2019

DANDRITE ANNUAL REPORT

AARHUS UNIVERSITY

DANDRITE
Danish Research Institute of Translational Neuroscience
Nordic EMBL Partnership for Molecular Medicine

Words from the Director

Photo by the Novo Nordisk Foundation, Denmark

Welcome to the 2019 annual report from DANDRITE – the Danish Research Institute of Translational Neuroscience funded by the Lundbeck Foundation and hosted by the Departments of Biomedicine and the Department of Molecular Biology and Genetics at Aarhus University.

DANDRITE is the Danish node of the Nordic EMBL Partnership for Molecular Medicine and a proud host of many individual and center-based research programs and the PROMEMO center of excellence of the Danish National Research Foundation.

2019 has been a very busy year with all group leader extensions now successfully completed. The DANDRITE research community has reached a stable level of around 130 researchers in the group leader and team leader laboratories. Our affiliated researchers also take advantage of joint initiatives to expand on neuroscience initiatives and bold new research questions. With the EMBL-inspired group leader research program and the Nordic EMBL Partnership to support it, DANDRITE has sprouted in many different, yet coherent directions and forms an expanding and dedicated community that allows interdisciplinary and innovative ideas to unfold and flourish – both within and around DANDRITE.

DANDRITE also has a growing community of alumni all across the globe – in 2019 alone a total of 12 DANDRITE PhD students graduated. In the coming years DANDRITE will develop our international alumni network to support an interspersed community of our alumni with current DANDRITE researchers, Danish neuroscience, the Nordic EMBL Partnership, and private sector enterprises. We will pave the road for mutual interactions in neuroscience and research-based careers. In this year's report, we feature three DANDRITE PhD graduates. We hope you will enjoy reading about their different career paths – past, present and pointing into the future.

DANDRITE is devoted to introducing new, original lines and methods of research in Danish neuroscience and to strengthening those that we already established. The Danish national cryo-EM facility network (EMBION) is established and a new flagship Titan-Krios electron microscope is currently being installed that will expand dramatically our capacity for research into molecular and cellular mechanisms in brain. In collaboration with our hosting departments, and the Departments of Engineering, Chemistry, Biology, Physics, Computer Science, and the iNANO center at Aarhus University and other Danish and international partners we see exciting developments of technologies and scientific questions that inquire brain function at single cell and single molecule level and at organismal level and in social context. Community science and gaming, and the use of deep learning and other artificial intelligence approaches have entered our quantitative modeling of behavior and extraction of complex patterns and correlations from large data sets and images. Behavior, neuronal circuits, genetics, and molecular interactions are approached from several different angles with the aim of understanding mechanisms of brain and brain diseases at multiple, connecting scales.

Several publications of 2019 report on exciting discoveries in basic and translational neuroscience and have opened new avenues of research in Denmark. Exciting research grants were awarded in 2019 to our researchers, for example Lundbeck Experiment and Villum Experiment grants for Team Leader Magnus Kjærgaard, grants from the Michael J. Fox Foundation for core Group leader Poul Henning Jensen, and grants from the Parkinson's Foundation for Group leader Mark Denham and core Group leader Poul Henning Jensen. Several talented young researchers attracted fellowships including Lundbeck Foundation fellowships to Ronja Driller and Kathrine Gill, PhD stipends to Katia Soud and Karen Marie Juul Sørensen, and many DANDRITE young investigators received travel awards and bursaries. I personally had the great honor of receiving the Novo Nordisk Foundation Distinguished Investigator grant and the Lundbeck Foundation professorship launching long-term research programs.

DANDRITE continues to strengthen our interactions with the Danish neuroscience community through appointments and renewals of affiliated researchers. This is a cornerstone of the DANDRITE mission, and we maintain a commitment to NeuroCampus Aarhus, the Danish Society for Neuroscience, and the Brain Prize activities supported by the Lundbeck Foundation, and exploit also many international platforms for neuroscience, such as EMBO, FENS and FEBS. In 2019, DANDRITE entered into a new collaboration with the Brain Research Institute (BRI), Niigata University, Japan.

In September 2019, EMBL Barcelona hosted the 3rd EMBL Partnership Conference "Perspectives in Translational Medicine", which is arranged every 3-4 years. The Nordic EMBL Partnership participated along with other EMBL Partnerships such as BRAINCITY in Poland, the Hubrecht Institute in the Netherlands, and HCEMM in Hungary. The conference marked a good opportunity to exchange expertise and build new interactive structures across the EMBL partnerships. As an outcome of the conference, the different Institutions and EMBL will organize workshops within shared research themes to enhance collaborations across partnerships.

DANDRITE outreach activities included the annual DANDRITE Encounters, where students meet our research groups, and the co-organization of the Neuroscience Day and Brain Prize outreach activities. Every year DANDRITE has a grand display at the Festival of Research ("Forskningens Døgn"), and engage year-round in public outreach lectures and social media outlets.

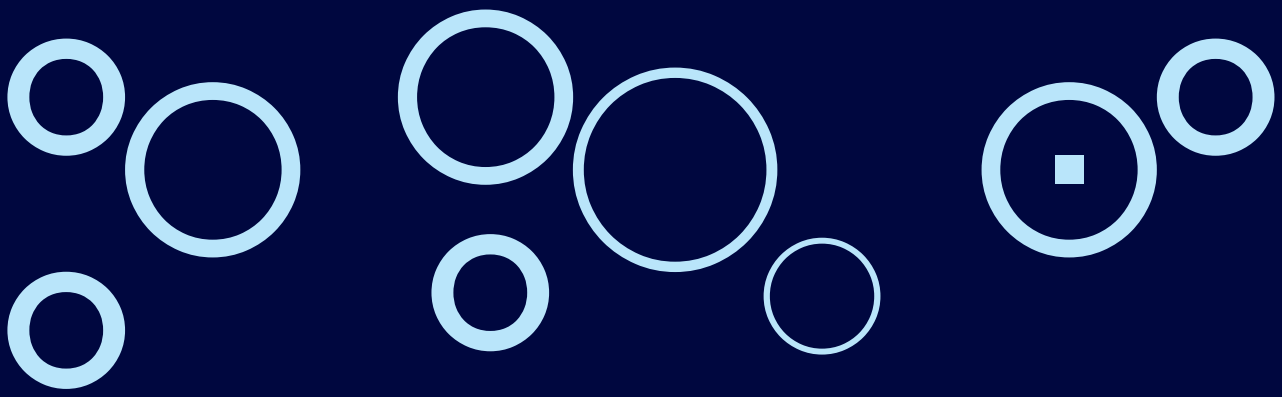
It remains a key mission of DANDRITE to spur everyone's interest in the depth and width of neuroscience, and we invite you to spend a few moments to learn more about our activities on the following pages.

With my warmest regards,

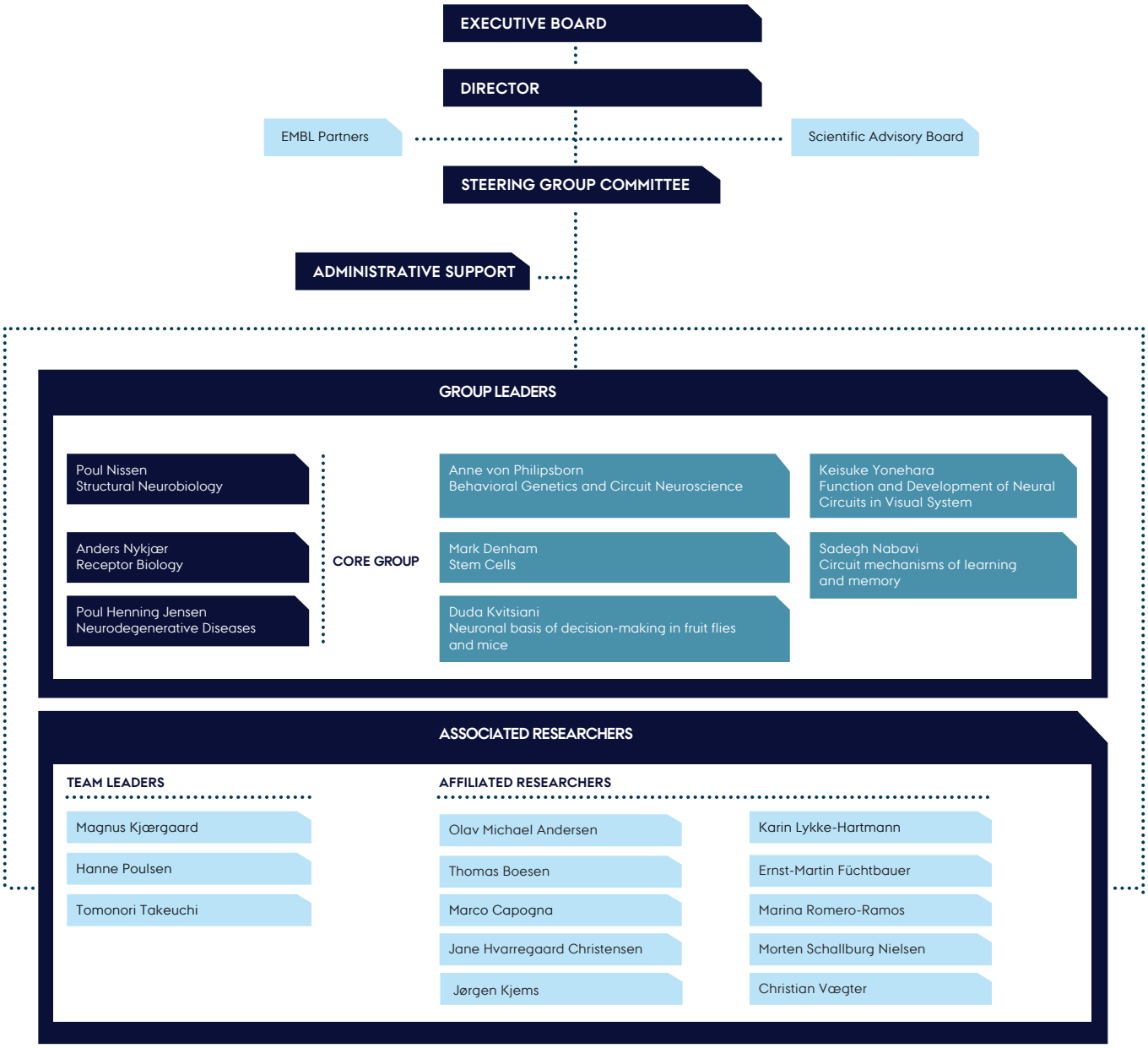
Poul Nissen, Director and Core Group Leader

01

Organization Structure



Organization Structure



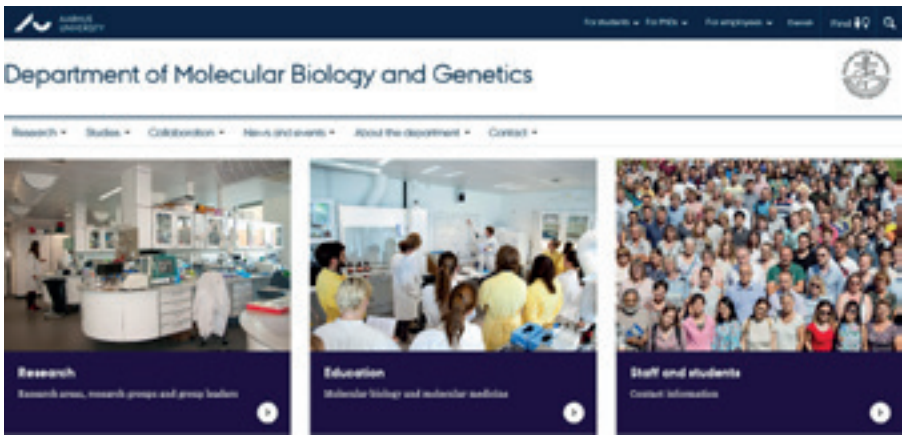
Hosting Departments

DANDRITE's executive hosting institution is Aarhus University and with neuroscience research being an innately interdisciplinary endeavor DANDRITE is placed as an Interfaculty center at the University and hosted fruitfully by the departments: Department of Biomedicine (Faculty of Health) and Department of Molecular Biology and Genetics (Faculty of Natural Sciences).

Research at Department of Biomedicine bridges the divide between natural science and clinical medicine, and the results are used to improve diagnosis, counselling and treatment of patients. The department's research covers a wide range of research areas of which Neuroscience is one of the major focus areas.

→ biomed.au.dk/en

Research at Department of Molecular Biology and Genetics spans from basic to applied research within molecular biology and genetics. Several focus areas at the departments are involved in neuroscience research – specifically Structural Biology, Gene Expression, and Gene Medicine.



→ mbg.au.dk/en

Executive Board

The Executive Board meets twice a year and consists of the Chairman, the Deans of the two founding faculties, the Director, the leaders of the Core Teams, observing representatives from The Lundbeck Foundation, and the Chief Administrative Officer. The Executive board approves significant decisions influencing DANDRITE as a research centre, including the annual budget and changes to the Research Plan. Together with the Director, the Executive Board will ensure the coordination of activities with the Nordic EMBL Partners and EMBL.

Chair: Clinical Professor **Jens Chr. Hedemann Sørensen**, Department of Clinical Medicine, Aarhus University (chair from December 2016)

Acting Dean **Lars Henrik Andersen**, The Faculty of Science and Technology (from February 2019) (From April 2020, Kristian Pedersen is new Dean Faculty of Natural Sciences).

Dean **Lars Bo Nielsen**, The Faculty of Health, Aarhus University

Director Professor **Poul Nissen**, DANDRITE

Professor **Anders Nykjær,** DANDRITE

Professor **Poul Henning Jensen**, DANDRITE

Lundbeckfonden Senior Vice President, Grants & Prizes, Director of Science
Jan Egebjerg (non-voting)

Programme Manager **Lars Torup**

Administrative support from Chief Administrative Officer **Maria Thykær Jensen**, DANDRITE (New member since August 2019, cover for Else Magård)

Management

STEERING COMMITTEE
The steering committee meets every Monday at 10-11 AM and consists of the director, the core group leaders and two representatives of the group leaders (internally elected for two-year terms). DANDRITE's administrative personnel also attends the meetings. The steering committee is responsible for strategic developments and implementation of research, the planning and coordination of activities, and the distribution of running budget. The steering committee will also be overseeing public dissemination and outreach of DANDRITE research and activities. The committee in 2019 consisted of the following members:

- Professor **Poul Nissen**, Director
- Professor **Anders Nykjær**
- Professor **Poul Henning Jensen**
- Group Leader **Mark Denham** (took over from Duda Kvitsiani in August 2019)
- Group Leader **Anne von Philipsborn**
- Chief Administrative Officer **Maria Thykær Jensen** (took over in August from Else Magård)

Furthermore, the steering committee meetings are attended by:

- Communications Assistant & Director PA, **Karen Bech**
- Research Group Coordinator and Communications Assistant, **Kathrine Hennings** (took over from Maria in August 2019)
- Center Administrator (PROMEMO) & Professor PA **Susanne Schousboe Sjøgaard**
- Communications and Scientific Research Coordinator, **Aisha Rafique** (From June 2019)

MONTHLY EXTENDED STEERING COMMITTEE MEETING
Every second Monday of each month the steering committee meets for an extended steering committee meeting taking place from 10:30 AM to 11:30 AM. The extended committee consists of all Group Leaders and Team leaders, and spokespersons for each personnel category at DANDRITE. In 2019 the participants were:

- All DANDRITE Group Leaders
- All DANDRITE Team Leaders
- Affiliated Researcher spokesperson: Jørgen Kjems (second half year)
- Affiliated Researcher spokesperson: J**ane Hvarregaard Christensen** (first half year)
- Postdoc spokesperson: **Alena Salasova**
- PhD student spokesperson: **Rune Rasmussen**
- Technician spokesperson: **Anne-Katrine Vestergaard**

MONTHLY COORDINATION MEETING
Monthly the DANDRITE core Group Leaders and chief administrator meet with the heads of the two hosting department (Thomas G. Jensen, Department of Biomedicine and Erik Østergaard Jensen, Department of Molecular Biology and Genetics) for coordination of activities, teaching, infrastructural matters, and strategies.

Scientific Advisory Board

The scientific advisory board convenes biannually and provides independent advice on scientific and strategic matters, and evaluations of achievements, ideas and strategies. SAB members are international, highly reputed researchers. The fourth DANDRITE advisory board meeting will take place 27-29 May 2020. The current members of the DANDRITE SAB are:

- Professor and chair of DANDRITE SAB, **Mart Saarma**, University of Helsinki
- Director **Matthias Wilmanns,** EMBL Hamburg
- Professor **Yang Dan**, University of California, Berkeley
- Professor **Glenda Halliday**, Neuroscience Research Australia (NeuRA)
- Professor **Ole Kiehn**, University of Copenhagen
- Professor **Rüdiger Klein**, Max-Planck-Institute of Neurobiology
- Professor **Carl Petersen**, École polytechnique fédérale de Lausanne EPFL

New members who will take part in the planned SAB meeting in May 2020:
- Professor **Elena Cattaneo,** University of Milan, Italy
- Professor **Veerle Baekelandt**, KU Leuven - Center for Molecular Medicine, Belgium

Associated Researchers

Associate Membership serves a strategic tool for the further development of DANDRITE's research focus areas and must be of mutual benefit. Selection criteria for associating a researcher is foremost on scientific excellence and scientific complementation.

A team leader holds a non-tenured junior group leader position/assistant professorship at Aarhus University. The appointment as DANDRITE team leader is for 3 years with possible extension for a total of maximum 6 years.

An affiliated researcher is typically, an Aarhus University researcher with permanent position that is tightly associated to DANDRITE group leader(s) for mutual benefits on research aims (e.g. through joint grants/research centers, shared laboratories etc.). The affiliation can also serve to strengthen strategic infrastructures that are of key importance to DANDRITE. Affiliated researchers (AR) have qualifications and position at associated professor level or higher.

In 2019 Professor Ernst-Martin Füchtbauer joined as Affiliated Researcher to DANDRITE.

ADMINISTRATIVE SUPPORT TEAM

The Support Team aims at ensuring a cohesive, efficient and professional administration and research support for employees and students connected to DANDRITE. The Support Team strives for providing the framework needed for the single DANDRITE researcher to reach their full potential.

As DANDRITE is an interfaculty unit, an important task for the support team is to bridge different administrative procedures among various entities and cultures and the work is done in tight collaboration with colleagues in the two hosting departments.

To streamline and keep high quality in the undertaking of administration tasks, DANDRITE's local support team links and draw on the administrative colleagues and services in the grand university's administrative organization e.g. the HR units, the accounts units, procurement unit, the communication units, and the research support unit. In this way, the support team ensures that DANDRITE gains the full advantage of the AU administrative organization, infrastructure and resources provided at the department levels, the faculty levels, and the university level.

ANNUAL CYCLE

Since the inauguration of DANDRITE in 2013, many of the annual activities and organizational structures have settled as recurring events, illustrated here by the annual cycle.

Figure: DANDRITE Annual Cycle
* SAB Meetings take place every 2nd year
** Executive board meetings takes place every half year; June/July and December
*** Not included in annual cycle: weekly Business Meetings, bi-weekly Internal Meetings, monthly Extended Business Meetings

Career café on 'what do people do with a research background' by Ph.D. Career Consultant Vibeke Broe

Young DANDRITE

– The PhD & Postdoc association at DANDRITE

During 2019, Young DANDRITE 'reinvented' their organization with the aim to facilitate interaction and unity among PhD students and Postdocs at DANDRITE, and support professional development of young researchers. The organizing committee recruited additional members and now meets every month to arrange both social and scientific events throughout the year. In 2019, the Young DANDRITE organizing committee hosted several events. The scientific events included a workshop on 'How to write a good funding application' by Scientific Research Coordinator Aisha Rafique and a seminar on 'what do people do with a research background?' by Ph.D. Career Consultant Vibeke Broe. There have also been social gatherings, which included pub-crawls, Friday bars and board game nights. The Young DANDRITE organizing committee is currently working hard to schedule their program for 2020.

Besides organizing their own events, Young DANDRITE is contributing with input to general DANDRITE events, such as the Scientific Advisory Board meeting and DANDRITE retreat, to ensure that they stay relevant and exciting to the young DANDRITE community. The opinions from Young DANDRITE are highly valued and their engagement in DANDRITE events is crucial to the innovation and unity of DANDRITE.

YoDa.
Illustration by: PhD student Sophie Seidenbecherr

Current members of the Young DANDRITE organizing committee:
Katia Soud, PhD student
Karen Marie Juul Sørensen, PhD student
Lucie Woloszczuková, Research Assistant
Lixiang Jiang, PhD student
Emil Gregersen, PhD student
Meike Sieburg, Postdoc
Mads Christensen, PhD student
Admin. Support representative: Kathrine Hennings (Research Group Coordinator & Communications Assistant)
PhD representative: Rune Rasmussen
Postdoc representative: Alena Salasova

Group photo from the third EMBL Partnership Conference "Perspectives in Translational Medicine" in Barcelona on 25–27 September 2019.
Photo: Christine Panagiotidis

THE NORDIC EMBL PARTNERSHIP FOR MOLECULAR MEDICINE

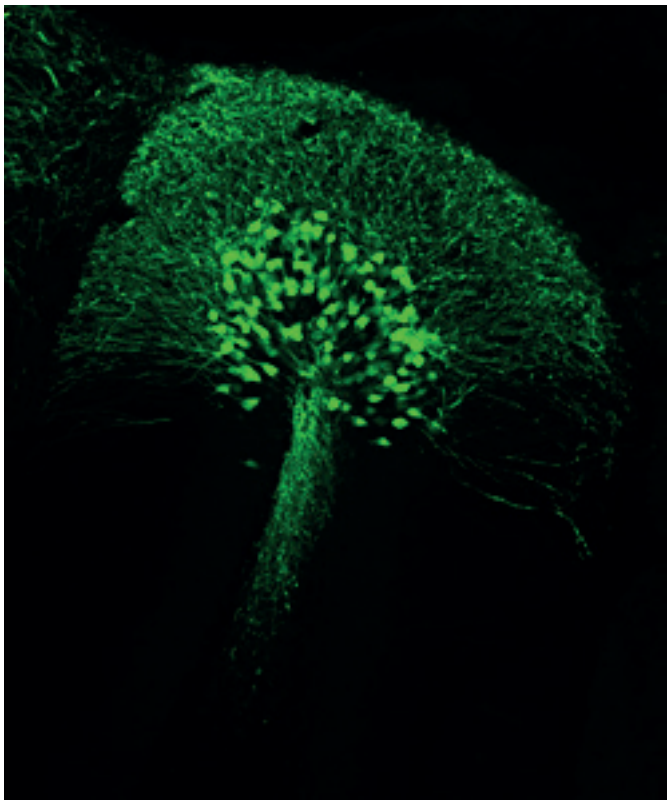
The Nordic EMBL Partnership for Molecular Medicine is a unique association of four national research centres that run complementary translational molecular medicine research in the Nordic countries using the operational model and core principles of the European Molecular Biology Laboratory (EMBL). The national research centres are hosted by universities in Denmark, Finland, Norway and Sweden and constitute a major strategic player in European research of disease mechanisms and biomedical research in the Nordic and global biomedical research community. By combining the complementary strengths of the centres including biobanks, health registries, industrial collaborations and core facilities, the partnership has created a vibrant and an open international collaboration in translational molecular medicine research and share the common mission to address some of the biggest challenges in biomedicine today.

The Nordic EMBL Partnership for Molecular Medicine was established in 2008 as a united venture between EMBL and three Nordic countries; Finland, Sweden and Norway. It initiated the building of national institutions namely the Institute for Molecular Medicine Finland (FIMM, www.fimm.fi) at the University of Helsinki, the Laboratory for Molecular Infection Medicine Sweden (MIMS, www.mims.umu.se) at Umeå University, and the Centre for Molecular Medicine Norway (NCMM, www.ncmm.uio.no) at the University of Oslo.

Concurrently with a renewed partnership agreement with EMBL in 2013, the Nordic EMBL Partnership was expanded by a fourth node, the Danish Research Institute of Translational Neuroscience (DANDRITE, www.dandrite.au.dk). Today, the four nodes in the Partnership support over 63 group and team leaders and house over 60 different nationalities of staff and researchers.

"The national institutes have complementary strengths with each partner bringing a unique profile of field expertise, skills and core facilities that incorporate research within molecular, cellular and developmental biology, human genetics, bioinformatics and structural biology. NCMM's proficiency in molecular mechanisms of disease, MIMS' focus on microbial pathogenicity and molecular infection medicine, FIMM's expertise in human genomics and medical systems biology and DANDRITE's strength in neurobiology and structural biology, complement and equip the nodes to tackle some of the biggest challenges of biomedicine today. Alongside the collaboration between the nodes, the national institutes cooperate with their host universities, university hospitals, local and national research institutes, public health institutes, and research councils. This has developed a strong multidisciplinary and cross-organizational Nordic network for molecular medicine research.

DANDRITE contributions to The Nordic EMBL Partnership Calendar Competition 2019



CALENDAR IMAGE FOR JANUARY 2020

HIPPOCCOLI
By Meet Sanjakumar Jariwala, DANDRITE.

"The image represents specifically labelled green fluorescent protein (GFP) positive neurons in CA1 region of dorsal Hippocampus in mouse brain. The picture represents only half hemisphere of the brain, while the cortex starts from left and ventral part of brain is in right. This image represents the neurons activated during fear behavior. The virus injection has spread from Lateral Habenula (nearby region) to CA1 region of Hippocampus, giving it a beautiful shape of Broccoli."

