2015

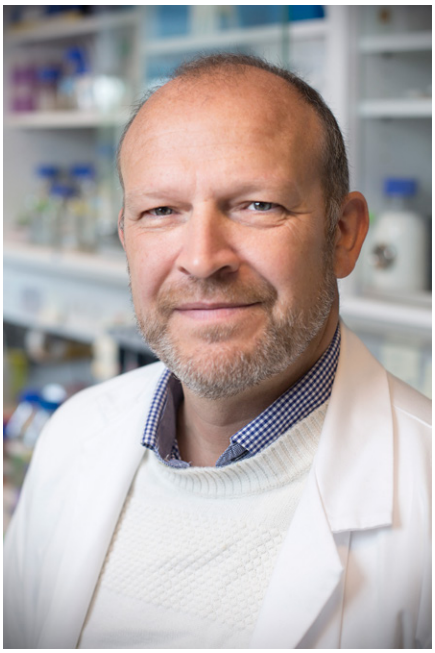
DANDRITE ANNUAL REPORT

AARHUS UNIVERSITY

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

Words from the Director

We are proud to present the 2015 annual report - our third from DANDRITE. We hope that as a reader you will share our enthusiasm of a unique and thriving research environment building up in Danish and international neuroscience. We are also proud to present the powerful impact of the Nordic EMBL Partnership for Molecular Medicine and EMBL model, which define our mission and ambition through the activity of young group leaders with original research and bold aims that challenge our current understanding of brain and neuroscience.



2015 was a very busy year with group leader searches concluding, large research programs initiating, infrastructures unfolding, and many new collaborations. Group leaders Keisuke Yonehara and Sadegh Nabavi began their activities in January and July 2015, respectively, and were both further supported by prestigious ERC starting grants. More than 30 new students and staff members were added during 2015 reaching a total number of 100 students and staff members. DANDRITE hosted more than 45 visiting speakers and researchers and organized several meetings including our first retreat. Among prominent speakers that were included in AU lecture series, we hosted Prof. Raimund Dutzler from the University of Zürich, Dr. Jason Chin from the MRC-LMB in Cambridge, and Prof. Michael Rosbash from Brandeis University. DANDRITE was also the host of the 2015 meeting of the Nordic Molecular Medicine Network Meeting of the Nordic EMBL Partnership, gathering more than 170 attendees from the four Nordic nodes (DANDRITE-Aarhus, MIMS-Umeå, NCMM-Oslo, and FIMM-Helsinki). The meeting had very well-attended open keynote lectures by the EMBL Group Leader Carsten Sachse and EMBL head of Cell Biology and Biophysics Unit Jan Ellenberg and Prof. Gary Lewin of the Max-Delbrück Center on new frontiers in electron microscopy, quantitative high-throughput imaging, and physiological models of the mole rat, respectively. This great event was preceded by a very successful first Young Investigator Meeting featuring talks on science and career opportunities.

Research infrastructure was also a big part of our 2015 activities. DANDRITE took a leading role in defining an electron microscopy infrastructure in Denmark resulting in the EMBION proposal, which was included on the Danish roadmap. DANDRITE also co-organized the Danish ESFRI-INSTRUCT membership and sponsored the EU-OpenScreen ESFRI initiative in Denmark. Together with assoc. prof. Morten S. Nielsen, Department of Biomedicine, we initiated the organization of imaging facilities at Aarhus University in coordination with the Danish Bioimaging and ESFRI-EuroBioImaging networks. We also took the first steps to form our large, interactive workshop for advanced electrophysiology, optogenetics and in vivo imaging, called the JOINT, and thanks to the large equipment investments made by our group leaders with their wish to form a creative and synergistic environment.

Much more has happened and developed beyond our expectations, and the following pages will present a selection of the many DANDRITE activities – please take a moment to read and enjoy!

With my warmest regards,

Poul Nissen, director and core group Leader.

01

Events, Visitors, Guests & Seminars

Events, Visitors, Guests & Seminars

DECEMBER

Erasmus Student **Akhil Pukkattu John**, University of Skövde, Sweden, hosted by Philipsborn Group (6 months)

DANDRITE Topical Seminar, Postdoc **Trine Kvist Carlino**, University of Copenhagen, hosted by Nissen Group (Hanne Poulsen) (Two days), *Structure-based discovery of antagonists for GluN3-containing NMDA receptors*

NOVEMBER

DANDRITE Topical Seminar, Reader **Jarema Malicki**, University of Sheffield, United Kingdom, hosted by Nykjær Group (Olav Andersen) (One day), *Cilium - a Unique Subcellular Compartment that Functions as a Signal Detection Device*

DANDRITE Topical Seminar, Microscopy Specialist **Jutta Bulkescher**, University of Copenhagen, Denmark, hosted by Nissen Group & Yonehara Group (One day), *The Danish BioImaging Network/Imaging resources at the CPR and Danstem Imaging Platform*

OCTOBER

DANDRITE Topical Seminar, Postdoc **Laura Marchetti,** The Scuola Normale Superiore, Pisa, Italy, hosted by Nykjær Group (Two days), *Single molecule imaging and tracking of neurotrophins and their receptors in living neuronal cells*

JOINT DANDRITE & KJELDGAARD LECTURE, Group Leader **Francesco Roselli**, Ulm University, Deutschland, hosted by Philipsborn Group & Yonehara Group (Two days), *Controlling neuronal and non-neuronal components of net-works in neurodegeneration*

Guest **Abhijith Yenikekaluva**, University of Bordeaux, France, hosted by Kvitsiani Group (One day)

Professor **Michael Rosbash**, Brandeis University, USA, hosted by Nissen Group & Philipsborn Group (One day), *The Circadian Clock and Sleep in Flies: Molecules, Neurons and Circuits*

DANDRITE LECTURE Associate professor **Sarang Dalal**, University of Konstanz, Germany, hosted by Nissen Group & Yonehara Group (One day), *Associating Neuromagnetic Oscillations with Perception and Awareness*

Research Engineer **Zoltan Raics**, Friedrich Miescher Institute, Germany, hosted by Yonehara Group (Three days)

Guest Student **Cristina Batlle Carreras**, Institute of Biotechnology and Biomedicine of Barcelona, SERHS, Spain, hosted by Jensen group (4 months)

EVENT: Establishment of The JOINT - Electrophysiology, Optogenetics, and Behavior Workshop, Aarhus University, building 1182, room 319

SEPTEMBER

Erasmus Student **Quentin Rott**, Université de Strasbourg, France, hosted by Philipsborn Group (6 weeks)

Visiting Senior Engineer **Rajeevkumar Raveendran Nair**, Norwegian University of Science and Technology, hosted by Yonehara Group (Three days)

EVENT: 6th Annual Network Meeting of the Nordic EMBL Partnership for Molecular Medicine (Three days), Aarhus University & Moesgaard Museum

EVENT: Young Investigator Meeting in connection to the 6th Annual Network Meeting of the Nordic EMBL Partnership for Molecular Medicine (Two days), Aarhus University

INVITED LECTURE at the 6th Annual Network Meeting, EMBL head of Cell Biology and Biophysics Unit **Jan Ellenberg**, European Molecular Biology Laboratory (EMBL) Heidelberg, Germany, hosted by DANDRITE (Three days), *Systems biology of human cell division using light microscopy*

INVITED LECTURE at the 6th Annual Network Meeting, Group Leader **Carsten Sachse**, European Molecular Biology Laboratory (EMBL) Heidelberg, Germany, hosted by DANDRITE (Three days), *Structural basis and mechanism of the selective autophagy receptor p62/SQSTM1*

KEYNOTE LECTURE at the 6th Annual Network Meeting, Group Leader **Gary Lewin**, European Molecular Biology Laboratory (EMBL) Heidelberg, Germany, hosted by DANDRITE (Three days), *Extremity as the mother of metabolic invention: The neurobiology of the naked mole-rat*

Visiting PhD Student **Jaroslava Geleticova**, Palacky University Olomouc, Czech Republic, hosted by Nissen Group (3 month)

PhD Student **Saida Said,** Aarhus University, hosted by Nissen Group (1 month)

AUGUST

DANDRITE LECTURE, Associate Research Scientist **Oliver B. Clarke**, Columbia University, NY, USA, hosted by Nissen Group (Two days), *Structural studies of ryanodine receptor gating by cryoelectron microscopy*

Erasmus Student **Yanan Zhang,** University of Konstanz, Germany, hosted by Philipsborn Group (6 weeks)

DANDRITE Topical Seminar, Associate professor **Kim Furbo Rewitz**, University of Copenhagen, hosted by Philipsborn Group (One day), *A genome-wide in vivo RNAi screen in Drosophila identifies regulators of cholesterol-dependent steroid production*

DANDRITE Topical Seminar, Group Leader **Andreas Neef**, Max Planck Institute for Dynamics and Self-Organization, hosted by Nissen Group (Three days), *The biophysical basis of the high-bandwidth information encoding in cortical neurons*

Erasmus Student **Jennet Baltayeva**, IMC Fachhochschule Krems, Austria, hosted by Denham Group (6 months)

JULY

DANDRITE Topical Seminar, PhD student **Katja Reinhard**, University of Tübingen, Germany, hosted by Yonehara Group (Two days), *Illuminance-dependent variability in response properties of retinal ganglion cells*

JUNE

DANDRITE Topical Seminar, Senior Lecturer **Kouichi Hasegawa**, Kyoto University, Japan, hosted by Denham Group (Two days), *Understanding and Controlling Human Pluripotent Stem Cell Renewal and Differentiation with Materials*

MAY

EVENT: DANDRITE retreat 2015 (Two days), hosted by DANDRITE at Sandbjerg Manor, Denmark

KEY NOTE LECTURE at DANDRITE retreat 2015, Professor **Hannes Lohi**, University of Helsinki, Finland (Two days), *Canine neurological and neuropsychiatric conditions*

INVITED LECTURE at DANDRITE retreat, Associate professor **Morten Schallburg Nielsen**, Aarhus University (Two days), *Receptor Trafficking in the BloodBrain Barrier*

Crash course at DANDRITE retreat 2015, Associate Professor **Rikard Blunck**, University of Montréal, Canada, hosted by Nissen Group (5 months), *Voltage clamp electrophysiology & flurometry*

JOINT DANDRITE & KJELDGAARD SEMINAR, Professor **Jason Chin**, MRC Laboratory of Molecular Biology, Cambridge, UK, hosted by DANDRITE (Three days), *Reprogramming the Genetic Code*

APRIL

EVENT: Festival of Research 2015 at Navitas hosted by Aarhus University (One day)

EVENT: Neuroscience Day 2015 - Bridging Basic and Clinical Research, hosted by NeuroCampus, Aarhus University (One day)

Joint iNANO & DANDRITE Topical Seminar, Guest Researcher **Arek Kulczyk**, Harvard Medical School, hosted by Nissen Group (Arne Möller) (One month), *Single-molecule studies of the replisome structure and dynamics*

JOINT DANDRITE & INANO LECTURE, Editor **Anne Fœrch Nielsen**, The EMBO Journal, hosted by Nissen Group (Two days), *Behind the Scenes of Scientific Publishing*

DANDRITE Topical Seminar, Visiting Student **Irene Caprara**, University of Rome, Italy, hosted by Kvitsiani Group (Three days), *Attention and motor planning in the frontal cortex of primates*

DANDRITE Topical Seminar, Visiting Student **Dmytro Cherepakha**, National Technical University of Ukraine, Ukraine, hosted by Kvitsiani Group (Three days), *Visualization of result of calcium influx through low-voltage activated calcium channels*

MARCH

BRIAN CLARK BIOTECH LECTURE, Professor **Michael Sundstrøm**, Karolinska University Hospital and Karolinska Instituttet, Sweden, hosted by Nissen Group (One day), *Open Access Research Tools (Proteins, Structures, Probes and Assays) for Pre-Clinical Target Validation*

DANDRITE Topical Seminar, Visiting Student **Aimilia Lydia Kalafateli**, Utrecht University, Netherlands, Kvitsiani Group (Three days), *Pharmacological Inactivations of the mPFC in Rats Performing a Reward-Related Delayed Spatial Alternation Task and mTOR signaling in genetic mouse models for distinct autism-related behavioral domains*

DANDRITE Topical Seminar, Visiting Student **Juliane Martin**, Dresden University of Technology, Germany, Kvitsiani Group (Three days), *Interleukin-1 Regulates Adult Hippocampal Neurogenesis and Spatial Learning Independently*


Molecular machines governing exocytosis of synaptic vesicles
Molecular machines governing exocytosis of synaptic vesicles

FEBRUARY

EVENT: DANDRITE encounters 2015 (One day), hosted by DANDRITE at Aarhus University.

