RESEARCH CATALOGUE

RESEARCH WITHIN THE HEALTH SCIENCES AT AARHUS UNIVERSITY

AARHUS UNIVERSITY

Research Catalogue
Research within
the Health Sciences
at Aarhus University

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HEALTH AT AARHUS UNIVERSITY

FOCUS ON KNOWLEDGE EXCHANGE

In 2011, Aarhus University went through the most extensive reorganization in the institution's eighty-three-year history. Faculties and departments have been combined to form larger entities, and the entire university administration has been radically altered.

In the process Health, the main academic area embracing the health sciences, has also undergone change – especially with respect to the "basic" departments formerly existing as the Department of Anatomy, the Department of Physiology and Biophysics, the Department of Medical Biochemistry, the Department of Pharmacology, the Department of Human Genetics, and the Department of Medical Microbiology and Immunology. These legacy departments are now united in a single entity: the Department of Biomedicine.

The modifications to the other four departments at Health – the Department of Dentistry, the Department of Public Health, the Department of Clinical Medicine, and the Department of Forensic Medicine – have been modest.

An important element in this change process is a new professional and academic mindset that has enabled us to complement the university's existing core services – Research and Education – with two new, parallel services: Talent Development and Knowledge Exchange. Here at Health, we have created the Research Catalogue you have before you as our first step in promoting Knowledge Exchange, thereby offering a single comprehensive publi-cation that presents all of our areas of research skill and expertise. The subsequent steps in this process will be electronic, and will involve upgrading the university's Web site as a knowledge-sharing platform, incorporating video and other types of presentations.

This Research Catalogue is mainly addressed to our collaborating partners, including public authorities and the business community. Its aim is to briefly and succinctly show how, at one and the same time, the research environment at Health accommodates extremely specialized areas of expertise that make world-class contributions, and also fosters strong collaborations that transcend departmental boundaries. This publication went from idea to tangible reality in record time. The concept was set out in June 2011, and the catalogue was ready to go to press in December 2011. Completing this extensive undertaking was only possible thanks to contributions from a large number of key individuals, all of whom have done a huge job throughout the process. This bears witness to an exceptional spirit of commitment, and to a dedication that

demonstrates yet another area of special competence here at Health: the will to deliver results. It also shows that exchanging knowledge is something that all of our researchers take very seriously.

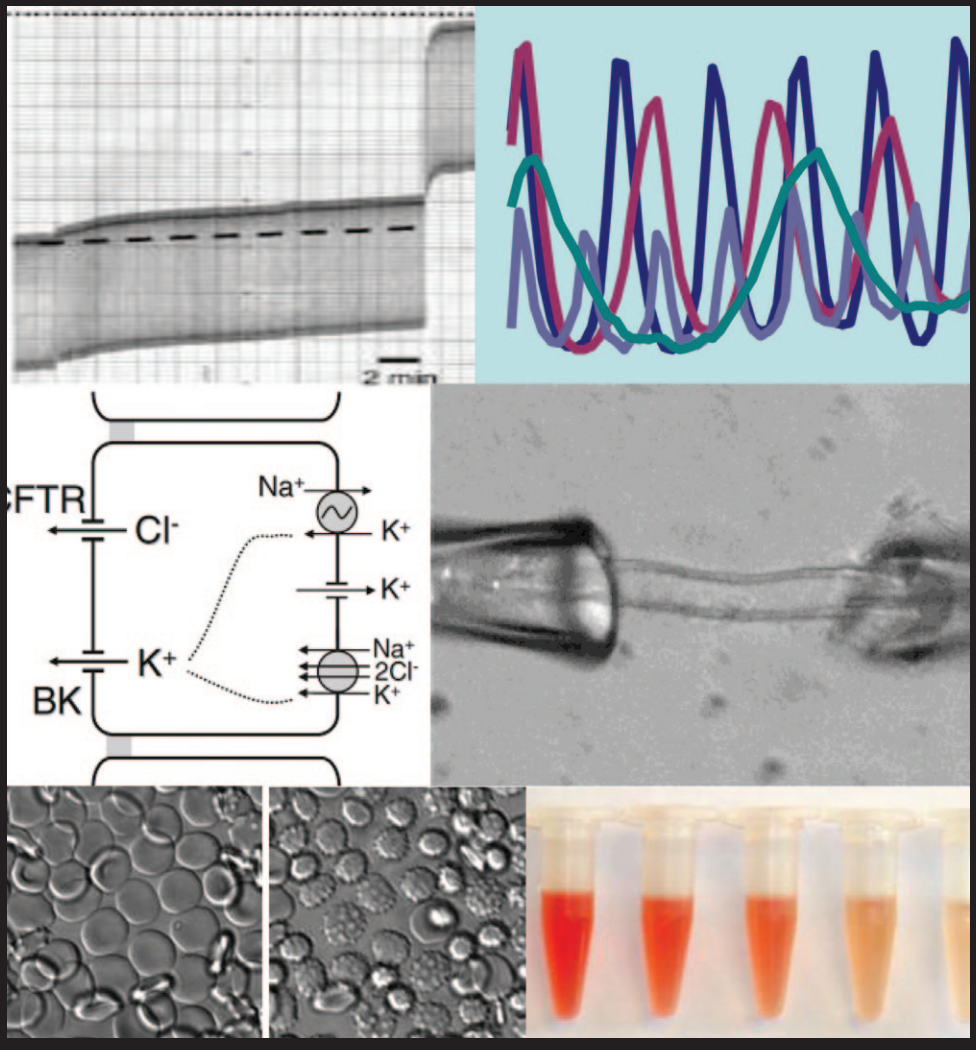
During the preparation of this Research Catalogue, the working group has also mapped the collaborative relationships that Health researchers have with other academic and scientific colleagues, and with partners in the private sector. This mapping has revealed an enormous network of cooperation and partnerships involving a wide variety of stakeholders and participants. This, too, reflects our strong commitment to knowledge exchange.

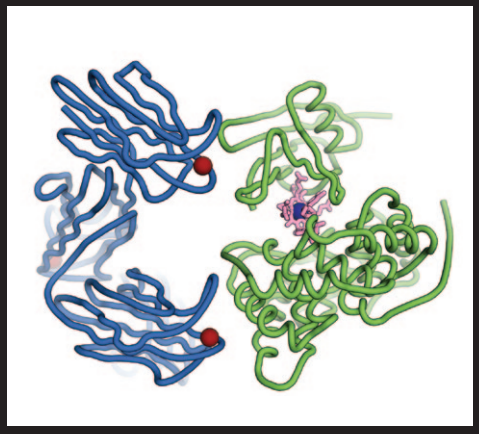
It is important to point out that this catalogue, with its brief and somewhat popularized form of expression, does not provide an exhaustive or fully detailed description of all the research activities and expert competencies at Health. Rather, it is an appetizer that takes a fresh approach to introducing people outside the university to the highly specialized areas in which our researchers and scientists work and excel. Hence, this catalogue can also be used by those wishing to contact, or learn more about, the special research expertise and competence that Aarhus University has to offer in the health sciences.

Extending my personal thanks to all those who have contributed to this publication is an impossible task. Six people do, however, merit special mention for their enormous efforts in the successful completion of the project: Michael J. Mulvany, Michael Pedersen, Vivi Schlünssen, Andreas Stavropoulos, Lars Uhrenholt, and Kirsten Olesen. They most particularly deserve credit and thanks for their part in ensuring that this complex project has now been brought to fruition.

Vice-Dean for Knowledge Exchange
J. Michael Hasenkam

BIOMEMBRANES

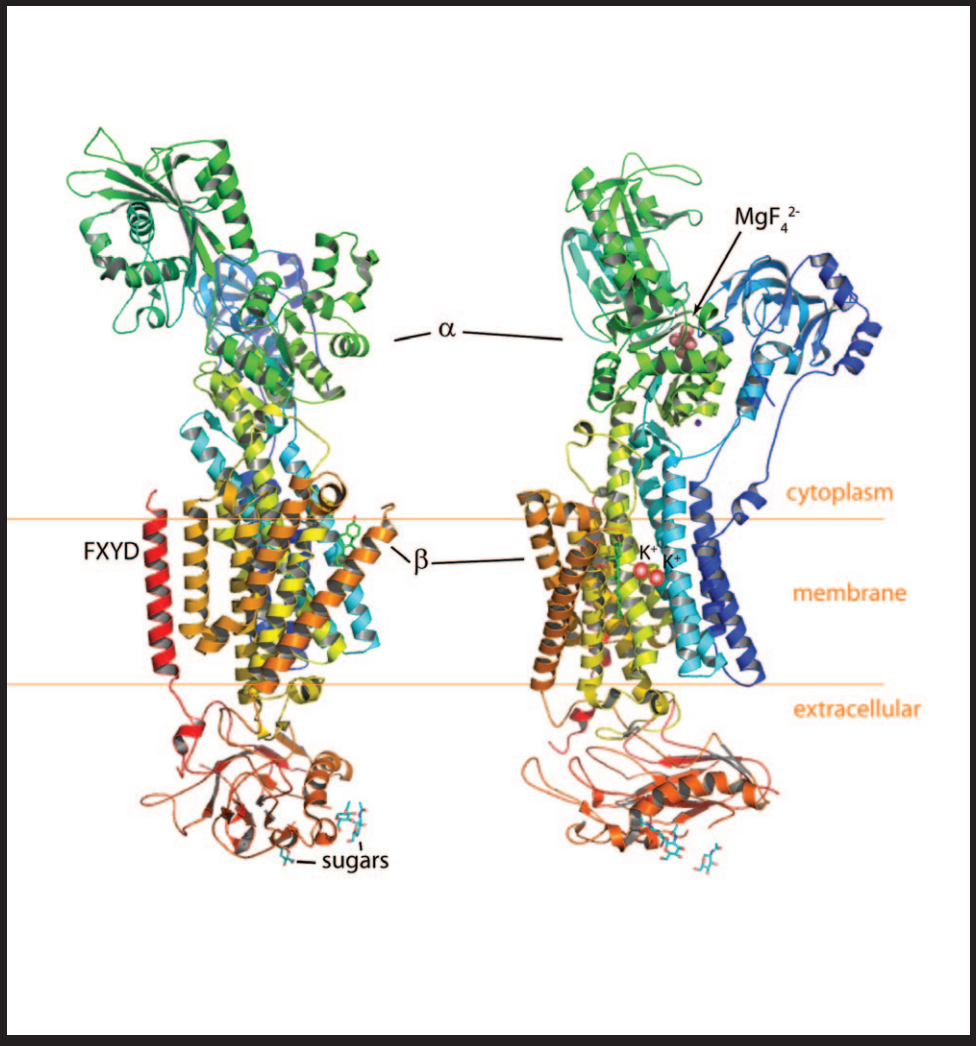




▲ Intrinsic factor (green) with bound vitamin B12 (pink) is recognized by the receptor cubilin (blue) in human intestinal tissue. The red spheres are calcium ions, essential to the bond.

◄ Collage of membrane transport in kidney, red blood cells, and intestinal tissue.

► The structure of Na+,K+-ATPase with bound phosphate analogue (MgF42–) and K+. The three units of the Na+,K+-ATPase – a, b, and the regulatory FXYD protein – are shown from two different angles.



MAKING THE LEAP **FROM 2D TO 3D**

Ever since the discovery of the Na+,K+-pump in 1957, research groups around the world have been studying its crucial significance for the vital transport of the sodium and potassium ions Na+ and K+ in every single cell in the body. And for just as long, one of the great unanswered questions has been: What does the Na+,K+-pump look like?

The scientific breakthrough

In 2007, researchers from Health, collaborating with colleagues from The Faculty of Science and Technology at AU, succeeded in obtaining a crystal structure of the Na+,K+-ATPase protein – enabling them to create a three-dimensional image. This was a scientific breakthrough that was featured on the cover of NATURE, and which very aptly coincided with the anniversary of Jens Christian Skou's initial discovery of the Na+,K+-pump at Health 50 years earlier. Knowledge of the structure of the Na+,K+-ATPase protein has made it possible to identify completely new areas of interest to this research field.

"The crystal structure showed us where the K+ ions are bound within the a-unit, and it also revealed something we weren't expecting: that the C-terminal tail is arranged in a very strategic way. This would turn out to be an important discovery," the researchers at Health recall. That discovery inspired a series of experiments at Health demonstrating that mutations in the tail area have a decisive impact on the transport of Na+. This new knowledge has helped researchers and clinicians all over the world to better understand the implications of the pathological mutations causing the neurological diseases rapid-onset dystonia parkinsonism and hemiplegic migraine.

In 2009, researchers at Health were able to obtain yet another crystal structure of the Na+,K+-ATPase protein, this time working with crystallographers at the University of Tokyo. Their work made it possible to explain the function of the so-called b-unit, as well as the structure of the binding site for cardiac glycosides; substances that have been used as drugs to treat cardiac diseases for two centuries.

The crystal structure showed us where the K+ ions are bound within the a-unit, and it also revealed something we weren't expecting: that the C-terminal tail is arranged in a very strategic way. This would turn out to be an important discovery.

FACTS

Professor Jens Christian Skou discovered and described the Na+,K+-pump in 1957. This pump functions as the cell's "nano engine", transporting the sodium and potassium ions Na+ and K+ through the cell membrane, and it is powered by energy from the hydrolysis of ATP molecules. In 1997, Professor Skou received the Nobel Prize in Chemistry for his discovery.

MEMBRANE PUMPS

The research in membrane pumps aims to explain the workings of Nature's smallest cellular engines and how, by interacting with other proteins in the cell, they are controlled in and through their cellular environment.

These processes are critical for the functions that power a number of the body's organs, including the brain, kidneys and muscles. In fact, the functioning and growth of all cells is dependent on the presence of membrane pumps. That is why membrane pumps are such vital biological mechanisms, and why their dysfunction often leads to illness.

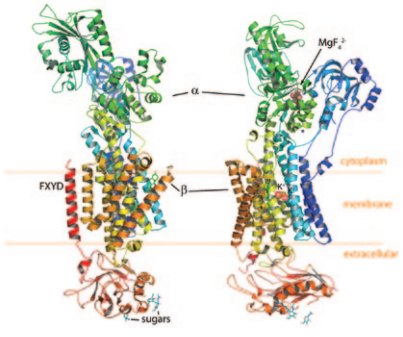
Today we know that many illnesses are associated with mutations and defects in the Na+,K+ (sodium–potassium) pump and the body's other membrane pumps; even diseases we have known and attempted to treat for many years, though without fully understanding their cause and development. Examples are the neurological diseases rapid-onset dystonia parkinsonism and hemiplegic migraine.

Ground-breaking snapshots

The goal is to gain a more thorough comprehension of membrane-pump functions, so that in the future we can use them to better understand and treat diseases. Also, and in quite a different context, we hope to find ways to more efficiently utilize energy in man-made engines.

In 2007 researchers at AU Health, working with colleagues at AU SCIENCE AND TECHNOLOGY, succeeded in determining a crystal structure of the Na+,K+-ATPase protein. This meant that suddenly we had access to a three-dimensional picture of the molecule behind the sodium–potassium pump, thus providing a completely new way to view the transport mechanism and pathogenic mutations. This enabled us to demonstrate that the protein's "tail" fulfils a pivotal role in the transport of Na+, which in turn explains the underlying pathophysiology in some of the patients suffering from rapid-onset dystonia parkinsonism.

In 2009 and 2011 we were able to create several snapshots of the Na+,K+-pump, and one of the forms captured has been shown to bind drugs used in the treatment of cardiac failure. Ongoing research efforts aim to generate and collect snapshots of the protein structure, and to compare this information with studies of functional changes induced by means of mutations. Ultimately, we hope to draw a clear picture of the pump's mechanism, its regulation, and its significance to disease.



The structure of Na+,K+-ATPase with bound phosphate analogue (MgF_4^{2-}) and K+. The three units of the Na+,K+-ATPase – a, b, and the regulatory FXYD protein – are shown from two different angles.

PROJECTS

1. The crystal structure of Na+,K+-ATPase has already been determined for the K+-bound form. Researchers are now attempting to crystallize the Na+-bound form in order to identify the Na+ binding sites, and understand the structural basis for alternation of the pump between selective binding of Na+ and K+, respectively.

2. Na+,K+-ATPase mutations found in patients with rapid-onset dystonia parkinsonism affect the binding of Na+. One of these mutations is localized in the C-terminal tail, while another is found in a channel-like structure in the Na+,K+-ATPase. Current investigations are clarifying whether the channel-like structure forms the transport path for Na+, and whether the opening of the transport path is regulated by interaction with the C-terminal tail.

3. In cardiac muscle cells, Na+,K+-ATPase is regulated by a small membrane protein – phospholemman (PLM) – that acts as an inhibitor. In connection with the phosphorylation of PLM via protein kinases, the inhibition is relieved. The interaction between PLM and Na+,K+-ATPase is now being studied with a view to influencing this mutual interaction as part of a new therapeutic goal for treating cardiac disease.

4. A newly discovered group of membrane pumps called "flippases" transport, or "flip", amino phospholipids from the outer part of the cell membrane's lipid bilayer to the inner part, thereby creating the asymmetrical lipid distribution that enables fertilization, cell division, and other processes. Our hypothesis is that these flippases function by means of a mechanism similar to that of the Na+,K+-pump, and we are investigating this by identifying the functional changes that result from inserting a series of strategically positioned mutations.

METHODS

Scientists at Health use these and other methods to study the structure and mechanisms of membrane pumps:

- Differential and gradient centrifugation, and detergent extraction of membranes from kidneys and shark rectal glands to produce highly purified Na+,K+-ATPase preparations that can be used, for instance, for crystal-structure determination. Similar centrifugation procedures and immune affinity purification for other membrane pumps (including Ca2+-ATPase, H+,K+-ATPase, and flippases).
- Insertion of purified detergent solubilized pump protein in well-defined lipid vesicles, and transport studies of same.
- Site-directed mutagenesis (introduction of selected mutations into DNA), followed by the expression of mutant pump proteins in cell cultures and animal models.
- Investigation of the individual reaction steps in the pump process, including phosphorylation and dephosphorylation, binding and dissociation of ions, nucleotides and specific inhibitors by means of enzyme-kinetic methods (including the use of radioactive isotopes and fluorescent probes in conjunction with stopped-flow and quenched-flow techniques).
- Investigation of conformational states in pump proteins and their interaction with ATP and membrane lipids using spectroscopic methods (including fluorescence, nuclear magnetic resonance, and electron-spin resonance) and proteolytic cleavage.

MILESTONES

Discovery of Na+,K+-ATPase, published in a historical article from Health that was later awarded a Nobel Prize
(Skou JC. Biochim Biophys Acta. 1957;23:394–401)

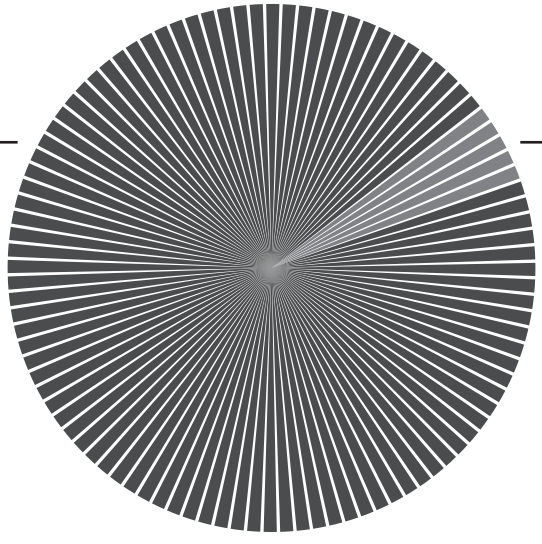
Determining which amino acids in Ca2+-ATPase bind either of the two Ca2+ ions during transport
(Andersen JP, Vilsen B. J Biol Chem. 1994;269:15931–6)

Presenting the crystal structure of Na+,K+-ATPase, and demonstrating the C-terminal tail's role in Na+ binding by means of mutational analysis
(Morth JP, et al. Nature. 2007;450:1043–9. Vilsen B and Nissen P both corresponding authors)

Presenting the crystal structure of Na+,K+-ATPase in very high resolution, showing the role of the b-subunit in K+ binding
(Shinoda T, et al. Nature. 2009;459:446–50)

Presenting the crystal structure of Na+,K+-ATPase, showing the binding site for cardiac glycoside
(Yatime L, et al. J Struct Biol. 2011;174:296–306)

OVERVIEW



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MEMBRANE TRANSPORT

The membrane of a cell constitutes the boundary between the cell's interior and its surroundings. The membrane is therefore necessary to guard the internal cell environment. All exchanges with the cell's surroundings take place through its membrane by means of special channels or transport proteins.

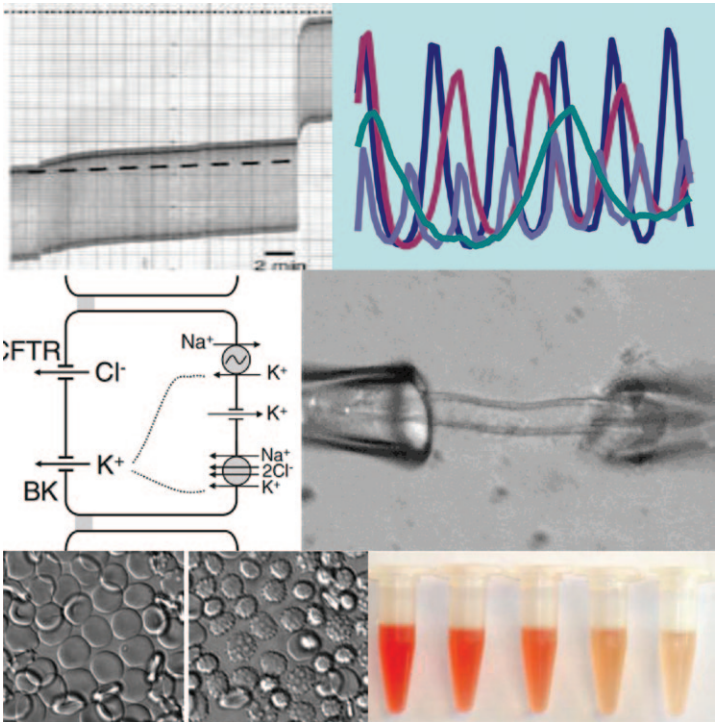
Deviations can lead to grave illness. One example is the hereditary condition cystic fibrosis, in which a failure to transport ions leads to serious respiratory problems. The inadequate transport means that the mucus formed in the lungs cannot be led upwards and out of the respiratory tract.

Because the altered functioning of membrane transporters often results in illness, it is important to scientifically investigate how transport and communication processes across the cell membrane take place. This understanding is fundamental to implementing a rational strategy for treatment.

Working across research groups and fields
Aarhus University holds a strong international position in the field of membrane transport, and this has created a particularly conducive and inspirational local research environment. Although we do research on membrane transport on a molecular and cellular scale, we consistently see our scientific efforts in the light of pathology and treatment. One reason for this is that physicians, with their knowledge of clinical work, hold a pivotal position within the group, which also includes biologists and molecular biologists.

When seeking to understand a disease in relation to transport across the cell membrane, we frequently collaborate with other research areas, such as genetics. Often the geneticists have already identified the defective gene that causes a particular condition. Animal models and other methods are used to investigate the functional significance of the genetic defect, and in this way our group can help to explain the consequences of specific genetic defects.

The transmembranal processes in our cells are of paramount importance to all of the body's systems. That is why the membrane transport group embraces many organ-specific research areas. And it is precisely this inspiration – passing across boundaries, to and from other fields – that promotes our scientific endeavours to find basic explanations for the interactions running from molecular level to disease manifestation and treatment.



Collage of membrane transport in kidney, red blood cells, and intestinal tissue.

PROJECTS

1. **Pore-mediated cell damage.** Many types of bacteria secrete toxins that form pores in the membranes of other cells, thereby destroying them. We have demonstrated that the pore does not cause any actual cell damage in itself, but that the toxins activates specific membrane signals that lead to cell damage. Our particular concern is to prevent this type of cell damage from occurring by affecting the cell's own signal pathways.

2. **The kidney's transport function.** The kidney is a vital organ responsible for the excretion of waste materials, water, and salt. We have found that urine excretion is regulated by the local signal substance ATP. This project aims to determine when and how ATP is released from the kidney's cells.

3. **The colon's excretion of potassium.** Like the kidney, the colon plays a central role in the body's salt and water balance. The intestine is particularly important for the potassium (K) balance. The unit's researchers have established that the colonic excretion of K+ solely takes place through specific "BK channels". In other words, this type of channel is an excellent point of attack when seeking to either stimulate or inhibit intestinal excretion. Intensive efforts are under way to establish the significance of local regulators for the excretion of K+ in the colon.

MILESTONES

Discovering the primary cilium as a flow sensor
(Praetorius HA. J Membr Biol. 2001;184:71–9)

Luminal ATP as antidiuretic signalling factor in the kidney
(Leipziger J. Am J Physiol. 2003;284:F419–F432)

BK channels in epithelial K+ secretion
(Sausbier M. JASN. 2005;17:1275–12)

Extracellular ATP signalling in red blood cells
(Skals M. Proc Natl Acad Sci USA. 2009;106:4030–5)

METHODS

Membrane transport is studied and quantified using methods optimized for direct observation in living tissue. These methods include:

- Live cell imaging: Wide-field/confocal and total internal reflection microscopy, and other techniques, to measure intracellular ion concentrations and determine vesicular release
- Electrophysiological methods: Patch clamp, Ussing chamber, microelectrodes to determine ion transport
- Flow cytometry: Alterations in cell volume, surface, and apoptose markers

OVERVIEW

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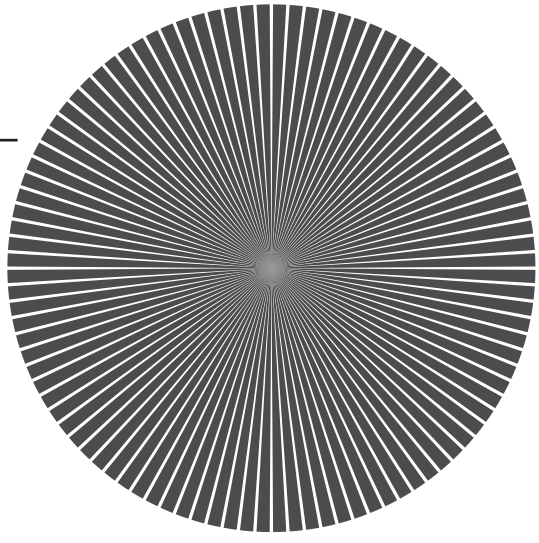
Basic research



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RECEPTOR RECOGNITION

Cells are constantly interacting with their surroundings. This is an essential process enabling the absorption, excretion, and transport of nutrients and waste materials, not only at a cellular level but also for the body as a whole. The receptor research conducted at Health has been instrumental in the discovery and characterization of previously unknown receptors, co-receptors, and other transport mechanisms relating to the absorption of such substances as haemoglobin and vitamin B12, as well as various enzymes and therapeutic drugs.

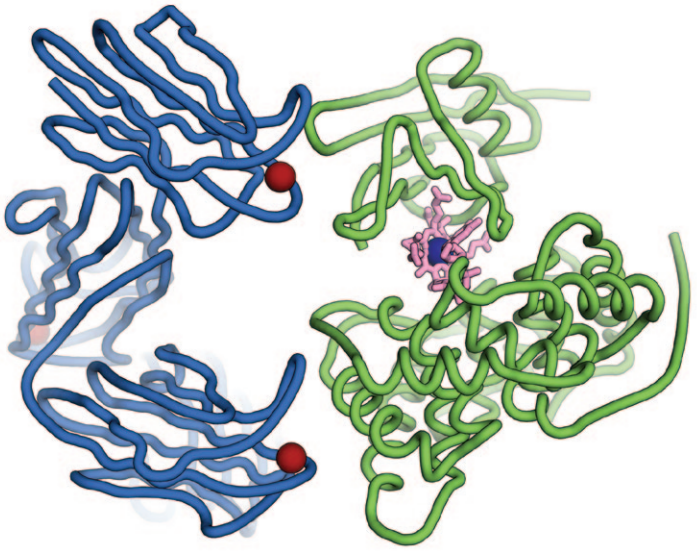
Part of this process is carried out by a variety of receptors that circulate between the surface and the interior of the cell. It is important to identify the receptors linked to the relevant substances and to characterize their structure in order to understand the fundamental mechanisms at work. This is because such mechanisms can explain biological phenomena and diseases that arise when receptors do not work properly. A well-know example is the serious hardening of the arteries caused by a defect in the receptor for cholesterol uptake. Furthermore, the new information on these receptors can lead to new medical therapies – for instance by exploiting the transport function of receptors to deliver drugs to the appropriate cells, thereby avoiding or reducing undesirable side effects. In its programme for developing new receptor-targeting drugs, the research team focuses on cancer and inflammatory diseases.

Improving medical treatment and diagnostics

The receptor research conducted addresses questions like:

- What is the structure of a particular receptor?
- How does the receptor interact with substances in its surroundings?
- How can receptors help us to better diagnose disease?
- How can receptors help us to increase the therapeutic effect of medications and reduce side effects?

In 2006 the receptor researchers at Health made a discovery that unexpectedly led to interesting findings and new developments relating to trypanosomiasis, commonly known as sleeping sickness. Refuting previous assumptions, they demonstrated that haptoglobin-related protein binds haemoglobin from red blood cells. Based on their findings the team began collaborating with a group of Belgian researchers, leading in turn to the discovery of hitherto unknown immune-system defence mechanisms against sleeping sickness. In time, this discovery may help scientists develop drugs against a disease that incapacitates tens of thousands of people in Africa every year. The Danish–Belgian research team is now also working in this direction.



Intrinsic factor (green) with bound vitamin B12 (pink) is recognized by the receptor cubilin (blue) in human intestinal tissue. The red spheres are calcium ions, essential to the bond.

PROJECTS

1. Identification of the 3-dimensional structure of the haptoglobin–haemoglobin receptor complex in mammals and in trypanosomiasis parasites.
2. Investigation of the haptoglobin–haemoglobin system in mice using genetic knock-out models.
3. Use of endocytic receptors to direct therapeutic drugs to specific cells, including use of the receptor CD163 to direct anti-inflammatory drugs to macrophages involved in infection; studies of inflammatory animal models (for example regarding arthritis and hardening of the arteries).
4. Development of liposomes for receptor-mediated drug delivery.
5. Use of receptors, including CD163, for imaging of inflammatory processes.

MILESTONES

Identification of the haemoglobin scavenger receptor
(Kristiansen M, et al. Nature. 2001;409:198–201)

The functional cobalamin (vitamin B12)-intrinsic factor receptor is a novel complex of cubilin and amnionless
(Fyfe JC, et al. Blood. 2004;103:1573–9)

Discovery of hitherto unknown immune-system defence mechanisms against sleeping sickness
(Vanhollebeke B. Science. 2008;320:677–81)

Resolving the three-dimensional X-ray structure of a receptor–receptor complex
(Andersen CB, et al. Nature. 2010;464:445–8)

Identification of multidrug resistance protein 1 (MRP1/ABCC1) as a molecular gate for cellular export of cobalamin
(Beedholm-Ebsen R, et al. Blood. 2010;115:1632–9)

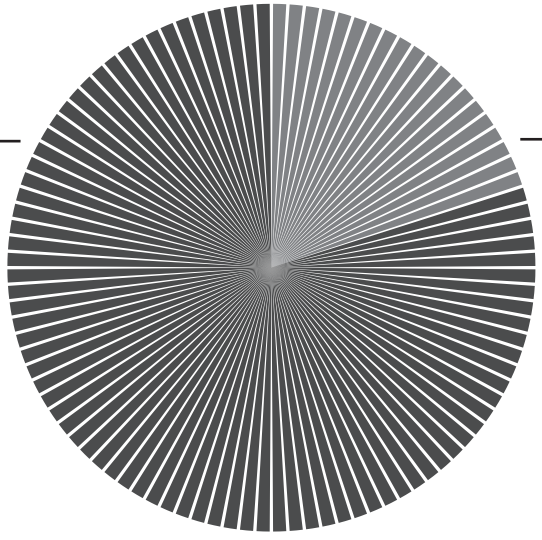
METHODS

The receptor research labs at Health use X-ray crystallography to study the three-dimensional structure of receptors, their recognition of ligands, and their function.

These studies form the basis for further investigations into how endocytic receptors can be used to augment the therapeutic index of the drugs examined. The research group also explores how receptors can be used in diagnostics through the development of in vivo imaging techniques and new biomarkers. Our methods include:

- Creation of recombinant proteins using biotechnological processes that involve bacteria, yeasts, and mammalian cell cultures
- Examination of proteins, DNA, and RNA using methods from the field of molecular biology
- Cell culturing
- X-ray crystallography studies of receptors' three-dimensional structure and ligand recognition
- Confocal scanning
- Live imaging
- Surface plasmon resonance
- Gene modification

OVERVIEW



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WATER AND SALT IN HEALTH AND DISEASE

Tight regulation of water and salt balance is of crucial importance. Several diseases are associated with large alterations in body water and salt balance. Investigating the channels and transport proteins that are responsible for regulation of water and salt balance is a field that has made substantial progress over the past 20 years. The molecular identification of the key players, along with the integrated regulation of these in the kidney and other organs, has been a major breakthrough.

We study how water and salt are transported across cell membranes in the kidneys and other organs, and explore how this transport is regulated at the molecular, cellular, and integrated levels. The aim of our research is to more fully understand the molecular and cellular mechanisms that control these processes.

Our efforts have yielded profound insights into the water channels and sodium transport proteins responsible for water and salt balance, which in turn creates entirely new opportunities for improving the treatment of serious imbalances of this nature. One key goal is to learn more about the dysregulation of these processes in connection with a number of commonly occurring diseases, including kidney and cardiovascular diseases, hypertension, and diabetes.

Research leaders
Our researchers already work with a wide variety of methods, ranging from molecular structural analyses that apply electron microscopy techniques, to methods from molecular and cell biology, and functional physiological methods that include the development of transgenic animal models. We also work with a series of disease models in experimental animals to better understand how our research findings fit into a clinical context, and how they can enable us to improve treatment of the diseases associated with serious water and salt imbalances.

Our special skills and expertise in this field rank at an international level, and this has enabled Aarhus University to attract leading international researchers. This is not solely due to the merits of the research community that has evolved around the Water and Salt Research Center (a basic-research centre of excellence founded and supported by the Danish National Research Foundation); it is also, most particularly, due to the excellent international reputation of the university's membrane-protein research environment at large.

Internationally, we collaborate very closely with leading researchers abroad, one notable example being our 20-year cooperation with Professor Peter Agre of Johns Hopkins University. In 2003, Professor Agre received the Nobel Prize in Chemistry for his discovery of aquaporin water channels. These and other international research partnerships have played a central role in the founding and expansion of this new research field.

PROJECTS

1. Identifying the molecular mechanisms involved in regulating water channels in the kidney and other organs, through the application of methods from molecular biology, cell biology, proteome/bioinformatics, and high-resolution structural biology.

2. Developing transgenic animal models to yield insights into the significance of new aquaporins and aquaglyceroporins in the kidney, liver, pancreas, and brain. The aim is to understand their physiological role, and their role in diseases such as cerebral oedema and metabolic diseases (diabetes).

3. Developing aquaporin and aquaglyceroporin inhibitors. Such inhibitors are essential tools if we are to understand the fundamental significance of these channels and, looking forward, if we are to identify new targets that can advance the development of new medications.

4. Functionally characterizing transporters of sodium bicarbonate, for instance in transgenic mice, to understand their physiological significance in the kidney, central nervous system, and elsewhere.

5. Clarifying (parallel to the analysis of water channels) the molecular mechanisms involved in regulating the epithelial sodium channel (ENaC) and sodium co-transport proteins, including structural and functional analyses.

MILESTONES

Vasopressin increases water permeability in the kidney's collecting tubule by translocating aquaporin-2 water channels to the plasma membrane – consequently demonstrating a fundamental process that is decisive to the kidney's regulation of the body's water balance (Nielsen S, et al. Proc Natl Acad Sci USA. 1995;92:1013–17; and Rojek A, et al. Proc Natl Acad Sci USA. 2006;103:6037–60; and Fenton RA. Proc Natl Acad Sci USA. 2008;105:3134–39)

Aquaglyceroporin AQP9 controls the liver's absorption of glycerol, and is regulated by insulin. This shows a fundamental new function of aquaglyceroporins, which potentially play an important role for diabetes (Rojek AM, et al. Proc Natl Acad Sci USA. 2007;104:3609–14; and Carbrey JM, et al. Proc Natl Acad Sci USA. 2003;100:2945–50)

Vasopressin stimulates phosphorylation of AQP2 for the regulation of intracellular traffic of AQP2, and the regulation of water transport in the kidney's collecting tubule (Hoffert JD, et al. J Biol Chem. 2008;283:24617–27; and Moeller HB, et al. Kidney Int. 2009;75:295–303; and Moeller HB, et al. Proc Natl Acad Sci. 2010;107:424–9)

Development of inhibitors for specific inhibition of certain aquaporin isoforms. These can be used to clarify the significance of aquaporins to specific organ systems, and to gain insight into the potential significance of aquaglyceroporins for a number of diseases, and as a target for treatment of metabolic and other diseases (Jelen S, et al. J Biol Chem. 2011; 286:44319-25)

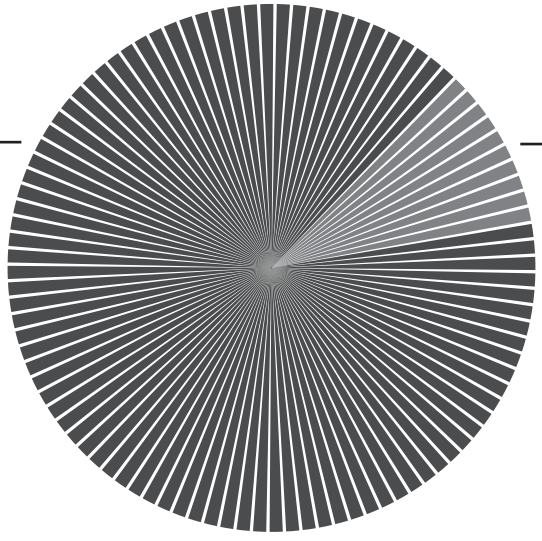
Transgenic mouse models have shown that expression of the sodium channel ENaC in a particular segment of the kidney's tubule system is of crucial importance to maintaining the body's salt balance (Christensen BM, et al. J Am Soc Nephrol. 2010;21:1942–51)

METHODS

We employ many diverse methods to analyse membrane channels and transporters: molecular and cell biology, structural biology, transgenic mice, physiology, and pathophysiology.

- Cell expression systems
- Confocal/microscopic analyses of intracellular traffic of membrane proteins in live or fixated cells
- Electron microscopy
- Single-particle cryoelectron microscopy
- Immunocytochemistry, immunohistochemistry, immunoblotting and similar techniques
- Biochemical and imaging analyses of intracellular protein trafficking
- Development and phenotyping of transgenic mouse models
- Functional studies at different levels: cellular, organ, and organism
- Disease models/pathophysiological animal experiments
- Design, development, and functional characterization of pharmacological inhibitors of channel proteins

OVERVIEW



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Basic research

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Clinical research

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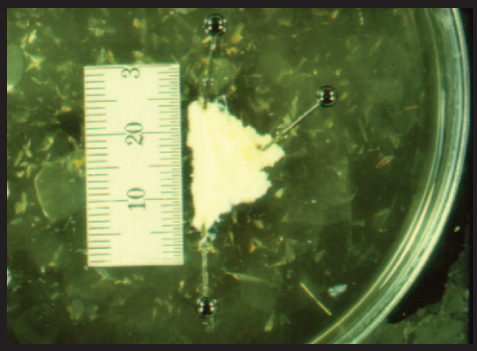
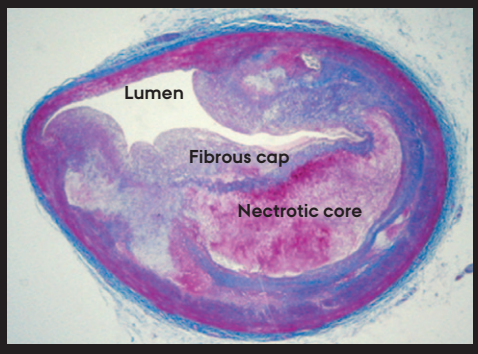
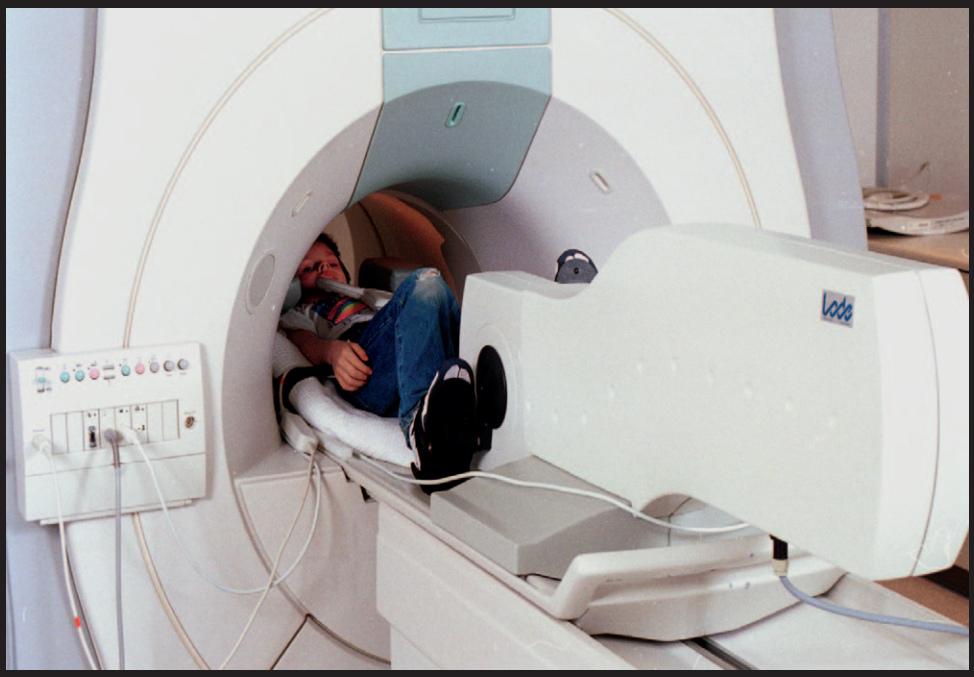
CARDIOVASCULAR



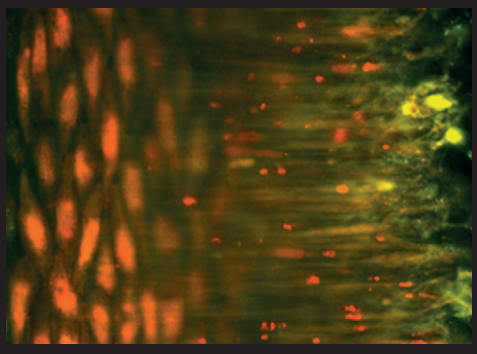
▲ Skin biopsy containing small arteries (0.2 mm in diameter) in fatty tissue (at right). The arteries are studied using a myograph. Biopsy taken from a human subject in local anaesthesia. Scale shows millimetres.

▼ Atherosclerosis lesion in a coronary artery from a pig with elevated plasma cholesterol. This lesion resembles a "vulnerable plaque", which in humans gives rise to life-threatening thrombus formation in the coronary and cerebral arteries.

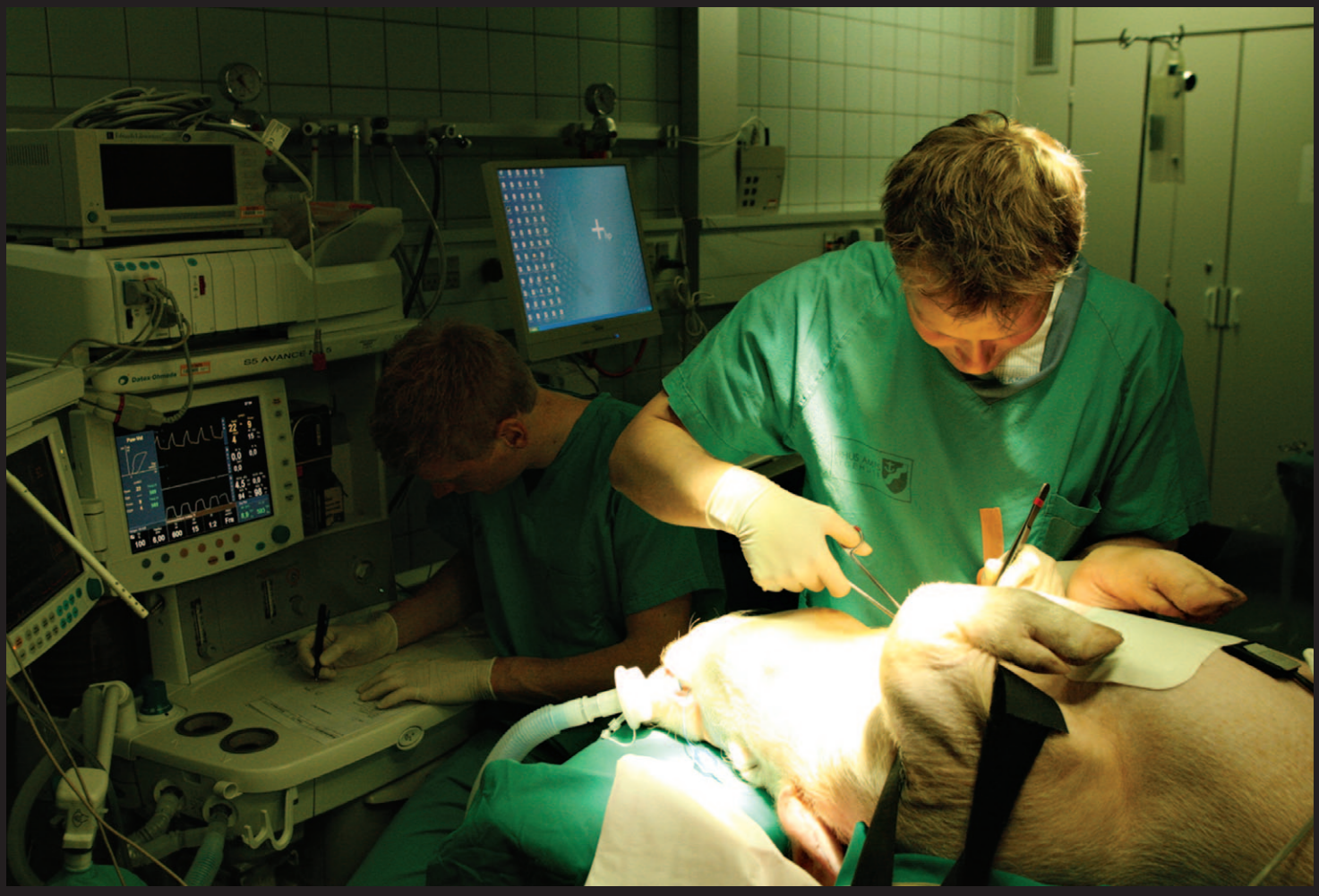




▲ Modern diagnostic techniques help children with heart disease.



► Simultaneous Ca2+ signals in endothelial cells (left), smooth muscle cells (middle), and nerves (right) obtained with confocal microscope."



▲ Research-year medical students preparing renal transplantation.

ATHEROSCLEROSIS

The development of fatty plaques in the arteries – atherosclerosis – is a common cause of death and disability. The burden of disease is enormous, both on an individual level for affected patients and in socio-economic terms. The benefits of improving prevention, diagnosis, and treatment are therefore considerable. Our aim is to shed light on the fundamental molecular, cellular, and physiological mechanisms associated with this disease. Better treatment calls for better diagnostic and therapeutic medications, and their development depends on good animal models, expert competence, and the right tools for studying arterial plaques. Because atherosclerosis is linked to several other major life-style diseases, its association with such conditions as diabetes, obesity, and hypertension is explored.

A core facility with unique animal models
The atherosclerosis research at Health has excellent scientific opportunities by virtue of the faculty's strong position and expertise in the basic-research capabilities that our field requires – in conjunction with our invaluable access to cloned pig models that develop hypercholesterolaemia and atherosclerosis mimicking the arterial disease observed in humans. These porcine models were developed after years of research, based, among other things, on our solid experience with corresponding mouse models that enabled us to describe the process of arterial-plaque development. This has paved the way for conducting relevant preclinical trials on pigs that physiologically resemble patients with the corresponding condition, putting atherosclerosis research at Health at the forefront of its field worldwide. We are helping to develop new diagnostic technologies (based on imaging) and new therapeutic principles to ensure rapid and effective implementation in the treatment of patients (translational research).

Our research group ranks alongside the best of its international peers. In addition to the faculty's unique porcine models, we also have access to state-of-the-art laboratories and technologies such as MRI, ultrasound, CT, SPECT, and PET. And working closely with cardiologists, we can conduct diagnostic and therapeutic investigations of porcine coronary arteries, applying advanced interventional techniques and devices that include stenting, IVUS, OCT, and NIRS. We further collaborate with other groups and units at Health, and with recognized research groups from Denmark and abroad.

MILESTONES

Cloning of the world's first transgenic minipig with high cholesterol and spontaneous development of atherosclerosis
(Bentzon JF, et al. Submitted. Dec 2011)

Invited comment in one of the world's leading medical journals, substantiating the advantages of imaging in screening for atherosclerosis
(Sillesen H, et al. Lancet. 2011;378:645–6)

Newly developed mouse models controvert the prevalent hypothesis that the endothelial cells in blood vessels may originate from circulating progenitor cells
(Hagensen MK, et al. Circulation. 2010;121:898–905)

A widespread imaging technique for detection of vulnerable atherosclerotic plaques (Virtual Histology) is tested in porcine coronary arteries and found to be unreliable
(Thim T, et al. Circ Cardiovasc Imaging. 2010;3:384–91)

Original mouse models reject the prevalent hypothesis that the smooth muscle cells in atherosclerotic plaques may originate from circulating progenitor cells
(Bentzon JF, et al. Circulation. 2007;116:2053–61)

PROJECTS

Developing and studying transgenic animal models for:

1. **Hypertension and atherosclerosis:** Studies of newly developed pig and mouse models to find out why hypertension promotes the development of arterial plaques, with special focus on cellular and molecular mechanisms. Hypertension is induced in hypercholesterolaemic pigs by constricting the abdominal aorta just above the renal arteries.

2. **Diabetes and macrovascular disease (atherosclerosis):** It is unknown why diabetes accelerates the development of arterial plaques. We are studying this in pigs and mice with elevated cholesterol levels, in which the insulin-producing cells of the pancreas are medically destroyed.

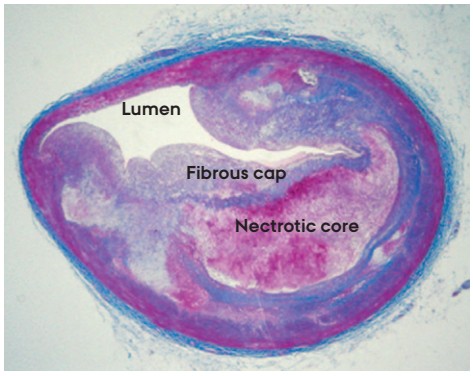
3. **Obesity and atherosclerosis:** The links between obesity, insulin resistance, and atherosclerosis are being studied in a newly developed pig model.

4. **Atherosclerosis imaging:** Both invasive and non-invasive imaging techniques are used in all projects to monitor the development of atherosclerosis in live pigs, and to subsequently compare imaging results with findings post-mortem.

5. **Atherosclerosis treatment:** Potential new treatments for atherosclerosis and vulnerable plaques are tested in the preclinical phase.

METHODS

- Animal models of atherosclerosis, particularly transgenic mice and pigs
- Cell culturing
- Techniques from molecular biology
- Pathology, including immunohistochemistry
- Non-invasive imaging (MRI, ultrasound, CT, SPECT, and PET)
- Invasive imaging (IVUS, OCT, NIRS, and other techniques)
- Percutaneous coronary intervention (PCI)



Atherosclerosis lesion in a coronary artery from a pig with elevated plasma cholesterol. This lesion resembles a "vulnerable plaque", which in humans gives rise to life-threatening thrombus formation in the coronary and cerebral arteries.

OVERVIEW

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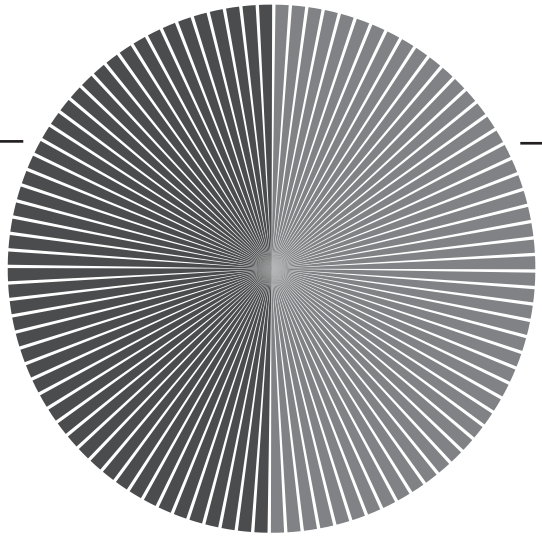

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Epidemiological research

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NEPHROLOGY

Kidney disorders, both acute and chronic, increase the risk not only of kidney failure, which ultimately requires dialysis treatment, but also of attendant conditions such as heart problems and premature death. Chronic kidney disorders affect about 10% of the Danish population and the incidence of acute kidney failure is on the rise. Both types of conditions therefore take their toll, personally and socio-economically.

We must uncover the underlying mechanisms if we are to prevent the type of damage that can develop into kidney failure. Treatment of kidney failure is demanding and costly, both for the individual patient and for society as a whole. This applies to surgical transplant procedures and to dialysis treatment, which uses technical equipment to remove waste substances and regulate the body's water-salt balance, and it also applies to the therapeutic drugs needed to rectify some of the numerous body-function disorders that accompany renal conditions.

Based on issues raised in the clinic, researchers plan and conduct investigations that range from cell function and control, over animal models involving gene-manipulated mice and pig experiments, and finally to clinical studies. At present we are setting up biobanks with samples of kidney tissue, blood, and urine, which will allow us to pursue new hypotheses using the latest scientific methods.

Ground-breaking research in renal protein treatment

Health has earned recognition in the international research community for determining the excretion of proteins in urine – one of the earliest signs of kidney damage. Research efforts mainly concentrate on the receptors megalin and cubilin, which are responsible for protein reuptake in the kidneys. In recent years our investigations of these two receptors, conducted using receptor-knockout mice, have resulted in frequently cited articles in well-reputed international journals.

A different, and new, research area that holds great promise is the prevention and treatment of Acute Kidney Injury (AKI). This condition can arise if, for instance, the body is subject to a surgical procedure or a serious infection, or in connection with a kidney transplantation. When AKI occurs, the kidney stops excreting urine and waste substances as it should, and this can have serious consequences for the patient. One aim of our research is to minimize complications and improve the long-term results of kidney transplantation.

High blood pressure damages the kidneys, and a reduction in kidney function in turn damages the body's arteries. Studies are under way to assess the value of various therapeutic drugs combined with removal of the nerves leading to the kidneys, and scientists are seeking to develop good methods for assessing blood-vessel function.

PROJECTS

1. **The significance of receptor-mediated endocytosis (megalin/cubilin) for the progression of proteinuria:** Clarifying the impact of the kidney's ability to absorb proteins as a chronic kidney disease progresses.

2. **Receptor-mediated endocytosis as a therapeutic goal:** Using megalin, cubilin, and other receptors as mediators for the absorption, "uptake", of therapeutic drugs in the treatment of kidney disorders and other conditions.

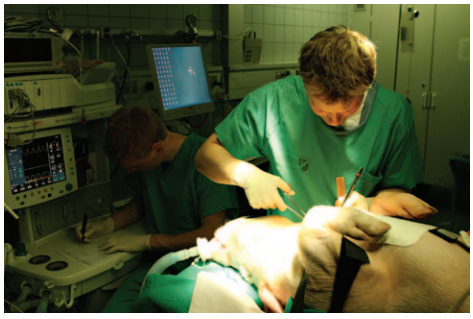
3. **The significance of receptor dysfunction in human illness:** Clarifying the human phenotype by looking at congenital defects in the body's megalin/cubilin function, thereby also clarifying the physiological significance of these proteins to humans.

4. **The CONTEXT study:** Can Acute Kidney Injury in kidney transplants be prevented by remote ischaemic conditioning, by means of brief, repeated clamping of the blood supply to one leg before opening the blood supply to the transplanted kidney?

5. **The SAFIR study:** Can renal and cardiac functioning be stabilized among

dialysis patients by using an angiotensin-II receptor antagonist (a drug that reduces blood pressure)?

6. **The RenVas project**: Investigating whether the structure of the body's tiniest blood vessels affects the loss of renal function, by examining blood-vessel resistance and blood flow to the kidneys and by precisely measuring renal filtration capacity.



Research-year medical students preparing renal transplantation.

MILESTONES

Description of the uriniferous tubule: structural and functional organization
(Christensen EI, et al. In: Pollock DM, Garvin J, editors. Comprehensive Physiology. Renal Physiology. Wiley-Blackwell: 2012:2,1–56)

Study of a patient with cubilin deficiency
(Storm T, et al. N Eng J Med. 2011;364:89–91)

Mouse model of proximal tubule endocytic dysfunction
(Weyer K, et al. Nephrology, Dialysis, Transplantation. 2011;26:3446–51)

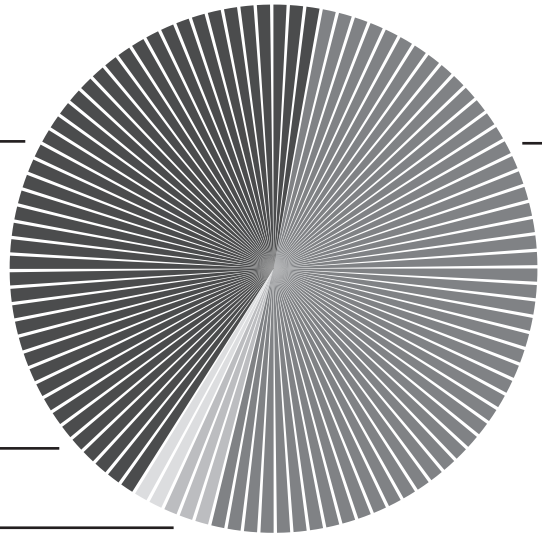
Preserving residual renal function in dialysis patients; an update on evidence to assist clinical decision-making
(Kjærgaard KD, et al. Nephrology Dialysis Transplantation Plus. 2011;4:225–30)

Effect of remote ischaemic conditioning on dendritic cell number in blood after renal transplantation – flow cytometry in a porcine model
(Ravlo K, et al. Transpl Immunol. 2011; Epub ahead of print)

METHODS

- Experimental animal models: tissue-specific constitutive and inducible gene knockout mice, and ischaemia/reperfusion and transplantation models using pigs
- Clinical randomized studies and analyses of patient material, and epidemiological studies
- Measurement of renal function using tracer-substance techniques; measurement of pulse-wave velocity, central blood pressure, and heart rate variability, plethysmography; measurement of blood flow in the renal arteries, and of the oxygen content in renal tissue using contrast-free MR scanning
- Establishment of biobanks with tissue, blood, and urine samples
- Cell-culture studies, light and electron microscope analyses, immunohistochemistry; biochemical analyses of blood, urine, tissue, and cells; and molecular-biology analyses (mRNA purification, Q-PCR, mutation analyses).

OVERVIEW



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PULMONARY AND CARDIOVASCULAR PHARMACOLOGY

Although world-wide hundreds of millions of people live with high blood pressure, we just need to go back a few decades to find a time when hypertension could only be registered with a blood-pressure cuff, or as a variety of serious attendant illnesses in patients suffering from this condition.

Scientists lacked conclusive knowledge of the pathological mechanisms in the human organism that cause hypertension. Today we know that the structure and reactivity of the body's smallest arteries plays a decisive role, not just to our entire circulatory system but also in the development of hypertension. And we know this thanks to research done at Aarhus University, where colleagues working in the 1970s and 1980s developed a series of ground-breaking methods to extract biopsies and examine what goes on in the small arteries. Up until that time these arteries – being extremely small; about 1/10 mm in diameter – were a terra incognita in the human organism. Now the methods pioneered in Aarhus are used around the world.

Because we are now capable of investigating the human body's smallest arteries in minute detail and studying their structure and function, we can address such questions as:

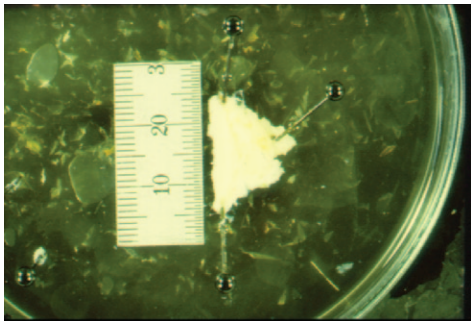
- To what extent are abnormalities in the small arteries a root cause of hypertension?
- How can these abnormalities be normalized?
- Can normalizing abnormalities reduce the risk of contracting diseases of the heart, lungs, and circulatory system?

New therapeutic drugs and treatments

These days we are utilizing this knowledge as we work to develop medication that not only reduces blood pressure but also specifically works to normalize blood vessel structure, or to prevent abnormalities from developing in, for instance, the innermost cell layer of the blood vessels (endothelial-cell dysfunction).

Knowledge about the small blood vessels also offers new perspectives for the treatment of pulmonary hypertension – excess pressure in the pulmonary circulatory system . This is a condition that currently cannot be treated, and which typically reduces by half the life expectancy of patients with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD).

We also monitor population groups over time to investigate the correlation between abnormalities in blood-vessel structure and the development of hypertension.



Skin biopsy containing small arteries (0.2 mm in diameter) in fatty tissue (at right). The arteries are studied using a myograph. Biopsy taken from a human subject in local anaesthesia. Scale shows millimetres.

PROJECTS

1. Development of treatment strategies to normalize blood-vessel structure in individuals with hypertension, and prospective studies to examine whether these strategies can reduce the risk of cardiovascular diseases.

2. Investigation of molecular mechanisms responsible for abnormal blood-vessel structure in individuals with hypertension.

3. Description of the scope and development of treatments for pulmonary hypertension in patients with COPD and ILD. These activities take place at the Pulmonary Vascular Centre at Aarhus University Hospital.

4. Examination of hydrogen-sulphide donors for treatment of cardiovascular disease.

5. Examination of channel modulators and olive-oil derivatives for treatment of endothelial-cell dysfunction. The main aim is to develop a new treatment strategy for endothelial-cell dysfunction building on knowledge about cation channels and potassium channels localized in the plasma membrane of the endothelial cells.

MILESTONES

Development of methods for in vitro examinations of small arteries
(Mulvany MJ, Halpern W. Nature. 1976;260:617–9)

Development of methods for in vitro examinations of small arteries from individuals with essential hypertension
(Aalkjær C, et al. Circ Res. 1987;61:181–6)

Demonstration of correlation between abnormal blood-vessel structure and cardiovascular risk
(Mathiassen ON, et al. J Hypertens. 2007;25:1021–6)

The significance of potassium channels in the endothelial-cell layer for the release of nitrogen oxide
(Stankevicius E, et al. Br J Pharmacol. 2006;149:560–72; and Dalsgaard T, et al. Expert Opin Ther Targets. 2010;14:825–37)

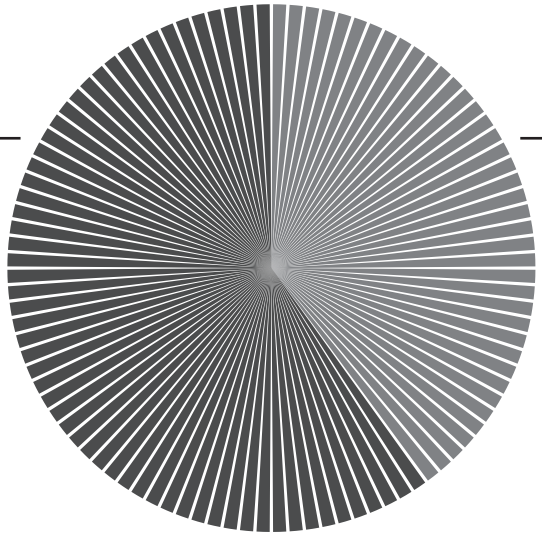
Demonstration of the impact that pressure-load has on circulation in the lungs and right ventricle in patients with pulmonary hypertension
(Baandrup U, et al. PLoS One. 2011;6:e15859; and Ostergaard L, et al. Proteomics. 2011;11:4492–502).

METHODS

Various microvascular myography and in vivo techniques are used to investigate the structure and function of small blood vessels.

- Measurement of dimensions, contraction, membrane potential, cytoplasmic ion concentrations, protein expression, protein phosphorylation
- In vivo examinations in animal models; Telemetric measurement of blood pressure and other haemodynamic parameters, and examination of lung function in mice and rats
- Clinical studies using non-invasive examinations of small-blood-vessel structure; plethysmography
- Molecular studies of cells to test new chemical structures in animal models for hypertension, diabetes, and pulmonary hypertension; also in transgenic animals
- Use of electrochemical microsensors and nanosensors to measure nitric oxide, hydrogen sulphide, and other substances.

OVERVIEW



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Clinical research

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TRANSLATIONAL CARDIOLOGY

Cardiovascular diseases, the most common type of medical condition amongst the Danish population, often lead to disability or death. Hence, rapid diagnosis and effective treatment are crucial, but prevention is equally important to make sure that fewer people become affected and more survive.

We aim to improve treatment of these patients by using new and more effective medications, new surgical techniques such as acute angioplasty (emergency balloon treatment of the coronary artery) and cardioprotective interventions with removal of the blood clot (thrombectomy), as well as remote ischaemic conditioning in patients with acute heart attacks – a field in which we are a world leader. However, it is also important to study why atherosclerosis and blood clots occur in the individual patient, for example due to genetic characterization, so that we will be able to customize treatment and introduce appropriate preventive measures in the future.

We use a wide spectrum of advanced methods in our research in the form of traditional, complex, and genetic blood analyses; haemodynamic monitoring; and invasive and non-invasive imaging techniques in animal models and preclinical human models, and in the clinical setting. We use cell cultures, mice, rat, rabbit, and pig models to study the development of atherosclerosis, the initiation of blood clots, and the characterization of myocardial metabolism during ischaemia and reperfusion. Pig models are also used for initial evaluation of interventional treatment for ischaemic and valvular heart disease (coronary and valvular stenting) and arrhythmias (pacemaker and implantable defibrillator device technology).

We have the facilities to carry out randomized clinical trials, which gives us the broadest possible research competence, spanning all the way from hypothesis, over basic research and translational research, and through to clinical treatment. Furthermore, we have access to validated data through our partners in epidemiology research, enabling us to assess the public benefit of new interventions.

We are leading in the research of paediatric cardiology, platelet function, atherosclerosis, ischaemic heart disease, valvular disease, heart failure, arrhythmia, arterial hypertension, interventional cardiology, and cardiac imaging, as well as referral logistics for rapid hospital admission for patients with acute cardiac disease. We have also recently established facilities for research within cardiac nursing.

Breakthrough in acute heart attack research

A recent trial, the DANAMI-2 trial, demonstrated the superiority (over medical therapy) of transporting patients with an acute blood clot to balloon angioplasty at a interventional heart centre. In a more recent trial, we measure platelet inhibition over time in patients with an increased risk of developing a blood clot. In this way we can check whether a blood clot is developing, and our aim is to be able to predict a blood clot before it occurs.

In the field of remote ischaemic conditioning, we have developed an effective preventive treatment for averting the tissue damage caused by blood clots. Our initial results based on animal experiments have been translated into clinical practice. While transporting the patient to acute angioplasty, the ambulance staff performs remote conditioning by blocking the blood flow to one arm for five minutes, four times at five-minute intervals. This saves around one third of the cardiac muscles that would otherwise have been lost. Researchers are studying whether a similar effect can be obtained in connection with blood clots in the brain.

PROJECTS

1. **Pre-admission diagnostics, treatment, and referral logistics**
   Telemedical diagnosing prior to hospital admission has enabled us to refer our heart patients directly to a cardiac centre for relevant treatment. We are now working on expanding this diagnostic procedure with biochemical examinations, and introducing in-ambulance treatment.

2. **Remote ischaemic conditioning – mechanisms and clinical application**
   We are investigation the methods and mechanisms behind the activation of the body's own immune defence

against the repercussions of a blood clot in the heart.

3. **Stenting, thrombosis, and embolisms**
The project compares stent types, implantation techniques, and medical treatment in studies with clinical endpoints (morbidity and mortality), using clinical databases (the West of Denmark Heart Database, the National Patients Register, and the Danish Causes of Death Register). Biochemical evaluations of blood platelet function, aimed at customizing anticoagulant treatment for the individual patient.

4. **Arrhythmia**
Researchers are studying the effect of customized positioning of the pacemaker electrode, also in patients treated for heart failure with a triple-chamber pacemaker.

5. **Heart failure and valve disease, including genetic diagnostics and pulmonary hypertension**
This project studies diagnostics, causes, mechanisms, and treatments in connection with heart failure, including enlargement and failure of the right ventricle.

METHODS

Facilities for randomized clinical trials:

- Clinical trial unit with secretariat, statistics, and epidemiology
- Imaging modalities, echocardiography, heart CT, CMR, PET, and SPECT
- Walking and cycling test, endothelium studies, ECGs, telemedicine
- Biochemical blood and tissue tests

Experimental facilities include:

- Tissue cultures and animal test models (mice, rats, rabbits, and pigs)
- Transfer of human dialysed plasma to animal models
- Traditional analytical techniques, Western blot, PCR, mass spectrometry
- Tracer kinetic metabolism studies
- Imaging techniques

MILESTONES

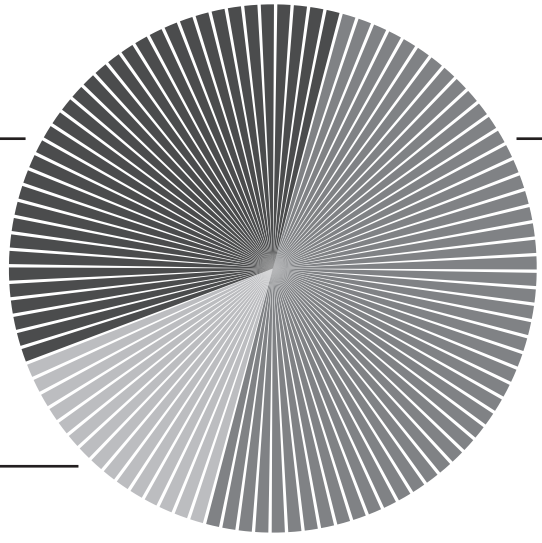
Effect and implementation of primary balloon treatment in connection with blood clots in the heart
(Andersen HR, et al. N Engl J Med. 2003;349:733–42)

Clinical demonstration of myocardial protection in connection with remote ischaemic conditioning
(Bøtker HE, et al. Lancet. 2010;375:727–34)

Implantation of wires in both the atrium and the ventricle reduces the occurrence of atrial fibrillation, and the need for reimplantation, compared with a single wire for pacing the heart in connection with sinus node dysfunction with bradycardia
(Nielsen JC, et al. Eur Heart J. 2011;32:686–96)

Reduced occurrence of heart failure following primary percutaneous coronary intervention
(Terkelsen CJ, et al. Ann Intern Med. 2011;155:361–7)

OVERVIEW



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Clinical research

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Epidemiological research

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CARDIOTHORACIC AND VASCULAR SURGERY

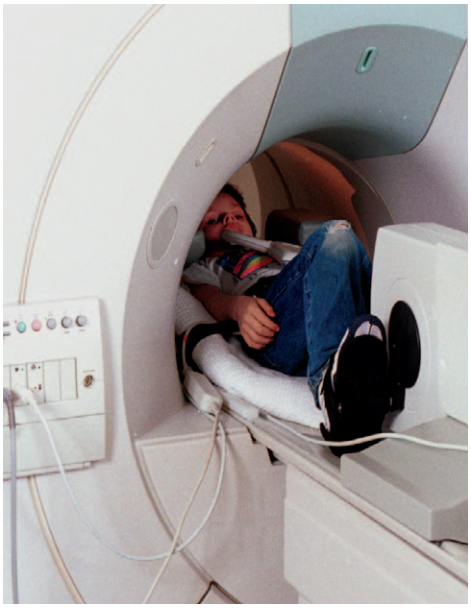
Cardiothoracic and vascular diseases are among the most common diseases in the Western world. Problems can be caused by lifestyle diseases, but also by congenital conditions such as pigeon chest. The scope of our research is broad: from vascular surgery to heart surgery and classic thoracic surgery.

We study how such diseases affect patients over time, which enables us to assess their long-term prognosis. This applies to congenital diseases and to acute conditions that require surgery. Our research topics include improved prognosis and treatment of:

- patients with arteriosclerosis
- children with congenital heart diseases
- patients with heart valve diseases
- patients taking anticoagulant medication

Technical expertise and useful tools
The high volume of surgical procedures performed at our department means we are in a position to include large numbers of patients in randomized tests, epidemiological studies and similar research.

We have unique skills and experience in the field of experimental heart surgery. Experience aside, this special competence and expertise lies in our unique opportunities for practical training on pig models, which ensures successful translation from research to the clinic.



Modern diagnostic techniques help children with heart disease.

MILESTONES

Congenital heart defects and developmental and other phychiatric disorders. A Danish nationwide Cohort Study.
(Olsen M, et al. Circulation. 2011;124(16):1706–12)

Saddle-shaped mitral valve annuloplasty rings improve leaflet coaptation geometry.
(Jensen MØ, et al. J Thorac Cardiov Surg. 2011;142(3):697–703)

Compromised cardiac function in exercising teenagers with pectus excavatum.
(Lesbo M, et al. Interact Cardiovasc Thorac Surg. 2011;13(4):377–80)

Practical Regimen for Amiodarone Use in Preventing Postoperative Atrial Fibrillation.
(Zebis LR, et al. Ann Thorac Surg. 2007;83:1326–31)

Long-term incidence of myocardial infarct, stroke, and mortality in patients operated on for abdominal aortic" aneurysms.
(Eldrup N, et al. J Vasc Surg. In-press)

PROJECTS

1. The Department of CardioThoracic and CardioVascular Surgery studies the occurrence and causes of mortality and morbidity from such conditions as arrhythmia, renal failure, impaired heart-pumping function, brain damage, and lung-related effects in surgery to correct congenital heart diseases. Other studies include psychiatric, educational, and family and lifestyle-related conditions in teenagers and adult patients with heart defects.

2. The department is also seeking to reduce the risk of atrial fibrillation following heart or lung-cancer surgery.

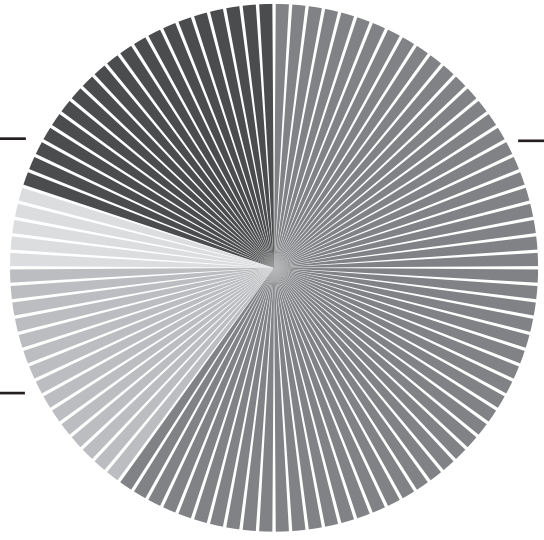
3. Aortic aneurysm surgery entails a 5–10% risk of serious complications in the heart, kidney, and intestines. Two randomized trials have been initiated to explore whether perconditioning can prevent such complications from arising.

4. We also conduct experimental clinical research in reconstructive heart-valve surgery, with special focus on biomechanical studies of heart-valve function and interaction with the heart's pumping function. This research work represents a translational aspect of the collaboration between clinical doctors, researchers specializing in biomedical techniques, and researchers with experience in animal testing – all with the aim of translating experimental studies into clinical practice.

METHODS

- Experimental surgery on pig models: The pig is well-suited for performing experimental coronary surgery, and we have an excellent experimental unit that is unique to our facility.
- Clinical studies (mainly randomised controlled studies): Used in all branches of our research, such as reducing coronary arrhythmia after thoracic surgery and applying various methods to control anticoagulant treatment.
- Epidemiological methods: In Denmark everyone has a unique personal- identification number in the "central person register" (CPR) system, and extensive information is registered electronically: diagnoses, causes of death, prescriptions (in the National Prescription Database), employment (Database for Labor Market Research) work injuries (with the National Board of Industrial Injuries), and much more. Researchers can collate and compare information from the various registers and databases (in cooperation with the university hospital's Department of Clinical Epidemiology) to find links between risk factors (say, a certain type of surgical procedure) and the course of the illness.
- Participation in numerous national and international multi-centre studies, for example on different procedures for bypass surgery, and different methods for implanting heart valves.

OVERVIEW



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VASCULAR PHYSIOLOGY

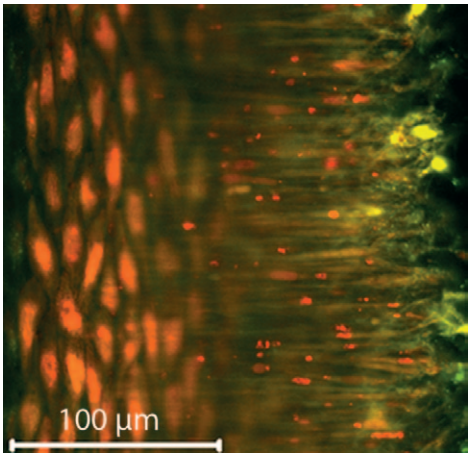
Diseases of the body's blood vessels are responsible for about one third of all deaths in the Western world, so it is imperative that we increase our knowledge of how blood vessels work. Vascular physiology research concentrates on the function of the body's small blood vessels.

By learning more about how small blood vessels regulate blood pressure and the flow of blood, we can advance our understanding of their significance for medical conditions such as diabetes, hypertension, coronary thrombosis, and circulatory insufficiency.

Gaining new insights through cooperation
The researchers in Aarhus have made unique discoveries that help us understand the ion-transport mechanisms in blood vessels. Among these are first-ever descriptions of specific chloride currents and bicarbonate transport mechanisms, as well as the identification of the relevant coding genes. Current investigations are trying to clarify their importance for blood vessel function and blood pressure regulation.

There are slight variations in genetic material from one person to another. Cooperating with geneticists, researchers have gained several new insights. One is that people with hypertension (chronically high blood pressure) have an increased likelihood of bearing a certain variant of the gene coding for the bicarbonate transporter. The same has been found to apply to women with breast cancer. This points not only to a new understanding of these diseases, but also to the value of intensifying collaborations with geneticists.

Among patients with depression receiving medical treatment, researchers have demonstrated an increased prevalence of cardiovascular disorders. To shed more light on this area, we have embarked on a research-based project in alliance with the Risskov psychiatric branch of Aarhus University Hospital. The aim is to better understand the link between depression and the function of the body's small blood vessels.



Simultaneous Ca2+ signals in endothelial cells (left), smooth muscle cells (middle), and nerves (right) obtained with confocal microscope.*

PROJECTS

1. Clarifying the significance of Na+-coupled HCO3- transport and intracellular pH for the function of large and small blood vessels and other tissues in connection with major diseases afflicting Danes, including atherosclerosis, high blood pressure, and cancer.