CALENDAR IMAGE FOR JULY 2020

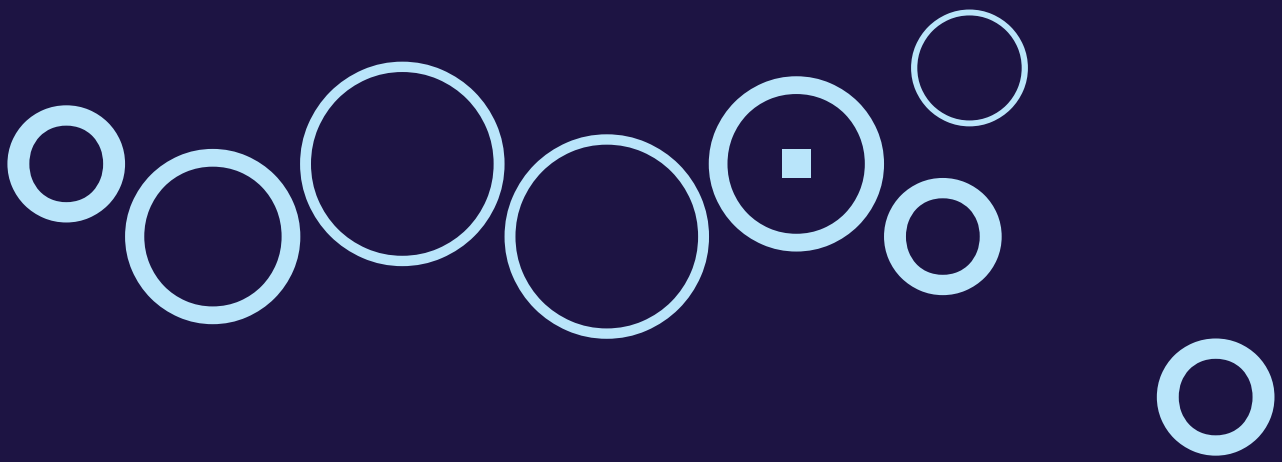
PURIFYING PROTEIN
By Mateusz Dyla, DANDRITE.

"Protein purification is a common process in many protein-oriented labs. In my picture, I wanted to show a final stage of this process, i.e. purified protein dripping down from a purifier. I used a 3D-printed model of a sodium/potassium pump to visualize this concept. I used a syringe and AKTA system connectors to control the size and position of a water drop, and I placed the protein model directly behind the drop. The result was refraction of the model in the drop, looking as if it was contained within the drop. I used a macro lens to capture the picture, and the background was the actual out-of-focus protein model."

CALENDAR IMAGE FOR SEPTEMBER 2020

IDEA
By Mette Richner, DANDRITE
"When an idea germinates – an artistic interpretation."

02 Research Activities



Nissen Group

Structural neurobiology

Professor
Poul Nissen

The Nissen lab focuses on structural neurobiology and in particular on membrane transporters and neuronal membrane ultrastructures. The laboratory uses primarily cryo-electron microscopy (cryo-EM), protein crystallography, biochemistry, and biophysics, and includes also collaborative studies through e.g. molecular dynamics simulations, fluorescence microscopy, and electrophysiology. Main subjects include P-type ATPase ion pumps and lipid flippases, Na+ dependent transporters of neurotransmitters and chloride, and metabolic receptors. Derived activities include also structure-based drug discovery. A major, long-term goal is to investigate neuronal ultrastructures and model higher-order networks and mechanisms in the Axon Initial Segment that integrate circuit inputs and generate action potentials, and downstream of that the synaptic structures associated with memory and learning, and molecular mechanisms underlying direction-selective function in the visual system.

The P-type ATPase ion pumps, such as the Na+,K+-ATPase and Ca2+-ATPase, maintain constantly the vital ion gradients that potentiate e.g. ion channels, membrane potential, secondary transporters, membrane dynamics, and regulation of cell volume, ion homeostasis, and pH control. Structural studies of sarco-endoplasmic reticulum Ca2+-ATPase 2a (SERCA2a) revealed basic mechanisms of function, pathological mechanisms of disease-mutations, regulation through intra- and intermolecular interactions, and post-translational modifications. Furthermore, the integral role of SERCA in cell death mechanisms were investigated in a collaboration with researchers from NCMM of the Nordic EMBL partnership.

First structures of a P4-ATPase lipid flippase were determined by cryo-EM in collaboration with previous DANDRITE team leader Arne Möller and revealed the basis of lipid interaction and autoregulation of lipid flippases.

Cryo-electron tomography studies are ongoing and have revealed the first 3D tomograms with gold labeling of key determinants (unpublished).

TRANSLATIONAL STUDIES
The work on lipid flippases pointed to important regulatory mechanisms that may also be manipulated to affect lipid homeostasis and membrane dynamics.

Nissen group members.
Photo: Lisbeth Heilesen.
Due to the Corona lockdown, a photo with all lab members present was not possible to get

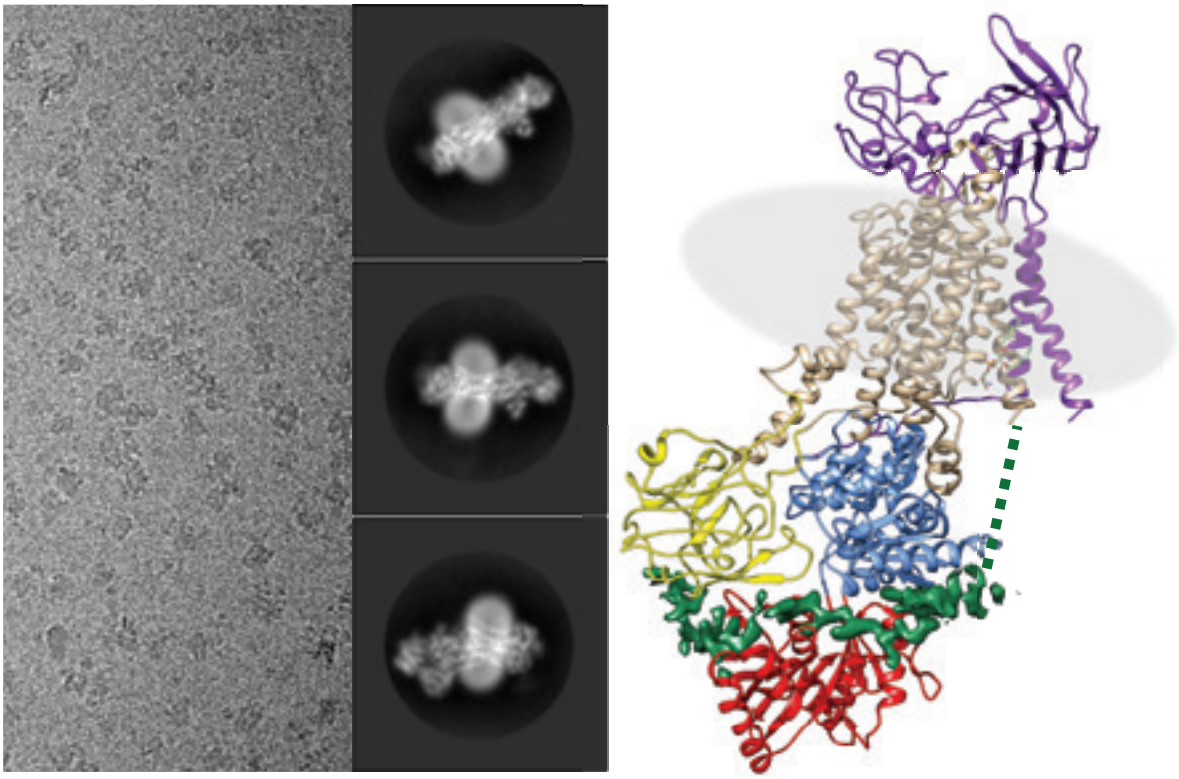


Figure 1: First structure of a P4-ATPase lipid flippase. The 3D reconstruction and structure determination of a P4-ATPase lipid flippase - the phosphatidylserine lipid flippase Drs2:CDC50 (Timcenko, Lyons, Januliene et al. 2019, Nature 571, 366-370). Left: micrograph showing individual lipid flippase molecules. Middle: 2D class averages showing clear structural features. Right: final structure shown in cartoon representation combined with the EM map (in green) for the autoinhibitory domain and revealing the mechanism of autoinhibition – an entry point for functional intervention.

SELECTED PUBLICATIONS 2019

Dyla M, Kjærgaard M, Poulsen H, Nissen P (2019). Structure and Mechanism of P-Type ATPase Ion Pumps. *Annu Rev Biochem.* 2019 Dec 24.

Timcenko M, Lyons JA, Januliene D, Ulstrup JJ, Dieudonné T, Montigny C, Ash MR, Karlsen JL, Boesen T, Kühlbrandt W, Lenoir G, Moeller A, Nissen P (2019). Structure and autoregulation of a P4-ATPase lipid flippase. *Nature* 571, 366-370

Sitsel A, De Raeymaecker J, Drachmann ND, Derua R, Smaardijk S, Andersen JL, Vandecaetsbeek I, Chen J, De Maeyer M, Waelkens E, Olesen C, Vangheluwe P, Nissen P (2019). Structures of the heart specific SERCA2a Ca2+-ATPase. *EMBO J 38*, pii: e100020

PERSONNEL LIST NISSEN GROUP

Senior Researcher **Thomas Lykke-Møller Sørensen**
Assistant Professor **Esben Quistgaard**
Assistant Professor **Joseph Lyons**
Assistant Professor **Michael Voldsgaard Clausen**
Assistant Professor **Azadeh Shahsavar**
Postdoc **Antoni Kowalski**
Postdoc **Michael Habeck**
Postdoc **Milena Timcenko Tronsgaard**
Postdoc **Montana Caballero Bermejo**
Postdoc **Ronja Driller**
PhD Student **Aljona Sitsel**
PhD Student **Caroline Marie Teresa Neumann**
Industriel PhD Student **Jeppe Achton Nielsen**
PhD Student **Jonathan Juhl**
PhD Student **Josephine Nissen**
PhD Student **Line Marie Christiansen**
PhD Student **Mads Eskesen Christensen**
PhD Student **Marlene Uglebjerg Fruergaard**
PhD Student **Paula Szalai**
PhD Student **Samuel Hjorth-Jensen**
PhD Student **Sigrid Thirup Larsen**
PhD Student **Sofia Trampari**
Laboratory Technician **Anna Marie Nielse**n
Laboratory Technician **Tanja Klymchuk**
Research Assistant **Temitope Ibironke Ayeotan**
Research Assistant **Christine Juul Fælled Nielsen**
Student Assistant **Søren Brag**
Student Assistant **Jonathan Søholm-Boesen**
Scientific computing **Jesper Lykkegaard Karlsen**
Communications Assistant & Personal Assistant **Karen Bech-Pedersen**
Nordic EMBL Partnership Communications Officer and Scientific Research Coordinator **Aisha Rafique**
Group Leader, Professor **Poul Nissen**

Jensen Group

Neurodegenerative Diseases

Professor
Poul Henning Jensen

The Jensen group is studying how alpha-synuclein contributes to the neurodegenerative processes in Parkinson's disease, Lewy body dementia and multiple systems atrophy, which are hallmarked by prion-like spreading of intracellular aggregates of aggregated alpha-synuclein in the nervous system. This is investigated in studies of alpha-synuclein aggregates in vitro, in cell models, transgenic animals and human tissue and involve development of new tools, and methods.

Focus areas are:

- How the early phase of the alpha-synuclein aggregate build-up sculpts the degenerative process in and between neurons thereby contributing to patients' symptomatology by making neurons dysfunctional thereby contributing to abnormal circuitries. Investigations probe the molecular structure of alpha-synuclein aggregates generated in cells and brains, how they impact on cellular signalling pathways, and how the aggregate pathology is passed between cells. Mechanism-based disease interventions are conducted in cellular and in vivo models.
- How cell- and environmental factors are contributing to the specific strains of alpha-synuclein aggregates that displays different properties with respect to cellular effects in in vivo propagation and toxicity. In vitro formed aggregate strains are compared to aggregate-strains amplified from patient samples.
- New antibody-based methods developed with the aim of identifying and characterizing novel alpha-synuclein-based pathology in brain tissue from human patients and in vivo models are used in clinical investigations
- The expression level of brain alpha-synuclein represents a clinical risk factor. We study how different kinases and environmental stress factors regulate expression of alpha-synuclein.

Jensen group members
Photo: Kathrine Hennings

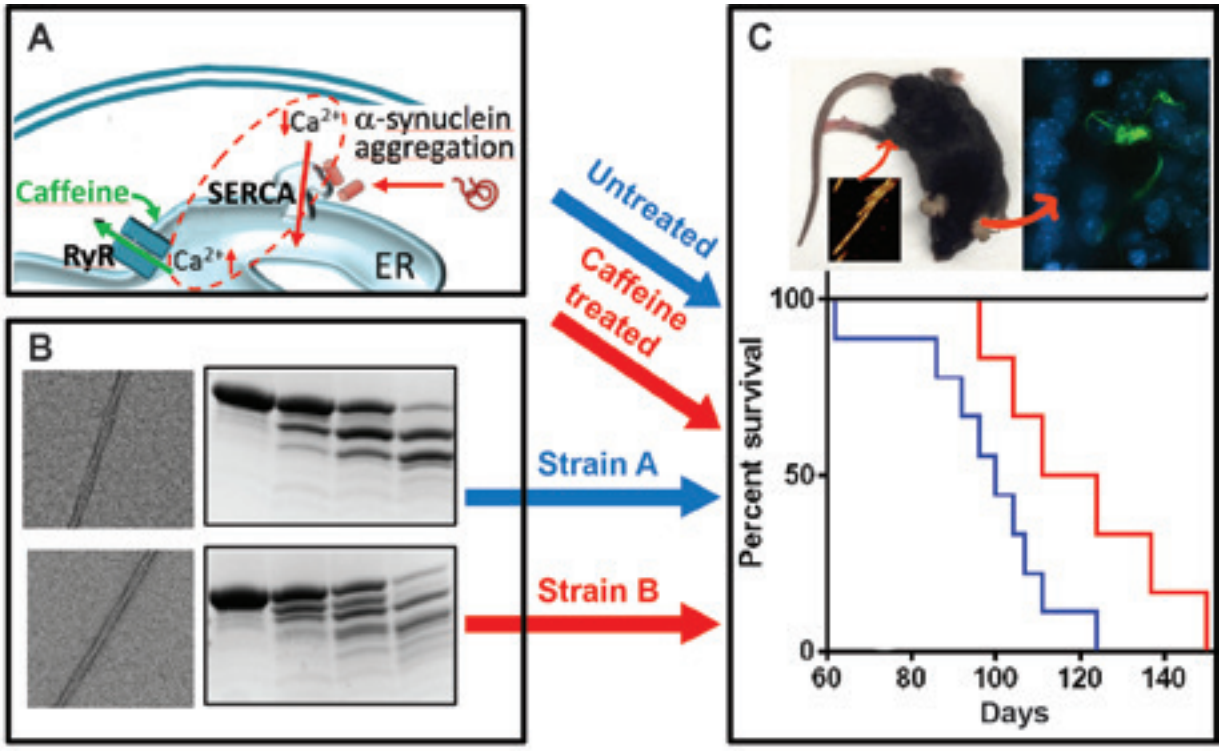


Figure 1: Investigating disease mechanisms in Parkinson's disease. A) Hypothetical mechanism behind the cytotoxicity of alpha-synuclein aggregates that stimulate calcium pump SERCA and pumps calcium from cytosol to the endoplasmic reticulum (ER). Caffeine can counteract the calcium flow by increasing efflux from ER via ryanodine receptor channels (RYR). B) Folding strains of preformed alpha-synuclein aggregates (A and B) are produced and analysed by electronmicroscopy (left) and proteolytic peptide mapping (right). C) Disease mechanisms are investigated in an alpha-synuclein transgenic mouse model. Injection of preformed alpha-synuclein aggregates in the hind limb muscle causes the development of a progressive prion-like spreading of alpha-synuclein aggregate pathology that ultimately kills the animals. Caffeine treatment protect the animals thus corroborating the hypothesis in panel A and the strains A and B displays different disease causing properties with strain A being most aggressive.

SELECTED HIGHTLIGST 2019

Ruesink H, Reimer L, Gregersen E, Moeller A, Betzer C, Jensen PH. (2019) Stabilization of a-synuclein oligomers using formaldehyde, *PLoS One* 14(10):e0216764

Elfarrash S, Jensen NM, Ferreira N, Betzer C, Thevathasan JV; Diekmann R, Adel M, Omar NM, Boraie MZ, Gad S, Ries J, Kirik D, Nabavi S, Jensen PH. (2019) Organotypic slice culture model demonstrates interneuronal spreading of alpha-synuclein aggregates. *Acta Neuropathologica Communications* 7(1):213

Kofoed RH, Betzer C, Ferreira N, Jensen PH (2019) Glycogen synthase kinase 3 β activity is essential for Polo-like kinase 2- and Leucine-rich repeat kinase 2-mediated regulation of α-synuclein *Neurobiol Dis.* 136, 104720

Jan A, Richner M, Vægter CB, Nyengaard JR, Jensen PH (2019) Gene Transfer in Rodent Nervous Tissue Following Hindlimb Intramuscular Delivery of Recombinant Adeno- Associated Virus Serotypes AAV2/6, AAV2/8, and AAV2/9, *Neuroscience Insights*, 14: 1–12

PERSONNEL LIST JENSEN GROUP

Assistant Professor **Cristine Betzer**
Assistant professor **Nelson Ferreira**
Postdoc **Asad Jan**
Postdoc **Fikret Emre Kapucu**
Postdoc **Lasse Reimer**
PhD Student **Emil Gregersen**
PhD Student **Lixiang Jiang**
PhD Student **Sara Elfarrash**
PhD student **Hjalte Gram**
Research Assistant **Nanna Møller Jensen**
Bioanalyst **Jette Bank Lauridsen**
Laboratory Technician **Golshah Ayoubi**
Group Leader, Professor **Poul Henning Jensen**

Nykjær Group

Receptor Biology

PROMEMO
CENTER FOR PROTEINS IN MEMORY

Professor
Anders Nykjær

Research activities of the Nykjær lab are focused towards the functional characterization of a family of neuronal type-1 receptors denoted Vps10p-domain receptors or sortilins. Members of this gene family, which comprises sortilin, SorCS1, SorCS2, SorCS3, and SorLA are most highly expressed in neurons but are also present in some specialized cell types outside the nervous system.

All the receptors are multifunctional as they can bind a vast number of ligands including neurotrophins, receptor tyrosine kinases, amyloid precursor protein, progranulin, and neurotransmitter receptors and engage in cellular trafficking and signaling dependent on the cellular context. Accordingly, sortilin receptors have surfaced as risk genes in both psychiatric, neurological, and metabolic diseases.

We aim to understand the molecular mechanism by which sortilin receptors control neuronal development, synaptic plasticity, survival, and memory and what goes wrong in patients with mental disorders and neurodegenerative diseases. To achieve this, we take advantage of a broad repertoire of techniques including transgenic animal models, viral-mediated gene transfer, electrophysiology, mouse behavioral testing, cell biology, and advanced imaging systems, as well as close collaborations with structural biologists and geneticists.

Memory is the single most important brain process that determines our personality. Some experiences we remember strongly whereas other instances rapidly faint. A major effort in the group is to understand the molecular mechanisms that govern consolidation and recall of a memory, its selectivity, and what may go wrong when cognitive function fails. Sortilin acts as a thermostat to control the neuronal communication in brain regions that are critical to consolidate a memory. Scientists at University-Wisconsin Madison recently identified in the Amish population the first mutation in the gene. Using a genetically engineered mouse model we find that the sortilin mutation impacts on learning and memory, and current efforts are directed to understanding the underlying mechanism at the level of the molecule and in neuronal circuits.

Curiously, sortilin also regulates certain types of sensation. Neuropathic pain is a condition where a normally innocuous stimulus like touching a cup is associated with very painful and disabling sensation, so-called allodynia. We found that neuronal communication in the peripheral nervous system is disturbed leading to increased transmission of pain stimuli to the brain. Importantly, treatment with a sortilin antagonist completely normalized sensation. This finding provides an unprecedented opportunity for development of a new class of drugs to alleviate this painful condition.

"Motor neuron development is a complex process that requires a concerted action of trophic factors and guidance cues for the axons to reach their targets and develop functional neuromuscular junctions. Using transgenic zebrafish and mice, we have studied the role of sortilin receptors in development of motor neurons and their regeneration following a nerve injury. The first data suggest that the receptor family may subserve critical functions in controlling axon outgrowth. (Figure 1). Curiously, the molecular mechanisms involved in patterning of neuronal circuits is overlapping with those controlling vascular development. Hence, like motor neuron development, angiogenesis also requires sortilin receptors, and in fish lacking this receptor, vascular outgrowth in the brain as well as in the periphery is affected (Figure 2)".

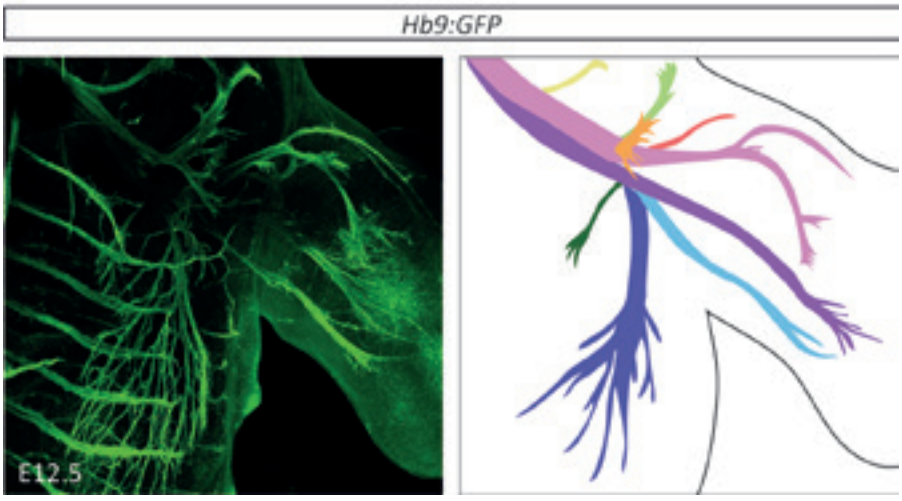


Figure 1: Whole-mount GFP staining of the motor neurons in the right forelimb of a 12-days old transgenic mouse embryo. The drawing represents the innervation pattern with the different forelimb nerves color-coded. Credits: Pernille Thomasen.

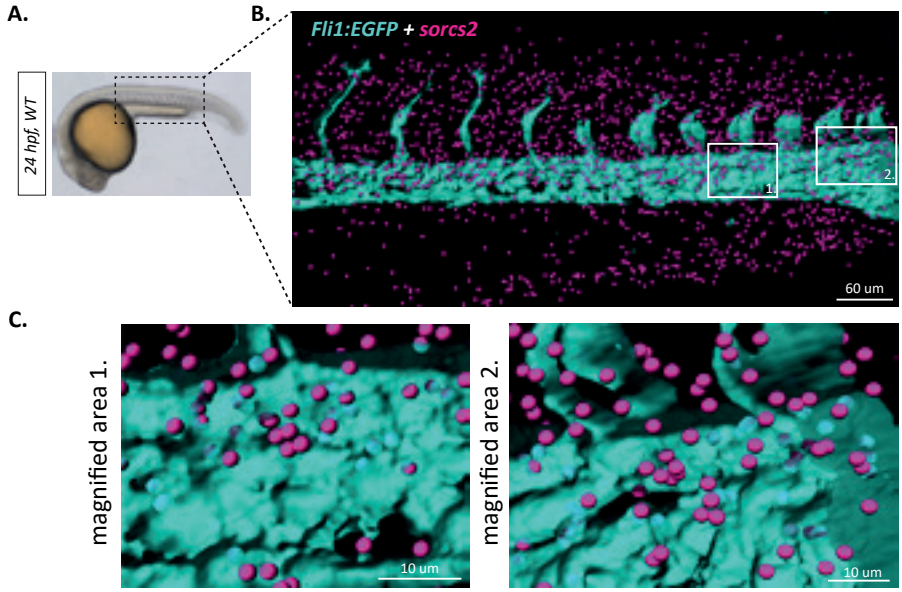


Figure 2: Single mRNA molecule detection of sorcs2 in vessels of transgenic zebrafish. A. 24hpf zebrafish embryo with highlighted region of interest. B. 3D reconstruction of vessels (labelled by Fli1:EGFP in green) and single molecules of sorcs2 mRNA (purple) in the fish trunk. C. When zoomed in, one can determine the exact number and location of sorcs2 molecules outside and inside of the vessels. Credits: Alena Salasova.

Nykjaer group members
Photo: Mathias Voetmann

Selected publications 2019

Richner M, Pallesen LT, Ulrichsen M , Poulsen ET , Holm TH , Login H , Castonguay A, Lorenzo L-E, Gonçalves NP, Andersen OM, Lykke-Hartmann K, Enghild JJ, Rønn LCB, Malik IJ, De Koninck Y, Bjerrum OJ, Vægter CB, Nykjær A (2019) Sortilin Gates Neurotensin and BDNF Signaling to Control Peripheral Neuropathic Pain. *Science Adv*, 5 (6), eaav9946.

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Denham Group

Stem Cells

Group Leader
Mark Denham

We study how the human nervous system develops and the processes involved in neurodegeneration. To do this, we use human pluripotent stem cells, which have the unique ability to give rise to all cell types of the body, and by differentiating them into particular neuronal lineages, we investigate developmental or disease processes, in a human context. Specifically, our laboratory is interested in understanding how mesencephalic dopaminergic (mesDA) neurons develop, the cells that are predominantly affected in Parkinson's disease (PD) patients. Furthermore, we are using patient-specific induced pluripotent stem cells (iPSCs) to generate diseased neurons, and by combining in vitro neuronal activity analysis with next-generation sequencing, we aim to detect early pathological gene-expression changes. The overall goals are to identify new disease mechanisms that may be used in the development of novel drug targets for treating PD and other neurodegenerative disorders.