Erasmus Student **Leire Recalde Percaz,** University of Barcelona, Spain, hosted by Denham Group (5 months)

DANDRITE Topical Seminar, PhD Student **Ana Oliveira**, University of Coimbra, Portugal, Yonehara Group (Three days), *Regulation of the Ras pathway by neurofibromin in dendritic spines*

DANDRITE Topical Seminar, PhD Student **Szilard Sajgo**, National Institutes of Health (NIH), USA, hosted by Yonehara Group (Three days), *Transcriptional codes that drive neuronal diversity*

Visiting Student **Inês Costa Laranjeira**, Universidade do Porto, hosted by Nykjær Group (Christian Vægter) (4 months)

DANDRITE Topical Seminar, PhD Student **Nami Ohmura**, Tottori University Graduate School of Medical Sciences, Japan, hosted by Yonehara Group (Three days), *A novel electroporation technique to analyze fine neuronal structures in postnatal mammalian brain*

JANUARY

DANDRITE Topical Seminar, PhD Student **Emilienne Repak**, Institut Pasteur, France, hosted by Yonehara Group (Three days), *Optical control of NMDA-receptors with a diffusible photoswitch*

JOINT DANDRITE & MEMBRANES LECTURE, Professor **Raimund Dutzler**, University of Zurich, hosted by Nissen Group (Three days), *Structural basis for Ca2+-activation in TMEM16 chloride channels and lipid scramblases*

Visiting Researcher **Fabia Febbraro**, Karolinska Institute, Stockholm, Sweden, hosted by Denham Group (12 months)

Visiting Researcher **Amir Tayaranian Marvian**, University of Teheran, Iran, hosted by Jensen group (6 months)

Visiting Student **Andreas Brydenfelt Wulff**, Aarhus University, hosted by Philipsborn Group ,(3 months)

Visiting Researcher **Matthijs Wopke de Boer**, VU University Amsterdam, the Netherlands, hosted by Philipsborn Group, (5 months)


BANDRITE

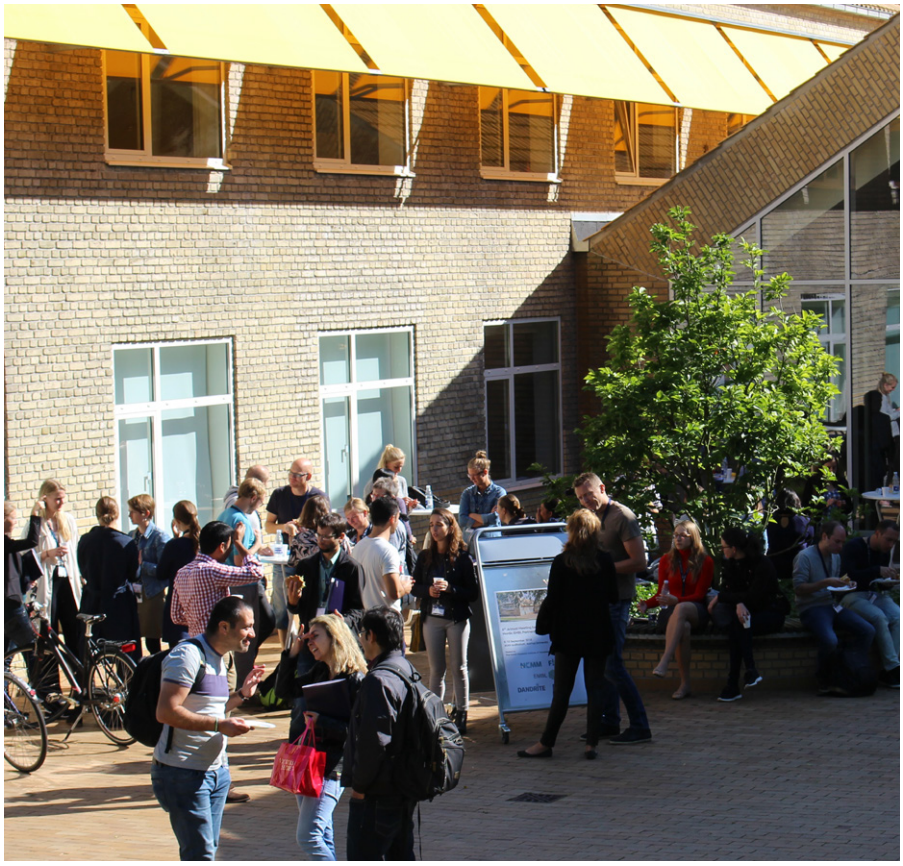
6th Annual Network Meeting of the Nordic EMBL Partnership for Molecular Medicine

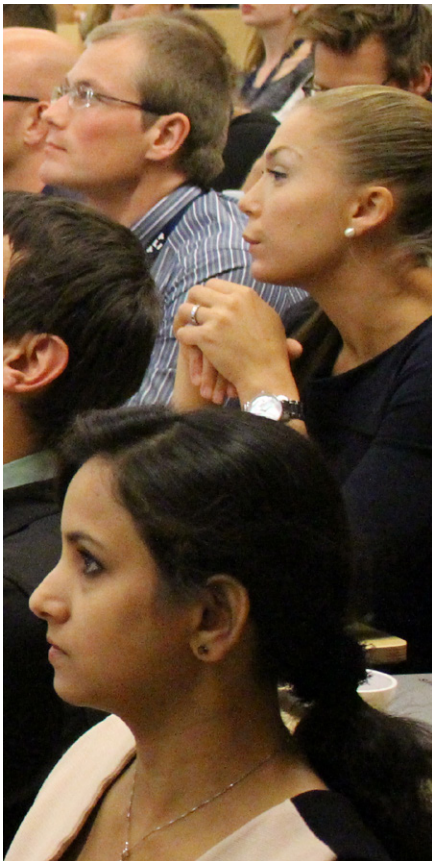
In 2015 the 6th Annual Network Meeting of the Nordic EMBL Partnership for Molecular Medicine was hosted by DANDRITE, taking place from 8.-10. September, where new and established researchers from EMBL and its four Nordic partnership nodes convened at Aarhus University to focus on scientific interaction, scientific synthesis and collaborative openings between the partnership nodes. 170 participants gathered in the campus setting, with a half-day detour to the auditorium of the inspiring Moesgaard Museum of human evolution and culture.

The programme included dedicated presentations by the new Group leaders at the 4 nodes, short topical presentations by postdocs or PhD students with a newly published paper (or soon to be), a scientific "speed dating" session, and a poster session. The invited speakers for the meeting included keynote speaker Gary Lewin from the Max-Delbrück Center for Molecular Medicine in Berlin, and invited speakers EMBL head of Cell Biology and Biophysics Unit Jan Ellenberg and Group Leader Carsten Sachse both from EMBL Heidelberg. During the meeting the partnership nodes also arranged their first common Science&Art contest, where participants were invited to submit their artistic pictures, graphics, or illustrations, to be displayed and compete during the annual meeting to be included in the calendar for 2016, where the 3 best images from each node was presented.

Young Investigator Meeting of the Nordic EMBL Partnership

As the tradition invites, the Young Investigators (postdocs and graduate students) from the Nordic EMBL Partnership for Molecular Medicine met for a pre-meeting from 7.-8. September, before the annual meeting started. Volunteers from the Young Investigator forum of the partnership (Postdoc Florian Hilbers, postdoc Joseph Lyons, Postdoc Alessia Arduin, PhD student Jakob Ulstrup and PhD student Sigrid Thirup Larsen) put together a great programme, where they had their own time for networking, socializing, and career discussions.






EMBL


Genome sequence and tools
DANDRITE

Retreat

DANDRITE's staff and students had their first retreat 20.-21. May 2015 at the university conference venue Sandbjerg Manor in southern Denmark, a very beautiful old manor from the 16th century placed right down to the water and surrounded by forest. During 2 days with summer weather, we had great opportunities for knowledge exchange of lab activities, methods, ideas and fun, which will nurture our interactions and collaborations ahead. With over 70 people attending, it was also a good opportunity to get to know many of the new faces at DANDRITE, which had been recruited by the new Group leaders during the year. The programme included invited keynote speaker Hannes Lohi from the University of Helsinki, invited crash courses from DANDRITE staff members on specific relevant topics for everyone, elevator talks by postdocs and graduate students, as well as a poster session. The retreat also focused on social interactions, facilitated by team building challenges of various topics and a festive dinner in the evening.

Symposium "DANDRITE encounters"

In February 2015 DANDRITE invited everyone interested to attend the newly established annual afternoon symposium "DANDRITE encounters", where the Group leaders at DANDRITE presented their research. The audience was fellow scientists and prospective students from Aarhus University, and a group of invited American neuroscience students from Danish Institute for Study Abroad also attended. The presentations focused on the Group leaders' field of expertise, techniques, collaboration possibilities, and available student projects. The aim was to spark interest and curiosity about the new activities and possibilities in neuroscience at Aarhus University offered by DANDRITE.

Festival of Research

DANDRITE attended the Festival of Research 2015, where the theme was "Technologies of the Future". Group leaders and students from DANDRITE communicated their research to the general Danish public, including demonstration of stem cells that are used in brain research of diseases such as Parkinsons, and behavioural studies of the fruit fly, which is used as model organism for studies of the brain and nervous system.

Establishment of "The JOINT - The Electrophysiology, Optogenetics & Behavior Workshop"

The JOINT is an interactive workshop facility at Dept. Biomedicine, Aarhus University, for neuro-scientific research using electrophysiology, optogenetics, and behavioral experimental set ups. The JOINT workshop facility houses state-of-the-art equipment, such as electrophysiological/imaging set ups allowing simultaneous imaging/multiple whole-cell recordings in vitro and in behaving rodents, as well as optogenetics and behavioural set ups. Further expansions such as installing high-end 2-photon laser scanning microscopy for in vitro and behaving studies have been envisioned. The facility is organized as a large shared room with electrophysiology rig spaces, a separate slicing area, and neighboring animal storage and test rooms. Furthermore a separate High-end Optogeneitcs Workshop is available for instrumentation and design of holographic imaging and stimulation experiments.
At the JOINT interested users can get information how to fabricate electrodes, build optrode microdrives for chronic implantation and print 3D objects. The JOINT welcomes and facilitates new collaborations. The JOINT workshop facility has a number of in-house main users, with which collaborations can be agreed, and the facility may also be open to individuals after agreement. The establishment and daily management of the JOINT has been facilitated by DANDRITE.

Read more about The JOINT here: **www.dandrite.au.dk/the-joint/**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RESEARCH
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02 Research Activities

Nissen Group

Structural and Functional Studies of Membrane Transporters in Brain

Professor
Poul Nissen

The Nissen lab investigates molecular mechanisms of membrane transport processes and biomembrane structures in brain. Activities are mainly focused on protein crystallography, electron microscopy and biochemistry, and include also collaborative studies on small-angle X-ray scattering, molecular dynamics simulations, electrophysiology, cell biology, animal models, and clinical research. Main subjects of research focus on P-type ATPases (ion pumps and lipid flippases) and Na+ dependent amino acid/neurotransmitter transporters, and include also structure-based drug discovery and protein engineering.

The P-type ATPase ion pumps and lipid flippases consume some 40-80% of ATP in the brain and maintain constantly the vital lipid distributions and ion gradients that power secondary transporters, and control of e.g. cell volume and morphology, ion homeostasis, and pH. Na,K-ATPases also interact with the extracellular matrix, and control for example potassium in the narrow, interstitial space of brain. Structures of Na,K-ATPase with cardiotonic steroids were published showing substantial differences between bufadienolide and cardenolide steroids and how they bind cooperatively with potassium and magnesium, respectively. New insights into the transport pathway and regulation of copper transporting Cu+-ATPases were obtained through an interdisciplinary. program on copper binding and activity. First results were presented for detailed, structural studies of Ca2+-ATPases using an X-ray Free Electron Laser (XFEL) that will pave the road for future, possibly time-resolved studies of membrane transport and signaling.

Early stage lead discovery and development research is being conducted through structural and biochemical approaches on RSK/MSK kinases and developing new classes of allosteric inhibitors. The dysfunctional Cu+-ATPase ATP7B in Wilson's disease is being targeted through a research program in collaboration with the Danish Wilson's Disease Center at Aarhus University Hospital.