2. Determining the significance of chloride channels and the sodium–potassium pump for the coordination of the smooth muscle cells in small blood vessels.

3. Defining the significance of the voltage-dependent calcium channels for the contractile properties of smooth muscle cells, including phenotypic shifts; and for the function and structure of the small blood vessels.

4. Identifying the significance of potassium channels for the function of the endothelial cells in small blood vessels, particularly in connection with obesity, diabetes, and kidney failure.

5. Examining the mechanisms that control the function of human lymphatic vessels, notably those mechanisms ensuring the coordination of smooth muscle cell tone.

MILESTONES

Description of a new transmembrane transport for HCO_3^-, coupled with Na^+ transport
(Aalkjaer C, et al. J Physiol. 1991; 436:57–73)

Cloning of the gene that codes for the HCO_3^- transporter
(Choi I, et al. Nature. 2000; 405: 571-5)

Development of HCO_3^- transporter knock-out mice, and demonstration of the significance of the HCO_3^- transport and intracellular pH for the functioning of blood vessels and for blood-pressure regulation
(Boedtkjer E, et al. Circulation. 2011; 124:1819–1829)

Description of a model for oscillations in vessel tone, known as vasomotion
(Peng H-L, et al. Circ Res. 2001; 88: 810–815)

Demonstration, derived from vasomotion findings, of a new cGMP-dependent, Ca^{2+}-activated chloride current in smooth muscle cells
(Matchkov V, et al. J Gen Physiol. 2004; 123: 121–134)

Demonstration of bestrophins as being essential to this chloride current
(Matchkov V, et al. Circ Res. 2008;103: 864–172)

Demonstration of this chloride current as being decisive to the development of vasomotion
(Broegger T, et al. Cardiovasc Res. 2011; 91:685–693)

METHODS

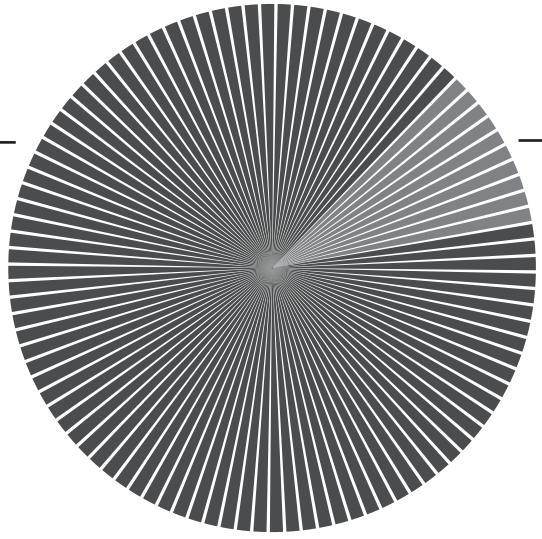
Our research work is based on myography techniques used to determine isometric and isobaric tone in the walls of isolated small blood vessels, typically around 0.2 mm in diameter. A wide variety of methods are used to measure the structure and function of these blood vessels:

- Determining in vivo vessel tone in sedated rats and mice
- Live-cell confocal imaging of intact blood vessels to detect changes in the intracellular calcium concentration and intracellular pH in smooth muscle cells, endothelial cells, and nerve cells; these parameters are also measured in other tissue and cell types
- Determining ion currents and membrane potentials in smooth muscle cells and endothelial cells using patch-clamp techniques and sharp glass electrodes
- Determining enzyme activity in smooth muscle cells and endothelial cells
- siRNA technology for downregulation of specific genes in blood vessels in vivo
- Quantitative determinations of mRNA and protein levels in small blood vessels
- Immunohistochemistry, to determine localization of proteins in small blood vessels
- Stereology, to determine cell numbers and sizes in blood vessel walls
- Blood pressure measurements on mice and rats using telemetry and tail-cuff techniques

OVERVIEW

90 %
Basic research

10 %
Clinical research



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Qualitative research

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Epidemiological research

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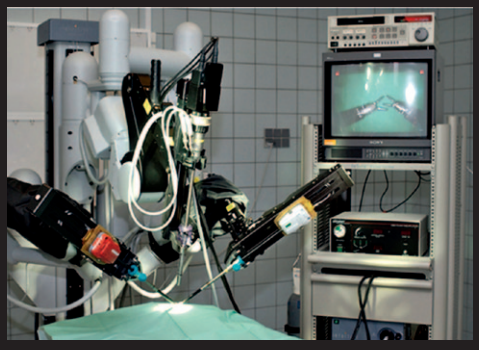
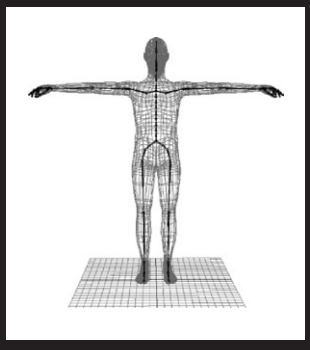
CLINICAL MEDICINE

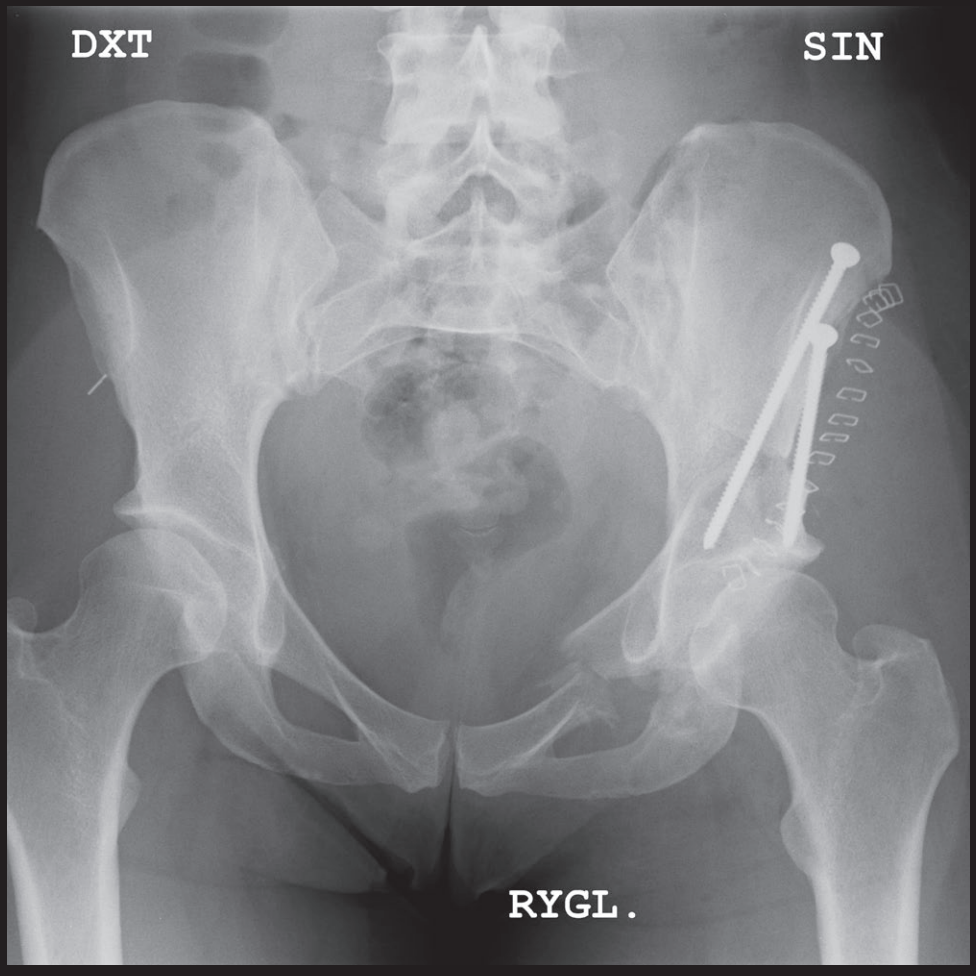
▲ Full-shift noise level and ambulatory blood pressure are measured in a slaughter-house worker participating in an epidemiological study.

► The mathematical models used around the world for PET scans of the liver were developed at the Department of Hepatology and Gastroenterology at Aarhus University Hospital. Photo: Lars Kruse, AU Kommunikation.

▼ Robotic equipment used to develop new surgical procedures for children with congenital malformations of the urinary tract and genitals.

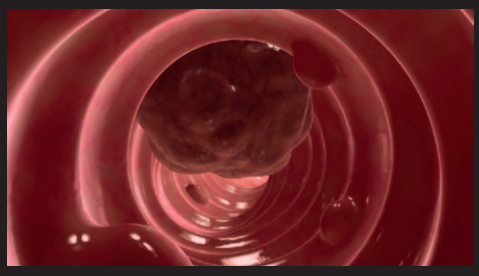






▲ X-ray of a patient with hip dysplasia following a joint-preserving procedure (periacetabular osteotomy, PAO) using minimally invasive techniques. Two screws are inserted to fix the acetabulum.

▲ Research in orthopaedic surgery studies prevention and treatment relating to the musculoskeletal system.



CENTRE FOR PHARMACOLOGY AND PHARMACOTHERAPEUTICS

When striving to ensure that the public has the best possible treatment options, our task is not only to develop new pharmaceutical drugs that can respond to the health challenges of our day and age. We must also gain a better understanding of the effects caused by the medications already on the market, and learn more about their uses.

Besides following the life cycle of individual drugs, here at the Centre for Pharmacology and Pharmacotherapeutics we also do research that ranges from the most basic investigations at cellular and molecular level, over animal experiments and clinical drug trials, and all the way through to extensive population studies and advisory services for national and international forums and bodies. Among the tasks handled at our centre are the facilitation and support of basic research that aims to develop new drugs, carried out in various Danish and international constellations. Furthermore, we develop therapeutic substances in collaboration with other research groups and with the pharmaceutical industry. Finally, we work with public authorities and medicine agencies in Denmark and abroad to assess the wider impact of drugs on health and disease.

Studying a drug from every angle

Drug research studies each and every aspect of a given medication, beginning in the laboratory to describe its mechanisms of action, moving on to initial trials in human test subjects, and finally reaching the point where a decision is made to use the drug for groups of patients. This enables us to provide a comprehensive assessment of how drugs can best be used – including descriptions of which drugs have the fewest side-effects and studies of patient groups with special therapeutic needs.

We also do research in using well-known drugs for multiple diseases. Furthermore, we provide advice and guidance regarding the use of drugs for particular patients and patient groups, for instance about the simultaneous use of several types of medication, or about patients that require special interventions. Each year we handle between 300 and 400 contacts regarding drugs from doctors who wish to discuss specific, individual courses of treatment. Several of these contacts require specialist advice about individual patients taking several types of drugs at the same time.

PROJECTS

1. **Can a better understanding of type-2 diabetes (T2D) lead to new and improved treatment options for patients with Alzheimer's disease?** Population studies have shown a certain correlation between patients with T2D and Alzheimer's disease. The Centre for Pharmacology and Pharmacotherapeutics participates in studies seeking to map the reasons for this, and to determine whether drugs used to treat T2D can improve brain function.

2. **Project Meris.** This project aims to develop an algorithm that can help identify drugs, or combinations of drugs, that lead to an increased risk of undesirable side-effects. This will enable us to improve the standards we set for the use of drugs today.

3. **Modulation of kation channels for treatment of endothelial and erectile dysfunction.** Erectile dysfunction more frequently afflicts patients with risk factors for cardiovascular disease. This project is searching for an effective treatment for endothelial and erectile dysfunction in diabetes patients.

4. **The influence of environmental factors and drugs during early foetal development.** In this context we are helping to map the extent to which drugs, substances linked to hormone disruption, and environmental toxins (including tobacco smoke and its constituents) can be shown to be present in the foetus, and to determine how they influence foetal development.

MILESTONES

The effect of potassium-channel modulation on erectile function
(Simonsen U, et al. Br J Pharmacol. 1995;116:2582–90; and Kun A, et al. Br J Pharmacol. 2009;158:1465–76)

Clinical pharmacological aspects of growth-hormone administration
(Laursen T. Growth Horm IGF Res. 2004 Feb;14:16–44)

SLC30A3 responds to glucose and zinc variations in beta-cells and is critical for insulin production and in vivo **glucose metabolism during beta-cell stress**
(Smidt K, et al. PLoS One. 2009;4:e5684)

The effect of systematic medication review in elderly patients admitted to an acute ward of internal medicine
(Lisby M, et al. Basic Clin Pharmacol Toxicol. 2010;106:422–7)

Development of a unique drug candidate for treatment of erectile dysfunction
(Peters D, et al. Patent file. 2011; and Gratzke C, et al. J Sex Med. 2010;7:445–75)

Targeting amyloid-beta by glucagon-like peptide-1 (GLP-1) in Alzheimer's disease and diabetes
(Bak AM, et al. Expert Opin Ther Targets. 2011;15:1153–62)

Antidiabetic treatments and risk of hospitalization with myocardial infarction: a nationwide case-control study
(Horsdal HT, et al. Pharmacoepidemiol Drug Saf. 2011;20:331–7)

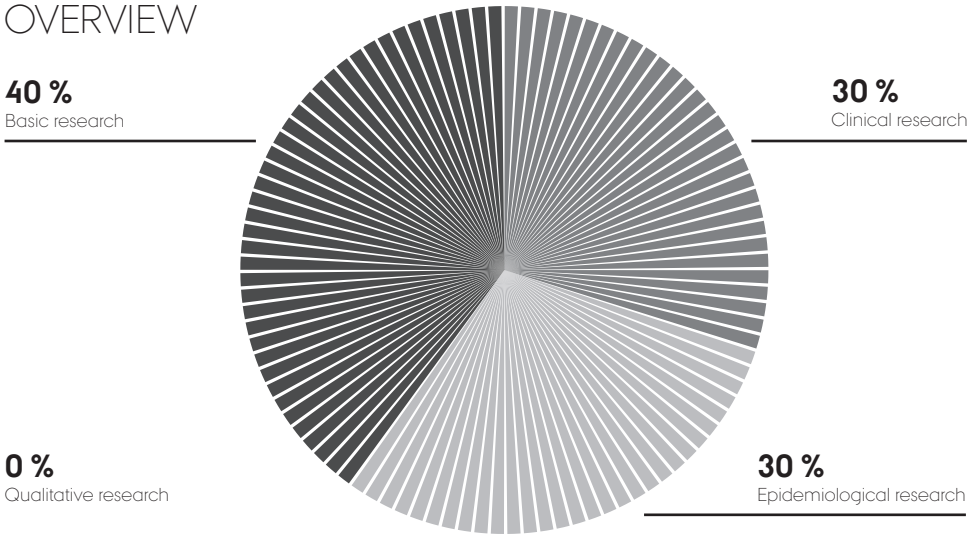
Uptake of silver from metallic silver surfaces induces cell death and a pro-inflammatory response in cultured J774 macrophages
(Locht LJ, et al. Histol Histopathol. 2011;26:689–97)

METHODS

Our centre's research into the use of drugs ranges from basic research, over clinical research, and to epidemiological studies and health research.

- Cell studies in vitro and ex vivo, notably including toxicological examinations of cell survival
- The influence of drugs and heavy metals on genes and other regulatory mechanisms
- Functional studies of insulin-producing cells, including the influence of metals on their activity and survival
- The effect of drugs in animal models and in isolated specimens ex vivo
- Investigator-initiated clinical intervention studies
- Epidemiological studies
- Intervention via systematic medication review during patient admission

OVERVIEW



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CLINICAL EPIDEMIOLOGY

Clinical epidemiology forms the very foundation of evidence-based medicine. By applying modern epidemiological methods in a clinical setting, clinical epidemiology seeks to answer important clinical questions about the prognosis of patients, and to guide clinical decision-making with the best available evidence.

The Department of Clinical Epidemiology is a highly specialized research department at Aarhus University Hospital that works with clinical epidemiology at an international level. The department's mission is to contribute to improved diagnostics, quality of care, and treatment, and thus to improve patient prognosis. The department seeks to fulfil its mission by means of four activities: 1) conducting free and independent world-class research within diagnostics, treatment and prognosis; 2) developing strong epidemiological research methods; 3) implementing a postgraduate programme in clinical epidemiology; and 4) counselling clinical departments and advising public authorities. Our department strives to maintain a stimulating, international work environment with highly qualified employees who have good social skills.

We have an extensive international research network that includes Boston University, the University of North Carolina, Leiden University, Stanford, Karolinska Institutet, Harvard Medical School, and Ohio State University.

PROJECTS

1. **Colon Polyp project.** The association between hyperplastic polyps and cancer.
2. **NSAID use and risk of atrial fibrillation or flutter: a population-based case-control study.** The risk of atrial fibrillation or flutter associated with use of nonselective NSAIDs or COX-2 inhibitors.
3. **Prognosis of Barrett's oesophagus.** The incidence of oesophageal adenocarcinoma and high-grade dysplasia among patients with Barrett's oesophagus.
4. **Adverse drug effects project.** Development of an innovative computerized system to detect adverse drug reactions (ADRs), supplementing spontaneous reporting systems.
5. **The type 2 diabetes cohort.** The relation between diabetes and subsequent risk of surgical procedures, dialysis, socio-economic outcome, and mortality.
6. **Intensive care epidemiology.** Association between intensive care unit admittance and risk of death and long-term complications such as somatic and psychiatric illness.
7. **Statins and breast cancer.** Effect of statins on breast-cancer recurrence patients.
8. **Statins and ALS.** The association between patients suffering from amyotrophic lateral sclerosis and the use of statins.
9. "**Soon Parents**". This internet cohort study of parents-to-be aims to evaluate the possible impact of several lifestyle, behavioural, and environmental factors on the time to pregnancy, as well as the relationship between several exposures and the risk of miscarriage and low infant birth weight.

MILESTONES

Arthritis medication and arrhythmia: Non-steroidal anti-inflammatory drug use and the risk of atrial fibrillation or flutter – a population-based case-control study
(Schmidt M, et al. BMJ. 2011;343:d3450)

Statins and the prognosis after intensive treatment: Statin use and mortality within 180 days after bacteremia – a population-based cohort study
(Thomsen RW, et al. Crit Care Med. 2006;34:1080–6)

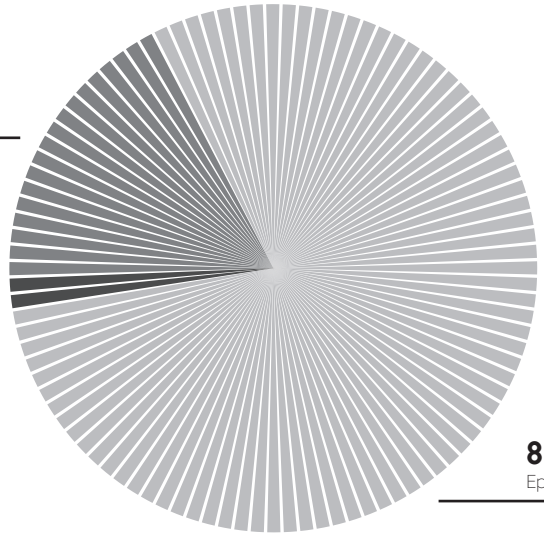
Blood clots in legs and lungs, acute myocardial infarction, and stroke: Venous thromboembolism and subsequent hospitalization due to acute arterial cardiovascular events – a 20-year cohort study
(Sørensen HT, et al. Lancet. 2007;370:1773–9)

Blood clots in legs and lungs as a prognostic factor in connection with cancer: Prognosis of cancers associated with venous thromboembolism
(Sørensen HT, et al. N Engl J Med. 2000;343:1846–50)

METHODS

The Department of Clinical Epidemiology possesses a unique capability in linking data from a wide range of biobanks and electronic registries: the CPR civil registration system, the Danish Cancer Registry, the National Patient Register, the Laboratory Information System (LABKA), and many others.

OVERVIEW



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Clinical research

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Basic research

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Qualitative research

80 %
Epidemiological research

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CLINICAL NEUROMODULATION WITH DEEP BRAIN STIMULATION

Parkinson's disease (PD) affects 6 million people worldwide. The older the population becomes, the larger this number will grow. PD is very costly both in human terms for PD patients and their family and friends, and in economic terms for society. In 1996 we spearheaded the introduction of an advanced neuromodulation technique called Deep Brain Stimulation – DBS – in Denmark to treat patients with PD, essential tremor, and dystonia. DBS significantly increases patient quality of life for a number of years.

Using sophisticated scanning techniques, electrophysiological equipment, and computer technology, we can surgically implant electrodes with extreme precision to stimulate areas that lie deep within the brain. The aim of applying DBS to a given target area is to reduce the motor symptoms associated with the neurological diseases mentioned above.

We currently lack a full understanding of how DBS works; clarifying its mechanism of action is our main research area. The opening of this field has moved our focus: While previously we regarded this type of neurological disease as a result of neurochemical disturbances in the brain, today we are exploring the electrophysiological disturbances in the neuronal pathways that these diseases produce.

Neurons communicate with one another along certain pathways, by means of chemical and electrical impulses. The electrical impulses produce a magnetic field that is weak but detectable. We are now able to measure this field using a new and amazing technique – magnetoencephalography (MEG). Once again at the forefront our department, as part of the Danish Neuroscience Centre (DNC), is the first place in Denmark to employ this technology, thanks to equipment made available by a large donation from the Velux Foundation. DBS therapy involves stimulating small, deeply seated target areas in the patient's brain. By using MEG scanning, we can measure signal alterations in the cerebral cortex caused by Deep Brain Stimulation in target areas deeply embedded in the brain and communicating with the cerebral cortex through neuronal pathways.

DBS techniques give us an unparalleled opportunity to tailor treatments for individual patients and specific diseases, and to investigate therapies for a number of diseases that are currently untreatable. Perhaps in the future it will be possible to apply external stimulation to the cerebral cortex using Transcranial Magnetic Stimulation (TMS) – a technique available today – thereby avoiding brain surgery and the risks and complications associated with the procedure.

PROJECTS

1. **Abnormal oscillatory synchronization in PD – a potential target for optimizing symptomatic and neuroprotective treatment with DBS**. Collaboration between Professor Karen Østergaard and Postdoc, PhD Erik Johnsen, MD. Funding for the project is provided by: the Danish Council for Independent Research – Medical Sciences; the Lundbeck Foundation; and the Danish Parkinson's Disease Association.

2. **Long-term follow-up of PD patients treated with STN DBS**. This project was approved by the National Committee on Health Research Ethics in September 2011. Supported by funding from the Danish Parkinson's Disease Association. Collaboration between Professor Karen Østergaard, Postdoc Erik Johnsen, and medical student Ane Vas.

3. **PET study of glucose metabolism in small basal ganglial structures in PD patients treated with DBS**. Collaboration between Professor Karen Østergaard and Specialist Registrar in Training Per Borghammer, the Department of Nuclear Medicine. The latter is the project's principal applicant. The project has been approved by the National Committee on Health Research Ethics. The Danish Parkinson's Disease Association is supporting this project with a grant of DKK 400,000.

4. **Evaluation of MR-based fibre tracking as a tool in 1) DBS for movement disor-**

ders, and 2) differentiating sub-groups and estimating prognosis in movement disorders. The Lundbeck Foundation is supporting the project with a grant of DKK 1.8 million. It is being carried out in collaboration between Professor Karen Østergaard and Specialist Registrar in Training Frederikke Rosendal, the Department of Neurosurgery, Aarhus University Hospital. The latter is the project's principal applicant.

5. **Coping with life changes – PD patients after DBS**. This study is being conducted by Assistant Professor, PhD, cand.cur. Anita Haahr, RN, in collaboration with Professor Karen Østergaard. The project is supported with funding from AU, Aarhus University Hospital, and several private foundations.

MILESTONES

Demonstrating the significant effect of subthalamic nucleus (STN) DBS for the treatment of motor symptoms and complications in PD (Østergaard K. Mov Disord. 2002;17:693–700)

Quality of life is significantly improved in PD patients treated with STN DBS (Just H. Mov Disord. 2002;17:539–45)

Long-term effects of STN DBS after 4 years are shown to be sustained in alleviating motor complications, but the disease progresses as expected with deterioration, for example, of gait and balance functions (Østergaard K. Mov Disord. 2006;21:624–31)

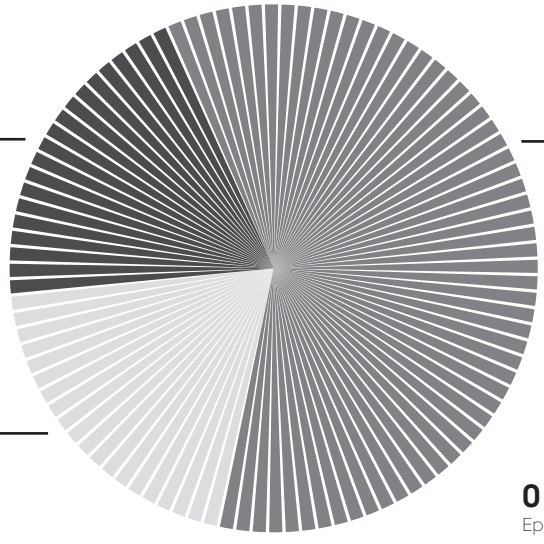
MR-verified correlation between localization of the stimulus and clinical outcome (Johnsen EL. Eur J Neurol. 2010;17:746–53, Incl. Editorial by Wharen R. Eur J Neurol 2010;17:639–40).

The first description in the world of the patient's experience of treatment with STN DBS (Haahr A. Int J Nursing Studies. 2010;47:1228–36)

METHODS

- Deep Brain Stimulation (DBS)
- Magnetoencephalography (MEG)
- Magnetic resonance imaging (MRI) is used to obtain an anatomical representation of the target areas into which the electrodes are surgically implanted. Prior to scanning, a frame is placed around the patient's head. Markers in the frame will be visible along the edges of the MR image, positioning the brain within a system of reference coordinates. Computer software is used to calculate the precise coordinates for adjusting the frame and placing the electrode within a specific target area.
- Electrophysiology. Using reference coordinates, a microelectrode is introduced into the planned target area for recording neuronal firing frequency and patterns. Because each target area has its own characteristic pattern, we can hear when we have reached the target.
- Positron emission tomography (PET) scans. The hospital's new HRRT PET scanner has such high resolution (approx. 2 mm) that we can now measure glucose metabolism in the deep target areas with and without DBS. This indicates which areas are activated by DBS.
- MRI fibre tracking. This method is used to map the nerve fibre pathways stimulated by DBS. The correlation between the clinical effect and the stimulated neural-pathway map will help us to place the electrodes in optimum position.

OVERVIEW



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Clinical research

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Qualitative research

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Epidemiological research

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CRITICAL CARE

Our research concentrates on acute conditions and critical illnesses that call for urgent intervention. Examples are patients with heart failure, haemorrhagic shock, sepsis, and serious injury. It further covers patients undergoing surgical procedures aimed at optimizing circulation, lung function, and pain relief.

One focus area is the establishment of experimental animal models for the acute conditions outlined above. We use unique pig models, in which we induce, observe, and modify the body's response to different types of pathological insults. The animal models can give us valuable knowledge about what happens in the individual organs during heart failure, haemorrhagic shock, brain death, hypothermia, sepsis, and similar acute conditions. We can subsequently intervene with the aim of preventing organ dysfunction; a dreaded complication in critically ill patients.

Another focus area for our research efforts is ultrasound diagnosis and intervention. The use of ultrasound makes it possible to actually visualize the organs, which provides important information about circulatory system. This research contributes to the development of new methods for diagnosing acute conditions.

Our efforts also move into the field of clinical epidemiology, where we use the information available in Denmark's many public registers and clinical databases to describe the prognosis for critically ill patients, and the outcome of intensive therapy.

The research at the department is carried out in close collaboration with international partners and a number of basic research centres at Aarhus University.

PROJECTS

1. We collaborate with researchers at Emory University, Atlanta, on projects concerning the phenomenon of ischaemia reperfusion. Interventions are used on heart-failure and haemorrhagic-shock animal models with a view to improving patient survival.

2. Studies of how critical illness and intensive therapy affect patients and relatives.

3. One research study focusses on sedation, delirium, and subsequent psychological problems, while another focusses on how the period of convalescence is perceived by patients and relatives.

4. Collaborating with researchers at St Thomas Hospital, London, we examine coagulation disorders in connection with brain death, using a pig model created at the Department of Clinical Medicine's experimental animal facilities.

5. In collaboration with the Danish Pain Research Centre, our department is investigating the development of chronic pain after surgery. In addition, we study the development of chronic pain in children after surgery.

6. Studies of age-related changes in the coagulation system in normal children and in children with congenital heart disease.

7. Validation of haemostatic intervention after heart surgery in children with congenital heart disease.

MILESTONES

Hyponatraemia triggers heart oedema
(Overgaard-Steensen C, Am J Physiol Regul Integr Comp Physiol. 2010, 299(2):R521-32)

Insulin inhibits the inflammatory response to sepsis
(Brix Christensen V, et al. Anesthesiology. 2004;100: 861–70)

Statin treatment reduces mortality in critical illness
(Christensen S, et al. Crit Care. 2010;14:R29)

Brain death triggers severe coagulation disturbances
(Barklin A, et al. Anesthesiology. 2009;110;1287–92)

Prediction of acute and chronic pain following hysterectomy
(Brandsborg B, et al. Br J Anaesth. 2011;107:940–7)

Ectopic tachycardia following operation for congenital heart defect in children
(Andreasen JB, et al. Crit Care Med. 2008;34:894–902)

Changes in haemostatic intervention following implementation of thromboelastometry
(Hvas AM, et al. J Cardiothorac Vasc Anesth. In press)

METHODS

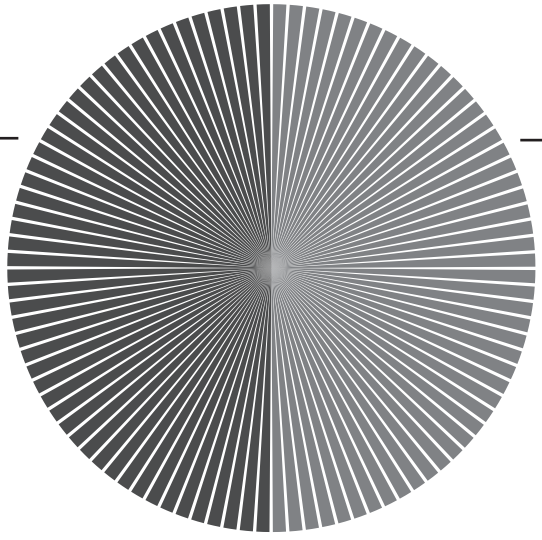
Research involves intensive therapy, anaesthetics, pain treatment, and acute medication.

- **Clinical studies:** pain treatment, long-term effects of intensive therapy, sepsis, remote conditioning
- **Experimental animal models:** sepsis, heart failure, haemorrhagic shock, hyponatraemia, heart failure in newborns, measurement of ventricular function and myocardial metabolism, therapeutic hypothermia
- **Clinical epidemiology studies:** prognosis and outcome of critical illness and intensive therapy
- **Ultrasound:** clarification of cardiopulmonary issues; development of new methods for diagnosing acute conditions

OVERVIEW

50 %
Basic research

50 %
Clinical research



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Qualitative research

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Epidemiological research

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EXPERIMENTAL ORTHOPAEDIC RESEARCH

Core research areas include the aetiology, prevention, and treatment of illnesses in joints and muscles. Our experimental unit carries out research into innovative treatment methodologies, and its primary research areas are improved joint prosthetics, bone healing, and cartilage repair.

This includes the investigation of surgical methods, implant surfaces, wear debris, growth factors, stem cells, and gene therapy methodology.

The research activity in the group is greatly increasing. The total number of published articles is 280, 97 of which have been published within the last five years. In 2010 alone the group published 29 peer-reviewed articles.

Clinical orthopaedic research
The Orthopaedic Surgical Research Group does clinical research on a considerable number of patients every year, particularly regarding total joint prostheses.

The group commands specialist knowledge in the testing of new treatment strategies and methods including RSA, MRI, DEXA, rehabilitation, and clinical follow-up.

Currently, the research group is conducting 25 randomized studies with Aarhus University Hospital as the central organizer.

PROJECTS

1. Epidemiology of total joint replacements.
2. Experimental implant model in dogs.
3. Bone growth factors in experimental animals.
4. Revision models for implant loosening.
5. RCTs on total joint prostheses, based on RSA and DEXA.
6. Rehabilitation before and after total joint arthroplasty.
7. Hip dysplasia, new surgical techniques.

MILESTONES

We have succeeded in setting up a research laboratory containing biomechanical test facilities, a hard tissue laboratory, an image diagnostics unit with micro-CT scanners and a QCT scanner, a first-class cell laboratory for the handling of gene-modified material, and a new confocal microscopy unit.

We have developed well-controlled experimental animal models to study bone ingrowth into cementless implants, including a micromotion device, and also a documented revision model.

The most striking results have been in the effect of surface coatings, but we also have interesting data on new surgical methods for implantation, new implant surfaces, the effect of wear particles, growth factors, stem cells, and gene therapeutic methods.

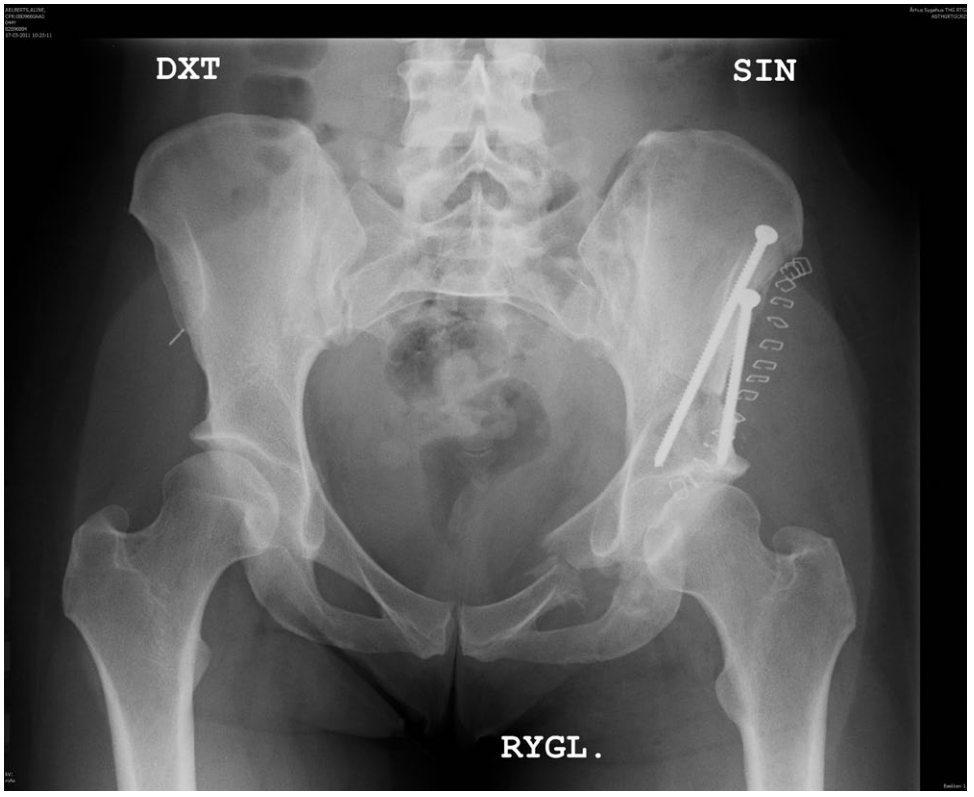
For the clinical research, we use the newest development within the RSA method (Model- Based RSA), which makes it possible to match a model of the prosthesis (CAD or reverse engineered) on the radiostereometric picture of the patient's implant.

The most remarkable results from our RSA analyses have been data from RCTs on new materials (tantalum), which improves fixation of cementless knees significantly, but we also have generated data on a very small finger implant, which showed that cementless technique is superior to that using cement.

The Ganz (PAO) osteotomy can prevent or postpone the development of osteoarthritis in the dysplastic hip, and total hip replacement can be avoided. A new minimally invasive approach developed in our department has dramatically improved the results from this operation, and the technique has gained international interest, with many foreign surgeons visiting our site to learn the new procedure.

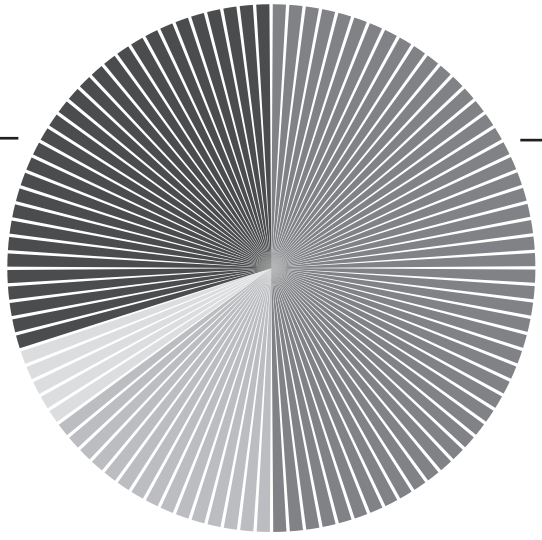
METHODS

- Non-invasive diagnostic techniques: Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scanning, radio stereophotogrammetric analysis (RSA), radio frequency ablation, gait analysis, pressure plates
- Invasive interventions: arthroscopy, osteotomies, artificial-bone grafts
- Cellular studies: toxicology, histology, microscopy
- Experimental animal models for bone ingrowth
- Epidemiology
- Qualitative methods: objective methods of measurement for the assessment of pain following surgical procedures
- Experimental research laboratories for hard-tissue specimen preparation, stem-cell research, and gene therapy
- New surgical techniques for joint preserving procedures



X-ray of a patient with hip dysplasia following a joint-preserving procedure (periacetabular osteotomy, PAO) using minimally invasive techniques. Two screws are inserted to fix the acetabulum.

OVERVIEW



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Basic research

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Clinical research

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Qualitative research

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Epidemiological research

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GASTROENTEROLOGY

At some point in their lives, most Danes will experience complications involving their gastrointestinal system. One condition, irritable bowel syndrome (IBS), which is characterized by constipation, diarrhoea, and stomach pains, occurs in up to 20% of the population.

Some women sustain potentially debilitating sphincter injuries in connection with childbirth, and more and more people are also being diagnosed with colorectal cancer. These are just some of the many focus areas for the treatment and research being done by the gastroenterology groups at the Department of Clinical Medicine. The department has a laboratory with some of the most sophisticated modern equipment and methodologies available for analysing, treating, and scientifically studying diseases of the oesophagus, stomach, liver, spleen, and other internal organs. The goal of this research is to optimize treatment and find methods for quicker and better diagnosis.

Innovating clinical treatment

One extremely interesting project that is currently under way is the effort to clarify whether chronic stimulation of the sacral nerve can be used to treat patients with severe IBS. The treatment involves implanting a thin electrode that runs through the small holes in the sacrum and on to the sacral nerves. This electrode is hooked up to a pacemaker, which enables constant stimulation of the relevant nerves. Preliminary studies indicate that this chronic stimulation modulates the central nervous system, thereby alleviating the symptoms of IBS.

Another project targets patients with childbirth-related ruptures of the anal sphincter. Such patients are normally treated by means of suturing, but a new ongoing study examines whether better results can be achieved using chronic nerve stimulation.

At Aarhus University Hospital we have also developed a special system that treats both faecal incontinence and constipation by means of colonic irrigation. The Danish company Coloplast has further develop the system, making it more user-friendly and enabling patients to carry out the treatment at home.

The surgical department at Aarhus University Hospital contributes to these and many other research projects in collaborations that reach across professional and geographical boundaries and include external stakeholders and numerous international research partners in the UK, the US, Spain, Germany, Sweden, Australia, and elsewhere.

PROJECTS

1. Randomized study comparing anterior and posterior suturing in connection with rectal prolapse.
2. Randomized cross-over trial involving treatment with sacral-nerve stimulation for IBS.
3. Randomized study for optimization of stimulation parameters (frequency and amplitude) in sacral-nerve stimulation for bowel incontinence.
4. Randomized study concerning optimum stimulation effect in the sacral-nerve stimulation.
5. Randomized multi-centre study of sphincter reconstruction versus sacral-nerve stimulation following childbirth trauma.
6. Randomized study: Can transanal irrigation alleviate bowel symptoms following surgery for rectal cancer?

MILESTONES

The department has made significant contributions to understanding normal, age-related changes in the function of the colorectal region, and also shed light on bowel complications linked to a wide variety of situations and conditions, including childbirth, surgery, spinal-cord injury and scleroderma. Our department hosts a centre that is an international leader in treatments that apply sacral-nerve stimulation.

Sacral nerve stimulation for faecal incontinence alters colorectal transport.
(Michelsen HS, et al. Br J Surg. 2008;95(6),79–84)

Temporary sacral nerve stimulation for treatment of irritable bowel syndrome: a pilot study.
(Lundby L, et al. Dis Colon Rectum. 2008;51(7),1074–8)

Long-term outcome and safety of transanal colonic irrigation for neurogenic bowel dysfunction.
(Faaborg PM, et al. Spinal Cord. 2009;47(7),545–9)

Rectal motility after sacral nerve stimulation for faecal incontinence.
(Michelsen HS, et al. Neurogastroenterology Motil. 2010;22(1),36–41)

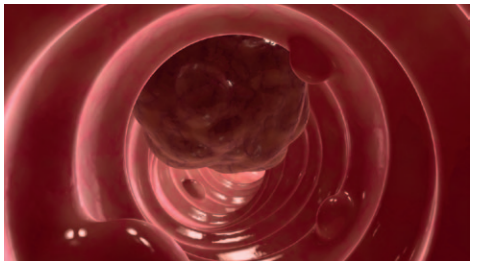
Suboptimal outcome following sacral nerve stimulation for faecal incontinence.
(Maeda Y, et al. Br J Surg. 2011;98(1),140–7)

Do gastrointestinal transit times and colonic dimensions change with time since spinal cord injury?
(Faaborg PM, et al. Spinal Cord. 2011;49(4),549–53)

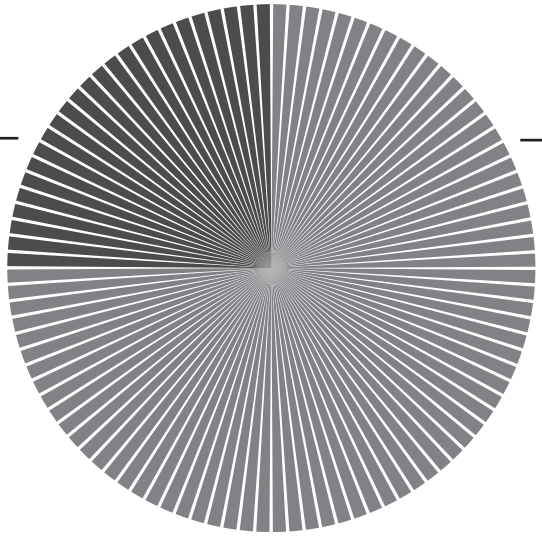
METHODS

Our department has the most advanced equipment available to shed light on the functioning of the small and large intestines and the colon, and on the complex interaction between colon and sphincter:

- A magnetic tracking system for quantitation of motility in the small and large intestine
- Advanced multi-site pressure system for quantitation of pressure throughout the colorectal area
- Multimodal sensory system to clarify sensitivity to temperature, pressure, and pain
- Scintigraphic technique to clarify defecation
- An impedance planimetry system
- Anorectal physiological equipment
- Neurophysiological equipment



OVERVIEW



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Epidemiological research

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LIVER AND GASTROINTESTINAL MEDICINE

The hepatogastroenterology research unit at the Department of Clinical Medicine does research into a variety of issues related to the function and diseases of the liver and the gastrointestinal tract, which are studied using functional, imaging, laboratory, and clinical epidemiological methods.

The unit works under the motto "Research-based intervention against disease", investigating topics that spring from the field of internal medicine: gastroenterology and hepatology.

Our efforts have clear links from the hospital bed to the laboratory test bench, and vice versa. As part of our research strategy, we endeavour to study our selected research questions from as many angles as possible. We consequently work with equipment, expertise, and alliances that use techniques ranging from molecular medicine over guinea pig testing and patient trials, and to population-based clinical epidemiology. Our unit also comprises a clinical trial unit, which handles investigator and sponsor-initiated drug testing, a clinical laboratory with catheterization and functional equipment, and a research laboratory with associated technical staff. We adhere to our motto by keeping abreast of scientific news, and by consistently welcoming progress and new opportunities. Our unique competence within the medical hepato-gastroenterology unit is our ability to gather and embrace the many research disciplines – thereby creating a unified entity that enables projects dealing with complex research topics to be carried out within a single infrastructure.

We focus on the metabolic changes caused by liver disease, and on assessing the effects of growth factors on chronic liver disease and portal hypertension. Our research work includes the use of PET scans to study the function and metabolism of the liver. The metabolic impacts of portal hypertension are investigated through the creation of transjugular intrahepatic porto-systemic shunts (TIPS).

In future, some of the answers to these liver and gastroenterology issues may be found in comparative biological studies. For instance, the digestive mechanisms in the boa constrictor; an animal that can virtually deactivate its intestinal system for extended periods of time without food ingestion, but which can reactivate its entire digestive apparatus with amazing speed when resuming food intake.

PROJECTS

1. The effect of Kupffer-cell activation on portal hypertension.
2. The effect of regulating the liver's genetic expression on inflammatory catabolism.
3. The effect of mucosal T-cell differentiation on the response to biological therapy for inflammatory bowel disease.
4. The effect of changes in the intestinal motility on inflammatory diarrhoea.
5. The effect of neuronal alanine synthesis on the osmotic status of astrocytes

MILESTONES

Kupffer cells are activated in cirrhotic portal hypertension and not normalized by TIPS
(Holland-Fischer P, et al. Gut. 2011;60:1389-93.)

Hepatic galactose metabolism quantified in humans using 2-18F-fluoro-2-deoxy-D-galactose PET/CT
(Sørensen M, et al. J Nucl Med. 2011;52:1566-72)

Infliximab induces clonal expansion of gamma-delta-T cells in Crohn's disease: a predictor of lymphoma risk?
(Kelsen J, et al. PLoS One. 2011;6:e17890)

The acute effect of dorsal genital nerve stimulation on rectal wall properties in patients with idiopathic faecal incontinence
(Worsøe J, et al. Colorectal Dis. 2011;13:e284)

Unchanged capacity of urea synthesis during acute phase response in rats
(Thomsen KL, et al. Eur J Clin Invest. 2011;41:16-22)

Incidence and mortality of alcoholic hepatitis in Denmark 1999–2008: a nationwide population-based cohort study
(Sandahl TD, et al. J Hepatol. 2011;54:760-4)

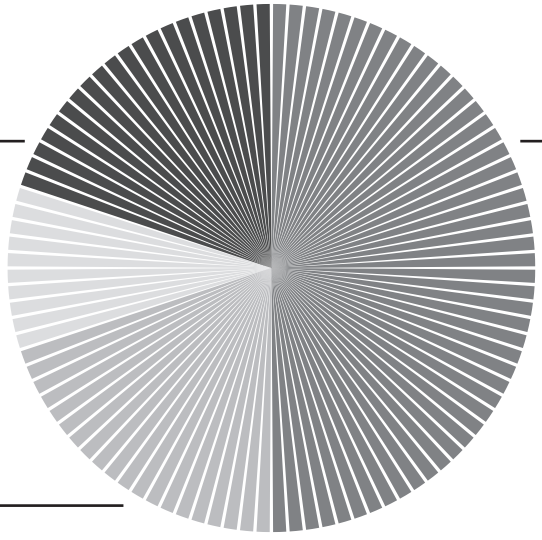
The mathematical models used around the world for PET scans of the liver were developed at the Department of Hepatology and Gastroenterology at Aarhus University Hospital. Photo: Lars Kruse, AU kommunikation.

METHODS

Our research is defined based on the clinical problems afflicting patients. Quite often, a research project begins with an epidemiological population survey based on public-register and database information – for instance in relation to fatty liver disease. The next step will typically apply physiological methodology – aimed, for instance, at revealing the effects of fatty liver disease on the metabolism of insulin. At the molecular level, the researchers delve deeper into the details, trying to answer such questions as: What functions work poorly in cells that contain fat? How can this trigger an inflammatory reaction in the cell's surroundings? And why does this increase the risk of cancer?

We use a wide variety of research methods, ranging from molecular to full-body research, and from experimental to clinical research. This allows us to run cyclic tests of the mechanisms at work, and their effects.

OVERVIEW



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OCCUPATIONAL EPIDEMIOLOGY AND REPRODUCTIVE TOXICOLOGY

The workplace environment is a significant contributory factor in chronic diseases, sick leave, and premature exit from the labour market. The costs of work-related illness run into billions of Danish kroner annually. At work, people are often subjected to significantly higher exposure levels than they are elsewhere. This makes studies of occupational health exceptionally well suited to reveal causes of disease as well as reproductive health problems that are found not only in the working environment, but also in the world around us.

The research group for occupational medicine and reproductive toxicology investigates a variety of topics:

1. How do chemical and psychosocial exposures affect the risk of reduced fertility, miscarriage, foetal growth inhibition, and other negative pregnancy outcomes?
2. What are the threshold levels for the relation between ergonomic exposures and musculoskeletal disorders?
3. How do psychosocial exposures affect the risk of mental illness and biological stress markers?
4. How can we help people with common health problems to keep working?
5. How do light and noise levels, in conjunction with personal factors, affect the risk of mental and somatic illness?

The general aim of our research is to detect and elucidate environmental causes of disease. We also study the significance of health for the individual's ability to work, and assess preventive measures in the workplace. The identification of environmental risk factors calls for independent and objective measurements of physical, ergonomic, chemical, biological, and psychosocial exposures. Across research areas we are working to constantly develop and improve measurement methods. We have acquired special skills in field investigations that involve the collection of exposure data and biological markers. We use this as a basis for studies that also draw on Denmark's many public registers and electronic databases, for instance the National Patients Registry and the Medical Birth Registry under the National Board of Health. We also use information registered in national employment databases to study occupational prognoses after treatment has been concluded.

Since 2008, our research efforts have been planned and coordinated within the framework of Dansk Ramazzini Centre, which is a network for occupational and environmental medical research. Collaborations involve researchers in the fields of environmental and occupational epidemiology, as well as medical departments of rheumatology, gynaecology and obstetrics, paediatrics, and pulmonary medicine.

PROJECTS

1. **CLEAR – Climate change, environment and reproductive health**. The aim is to assess whether climate changes are leading to shifts in the release of pollutants into the environment, and whether these substances exert an influence on human reproductive health. Supported by the EU's Seventh Framework Programme for Research (FP7).
2. **SKULDER – work-related risk factors in connection with shoulder disorders requiring surgical intervention.** Here we examine the link between occupation, occupational exposures, and shoulder disorders that require surgical intervention, based on a job-exposure matrix tailored to shoulder exposure and conducted with the aid of expert assessments and technical measurements. The project is supported by the Danish Working Environment Authority, the Danish Agency for Science, Technology and Innovation, and the Danish Arthritis Association.
3. **LUX@R – The health consequences of the lighting environment during indoor work and night-shift work.** The general

aim is to investigate whether the lighting provided for indoor work and night-shift work increases the risk of depression, breast cancer, and disturbances of the circadian rhythm. This project is supported by the Danish Working Environment Authority.

4. **STØJSTRESS and STØJRISK – Noise and health.** These projects explore the interaction between noise, genetic markers, and other individual factors and risks for auditory and extra-auditory effects in health, including hypertension and cardiovascular disorders, as well as biological markers for stress. Both projects are supported by the Danish Working Environment Authority.

Full-shift noise level and ambulatory blood pressure are measured in a slaughter-house worker participating in an epidemiological study.

MILESTONES

Establishment of a university chair in occupational medicine
2002

Danish Ramazzini Centre, a collaborative centre for research in occupational medicine, 2008

Exposure to monoethylhexyl phthalate is linked to an increased risk of miscarriage
(Toft G, et al. Environ Health Perspect. In-press)

A simple and effective method for helping patients with low back pain to remain at work
(Jensen LD, et al. Occup Environ Med. 2012;69(1):21-8)

Independent method for assessing the psychosocial workplace environment
(Kolstad HA, et al. Am J Epidemiol. 2011;173(1):94–102)

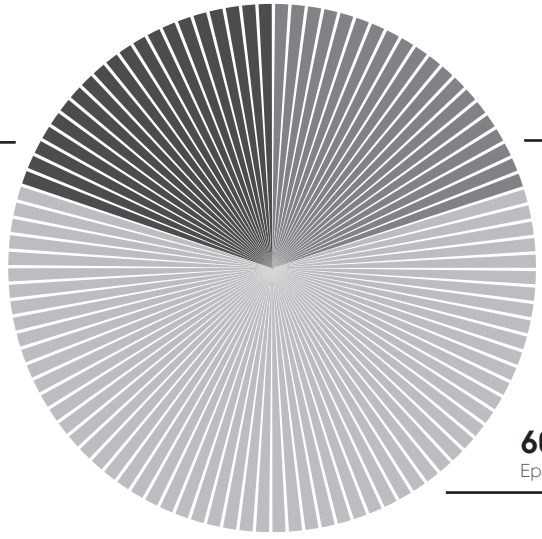
No evidence of malignant cells in ovarian tissue of patients with breast cancer
(Rosendahl M, et al. Fertil Steril. 2011;95(6):2158–61)

METHODS

Our research is partly based on epidemiological investigations – in which independent, objective, and quantitative measurements of environmental exposures figure very prominently – and partly on animal models for assessing the effects of potentially gonadotoxic substances.

- Occupational epidemiology
- Environmental epidemiology
- Toxicology
- Gene–environment interaction
- Cryopreservation
- Semen analyses
- Exposure assessments
- Risk assessments
- Intervention studies

OVERVIEW



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PAEDIATRIC ORTHOPAEDICS

Research in orthopaedic surgery studies the prevention and treatment of conditions relating to the musculoskeletal system. Our experimental unit carries out research into innovative treatment methodologies, and its primary research areas are improved joint prosthetics, bone healing, and cartilage development. This includes the investigation of surgical methods, implant surfaces, wear debris, growth factors, stem cells, and gene therapy methodology.

The field of paediatric orthopaedics includes research into, and treatment of, hips, knees, and feet in children suffering from deformities, bent toes, hip dysplasia, flat-foot, or claw-foot. In addition, the unit studies neuromuscular disorders in patients with impaired brain-to-muscle communication, as well as severe deformities following bone fractures. Other noteworthy areas of research are the anabolic effects of zinc, the development of artificial bone components, and affecting of bone-eroding cells. Yet another area is the treatment of children with growth disorders, where we are focussing on the development of new treatment methods. We are currently exploring a new method that regulates growth by means of thermal impact, induced by a probe inserted near the bone tissue.

Health economics research

We carry out health-economics analyses to project the consequences of changing procedures for orthopaedic surgery patients. Our unit has the professional and technical expertise needed to analyse cost-of-illness, cost-effectiveness, cost-utility, and cost-benefit aspects. We also have specialized software that enables us to analyse decision-making based on decision trees or Markov models. At present we are conducting cost-efficacy and cost-effectiveness analyses regarding the introduction of new post-operative rehabilitation procedures for patients who have undergone hip and knee prosthetic surgery. Health economics analyses take both a socio-economic and a class-economic perspective. Similarly, it is interesting to know whether pre-operative intervention during the waiting period prior to hip or knee prosthetic surgery will benefit the patient and/or the hospital, and whether the added cost should be borne by the hospital or the municipal authority.

PROJECTS

1. New bone-grafting technique in paediatric foot surgery. Validation of outcome measures.
2. Reversible Hemiepiphysiodesis – stapling versus eight-plate.
3. Reversible Hemiepiphysiodesis – a prospective clinical randomized study.
4. Epiphysiodesis performed using radio frequency ablation – an innovative technique.
5. Establishment of an experimental osteotomy model in pigs.
6. Cerebral palsy. Corrective osteotomies of the ilium and proximal femur.
7. Hip arthroscopy in children. Study of clinical outcomes, development of an animal model, and application for specific paediatric disorders.
8. Management of claw-foot (pes cavus) by integration of clinical assessments, functional status, and socio-environmental evaluations.

We have a large network of partners, including manufacturers of implants and surgical equipment, as well as centres of orthopaedic surgery in a variety of countries including Austria, France, the UK, Italy, New Zealand, Finland, the Netherlands, and Ireland.

MILESTONES

Intra- and interrater agreement of pressure pain thresholds in children with orthopedic disorders
(Nikolajsen L, et al. J Child Orthopaedics 2011:5(3),173-8)

Neonatal jaundice, autism, and other disorders of psychological development
(Maimburg RD, et al. Pediatrics. 2010;126(5):872–8)

Autometallographic tracing of zinc ions in growing bone
(Ovesen J, et al. J. Musculoskelet Neuronal Interact. 2004;4(4):428–35)

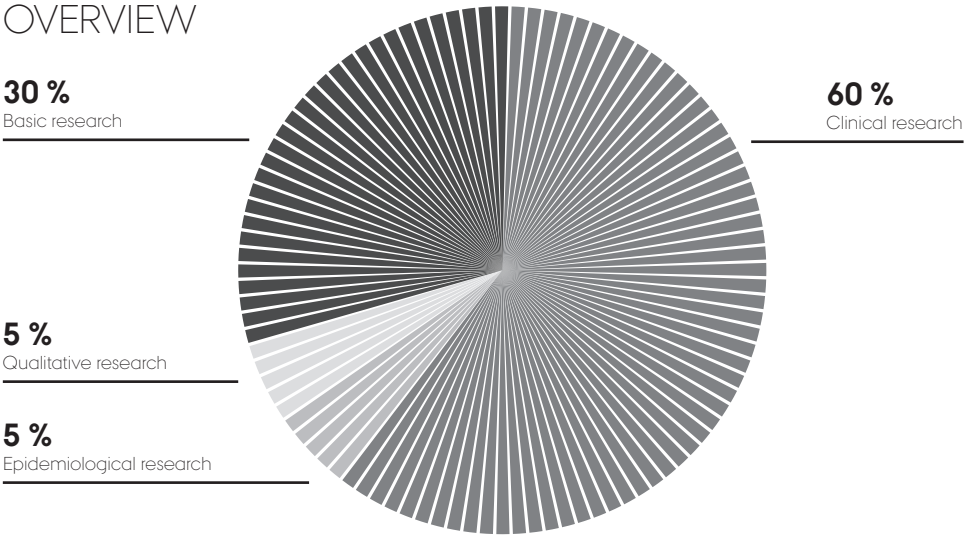
The positive effects of zinc on skeletal strength in growing rats
(Ovesen J, et al. Bone. 2001;29(6):565–70)

Research in orthopaedic surgery studies prevention and treatment relating to the musculoskeletal system.

METHODS

- Non-invasive diagnostic techniques: Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scanning, radio stereometry assay, radio frequency ablation, gait analysis, pressure plates
- Invasive interventions: arthroscopy, osteotomies, artificial-bone grafts
- Cellular studies: toxicology, histology, microscopy
- Experimental animal models
- Epidemiology, drawing upon Denmark's extensive registration of citizen and patient data: The Danish Orthopaedic Common Database, which comprises the Danish Hip Arthroplasty Registry, the Danish Knee Arthroplasty Registry, the Danish Shoulder Alloplasty Registry, the Danish Cruciate Ligament Registry, and the Ganz Database
- Qualitative methods: objective methods of measurement for the assessment of pain following surgical procedures
- Experimental research laboratories facilitate, for instance, hard tissue specimen preparation, stem cell research, and gene therapy

OVERVIEW



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PAEDIATRIC UROLOGY

Paediatric urology deals with congenital deformities and functional disorders in the upper and lower urinary tract, as well as deformities of the inner and outer genitals. These conditions exist in 0.5% of all newborns. Most urinary-tract deformities are malformations of the male genitals, while other conditions are rarer.

Paediatric urology research at the Department of Clinical Medicine covers the entire spectrum, from basic research to clinical trials, and contributes actively to the implementation of new treatments modalities. In terms of translational research we have developed a number of unique pig models, and our special expertise lies in studying the dynamic properties of the upper and lower urinary tract. Examples include transit-time ultrasound measurement of urinary flow, and monitoring of the renal function, including the use of microdialysis techniques after kidney transplant. For children with urogenital conditions, many of these techniques should make diagnosing and follow-up much easier and more comfortable in the future.

We have developed special skills in robotic surgery, and our paediatric urology research group was the first in Denmark, and one of the first in the world, to introduce this surgical technique. The new methods were developed early in the new millennium and today, along with Harvard University, we are at the cutting edge of robotic surgery as applied in paediatric urology.

PROJECTS

1. The development of a pig model with increasing outlet obstruction immediately after birth, providing a basis of treatment for several congenital bladder and urinary-tract deformities.

2. The replacement of bladder tissue with artificially cultivated bladder-wall cells for children with serious bladder malformations (in connection with spina bifida conditions, for instance).

3. Bladder diversion surgery by means of robotic surgery technique for children with severe bladder malformations.

4. The use of unique urodynamic techniques, including transit time ultrasound, for diagnosing and monitoring children with voiding dysfunction.

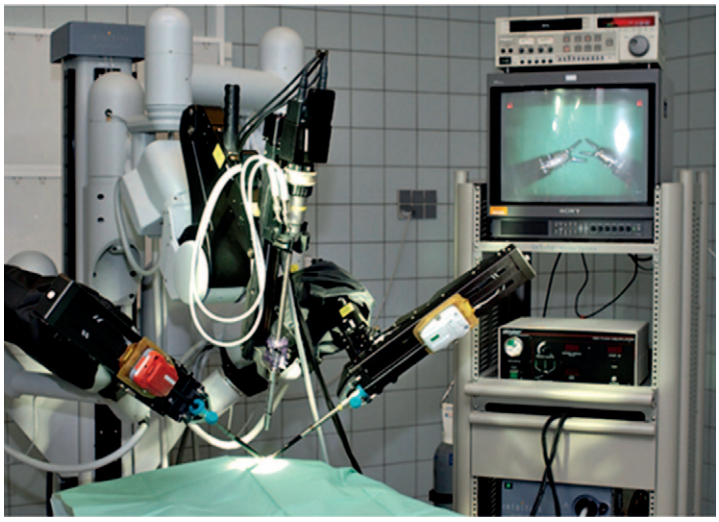
5. Biomarkers in connection with outlet obstruction in the upper urinary tract, and the clinical consequences of findings.

MILESTONES

Robotic surgery is feasable in children with congenital anomalies of the kidneys
(Olsen LH, et al. Urol. 2004;171(6 Pt 2):2660–3)

The development of voiding in the fetus – an experimental model
(Olsen LH, et al. J Urol. 2001;165:2331–4)

Microdialysis can indicate complications after renal transplantation
(Keller AK, et al. J Urol. 2009;182(4 Suppl):1854–9)



Robotic equipment used to develop new surgical procedures for children with congenital malformations of the urinary tract and genitals.

METHODS

Most of our techniques were developed using pig models, with the knowledge later applied in clinical studies.

- Robotic surgery, including retroperitoneal pyeloplasty and transvesical urethral implantation
- Experimental pig models with outlet obstructions in the upper and lower urinary tract
- Microdialysis for the monitoring of renal function following kidney transplant
- Describing the development of urinary function from embryonic phase to infancy, including transit-time ultrasound measurement of urination speed

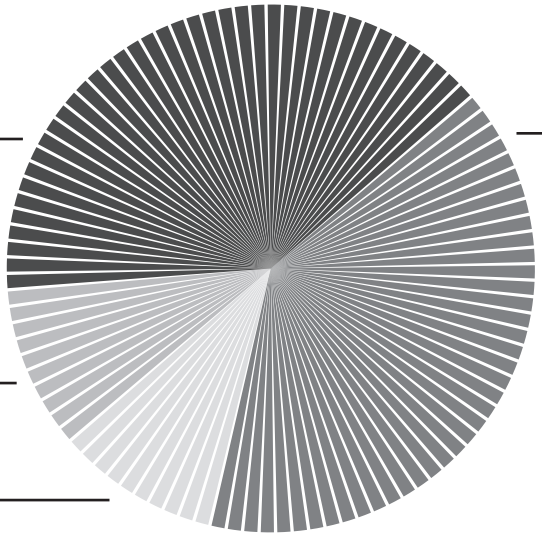
OVERVIEW

40 %
Basic research

40 %
Clinical research

10 %
Epidemiological research

10 %
Qualitative research



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SPINE SURGERY AND TRANSLATIONAL ORTHOPAEDIC RESEARCH

Worldwide, disorders of the musculoskeletal system are among the most prevalent and costly of medical conditions. Examples are temporary or permanent disability due to chronic back pain and/or neurodeficit, which can occur as consequences of spondylosis, trauma, cancer, infections, developmental diseases, and fractures caused by osteoporosis.

Aarhus Orthopaedic Centre, under the Institute of Clinical Medicine, is internationally recognized as a leader in medical care, research, education, and innovation in issues relating to the musculoskeletal system. The research at the centre consists of a comprehensive package of state-of-the-art novel imaging modalities for diagnosing and monitoring diseases, cell-based therapy and scaffold-based tissue engineering, and nanoparticle-functionalized implants for skeletal reconstruction. Our aim is to accelerate the application of medical, imaging, engineering, and nano-based technologies in the life sciences, by combining the new research tools with wide-ranging scientific, technical, and clinical expertise. Our educational scientific activities have led to 63 completed theses over the last few decades, and to more than 300 publications cited on PubMed.

One of our strategies for success is the integration of individually tailored cell- and molecular-based tissue substitution. This is expected to play a significant role in developing and monitoring the efficacy of treatment.

Our laboratory is highly specialized and considered to be one of the world's leading facilities in hard-tissue histology, cell culturing (including stem cells in 3D perfusion bioreactors and hypoxia incubators), µCT scanning, confocal microscopy, scanning electron microscopy, qRT-PCR, and gene array technology. Highly advanced MRI and PET/CT technologies for visualization have been developed for monitoring specific cellular mechanisms and visualizing therapeutic interventions on a molecular scale, and here our group has moved its expert competence into translational clinical research. In a clinical perspective, our patient databases have facilitated multiple RCTs and high-level research in spinal outcomes.

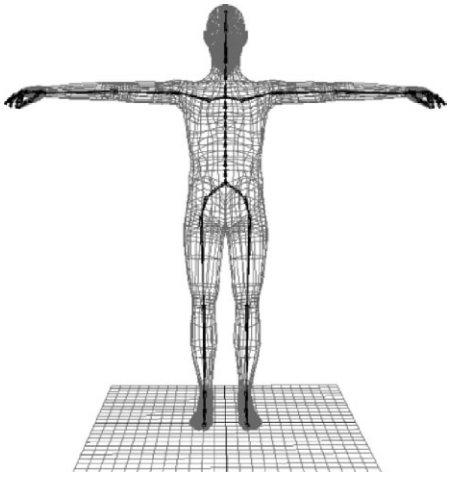
PROJECTS

Examples of funded large-scale projects:

1. Cost-effectiveness of new treatment strategies in spine surgery: evaluation of patient-based outcome, health and socio-economic consequences in Denmark
2. Advanced 3D tissue engineering, focussing on regeneration and reconstruction of degenerative spinal diseases
3. Improved treatment of disc degeneration by means of modern gene therapy and traditional Chinese medicine
4. Individualized musculoskeletal regeneration and reconstruction

Examples of ongoing projects:

1. Optimized chondrograft implantation on small and large-scale cartilage defects
2. Cost-effectiveness is spinal metastasis surgery
3. Stem-cell transplantation in degenerative disc disease
4. Instrumentation strategies in spinal deformities
5. Intervertebral disc regeneration
6. Functionalized implants for skeletal reconstruction
7. Bone-tumour treatment through targeted drug delivery of gene silencers



MILESTONES

Aarhus Orthopaedic Centre has been involved in establishing numerous centres:

Orthopaedic Research Laboratory (1979)

The Clinical Center for Cell-Based Therapy

Crossdisciplinary Nanoscience and Biocompatibility Center

Centre for Molecular Orthopaedics

Centre for Individualized Musculoskeletal Regeneration

Centre for Cost-Effectiveness Analysis of New Treatment Strategies in Spine Surgery

The Lundbeck Foundation Nanomedicine Centre for Individualized Management of Tissue Damage and Regeneration

METHODS

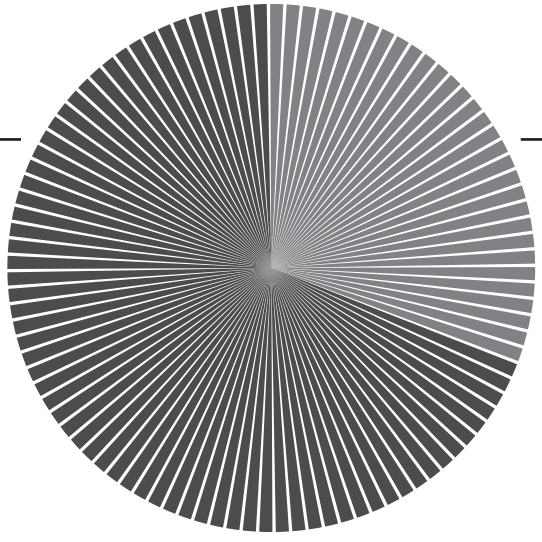
We use a wide variety of techniques including:

- Advanced 3D tissue culturing techniques, including a perfusion bioreactor, hypoxic
- environments, growth factors, co-cultivation with different cell types to optimize cell-based therapy and tissue
- Engineering for bone, cartilage, and intervertebral disc regeneration
- Finite element modelling
- Diagnostic modalities
- Nanoparticles and specific siRNAs and micro RNA
- Biobanks
- Quantitative RT-PCR and, at protein level, Western blotting and flow cytometry
- Dedicated animal models
- Large animal models to mimic spinal deformity, fractures, spinal stenosis, cancer, and other implant and fusion scenarios

OVERVIEW

70 %
Basic research

30 %
Clinical research



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Qualitative research

0 %
Epidemiological research

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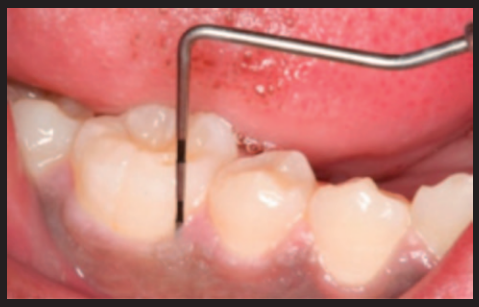
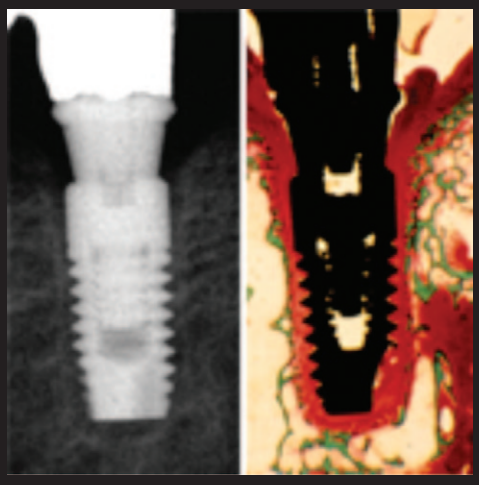
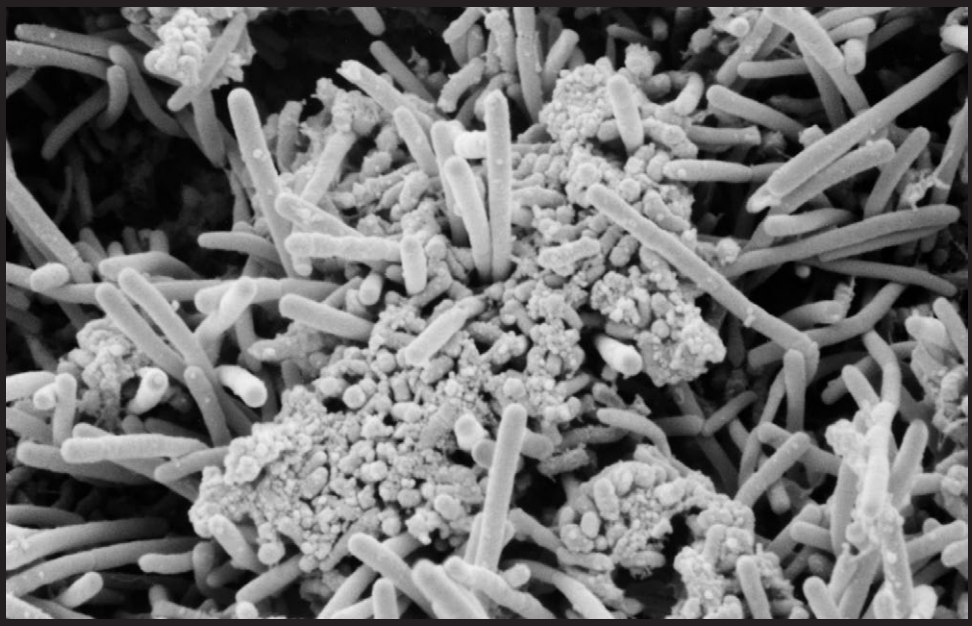
DENTISTRY



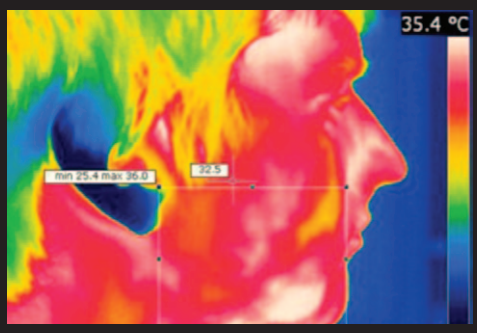
▲ One manifestation of marginal periodontitis is a loss of attachment around the teeth. This can be diagnosed by clinical examination.

▼ Radiological (on left) and histological image of an implant that has lost osseointegration due to forceful compression .



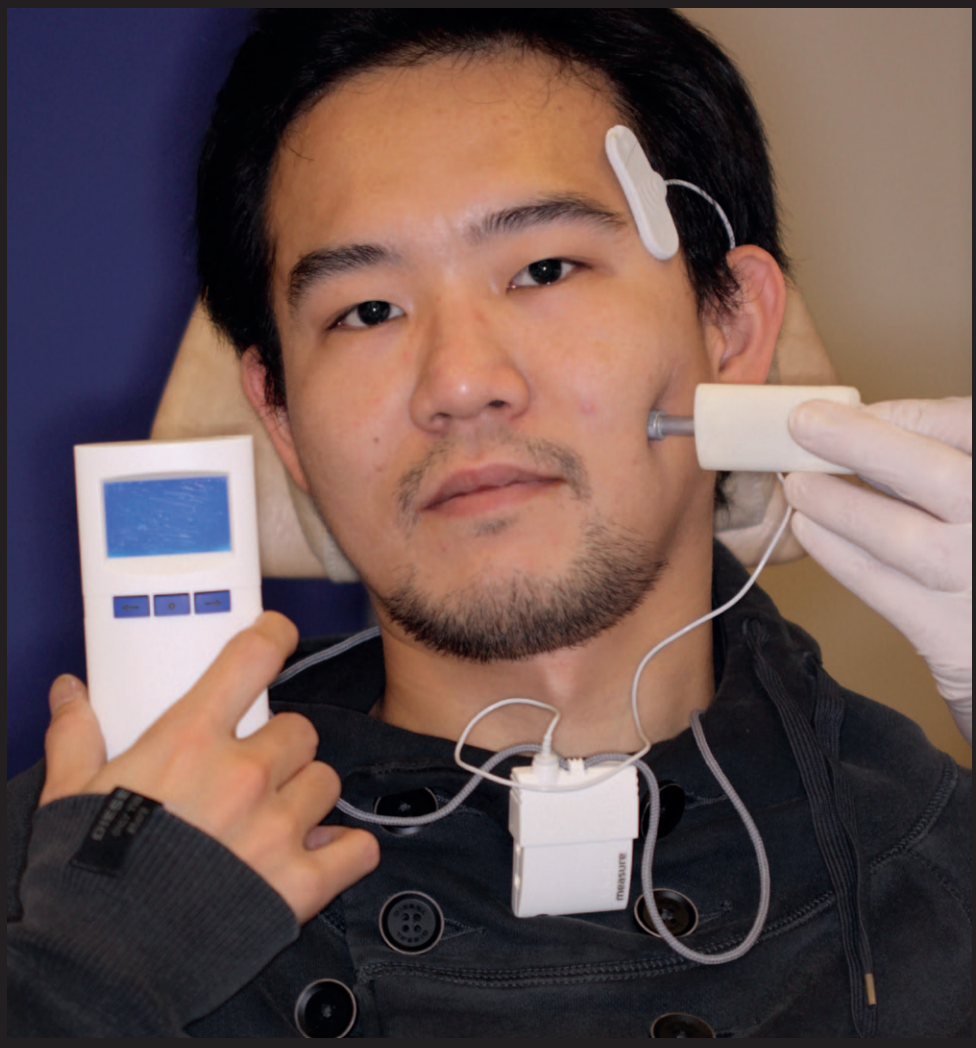


▲ Dental biofilm. Courtesy of Skaaring, Fejerskov & Nyvad. Aarhus University.



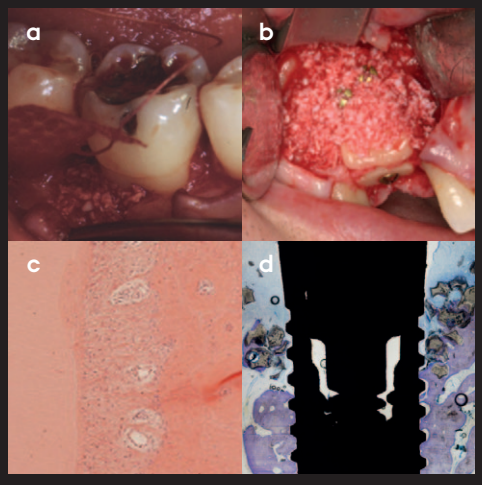
▲ Thermogram of patient following removal of a wisdom tooth. White colour indicates warmest skin area.

TEXT



◄ Illustration of ambulatory recording of jaw muscle activity with the use of Grindcare (Medotech A/S) and standardized assessment of jaw muscle pain sensitivity with a so-called palpometer.

▼ Regenerative treatment in periodontal (a) and bone defects (b), involving implantation of bone biomaterials, may facilitate complete periodontal regeneration (c) and installation of oral implants (d).



GENERATING **THE MISSING BONE**

A major component in many procedures to regenerate lost oral tissue is the use of biomaterials. The aim is to promote bone formation whilst limiting or eliminating the need for autogenous bone harvesting from the patient.

A biomaterial should be biocompatible and/or bioactive and exert minor or no adverse reactions; it should promote tissue formation in a timely manner and, ideally, it should disappear from the tissues after having completed its function. However, the bone substitute materials widely used in the clinic today show a significant disadvantage: After successful regenerative procedures, they remain in the peri-implant tissues for a long period of time.

New perspectives for treatment

Until recently, no evidence existed on what role the presence of these bone substitute materials play in the event of infection or inflammation: "Not long ago we concluded a preclinical in vivo study suggesting that the presence of bone-substitute materials within the peri-implant tissues may be detrimental in the event of peri-implantitis, leading to more bone loss compared to implants installed in pristine bone. If this can be conclusively confirmed, then the clinical indications for use of such non-degradable bone substitutes will probably be changed," Associate Professor Andreas Stavropoulos explains.