MOLECULAR MECHANISMS CONTROLLING PARKINSON'S DISEASE SUSCEPTIBILITY

To investigate mechanisms involved in initiating PD, we generated eight PD iPSC lines reprogrammed from a diverse range of familial Parkinsonian patient skin samples (Chen et al., 2019; Figure 1). With these cell lines, we are investigating genetic mechanisms that contribute to disease susceptibility. In particular, we are interested in glucocerebrosidase (GBA) variants that result in a compromised lysosomal/autophagic pathway. GBA mutations are the most common risk factor for developing PD, and the pathology is similar to idiopathic PD. However, not all GBA carriers develop the disorder, and the reason for the variability in penetrance is unknown. As such, we are investigating what mechanisms in addition to GBA regulate disease severity. To date, we have successfully generated GBAhet neurons from iPSCs and developed a culture system whereby we can detect deficits in synaptic activity using a multi-electrode array. Furthermore, by performing RNA sequencing, we have identified an RNA binding protein that is dysregulated in GBAhet neurons and shown that this imbalance can lead to an increase in Alpha-synuclein, the principal protein that is misfolded and aggregated in PD. Using ATAC sequencing, we are now

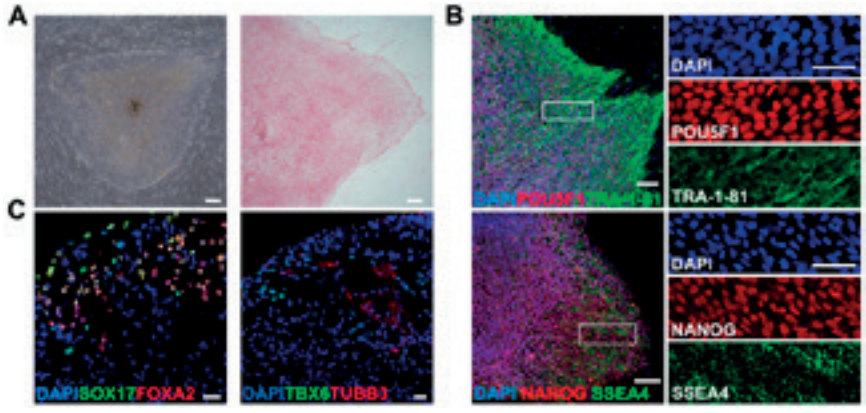

Figure 1: Induced pluripotent stem cell line. A) Colony growing on feeders. B) Expression of pluripotent markers. C) Germ layer differentiation. Illustration by Muwan Chen.

further investigating what mechanism is responsible for this dysregulated expression. Overall, understanding the genetic mechanisms that contribute to the risk of developing PD is highly relevant for sporadic cases and can lead to new therapeutic targets.

REGIONAL SPECIFICATION OF NEURONS FROM iPSCs

We are investigating the processes involved in the differentiation of iPSCs into subtype-specific neurons. Neurological disorders such as PD target specific neuronal subtypes; therefore, being able to control the differentiation of iPSCs will allow us to uncover neuronal subtype-specific phenotypes. Numerous transcription factors are known to be involved in dictating cell fate; however, the regulatory mechanism that controls transcription factor expression is poorly understood. To better understand these events, we mapped the transcriptome during the early stages of neuronal development under specific growth factor conditions (Chen et al., 2018), and identified distinct expression patterns that correspond to specific developmental regions of the CNS. From this analysis, we developed a combined differentiation and conversion method that generates regionally specified neurons. Currently, we are characterising two distinct neuronal subtypes that correspond to the forebrain and hindbrain regions of the CNS (Figure 2). Overall, determining the factors that regulate cell fate and how the interplay between extrinsic and intrinsic factors is regulated is crucial for understanding developmental processes and will allow us to generate pure neuronal populations for disease modelling.

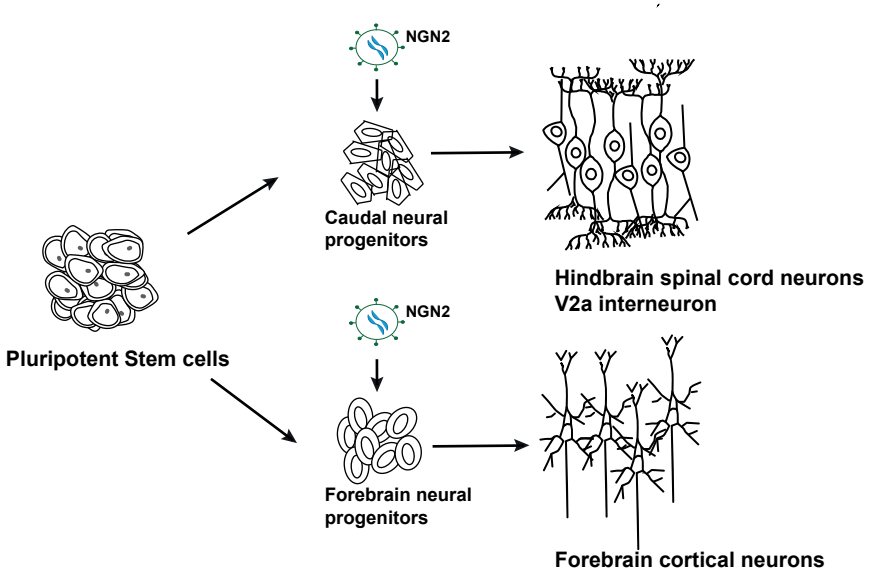

Figure 2: Combined differentiation and direct conversion with a single factor NGN2 yield regional-specific neurons along the rostral-caudal axis. Illustration by Muwan Chen.

Denham group members
Photo: Kathrine Hennings

SELECTED PUBLICATIONS 2019

Chen M, Maimaitili M, Buchholdt SH, Jensen UB, Febbraro F. Denham M. (2019). Generation of eight human induced pluripotent stem cell lines from Parkinson's disease patients carrying familial mutations. *Stem Cell Research.*

Habekost M, Jørgensen AL, Qvist P, Denham M. (2019). Transcriptomic Profiling of Porcine Pluripotency Identifies Species-specific Reprogramming Requirements for Culturing iPSCs. *Stem Cell Research.*

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Kvitsiani Group

Neuronal basis of decision-making in fruit flies and mice

Group Leader
Duda Kvitsiani

We investigate genetic and neural circuit mechanisms of foraging decisions. The methods we use include molecular genetics, psychophysics, behavioral electrophysiology, optogenetics and computational modeling.

To characterize behavior we build predictive and quantitative models that help us capture key decision variables. To understand genetic basis of decisions we focus our research on fruit flies and using extracellular electrophysiology and cell-type specific recordings we investigate how neural circuits guide value based decisions in rodents. Overall, our long-term goal is to use ecology inspired quantitative behavioral models to guide and sharpen scientific questions.

MAJOR ACHIEVEMENTS

In the past we have studied probabilistic reward foraging decisions in fruit flies using closed loop optogenetic reward delivery system (Fig.1a). Using this system we discovered that flies combine navigation and value based decision making strategies to forage for fictive rewards. We arrived to this conclusion by analyzing walking paths of flies in response to sugar receptor optical stimulation and using computational modelling approaches (Fig.1b).

In mice and humans using probabilistic reward foraging task (Fig.2) we discovered that animals rely both on their past reward and choice history to make decisions. Using normative framework we show that choice history integration

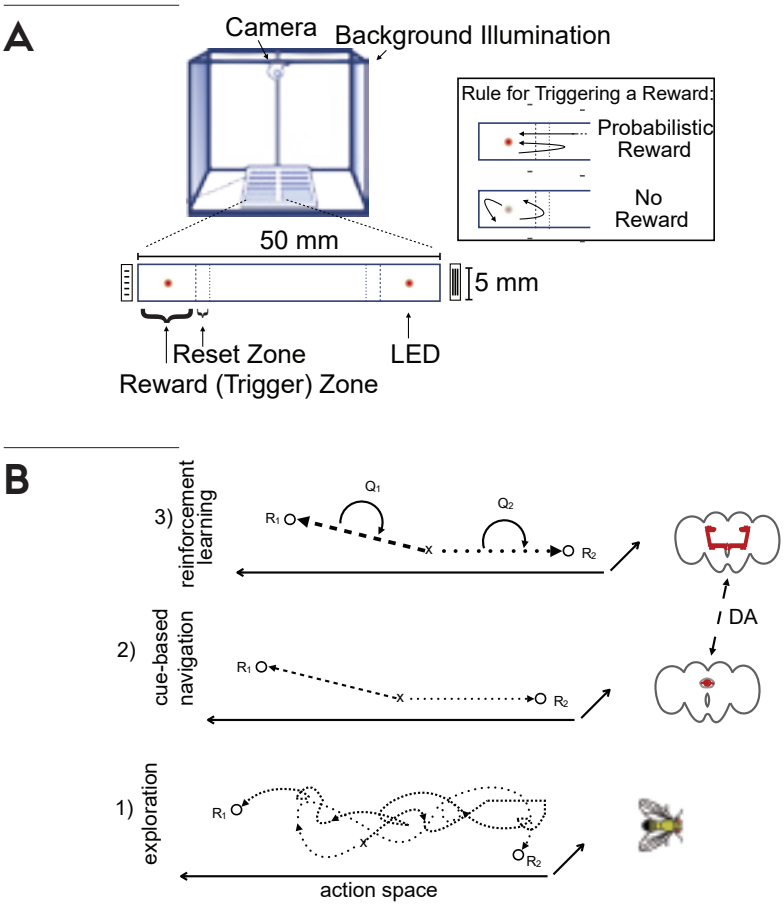

Figure 1:

A Single fly optogenetic foraging setup. A system of 12 linear track arenas is placed in a behavior box with uniform white background illumination and monitored by a webcam from above. Each arena contains two stimulating LEDs (λ = 624 nm) mounted below each of the track. Reset and trigger zones (short and long dash) are not visible to the flies. Distal visual cues were drawn behind each trigger zone: black and white stripe patterns with different orientations on each side. Inset: Rule for triggering a probabilistic flash of light. A flash is triggered only when the fly enters the reset and the reward zones in that order.

B Proposed schematic of the interaction of navigation and learning in a foraging task.

1) A foraging fly starts navigation in a new environment with the sequence of actions (dashed) thatleads to reward R1. After that, the fly continues to forage on a path (dotted) experiencing another reward R2.
2) After leaving R2, the fly can make a decision to return to the R1 or R2 rewarded site via the already executed and rewarded path (dashed or dotted) or, using representation-based navigation, travel on shortcuts to the rewarded locations.
3) Combined with reinforcement learning, values are assigned to those shortcuts and updated with the collected rewards.

into decision-making process is optimal and computational models that incorporate choice history effects outperform existing models that ignore choices history effects.

We also carried out single unit recordings to understand how decision variable are computed by cortical neurons. We can demonstrate that individual neurons in medial prefrontal cortex represent past rewards and choices up to 10 trials back in the history.

FUTURE PLANS

We are aiming to manipulate activity of neurons with the millisecond precision. For this we have developed the real-time spike sorting feedback system that allows us to trigger any arbitrary stimulus when a single spike is detected from a well isolated single unit. We plan to use this method to investigate spike timing based plasticity and how it is controlled by neuromodulators. The method will allow us for the first time to probe plasticity mechanisms in intact animals.

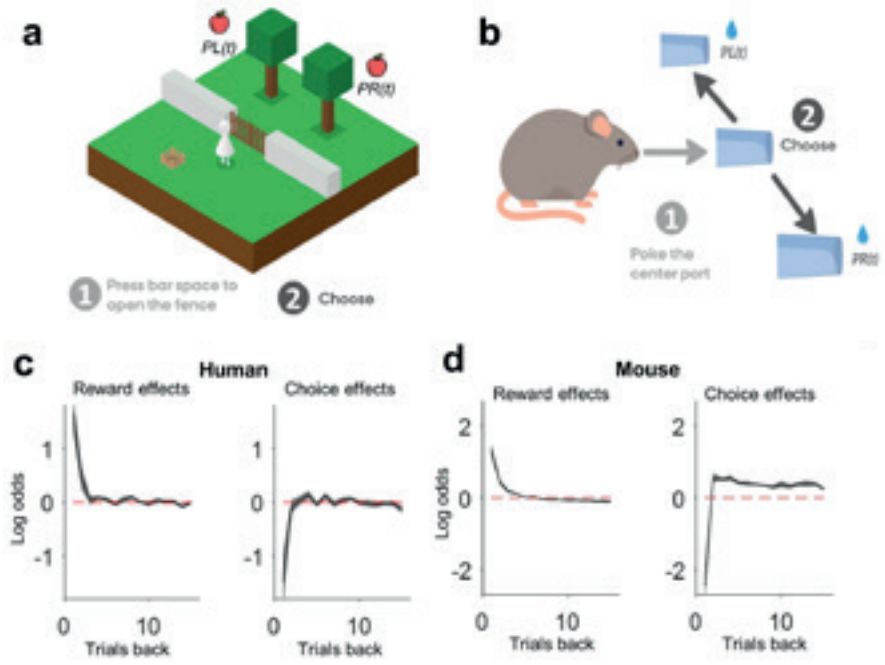

Figure 2: A Snapshot of the computer game played by the human participants. The subjects had to wait between 0s and 5s after opening a virtual fence by pressing on a keyboard before making the decision to press on the left or right key. **B** The scheme of the task adapted for mice. The rodents had to poke the center port to start a trial and wait in the center port 0.2-0.4s before choosing the right or left port. For and (b), the reinforcement is assigned probabilistically to the alternative options independent of whether or not an agent visits the option in the given trial, and it remains to be collected until an agent chooses that option. In other words, reinforcements are allocated under a baiting schedule. The influence of past rewards and choices on the current choice for humans **C** and mice **D**, rodents.

Kvitsiani group members
Photo: Islam Faress

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Seidenbecher, SE, Sanders JI, von Philipsborn AC, Kvitsiani D. "Foraging fruit flies mix navigational and learning-based decision-making strategies". 2019 September 15.

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Nabavi Group

Circuit mechanisms of learning and memory

Group Leader
Sadegh Nabavi

Synaptic plasticity remains an (almost) indisputable candidate for learning and memory. For this reason, a large body of works is devoted to the mechanisms underlying plasticity; with the majority of these works take in vitro preparation as their working model. However, many behavioral phenomena either cannot be studied in slice preparation or are inconsistent with the findings. The main theme of our research is to understand the rules that govern synaptic plasticity in vivo, in respect to associative learning. We will give a particular emphasize to the types of associative learnings (and forgetting!) that cannot be reconciled with the currents models that are inspired by in vitro studies. Our investigation is confined between synaptic and circuit levels. For the behavioral model, we take a reductionist approach that is we study only the associative learnings that can be monitored and manipulated at the cellular and synaptic scales in rodents. Although we remain focused at the level of the questions, we do not confine ourselves to a particular set of techniques. In vitro and in vivo electrophysiology as well as in vitro and in vivo imaging and brain-circuit mapping will be indispensable to our investigation.

FUTURE PROJECTS

- Synaptic Mechanisms Underlying Memory Decay. The mechanisms underlying memory decay have been largely neglected, in part due to the technical difficulties as the process occurs in a much slower time scale. We test the hypothesis of whethe synaptic depotentiation is a substrate for weakening memories. This is based on our previous works, where we demonstrated: A) induction of LTD weakens a memory; B) beta-amyloid, a causative agent in Alzheimer's disease, induces synaptic depression through a mechanism similar to LTD; C) pre-synaptic release of glutamate can induce an NMDAr-dependent LTD if the calcium influx through the receptor is blocked. We test our hypothesis using optogenetic viral approaches combined with pharmacological manipulation and in vivo electrophysiology in behaving animals.

MAJOR ACHIEVEMENTS

- Identifying plasticity-related proteins: It is believed that during the formation of a memory or in¬duction of long-term potentiation (LTP), a group of proteins (plasticity-related proteins or PRPs) are synthesized. These proteins, it has been proposed, are essential for stabilization of memories and LTP. To identify these proteins, we used a novel biochemical technique that can specifically label newly synthesized proteins. We induced LTP in slices as well as in anesthetized animals. We confirmed the LTP expression biochemically or electrophysiologically. The proteins extracted from the LTP experiments were characterized using mass spectrometry in the lab of Dr. Yates (UCSD). This was achieved using a robust proteomic method known as Tandem Mass Tag (TMT) that quantifies the overall changes in the entire proteome. We are currently analyzing the mass spectrometry results to identify the proteins with significant quantitative changes after LTP induction. Using knockdown assay, imaging and electrophysiology, these proteins will be further tested for their relevance in plasticity.
- Functional mapping of brain circuits using activity-depen¬dent retrograde tracing: There is a keen interest in identifying the functional connectivity between different brain regions during a behavioral experience as this reveals the underlying circuit as well as it provides a basis for further mechanistic and genetic investigation. To achieve this, current approaches need to rely on prior knowledge of candidate regions that are pre-selected based on previous results. We developed an unbiased strategy to identify synaptic inputs, which convey behavioral information. It combines virus-mediated retrograde labelling and activity-dependent immediate early gene promoters. We demonstrate that this method effectively labels four brain areas after the exposure of the animals to three different behaviors.
- Mapping the neural circuit for an innate fear behavior: Fears are either innate (fear of snakes) or learned (fear of a gun). It is widely accepted that the expression of learned fears relies on the amygdala activity. Recent findings in our lab, obtained using electrically and genetically induced lesions, suggest that the integrity of the amygdala is also required for the expression of an innate fear. In corroboration with this finding, our preliminary data using bulk calcium imaging (fiber-photometry) shows the activity within the amygdala upon exposure to both learned and innate fears. This raises a dilemma: how the amygdala harbors two qualitatively different fears one requires plasticity (learned fear) whereas the other is hard-wired (innate fear). The next step in our work is to confirm our finding with reversible inactivation of the amygdala.
- Tracing the plasticity for behaviorally realistic associative learning: A fundamental, yet unresolved question in the field of learning and memory is how the brain associates events separated in time. This requires the brain to maintain the trace of the first event until the arrival of the next event, seconds later; and yet synaptic plasticity runs on the scale of milliseconds. Currently, there is no theoretical model or experimental paradigms that captures the problem of, as we phrase it, "behaviorally realistic associative plasticity", without leading to biologically implausible predictions. As the first step to tackle this problem, we have used tetrode recording in freely moving mice during a

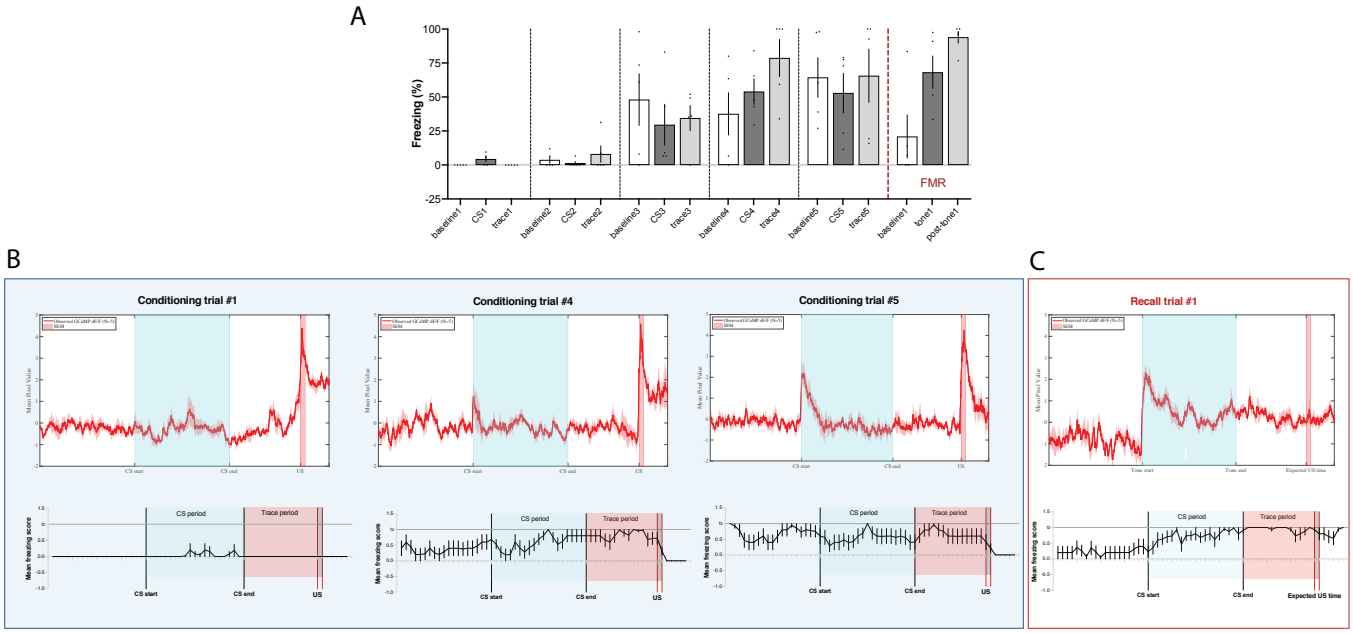

Figure 1: DAT::Cre mice (N=5) were injected with AAV-DJ EF1a-DIO-GCaMP6f into the VTA . Afterwards, they were subjected to a trace fear conditioning session, consisting of 10 pairings of a tone and a footshock separated by an empty 15s-long trace interval. A fear memory recall session (FMR) was administered 24h later in a novel context, where 3 presentations of the tone alone given. Fiber photometry recording of GCaMP6f was achieved with a 470-nm excitation. A) Mice showed trace fear conditioning learning by exhibiting greater freezing responses during the CS (dark grey bars) and trace (light grey bars) periods, compared to a baseline period (white bars). Mean ± SEM. B) Top, VTA calcium responses to the CS and footshock during the first, fourth and fifth CS-US pairings of the conditioning session (N=5). Activity in VTA dopaminergic neurons increased as subjects learned a trace fear conditioning task. Bottom, Mean freezing scores (1s-long bins) during the same conditioning trials for the same subjects (N=5). Greater values indicate a stronger freezing response. Mean ± SEM. C) Top, VTA calcium responses to the CS during the first trial of the FMR session (N=5). The aversive cue evoked a strong calcium response in the VTA, which persisted throughout the trace period. Mean ± SEM. Bottom, Mice exhibited conditioned fear learning by displaying a strong freezing response to the aversive cue in a novel context. Importantly, freezing also persisted high during the trace period. Mean ± SEM.

trace fear conditioning, an associative learning wherein two events- the tone and shock- are separated by many seconds. Our recording has allowed us to identify putative monosynaptic connections during the learning process. Currently, we are investigating whether there is a change in synaptic strength between pre-and postsynaptic pairs of neurons. Our next step is to use high-density silicon probs in our learning paradigm to increases the likelihood of detecting monosynaptic connections by orders of magnitude. On this project, we heavily rely on our collaboration with Duda Kvitsiani.

Nabavi group members
Photo: Kathrine Hennings

BKEY PUBLICATION

Nabavi S, Fox R, Proulx CD, Lin JY, Tsien RY, and Malinow R (2014) Engineering a memory with LTD and LTP. *Nature* 511, 348-352

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Philipsborn Group

Behavioral Genetics and Circuit Neuroscience

Group Leader
Anne von Philipsborn

We are interested in how the nervous system generates and controls behavior- at the level of genes and molecules, cells and neuronal circuits. Our model system is Drosophila melanogaster, which has a relatively small and stereotyped nervous system, but displays complex and fascinating behaviors.

By studying the neuronal circuits underlying Drosophila behavior, we aim at understanding general principles of motor control, behavioral organization and action selection. We focus on circuits for motor pattern generation and the architecture of neuro-muscular networks, as well as the mechanisms of higher order coordination of complex motor behaviors and behavioral sequences.

As a model behavior, we use Drosophila acoustic signaling during reproductive behavior. Identified neurons are dedicated to generation of male courtship song, an elaborately patterned signal. We investigate how the sex-specific song pattern is generated, and how the song circuit is modulated during other motor behaviors. We use audio recording as a highly sensitive, high throughput measurement for motor behavior at millisecond timescale as well as genetic tools for neuronal activity imaging and optogenetic activation and silencing in intact animals.

Simultaneously, we scrutinize the genetic and molecular basis of circuit dynamics. We are interested in genes pivotal for computational performance and configuration of ensembles of interconnected neurons, namely, genes encoding ion channels, membrane transporters and molecules implicated in neuromodulation.

MECHANISMS OF MULTIFUNCTIONAL MOTOR CONTROL
Multifunctional motor systems produce distinct output patterns dependent on behavioral context, posing a challenge to underlying neuronal control. Flies use their wings for flight and the production of a patterned acoustic signal, the male courtship song, employing in both cases a small set of wing muscles and corresponding motor neurons. We investigated the neuronal control mechanisms of this multifunctional motor system by live imaging of muscle ensemble activity patterns during song and flight and establish the role of a comprehensive set of wing muscle motor neurons by functional manipulations. Song and flight rely on distinct configurations of neuromuscular activity, with most, but not all flight muscles and their corresponding motor neurons contributing to song and shaping its acoustic parameters. The two behaviours are exclusive, and the neuronal command for flight overrides the command for song (O'Sullivan et al. 2018).

Mechanisms of Motor Pattern Generation and GABAergic Signaling
Almost all behavior is shaped by both excitatory and inhibitory neuronal control. We find that GABAergic inhibitory signaling impacts on song motor behavior on multiple levels, tuning fine motor structure, intensity and overall coordination of the behavior. With cell specific RNAi mediated knock- down of genes involved in GABAergic signaling, we are elucidating the mechanisms of inhibitory control and its role in pattern generation. Our efforts are directed at integrating data from genetic and neuronal screens and at building a model of how the song pattern is generated at the level of interneurons. We are establishing connectivity patterns of the various circuit components by GRASP (Gfp reconstitution across synaptic partners) and neuronal epistasis experiments.