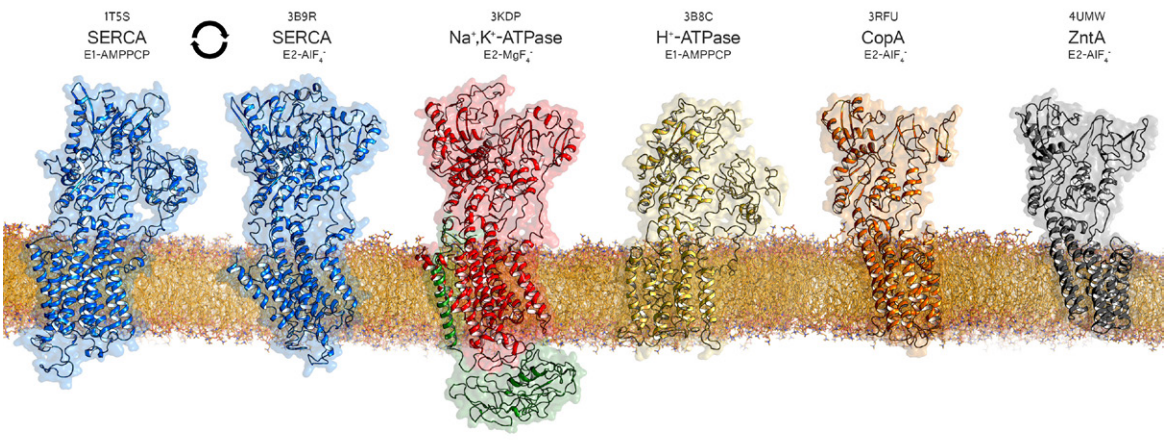


Fig.1. A collection of P-type ATPase structures characterized by the Poul Nissen lab. Figure by Oleg Sitsel.

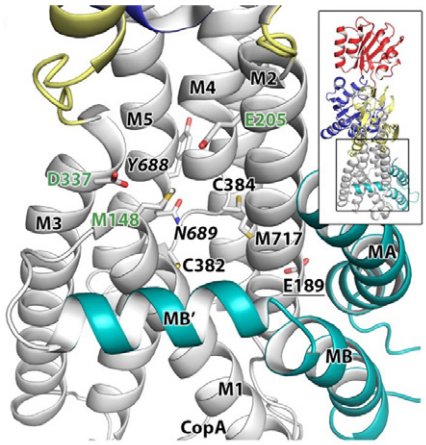


Fig. 2. The metal ion entry in the copper pump. Close-up of the entry pathway of CopA. From Sitsel O et al. (2015) Biochemistry, 54 (37), pp 5673–5683

Selected publications 2015

Laursen M, Gregersen JL, Yatime L, Nissen P, Fedosova NU (2015) Structures and characterization of digoxin- and bufalin-bound Na+,K+-ATPase compared with the ouabain-bound complex. *Proc Natl Acad Sci U S A* 112, 1755-60

Mattle D, Zhang L, Sitsel O, Pedersen LT, Moncelli MR, Tadini-Buoninsegni F, Gourdon P, Rees DC, Nissen P, Meloni G (2015) A Sulfur-Based Transport Pathway in Cu+-ATPases. *EMBO Rep* 16, 728-40

Bublitz M, Nass K, Drachmann ND, Markvardsen AJ, Gutmann MJ, Barends TR, Mattle D, Shoeman RL, Doak RB, Boutet S, Messerschmidt M, Seibert MM, Williams GJ, Foucar L, Reinhard L, Sitsel O, Gregersen JL, Clausen JD, Boesen T, Gotfryd K, Wang KT, Olesen C, Møller JV, Nissen P, Schlichting I (2015). Structural studies of P-type ATPase-ligand complexes using an X-ray free-electron laser. *IUCrJ* 2, 409-20

Personnel List Nissen Group

Postdoc **Anne-Marie Lund Winther**
Postdoc **Azadeh Shahsavar**
Postdoc **Alessia Arduin**
Postdoc **Jacob Lauwring Andersen**
Postdoc **Ingrid Dach**
Postdoc **Joseph Lyons**
Postdoc **Antoni Kowalski**
Postdoc **Magnus Kjærgaard**
PhD Student **Dorota Focht**
PhD Student **Aljona Kotsubei**
PhD Student **Milena Laban**
PhD Student **Sigrid Thirup Larsen**
PhD Student **Caroline Marie Teresa Neumann**
PhD Student **Lars Sørensen**
PhD Student **Marlene Uglebjerg Sørensen**
PhD Student **Jakob Ulstrup**
PhD Student **Mateusz Dyla**
PhD Student **Peter Aasted Paulsen**
Research Assistant **Rasmus Pihl**
Research Assistant **Oleg Sitsel**
Laboratory Technician **Lotte Thue Pedersen**
Laboratory Technician **Anna Marie Nielsen**
Academic employee **Christine J. F. Nielsen**
Senior Advisor **Claus Olesen**
Communications Assistant**, PA Karen Bech**
Professor **Poul Nissen**

NISSEN GROUP (ARNE MÖLLER)
Postdoc **Dovile Januliene**
Team Leader **Arne Möller**

NISSEN GROUP (HANNE POULSEN)
Postdoc **Florian Hilbers**
Team Leader **Hanne Poulsen**

NISSEN GROUP (THOMAS BOESEN)
Affiliated Researcher **Thomas Boesen**

Jensen Group

Neurodegenerative Disease

Professor
Poul Henning Jensen

The Jensen group is interested in understanding how alpha-synuclein contributes to the neurodegenerative processes in Parkinson's disease, Lewy body dementia and multiple systems atrophy, which are hallmarked by the development of intracellular aggregates of alpha-synuclein. This is investigated in studies of alpha-synuclein aggregates in vitro, in cell models, transgenic animals and human tissue and involves development of new aggregate selective tools.

Based on unbiased screens for misfolded alpha-synuclein effect on 1) proteins interactions and 2) gene expression, 3) kinases regulating cellular alpha-synuclein function and cellular toxicity and antibodies recognizing misfolded alpha-synuclein we collaborative widely with experts on in vivo modelling, human brain tissue, biophysics and proteomics.

The aim is to decipher how cells respond to misfolded alpha-synuclein with respect to cytotoxic and protective mechanisms that can be targeted by therapy. This involves proteostatic mechanisms like autophagy, unconventional secretion, prion-like intercellular propagation and susceptible homeostatic cellular mechanisms being offset by alpha-synuclein aggregates.

The main focus in 2015 was to establish the in-vivo mouse model of prion-like alpha-synuclein spreading, identify novel kinases regulating alpha-synuclein functions and clarify the impact of alpha-synuclein on neuronal calcium homeostasis.

Future studies will expand these focus areas and based on our mechanistic insight to conduct preclinical in vivo experiments for disease modifying strategies.

Selected publications 2015

Betzer C, Movius AJ, Shi M , Zhang J, Jensen PH (2015) Identification of Alpha-Synuclein Interacting Synaptosomal Proteins. *Plos One.* 10(2):e0116473

Stewart T, Sossi V, Aasly JO, Wszolek ZK, Uitti RJ, Hasegawa K, Yokoyama T, Zabetian CP, Leverenz JB, Stoessl A, Wang Y, Ginghina C, Liu C, Cain KC, Auinger P, Kang U, Jensen PH, Shi M, Zhang J. (2015) Phosphorylated -synuclein in Parkinson's disease: correlation depends on disease severity. *Acta Neuropathol Commun.* 3:7

Personnel List Jensen Group

Postdoc **Cristine Betzer**
Postdoc **Nelson Ferreira**
Postdoc **Louise Berkhoudt Lassen**
PhD Student **Michael Aagaard Andersen**
PhD Student **Rikke Hahn Kofoed**
PhD Student **Lasse Reimer**
PhD Student **Jin Zheng**
Laboratory Technician **Jette Bank Lauridsen**
Professor **Poul Henning Jensen**

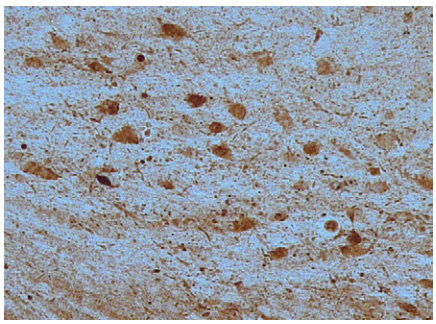


Fig. 1. Accumulation of misfolded alpha-synuclein in brain tissue from transgenic mouse using novel conformational specific antibody. Neurodegenerative model studied by post doc Louise B. Lassen who also made the photo.

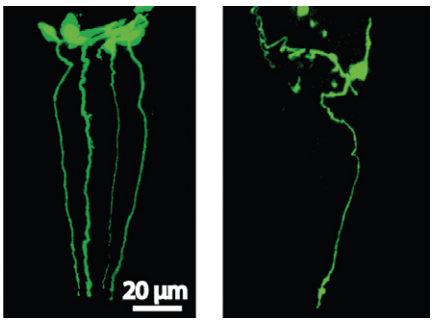


Fig. 2. Fluorescent alpha-synuclein expressing neurons in C. elegans. Photo by Cristine Betzer

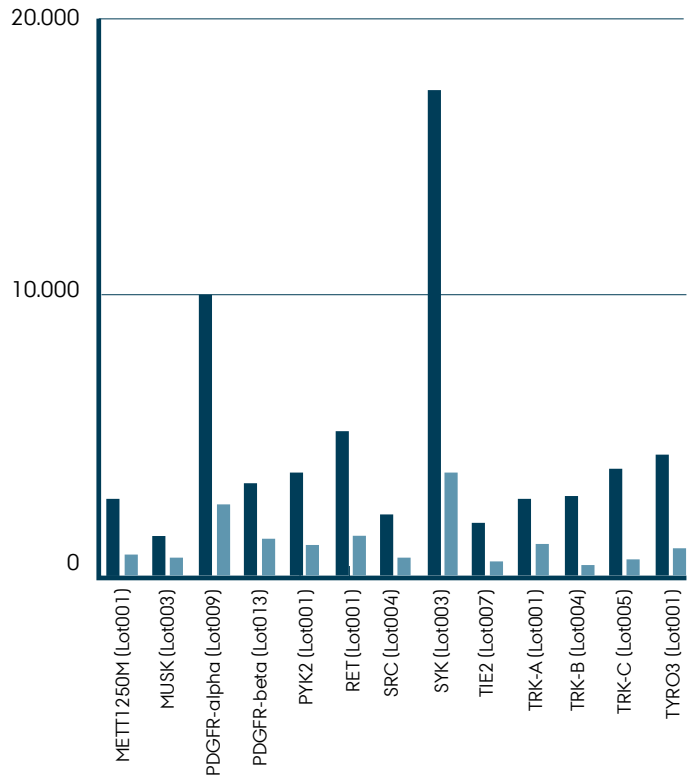
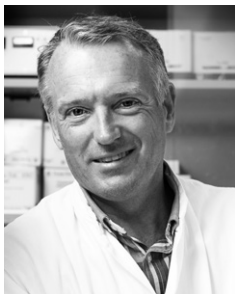


Fig. 3. Part of data from a kinase screen on synuclein pathophysiology. Data by Lasse Reimer

Nykjær Group

Receptor Biology



Professor
Anders Nykjær

Research activities of the Nykjær Group 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, predominate in neurons but are also present in specialized cell types outside the nervous system.

The receptors are considered multifunctional as they bind a vast number of ligands including neurotrophins and their receptors, neuropeptides, Alzheimer's precursor protein, progranulin, ApoE, and VLDL and engage in cellular trafficking and signaling dependent on the cellular context (reviewed in Trends in Neurosci 2012; Nat Rev Neurosci 2008).

Using a broad repertoire of molecular, cellular and genetic tools combined with transgenic mouse models, we aim to unravel the function of the receptor family in health and disease and to evaluate the potential of the receptors as drug targets. Studies by us have demonstrated that sortilin receptors are critical regulators of neuronal survival, differentiation, functionality, and cholesterol metabolism, and that their dysfunction may cause diseases both inside and outside the nervous system (e.g. Nature 2004, Nat Neurosci 2007 and 2011, Neuron 2011 and 2014, Cell Metab 2010, and Mol. Psych 2016). Accordingly human genetic association studies and gene targeting in mice have linked dysfunction of the receptors to schizophrenia, bipolar disorders, ADHD, Alzheimer's Disease, fronto-temporal-lobar dementia, cardiovascular disease, and type 2 diabetes.

Competences include confocal and two-photon imaging, development of transgenic mouse and zebrafish models, neuronal culture systems, *in situ* hybridization, behavioral phenotyping of mice, electrophysiology, animal models of peripheral neuropathies, *in vivo* gene transfer, and *in utero* electroporation. Optogenetics is currently being established in the laboratory.