Another aspect in this context is the influence that systemic conditions, such as diabetes and osteoporosis, have on the outcome of regenerative procedures involving the use of bone substitutes. As Professor Søren Schou points out, "One has to keep in mind that we're facing a population that's growing older, and we'll be treating more and more patients with systemic conditions – potentially influencing treatment outcomes and susceptibility to disease or tissue loss."

If this can be conclusively confirmed, then the clinical indications for use of such non-degradable bone substitutes will probably be changed.

ASSOCIATE PROFESSOR
ANDREAS STAVROPOULOS

FACTS

The biomaterials used today, with variable success, range from bone substitutes and guided tissue regeneration membranes to growth and differentiation factors and, more recently, cells and scaffolds. These can be used as stand-alone protocols or in various combinations.

IMAGING TECHNIQUES IN DENTISTRY

Radiography is the most significant paraclinical diagnostic method employed in connection with dental treatment. Radiographic examinations are used to diagnose pathological conditions in the jaw bone and those parts of the teeth that are not visible in the oral cavity.

Radiography is used before, during, and after treatment, for instance to diagnose caries lesions before treatment of periodontal disease; before the removal of wisdom teeth; before and after the insertion of dental implants; and before, during, and after root-canal treatment of a tooth. Moreover, orthodontic specialists use radiography to decide on a course of treatment and to assess the results achieved.

Most of the research done in imaging techniques is clinical, and therefore relevant to dental practice. Digital radiographic techniques have been gaining ground in general dental practice, not only to examine teeth, but also to carry out extensive examinations of the jaws, the temporomandibular joint (TMJ), and the skull. We are conducting intensive research to clarify the diagnostic accuracy and image quality obtained with digital receptors, and in recent years dental CT scanning has taken a high priority as a research field. CT scanning is often used prior to the removal of wisdom teeth in the lower jaw in order to assess tooth position and avoid nerve damage during the procedure. Also, when analysing results after orthodontic and surgical treatment of skeletal deviations, we combine information from CT images and from 3D virtual tooth models. We also stay abreast of new imaging techniques that are not based on ionizing radiation. One technique we are currently working on is thermography, which measures the temperature of a surface and displays a thermogram (see below) where each colour represents a temperature. With measuring of the facial skin, this method can be used to assess the effect of medication administered to reduce swelling or infection after the removal of wisdom teeth.

We also study patient discomfort and the working processes associated with the introduction of new technology. One way of doing this is to conduct a Medical Technology Assessment (MTA), and such projects notably concern equipment involving high radiation doses to the patient (as CT scanners do). The objective of an MTA can be to compare, on the one hand, the efficacy of the new diagnostic method on patient treatment and, on the other, the increased costs and other socio-economic aspects of the method, and the radiation exposure it entails for the population. The underlying cost-benefit analyses are carried out in co-operation with health economists.

Moreover, as a research method for in vitro studies we use micro-CT scanning for volumetric analyses of animal and human bone and tooth specimens. The volumetric data thus obtained forms the basis of finite-element analyses, which in turn are used to assess modelling and remodelling of bone at a cellular level, and also to perform experimental studies of caries lesions and the quality of root-canal fillings.

PROJECTS

1. **Assessing the diagnostic value of various imaging methods (their sensitivity, specificity, and so on)**:
   - The value of radiological methods prior to removing wisdom teeth
   - The value of radiological methods in assessing bone prior to inserting tooth implants
   - The correctness of digital receptors in assessing caries lesions, root fractures, and the quality of root-canal fillings
   - The value of tomography in assessing the TMJ, and its effect on the treatment plan

2. **Clinical longitudinal studies**:
   - Using thermography to assess inflammation after removal of wisdom teeth
   - The effect of CT image quality following patient movement during examination
   - CT scanning to assess the effect of treatment of the TMJ: a) in juvenile arthritis patients; and b) when applying various ortho-surgical principles

3. **Randomized clinical trials with long-term follow-up**:
   - Assessment of various tissue-regeneration methods, including bone transplants, in connection with implant treatment
   - Assessment of nerve damage following removal of wisdom teeth, investi-

gated pre-operatively using various radiographic methods
- The success of implant treatment,
- assessed pre-operatively using various radiographic methods
- Comparison of various treatment principles used for dento-alveolar bone modelling

4. **MTA studies**
   - Socio-economic aspects of using high-technology, dose-intensive CT methods instead of conventional radiographic examination for dental diagnostic tasks

MILESTONES

The Department of Dentistry at AU was the first dental school in the world to replace conventional radiographic film methods with digital receptors in its clinical education programmes.

Our dental school was also the first dental clinic in Denmark to implement advanced 3D techniques such as dental CT scanning. We initially did so when treating orthodontic patients with special needs, such as juvenile idiopathic arthritis.

The influence of computerized information technologies on image quality in dental radiographs
(Wenzel A. Dr. odont. thesis. Danish Dental Journal. 1991;95:527–59)

Radiography for the detection of dental caries lesions
(Hintze H. Dr. odont. thesis. Royal Dental College. University of Aarhus, 2004)

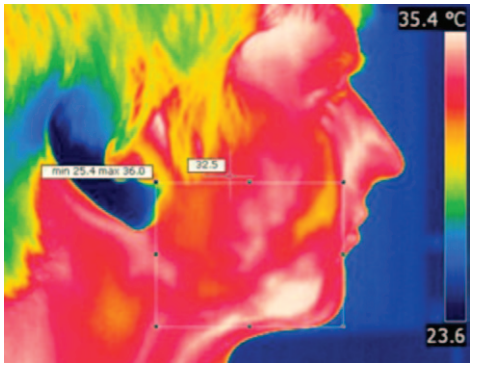
Synchrotron radiation-based microtomography of alveolar support tissues
(Dalstra M. Orthod Craniofacial Res. 2006;9:199–205)

Cross-sectional tomography and temporomandibular joint disorders
(Wiese M. PhD thesis. School of Dentistry. University of Aarhus, 2008)

Work-flow with intraoral digital radiography: A systematic review
(Wenzel A. Acta Odontol Scand. 2010;68:106–14)

METHODS

- Assessing the diagnostic accuracy of new techniques
- Longitudinal clinical studies
- Randomized clinical studies
- Clinical cross-over experiments
- MTA studies.



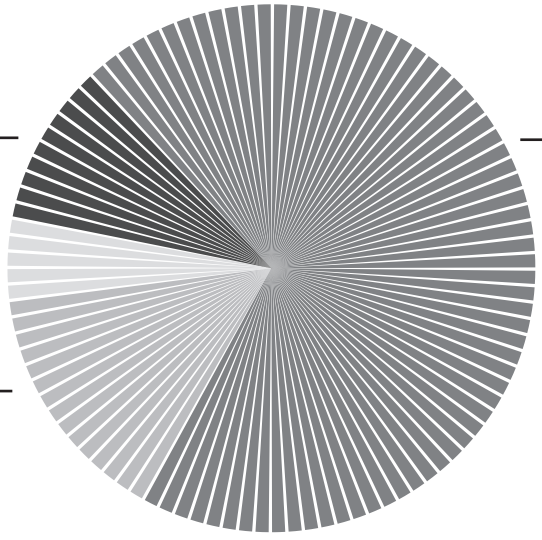
Thermogram of patient following removal of a wisdom tooth. White colour indicates warmest skin area.

OVERVIEW

10 %
Basic research

5 %
Qualitative research

15 %
Epidemiological research



70 %
Clinical research

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ORAL DISEASES / EPIDEMIOLOGY AND AETIOLOGY

The manifestation, diagnosis, aetiology, pathogenesis, and epidemiology of oral diseases are topics of fundamental importance to the field of dentistry. The term "Oral diseases" covers pathological conditions in both the soft and hard tissues of the oral cavity. For decades, the Department of Dentistry at Health has made internationally recognized research contributions within a wide range of oral diseases. These include diseases in the supportive tissues around the teeth (periodontal disease) and in the hard tissues of the teeth themselves (dental caries, erosion, mineralization disturbances, and tooth anomalies).

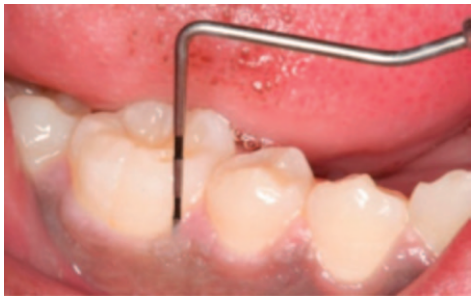
Nevertheless, many unresolved questions continue to call for intensive research in oral diseases. Given that the oral cavity is an important entryway into the body, and that functional teeth and healthy oral tissues are preconditions if people are to function well and thrive in the broadest sense of the word, studies of oral diseases are and will remain important and ever relevant. In addition, new questions and issues that also require research regularly arise, instigated by such factors as the rapid pace of change in our modern world. This pace leads to changes in the way people interact and behave, and it influences health, living conditions, and lifestyles.

Research on global oral health and disease

The research carried out at the Department of Dentistry focusses on clinical manifestations and variations of diseases in the oral tissues. Studies are conducted in Denmark and elsewhere around the globe. We especially focus on oral bacteria implicated in the initiation and progression of disease – such as the development of cavities (caries) or loose teeth (periodontal disease) – but also focus on other factors – hereditary, environmental, health-related, behavioural, and social – which may be implicated in the development of disease.

In recent years, research on an aggressive form of periodontal disease has gained international attention. Over decades, we have accumulated extensive knowledge about a virulent bacterial clone of the oral microorganism Aggregatibacter actinomycetemcomitans (more specifically called the JP2 clone). The prevalence of this particular clone is very high in the northern and western parts of the African continent, but it is also frequently found in individuals of African origin, living in Denmark and in other countries that are geographically widespread.

People who carry this bacterial clone in the oral cavity have an 18-times higher risk of developing an aggressive form of periodontal disease, compared to those who do not carry this clone. Based on our findings we can contribute to early diagnosis of this disease in the young, enabling preventive efforts to begin in a timely fashion. In cases where the disease has already become evident, we can help to organize and carry out a more specifically targeted treatment regimen for this aggressive form of periodontal disease.



One manifestation of marginal periodontitis is a loss of attachment around the teeth. This can be diagnosed by clinical examination.

PROJECTS

1. The Department of Dentistry is conducting a variety of interesting and noteworthy projects that primarily focus on diagnostics of oral diseases, including clinical, radiographic, functional, microbiological, and genetic examinations. Many of these projects are based on interdisciplinary and intersectorial collaboration with researchers from other universities and other types of institutions and organizations, within Danish borders and beyond.

2. Periodontal attachment loss in children and adolescents. Collaborative projects involve departments at Aarhus University and universities on the African continent and in Europe, North America, South America, and Asia.

3. Diagnostic research relating to dental caries and periodontal diseases.

4. Factors relating to the treatment, development, and healing of apical periodontitis, and the development of the endodontic status in an adult Danish population.

5. Molar Incisor Hypomineralization. Collaborative projects involve Danish municipal services, paediatric departments at Danish hospitals, and international universities.

6. Oral manifestations of rare diseases, such as hereditary rickets, amelogenesis imperfecta, and osteogenesis imperfecta.

MILESTONES

Increased risk for development of periodontal attachment loss in carriers of the JP2 clone of Aggregatibacter actinomycetemcomitans
(Haubek D. Lancet. 2008;371:237–42)

Microevolution and patterns of dissemination of the JP2 clone of Aggregatibacter (Actinobacillus) actinomycetemcomitans.
(Haubek D. Infect. & Immun. 2007;75:3080–8)

Implications of caries diagnostic strategies for clinical management decisions
(Baelum V. Community Dent Oral Epidemiol. 2011 Epub ahead of print)

Risk factors for developing apical periodontitis in a general population
(Kirkevang L-L. Int Endod J. 2007;40:290–9)

Defining a periodontitis case: analysis of a never-treated adult population
(Baelum V. J Clin Periodontol. 2011. Epub ahead of print)

Clinical variation of amelogenesis imperfecta – mutations of the genes involved in the amelogenesis
(Haubek D. Int J Paediatr Dent. 2011;21:407–12)

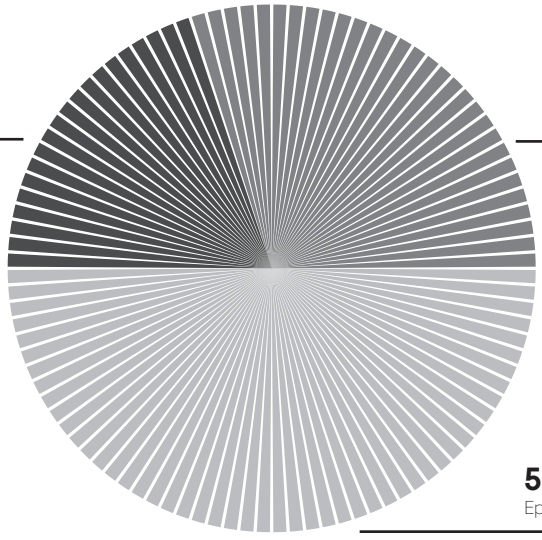
Manifestation of hereditary rickets in oral and craniofacial tissues
(Gjørup H. Am J Med Genet. 2011;155:2654–60)

METHODS

Research in the field of oral diseases comprises a wide range of methods used to perform clinical, radiological, microbiological, genetic, histological, functional, and epidemiological investigations. Some of the scientific methods and special skills are:

- Design and analysis of clinical trials, case-controlled studies, and cohort studies
- Systematic collection of clinical data related to oral conditions and/or diseases
- Generation and interpretation of radiographic images, and scientific handling of radiological data
- Analysis of biological materials, such as teeth, dental plaque, saliva, and tissue and blood samples
- Scientific handling of data from various Danish electronic public registers and databases, and combination of these with scientific data within the field of odontology
- Qualitative and quantitative methods
- Epidemiological and statistical methods.

OVERVIEW



20 %
Basic research

30 %
Clinical research

0 %
Qualitative research

50 %
Epidemiological research

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ORAL ECOLOGY

The Department of Dentistry at Health has been studying the biofilm of human teeth for more than three decades. This makes the department an international pioneer in its field, and we possess profound and extensive knowledge about the life of bacteria on dental surfaces.

Our research group seeks to answer many questions, including:

- Which biological mechanisms underlie the generally peaceful relationship between us and the microflora in our mouths?
- Which changes in the composition of dental plaque (biofilm) can explain the development of periodontal disease?
- How do various environmental factors affect the composition and structure of the dental biofilm and its potential for producing acid?
- How can our scientific findings be converted into new strategies for preventing dental caries and periodontal disease?

The aim of doing research in oral ecology is to expand and diversify our knowledge about the oral microflora, and about its interaction with saliva, diet, and the immune system. By increasing our knowledge in these areas we become more able to understand what causes dental diseases, and more qualified to suggest how best to prevent them from occurring. Our basic working hypothesis is that caries and periodontal disease are caused by changes in the oral environment. If the mouth is supplied with sugar, its environment will favour acid-producing bacteria, which leads to cavities. If bacterial build-up is allowed to proceed along the gums, this leads to gingivitis, which can ultimately develop into periodontal disease.

Ecological imbalances lead to disease
One of the questions our research explores is how the composition, structure, and metabolic processes in plaque can explain why some people are more prone to develop pathological conditions than others. In short, we regard dental disease as the result of an imbalance in oral ecology – an imbalance that can be rectified, provided we intervene at an early stage, before it manifests as cavities or loosening of the teeth.

PROJECTS

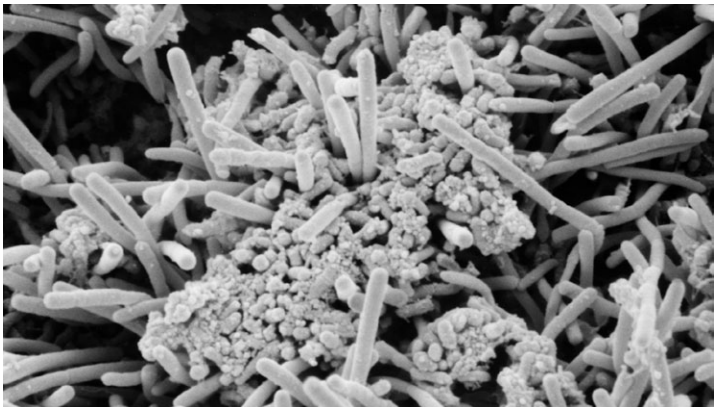
Research in oral ecology is conducted in close collaboration with other groups, both in Denmark and from the international research community.

1. ProSurf. One noteworthy project is our interdisciplinary cooperation with AU SCIENCE AND TECHNOLOGY (iNANO) and industrial partners on a platform called "ProSurf – proteins and nanotechnology". The objective of ProSurf is to develop nanoparticles based on milk protein for use in dental-hygiene products. ProSurf is partly funded by the National Danish Advanced Technology Foundation.

   Other ongoing projects are:

2. Studies of the structural composition and metabolic potential of young dental biofilms studied in vivo, with and without influence from sucrose.
3. Investigations to explain why certain periodontal-disease bacteria evade the effect of high antibody concentrations that they themselves generate in the host.
4. Investigation of the biochemical mechanisms by which toxins from periodontal-disease bacteria can kill our immune cells.

Dental biofilm.
Courtesy of Skaaring, Fejerskov & Nyvad.
Aarhus University.



METHODS

In recent years, molecular and microscopic methods using fluorescent biomarkers have made it possible to analyse the bacterial composition and pH of intact biofilms without removing them from the tooth. This means that we can now examine the biofilm in its natural surroundings, along with the surface on which it grows and in interaction with the local environment in the oral cavity. Such methods are employed today to study whether various types of "environmental therapy" using nanoparticles are able to inhibit the potential of the biofilm to generate pathological conditions.

We use the following analytical methods:

- DNA sequencing
- Metabolomics
- Immunochemistry/immunocytochemistry
- FISH (Fluorescence In Situ Hybridization)
- Biofilm pH real-time imaging
- CLSM (Confocal Laser Scanning Microscopy)
- SEM (Scanning Electron Microscopy)
- Microradiography
- Flow-cell experiments
- In situ experiments.

MILESTONES

Actinomyces naeslundii in initial dental biofilm formation
(Dige I. Microbiology. 2009;155:2116–26)

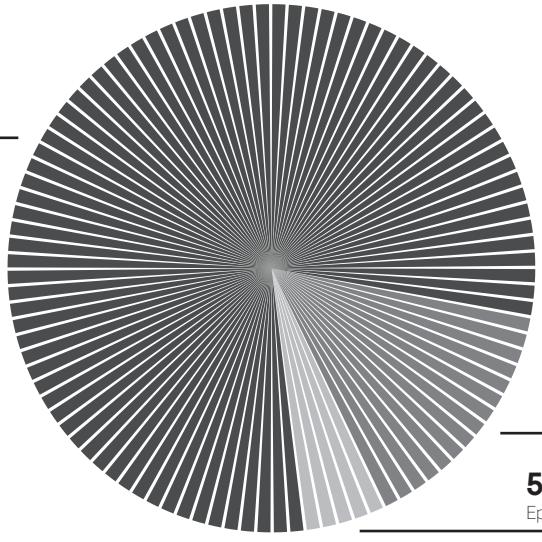
pH landscapes in a novel five-species model of early dental biofilm
(Schlafer S. PLoS One. 2011;6(9):e25299. Epub 2011 Sept 23)

The role of bacteria in the caries process: Ecological perspectives
(Takahashi N. J Dent Res. 2011;90:294–303)

IgA and mucosal homeostasis
(Reinholdt J. In: Morteau O, editor. Oral Tolerance: The response of the intestinal mucosa to dietary antigens. Plenum Publishers, 2004, New York, pp. 81–98)

Microbiological and immunological characteristics of young Moroccan patients with aggressive periodontitis with and without detectable Aggregatibacter actinomycetemcomitans JP2 infection
(Rylev M. Mol Oral Microbiol. 2011;26:35–51)

OVERVIEW



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ORAL REHABILITATION

Oral rehabilitation relates to the diagnostic process, treatment planning, and rehabilitation of oral function, and to its maintenance. This field encompasses elements from most of the disciplines normally associated with dental treatment: filling and crowning teeth damaged by dental caries, erosions (acid damage), wear and abrasion (caused by tooth-grinding, for instance), and trauma (blows). The damage can be so extensive that root-canal treatment becomes necessary.

The field also covers the replacement of teeth that have been lost as a result of caries, periodontal disease, or trauma, or which are lacking due to hereditary conditions. Tooth replacements are made using biocompatible materials, and they can be fastened on existing teeth (bridges) or implants, or be supported by existing teeth, implants, and the oral mucous membrane (dentures). We conduct research to optimize the methods and techniques used for these dental treatments. Our research is many-faceted, and in our work we test various hypotheses using methods such as mechanical testing in a laboratory environment, computer simulation, and animal models. In addition, much of our activity takes place as clinical studies where in some areas we have been following our patients for 20 years.

When correcting poor dentition and abnormal or defective mandibular growth, we use orthodontics and, in more challenging cases, a combination of orthodontic appliances and jaw surgery. One element of oral rehabilitation therefore involves clinical and experimental animal testing as we seek to develop and improve the treatment options for correcting congenital or acquired deformities of the maxillofacial skeleton. As part of these efforts, bone growth, modelling and remodelling are assessed in relation to mechanical forces exerted upon the bone (which can be around teeth, for example, or oral mini-implants). Tests are done partly on humans, partly as animal experiments, and partly on cell cultures. Through these investigations we can learn how to optimally exert force on teeth and bone tissue when providing orthodontic treatment.

Weighing the risks gives the best outcome

Whether we are working to rehabilitate the teeth of a senior citizen or an adolescent, the crucial question is: Which treatment methods will yield the best results, with the fewest complications in the long term? In some cases we strive to maintain the tooth in the patient's mouth. In other cases, treatment may aim to improve the patient's ability to chew, smile, or speak – the issue being improved quality of life. Consequently, when testing principles we also seek to determine how dentists can give their patients the best possible treatment, even while considering the potential risks that dental treatment can entail.

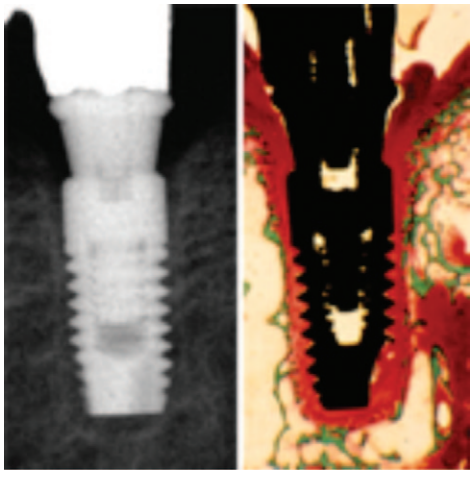
PROJECTS

1. Clinical, radiological, and histological evaluation of bone reactions at immediately loaded free-standing implants in monkeys. Immediately loaded implants are compared both with implants that have healed prior to occlusal loading and with non-loaded implants.

2. Long-term observations of tooth replacements (single-tooth implants, bridges, or adhesive bridges). Survival and complications are assessed for several groups of patients, including persons with tooth loss due to aggressive marginal periodontal disease; some patients have been followed for 20 years.

3. Research concerning patients with disturbances in dentofacial growth and mandibular function caused by pathological conditions in the temporomandibular joints, including patients diagnosed with juvenile idiopathic arthritis; for instance the evaluation of bone distraction in patients with juvenile idiopathic arthritis.

4. Studies of bone reaction to various biomechanical loads; for instance specific bone tissue reactions under certain physiological and pathological conditions in an animal model, using orthodontic biomechanical loading.



Radiological (on left) and histological image of an implant that has lost osseointegration due to forceful compression .

MILESTONES

Excessive masticatory force can cause osseointegrated oral implants to lose osseointegration
(Isidor F. Clin Oral Impl Res. 1997;8:1–9)

The greatest reduction in alveolar bone volume after tooth extraction takes place within the first year
(Schropp L. Int J Periodont Rest Dent. 2003;23:313–23)

3D analysis and evaluation of orthopaedic treatment of abnormal mandibular growth pattern
(Cattaneo PM. Comput Meth Biomech Biomed Engin. 2005;8:157–65)

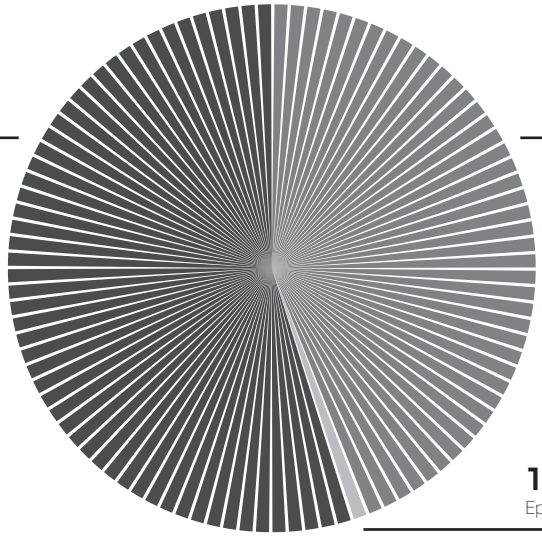
Investigations relating to biomechanics, bone biology, and orthodontic treatment of adult patients
(Melsen B. Editor. Adult Orthodontics. Wiley-Blackwell, Chichester, West Sussex, UK. ISBN: 978-1-4051-3619-8)

METHODS

Clinical evaluation and animal experiments (with subsequent histological evaluation), mechanical testing and similar tests in the laboratory, and also computer simulation.

- Clinical assessment of treatment outcomes: function, aesthetics, patient satisfaction, complications, survival of tooth/implant, and restoration
- Radiological evaluation of treatment outcomes
- Hard-tissue histology of bone reactions to mechanical loads
- Tensile and fracture strength of test specimens subject to static and dynamic load
- Computer simulation of the effect that load on teeth and implants has on the surrounding tissues, and particularly on bone.

OVERVIEW



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ORAL TISSUE REGENERATION

BIOMATERIALS

Loss of oral tissues can be due to disease, trauma, therapeutic interventions, or developmental aberrations. Standard therapeutic interventions result most frequently in a reparative type of healing, which in turn often results in functionally and aesthetically compromised conditions. A variety of biomaterials and approaches have been used aiming at regenerating the oral tissues, including bone grafts/substitutes, guided tissue regeneration membranes, growth and differentiation factors, bioactive molecules, scaffolds, cells, and various combinations of these elements.

Periodontal disease, for example – an inflammatory disease of microbial aetiology – results in loss of the tissues surrounding the teeth, including bone, and in its advanced stages it leads to tooth loss as well. Greater clinical improvements and better aesthetic outcomes may be achieved with procedures aiming at regenerating the lost tissues around teeth. In addition, in cases where oral implants are planned for replacing missing teeth, regeneration of the lost or missing bone is often required. Similarly, regenerative procedures are often needed for treating peri-implant inflammatory lesions (known as peri-implantitis).

What works, and what works better?
There is a constant search for the ideal biomaterial, and the ideal approach to regenerate the missing tissues. Autogenous bone (which is bone taken from the same patient) has been considered for many years to be the "gold standard" in grafting materials. Autogenous bone harvesting is, however, associated with some drawbacks, such as additional patient suffering, surgical complications related to the donor site, and limited graft availability, as well as graft resorption. To replace or reduce the need for autogenous bone grafting and to optimize the regenerative outcome, various biomaterials and approaches have been developed.

Pioneering studies by researchers at the Department of Dentistry have led to the development of a treatment strategy for regenerating the lost tissues around periodontally compromised teeth. The technique, called Guided Tissue Regeneration (or simply the "membrane" technique), is still applied in the clinic all over the world. Currently, focus is placed on tissue engineering approaches involving combinations of scaffolds, bioactive molecules, and cells. Issues addressed by current research include tissue-biomaterial interactions, functionalizing biomaterials for enhancing the regenerative outcome, and evaluating systemic conditions (such as diabetes and osteoporosis) that may aggravate tissue loss and/or influence the outcome of regenerative procedures. In collaboration with national and international partners, including the dental industry, studies are being performed – using a variety of in vitro and preclinical in vivo models, and also randomized clinical trials and human histological evaluations – to assess such technologies and approaches that aim at regenerating tooth and periodontal tissues, as well as bone in association with oral implant therapy.

PROJECTS

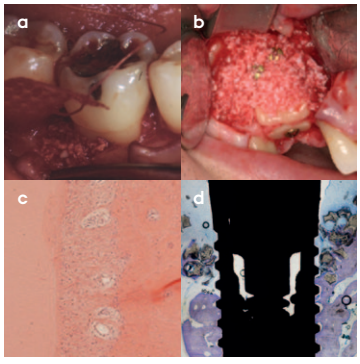
1. Growth and differentiation factors (GDFs). GDFs are potent regulators of many processes relevant to tissue regeneration. We perform preclinical in vivo, clinical, and human histological evaluation of such factors for orofacial tissue regeneration, including pulp, dentin, and periodontal regeneration, and for bone regeneration in association with oral implants.

2. Bone substitute materials. Bone-derived and synthetically produced bone substitute materials are suggested, either alone or in combination with autogenous bone grafting, for eliminating or reducing, respectively, the amounts of autogenous bone needed. Such materials are constantly evaluated in preclinical in vivo experiments and clinical studies for periodontal indications and in association with oral implants.

3. Systemic conditions and tissue regeneration. Diabetes and osteoporosis seems to compromise the outcome of bone regenerative procedures. Preclinical in vivo studies explore the influence of such systemic conditions on bone regenerative procedures and in association with oral implants.

4. Innovative dental materials. Preclinical testing of dental materials for hard tissue regeneration in and around the tooth.

5. Bone Tissue Engineering. We perform preclinical and clinical studies testing different scaffold materials, designs, and nano-surface topographies, various biomolecules and types of cells (for instance autogenous bone cells, mesoangioblasts, mesenchymal bone-marrow-derived cells, and dental-pulp-derived cells) for their potential to enhance bone regeneration.



Regenerative treatment in periodontal (a) and bone defects (b), involving implantation of bone biomaterials, may facilitate complete periodontal regeneration (c) and installation of oral implants (d).

MILESTONES

Development of the guided-tissue regeneration technique for periodontal regeneration, which is applied worldwide in the clinic
(Karring T. Perio. 2000;1993,1:26–35)

Co-editing several editions of Textbooks on Clinical Periodontology and Implant Dentistry
(Eds: Lindhe J, Karring T, Lang NP. 5th edition, Blackwell-Munksgaard, 2008)

Co-editing the only existing Textbook on Biocompatibility of Dental Materials
(Schmalz G, Arenholt-Bindslev D. 1st edition, Springer, 2008)

Peri-implantitis: pathogenesis, diagnosis, and treatment as evaluated in cynomolgus monkeys
(Schou S. Dr. odont. thesis, University of Copenhagen, 2004)

Deproteinized bovine bone in periodontology: animal experiments and clinical studies
(Stavropoulos A. Dr. odont. thesis, Aarhus University, 2010)

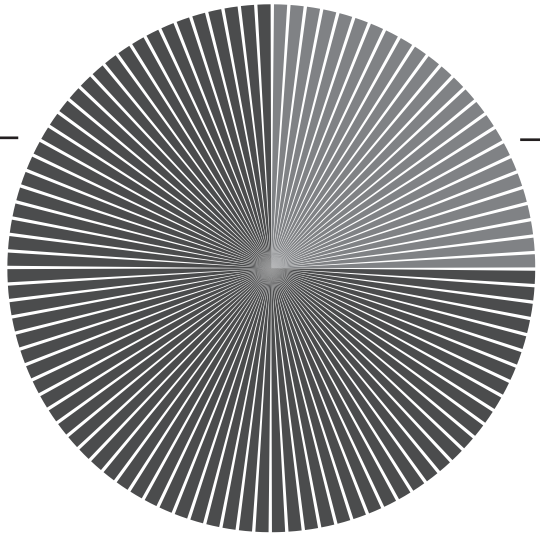
METHODS

- In vitro methods
  - Cell cultures; cell sorting and differentiation assays
  - Elisa; Real-time PCR
- Preclinical in vivo evaluations in rodent, porcine, and canine platforms
- Histology
  - Decalcified (paraffin) embedded tissues
  - Plastic non-decalcified embedded tissues, including biomaterials and/or oral implants (thin – thick sections)
- Micro-CT scanning
- Stereology as a method for obtaining unbiased estimates of tissue regeneration
- Randomized controlled clinical trials.

OVERVIEW

75 %
Basic research

25 %
Clinical research



0 %
Qualitative research

0 %
Epidemiological research

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OROFACIAL PAIN AND DYSFUNCTION

Pain and functional jaw disorders are an inadequately recognized problem in Denmark, despite the fact that they affect 10% of the Danish population. For some the pain is so debilitating that they are ultimately declared medically unfit to work.

One ambition for the Department of Dentistry and its unit for clinical oral physiology is to help relieve severe pain of this nature. Our research therefore revolves around finding better diagnostic and therapeutic methods to treat patients suffering from oral and jaw pain.

The unit has a particularly high level of competence in the field of Quantitative Sensory Testing (QST) and orofacial pain. We are world leaders in the technical aspects of QST and have developed a special device – a palpometer – which, by "feeling" the muscles, can standardize pressure, thereby reducing the variation in the clinical examination of different muscles and joints. This small device gives greater certainty in the diagnostic process and thus benefits patient treatment. The palpometer is patented, and commercial production has begun.

Another specialized skills area is our work with a wide variety of techniques used to measure motor function. In this context we measure reflexes and evoked potentials, as well as other biological muscle reactions. Combined with various brain-scan techniques this gives us a new way of looking at the brain of patients suffering from severe pain. An added advantage is that we can look not only at the teeth, but more broadly at the patient as a whole.

An international partner

Within our professional area we collaborate with many other groups based in the fields of neurology, rheumatology, psychology, and anaesthesiology. However, we are also strong on international partnerships, uniting our efforts with researchers and units in Europe, Japan, and Canada. In Nanjing, China, we co-founded the Sino-Denmark Orofacial Pain & TMD Research Center in 2011.

As an active participant in the international research community, we help to create a consensus about what topics are most relevant for research in our field. Here, our unit at AU Health is one of the international heavyweights measured, for instance, in terms of research output, but also by virtue of the emphasis our voice carries in international bodies and discussions. We play a very active role in special interest groups for facial pain, and we hold the chairmanship in an international forum on temporomandibular disorder pain.

PROJECTS

1. **Motor learning/cortical plasticity.** This heading covers a series of projects in which repeated jaw or tongue movement is practiced to obtain a high degree of accuracy in execution, and in which precision can be measured simultaneously with the brain's altered control of the muscles in question. This is an important part of relearning functions, for example for people learning to swallow again after a stroke, or for those internalizing jaw exercises in connection with physical therapy.
2. **QST and orofacial pain.** Quantitative Sensory Testing is a "window" that can reveal many things about the pain-related nervous system: By systematically describing the function of various sensory nerves, we are able to form an impression of the background of orofacial pain. Therefore QST can also be used to document damage to the nervous system and form a prognosis on how orofacial pain will develop.
3. **Bruxism – causes and effects.** Tooth-grinding and clenching – bruxism – is a frequently occurring phenomenon. It can not only wear down teeth, but can also result in headaches or pain and tenderness in the jaws. Working with commercial firms, we have developed EMG measuring apparatuses and therapeutic devices for diagnosing and treating bruxism. This equipment can also be used to investigate basic circumstances relating to the condition.
4. **Autonomous reactions to orofacial pain.** Leading a stressful life can aggravate orofacial pain. This project employs several physiological, psychological, and genetic measurements of pain sensitivity to assess the autonomous nervous system's significance for orofacial pain.

5. **Brain scans.** We are collaborating with the university's Center of Functionally Integrative Neuroscience (CFIN) and the Danish Pain Research Centre to conduct several studies that explore the interaction between pain, brain activity, and emotions. We expect to identify critical areas in the brain that give rise to an intensified feeling of pain, as well as areas that can alleviate pain.

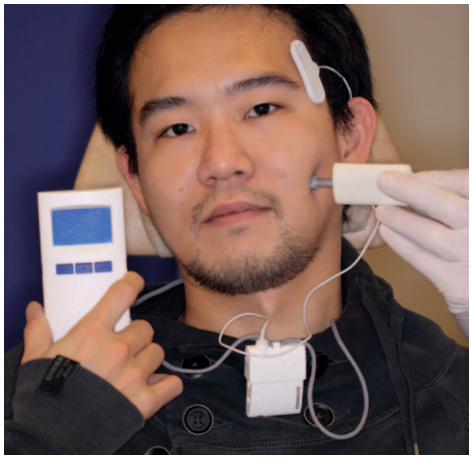


Illustration of ambulatory recording of jaw muscle activity with the use of Grindcare (Medotech A/S) and standardized assessment of jaw muscle pain sensitivity with a so-called palpometer.

MILESTONES

Our goal is to make high-profile contributions to the internationally recognized literature on orofacial pain and functional disorders. Furthermore, our ambition is to continue to obtain research funding from Danish and foreign sources, and to attract visiting researchers from abroad.

Development, patenting, and validation of the new palpometer
(Futarmal S. J Dent Res. 2011;90:918–22)

Guidelines and recommendations for assessment of somatosensory function in orofacial pain conditions
(Svensson P. J Oral Rehabil. 2011;38:366–94)

Demonstration of lower levels of pain perception during hypnosis
(Abrahamsen R. Pain. 2010;151:825–33)

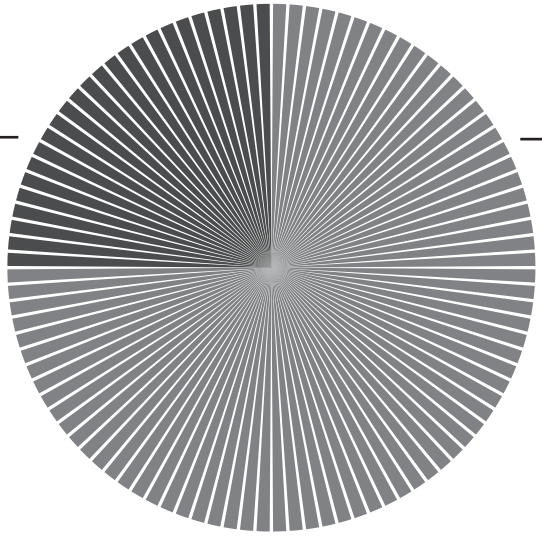
METHODS

The research done on pain and functional jaw problems involve techniques for systematically assessing sensory functions – as this gives us a window to understanding how the pain system works. For this purpose we use Quantitative Sensory Testing (QST). Our research unit at Health has drawn up guidelines for the use of QST on orofacial areas.

We also employ a variety of other scientific methods, including:

- Electrophysiology (EMG, reflex, EEG)
- Autonomous measurements (EKG variability)
- Brain scans (fMRI)
- Experimental pain investigations – models for pain in, for instance, muscles or joints
- Standardized clinical functional assessments (Research Diagnostic Criteria for Temporomandibular Disorders)
- Assessment of bruxism (tooth-grinding) using Grindcare

OVERVIEW



25 %
Basic research

75 %
Clinical research

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Qualitative research

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Epidemiological research

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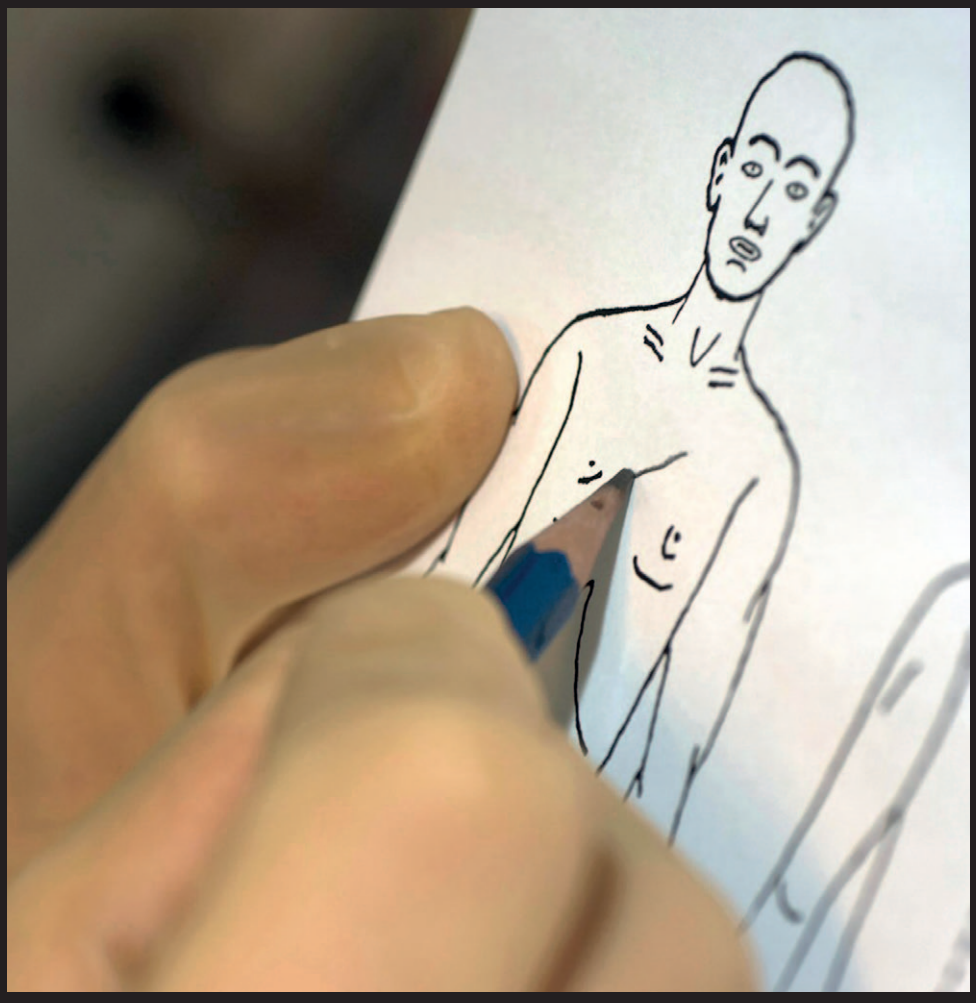
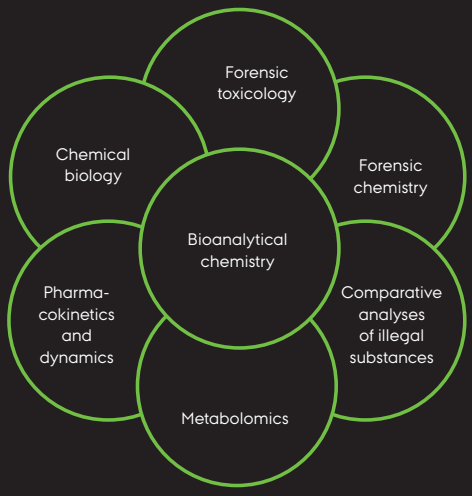
FORENSIC MEDICINE



▲ Documenting findings. Photo: Zebra Media

▼ The Unit for Bioanalytical Chemistry covers research and development within the six overlapping areas. Activities revolve around our core competence: advanced bioanalytical chemistry.



▲ Sampling of trace evidence. Photo: Zebra Media

HERE DEATH BENEFITS **THOSE WHO LIVE**

We know today that the mortality rate among people with a psychiatric diagnosis is twice as high as it is among the rest of the population. But we do not know why – and currently, after autopsy the cause of death remains unexplained for 15.5 per cent of the deceased psychiatric patients in Denmark.

New optimized autopsy method

The ambition of the researchers behind the project SURVIVE: "Here Death benefits those who live", which is anchored at the Departments of Forensic Medicine in Denmark, is to optimize autopsies by employing molecular biology methods. This will enable us to understand the causal relations of these deaths far better than we do today. Our improved knowledge will be useful in identifying the greatest risk factors. This, in turn, will allow us to identify areas of intervention and prevention that can benefit psychiatric patients and thereby reduce the mortality in this group. "When we perform an autopsy, we play a part in detailing a story. In the long term, the knowledge that we obtain can help prevent future deaths," Professor Jytte Banner points out.

Mapping five decisive factors

Over a period of two years the researchers in the SURVIVE project will examine all of the deceased psychiatric patients in Denmark, expected to be about 500 individuals, for whom a forensic autopsy has been requested. The researchers are focussing, in particular, on five factors that are believed to play an essential role in mortality among psychiatric patients:

1) somatic disease; 2) metabolic syndrome and risk factors for developing cardiovascular diseases; 3) the use and abuse of alcohol, medication, and illegal drugs; 4) the body's metabolism of medication; and 5) hereditary predisposition for sudden death by cardiac arrest.

"Many preventive measures are based on the theory that lifestyle plays an important role. But through autopsy studies we can more precisely determine the causal relations, and in that way give a much better picture of areas in which interventions could make a difference," explains Professor Banner.

The data collection and the subsequent analysis begin in 2012, and the results are expected to be ready for presentation in the latter half of 2014.

> **When we perform an autopsy, we play a part in detailing a story. In the long term, the knowledge that we obtain can help prevent future deaths.**
>
> PROFESSOR JYTTE BANNER

FACTS

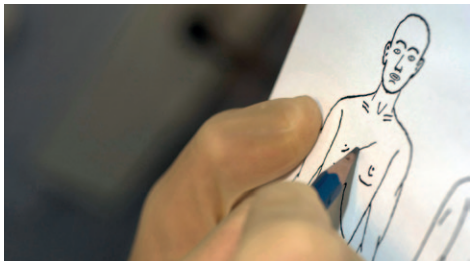
We know today that approximately one third of deaths among people with mental illnesses are caused by suicide and accidents. The remaining two thirds die of natural causes, with cardiovascular diseases accounting for almost half of the cases.

FORENSIC PATHOLOGY AND CLINICAL FORENSIC MEDICINE

In cases of criminal acts, suicides, and accidents, or in the event of sudden unexpected death, consulting forensic experts is a legislative and necessary step. In the fields of forensic pathology and clinical forensic medicine we examine dead and living persons to provide thoroughly documented expert assistance to the police, legal authorities, and the Danish national health service.

We perform autopsies in order to elucidate the manner and cause of death, but also to continuously increase our insights into issues relevant for the health profession, thereby benefitting both the common health and the development of preventive measures. Examples include traffic safety and sudden unexpected death. In the field of clinical forensic medicine we also work to document injuries sustained by victims of violence and sexual abuse.

Professional expertise and useful tools
The focus of our research is to aid preventive efforts. At the same time we continue to develop our cooperation with other research units. We work very closely, for instance, with other departments in the Health faculty, and with Aarhus University Hospital and other regional hospitals.



Documenting findings. Photo: Zebra Media

Our department was among the first in the world to introduce advanced post-mortem imaging when we acquired a high-end CT scanner. This scanner enables us to visualize details that an autopsy alone would not reveal.

The research done in traffic medicine has influenced preventive legislation and increased our understanding of whiplash and fatal injuries sustained in traffic accidents. Our research on infant mortality has influenced the decision made by the National Board of Health to change guidelines on the positioning af infants during sleep, and it has also played a role in expanding the Danish national neonatal screening programme (heel prick test), which now includes screening for more diseases than previously.

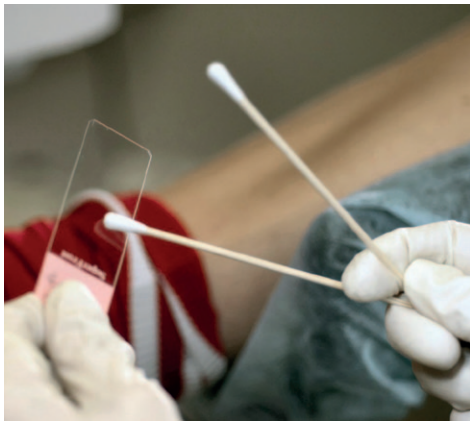
PROJECTS

1. **National strategy for sudden unexpected death – Focus on hereditary cardiac diseases and stress-related conditions (heat shock and oxidative stress):** Involves three PhD projects, currently ongoing, which aim to develop prognostic markers.
2. **Survive: "Here Death benefits those who live" – Autopsy-based strategy for mapping the risk markers for deaths among people with mental illness:** A nationwide interdisciplinary project that involves five planned PhD projects focussing on metabolic syndrome, hereditary predispositions, and the metabolizing of medication.
3. **Injury Pattern Analysis:** Examines deceased trauma victims using CT scans, histomorphometry, and histological analyses of undecalcified bone tissue.
4. **Development and implementation of post-mortem CT scans with angiography:** Intended for use in forensic pathology and forensic archaeology.
5. **Clinical forensic medicine – Characterization of abuse:** Three PhD projects, including studies of drug rape; examination of communication with children and parents in the event of suspected sexual abuse; and determination of findings from medical examinations of children who are victims of sexual abuse.

MILESTONES

Impact on Danish society

- Improved safety equipment in traffic; altered recommendations from the National Board of Health on infant care regarding infant sleeping position and expanded metabolic-disorder screening offered to newborns.



Sampling of trace evidence. Photo: Zebra Media

Collaborative efforts and units established

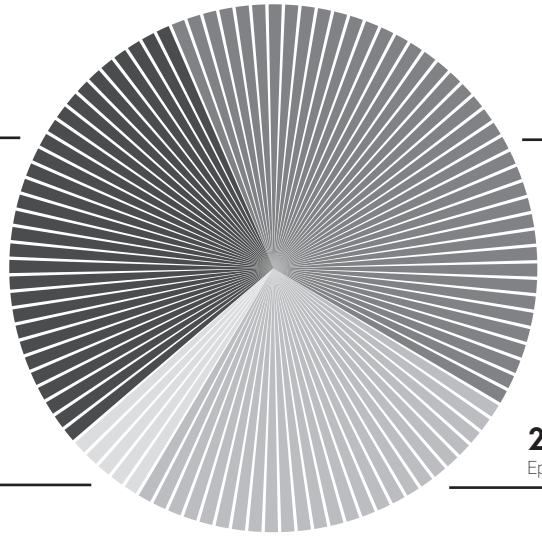
- Extensive national and international collaborations on sudden infant death syndrome (SIDS) and cardiac arrest among young adults, deaths among people with mental illness, forensic epidemiology, and traffic medicine.
- Regional imaging cooperation: a broad, innovative research network on post-mortem diagnostic imaging of the musculoskeletal system and traumatic lesions.
- The Centre for Rape Victims (CfV): founded in 1999 in Aarhus, Herning, and Aalborg, with Aarhus serving as the knowledge and learning centre for the western regions of Denmark.
- The Child Protection Centre (CBO): founded in 2007 as a national knowledge and learning centre.
- Establishment of a national interdisciplinary working group focussing on the prevention of rape and abuse.

METHODS

In connection with autopsies and examinations of individuals we use accredited investigative techniques, supplemented by interdisciplinary centre functions and investigations done at or done by:

- The Histology and Bone Laboratory: General histopathology, production of undecalcified histological sections, stereological analyses (newCAST)
- The Molecular Pathology Laboratory: Experimental intervention of human cells, extraction of DNA and RNA, preparation for proteomics and metabolomics
- The Anthropology Laboratory: Collaboration with forensic archaeologists and anthropologists
- Imaging and Injury Pattern Analysis: Traumatology, pathology, and CT scans

OVERVIEW



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SECTION FOR TOXICOLOGY AND DRUG ANALYSIS – BIOANALYTICAL CHEMISTRY

It is absolutely crucial to possess detailed knowledge of small molecules like those that constitute pharmaceuticals, metabolites, and illegal narcotics if we are to understand the mechanisms and processes at work in diseases, and if we are to prevent deaths and crime.

At the Unit for Bioanalytical Chemistry – which is the scientific research unit at the Section for Toxicology and Drug Analysis – our overall engagement involves analysing the composition of endogenous and exogenous molecules in the body. Our aim is to do basic research as well as to provide assistance to the authorities.

On the research side, one main area is the body's reactions to pharmaceuticals and narcotics. In addition, metabolomic analyses also examine how the body's own molecules, the so-called metabolites, play a significant role in diseases and ageing.

The services we provide to the authorities most notably deal with toxicology and illegal substances. Additionally, we develop new analyses and investigative methods that benefit the police and legal system. The Section for Toxicology and Drug Analysis has achieved ISO 17025 accreditation.

New interdisciplinary unit with excellent research facilities

The research unit that deals with bioanalytical chemistry is new and very diverse. It covers research and development within 6 overlapping areas (see Figure 1), all of which arise from our key analytical expertise and potentials. Newly established in 2007, the unit has been able to gather various technologies and facilities under one roof.

Bioanalytical chemistry work requires expensive equipment and specially trained staff. As a result, other health research units often call upon our unit's skills and expertise, which also means there is a considerable potential for external crossdisciplinary collaboration within natural and health science.

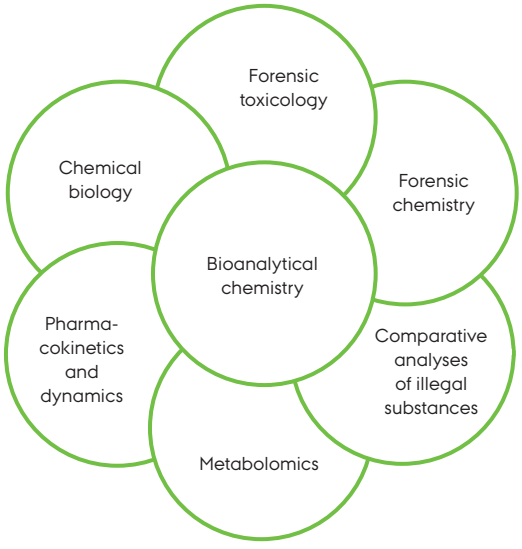
PROJECTS

1. **Pharmacokinetics:** Clarification of pharmacokinetic issues in deaths among patients with psychiatric illnesses, using measurements on pharmaceuticals and abuse substances and determination of genotype and phenotype in relation to pharmacokinetics. (Project cooperation with the Department of Forensic Pathology, described in an article p.76.)

2. **Chemical profile analysis:** This research project is working towards establishing a

FIGURE 1:

The Unit for Bioanalytical Chemistry covers research and development within the six overlapping areas. Activities revolve around our core competence: advanced bioanalytical chemistry.



national database for chemical profiles of illegal narcotic substances. We actively cooperate with police investigation units, which will eventually be the end-users of the knowledge and information gathered. At present we are also working to acquire skills in comparing illegal doping substances and new mind-altering drugs.

3. **Metabolomics:** Targeted and untargeted metabolomics methods are being developed and used to gain insight into the human metabolism, and to identify markers and mechanisms behind ischaemic heart disease (blood clots) and other diseases.

4. **Chemical biology:** Understanding the link between, for instance, lipid metabolism and disease/biological ageing, with special focus on the role of glycations and ketone bodies.

5. **Chemical biology:** The development of chemical probes that can be used to clarify how the modification of genes and proteins (post-translational) is linked to the human metabolism and various pathological changes.

MILESTONES

Introduction of lower-limits of significance for the presence of illegal substances in traffic in Denmark.

Interdisciplinary translational research/collaboration, ranging from the synthesis laboratory at the Department of Chemistry, across the Research Unit for Molecular Medicine at the Department of Clinical Medicine, and to the Department of Cardiology at Aarhus University Hospital.

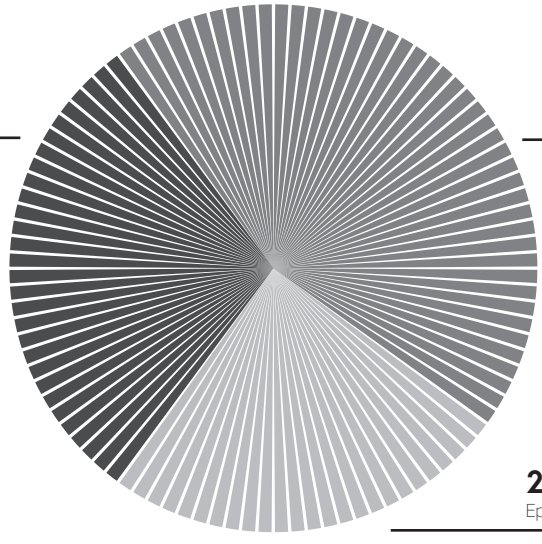
Collaboration with the police and the National Board of Health (as well as the Danish customs authorities). Our unit acts as a strong link between the research community and the authorities and other vital institutions in society. We also serve as the national coordinator monitoring the Danish market for illegal substances.

METHODS

Both the forensic services that assist the Danish authorities and the Unit for Bioanalytical Chemistry rely on exact measurements of small molecules, and on conclusive assessments and interpretations of the findings. Such investigations employ a variety of tools:

- Advanced chromatographic analysis techniques: LC-MS/MS, LC-TOF-MS, GC-MS, and others.
- Metabolomics and chemical profiling: "chemical" profiles of illegal substances or biological profiles from cells or similar material.
- Chemical biology: Chemistry is used to understand and decode the biological world.
- Toxicological and chemical assessments: performed, for example, on pharmaceuticals and narcotics to clarify how, by interacting, these substances affect the body in which they are present.

OVERVIEW



30 %
Basic research

45 %
Clinical research

0 %
Qualitative research

25 %
Epidemiological research

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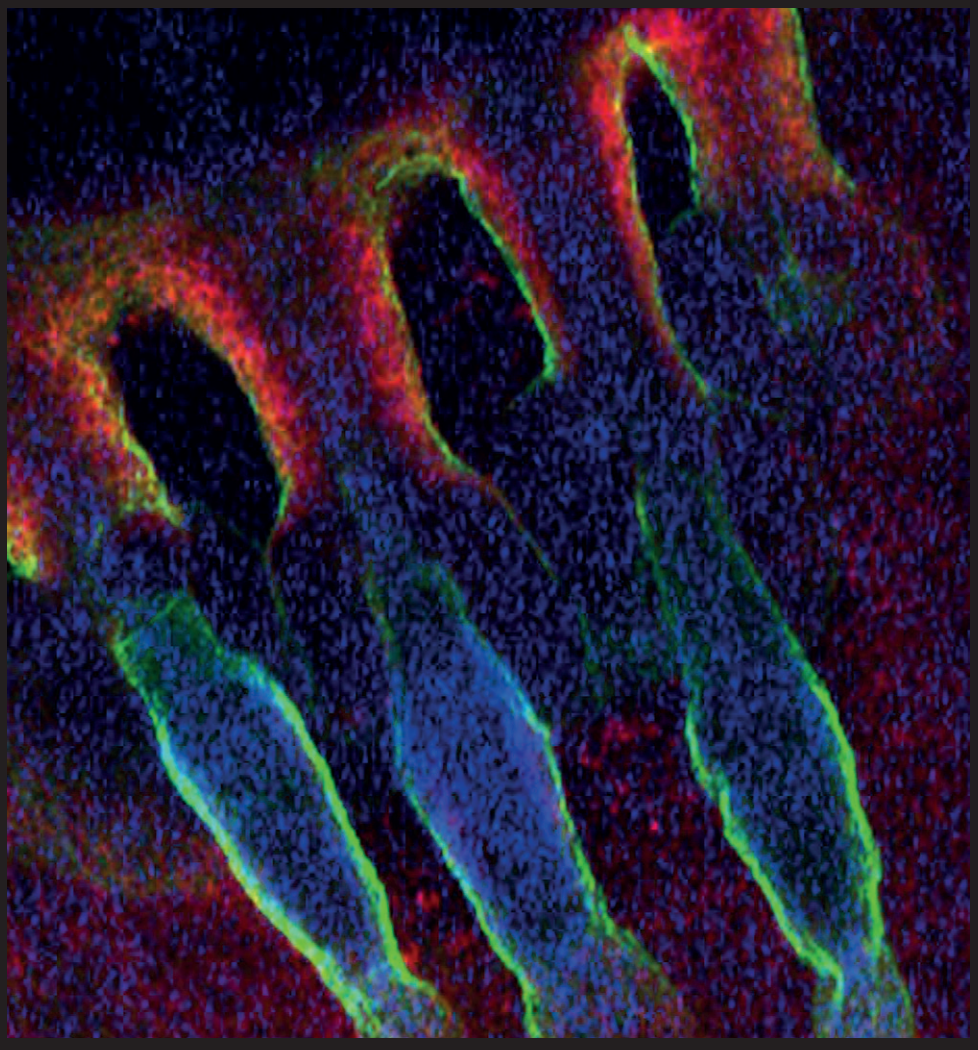
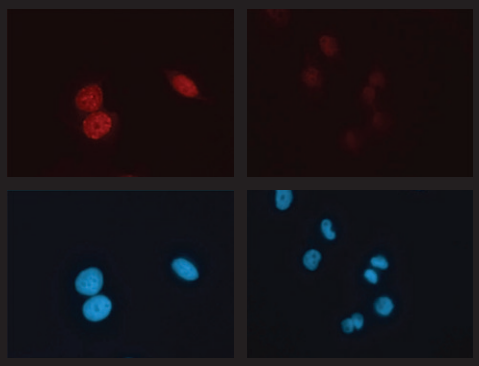
GENETICS

◄ Genetically modified piglets reared at Aarhus University in Sino-Danish collaboration.

► Epidermal "whole mount" prepared from mouse skin. Expression is visible of a6 integrin (green), Sca-1 (red), and CD34 (blue). The upper isthmus region is negative for CD34 and Sca-1, and expresses low levels of a6 integrin. This region includes the most immature skin stem cell observed so far.





▲ Expression in non-metastasizing (left) and metastasizing (right) breast-cancer cell nuclei (blue) of the epigenetic key protein HP1-alpha (red).

THE WORLD'S FIRST **GENETICALLY MODIFIED MINIPIGS** WITH ATHEROSCLEROSIS

Researchers at the Department of Clinical Medicine have successfully developed the first genetically modified minipig animal models in the world destined for research into atherosclerosis.

"Genetically modified mice have been the standard research model for 20 years, but some of the biggest challenges in studying atherosclerosis can't be addressed by looking at mice. Not just because they are too small, but also because the atherosclerosis they develop is different from what we see in humans on several key points," explains Associate Professor Jacob Fog Bentzon, who holds a PhD and a degree in medicine.

The project, which has been underway since 2006, has encountered a variety of obstacles along the way. The researchers at the Department of Clinical Medicine are fairly persistent, however, and finally in 2010 their determined efforts resulted in the successful cloning of the first strain of transgenic minipigs in the project. They are currently working on another exciting atherosclerosis model, created by their colleagues at the Department of Biomedicine.

"It has just very recently become possible to produce genetically modified pigs, and at present, worldwide, only a handful of different disease models have been made," Associate Professor Bentzon continues. "The hard part is that you have to use cloning in the process – and cloning is a sophisticated technique that only a limited number of research groups master to perfection. But here at Aarhus University we're fortunate enough to have one of the world's best groups in porcine cloning, at the Department of Animal Science."

The next step is that Health's Department of Clinical Medicine will use the minipigs to develop and test new methods for visualizing atherosclerosis in patients in collaboration with researchers from the MR Centre and the Department of Nuclear Medicine at Aarhus University Hospital. The transgenic pigs are commercially available to others through the company Pixiegene, which has a licensing agreement with Aarhus University.

> **It has just very recently become possible to produce genetically modified pigs, and at present, worldwide, only a handful of different disease models have been made.**
>
> ASSOCIATE PROFESSOR JACOB FOG BENTZON

PIG FACTORY

FACTS

The Department of Clinical Medicine has set up a Core Facility for porcine research that enjoys international recognition for its high standard. Besides having access to unique pig models, researchers working here have state-of-the-art technologies – including MRI and PET/CT scanners – at their disposal.

CLINICAL GENETICS

The foundation of good genetic diagnostics and counselling is basic genetic research. Our unit does research on stem cells, fertilization, embryonic development, and how cell differentiation and cell growth are regulated throughout a person's lifetime.

Basic research is also the foundation of clinical work and is, at the same time, a precondition for developing new treatment methods, for instance gene therapy.

The research we do deals with questions like these:

- What can we learn about cancer by studying stem cells?
- How can stem-cell research lead to better diagnostics for hereditary diseases?
- What genetic mechanisms regulate normal fertilization, growth, and development?
- What changes in these mechanisms trigger infertility, abnormal development, and/or disease?

Cutting-edge biobank
Stem-cell and fertilization research are two of the fields in which we have earned special notice.

A number of hereditary diseases are caused by the loss of tissue that is dependent on stem cells. Part of our research focusses on stem cells from the skin, which is one the few organs from which normal human tissue can be obtained. Here we endeavour to clarify the link between stem-cell mechanisms and their role in the development of diseases such as cancer and Alzheimer's disease. Understanding this link can help to improve treatment. Besides research into human cell systems, the unit also works with animal models and, in that context, has demonstrated the most immature stem-cell population in the skin.

Our fertilization research shows that the risk of cancer after hydatididform moles is linked to cells with two sets of genomes. Based on this finding, Denmark – as the first country in the world – now recommends that women who have had mole pregnancies with three genome sets are spared an extended regimen of controls and, possibly, preventive cancer chemotherapy.

Since 1986 we have been building up a biobank with tissue samples from hydatidiform moles. This biobank – the largest and most representative in the world – is an important international resource for scientists doing research in this particular area.

PROJECTS

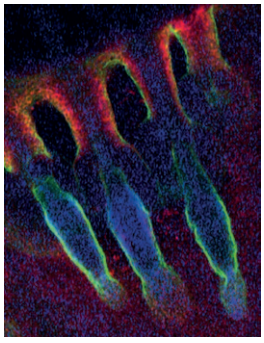
1. **Clarifying the significance of NLRP genes for early differentiation and carcinogenesis.** Mutation of NLRP7 in a woman leads to abnormal methylation and mole differentiation in her pregnancies. We wish to study the significance of NLRP genes for normal differentiation in the next generation, for instance using knock-out in an animal model.

2. **Mapping of genes regulated by genomic imprinting** (the marking of genes in a parent-of-origin dependent way). Among other things, we will compare the imprinting in mole pregnancies with chromosomes solely from the father, with the imprinting of normal pregnancies with one chromosome set from the father and one from the mother.

3. **How does a pregnancy with chromosomes solely from the father arise?** Our observations in mosaics indicate that diploid androgenetic hydatidiform moles arise from an egg cell with one chromosome set from the mother and two from the father. This hypothesis is being tested by studies of such egg cells that are occasionally observed in fertility clinics.

4. **It is common to all stem-cell populations in mouse skin that they do not express the gene Stem Cell Antigen-1, Sca-1**. We have developed transgenic mice in which, at multiple levels, we can activate Sca-1 in the regions that do not normally express this gene. Early experiments show that the ability to form tumours is reduced when Sca-1 is expressed in stem cells.

5. **Charcot-Marie-Tooth (CMT)** is a degenerative disease in the long nerves. The disease is hereditary and can be caused by mutations in more than 40 genes. In this project we make use of massive parallel sequencing (Next Generation Sequencing), aiming to sequence all candidate genes in one analysis in patients with CMT. This technique can also be used to find new genes that may be of importance for this disease.



Epidermal "whole mount" prepared from mouse skin. Expression is visible of α6 integrin (green), Sca-1 (red), and CD34 (blue). The upper isthmus region is negative for CD34 and Sca-1, and expresses low levels of α6 integrin. This region includes the most immature skin stem cell observed so far.

MILESTONES

A significant proportion of the hydatidiform moles that were previously assumed to have a normal genome were shown to be mosaics with one cell line that is androgenetically diploid and the other is normal
(Sunde L, et al. Eur J Hum Genet. 2011;19:1026–31)

The risk of neoplasia after a mole pregnancy is, by far, most often associated with the diploid form of hydatidiform mole
(Niemann I, et al. Gynecol Oncol. 2007;104:411–15)

Family history (the family tree) is a better predictor for the risk of bowel cancer than instability in DNA and chromosomes
(Sunde L, et al.Cancer Biomarkers: Section A 2009;5:197–205)

Whole-mount technology, combined with confocal microscopy, can be used to map the three-dimensional localization of stem cells in the epidermis
(Jensen UB, et al. Development. 1999;126:2409–18)

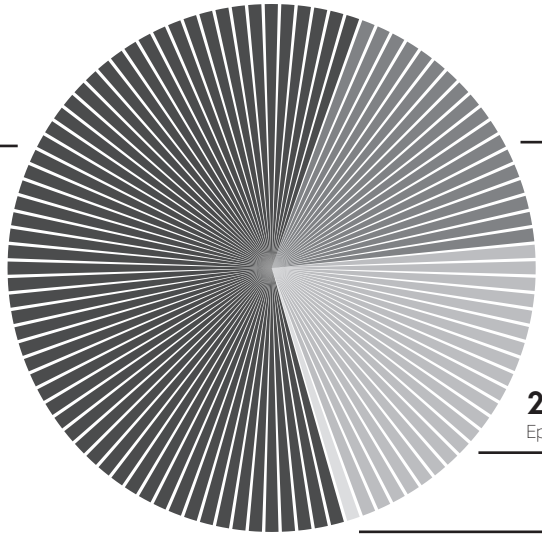
Demonstration of a new and immature stem-cell population in the hair follicles of the skin: The first indication of the presence of a hierarchy of stem cells
(Jensen UB, et al. Journal of Cell Science. 2008;121:609–17)

METHODS

Genetic analyses of individual cells and of human DNA/RNA using these and other methods:

- Cytogenetics
- Flow cytometry, including cell sorting
- DNA-marker analysis
- Chromosome analyses
- Micro-array techniques
- DNA sequencing
- Transgenic animal models, including sophisticated cell transplant technology
- DNA-cloning techniques

OVERVIEW



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MEDICAL GENETICS AND EPIGENETICS

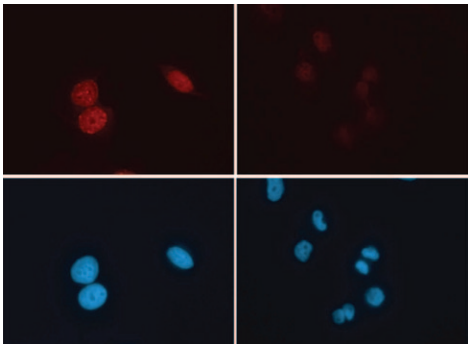
Researchers working in the field of medical genetics identify and investigate genes that hold significance for health and disease. Some diseases arise because of a mutation in a single gene, but in the vast majority of cases a disease will develop because of mutations or variations in several genes, often in interaction with environmental influences.

The human genome contains millions of genetic variants. In order to identify the variants that influence the development of diseases, we carry out detailed genetic scans that often include thousands of individuals, sick and healthy. Our results are used to determine the genetic foundation for the development of the disease, and to determine its root cause at a molecular level. Doing so can be decisive to the patient's diagnosis and the treatment option chosen. In some cases it can also be important to the counselling of people who have the same gene mutation, but in whom the disease has not yet been expressed. The gene variants we have identified include some that are involved in the development of cancer, heart disease, and psychiatric illnesses.

Epigenetic changes

On top of the genetic understanding of diseases lies the field of epigenetics – which studies modifications of the genes and associated proteins that do not change the fundamental base sequences in the DNA. Certain events can affect the cell epigenetically, damaging its normal function. This effect can be inherited by newly formed cells and have serious consequences for the human organism. In this context we study how epigenetic changes are involved in the development of disease, and how environmental effects influence the epigenetic landscape. For instance, based on the information registered in the national patient databases and biobanks, epigenetic investigations can be made of the link between early traumatic events and an increased risk of mental illness. Similarly, we examine the epigenetic changes as causes of cancer, as well as their significance for diagnosis and treatment. Further, based on animal models we examine the impact of genetic and environmental factors on the development of diseases through epigenetic modifications.

To gain a better understanding of genetic and epigenetic disease mechanisms we do research at multiple levels: molecular, cellular, organ, and entire individual. We may use DNA and RNA samples collected from large patient and control groups; or cells cultured in the laboratory, for example from human brain, kidney, and heart tissue; or animal models. Our research efforts are often multidisciplinary, with clinicians, epidemiologists, molecular biologists, statisticians, and bioinformatics specialists working in close collaboration.



Expression in non-metastasizing (left) and metastasizing (right) breast-cancer cell nuclei (blue) of the epigenetic key protein HP1-alpha (red).

PROJECTS

1. Clarifying the genetic and epigenetic background for a number of frequently occurring disorders: psychiatric, cancerous, allergy and immune-related, neurodegenerative, metabolic, and processes related to healthy ageing.

2. Development of molecular-medicine methods: New methods for identifying genetic and epigenetic factors, and for processing the resulting data.

3. Interdisciplinary research based on an integrated sequencing methodology. A multidisciplinary centre at Aarhus University, working across the main areas of Health, Science and Technology, and Business and Social Sciences and collaborating with BGI (the Beijing Genomics Institute) will seek to clarify complex molecular systems governing biological functions and human illnesses.

MILESTONES

Loss of chromosome area is shown to be significant for breast-cancer prognosis
(Hansen LL, et al. Cancer Res. 1998;58:2166–9)

Identification of epigenetic mechanisms in gene regulation
(Nielsen AL, et al. Mol Cell. 2001;7:729–39)

First complete genome scan of asthma and allergy in Denmark, and subsequent detailed genetic mapping
(Haagerup A, et al. Allergy. 2002;57:680–6; and Allergy 2004;59:88–94)

Mapping of the human genome
(International Human Genome Sequencing Consortium. Nature. 2001;409:860–921; and Nature. 2004;431:931–45)

First identification of a gene for both schizophrenia and bipolar disorder based on scanning of individuals from the isolated Faeroese population
(Severinsen JE, et al. Mol Psychiatry 2006;11:1126–38)

First complete genome of an Asian individual
(Wang J, et al. Nature. 2008;456:60–5)

Development of a sensitive method for detecting epigenetic variation with application in clinical cancer management
(Wojdacz TK et al, Nat Protoc 2008;3:1903-1908)

Contributing to the largest international genetic scans that identify genes for schizophrenia
(Stefansson K, et al. Nature. 2009;460:744–7; and Ripke S, et al. Nature Genetics. 2011;43:969–76)

Extensive sequencing and mapping of the human exome and its variation
(Li Y, et al. Nature Genetics. 2010;42:969–72)

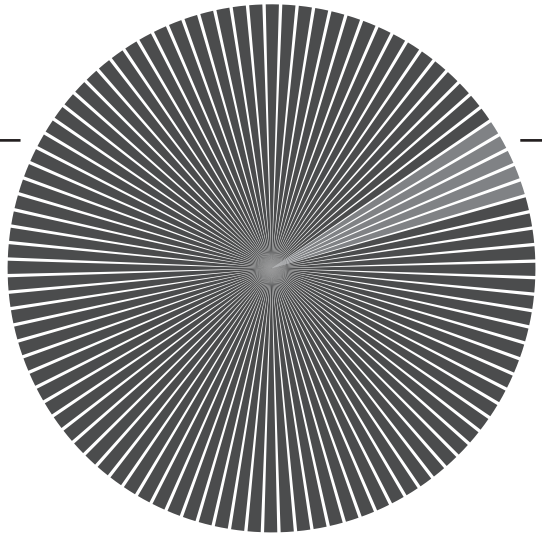
First Danish genome scan of a neurodevelopmental syndrome, and the subsequent identification and characterization of the specific disease gene
(Børglum A, et al. Eur J Hum Genet. 2001;9:753–7; and Qvist P, et al. PLoS Genet. 2011;7:e1002310)

METHODS

The research in medical genetics and epigenetics identifies genes, gene variants, and gene modifications that are involved in a wide variety of human diseases. Further, through basic research it provides functional characterizations of their significance, from the level of the cell to that of the entire individual. The scientific methods used include:

- Genetic scans and next-generation sequencing of genome, epigenome, and transcriptome.
- Bioinformatics and statistical genetics.
- Methylation Sensitive-High Resolution Melting (MS-HRM).
- Chromatin immunoprecipitation (ChIP) analyses.
- Sequenom MassArray platform for high-throughput analysis of DNA/RNA fragments, SNP, CNV, and DNA methylation.

OVERVIEW



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Basic research

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Clinical research

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Qualitative research

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Epidemiological research

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TRANSLATIONAL GENETICS

Today we possess enough knowledge to understand the human genome not merely as a static volume of code that needs to be mapped – but rather as an inconstant structure that can be affected and altered. This opens a whole new array of perspectives for preventing and treating disease.

Our basic studies of genetic and epigenetic processes (where the latter refers to the functional development of our genes during our lifetime) examine gene variants that cause disease. However, they also investigate the mechanisms that protect the genome, thereby keeping our organism healthy and promoting successful ageing in a world where human living conditions and lifestyles change far more rapidly than humankind's genetic makeup.

The overall goal of our work in the long term is to prevent the genes from sustaining damage or degenerating throughout our lifespan, also when we are ill. This does not necessarily mean prolonging life. But it does mean that while we are alive we should remain as healthy and as free of afflictions as possible. This is what we call "Healthy Ageing".

The research we do is based on close collaboration with partners such as the Beijing Genomics Institute (BGI) in Shenzhen, China, which over the past 12 years has grown into the world's largest genome research centre.

In this context we study topics such as:

- congenital and acquired genetic changes, by comparing groups of genomes, epigenomes, and expression of the genetic information.
- how genes change, and how cells are selected and adapt throughout the lifespan
- how common and rare gene variants can lead to susceptibility or resistance in disease processes
- the use of genetically designed pig models, in order to analyse, diagnose, and prevent common disease processes associated with ageing

Moving towards personalized medicine
Each day, researchers at Health work along with their Chinese colleagues at BGI-Shenzhen to sequence the billions of building blocks that make up the human DNA. This means that each day, we develop a more and more profound understanding of the human genome.

The more we know about the human genome, the more attuned we become to identifying variations and characteristics in the unique genetic makeup of each individual person. This gives us an ever-deeper understanding of patients, treatments, and prevention initiatives, which enables us to increasingly adapt interventions to suit more and more diversified and well-defined patient groups. This is moving us towards what is known as "personalized medicine". Members of our expert research group have received the August Krogh Prize (1996) and the Chinese National Friendship Award (2009), and recent years have seen the publication of about 10 of our articles in Nature and Science.

PROJECTS

1. Investigating the genetic background of metabolic syndrome. This Sino–Danish project is supported by the Lundbeck Foundation.

2. Establishing a large-scale sequencing and supercomputing centre in Denmark in collaboration with BGI-Europe. (Supported by the Danish Advanced Technology Foundation).

3. "GEnetics of Healthy Ageing (GEHA)", an EU Integrated Project that is searching for "wellness" gene variants rather than "illness" gene variants.

4. Establishing the platform "Pigs & Health" for pig-genome sequencing, genetic design, and cloning to develop and characterize porcine models of human diseases. (Supported by the Danish Advanced Technology Foundation.)

5. Establishing induced pluripotent stem cells (iPS cells) from patients with neurodegenerative diseases. These cells should be differentiated into neuronal cell types and serve as models for the study and prevention of degenerative processes. Much of the analytical work is based on the sequencing of epigenomes and transcriptomes. (Supported by the Danish Advanced Technology Foundation.)

6. A Sino-Danish Breast Cancer Research Centre and a Sino-Danish Colorectal Cancer Research Project. Both endeavours focus on the genetic/epigenetic background for the development of drug resistance. (Supported by the Danish National Research Foundation and the Chinese National Natural Science Foundation, as well as the "Food and Health Commission" of the Danish Council for Strategic Research.)

7. Cancer genomics/epigenomics, temporal dissection of the accumulation of somatic aberrations, and the study of somatic (normal and tumour) cell selection and adaptation (supported by funding from the US and China).

Genetically modified piglets reared at Aarhus University in Sino-Danish collaboration.