BEHAVIORAL HIERARCHY AND COORDINATION- STATE DEPENDENT ACTION SELECTION
How do different behaviors interact and influence each other on a circuit level? During courtship, some behavioral elements are combined and others exclude each other or occur in a preferred sequence. We discovered that dependent on the state of the animal and the behavior it is engaged in, activation of

PUBLICATIONS 2019

Foraging fruit flies mix navigational and learning-based decision-making strategies Sophie E. Seidenbecher, Joshua I. Sanders, Anne C. von Philipsborn, Duda Kvitsiani, *BioRXiv* 2019, doi: https://doi.org/10.1101/842096

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Group Leader A**nne von Philipsborn**

Fig. 1: *Drosophila* courtship song. A male fly sings to a female by extending and vibrating one wing. Song is recorded by small microphones: the oscillogram shows sine and pulse bouts. Photo and illustration by Anne von Philipsborn

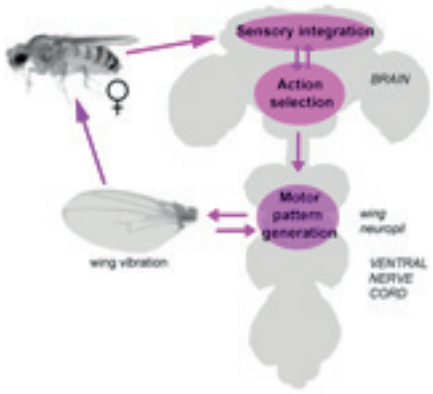


Fig. 2: Schematic of the neuronal circuits for courtship song. Illustration by Anne von Philipsborn

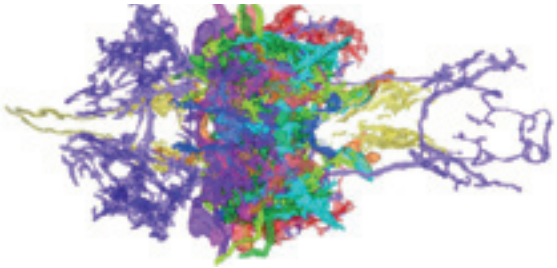


Fig. 3: Reconstruction of 3D arborization patterns of wing motor and premotor interneurons contributing to the patterning of wing movements. Illustration by Anne von Philipsborn

neuronal classes has drastically different motor outcomes. By using optogenetic circuit interrogation, we explore the neuronal and genetic basis of state dependent action selection, aiming at identifying circuits and neuromodulators for behavioral hierarchy and coordination. Our findings highlight inhibition as an important mechanism for structuring behavioral sequences, ensuring appropriate, context dependent response to sensory stimuli.

SEX SPECIFIC MOTOR CIRCUITS FOR COMMUNICATION

We discovered that during reproduction, not only male, but also female flies use rhythmic acoustic signals for communication. While males produce a pre-copulatory courtship song, females sing during copula. Female copulation song depends on transfer of specific seminal fluid components. Our research indicates that this newly discovered female behavior impacts sperm competition Kerwin et al. 2020, Nature Communications 11 (1):1430.Females lack most of the male's song neurons and show differential gene expression, which might explain striking differences in the motor output shaped to produce sex-specific sound patterns. Current effort are directed at unraveling the circuits for female singing and understanding how males hear, detect and act upon female song.

Philipsborn group members. From left to right: Peter Kerwin, Per mogensen, Bijayalaxmi Swain, anna Prudnikova, Kawtar Cherkaoui, Anne von Philipsborn. Photo: DANDRITE

MOLECULAR AND CELLULAR MODELS FOR NEUROLOGICAL DISEASE IN DROSOPHILA

Fundamental mechanisms of nervous system function on the molecular, cellular and circuit level are conserved and shared across vertebrates and invertebrates. Drosophila is a convenient and genetically accessible in vivo model for analyzing the effect of pathological mutations on neuronal physiology. Together with the Kvitsiani group, we harness the potential of genetic screens in Drosophila to study genes, molecules and neurons for reward processing and foraging strategies in an operant behavior task, which will give insight into circuits for motivation, addiction and decision making. Furthermore, we are collaborating with Poul Henning Jensen to explore calcium dynamics during alpha-synuclein mediated neurodegeneration and trans-synaptic spreading of alpha-synuclein aggregation.

Yonehara Group

Function and Development of Neural Circuits in Visual System

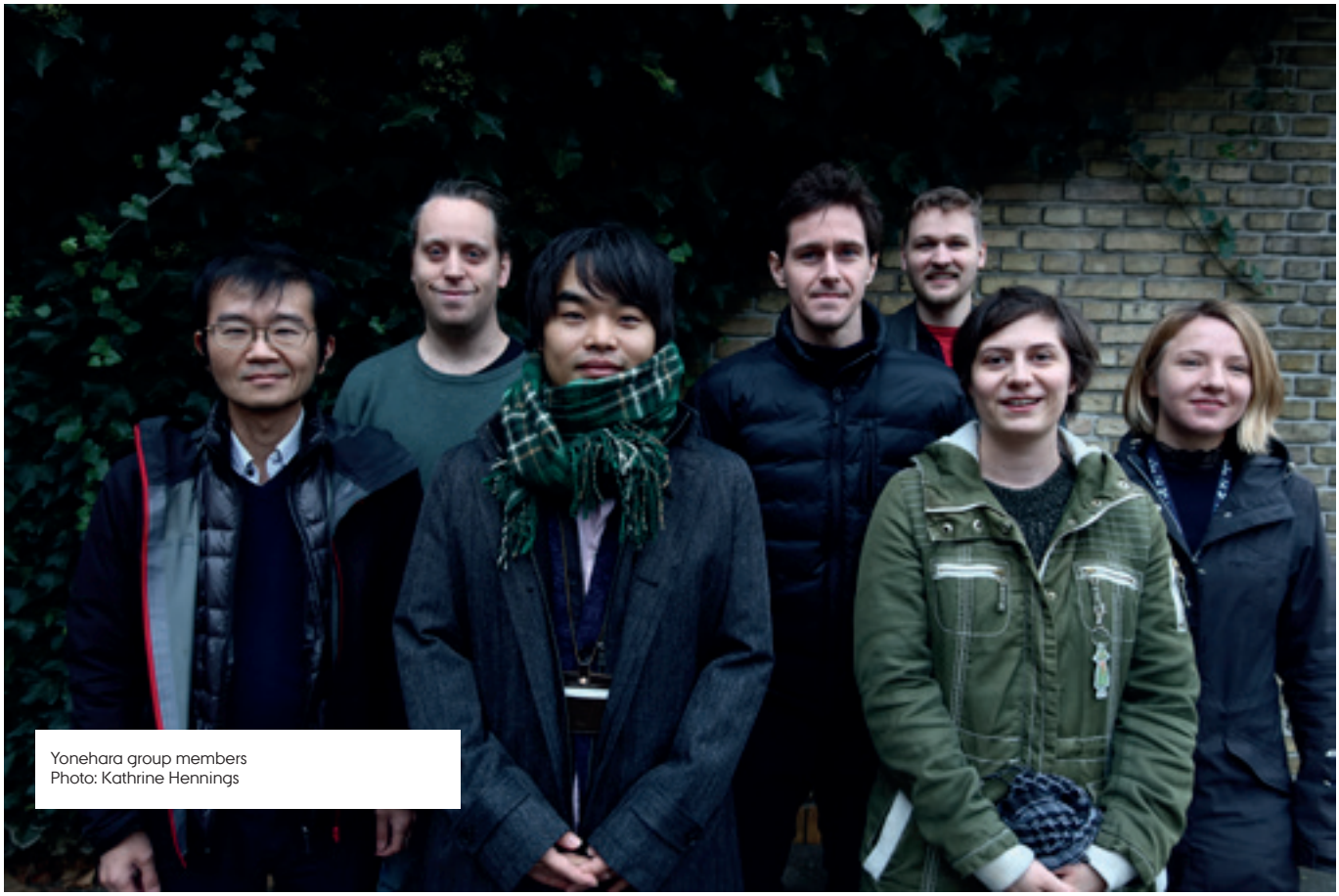
Team Leader
Keisuke Yonehara

The Yonehara group investigates how cell types in the central nervous system are organized into neural circuits for extracting sensory information and how specific connectivity in the neural circuits arises during development using mouse visual system as a model.

We mainly focus on neural circuits for visual motion processing across retina, superior colliculus, thalamus and visual cortex of mice. The logic of our research plan is to first identify a computation performed by a given neuronal circuit comprising distinct cell types in the adult brain. Second, to investigate how the computation is performed by linking the activity and synaptic connectivity of individual cell types in the circuit to the computation that the circuit achieves. Third, to examine the role of individual cell types in transforming the sensory input into output behavior. Finally, to study the genetic mechanisms by which the elementary circuit motifs are assembled, and how its dysfunction can lead to disease.

DYNAMIC INTEGRATION OF SYNAPTIC INPUTS FOR COMPUTING VISUAL MOTION

The direction of visual motion is first extracted by retinal direction-selective circuits and further processed in downstream areas such as thalamus or visual cortex. In the retina, we identified a new circuit mechanism for computing the direction and speed of visual motion in the mammalian retina by combining two-photon glutamate imaging, patch-



Yonehara group members
Photo: Kathrine Hennings

clamp recordings, and 3D electron microscopy (Fig. 1; Matsumoto et al., Curr Biol 2019). In the visual cortex, we identified a segregated processing stream for signaling originated from retinal direction-selective cells by in vivo two-photon calcium imaging and genetic manipulation of retinal computation. In the next years we aim to understand the temporal dynamics of circuit components involved in those circuitries and how they are wired together during development.

MOLECULAR MECHANISMS UNDERLYING THE SPATIALLY ASYMMETRIC NEURONAL CONNECTIVITY

Spatially asymmetric neuronal connectivity is the fundamental building block of neuronal computation. We use retinal direction-selective circuits as a model to study how spatially asymmetric neuronal connectivity is assembled by genetic mechanisms. In addition to congenital nystagmus gene FRMD7 (Yonehara et al., Neuron 2016), we have identified some key molecules for establishing spatially asymmetric inhibitory input from an inhibitory amacrine cell type to the direction-selective cells in the retina. Our aim is to understand fundamental mechanisms underlying the establishment of neuronal polarity and synaptic specificity by further investigating the role of genes we identified.

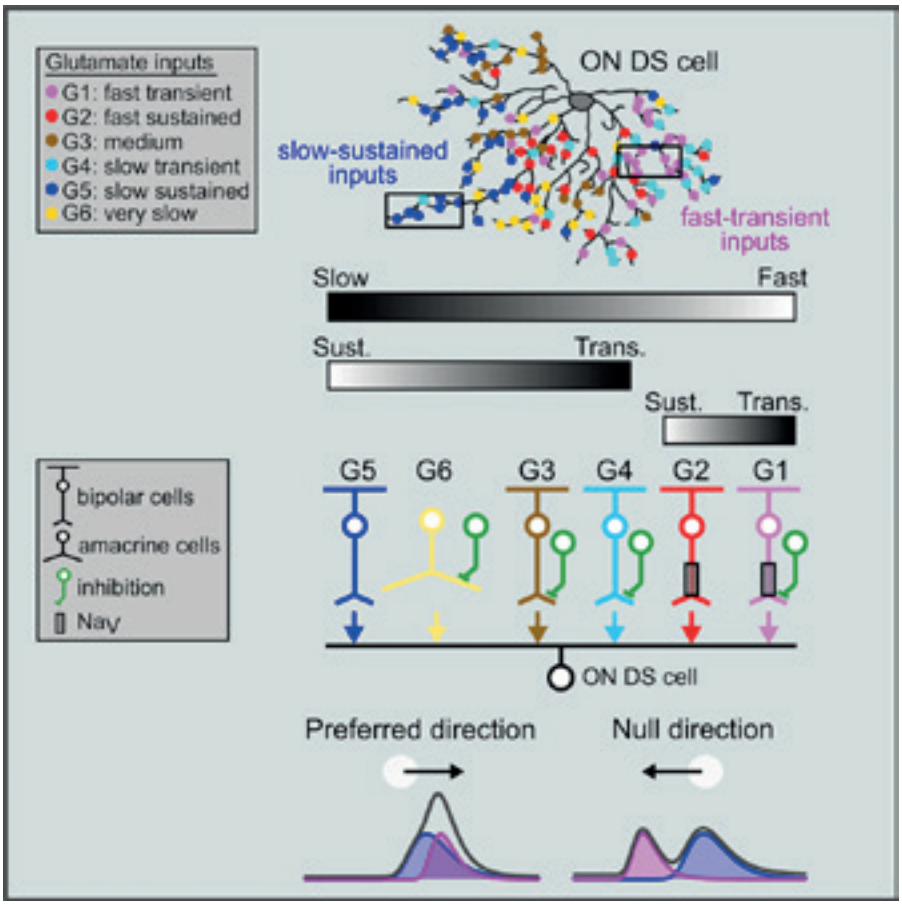


Fig. 1: Spatiotemporally asymmetric excitation supports mammalian retinal motion sensitivity. Space-time wiring between ON direction-selective cells and bipolar cells was identified in the mouse retina. Preferred direction enhancement supports the tuning to direction and slow speed. Graphical abstract from Matsumoto et al., 2019.

SELECTED PUBLICATIONS 2019

Matsumoto A, Briggman KL, Yonehara K. (2019) Spatiotemporally asymmetric excitation supports mammalian retinal motion sensitivity. *Curr Biol* 29: 3277-3288.

Krabbe S, Paradiso E, d'Aquin S, Bitterman Y, Courtin J, Xu C, Yonehara K, Markovic M, Müller C, Eichlisberger T, Gründemann J, Ferraguti F, Lüthi A. (2019) Adaptive disinhibitory gating by VIP interneurons permits associative learning. *Nature Neurosci* 22: 1834-1843.

PERSONNEL LIST YONEHARA GROUP

Postdoc **Akihiro Matsumoto**
Postdoc **Ana Oliveira**
Postdoc **Szilard Sajgo**
Postdoc **Yutaka Shimizu**
PhD Student **Monica Dahlstrup Sietam**
PhD Student **Ole Søndergaard Schwartz**
PhD Student **Rune Rasmussen**
Laboratory Technician **Bjarke Thomsen**
Laboratory Assistant **Misugi Yonehara**
Student Assistant **Simon Arvin**
Group Leader **Keisuke Yonehara**

Kjærgaard Team

Synaptic Plasticity and Intra-cellular Signaling Complexes in Memory Formation

Team Leader
Magnus Kjærgaard

We are interested in understanding how proteins in the post-synaptic density modulate the dynamics of synaptic proteins and signalling pathways. We study how long-term potentiation change the structure of the post-synaptic density and recruit new proteins to the synapse and change the signalling output from the synapse. We use a range of biophysical techniques including NMR spectroscopy and single molecule FRET spectroscopy to answer mechanistic questions about brain proteins.

A key mechanism in memory is the modulation of ionotropic glutamate receptors by their intra-cellular ligand occupancy and phosphorylation state. The intra-cellular domains of these receptors coordinate many binding partners and affect the conductivity of the channels, but are difficult to study by traditional structural techniques as they are flexible and devoid of fixed structures, so-called intrinsically disordered proteins. We use spectroscopic and biophysical techniques to study the interactions of the intra-cellular domains of the NMDA receptor with post-synaptic proteins. We recently discovered that synaptic proteins interact through a mechanism called liquid-liquid phase separation, where the proteins form small droplets in the cell. We are investigating this mechanism to understand how proteins are recruited specifically to active synapses.

Receptor activation leads to different downstream events depending on the cellular context, e.g. which other signaling pathways are active. Large flexible molecular assemblies called signaling complexes organized by scaffolding proteins coordinate signaling pathways. These complexes connect receptors to enzymes and substrates. The signaling complexes act as molecular matchmakers by determining which molecules encounter each other. We have developed a quantitative framework for investigating how signalling complexes control intra-complex reactions (Sørensen et al. 2019a,b). We are using this framework for describing how synaptic kinases are affected by targeting to the post-synaptic density. This has suggested that intrinsically disordered proteins may have unrealized potential in protein biotechnology, which we are currently doing proof-of-principle tests of.

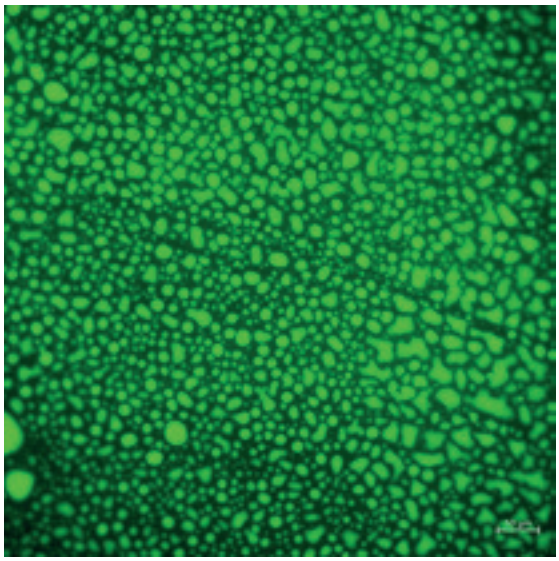


Fig 1: Liquid-liquid phase separation by synaptic scaffolding proteins.
Picture by: Postdoc Xavier Warnet

Kærgaard team members February 2020.
Back row (left to right): Mateusz Dyla, Mikkel Juul Thomsen, Emily C. Pheasant, Anders Lenstrup, Dirk Hoffmann. Front row: Xavier Warnet, Magnus Kjærgaard.

KEY PUBLICATION 2019

Dyla, M., Basse Hansen, S., Nissen, P. and Kjaergaard, M. (2019) Structural dynamics of P-type ATPase ion pumps. *Biochem. Soc. Trans.* 47 (5), 1247-1257

Sørensen, C.S. and Kjaergaard, M. (2019) Effective concentrations enforced by intrinsically disordered linkers are governed by polymer physics *PNAS* 2019 116 (46) 23124-23131

Sørensen, C.S., Jendroszek, A. and Kjaergaard, M. (2019) Linker dependence of avidity in multivalent interactions between disordered proteins. *J. Mol: Biol.* 431(24):4784-4795

Karlsson, E., Andersson, E., Jones, N.C., Hoffmann, S.V., Jemth, P. and Kjaergaard, M. (2019) Coupled Binding and Helix Formation Monitored by Synchrotron-Radiation Circular Dichroism. *Biophys. J.* 117(4):729-742

PERSONNEL LIST KJÆRGAARD TEAM

Postdoc **Agnieszka Jendroszek**
Postdoc **Charlotte Skovgaard Sørensen**
Postdoc **Mateusz Dyla**
Postdoc **Xavier Warnet**
PhD Student **Sara Basse**
Team Leader **Magnus Kjærgaard**

Poulsen Team

Electrophysiology of Electrogenic Transporters and Ion Channels

Team Leader
Hanne Poulsen

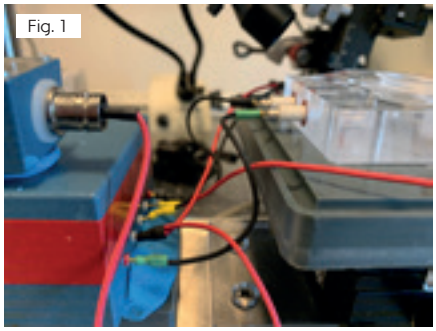


Fig. 1

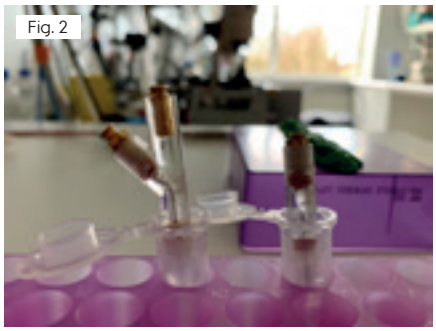


Fig. 2

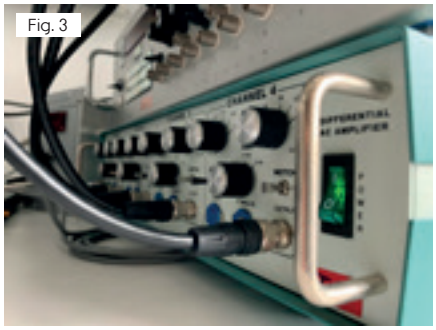


Fig. 3

We are interested in the molecular functions of ion channels and transporters and their roles in health and disease. These membrane proteins are essential for nerve cell communication, and it causes various neurological diseases if they do not function optimally. To study these fascinating molecules, we use various methods, including electrophysiology, voltage-clamp fluorometry and transgenic mice.

Neuronal firing depends on a series of ion sluices opening and closing in the membrane, allowing in particular sodium, potassium and calcium to flow into and out of the cell. Ion pumps are therefore necessary to reestablish the gradients. We aim at describing the membrane proteins in molecular detail, to understand how these tiny channels and pumps can function and how they are regulated, and to see them as players in the larger context of cellular networks.

The method of choice for studying electrogenic membrane proteins like ion channels and many of the pumps and transporters has long been electrophysiology, but fluorescence-based approaches are currently expanding the toolbox and broadening the field of membrane proteins that can be studied with a real-time read-out, while they are embedded in intact membranes. Methods using fluorescence measurements allow studies of ligand and drug binding, conformational changes, protein dynamics, single molecule kinetics, and they may be combined with, make use of and even replace electrophysiology.

Figure 1: In the cut-open voltage-clamp fluorometry set-up, the protein of interest is labelled with an environmentally sensitive fluorophore, and the protein activity (measured as changes in current) and dynamics (measured as changes in fluorescence) can be determined simultaneously.

Figure 2: Silver wires are chlorinated so that the electrodes can transduce currents of ions in solution to electron currents.

Figure 3: The small electrical currents measured in e.g. an oocyte or on the skull of a mouse must be amplified and digitalised.

We use these techniques to study the functions of two groups of neuronal membrane proteins, both of which are vastly important for human physiology and pathophysiology, namely transporters including the Na,K-ATPases and the GABA transporter and the NMDA receptor.

MAJOR ACHIEVEMENTS & FUTURE PLANS

The fluorescent unnatural amino acid Anap has been incorporated into several positions in the Na,K-ATPase and the GABA transporter, where we can see that pumping activity causes fluorescence changes. We will continue these studies with the aim of shedding light on the intrinsic relationship between molecular dynamic movement of segments of the protein and its activity to understand both the basic function and what happens, when mutations cause diseases. We have also set up studies of the NMDA receptor with special focus on their structurally disordered intrinsic tails, where we will include studies using Anap.

The brain makes several versions of the Na,K-ATPase including a3 in neurons. Mutations in the gene encoding a3 are connected with severe neurological diseases. One of them is CAPOS (cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss), which is associated with a single amino acid change, namely E818K. Patients with CAPOS have distinctive auditory and visual impairments, which have not been reported for two other syndromes caused by mutations in the same gene, suggesting that the mutation causing CAPOS alters protein function in a manner that has particular effects on vision and hearing. We found that the mutation alters the kinetics of particular steps in the catalytic cycle, though it remains to be determined why these changes are detrimental to the visual and auditory systems. In order to study this, we have generated a mouse with the mutation that we will study, and we will continue examining the basic functional consequences of the mutation on the protein.

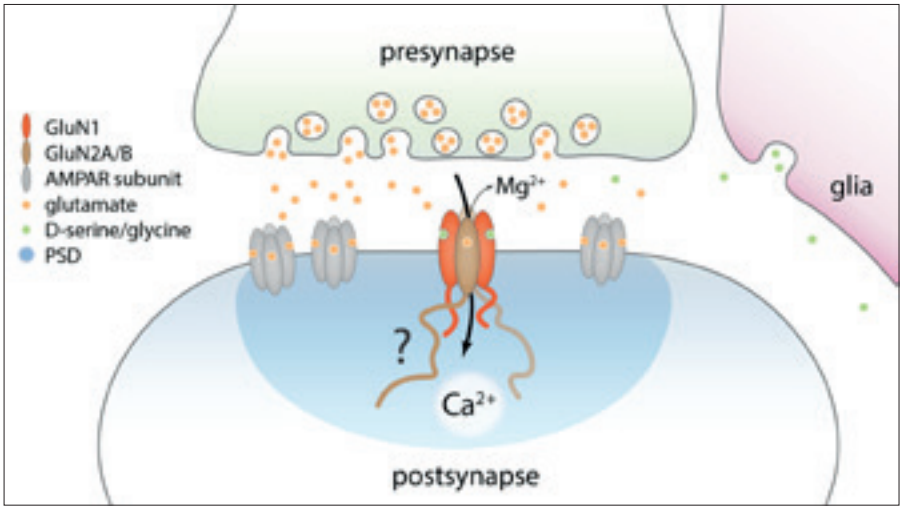


Figure 6: Overview of the role of the NMDAR in synaptic plasticity. The NMDAR in the postsynaptic density (PSD) allows the influx of calcium when activated by glutamate released from the presynapse and D-serine or glycine. Opening of the NMDAR is strictly regulated and requires release of a channel-blocking magnesium, which is only achieved upon activation of AMPA receptors by glutamate causing depolarization of the membrane. Intracellular calcium will turn on a wide array of signaling pathways, and this can lead to strengthening or weakening of the synapse, depending on the timing and extent of NMDAR activation. The C-termini of the NMDAR subunits are intrinsically disordered domains and only little is known about their function and regulation, except that they interact with a number of proteins important for synaptic plasticity.