Our current work focuses on three main topics. In one research program, we characterize the roles of sortilin and SorCS2 in neurotrophin signaling, synaptic plasticity, and mental disorders. In a second approach, we investigate how Vps10p-domain receptors expressed in satellite cells and neurons of the peripheral nervous system engage in neuropathic pain and diabetic neuropathies. Finally, we study the structure and transcriptional regulation of the Alzheimer's disease gene SORL1, and characterize the physiological function of the encoding receptor SorLA in development of the eye.

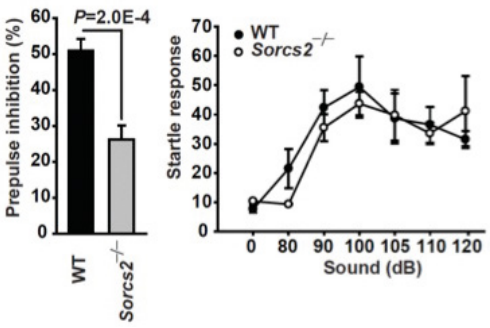


Fig. 1. Prepulse inhibition. Normal startle response but attenuated prepulse inhibition in SorCS2 knockout mice. Illustration from Glerup, Bolcho et al. Mol Psych 2016 (in press)

Fig. 2. Brain filling. Micro-CT scan of mouse cerebrovasculature. Illustration by Hande Login (unpublished data

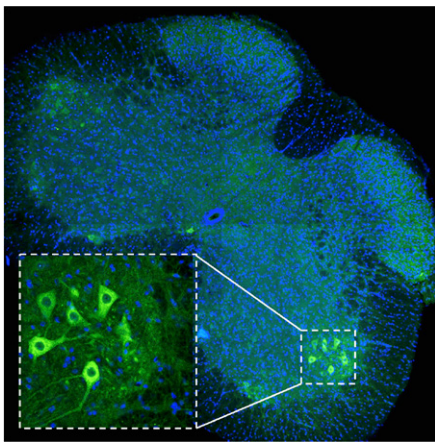


Fig. 3. SorCS2 expression. Expression of SorCS2 in motor neurons in murine spinal cord. Illustration by Pernille Thomasen (unpublished data)

Selected publications 2015

Coulson EJ, Andersen OM (2015) The A-B-C for SORting APP. *J Neurochem.*135(1):1-3

La Rosa LR, Perrone L, Nielsen MS, Calissano P, Andersen OM, Matrone C (2015) Y682G Mutation of Amyloid Precursor Protein Promotes Endo-Lysosomal Dysfunction by Disrupting APP-SorLA Interaction. *Front Cell Neurosci.* 9:109

Buttenschøn HN, Demontis D, Kaas M, Elfving B, Mølgaard S, Gustafsen C, Kaerlev L, Petersen CM, Børglum AD, Mors O, Glerup S (2015) Increased serum levels of sortilin are associated with depression and correlated with BDNF and VEGF. *Transl Psychiatry.* 5:e677

Mehmedbasic A, Christensen SK, Nilsson J, Rüetschi U, Gustafsen C, Poulsen AS, Rasmussen RW, Fjorback AN, Larson G, Andersen OM (2015) SorLA complement-type repeat domains protect the amyloid precursor protein against processing. *J Biol Chem.* 90(6):3359-76

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Denham Group

Stem Cells

Group Leader
Mark Denham

Our laboratory is interested in understanding how the nervous system develops and the processes involved in neural degeneration. We use human embryonic stem (ES) cells and induced pluripotent stem (iPS) cells to study the signalling pathways required for their differentiation into precise neural progenitor cell types. In particular, our group is interested in the specification of mesencephalic dopaminergic neurons, the major cell type affected in Parkinson's disease (PD).

The objective is to develop in vitro models for studying neural development and disease processes and to identify early cellular changes that underlie the onset of neurodegenerative diseases such as Parkinson's disease. Furthermore, we are also interested in how different neural progenitor subtypes survive and function after transplantation in an adult rodent brain. Our overall goals are to develop potential new treatment strategies for neurodegenerative disorders.

Major Achievements and Future Plans
Our group has successfully reprgrammed fibroblast cells, from a diverse range of familial Parkinsonian patients, into iPS cells. These cell lines encompass most of the known familial PD mutations, which will be used for our subsequent experiments. Using a state of the art genetic engineering technique CRISPR, to facilitate homologous recombination, we are currently in the process of correcting the mutations in the iPS cells. The reprogrammed cell lines along with the isogenic controls serve as a valuable tool for examining the pathway that each mutation perturbs. To investigate this we are currently subjecting neurons derived from the iPS cell lines to various stress conditions to identify cellular mechanisms associated with PD and we intend to use next generation sequencing to analyse these disease states.

Additionally our group is investigating the processes involved in regulating a stem cell's fate down defined neural lineages and the factors involved in self-renewal versus differentiation. Uncovering these mechanisms will lead to improved in vitro differentiation protocols that can be used to generate new human cellular models of neural development and neurodegenerative diseases.

Selected publications 2015

Denham M, Hasagawi K, Zhang D, Hough S, Menheniott T, Leung J, Rollo B, Newgreen D, Pera M, Dottori M (2015) Identification of a multipotent neural progenitors that give rise to the central and peripheral nervous system. *Stem Cells*

Arenas E, Denham M, Villaescusa JC (2015) How to make a midbrain dopaminergic neuron. *Development*

Rollo BN, Zhang D, Stamp LA, Menheniott TR, Stathopoulos L, Denham M, Dottori M, King SK, Hutson JM, Newgreen DF (2015) Enteric Neural Cells from Hirschsprung Disease Patients form Ganglia in Autologous Aneuronal Colon Muscle Tissue. *Cellular and Molecular Gastroenterology and Hepatology*

Personnel List Denham Group

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Laboratory Technician **Susanne Hvolbøl Buchholdt**
Group Leader **Mark Denham**

NEURAL DIFFERENTIATION

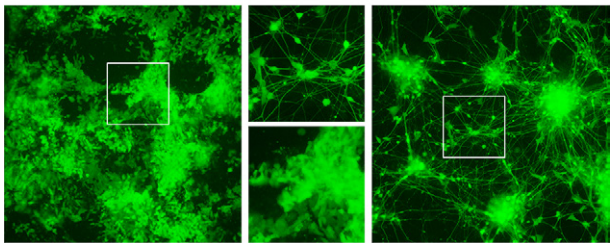

Fig. 1. Neuronal differentiation of human Parkinson's diseased induced pluripotent stem cells. Left image shows cells under control condition and right image shows cells after differentiation. Image by: Mark Denham.

REPROGRAMMING

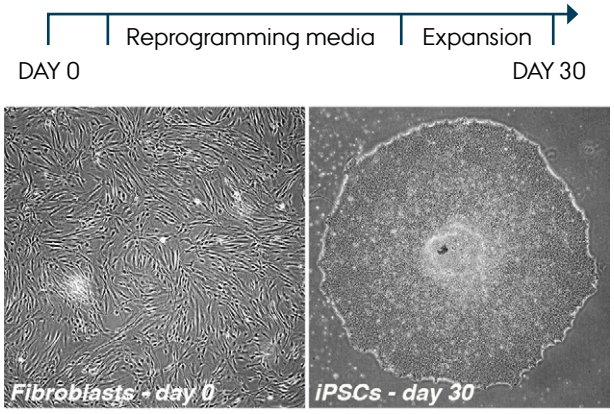

Fig. 2. 30 day sendai virus reprogramming protocol used to convert human patient fibroblast cells into induced pluripotent stem cells in defined media. Left image shows human fibroblast cells prior to reprogramming and right image shows a successfully reprogrammed cell colony. Image by: Susanne Buchholdt.

Kvitsiani Group

Neuronal Circuits and Molecular Basis of Effort Based Decision-making

Group Leader
Duda Kvitsiani

We investigate genetic and neural circuit mechanisms underlying decision-making in flies, rodents and humans. The aim of our research is to build predictive and quantitative models of behavior that will help us uncover mechanistic insights into decision-making. The methods we use include molecular genetics, psychophysics, behavioral electrophysiology and optogenetics.

Our research is centered on a simple basic question: How do animals and humans choose better options? Our aim is to understand biology of decisions on multiple levels: from molecules to neural circuits. In fruit flies we are undertaking genetic screens to discover single molecules controlling foraging decisions and using extracellular electrophysiology and cell-type specific recordings in rodents we plan to identify circuit level computations in mouse brain that represent value.

We also aim to see how humans make simple decisions and if behavioral diversity within a population can be explained by genetic make-up of individuals. Overall our long-term goal is to use ecology inspired quantitative behavioral models to guide and sharpen scientific questions.

Last year we have set up trial based single fly reward foraging assay to study how animal's choices are affected by reward history. In our behavioral set up animals are freely walking back and forth in a linear arena (Fig.1a). At the end of the arena (light blue rectangle) animals experience reward delivered by optogenetic activation of sugar receptors on the labellum of the fly in a probabilistic fashion. This allows us to estimate how reward history affects fly's decision to enter the rewarded area (light blue rectangle). We have used linear model to show that contribution of past rewards (Choice Triggered Reward Average) to current choices has exponential decay. Currently we are undertaking RNAi based genetic screen to discover molecules that control reward foraging decisions.

Key publications

Stockinger P*, Kvitsiani D*, Rotkopf S, Tirian L, Dickson BJ (2005) Neural circuitry that governs Drosophila male courtship behaviour *Cell.* 121(5):664-6. * These authors contributed equally

Taniguchi H, He M, Wu P, Kim S, Paik R, Sugino K, Kvitsiani D, Fu Y, Lu J, Lin Y, Miyoshi G, Shima Y, Fishell G, Nelson SB, Huang ZJ (2011) A resource of Cre driver lines for genetic targeting of GABAergic neurons in cerebral cortex. *Neuron.* 71(6):995-1013

Kvitsiani D, Ranade S, Hangya B, Taniguchi H, Huan Kepecs A (2012) Distinct behavioural correlates and network interactions of two interneuron classes in mouse prefrontal cortex. *Nature.* 498(7454):363-6

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Research assistant **Sophie Seidenbecher**
Group Leader **Duda Kvitsiani**

Similar to flies we have established dynamic foraging task in mice where water rewards are given to animals either from left or right port in a probabilistic fashion (Fig. 2a). Over the course of the behavioral session reward probabilities change and we monitor how animals adjust their choices to changing probabilities. Using the same analysis tools as in flies our initial results tell us that mice can quickly adapt their choices (within 3-4 trials) to changing probabilities (Fig. 2b). In further experiments we have used electrophysiological recordings from neurons in mouse Anterior Cingulate Cortex to reveal how cells in this area represent value of upcoming options.

In collaboration with Søren Keiding's lab at Chemistry Department at AU we decided to develop a method to generate movable focused beam of light through optical fibers in awake mouse brain. This method aims to overcome the limitation of all current optogenetic experiments where optical stimulation activates large number of neurons within one millisecond interval, something that has never been seen in unperturbed brain. Our plan is to mimic natural patterns of brain activity using light in behaving animals and ask fundamental questions about how neurons are causally linked to decision variables.

Finally we are planning to test human subject on virtual reward foraging tasks using computer games. Our goal is to see if genetic makeup of individuals can account for behavioral performance of our test subjects.

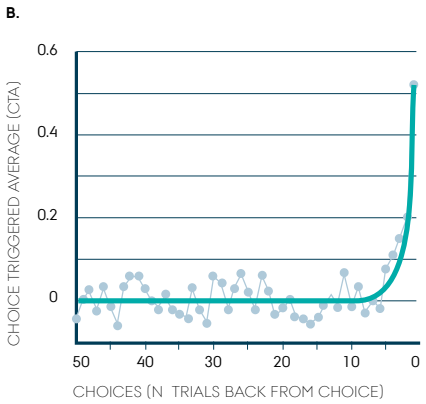
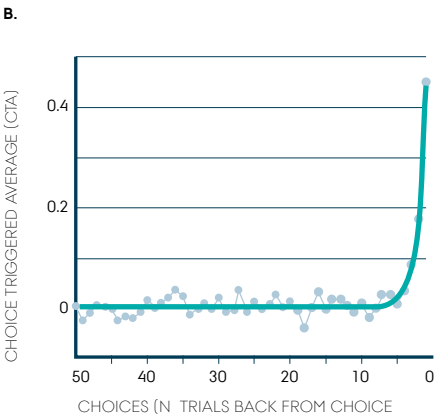


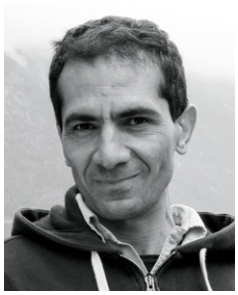
Fig.1 Reward foraging task in fruit flies. a). Behavioural arena for single fly foraging task consists of "reward zone" illustrated in light blue rectangles at the end of a linear track. Each of this zone can deliver probabilistic reward in the form of short light pulses that activate Channelrhodopsin molecule expressed on the sugar receptors of the fly's labellum. b) Fly's choices depend on reward history. X axis depicts trials back from a decision to deliver light stimulation by individual fly and Y axis contribution of the reward on that trial to animals choice.