MILESTONES

Co-development of, and large scale international collaboration with, BGI in China. The centre has 137 HiSeq machines, as well as other instruments and supercomputing facilities, and more than 4000 employees. (http://en.genomics.cn)

Development of world-leading software for de novo assembly of sequenced DNA fragments. This has made us realize that human genetic variation is vastly greater than previously assumed. (Ruiqiang Li, et al. Nature Biotechnology. 2010;28:57–63; and Yingrui Li, et al. Nature Biotechnology. 2011;29:723–30)

The development of technology for genetic design and cloning. This has allowed us to create tissue and animal (pig) models for a number of disease processes. Atherosclerosis models now show pathological phenotypes that may enable scientists to study and prevent the pathogenesis. (Kragh PM, et al. Transgenic Research. 2009;18:545–58; and Yonglun Luo, et al. Transgenic Research. 2011;20:975–88)

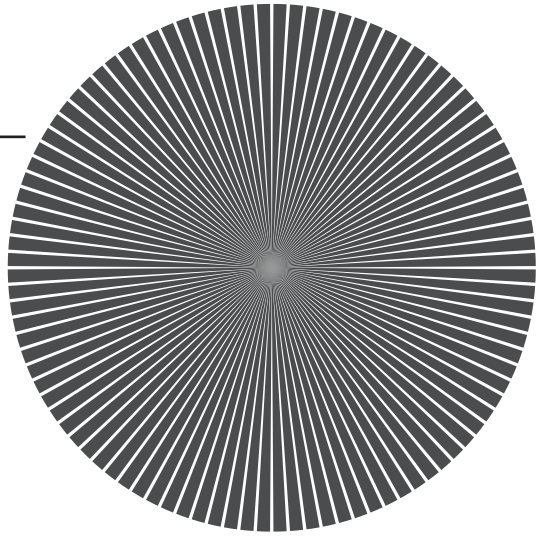
METHODS

We have established methods for large-scale sequencing of entire genomes and their function –in patients and in healthy subjects, as well as in genetically designed cellular and animal models for the relevant disease processes.

- Massive parallel sequencing of DNA (genome sequencing), bisulphite-treated DNA (epigenetic, methylome, sequencing) and cDNA (transcriptome sequencing)
- Genetic design of cells using gene transposition and homologous recombination
- Cloning using somatic-cell nuclear transfer from genetically designed pig cells to create tissue models and live pigs
- Characterization, using sequencing technologies, of pathological disease processes and cellular or animal model systems in relation to different forms of intervention

OVERVIEW

100 %
Basic research



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Qualitative research

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Epidemiological research

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Clinical research

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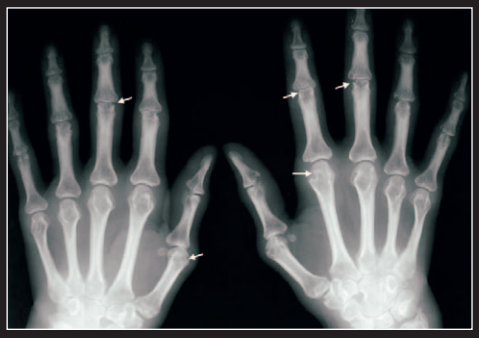
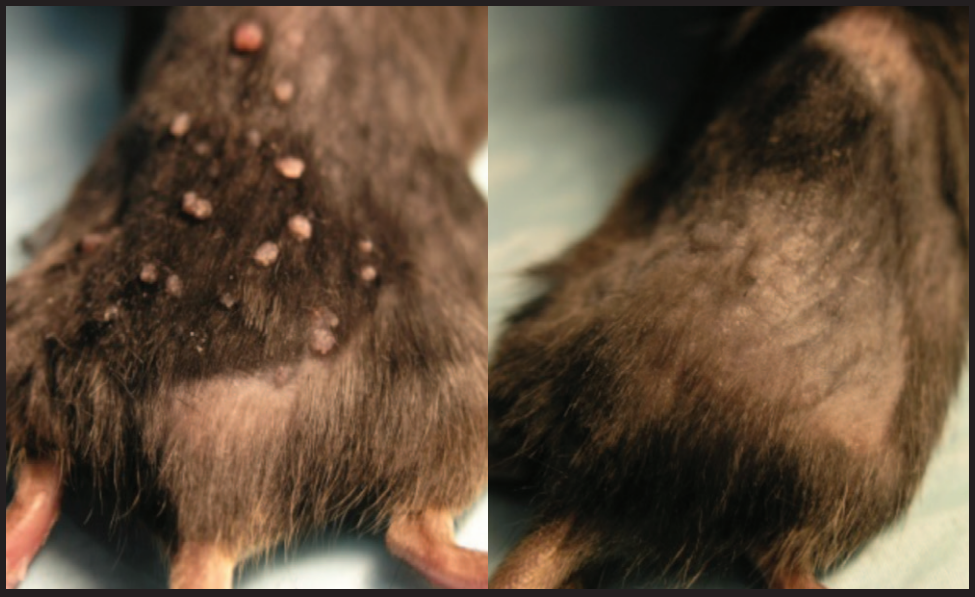
INFLAMMATION AND INFECTION



◄ Chemically induced tumour development is inhibited in MK2 knockout mice compared with wild-type mice.

▲ Flexibility: from biosafety class 3 to the clinic – and back again.



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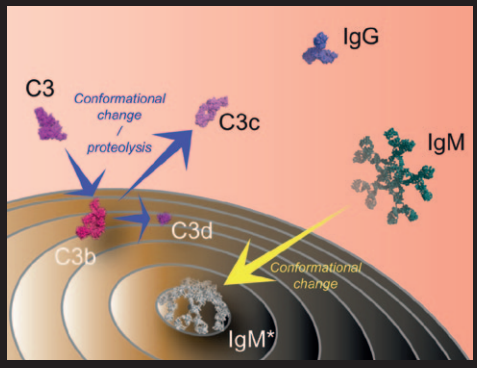
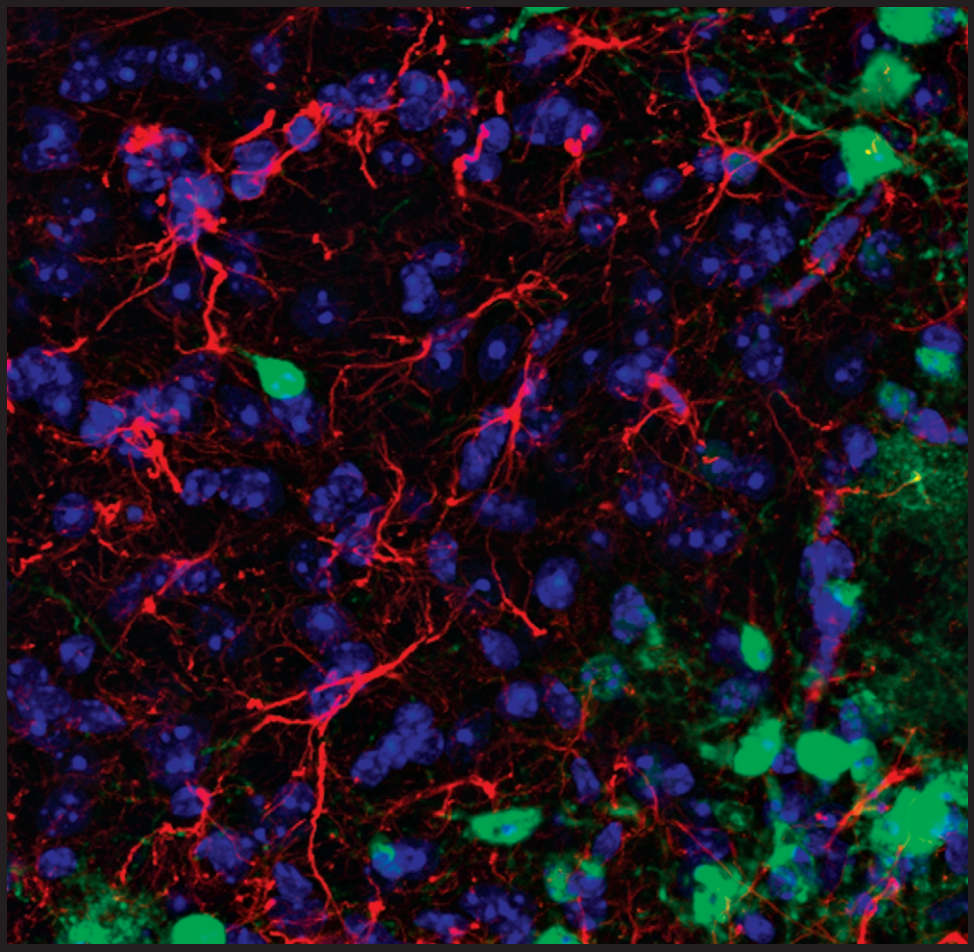
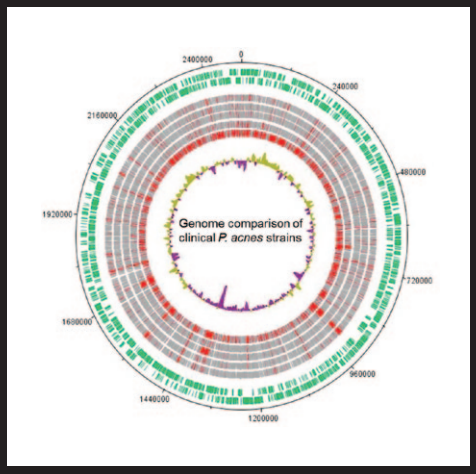


▲ The binding of blood proteins to microbial surfaces is decisive for the ability of such proteins to protect against infection.



◄ Confocal microscopy image of a section of a spinal cord following infection with herpes simplex virus type 2. The picture shows herpesvirus (green), astrocytic filaments (red), and cell nuclei (blue).



▲ The pan-genome of Propionibacterium acnes. Comparison of 6 geno-mes shows common and flexible gene pools in this species.

HEALTH, ILLNESS, AND MICROORGANISMS

As humans, we exist in harmony with millions of bacteria and other microorganisms that live all around us and colonize the human body. They play a vital role in keeping us healthy and have done so throughout the evolutionary process.

However, the choreography of our microflora is complex and unpredictable. While some bacteria are beneficial to human health, others – often within the same group or species – can be detrimental to our health and cause infection. According to the WHO, infectious diseases are responsible for about one third of all deaths worldwide.

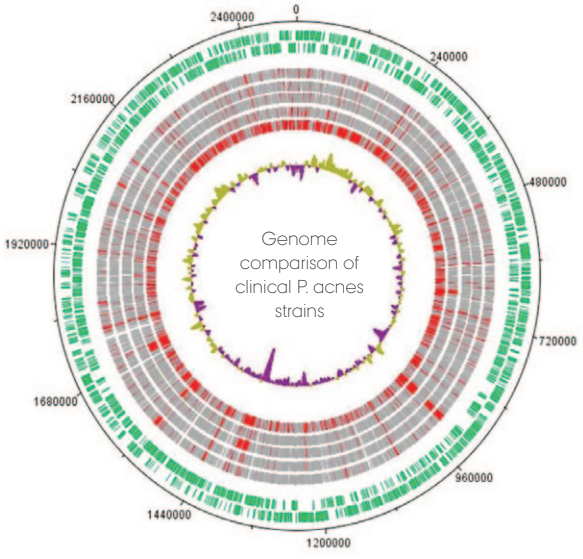
Generally speaking, our research seeks to understand why humans live in harmony with some bacteria while others lead to infections. We also examine the molecular mechanisms behind medical conditions such as acne, meningitis, and pneumonia, and investigate possible links between certain bacteria and cancer.

The superorganism

Scientists in the field of microorganism research employ a concept that understands the human organism as a single entity; an entity that also includes the microflora living upon its surfaces. We call this the superorganism.

If we come to understand the interactions taking place within the superorganism, we can potentially develop alternatives to antibiotics that do not wage war on our natural microflora. Such therapies could, instead, stimulate and promote the processes that are beneficial to our health, thereby using the body's own immune defence system to prevent and fight infections. The perspectives this research offers are many, and they hold relevance for a wide range of diseases and conditions related to infection, including acne, meningitis, periodontal disease, pneumonia, and certain types of cancer.

The pan-genome of Propionibacterium acnes. Comparison of 6 genomes shows common and flexible gene pools in this species.



PROJECTS

1. Detailed longitudinal mapping of Propionibacterium acnes on the skin of acne patients and healthy individuals, with a view to clarifying the pathogenesis of the condition.
2. Investigating a possible link between Propionibacterium acnes and prostate cancer.
3. Transcriptome analyses of Propionibacterium acnes in both in vitro and in vivo environments.
4. Investigating normal-flora Streptococcus bacteria as a gene pool, enabling genetic variation and development of antibiotic resistance of the pathogenic Streptococcus pneumoniae.

MILESTONES

First complete genomic analysis of the species Propionibacterium acnes, which is an important part of normal human skin flora, as well as the cause of acne and a variety of other infections
(Brüggemann H, et al. Science. 2004;305:671–3)

Demonstration of genetic diversity within the species Propionibacterium acnes, and identification of clones specifically associated, respectively, with disease and health
(Lomholt H, Kilian M. PLoS ONE. 2010;5(8):e12277)

Demonstration that the important pathogenic bacterium Streptococcus pneumoniae is a specific evolutionary lineage evolved within the normal-flora bacterium S. mitis, and mapping of the evolutionary background
(Kilian M, et al. PLoS ONE. 2008 Jul 16;3(7):e2683)

Comparative genome analyses of P. acnes isolates with different backgrounds, and demonstration of genetic mechanisms behind differences in disease association
(Brzuszkiewicz E, et al. PLoS One. 2011;6(6):e21581)

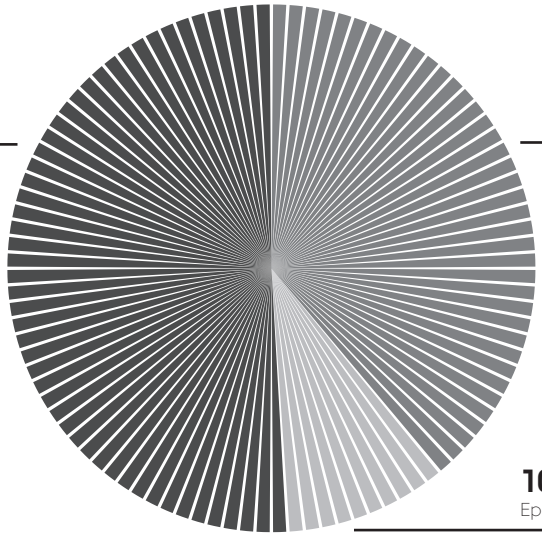
Mapping of the evolutionary mechanisms behind an important source of infection in newborns (Streptococcus agalactiae)
(Sørensen UBS, et al. mBio. 2010 Aug 24;1(3). pii:e00178–10)

METHODS

The research group uses molecular DNA-based and protein-based methods to study bacterial activities in relation to sickness and health.

- Comparative genome analyses of bacteria
- Transcriptome analyses using sequencing
- Sequence-based mapping of complex microfloras
- Mutagenesis, cloning, overexpression of bacterial genes
- Bacterial infections in cell cultures and animal models
- Population-genetics analyses of bacteria
- Purification and analysis of bacterial proteins
- Proteome analyses

OVERVIEW



50 %
Basic research

40 %
Clinical research

10 %
Epidemiological research

0 %
Qualitative research

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INFECTIOUS DISEASES

Infections account for a large part of the overall pathological picture in Denmark and worldwide. By studying infectious diseases, we aim to improve the general state of health, so that fewer infectious diseases occur, and so we can give those suffering from infections the best possible treatment.

The focus of our research is to understand the interaction between microorganisms and the human immune system. By improving our understanding of this relationship, we can develop new drugs and vaccines that work better than those available to us today.

Our research work includes projects on the treatment and prevention of HIV, hepatitis, meningitis, cystic fibrosis, and diseases related specifically to third-world countries.

PROJECTS

1. **HIV**
   New insights into the interaction between microbes and the immune system now enable us to understand how the signal pathways in the immune system's cells work when a person contracts HIV. This basic understanding has also contributed to the development of a brand-new HIV vaccine concept that builds on gene technology, achieved in collaboration with the Department of Molecular Biology, and it has led to a new concept for an actual "HIV cure". The short time it takes for new ideas to move from the laboratory via animal testing to testing on humans has also enabled us to test some of our ideas in large randomized trials, which we plan and organize from the bottom up.

   Our research has also contributed to the development of new drugs. As a result, the course of certain infections has changed considerably. For example, patients with HIV now live a lot longer than they did just a few years ago. It is important, however, that patients take their medicine very regularly, and we also study patients' ability to manage their own disease.

2. **Hepatitis**
   In the case of hepatitis we also study the relationship between the virus and the immune system, also attempting to alter the immune system to make it better at fighting the hepatitis virus. In addition, we study new treatment modalities in clinical trials and, in particular, their impact on the central nervous system. We have moreover developed a database system (InfCare) that makes it possible to carry out ongoing research based on data from the routine treatment of patients.

3. **Meningitis**
   We are working on developing new, improved treatment modalities both for patients in intensive care and patients with acquired brain damage following meningitis. We have also developed a new and more effective vaccine against pneumococcal meningitis, and conducted a large number of clinical trials with meningococcal meningitis as well.

4. **Cystic fibrosis**
   Today, patients with cystic fibrosis live much longer than they used to, thanks to effective prophylactic treatment with antibiotics. We are additionally collaborating with the Department of Molecular Biology and the Department of Genetics and Biotechnology to develop a gene therapy based on downregulation using siRNA.

5. **Third-world countries**
   In some of our tropical-disease research we cooperate with the Department of Public Health, and together we have established the Centre for Global Health. We also work closely with the Bandim Health Project in Guinea Bissau, carrying out a large number of research projects there on tuberculosis, HIV, and hepatitis.

MILESTONES

Endotoxaemia is found to be associated with altered innate and adaptive immune responses in untreated HIV-1-infected individuals
(Bukh AR, et al. PLoS One. 201;6:6,s.e21275)

A tetravalent meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine is immunogenic and well-tolerated when co-administered with Twinrix ® in subjects aged 11–17 years, in an open randomized and controlled trial
(Ostergaard L, et al. Vaccine. 2011. Epub ahead of print)

Flexibility: from biosafety class 3 to the clinic – and back again.

Improving the immunogenicity of pneumococcal conjugate vaccine in HIV-infected adults with a toll-like receptor 9 agonist adjuvant, in a randomized controlled trial
(Søgaard OS, et al. Clin Infect Dis. 2010;51:42–50)

Transmission of HIV-1 drug-resistant variants: prevalence and effect on treatment outcome
(Jakobsen MR, et al. Clin Infect Dis. 2010;50:566–73)

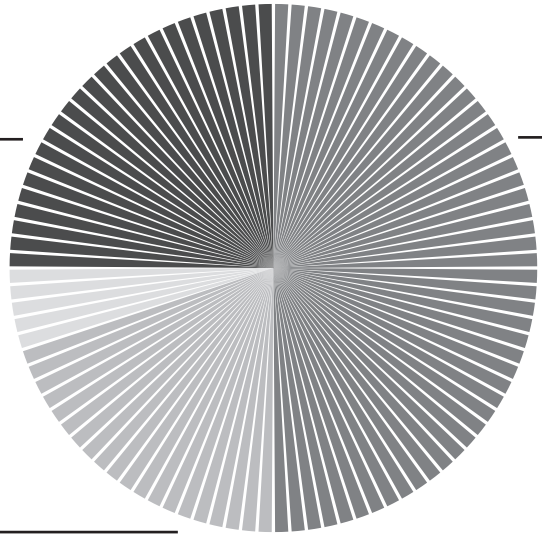
Induction of partial protection against infection with Toxoplasma gondii genotype II by DNA vaccination with recombinant chimeric tachyzoite antigens
(Rosenberg C, et al. Vaccine. 2009;27:2489–98)

METHODS

We combine laboratory and clinical work with data processing using the following methods:

- Biosafety class-3 laboratory
- 8-channel flow cell sorter with high sensitivity
- DNA transfection, real-time PCR, sequencing
- Analysis of intra-cellular signal transduction
- Animal experiments on mice
- Experimental clinical immunomodulation (vaccines and biological drugs)
- Design and implementation of randomized, controlled clinical trials
- Research using correlations found in databases and public registers

OVERVIEW



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INFLAMMATORY DISEASES

All of the body's organs can become infected, and basically our work is aimed at understanding the immune system and why inflammatory conditions arise. We work with functional inflammation at the most fundamental level, studying how cells move and behave when influenced in different ways.

Through this understanding we seek to optimize treatment. Sometimes our understanding can lead to better diagnoses, or to better monitoring techniques – all of which will benefit the patient.

Because basic research and clinical work are intimately linked, our research environment is quite unique. It is easy for us to test a hypothesis thanks, among other things, to the direct access we have to extensive biobanks and electronic registers containing patient information. And when we do identify a better method, the path to introducing it in clinical practice is also very short.

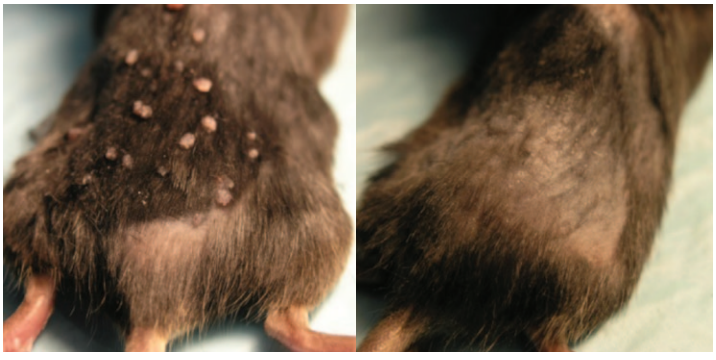
Promising prospects for better therapies
Understanding how the immune system works can also serve other purposes than improving and developing the treatment of inflammatory conditions. As an example, we have developed a strain of mice in which the gene that prevents the mouse from getting skin cancer has been removed. It turns out that infection can destroy the cancer. In other words, the mouse's own immune system can exfoliate, or shed, the cancer. Each year 6000 Danes are diagnosed with this particular type of skin cancer, and so we are intent on bringing this research into the clinical phase.

We collaborate with many different fields, such as iNANO – the Interdisciplinary Nanoscience Center at AU – which has developed nanoparticles for us that can be transported by the immune system, meaning that they only end up in the body's diseased joints, not in the unaffected joints. Having made this technology work in mice, we are now going to adjust it to work in humans as well. From that stage on, the project will be further developed in association with a pharmaceutical company.

In our area of expert competence we expect to make great progress in fundamentally understanding inflammatory conditions, one reason being that we will be accessing many new techniques. Among these will be newly developed biological therapies that enable us to target precisely those molecules that are dysfunctional. At the moment more than 300 biological therapies are being tested worldwide. For patients with articular rheumatism, a biological therapy will mean that they are treated more specifically and, not least, with fewer side effects.

PROJECTS

1. Assessing the effect of adalimumab on Crohn's disease (in collaboration with the University of Gothenburg).
2. The effect of bovine macropeptide ulcerative colitis, clinically as well as immunologically using biopsies and flow cytometry on blood and intestinal tissue.
3. Testing of high-dose intravenous infusions of iron (MonoFer) to counter anaemia in patients with Crohn's disease or ulcerative colitis.
4. The interaction between signal molecules in the immune system (IL-19, -20, -21, -23, and -24) and their significance to the development of arthritic diseases.
5. Study of viral DNA as a cause of connective-tissue diseases.



Chemically induced tumour development is inhibited in MK2 knockout mice compared with wild-type mice.

6. Study of the effect of biological treatment on intracellular signals in psoriasis, and the interaction between the signals. This project also focuses on the development of skin cancers.

7. The role of the immune system in atopic eczema. The interaction between skin cells and the immune system.

8. The allergen-specific sensitivity of basophilic granulocytes during subcutaneous immunotherapy to counter grass-pollen allergy.

9. Changes in function, structure, and receptors during culturing of mast cells from blood stem cells. The influence of IgE receptor function and activity. Cytokine release assays for assessment of T-cell sensitization in tuberculosis and allergenic diseases.

10. The role of magnesium in the human organism, including its distribution and its biochemical relations/mechanism of action relative to respiratory inflammation and bronchial hyperreactivity.

MILESTONES

The significance of vitamin D3 liver damage
(Malham M, et al. World J Gastroenterol. 2011;17:922–5)

Supplements of vitamin D3 are shown to have an effect on Crohn's disease
(Bendix-Struve M. Aliment Pharmacol Ther. 2010;32:1364–72)

Antibody treatment of ulcerative colitis
(Vermeire S. Gut. 2011 Aug;60:1068–75)

Reactions to viral infections can turn the immune system in a direction that may lead to arthritic diseases
(Holm C, et al. J Immunol. 2009;183:4422–31)

The significance of IL-21 to the development of arthritic diseases
(Rasmussen T, et al. J Rheumatol. 2010;37:2014–20)

The significance of intracellular signals to the development of psoriasis
(Johansen C, et al. J Biol Chem. 2011;286:25487–94)

Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis
(Dahl R. Allergy. 2006;61:185–90)

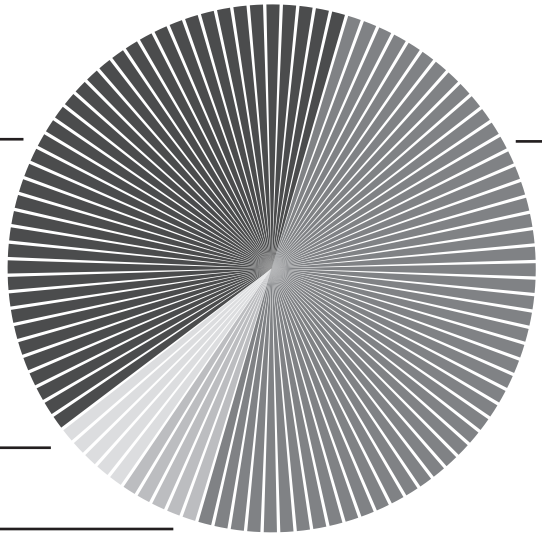
Caspase-5 expression is upregulated in lesional psoriatic skin
(Salskov-Iversen ML, et al. J Invest Dermatol. 2011;131:670–6)

IL-25 in atopic dermatitis: a possible link between inflammation and skin barrier dysfunction?
(Hvid M. J Invest Dermatol. 2011;131:150–7)

METHODS

- Gene chip analyses
- Biobanks
- Ex vivo examination of human tissue on an animal model
- Cellular experiments to study mechanisms that control cells
- Biological therapy, assessed in controlled clinical studies
- Effect of vitamin D on the adaptive immune system in the intestine, partly in clinical controlled studies, and partly in basic research (cell cultures, flow cytometry on blood, and intestinal biopsies)
- Serial biopsies taken before and after treatment
- Immunohistochemical analyses

OVERVIEW



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INNATE IMMUNOLOGY

The immune system fights external microorganisms that are foreign to the body. At the same time, it also helps to maintain the body in its normal state.

We work with basic research analyses of the innate immune system's functions, examining how it protects us against infection and what role it plays in connection with chronic infections. Our research therefore looks at factors that both promote and inhibit the functioning of the innate immune system.

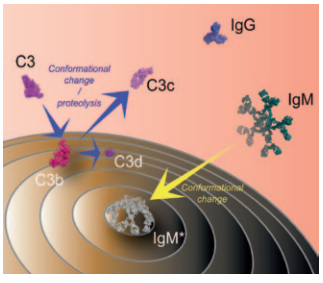
Generally speaking, we explore the links between the biochemical characteristics of proteins and the significance of these characteristics for a given protein's role in the body's immunological defences. The immune system is made up of various proteins that work together, and in our field of research we look at what other proteins the individual immune-related molecule is interacting with. At the same time we also try to determine which particular bacteria and viruses the proteins bind to, in order to identify the microorganisms against which the various parts of the immune system are effective.

The link in patients between protein deficiency and immune system

Today, scientists do not know what mechanisms of action lie behind many of the pharmaceutical therapies used to treat immune-related diseases. This is true, for instance, of multiple sclerosis (MS). By analysing patient material we have discovered that when MS is treated, changes occur in the molecules of the immune system. This discovery may pave the way for new insights into the mechanisms of action producing therapeutic effects, potentially opening an avenue to improved treatments for MS patients.

Based on our measurements we carry out statistical studies to map correlations between our focus proteins and the patient's condition. In this fashion, our basic research is linked to the work of the clinicians on an ongoing basis.

In the years to come we expect to enhance our understanding of the mechanisms of action at work in the therapies currently being used. Our aspiration is to aid in the development of new biological drugs that can promote and inhibit the functioning of the innate immune system, making the treatments of the future more effective – and less fraught with side effects.



The binding of blood proteins to microbial surfaces is decisive for the ability of such proteins to protect against infection.

PROJECTS

1. **The significance of ficolins in the innate immune system:** Ficolins are an element in the innate immune system that was discovered fairly recently. Our work seeks to understand their role in activating the antimicrobial functions of the blood proteins, as well as their role in relation to other cellular components in the immune system.

2. **The release of cell-binding molecules in connection with rheumatoid arthritis and MS:** Cell-binding molecules, such as integrins, play a significant part in regulating the immune system, and they are the target of several important therapies for chronic inflammatory diseases, including rheumatoid arthritis and MS. Measuring the release of integrins from immune cells opens new perspectives in the understanding of disease progression and treatment.

3. **Ligon-binding studies of mannan-binding lectin and ficolins:** When it comes to understanding the functions of the immune system, molecular binding reactions are pivotal. Characterizing these bindings not only involves finding new binding partners on the surface of microbial organisms, but also chemically characterizing the strength of the bond.

MILESTONES

Discovery of mannan-binding lectin-associated serine protease-2 – significantly augmenting our understanding of the significance of blood proteins in immune-system activation
(Thiel S, et al. Nature. 1997;386:506–10)

Discovery of mannan-binding lectin-associated serine protease-3 – paving the way for new insight into how a single gene can express multiple blood proteins with different functions in the immune system
(Dahl M, et al. Immunity. 2001;15:127–35)

Characterization of mannan-binding lectin-associated serine protease-2 deficiency in humans – describing the first known defect in humans in the functioning of the mannan-binding lectin-associated serine proteases
(Steengaard-Pedersen K, et al. N Engl J Med. 2003;349:554–60)

Release of cell-binding molecules (integrins) in connection with rheumatoid arthritis – creating a potential for measuring integrins as a tool for clarifying disease progression in patients with rheumatoid arthritis, and possibly for clarifying the effectiveness of the treatment given
(Gjelstrup LC, et al. J Immunol. 2010;185:4154–68)

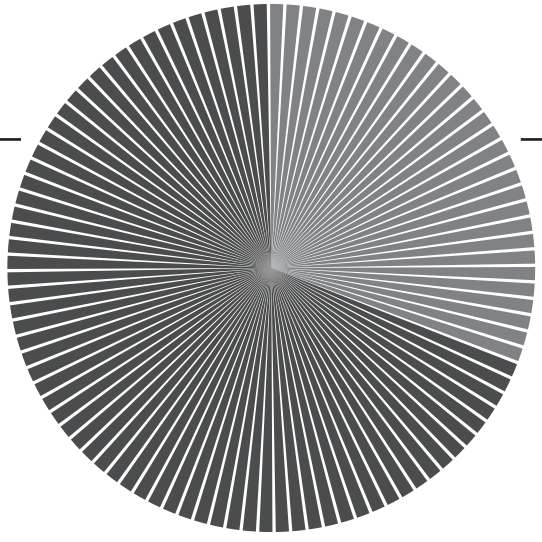
Demonstration that "natural nanoparticles" are formed based on fragments of material in their cell wall; these particles activate immunological mechanisms with particular efficacy, whereby the intact bacterium limits, or perhaps avoids, attack from the immune system
(Pedersen MB, et al. J Immunol. 2010;184:1931–45)

METHODS

Our laboratories apply a variety of state-of-the-art technologies to study the activities of the immune system:

- Time-resolved immunofluorometric assays of protein components in blood and other bodily fluids to determine volumes of key proteins in these fluids
- Low-angle X-ray scattering to determine the approximate structure of blood proteins in a solution, which corresponds to their environment in blood
- Flow cytometry (measurements of cells) to follow the activity and function of the cellular components in the immune system
- Cell-binding studies to understand the capabilities of immune cells, for instance to bind to components of infected nerve tissue

OVERVIEW



70 %
Basic research

30 %
Clinical research

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Qualitative research

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Epidemiological research

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RHEUMATOLOGY

Just over 100,000 Danes, of the country's less than 5.7 million, suffer from an inflammatory disease of the joints. Chronic rheumatoid arthritis, which is the most common and the most serious type of rheumatism, can be debilitating and also lead to premature death.

The rheumatology research groups at the Department of Clinical Medicine are leaders in the field, particularly in the study of chronic rheumatoid arthritis. We handle the organizational framework and supervision of large clinical pharmacological studies to examine this type of disease. The aim is to document the effects and side-effects of new treatments. Moreover, by gaining insight into the immune defence system we aspire to identify biomarkers that can predict, for the individual patient, the course of the disease, the development of permanent damage to joints, and the efficacy and possible side-effects of medication.

We also possess considerable expertise in studying, understanding, and using the biomarkers in blood and tissue that play a part in promoting or inhibiting inflammatory processes. Studies of cartilage and bone are carried out with a special view to understanding how the processes of regeneration and deterioration work under the influence of rheumatoid inflammation.

Rheumatology research employs diagnostics, both at a cellular level and at patient level. For instance, we now use X-ray and MR imaging to assess the pathological progression of permanent joint damage.

A strategy that helps 70 per cent for years
The rheumatology research groups at the Department of Clinical Medicine also work with epidemiological investigations based on long-established databases for patients with chronic rheumatoid arthritis. We look at how these databases can be correlated with information from other of Denmark's many clinical electronic registers and records: the National Patient Register and the National Prescriptions Database. This has enabled us to map patient behaviour concerning medication, as well as rare and serious side-effects such as increased prevalence of cardiovascular diseases and tumours.

The implementation of new therapeutic strategies has changed the way rheumatoid arthritis is treated, both in Denmark and abroad, based on a triad of principles: early diagnosis, rapid treatment of swelled joints, and early intervention with preventive medication (methotrexate). Our experience shows that this specific strategy helps more than 70% of our patients with rheumatoid arthritis.

PROJECTS

Clinical RCT studies of early-stage rheumatoid arthritis.

1. CIMESTRA: MTX + cyclosporin versus MTX + placebo, with results published up to year 5. Currently and open cohort study up to year 10. This project gives us a unique opportunity to assess the long-term effects of early aggressive and effective treatment, and to asses the prognostic value of biomarkers.
2. OPERA: MTX + adalimumab versus MTX + placebo. Year-1 data shows a 20% improvement in remission when used in combination. The project is being extended as an open cohort study for several years with a clinical database, biobanks, and image banks.
3. A new RCT study that would test MTX + tocilizumab versus MTX + placebo for treating early rheumatoid arthritis is currently being assessed by the European Medicines Agency.
4. In all of these studies, the participants include the majority of Danish rheumatology departments. The typical design is a 1–2-year RCT study, and subsequently an open cohort study. There is a central clinical database that holds the associated statistics, an image database for serial X-rays, MRI, ultrasound, and dual energy X-ray absorptiometry scans, and biobanks for serum/plasma, DNA, and cell samples.

MILESTONES

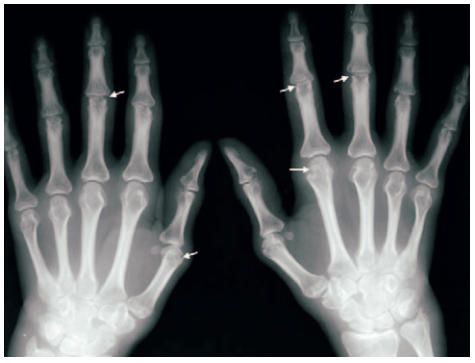
A new treatment strategy for chronic rheumatoid arthritis, based on the CIMESTRA study, is established in Denmark, and arouses international attention
(Hetland ML, et al. Arthritis Rheum. 2006;54:1401–9; and Hetland ML, et al. Ann Rheum Dis. 2008;67:815–22)

Interleukin 21 measured in the blood is a good marker for future disease activity and permanent joint damage
(Rasmussen TK, et al. J Rheumatol. 2010;37:2014–20)

Japanese–Danish collaboration enables researchers to follow the entire course of chronic rheumatoid arthritis in a special mouse model, in which new treatment modalities are also being tested
(Keller KK, et al. Clin Exp Rheumatol. 2011;29:536–43)

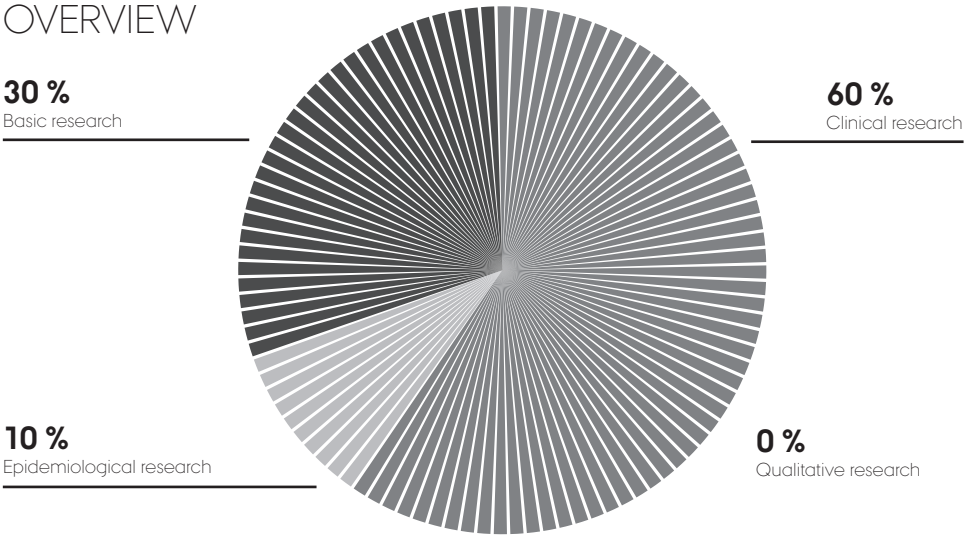
METHODS

- Organization and supervision of RCT design: double-blind, placebo-controlled studies of new pharmaceuticals, as well as data collection (blood, cells, and genetic material) in large databases, biobanks, and image banks
- ELISA technique for quantitative measurement of cytokines, chemokines, growth factors, vitamin-D metabolites, and so on; in plasma, serum, and synovial fluid.
- Immunocytochemical technique for localizing cytokines, chemokines, and so on, in the normal and the inflamed synovium
- Flow-cytometric technique for characterizing receptors and other molecules on the surface of T-lymphocytes, B-lymphocytes, and monocytes
- Gene analyses, partly using SNIP techniques and partly using whole-genome scanning
- Quantitative histomorphometric analyses of cartilage and bone tissue
- Experimental animal-based arthritis studies using the zap-70 mouse (a model for rheumatoid arthritis)
- Clinical epidemiological techniques for cohort studies of rheumatoid arthritis patients



Chemically induced tumour development is inhibited in MK2 knockout mice compared with wild-type mice.

OVERVIEW



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VIRAL-HOST INTERACTIONS

The crucial question motivating our research is: How can viruses cause disease? That is why our paramount concern is investigating the mechanisms that come into play between a virus and its host. This type of interaction is a dynamic and complex thing.

In the short term, our research is all about understanding the principles underlying the viral–host interaction. In the longer term, we aspire to create a platform for developing new treatments and vaccines against chronic and acute illnesses caused by viral infection.

Within this complex of topics we mainly work on problems addressed through basic research, and this calls for a wide range of techniques and special skills.

Interdisciplinary basic research
Conducting basic research that focuses on virus and human requires coordinated research efforts among several disciplines working together. This field cannot exist without a well-established interactive research environment that stretches across faculties, departments, and laboratories. Therefore knowledge-sharing, cooperation, and the horizontal structure of the organization are decisive factors in fostering the special kind of dynamism, understanding, and innovation that it takes to achieve results.

One specific area we are working on is understanding the earliest processes initiated upon infection with two types of virus that are, in principle, different – with one group's genetic material consisting of DNA and the other group's of RNA. This research is revealing to us how a virus behaves when interacting with different types of cells. In one of the methods used in this context, we develop models where cell cultures are infected with virus, using this to shed light on potential mechanisms in the development of disease. Sometimes we are able to work with animal models and thereby uncover more complex interactions.

In 2011 one of our researchers received the prestigious Danish Elite Research prize and Anders Jahre Prize for Young Scientists, awarded for research excellence, for exploring the immune system's recognition of microorganisms. The work dealt with identifying immunological receptors that recognize a virus, which is precisely what enables the host organism to defend itself against that virus. Conversely, the virus has different strategies to avoid being recognized, incapacitating certain mechanisms within the cell. Attaining a better understanding of how the body recognizes viruses, and what strategies viruses use to avoid the body's defence mechanisms, may prove to be important for gaining insight into the development of disease – and for the development of better diagnosis, treatment, and prevention options in the future.

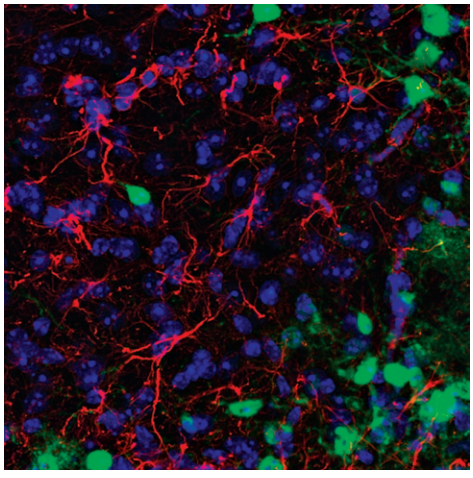
PROJECTS

1. **Identifying mechanisms used by the virus to prevent cell death.** This project examines basic aspects of cell biology by studying the interaction between the virus and the infected cell.

2. **Investigating disease mechanisms in patients with multiple sclerosis.** In this project we explore virological, immunological, and genetic mechanisms using cells and serum from patients, and using a variety of model systems.

3. **Describing the role and mechanisms of action for innate immunological receptors in the organism's defence against herpesvirus infections.** Here we are seeking to identify the earliest steps in the human immune system's molecular recognition of viral infection and the defence reactions to which they give rise.

4. **Identifying mechanisms to show how virus (including retrovirus) evade, or avoid, immunological recognition and inhibit the organism's defences.** The aim of this project is to identify the mechanisms developed by viruses to establish infection, despite the body's attempts to eliminate them.



Confocal microscopy image of a section of a spinal cord following infection with herpes simplex virus type 2. The picture shows herpesvirus (green), astrocytic filaments (red), and cell nuclei (blue).

MILESTONES

Demonstration of inactivation of the p53 function in T cells following infection with human herpesvirus 6B
(Øster B, et al. J Virol. 2005;79:1961–5)

Identification of a new mechanism for inhibiting TNF-receptor signalling
(Höllsberg P, Kofod-Olsen E. Polypeptide and polynucleotides for use as medicament or diagnosticum. PCT/DK2011/050032)

Demonstration of correlation between disease activity and increased expression of human endogenous retrovirus proteins on mononuclear cells from the blood of patients with multiple sclerosis
(Brudek T, et al. Retrovirology. 2009;6:104)

Identification of IFI16 as an intracellular immunological sensor of viral DNA
(Unterholzner L, et al. Nat Immunol. 2010;11:997–1004)

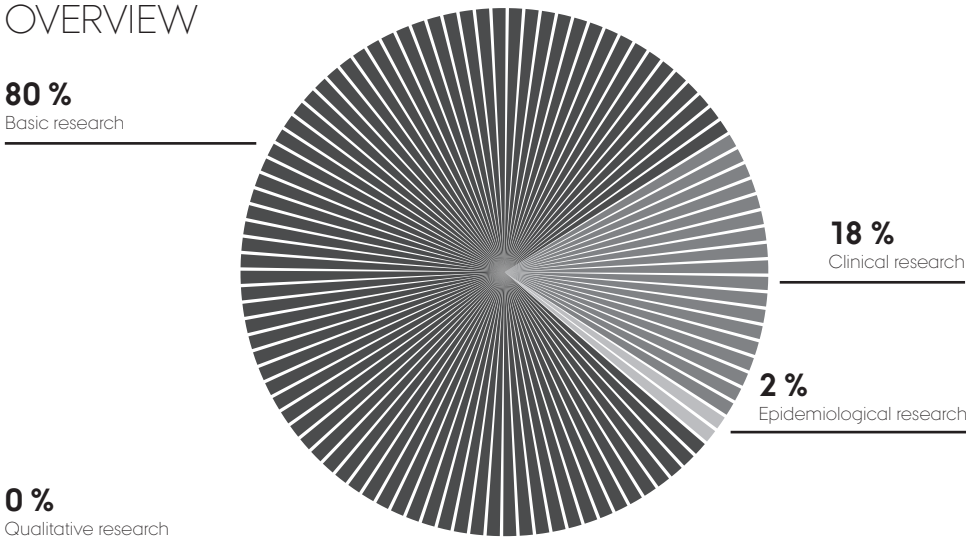
Description of mechanisms for innate immunological recognition of herpesvirus
(Paludan SR, et al. Nat Rev Immunol. 2011;11:143–54)

METHODS

Our specialist skills revolve around virological and cell-biological techniques and investigative methods, including:

- Cell culturing and handling of virus-infected cells
- Animal models and viral infections
- Confocal microscopy
- Flow cytometry
- Real-time qPCR
- Western blotting
- Immune precipitation
- Transfection

OVERVIEW



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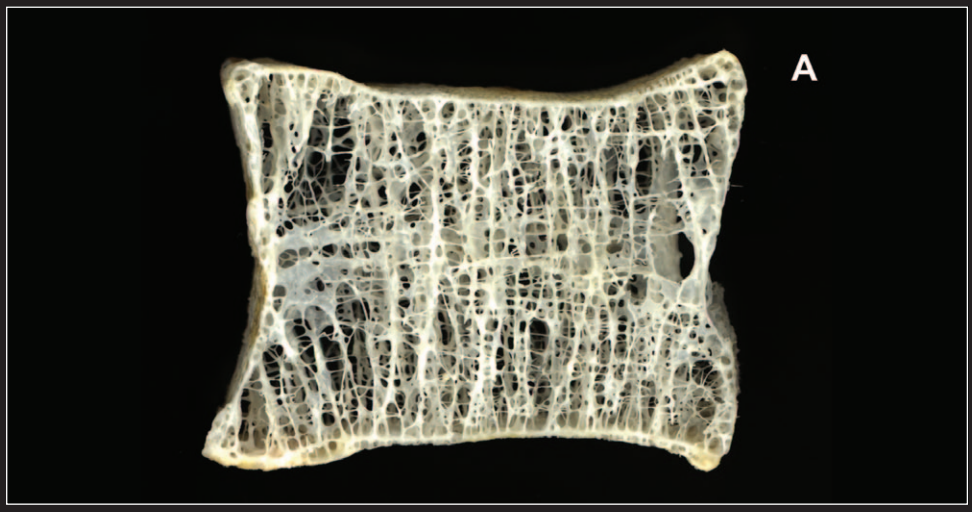
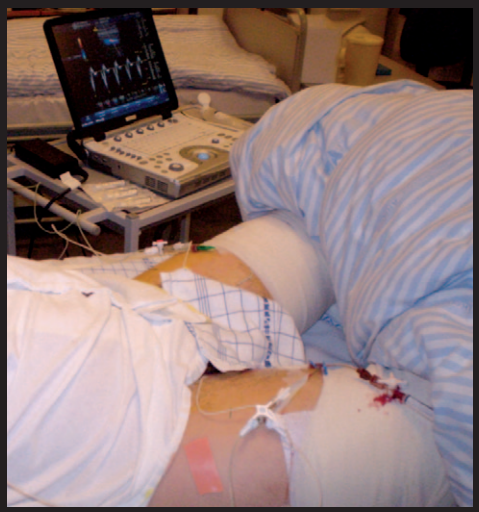
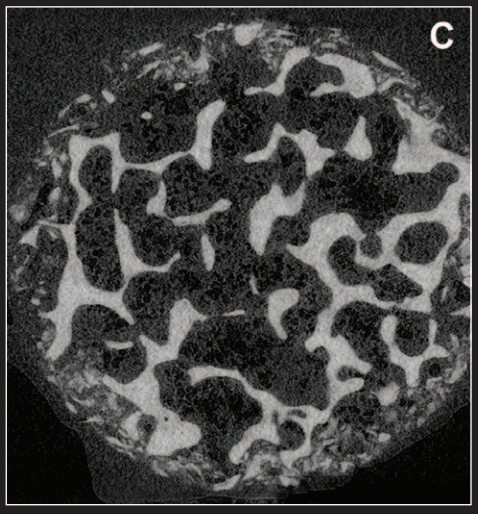
METABOLIC DISEASES

► A: Vertebra without osteoporosis.
B: Vertebra with osteo-porosis

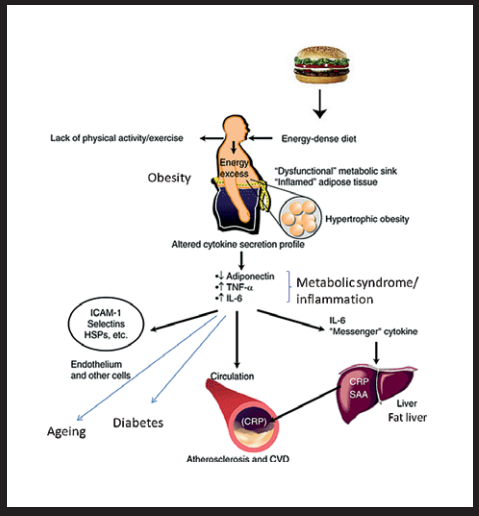


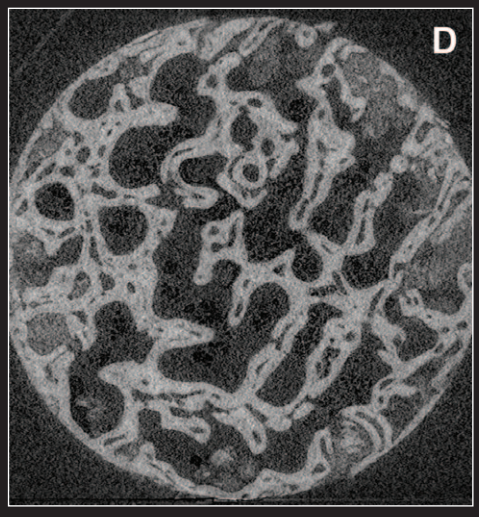
▼ A young diabetes patient is examined to clarify the causes of reduced insulin sensitivity.





◀ C: Trabecular bone from patient with hypopara-thyroidism





◀ D: Trabecular bone from patient with hypoparathyroidism receiving parathyroid hormone therapy.

BONES

It has been estimated that about 400,000 Danes suffer from osteoporosis. This condition affects 1 in 3 women, and 1 in 5 men. Osteoporosis is associated with increasing age, but factors such as inheritance, lifestyle, pregnancy, and breast-feeding also influence bone mass, structure, and turnover. Other diseases, such as increased activity of the parathyroid glands, and certain pharmaceuticals, also influence bone strength and hence the risk of bone fractures.

Our research into the structural and hierarchical composition of bone, as well as its deterioration, regeneration, and mechanical strength, improve our scientific knowledge about osteoporosis, which in turn can help develop new methods for prevention and treatment. Research efforts also focus on how bone fractures and defects heal. By learning more about how fractures heal, we can improve treatments and reduce the risk of new fractures.

We are particularly interested in developing methods to predict the risk of fractures and assess the efficacy of new treatment regimens. The goal is to ensure early identification of people in need of preventive treatment, and to assess the effect of the treatment they receive.

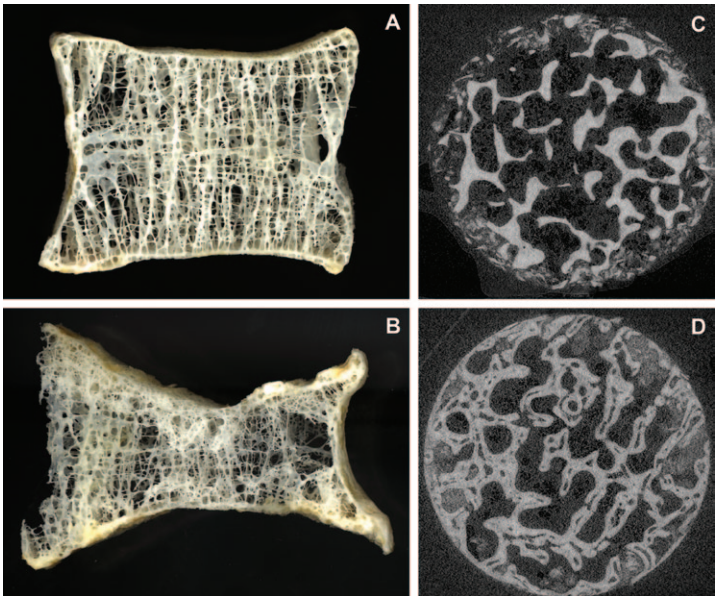
Building bones effectively
In our research there is a constant interaction between treatment programmes and clinical and basic research. One of the great challenges is that at present no in-depth knowledge is available about the biological mechanisms behind several of the treatment regimens.

That is why one project has monitored patients with reduced parathyroid-gland function, treating one group with the lacking hormone, whereas the other group was treated with placebo. The parathyroid hormone regulates both the amount of calcium in the blood and the speed at which bone tissue is replaced. The aim is to develop a more effective treatment. Investigations into the effect of hormones on bone regeneration and structure has led us to cooperate with an American pharmaceutical company. Generally, expectations are high that the coming years will see the development of drugs that can effectively regulate the building of bone tissue and calcium homeostasis.

When developing new forms of therapy we begin at cell-culture level, then move on to animal models, and ultimately involve patients. We also collaborate with geneticists to study genetic predisposition and the risk of losing bone mass.

PROJECTS

1. The influence of immobilization on bone:
   - Examination of bone biopsies from a bed-rest experiment lasting 370 days
   - The effect of various pharmaceutical drugs on bone loss in an experimental immobilization model.
2. The structural and hierarchical composition of bones, and the significance of these factors for bone strength and fracture risk.



A:
Vertebra without osteoporosis

B:
Vertebra with osteoporosis

C:
Trabecular bone from patient with hypoparathyroidism

D:
Trabecular bone from patient with hypoparathyroidism receiving parathyroid hormone therapy.

3. The effect of exogenous parathyroid hormone on bone structure, mineral density, and bone regeneration and structure in patients with hypoparathyroidism.

4. Changes in bone structure, mineral density, and bone regeneration and structure during normal pregnancy and breast-feeding.

5. The effect of parathyroid hormone, CaSR gene mutation, and thyroid hormones on bone mineral density, and on bone regeneration and structure in patients with primary hyperparathyroidism, familial hypercalciuric hypercalcemia, and hypo- or hyperthyroidism.

6. Association between genetic mutations, clinical profile, bone regeneration, and bone structure and mineral density (phenotype) in patients with osteogenesis imperfecta

MILESTONES

Vitamin D metabolites and skeletal consequences in primary hyperparathyroidism
(Moosgaard B, et al. Clin Endocrinol. (Oxf) 2008;68:707–15)

Three-dimensional quantification of structures in trabecular bone using measures of complexity
(Marwan N, et al. Phys Rev E. 2009;79:021903-1–021903-11)

Strontium is incorporated into the fracture callus but does not influence the mechanical strength of healing rat fractures
(Brüel A, et al. Calcif Tissue Int. 2011;88:142–52)

The effect of adding PTH(1–84) to conventional treatment of hypoparathyroidism: a randomized, placebo-controlled study
(Sikjaer T, et al. J Bone Miner Res. 2011;26:2358–70)

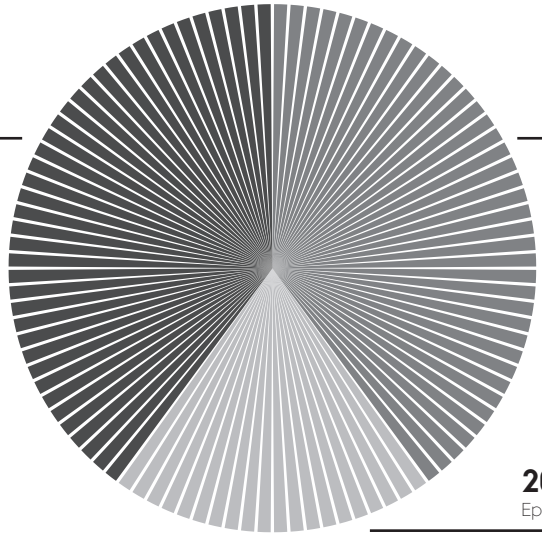
Changes in bone mineral density and body composition during pregnancy and post partum: a controlled cohort study
(Møller UK, et al. Osteoporosis Int. 2011. Epub ahead of print)

METHODS

Our research involves a wide variety of invasive and non-invasive methods used on patients and experimental models:

- Biomechanics
- µCT, pQCT, QCT, and DEXA
- 3D visualization
- Histomorphometry after intravital tetracycline double-labelling and stereology
- ELISA, collagen analysis
- Animal-experiment models involving rodents: immobilization (disuse); fracture healing; ovariectomy
- Biochemical bone markers for bone deterioration and regeneration in plasma and urine
- Calcitrope hormones (parathyroid hormone (PTH) and calcitonin), vitamin-D metabolites
- Genetic analyses for osteoporosis and rare metabolic bone disease
- Examination of muscle function (determination of strength) and balance, with a view to assessing fall and fracture risks

OVERVIEW



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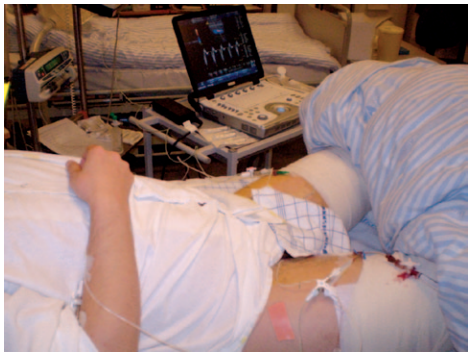
DIABETES AND ENDOCRINOLOGY

Our research deals with the occurrence, background, development, and treatment of major lifestyle diseases such as diabetes and hypertension, and with certain rare endocrine diseases.

We focus on determining the characteristics of these diseases, in particular the mechanisms that cause diabetes and the endocrine diseases to develop – working not only at a molecular level, but also looking at pathophysiology and demographic factors. Therapeutic methods for patients with all stages of diabetes, hypertension, and endocrine diseases are developed and tested at an integrated centre that has basic and clinical research units, often in collaboration with academic and industrial partners.

Besides diabetes and hypertension our research focusses on diseases relating to the pituitary and adrenal glands, and on conditions like Turner's syndrome and Klinefelter's syndrome, which relate to the glands producing gender-specific hormones. A number of very rare diseases, for example Prader-Willi syndrome, have been characterized using our methods, and possible avenues of treatment have been explored.

Professional expertise and useful tools
The research-based approach to endocrine diseases, using the methods described below and many more, has been systematically applied in relation to patient diagnoses and the interventions provided by the health system. Based on the fundamental assumption that all patients are different, the research unit has set up evidence-based clinical pathways for the various diseases. The unit plays a national and international role in operationalizing the data produced in the laboratory (for instance by establishing practice guidelines). A key element in our research is to monitor the effects and side effects of new and well-established treatments.



A young diabetes patient is examined to clarify the causes of reduced insulin sensitivity.

PROJECTS

1. **DD2:** The DD2 project tests the hypothesis that by using treatment guidelines and structured regimens it is possible to normalize the risk profile and avoid diabetes complications. The project continuously monitors information registered in Danish public-health databases, thereby obtaining long-term knowledge about indicators for diabetes complications. This will enable us to set objectives for new interventions. So far the project has been funded with DKK 55 m from the Danish Council for Strategic Research and a number of foundations.

2. **Insulin production:** Beta-cell function during metabolic stress from nutrients and hypoxia is one example of our basic methodologies.

3. **Insulin resistance:** We examine insulin resistance, for instance using the clamp method in muscles subjected to stress.

4. **Fat metabolism:** Isotopic methods are used to study the metabolism of VLDL-TG and triglycerides.

5. **The prognosis for treatment with anti-diabetic medication:** Research in national Danish databases enables us to determine morbidity and mortality rates.

6. **Diseases and chromosome aberrations:** Metabolism and morbidity are studied in groups of people with chromosome aberrations, including Turner's syndrome.

MILESTONES

The body's release of insulin is regulated and inhibited by somatostatin.
(Alberti KG, et al. Lancet. 1973;2:1299–1301)

Microalbuminuria is an early risk marker that warns of kidney failure and death in patients with type-2 diabetes
(Mogensen CE, et al. N Engl J Med. 1984;310:356–60)

Measurement of glucose in the subcutis shows the sugar level in the brain
(Nielsen JK, et al. Diabetes. 2005;54:1635–9)

Certain proteins reduce the content of harmful fat in the blood after a meal
(Mortensen LS, et al. Am J Clin Nutr. 2009;90:41–8)

The development of serious vascular complications accompanying diabetes can be explained by changes in parts of the immune system
(Flyvbjerg A. Nat Rev Endocrinol. 2010;6:94–101)

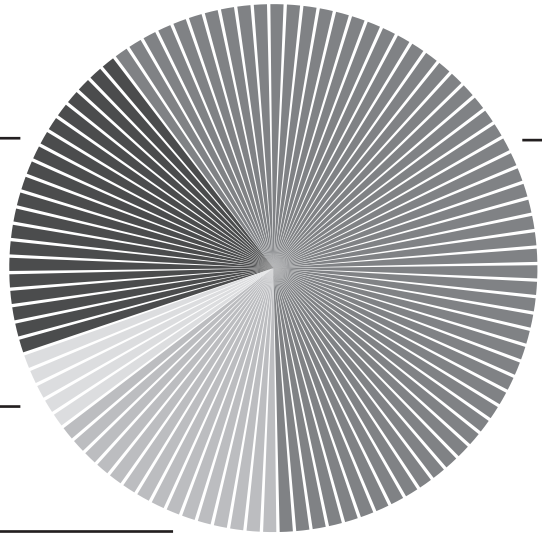
Insulin also has an affect on diabetes patients with serious insulin resistance
(Kampmann U, et al. Diabetes Obes Metab. 2011;13:511–6)

METHODS

Our methods include a wide array of immunoassays to measure peptides and hormones, blot analyses to measured tissue proteins and mRNA, and more traditional chemical methods to measure low-molecular metabolites.

- Imaging techniques that quantify muscles, fat, bone, and liver
- Administration, during clinical examinations, of labelled isotopes to measure the metabolism of glucose and other substances, for instance in brain and muscle tissue
- Tissue samples from muscle and fat to investigate at signal levels
- Clamp testing to clarify insulin sensitivity (see illustration), during which plasma glucose and other values are maintained at a stable level under various influences
- Animal models and cell cultures, which are used for much of the unit's basic research

OVERVIEW



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GROWTH

Body growth and regeneration are processes essential to our health – from before birth and until we reach old age. The growth and healing processes in our body are therefore controlled with extreme precision, regulated by a complex interplay between genes, nutrition, and a number of hormones that promote growth.

When the delicate balance of this interplay is disrupted, it can result in diseases. Imbalances can arise due to insufficient or excessive production of growth-promoting hormones, for instance, or when the body reacts abnormally to these hormones as a result of genetic miscoding or the person's nutritional state.

In children, reduced production of growth-promoting hormones will lead to low height, whereas excess production will lead to gigantism. In adults, a production deficit of growth-promoting hormones leads to a shift in the distribution of body fat – with more dangerous fat between the internal organs, reduced muscle volume, and reduced quality of life – whereas excess production causes problems with the bones, the heart, and the glucose balance (diabetes). Growth hormone imbalances further entail a heightened risk of developing cancer and cardiovascular diseases, and of premature death. At the Medical Research Laboratory, we map the mechanisms influencing the interaction between the body's nutritional state, genes, and growth-promoting hormones. We take a particular interest in investigating changes in the body resulting from insufficient or excessive growth hormone production, and in studying the balance of growth-promoting hormones in cancer patients. We also study why obesity is harmful, whereas caloric restriction seems to be beneficial to the body. Finally, we explore how genetic diseases affect the body's growth-promoting hormones.

A unique laboratory

As a part of Aarhus University Hospital, we work with the newest treatment principles and develop new diagnostic methods for diseases arising from deficient or excess production of growth-promoting hormones. Furthermore, we use advanced scientific methods to investigate the body's nutritional state, and to measure how changes in growth-promoting hormones can affect the genes.

Within the Medical Research Laboratory we also do research on using the level of hormones in the blood as biomarkers. Such biomarkers will make it possible to predict which individuals have a special risk of developing a particular disease over time, and will additionally enable us to monitor the effects of treatment. This not only means that treatment can be individualized to solely include those with a high risk of developing disease; it also enables us to initiate timely treatment, and to avoid unnecessary side-effects.

The Medical Research Laboratory, located Aarhus University Hospital, provides exceptional opportunities for combining bedside and laboratory-based research. We also have access to a Clinical Research Unit, which, among other things, makes it possible to carry it out 24-hour examinations of admitted patients. This close contact between research and patients allows for the rapid transfer of new knowledge and scientific findings, and also enables us to continuously monitor treatments and clinical trials.

PROJECTS

1. The significance of caloric restriction (CR) and growth hormone (GH) on the mechanisms that control body ageing. GH exerts a double function relative to ageing: It promotes growth and reproduction by activating IGF-I, which accelerates the ageing processes in the body. At the same time, GH stimulates the fat metabolism during fasting, and during physical activity – yielding effects that protect against ageing. We are conducting a number of projects on healthy test subjects and overweight individuals in order to understand how, at a molecular level, GH is capable of switching between these two functions.

2. Turner's syndrome (TS) leads, among other things, to a deficit of female sex hormones, infertility, osteoporosis, and bone fractures. Patients with TS have lower bone-mineral density (BMD). Bone structure is interesting, because the ultimate strength of the bone, and consequently the risk of fractures, depends not only on bone mass, but also on bone quality and structure. We are seeking to use a new method – high-resolution peripheral quantitative computed tomography – to visualize and structurally characterize the long tubular bones of the forearm and leg. This new technique permits us to reproduce imaging details in extremely high resolution (cross-sections 80 micrometres

thick), and simultaneously enables 3D recording. This gives us new knowledge of the interaction between bones and hormones.

3. Studies of tumours and blood have shown that insulin-like growth factors (IGFs) are capable of stimulating the development and growth of malignant cells. When measuring IGF content in the blood, however, methods have so far been used that do not enable us to distinguish between active and inactive forms of IGF. We have therefore developed new, sophisticated biological methods enabling measurement of only the active IGF-forms. Efforts are currently ongoing to clarify the activity of IGF-I in the blood of patients with breast, lung, and liver cancer.

4. A clinical investigation to determine what significance the administration method for GH has on its biological effects in patients with growth hormone deficiency. GH is partially absorbed via the lymphatic system. Consequently, factors that influence lymphatic flow, including physical activity, may play a role in the systemic absorption of GH. To learn more about this issue, we compare GH blood profiles in a group of patients without GH, partly after injection into the subcutis, and partly after constant infusion into the subcutis. Investigations take place during flat bedrest and during physical activity.

METHODS

We clarify the significance of growth-promoting hormones in human health and disease, comparing blood-concentration levels of these hormones, their biological effects within the body, and the signal pathways they activate in the cells. In addition we conduct epidemiological studies of the correlation between an individual's hormone levels and the risk, over time, of developing cancer, cardiovascular disease, and other diseases.

- Measurement of cellular signal proteins and mRNA in tissue samples
- Measurement of hormonal effects in the body (for instance using clamp techniques)
- Development and clinical testing of new hormone/biomarker analyses
- Randomized clinical trials of new hormone treatments

MILESTONES

Wick chromatography for rapid and reliable immunoassay of insulin, glucagon, and growth hormone
(Ørskov H, et al. Nature. 1968;13:193–5)

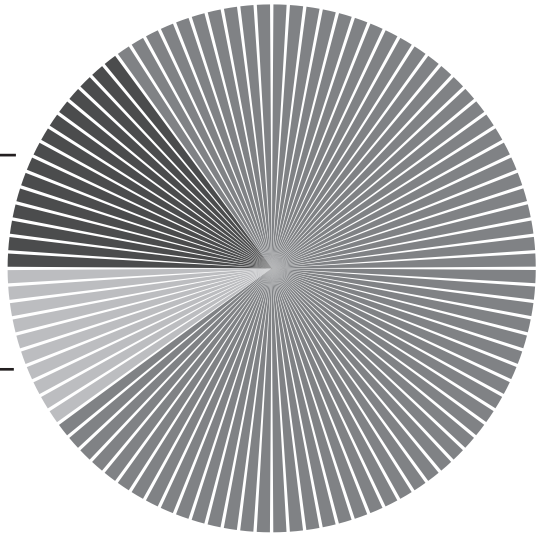
Beneficial effects of GH substitution in GH-deficient adults: a placebo-controlled trial
(Jørgensen JO, et al. Lancet. 1989;1:1221–5)

Free insulin-like growth factors (IGF-I and IGF-II) in human serum
(Frystyk J, et al. FEBS letters. 1994;348:185–91)

Long-term effects of continuous subcutaneous (sc) infusion versus daily injections of growth hormone (GH) on the insulin-like growth factor system, insulin sensitivity, body composition, bone and lipoprotein metabolism in GH-deficient adults
(Laursen T, et al. J Clin Endocrinol Metab. 2001;86:1222–8)

Prevalence, incidence, diagnostic delay, and mortality in Turner's syndrome
(Stocholm K, et al. J Clin Endocrinol Metab. 2006;91:3897–902)

OVERVIEW



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OBESITY AND NUTRITION

Research into obesity and nutrition is relevant to a large part of Danish society. Of the country's roughly 5.6 million inhabitants, around 400,000 are seriously overweight. Obesity is associated with a number of complications such as metabolic syndrome, diabetes, and cardiovascular diseases.

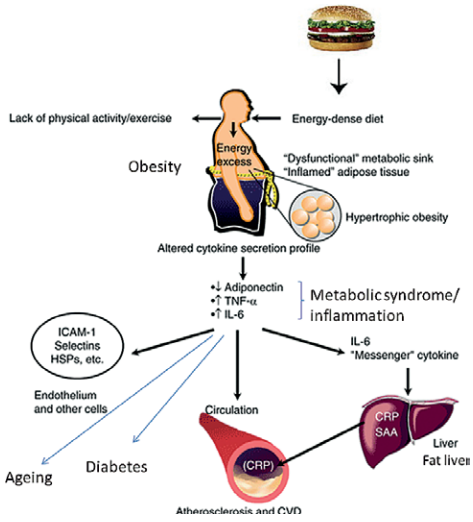
Nutrition is relevant for all the major lifestyle diseases and for the human body's development and ageing, which makes nutrition particularly interesting in connection with the concept of "healthy ageing".

As researchers we work at a very basic level, analysing tissue samples and cells in the laboratory but also in the clinic, where we study patients for purposes of diagnosis, pathophysiology, and treatment. We have specialized in different techniques for biopsies from humans. In addition, we test human insulin sensitivity to explain what factors might improve or impair it. Finally, we use specific methods and techniques to measure energy conversion, energy consumption and other values. This improves our understanding of the metabolism – which determines the amount of energy deposited and hence the degree of obesity.

Focus on excess weight and nutrition

In our obesity research we are currently focussing on the point at which excess weight becomes a pathological condition, and on the complications to which it can give rise. In this context we study questions like why fatty tissue, in and of itself, can cause disease and problems (in some cases resulting in "fat poisoning"), and we also study the location of fatty deposits on the body. One hypothesis is that inflammation in the body's fatty tissues, and inappropriate deposit locations, play an important role in the health issues associated with carrying excess weight.

In terms of nutrition, we concentrate on how certain nutritional factors affect obesity, metabolic syndrome, diabetes, cardiovascular diseases, and ageing processes. Examples are the identification of micronutrients that have health-promoting properties, and the effect of other nutritional factors such as protein quality, "New Nordic cuisine", and so on, with a view to preventing and treating lifestyle diseases.



PROJECTS

1. Studies of the nutrient resveratrol as a factor in preventing obesity complications and the ageing process (animal and human interventions). The Danish Council for Strategic Research, DKK 19 million.
2. The quantity and quality of protein, including the role that specific amino acids play in metabolic syndrome and lifestyle diseases. The Danish Council for Strategic Research, DKK 13 million.
3. Different types of diet, including healthy "New Nordic" food versus conventional Western food. Human studies.
4. Studies of different inflammatory biomarkers for the development of diabetes and cardiovascular diseases. The Danish Council for Strategic Research, DKK 13 million.
5. Studies of the role of sugar/fructose in the development of obesity, fatty liver, and metabolic disease. A human intervention study. The Danish Council for Strategic Research, DKK 5 million.
6. Basic research: The importance of polyphenols for inflammation and macrophage infiltration of fatty tissue. The Danish Council for Strategic Research, DKK 3 million.

MILESTONES

Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat. A 6-month randomized intervention study
(Maersk M, et al. Am J Clin Nutr. 2011)

Diet-induced weight loss and exercise, alone and in combination, enhance the expression of adiponectin receptors in adipose tissue and skeletal muscle; but only diet-induced weight loss enhanced circulating adiponectin
(Christiansen T, et al. J Clin Endocrinol Metab. 2010;95:911–9)

Anti-inflammatory effect of resveratrol on adipokine expression and secretion in human adipose tissue explants
(Olholm J, et al. Int J Obes. 2010;34:1546–53)

Differential effects of protein quality on postprandial lipaemia in response to a fat-rich meal in type 2 diabetes; comparison of whey, casein, gluten, and cod protein
(Mortensen LS, et al. Am J Clin Nutr. 2009;90:41–8)

Weight loss larger than 10% is needed for general improvement of levels of circulating adiponectin and markers of inflammation in obese subjects; a three-year-weight loss study
(Madsen EL, et al. Eur J Endocrinol. 2008;158:179–87)

Effect of orlistat on weight regain and on cardiovascular risk factors following a very-low-energy diet in abdominally obese patients; a three-year-randomized placebo controlled study
(Richelsen B, et al. Diabetes Care. 2007;30:27–32)

Differential effects of saturated and monounsaturated fat on postprandial lipaemia and glucagon-like peptide 1 responses in patients with type 2 diabetes
(Thomsen C, et al. Am J Clin Nutr. 2003;77:605–11)

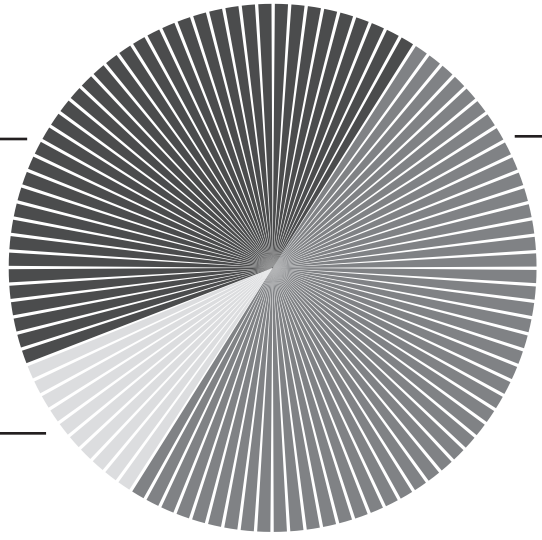
Substituting dietary monounsaturated for saturated fat improves insulin sensitivity in healthy men and women – The KANWU study
(Vessby B, et al. Diabetologia. 2001;44:312–9)

METHODS

We take different types of biopsies and test human insulin sensitivity in various ways. Also, we apply specific methods and techniques to measure energy conversion and consumption.