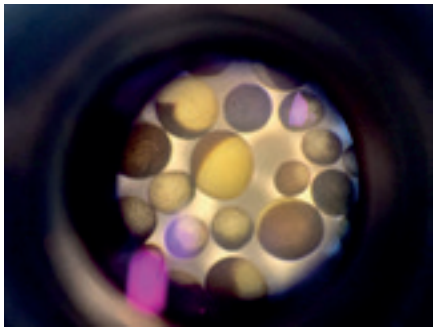
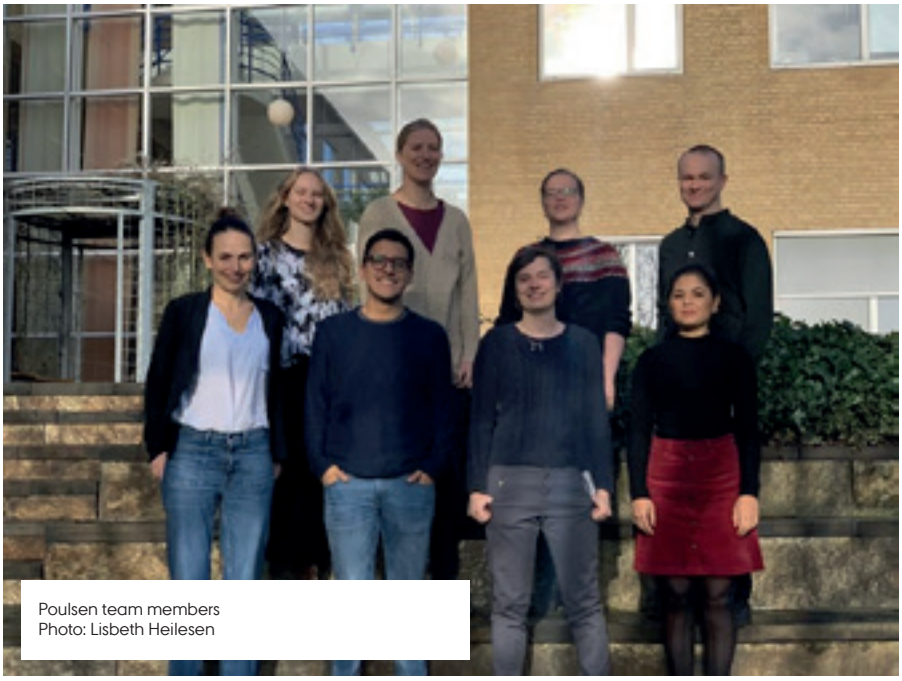


Figure 4-5: Oocytes surgically removed from the African clawed frog Xenopus laevis have been enzymatically treated to remove the follicle layer and washed. For electrophysiological experiments, we then select stage V-VI oocytes, which have even colouring in the animal (dark) and vegetal (light) poles and are around 1 mm in diameter.



Poulsen team members
Photo: Lisbeth Heilesen

PUBLICATIONS 2019

Dyla M, Kjærgaard M, Poulsen H, Nissen P, Structure and mechanism of P-type ATPase ion pumps. *Annual Review of Biochemistry* Vol 89

Warnet XLCA, Krog HB, Quispe OGS, Poulsen H, Kjærgaard M, Functions of the C-terminal domains of the NMDA receptors – How intrinsically disordered domains affect interaction networks, plasticity and disease. *European Journal of Neuroscience* edition 'Proteins and circuits in memory'

PERSONNEL LIST POULSEN TEAM

Postdoc **Helle Bakke Krog**
Postdoc **Tommi Miikael Anttonen**
PhD Student **Mette Ozol**
PhD Student **Monica Dahlstrup Sietam**
PhD Student **Oscar Gabriel Sevillano Quispe**
PhD Student **Saida Said**
Team Leader **Hanne Poulsen**

Takeuchi Team

Memory selectivity and knowledge updating

Team Leader
Tomonori Takeuchi

Knowledge plays a central role in human life. Indeed, we are who we are largely because of what we remember. The Takeuchi lab is focused on the overall goal to elucidate our knowledge on how memories of events and facts are initially processed in the hippocampus and subsequently stored as long-term memory in the neocortex.

The research is divided in two overall research themes

- **Novelty-induced enhancement of memory retention**, is now an established phenomenon, but the underlying molecular mechanisms remains to be elucidated. In our team, we now have the behavioral setup including the hippocampus-dependent object dislocation task and everyday memory task in rats to investigate this subject in further detail. Further, we have an advanced fiber photometry setup, where we are able to detect novelty-induced dopamine release using a genetically encoded fluorescent sensor in free-moving rats. Finally, we are doing experiments to identify key proteins critical for novelty-induced memory enhancement. Identification of proteins that enhance memory retention will have the potential to reveal new drug targets for treatment of lost memory function.

- **Assimilation of new memory into neocortical schemas**, has been shown to be a much faster process, than initially believed. In our team, we aim to secure definitive information about the neocortical networks and neuromodulation involved in the assimilation of new memory into the neocortical schemas. Understanding the molecular- and circuit-mechanisms of assimilation of new memories into schemas may lead to the development of efficient educational methods.

MAJOR ACHIEVEMENTS 2019
In 2019, we succeeded to develop a red-shifted fluorescent dopamine sensor, which has not been accomplished previously. This sensor will be a valuable tool for our future studies.

Further, we have built two event arenas for everyday memory task and schema task, respectively. In addition, we tried to find an optimal training protocol for the object dislocation task. All of which are now being used for experiments to reach our research goals.

Finally, our fiber photometry setup has provided the first measurements, where optogenetic stimulation of the ventral tegmental area induced fluorescence increases of the dopamine sensor in the striatum confirming that dopamine was released from VTA axons in the striatum in vivo.

FUTURE PLANS
In 2020, we plan to use one of our event arenas to investigate molecular and circuit mechanisms of novelty-induced memory boost in the hippocampus. Specifically, we will investigate how dopamine release from axons of the locus coeruleus in the hippocampus.

In collaboration with Bordeaux University in France and the Nabavi lab at DANDRITE, we will continue our studies on finding and assessment of functions of plasticity-related proteins that is critical for novelty-induced memory boost.

The second event arena will be used to replicate our previous finding on assimilation of new memory into schema. Our new event arena has been modified to increase reliability and objectivity, whilst also decreasing the intensive labour costs currently associated with this task.

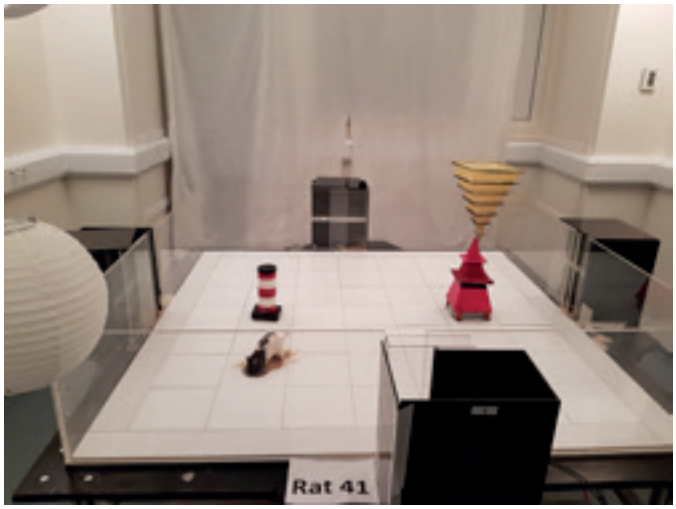


Figure 1: An event arena in the rats. Photo by Tomonori Takeuchi.

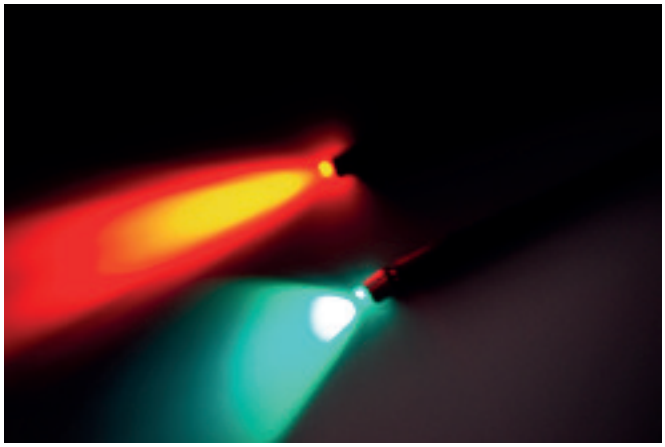
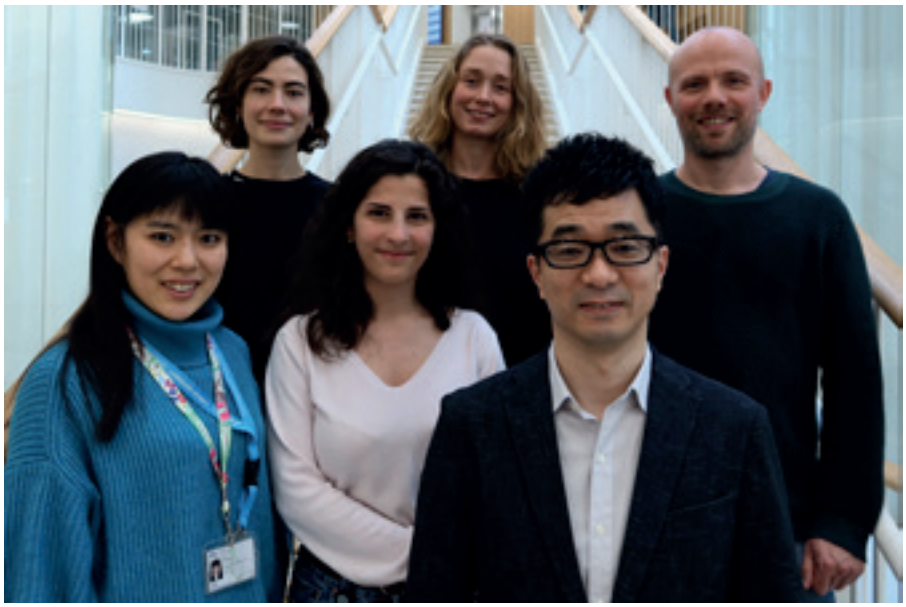


Figure 2: Laser and LED light. Photo by Kim Henningsen.



Takeuchi team members
Photo: Emma Kathrine Sommer

PUBLICATIONS 2019

Duszkiewicz, A.J., McNamara, C.G., Takeuchi, T.§ and Genzel, L.§ (2019) Novelty and Dopaminergic Modulation of Memory Persistence: A Tale of Two Systems. *Trends in Neurosciences*, 42: 102–114. §Co-last authors.

Broadbent, N., Lumeij, L.B., Corcoles, M., Ayres, A.I., Ibrahim, M.Z.B., Masatsugu, B., Moreno, A., Carames, J-M., Begg, E., Strickland, L., Mazidzoglou, T., Padanyi, A., Munoz, M., Takeuchi, T.§, Peters, M.§, Morris, R.G.M.§ and Tse, D.§ (2019) A stable home-base promotes allocentric memory representations of episodic-like everyday spatial memory. *European Journal of Neuroscience*. In press. §Co-last authors.

Nakamoto, C., Kawamura, M., Nakatsukasa, E., Natsume, R., Takao, K., Watanabe, M., Abe, M.§, Takeuchi, T.§ and Sakimura, K. (2019) GluD1 knockout mice with a pure C57BL/6N background show impaired fear memory, social interaction, and enhanced depressive-like behavior. *bioRxiv*, https://doi.org/10.1101/826768. Accepted for publication in *PLoS ONE*. §Co-last authors.

PERSONNEL LIST TAKEUCHI TEAM

Postdoc **Chihiro Nakamoto**
Postdoc **Mai Iwasaki**
Postdoc **Okuda Kosuke**
PhD student **Kristoffer Højgaard**
Research Assistant **Katia Soud**
Lab Manager **Kim Henningsen**
Laboratory Technician **Trine Rohde**
Team leader **Tomonori Takeuchi**

DANDRITE Affiliated Researchers

DANDRITE is proud to enter year 2019 with ten active Affiliated Researchers:

CHRISTIAN VÆGTER

Glia reactivity in the PNS
The peripheral sensory neurons are completely covered by glial cells, with satellite glial cells (SCG) covering the neuronal soma and Schwann cells covering the length of the axon. It is therefore obvious that these glia cells play major roles in how the neurons function. Our aim is to understand how peripheral glia calls affect neuronal functionality in health but also following nerve injury or in diseases such as diabetes.

Highlights from 2019
- Christian Vægter awarded the Lundbeckfonden Ascending Researcher Grant (5 mio)
- Publication of study: Sortilin gates neurotensin and BDNF signaling to control peripheral neuropathic pain in *Science Advances (Richner et al., 2019)*
- Publication of study: Peripheral Nerve Regeneration Is Independent From *Schwann Cell* p75NTR Expression in *Frontiers in Cellular Neuroscience* (Goncalves et al., 2019).

ERNST-MARTIN FÜCHTBAUER

Genetically modified mice
We collaborate with several DANDRITE researches in the generation of genetically modified mice and differentiation of murine ES cells. In particular, we had a DARE collaboration with the group of Keisuke Yonehara to establish the exchange of genetic element using CRISPR technology.

Highlights from 2019
- Using CRSIPR mutagenesis we created mice that are expected to express exclusively or predominantly either the one or two chain form of SorCS2

JANE HVARREGAARD CHRISTENSEN

Mental disorders - Genes and disease mechanisms
Our primary focus is to discover genetic risk factors and disease mechanisms in mental disorders. We study how core schizophrenia and autism risk genes involved in gene regulatory processes operate in the cell and the brain. We are also mapping novel risk genes in nocturnal enuresis (bedwetting). These are investigated along with genes causing rare disorders of the water balance to understand their interplay in regulating urine production, bladder activity and sleep.

Highlights from 2019
- Publication: Paternoster, V; Svanborg, M; Edhager, AV; Rajkumar, AP; Eickhardt, EA; Pallesen, J; Grove, J; Qvist, P; Fryland, T; Wegener, G; Nyengaard, JR; Mors, O; Palmfeldt, J; Børglum, AD; **Christensen, JH**, Brain proteome changes in female Brd1+/- mice unmask dendritic spine pathology and show enrichment for schizophrenia risk, Neurobiology of Disease, Vol 124, 04.2019, p. 479-488

Nanomedicine

The Kjems lab investigates the function and biomarker potential of non-coding RNA in the nervous system. In particular, they study how microRNAs and circular RNAs act in neuronal development and test their potential role in diseases such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease and temporal lobe epilepsy. The lab also develops methods to deliver drugs across the blood brain barrier using multivalent nanoscaffold and exosomes.

Highlights from 2019
- Proof of concept grant awarded from BII: Improved technology for miRNA inhibition using circular RNA

- Paper published: Andersen, L.A.; Vinther, M., Kumar, R., Ries, A., Wengel, J., Nielsen, J.S., Kjems, J.: A self-assembled, modular nucleic acid-based nanoscaffold for multivalent theranostic medicine. *Theranostics* 9(9):2662-2677
- Preprint posted: Venø, M.T., Reschke, C.R., Morris, G., Connolly, N.M., Su, J., Yan, Y., Engel, T., Jimenez-Mateos, E.M., Harder, L.M., Pultz, D., Haunsberger, S.J., Pal, A., Norwood, B.A., Costard, L.S., Neubert, V., Del Gallo, F., Salvetti, B., Vangoor, V.R., Rodriguez, A.S., Muilu, J., Fabene, P.F., Pasterkamp, R.J., Prehn, J.H., Schorge, S., Andersen, J.S., Rosenow, F., Bauer, S., Kjems, J., Henshall, D.C.: Ago2-seq identifies new microRNA targets for seizure control.
- Preprint posted: Lo, IJ., Hill, J., Vilhjálmsson, B.J., Kjems, J.: Linking the association between circRNAs and Alzheimer's disease progression by multi-tissue circular RNA characterization.

KARIN LYKKE-HARTMANN

Atp1a3 disease knock-in mouse modeling
Autosomal dominant mutations in the human ATP1A3 gene encoding the neuron-specific Na+/K+-ATPase α3 isoform cause neurological diseases including rapid-onset dystonia-parkinsonism (RDP) and alternating hemiplegia of childhood (AHC). Main symptoms include hemiplegia, dystonia, ataxia, hyperactivity, epileptic seizures, and cognitive deficits. Mice harboring the D801Y mutation (α3+/D801Y) were shown to represent several of the ATP1A3 disease-related symptoms including hyperactivity, increased sensitivity to chemically induced epileptic seizures, cognitive deficits, hypothermia-induced dystonia and ataxia.

Highlights from 2019
- Organizer of the 8th Annual Symposium on ATP1A3 in Disease, Reykjavík, Iceland.
- Member of ATP1A3 Standing Committee

MARCO CAPOGNA

Neuronal circuits of human and rodent cerebral cortex, amygdala and hippocampus
We define the neuronal circuits of human and rodent cerebral cortex and connected brain areas, as they are cellular regulators of cognitive process. We explore what neuronal circuitry guides emotional-dependent memory, and how it is modified in animal models of psychiatric disorders. Major focus is on GABAergic neuron types because of their critical role in controlling brain networks. We use electrophysiology, pharmacology, optogenetic, imaging, and anatomy.

Highlights from 2019
- Collaboration with AUH to investigate human cortex in vitro
- Publication with Oxford group on mGluRs at human cortical synapses (Bocchio et al, Frontiers in Cell Neurosci 2019)
- Lundbeck Foundation-NIH grant award with Soltesz group, Stanford (3M DKK) to investigate behavioral role of hippocampal GABAergic neurons in rodents
- Lundbeck Foundation-NIH grant award with Ting group, Allen Seattle (3,5M DKK) to investigate the role of GABAergic neuron types in human cortex

MARINA ROMERO-RAMOS

Study and Characterization of the neurodegenerative event in Parkinson's Disease and the associated immune response

CNS Disease Modelling Group
My lab works on understanding the progressive changes in the immune cells associated to the neurodegenerative process of α-synucleinopathies, such as Parkinson's Disease. Our hypothesis is that the immune response in Parkinson involves both: brain and periphery and that especially myeloid cells, such as microglia and monocytes, play an active role in the neuronal fate.

In our studies we perform experiments in rodent models, but also analysis of human derived samples. Our main focus is to further understand, the different cell populations as well as the proteins involved in the neuroinflammatory process of the disease with an ultimate focus on describing novel targets for therapy and define disease biomarkers.

Highlights from 2019
- Invited review describing the current understanding on the dynamic immune response in Parkinson's Disease (Tansey & Romero-Ramos, 2019).
- Dr Romero-Ramos, was awarded a grant from the AUFF NOVA and a second one from the Independent Research Fund, Denmark.
- The lab has shown that Parkinson's disease patients have a modified monocytic population in blood. Patients monocytes showed lower viability but higher proliferative capacity. In addition, they were less able to react to α-synuclein that those monocytes form healthy individuals (Nissen el at., 2019).
- During 2019 Dr. Romero-Ramos became the Co-chair of the Basic Science Subcommittee for the World Parkinson Congress 2022, Barcelona, Spain

MORTEN SCHALLBURG NIELSEN

Receptor mediated drug delivery to the brain

The use of receptors to deliver drug from blood to brain is the major research focus in our group. We are using advanced in vitro models of the blood brain barrier, based on primary brain endothelial cells, astrocytes and pericytes. In the recent year, we have usefully established a new human model based on human induced pluripotent stem cells. Together with our partners in the Horizon2020 IM2PACT program we will continue to develop BBB models from patients with different neurodegenerative diseases.

Highlights from 2019

- Publication in Fluids and Barriers of the CNS
- Hiring two new post docs; Mikkel Holst and Diana Hudecz
- Establishing a new human BBB models based on iPSC

OLAV MICHAEL ANDERSEN

Transport receptors in neurodevelopment and degeneration

We study how the SORL1 gene (and its translation product, SORLA) is associated with Alzheimer's disease. There is continuously being identified new SORL1 gene variants in Alzheimer's patients, but it has proved challenging to determine whether these novel variants are benign or disease causing. We are developing tools aiming to determine the pathogenecity of SORL1 variants based on new biochemical, cell biological and animal models.

Highlights from 2019

- Co-authoring the first study to identify a role of SORLA in cancers; Mike Pietila et al, Nat. Comms.
- Champion for honorary professor Scott Small, Columbia University, New York, USA
- Partner of EU-funded JPND-project "SORLA-FIX"

THOMAS BOESEN

Cryo-EM on membrane transporters and receptors

I am involved in research projects centered on nanodisc technology and structural biology of membrane protein transporters and receptors. New avenues are cryo-EM data processing software development and implementation of new cryo-EM methods in DANDRITE projects. As cryo-EM Facility Manager at iNANO-AU, I enable easy access and training on equipment and in cryo-EM and negative stain methods for DANDRITE researchers. The iNANO cryo-EM facility is becoming an important strategic infrastructure in key DANDRITE projects.

Highlights from 2019

- Timcenko, M., Lyons, J.A., Januliene, D., Ulstrup, J.J., Dieudonné, T., Montigny, C., Ash, M.R., Karlsen, J.L., Boesen, T., Kühlbrandt, W., Lenoir, G., Moeller, A., Nissen, P. (2019). Structure and autoregulation of a P4-ATPase lipid flippase. *Nature*. (DOI: 10.1038/s41586-019-1344-7)

Endeavor by Yonehara group

Towards understanding neural circuits

Text by Group Leader Keisuke Yonahara
Edited by Aisha Rafique, Communications and Scientific Research Coordinator

The brain is one of the most complex biological machines in the world; it generates our perception, thoughts, memory, emotion, and curiosity. Yet, we know so little on how the brain functions and causes neurological and psychiatric diseases. The Yonehara group at DANDRITE addresses these fundamental questions of science by combining state-of-the-art multidisciplinary approaches such as two-photon imaging (Figure A), electrophysiology, trans-synaptic tracing, transcriptomics, proteomics, mouse genetics, and behavioral studies.

How can we understand the brain with the tools available at this stage? The strategy of Yonehara's group is to focus on a relatively simple structure in the central nervous system: the mammalian retina. The retina is a thin neural sheet attached to the inside of the eyeball and it operates the first steps of our visual processing. Photoreceptors generate neuronal signals in response to light patterns hitting them and transmitting the signals to downstream retinal neurons. As the signals move through the retinal neural circuits, visual features such as color, contrast, and motion, are extracted and are encoded in the output neurons of the retina so-called retinal ganglion cells. The extracted visual features are then sent to different brain areas by the axons of retinal ganglion cells for further processing.

One major approach to understand the function and development of neural circuits is to focus on a particular computation, and try to understand it at all the different hierarchical levels from molecular to cellular, circuits to organs and systems level. The Yonehara group focuses on motion sensitivity of the visual neurons – a fundamental characteristics of our visual system. Inferring the speed and direction of image motion is essential for animal survival: it helps them to find food, mate, spatially navigate, and escape from predators. Neurons that are sensitive to speed and the direction of image motion are located in the retina, which is the very first stage of visual processing along the visual hierarchy. By using this neural system as a model, Yonehara group wants to understand how neurons are organized into neural circuits to generate behaviorally relevant functions.

Since Yonehara lab started five years ago, it has produced two key scientific findings. The first important finding is about how retinal neurons compute image motion. Inferring motion speed, e.g. slow or fast, is critical for animals to make motion information useful for their behaviors; for example, eye movements for gaze stabilization must occur in the speed of visual motion for precise tracking. Akihiro Matsumoto, a postdoctoral fellow in Yonehara group, identified, in collaboration with Dr. Kevin Briggman in Germany, a novel neural circuit structure that makes retinal neurons sensitive to speed and direction of the visual motion. Thus, this work provided the first mechanistic understanding of how visual system analyses visual motion speed (Matsumoto et al., Curr Biol 2019).

The second important finding was about how visual motion signals extracted by retinal circuits are further processed in the cerebral cortex. Rune Rasmussen, a PhD student in Yonehara group, and his colleagues discovered a dedicated neural information highway in the cerebral cortex that carries retinal motion signals up to an area in the posterior parietal cortex, a cortical area which is known to be important for the computation of self-motion, spatial navigation, and decision making (Figure B; Rasmussen et al., Nat Commun 2020). Our finding points to an intriguing hypothesis that signals from retinal motion sensitive neurons contribute to the creation of neuronal representation of self-motion in this cortical area, and this representation would be further utilized for spatial navigation of the animals. Interestingly, our studies revealed that, cortical motion responses, which have been thought as a result of cortical functioning, turned out to heavily rely on the retinal computation. We therefore propose that, in order to fully understand the visual system, we have to study the entire visual system spanning from the retina to the cortical areas as one coherent system, rather than studying them separately as researches have done until now.

The Yonehara group has three main research directions for the near future. Firstly, to understand how retinal circuits develop and work for extracting visual motion. They have recently discovered that some congenital nystagmus-related genes cooperate to establish the retinal circuits for motion sensitivity, providing biomedical insights to the etiology of this common visual disorder. Second, to understand how visual motion signals extracted by retinal circuits are used for spatial cognitive function in the cerebral cortex and the superior colliculus (a major component of the mammalian midbrain). Third, to develop new genetic approaches for restoring lost visual function in visual neurodegenerative disorders such as glaucoma and optic nerve trauma. We predict that more and more new exciting findings will be brought about from the lab in the coming years, driven by the strong curiosity of young scientists and satisfactory lab resources.

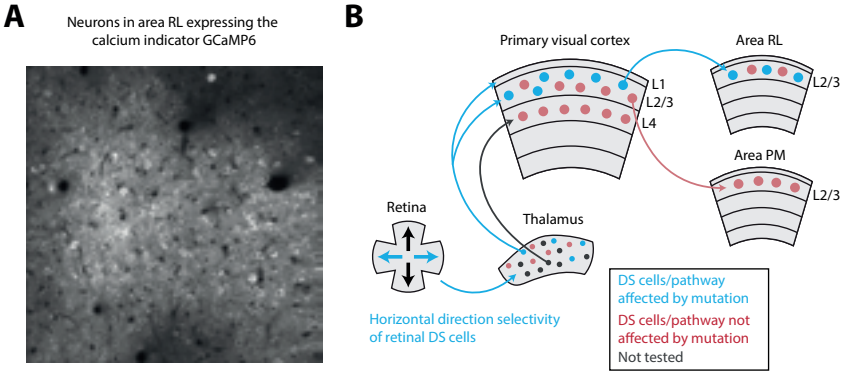


Figure A. Example of in vivo two-photon image of RL neurons labeled with fluorescent calcium indicator GCaMP6.
Figure B. Schematic diagram of proposed neural pathway linking retinal DS cells to RL DS cells.