Fig. 2. Dynamic Matching task in mice. a). Behavioral box for mice. Each box is equipped with ports that deliver water to thirsty mice on a probabilistic schedule. Task of the mouse is to figure out which port is associated with higher probabilities and choose that port over the others. b) The same analysis as for flies in Fig1 b). Here contribution of past rewards to choices is plotted.



Nabavi Group

Memory Formation and Consolidation at the Synaptic and Circuit Levels



Group Leader
Sadegh Nabavi

Memories are formed by changes in the strength of connections between neurons, a process known as synaptic plasticity. However our memories are not all created equally strong: Emotional experiences are well remembered while more trivial events are remembered poorly, if at all. Our lab investigates the neurobiological processes that contribute to such differences in the strength of our memories. One of our main interests is to understand how neuromodulators contribute to strength of a memory as all emotional experiences trigger the release of neuromodulators.

To this point fear memory provides an excellent case study since its underlying circuit is remarkably simple (by the brain's standard). What we know is that fear triggers the release of the neuromodulator norepinephrine, with ample evidences pointing out to its contribution to the memory strength. However, we don't know whether the neuromodulator is engaged during the formation of the memory or its consolidation. One of our goals for this year is to investigate this. To do so we will manipulate the release of the neuromodulator with high temporal and spatial resolution during different stages of the memory. To this end we will use optogentics (by expressing different variants of channelrhodopsin) to activate and suppress norepinephrine release in wild type and transgenic mice. In vitro and in vivo electrophysiology combined with behavioral studies are our means to detect and quantify changes in the synaptic as well as memory strength (Figure 1).

As mentioned above optogenetics is our method of choice for manipulating neuronal activity as it offers unprecedented temporal and spatial resolution. However, a major limitation in the use of optogenetics is the inability to activate two distinct neural populations independently. As the action spectra in Figure 2 shows red shifted variant of channelrhodopsin (ChrimsonR) displays partial activity at the peak response of the blue-shifted variant (oChIEF).

Our other goal for this year is to invest on developing a system which allows activation of the two variants independently.

Key publications

Nabavi S, Fox R, Proulx C D, Lin J Y, Tsien R Y, and Malinow R (2014) Engineering a memory with LTD and LTP. *Nature.* 511, 348-352

Nabavi S, Kessels H W, Alfonso S, Aow J, Fox R, Malinow R (2013) Metabotropic NMDA receptor function is required for NMDA receptor-dependent long-term depression. *Proc Natl Acad Sci U S A.* 110, 4027-4032

Kessels H W, Nabavi S, Malinow R (2013) Metabotropic NMDA receptor function is required for-amyloid-induced synaptic depression. *Proc Natl Acad Sci U S A.* 110, 4033-4038

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Research Assistant **Sherif Idriss**
Laboratory Technician **Anne-Katrine Vestergaard**
ERASMUS student **Agnieszka Gawda**
Group Leader **Sadegh Nabavi**

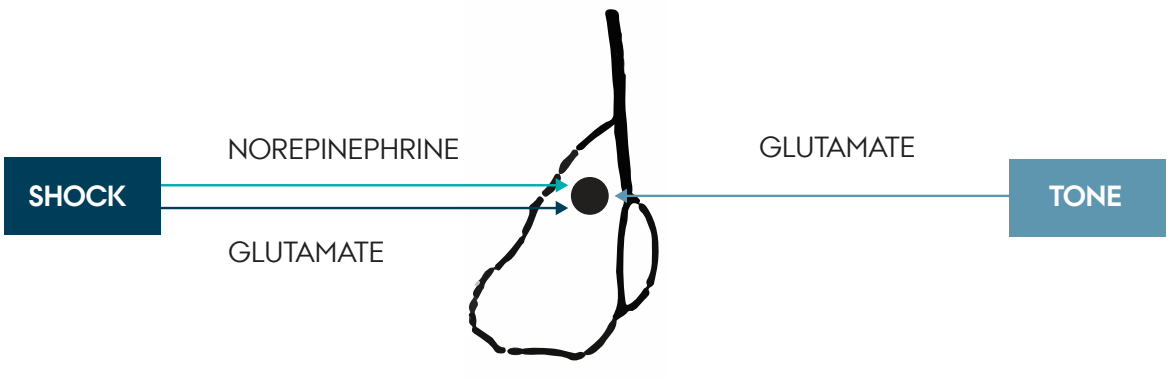

Fig. 1. Our proposed model for a fear memory circuit. The amygdala, the fear center of the brain, plays a central role in long-term memory consolidation. An essential part of this stress-hormone induced memory formation is the release of signals going out from the shock and from the tone inputs. A significant role is played by norepinephrine and the activation of noradrenergic receptors in the amygdala. Credit: Nathalie Krauth

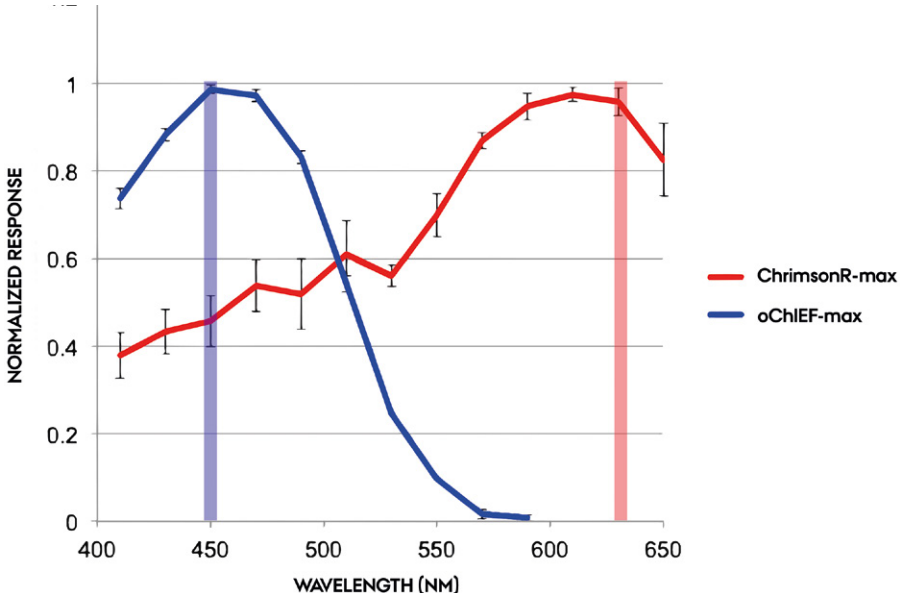

Fig. 2. Channelrhodopsin action spectra (HEK 293 cells). Blue-shifted channelrhodopsin oChIEF shows no detectable activity by exposure to red light. In contrast, blue light partially activates red-shifted ChrimsonR (see the red tail at wavelength 450nm). Credit: John Lin

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. 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 behaviours and behavioural sequences.

As a model behaviour, we use Drosophila male courtship. Previously, we identified neurons and subcircuits dedicated to generation of male courtship song, an elaborately patterned acoustic signal.

Currently, we investigate how already described and newly identified song neurons interconnect, signal to each other and control the sex-specific song pattern and related non- sex specific motor behaviours. We use audio recording as a highly sensitive, high throughput measurement for motor behaviour at millisecond timescale as well as genetic tools for neuronal activity imaging and optogenetics.

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

Flies use their wings for flight as well as for acoustic communication, e.g. the production of male courtship song. The two behaviours show different movement patterns, but rely both on wing muscle motor neurons. We aim at investigating cellular and genetic mechanisms of this multifunctionality.

With intersectional techniques (Split-GAL4), we gained genetic access to single classes of wing control muscle motor neurons and are assembling an anatomical and functional atlas of the wing motor neuropil. In collaboration with Michael Dickinson at the Caltech, US, we are investigating neuromuscular calcium activity patterns during different wing behaviours in intact behaving animals.

Key publications

Verzijden MN, Abbott JK, Philipsborn A, Loeschcke V (2015) Male Drosophila melanogaster learn to prefer an arbitrary trait associated with female mating status. *Current Zoology*, Vol. 61, No. 6, p. 1036-1042

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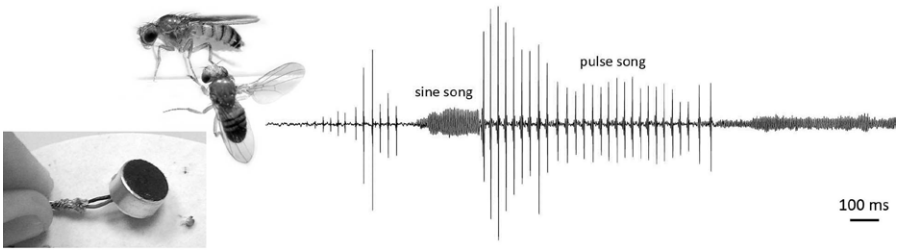


Fig.1. Drosophila courtship song. A male fly sings to a female by extending and vibrating one wing. Song is recorded by small microphones: the oscillogram shows sine and pulse bouts. Photo by Anne von Philipsborn.

Inhibitory signaling in motor control

Almost all behaviour 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 behaviour.

With cell specific RNAi mediated knockdown of genes involved in GABAergic signaling, we are elucidating the mechanisms of inhibitory control and its role in pattern generation.

Behavioural hierarchy and coordination

How do different behaviours interact and influence each other on a circuit level? During courtship, some behavioural elements are combined and others exclude each other. We discovered that dependent on the state of the animal and the behaviour it is engaged in, activation of neuronal classes has drastically different motor outcomes.

By using optogenetic circuit interrogation, we explore the neuronal and genetic basis of this behavioural hierarchy and coordination.

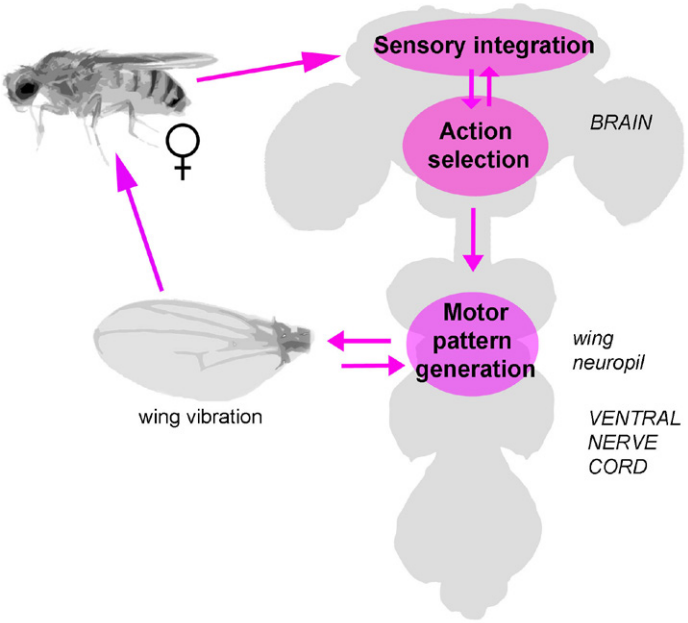


Fig. 2. Schematic of the neuronal circuits for courtship song. Illustration by Anne von Philipsborn.

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 can serve as a convenient and genetically accessible in vivo model for analyzing the effect of pathological mutations and protein modifications on neuronal physiology.

For example, we are currently collaborating with Hanne Poulsen at DANDRITE to study disease causing mutations of ATP1A3 in a Drosophila model system.