- Clinical research: Human intervention studies (nutrition and pharmaceuticals), appetite regulation, insulin sensitivity tests (clamp), indirect calorimetry, biopsies (fat, muscle, and liver)
- Imaging: CT, MR, DXA, SpectMRI (to determine body composition, fat storage in the liver and muscles, visceral fat, and so on)
- Animal models – including food consumption and insulin sensitivity
- Postprandial lipaemia (blood lipid contents after eating), microdialysis of fatty tissue, protein and fat metabolism
- Molecular-biology tests and functional tests in vitro; performed in our fatty-tissue/fat-cell laboratory and β-cell laboratory

OVERVIEW



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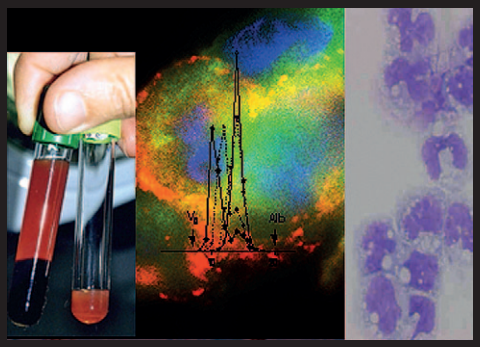
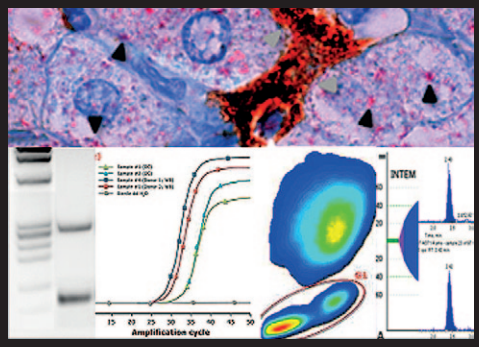
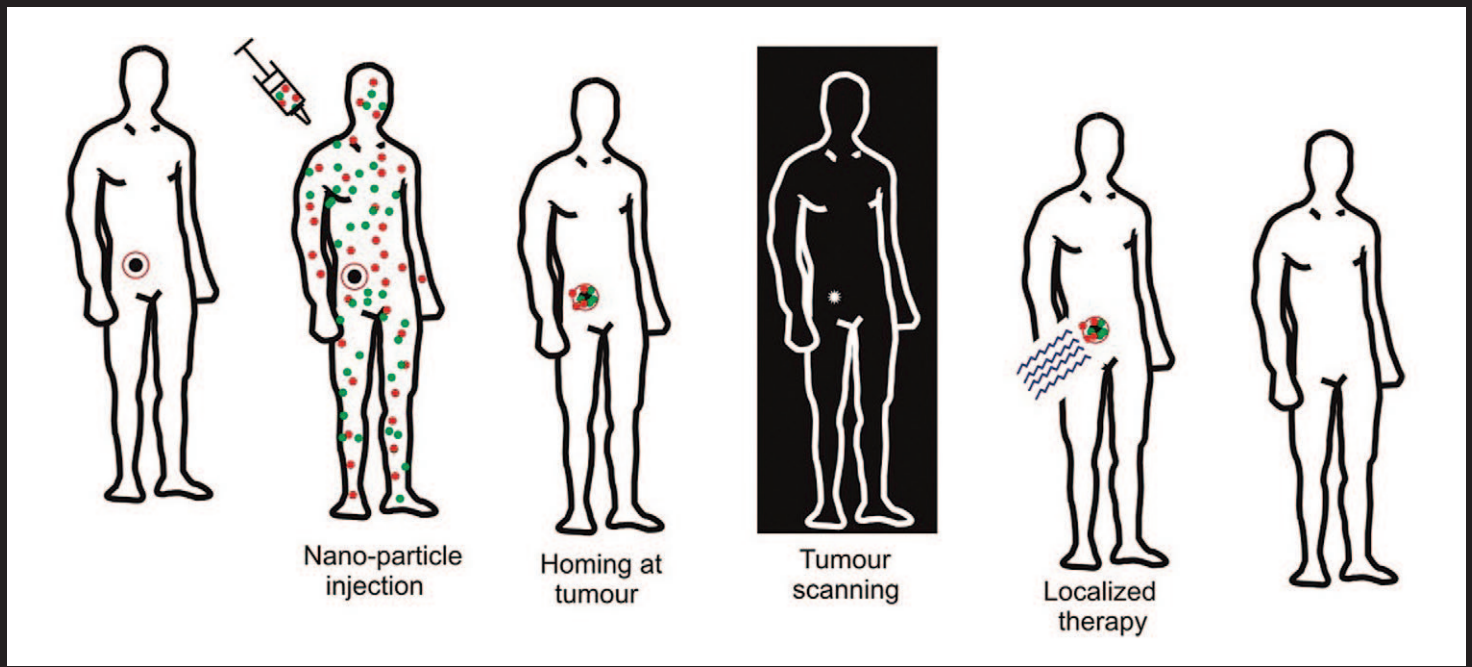
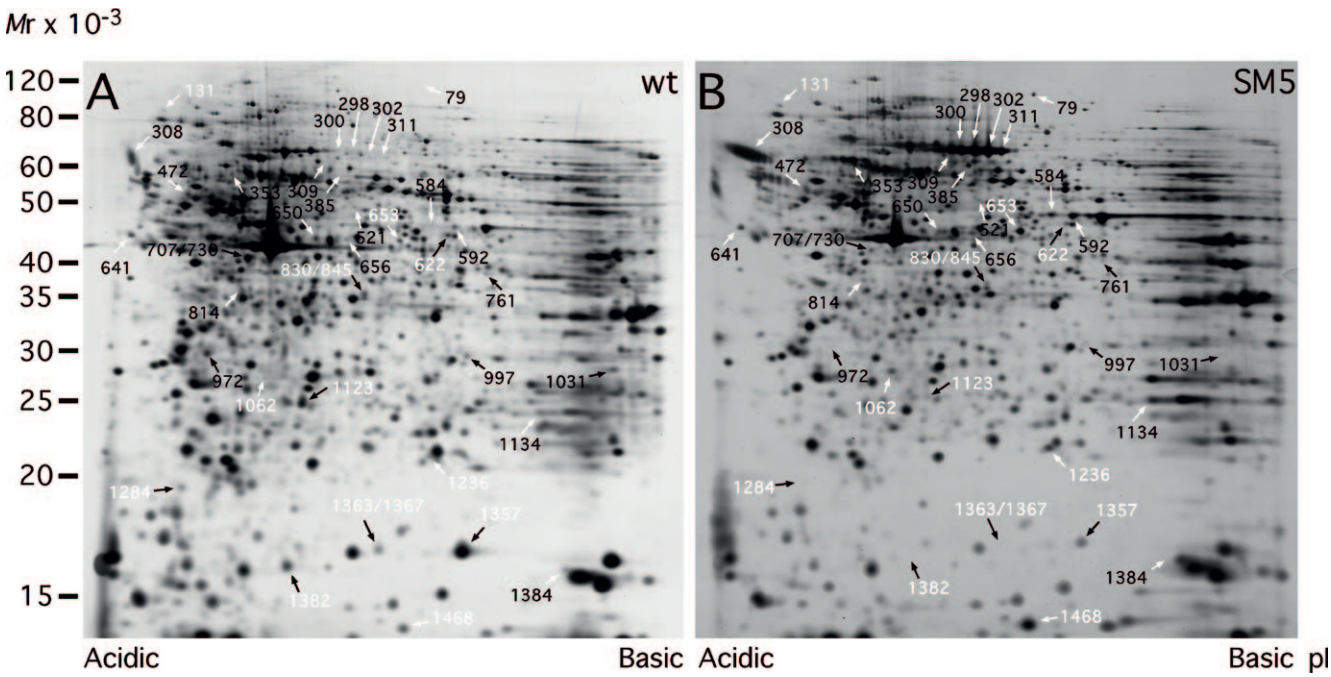
MOLECULAR DIAGNOSTICS AND BIOMARKERS





▼ Principles of molecular imaging.





▲ Two-dimensional gel electrophoresis of normal cells (A) and tumour cells (B). Identified differentially regulated proteins are incidated with arrows. (Honoré B, et al. Proteome Sci. 2008;6:18)

BIOMARKERS AND CLINICAL BIOCHEMISTRY

At the Department of Clinical Biochemistry we perform more than 10 million analyses of blood samples and other biological fluids every year. However, there is a constant demand for exploring new biomarkers in order to improve the diagnosis and treatment of patients.

Our expertise covers the development and validation of new biomarkers. Activities at the department include basic research, development of analytical methods, and clinical studies aiming at the final validation of how to use biomarkers in clinical medicine. We have expert competence at a high international level within the areas of vitamins, notably vitamin B12 and vitamin D, thrombosis and haemostasis, inflammation and macrophages, neonatal screening, and the epidermal growth-factor system in relation to cancer.

In addition, our ISO15189 accredited department assists at the highest professional level with the analysis of biomarkers, and thereby our results thereby contribute to numerous clinical studies.

PROJECTS

Our **projects** are performed in local, national, and/or international collaboration, and they are mainly financed by soft money. In addition, we support the research of others and collaborate with industrial partners.

- **CORE facility**
  Currently we are contributing to more than 150 clinical studies.

- **Industrial collaborations**
  Validation of analyses for vitamin D, active B12, trefoil peptides, and prenatal biomarkers.

  Development (and our own patenting) of labelled erlotinib.

  Cytoguide: a spin-off biotech company, based on local know-how.

Independent research projects, selected examples being:
HoloTC and markers of vitamin B12 metabolism. Part of three EU-financed projects. Key results: development and validation of assays for holoTC and a B12 absorption test.

Haemostasis and thrombosis: prediction of 1) the effect of antiplatelet therapy; 2) haemostasis during cardiac surgery, and; 3) thrombosis during fertility treatment and pregnancy.

Early Tracing and Intervention in Obesity-associated Life-style Diseases (TRAIN). A collaborative study financed by the Strategic Research Council, which aims to explore the clinical usefulness of macrophage-derived biomarkers.

The role of the epidermal growth-factor system in relation to lung cancer, notably relating to mutated receptor and affects of the accumulation of erlotinib on treatment outcome.

MILESTONES

Some recent publications:

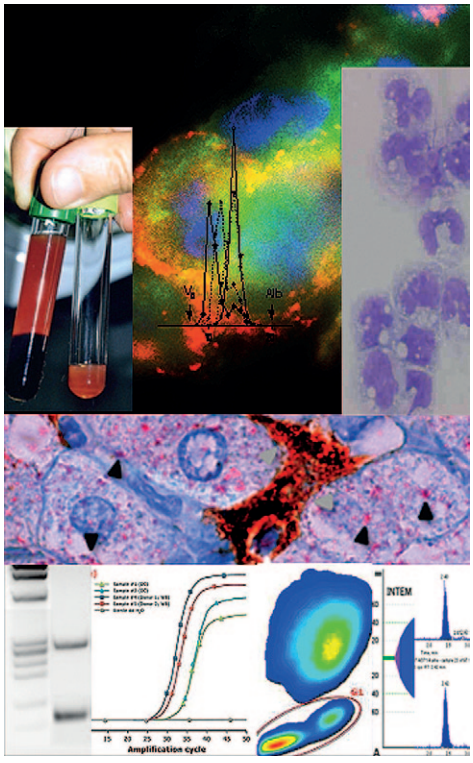
Association of cognitive impairment with combinations of vitamin B12-related parameters
(Lildballe DL, et al. Clin Chem. 2011;57:1436–43)

Influence of renal function and platelet turnover on the antiplatelet effect of aspirin
(Würtz M, et al. Thromb Res. 2011 Aug 10. Epub ahead of print)

Serum-soluble CD163 predicts risk of type 2 diabetes in the general population
(Møller HJ, et al. Clin Chem. 2011;57:291–7)

Erlotinib accumulation in brain metastases from non-small-cell lung cancer: visualization by positron-emission tomography in a patient harbouring a mutation in the epidermal growth-factor receptor
(Weber B, et al. J Thorac Oncol. 2011;6(7):1287–9)

First-trimester screening for trisomy 21 in gestational week 8–10 by ADAM12-S as a maternal serum marker
(Tørring N, et al. Reprod Biol Endocrinol. 2010 29;8:129)

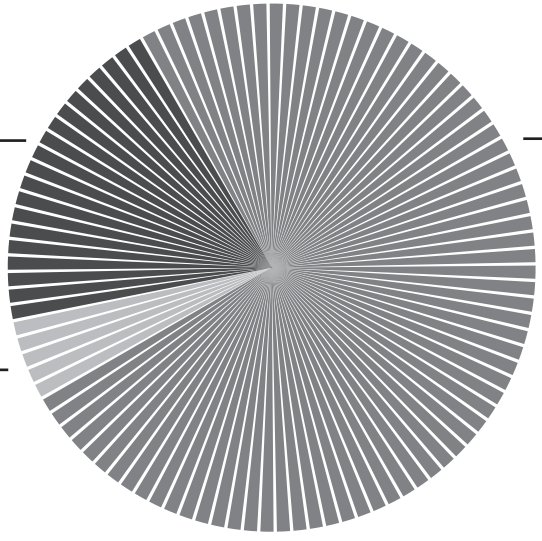


METHODS

We are **equipped** with highly specialized analytical instruments, and with high-throughput platforms. The department's core specialized methodologies are:

- Measurement and characterization of proteins, including ELISA, FPLC, and gel electrophoresis
- Measurement of low molecular weight substances using HPLC and tandem LC-MS/MS
- Cells in culture, including classified laboratory for transfection, flow cytometry, and fluorescence microscopy
- Analysis of platelet function (impedance and turbidimetry), and whole blood-clot formation (thromboelastometry)
- RNA and DNA analysis, including RT-PCR and next-generation sequencing

OVERVIEW



20 %
Basic research

75 %
Clinical research

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Epidemiological research

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Qualitative research

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INTERVENTIONAL SYSTEMS FOR ADVANCED BIO-IMAGING AND THERAPY

The concerted action of the research network "Interventional Systems for Advanced Bio-Imaging and Therapy" is heading towards the development of new bio-imaging techniques, firstly to exploit the improved specific sensitivity in diagnostics, and secondly to develop new targeting therapies. Diagnostics with a higher sensitivity and specificity can form the basis of new interventional systems for therapy. Examples of our techniques are biomarkers, or bioprobes, that all have the capacity to interact with specific tissues or metabolic processes.

The Department of Clinical Medicine provides a wide range of advanced imaging facilities for experimental applications, facilitating bench-to-bed studies, and including ultrasound, X-ray based systems (CT), magnetic resonance (MR), and isotope-based modalities (SPECT, PET). Further, we take advantage of interventional systems for bio-imaging and therapy based on biotargeting, contrast design and focussed targeting. Our research promotes the design, production and testing of interventional systems that bind to specific tissue types, such as cancer cells or stroke tissue, or couples to specific biochemical processes. These interventional systems will furthermore carry therapeutic substances directed towards specific pathologies, which can then exert their effect locally.

Broad scientific collaboration

The imaging research groups at the Department of Clinical Medicine are conducting numerous preclinical and clinical research programmes, particularly within oncology, renal physiology, brain and cardiovascular functionality, orthopaedics, stem cells, and tissue regeneration. In addition, we have access to advanced facilities (housing and intervention) for experiments that involve animals. These research activities are generated in close partnerships with groups at Aarhus University, and with other institutions addressing biomedical, technological, and biological topics. The peer-reviewed publication rate for bio-imaging research at the Department of Clinical Medicine is, on average, 55.

MILESTONES

Bøtker HE, et al. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. (Lancet. 2010,375(9716),727-34.)

Borghammer P, et al. Cerebral oxygen metabolism in patients with early Parkinson's disease. (J Neurol Sci. in-press)

Stødkilde L, et al. Bilateral ureteral obstruction induces early downregulation and redistribution of AQP2 and phosphorylated AQP2. (Am J Physiol Renal Physiol. 2011,301(1),F226-35.)

Andersen TB, et al. GFR Prediction From Cystatin C and Creatinine in Children: Effect of Including Body Cell Mass. (Am J Kidney Dis. 2012,59(1),50-7.)

Chondrocyte gene expression is affected by very small iron oxide particles-labeling in long-term in vitro MRI tracking. (Foldager CB, et al, J Magn Reson Imaging. 2011,33(3):724-30)

CMR Assessment of endothelial damage and angiogenesis in porcine coronary arteries using gadofosveset. (Fjord S, et al. J Cardiovasc Magn Reson. 2011,13(1),10)

First in vivo demonstration of coronary edema in culprit lesion of patient with acute coronary syndrome by cardiovascular magnetic resonance. (Kim WY, et al. Circ Cardiovasc imaging. 2011,4(3), 344-6.)

Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. (Nielsen MM, et al. Am J Clin Nutr. In-press)

The Power of Charisma: Perceived charisma inhibits the frontal executive network of believers in intercessory prayer. (Schjødt U, et al. Soc Cogn Affect Neurosci. 2011, 6, 119-127.)

Vascular effects of plinabulin (NPI-2358) and the influence on tumour response when given alone or combined with radiation. (Bertelsen LB, et al. Int J Rad Biol 2011, 87(11), 1126-1134.)

PROJECTS

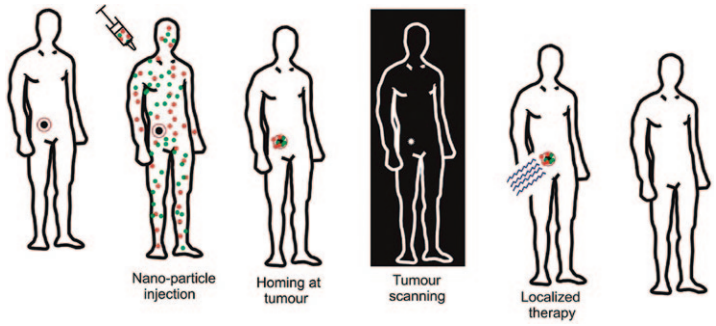
1. **Atherosclerosis:** New technology for preventing cardiac and cerebral stroke
2. **Regeneration:** Stem cells in regeneration and functional repair following tissue damage.
3. **Neo-vascularisation:** Progenitor cells in re-vitalisation of ischemic tissue and for preventing tumour re-growth.
4. **Comparative physiology:** Genetically engineered experimental models for understanding human diseases
5. **Growth and Metabolism:** Lipid metabolism/accumulation in organs and diseases in the musculoskeletal system.
6. **Molecular physiology of kidney diseases:** Molecular biology and physiology of transport systems broadly relevant to renal function and disease
7. **Brain PET imaging:** Target-specific PET probes for neurodegenerative disorders
8. **Nuclear cardiology:** Provides important anatomical and physiological information about the heart
9. **Molecular imaging in oncology:** Non-invasive imaging of the key molecules and molecular-based events that are fundamental to human tumor biology

METHODS

Modern radiology and nuclear-medicine scanner technologies offer new diagnostic and therapeutic possibilities by virtue of innovative, dynamic scanner modalities. This enables us to monitor and quantify organ function and biochemical processes over a period of time. These longitudinal datasets add substantial value to diagnostics and therapy based on interventional principles.

Our expert research competence mainly lies within cardiovascular pathology, general organ functionality, oncology, growth and metabolism, and stem-cell and progenitor-cell tracing and functionality.

Molecular imaging



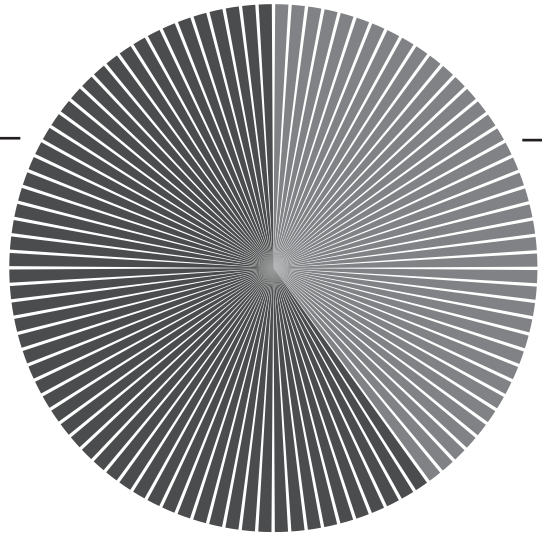
Principles of molecular imaging.

- Aspects of the development of atherosclerotic plaques
- Brain functionality during controlled thinking in arrays
- Use of reptiles for tissue regeneration
- Tumour metabolism and blood supply
- Stem cells in growth
- Energy metabolism and lipid metabolism
- Models for stem cells and progenitor studies
- Tracing of cells

Partnerships

- Extensive partnerships within the European framework of concerted action.
- Very strong crossdisciplinary partnerships.
- Organizer of ad hoc working groups for specific research efforts.

OVERVIEW



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Basic research

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Clinical research

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Qualitative research

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Epidemiological research

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MOLECULAR AND CELLULAR PATHOLOGY, AND STEREOLOGY

Pathology research covers a wide spectrum, ranging from basic biomedical to applied clinical research.

The field is expanding rapidly as a result of advances in molecular biology. There is an emphasis on translational research – involving both the speedy transfer of basic scientific findings to the clinic and the effective investigation of clinical problems in the laboratory. While we work with all major disease categories, the main focus of our applied clinical research is on cancer. Our research identifies biomarkers that can improve diagnosis (for example by distinguishing between cancer cells and other cell types), predict the development of diseases (for example in cancer prognosis), and make treatment more effective (for example by identifying patients who will benefit from targeted cancer therapy). The presence of biomarkers in tissue is demonstrated by combining traditional microscopy with advanced molecular methods, a combination that has given rise to a new area of expertise: molecular morphology. At the same time, we use novel scanning and digital-imaging techniques to increase the precision of marker identification and measurement, and to automate the process.

Stereology derives quantitative information from planar images (such as tissue samples and scanned images). This technology makes it possible, for instance, to count neurones in a tissue sample, and then use this to estimate the number of neurones in the entire brain. Similarly, stereology can be used to determine numbers, volumes, surfaces, lengths, connections, and 3-dimensional spatial distribution. Aarhus University is a global leader in the field, and one notable research contribution has been a targeted effort to integrate stereology with automatic image analysis.

Unique biobanks

An important element in our research is having access to biobanks. The Institute of Pathology has regional responsibility for collecting tissue samples for the newly established Danish Cancer Biobank. In addition, we house one of the largest biobanks that exists in Denmark. As part of our diagnostic work, we have been collecting formalin-fixed, paraffin-embedded (FFPE) tissue samples for decades, and our archive now holds millions of such samples. In Aarhus and elsewhere, novel methods have been developed that enable molecules extracted from FFPE tissue to be used in advanced molecular techniques, whilst the same tissue can be used for state-of-the-art molecular morphological studies. This unique scientific resource is made even more valuable when we link the biobank data with information from Denmark's many comprehensive clinical databases. This allows us to correlate pathological findings with patients' clinical courses, ultimately enabling us to identify molecular signatures of diagnostic, prognostic, or predictive significance.

PROJECTS

1. **Large-scale use of formalin-fixed, paraffin-embedded (FFPE) tissue in molecular analyses.** The project is supported by the Danish National Advanced Technology Foundation.

   The archives of the world's pathology institutes contain more than a billion FFPE blocks – an invaluable scientific resource for this field. However, no robust methods yet exist for using FFPE tissue samples for large-scale molecular analyses. Our aim is to develop routine platforms for using FFPE tissues on a large scale, applying next-generation sequencing.

2. **Stress-induced glutamatergic dysfunction in a rat model with behavioural stress, with particular emphasis on prefrontal synaptic vesicles.**

   Acute behavioural stress is capable of producing an increase in glutamate release in the prefrontal cortex region of the rodent brain. This increase can be completely normalized by means of chronic antidepression treatment. The project's aim is to further clarify this mechanism using electron-microscopy studies.

3. **Molecular epidemiological studies of breast cancer.** The project is supported by the Danish Cancer Society and the National Cancer Institute, USA.

Primary FFPE tissue samples have been collected from several thousand Danish breast-cancer patients. These samples are studied using molecular pathological techniques, and the results are correlated with data from epidemiological and clinical databases in an effort to identify new biomarkers of importance for prognostication and treatment.

4. **Epidemiological and clinical differences between Epstein-Barr virus (EBV)-positive and EBV-negative Hodgkin's lymphoma (HL).** This project is also supported by the Danish Cancer Society.

   The Institute of Pathology at Aarhus University Hospital has long experience in working with EBV-related cancer. We are currently conducting the world's largest cohort study to describe epidemiological and clinical differences between EBV-positive and EBV-negative HL, and to demonstrate whether the two diseases have different prognoses and should be treated differently.

MILESTONES

The unbiased estimation of number and sizes of arbitrary particles using the dissector (Sterio DC. J Microsc. 1984;134:127–36)

Characteristics of Hodgkin's lymphoma after infectious mononucleosis (Hjalgrim H, et al. New Eng J Med. 2003;349:1324–32)

Automatic sampling for unbiased and efficient stereological estimation using the proportionator in biological studies (Gardi JE, et al. J Microsc. 2008;230:108–20)

Macrophage markers in serum and tumour have prognostic impact in American Joint Committee on Cancer stage I/II melanoma (Jensen TO, et al. J Clin Oncol. 2009;10:3330–7)

Automated digital volume measurement of melanoma metastases in sentinel nodes predicts disease recurrence and survival (Riber-Hansen R, et al. Histopathology. 2011;59:433–40)

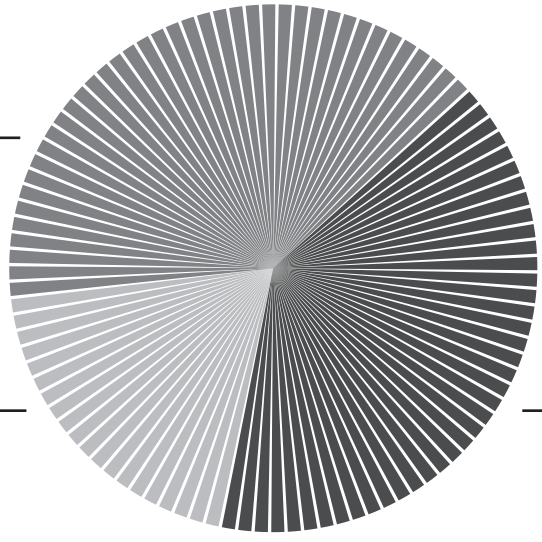
CYP2D6 inhibition and breast-cancer recurrence in a population-based study in Denmark (Lash TL, et al. J Natl Cancer Inst. 2011;103:489–500)

METHODS

Molecular pathology techniques, particularly used to study tissue sections or molecules extracted from samples of FFPE tissue:

- Light microscopy (histology and cytology) and confocal laser scanning microscopy
- Electron microscopy and immuno-electron microscopy
- Immunohistochemistry; chromogenic in situ hybridization; fluorescence in situ hybridization (FISH)
- Tissue microarray construction, staining, and interpretation
- Laser-based microdissection
- Stereology, morphometry; virtual microscopy
- PCR; RT-PCR; RQ-PCR, particularly used on FFPE tissue samples
- DNA/RNA extraction from FFPE tissue samples; production of molecules for next-generation sequencing
- Biobanking

OVERVIEW



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Basic research

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Epidemiological research

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Qualitative research

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Clinical research

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MEDICAL PROTEOMICS

The protein composition in our bodies plays an important role in the mechanisms that make our biological processes work – when we are well and, not least, when we are ill.

Proteomics – the study of the human proteome, or total protein make-up – can therefore help scientists understand the body's most basic mechanisms and so discover how diseases develop. Research can consist in studying changes in the proteome as a condition progresses in severity, or in comparatively studying the protein make-up in the tissue of healthy individuals and affected patients.

Our researchers seek to track down the proteins that are regulated up or down in the body in pathological conditions; to identify these proteins using mass spectrometry; and to characterize and analyse them. This will enable us, for instance, to examine the effect of these proteins on the body's cells.

Improving diagnostics and treatment
The long-term goal is to identify protein biomarkers for a range of diseases such as cancer, and eye and cardiovascular disorders, and to identify diagnostic tools and ways of monitoring treatment by measuring the relevant biomarkers.

Cooperating with the Department of Haematology and the Department of Pathology at Aarhus University Hospital, our researchers have carried out a study investigating the survival chances of 143 patients with lymph cancer. Basically the study used proteomics to explain why one group of patients responded well to cancer treatment, whereas the other group experienced a more limited effect. The investigation showed a correlation between survival chances for younger patients and the concentration of a particular protein.

This knowledge forms the foundation for new hypotheses, and for new experiments that can lead scientists onward to improved diagnostic practices and therapies that more specifically target patients with lymph cancer.

PROJECTS

1. We cooperate with clinical units on cancer research projects, notably regarding lymph and colon cancer. Tissue samples representing different lymphoma types are compared with normal tissue to identify proteins expressed in various concentrations. A completed study on Hodgkin's lymphoma has identified a series of biomarker candidates. One protein has been analysed in detail and a link with patient survival demonstrated. This protein and others are being further investigated for their suitability as biomarkers. Several other groups of diseases are under examination, and tissue studies are supplemented with cell models.
2. Our unit also collaborates with national ophthalmology units and international research groups to study a wide range of eye diseases. Among these are uveal melanoma, retinal detachment, and retinal changes caused by diabetes. Methods include examination of material from human patients and animal models.
3. Selected biomarker candidates are subjected to a detailed investigation of their biological function. We are especially focussing on a number of calcium-binding proteins in the CREC protein family, mapping their protein-binding partners, effect on cells, and so on by means of biochemical, cell-biology, and molecular-biology techniques.

MILESTONES

Identification of differentially expressed proteins in patients with ruptured and non-ruptured aortic aneurysms
(Urbonavicius S, et al. J Vasc Surg. 2009;49:455–63)

Identification and characterization of new ERC-55-binding proteins
(Ludvigsen M, et al. Proteomics. 2009;9:5267–87)

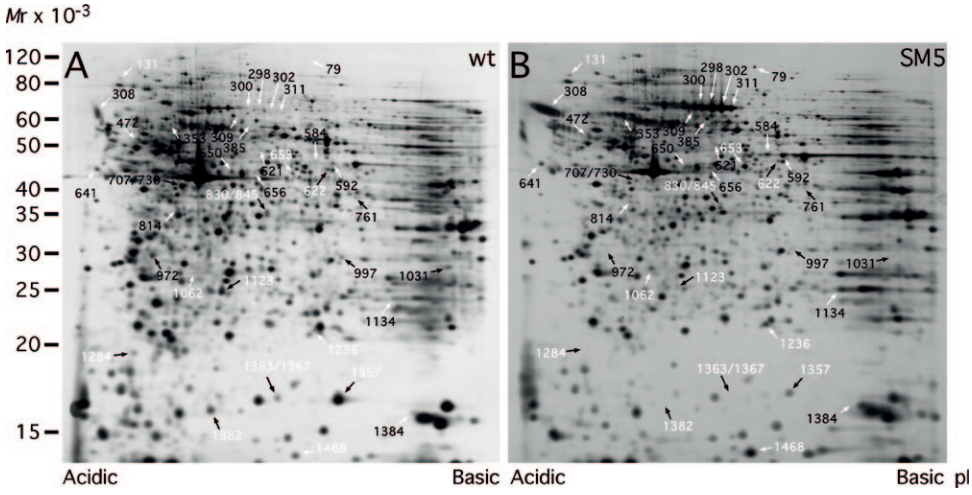
Proteomics applied to identify galectin-1 as a prognostic biomarker in patients with classical Hodgkin's lymphoma
(Kamper P, et al. Blood 2011;117:6638–49)

Protein alterations in the retina, resulting from experimentally induced retinal detachment in rabbits
(Mandal N, et al. Mol Vis. 2011;17:2634–48)

METHODS

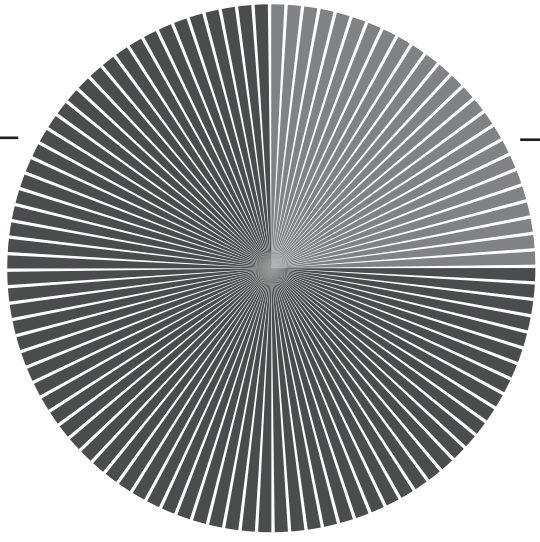
A variety of methods are used for high-resolution separation, identification, and characterization of proteins.

- Two-dimensional polyacrylamide gel electrophoresis (2D-PAGE)
- Tandem mass spectrometry (LC-MS/MS)
- Cell-biology techniques, including cell culturing, immunofluorescence light microscopy, transfection, and Western blotting
- Recombinant DNA technology, including heterologous expression, and purification of recombinant proteins from Esherichia coli
- Biochemistry techniques, including column affinity-chromatographic purification of proteins



Two-dimensional gel electrophoresis of normal cells (A) and tumour cells (B). Identified differentially regulated proteins are incidated with arrows. (Honoré B. et al. Proteome Sci. 2008;6:18)

OVERVIEW



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Basic research

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Clinical research

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Qualitative research

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Epidemiological research

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TRANSLATIONAL MOLECULAR MEDICINE:

MOLECULAR PATHOGENESIS AND PATHOPHYSIOLOGY

The Department of Clinical Medicine contributes to molecular-genetic and pathogenetic elucidation and diagnosis of a large number of hereditary diseases. This research is primarily carried out by the Research Unit for Molecular Medicine (Molekylær Medicinsk Forskningsenhed, MMF), which conducts its own research programmes and also collaborates on projects with local, national, and international scientists and clinicians.

The technologies we employ are used to study mechanisms of disease at the level of DNA, RNA and cellular proteins. Protein studies mainly investigate quantitative proteomics and are carried out using sophisticated mass-spectrometric techniques. Furthermore, our research unit serves as the expert competence centre for molecular medicine in connection with the PhD programme at Health.

At MMF we investigate disturbances in the energy metabolism in the cellular powerhouse: the mitochondria. We also study the interplay between the cell's genetic apparatus and the mitochondrial energy metabolism, further utilizing our knowledge and methods to identify new protein-based biomarkers under pathological conditions.

The unit acts as an international centre for molecular-genetic diagnosis of patients with hereditary disturbances in mitochondrial energy metabolism, and we are therefore also an important player in the Danish and other national screening programs that examine newborns for such diseases. A weakening or dysfunction of the energy metabolism is a central element in the normal ageing process, but also in the pathophysiology of diabetes, cardiovascular disease and similar conditions, as well as neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease.

MILESTONES

MMF has earned international recognition for its cutting-edge research in the following areas, exemplified by selected publications:

Contributions to diagnosing and investigating genetic defects in the mitochondrial metabolism
(Andresen BS, et al. Am J Hum Genet. 2001; 68:1408–18; and Olsen RK, et al. Brain 2007;130: 2045–54)

The consequences of genetic errors in protein structures, and analysis of the metabolism of mitochondrial proteins
(Bross P, et al. J Biol Chem. 1995;270:10284–90; and Gregersen N, et al. Ann Rev Genom Human Genet. 2006;7:103–24)

Analysis of disturbances in the mitochondrial protein pattern in cell stress and metabolic diseases
(Pedersen CB, et al. J Inherit. Metab Dis. 2010;33:211–22; and Palmfeldt J, et al. Journal of Proteome Research. 2011;10: 2389–96)

Working with clinicians at Aarhus University Hospital to detect and explore the consequences, at protein level, of genetic defects that cause such disorders as familial hypercholesterolaemia, hypertrophic cardiomyopathy, and diabetes insipidus.
(Hansen PS, et al. J Lipid Res. 1991;32:1229–33; and Mogensen J, et al. J Clin Invest. 1999;103:R39–43; and Faerch M, et al. Am. J Physiol Renal Physiol. 2009;297:F1518–F1525)

PROJECTS

Molecular genetics

1. Molecular genetic characterization of medium-chain acyl-CoA dehydrogenase (MCAD) defi¬ciency in clinically affected patients and in newborns identified by tandem MS-based newborn screening.
2. Clinical, genetic, and protein studies in arrhythmogenic right-ventricular cardiomyopathy, and in nephrotic syndrome

Molecular pathogenesis

1. Protein processing and mitochondrial dysfunction: identification of protein factors important for maturation of active short-chain acyl-CoA dehydrogenase (SCAD) using RNA interference.

2. Understanding the interdependency between vitamin B2 (riboflavin) supply and mitochondrial function.

Molecular cell pathology

1. Novel technologies to study mitochondrial dysfunction in patient-specific cell models.
2. Plasma and urine proteome profiles in children with idiopathic nephrotic syndrome.
3. Chronic cell stress in cultured fibroblasts from patients with inherited mitochondrial fatty acid oxidation disorders.
4. Pathophysiology of neurodegenerative diseases due to mutation in the mitochondrial Hsp60 chaperone.
5. Hippocampal biomarkers of susceptibility and resilience to stress in a rat model of depression.
6. Does acetoacetate have a protective role against methylglyoxal-based formation of advanced glycation end-products (AGEs)?
7. Urinary proteome analysis in congenital bilateral hydronephrosis.
8. Proteome analysis of cholesteatoma.

METHODS

We use both advanced and traditional methods from chemistry, biochemistry, and molecular biology in our research projects.

Protein analysis:

- using advanced mass spectrometry – both to detect biomarkers (untargeted) and to identify specific protein patterns (targeted)
- using antibody-based methods – both to identify specific protein patterns (Luminex technology) and for single-protein analyses (Elisa and Western blot)

Gene-expression analysis:

- using quantitative polymerase chain reaction (PCR) analyses

Genetic analysis:

- using capillary-based and fluorescence-based DNA sequencing and analysis of melting curves.

These methodologies are used on cells from patients, most often cultured epithelial cells (fibroblasts) which, in some cases, are transformed into the cell types relevant to the disease. The methods are also used in connection with experiments on cell models and laboratory animals. Protein analysis is furthermore used to analyse blood and urine samples.

Both in terms of methods and expert skills, we work in close collaboration with other researchers from the Department of Biomedicine (Professor Thomas G Jensen and Associate Professor Thomas J Corydon), who contribute with virus-based recombinant methods; and from the Unit for Bioanalytical Chemistry, under the Department of Forensic Medicine (Professor Mogens Johannsen), who supplements our protein analyses with metabolite analyses. Together, the Unit for Bioanalytical Chemistry and the Research Unit for Molecular Medicine (MMF) serve as a proteome/metabolome core facility at Health.

OVERVIEW

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Basic research

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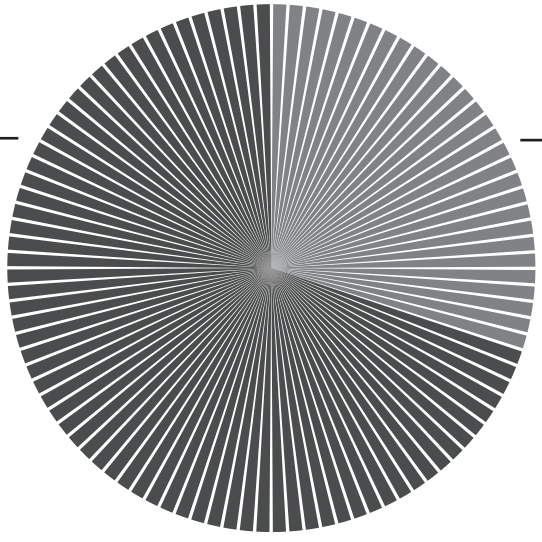
Clinical research



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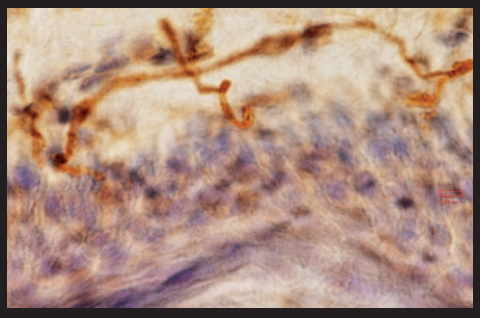
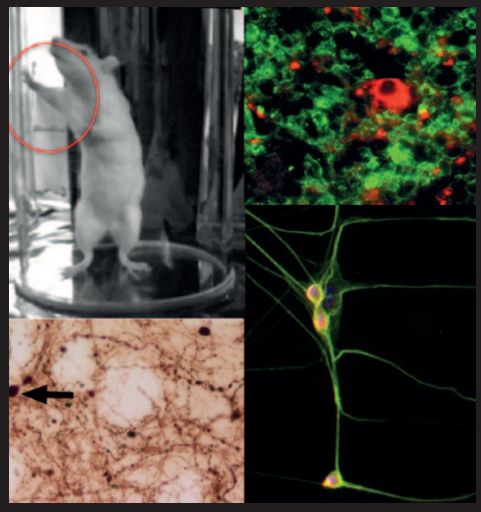
NEUROSCIENCE

▲ Stereotaxic embedding of electrode for deep brain stimulation to treat chronic pain.

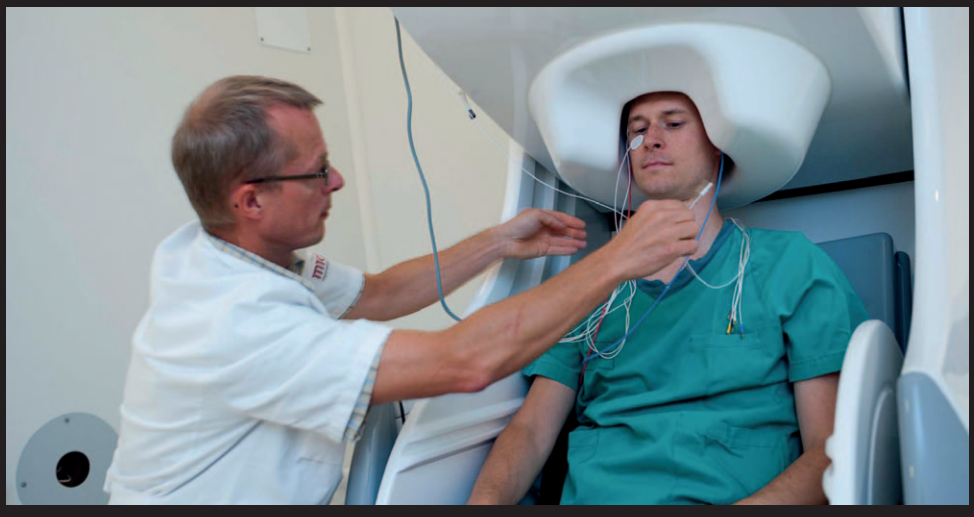
▼ Dermal microdialysis to determine noradrenaline.



► Neurodegeneration is studied at many levels: in the human brain, via animal behaviour and cerebral changes, and in the individual nerve cell.



▼ Simultaneous recording of MEG and EEG. (Photo: Michael Harder, Aarhus University Hospital)

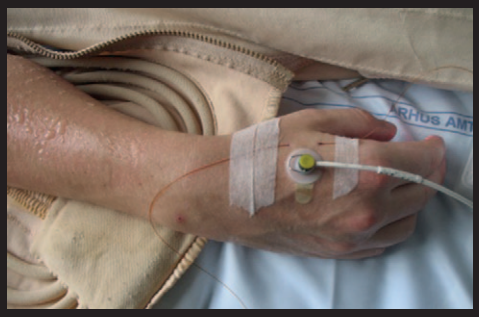


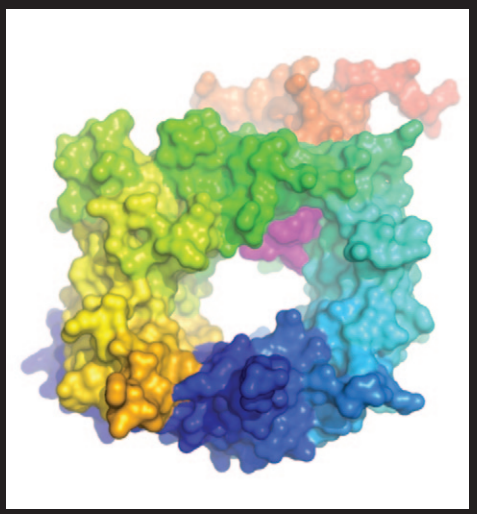
25 OF

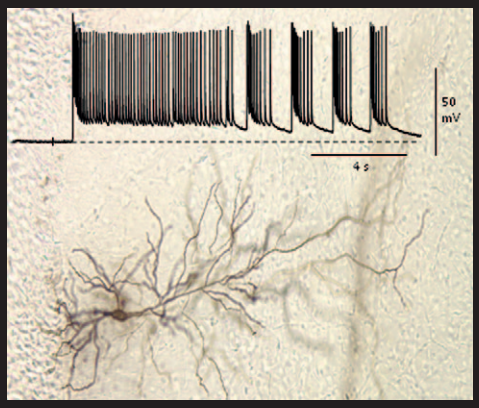
▲ Determination of nerve and muscle functions.

► Structure shown with the ligand-binding b-propeller in the foreground.

▼ Small (C/Ad) [HFL1] nerve fibres in the skin.

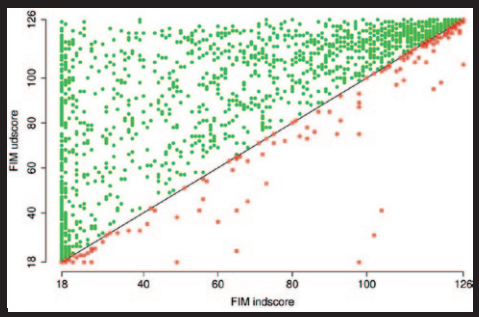






▲ Epileptic activity in (upper), and structure of (lower), a hippocampal pyramidal cell

▼ Plot of patient progress (acquired brain injury) at Hammel Neurorehabilitation Centre during the period 2002–2009. The X axis shows the function score (Functional Independence Measure) upon hospitalization, and the Y axis shows the function score upon discharge. The green colour indicates improvement; red indicates no improvement, or impairment.



CLINICAL NEUROPHYSIOLOGY

The human brain produces electromagnetic signals, both spontaneously and in reaction to sensory stimuli. Using a sophisticated magnetoencephalography (MEG) scanner it is possible to measure the magnetic fields by means of 306 sensors positioned on the head of a subject, thereby measuring brain-cell activity.

The MEG scanner is just one of many advanced technologies used at the Department of Neurophysiology to diagnose diseases and disorders of the brain, spinal cord, peripheral nerves, and muscles, and in the transmission between nerves and muscles.

One of the diseases we study at our department is amyotrophic lateral sclerosis (ALS), a rare disease which today carries a very poor prognosis and is fatal. Another main research area is epilepsy, a disease afflicting 50,000 Danes today. Most find some relief with medication, but surgery can become necessary if fits cannot be adequately controlled with drugs. At the department we are therefore seeking to identify the best and safest methods for selecting epilepsy patients for neurosurgical intervention.

Combining knowledge and technical skills
When assessing patient eligibility for epilepsy surgery, it used to be necessary to surgically open the skull so that electroencephalography (EEG) electrodes could be applied directly to the brain surface. With MEG scanning, which is unaffected by the skull, we expect to be able to obtain the necessary signals from the brain without surgical intervention during assessment – a considerably less invasive examination method. The MEG scanner is also used to map the brain's motor centres and sensory centres with a view to customizing brain-tumour surgery.

Aarhus University Hospital collaborates across departments to combine the hospital's extensive knowledge of the brain, and the many measurement methods applicable to the brain – MEG, EEG, transcranial magnetic stimulation, fMRI, CT, PET and SPECT, and more – to achieve the synergies that multimodal imaging of the brain's anatomy and functions can generate.

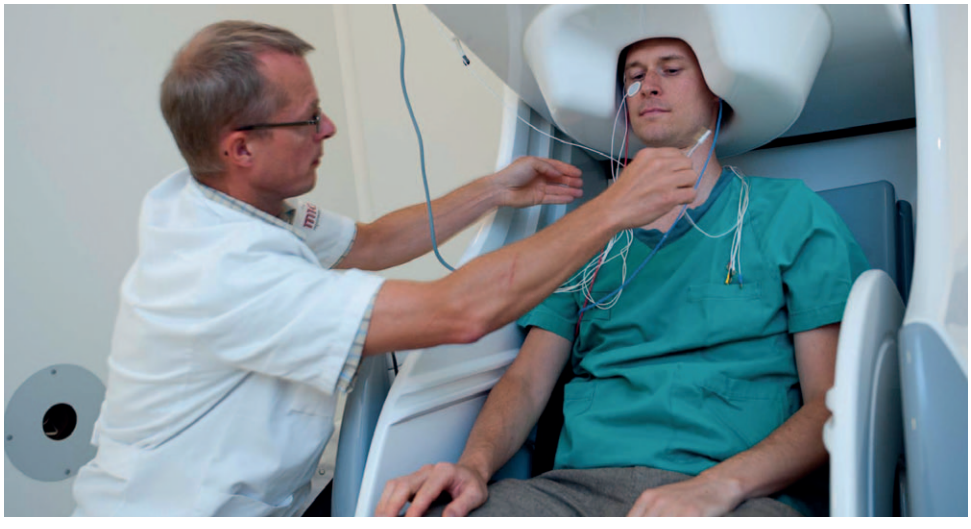
In the long term, research at the Department of Neurophysiology is expected to lead to greater insight and better treatments for other chronic diseases such as chronic pain, schizophrenia, depression, Parkinson's disease, movement disorders, and dementia.

PROJECTS

1. ALS and inflammatory polyneuropathies: electrodiagnostics, pathophysiology, and pathology are used to improve our understanding, and possible treatment, of the diseases.

2. ESTEEM, a European multicentre network for diagnostic guidelines and rare diseases in connection with nerve and muscle disorders (headed by Anders Fuglsang-Frederiksen).

3. SCORE, a European multicentre network for EEG in epilepsy (headed by Sándor Beniczky).



Simultaneous recording of MEG and EEG. (Photo: Michael Harder, Aarhus University Hospital)

4. MEG in connection with epilepsy: Exploring whether MEG can supplement EEG in diagnostic evaluation with a view to improved medical and surgical treatments.

5. Evaluation of peripheral and central factors in muscular pain by means of MEG, EEG, ENG, and EMG.

MILESTONES

The muscle's endplate, where the nerve branch attaches to the muscle fibre, is more sensitive to pain than other areas of the muscle – which may be part of the mechanism behind muscular pain conditions
(Qerama E, et al. Muscle and Nerve. 2004;39:393–400)

Automatic quantitative EMG in muscular dystrophy and other neuromuscular disorders is important for early diagnosis and potential treatment
(Fuglsang-Frederiksen A. Clinical Neurophysiology. 2006;117:1173–89)

In some patients with ALS, the sensory system appears to be affected, which can have an impact on prognosis and treatment
(Pugdahl K, et al. J Neurol Neurosurg Psychiatry. 2007;78:746–49)

The action potential in nerves and muscles is often used to determine the pathophysiology, and therefore the potential treatment, of polyneuropathy, but is shown here to be of no use for this purpose
(Tankisi H, et al. Clinical Neurophysiology. 2007;118:2383–92)

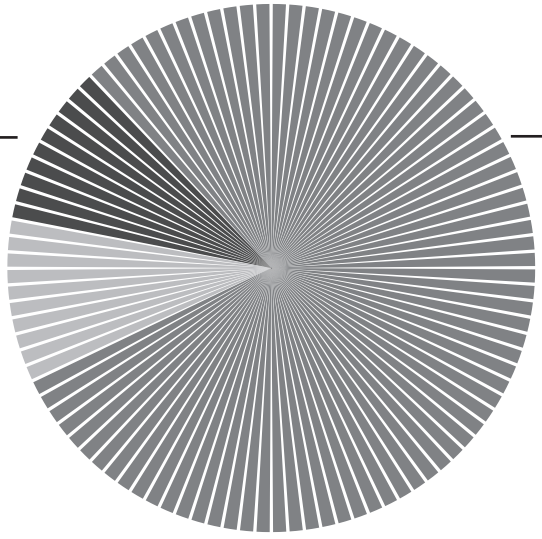
In the future, the changes in EMG compared with EEG during epileptic seizure can be used for diagnostic purposes
(Ilsa Conradsen, et al. Epilepsia. 2011;52:2125–32)

METHODS

The Department of Neurophysiology employs a wide range of advanced technologies to diagnose and study dynamic disturbances and diseases in the brain, nerves, and muscles.

- MEG – Magnetoencephalography
- EEG – Electroencephalography (24-hour video during EEG)
- IOM – Intraoperative monitoring
- EP – Evoked potentials
- MEP – Motor-evoked potentials
- ENG – Electroneuronography
- EMG – Electromyography
- Neurophysiological pelvic-floor examinations
- Neurophysiological eye examinations
- Ultrasound examinations of nerve entrapment

OVERVIEW



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EYE DISEASES

Vision is one of our most important senses, which makes the prevention and treatment of eye diseases and visual impairment extremely important. The eye can be divided into two parts: The anterior part consisting of the cornea, the pupil, and the lens, projects an image of the surrounding world onto the retina on the inner back wall of the eye. The posterior part of the eye consists of the retina, which converts the physical image into nerve impulses and sends these impulses to the brain. Our research is similarly divided into activities that target diseases in these two parts of the eye.

Research into the optics of the eye
We are leaders in femtosecond laser-based refractive surgery; a technique we have perfected to make it as minimally invasive as possible. Accordingly, we can now provide safe, precise, and effective treatment of refraction abnormalities in the eye. We also study the biomechanics of the cornea and have developed photochemical modelling of the cornea's mechanical properties. We extract stem cells from the peripheral surface of the cornea for cultivation. Our long-term aim is to be able to treat corneal diseases with cultivated stem cells, replacing the current procedure of corneal transplant from donor to recipient. We have established a cornea biobank for the purpose of extracting and cultivating stem cells. Our research into the lens and its diseases is aimed at improving the methods for calculating the refractive properties of artificial lenses inserted into the eye during cataract surgery.

Research into retinal diseases
Diseases in the anterior part of the eye are the most common cause of visual impairment and blindness in the Western world. These diseases are related to impairment of retinal blood flow. We have therefore set up a laboratory for vascular physiology where we investigate the regulation of retinal blood flow on porcine retinal tissue. The results of these studies have been translated into clinical trials.

The department also works with new optical methods to measure retinal oxygenation and diagnose morphological changes in individual retinal cells. We are furthermore developing new treatments of retinal diseases using gene therapy. Finally, we are working with mathematical models to calculate how often patients with chronic eye diseases should come for follow-up, to ensure that diseases are diagnosed while they are still treatable.

Proteome analysis
The purpose of our biochemical research is to identify proteins in the eye that can predict the risk of developing eye diseases. We are mapping markers for malignant melanoma of the eye with the purpose of preventing and treating this disease. In a recently completed project, we identified proteins that are particularly active in patients who develop retinal detachment.

PROJECTS

We collaborate with a wide range of partners:

Carl Zeiss Meditec, Jena, Germany; Schepens Eye Institute, Boston, USA; and the Laboratory for Stem Cell Research, Aalborg University.

Novo Nordisk, Denmark; ImagineEye, Paris; Oxymap, Reykjavik; University of Vienna; and Imedos, Leipzig.

University of Liverpool, UK; University of California, Santa Barbara, USA

Our many projects include the following:

1. Prospective study of femtosecond laser lensectomy.
2. The effect of UV riboflavin treatment on corneal swelling pressure and shear modulus.
3. Transcriptional profiling of corneal epithelial subpopulations in situ of Limbal Epithelial Stem Cells in culture under different growth conditions, using LCM and modified SAGE.
4. Autologous conjunctival ex vivo epithelial and goblet-cell expansion and matrix substitution for ocular surface transplants.
5. Studies of tone regulation in retinal arterioles and capillaries.
6. Studies of tone regulation in ciliary vessels.
7. Confocal microscopy of cellular components in retinal blood vessels.

8. Optimization of control intervals for patients with diabetic retinopathy.
9. Prognostic factors in the development of exudative age-related macular degeneration (AMD), for patients requiring treatment.
10. VEGF Trap treatment in diabetic retinopathy.
11. Diagnosis of retinal diseases using adaptive optics scanning.
12. Prevention of diabetic retinopathy using topical latanoprost.
13. Quantitation of fixation saccades.
14. Gene therapy for AMD.
15. Pharmacotherapy for pseudoxanthoma elasticum.
16. Proteome analysis as a diagnostic marker in choroidal melanomas.
17. Proteome analysis as a diagnostic marker in retinal detachment.

MILESTONES

ATP-induced relaxation of porcine retinal arterioles in vitro depends on prostaglandin E synthesized in the perivascular retinal tissue
(Holmgaard K, et al. Invest Ophthalmol Vis Sci. 2010;51:5168–75)

Topical treatment for 1 week with latanoprost, but not diclofenac, reduces the diameter of dilated retinal arterioles in patients with type 1 diabetes mellitus and mild retinopathy
(Tilma KK, et al. Acta Ophthalmol. 2011. Epub ahead of print)

A retrospective comparison of efficacy and safety of 680 consecutive lasik treatments for high myopia performed with two generations of flying-spot excimer lasers
(Gazieva L, et al. Acta Ophthalmol. 2011;89:729–33)

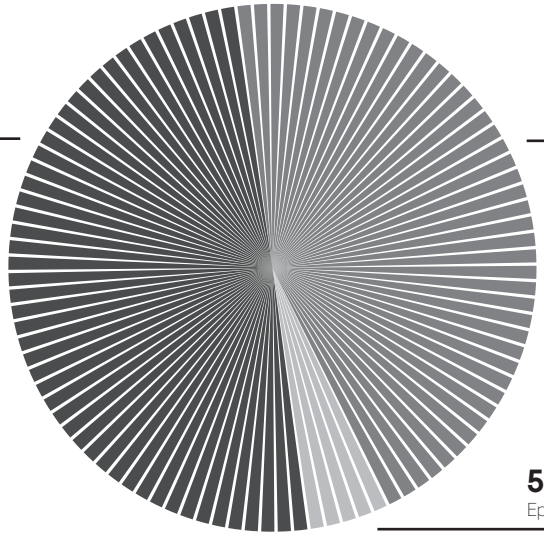
Visual acuity and contrast sensitivity after posterior lamellar keratoplasty
(Nielsen E, et al. J. Acta Ophthalmol. 2011)

Ocular proteomics with emphasis on two-dimensional gel electrophoresis and mass spectrometry
(Mandal N, et al. Biol Proc Online. 2009;12:56–88)

METHODS

- Cornea biobank – organ cultivation, ex vivo stem cell enrichment
- Femtosecond laser-based refractive surgery – methods for measuring the physiological, optical properties of the eye
- Corneal biomechanics – micro-material test equipment
- Ray-tracing-based calculation of the strength of individual artificial lenses in connection with removal of the eye's natural lens
- Methods for studying retinal blood flow in vitro. The method covers studies ranging from isolated vessels, over vessels with preserved perivascular tissue, and to the blood flow in complete microcirculatory units
- Retinal oximetry
- Adaptive optic scanning
- In vivo determination of diameter changes in retinal vessels
- Proteome analysis

OVERVIEW



50 %
Basic research

45 %
Clinical research

0 %
Qualitative research

5 %
Epidemiological research

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MULTIFUNCTIONAL BRAIN RECEPTORS

At Research Center MIND we are working to map the structure of the Sortilin/Vps10p-receptor family and shed light on cell biology and physiological functions. Cells – the smallest living units in all organisms – are surrounded by a cell membrane, and this membrane contains proteins that carry out various functions. One function is to act as receptors, which simply means they act as the body's signal receivers.

Sortilin/Vps10p-receptors were originally discovered at the Department of Medical Biochemistry at AU. They are located precisely in the cell membrane, notably in brain cells. These receptors play a role in transporting proteins through the cell membrane, and also in receiving signals destined for the cell. They are, for instance, involved in the human sensing of pain and tactile impulses; in the transmission of signals to the brain; and in the development of several diseases, among them Alzheimer's disease and ADHD. Furthermore, these receptors influence the amount of cholesterol in the blood, and the body's sensitivity to insulin. Consequently our research is not solely concerned with disorders of the nervous system, but also with other types of diseases.

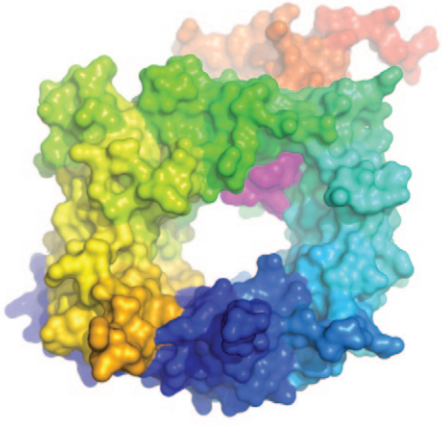
New knowledge about receptors in nerve cells

MIND mainly does basic research, for example in our cell-research projects, but we also serve as a central site that brings in other research done on the five known sortilins/Vps10p-receptors. Such projects may deal with genetically modified animal models, for example, or analyses of patient populations. MIND is the link that facilitates close contact among researchers in the field, thereby promoting the exchange of ideas and tools, as well as the exploitation of techniques and expertise aimed at eventually achieving an exhaustive description of the functions of these receptors in nerve cells and nerve tissue.

The close collaboration on sortilins among researchers at AU has already led to several breakthroughs in understanding the functions of this receptor family and their potential significance to the development of disease. Based on our results, the Lundbeck Foundation has provided funding in the form of two substantial five-year grants, enabling us to set up Research Center MIND and found a new field of international research, the epicentre of which lies at Aarhus University. In 2010, MIND hosted the first international conference on sortilins/Vps10-receptors; a gathering that attracted researchers from 20 different countries. The research results achieved thus far have paved the way for new insights into a number of disease mechanisms, and for possible treatments opportunities in the future.

PROJECTS

1. The role of sortilins/Vps10p-receptors in synaptic plasticity and memory processes in animal models, and their significance for the development of mental illnesses in humans.
2. Sortilins/Vps10p-receptors in the development of neuropathic pain in animal models, and the potential of receptors as drug targets in patients.
3. Crystallographic characterization of the molecular structures involved in receptor–ligand interactions.
4. The role of Vps10p-D receptors in the metabolism and regulation of neurotrophic ligands (such as NGF, BDNF, GDNF, and CLC/CLF) and their primary receptors.



Structure shown with the ligand-binding b-propeller in the foreground.

MILESTONES

The first identification and description of sortilins/Vps10p-receptors
(Jacobsen L, et al. JBC. 1996;271:31379–83; and Petersen CM, et al. JBC. 1997;272:3599–605)

Characterization of the conversion of newly-formed sortilin to the mature ligand-binding receptor, and of the receptor's sorting in cells
(Petersen CM, et al. EMBO J. 1999;18:595–604; and Nielsen MS, et al. EMBO J. 2001;20:2180–90)

Demonstration that Sortilin, along with (pro)NGF and its receptor p75, form a complex that induces death in nerve cells, both in vitro and in vivo
(Nykjær A, et al. Nature. 2004;427:843–8; and Jansen P, et al. Nature Neurosci. 2007;10:1449–57)

Determination of sortilin's crystal structure
(Qvistgaard E, et al. Nature Struct. & Mol. Biol. 2009;16:96–8)

Demonstration that Sortilin also mediates effects that promote growth and function in nerve cells
(Vægter C, et al. Nature Neurosci. 2011;14:10–24)

Establishment of Research Center MIND (in 2005) to investigate the function of sortilins/Vps10p-receptors. The activities at MIND are essentially funded by two five-year grants from the Lundbeck Foundation, awarded in 2005 and 2011, respectively, and each amounting to DKK 50 million.

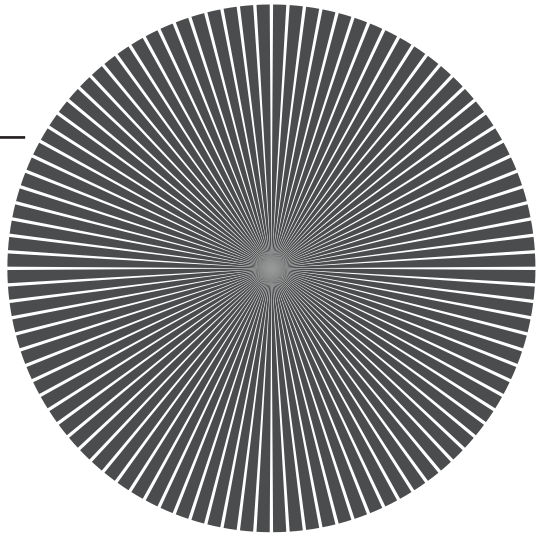
METHODS

We apply various techniques to clarify the molecular structure of the receptors we work with, their interaction with other proteins, and their function(s) within cells and within the living organism.

- Phenotypic characterization (including behavioural studies) of transgenic mouse models
- Cell biology studies Vps10p-D receptors in tissue and cultured wild-type cells, and in transfected and untransfected immortalized cell lines
- Large-scale affinity purification of receptors from tissue and cell lines
- Machine-based analyses of protein–protein interaction (using Surface Plasmon Resonance and Isothermal Titration Calorimetry)
- Immunofluorescence microscopy, including high-content screening microscopy
- Yeast two-hybrid screening

OVERVIEW

100 %
Basic research



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Qualitative research

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Epidemiological research

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Clinical research

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NEURODEGENERATIVE DISEASES

One of the great challenges facing the Danish health system is that we, the population as a whole, are becoming older and older – and that the understanding medical science has of the human brain largely builds upon research based on the young, smoothly working brain.

The research we have today lacks knowledge about the ageing, stress-affected, and dysfunctional brain and its relationship to the ageing body. In actual fact, no one knows what causes the death of cerebral nerve cells in patients with dementias or motor diseases like Alzheimer's and Parkinson's.

That is why we are asking questions such as these:

- How do we identify biomarkers that can reveal the early stages of neurodegenerative disease?
- Why is the brain unable to function properly if it accumulates misfolded proteins? Which types of misfolded proteins are detrimental, what damage do they cause, and how?
- How can we counteract disease that is already in progress – for instance using medication and vaccines?

Stressed-out nerve cells are better than dead ones to teach us about life

To learn more about neurodegenerative diseases, our research is probing into new territory, moving in directions that concentrate less on the nerve cell's moment of death, and more on the previous stages during which stress levels are on the rise. One of the common characteristics of dysfunctional cells is that they accumulate a number of misfolded proteins.

That is why some of our research investigates how brain cells interact with these misfolded proteins, as we seek to discover why they apparently act as a stress factor on the cells, and hence cause damage. Another important new insight into the ageing human brain is that the support cells that maintain a proper environment around the nerve cells seem to play a more important role than previously assumed, perhaps even driving the development of disease.

PROJECTS

1. To initiate effective treatment of Alzheimer's disease using the neuroprotective therapies of the future, the first step is to identify markers that can reveal the very early disease manifestations, before actual cognitive symptoms have yet arisen. We are therefore studying changes that take place in the early phases of Alzheimer's disease, examining brains from patients and from transgenic mouse models.

2. Parkinson's disease is caused by the slow-onset degeneration of dopamine-producing and non-dopamine-producing nerve cells. The consequences of α-synuclein being present in non-dopamine-producing neurones is being studied to understand the symptoms triggered by the two types of nerve cells (dopaminergic and non-dopaminergic).

3. Mishandling of α-synuclein in the nerve cells is decisive for the development of Parkinson's disease. We are therefore seeking new treatment goals based on modulating the aggregation and phosphorylation of α-synuclein, and also studying the dysfunctions triggered by α-synuclein.

   Because the immune system plays a part in the development of Parkinson's disease, we are studying the significance of the peripheral immune system and its interactions with the brain's own immune cells (microglia) when Parkinson's is present. The aim is to develop an immune-based therapy.

4. Parkinson's disease and Alzheimer's disease primarily develop in ageing brains. This project therefore studies whether disease causes dysfunction in specific age-dependent, neuron-protecting mechanisms, and whether they can be activated to safeguard the brain.

MILESTONES

Demonstration that the CA1 region of the hippocampus, in particular, suffers nerve-cell loss in Alzheimer's disease
(West MJ, et al. Lancet. 1994;344:769–72)

Demonstration that disease mutations inhibit α-synuclein in binding to brain vesicles
(Jensen PH, et al. J Biol Chem. 1998;273:26292–4)

Demonstration that axonal transport of α-synuclein primarily takes place as slow transport
(Jensen PH, et al. Eur J Neurosci. 1999;11:3369–76)

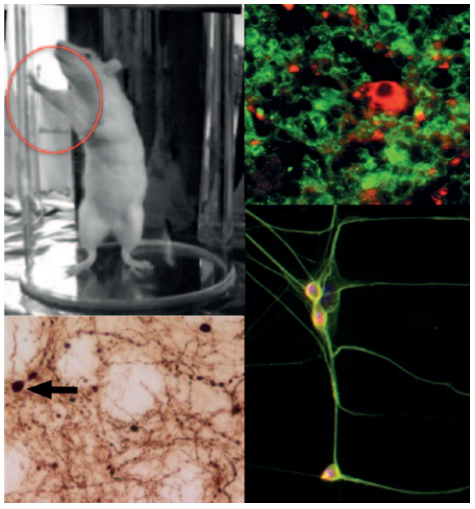
Demonstration that both aggregation and Serin129 phosphorylation is necessary for α-synuclein-dependent cell death
(Kragh CL, et al. J Biol Chem. 2009;284:10211–22)

The degree of α-synuclein-triggered neuropathology is shown to lead to different microglial activation patterns, which suggests that neuroinflammation is an active participant in the process
(Sanchez-Guajardo V, et al. PLoS One. 2010;5:e8784)

METHODS

To model Alzheimer's disease and Parkinson's disease, we use techniques that transfer genes coding for disease-regulating proteins to cultured brain cells and rodent models. Responses are subsequently determined at various levels, ranging from the genes themselves and all the way up to behavioural patterns.

- Development of viral and conventional gene expression vectors
- Development of antibodies against disease proteins
- Culturing, co-culturing, and genetic manipulation of cultured brain cells
- Transgenic mouse models and viral transgenic rat models based on stereotactic virus injection
- Gene expression analyses
- Proteome-based protein interaction analyses
- Immunomodulation, vaccination, and cell transplantation
- Motor-behaviour analyses of rodents
- Immunofluorescence microscopy, immunohistochemistry, and stereotaxis
- Cell-based screening of inhibitors of specific steps in pathological processes
- Histological and anatomical analyses of the nerve-cell pathology in human and animal brains
- Integrative analyses of behavioural, biochemical, gene-expression, and anatomical data from animal experiments

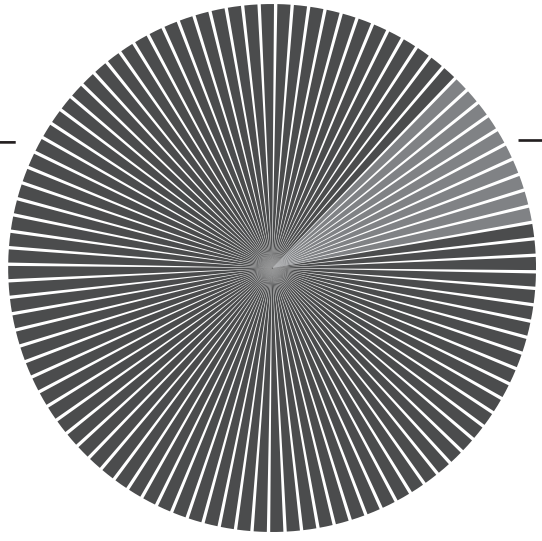


Neurodegeneration is studied at many levels: in the human brain, via animal behaviour and cerebral changes, and in the individual nerve cell.

OVERVIEW

90 %
Basic research

10 %
Clinical research



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Qualitative research

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Epidemiological research

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NEUROPHYSIOLOGY AND MUSCLE PHYSIOLOGY

The research conducted in this special competence area seeks to learn more about the principles of information transfer in neural networks, and about the activation mechanisms and function of skeletal muscles.

Most of the research revolves around two topics: The mechanisms underlying rhythmic brain activity in normal and pathological conditions such as epilepsy; and the fundamental principles for activating skeletal and cardiac muscle, with particular focus on what causes a loss of function in relation to diseases, strenuous work, and strain injuries.

For both of these focal topics, the research is aimed at clarifying the basic principles behind interneuronal communication and the activation of muscle cells. This involves electrophysiological, biochemical, and morphological investigations of the properties of individual nerve cells, neuronal networks, and muscle cells. The results from these investigations are, in turn, used to gain greater insight into the disorders and disturbances that cause neuronal and muscular dysfunction. The long-term goal and aspiration is to create a better basis for new treatment strategies and interventions targeting diseases of the brain and muscles.

Disrupted communication between nerve cells

Nerve cells primarily communicate by means of electrical signals, the transferral of which is normally subjected to rigid control. If signal transferral is disrupted, the result is dysfunction – for example hyperactivity – in the neuronal networks. Depending on which areas of the brain are affected, this can lead to epileptic seizures. A fundamental understanding of the dynamic processes that regulate neuronal communication is therefore a prerequisite for identifying new strategies in treating epilepsy.

Compromised muscle activation

Our research seeks new insights into the electrical function of cell membranes, and their significance for muscular function. Regardless of their origin, all conditions that cause the body's muscles to react inadequately to the brain's signals will give rise to increased fatigue and reduced functional capacity. In this context, our most recent findings suggest that in many cases, a loss of function arising from disease, work, or strain is associated with compromised activation of the muscles, rather than with an actual loss of their ability to contract. These findings include the first-ever demonstration that when muscle fibres are activated, the activation itself triggers the rapid closure of chloride channels in the cell membrane – implying that this regulation is critical in maintaining the electrical function of the body's muscles.

PROJECTS

1. Clarifying the role of dendritic L-type calcium channels in the formulation of theta oscillations in hippocampal CA1 pyramidal cells.
2. Clarifying the fundamental mechanisms behind the dissemination of epileptic seizure activity within, and between, cortical areas. Here the focus is on synaptic as well as non-synaptic factors.
3. Determining the significance of inadequate activation to the functional loss in muscles seen in connection with strain injuries, work, and pathological conditions such as myasthenia gravis, critical-illness myopathy, and hypothyroidism. This includes the development of a new treatment modality for myasthenia gravis.
4. Exploring the links between the electrical activation of muscles and the regulation of their function.
5. Developing mathematical models to describe the excitability of muscle fibres.

MILESTONES

Active propagation of action potentials in the dendrites of pyramidal cells
(Andreasen M, et al. Hippocampus. 1996;6:79–95)

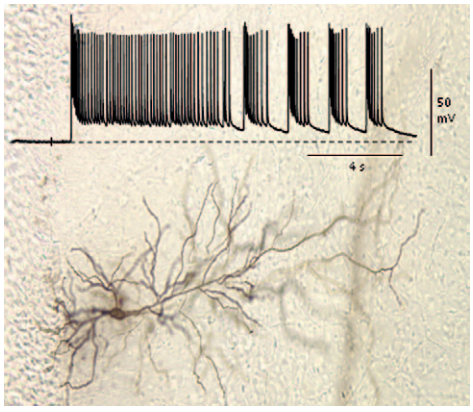
Demonstration of positive effects of lactic-acid accumulation on muscle function
(Nielsen OB, et al. Science. 2004;305:1144–7)

Demonstration of a positive effect of reduced pH and lactic acid on the electrical signalling in muscles
(Pedersen TH. J Gen Physiol. 2005;125:237–46)

Demonstration of an activity-induced regulation of the electrical signalling in muscles
(Overgaard K. Am J Physiol. 2001;280:R48–R55; and Pedersen TH, et al. J Gen Physiol. 2009;134:309–22; and Pedersen TH, et al. J Gen Physiol. 2009;134:323–37)

New principal for the regulation of neurotransmitter release in glutamatergic synapses
(Skov J, et al. Cell Mol Neurobiol. 2011;31:587–96)

The behaviour of individual neurons during epileptic seizure activity
(Andreasen M, et al. J Neurophysiol. 2011)



Epileptic activity in (upper), and structure of (lower), a hippocampal pyramidal cell

METHODS

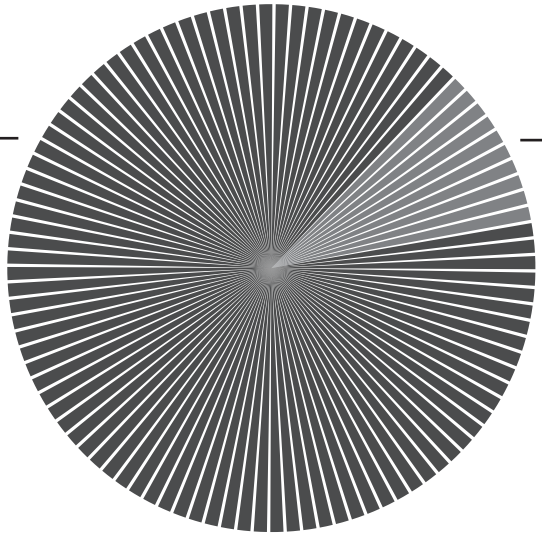
Highly advanced electrophysiological and histochemical techniques are used to examine fresh specimens from humans and laboratory animals.

- Electrophysiological recording techniques
- In vitro and in vivo cell studies
- In vitro epilepsy models
- In vitro models for muscular diseases
- Histochemical analyses
- Measurement of contractile force
- Measurement of ion channel function
- Isotope flux measurements
- Fluorescence microscopy

OVERVIEW

90 %
Basic research

10 %
Clinical research



0 %
Qualitative research

0 %
Epidemiological research

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NEUROREHABILITATION

Each year, approximately 19,000 Danes suffer an acquired brain injury, many as a result of stroke or trauma, for example in connection with an accident. In the short term, brain injuries can be life-threatening, but for most patients it is the physical and cognitive repercussions (or sequelae) that account for most of the complications. Examples are paralysis and walking difficulties, problems with loss of memory or speech, and loss of consciousness.

At Hammel Neurorehabilitation Centre, activities include prognostication, treatment of physical and cognitive sequelae following brain damage, and research into the pathophysiological mechanisms. The centre therefore offers a wide range of treatment modalities that employ a variety of special skills sets, methods, and techniques. Treatments include gait training using advanced technologies such as walking-rehabilitation robots, measurement of spinal reflexes in patients with physical impairments, and electrical measurements and imaging techniques for prognostic assessment of patients with cognitive brain damage.

Beyond the confines of the hospital

Clinical treatment and research are closely interconnected and also draw heavily on basic research. Hammel Neurorehabilitation Centre's multidisciplinary research and treatments involve physiotherapists and occupational therapists, neuropsychologists, speech therapists, and other staff groups. What is unique about the translational research at the centre is the way it combines crossdisciplinary quantitative research with more humanistic qualitative research. This combination brings new approaches to treatments, methods, techniques, and regimens.

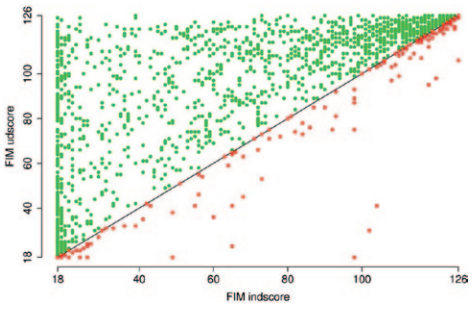
Most recently Hammel Neurorehabilitation Centre, along with the Department of Neurology at Health, has received a research grant to study motor rehabilitation of patients with paralysis, with special focus on physical training and gait training. In 2010 the centre in Hammel received the European Research Council Starting Grant for a research programme (MindRehab) that combines basic consciousness research with rehabilitation. We look at the treatment in its transitional phase: from intensive care to rehabilitation, and later to municipal care. There is a need for better coordination of the transitional stages between the different levels, especially in the handover to the municipal service providers. We therefore work with training regimens that reach beyond the confines of the hospital and also look at continuing education and competence development at a municipal level.

In the long term this will lead to better, cheaper, and more effective treatment of patients, both in and out of hospitals.

PROJECTS

Examples of current and future projects:

1. A combination of concentrated resistance training and treadmill training as part of municipal rehabilitation programmes
2. Changes in GABA activity before and after focussed hand training (fMRI and spectroscopy studies)
3. The effect of neurological rehabilitation on patients with sequelae from subarachnoid haemorrhage
4. Studies involving blindsight and visuospatial neglect in patients with impaired consciousness



Plot of patient progress (acquired brain injury) at Hammel Neurorehabilitation Centre during the period 2002–2009. The X axis shows the function score (Functional Independence Measure) upon hospitalization, and the Y axis shows the function score upon discharge. The green colour indicates improvement; red indicates no improvement, or impairment.

MILESTONES

Short-latency crossed spinal responses are impaired differently in subacute and chronic stroke patients
(Stubbs PW, et al. Clin Neurophysiol. 2011. Epub ahead of print)

Impulses of activation but not motor modules are preserved in the locomotion of subacute stroke patients
(Gizzi L, et al. J Neurophysiol. 2011;106:202–10)

Baseline GABA concentration and fMRI response
(Donahue MJ, et al. Neuroimage. 2010;53:392–8)

Phase modulation of the short-latency crossed spinal response in the human soleus muscle
(Stubbs PW, et al. J Neurophysiol. 2011;105:503–11)

Measuring consciousness: task accuracy and awareness as sigmoid functions of stimulus duration
(Sandberg K, et al. Conscious Cogn. 2011;20:1659–75)

Measurements of consciousness in the vegetative state
(Overgaard M, et al. Lancet. 2011;Nov 9. Epub ahead of print)

Integrating situated learning theory and neuropsychological research to facilitate patient participation and learning in traumatic brain injury rehabilitation patients
(Aadal L, et al. Brain Inj. 2011;25:717–28)

Aspects affecting occupational therapists' reasoning when implementing research-based evidence in stroke rehabilitation
(Kristensen HK, et al. Scand J Occup Ther. 2011. Epub ahead of print)

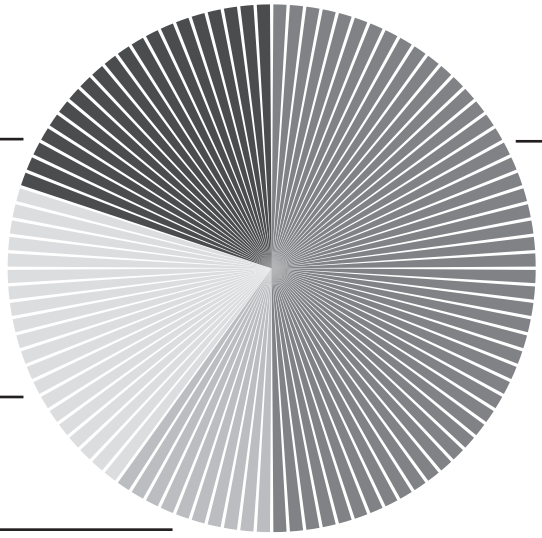
Increased power generation in impaired lower extremities correlated with changes in walking speeds in subacute stroke patients
(Brincks J, et al. Clin Biomech. 2011. Epub ahead of print)

METHODS

We use various methods to illustrate motor control, neuroplasticity, and consciousness phenomena, and also apply qualitative research methodologies.