03
Events of the year 2019

EVENTS, VISITORS, GUESTS AND SEMINARS

The PROMEMO conference *"Proteins and Circuits in Memory"*
Photo: Susanne Schousboe Sjøgaard

01

JANUARY

EVENT: **DANDRITE Mini Symposium**, Aarhus University
Lectures by:

- Associate Professor **Andrew Huberman**, Stanford University School of Medicine Stanford, CA., USA, "*Brain circuits that link perceived threats with action responses.*"
- Director, EMBL-EBI **Rolf Apweiler**, The European Bioinformatics Institute (EMBL-EBI), Welcome Genome Campus, United Kingdom, "*Bioinformatics goes Translational: The Open Targets example.*"
- PhD, DSc – Principal investigator **Gábor Tamás**, University of Szeged, "*Novel cellular components and network mechanisms in human and rodent neocortical microcircuits.*"
- Associate Professor and DANDRITE Group Leader **Sadegh Nabavi**, Department of MBG, Aarhus University, "*An approach for activity-dependent retrograde mapping.*"
  Host: Group Leader Sadegh Nabavi

02

SEMINAR: **DANDRITE Topical Seminar** with **Maria Luísa Vasconcelos**, Champalimaud Centre for the Unknown Lisboa, Portugal, "*Female responses to male courtship in flies*", Host: Group Leader Anne von Philipsborn

03

FEBRUARY

SEMINAR: **Biomedicine Seminar**, Team Leader **Tomonori Takeuchi**, "*Selective memory retention and updating schematic knowledge*"

04

SEMINAR: MBG Focus Talk, Professor **Jakob Nilsson**, NNF Center for Protein Research, University of Copenhagen, "*Regulation of signaling by phosphoprotein phosphatases*", Host: Group Leader Poul Nissen

05

EVENT: **DANDRITE Student Encounters 2019**, Aarhus University

06

MARCH

EVENT: The PROMEMO conference "**Proteins and Circuits in Memory**", took place on 5-7 March 2019. The conference brought together world-leading neuroscientists who discussed their latest research uncovering novel mechanisms that underlie memory formation, storage, and recall. The program included the official announcement of The Brain Prize Awardee(s) 2019

07

SEMINAR: **Biomedicine Seminar**, Group Leader **Mark Denham**, "*Identifying disease susceptibility variances in Parkinson's disease with human induced pluripotent stem cells*"

08 SEMINAR: **Joint KJELDGAARD & DANDRITE Lecture** with Senior Group Leader **Andreas Luthi**, Friedrich Miescher Institute for Biomedical Research, Basel, "*Neuronal circuit mechanisms for learning and memory*", Host: Affiliated Researcher at DANDRITE Macro Capogna

09 SEMINAR: **DANDRITE Topical Mini Symposium** with Professor Jean-Christophe Billeter, Groningen University, "*Modulation of individual behaviour by social experience in Drosophila melanogaster*" and Professor Marion Silies, Mainz University, "*A luminance-sensitive pathway in Drosophila is required for image processing in low light conditions*", Host: Group Leader Anne von Philipsborn

10 EVENT: **DANDRITE Spring Party**

11 EVENT: **Board Game Night**, organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE")

APRIL

12 EVENT: **Festival of Research 2019 – FASCINATING RESEARCH**. DANDRITE research groups attending

13 SEMINAR: **DANDRITE Topical Seminar** by Assistant Professor **Ali Haydar Cetin**, University of Washington, "*Circuit mapping with novel molecular genetic tools*", Host: Group Leader Keisuke Yonehara

14 SEMINAR: **DANDRITE Topical Seminar** by PhD **Naoya Takahashi,** Humboldt University of Berlin, "*Cellular and circuit mechanisms for somatosensory perception*", Host: Group Leader Keisuke Yonehara

15 SEMINAR: **Neuroscience Seminar** by Professor **Chris Meisinger,** Institute of Molecular Medicine and Cell Research, Faculty of Medicine, University of Freiburg, "*Signalling pathways targeting the mitochondrial import machinery: control of cell cycle, metabolism and oncogenesis*", and Dr. **Nora Vögtle,** Institute of Molecular Medicine and Cell Research, Faculty of Medicine, University of Freiburg, "*Quality control by the mitochondrial presequence processing machinery in health and disease*". Host: Group Leader Poul Henning Jensen

16 SEMINAR: **Neuroscience Seminar** with Postdoc **Anne M. Klawonn**, Stanford Universitet, "*Neuromodulators of Motivational and Affective Neurocircuits – Aversive, Rewarding and anhedonic features*" Host: Group Leader Anders Nykjær

17 SEMINAR: **DANDRITE Topical Seminar** with Dr. **Gergely Szabo**, Stanford University, "*GABA-ergic inhibition coincident with sharp wave-ripples broadcasts within the hippocampal formation and beyond*", Host: DANDRITE affiliated researcher Marco Capogna

18 EVENT: The first **DANDRITE writing club**, organized by Team Leader Magnus Kjærgaard

19 EVENT: **Board Game Night**, organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE")

MAY

20 EVENT: **Neuroscience Day 2019: Brain Jam**. Organized by NeuroCampus Aarhus

21 SEMINAR: **PROMEMO/DANDRITE Topical Seminar** with Associate Professor **Enrico Tongiorgi,** University of Trieste, "*BDNF mRNA variants in neuronal development: the "spatial & quantitative code model*", Host: Affiliated DANDRITE researcher and PROMEMO Group Leader Marco Capogna

22 SEMINAR: **AIAS Fellows' Seminar** by **Tomonori Takeuchi**, Aarhus University, "*Memory modulation by light.*"

JUNE

23 SEMINAR: **DANDRITE Lecture** with Professor and Senior Principal Investigator at the ZIINT and School of Medicine at Zhejiang University, **Hailan Hu**, "*Neural mechanism of social and emotional behavior – from pecking order to ketamine*", Host: Young DANDRITE and Group Leader Sadegh Nabavi

24 SEMINAR: **DANDRITE Topical Seminar** with Professor **Helmut Kessels**, University of Amsterdam, "*AMPA-receptor plasticity in control of memory formation and retrieval*", Host: Group Leader Sadegh Nabavi

Visit by two preschool classes from Samsøgade School
Photos by: Student Assistant Emma Kathrine Sommer

25 SEMINAR: **DANDRITE Lecture** with Dr. **Hiroshi Ito**, Frankfurt am Main, "*A prefrontal-thalamic circuit for route planning*", Host: Team Leader Tomonori Takeuchi

26 SEMINAR: **DANDRITE Topical Seminar** with PhD **Carl E. Schoonover**, Columbia University, "Unstable odor responses in piriform cortex" and PhD **Andrew J.P. Fink**, Columbia University, "*A virtual burrow assay for head–fixed mice measures habituation, discrimination, exploration and avoidance without training*", Host: Group Leader Duda Kvitsiani

27 EVENT: **DANDRITE Mini Symposium**, Aarhus University Lectures by:

- EMBL Group Leader **Paul Heppenstall,** "New technology to control itch and pain"
- Professor **Clive Bramham**, University of Bergen, *"Arc protein: signal hub or retrovirus-like capsid?"*
- Professor **Eric Hanse**, University of Gothenburg, "*Modulation of synaptic and neuronal function by cerebrospinal fluid*".
- Associate Professor and DANDRITE Group Leader **Mark Denham**, Aarhus University, "*Identifying risk variances in GBA-associated Parkinson's disease*"

Host: Group Leader Mark Denham

28 SEMINAR: **DANDRITE Topical Seminar** with Professor Emre Yaksi, Trondheim, "*Function and development of habenular networks*", Host: Group Leader Duda Kvitsiani

29 SEMINAR: **DANDRITE Topical Seminar** with Group Leader **Kentaroh Takagaki**, Otto-von-Guericke University Magdeburg, "*Chronic Massively-Parallel Recording of Single-Unit Activity in the Rodent Brain*", Host: Team Leader Tomonori Takeuchi

30 EVENT: **Final rainbow club**, "Bitcoins", organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE")

31 GUESTS: **Visit by two preschool classes from Samsøgade School**, host: Postdoc Stella Solveig Nolte

32 EVENT: **NEUROSCIENCE/DANDRITE WORKSHOP** on Parkinson's disease and alpha-synuclein. Lectures by:

- Associate Professor **Hilal Lashuel**, Brain Mind Institute, Switzerland, "*Deconstructing and r econstructing the process of lewy body formatin in Parkinsn's disease. The issue is in the tissue*".
- Associate Professor **Kostas Vekrellis**, Biomedical Research Foundation Academy of Athens, Center for Basic Neurosciences & Visiting Professor, Oxford University Medical School, Dept. of Experimental Medicine, Radcliffe Dept. of Medicine, UK: "*Hitching a ride to the next cell: Extracellular alpha synuclein and the spread of the disease pathology*"

JULY

33 SEMINAR: **DANDRITE Topical Seminar** with **Morteza Abbaszadeh**, *"Latent Components of Neurodegeneration: Two Short Stories from Alzheimer's and Parkinson's Diseases"*, Host: Group Leader Keisuke Yonehara

34 SEMINAR: **DANDRITE Topical Seminar** with **John L. Rubinstein**, University of Toronto, *"CryoEM of macromolecular machines at energized membranes"*, Host: Group Leader Poul Nissen

Talk by Strategic Development Partner Mikkel Hougaard Orlovski from DTU on Cultural intelligence

AUGUST

35 EVENT: SYNDI **Conference 2019**: neural mechanisms of decision-making, learning and other cognitive processes. Organized by Group Leader Duda Kvitsiani

36 EVENT: **DANDRITE Retreat 2019**

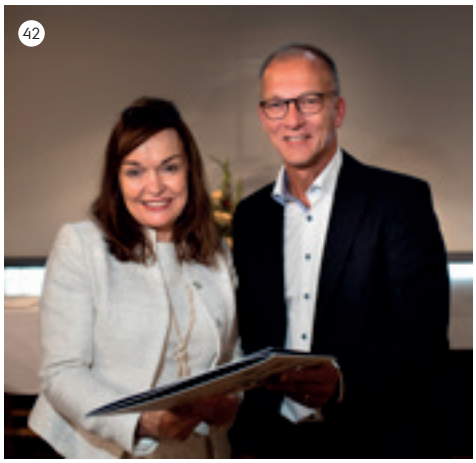
37 SEMINAR: **PROMEMO/DANDRITE Topical Seminar** with Senior Research Fellow **Lilian Kisiswa**, National University of Singapore, *"Deciphering proteins involved in neuronal survival and the growth of neurites in developing nervous system"*, Host: Group Leader Anders Nykjaer

38 SEMINAR: **Joint KJELDGAARD & DANDRITE Lecture** with **Yulong Li**, Peking University, *"Spying on neuromodulation by constructing new genetically encoded fluorescent sensors"*, Host: Group Leader Keisuke Yonehara

SEPTEMBER

39 SEMINAR: **PROMEMO/DANDRITE Double Topical Seminar** with Postdoctoral Researcher **Priyanka Rao-Ruiz**, VU University Amsterdam, *"Elucidating the Engram-specific Molecular Architecture of Memory Consolidation"* and Lead Data Scientist **Ben Dichter**, Stanford University, *"Using the Neurodata Without Borders: Neurophysiology Standard to Access Tools and Drive Collaboration"*, Host: PROMEMO Group Leader and DANDRITE affiliated researcher Marco Capogna

40 SEMINAR: **DANDRITE Topical Seminar** with Professor **Hajime ("Haj") Hirase**, University of Copenhagen, *"Heterogeneity of astrocytes in glycogen distribution and GPCR-driven dynamics"*, Host: Group Leader Keisuke Yonehara



Honorary Doctor Carol Robinson and Dean of ST Lars Henrik Andersen. Photo: Lars Kruse

41 SEMINAR: **DANDRITE Topical Seminar** with Assistant Professor **Cristina Paulino**, University of Groningen, *"The flips and flops of a scramblase story – proteins in nanodiscs and electrons at 200kV"*, Host: Group Leader Poul Nissen

42 SEMINAR: **Aarhus University Honorary Doctorate Seminar** by Professor **Dame Carol Robinson** from the University of Oxford. Prof. Robinson was appointed honorary doctorate at the Faculty of Science of Technology, Aarhus University 2019. *"From peripheral proteins to membrane motors – mass spectrometry comes of age"*. Host: Group Leader Poul Nissen and Prof. Birgit Schiøtt

Honorary doctor Mark Daly and Dean of HE Lars Bo Nielsen.
Photo: Lars Kruse

DANDRITE's attending a match between FC Barcelona - Villarreal CF.
Photo: Postdoc Mateusz Dyla

43 SEMINAR: **Honorary doctor Mark Daly** by Professor Mark Joseph Daly, Director of the Institute of Molecular Medicine Finland (FIMM), the Finnish node of the Nordic EMBL Partnership. Prof. Daly was appointed honorary doctorate at the Faculty of Health, Aarhus University 2019. *"Global partnerships: From Psychiatric Genetics to FinnGen and opportunities in discovery, prevention and personalized medicine"*

44 EVENT: **The 3rd EMBL Partnership Conference** *"Perspectives in Translational Medicine"*, hosted by The European Molecular Biology Laboratory (EMBL), EMBL Barcelona, Spain. Attended by DANDRITE researchers and students

OCTOBER

45 EVENT: **The 8th Symposium on ATP1A3 in Disease 2019** took place on 3-4 October 2019 at the beautiful and conveniently located Grand Hotel Reykjavik on Iceland. The hosts were the AHC Association of Iceland supported by an organizing committee that consisted of European scientists that have been working on ATP1A3 related diseases for many years, including DANDRITE Group Leader Poul Nissen, Affiliated Researcher Karin Lykke-Hartmann, and Team Leader Hanne Poulsen

The 8th Symposium on ATP1A3 in Disease 2019 organizing team

46 SEMINAR: **DANDRITE Topical Seminar** with **Charlott Stock**, Goethe University Frankfurt, *"Structures of KdpFABC reveal K+ transport mechanism via two inter-subunit half-channels"*, Host: Group Leader Poul Nissen

47 SEMINAR: **Joint iNANO-DANDRITE Workshop** with Dr. **Celiné Galvagnion**, University of Copenhagen, *"Amyloid protein – membrane interactions: the influence of the lipid composition on the kinetics of protein aggregation"* and Professor **Alexander K. Buell**, DTU, "Mechanistic insight into the growth and autocatalytic amplification of amyloid fibrils", Host: Group Leader Poul Henning Jensen

NOVEMBER

48 SEMINAR: **DANDRTE Topical Seminar** with Professor **Jan Gründemann**, University of Basel, *"Imaging deep: State and sensory coding in subcortical circuits"*, Host: Group Leader Sadegh Nabavi

49 SEMINAR: **DANDRITE Lecture** with Professor **Michael Sendtner**, University of Würzburg, *"Subcellular neurotrophic signaling for neuronal development and presynaptic function"*, Host: Group Leader Anders Nykjaer

50 EVENT: **Visit by Brain Research Institute, Niigata University, Japan. Incl. Mini Symposium**

51 SEMINAR: **DANDRITE Topical Seminar** by Group Leader Armin Lak, Oxford University, *"Dopaminergic and prefrontal basis of learning from sensory confidence and reward value"*, Host: Group Leader Duda Kvitsiani

52 EVENT: **Le Tour de Skou** – a tour of the Skou building, the laboratories & facilities

53

54

55

EVENT: **DANDRITE Internal Meeting**, inaugural presentation by DANDRITE's newly appointed Affiliated Researcher; Professor **Ernst-Martin Füchtbauer**

DECEMBER
EVENT: **DANDRITE Christmas get-together** with spouses and children

SEMINAR: **Joint DANDRITE-Biomedicine/Neuroscience Seminar** with **Rikke Hahn Kofoed**, Sunnybrook Research Institute, *"Non-invasive delivery of gene therapy to the CNS using MRI-guided focused ultrasound and microbubbles"*, Host: Poul Henning Jensen

SYSTEMS NEUROSCIENCE AND DECISION MAKING CONFERENCE

In August 2019, DANDRITE Group Leader Duda Kvitsiani and Balazs Hangya from Institute of Experimental Medicine in Hungary organized Systems Neuroscience and Decision Making (SYNDI) conference at Aarhus University. The general topic was neural mechanisms of decision-making, learning and other cognitive processes. One of the aims of the meeting was to bring together labs working on different levels: from molecules to cells and circuits as well as using variety of model organisms and approaches to answer fundamental questions in behavioral neuroscience.

INVITED SPEAKERS

- Armin Lak, Associate professor, Department of Physiology, Anatomy and Genetics, Oxford University.
- Junya Hirokawa, Associate professor, Graduate School of Brain Science, Doshisha University, Kyoto.
- Adil Khan, Group leader, Kings College, London
- Hyun Jae Pi, postdoctoral fellow, Dept. of Biology, Volen Center for Complex Systems, Brandeis University
- Oliver Hulme, Senior Researcher, Danish Research Centre for Magnetic Resonance ,Copenhagen University, Hospital Hvidovre
- Ebru Demir, postdoctoral fellow, Department of Neuroscience, Columbia University

PUBLIC OUTREACH

Neuroscience Day 2019 Participants. Photo by Lars Kruse, AU Photo

NEUROSCIENCE DAY

EVENT: Neuroscience Day 2019: Brain Jam. Organized by NeuroCampus Aarhus (NCA). NCA is a cross-disciplinary research network at Aarhus University and Aarhus University Hospital open for all interested in the brain. DANDRITE strongly supports and are involved both the NCA network as such and in the organizing of the Neuroscience Day 2019 in particular.

Keynote lecturers were:

- 2018 Brain Prize Winner Professor **Michel Goedert**, *"Conformers of assembled Tau"*
- Professor **Jørgen E. Nielsen**, Rigshospitalet, University of Copenhagen, *"Frontotemporal Dementia Linked to Chromosome 3: Mutation, Mechanisms, Markers and Modifiers"*
- Professor **Johan Jakobsson**, Wallenberg Neurosci. Center, Lund University, Sweden, *"Using patient-derived aged neurons to study Huntington's disease."*

Presentations by DANDRITE researchers:

- DANDRITE Group Leader **Poul Henning Jensen,** Aarhus University, *"A-syn aggregation in cells during synucleinopathies"*
- DANDRITE Group Leader **Mark Denham**, Aarhus University, *"Investigating early causative mechanisms that lead to Parkinson's Disease in GBA heterozygous carriers"*
- DANDRITE Affiliated Researcher **Marina Romero-Ramos**, Dept. of Biomedicine, Aarhus University, *"Immune response to a-syn aggregation"*
- DANDRITE Affiliated Researcher Prof **Olav Andersen**, Dept. of Biomedicine, Aarhus University, *"Novel functions of the APP-sorting receptor SORL1"*

FESTIVAL OF RESEARCH

DANDRITE researchers always take part in the annual recurring nationwide Festival of Research and not least in 2019. At Aarhus University's campus, the Festival is each year a day-event where the general Danish public is invited to meet researchers first hand. It was also in 2019 busy and enjoyable day where students from DANDRITE demonstrated their research areas. Four labs were represented: Poul Nissen lab, Magnus Kjærgaard lab, Sadegh Nabavi lab and Anne Philipsborn lab.

Researchers from Sadegh Nabavi's lab showed how our brain controls our body by inviting the public to try a neuroprosthetics device that transfers one person's electrical muscle impulses to another person's muscles by delivering the same current to the nerves. At Poul Nissen and Magnus Kjærgaard's stand, the public could learn how proteins are built via. LEGO bricks. Finally, Philipsborn's lab brought the audience into the mind of a fruit fly and showed how Drosophila neuroscience helps us understand the brain.

DANDRITE STUDENT ENCOUNTERS 2019

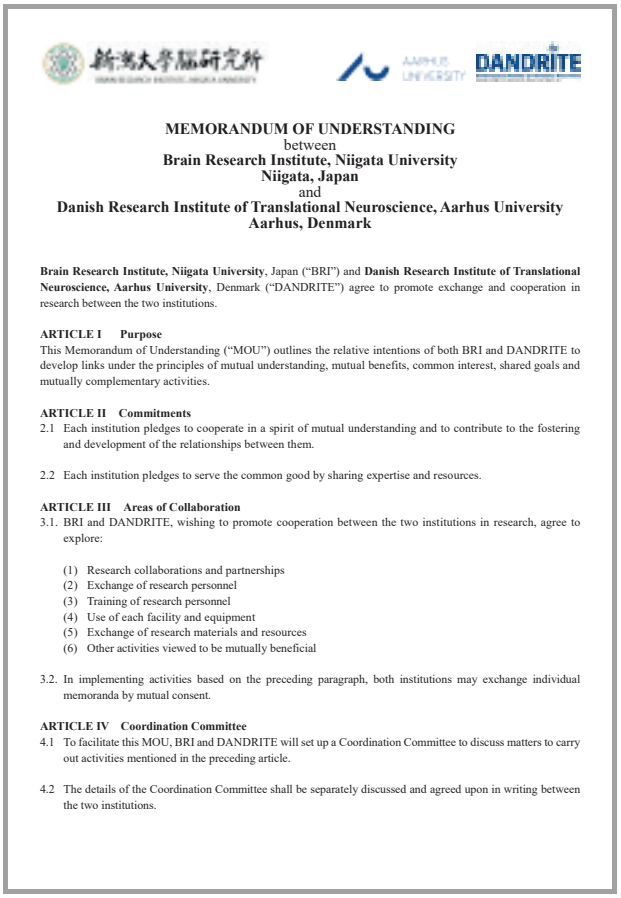
In 2019, we repeated last year's success with guided lab tours. The new format is highly appreciated and 80 students showed up to look for opportunities for student projects in one of DANDRITE's different research groups.

Assistant Professor Andrea Tóth at DANDRITE Student ENCOUNTERS 2019

VISIT BY BRAIN RESEARCH INSTITUTE, NIIGATA UNIVERSITY, JAPAN

During 2019, DANDRITE established a new collaboration with Brain Research Institute (BRI) from Niigata University, Japan. Group leader Keisuke Yonehara and Team Leader Tomonori Takeuchi initiated the contact with BRI. On November 24-26, a delegation from BRI visited DANDRITE where a Memorandum of Understanding was signed to promote research exchange and cooperation between the two institutions.

During the visit, the delegation visited DANDRITE facilities such as 'The Joint' and the '2photon', they meet with several DANDRITE Group Leaders, and finally they took part in a joint Mini Symposium where researchers from both institutes gave research presentations of their work.



MEMORANDUM OF UNDERSTANDING
between
Brain Research Institute, Niigata University
Niigata, Japan
and
Danish Research Institute of Translational Neuroscience, Aarhus University
Aarhus, Denmark

Brain Research Institute, Niigata University, Japan ("BRI") and **Danish Research Institute of Translational Neuroscience, Aarhus University**, Denmark ("DANDRITE") agree to promote exchange and cooperation in research between the two institutions.

ARTICLE I Purpose
This Memorandum of Understanding ("MOU") outlines the relative intentions of both BRI and DANDRITE to develop links under the principles of mutual understanding, mutual benefits, common interest, shared goals and mutually complementary activities.

ARTICLE II Commitments
2.1 Each institution pledges to cooperate in a spirit of mutual understanding and to contribute to the fostering and development of the relationships between them.

2.2 Each institution pledges to serve the common good by sharing expertise and resources.

ARTICLE III Areas of Collaboration
3.1. BRI and DANDRITE, wishing to promote cooperation between the two institutions in research, agree to explore:

(1) Research collaborations and partnerships
(2) Exchange of research personnel
(3) Training of research personnel
(4) Use of each facility and equipment
(5) Exchange of research materials and resources
(6) Other activities viewed to be mutually beneficial

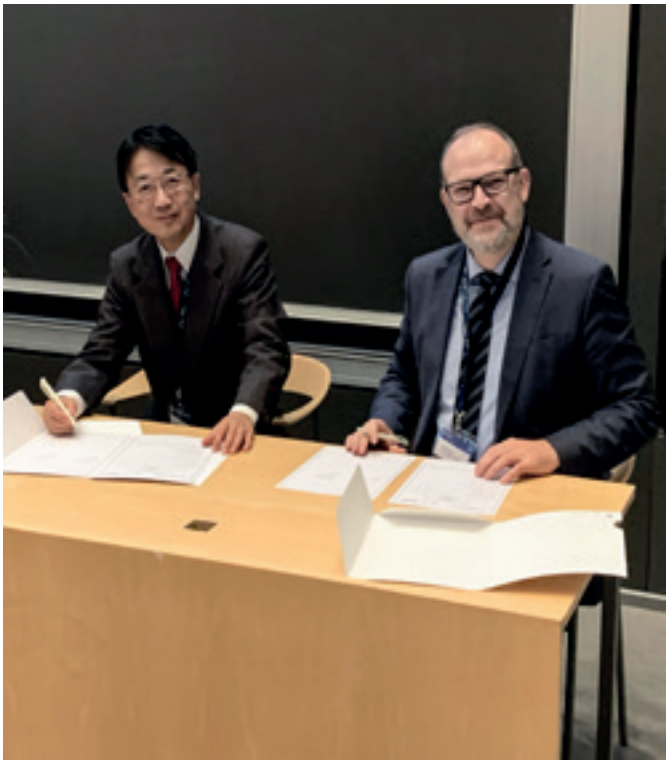
3.2. In implementing activities based on the preceding paragraph, both institutions may exchange individual memoranda by mutual consent.

ARTICLE IV Coordination Committee
4.1 To facilitate this MOU, BRI and DANDRITE will set up a Coordination Committee to discuss matters to carry out activities mentioned in the preceding article.

4.2 The details of the Coordination Committee shall be separately discussed and agreed upon in writing between the two institutions.