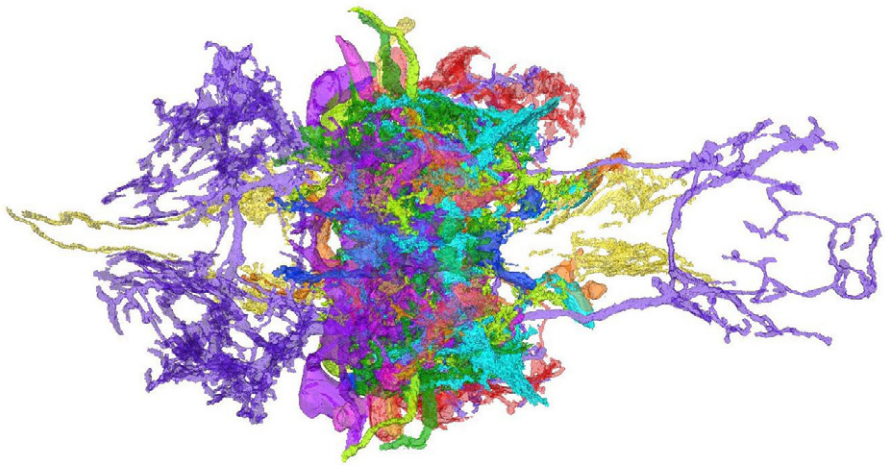
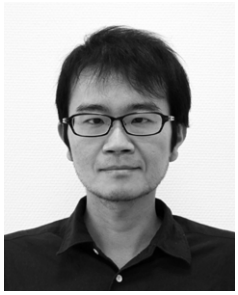


Fig. 3. Reconstruction of 3D arborization patterns of wing motor and premotor interneurons contributing to the patterning of wing movements. Illustration by Anne von Philipsborn.

Yonehara Group

Structure, Function and Development of Neural Circuits in Visual System



Group Leader
Keisuke Yonehara

The Yonehara group investigates the structure, function and development of neural circuits in the visual system. We are interested in the role of different cell types in neuronal circuits and the genetic and molecular mechanisms of how those circuits are assembled during development. The methods used include two-photon imaging, electrophysiology, optogenetics, trans-synaptic virus, genetic labeling, molecular biology, genomics and behavioral analysis.

Our research is based on the central hypothesis that functionally important neuronal circuit motifs are repeatedly used across various brain regions and species, and therefore identifying and understanding the structure and function of such motifs could give insights into the functional organisation of the brain. The mouse visual motion circuits, particularly the retina and its direct brain target the superior colliculus, provides us with an approachable substrate to work towards this goal, given its functionally and genetically well-defined cell types, multi-layered organization and tractable visually-guided behaviors. Two key organising principles that characterize not only the visual motion circuits of mammals and insects, but also other neuronal systems, are 1) parallel processing and 2) asymmetry of neuronal connectivity. We have focused, and will continue to focus, on questions relevant to these organising principles (Yonehara et al., Nature, 2011; Yonehara et al., Neuron, 2013).

The research plan is firstly to identify a computation performed by a given neuronal circuit comprising distinct cell types in the adult brain. Secondly, 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. Thirdly, to examine the role of individual cell types in transforming the sensory input into output innate behavior or eye movement control. Finally, to study the genetic mechanisms by which the elementary circuit motifs are assembled, and how its dysfunction can result in disease. Ultimately, by these experiments we aim to link genes to behavior. We will also develop new genetic and viral technologies that facilitate probing circuit function in healthy and diseased systems.

Dissecting the functional organization of mouse visual circuits

In the visual system, sensory processing begins in the retina where the visual scene is divided into 20 information channels before reaching the brain.

The superior colliculus is one of the main recipients of retinal output and mediates visually-guided behaviors. However, it remains unknown how visual signals from individual retinal ganglion cell types are processed by collicular neurons to achieve specific computations relevant to behaviors.

Using cell-type-labeled transgenic mouse lines, retrograde viral tracing, two-photon imaging, optogenetics and behavioral assays, we will characterize the response properties of individual classes of collicular neurons. Next we will examine which retinal ganglion cells project to specific collicular neurons and we will evaluate the degree of parallelism in retino-collicular circuits. Finally, we will dissect the role of collicular neurons in visually-guided behavior and investigate the developmental mechanism of circuit connectivity. This work will provide mechanistic insights into how our visual system works and develops.

Pathway-specific function of individual retinal ganglion cell types

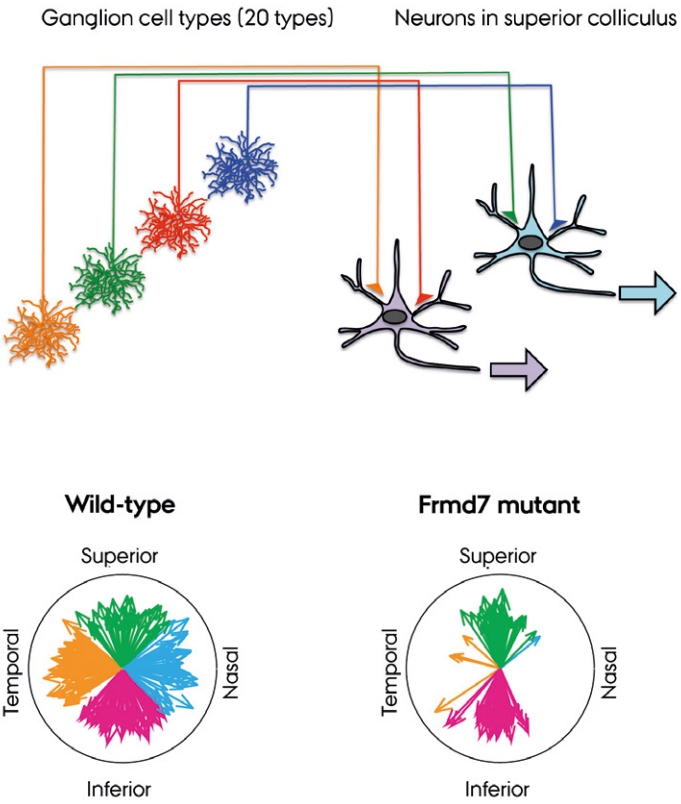
The brain is assembled from thousands of cell types, which are organized into distinct neuronal circuits to perform neural computations for analysing the sensory environment. Investigating structure and function of individual cell types is critical to the understanding of how our brain works, however, a systematic genetic approach that allows to manipulate the activity of a defined cell type is presently unavailable. The main aim of our project is to develop a new

genome engineering technique that allows us to change the visible labelling of specific cell types into a functional tool to regulate neuronal activity.

An investigation of the roles of genes associated with congenital nystagmus in retinal circuit assembly

Idiopathic congenital nystagmus, a disease that severely impacts eye movement, leaves approximately 1 in 1500 people with seriously impaired vision. Today, there is no cure or reliable treatment for this disease. In 70% of cases studied, mutations have been found in the FRMD7 gene. For the first time, this year, we published results linking mutations in FRMD7 to defects in retinal circuits underlying motion detection and the control of eye movement (Yonehara et al., Neuron). By combining trans-synaptic viral tools, two-photon imaging, and genome engineering, we aim to reveal the role of FRMD7 signaling cascades on the establishment of the retinal circuit implicated in congenital nystagmus. Our work will extend the scope of the investigation of the etiology of congenital nystagmus beyond FRMD7. In collaboration with international experts in biochemistry, virology, optics, and genome engineering, we will explore the role of FRMD7-interacting genes in the retinal direction-selective circuit.

A schematic of the retino-cellicular projection



Direction-selective responses in the retinas of wild-type and Frmd7 mutant mice. Mutant mouse retinas lack horizontal direction selectivity.

Key publications

Yonehara K, Fiscella M, Drinnenberg A, Esposti F, Trenholm S, Krol J, Franke F, Scherf BG, Kusnyerik A, Müller J, Szabo A, Jüttner J, Cordoba F, Reddy AP, Németh J, Nagy ZZ, Munier F, Hierlemann A, Roska B (2016) Congenital nystagmus gene FRMD7 is necessary for establishing a neuronal circuit asymmetry for direction selectivity. *Neuron.* Vol. 89, No. 1, 06.01.2016, p. 177-93

Wertz A, Trenholm S, Yonehara K, Hillier D, Raics Z, Leinweber M, Szalay G, Ghanem A, Keller G, Rózsa B, Conzelmann KK, Roska B (2015) PRESYNAPTIC NETWORKS. Single-cell-initiated monosynaptic tracing reveals layer-specific cortical network modules. *Science.* 349: 70-74

Yonehara K, Farrow K, Ghanem A, Hillier D, Balint K, Teixeira M, Jüttner J, Noda M, Neve RL, Conzelmann KK, Roska B (2013) The first stage of cardinal direction selectivity is localized to the dendrites of retinal ganglion cells. *Neuron.* 79: 1078-1085

Yonehara K, Balint K, Noda M, Nagel G, Bamberg E, Roska B (2011) Spatially asymmetric reorganization of inhibition establishes a motion-sensitive circuit. *Nature.* 469: 407-410. Commentary in Nature Reviews Neuroscience.

Personnel List Yonehara Group

Postdoc **Ana Oliveira**
Postdoc **Emilienne Repak**
Postdoc **Szilard Sajgo**
Research Assistant **Oleg Sitsel**
Laboratory Technician **Gurmeet Kaur Singh**
Laboratory Assistant **Misugi Yonehara**
Group Leader **Keisuke Yonehara**

Möller Team

A Direct View on Macromolecular Machines

Team Leader
Arne Möller

We use electron cryo-microscopy (cryoEM) to study the architecture of sortilins, key players in neurodegenerative diseases. In addition we are actively developing methods to visualize small or otherwise difficult samples by cryoEM. To this end we are engineering DNA scaffolds as carriers for small proteins. CryoEM is unique as it allows us to immediately see individual proteins, even in a native lipid environment.

In the past years cryoEM underwent a true revolution, as with the advent of direct electron detectors (novel EM-cameras that can detect the impact of an individual electron) it is now possible to analyze the 3D-architecture of macromolecular complexes at atomic resolution.

We employ this technology to structurally characterize sortilin complexes (in collaboration with Anders Nykjær). Sortilins are neuroreceptors involved in many mental disorders such as Alzheimer's and Huntington's disease and Schizophrenia. Sortilins bind to a large variety of macromolecular ligands and the specific binding partner defines sortilins function. Structural determination of these complexes, the mode and stoichiometry of binding and the identification of binding sites is crucial to understand sortilins function and to develop site-specific drugs. In contrast to X-ray crystallography cryoEM requires only minute sample amounts and is not limited to crystallization.

In our second project we nano-engineer DNA and RNA strands and utilize the constructs as carries for small proteins that would typically be too small to be visualized by cryoEM. However, when bound to the large RNA/DNA scaffold they become visible.

Selected Publications

Kang Y, Zhou XE, Gao X, He Y, Liu W, Ishchenko A, Barty A, White TA, Yefanov O, Han GW, Xu Q, Waal PW, Ke J, Tan MHE, Zhang C, Moeller A, West GM, et al. (2015) Crystal structure of rhodopsin bound to arrestin by femtosecond X-ray laser. *Nature.* 523, 561–567

Leung JH, Schurig-Briccio LA, Yamaguchi M, Moeller A, Speir JA, Gennis RB, Stout CD (2015) Division of labor in transhydrogenase by alternating proton translocation and hydride transfer. *Science 347 Issue* 6218, 178-181

Moeller A, Lee SC, Tao H, Speir JA, Chang G, Urbatsch IL, Potter CS, Carragher B, Zhang Q (2015) Distinct conformational spectrum of homologous multidrug ABC transporters. *Structure 23*, Issue 3, 450–460

Yang L, Yang D, de Graaf C, Moeller A, West GM, Dharmarajan V, Wang C, Siu FY, Song G, Reedtz-Runge S, Pascal BD, Wu B, Potter CS, Zhou H, Griffin PR, Carragher B, Yang H, Wang MW, Stevens RC, Jiang H (2015) Conformational states of the full-length glucagon receptor. *Nature Communications.* 6, 7859

Ye Q, Rosenberg SC, Moeller A, Speir JA, Su TY, Corbett KD (2015) TRIP13 is a protein-remodeling AAA+ ATPase that catalyzes MAD2 conformation switching. *eLife.* 015;4: e07367

Fig. 1. The TITAN Krios TEM available at AU provides a state-of-the art facility and can be used to obtain high-resolution images from macromolecular machines. Data collection is fully automated and images are processed in a highly streamlined manner on a powerful computer cluster. Photo by Lars Kruse, AU Komm.

Poulsen Team

Electrophysiology of Electrogenic Transporters and Ion Channels

Team Leader
Hanne Poulsen

Major achievements

In 2015, we bought the set-up for doing voltage-clamp fluorometry, and Rikard Blunck had a sabbatical for half a year at AU from Montreal to help establish the technique. We are still working on establishing the technique, since there have been technical problems with the amplifier. We finished a few projects and wrote manuscripts describing -the beta subunit of the Na,K-ATPase plays a previously unrecognized regulatory role. Using electrophysiology and molecular dynamics we could functionally and structurally explain the differences between different beta subunits -the alpha4 subunit of the Na,K-ATPase is exclusively found in sperm cells, and it is the most divergent of the alpha subunits by far. We found that it has a releatively low activity, but that the activity is much less affected by changing environment than for alpha1, suggesting that the pump is optimized for the extreme changes that a sperm cell faces when traversing another organism -the most used antimalarial drug, artemisinin, has been proposed to antagonize PfATP4, a P-type ATPase in Plasmodium falciparum. Using PfATP4 expressed in Xenopus oocytes, we could show that it is not active and not effected by artemisinin. Concurrently, others showed interesting novel results suggesting the true mechanism-of-action of artemisin.