- Methods for quantifying spinal gait reflexes (stretch reflex/H-reflex)
  Event-related potentials (ERP and MMN)
  Quantitative EEG
  Optokinetic gait analysis
  Clinical function scores, cognitive scores and test batteries
  Transcranial magnetic stimulation (TMS)
  Direct current stimulation
- MRI spectroscopy
- Semi-structured interviews focussing on the relationship between patients and relatives
- Questionnaire survey of long-term effects

OVERVIEW



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NEUROSURGICAL INTERVENTIONS

The focus of our research is the study of neurosurgical treatments for a number of different brain diseases and nervous-system injuries. This covers everything from neurosurgical treatment of serious brain damage following haemorrhage or traffic accidents to brain tumours and minor surgical procedures such as slipped discs and osteoarthritis of the back. We also study malformations of the central nervous system, hydrocephalus, chronic pain, and neurodegenerative diseases such as dementia and Parkinson's disease. We use neuromodulation with spinal-cord stimulation to treat chronic neurogenic pain.

We constantly strive to improve treatments. Consequently, we conduct basic research into the brain's functions at cellular and molecular levels – both to understand the effect of existing forms of treatment and to develop new treatment modalities.

New technology paves the way for new treatment modalities

Surgical intervention in the brain requires precision and the use of advanced technical equipment such as MRI scanning to create three-dimensional modelling of the head. We use the latest technology in our treatments, and in our research as well. Advanced computer calculations based on MRI scans can produce images of the fibre pathways in the brain. That means we can now perform high-precision brain surgery that bypasses the fibre pathways, thereby reducing the risk of permanent damage to the patient. It is also possible to remove malignant brain tumours with a high degree of precision using MRI scanning, microscopic fluorescence, and microsurgery techniques. Moreover, keyhole surgery now enables us to look into the cranial cavity to remove tumours and cysts and create new drainage pathways for removal of excess fluid in hydrocephalus patients.

Neuromodulation treatment with spinal-cord stimulation and Deep Brain Stimulation (DBS) can be used in a number of areas. We use the methods in large animal models for neurodegenerative diseases such as Parkinson's disease and dementia, and also in models for pain, eating disorders, bladder dysfunction, and high blood pressure. Neuromodulation with spinal-cord stimulation can also be employed to treat pain and depression. We are currently developing new DBS techniques in collaboration with Oxford University and several private-sector companies.

A multidisciplinary research function

The Department of Neurosurgery has established a multidisciplinary research function to promote mutual inspiration and collaborative research and development efforts among medical and nursing staff, which will benefit future patients and their relatives. This includes targeted development of nursing care through research, quality improvement, quality assurance, and documentation.

PROJECTS

1. Optimization and development of stereotactic techniques for DBS treatment of patients with Parkinson's disease.
2. Development of minipig models to illustrate the mode of operation, neuroprotective aspects, and future fields of application for DBS.
3. Development of a microinjection device for transplanting stem cells to the central nervous system.
4. Development of MRI-compatible equipment for stereotaxic surgery on large experimental animal models.
5. Spinal Cord Stimulation (SCS) for chronic pain conditions, including the development of a minipig model for SCS.
6. Development of computer-assisted neurosurgery for resection of brain tumours using advanced imaging modalities.
7. Implantation of encapsulated growth-factor-producing cells in the brains of minipigs. A preclinical model for the treatment of dementia, Parkinson's disease, and epilepsy.
8. Bladder reinnervation in patients with spinal-cord injuries.
9. Early rehabilitation of patients with post-traumatic amnesia.

MILESTONES

1996: Introduction of DBS in treating Parkinson's disease and essential tremor in Denmark
(Ostergaard K, et al. Ugeskr Laege. 2000;162:5491–6)

2004: Development of MRI-guided stereotaxic surgery on large animal models
(Bjarkam CR. Dan Med Bull. 2004;51:311. PhD thesis, Aarhus University)

2008: Establishing a large animal model for Parkinson's disease
(Nielsen MS, et al. Deep Brain Stimulation: Applications, Complications and Side Effects. Nova Science Publishers; 2008)

2008: Proof of safety in nerve growth treatment (NGF) of Alzheimer's disease in a large animal model – collaboration with NsGene
(Fjord-Larsen L, et al. Mol Ther. 2010;18:2164–72)

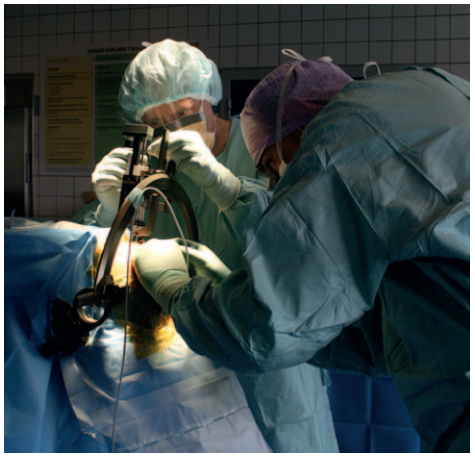
2009: Establishing a large animal model for neurostimulation treatment of bladder dysfunction
(Jensen KN, et al. Acta Neurochir. (Vienna) 2009;151:785–94)

2010: Efficacy of reality-oriented nursing care of patients with post-traumatic amnesia (PTA)
(Langhorn L. PhD thesis, Aarhus University)

METHODS

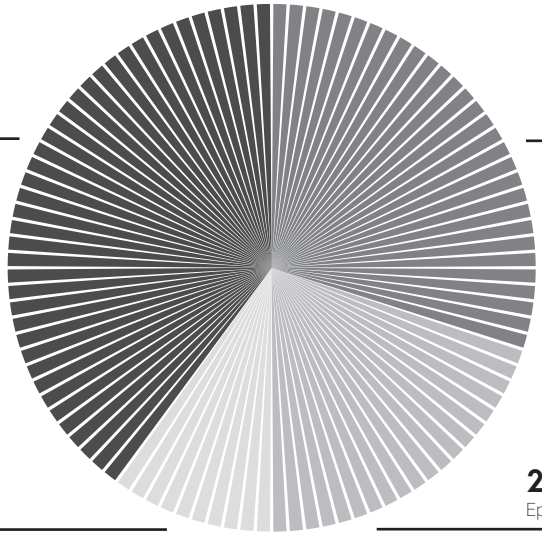
The Department of Neurosurgery has expert capabilities in all the standard neurosurgical techniques, supported by advanced imaging diagnostics, computer navigation and keyhole surgery.

- Microscopic, microsurgical and fluorescence-guided removal of malignant glioma
- Stereotaxic surgery for brain biopsies and embedding of depth electrodes for DBS
- Neuronavigation for high-precision surgery, including the treatment of brain tumours. Diffusion Tensor Imaging (DTI) for fibre tracking of nerve pathways in the central nervous system
- Craniofacial surgery for facial skeletal malformations and facial trauma
- Bypass surgery of complicated vascular malformations in the brain
- Keyhole surgery to treat hydrocephalus conditions
- SCS and DBS to treat chronic pain conditions
- Reality-oriented nursing care in the treatment of patients in the post-traumatic amnesia (PTA) phase
- Animal modelling of neurological and psychiatric conditions.



Stereotaxic embedding of electrode for deep brain stimulation to treat chronic pain.

OVERVIEW



40 %
Basic research

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Clinical research

10 %
Qualitative research

20 %
Epidemiological research

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PAIN

Pain can be a normal sensation as well as a symptom of disease. According to the International Association for the Study of Pain (IASP), pain is defined as "a sensory and emotional experience of actual or potential tissue damage or an experience expressed in such terms". Due to its subjective nature, pain is difficult to measure and observe objectively.

Pain is never the same, and many factors influence our perception of it. In addition to physical factors, the body's own pain-relieving mechanisms, in the form of morphine-like signal substances called endorphins, also greatly affect our pain perception. The placebo effect, which plays a key role in many chronic pain conditions, involves the activation of the human body's own endorphins.

At the Danish Pain Research Centre, we try to objectively describe subjective pain and understand some of the many mechanisms behind it. We especially work with issues relating to nervous-system injuries, including pain in the central and peripheral nervous systems. Examples are pain following surgery, phantom pain, spinal cord injuries, multiple sclerosis (MS), and patients experiencing pain after a stroke. Another major focus area for the pain research group involves signal substances that play a role in migraine and other types of headache.

A multi-pronged attack

We are a leader in the field of neurogenic pain, thanks to the excellent multi-disciplinary collaboration involving clinical work and patient care, as well as more basic laboratory research that works with animal models and the identification of biomarkers. The nervous system is selective, and it sends different forms of sensory messages to the brain via specific nerve pathways. That is why we also use a number of different forms of sensory exposures such as heat/cold stimuli and chemical, electrical, and mechanical exposures. To understand the nervous system's reaction to pain, it is necessary to study both healthy subjects and patients. In that way we can quantify pain and measure pain thresholds and pain perception under different circumstances.

We have several areas of expert competence. One area is the so-called autonomous nervous system – the part of the nervous system that lies beyond our control. Another area involves the brain's reaction to pain. Here we use neurophysiological methods and imaging techniques like MRI and PET. These techniques make it easier for us to understand the complex relationship between different parts of the brain, and we hope this will enable us to understand how fear, pleasure, and anxiety affect our perception of pain.

PROJECTS

1. **Pain after surgery** (thoracotomy, hip surgery, and amputation, for example). We study the occurrence of chronic pain following surgery. We examine signal substances in severed nerves after different surgical procedures; the potential importance of these signal substances for pain and changes in sensitivity; and how they can be inhibited using sodium-channel blockers.
2. **Chemotherapy-induced pain.** Platinum, taxane, and a number of other chemotherapy drugs are neurotoxic and in some cases cause nerve pain due to neuropathy. We are studying the occurrence of pain and the potential correlation between sensitivity thresholds and the number of nerve fibres in the skin of patients receiving chemotherapy treatment.
3. **Pharmacological treatment of sensitized nociceptors.** Previous studies have shown that the sensitization of pain-sensitive nerve endings (nociceptors) and so-called central sensitization are key mechanisms in the development of pain following nerve damage. A large multi-centre study, which we are managing in an EU-financed project, looks at the role of "sensitized" versus "non-sensitized" nociceptors in the development of neurogenic pain.
4. **Emotions and pain.** We study the correlation between emotions and pain in experimental studies in humans and animals. In human studies we test whether unpleasant and pleasant visual and gustatory stimuli can affect the pain threshold, and in animal experiments we also study this complex relationship in other models.

MILESTONES

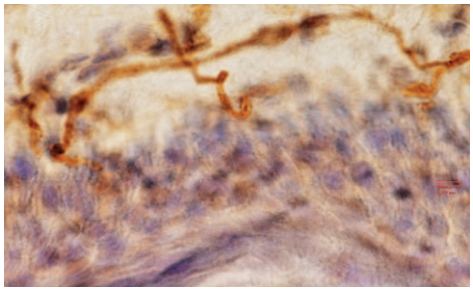
The occurrence of central pain following cerebral apoplexy
(Klit H, et al. PLoS One. 2011; 6: e27607. Epub)

Demonstration of the reaction of the autonomous nervous system to mental stress and tilt-table testing, in patients with reflex dystrophy and healthy subjects
(Terkelsen AJ, et al. Anesthesiology. 2011. Epub)

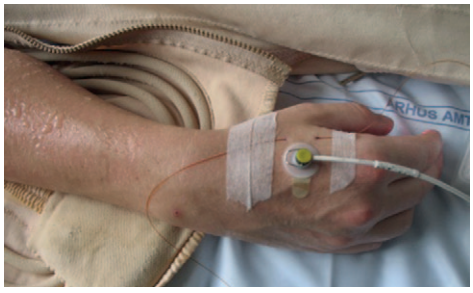
A reduction of excitatory substances in the nervous system can reduce the pain reaction in rats with experimental bone-marrow injury
(Baastrup C, et al. Brain Res. 2011;1370:129–35)

The cognitive condition of the brain can affect the neurophysiological reaction of the bone marrow to mechanical stimuli in patients with phantom pain following amputation
(Vase L, et al. Pain. 2011;152:157–62)

Meta-analysis that documents the effect of pharmaceuticals in the treatment of neurogenic pain conditions on the basis of NNT and NNH
(Finnerup NB, et al. Pain. 2010;150:573–81)



Dermal microdialysis to determine noradrenaline.



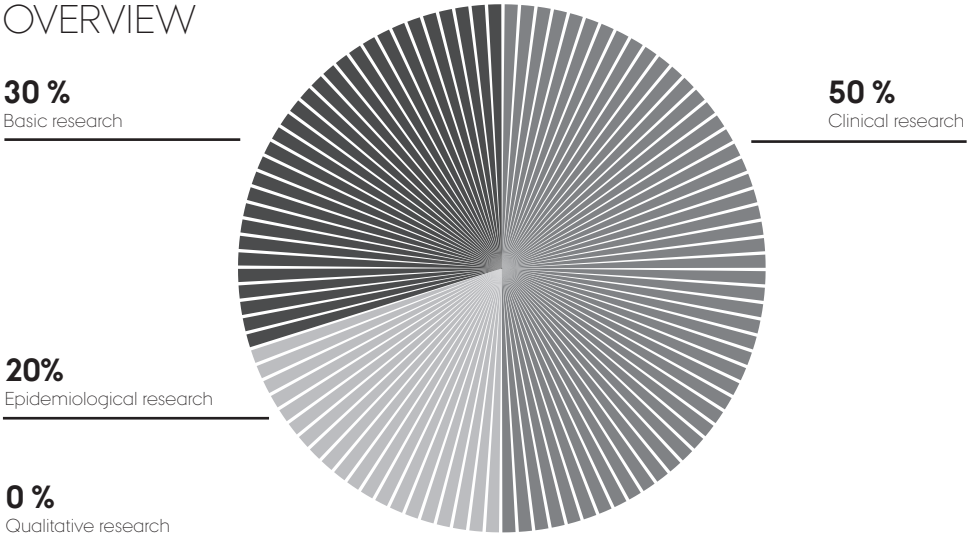
Small (C/Ad) [HFL1] nerve fibres in the skin.

METHODS

A number of different methods are used to record the body's reaction to pain stimuli.

- The brain's response to contact-heat evoked potentials (CHEPS response)
- 3-mm skin biopsies for quantification of the density of nerve fibres (c-fibres)
- Sweat response (QSART), muscle oxygenation (NIRS), heart-rhythm measurement, and tilt-table testing
- Dermal microdialysis, including catecholamine measurements
- Whole-body cooling/warming ("physiological locking" of the autonomous nervous system)
- Quantitative sensory testing (QST)
- Capsaicin tests and other pharmacological provocation studies of impacts on small nerve fibres
- Reflex and behaviour as measurement parameters in rodents with experimental nerve injury

OVERVIEW



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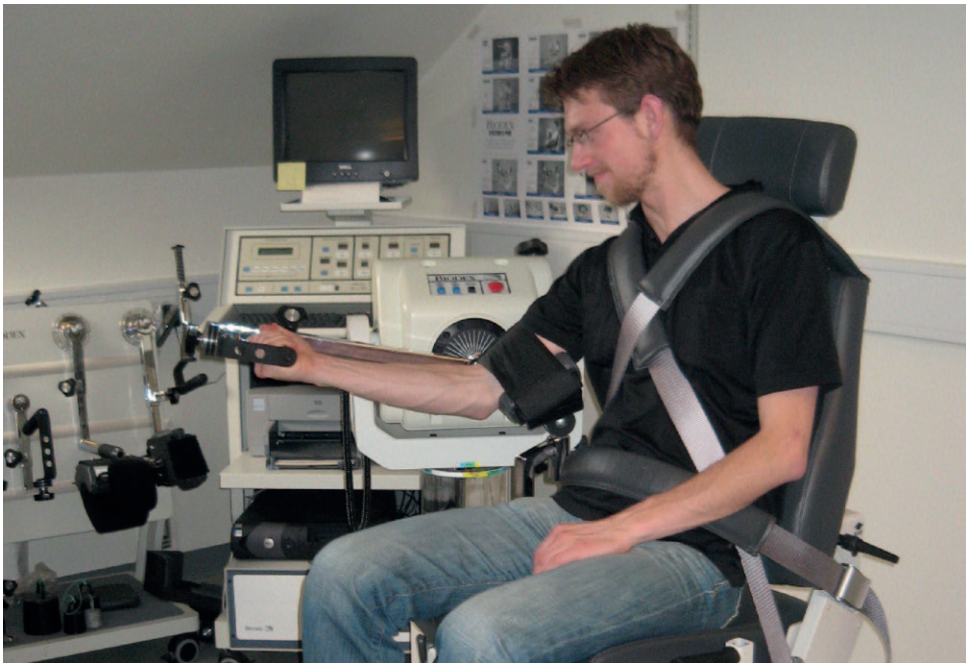
TRANSLATIONAL NEUROSCIENCE

Neurological diseases lead to increased mortality and severe physical and mental disabilities, making such conditions a challenge for individual patients and for society. Each year about 12,000 Danes suffer cerebral thrombosis (a blood clot in the brain), and approximately the same number are affected by dementia. The country has 8000 citizens living with multiple sclerosis (MS), and over 20,000 with neuromuscular diseases.

In our field, research and treatment are intimately linked, and we particularly focus on treatment of these three types of disease.

A leader in cerebral thrombosis
In the treatment of cerebral thrombosis we are currently implementing a decisive new development, the goal of which is that stroke patients recovering from cerebral thrombosis can avoid paralysis and speech difficulties. The quicker treatment is initiated, the quicker we can dissolve or extract the blood clot, thereby limiting damage to the brain. We are at the international forefront in this area, having put in place a rapid-response service that can carry out treatment within six hours, regardless of where the patient is physically located in western Denmark. The regional emergency helicopters are a part of this rapid-response service.



Determination of nerve and muscle functions.

As concerns neuromuscular diseases, we focus on the complications arising from diabetes and in connection with the immune-mediated neuropathies that lead to muscular dystrophy. Here we are interested in determining which growth factors and which immune-regulating molecules affect the nerves and muscles, seeking in this way to develop a treatment for these types of muscular dystrophy and paralysis.

We also conduct research in the treatment of MS, a diagnosis that almost 500 Danes receive every year. A variety of different treatments are available today, and are usually effective, but they can lead to serious side-effects and attendant conditions. Our goal is to develop one treatment that has no undesirable effects. In order to achieve this, we must attain a better understanding of why some people develop MS, so that in the long term we will be able to cure patients when they initially become ill, or before they develop symptoms.

PROJECTS

1. A placebo-controlled randomized study examines whether brief periods of ischaemia in the extremities (remote conditioning) reduces the size of the infarction following apoplexy.

2. A placebo-controlled randomized study investigates whether subcutaneous treatment with immunoglobulin is effective in chronic inflammatory demyelinating polyneuropathy (CIDP).

3. A clinical physiological study explores muscle strength and fatigue in patients with myasthenia gravis, and the effect of pyridostigmine.

The significance of sub-groups of "natural killer" cells is examined by means of multicolour flow cytometry and a developed dose-response model in patients with MS.

MILESTONES

MRI scanning with determination of water diffusion predicts the effect of thrombolysis during the 3-hour window following apoplexy
(Sølling C, et al. Cerebrovasc Dis. 2009;27:223–9)

Demonstration of a lack of neutroph-3 in weak muscles in connection with diabetes
(Andreassen CS, et al. Brain. 2009;132:2724–33)

Treatment with immunoglobulin in patients with chronic immune-mediated polyneuropathy reduces the number and the toxicity of "natural killer" cells
(Bohn AB, et al. Eur J Neurol. 2011;18:919–24)

Treatment with subcutaneous infusion of immunoglobulin in patients with chronic immune-mediated polyneuropathy (multifocal motor neuropathy, MMN) reduces the loss of muscle strength
(Harbo T, et al. Neurology. 2011;75:1377–80)

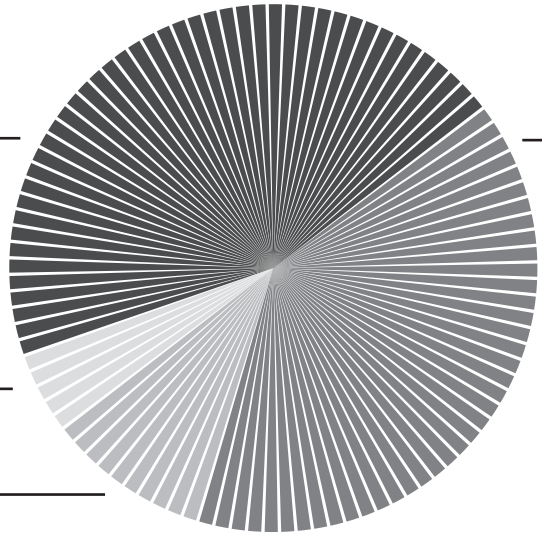
In patients with MS, immunocompetent cells recognize a peptide fragment of the Epstein-Barr virus
(Jørgensen PB. In press)

METHODS

The methods applied are partly used to define markers and key factors in the development of disease, and partly used to test whether new pharmacological and physical principles can be employed to treat patients.

- Clinically controlled treatment studies and clinical pathogenic studies in all three disease areas
- Imaging using MR technology to determine infarction formation in cases of apoplexy, the volume of plaque in MS, and the loss of muscle tissue in neuromuscular diseases
- Determining receptor binding and signal-molecule metabolism using positron emission tomography (PET) to characterize the significance of serotonin in apoplexy, dementia, and depression
- Determining the role of the immune mechanisms in MS by characterizing peptides and epitopes that are a part of the Epstein-Barr virus
- Determining nerve and muscle functions using electrophysiological methods and dynamometry to study neuromuscular diseases

OVERVIEW



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Basic research

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Clinical research

5 %
Qualitative research

10 %
Epidemiological research

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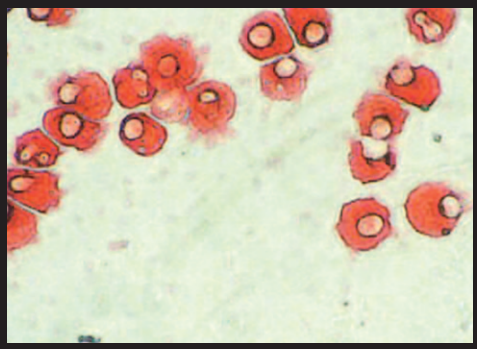
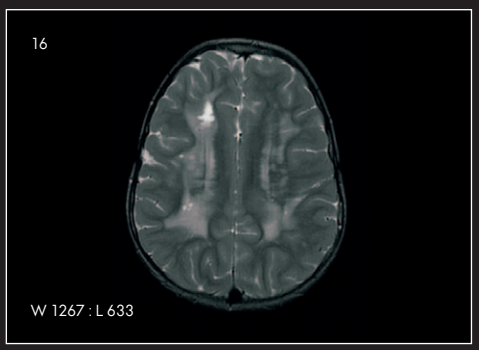
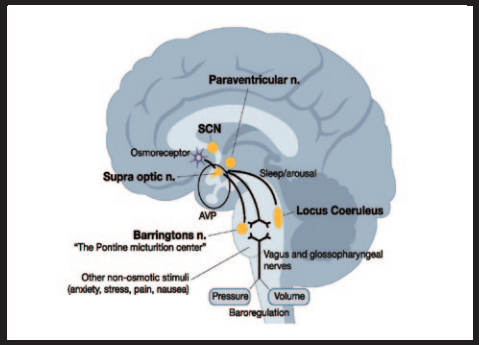
OBSTETRICS AND PAEDIATRICS

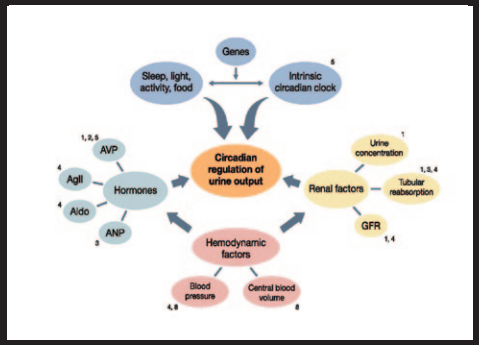


▲ We can cultivate mast cells by the millions and examine them to shed light on their activation mechanisms.

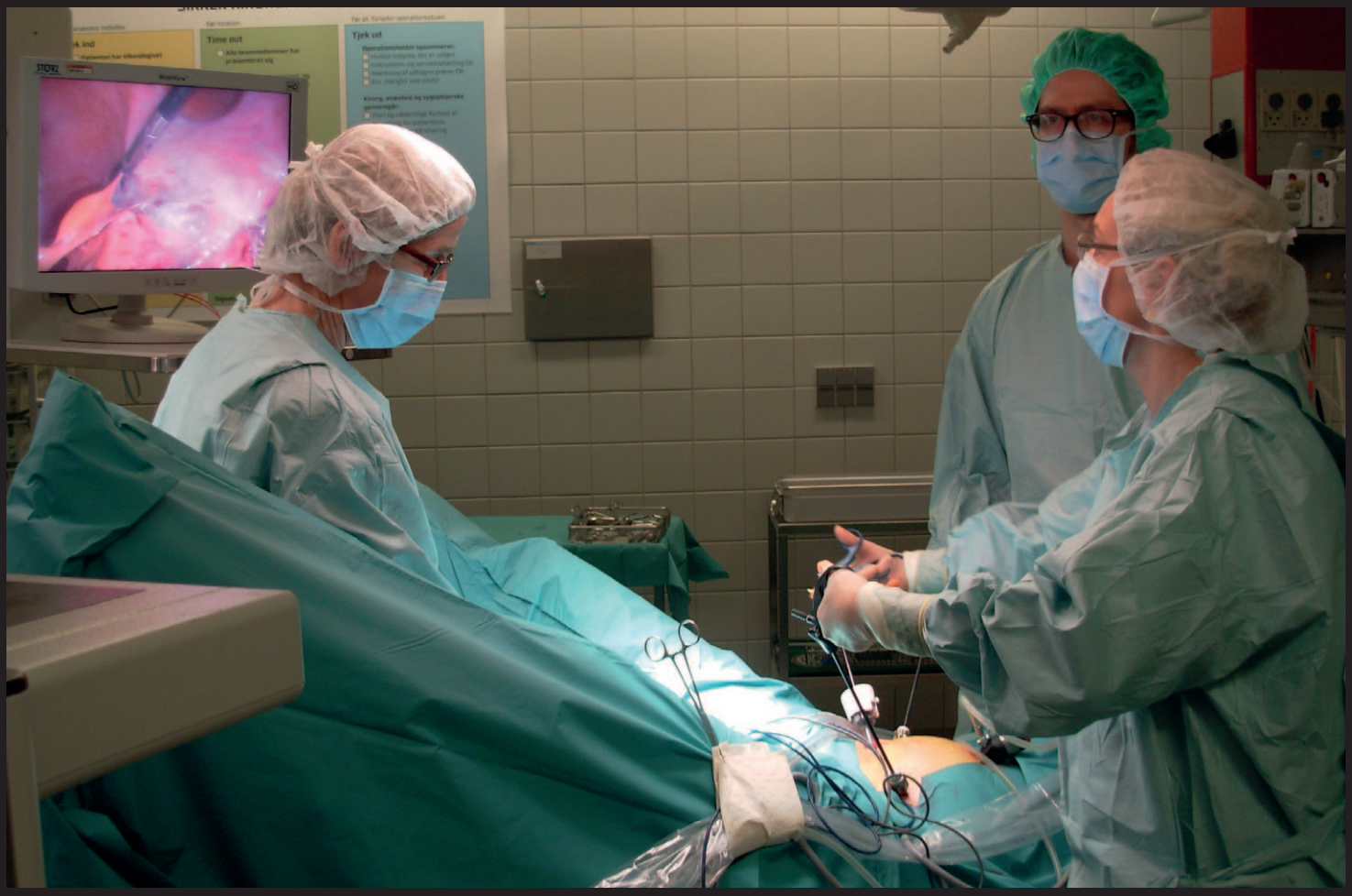


▲ White matter signal changes due to a cerebral angiopathy in a child with ACTA 2 R179H mutation.





◄ Our research group has focused on mechanisms behind nocturnal polyuria in enuresis such as genes, the antidiuretic hormone, renal factors, and nocturnal blood pressure regulation.



▲ Laparoscopic surgery for deeply infiltrating endometriosis

CHILD NEUROLOGY

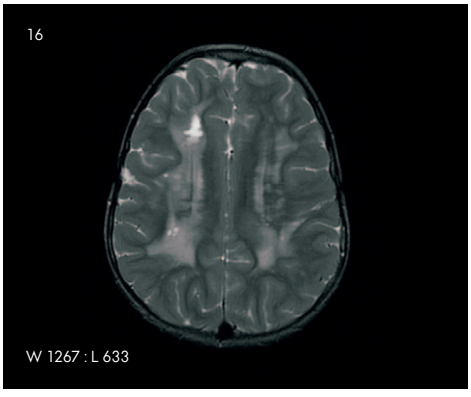
Developmental disabilities in children can be regarded as a product of genes and, to a lesser extent, of intrauterine life. Brain and heart development occur simultaneously in the human foetus through the orchestration of complex genetic programmes, followed by periods of morphological refinement in response to physiological function.

The developing brain is highly metabolic and dependent upon the heart for delivery of oxygen and nutrients. The heart in turn receives innervations and control from the autonomic nervous system. Given the complexities of these shared morphogenetic programmes, it is not surprising that disruption of organogenesis in one organ can have significant effects for the other.

To evaluate the genetic impact on brain organogenesis in children with congenital heart disease (CHD), we investigate brain growth in CHD-children with and without genetic abnormalities. Especially imprinted genes have a great impact on intranatal and postnatal growth and brain development. Another scientific focus area is making comparisons between genotype and phenotype in developmental disability syndromes with either an absence or a surplus of imprinted genes, as in Angelman syndrome and Prader-Willi syndrome. These studies yield new information about language development, the occurrence of epilepsy, and behavioural disorders.

Cerebrovascular diseases

Recently, we reported that de novo mutation in ACTA2 (R179H) causes a syndrome characterized by dysfunction of smooth muscle throughout the body, leading to aortic and cerebrovascular disease, fixed dilated pupils, hypotonic bladder, malrotation, and hypoperistalsis of the gut, as well as pulmonary hypertension (Multi Systemic Smooth Muscle Dysfunction Syndrome; OMIM #613834). The distinctive cerebrovascular features observed were dilatation of the proximal internal carotid artery (ICA), occlusive disease of the terminal ICA, and an abnormally straight course to the intracranial arteries, which therefore resembled the foetal brain arteries. A transgenic mouse model is on the drawing board and may provide a basis for in vivo and in vitro studies of this newly discovered condition.



White matter signal changes due to a cerebral angiopathy in a child with ACTA 2 R179H mutation.

PROJECTS

Other ongoing projects include:

1. 22q11.2 deletion and duplication: Cardiac and epidemiological aspects.
2. Moebius syndrome: The incidence and course of the disease.
3. Effects of the increased use of gestures and body language in social interaction by individuals with Moebius syndrome.
4. Genetic studies on HEMS (Hypomyelination of Early Myelinating Structures), a novel leukoencephalopathy affecting early myelinating brain structures.
5. Behavioural disturbances in children with neurofibromatosis type 1.
6. Neurocognitive phenotype, neuroradiological and genetic aspects of Klinefelter syndrome.
7. Disturbances in tooth development in children prenatally exposed to antiepileptic drugs.
8. Gross motor function and its correlation to accompanying disabilities in children with Cerebral Parese.

MILESTONES

Scientific landmarks:

Risk factors in intracranial saccular aneurysms
(Østergaard JR. Acta Neurol Scand. 1989;80:81–98)

A different view of ophthalmoplegic migraine
(Østergaard JR, et al. Cephalalgia. 1996;16:276–9)

Autism and Angelman syndrome
(Trillingsgaard A, Østergaard JR. Autism. 2004;8:163–74)

Mortality in children with febrile seizure
(Vestergaard M, et al. Lancet. 2008:372:457-463)

Multisystemic smooth muscle dysfunction syndrome
(Milewicz DM, et al. AmJ Med Genet. 2010;152A:2437–43)

Cardiac involvement in Battens disease
(Østergaard JR, et al. Neurology. 2011;76:1245–51)

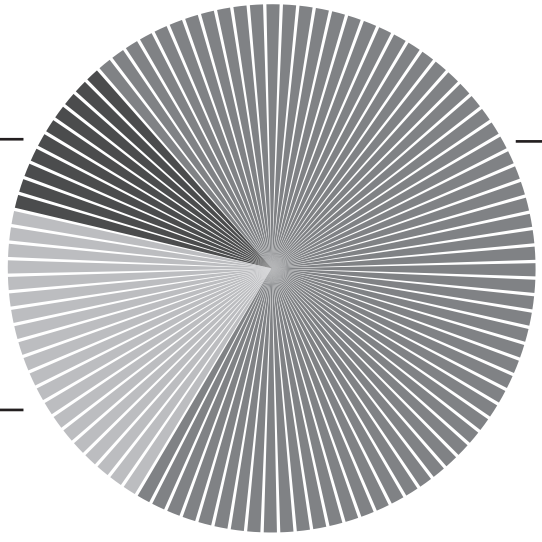
Scientific acknowledgements:

Membership of the "Hall of Fame" within the European Association of Rare Diseases (2010)

UCB Nordic Epilepsy Award (EUR 15,000) (2010)

Nomination for the Eurodis Scientific Award (2011, 2012)

OVERVIEW



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Basic research

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Clinical research

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Epidemiological research

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Qualitative research

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john.oestergaard@skejby.rm.dk

GYNAECOLOGY

Lower abdominal and pelvic pain in women is a prevalent phenomenon, and one of the main things causing it is endometriosis. Normally, the mucosal lining of the uterus (the endometrium) is discharged during menstruation, and in many women some of the resultant menstrual flow exits through the fallopian tubes, accompanied by tiny endometrial fragments.

These fragments of tissue lodge within the abdominal cavity, causing bleeding and local inflammation, and potentially leading to chronic pain and an inability to conceive.

Research into the causes of the condition, and new types of diagnosis and treatment
We know that endometriosis is, to a certain extent, hereditary. However, we do not yet fully understand the disease mechanisms behind it. The gynaecology and obstetrics research group at the Department of Clinical Medicine, working with the university hospital's clinical and immunology departments, has identified a gene that (most probably in combination with other genes, as yet unknown) indicates a predisposition for endometriosis. We have further been able to demonstrate changes in growth factors in the endometrium – following an extensive research project based on meticulous examinations of tissue and blood samples from patients and healthy control subjects. We will also be participating in an international collaborative effort to further investigate this topic. In addition, we are seeking to find out why the uterus transports blood and tissue fragments through the fallopian tubes and into the abdominal cavity, which may enable us to prevent endometriosis from arising, if we can block it at this early stage.

Diagnosing severe endometriosis involves the application of magnetic resonance (MR) diagnostic techniques. In connection with endometriosis we have demonstrated that the endometrium itself prominently infiltrates the uterine musculature, substantiating the theory of a particularly aggressive growth pattern.

Very early on we introduced laparoscopic surgery for endometriosis intervention and today, in cooperation with leading colorectal surgery departments, we also use more radical surgical procedures.

Finally, we conduct research to improve life for those patients who, despite the application of all known interventions, still end up with a chronic pain condition. Working alongside clinical psychologists, we have conducted a pilot study to test whether mindfulness therapy can improve patient quality of life. This work is now being followed up with a randomized clinical trial. We are moreover collaborating with a leading medical centre in Switzerland on research to block pain signal pathways using electrostimulation of the pelvic nerves.

PROJECTS

1. **Laparoscopic rectal resection in cases of rectovaginal endometriosis.** Detailed characterization of the clinical course of treatment, the effect on pain levels and sexual function, and the effect on bladder and bowel function.
2. **Ultrasound-based assessment of the prevalence, and the invasive depth, in cases of rectovaginal endometriosis.** This includes a systematic comparison of findings from ultrasound examinations and the tissues surgically extracted during rectal resection.
3. **The shift in coping strategies following mindfulness therapy.** Based on the results of a now-concluded pilot study, the research group is planning a cross-disciplinary prospective randomized controlled study of the effects of mindfulness techniques upon chronic pain syndrome in endometriosis patients. The crossdisciplinary therapist group will include clinical psychologists and nurses with specialist training.
4. **Physiological and pharmacological characterization of the innermost layer of the myometrium.** Following basic characterization, the project clarifies the effect of and/or activated substances and the presence of -adrenoceptors. In continuation of this, we will examine the possibility of selectively relaxing this muscle layer to block retrograde menstruation.
5. **Establishment of a tissue biobank** for molecular-biology characterization of endometriosis-patient genotype, for comparison with a local phenotype.

MILESTONES

(Riiskjaer M, et al. Am J Reprod Immunol. 2011;65(1):13–9)

(Ejskjaer K, et al. Gynecol Obstet Invest. 2009;67(2):118–26)

(Larsen SB. Eur J Obstet Gynecol Reprod Biol. 2011;157(2):206–11)

(Kruse C, et al. Acta Obstet Gynecol Scand. In press)

METHODS

Minimally invasive surgical treatment for deeply infiltrating endometriosis

- Laparoscopic rectal resection for rectovaginal endometriosis

Imaging techniques for infiltrating endometriosis

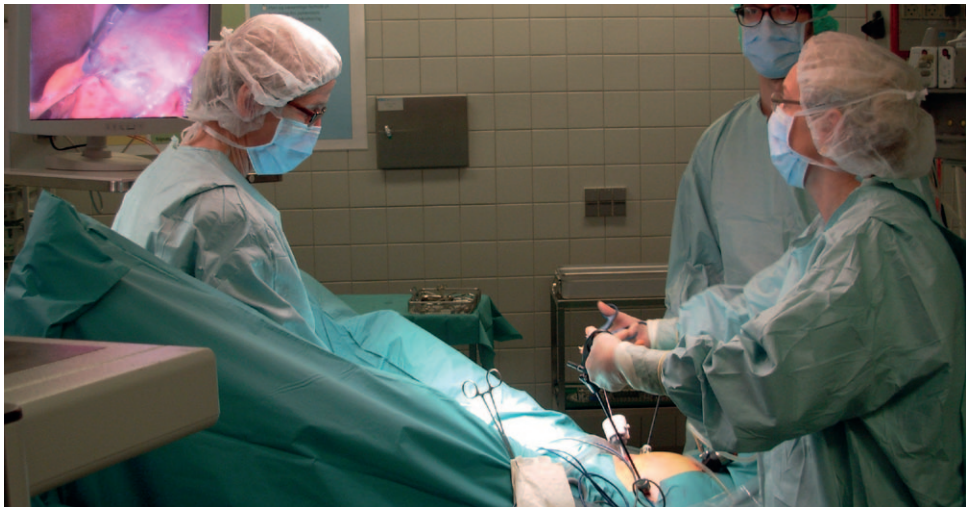
- Assessment of occurrence and invasive depth using vaginal ultrasound

Improved coping strategies for patients suffering from chronic pain

- Use of mindfulness therapy to activate the pain-afflicted patient

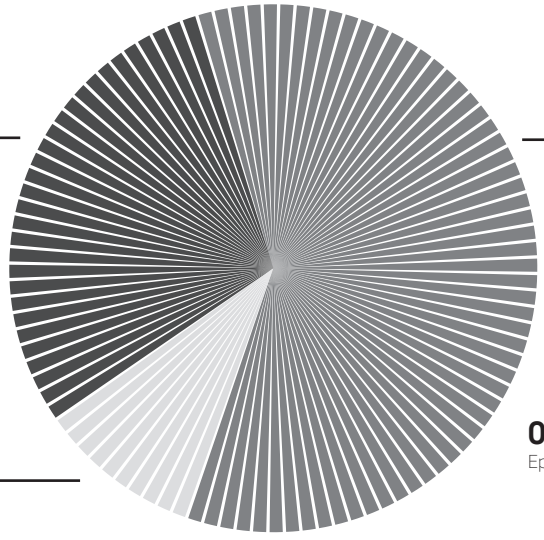
Characterizing the mechanisms behind retrograde menstruation, and the possibilities for blocking it

- Examining isolated myometrium using an organ-bath technique
- Establishing endometriosis in the autologous mouse model



Laparoscopic surgery for deeply infiltrating endometriosis

OVERVIEW



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Basic research

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Epidemiological research

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PAEDIATRIC NEPHROLOGY

The team of researchers behind the Centre for Child Incontinence at the Department of Clinical Medicine were the first in the world to explain several of the mechanisms behind nocturnal incontinence (enuresis nocturna). This is a condition that affects many children, and one out of ten seven-year-olds wet their bed at night.

It was therefore ground-breaking news when researchers discovered that many children produce excessive amounts of urine during the night because of disturbances in the circadian rhythm of the body's antidiuretic hormone. The group has also demonstrated that low nocturnal bladder capacity plays a role in the condition. Discovering the importance of the nocturnal deficiency of antidiuretic hormone has changed enuresis treatment on a global scale, shifting interventions to an artificial hormone analogue (desmopressin). The antidiuretic hormone is also responsible for other disturbances of the body's water balance. Yet another focus area is the study of patients who lack this hormone, or whose bodies do not react normally to the hormone by allowing it to inhibit urine production in the kidneys. A condition called diabetes insipidus, which leads to excessive thirst, causes patients to pass up to 10–15 litres of urine each day.

Focus on genetic factors

We are investigating the genetic factors that play a role in families in which multiple members experience problems with nocturnal enuresis. The aim is to identify specific genes that may cause either late maturation of bladder function or an abnormal circadian rhythm in the antidiuretic hormone. Successful identification of the pathogenic gene – which may, for example, be a neurotransmitter – could unlock significant new potentials for treatment.

Some patients with diabetes insipidus have hereditary mutations in the antidiuretic hormone itself, or in the kidney receptor that reacts to the hormone. The researchers at the Department of Clinical Medicine have identified almost half of all known mutations and clarified how they result in an accumulation of malformed hormones in the cells.

Our most important research partners include North Western University in Chicago, the University of Denver, the University of Ghent, and Nagoya University.

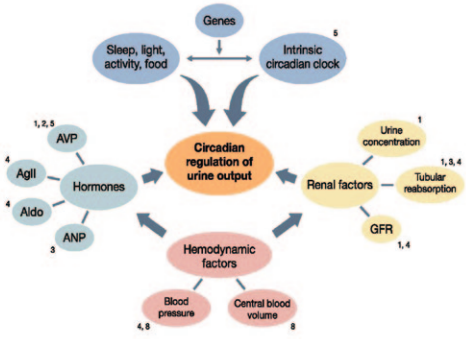
PROJECTS

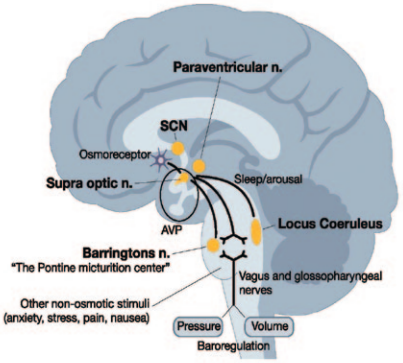
1. **Enuresis nocturna – clinical and genetic aspects.** Study of newly identified candidate genes; establishment of an international enuresis biobank.

2. **Gender differences in antidiuretic function.** The renal response to graded desmopressin infusion. A study of the importance of X-inactivation on renal AVP sensitivity. Determination of AVPR2 density using PET scans.

3. **Pathogenetic mechanisms behind over-active bladder (OAB) in children.** Microarray studies of the OAB detrusor muscle. Functional MR scans of OAB. The effect of TENS (Transcutaneous Electric Nerve Stimulation) and anticholinergic medication on OAB in children.

4. **Improved treatment of neurogenic diabetes insipidus.** Modulation of the protein quality control in cells. Gene therapy in the treatment of adFNDI.





Our research group has focused on mechanisms behind nocturnal polyuria in enuresis such as genes, the antidiuretic hormone, renal factors, and nocturnal blood pressure regulation.

MILESTONES

Founding of the Centre for Child Incontinence, under the Department of Clinical Medicine.
(Aarhus University Hospital, 1999)

The first controlled study to show that children with nocturnal enuresis produce excessive amounts of dilute urine during night due to low plasma levels of antidiuretic hormone.
(Rittig S, et al. J Am Physiol. 1989;256(4 Pt 2):F664–71)

The largest study of the genetic background behind familial neurogenic diabetes insipidus (FNDI) identifying 13 new disease causing genes.
(Rittig S, et al. J Am Hum Genet. 1996;58(1):107–17)

The first demonstration of linkage between non-monosymptomatic nocturnal enuresis and a specific area of chromosome 4.
(Elberg H, et al. J Urol 2001;166(6):2401–3)

Using 'state of the art' molecular techniques this study demonstrated accumulation of misfolded vasopressin prohormone in cells expressing diabetes insipidus mutations.
(Christensen JH, et al. J Clin Endocrinol Metab. 2004;89(9):4521–31)

The first demonstration of a new enuresis patient subgroup with increased nocturnal natriuresis, excretion of PGE2, and desmopressin resistance.
(Kamperis K, et al. Am J Physiol Renal Physiol. 2006;291(6):F1232–40)

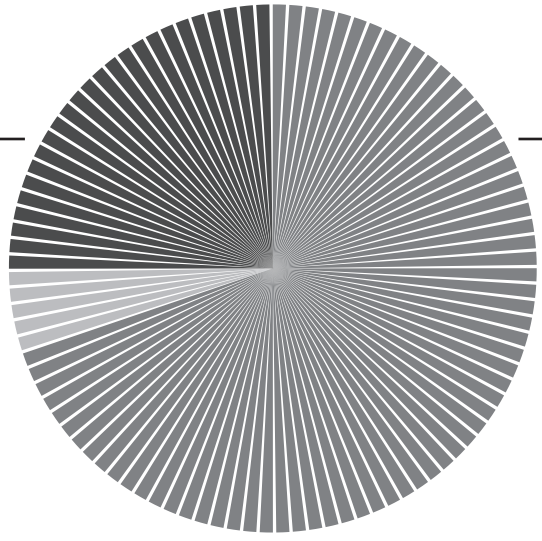
This study characterized clinically and genetically a newly recognized form of nephrogenic diabetes insipidus with mutations in the vasopressin AVPR2 receptor causing a partial phenotype.
(Faerch M, et al. Am J Physiol Renal Physiol. 2009;297(6):F1518–25)

Acute sleep deprivation in children causes significant polyuria and suppression of baroregulatory hormones. This study points towards a link between high nocturnal blood pressure and nocturnal polyuria.
(Mahler BT, et al. Am J Physiol Renal Physiol. 2012;302(2):F236-43)

METHODS

- Genetic and molecular techniques
- Detailed clinical studies of the circadian rhythm of urinary excretion, of the plasma level of hormones (radioimmunoassay) that regulates this rhythm, and of other factors such as circadian blood pressure and sleep pattern
- Clinical tools to characterize nocturnal polyuria and reduced bladder capacity, based on data recorded at home
- Advanced physiological studies of antidiuretic hormonal function, including thirst test, infusion of hypertonic NaCl, and infusion of dDAVP
- Randomized placebo-controlled studies of new treatment modalities for child incontinence
- Genetic analyses of large families with hereditary enuresis nocturna, identification of candidate genes, and sequencing of the genes (including GWAS:Genome-Wide Association Studies)
- Sequencing of all diabetes insipidus genes (AVP, AVPR2, and AQP2) in families with hereditary diabetes insipidus
- Expression studies of diabetes insipidus mutations in cell lines with a view to studying intracellular mechanisms, AVP secretion, and AVPR2 and AQP2 function.

OVERVIEW



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PERINATOLOGY AND NEONATOLOGY

Organ formation and development mainly takes place during foetal life, but a few organs continue this process after birth. For babies born very preterm, some of this development happens during their stay in the neonatal intensive care unit.

A variety of exposures during the time-window of organ development may permanently change later organ function and influence the likelihood of diseases in childhood or adult life. The highest mortality and morbidity from birth until the age of 60 are found in the newborn period; and 10% of all newborns require hospitalization. Identification of causes or early treatment with minimal adverse effects is the first step towards primary or secondary prophylaxis, and thus towards long-term handicap-free survival. Little is still known about the consequences of exposures during foetal and newborn life. This goes for environmental exposures, medical treatment, and the potential interaction with genetic constitution. Likewise, little is known about what causes serious problems in early life, such as preterm delivery and malformations.

Unique biobank

Within Health, we collaborate with experts from toxicology, clinical genetics, molecular biology, epidemiology, clinical biochemistry, and psychiatry. We also work with several international partners. We have established a cohort of all pregnant women and their newborns delivered in AUH from 1989 and onwards; the Aarhus Birth Cohort: one of the world's largest pregnancy cohorts. It now holds information on some 100,000 pregnant women and their children. Several international collaborations are based on information from this cohort. We have also established a biobank of biological samples from both parents and the newborn, which will allow studies on genetics and interactions between genes and environment, as well as pregnancy outcome and child health. A number of randomized studies to either prevent or treat newborn disease have also been initiated, or are chaired or monitored (steering or data-monitoring committee), by our research group. Clinical observational studies on various newborn diseases, their investigation, or treatments are also under way. These include studies on hyperbilirubinaemia, biomarkers of brain damage in perinatal asphyxia, echocardiography and biomarkers in the prediction of haemodynamically significant ductus arteriosus in preterm newborns, and comparison of various treatment strategies in preterm newborns with respiratory distress.

PROJECTS

Noteworthy projects include:

1. A randomized controlled trial of the timing of elective Caesarean section and admission to the neonatal intensive care unit.
2. A study on point-of-care ultrasound in sick newborns. Can we decrease diagnostic delay for life-threatening conditions in sick newborns by introducing point-of-care ultrasound, and placing this in the hands of the neonatologist on call?
3. A randomized controlled trial on how to discontinue respiratory support in very preterm newborns.
4. Controlled study on executive functions in children with extreme neonatal hyperbilirubinaemia.

MILESTONES

Lifestyle factors, interaction with genetics, and medication during pregnancy may influence the physical and mental health of offspring:

Is maternal smoking during pregnancy a risk factor for hyperkinetic disorder? Findings from a sibling design
(Obel C, et al. Int J Epidemiology. 2011;40:338–45)

Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: a population-based cohort study
(Pedersen LH, et al. Br Med J. 2009;339:b3539)

Stillbirth and slow metabolizers of caffeine: comparison by genotypes
(Bech BH, et al. Int J Epidemiology. 2006;35:948–53)

Risk factors for, and consequences of, preterm delivery:

Preterm delivery is associated with behaviour and learning problems in early school age. Gestational age and birth weight in relation to school performance of 10-year-old children: a follow-up study of children born after 32 completed weeks
(Kirkegaard I, et al. Pediatrics. 2006;118:1600–6)

Cryptorchidism and hypospadias in a cohort of 934,538 Danish boys: The role of birth weight, gestational age, body dimensions and foetal growth
(Jensen MS, et al. Am J Epidemiology. 2011. In press)

Delivery and newborn disease:

Risk of respiratory morbidity in term infants delivered by elective Caesarean section: cohort study
(Hansen AK, et al. Br Med J. 2008;336:85–7)

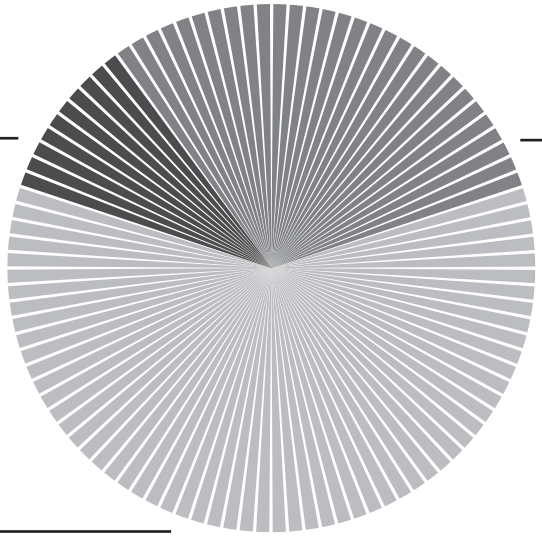
Neonatal non-haemolytic hyperbilirubinaemia: a prevalence study of adult neuropsychiatric disability and cognitive function in 463 male Danish conscripts
(Ebbesen F, et al. Arch Dis Child. 2010;95:583–7)

Follow-up on neonates with total serum bilirubin levels ≥ 420 µmol/L: a Danish population-based study
(Vandborg P, et al. Pediatrics. In press)

METHODS

- Perinatal epidemiology
- Genetic epidemiology
- Randomized controlled clinical trials
- Cohort studies
- Clinical epidemiology
- Ultrasound measures in newborns
- Biomarkers

OVERVIEW



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Qualitative research

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REPRODUCTIVE MEDICINE

In Denmark 30,000 fertility treatments are carried out each year. Our core research at the Fertility Clinic investigates techniques that can identify the embryo with the best chance of implantation and subsequent pregnancy.

Improving the chances of successful conception will make treatments less expensive, since each woman must undergo fewer treatment cycles to conceive. It will also support the practice of transferring only one embryo, eliminating risks associated with twin pregnancy. Early identification of the embryo with the greatest chance of success will also reduce in vitro cultivation time, thereby minimizing possible undesirable effects that the environment outside the uterus may have on the genetic programming of the embryo.

One technique we use in this research is time-lapse imaging, which allows dynamic monitoring of embryonic development. Surprisingly, we have found indications that embryos that lead to successful conception and pregnancy may not be the ones that look most healthy and viable at first glance. Further, we investigate Nuclear Magnetic Resonance (NMR) spectroscopy as a tool to examine embryonic metabolism as a possible predictor of implantation. Gene-expression analysis is also studied to evaluate gene expression in preimplantation embryos.

In the field of qualitative research, we have shown that there seems to be an association between the woman's psychological profile and her chances of conceiving. We are currently trying to reduce stress in infertile patients by using a technique called Expressive Writing in a large randomized intervention study. Another focus area is the significance of lifestyle factors on fertility, which we are examining using data collected from fertility treatments carried out over the past 10 years.

The Fertility Clinic also contributes to projects that explore pathogenic factors relating to Polycystic Ovary Syndrome (PCOS) using gene-expression studies of the ovarian follicular apparatus in normal subjects and in PCOS patients, and to studies of the correlation between viral infections and male infertility.

Important technology assessments:
Our use of Medical Technology Assessments (MTAs) has contributed to evaluations of hormone stimulation models, preimplantation diagnostics, and Single Embryo Transfer. These MTAs have been performed in close collaboration with researchers from a variety of fields. Our joint efforts have enabled us to assess not only the medical consequences but also the broader economic and personal implications of assisted conception and fertility treatment.

PROJECTS

Our research investigates infertility in women, clarifying the mechanisms behind defective blastocyst implantation, and also studies the significance of viral infections on semen quality for infertile men.

1. **The pathogenesis behind hydatidiform moles.** Exploring the causes and development of hydatidiform mole in the uterus.

2. **A randomized controlled intervention study of the effects of expressive writing** on psychosocial stress and in vitro fertilization (IVF) outcomes for childless couples undergoing IVF treatment to conceive.

3. **Improving the chances of pregnancy following IVF treatment:** Identification of candidate genes exhibiting variations in genetic expression as markers for selecting viable embryos.

4. **Is the Anti-Müllerian Hormone (AMH) responsible for inadequate follicle maturation in patients with PCOS?**

MILESTONES

Our main research partners are:

Professor Robert Zachariae
Research Unit for Psychooncology, Department of Psychology, AU

Professor Niels Christian Nielsen
Laboratory for Biomolecular NMR Spectroscopy, Department of Chemistry, AU

Professor Per Höllsberg
Medical Microbiology and Immunology, AU

Associate Professor Karin Lykke-Hartmann
Department of Medical Microbiology, AU

Associate Professor Niels Tørring
Department of Clinical Biochemistry, Aarhus University Hospital

Professor Steen Kølvraa
University of Southern Denmark

Important publications include:

Patient attitudes towards twin pregnancies and single embryo transfer: a questionnaire study
(Højgaard A, et al. Hum Reprod. 2007;22(10):2673–8.)

Stressful life events are associated with a poor in vitro **fertilization (IVF) outcome: a prospective study**
(Ebbesen SM, et al. Hum Reprod. 2009;24(9):2173–82.)

Stress, distress, and outcome of assisted reproductive technology (ART): a meta-analysis
(Matthiesen SM, et al. Hum Reprod. 2011;26(10):2763–76)

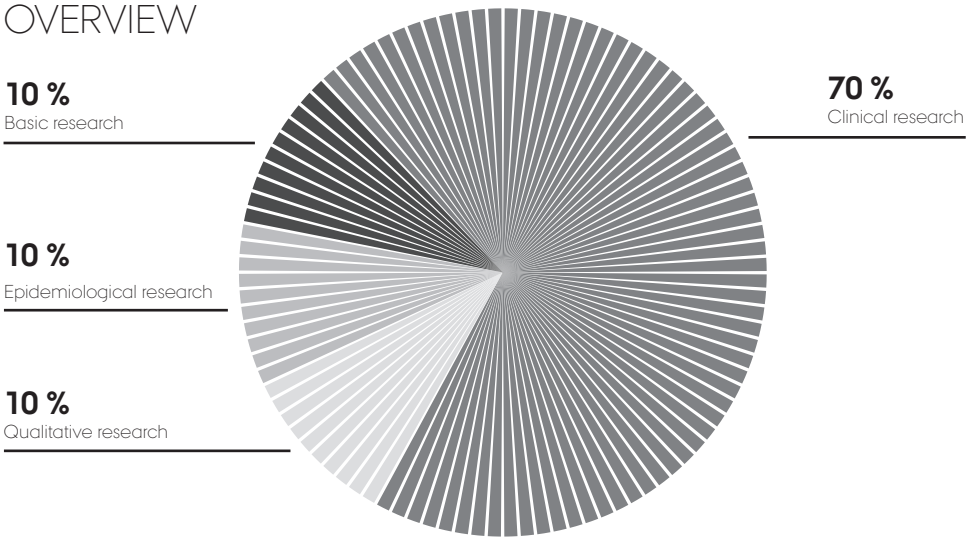
Identification of multiple HPV types on spermatozoa from human sperm donors
(Kaspersen MD, et al. PLoS One. 2011 Mar 29;6(3):e18095)

METHODS

Our research takes place in close crossdisciplinary cooperation between the Fertility Clinic and external partners whose know-how, technology, and professional expertise create valuable synergetic effects. Our research therefore uses an extremely wide range of methods and technologies, some of which are handled locally while others are handled by partners and associates within and outside the university.

- Expressive Writing
- Time-lapse imaging
- NMR
- Polymerase Chain Reaction (PCR)
- Array technology
- Questionnaire studies
- Epidemiological research methodologies

OVERVIEW



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PAEDIATRICS

The paediatric research concerning pulmonary disease carried out at the Department of Clinical Medicine is particularly concerned with explaining and investigating two lung diseases:

- Asthma
- Cystic fibrosis.

Asthma
Research in asthma at the Department of Paediatrics at Aarhus University Hospital essentially concentrates on the mast cell, which releases signal substances that trigger allergic reaction when the cell is activated. Based on stem cells, we have developed a method that allows us to culture mature mast cells. Using this technique we can now cultivate mast cells by the millions, then examine them to shed light on their activation mechanisms.

Understanding the mechanisms of cellular activation and inhibition is a decisive step in developing rational forms of pharmacotherapy.

Cystic fibrosis
Regarding cystic fibrosis, it has been known for some years that the lungs of patients are damaged partly by infections, and partly by oxidative stress. While infections can largely be held in check using conventional antibiotics, it has recently been demonstrated that intensive therapeutic doses of antioxidants can help cystic-fibrosis patients by alleviating or completely eliminating their pulmonary oxidative stress. This will improve the functioning of the neutrophile granulocytes in their lungs, thereby strengthening their own immune defences against bacterial infection. This treatment is currently being implemented at Aarhus University Hospital.

MILESTONES

The establishment of a combined serum-free and serum-supplemented culture method of obtaining functional cord blood-derived human mast cells.
(Dahl C, et al. J Immunol Methods. 2002:1;262(1-1):137-43)

Human mast cells express receptors for IL-3, IL-5 and GM-CSF; a partial map of receptors on human mast cells cultured in vitro.
(Dahl C, et al. Allergy. 2004;59(10):1087–96)

Identification of tryptase- and chymase-related gene clusters in human mast cells using microarrays.
(Dahl C, et al. Allergy. 2006;61(3):276–80)

Prizes and awards:
The Danish Order of Odd Fellows research prize
1997 (DKK 125,000)

The Lions Club Denmark prize
1999 (DKK 250,000)

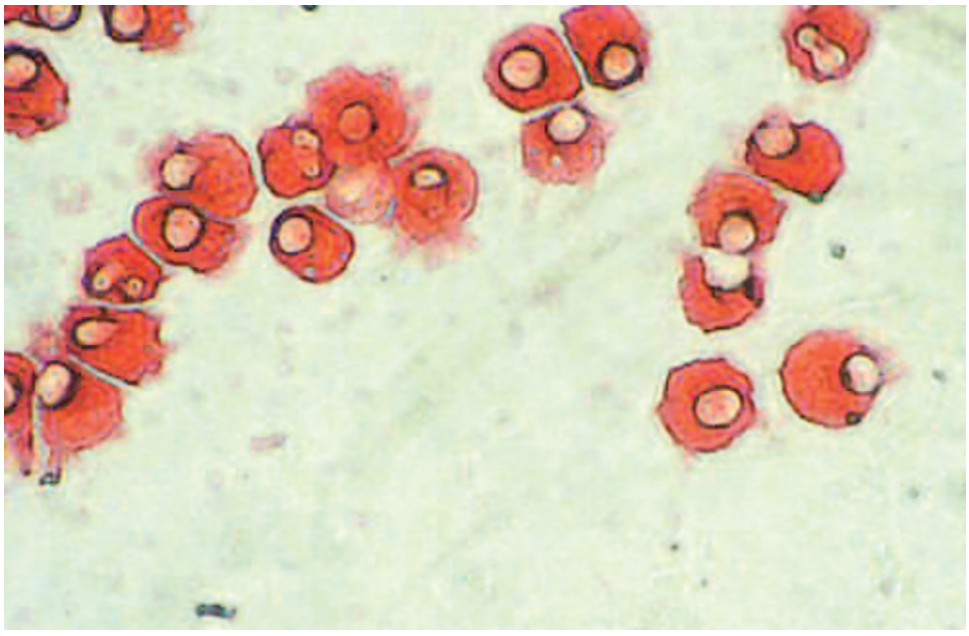
Danish Society for Allergology's award for best-and-brightest young Danish researcher (sponsored by Schering-Plough)
1993, 1995, 2003, and 2005 for our work on mast cells

Seven week culture of functional human mast cells from buffy coat preparations.
(Holm M, et al. J Immunol Methods 2008:336(2):213-21)

Cultured Human mast cells are heterogenous for expression of the high-affinity IgE receptor FceRI.
(Hoffmann HJ, et al. Int. Arch Allergy Immunol 2011:157(3):246-250)

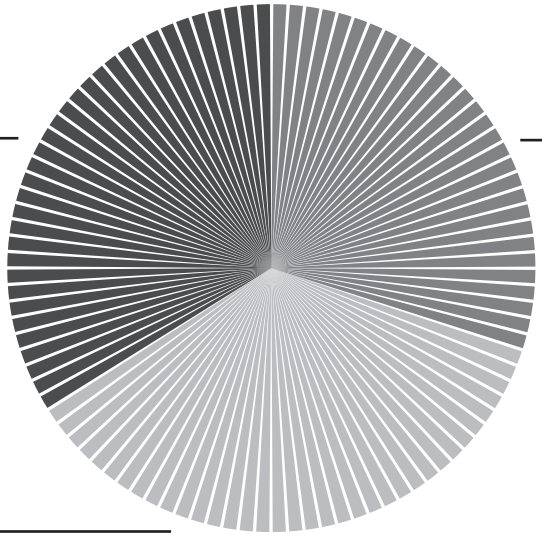
PROJECTS

1. Antioxidant treatment of patients with cystic fibrosis, systemically and locally.
2. Research on mast-cell activation.



We can cultivate mast cells by the millions and examine them to shed light on their activation mechanisms.

OVERVIEW



34 %
Basic research

33 %
Clinical research

33 %
Epidemiological research

0 %
Qualitative research

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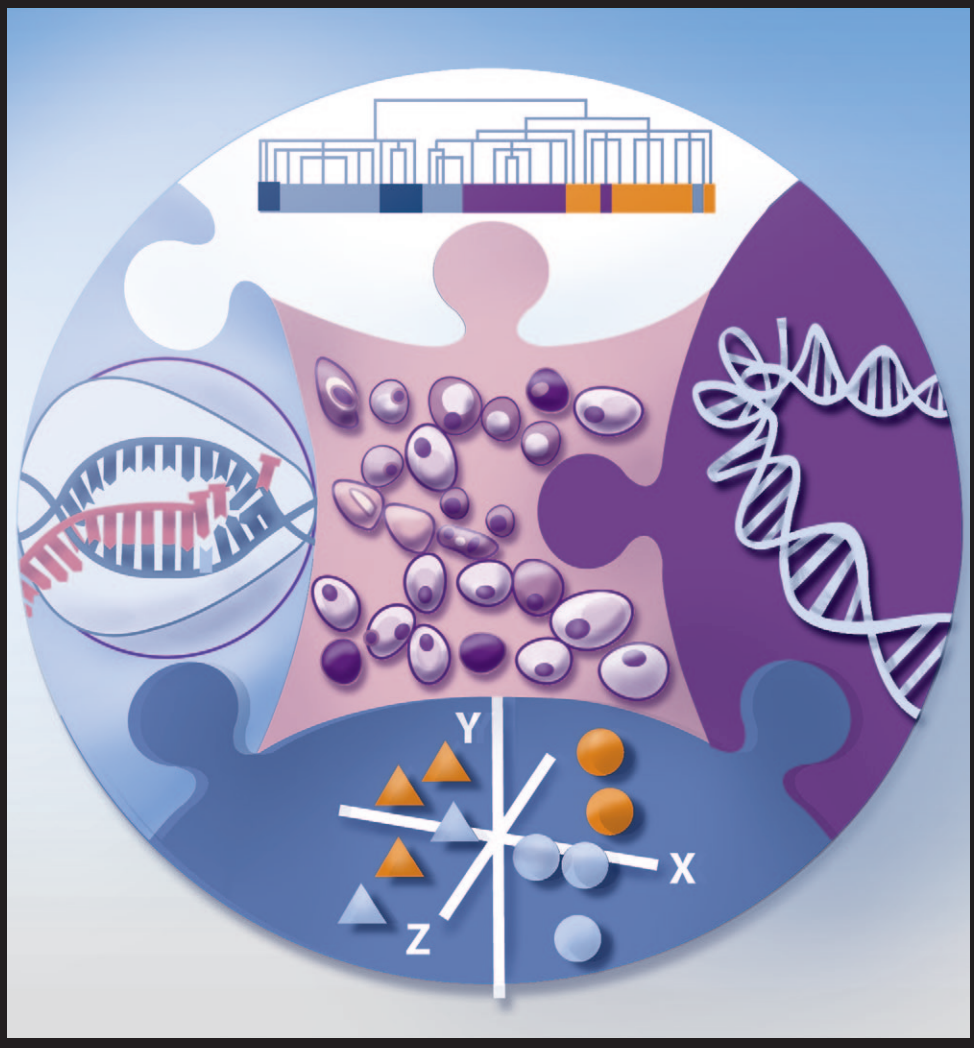
ONCOLOGY



◄ The integration of genomic, cytomic, and biostatistical approaches to modern haematological pathogenesis research in the laboratory.

CLINICAL ONCOLOGY

Clinical oncology research is done in close collaboration with surgical departments, studying the treatment of a wide range of cancers, including intestinal, prostate, and ovarian cancer. By ensuring the implementation of basic and clinical research in clinical practice, we combine strong skills in basic research with excellent clinical work, including a laboratory with highly advanced equipment.

Cancer of the colon, rectum, bladder, and prostate gland are life-threatening diseases, and all carry a high mortality rate. Each year, approximately 4100 Danes are diagnosed with cancer of the colon or rectum, and one out of three males over 50 will be diagnosed with prostate cancer at some point. We have commenced research into new diagnostic methods, seeking to develop optimized therapies for these diseases.

Ovarian cancer is often diagnosed late, and here, too, mortality is high. The cause of the disease is not known, which has made screening and early diagnosis efforts inadequate. The section for oncological gynaecology performs basic and clinical research on ovarian, endometrial, cervical, and vulvar cancer. Our ovarian cancer research is internationally renowned, and we have developed a ground-breaking new infection theory, which indicates that an ascending infection could be causing this disease.

Studying biomarkers

No optimal screening method currently exists for detecting the early stages of prostate cancer. Although we can measure the amount of Prostate Specific Antigen (a strong indicator) in the blood, PSA measurement is associated with considerable uncertainty. Accordingly, some men are overtreated, which entails the risk of serious side-effects: incontinence and impotence.

A key challenge is therefore to become able to identify the disease at an earlier stage. To this end we are studying biological markers in the genes, such as enzymes that can more clearly identify the risk group.

The clinical oncology research group has created a unique tissue and data bank, which can be used for epidemiological studies that clarify, for instance, correlations between men who have been screened and treated for prostate cancer, and who also suffer from various other cancer diseases of the intestines and bladder.

PROJECTS

1. Multidisciplinary rehabilitation in bladder cancer.
2. Multidisciplinary intervention in early prostate cancer (NILS).
3. Translational/clinical research – lifetime risk of PCa (MolPros).
4. Focal therapy in PCa (Freeze-focal).
5. DAPROCA-1.
6. Medical phase-II and phase-III studies.
7. Epithelial ovarian cancer – an abdominal infection?
8. Evidence-based follow-up on cancer patients. Focus on gynaecological forms of cancer.
9. Connection between dental agenesis and epithelial cancer – including, in particular, ovarian cancer.
10. Cellular immunity and the development of the Human Papilloma Virus (HPV), related secondary cancers following immunosuppression.
11. Long-term outcomes after surgery for locally recurrent and advanced rectal cancer.
12. Chronic pain, and bladder, sexual, and intestinal dysfunction after treatment for intestinal cancer.
13. Cancer risk after surgery for ulcerative colitis.
14. Quality of life after treatment for intestinal cancer.
15. Can preoperative chemotherapy improve outcomes after locally advanced colon cancer? A randomized, international multicentre study.

MILESTONES

The oncology department has contributed to important research results, including the understanding and clarification of: mortality in prostate cancer, identification of biomarkers in prostate cancer, the connection between hormone supplements and the development of ovarian cancer, the risk of premature birth following conization of the cervix, and identification of ovarian cancer as a peritoneal infection.

The natural history of prostate carcinoma based on a Danish population treated with no intention of cure
(Borre M, et al. Cancer. 1997;80:917–28)

The dilemma of prostate cancer: a growing human and economic burden irrespective of treatment strategies
(Borre M, et al. Acta Oncol. 1997;36:681–7)

Intrinsic markers of tumour hypoxia and angiogenesis in localized prostate cancer predict the outcome of radical treatment
(Vergis R, et al. Lancet Oncol. 2008;9:342–51)

Screening by lower urinary tract symptoms versus asymptomatic prostate-specific antigen levels leading to radical prostatectomy in Danish men: tumour characteristics and treatment outcome
(Borre M. BJU Int. 2009;104:205–8)

Seven prostate cancer susceptibility loci identified by a multi-stage genome-wide association study
(Kote-Jarai Z, et al. Nat Genet. 2011;43(8):785–91)

Hormone therapy and the impact of oestrogen intake on the risk of ovarian cancer
(Glud E, et al. Arch Intern Med. 2004;164(20):2253–9)

After conization of the cervix, the perinatal mortality as a result of preterm delivery increases in subsequent pregnancy
(Ørtoft G. BJOG. 2010;117(3):258–67)

The missing link in epithelial ovarian cancer: an aetiological unifying theory
(Dinesen JG. Nat Med. In press)

Long-term colorectal function after postoperative radiotherapy for colorectal cancer
(Lundby, et al. Lancet 1997;350:564–5)

Multicentre experience with extralevator abdominoperineal excision for low rectal cancer
(West, et al. Br J Surg. 2010;588–99)

Self-expanding metallic stents as bridge to surgery in obstructing colorectal cancer
(Iversen, et al. Br J Surg. 2011. 275–81)

Cause-specific colostomy rates after radiotherapy for anal cancer: a Danish multicentre cohort study
(Sunesen, et al. J Clin Oncol. 2011;3535–40)

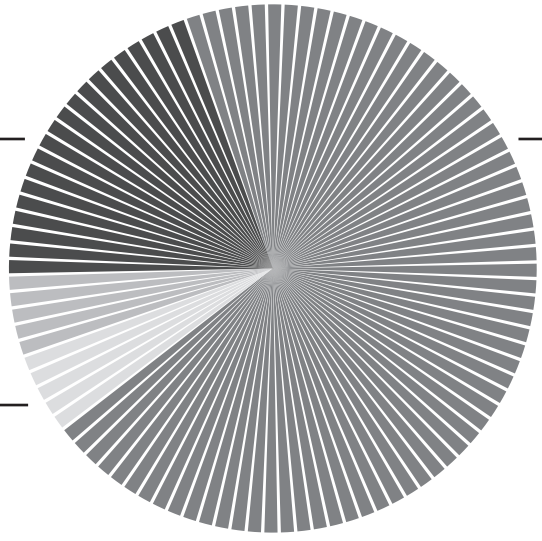
Next-generation stool DNA test accurately detects colorectal cancer and large adenomas
(Ahlquist, et al. Gastroenterology. In press)

METHODS

Our research deals with epidemiological and anthropological studies, basic research work, and clinical studies, employing methods from:

- Epidemiology
- Genetics
- Immunology/haematology
- Infection medicine
- Nuclear medicine
- Cellular in vitro studies
- Anthropological field studies
- Molecular biology
- Pathology

OVERVIEW



20 %
Basic research

70 %
Clinical research

5 %
Epidemiological research

5 %
Qualitative research

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HAEMATOLOGY

Haematology covers a number of disorders in the blood-forming system. Most of these are malignant diseases, which account for approximately 10% of cancer in the population. Each year, more than 2000 Danish children and adults are diagnosed with cancer of the blood-forming system. Today approximately 15,000 people are patients at haematology departments because of their cancer.

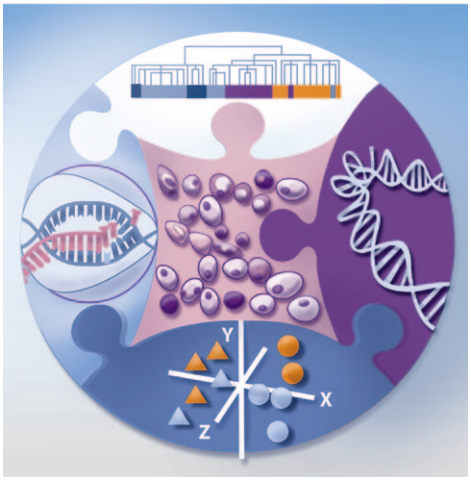
Haematology is traditionally at the forefront of research and implementation of new treatment modalities, including the identification of new relevant biomarkers.

From the laboratory to the clinic
Haematology is consistently at the cutting edge of translational research in both adults and children under these general headings:

1. Clinical trials
2. Individualized patient treatment – with focus on the significance of Minimal Residual Disease
3. Improved diagnostics – new technologies permit individual patient diagnosis
4. Pathogenesis research – with focus on identifying new biomarkers
5. Pharmacology and pharmacogenetics
6. Mapping of late offside effects of cancer treatment
7. Rehabilitation

Haematology research is supported by a strong infrastructure:

- Specialized laboratories equipped with advanced technology
- Biobanks with material and samples from thousands of patients
- Well-functioning clinical research units that serve as the basis for clinical studies
- Excellent databases with clinical data from selected patient histories
- A strong network of national and international partners
- Researcher education and training



The integration of genomic, cytomic, and biostatistical approaches to modern haematological pathogenesis research in the laboratory.

PROJECTS

1. hMICL as a marker for leukaemia stem cells.

2. Focussed array techniques as a means to identify individual genetic mutations in connection with haematological malignancy.

3. The effect of CAMPATH antibody treatment of T-cell lymphoma.

4. Identification of myeloma cancer stem cells; MSCNET: Coordinator of the European Myeloma Stem Cell Network. Funded with EUR 3 million by the sixth EU Framework Programme (http://www.myeloma-europe.org/mscnet/index.php) .

5. Chemo prediction for malignant B-cell diseases; chemotherapy screening of human malignant B-cell lines in view of chemotherapy; predictive gene profiles and their validation; biostatistical models for analysis of array and sequencing data; Coordinator for a grant from the Danish Council for Strategic Research, DKK 8.2 million (http://www.blodet.dk (CHEPRE 2008–2015).

6. Resistance and targeted treatment; RESTART: Coordinator of "Translational research on cancer with poor prognosis".

7. The pathogenetic importance of hereditary polymorphs, MyelomaA Genetics International Consortium (MAGIC 2011–2015).

8. Pathogenesis and clinical characteristics in AML and MDS/JMML.

9. Phage display techniques as a method to develop new diagnostic reagents in chronic myeloid leukaemia.

10. Optimized treatment support.

MILESTONES

The kinetics of Minimum Rest Disease in recurrent acute myeloid leukaemia (AML)
(Ommen HB, et al. Blood. 2010;115:198–205)

New biomarker (Galectin) in Hodgkin's lymphoma
(Kamper P, et al. Blood. 2011;117:6638–49)

New stem cell marker (hMICL) in AML

Improved survival rate in juvenile AML

New pathogenetic understanding of juvenile AML and MDS/JMML
(Niemeyer CM, et al. Nature Genetics. 2010;42:794–800)

Atlas of the differentiation profiles of B-cells
(Kjeldsen MK, et al. Am J Clin Pathol. 2011;136:960–9)

Gene expression profiles predicting chemotherapy response
(Boegsted M, et al. PLoS One. 2011;6:e19322)

METHODS

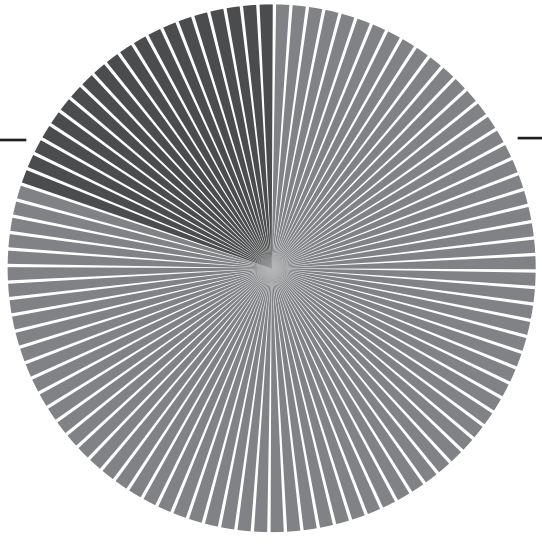
Haematology research uses the latest methods to study patients in clinical trials and to conduct laboratory studies of biological samples of blood, bone marrow, and lymph-node tissue. The laboratory research benefits from a number of core functions and areas of expert competence in the form of:

- Advanced cell-culture systems
- Flow cytometry and fluorescence-activated cell sorting
- Genome screening using array technologies
- Bioinformatics
- Specialized quantitative PCR assays
- Gene-function assays

Our areas of special professional competence within clinical research are:

- Clinical trials with patient monitoring
- Recording and registering of clinical data
- Biobank and public-register databases
- Biostatistics

OVERVIEW



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Basic research

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Clinical research

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Epidemiological research

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Qualitative research

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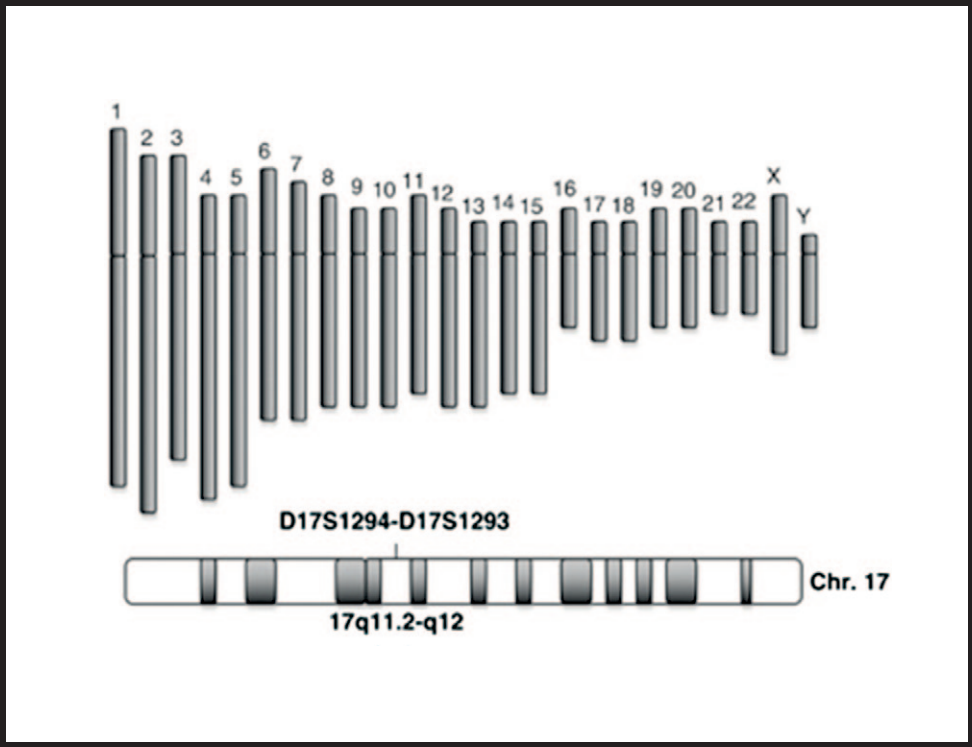
PSYCHIATRY

► Genome-wide scan to detect association between PD and a two-marker segment on chromosome 17. This was followed up on 17q11.2-q12, which revealed significant association between PD and several markers and suggested ACCN1 as a possible candidate gene. This was analysed using tag-SNPs.