MoU agreement

Photo: Azuza Yamada



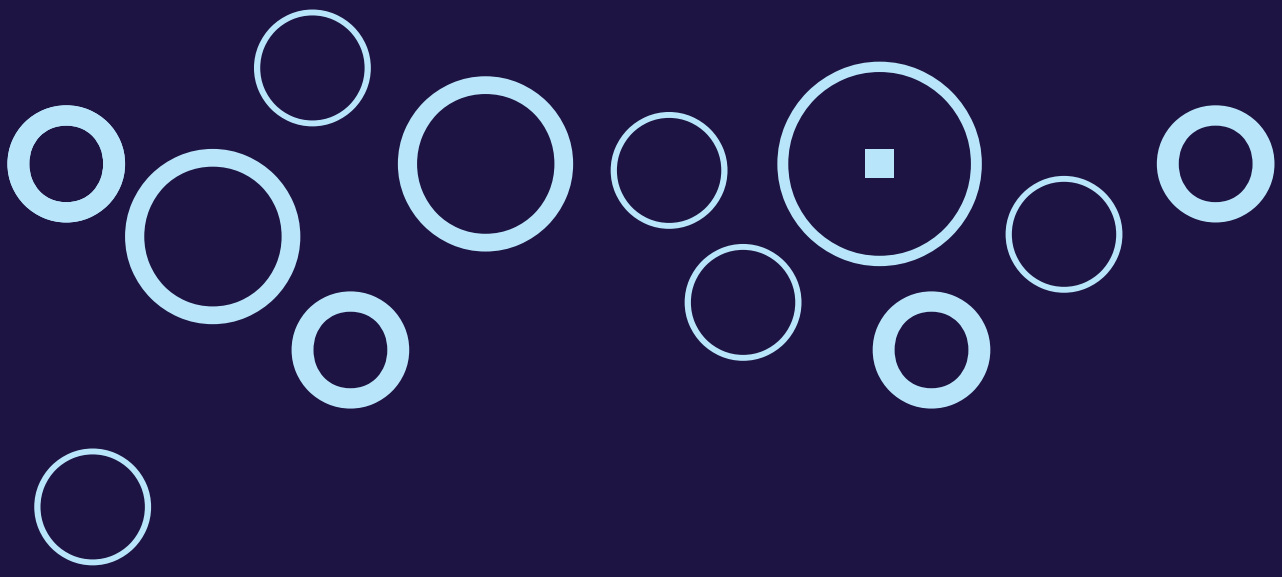
Signing of MoU agreement by Niigata Director Prof. Hiroyuki Nawa and DANDRITE Director Prof. Poul Nissen. Photo: Azuza Yamada.

DANDRITE RETREAT 2019
(PHOTOS)

Photo: Sadegh Nabavi

Photo: Sadegh Nabavi

04 Personnel

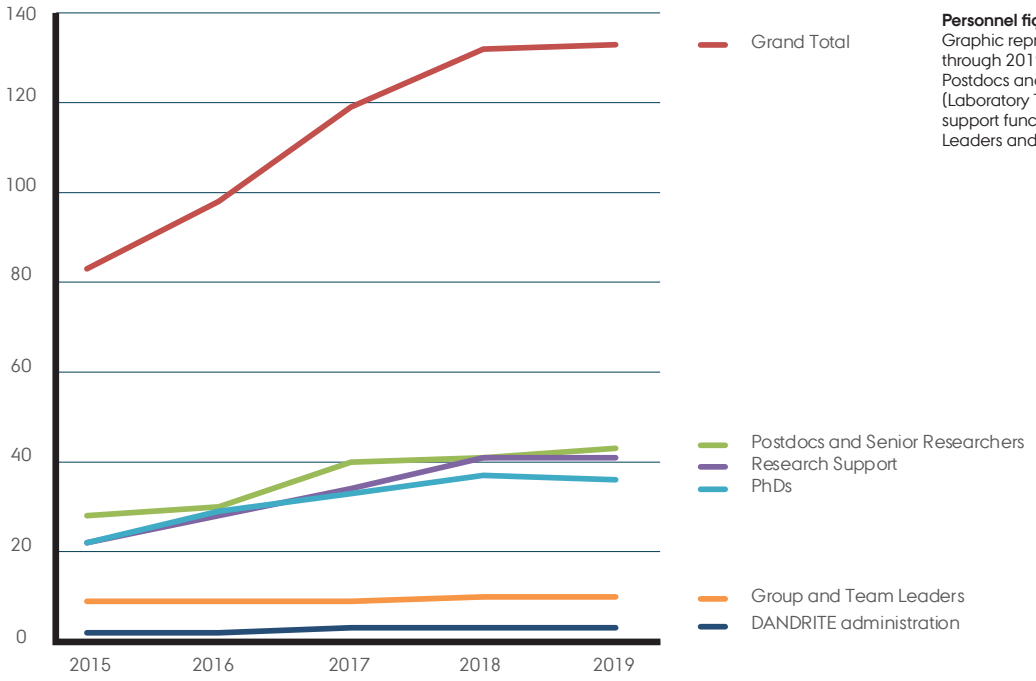


Personnel

Since DANDRITE's inauguration in 2013, staff development has been characterized by considerable growth each year. In 2019, the personnel development at DANDRITE reached a steady state with a grand total of 133 employees (excluding affiliated researchers).

All the five young group leaders are now well established at DANDRITE, and they have all entered their second period (following the EMBL model). Further, DANDRITE begins to experience an increasing number of alumni.

The following pages display different graphical presentations of DANDRITE statistics. All counts excludes affiliated researchers



Personnel figure 1:
Graphic representation of personnel progression 2015 through 2019 for appointed categories summarized: Postdocs and Senior Researchers, Research Support (Laboratory Technicians, Research Assistants and other support functions), PhD students, Group and Team Leaders and administration.

FIGURE 2
COUNT OF NUMBER AND PERCENTAGES OF PERSONNEL EMPLOYED DURING 2019 GROUPED BY APPOINTMENT CATEGORY AND GENDER

DANDRITE Personnel categories	Female	Male	Total	%
Group and Team Leaders	2	8	10	8 %
Postdocs and Senior Researchers	19	24	43	32 %
PhDs	23	13	36	27 %
DANDRITE administration	3	0	3	2 %
Research Support	32	9	41	31 %
Grand Total	79	54	133	100 %
% Male/Female	59	41	100	

Figure 3:
Graphic representation of the personnel counts for 2019 (numbers grouped by appointment category and gender)

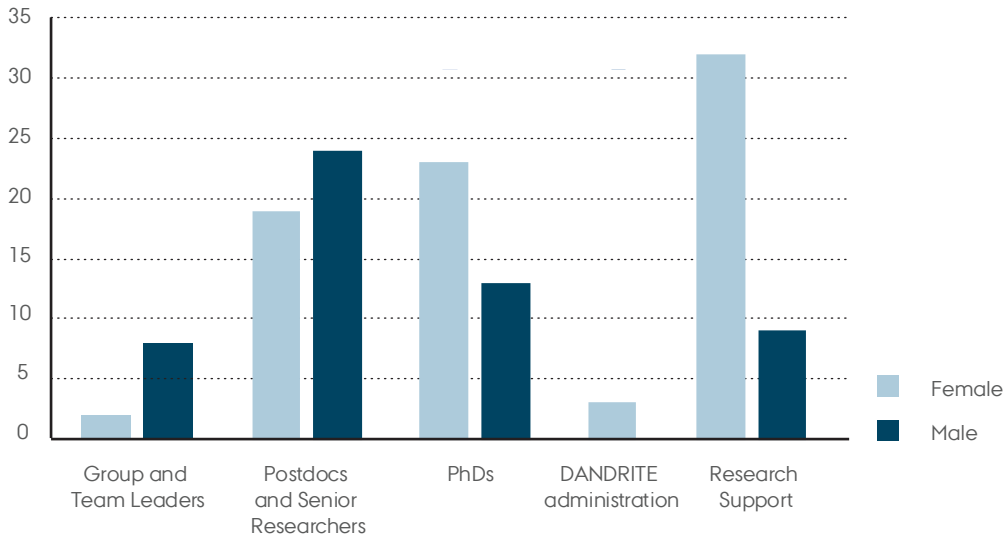
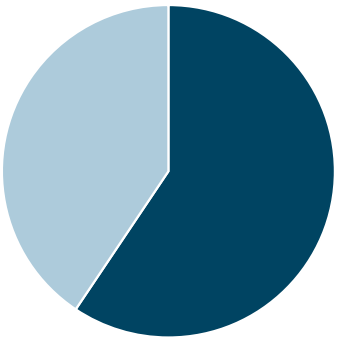


Figure 4:
Graphic representation of the personnel counts for 2019 grouped gender



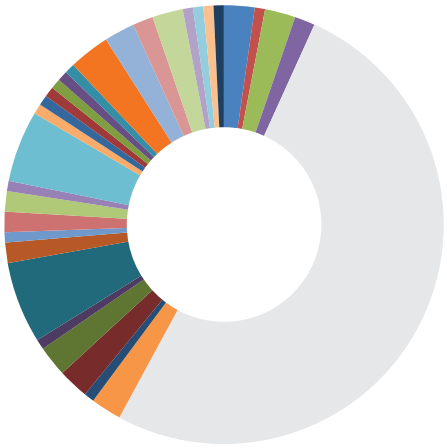
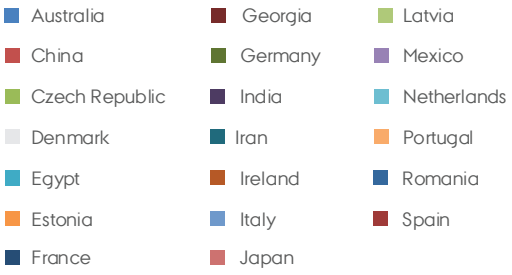


Figure 5:
Graphic representation of the nationality distribution of all employees

Figure 6:
Graphic representation of the nationality distribution of the employees in DANDRITE's five young research groups



DANDRITE Alumni

Aisha Rafique, Communications and Scientific Research Coordinator
edited all features

In 2019, DANDRITE entered the seventh year of operation, and has a fast-growing number of Alumni. PhDs are graduating and the many post-docs are completing their positions at DANDRITE and move to new career stages. In the coming years DANDRITE will establish an alumni network for the mutual benefit of active researchers at DANDRITE and DANDRITE alumni in science careers and neuroscience.

Some DANDRITE alumni stay in academia others go to private sector research or consulting, and some to public sector teaching and administration. Many stay within Denmark, many others go abroad. On the following pages, we present the different career paths of three DANDRITE PhD graduates, namely Dr. Sara Elgaard Jager (former PhD student in Affiliated Researcher Christian Vægter's group), Dr. Juliane Martin (former PhD student in Group Leader Duda Kvitsiani's group) and Dr. Rikke Hahn Kofoed (former PhD student in Group Leader Poul Henning Jensen's group).

ALUMNI FEATURE
/ Text: Sara Elgaard Jager

Sara Elgaard Jager, Postdoctoral Research Fellow with Lundbeck Fellowship at King's College London

In brief, tell me about your specific field of research and explain why you are interested in this particular area?
I do basic research in relation to pain and chronic pain after a nerve injury. I am interested in the interplay between neurons, glial cells and immune cells and how this possibly contributes to the development of chronic pain. Chronic pain is a global problem with limited treatment options that are inadequate in providing pain relief. The lack of efficient medication is rooted in a poor understanding of why pain becomes chronic. With a better understanding of the cellular mechanisms behind chronic pain we will be able to develop efficient medication and help the patients to a pain free life.

What was most memorable to you about your experiences in your PhD and postdoctoral program, and what was most memorable to you about your experiences at DANDRITE and Aarhus University?
I did my PhD at Associate Professor Christian Vægter's lab where I had freedom to plan my own time and research project. The Vægter lab is affiliated to DANDRITE, which allowed me to participate in the international environment at DANDRITE. Looking back, I specifically remember the first time I had to present my research at the biweekly internal meeting – a forum where students, young researchers and PI's have the opportunity to discuss their research and provide feedback. I was very nervous and had spent a lot of time preparing and I failed miserably. I lost the audience within the first minute and the questions I received after my presentation had nothing to do with what I intended to communicate. I talked to Susanne Sjøgaard about my frustrations and she told me that my slides where beautiful. That made me realize that not everything was lost and that it would be possible for me to become a better communicator. I started by participating in PhD courses for research presentation provided by Health and Aarhus University. I especially learned a lot from the course "Research presenter" taught by Mads Ronald Dahl. I think this course was helpful for me because I had an open mind and was very eager to learn. Following that course, I kept challenging myself by doing various type of communication including talks to lay people at the Danish science festival, written communication on videnskab.dk and of course scientific talks and presentations. Most recently, I participated in the Danish PhD cup 2019, which was an amazing and challenging experience. I learnt how other people perceive me when I give a presentation and how to connect with the audience.

How have you used your skills and experiences gained at DANDRITE and Aarhus University in your subsequent positions? What advice would you give to someone who is considering pursuing a doctorate within science?
For me it has been fulfilling to identify a weakness (my presentation skills) that I could work on improving in parallel with my research in the lab. As I see it, improving my scientific communication skills have been key in securing my current funding, and in transforming my scientific presentations into fun instead of something, I fear.

Describe your career path since completing your education at Aarhus University? Where are you now?
During my PhD I spent 6 months at King's College London with Professor Stephen McMahon and Dr. Franziska Denk. During this time, I realized that I would like to do a postdoc at King's College London. I discussed this with Dr. Denk and she was happy to help with writing the application to secure the funding. I submitted to various Danish funds and was lucky to get a 3-year Lundbeck Fellowship via their International Neuroscience programme. I have just completed my first year in Denk lab and I am very excited that I have at least two more years here.

ALUMNI FEATURE
/ Text: Juliane Martin

In this feature, Juliane Martin sheds a light on her skills and memorable experiences gained at DANDRITE and Aarhus University and how this led her to pursue a career in the industry.

When I started my PhD at DANDRITE, I would have never thought that it would lead me to where I am now. I was certain I would stay in academia. Yet, today, I'm in Copenhagen, about to start my new job as an Assistant Consultant at Boston Consulting Group. As a consultant, I will provide strategic advice to companies of various industries.

Juliane Martin, Associate Consultantat Boston Consulting Group

I often get the question, what this has to do with my education, molecular biology. Frankly, nothing. But it got to do with who I am as a person and my

hitherto made experiences (inside and outside of work). So, never underestimate your soft skills!

My experiences during my PhD, specifically my personal development, helped me to understand where my strengths lie and how I would like to use these at work. So, if I would have to give advice to young researchers, it would be to pause once in a while and reflect on your current situation. Is this still where you want to be in life? What do you like most at your current position? What does your work environment need to comprise in order for you to thrive? I asked myself exactly these questions at the end of my PhD, and they were a good starting point to think about my skills, strengths and needs. I realized that what I liked most about my PhD was the steep learning curve, structuring and discussing projects (independent of whether it was my own or other's), and the constant trouble-shooting. I also realized that I prefer to work in a team, and that I love to be an active member of a community. Especially, for the latter, DANDRITE provided the necessary freedom to propose and implement my ideas. I think my involvement in Young DANDRITE (YoDa) and co- founding the rainbow club were crucial turning points in my career. Of course, the above-mentioned attributes are important in science, but all of them are also highly valued and nurtured in my current position. So, a second advice I would give is to look outside the box. As scientists, we don't always see or know about the doors actually open to us and industry can be surprising flexible and has space for many qualities and personalities.

After I identified my qualities, I took advantage of the career services offered by Aarhus University to narrow down my next career step. Specifically, I went to a career fair and to career counselling, which then put me into contact with people who already accomplished what I desired, i.e. transitioning from academia to consulting. I talked to at least one employee of each company I applied to. This gave me a much better understanding of the job, its requirements, challenges and perspectives. It also gave me the opportunity of a first glance at the company's atmosphere and values. The latter is an often overseen, but crucial criteria. Only if you and your employer (company or public institution) are a good fit, can your potential be completely unlocked. In all of my interviews, 50% of the time were spent on getting to know me as a person and evaluating my fit for the company. The remaining 50% were then used to test my skills.

I know my career choice looks unusual from the outside. But in retrospect, it completely makes sense to me. So, the last advice I would like to give here is: be confident about your own skills and personality traits!

ALUMNI FEATURE
/ Text: Rikke Hahn Kofoed

What was most memorable to you about your experiences in your PhD and postdoctoral program, and what was most memorable to you about your experiences at DANDRITE and Aarhus University?
I was enrolled as a student at Aarhus University from 2009 to 2018 during which I obtained my bachelor, master, and PhD degree in molecular medicine. My PhD focused on Parkinson's disease and cell signaling using cell culture models. A year before finishing my PhD I started looking for a post-doctoral position abroad. I met a professor from Canada at a conference in Vienna and I was intrigued by her research. I joined her group 3 months after defending my PhD – in Toronto, Canada. Now, my research focuses on delivery of Gene Therapy to the central nervous system in preclinical animal models.

Rikke Hahn Kofoed, Postdoctoral Research Fellow at Sunnybrook Research Institute, Toronto, Canada

Looking back at my time as a bachelor and master student at Aarhus University, I really enjoyed that period of my academic career. The structure of the campus creates a feeling of a little town within the city, with a focus on learning and innovation. It has always fascinated me that no matter the time or day, there's always someone present at Aarhus University, either conducting an experiment or deeply concentrated in studying for an exam (or just in early for "Kapsejladsen"). To me, this symbolized a passion for research and learning, and it was a very inspiring environment to study and grow in.

What I find unique about DANDRITE, in particular, is the opportunity to gain knowledge on a great variety of neuroscientific areas. DANDRITE gave me the opportunity to connect with other neuroscientists outside of biomedicine, which really broadened my idea of neuroscience in general. For example, our biweekly internal meetings created a strong foundation for collaborations as well as a relaxed atmosphere for students to present their work and to interact with other researchers at all levels. The DANDRITE community provided me with a great sense of belonging, and after having left DANDRITE, I have really come to appreciate how unique this was.

How have you used your skills and experiences gained at DANDRITE and Aarhus University in your subsequent positions?
Looking back at my PhD program, I grew dramatically from a newly enrolled PhD student to a much more independent researcher. What I especially remember from my training is how I learned to always ask questions along the way during an experiment and never assume that anything in science is set in stone. DANDRITE and Aarhus University also provided several opportunities for me to present my work and to teach other students e.g. by participating in the Nordic EMBL Partnership conferences, internal meetings, and the mandatory teaching tasks as a PhD student. These experiences allowed me to develop my communication skills – a skill which I am highly dependent upon in my current and future positions e.g. when supervising students in the laboratory or presenting my work at conferences.

At first, obtaining a PhD degree might seem like many years of education, but the time as a PhD student is exciting and you will do research from day one. Doing a PhD is also not incompatible with having a life outside of the laboratory and I strongly believe that having other interests makes a better scientist. In a research environment like DANDRITE, you will also experience a great community among the PhD students, both in and outside of the laboratories. What advice would you give to someone who is considering pursuing a doctorate within science?

It has been a highly valuable experience for me to go from an in vitro based PhD to a postdoc focusing on treatments and preclinical models, and I will strongly recommend others to also dare change their research area. Even though I initially had to learn many new things, I believe that the mixture of my PhD background and current postdoctoral training is exactly what will enable me to create a unique profile for myself as a future scientist.

A career in academia is exciting and, I believe, should be driven by a passion for knowledge and data. As soon as you come to terms with the fact that research success will go up and down, science will always be fascinating. As a scientist you get to spend your time developing new knowledge and you can work almost anywhere in the world. Living in a different culture has made me grow quicker than I thought possible, both in regards to my career and my personal life. It has been a life-changing experience and I will highly recommend it to others.

Awards

Photo by Lundbeck Foundation

DANDRITE Director and Group Leader **Poul Nissen** was awarded the Novo Nordisk Foundation Distinguished Investigator grant 2019 within "Bioscience and Basic Biomedicine" on DKK 10 million. The grant is given to researchers who have shown their ability to carry out and lead research at the very highest international level.

Affiliated researcher **Christian Vægter** received Lundbeckfonden Ascending Investigator grant of DKK 5 million to his research into chronic nerve pain. The aim of the Ascending Investigator programme is to support established, experienced and talented scientific researchers, to boost their careers and, potentially, to make a significant contribution to biomedical science.

Postdoc **Ronja Driller** was awarded one of 46 prestigious Lundbeck postdoctoral fellowship for 2019. The fellowship is fully-funded for 3 years, amounting to 2,4 million DKK. The grant was awarded to Ronja in order for her to investigate the structure and function of endosomal and lysosomal P5-ATPases such as ATP13A2 (PARK9), which is tightly linked to lysosomal function and Parkinson's disease, but through unknown mechanisms.

Postdoc **Katherine Gill** was awarded one of 46 prestigious Lundbeck postdoctoral fellowship for 2019. The fellowship is fully-funded for 3 years, amounting to 2,4 million DKK. The grant was awarded for Katherine's work in investigating the early-stage mechanisms of Parkinson's Disease using a human stem-cell derived neuron model system.

DANDRITE DIRECTOR AND GROUP LEADER POUL NISSEN RECEIVES THE LUNDBECK FOUNDATION'S PROFESSOR GRANT

In December 2019, the Lundbeck Foundation announced six professorship grants worth DKK 232 million (USD 34 million). The aim of the Lundbeck Foundation Professorships programme is to promote the development of strong brain research environments, centered on leading, internationally renowned researchers. A Lundbeck Foundation professor is not only expected to contribute to ground-breaking research, but also to be a dedicated mentor for the next generation of talented scientists.

DANDRITE director Poul Nissen received one of these six-year grants, worth DKK 40 million to investigate the three-dimensional structure and dynamics of specific protein complexes in the cell membrane of neurons, going from atomic to sub-cellular levels of scale. He will analyse and establish models of complex membrane proteins to gain a deep, mechanistic understanding of how they sustain and organise neuron functions and their circuits. He will use sophisticated techniques such as cryo-electron tomography to study the axon initial segment. This is where nerve activity is generated, and it is therefore crucial for neuronal signaling.

"With this very prestigious grant from the Lundbeck Foundation, we can seriously think long-term and invest in important topics and methods, which are crucial for Danish brain research, such as electron microscopy. I am immensely grateful for the trust and impact the Lundbeck Foundation has with their professorship programme, and I look forward to exciting projects with outstanding colleagues in neuroscience," says Poul Nissen.

Grants


2


6


23


25


26


27

1. Affiliated Researcher **Olav Andersen**: Funktonel karakterisering af ny SORLA-variant som giver Alzheimer's demens, DKK 45.000, A.P.Møller Fonden (Lægefonden)

2. Postdoc **Krutika Bavish**i: Cross border science and society project, DKK 170.000, HALOS

3. Affiliated **Researcher Marco Capogna**: Neuron types in human cerebral cortex, DKK 3.5 million, Lundbeck Brain NIH intiative grant

4. Group Leader **Mark Denham**: Investigating GBA-associated Parkinson's disease using human IPSCs, DKK 100.000, Bjarne Saxhofs Foundation facilitated by the Parkinsons Association

5. Professor **Kai Finster** (Thomas Boesen as co-applicant): Interdisciplinary Synergy Grant, DKK 15.0 million, Novo Nordisk Foundation

6. PhD Student **Mariam Gamaledin**: Travel grant, DKK 26.000, Boehring Ingelheim

7. Group Leader **Poul Henning Jensen**: Perform quality control on up to three rounds of aSyn monomer and filament protein from Abcam, DKK 67.000, Michael J Fox Foundation

8. Group Leader **Poul Henning Jensen**: Generation, Characterization, and Small Batch Production of WT aSyn Oligomers for Use in the Development of aSyn Oligomeric Assays, DKK 575.000, Michael J Fox Foundation

9. Group Leader **Poul Henning Jensen**: Development and characterization of an animal model to study Parkinson's associated pain based on α-synuclein aggregation, DKK 280.000, Parkinsonforeningen

10. Affiliated Researcher **Jørgen Kjems**: Circular RNA as potential biomarkers for neurodegenerative diseases : postdoc salary and consumables, DKK 2.8 million, Danmarks Frie Forskningsfond

11. Affiliated Researcher **Jørgen Kjems** & **Thomas Hansen**: Improved technology for miRNA inhibition using circular RNA, DKK 800.000, BioInnovation Institute

12. Team Leader **Magnus Kjærgaard**: Self-assembled protein droplets as reaction platforms for biotechnology, DKK 2.0 million, Villum Foundation

13. Team Leader **Magnus Kjærgaard**: De novo engineering of plasticity-related proteins, DKK 2.0 million, Lundbeck Foundation

14. Team Leader **Magnus Kjærgaard**, Professor Gregers Rom Andersen and Novo Nordisk: Avidity and multivalent target engagement in antibodies, DKK 1.0 million, Innovation Fund Denmark

15. Group Leader **Duda Kvitsiani** and PI **Balazs Hangya**: Organizing a scientific meeting SYNDI 2019 in Aarhus, DKK 118.000, Lundbeck Foundation

16. Professor **Poul Nissen**: BRAINSTRUC center (director: Kresten Lindorff Larsen, Univ. Copenhagen), second tranch, DKK 3.8 million, Lundbeck Foundation

17. Affiliated Researcher **Morten Nielsen**: Drug delivery to the brain and blood-brain barrier transport mechanisms, DKK 3.45 million, Lundbeck Foundation

18. Affiliated Researcher **Morten Nielsen**: Investigating Mechanisms and Models Predictive of Accessibility of Therapeutics (IM2PACT) Into The Brain, DKK 3.6 million, Horizon2020 IMI2

19. Group Leader **Anders Nykjær**: SORCS1 – the crossroad between type 2 diabetes and dementia, DKK 500.000, Alzheimer-forskningsfonden

20. Affiliated Researcher **Marina Romero-Ramos**: Progressive monocytic response in Parkinson's Disease, a role for the peripheral immune system in the disease, DKK 2.880.000, FSS

21. Affiliated Researcher **Marina Romero-Ramos**: Single cell RNA analysis of the myeloid response in brain during alpha-synuclein neurodegeneration, DKK 600.000, AUFF NOVA

22. Lector **Alberto Scoma** (Thomas Boesen as co-applicant): Nova, DKK 2.5 million, Aarhus University Research Foundation

23. Postdoc **Azadeh Shahsavar**: NNF glycin-transporter grant, DKK 1.65 million, Novo Nordisk Foundation

24. PhD Student **Katia Soud**: Unraveling of mechanisms of dopaminergic memory retention by the locus coeruleus-hippocampus circuit, DKK 200.000, Augustinus foundation

25. PhD Student **Katia Soud**: PhD fellowship, DKK 1.5 million, Graduate School of Health

26. PhD Student Karen **Marie Juul Sørensen**: 1/3 PhD Stipend: VPS10P domain receptors in astrocyte-synapse interaction and memory formation, DKK 550.000, Graduate School of Health Sciences, Aarhus University