Future plans

In 2016, the main focus will be on establishing voltage-clamp fluorometry using the unnatural amino acid Anap to study the Na,K-ATPase, the GABA transporter and NR3 NMDA receptors. I mention here a couple of the projects that we will be addressing:

-Three different neurological phenotypes arise from mutations in the gene encoding the Na,K-ATPase alpha3. This is intriguing and suggests that the mutations have different effects, possibly causing both loss- and gain-of-function. We have tested all three, RDP, AHC and CAPOS causing mutations, and none of them cause as severe gain-of-function as we showed previously for the somatic disease-causing mutations in ATP1A1. However, fever appears to be a trigger for many of the alpha3 diseases, suggesting that temperature may trigger the aberrant behaviour. Concomitant loss of sight and hearing as observed in CAPOS (but not the other syndromes) has previously been linked most often to mitochondrial effects, making it possible that the CAPOS mutation has a unique effect on mitochondria. Hopefully, our studies will provide insight into the molecular mechanisms that cause neurological diseases associated with ATP1A3 and may provide more general information about symptoms such as ataxia and loss of sight and hearing.

-When we sense pain, warmth, cold, the taste of chili, menthol, mustard, or pressure, the molecule translating the stimulus into an electrical signal is often a TRP channel. The TRPs play numerous roles in physiology and pathophysiology, but they have been far less studied than many of the voltage- and ligand-gated channels, although the roles of TRPs in nociception, pain and diseases make them highly relevant targets for drug discovery and drug screening. A major, yet unanswered question is what the molecular mechanism of temperature sensation is, and how it differs from ligand mediated gating. We will incorporate Anap to track physical movement in the channel and correlate that with channel activity in order to build a model for the molecular mechanism.

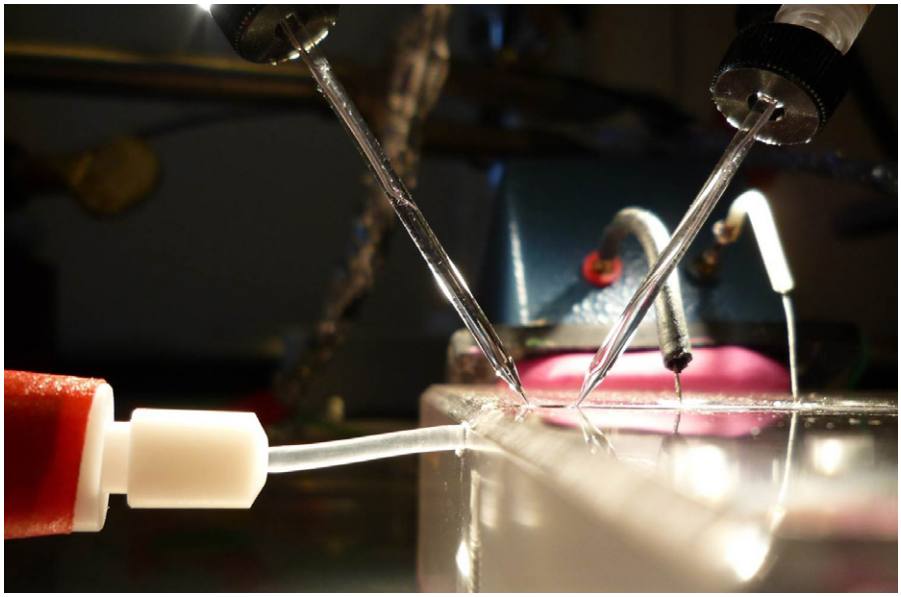


Fig. 1. Two-electrode voltage clamping. The two glass electrodes are in a Xenopus laevis oocyte, and the external buffer is controlled at the inlet to the left. Photo by Hanne Poulsen

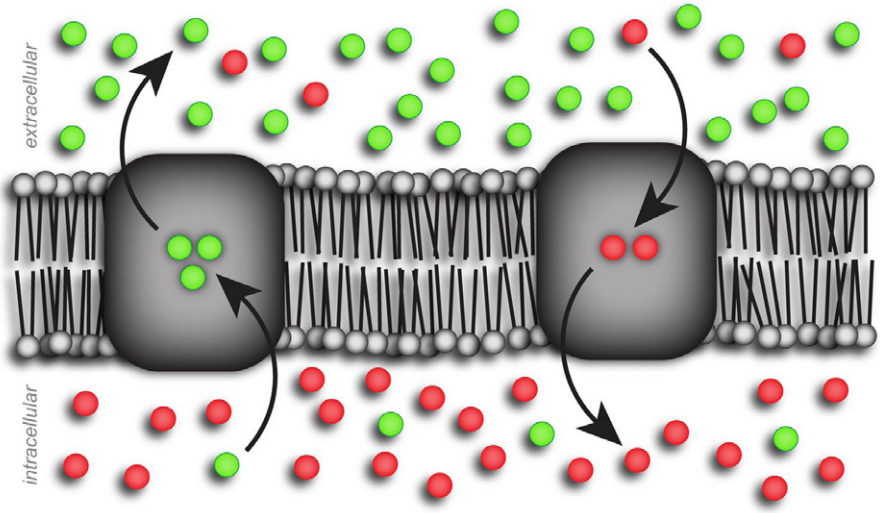


Fig. 2. Schematic illustration of the Na,K-ATPase actiity. Outside a cell, the concentration of sodium (green spheres) is high, inside a cell, the concentration of potassium (red spheres) is high due to the pumping of the Na,K-ATPase. In each round, the pump transports three sodium ion out of and two potassium ions into the cell at the expense of one ATP molecule. Illustration by Hanne Poulsen.

Key publications

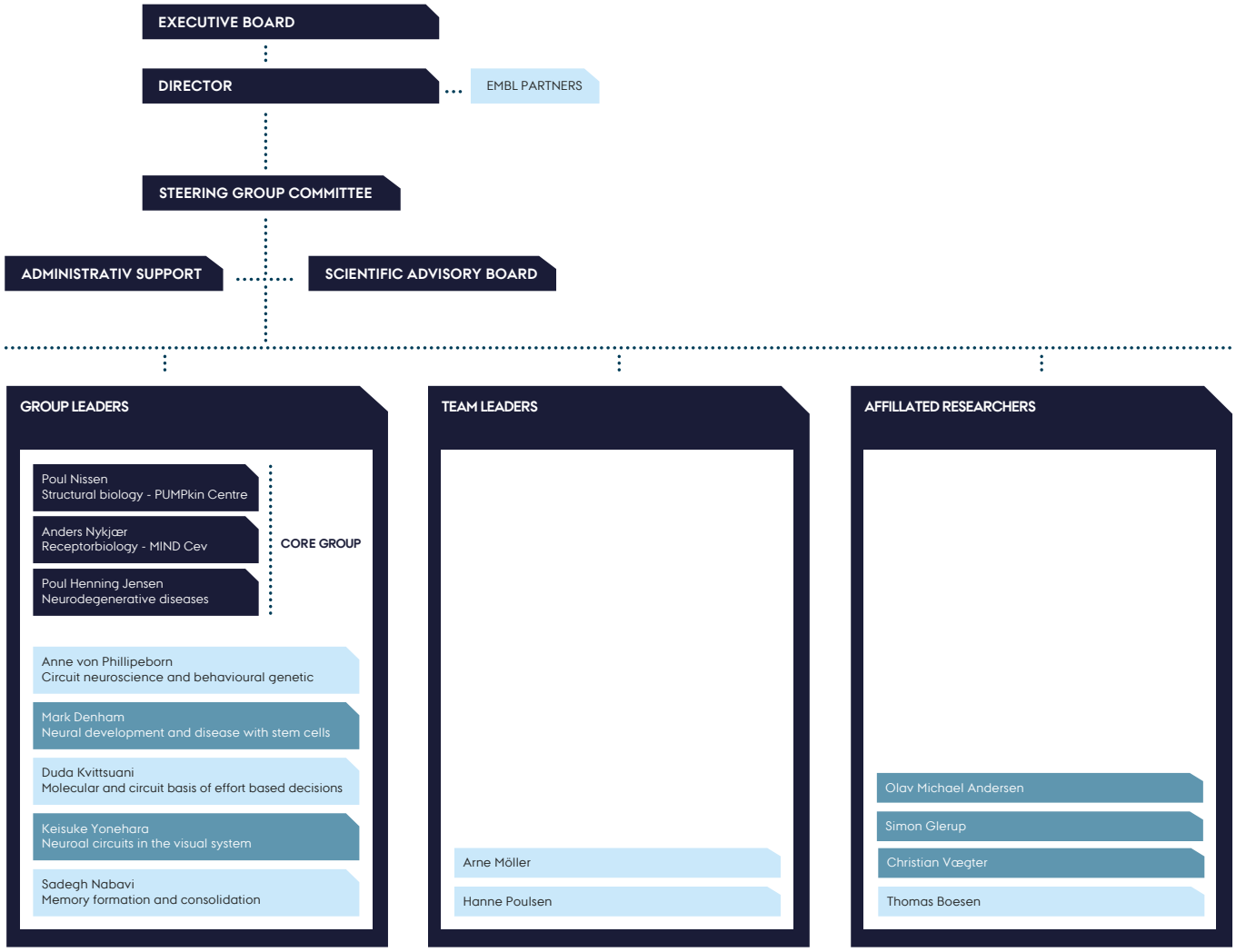
Voldsgaard MC, Nissen P, Poulsen H (2016) The alpha4 isoform of the Na,K-ATPase is tuned for changing extracellular environments. *FEBS J.* 283, 282-93

Heinzen EL, Arzimanoglou A, Brashear A, Clapcote SJ, Gurrieri F, Goldstein DB, Jóhannesson SH, Mikati MA, Neville B, Nicole S, Ozelius LJ, Poulsen H, Schyns T, Sweadner KJ, van den Maagdenberg A, Vilsen B; ATP1A3 Working Group. (2014) Distinct neurological disorders with ATP1A3 mutations. *Lancet Neurol.* 13(5):503-14

Azizan EA, Poulsen H, Tuluc P, Zhou J, Clausen MV, Lieb A, Maniero C, Garg S, Bochukova EG, Zhao W, Shaikh LH, Brighton CA, Teo AE, Davenport AP, Dekkers T, Tops B, Küsters B, Ceral J, Yeo GS, Neogi SG, McFarlane I, Rosenfeld N, Marass F, Hadfield J, Margas W, Chaggar K, Solar M, Deinum J, Dolphin AC, Farooqi IS, Striessnig J, Nissen P, Brown MJ (2013) Somatic mutations in ATP1A1 and CACNA1D underlie a common subtype of adrenal hypertension. *Nat Genet.* 245(9):1055-60

03 Organization Structure

Organization Structure



Employed at Dept. Biomedicine

Employed at Dept. Molecular Biology and Genetics

Executive Board

The Executive Board meets twice a year and consists of a chair, the deans of the Faculty of Science & Technology and the Faculty of Health, the director of research from the Lundbeck Foundation, and the core group leaders from DANDRITE. The chief administrative officer at DANDRITE provides support. The board currently consists of the following people:

Chair, Professor David Brooks

Department of Clinical Medicine
Aarhus University and Aarhus University Hospital-Danish Neuroscience Center

Dean Allan Flyvbjerg

Faculty of Health Sciences
Aarhus University

Director of Research Anne-Marie Engel

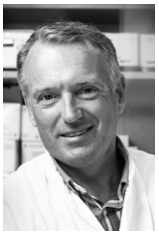
Lundbeck Foundation (non-voting)

Dean Niels Christian Nielsen

Faculty of Science & Technology
Aarhus University

Director, Professor Poul Nissen

DANDRITE
Aarhus University



Professor Anders Nykjær

DANDRITE
Aarhus University

Professor Poul Henning Jensen

DANDRITE
Aarhus University

Administrative support by
Chief Administrative officer Else Magård

DANDRITE
Aarhus University

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 2 year terms). DANDRITE's administrative personel also attends the steering committee meetings. The steering committee is responsible for strategic developments and implemenation of research, the planning and coordination of activities, and the distribution of the running budget. The steering committee also oversees the public dissemination and outreach of DANDRITE research and activities.