▲ MRI of depressive patients and control subjects. White-substance lesions are indicated in colour. Most of these occur in the orbitofrontal areas.

► Research in neuropsychological aspects of child psychiatric illnesses.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CHILD AND ADOLESCENT PSYCHIATRY

Mental illness in a child or adolescent not only severely affects the patient, it also profoundly affects the patient's family and friends. That is why we must achieve a better understanding of what causes these mental illnesses and how we can become better at treating them.

Mental illnesses are extremely complex conditions, given that they are associated with the patient's genes, brain, psyche, and environment. Our research therefore studies these individual factors and the ways in which they interact. Generally speaking, we investigate the genetic and environmental factors that influence mental illness, and in recent years we have increasingly begun to conduct intervention research as well.

More specifically, the Centre for Child and Adolescent Psychiatry, based at the Risskov branch of Aarhus University Hospital, is leading in the research and treatment of ADHD (attention deficit/hyperactivity disorder) and OCD (obsessive-compulsive disorder). However, we also have expert competence in the fields of eating disorders and autism spectrum disorders (ASD). In addition to being Denmark's largest national source of ADHD and OCD research, our daily work involves diagnosing, treating, and preventing various types of mental illnesses in children and adolescents.

Special expertise and hypotheses

At our department we conduct research that is close to the clinic and focusses on directly implementing our findings in clinical practice. The Risskov facility has a long history of doing biological research and cooperating across skills areas. Such cooperation involves not only medical, genetic, and brain research but also research in the fields of psychology, statistics, and paediatrics. In other words, our researchers have access to the newest knowledge from multiple areas and can therefore cover the entire scope of the diseases we investigate.

We possess special expertise in biological research, investigating the pharmacotherapeutic treatment of patients and also delving into neuropsychology, which focusses on the actual processes that take place in the brain. Not least, we investigate genetics, the most fundamental factor of all. Furthermore, we consider the environmental factors affecting the patient and study how interventions such as cognitive therapy and family training programmes can be used therapeutically. Our research unit is involved in many projects, collaborating nationally and internationally with other researchers to explore new aspects of therapeutic intervention, epidemiology, neuropsychology, and genetics.

PROJECTS

1. **Cognition and behaviour in school-aged children with and without ADHD:** This project studies the neuropsychological difficulties observed in connection with ADHD; how they can best be assessed and whether all children with ADHD encounter the same types of difficulties.

2. **Parental training programme for treating ADHD in toddlers and young children:** This is a randomized, controlled, multi-centre efficacy study of a parental training programme as applied to a large group of Danish preschool children with ADHD.

3. **Study of sleep patterns in children with ADHD before and after treatment:** Children with ADHD and sleep disorders are compared, in objective sleep studies, with a group of children with ADHD who do not have sleep disorders. After treatment with medication has been initiated, the studies are repeated.

4. **Early identification of ADHD and autism spectrum disorders (ASD) in toddlers and young children:** This study

builds on information from the Danish National Birth Cohort. The object is to determine whether parent-reported observations of differences in development and behaviour during the first two years of life can predict which children might later be diagnosed with ADHD or ASD.

5. **Nordic long-term OCD study**: A pan-Nordic study of psychotherapeutic and pharmacotherapeutic treatment of OCD (severe obsessions and compulsions) in children and adolescents. This study also includes investigations of neuropsychological markers for treatment efficacy and genetic investigations.

MILESTONES

OCD is often a chronic illness
(Thomsen PH. Eur Child and Adolesc Psychiatry. 1994;3:82–96)

Functional symptoms are also seen in preschool children
(Rask CU, et al. Eur J Epidemiol. 2009;24:625–34)

Not all children with ADHD have problems with their executive functions
(Lambek R, et al. J Child Psychol Psychiatry. 2010;51:895–904)

Many patients with anorexia develop other eating disorders
(Helverskov JL, et al. Eur Eat Disord. 2010;18:453–63)

Large increase in the number of ASD diagnoses
(Lauritsen MB, et al. J Autism Dev Disord. 2010;40:139–48)

METHODS

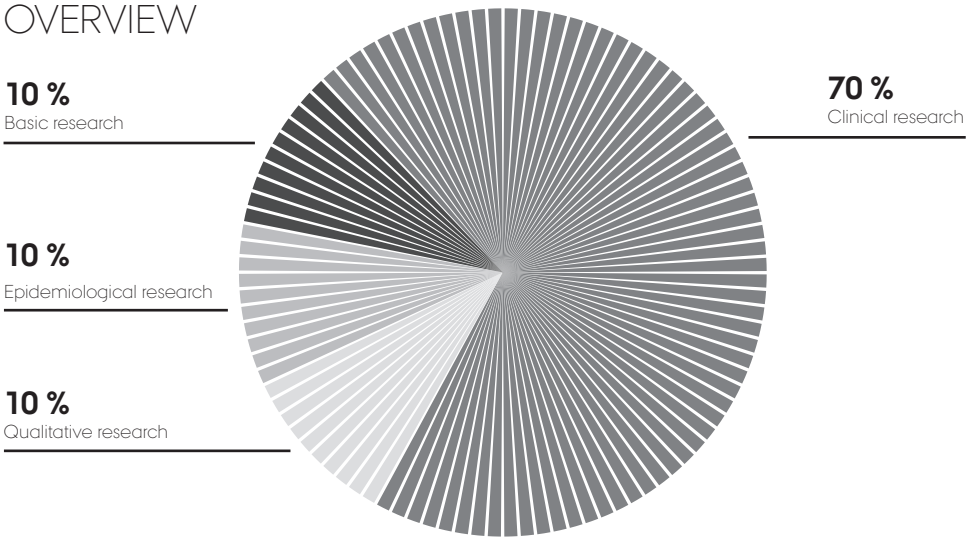
The scope of our research into the mental illnesses occurring in children and adolescents is broad, stretching from epidemiology to clinical research, also including the effects of interventions, neuropsychology, and genetic issues.

The scientific methods applied include:

- Epidemiology
- Intervention research
- Studies of clinical pathways
- Neuropsychology
- Genetics

Research in neuropsychological aspects of child psychiatric illnesses.

OVERVIEW



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NEUROPSYCHIATRY – FROM CLINIC TO MOLECULE AND BACK

Mental illnesses are among the most prevalent diseases in Denmark. They impose a heavy burden on those afflicted: personal suffering, reduced quality of life, and impaired social capabilities. They are therefore also detrimental to society at large.

The field of psychiatry covers a wide variety of illnesses, ranging from psychosis to anxiety and depressive disorders, as well as substance abuse and dependence. Our primary focus is on affective disorders (depression and bipolar disorder), but our research also studies schizophrenia, compulsive disorders, ADHD, and several other mental illnesses.

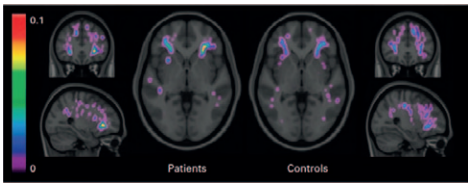
In general terms our research seeks to shed light on the causes and treatments of psychiatric morbidity, both in the clinic and all the way down to the molecular level. We do this by means of interdisciplinary research efforts based on neuroscientific front-line theories and by applying a wide array of modern neuroscientific techniques.

The brain in depression

The field of clinical neuropsychiatric research combines psychopathology and neuropsychology imaging technologies (PET and MR scans) that enable us to demonstrate structural and functional changes in the way the brain works. In depressed patients we have demonstrated an altered function in a particular part of the brain (the hippocampus) that plays a role in mood and intellectual functioning. Moreover, we have also demonstrated changes in the white substance in the brains of older patients, which indicates vascular damage and hence cerebral arteriosclerosis. This knowledge opens new opportunities for diagnostics as well as treatment.

In order to understand depression at an even more basic level, we study the hippocampus and other areas of the brain in animal models engineered for depression. We use these models to conduct detailed investigations of nerve cells, signal substances, transport molecules, and receptors, and to assess the effects of various psychoactive drugs. We also examine brain tissue from deceased patients, using samples from our brain collection, and scrutinize hippocampal cells using high-precision stereological methods. This basic research therefore seeks not merely to shed light on the mechanisms causing disease, but also to find new and better medication to treat affective disorders.

Because our clinical and basic research efforts are so intimately linked, we are in an excellent position to reinforce translational research – which means transferring new findings from basic research into the realm of daily clinical practice.



MRI of depressive patients and control subjects. White-substance lesions are indicated in colour. Most of these occur in the orbitofrontal areas.

PROJECTS

Correlation between depression and cardiovascular disease in first-episode depression patients over 50 years of age.

1. **Brain function in connection with obsessive–compulsive disorder (OCD):** An fMRI-based study.
2. **The hippocampus in severe unipolar depression:** A post-mortem stereological study of volume and cell numbers.
3. **A genetic rat model for depression:** Electrostimulation treatment and chronic stress; clarifying neuroplasticity by studying changes in neurotrophic factors; neurochemistry focussing on BDNF, VEGF, NO, and synaptic connections.
4. **The serotonin transporter:** Identification of molecular mechanisms for the ability of ligands to lock the transporter into specific configurations, and mapping of the binding sites for sodium and lithium.
5. **A chronic mild-stress animal model for depression:** Biomarkers, inflammatory response, chronobiology, GABAergic inhibition, and proteome analysis.

MILESTONES

The first Danish textbook on clinical neuropsychiatry
(Rosenberg R, et al. Lærebog klinisk neuropsykiatri. 2009. FADLs forlag)

Cerebral changes in the hippocampus in severe depression are reversible upon follow-up several years later; perhaps an effect of treatment with antidepressants
(Ahdidan J, et al. Acta Psychiatr Scand. 2011;123;211–9)

Small lesions in the white matter of the brain are associated with severe depression, because they compromise certain neuronal pathways in the brain
(Dalby RB, et al. Psychiatry Res. 2010;184:38–48)

Demonstration of an increased sodium-ion-channel level, and a deficient neurotransmitter release in a depression animal model under stress
(Henningsen, et al. Mol Cell Prot. In press)

In a genetic animal model for depression, the brain's content of growth factors is reduced whereas the level of growth factors in the serum is increased
(Elfing B. Int J Neuropsychopharmacol. 2010;13:563–72)

Demonstration in a rat model for depression of defective GABA neurotransmission, which is normalized by treatment with antidepressant (SSRI)
(Holm MM, et al. Hippocampus 2011;21:422–33)

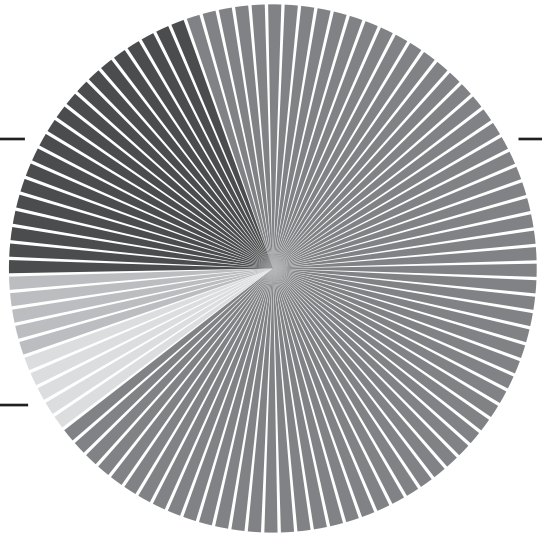
Stereological methods used to demonstrate cerebral changes in connection with schizophrenia, along with robust neurostereological findings from post-mortem schizophrenia studies
(Dorph-Petersen KA, et al. Biol Psychiatry. 2011;69:113–26)

METHODS

Our clinical research employs modern clinical methods, most notably standardized diagnostic and imaging techniques, and the neuroscientific methods used for experimental animal research conducted at behavioural, cellular, and molecular-biological levels.

- Imaging techniques: fMRI, PET scanning, MRI
- Neuropsychological tests: Stroop test, verbal fluency, trail making, and others
- Microscopic analyses of nerve and glial cells based on stereological techniques
- Studies of animal behaviour (depression and anxiety)
- Computer simulation of binding sites for ligands and transport molecules
- Microdialysis in relation to synaptic transmission, most particularly the nitrogen oxide (NO) system
- Proteome analysis of hippocampal synaptosomes
- Gene-expression profiling in specific animal models for depression
- Prenatal stress: behaviour, glucose metabolism, and stress feedback in the HPA -axis
- Electrophysiological studies of GABAergic inhibition in animal models of neuropsychiatric illnesses

OVERVIEW



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PSYCHIATRIC GENETICS

Schizophrenia, bipolar affective disorder, depression, anxiety, autism spectrum disorders, and ADHD are some of the costliest illnesses in the world, both at a personal level and for society as a whole. While these illnesses do share certain common risk factors, their causes are extremely complex, and their disease mechanisms remain largely unknown. Treatment with medication is often necessary, but unfortunately many patients do not respond to such treatment, which can also have severe side-effects.

The goal of our research group is to identify genetic and environmental causes of these debilitating mental illnesses, and to clarify the underlying disease mechanisms.

Based on the information available to us from Denmark's numerous public electronic registers and records, and from biobanks and clinical departments, our research group has built up a database and a biobank containing DNA from Danish (including Faeroese) patients and control subjects. This enables us to conduct extensive analyses of genetic and environmental risk factors relating to these severe psychiatric illnesses. In addition, we have collected similar data and DNA samples from patients in Cuba.

These unique resources, combined with new methods for detailed analysis of DNA, will enable us to identify risk variants in the entire human genome, and also enable us to analyse epigenetic factors, as well as gene–environment interactions – both for specific illnesses and across illnesses. New genetic risk variants will be tested using our own Danish and international patient material, as our group collaborates nationally and internationally with corresponding groups in a global effort to alleviate mental illness.

PROJECTS

1. **Sequencing schizophrenia.** The specific causes of schizophrenia remain unknown, although genetic predisposition is a significant background element. The objective of our research is to identify specific genetic causes and related neurobiological signal pathways:
   - identifying rare gene variants through sequencing the entire genome of 100 patients with schizophrenia from the Faeroe Islands, and
   - validating these gene variants in 3000 patients and 3000 control subjects from Denmark.

Pinpointing and identifying high-risk genetic variants for schizophrenia will assist in the clarification of important disease mechanisms relating to this illness.

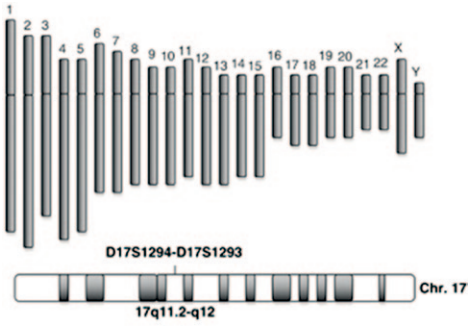
Furthermore, the interaction of these gene variants with environmental risk factors is also being investigated along with their significance for patient response to antipsychotic pharmacotherapy.

2. **Genomic Medicine for Schizophrenia (GEMS).** Schizophrenia is one of the most serious chronic mental illnesses. Antipsychotic medication is the mainstay of treatments today, but 30% do not respond to such drugs, and patients often experience severe side-effects. That is why there is an urgent need to find new types of antipsychotic drugs, and to move towards individualized treatment, thereby increasing therapeutic efficacy and reducing the side-effects and costliness of the disease. The objective of the project is to develop molecular medication to treat schizophrenia:
   - identifying and validating new targets for antipsychotic drugs
   - initiating the development of such drugs
   - initiating the development of diagnostic tests for individualized treatment.

A genetic study that covers all of the 2000 schizophrenia patients born in Denmark since 1982, comparing this cohort with a corresponding population-based control group and supplemented with public-register and database information about the course of illness, pharmacotherapy, and exposure to a number of specific environmental factors.

Our multidisciplinary research group encompasses internationally recognized expertise within the fields of psychiatry, epidemiology, genetics, molecular biology, bioinformatics, and statistics, and expertise from the pharmaceutical sector and the field of biotechnology as well.

These research projects can contribute extensive new knowledge about the causes and mechanisms of disease at work in psychiatric illnesses. Our scientific findings also hold prospects for clinical application, as we expect to identify new targets for drug development; to identify biomarkers for diagnosis and patient treatment; to point to preventive measures that can minimize environmental causes; and to provide a better basis for classifying these illnesses according to the factors that cause them.



Genome-wide scan to detect association between PD and a two-marker segment on chromosome 17. This was followed up on 17q11.2-q12, which revealed significant association between PD and several markers and suggested ACCN1 as a possible candidate gene. This was analysed using tag-SNPs.

MILESTONES

Evidence that frequently occurring gene variants in the population play a role in the development of schizophrenia
This supports the "Common disease – common variant" paradigm.

Common variants conferring a risk of schizophrenia
(Stefansson H, et al. Nature. 2009;460:744–7)

Identification, in a genome-wide association study, of five new schizophrenia loci
(Ripke S, et al. Nat Genet. 2011. Epub ahead of print)

Documentation of gene-environment interaction in schizophrenia
This includes demonstrating that certain genes can interact with antibodies in the mother, thereby altering the child's risk profile with respect to schizophrenia.

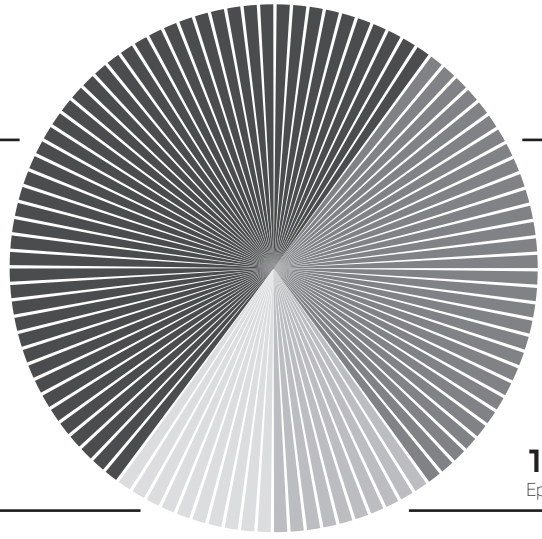
Association of GRIN1 and GRIN2A-D with schizophrenia and genetic interaction with maternal herpes simplex virus-2 infection, affecting disease risk
(Demontis D, et al. Am J Med Genet B Neuropsychiatr Genet. 2011. Epub ahead of print)

METHODS

Our research is based on an interdisciplinary effort that employs methods from the clinic, molecular biology, and epidemiology:

- In the clinic, we use research-based psychopathological characterization and diagnostics, and also examine courses of psychiatric treatment and therapeutic response in patients
- In molecular biology, we perform DNA extraction, focussed analyses of DNA markers, sequencing of entire genomes for patients and control subjects, and subsequent bioinformatic analyses and statistical genetic calculations
- Genetic epidemiology
- Denmark's many population-based registers and databases are used to identify environmental risk factors
- We use genetically modified animal models to study disease mechanisms in detail

OVERVIEW



50 %
Basic research

30 %
Clinical research

10 %
Qualitative research

10 %
Epidemiological research

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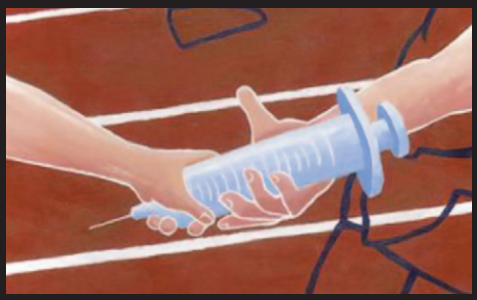
PUBLIC HEALTH

▲ Synchronic analysis of video recordings and physiological measurement data.

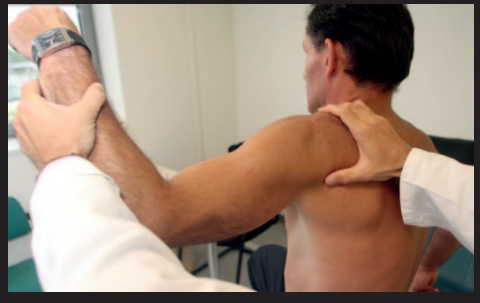
▲ Determining molecular and cellular bioeffects of environmental chemicals in the laboratory, Aarhus University.

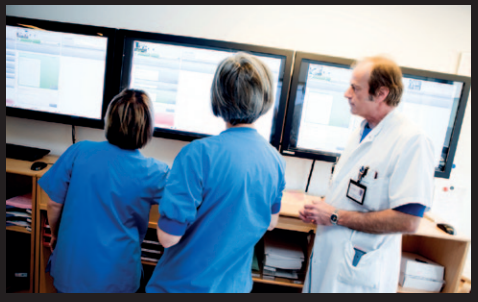


▲ The hypodermic needle is a powerful and widely used symbol when the media cover doping issues.

► Fears that performance-enhancing drugs will transform athletes into physical freaks is a weighty argument against doping.

◄ Preparing for systematic routine data collection for households at a Demographic Surveillance Site.





▲ The field of health service research is closely linked with daily practice, and its aim is to support qualified decision-making in health care.

▼ This image was part of the material used when collecting data for the Danish National Birth Cohort, which consists of almost 100,000 women and their children.

▲ 90 per cent of all contacts do not involve specialist care.

▲ Experimental evaluation of physical capacity

▲ Diet, Cancer and Health – an epidemiological study.

▲ Lung function in field studies

WORLD-CLASS CLIMATE CHAMBERS

In the climate chambers at Health, our researchers investigate how particles, gases, chemicals, and other substances affect our health – both on their own and when they interact. This knowledge is part of the basis used for setting limits for acceptable concentrations in indoor environments, and for setting health-and-safety standards. However, such investigations can also teach us how our reactions to environmental contaminants shift as climate change alters temperatures and ozone concentration in the atmosphere.

Research with an international impact

What sets our climate chambers apart is the ability to control exposure with tremendous precision, and to maintain exposure at a constant level for prolonged periods of time. Moreover, our specially trained staff has extensive experience and expertise in planning and conducting climate-chamber studies. This enables us to examine the significance of even very small concentrations, which is relevant because that is exactly what we are subjected to in our daily lives. On this background we can also conduct dose-response studies – a capability that is quite unique. "The climate chambers at Health are among the best in the world. This means that we can carry out projects that really have an international impact," explains Professor Torben Sigsgaard.

Research on synergies and particularly vulnerable groups

Our climate-chamber research pursues two tracks. One investigates how simultaneous exposure to several different substances affects the human body. For example: How do increases in atmospheric ozone influence our reaction to air pollution or household dust? The other track investigates the effects of environmental contaminants on particularly vulnerable groups, such as pollen-allergy sufferers and their reaction to rising atmospheric ozone concentrations. "We work to improve quality of life for people with allergies and respiratory diseases," Professor Sigsgaard stresses. "Our research suggests that as our climate gradually changes, in the future we may need to change the advice we give to people with allergies and COPD."

> **Our research suggests that as our climate gradually changes, in the future we may need to change the advice we give to people with allergies and COPD.**
>
> PROFESSOR TORBEN SIGSGAARD

FACTS

Experiments in the climate chambers at Health have guided decision-making on limits for a variety of substances, including formaldehyde in the workplace.

ARCTIC MEDICINE

The Inuit peoples of the Arctic originated in Asia – which means that not only their lifestyle but also their genetic makeup differs from that of Caucasians (ethnic Western peoples). The Inuit have previously exhibited a special pattern of illness and disease compared with, say, Western Europeans; a pattern that has changed over recent years.

Chemicals from activities in the industrialized world are transported to the Artic regions by atmospheric airstreams and ocean currents, causing the substances to accumulate upwards through the food chain. This is a factor that affects the lifestyle and the health of Arctic populations, and its impact is expected to increase in step with climate change.

If the Inuit population alters its diet, shifting from traditional marine-based foods in order to avoid chemicals, it may increase their risk of cancer, cardiovascular diseases, obesity, and diabetes – all of which occur less frequently among Arctic populations than among Western populations.

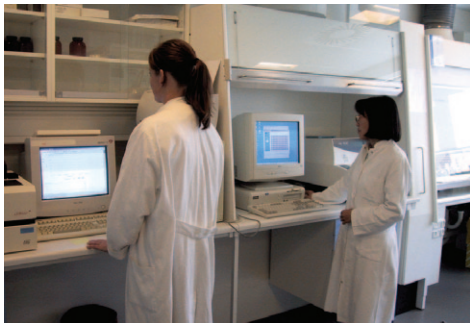
The Centre for Arctic Environmental Medicine is therefore monitoring the development of several diseases among the Arctic peoples, concentrating on the region's special conditions and influences. Part of our research also looks at gene–environment interactions, and at the genetic sensitivity of the Inuit people, given that their genetic background differs from that of ethnic Western populations.

Monitoring lifestyle changes

Since the 1990s the centre has monitored the heath of Greenland's people with focus on their particular conditions and the resulting effects. The knowledge obtained has, among other things, led to the prohibition of a series of substances. The centre is ever vigilant, checking whether new substances discovered in the food chain might constitute a health risk.

But chemical effects are not the only thing we are studying. The social structures and lifestyles of the Arctic are also changing. That is why we conduct interview studies that monitor how altered lifestyles are affecting the population's health.

Looking to the future, the centre is monitoring mothers and their children, right from pregnancy and as their lives unfold. This long-term data will allow investigations to disclose whether exposure during gestation can lead to diseases later in life. Findings are also compared internationally (among China, Norway, Greenland, and Denmark) and examined at different levels: molecular, cellular, and in overall child development.



Determining molecular and cellular bioeffects of environmental chemicals in the laboratory. Aarhus University.

PROJECTS

1. **FETOTOX:** Interaction between mother–foetus exposure to environmental toxicants and the risk of abnormal development. International interdisciplinary study (Greenland, Denmark, Norway, and China) funded by the Danish Council for Strategic Research (2011–2015).

2. **EPAKT:** Epidemiological assessment of the interaction between contaminant body burden, related xenobiotic serum activity, and health risks in Greenland. Funded by the Danish Environmental Protection Agency (2008–2011).

3. **BOC-risk:** Does Exposure to Persistent Organic Pollutants (POPs) Increase the Risk of Breast and Ovarian Cancer? (IPY) Focus on Arctic Women. Funded by the Commission for Scientific Research in Greenland (2008–ongoing)

4. **ACCEPT:** Adaptation to Climate Change, Environmental Pollution, and Dietary Transition. Establishment of a new Greenlandic Birth Cohort Study. Funded by the Danish Environmental Protection Agency (2009–ongoing)

5. **Time trend** of Perfluorinated Compounds (PFCs) in Arctic and Danish women. Supported by AU research funding and the Danish Environmental Protection Agency (2009–2011)

6. **SAM-TREND**: Comparison of contaminant data in humans, fauna, and the atmosphere in Greenland. Funded by the Danish Environmental Protection Agency (2011).

The Centre for Arctic Environmental Medicine works with the circumpolar Arctic Human Health Assessment Group (AMAP, www.Amap.no); the interdisciplinary Arctic-Health and Arctic Sci. & Tech. research groups, AU; and research groups at Danish universities SDU, KU, and DTU. The centre also acts as coordinator of the international interdisciplinary project FETOTOX, http://fetotox.au.dk/.

MILESTONES

Perfluorinated compounds are related to breast cancer risk in Greenlandic Inuit: A case control study
(Bonefeld-Jorgensen EC, et al. Environ Health. 2011 6;10(1):88)

Biomonitoring in Greenland: human biomarkers of exposure and effects – a short review
(Bonefeld-Jorgensen EC. Rural Remote Health. 2010;10(2):1362)

Global DNA hypomethylation is associated with high serum-persistent organic pollutants in Greenlandic Inuit
(Rusiecki JA, et al. Environ Health Perspect. 2008;116(11):1547–52)

Relation between serum xenobiotic induced receptor activities, DNA damage and sperm apoptotic markers in European and Inuit populations
(Long M, et al. Reproduction. 2007;133(2):517–30)

SPE-HPLC purification of endocrine-disrupting compounds from human serum for assessment of xenoestrogenic activity
(Hjelmborg PS, et al. Anal Bioanal Chem. 2006;385(5):875–87)

METHODS

We have expertise and experience in a variety of methods and technologies used for studying populations, measuring hormone disruption, and measuring cell stress and DNA changes.

- Monitoring the accumulation of chemicals (POPs) in the Greenlandic population
- Determining biological effects of serum POP mixtures (including PCB, DDT/DDE, and perflourinated chemicals (PFCs)) using SPE-HPLC fractioning
- Measuring cell stress and DNA changes (reactive metabolites, methylation and broken/damaged DNA)
- Epidemiological studies focussing on POP exposure, lifestyle, and diseases, correlated with reproduction, embryonic development, cancer, obesity, and allergies
- Comparative Artic exposure studies among Inuit, fauna, and the atmosphere
- Comparing genotypes among Inuit and Europeans.

OVERVIEW

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Basic research

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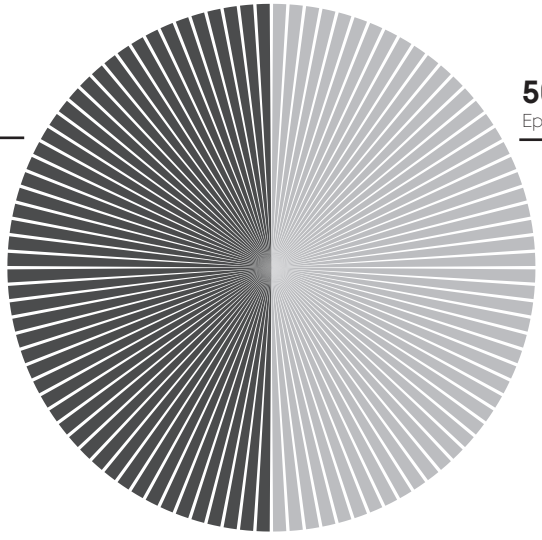
Epidemiological research



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Clinical research

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Qualitative research

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BIOSTATISTICS

The biostatistics section at the Department of Public Health helps to analyse and interpret the data gathered by the researchers at AU Health. We handle both clinical data and data extracted from Denmark's many public-health registers, such as the National Prescription Database and the National Patient Register. These electronic resources supply information that is essential for comprehensive population-wide studies.

Statistical analysis is used to get a grip on the large amounts of data that researchers assemble to shed light on a particular topic, and it indicates:

- What information is significant?
- What is not significant?
- Can many numbers be described in few numbers, without losing important information?

Biostatistics primarily deals with the statistical methods used in the health sciences and biology. Our field develops new methods, assesses their characteristics, and applies them to help resolve new, complex problems.

A team player for the whole faculty
Employees at the biostatistics section are involved in research projects at all of departments of the university's Health faculty, contributing to more than 40 projects each year. These include two comprehensive population studies concerning the prevalence of autism and diabetes, respectively. We have also assisted with risk assessments that will be a significant element in an upcoming study of patients with prostate cancer.

Data sources are never static. New and improved measurement methods are constantly being introduced, and new and more detailed electronic health databases being established, and this means there is a consistent need for ongoing development of new statistical methods. With the rapid pace at which computing capabilities continue to grow, we are constantly pushing the limits of the demands our calculation methods put on processing power. We therefore continually optimize our skills in order to be at the cutting edge of the field – and we pass these new methods on: All PhD students at Health take a mandatory course in methodology and statistics as part of their PhD programme.

PROJECTS

1. **Pharmacoepidemiology:** We are developing better methods to determine the treatment duration, based solely on when a prescription was filled and the amount of medication supplied. Based on the Danish National Prescription Database.

2. **Autism:** Studies of heritability, factors during pregnancy and delivery, and early symptoms relating to autism spectrum disorders (ASD). Based on data from public registers. These studies aim to help find the causes of ASD and contribute to early detection of the condition.

3. **Prostate cancer:** Calculation of individual life-time risk for prostate cancer patients. Based on genetic profiling.

4. **Assistance to the Danish Medicines Agency:** Our assistance is occasionally requested regarding the approval of new medication. We assess applicant compliance with the recommended statistical principles for clinical trials.

MILESTONES

Demonstration that the increased prevalence of autism in Denmark is related to earlier diagnosing
(Parner ET, et al. Arch Pediatr Adolesc Med. 2008;162:1150–6)

Detailed description of the occurrence of caries on dental surfaces among Danish children and adolescents
(Parner ET, et al. Eur J Oral Sci. 2007;115:491–6)

Development and application of methods to assess selection bias in cohort studies
(Nohr EA, et al. Epidemiology. 2006;17:413–8)

The diabetes epidemic of the 1990s shown to be caused not by obesity, but by fewer diabetics dying than the number of new diabetics being diagnosed
(Støvring H, et al. Lancet. 2003;362:537–8)

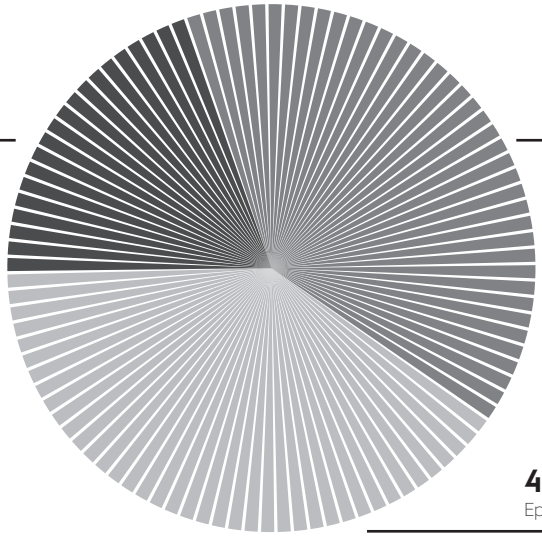
Development on the mathematical model to describe the occurrence of exposure-related cancer
(Pierce D, Væth M. Biostatistics. 2003;4:231–48)

METHODS

By using statistical models that reflect the health-science problem being examined, biostatistics makes it possible to distinguish biological variation, measurement errors, and other random variations from the systematic trends – the trends being what researchers are usually interested in identifying. To avoid misinterpretation, biostatistics focusses on diagnostic methods to reveal whether the parameters applied to a model are suitable in the specific context. These diagnostic methods are often graphical representations of noteworthy characteristics in the data. In constructing appropriate models, it is a crucial biostatistical skill to be able to adapt one's mindset to the relevant field and communicate the results in a form that is understandable and useful to other health researchers.

- Mathematics: statistics is a mathematical discipline
- Probability theory: uncertainties are described as probabilities
- Calculations: statistical calculations are done using computers with special software
- Graphical representations: a good chart is often the best way to describe results
- Common sense: some statistical methods are simply systematized common sense
- Communication: sharing knowledge amongst project participants ensures that analyses are relevant.

OVERVIEW



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Basic research

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Clinical research

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Qualitative research

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Epidemiological research

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CLINICAL SOCIAL MEDICINE AND REHABILITATION

The goal of clinical social medicine and rehabilitation is to maintain and develop optimum functional capacity in patients – despite disease, perceived illness, and physical, psychological, or social weakening. Interventions, which are based on the individual's entire life situation and decisions, are provided as a coordinated, coherent, and knowledge-based effort.

At the section of clinical social medicine and rehabilitation, our research areas include the implementation, monitoring, and assessment of rehabilitation interventions from municipal and regional authorities, which are offered to persons with chronic conditions, somatic and mental diseases, and disabilities. The groups covered are children, adults, and elderly people with a Danish or other ethnic background. We seek to answer questions like:

- How do we create a coherent rehabilitation trajectory from hospital, to general practice (GP), to municipal authority?
- How do we assess the need for, and the efficacy of, rehabilitation efforts?
- How do we help patients to keep working, even while they are ill?
- What is the best rehabilitative intervention targeted to the individual?

A significant proportion of the section's research activities revolve around the Regional Back Centre Silkeborg – Research unit for patients on sick leave. This unit was established in 2004, and it has since been run with financing from hospitals, a number of municipal authorities, and the Central Denmark Region (and the County of Aarhus, prior to 2007).

Regional and international collaboration
Working closely with the university departments of social medicine in Trondheim, Tromsø, and Oslo, we have established a Danish–Norwegian network in the field: Norsk–Dansk Trygde og Socialmedicinsk Netværk. The unit currently has six PhD students, all of whom are working with the consequences of illness for young people's functional capabilities in the workplace and elsewhere.

Our research-based work is done in close collaboration with a wide range of clinical departments at AU Health, and with a number of municipalities in the Central Denmark Region. Municipal cooperation includes counselling from physicians, psychologists, and social-service professionals. From the perspective of the individual citizen, our primary task is to coordinate the efforts of GPs, hospitals, municipalities, and workplaces.

The goal is that over the next few years we will develop useful tools that enable us to identify rehabilitation needs, and to differentiate the interventions for specific target groups at specific stages during the course of their disease.

PROJECTS

1. Working with the Regional Back Centre Silkeborg – Research unit for patients on sick leave, we have conducted a randomized controlled study (covering four municipalities in the mid-Jutland region) of a hospital-based, coordinated intervention for patients on sick leave who are diagnosed with unspecified disorders in the lower back, and neck/shoulder pain. The factors studied to assess their significance include social situation, mental illnesses, and functional impairments.

2. In a randomized study (Bodily distress syndrome, BDS, in the extensive Danish ReturnToWork intervention) focussing on persons with BDS on sick leave, we examine whether a new municipally coordinated, interdisciplinary intervention can improve their return-to-work prognosis. The study is being carried out in cooperation with the National Centre for the Working Environment.

3. In the Norwegian–Danish network, a PhD project seeks to clarify the development from 2000 to 2010 of sickness absence among young people. Comparing Danish and Norwegian data

and conditions, the project has special focus on employees of municipal care programmes for the elderly in the Municipality of Aarhus.

4. Another PhD project is studying the income situations of patients treated for haematological cancer in Denmark, shedding light on links between income situation and selected clinical, socio-economic, and demographic factors such as anxiety, depression, and fatigue.

5. Two PhD projects are part of a national Danish network (CE-Spine) involving several hospitals in the Central Denmark Region, and studying whether cognitive interventions and/or coordinator counselling prior to lumbar surgery can result in better restitution and returning to work. Both projects include health-care economy analyses.

6. An upcoming qualitative PhD examines why men diagnosed with cancer have a lower participation rate in municipal rehabilitation programmes.

MILESTONES

The research section, with its interdisciplinary staff, has effectively existed for 4½ years. Since its inception the unit has:

Hosted and assisted in the preparation and successful defence of 3 PhD dissertations

Taken on a further 6 graduates in our PhD programme (projects currently under way)

Grown to a total staff of 20, including 4 senior researchers

Established the Regional Back Centre Silkeborg – Research unit for patients on sick leave in 2004. The research is funded by an affiliation agreement between the Central Denmark Region and Aarhus University, which will provide DKK 8 m over a period of 4½ years (running until the end of 2012), and also by grants from TrygFonden and the Working Environment Research Fund. The latter has contributed DKK 5 million, which has been allocated to several projects in this context.

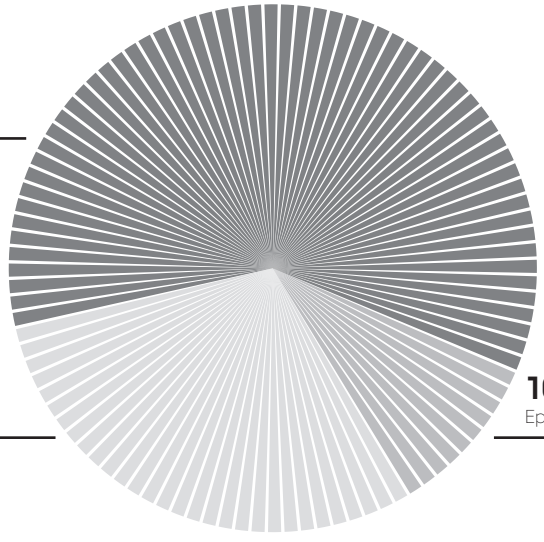
METHODS

Our research is multidisciplinary and seeks to combine:

- quantitative analyses (RCT, observational/epidemiological, and biostatistical)
- qualitative analyses (anthropological field observation, phenomenological/hermeneutic and other)
- data from all available sources: questionnaires (validated questions and scales), public registers and databases, clinical observations/paraclinical data, and interviews

New textbook in Social Medicine and Rehabilitation. FADL 2011.

OVERVIEW



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Clinical research

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Qualitative research

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Basic research

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Epidemiological research

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DIET AND HEALTH

The food that we eat constitutes the building blocks that make up our bodies. Every day, each Dane consumes an average of 3 kilogrammes of food and drink, corresponding to a whole tonne per year. Thus, from a quantitative point of view, diet is a person's most important environmental exposure. It almost goes without saying that diet is decisive to our state of health.

Central questions for this area of research include:

- Which components in our diet are associated with health?
- How can our diet help to prevent chronic diseases?

We combine our own epidemiological data from the study "Diet, Cancer and Health" with data from the European Prospective Investigation into Cancer and Nutrition, additionally drawing upon the extensive information available from Denmark's open public registers and databanks. In Denmark we are following 57,000 participants, and the pan-European project includes more than 500,000.

Diet, Cancer and Health – an epidemiological study.

Previously, dietary research mainly concentrated on individual components such as vitamins, minerals, and certain foodstuffs. By contrast, today's researchers look at the entire diet, for instance by examining the impact of replacing certain foods – say, replacing a large meat intake with a large amount of vegetables. One of our recent studies showed that at a detailed nutritional level there was no apparent difference in the frequency of ischaemic heart disease when saturated fats were replaced with carbohydrates. However, when we analysed the various types of carbohydrates, the same study showed that high-fibre carbohydrates were linked to lower morbidity, whereas refined carbohydrates were associated with higher morbidity rates.

Diet is a part of each person's aggregate lifestyle, and the importance of diet and lifestyle are partially a function of our particular genetic makeup. Many studies consequently explore the interaction between the three factors: diet, lifestyle, and genetics.

The main emphasis is on the significance of diet to the development of cancer, cardiovascular diseases, diabetes, obesity, and mortality.

PROJECTS

1. Numerous studies are based on "Diet, Cancer and Health", a follow-up study with 57,000 participants between 50 and 65 years of age at the time of recruitment. Information has been collected on diet and lifestyle, together with measures of anthropometry and biological material, including blood, adipose tissue, urine, and nail clippings.

2. "Diet, Cancer and Health" is part of the joint European Prospective Investigation into Cancer and Nutrition (EPIC), which follows a total cohort of 520,000 participants from 10 different countries. While the primary focus is on cancer, sub-studies are concentrating on type-2 diabetes (the InterAct programme) and cardiovascular diseases (EPIC-Heart).

3. The Danish Obesity Research Centre is a national interdisciplinary centre that investigates the causes and consequences of obesity. Data from the "Diet, Cancer and Health" project are used in studies dealing with diet's impact on the development of obesity, and with the significance of body-stature changes to the development of cardiovascular diseases and type-2 diabetes.

4. Causes of atrial fibrillation – particularly examining the intake and metabolism of fish and fatty acids in an interdisciplinary project financed by the Danish Council for Strategic Research. These projects are conducted in collaboration with fellow scientists in the UK and the US.

METHODS

Population studies

- Epidemiology
- Nutritional epidemiology
- Biostatistics
- Informatics.

MILESTONES

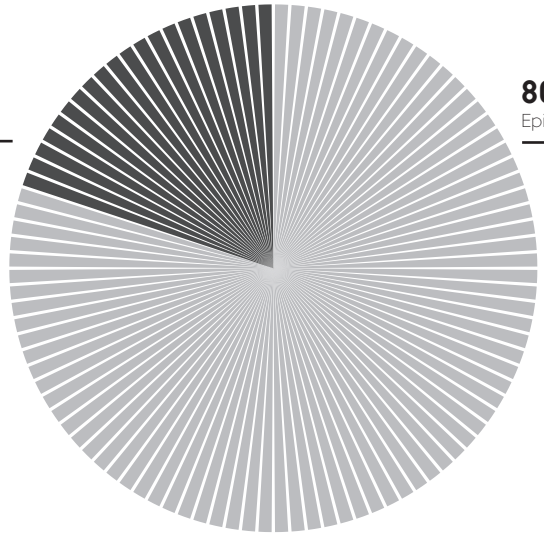
Marine n-3 polyunsaturated fatty acids in adipose tissue and the risk of acute coronary syndrome
(Joensen AM, et al. Circulation. 2011 Sep 13;124(11):1232–8)

Exploring dietary patterns by using the treelet transform
(Gorst-Rasmussen A, et al. Am J Epidemiol. 2011 May 15;173(10):1097–104)

Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycaemic index
(Jakobsen MU, et al. Am J Clin Nutr. 2010 Jun;91(6):1764–8)

Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark
(Tjønneland A, et al. Scand J Public Health. 2007;35(4):432–41)

OVERVIEW



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ENVIRONMENT AND RESPIRATORY HEALTH

Respiratory diseases, including asthma and airway allergies, are a largely overlooked public-health problem afflicting about 25 per cent of the Danish population. Quite apart from reducing patients' quality of life, such conditions are expensive to treat, both for society and for the individual. By learning more about the interaction between humans and the environment, indoors and out, and by identifying factors that may contribute to the development of respiratory ailments, we can also find better ways to prevent them.

That is why researchers in this field are asking questions like:

- How are respiratory illnesses contingent upon the gene–environment interaction?
- How do changes in our indoor and outdoor environment affect the development of allergies and respiratory ailments?
- Once new knowledge about the gene–environment interaction's significance for the development of respiratory diseases has been gained, how can it be used to prevent these ailments from occurring?

Working closely with a wide range of partners
Research into the impact of environmental factors on allergy and respiratory diseases is carried out in close collaboration with scientists from other university departments in Aarhus and elsewhere. Our partners include researchers from other universities and medical clinicians from departments for pulmonary and occupational medicine, who bring up clinical issues that help to define and develop new research areas.

The research has a strong end-user focus, with emphasis on transforming its findings into real benefits for the groups exposed to the adverse environmental conditions. That is why research projects often have an advisory group composed of key stakeholders, including ministries and labour-market organizations.

This makes it possible to put scientific results to practical use. In 2007, for example, the respiratory research at Health informed a decision to reduce the limits on wood dust in the workplace, thereby reducing the risk of lung diseases among employees in the woodworking and furniture industry.

Lung function in field studies

PROJECTS

1. Participation in CEEH – the interdisciplinary Centre for Energy, Environment and Health (www.CEEH.dk). CEEH utilizes knowledge about air pollution and its effects on human health, coupling scientific findings with energy economy, atmospheric chemistry, meteorology, demography and health economics to develop the energy utilities of the future – and to asses their impact on public health.

2. Numerous studies of acute toxicity. Conducted in the unit's advanced climate chamber, these studies enable scientists to directly examine inflammation in the respiratory tract after a subject's controlled exposure to environmental pollutants. The substances studied range from indoor contaminants to pollen and air pollution.

3. Leadership of CISBO – the interdisciplinary Centre for Indoor Air and Health in Dwellings, under the auspices of Realdania Research (www.CISBO.dk). This centre investigates the connection between indoor pollutants and health using many different approaches, from intervention to climate-chamber exposure.

4. The SUS project, studying indoor heath in farm buildings, has catalogued data on 2,400 young farmers over a period of 15 years. SUS has yielded a unique insight into the impact of gene–environment interaction on the development of allergy and respiratory diseases in the agricultural sector. Findings have demonstrated a lower prevalence of allergy and asthma among people born in rural settings, and identified genes that prove to be linked to a higher risk of developing asthma.

5. A study of potential links between wood dust and the development of respiratory diseases among 2,000 workers in the furniture industry. Detailed information on exposure and disease in this cohort, as well as detailed knowledge of the factors influencing exposure levels, has influenced the international research community and woodworking industries worldwide.

MILESTONES

Demonstration of gene–environmental interaction between agricultural exposure and genetic variants of alfa1 antitrypsin
(Sigsgaard T, et al. Eur Respir J. 2000;16:50–5)

Men and women are found to react differently following exposure to organic dust
(Jacobsen G, et al. Eur Respir J. 2009 Jun;33(6):1268–76)

Allergies are shown to occur less often among young farmers born in a rural setting
(Portengen L, et al. J Clin Exp Allergy. 2002 Feb;32(2):247–53)

Identification of risk factors for asthma among young farmers
(Omland O, et al. J Allergy Clin Immunol. 2011 Jul 11)

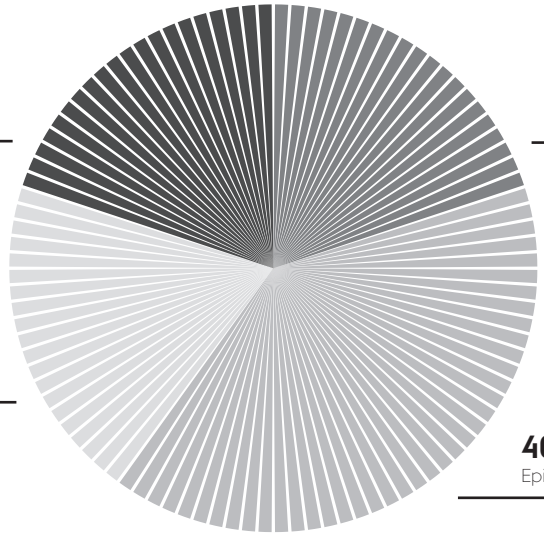
A large-scale, consortium-based, genome-wide association study of asthma
(Moffatt MF, et al. N Engl J Med. 2010 Sep 23;363(13):1211–21)

METHODS

Research into allergies and the human respiratory tract involves many different fields and activities, among them epidemiological studies, basic science, and clinical exposure studies using one of the most advanced climate chambers in the world. The scientific methods and fields employed include:

- Toxicology
- Human-exposure chambers equipped with state-of-the-art exposure facilities for particles and aerosols; further facilities for climate simulation
- Cellular studies in vitro and ex vivo
- Epidemiology, with emphasis on respiratory diseases and allergies
- Environmental epidemiology
- Occupational epidemiology
- Occupational exposure assessment focused on particles, microorganisms, and allergens
- Indoor and outdoor exposure assessment

OVERVIEW



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EXERCISE, TRAINING, AND PHYSICAL ACTIVITY

How does exercise affect the muscles? And how do athletes and patients organize their physical training to achieve maximum benefit? These are some of the big questions we are working on at the research unit for the Biology of Sport.

The research concentrates on five different areas that require very different skills, with a broad focus on both sport, clinical aspects, and basic research. Our core competences are planning, conducting, and assessing intervention programmes for physical training. Furthermore, we have great expertise in basic research, since most of our studies focus on a variety of biochemical, physiological, molecular-biology, and biomechanical methods to determine how the muscles and the circulatory system work.

One key area is research on physical training and optimizing athletic performances in the world of sports. The clinical aspects also relate to physical activity as a means to improve health – including physical activity aimed at reinforcing treatment and/or rehabilitation. Our basic research investigates muscle function and adaptation to activity and inactivity in terms of physiology, molecular biology, and biomechanics.

Principal investigator in a Nordic multi-centre study

In most projects we work with researchers outside our own unit, which has a wide-ranging and well-established network of numerous external partners. These include universities and university hospitals, notable examples being Aarhus University Hospital, the AU Department of Molecular Biology and Genetics, and the AU Department of Biomedicine, as well as research institutions in Norway, the United States, and Australia.

Currently the research unit is acting as principal investigator for a large Nordic multi-centre study of multiple-sclerosis patients undergoing a long-term physical training intervention. The study includes Norway, Sweden, and Finland and is being conducted in collaboration with a major pharmaceutical company.

PROJECTS

1. **Effects of acidification and increased extracellular potassium on dynamic muscle contractions in isolated rat muscles.** We are working with the Department of Biomedicine on multiple projects concerning the role that muscle ion balance plays for muscle fatigue during high-intensity dynamic work. Our collaborative results include a series of articles on the significance of potassium and hydrogen ions for muscle fatigue. It was previously believed that acidification with lactic acid was a significant cause of fatigue. These studies suggest, however, that in situations where muscle function is inhibited by increased levels of extracellular potassium, acidification can partially protect muscle from fatigue. This has led us to theorize that the formation of lactic acid during hard work has a primarily positive effect on muscle function during dynamic contractions.
2. **Fatigue, mood, and quality of life improve in MS patients after progressive resistance training.** This study demonstrates the importance of physical training (resistance training) for patients with multiple sclerosis (MS): It augments their muscle strength and functional capabilities and reduces fatigue, even while improving general mood and quality of life. The study's findings therefore controvert the long-standing practice of advising MS patients to avoid physical training. The study was done in close collaboration with neurologists at Aarhus University Hospital and with the Danish Multiple Sclerosis Society.
3. **Differentiated mTOR but not AMPK signalling after strength vs endurance exercise in training-accustomed individuals.** The biological processes taking place in the muscle cell at a molecular level have come strongly into focus as we seek to understand how different types of physical activity, and inactivity, can affect health and/or physical performance. This particular study exemplifies how only one training session can serve as a solid predictor for how, by virtue of its biological regulation mechanisms, the muscle is capable of adapting to changes in the physical activity level. This, in its turn, can help us to understand how beneficial development of functional muscle adaptations can best be promoted through prolonged physical activity.

MILESTONES

Effects of acidification and increased extracellular potassium on dynamic muscle contractions in isolated rat muscles
(Overgaard K, et al. J Physiol. 2010 Dec 15;588)

Fatigue, mood, and quality of life improve in MS patients after progressive resistance training
(Dalgas U, et al. Mult Scler. 2010 Apr;16(4):480–90)

Differentiated mTOR but not AMPK signalling after strength vs endurance exercise in training-accustomed individuals
(Vissing K, et al. Scand J Med Sci Sports. 2011. Epub ahead of print)

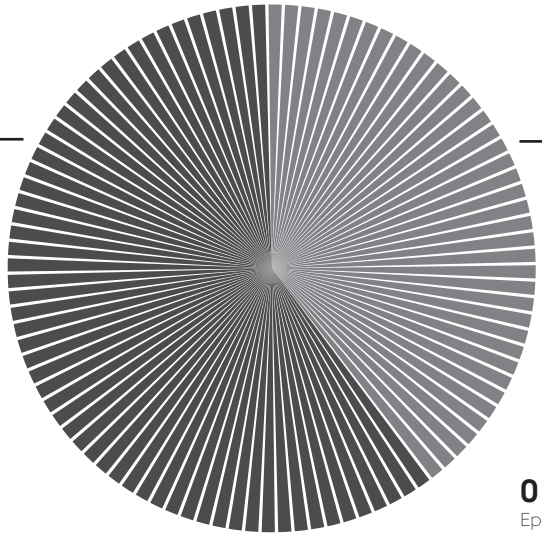
METHODS

Our competence spans the entire process of planning, carrying out, and assessing intervention programmes for physical training.

- Intervention programmes
- Physical testing of muscle function, circulation, and other health parameters
- In vitro models with isolated muscle groups
- Human muscle biopsies and blood sampling
- Biochemical and physiological measurements of blood and muscle tissue
- Molecular biology measurements of muscle tissue using real-time PCR, Western blot and other techniques
- Biomechanical methods using force platform, high speed camera, and inverse dynamics

Experimental evaluation of physical capacity.

OVERVIEW



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Basic research

40 %
Clinical research

0 %
Qualitative research

0 %
Epidemiological research

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GENERAL PRACTICE – COORDINATING ACROSS THE BOARD

The Research Unit for General Practice examines the patient–doctor encounter as it unfolds when citizen meets general practitioner, and also investigates the broader role of primary care. During a year, 98 per cent of Danes are in contact with their general practitioner (GP), and 90 per cent of all contacts do not involve specialist care.

In addition to handling common ailments, the GP must be capable of rapidly diagnosing serious and unusual conditions, including cancer. The unit conducts research that explores how patients can be provided with the best possible treatment, and how available resources can be put to the best use.

The unit's researchers answer questions such as:

- Why do patients consult their GP?
- How is cancer best diagnosed in the GP's office?
- How can GPs identify vulnerable patients?
- How do we speak with patients about risks?
- What is the role of general practice in treating people with mental illnesses?

From primary/secondary care to whole-system care

Most patients suffer from more than one medical condition, and there is a growing need to think of the various levels of heath service as parts of an integrated whole. Today, as Danish health services become increasingly specialized, the unit's researchers are seeking optimal solutions for organizing and coordinating treatment for patients with complex conditions.

In 2004, the Research Unit for General Practice showed that Denmark had excessively long delays for people diagnosed with cancer. Since then, the research unit has often provided valuable advice to the health authorities, and given feedback to augment the Danish health service's efforts to improve early diagnosing of cancer. Furthermore, the research unit is the founder of an international network for general-practice researchers, as well as an active participant in numerous transnational research projects.

90 per cent of all contacts do not involve specialist care.

PROJECTS

1. The Research Centre for Cancer Diagnosis in Primary Care (CaP) is one of the world's leading centres for research into diagnosing cancer early.
2. The Pattern of Contact and Illness project examines the reasons why some patients consult their GPs.
3. The COPD Treatment Pathway project looks at the impact of a specific treatment pathway for Chronic Obstructive Pulmonary Disease, and how it is implemented.
4. The Prostate Cancer Shared-Care project implement and evaluated a program for shared follow-up (urologist and GP) for prostate-cancer patients.
5. The Improved Follow-Up of Abnormal Cervical-Cancer Screening Test Results is an intervention project conducted to evaluate whether new communication tools will improve the results of the screening program.

MILESTONES

The general practitioner's role as gatekeeper can delay the diagnosing of cancer
(Vedsted P, Olesen F. Br J Gen Pract. 2011;61:e508–12)

The longer it takes for treatment to begin, the poorer the survival rates among patients with colon cancer
(Tørring ML, et al. Br J Cancer. 2011;104:934–40)

A systematic overview of delays in diagnosing cancer in Denmark
(Olesen F, et al. Br J Cancer. 2009;101:S5–8)

Why patients go to the doctor in Denmark
(Moth G, et al. Aarhus: The Research Unit for General Practice in Aarhus, Aarhus University; 2010)

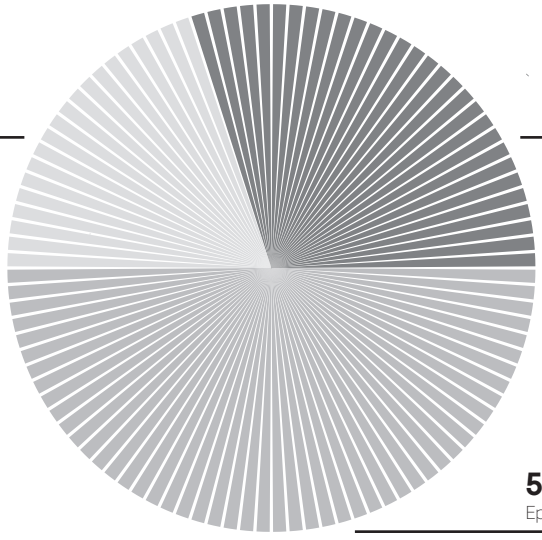
Bodily stress – a significant diagnosis in general practice
(Rosendal M, et al. Scand J Prim Health Care. 2005;23:3–10)

Screening for mental illness in general practice is not necessarily a good thing
(Christensen KAS, et al. Fam Pract. 2005; 22:428–34)

METHODS

- Clinical epidemiology
- Qualitative research
- Register-based research
- Intervention research
- Questionnaire studies.

OVERVIEW



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Qualitative research

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Clinical research

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Basic research

50 %
Epidemiological research

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GENERAL PRACTICE – PREVENTION FOCUSSING ON THE INDIVIDUAL

Lifestyle-related diseases such as diabetes, cardiovascular disorders, and certain types of cancer have increased the disease burden on individuals and on societies. Scientific findings indicate that healthy food, regular exercise, and tobacco cessation can reduce the prevalence of coronary heart diseases, stroke and diabetes by 80 per cent, and the prevalence of certain cancers by 40 per cent. Thus, the potential for improving public health is huge.

Prevention efforts can target structural changes in society, life-style changes for the individual, or both. In the course of a year, general practitioners (GPs) in Denmark come into contact with about 90 per cent of people registered with their practice. GPs are therefore in an excellent position to help individuals improve their health through life-style changes, in order to prevent diseases and premature death.

The Section for General Practice conducts work to solve question such as these:

- Can GPs help the individual to attain a better quality of life, reduce the risk of lifestyle-related diseases, and improve survival by giving people the opportunity to attend a medical health check followed by a health conversation?
- How can GPs motivate the individual to make healthier lifestyle choices?
- How can GPs best help individuals to make healthier choices and, when relevant, improve compliance with prescribed preventive medication?
- Which factors predict an unhealthy lifestyle, lifestyle diseases, and premature death?

Over the past 10 years we have conducted the ADDITION study, which evaluates the benefits and disadvantages of a high-risk screening program for diabetes in general practice. Some of our findings are now being incorporated into the clinical guidelines issued to Danish GPs.

In relation to health promotion, prevention, treatment, and rehabilitation we work with patient education, giving autonomy support and encouraging self-care and self-management. This education seeks to motivate and stimulate individuals to live with their disease, or to cope with the risk of becoming ill. Other research areas include childhood obesity, and living with several chronic conditions (multimorbidity).

We cooperate with national and international scientists from universities in Cambridge, Leicester, Utrecht, and elsewhere. In Denmark we also collaborate with the Danish Institute for Health Services Research, municipal authorities, and GPs across the country.

PROJECTS

1. The Ebeltoft Health Promotion Project began in the early 1990s. It offered 2,000 citizens living in the Municipality of Ebeltoft, and aged 30 to 50, medical check-ups and consultations with their own GP. The study, lasting 5 years, demonstrated that such an initiative could reduce the number of people at risk of cardiovascular diseases from 18% to 10%.

MILESTONES

2. The ADDITION study, initiated in Denmark, is an international study on the screening and treatment of people with asymptomatic diabetes. In Denmark, approximately 160,000 people ranging from 40 to 69 years of age were invited to sign up for screening. About 1,600 were identified with screen-detected diabetes; 2,300 had pre-diabetes; and 7,300 had a high risk of coronary heart diseases. The findings suggest that screening for diabetes is beneficial, and that screening for diabetes and screening for cardiovascular risk should be seen as integrated issues.

3. The Randers Health Promotion Project: "Check Your Health" is an extension of the project in Ebeltoft and the ADDITION study (both describe above), and it involves 36,000 citizens in the Municipality of Randers. "Check Your Health" seeks to further develop the concept of medical health checks in general practice.

Health tests and health consultations reduced cardiovascular risk without psychological strain, increased healthcare utilization or increased costs; an overview of the results from a 5-year randomized trial in primary care
(Lauritzen T, et al. The Ebeltoft Health Promotion Project (EHPP). Scand J Public Health 2008;36(6):650–61)

Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type-2 diabetes detected by screening (ADDITION-Europe); a cluster-randomized trial
(Griffin SJ, et al. Lancet. 2011 Jul 9;378(9786):156–67)

Effect on motivation, perceived competence, and activation after participation in the "Ready to Act" programme for people with screen-detected dysglycaemia: a 1-year randomized controlled trial (Addition-DK)
(Maindal HT, et al. Scand J Public Health. 2011 May;39(3):262–71. Epub 2011 Mar 22)

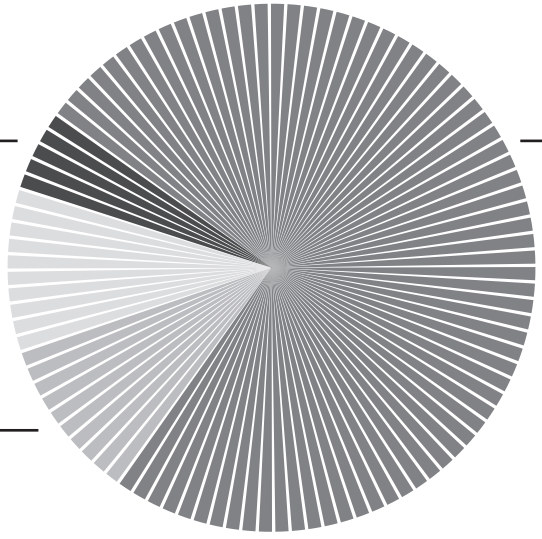
Stepwise screening for diabetes identifies people with high but modifiable coronary heart-disease risk (the ADDITION study)
(Sandbaek A, et al. Diabetologia. 2008 Jul;51(7):1127–34. Epub 2008 Apr 29)

MMR vaccination and febrile seizures – evaluation of susceptible subgroups and long-term prognosis
(Vestergaard M, et al. JAMA. 2004;292:351–7)

METHODS

- Clinical studies, randomized controlled trials (RCTs), and cohort follow-up studies
- Qualitative studies
- Register-based studies
- Health-service research

OVERVIEW



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GLOBAL HEALTH

Thanks to the field of health science, today we have a multitude of strategies designed to prevent, diagnose, and treat a wide range of the diseases occurring around the world. Experience shows, however, that the cost efficiency and the effectiveness of these strategies is highly dependent upon how they are implemented and – not least – where and in which health system.

The aim of global-health research is therefore to address health problems that cross national boundaries and hold political and economic significance on a global scale. Our research efforts study the health of entire populations seen in a global context, with emphasis on improving health across the board, reducing inequality, and safeguarding against global threats.

Research into global health addresses questions like these:

- What factors influence global health?
- What interventions are effective in improving global health?
- How can health systems be organized to generate maximum health benefits?

We not only look into concrete treatment strategies but also study the organization and financing of health systems, as well as the many pertinent factors at work outside the health system itself. These include environmental issues, education, nutrition, and economic growth. This enables us, for instance, to identify target groups for interventions and to create a basis for prioritizing health efforts in a way that incorporates measures that lie beyond the scope of the conventional health system.

Our research consistently seeks to address this challenge: that the best health solution in one country cannot always be duplicated in the rest of the world. We find that when working in areas with barely functioning health systems and no registration of the civilian population, it is not always possible to diagnose the diseases occurring there, or to describe their significance to the local population, since the baseline profile for the general population is unknown. Part of our work is therefore to develop simple tools – like a clinical score describing the severity of tuberculosis without using complicated laboratory analyses – and to help set up population-based public registers of citizens within so-called Demographic Surveillance Sites.

The way a health system is organized is, to some degree, defining for who uses that health system, how it is used, and which services it provides. Furthermore, in societies where resources are extremely scarce, becoming ill entails a significant financial risk that can be devastating for the individual. That is why one research aim is to identify the most suitable financing mechanisms in a given context. A study of health insurance programmes in Ghana and Tanzania examines various factors, including how different types of health insurance affect health behaviour, access to the health system, choice of treatment, quality of care, and financial risk for the citizens. Not least, our endeavours seek to determine whether this ultimately affects the health of the population at large.

PROJECTS

1. Health insurance in Ghana and Tanzania: Addressing equity and accessibility.
2. Cost effectiveness of vaccination strategies (sequence and bundling) and vitamin A supplements for children.
3. Economic consequences of the rising numbers of elderly citizens and the growing prevalence of chronic illnesses.
4. Multi-site studies within the INDEPTH network of risk factors for tuberculosis and of the clinical treatment of suspected cases of tuberculosis.
5. IRIPT – Isoniazid or Rifampicin/isoniazid as Preventive Treatment for Tuberculosis; a randomized clinical trial.
6. PIONA – Protease Inhibitor or NNRTI as first-line HIV treatment in a West African population; a randomized clinical trial.
7. Primary health-care reform in Palestine.
8. Introduction and evaluation of family and community medicine as a post-graduate study programme in Rwanda.
9. Founding of the Centre for Global Health at Aarhus University (GLOHAU), bringing together all competence areas

in the field of global-health research at AU. The aim is to pool the university's existing global-health capabilities in research and teaching, creating a framework for synergies to develop between the various professional disciplines represented.

10. Active participation in the Platform for Human Health under the auspices of the initiative "Building Stronger Universities in Developing Countries" – which aims to build up the research capabilities at, and collaboration with, selected universities in developing countries.

Preparing for systematic routine data collection for households at a Demographic Surveillance Site.

METHODS

The way that we work is fundamentally interdisciplinary, based on the needs of underprivileged populations and centred on building up capabilities. We conduct culture-sensitive, population-based studies in collaboration with local partners.

- Interdisciplinary approaches
- Randomized controlled clinical trials
- Cross-sectional, case-control, and follow-up studies
- Quasi-experimental designs
- Designing of surveys and preparation of questionnaires
- Qualitative studies
- Economic analyses.

MILESTONES

The significance of schistosomiasis co-infection for the pathological progression of HIV
(Kallestrup P, et al. Clin Infect Dis. 2006;42:1781–9)

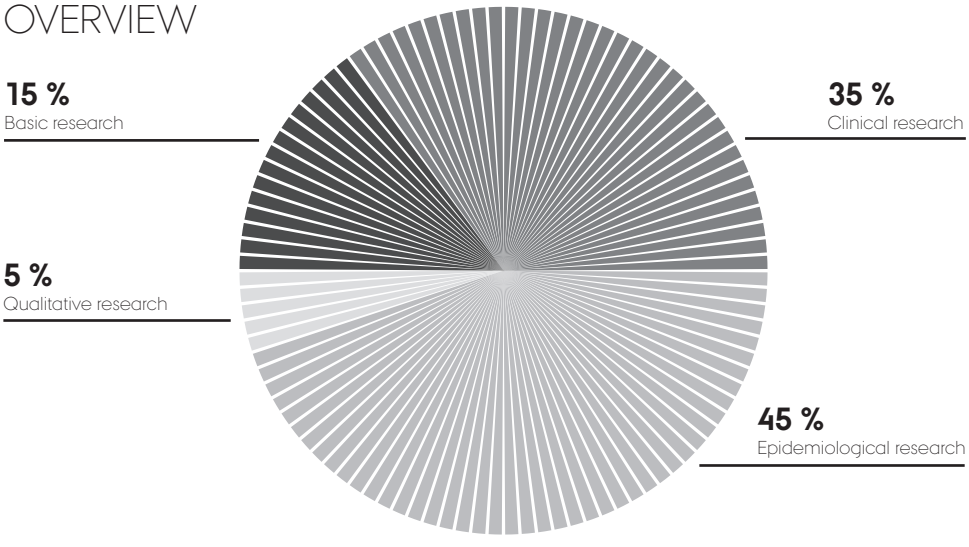
Development of a clinical score for assessing the severity of tuberculosis
(Wejse C, et al. Scand J Infect Dis. 2008;40:111–20)

Extensive phase-III clinical trial in Africa to study the effect of vitamin D on tuberculosis
(Wejse C, et al. Am J Respir Crit Care Med. 2009;179:843–50)

Demonstrating a substantial effect of tuberculosis on child mortality in exposed families in West Africa
(Gomes VF, et al. Thorax. 2011 Feb;66(2):163–7)

The dynamics of resource allocation and payment mechanisms, most particularly their impact on supplies of medicine
(Enemark U. In: Preker A, Langenbrunner J, editors. Spending Wisely: Buying Health Services for the Poor. World Bank: February 2005)

OVERVIEW



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HEALTH ECONOMICS

Does the price of medication influence patient health? What are the health-related consequences of hard physical labour? Do people take better care of their health if they have to pay for treatment themselves? These are just a few of the questions central to our research in the field of health economics.

This research takes place within a collaborative framework linking researchers at Health and at the university's Department of Economics, which gives us crossdisciplinary competence in understanding the effect of investments in health. One resource we use is the extensive data available to researchers from Denmark's many electronic public registers and databases. Furthermore, we have developed methods and techniques for register-based research.

We also have considerable expertise in conducting Medical Technology Assessments (MTAs), which involve complex economic analyses regarding the introduction of new treatments for patients. These assessments are carried out in close collaboration between the Department of Public Health and the Central Denmark Region.

Unique methods for register-based research

Thanks to the combination of data from Denmark's registers and databases (which are unparalleled in their coverage and level of detail) and a remarkably international research environment (which also draws upon the skills of a Nobel laureate from the Department of Economics), Aarhus University has many years of experience in studying register data and developing unique techniques and methods. This greatly contributes to our understanding of the cause-and-effect mechanisms that come into play between the investments made to promote public health, and their effect on public health at a societal level.

In the field of register-based research we possess special expertise in selecting variables and identifying correlations between specific changes during the various phases of life and their effects on health. In this way we can help to clarify whether specific health-policy measures and forms of treatment have achieved the desired effect, seen from a health-economics perspective.

Examples of our research include analysing the effectiveness of broadly targeted political health measures in relation to individuals and families. A specific example would be determining how treating children with ADHD with medication affects the patients' knowledge acquisition at school and, in a later phase of life, their adaptation to the labour market. We therefore focus not only on the clinical and societal effects of treatment, but also on the social effects that the interventions have on the patients in question and their immediate surroundings.

PROJECTS

1. 2011–2014 Sapere Aude Starting Grant, the Danish Council for Independent Research. Attention-Deficit/Hyperactivity-Disorder and Human Capital: The Lives of Children, Peers, and Families. DKK 5.6 million (Project investigator: Marianne Simonsen).

2. 2011–2012 The Danish Council for Independent Research. What are the determinants of patient behaviour? DKK 1.8 million (Project investigator: Niels Skipper).

3. 2009–2012 The Danish Council for Independent Research. The Impact of Education on Acquiring a Disability, Coping with Disability, and Disability-Related Labour Market Exit. DKK 1.8 million (Project investigator: Nabanita Datta Gupta).

MILESTONES

Price sensitivity of demand for prescription drugs: exploiting a regression kink design
(Simonsen M, et al. Working paper 2010–3, Aarhus University, School of Economics and Management. Under submission.)

Non-cognitive child outcomes and universal high-quality child care
(Datta Gupta N, et al. Journal of Public Economics. 2010;94:30–42)

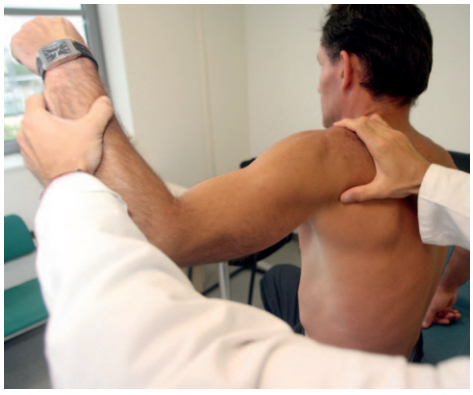
The effects of pharmacological treatment of ADHD on children's use of health services and risky health behaviour
(Dalsgaard S, et al. Work in progress)

Health-services use associated with emergency department closure
(Enemark U, et al. Journal of Health Services Research and Policy. 2011;16(3):161–6)

The impact of health on individual retirement plans: self-reported vs diagnostic measures
(Datta Gupta N, et al. Health Economics. 2010;19(7):792–813)

Collaborative efforts
Working with the Municipalities of Randers, Syddjurs, and Aarhus to develop a joint project for intermediary health-service programmes (between the primary and secondary sector: "comfort-and-care" hotels/ rehabilitation assistance units)

Center for Vitamins and Vaccines (a new basic-research centre headed by Christine Benn). The centre also does cost-effectiveness studies of interventions in Denmark (a randomized study at Kolding Hospital going forward; historically a quasi-experimental design) and in Guinea Bissau.

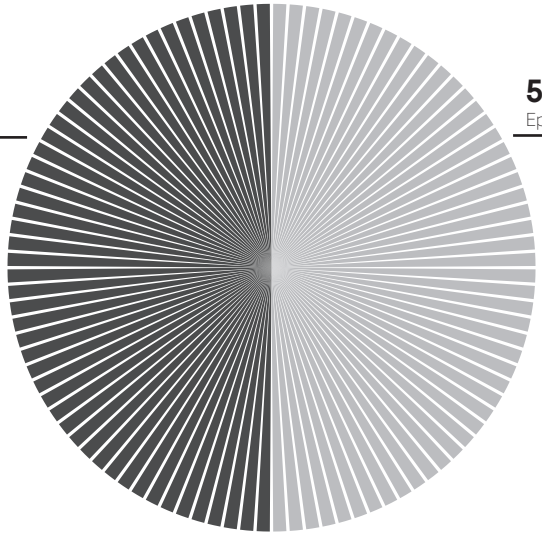


METHODS

Microeconometric methods used on electronic register data. Examples include instrument variables, regression kink designs, sibling comparisons, and other panel data methods.

- Economic assessment (cost-effectiveness, cost–benefit analysis)
- Time series and cross-sectional analysis of aggregated data
- Randomized and quasi-experimental designs
- Survey studies
- Crossdisciplinary approaches and 1triangulation

OVERVIEW



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Basic research

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Epidemiological research

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HEALTH SERVICES RESEARCH

When the time comes for politicians to lay down priorities and make decisions about the heath system, it is vital that they already have a solid foundation on which they can rely. The Unit for Health Services Research is part of that foundation.

We do research on the organization and efficiency of the Danish national health service, being broadly concerned with the arrangement of the health system, and the population's state of health. We address such questions as:

- What resources are available to us – as private citizens and as staff?
- Does the organization of the health system correspond to the Danish population's health-service needs?

Moreover, we assist the decision-makers obliged to choose one type of operation, or one type of medication, over another. In such cases our knowledge can be helpful in drawing a clear picture of the situation: You can choose this (or that) type of operation, at this (or that) cost, and it will have these (or these) side effects. Which would you prefer?

Health Technology Assessments yield results
Part of the work we do is carrying out a type of practice-based analysis and research projects called an HTA – a Health Technology Assessment. In this context we have succeeded in putting Denmark on the map by helping to develop and design the concept of the Mini-HTA. This concept means that HTAs no longer exist only in the form of exhaustive reports, but have become a mindset that can be used to prioritize and organize. Evaluations have already shown that many hospitals have used the Mini-HTA and subsequently rationalized the way they work.