27. Postdoc **Pernille Thomasen**: Travel stipend: SorCS2 i motor neuron udvikling og regeneration, DKK 10.000, Lundbeck Foundation

28. Postdoc **Pernille Thomasen**: Travel Stipend: SorCS2 as a regulator of axonal outgrowth – an in vivo study of mouse embryos, DKK 5.000, Biokemisk Forening

Invited Talks

JANUARY
Marco Capogna: *The necessity of GABAergic neuron diversity for brain function*, Lundbeck AS, Denmark

Poul Nissen: *Words of eulogy* , Thomas A. Steitz Scientific Symposium, Department of Molecular Biophysics and Biochemistry, Yale University & Memorial

Poul Nissen: *Structure and Dynamics of Active Transporters*, University of Gothenburg, Sweden

Tomonori Takeuchi: *Selective memory retention and updating schematic knowledge*, Mechanism of Brain and Mind-workshop, Rusutsu Resort Hotel, Hokkaido, Japan

FEBRUARY
Tomonori Takeuchi: *Selective memory retention and updating schematic knowledge*, Biomedicine seminar, Aarhus University, Denmark

Tomonori Takeuchi: *Selective memory retention and updating schematic knowledge*, Kavli Institute for Systems Neuroscience, NTNU, Trondheim, Norway

MARCH
Marco Capogna: *Role of amygdala inhibitory synaptic plasticity on fear memory*, PROMEMO SAB meeting, Copenhagen, Denmark

Mark Denham: *Identifying disease susceptibility variances in Parkinson's disease with hIPSCs*, Biomedicine seminar series, Aarhus University, Denmark

Poul Henning Jensen: *Project update, IMPRIND IMI consortium meeting, Lisbon*, Portugal

Joseph Lyons: *Structural Insights into the Function and Auto-Regulation of Lipid Flippases*, Biophysical Society Annual Meeting, Baltimore, USA

Poul Nissen: *Work Package 3 overview*, RAMP meeting, Hamburg, Germany

Poul Nissen: *Structure and dynamics of biomembranes and membrane proteins*, European XFEL Workshop, Hamburg, Germany

Tomonori Takeuchi: *Novelty-induced memory boost and plasticity-related proteins*, PROMEMO SAB meeting, Copenhagen, Denmark

Tomonori Takeuchi: *Dopaminergic memory boost by two distinct novelty systems*, The 9th Federation of the Asian and Oceanian Physiological Societies Congress, Kobe, Japan

Keisuke Yonehara: *Visual motion processing from retina to visual cortical areas in mice*, Nagoya University, Japan

APRIL
Marco Capogna: *GABAergic neuron diversity in the amygdala and hippocampus*, Max Planck Institute for Brain Research, Frankfurt, Germany

Samuel Hjorth-Jensen: *Proton pumping in sarco/endoplasmic reticulum Ca2+-ATPase studied by neutron crystallography*, British Crystallographic Association Spring Meeting 2019, University of Nottingham, UK

Keisuke Yonehara: V*isual motion processing from retina to visual cortical areas in mice*, Grad School of Veterinary Medicine, University of Tokyo, Japan

Keisuke Yonehara: V*isual motion processing from retina to visual cortical areas in mice*, Grad School of Medicine, University of Tokyo, Japan

Keisuke Yonehara: *Retinal circuit mechanisms for visual motion detection*, The 3rd sensory system study initiative symposium, Tokyo, Japan

MAY
Mark Denham: I*dentifying disease susceptibility variances in Parkinson's disease with hIPSCs*, Neuroscience Day, Aarhus University, Denmark

Poul Nissen: *Structure and Dynamics of Membrane Transport Proteins*, Instruct Biennial Structural Biology Conference 2019 Madrid, Spain

Poul Nissen: *Structural biology with neutrons – how and why?*, Swedish Neutron Week, Stockholm, Sweden

Christine Juul Fælled Nielsen: *A yeast-based assay for drug discovery on the H1069Q Wilson mutation*, Wilson Symposium, Aarhus, Denmark

Poul Nissen: *Structural studies by single-particle Cryo-EM*, Wilson Symposium, Aarhus, Denmark

JUNE
Marco Capogna: *Neuron diversity for brain functions*, Department of Biomedicine, Aarhus University

Mark Denham: *Identifying Genetic Risk Variants for Parkinson's Disease*, mini-symposium, Aarhus University, Denmark

Poul Nissen: *Structure and dynamics of membrane transporters*, Centre for Structural Systems Biology, Hamburg, Germany

Poul Nissen: *Structure and Mechanism of P4-ATPase Lipid Flippases*, Gordon Research Conference on Mechanisms of Membrane Transport, New Hampshire, USA

Anders Nykjær: *Regulated sortilin shedding balances synaptic input and mood states*, Neuroseminar, University of Copenhagen, Denmark

Tomonori Takeuchi: *Dopaminergic memory modulation by two distinct novelty systems*, Spring Hippocampal conference, Taormina, Sicily, Italy

Tomonori Takeuchi: *Memory consolidation, dopamine and two distinct novelty systems*, Impromptu Institute Seminar, Université de Bordeaux, Bordeaux Cedex, France

Keisuke Yonehara: *Visual motion processing from retina to visual cortical areas in mice*, NERF, KU Leuven, Belgium

JULY

Marco Capogna: S*leep Modulates the Spiking of Nitric Oxide Synthase Expressing*, Gordon Research Conference, Inhibition in the CNS, Maine, USA

Poul Henning Jensen: *Manipulating neuronal calcium homeostasis protect against*, FENS regional meeting, Beograd, Serbia

Poul Nissen: *Structure and Dynamics of Membrane Transport Proteins*, PSB Symposium on Macromolecules in Action, Grenoble, France

Anne von Philipsborn: *Multifunctional wing control in fly song and flight*, Kavli Workshop on Neural Circuits and Behavior of Drosophila, Crete, Greece

Keisuke Yonehara: *Visual motion processing from retina to visual cortical areas in mice*, Kyushu University, Fukuoka, Japan

Keisuke Yonehara: *Visual motion processing from retina to visual cortical areas in mice*, OIST, Okinawa, Japan

AUGUST

Poul Henning Jensen: *Mechanisms of synucleinopathies, 8th Scandinavian Conference*, Amyloid Diseases and Amyloid Mechanisms (ADAM 8), Lund, Sweden

Poul Henning Jensen: *Moderator for workshop on cellular models of synucleinopathies*, Synuclein Meeting 2019, Porto, Portugal

Katherine Gill: *Investigating Molecular pathways in GBA-associated Parkinson's disease,* BrainStem symposium, Lund University, Sweden

Poul Nissen: *Structure and function of membrane ATPases, FEBS advanced course in Biochemistry of Membrane Proteins – Structure*, Trafficking, Regulation, Budapest, Hungary

SEPTEMBER

Marco Capogna: *Neuron type diversity in the human cerebral cortex, Aarhus University Hospital*, Denmark

Mark Denham: I*dentifying Genetic Risk Variants for Parkinson's Disease, EMBL conference*, Barcelona, Spain

Poul Nissen: *Nordic EMBL Partnership*, 10th Annual Network Meeting of the Nordic EMBL Partnership for Translational Medicine, Barcelona, Spain

Poul Nissen: *Structural biology of membrane proteins, now and ahead*, VILLUM Center for Bioanalytical Sciences, University of Southern Denmark

Poul Nissen: *Structure and Dynamics of Active Transporters*, Institute for Research in Biomedicine, IRB Barcelona, Spain

Anne von Philipsborn: *Female song is modulated by seminal fluid*, EDRC (European Drosophila Research Conference) workshop: How context and internal state shape behaviour, Lausanne, Switzerland

Tomonori Takeuchi: *Memory consolidation, dopamine and two distinct novelty systems*, IDG/McGovern Institute for Brain Research, Peking University, Beijing, China

Keisuke Yonehara: *Visual motion processing from retina to visual cortical areas in mice*, European Retina Meeting 2019, Helsinki, Finland

Keisuke Yonehara: *Visual motion processing in mice: circuits and disease*, EMBL Barcelona, Spain

OCTOBER

Poul Henning Jensen: *Novel Alpha-synuclein Pathology in Parkinson's Disease and MSA and New Tools for Investigating Alpha-synuclein Aggregates*, The Michael J Fox Foundation, New York, USA

Poul Nissen: *Electron microscopy studies of membrane proteins – towards structures of ATP1A3*, The 8th ATP1A3 Symposium in Disease, Reykjavik, Iceland

Tomonori Takeuchi: *Memory consolidation, dopamine and two distinct novelty systems*, Central Pharmaceutical Research Institute, Osaka, Japan
Tomonori Takeuchi: Selective memory retention and updating schematic knowledge, Systems Neuroscience Seminar, Tohoku University, Sendai, Japan

Keisuke Yonehara: *Structure, function, and development of visual circuits, EMBL Heidelberg*, Germany

November

Mark Denham: *Identifying Genetic Risk Variants for Parkinson's Disease*, DANDRITE LUF site visit, Denmark

Mark Denham: *Identifying Genetic Risk Variants for Parkinson's Disease*, Parkinsonforeningen, Denmark

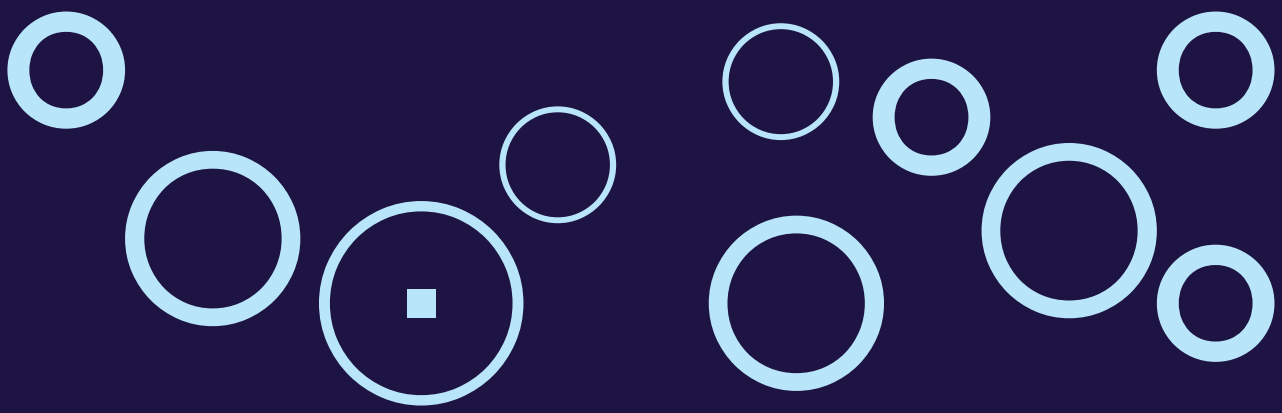
Poul Nissen: *Structure and Dynamics of Membrane Transport Proteins*, Folkeuniversitet, Lemvig, Denmark

Anders Nykjær: *Balancing synaptic strength and emotional state*, Site-visiit Niigata University, Aarhus University, Denmark

Keisuke Yonehara: *Spatially asymmetric excitation supports mammalian retinal motion sensitivity*, National Institute of Physiology, Okazaki, Japan
Keisuke Yonehara: Visual motion processing: cell types, circuits, and disease, Keio University, Tokyo, Japan

Keisuke Yonehara: *Eleventh year in Europe – Quest for basic principles underlying neuronal circuits,* University of Tokyo, Japan

05 Publications



Publications

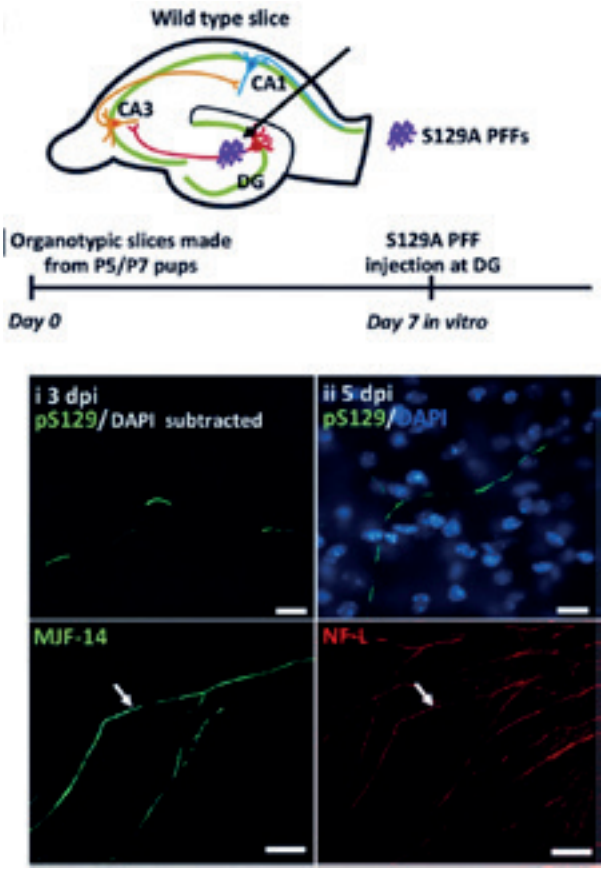
METHODOLOGY ARTICLE Open Access

Organotypic slice culture model demonstrates inter-neuronal spreading of alpha-synuclein aggregates

Abstract

Keywords: Alpha-synuclein, Prion-like spreading, Serine-129 phosphorylation, Organotypic slices

Introduction



(14)

1 **Asad, J, Richner, M**, **Vægter, CB**, Nyengaard, JR & **Jensen, PH** 2019, 'Gene Transfer in Rodent Nervous Tissue Following Hindlimb Intramuscular Delivery of Recombinant Adeno-Associated Virus Serotypes AAV2/6, AAV2/8, and AAV2/9', *Neuroscience Insights*, Vol. 14, no. November-December, p. 1-12.

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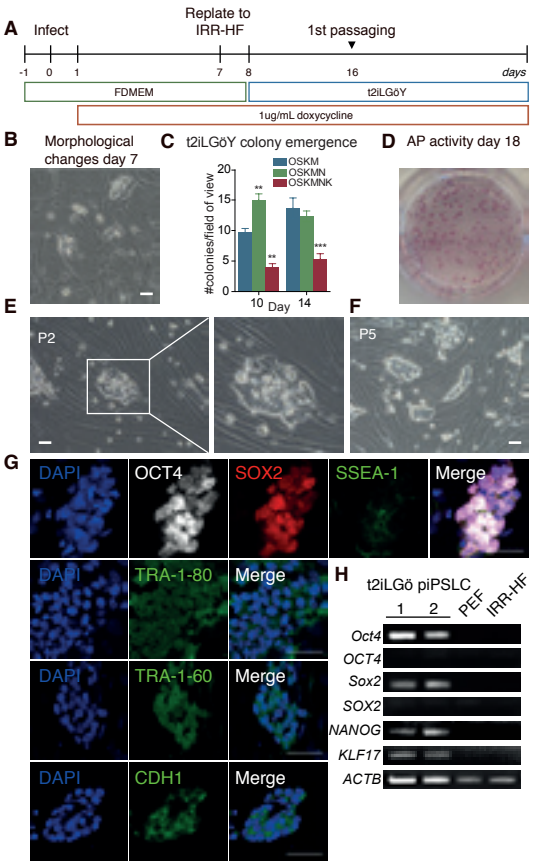

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Spatiotemporally Asymmetric Excitation Supports Mammalian Retinal Motion Sensitivity

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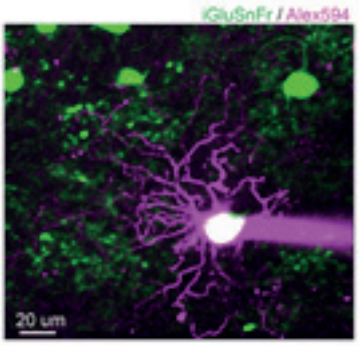
SUMMARY

The detection of visual motion is a fundamental function of the visual system. How motion speed and direction are computed together at the cellular level, however, remains largely unknown. Here, we suggest a circuit mechanism by which excitatory inputs to direction-selective ganglion cells in the mouse retina become sensitive to the motion speed and direction of image motion. Electrophysiological, imaging, and connectomic analyses provide evidence that the dendrites of ON direction-selective cells receive spatially offset and asymmetrically filtered glutamatergic inputs along motion-preference axis from asymmetrically wired bipolar and amacrine cell types with distinct release dynamics. A computational model shows that, with this spatiotemporal structure, the input amplitude becomes sensitive to speed and direction by a preferred direction enhancement mechanism. Our results highlight the role of an excitatory mechanism in retinal motion computation by which feature selectivity emerges from non-selective inputs.

glutamate imaging from the inner plexiform layer or calcium imaging from bipolar cell axon terminals have indeed suggested that individual glutamatergic synaptic inputs are not directionally tuned [10–12], favoring the hypothesis of voltage-clamping effect (but see [13]).

DS cells in the optic lobe of the fly [14] or the visual cortical layer 4 of the mouse [15] use preferred-direction enhancement mechanisms in which untuned excitatory synaptic inputs are summated in a specific spatiotemporal manner to create tuned outputs as described by the Hassenstein-Reichardt model (Figure 1A) [14, 16]. The minimum requirement of the model is two presynaptic units with distinct delays converging to a postsynaptic cell. If the temporal difference by which two units separated by a distance (Δ*S*) are activated by a moving stimulus matches the difference in their delays (Δ*T*), the postsynaptic cell could effectively summate inputs, resulting in direction selectivity not in the time integral (Figure 1A, ii) but in the peak amplitude of input (Figure 1A, i). The Hassenstein-Reichardt model predicts a speed optimum; motion that is too slow or too fast should degrade the summation. A similar mechanism is also predicted to operate at connections between bipolar cells and starburst cell processes in the mouse retina: this may support the centrifugal direction selectivity of starburst cell processes [17–19] (but see [20]). However, spatiotemporal structure in the excitatory inputs to DS cells, which may support retinal motion sensitivity, remains to be explored.



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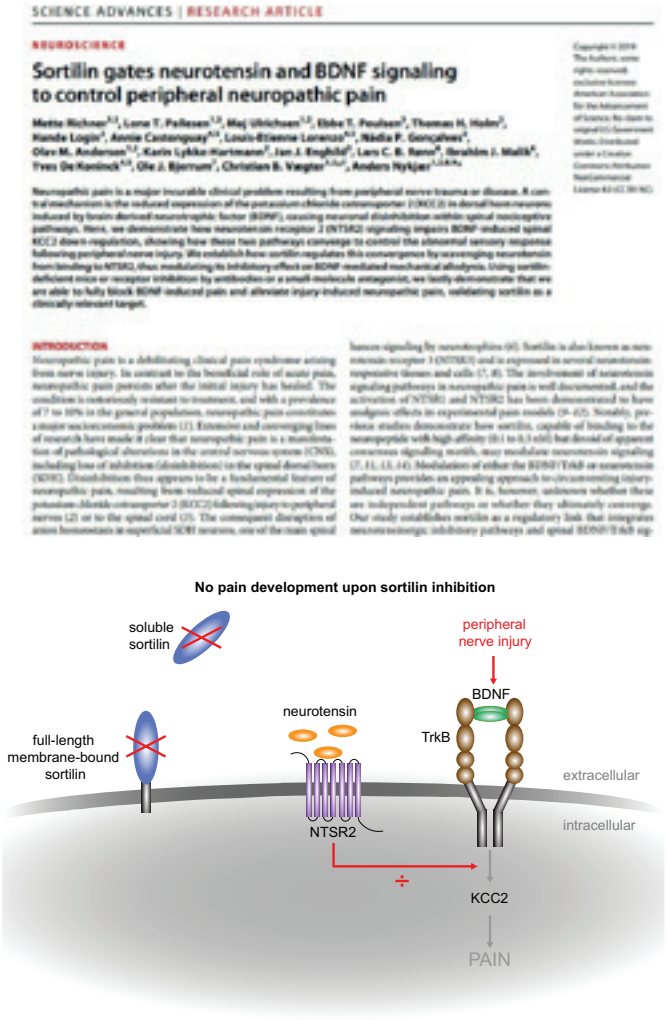

SCIENCE ADVANCES | RESEARCH ARTICLE

NEUROSCIENCE

Sortilin gates neurotensin and BDNF signaling to control peripheral neuropathic pain

Mette Richner[1,2], Lone T. Pallesen[1,2], Maj Ulrichsen[1,2], Ebbe T. Poulsen[3], Thomas H. Holm[3], Henrik Login[4], Annie Castonguay[4,5], Louis-Etienne Lorenzo[4,5], Nádia P. Gonçalves[1], Olav M. Andersen[1,2], Karin Lykke-Hartmann[3], Jan J. Enghild[3], Lars C. B. Renn[6], Ibrahim J. Malik[6], Yves De Koninck[4,5], Ole J. Bjerrum[7], Christian B. Vægter[1,2,*], Anders Nykjær[1,2,8,*]

Neuropathic pain is a major incurable clinical problem resulting from peripheral nerve trauma or disease. A central mechanism is the reduced expression of the potassium chloride cotransporter (KCC2) in dorsal horn neurons induced by brain-derived neurotrophic factor (BDNF), causing neuronal disinhibition within spinal nociceptive pathways. Here, we demonstrate how neurotensin receptor 2 (NTSR2) signaling impairs BDNF-induced spinal KCC2 down-regulation, showing how these two pathways converge to control the abnormal sensory response following peripheral nerve injury. We establish how sortilin regulates this convergence by scavenging neurotensin from binding to NTSR2, thus modulating its inhibitory effect on BDNF-mediated mechanical allodynia. Using sortilin-deficient mice or receptor inhibition by antibodies or a small-molecule antagonist, we identify and demonstrate that we are able to fully block BDNF-induced pain and alleviate injury-induced neuropathic pain, validating sortilin as a clinically relevant target.

INTRODUCTION

Neuropathic pain is a debilitating clinical pain syndrome arising from nerve injury. In contrast to the beneficial role of acute pain, neuropathic pain persists after the initial injury has healed. The condition is notoriously resistant to treatment, and with a prevalence of 7 to 10% in the general population, neuropathic pain constitutes a major socioeconomic problem (1). Extensive and converging lines of research have made it clear that neuropathic pain is a manifestation of pathological alterations in the central nervous system (CNS), including loss of inhibition (disinhibition) in the spinal dorsal horn (SDH). Disinhibition thus appears to be a fundamental feature of neuropathic pain, resulting from reduced spinal expression of the potassium chloride cotransporter 2 (KCC2) following injury to peripheral nerves (2) or to the spinal cord (3). The consequent disruption of axon homeostasis in superficial SDH neurons, one of the main spinal

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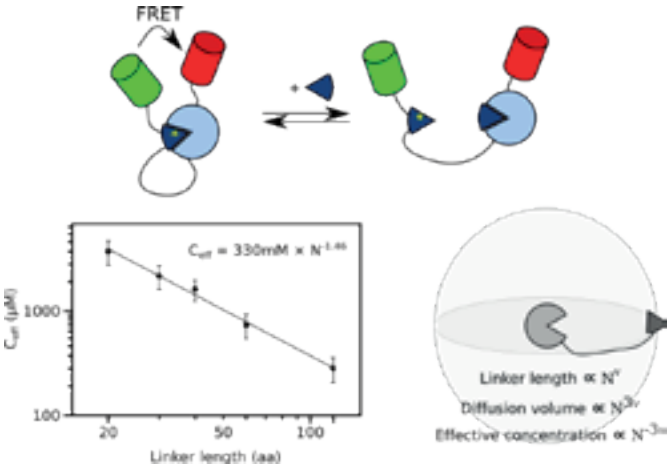

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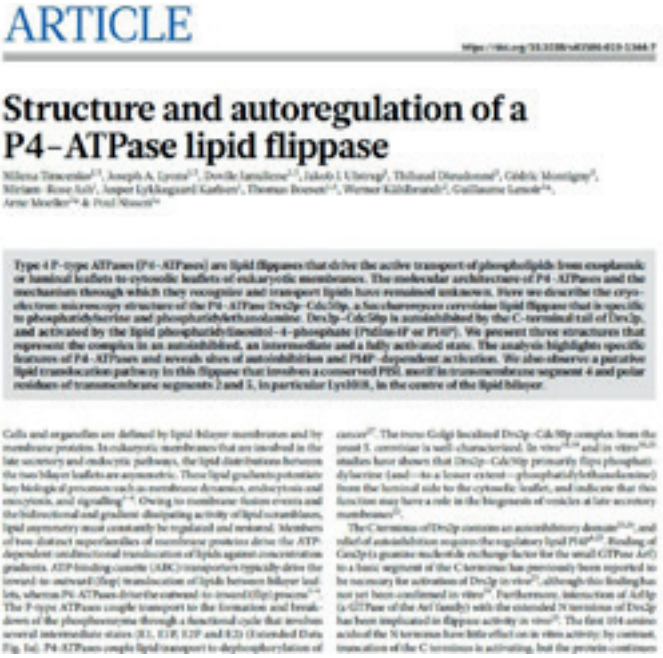
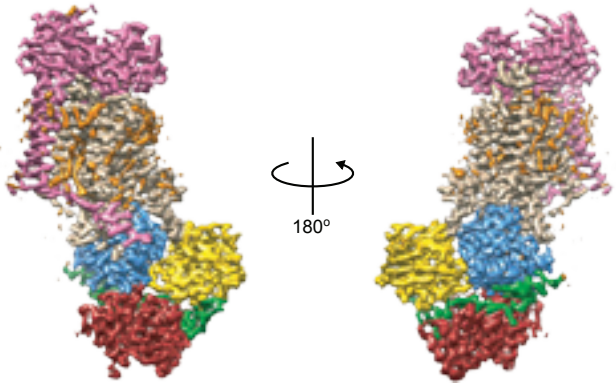


ARTICLE

Structure and autoregulation of a P4-ATPase lipid flippase



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PhD Dissertations 2019

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