We also work closely with the country's university hospitals and political administrative system. What is more, partnerships with the business community have produced positive results, including a well-documented HTA used by a small Danish IT consultancy firm that has invented a system to support working procedures related to the execution of the daily surgical programme.

We are also part of several international collaborative efforts – among them INAHTA (the International Network of Agencies for Health Technology Assessment). Over the coming years our goal is to become even more internationally oriented. At the same time, however, we will continue to help find answers to some of the pressing priority issues facing the Danish national health system. In short: How can we make the most of the money we spend on health?

PROJECTS

1. **Analysing the effects of a network family-support programme – a new service offering in social psychiatry.** This project is linked to a new, supplementary social-psychiatry service – the network family-support programme – which has been initiated in seven Danish municipalities. Its coverage is at least one local mental-health service centre in each of Denmark's five regions. The programme's target group is mental-health service clients suffering from prolonged and serious mental illness, who have an additional need for special social interventions. The basic idea is to bring these people into contact with "normal society". In practical terms, the mental-health clients in the programme are offered temporary stays with carefully chosen, well-functioning private families.

2. **HTA of rotavirus vaccination.** This is an HTA initiated and led by the National Board of Health. Our research unit is responsible for analysing the organizational opportunities and barriers involved in implementing one of the two rotavirus vaccines in the Danish child vaccination programme.

3. **Assessment and implementation of Aarhus EPR at the two branches of the Randers and Grenaa Regional Hospital.** This assessment evaluates the immediate consequences of fully rolling out the entire Aarhus Electronic Patient Record, also seeking to point out potential barriers relating to the end-users' application of Aarhus EPR.

MILESTONES

HTA of surgical treatment of patients with selected frequently occurring shoulder problems
(Løvschall C. HTA and the Unit for Health Services Research. The Central Denmark Region: 2011)

Analysis of cost-effectiveness of screening Danish men aged 65 for abdominal aortic aneurysm
(Ehlers L. BMJ. 2009;338:b2243)

HTA of "The Interactive Hospital" (iHospital) project
(Jensen LG. HTA and the Unit for Health Services Research. The Central Denmark Region: 2009)

Doing Mini-HTA in hospitals: A new concept of decision support in health care?
(Ehlers L. Int J Technol Assess. 2006;22:295–301)

Our unit has completed a series of HTA projects that have informed Danish decision-makers at a regional and national level. We have also contributed to developing new HTA methodologies, such as the concepts of Rapid HTA and Mini-HTA, which have gained a considerable international following. Today, both methods are seen as important tools in forming a basis for decision-making in the Danish health service system.

The Unit for Health Services Research has participated in collaborative international and European efforts concerning HTA, and will go on making valuable contributions to the development of international methods in the years to come.

In the specific field of health services research, the unit's most notable contributions consist in developing methods to assess the application of ICT (Information and Communications Technology) and in having performed high-quality assessments in this area.

METHODS

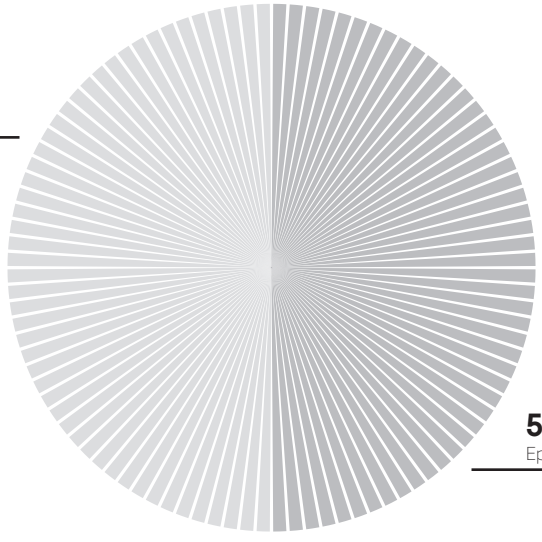
At the Unit for Health Services Research we take an interdisciplinary approach, often working with clinical researchers and other groups. We therefore employ all methods that can help to shed light on the problems we are addressing. Our scientific methods include:

- Quantitative methods (preparation of systematic reviews, RCT, observational/epidemiological and biostatistical methods)
- Qualitative methods (anthropological field observation, focus groups, interviews, and textual analysis)
- Organizational and health-economics analyses

Health service research utilizes all available sources: questionnaires (validated questions and scales), administrative registers and clinical databases, clinical observations/paraclinical data, interviews, and more.

The field of health service research is closely linked with daily practice, and its aim is to support qualified decision-making in health care.

OVERVIEW



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HUMANISTIC SPORT RESEARCH

The doping scandal during the 1998 Tour de France made the public acutely aware of how widespread the use of performance-enhancing drugs had become in the upper echelons of the sporting world. Developing medical techniques that can enhance a person's physical performance always entails a risk that they will be used to do just that.

Humanistic sport research delves into the dynamic interaction and the inherent contradictions between our ideas of the noble contest, the joy of social interaction, and the way top-level sports is run. In its research, the unit has shed light on taboos, dilemmas, and inconsistencies in sporting circles at the highest level, and on the public approach to sports – ultimately giving rise to considerable debate within and outside the Danish sports community.

Fan culture and extreme body cultures

Humanistic sport research is a young science, and its scope is expanding. Fascination and attraction are intrinsic elements of top-level sports. That is why the discipline examines how these special emotions are kept alive, and how the appeal of sports is cultivated in fan culture. One aspect of fan-culture research is a collaborative project being carried out with Liverpool University, and other activities include participation in a joint EU research project.

Humanistic sport research has also begun to study the prevalence of obesity as an expression of extreme body culture, asking, for instance, how and to what extent medical and psychological mechanisms can explain obesity.

Left: The hypodermic needle is a powerful and widely used symbol when the media cover doping issues.

Right: Fears that performance-enhancing drugs will transform athletes into physical freaks is a weighty argument against doping.

PROJECTS

1. Anti-Doping Strategies – An Interdisciplinary Research Programme with the Purpose of Improving Test and Educational Work. The fight against doping cannot be won by testing alone; real change calls for a whole new mindset. This project seeks ways to understand, and change, user attitudes toward doping.

2. Clean Results – Cultural analysis of socialization, fascination, training, diet, and exercise in elite cycling. The cycling sport is often associated with doping. This study investigates cyclists' own views on their sport, including their reasons for using, or refraining from using, doping.

3. "Everybody hates us". An analysis of "dangerous" Danish soccer fans. Violence and unrest at European football matches has been countered with massive police intervention. Examining football fan culture, this project looks for more effective, and less conflictual, ways of handling over-zealous football fans.

MILESTONES

Study on expanding anti-doping efforts through the testing of ordinary people training at the gym
(Christiansen, A.V. (2011) Bodily Violations – testing citizens training recreationally in gyms. In: McNamee M; Møller V, editors. Doping and Anti-Doping Policy in Sport: Ethical, legal and social perspectives. Vol. 3. London: Taylor & Francis, 2011. pp. 126–141)

The will to win is a more important motivating factor than money for athletes using doping substances
(Christiansen A.V. (2004) Ikke for pengenes skyld. Odense, University of Southern Denmark Press)

Anti-doping efforts are not suited for the moral redemption of sport; they increase corruption
(Møller V. (2010): The Ethics of Doping and Anti-Doping – Redeeming the Soul of Sport? London, Routledge)

Is the fight against doping built on myths?

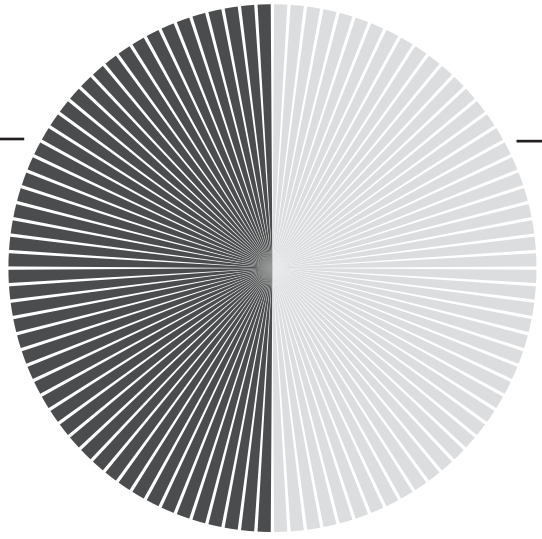
Investigation into the death of a famous Dane lacked evidence
(Møller V. (2005) "Knud Enemark Jensen's Death During the 1960 Rome Olympics: A Search for Truth?" in: Sport in History Vol. 25, London, Routledge)

Paradigm change in sport psychology
(Ryba, T. V., Schinke, R. J., & Tenenbaum, G. (2010). (Eds.) The cultural turn in sport psychology. Morgantown, WV: Fitness Information Technology)

METHODS

- Cultural analysis
- Literature studies
- Qualitative research
- Participant observation and interviews

OVERVIEW



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PRIMARY PREVENTION

The Research Unit for Primary Prevention looks at how the challenges and ailments that modern families face can be stopped before they develop. The focus ranges from pregnancy and childbirth to illness and hospitalization.

Primary prevention means investing resources during early childhood to act before problems and illnesses arise, thereby reducing the cost of health-service treatments later in life. Research in the field therefore explores how health professionals can best support and counsel individual families to promote their well-being and their infant's health, in everyday life and in exceptional situations.

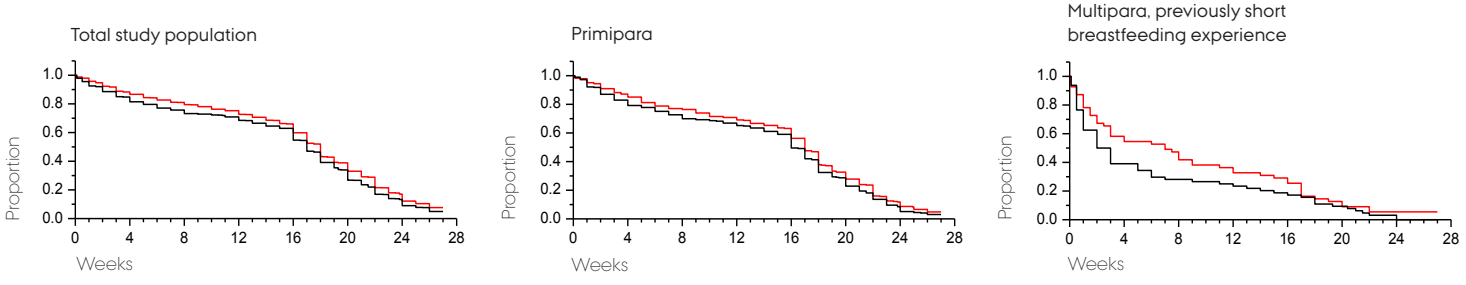
Focus on promoting family health

Unlike other research areas, this unit focusses on resolving challenges that other research has previously identified as problematic for the Danish national health service. Its preventive efforts are all about determining the needs of modern families for counselling during the various phases of life, and about developing and testing new initiatives that promote health and well-being for both the family and the child.

Research is done on health-promoting programmes for mothers, infants, and families at large. The Research Unit for Primary Prevention often conducts large randomized intervention studies. One study, involving 1,597 mothers, showed that by providing specific, practical counselling, public health nurses can help more women to successfully breastfeed their babies.

PROJECTS

1. The unit is initiator and anchor for a multi-centre study ensuring that all parents of premature babies are trained to use a specially designed care approach called NIDCAP. At the Skejby branch of Aarhus University Hospital, parents learn to more easily detect and decode signals from their premature infant. This helps them meet their child half-way. And even as the counselling from health professionals enhances the child's individual development and ability to interact, it also boosts the parents' self-esteem and personal resources.



Duration of full breastfeeding in a cluster-randomized intervention study. The intervention group received hands-on instruction and more practical education about breastfeeding.

Red line: Intervention group
Black line: Comparison group

2. Stretching over two separate periods of time, the unit completed a questionnaire study of 3,834 new mothers to assess the significance of home visits after they had given birth. The first period was while the Danish public health nurses were on strike; the second was after regular work had been resumed. This study clarified issues such as the new mothers' need of counselling, the impact of home visits on the duration of breastfeeding, and the increased use of other health services when home visits were not offered.

3. The unit has begun cooperating with social-science researchers to create new, interdisciplinary research angles from which to explore the importance of health-promoting measures early in life. This collaboration, AU RECEIV – the Aarhus University Research Centre for Early Interventions – is expanding the field to include studies based on electronic public-register information, and studies into the short-term and long-term effects of maternity leave, interventions to improve child-parent relations, and other programmes.

MILESTONES

How health professionals can best support the breastfeeding mother after she has been discharged from hospital
(Kronborg H, Kok G. Journal of Human Lactation. 2011;27:339–44)

Prenatal classes improve the ability of women to handle the process of giving birth
(Maimburg R D, et al. BJOG. 2010;117:921–8)

Family-centred nursing changes nurses' perceptions of the parent-child relationship
(Hall E, et al. Intensive and Critical Care Nursing. 2010;26: 307–13)

Interactive training improves support from public health nurses in addressing common breastfeeding problems
(Væth M, et al. European Journal of Public Health. 2008;18: 283–8)

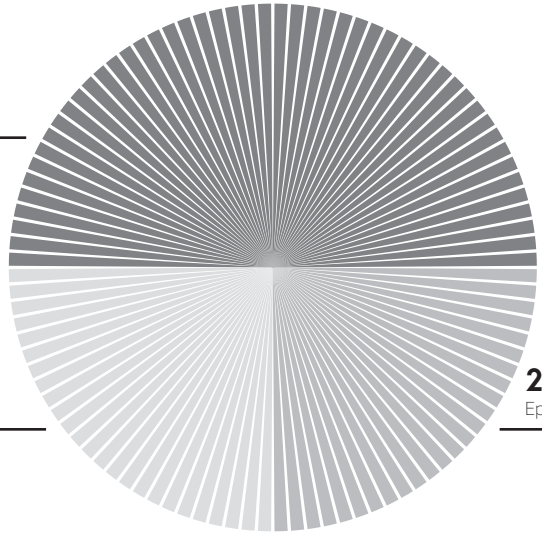
The many experiences mothers have on their way to developing motherhood of a premature baby
(Aagaard H, et al. Journal of Pediatric Nursing. 2008; 23: e26–36)

METHODS

Various methods are used to involve target groups and health professionals in the research process. The aim is twofold: to include practice-based experience, and to generate new knowledge that can facilitate change. Methods include:

- Individual interviews
- Focus-group interviews
- Observational studies
- Questionnaire studies
- Intervention studies
- Action research.

OVERVIEW



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Clinical research

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REPRODUCTIVE EPIDEMIOLOGY

Shortly after conception and throughout the period until a baby is delivered, vulnerabilities may develop that can lead to diseases that are either present at birth or manifest themselves later in life.

We are therefore mapping to what extent gestation – the time from conception to birth – influences foetal damage and disease, and are also seeking to identify some of the factors causing health conditions. The main focus is on prevention, which means our findings aim to help improve public health. Our research also covers factors that can lead to chronic illnesses – illnesses which may only become evident much later.

Examples of the diseases we study include birth defects, asthma, diabetes, reduced fertility, and obesity. Investigations look at a wide range of lifestyle factors, such as the pregnant woman's exposure to coffee, stress, and smoking, and exposure to occupational factors, illness, and medications.

Improving child health

Epidemiological studies of reproductive damage require access to data from large populations. In that respect we are very fortunate: In 1996, mainly with funding from the Danish National Research Foundation, we set up a database and began to recruit 100,000 pregnant women and their children and to register information about their state of health and other topics. This database is quite unique, and each year it supplies factual information to about 80 research groups around the world. Its fields of use are wide-ranging, from genetics and occupational medicine to studies of diet, medication use, and smoking and eating habits.

The research done using this database has provided many international contacts, one of which led the Centers for Disease Control and Prevention (CDC) to invest in expanding the database. We also use the registered data when providing expert advice to the National Board of Health and other public authorities that issue specific guidelines for pregnant women.

In addition to epidemiologists, this research group consists of biostatisticians, clinical specialists, neurologists, and IT professionals to handle the large amounts of data involved, as well as geneticists. This last group will become more strongly represented as the focus on gene–environment interaction intensifies in the future.

PROJECTS

1. **Exposure to serious stress as a factor in prenatal programming.**
   Women who lose a child or another close family member immediately prior to or during a pregnancy are in a state of elevated stress, which may affect the child's risk of disease or illness later in life. Animal experiments suggest that such a programming effect does exist; an effect that could potentially lead to obesity, diabetes, or mental problems during the child's adolescence or adult life.
2. **The use of pharmaceuticals during pregnancy.**
   Illnesses occurring during pregnancy must sometimes be treated with medication that could have unknown side effects on the unborn child. We know that certain pharmaceuticals can seriously affect the foetus, but we also know that untreated illness can do damage as well. The data resources we have at our disposal enable us to broaden and deepen our knowledge in this area.
3. **Is maternal obesity and alcohol consumption during pregnancy associated with poor semen quality in sons?**
   In order to investigate possible connections, we will be collecting blood and semen samples from about 500 young men. They are sons of mothers who, during their pregnancies, were included in the "Healthy Habits for Two" cohort (1984–87) and answered questions about alcohol consumption and other habits before and during pregnancy, and about their height and weight prior to conceiving. This study is expected to yield valuable information about the causes of impaired semen quality.
4. **Age of sexual maturity: Causes and consequences. A study among selected children in the "Better Health for Mother and Child" cohort.**

We will be collecting information about pubertal development from a group of approximately 14,000 children of mothers who, during their pregnancies in 1999–2002, agreed to participate in the "Better Health for Mother and Child" project (the DNBC), answering questions about a wide range of health and lifestyle factors. The resulting data, collected from the children every six months from the age of 11 and throughout puberty, will undergird numerous studies investigating the causes and consequences of changes in the age of puberty onset.

5. **Caffeine metabolites and the risk of miscarriage.**
The primary aim of this project is to examine the link between the plasma concentration of coffee and its metabolites and the risk of miscarriage. More specifically we will also study whether genotypes for metabolizing caffeine (CYP1A2 and NAT2) are associated with spontaneous abortion, and we will apply the principles of Mendelian randomization to approximate whether such an association (if evidenced) is causal.

MILESTONES

Apgar score predicts ADHD
(Li J, et al. J Pediatrics. 2011;158(5):775–9)

Pregnant women should adapt their weight increased during pregnancy to their pre-pregnancy weight
(Nohr EA, et al. Am J Clin Nutr. 2008;87:1750–9)

The structure and history of the Danish National Birth Cohort
(Olsen J, et al. Scand J Public Health. 2001 Dec;29(4):300–7)

Antidepressants given to pregnant women
(Pedersen LH, et al. BMJ. 2009 Sep 23;339:b3569. doi: 10.1136/bmj.b3569)

Alcohol and semen quality
(Ramlau-Hansen CH, et al. Hum Reprod. 2010 Sep;25(9):2340–5. Epub 2010 Jun 29)

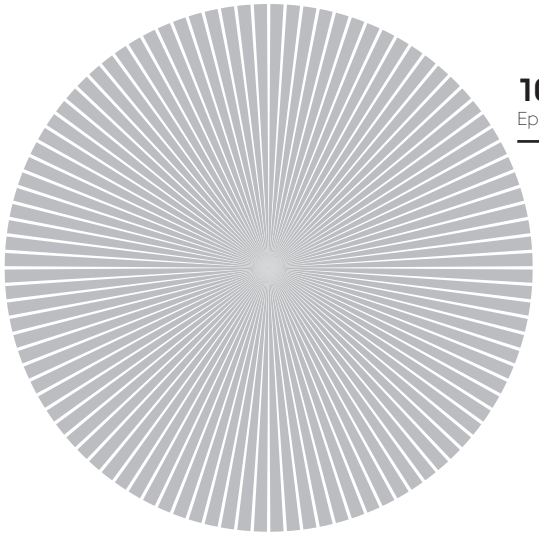
METHODS

In our work we apply both experimental and observational epidemiological methods. Much of our research is based on longitudinal studies, but we also use case-control studies, particularly for projects that rely on biological data.

We use existing population data as well as data gathered by our own unit. The various public registers and databases that exist in Denmark, and which hold information about the entire nation, can provide us with up to 30 years' follow-up time. Our own follow-up studies cover up to 25 years, in some cases with data collection still ongoing.

This image was part of the material used when collecting data for the Danish National Birth Cohort, which consists of almost 100,000 women and their children.

OVERVIEW



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SELF-CARE AND SELF-MANAGEMENT

Although patients may suffer from one or several chronic diseases or functional impairments, it is important for them to be able to do things on their own. And we, as health professionals, must become better at supporting them in achieving this. We must also become better at involving their families and social networks.

In a future where many citizens have chronic conditions or are elderly, where care staff is limited, and where health budgets are tight, there is a serious need for more knowledge and a better understanding of how care and treatment programmes can improve patients' self-care and well-being in their daily lives.

We need to find out how to differentiate health interventions so that they match the needs of each individual patient. One option is programmes that provide "help for self-help". Another is that a greater proportion of patients take responsibility for their own treatment in close dialogue with their health professionals.

Synchronic analysis of video recordings and physiological measurement data.

One challenge the system faces is moving patients out of the hospital and into their own homes, consequently creating a physical distance between the hospital-based expertise and the person requiring treatment. This in turn puts new demands on the interaction of care staff with patients, and on how staff utilize the available health and welfare technologies, such as robots and telemedicine.

Patient-centred care reinforces self-care in patients with COPD

A particular area that has been investigated in detail is the care of COPD patients, a group that consistently or periodically requires professional attention and care. Based on a qualitative study, we ran a trial programme at Aarhus University Hospital, changing the form of care given and educating front-line care staff to include the patient and to systematically plan and deliver care accordingly. In a subsequent study we then documented that the care staff had increased their skills levels and since then, in a randomized test, we have shown that patients who receive patient-centred care experience greater autonomy.

The general hypothesis is that all types of patients should become actively involved in their own care and treatment, thus becoming aware of what benefits them, and what does not. Moreover, care staff must begin by assessing each patient's own basic life situation and opinions about what they wish to do with their lives, and then adapt care and treatment to suit the circumstances. Here, the Department for Public Health has particular research competence in the field of qualitative methodology, and in using a variety of data-collection methods such as observation, interviews, and video documentation – methods well-suited to clarify the patient's point of view.

PROJECTS

1. By monitoring the rehabilitation of patients with spinal-cord injuries, the research unit has described their adaptation to a life altered by illness and disability. The project has identified relational, organizational, and political opportunities for optimizing rehabilitation.

2. A phenomenological investigation has clarified how persons with traumatic spinal-cord injuries living at home experience being dependent on care and assistance for all daily living activities, with special focus on meal-related dependency.

3. The research unit has developed the scientific method "Multi-modal grounded theory approach", which is applied to compare behavioural phenotypes with physiological parameters. Patients with COPD were video-filmed at the hospital and in their own homes while carrying out regular personal-grooming tasks in the morning. While doing so, they were attached to equipment that measured their energy consumption, blood-oxygen level, and other physiological measures, after which they were interviewed. The data were analysed synchronically and asynchronically.

4. Using observation and interview techniques, the research unit has studied how nurse communication and cooperation is decisive to COPD patients successfully carrying out and benefitting from non-invasive ventilation treatment (oxygen administered by mask).

5. A field study monitors patients participating in osteoporosis education classes at Aarhus University Hospital to see whether, and how, they integrate what they have learned into their daily-life habits.

MILESTONES

A new and expanded theoretical understanding of the nurse's role in the rehabilitation of apoplexy patients
(Kirkevold M. ANS. 2010 Jan;33(1):E27–E40)

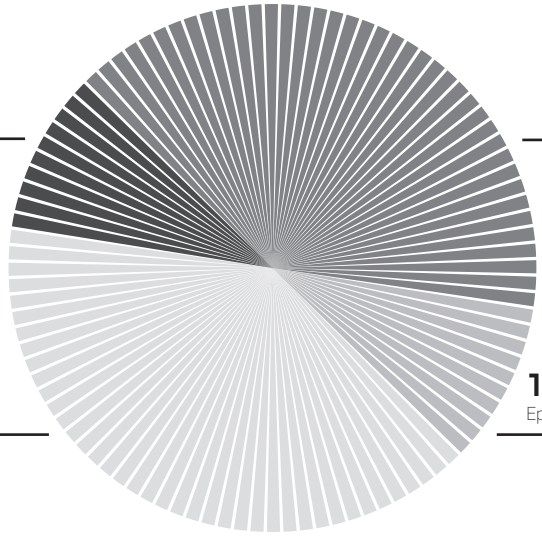
A study of patient autonomy and the maintenance of dignity and integrity
(Delmar C, et al. QHW. 2011; Epub ahead of print)

An innovative programme for nursing staff, dealing with patient-centred care of persons with COPD
(Lomborg K, et al. JCI. 2011;4:265–75)

METHODS

- Action research
- Grounded theory
- Interpretive description
- Intervention studies
- Phenomenology

OVERVIEW



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TOXICOLOGY

Chemical substances are a part of our everyday lives and our patterns of consumption. The main object of toxicology research is preventive, as scientists strive to more precisely determine when the levels of chemical substances become too high, making them hazardous to humans. However, some research also looks into how chemicals can make our daily lives easier.

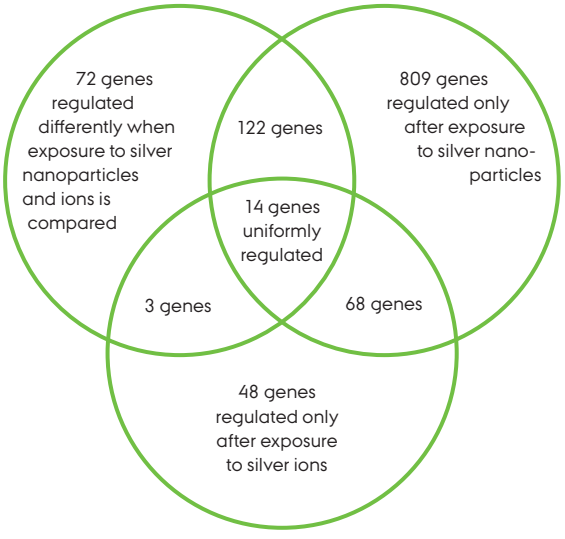
Research in the field of toxicology, which forms the basis of relevant political decision-making and also contributes to improving health services, is looking for answers to question like these:

- Which sections of the population are most susceptible to hazardous air pollution?
- How can chemicals be used to ease our daily lives?
- How and when is DNA damaged when affected by chemical substances?

How chemicals affect people

In recent years and today, nanotechnology has become increasingly important in toxicology research. Nanotechnology will allow us to replace dangerous substances in pharmaceuticals and other products. This will reduce the health risks associated with some of the products we know today. Yet our toxicology research looks beyond the chemical substances that are dangerous to us. It also investigates how chemicals can have a positive impact on our lives. One result was that in 2011, our research group's findings served to stop a bill, proposed in the Danish parliament, to prohibit the use of "silver-nano" in food products. Toxicology research has also played a role in Copenhagen's 1992 decision to have the city's busses change to environmentally friendly diesel fuel, thereby helping to reduce particulate pollution in the Danish metropolis.

And our research is not limited to looking at Danish issues. Scientific findings are passed on to decision makers in the EU through vice-chairmanship of the EU Scientific Committee on Health and Environmental Risks.



Investigation of cell reactions at gene level following exposure to silver nanoparticles.

PROJECTS

1. **Sidano – Assessing the safety of nanoparticles taking a parallelogram approach**
   The aim is to establish what physical-chemical properties are decisive in causing industrially manufactured nanoparticles to be hazardous. Experiments will be conducted on human and animal cells from various organs, with particular focus on carcinogenic effects.

2. **Nano3T – an EU project**
   Now concluded, this project sought to determine how surface treating iron-oxide nanoparticles with proteins affected their toxicity. Because these particles were intended for use in hyperthermia treatment of pancreatic cancer, the toxicological experiments were done on cancer cells of this type.

MILESTONES

Toxicity of silver nanoparticles – nanoparticle or silver ion?
(Beer C, et al. Toxicol Letters. 2012. In press)

Induction of intracellular communication in A549 cells by nanoparticles
(Deng F, et al. Nanotoxicology. 2010; 4:186–95)

Genetic susceptibility according to three metabolic pathways in cancer of the lung and bladder and in myeloid leukemias in nonsmokers
(Vinies P, et al. Ann Oncol. 2007;18:1230–42)

METHODS

- Cell culturing – examining cells in a tightly controlled environment
- Effect assessment – testing the biological effect in cells exposed to nanoparticles
- P32 isotope post-labelling – assay to assess chemically (nanoparticle-) induced damage to DNA and quantification of this damage
- Influencing gene expression using microarrays
- Assessment of genotoxic damage
- Microscopic analysis

OVERVIEW

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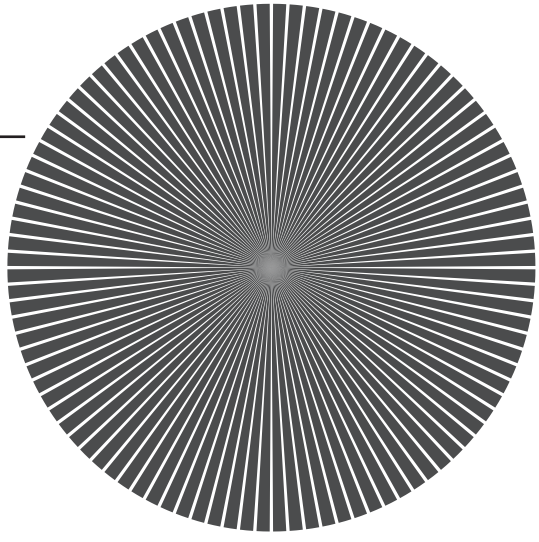
Basic research



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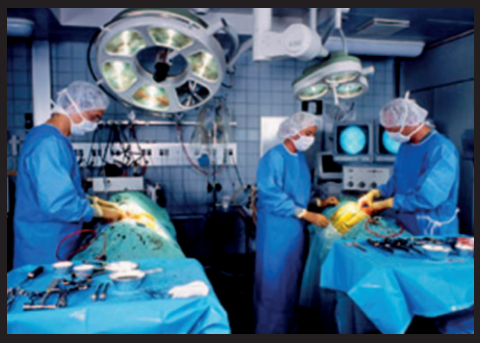
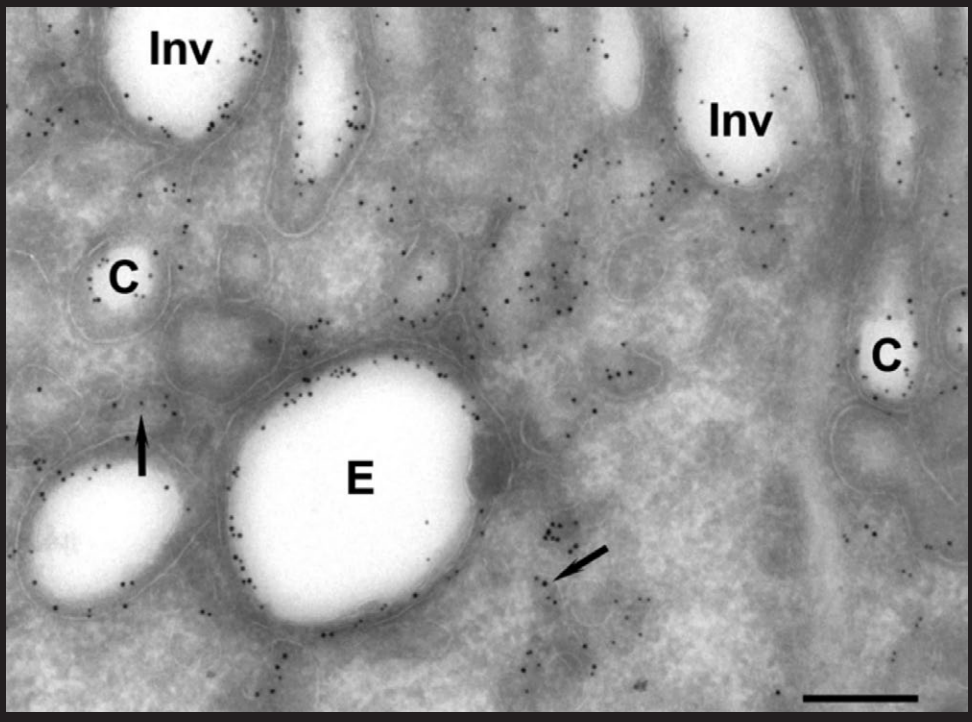
SPECIAL TECHNIQUES

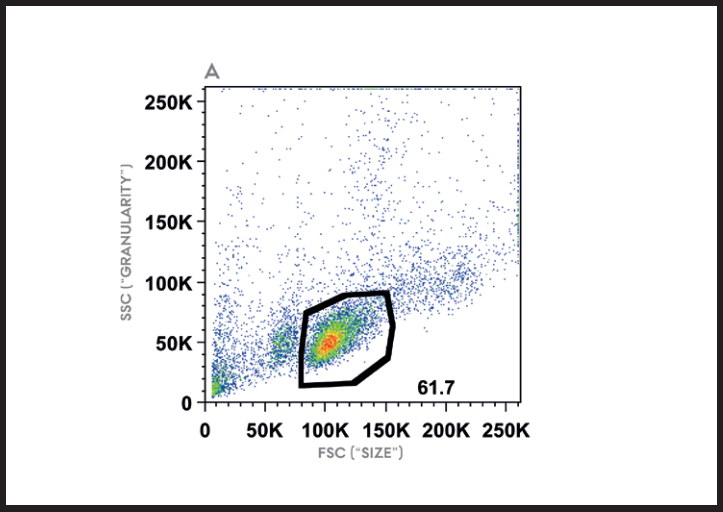


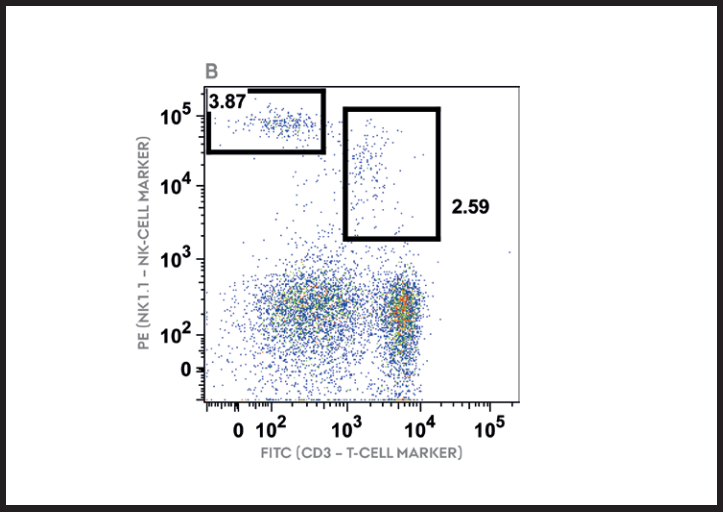
▲ The surgical facilities at the Department of Clinical Medicine used for experimental animal procedures.

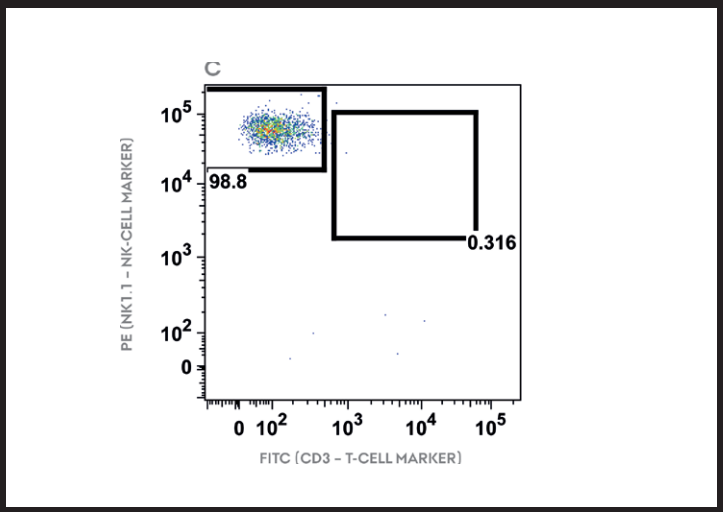
► Sorting of 2 cell populations from murine spleen.

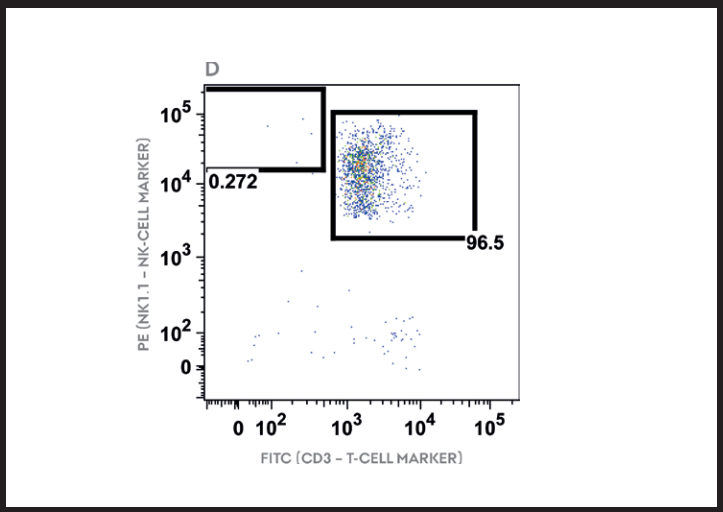


► Immunocytochemical localization of the endocytic receptors megalin (10 nm gold) and cubilin (5 nm gold) in the proximal tubule of the kidney, using electron microscopy. Ultra-thin frozen section. Inv: endocytic invaginations; C: coated pits; E: endosome; arrows: recycling dense apical tubules. Scale bar 0.5 µm.


A
250K
200K
150K
100K
50K
0
SSC ("GRANULARITY")
0 50K 100K 150K 200K 250K
FSC ("SIZE")
61.7


B
3.87
2.59
PE (NK1.1 – NK-CELL MARKER)
FITC (CD3 – T-CELL MARKER)


C
98.8
0.316
PE (NK1.1 – NK-CELL MARKER)
FITC (CD3 – T-CELL MARKER)


D
0.272
96.5
PE (NK1.1 – NK-CELL MARKER)
FITC (CD3 – T-CELL MARKER)

CORE FACILITIES: EXPERIMENTAL ANIMAL MODELS, AND ANIMAL HOUSING AND BREEDING

The Department of Clinical Medicine is one of Europe's leading biomedical institutions in the field of porcine experimentation, and we conduct and assist basic research in all organ systems within a regional and international framework. The department also has the largest laboratory in the Nordic region for surgical training, and it facilitates do research at all levels: from molecular studies, over imaging diagnostics, and to advanced robot-assisted surgery. The pig serves as a representative of the human organ functions.

Specialized animal models help us understand disease

The Department of Clinical Medicine began this type of work with the urinary tract, and its studies led to less aggressive treatments for children with urinary-tract problems – which cause difficulties that were known to be responsible for numerous cases of chronic kidney failure. The department also established an international assessment centre for artificial heart valves, then developed new revolutionizing treatments for coronary thrombosis, moving on to investigate the porcine brain and brainstem with the intent of developing new treatments for serious neurological and mental illnesses. In the process of achieving these medical breakthroughs, the Department of Clinical Medicine has come to host and breed a wide range of unique animal models dedicated to specific diseases: bow-legged pigs, brain-dead pigs, depressive rats, mice with HIV and psoriasis, and many others.

By way of example, one treatment modality developed at our experimental animal facility is used today to revive humans involved in drowning accidents. By cooling the pigs, we were able to establish that their heart continued to beat even though they showed no signs of life. These research findings are now used to successfully resuscitate humans subjected to hypothermia after prolonged immersion in or under water.

A unit for comparative biology

In addition, the Department of Clinical Medicine has an unparalleled cooperation with zoophysiology researchers, aimed at studying particular animals. This may, in time, lead to valuable new knowledge about diagnosing and treating diseases and developing new therapeutic drugs. The Mexican axolotl salamander, for instance, has a unique capacity to regenerate lost body parts. If, in the future, we become able to transfer this regenerative capability, it will unlock a huge potential for re-creating human limbs and organs that have been lost.

PROJECTS

1. A centre studying the development, diagnosis, and treatment of atherosclerosis, in collaboration with diagnostic researchers and the pharmaceutical industry.
2. A European heart-valve centre.
3. A centre for bone and prosthesis interfacing.
4. A centre for brain research and neurological treatment, for instance relating to Alzheimer's disease and spinal-cord injuries.
5. Managing ethical profiles for experimental animal research. All projects are approved by the Animal Experiments Inspectorate. Moreover, the department's veterinarians provide instruction and education in animal experiments and the correct handling of the animals. The researchers using animal models also receive supervision. In this way the department ensures compliance with clear, common guidelines among the employees and researchers who deal with the facility's animals.

MILESTONES

The Department of Clinical Medicine has assisted and contributed to significant developmental work in the field of animal experiments, including:

- The development and use of multiple-sclerosis mice
- The development and use of atherosclerosis in mice
- The development and use of an Alzheimer's disease pig
- The development and use of a pig model with urinary-tract obstruction
- The development and use of depression models in rats
- The development and use of a pig model with brain death
- The development and use of robot-assisted surgery on pigs

METHODS

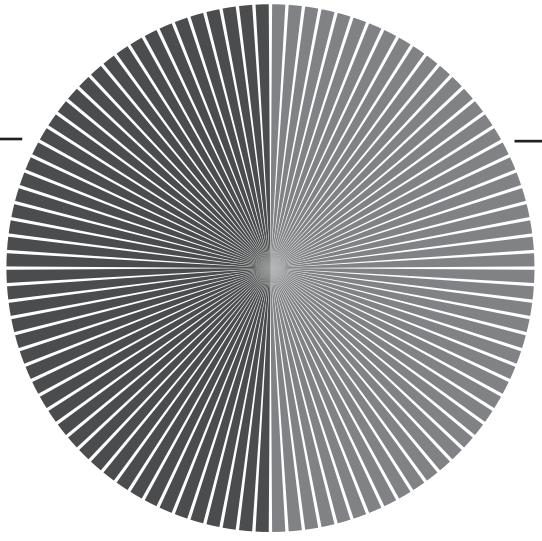
Our core facility has operating theatres that precisely correspond to those used in the clinic for surgical procedures performed on patients. Similarly, new types of instruments (for laparoscopy, robot-assisted surgery, telemedicine, new diagnostic methods, and so on) are tried and tested here preclinically, prior to any use on patients.

The surgical facilities at the Department of Clinical Medicine used for experimental animal procedures.

OVERVIEW

50 %
Basic research

50 %
Clinical research



0 %
Epidemiological research

0 %
Qualitative research

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ELECTRON MICROSCOPY

Electron microscopy permits exact and ultra-precise analysis of cells and their components, right down to the tiniest details. While a conventional light microscope has a resolution of 0.2 micrometres (0.0002 mm), the electron microscope (EM) has a resolution that is a thousand times smaller – 0.2 nanometres. This makes a huge difference for someone studying, say, the localization or structure of the cell's macromolecules.

Health has a special unit that works with transmission electron microscopy, immunoelectron microscopy, and cryo-electron microscopy. Its objectives include:

- Determining the localization and dynamic changes to proteins in cells under physiological and pathological conditions
- Studying the structure of the cell's various macromolecules
- Developing new and improved imaging-analysis methods for three-dimensional reconstruction

With forty years of research experience in biological electron microscopy our unit, which attracts researchers from all over the world, has made its mark, particularly in three areas:

Advice and consultancy
The brief point in time at which a tissue, cell, or molecular sample is photographed in an electron microscope is the culmination of a long process involving deliberations about the selection, handling, and preparation of the empirical material. The unit assists other scientists with specialist advice on evaluating study designs, fixating materials, purifying macromolecules, running pilot experiments, and many other issues. "We believe it's essential that the projects have a research potential that can make full use of the competencies available at our unit – because that's what creates synergies, and research at an international level."

Specialized technical staff
The unit's laboratory staff have spent years acquiring the special expertise needed to cut the ultra-thin sections photographed in the microscopes, using diamond and glass knives. The sections must be between forty and fifty millionths of a millimetre, so the staff's years of experience and extreme precision mean everything for the quality of the results.

Quantification and imaging
Preparing the samples to be photographed in the electron microscope takes an enormous amount of experience and patience. It is therefore essential that the samples studied using electron microscopy be representative of the problem they are intended to elucidate. Our unit has special expertise in designing studies in which the available material is limited. Often electron microscopy is combined with light microscopy, confocal microscopy, and 3D reconstruction to gain an understanding of the structural composition of tissues, cells, or molecules.

MILESTONES

Description of the uriniferous tubule: structural and functional organization
(Christensen EI, et al. In: Pollock DM, Garvin J, editors.Comprehensive Physiology. Renal Physiology. Wiley-Blackwell, 2012;2:1–56)

Demonstration by 3D cryo-EM of the structure of an active step in spliceosome, and localization of its catalytic core
(Golas MM, et al. Molecular Cell. 2010;40:927–38)

Vasopressin-induced phosphorylation of the thiazide-sensitive sodium chloride cotransporter in the distal convoluted tubule
(Pedersen NB, et al. Kidney Int. 2010;78:160–9)

Receptor-mediated endocytosis in the renal proximal tubule
(Christensen EI, et al. Pflügers Arch. 2009;458:1039–48)

Targeted disruption of the Cl-/HCO3- exchanger Ae2, resulting in osteopetrosis in mice
(Josephsen K, et al. Proc Natl Acad Sci U S A. 2009;106:1638–41)

Synaptic contact number and size in stratum radiatum CA1 of APP/PS1ΔE9 transgenic mice
(West MJ, et al. Neurobiol aging. 2009;30:1756–76)

PROJECTS

1. EM studies of receptor-mediated endocytosis (megalin/cubilin) in the development of proteinuria: clarification of the ability of the kidneys to absorb proteins during the progression of chronic kidney disease.

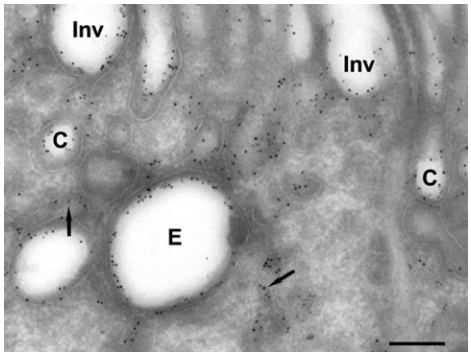
2. EM studies of kidneys in rats: reembedment of light-microscope serial sections for visualization of the structure of the nephron.

3. Development of single-cell visual proteomics. Use of micro-liquid systems for cell rupturing, cross-linking, and application of cell content onto EM grids, and subsequent EM labelling of multiprotein complexes.

4. Characterization of protein complexes involved in the development and function of nerve cells: complexes are purified from cell cultures to map composition and 3D structure using cryo-electron microscopy and imaging.

5. Collaborating with researchers from AU SCIENCE AND TECHNOLOGY, we are working to introduce a high-resolution microscope. This microscope is equipped with a number of new technologies that significantly improve the resolution of biological-sample images.

6. EM determination of whether iron nanoparticles accumulate in the body's cells and, if so, where (in which cells) they accumulate.



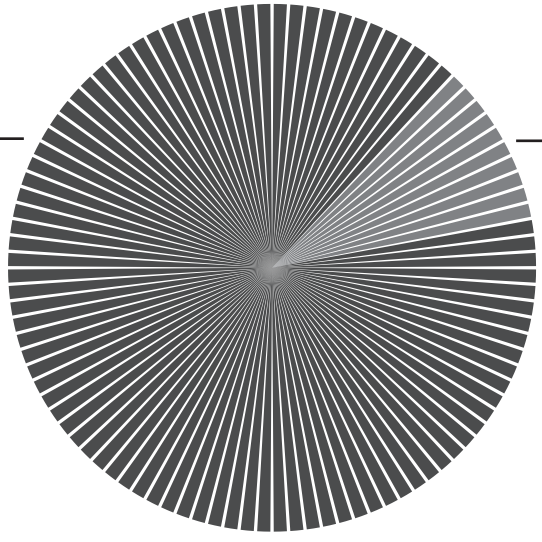
Immunocytochemical localization of the endocytic receptors megalin (10 nm gold) and cubilin (5 nm gold) in the proximal tubule of the kidney, using electron microscopy. Ultra-thin frozen section. Inv: endocytic invaginations; C: coated pits; E: endosome; arrows: recycling dense apical tubules. Scale bar 0.5 µm.

METHODS

The department employs all the techniques necessary for state-of-the-art electron microscopy, including:

- Tissue preparation for electron microscopy
- Immunocytochemistry and immuno-electron microscopy
- Serial sectioning of tissue samples
- Imaging and 3D reconstruction of the structure and ultra-structure of organs
- Quantitative morphometry and stereological quantitation
- Advanced imaging and image optimization
- "Single-particle" cryo-electron microscopy and 3D reconstruction of macromolecules

OVERVIEW



90 %
Basic research

10 %
Clinical research

0 %
Qualitative research

0 %
Epidemiological research

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Professor Ole Fejerskov
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Professor Søren Nielsen
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FLOW CYTOMETRY: THE FACS CORE FACILITY

The FACS core facility at Health was established in 2010, based on the long-standing and extensive expertise at the Department of Biomedicine in the field of flow cytometry (or, technically speaking: Fluorescence-Activated Cell Sorting, FACS). The facility receives requests for assistance in equal measure from the university's theoretical and clinical departments.

The most distinctive features of the FACS core facility are:

- its permanently employed and specially trained staff, which ensures stable and high-quality performance and further development of new FACS-based applications
- the research-based nature of the facility, which leads to continuous development of the technique, both in relation to the quality of results and to the introduction of new applications
- the facility's operational model, building on collaboration between the user and the core facility's staff – which in several cases has stretched from the initial formation of the hypothesis to the publication of the findings. In some cases, collaboration has developed into actual research partnerships
- the provision of consultancy services: The FACS facility is involved from the project earliest phases, helping to clarify the technique's potential and applicability to the project in question. In some cases, the FACS facility also helps in developing a study design and suggesting supplementary methodologies or reassessing the empirical material.

Flow cytometry gives unique capabilities
Flow cytometry is a highly sophisticated technique used for sorting and analysing cells. The technique is widely used for mapping and clarifying immunological, microbiological, haematological, and genetic issues. Among other things, flow cytometry plays an important role in the research of cellular immune responses and in the characterization of cancers stem cells. FACS is also a valuable element in daily clinical practice, where it is used for sorting and analysing at individual cell level, for instance to diagnose leukaemia and HIV and to monitor disease progression and therapeutic outcomes.

FACS technology enables us to isolate individual cells, and to combine certain cell populations with a very high degree of purity based on certain specific characteristics. It therefore gives us unique capabilities in studying particularly interesting types of cells, or extremely rare cells. Examples are bacteria, thrombocytes, leucocytes, endothelial cells, haematopoietic stem cells, and megakaryocytes, which can be analysed (and sorted) applying up to 14 different parameters, and at speeds of 20,000 cells or particles per second.

PROJECTS

The FACS core facility is used by a large number of research groups at Health and comprises applications such as:

1. Characterization of thrombocyte populations.
2. Characterization of cellular and protein interactions of innate immunity in relation to viral infection.
3. Development of new vector designs.
4. Characterization of cell-membrane transport mechanisms.
5. Characterization and cytogenetic identification of myeloid stem-cell populations.
6. Functional characterization of cell-mediated immune responses in relation to cancer.

METHODS

The FACS core facility at AU comprises:

Permanent staff
All staff are specially educated and trained, and have comprehensive and extensive experience in flow cytometry
- 1 full-time academic/technical project manager (head of daily operations)
- 2 part-time laboratory technicians

Equipment
- FACSAriaIII (3 lasers, 12 detectors) cell sorter
- FACSAriaIII (4 lasers, 14 detectors) cell sorter

- Outside the FACS facility itself, the Department of Biomedicine has 3 additional analysis units: a FC500 cell analyser, a Cell Lab Quanta SC, and a BD FACSCalibur

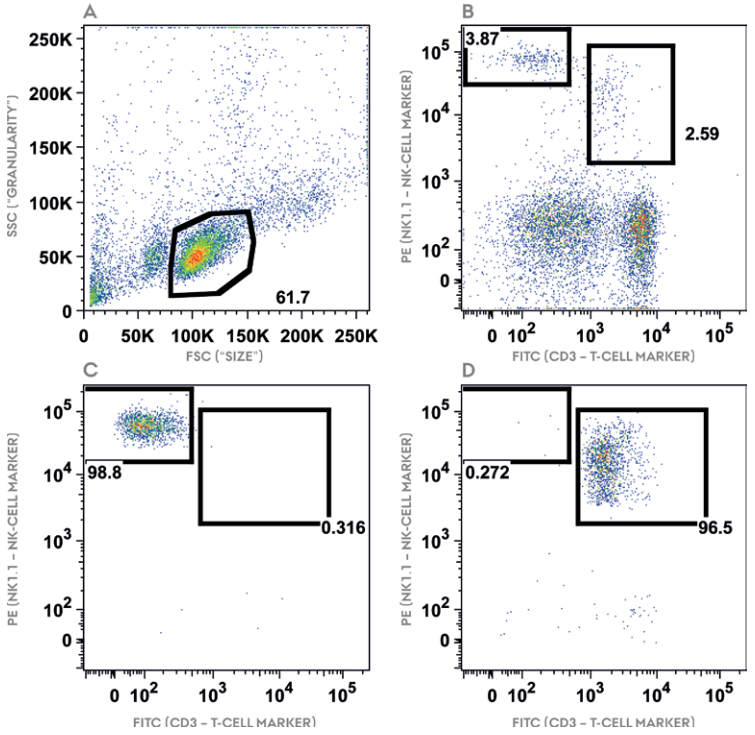
Specimen preparation facilities

Associated laboratory facilities for preparing specimens prior to analysis, including incubators, centrifuges, and other equipment.

Research environment

The FACS core facility is physically located in the immediate vicinity of research groups that take a special interest in, and frequently use, the flow cytometry technology.

SORTING OF 2 CELL POPULATIONS FROM MURINE SPLEEN



BEFORE SORTING

The figures show typical dot plot charts from a flow cytometric analysis, in which each dot represents a single cell from a murine (mouse) spleen. (The "warmer" the colour, the more numerous the cells.)

(A) shows the distribution of the various cell populations in murine spleen tissue, where the lymphocytes are delimited using an "electronic gate".

(B) shows the lymphocyte population from (A) and its distribution between NK (NK1.1+/CD3-) and NKT (NK1.1+/CD3+) cells. These 2 cell populations are then sorted and their purity determined by means of FACS analyses (C) and (D).

AFTER SORTING

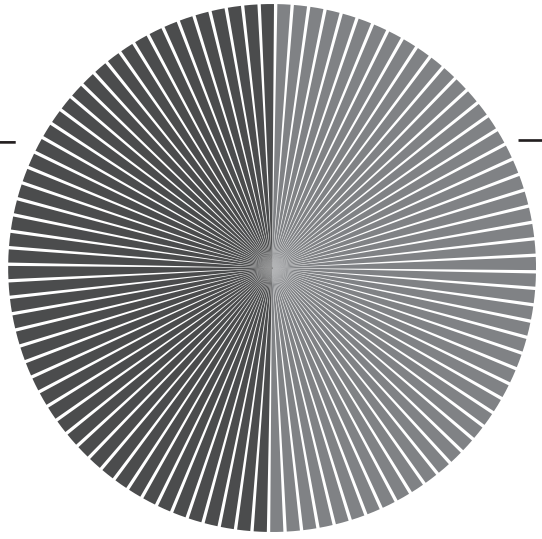
(C) shows that, after re-analysis of the sorted NK cells, the purity is 98.8% (based on an original concentration of approx. 2%).

(D) shows the re-analysis of sorted NKT cells with a purity of 96.5% (based on an original concentration of 1.5%).

OVERVIEW

50 %
Basic research

50 %
Clinical research



0 %
Qualitative research

0 %
Epidemiological research

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FACULTY OF **HEALTH**

The Faculty of Health at Aarhus University is the professional and academic umbrella for medical scientific research and education. Health is also one of the university's four columns, alongside Art, Business and Social Sciences, and Science and Technology.

In order to interrelate the scientific disciplines, we have defined four strategic interdisciplinary ties: Research, Education, Talent Development, and Knowledge Exchange. Within the Faculty of Health we have paralleled this organizational approach and have defined specific targets, in particular for Knowledge Exchange. One of the focal points within this target area is disseminating knowledge, and creating a heightened awareness of our full spectrum of health-professional scientific and research competencies.

In order to appropriately view these areas of competence in their organizational context, it is important to appreciate the complex nature of the matrix within which we work. Our research and educational backbone ranges from university campus-housed basic science, through hospital-operated applied science integrated with medical health care, and even into the field of epidemiological research.

Interdisciplinary collaboration
An important element in the organizational infrastructure of Health is our intimate collaboration with the regional authorities that own the university hospitals. This mutual relationship ensures seamless research cooperation between university and hospital, right from the top leadership to the individual researcher or health-care provider. The University–Region collaboration is a unique organization, in which we have formalized scientific responsibility as being governed by Aarhus University and clinical experimentation as being performed within hospital premises. In this way, the arrangement is mutually beneficial.

In practical terms, the research activities at Health are carried out in five departments:

1. **The Department of Biomedicine**
2. **The Department of Clinical Medicine**
3. **The Department of Forensic Medicine**
4. **The Department of Public Health**
5. **The Department of Dentistry**

Although they are allocated to specific departments, researchers at the departments interact intensively with one another, and throughout the entire university. We have even formalized dedicated research centres to house strategic research areas that require special expertise. With this strong infrastructure, all of our scientists and researchers have abundant opportunity to collaborate with their international counterparts, and to enter into close-knit partnerships with the business community.
With the new Aarhus University organization, it is our ambitious goal to further enhance our research and educational activities through talent development and knowledge exchange with society and the world at large.

We aim to intensify crossdisciplinary collaboration, which is already one of our overall key competencies – as materialized in the multidisciplinary centres sponsored by Aarhus University. Building on our solid physical and organizational infrastructure, we aim to reinforce translational research, from research laboratory to treatment and the prevention of disease.

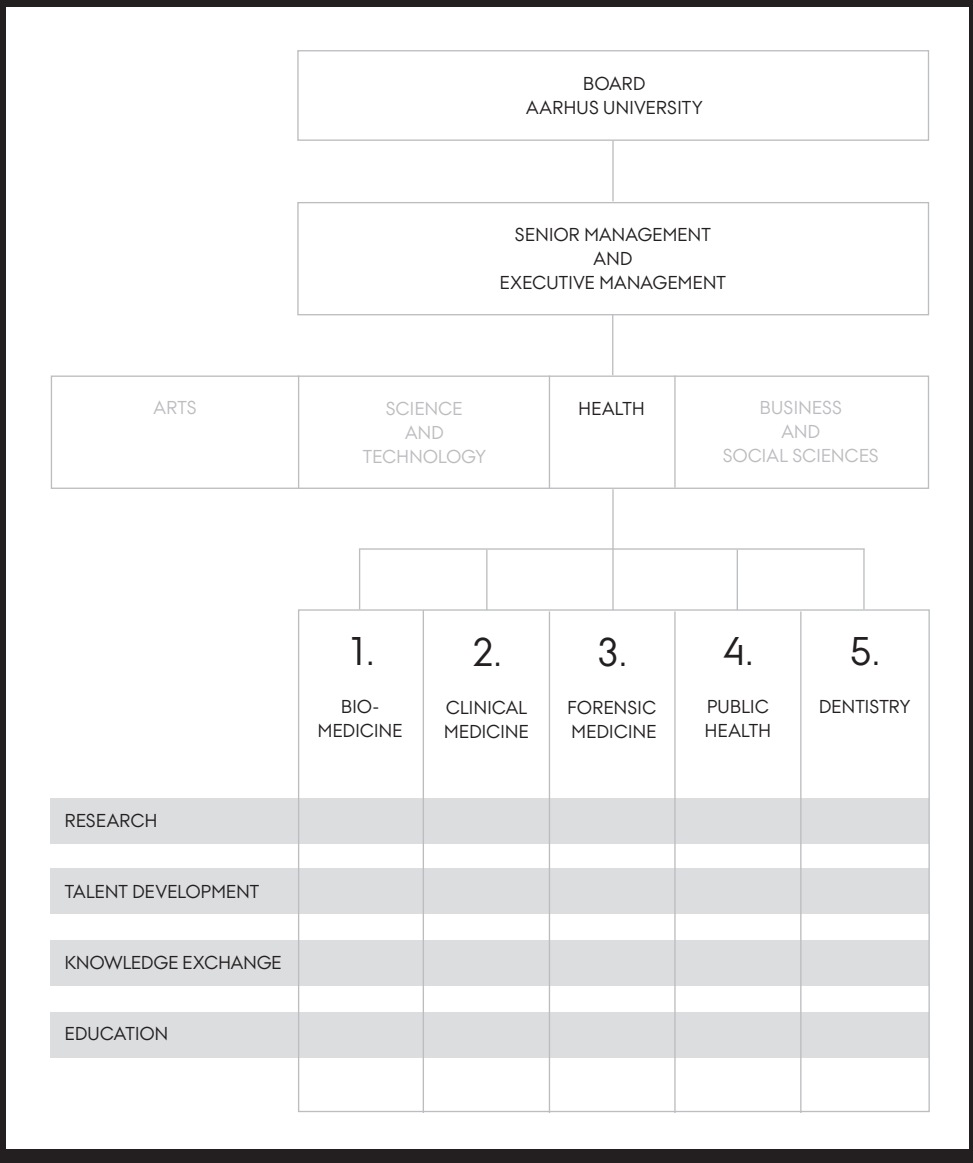
The purpose of this Research Catalogue is to bring our areas of expert competence into focus, and to present our capabilities in working across institutions, as well as openly collaborating with partners outside Aarhus University.

THE FACULTY OF HEALTH COMPRISES

5
DEPARTMENTS

1479
FULL-TIME EQUIVALENTS

612
ACTIVE PHD STUDENTS



DEPARTMENT OF **PUBLIC HEALTH**

The Department of Public Health consists of a number of scientific groups with skills relevant to the field. Research within the department is highly interdisciplinary and frequently involves collaboration with other researchers in Denmark and abroad.

We handle assignments that assist and promote the health of the Danish population at large, benefitting from a long-standing tradition for sharing knowledge and cooperating with public institutions, such as the municipal and regional authorities, the national health system, general practitioners, and stakeholder organizations. The Department of Public Health has a special relationship with the Central Denmark Region and also works closely with the Research Unit for General Practice.

We use our professional evidence-based knowledge to become involved in areas where we can influence the development of society. The staff members hold representative seats on a number of councils, boards and committees, and in associations where research points of view are of the utmost relevance.

We cover professional areas that include humanistic, biomechanical, and biological sport research; professional attention and care for the elderly; interaction between patient and (nursing) caregiver; health promotion; biostatistical and epidemiological method-based research; diet and health; reproductive research; environmental toxicology; occupational health; air pollution; the Arctic environment; prevention of public-health problems in general practice; rehabilitation; social medicine; health services and the economy; research in health services; physical activity and health; health among children and young people; qualitative methodologies; and international health.

Our research and society
Our vision is to help develop and promote the health of the population, nationally and internationally, through research and education. We disseminate our research findings to the public, to relevant research communities, and to other stakeholders, and we actively assist in implementing the research results.

The department assists in educating the university's medical students. We also organize a variety of courses in connection with the PhD programmes at AU Health, including the basic course in biostatistics and courses in research methodology.

Furthermore, we offer a number of study programmes in the field of public health: BSc and MSc in Public Health Science, BSc and MSc in Sport Science, MSc in Nursing Science, MSc (as well as a supplementary degree) in Health Science, and MSc in Clinical Nursing.

Photo: Lars Kruse, AU Kommunikation

EXPERT RESEARCH COMPETENCE

Arctic medicine
Biostatistics
Clinical social medicine and rehabilitation
Diet and health
Environment and respiratory health
Exercise, training, and physical activity
General practice – Coordinating across the board
General practice – Prevention focusing on the individual
Global health
Health economics
Health services research
Humanistic sport research
Primary prevention
Reproductive epidemiology
Self-care and self-management
Toxicology

CORE FACILITIES

1. Three climate chambers for human experimental studies
2. A data management unit
3. Laboratory equipment: Department facilities
4. include metering equipment for motion analyses, functional muscle-power measurements, metabolic testing, pulmonary function tests, and molecular-biology and toxicology measurements

NUMBER OF FTE

162

FULL TIME EQUIVALENT

98

ACADEMIC AND SCIENTIFIC STAFF

64

TECHNICAL AND ADMINISTRATIVE STAFF

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DEPARTMENT OF **DENTISTRY**

The clinical activities at the Department of Dentistry are organized in eight different fields: clinical oral physiology, oral surgery and oral pathology, orthodontics, periodontology, prosthetic dentistry, paediatric dentistry, oral radiology, and dental pathology. In addition there are two theoretical fields: oral microbiology and immunology, and oral epidemiology and public health. The department runs the Dental Hospital, where students receive their clinical education at a common clinic section covering four clinical fields, and at four speciality clinics. The hospital also treats patients referred for specialized dental procedures.

The overall mission of the Department of Dentistry is the promotion of oral health, nationally as well as globally.

We conduct high-quality dental research in interdisciplinary collaboration with other departments and strategic centres at Aarhus University, and with other national and international partners as well. Our goal is that the Department of Dentistry in Aarhus should continue to be recognized around the world for its strong international and interdisciplinary research environment, which operates in active interplay with other institutions to address the needs of society.

Dentists graduating from the Department of Dentistry are highly qualified, academically as well as clinically, on a background of research-based education. We will continue to innovatively develop the curriculum in response to the population's changing treatment needs and the advent of new treatment modalities. We also offer an advanced postgraduate programme in orthodontics at the highest international level, and the department contributes to the specialist training programme for oral and maxillofacial surgeons.

Our researchers are deeply involved in disseminating and sharing knowledge with the surrounding society. We provide expert assistance at the highest professional level to public advisory boards, to evidence-based postgraduate education programmes, and in the counselling of dentists – and we strive to create new forms of knowledge exchange. Our researchers hold seats on many boards, councils, and committees, and also in special-interest societies, and they are called upon to assist a wide array of public authorities.

The Dental Hospital in Aarhus serves as a referral centre for patients with complex orofacial conditions in association with several of the Danish administrative regions, and with Aarhus University Hospital. In addition, we receive patients referred to us for specialist treatment.

The department's buildings and interiors are currently undergoing extensive renovation. The transformation to state-of-the-art clinics and laboratory facilities will be completed over the next few years.

Photo: Lars Kruse, AU Kommunikation

EXPERT RESEARCH COMPETENCE

Imaging techniques in dentistry
Oral diseases / epidemiology and aetiology
Oral ecology
Oral rehabilitation
Oral tissue regeneration – Biomaterials
Orofacial pain and dysfunction

CORE FACILITIES

New, modern Dental Hospital (slated for completion in the summer of 2013), including central sterilization and a central laboratory as core facility for the department's clinical research.

Advanced X-ray equipment.

Research laboratories organized according to research methodologies in pain, dental materials, tissue culturing, histology (hard and soft tissue), microbiology and immunology, inorganic chemistry, and molecular biology.

NUMBER OF FTE

242

FULL TIME EQUIVALENT

139

ACADEMIC AND SCIENTIFIC STAFF

103

TECHNICAL AND ADMINISTRATIVE STAFF

ADDRESS

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DEPARTMENT OF **FORENSIC MEDICINE**

At the Department of Forensic Medicine we investigate deaths reported to the police, and we also examine living victims of assault and abuse, as well as persons charged with criminal violations. The aim of these examinations is to clarify the mechanisms leading to death and injury, and to establish causes of death and links between cause and effect. Forensic investigations shed light on medical queries, accidents, homicides, suicides, abuse, and bodily harm, and their main aim is to prevent the reoccurrence of such events. The field of forensic chemistry employs a wide variety of analytical methods supporting the associated fields of forensic pathology and forensic clinical medicine, examining samples for the presence of alcohol, pharmaceuticals, and illegal drugs. Independent examinations of objects are also performed to detect abusive substances.

Our areas of competence cover state-of-the-art research-based methods of investigation and analysis. We handle assignments for a number of public authorities, and part of our job is to present independent, impartial, and evidence-based findings for legal purposes. The department is accredited by DANAK – the Danish Accreditation and Metrology Fund – following an independent assessment, and based on an international standard for quality control. In order to actively promote Denmark as a secure society, we are represented in centres, boards, councils, societies, and committees to which forensic views are relevant.

The department's units cover forensic pathology and forensic chemistry. The staff includes forensic doctors, forensic technicians, laboratory technicians, chemists, molecular biologists, pharmacists, engineers, secretaries, and biomedical scientists. The majority of our assignments are commissioned by the police and the legal system, but we also do work for the National Board of Industrial Injuries in Denmark, the Refugee Appeals Board, and Denmark's national tax authority SKAT.

Research that actively contributes to the society

Our vision is to develop the profession of forensic medicine by using new methods of analysis, and by continuously improving each individual skills area. Furthermore, within selected areas we wish to achieve a special status as a centre of expertise. One example would be bioanalytical chemistry, where establishing a centre function could assist in addressing questions raised by health professionals. Similarly, we are currently establishing a centre-of-expertise function that can clarify sudden death from cardiac arrest among young adults.
The department educates and trains medical doctors to become specialists in forensic medicine. Forensic medicine is also part of the general curriculum for all medical students. Our activities outside the university include teaching and instructing laboratory technicians, police cadets and investigators, ambulance staff, nurses, and staff at crisis centres and similar institutions. We are also part of the team behind Denmark's first centre for rape victims. Another noteworthy achievement in collaboration with the police and the paediatric department at the Skejby branch of Aarhus University Hospital was the founding in 2007 of the Child Protection Centre (CBO).

Photo: Department of Forensic Medicine

EXPERT RESEARCH COMPETENCE

Forensic pathology and clinical forensic medicine
Section for Toxicology and Drug Analysis
– Bioanalytical chemistry

CORE FACILITIES

1. Laboratory for molecular forensic pathology, with special expertise in purifying RNA and DNA from autopsy material for use in molecular and genetic investigations of tissue from deceased persons.
2. Post mortem CT scans using the department's 64-slice dual-source CT scanner to visualize, for example, the skeletal system (including 3D reconstructions) in order to clarify and document lesions and mechanisms of injury.
3. Unit for Bioanalytical Chemistry, which offers advanced equipment and skills for bioanalyses and interpretation. Our focus areas lie within metabolomics, pharmacokinetics and dynamics, forensic toxicology, forensic chemistry, and comparative investigations, and also within chemical biology.
4. Laboratory for hard-tissue and bone biology, which can produce small and large undecalcified bone sections and work with special staining techniques; we also have equipment for quantitative and stereological measurements. The laboratory is accredited by DANAK.
5. Examinations of sexual offense victims. In this connection the Department of Forensic Medicine has played a crucial role in establishing the Centre for Rape Victims in Aarhus, and the Child Protection Centre (CBO), also located in Aarhus.

NUMBER OF FTE

55

FULL TIME EQUIVALENT

11

ACADEMIC AND SCIENTIFIC STAFF

44

TECHNICAL AND ADMINISTRATIVE STAFF

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CONTACT

Head of Department Annie Vesterby
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DEPARTMENT OF **CLINICAL MEDICINE**

The Department of Clinical Medicine
The Department of Clinical Medicine conducts basic research and clinical research within 37 of the 38 specialities in the medical profession at Aarhus University Hospital. Anchored in the hospital environment, the department brings together basic research, clinical research, and clinical application. We plan and carry out our research based on clinical, diagnostic, and treatment-related issues, which are studied and addressed by teams either associated with the relevant hospital department or located at a central research facility.

Our department is also responsible for the MSc programme in medicine, for MSc in biomedical engineering, and for a major part of the university's MSc programme in molecular medicine.

We promote talent development by hosting research activities for PhD students in virtually all medical and surgical specialities.

We also support and promote knowledge exchange by participating in further and higher education programmes for medical doctors; by providing the media with expert statements; by encouraging our staff to participate in postgraduate education programmes held outside Aarhus University; and by having staff members who are appointed members of various advisory councils, boards, and foundations. In a wider perspective, we share knowledge internationally by virtue of numerous appointments to international positions of trust, and through our participation in Danish and international conferences and symposiums.

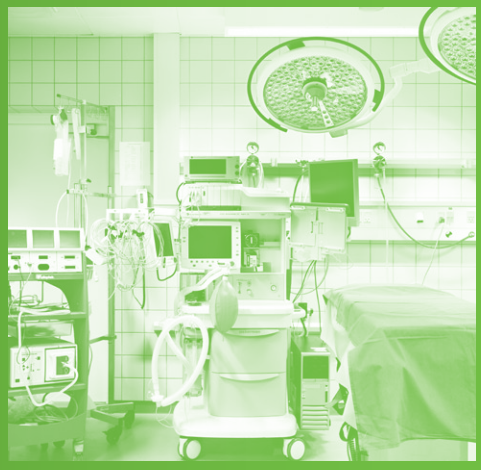

Photo: Roar Lava Paaske, AU Kommunikation

EXPERT RESEARCH COMPETENCE

Atherosclerosis
Biomarkers and clinical biochemistry
Cardiothoracic and vascular surgery
Child and adolescent psychiatry
Child neurology
Clinical epidemiology
Clinical neuromodulation with Deep Brain Stimulation
Clinical neurophysiology
Clinical oncology
Critical care
Experimental orthopaedic research
Eye diseases
Gastroenterology
Gynaecology
Haematology
Infectious diseases
Interventional Systems for Advanced Bio-Imaging and Therapy
Liver and gastrointestinal medicine
Molecular and cellular pathology, and stereology
Neuropsychiatry – From clinic to molecule and back
Neurorehabilitation
Neurosurgical interventions
Obesity and nutrition
Occupational epidemiology and reproductive toxicology
Paediatric nephrology
Paediatric orthopaedics
Paediatric urology
Paediatrics
Pain
Perinatology and neonatology
Psychiatric genetics
Reproductive medicine
Rheumatology
Spine surgery and translational orthopaedic research
Translational cardiology
Translational molecular medicine:
Molecular pathogenesis and pathophysiology
Translational neuroscience

Clinical Medicine / Biomedicine

Bones
Clinical genetics
Core facilities: Experimental animal models, and animal housing and breeding
Diabetes and endocrinology
Electron microscopy
Growth
Inflammatory diseases
Medical proteomics
Nephrology

CORE FACILITIES

The Department of Clinical Medicine has access to assistance from a variety of core facilities:

In the field of molecular research, the facilities we use are the Centre for Sequencing and Molecular Diagnostics (MOMA) and the Research Unit for Molecular Medicine (the Proteon Centre).

The FACS Centre is used in collaboration between the Department of Clinical Medicine and the Department of Biomedicine.

In the field of imaging, the MR Research Centre generates images for diagnostic and research purposes relating to the morphology and function of all organ systems.

The Danish Neuroresearch Centre handles morphological and functional investigations of the central nervous system.

The Medical Research Laboratories handle investigations relating to metabolic endocrine functions, normal and pathological.

The Surgical Research Laboratories deal with the development of diagnostic tools, procedures, and treatments using large animal models.

NUMBER OF FTE

577

FULL TIME EQUIVALENT

468

ACADEMIC AND SCIENTIFIC STAFF

109

TECHNICAL AND ADMINISTRATIVE STAFF

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CONTACT

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DEPARTMENT OF **BIOMEDICINE**

This department was formed in 2011 by combining the university's six biomedical departments: the Department of Anatomy, the Department of Medical Biochemistry, the Department of Physiology and Biophysics, the Department of Human Genetics, the Department of Medical Microbiology and Immunology, and the Department of Pharmacology. The new Department of Biomedicine is located on the central University Park campus in Aarhus, and its total staffing currently corresponds to 354 full-time equivalents.

The overall vision driving the department's work is to achieve a better understanding of diseases at a molecular and cellular level, and to exploit our findings to benefit patients. Thus, biomedicine is a research area that bridges the gap between natural science and clinical medicine.

The Department of Biomedicine brings together numerous areas of expert competence in cellular and molecular techniques, including cell biology, biomembrane transport, cell transport, epithelial transport, stereology, cellular genetics, human genetics and epigenetic techniques, proteomics, and mass spectrometry – areas that are relevant for a wide array of studies in cellular physiology and cellular pathology. The new organizational structure also brings together several areas of expertise in translational biomedicine. These include gene therapy research, disease modulation in cells and genetically modified animals, bioinformatics, various aspects of immune and infectional pathogenesis, immunoassays for studying the innate immune system's role in disease, and also a variety of pre-clinical and translational pharmacological techniques with general relevance for the clinic and biomedicine at large.

Reinforcing cooperation with external partners

The department will seek to expand and reinforce its cooperation with other research environments at AU Health – not least the research activities at the Department of Clinical Medicine – and its cooperation with external partners in the pharmaceutical industry, the business community and elsewhere. The Department of Biomedicine will also work to expand and intensify its cooperation with several of the departments at the university's new faculty of SCIENCE AND TECHNOLOGY, including the Department of Molecular Biology and Genetics and the Department of Animal Science. The Department of Biomedicine will also be in a position to participate as a valuable partner contributing to several interdisciplinary efforts at the university in neuroscience, biomembrane proteins, food, nutrition and health, and i-sequencing.

The Department of Biomedicine holds overall responsibility for the university's BSc programme in medicine, also contributing to study programmes for BSc in molecular medicine, odontology, MSc in biomedical engineering, and the civil-engineering degree in biomedical engineering and medical chemistry.

Furthermore, the department will continue to handle a variety of tasks and assignments done for, and with, public authorities. Examples are pharmaceutical consultancy for the Central Denmark Region and the North Denmark Region, and participation in various health committees.

Photo: Lars Kruse, AU Kommunikation

EXPERT RESEARCH COMPETENCE

Centre for Pharmacology and Pharmacotherapeutics
Flow cytometry: The FACS core facility
Health, illness, and microorganisms
Innate immunology
Medical genetics and epigenetics
Membrane pumps
Membrane transport
Multifunctional brain receptors
Neurodegenerative diseases
Neurophysiology and muscle physiology
Pulmonary and cardiovascular pharmacology
Receptor recognition
Translational genetics
Vascular physiology
Viral–host interactions
Water and salt in health and disease

Biomedicine / Clinical Medicine
Bones
Clinical genetics
Core facilities: Experimental animal models, and animal housing and breeding
Diabetes and endocrinology
Electron microscopy
Growth
Inflammatory diseases
Medical proteomics
Nephrology

CORE FACILITIES

In connection with the renovation and expansion of the Department's buildings on the University Park campus, emphasis will be given not only to basic research, but also to translational and interdisciplinary research. Increased internationalization will enable research students to increase their talents and broaden their scientific outlook. Another goal for the department is to attract top researchers from the international community, thereby retaining and attracting further talent and skill, and research funding.

The department's modern laboratories, along with their ancillary support, core, and animal housing and breeding facilities, constitute the physical scaffolding necessary for research. This scaffolding also supports the collaborative efforts that involve other departments, centres, groups, and individual researchers at AU and elsewhere, as well as commercial partners – in Denmark and abroad. Taken together the Department of Biomedicine has a solid platform for ensuring an attractive research environment and the ability to interact with the international research community.

NUMBER OF FTE

354
FULL TIME EQUIVALENT

190
ACADEMIC AND SCIENTIFIC STAFF

164
TECHNICAL AND ADMINISTRATIVE STAFF

ADDRESS

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