The committee currently consists of the following members:

- Professor Poul Nissen, Director
- Professor Anders Nykjær
- Professor Poul Henning Jensen
- Group Leader Sadegh Nabavi (took over after Anne von Philipsborn)
- Group Leader Mark Denham
- Chief Administrative Officer, Else Magård

Furthermore, the steering committee meetings are attended by:
Communications Assistant & Director PA, Karen Bech
Scientific Coordinator & Prof. PA, Susanne Schousboe Sjøgaard

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, with all Group leaders and Team leaders, and spokespersons present from every other category of staff at DANDRITE. In 2015 the participants were:

- All DANDRITE Group leaders
- All DANDRITE Team leaders
- Speaker for the Affiliated Researchers (Associate professor Olav Michael Andersen)
- Speaker for the Postdocs (Dr. Niels Wellner)
- Speaker for the PhD students (Sara Buskbjerg Jager)
- Speaker for the Technicians (Lotte Thue Pedersen)

Monthly Coordination Meeting

A monthly meeting of the DANDRITE core Group leaders and chief administrator with heads of hosting departments (Thomas G. Jensen, Dept. Biomedicine and Erik Østergaard Jensen, Dept. Molecular Biology and Genetics) for coordination of activities, teaching and infrastructural matters.

Young DANDRITE – The PhD & Postdoc Association at DANDRITE

The PhD & Postdoc Association at DANDRITE, called "Young DANDRITE", facilitates interactions and unity among the PhD students and postdocs affiliated with DANDRITE. The association meets several times a year for meetings and events, and activities are also planned ad hoc. The speakers of Young DANDRITE, PhD student Sara Jager and Postdoc Niels Wellner, also attend the monthly extended steering committee meetings.

Coordinators of Young DANDRITE:

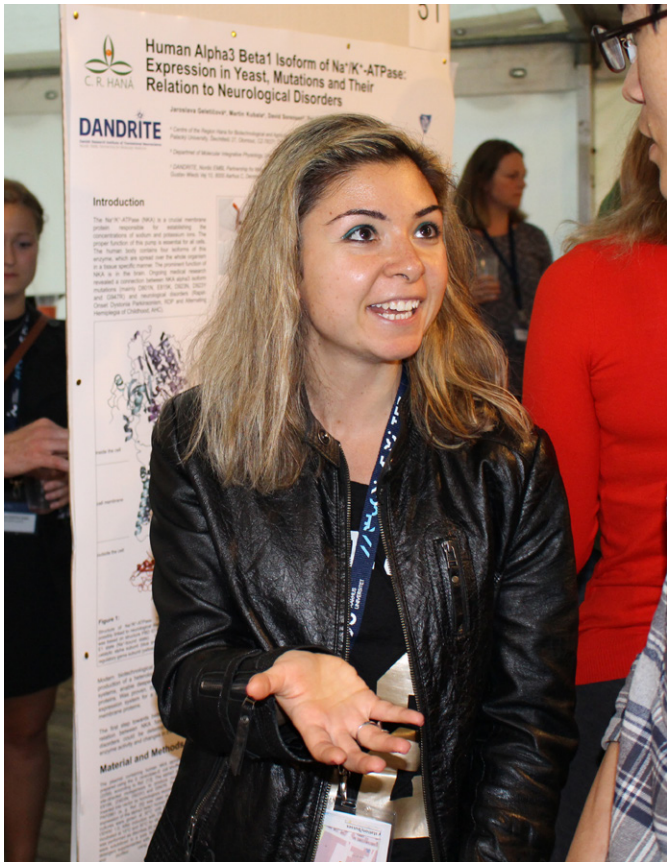
- PhD student Sara Buskbjerg Jager
- PhD student Milena Laban
- Postdoc Niels Wellner
- PhD student Juliane Martin

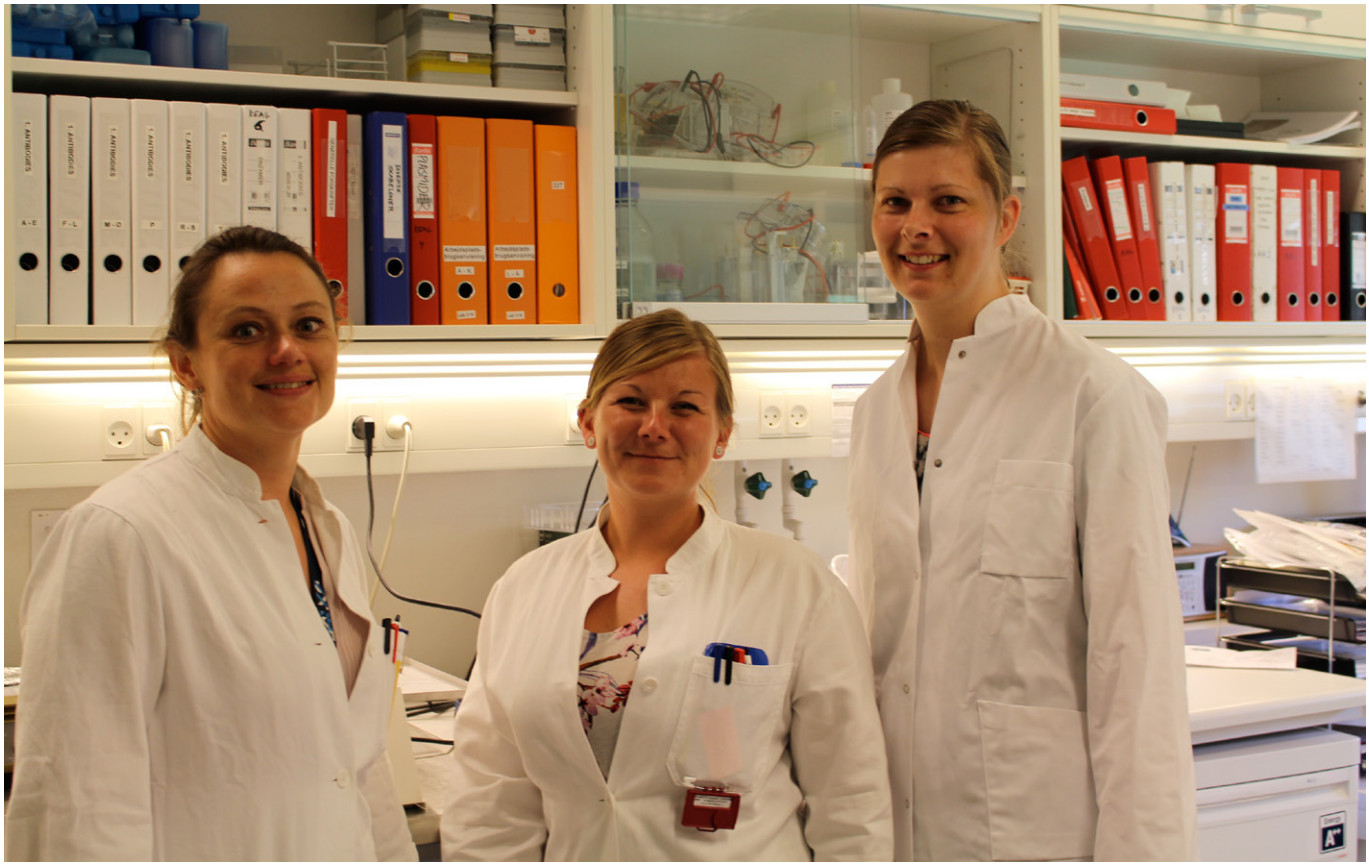
Network for Technicians

The laboratory technicians from all research groups affiliated DANDRITE have their own network and meet 2-3 times per year, to facilitate exchange of know-how, administrative and regulatory matters, practical informations, and informal networking. The speaker of the network, Lotte Thue Pedersen is also attending the extended steering committee meetings to communicate matters raised or discussed at the technician network.

Administrative Organization

As an interdisciplinary and cross-faculty research institute between Faculty of Science & Technology and Faculty of Health at Aarhus University, the research activities and administrative organization of DANDRITE are crossing borders. The DANDRITE administration serves as the single point of contact for administrative issues for all DANDRITE staff and students. The mission of the DANDRITE administration is to serve all needs connected to DANDRITE core activities and ensure that the research groups receive administrative support on a daily basis, drawing also from the general administrative support at AU. All DANDRITE's staff and students are therefore encouraged to consult with the DANDRITE administration on issues regarding e.g. employment/HR, visits, recruitments, salary, etc.


Human Alpha3 Beta1 Isoform of Na+/K+-ATPase: Expression in Yeast, Mutations and Their Relation to Neurological Disorders
DANDRITE
Introduction



04 Scientific Advisory Board

SCIENTIFIC ADVISORY BOARD

The scientific advisory board convenes biannually to provide independent advice on scientific and strategic matters, and evaluations of achievements, ideas and strategies. The members of the scientific advisory board are international, highly reputed researchers. The first advisory board meeting took place November 6, 2014, and the next will take place in September 2016.

DANDRITE's scientific advisory board members are:

- Professor Moses Chao, New York University
- Professor Kathleen Sweadner, Harvard Medical School
- Professor Mart Saarma, University of Helsinki
- Professor Glenda Halliday, Neuroscience Research Australia
- Director Matthias Wilmanns, EMBL-Hamburg
- Div. Director Jan Egebjerg, H. Lundbeck A/S
- Professor Rüdiger Klein, Max-Planck-Institute of Neurobiology
- Professor Carl Petersen, École Polytechnique Fédérale de Lausanne

DANDRITE's Scientific Advisory Board. From top left: Matthias Wilmanns, Mart Saarma, Rüdiger Klein, Jan Egebjerg, Moses Chao, Kathleen Sweadner, Glenda Halliday. SAB member Carl Petersen is missing in the photo.

05 Academic Organization

ACADEMIC ORGANIZATION

DANDRITE associates other research groups through three different instruments:

1. Team leaders (TL)
2. Affiliated Researchers (AFR)
3. DANDRITE Associate Research Program Investigators - (DARE)

Requests for TL or AFR status are approved by the DANDRITE steering committee, which also approves DARE applications on the basis of a peer-review.

DANDRITE Team Leaders (TL)

A maximum of 4 TL can be associated to DANDRITE and be supported by infrastructural or research-oriented strategies in DANDRITE.

- A TL holds a non-tenured junior Group Leader position/assistant professorship at Aarhus University (AU)
- The appointment as DANDRITE TL is for 3 years with possible extension for a total of maximum 6 years
- DANDRITE TL status is concluded earlier, if a permanent position at associate professor level is obtained
- Salaries and general running expenses are not funded by DANDRITE, but seed funding can be provided, and specific equipment and project expenses can be financed by DANDRITE as strategic investments
- TLs have access to the DANDRITE infrastructure (expertise and equipment) and administrative support on similar terms as Group leaders
- TLs participate in the monthlyextended steering committee meetings and internal activities at DANDRITE
- TLs qualify as internal DANDRITE applicants for DARE proposals. In addition to the general criteria for DARE programs, TL applications for DARE will be evaluated on their strategic value to DANDRITE

DANDRITE Affiliated Researchers

AFRs are typically AU researchers with permanent/senior positions that are tightly associated to DANDRITE core Group leaders for mutual benefits on research aims (e.g. through joint grants/research centers, shared laboratories). The affiliation can also support strategic structures of AU departments and infrastructures.

- AFRs are associated to DANDRITE via a core group Leaders and have qualifications at associated professor level or higher
- For projects associated with DANDRITE, AFRs have access to DANDRITE research infrastructures (expertise and equipment) on similar terms as Group leaders
- AFRs take part in internal DANDRITE activities
- AFRs are represented by a spokesperson at the monthly extended steering committee meetings
- AFRs have access to DARE programs through a core Group leaders as the formal applicant and grant holder. AFRs cannot be external partners of a DARE project
- AFRs can represent DANDRITE on collaborative initiatives, such as international networks

DANDRITE Associate Research Program Investigators - (DARE)

DARE Investigators are external collaborators with a DANDRITE GL/TL /AFR on a DARE project. DARE Investigators have qualifications at associated professor level or higher and are normally employed at a Danish research institution or company. DARE Investigators do not participate in the regular internal DANDRITE activities. DARE Investigators are invited to DANDRITE symposia and other larger scientific events. Depending on the type of project, the formal duration of a DARE investigator status is as follows.

- PhD projects: 4 years
- Postdoc projects: 3 years
- Equipment: 3 years

06
Personnel

Personnel

A major, initial goal of DANDRITE has been to recruit five outstanding young Group leaders in three recruitment campaigns following the EMBL model and finishing in 2015. Group Leader Mark Denham started his contract in December, 2013; Group Leader Anne von Philipsborn in January, 2014; Group Leader Duda Kvitsiani in November, 2014; Group Leader Keisuke Yonehara in January, 2015; and Group Leader Sadegh Nabavi in July, 2015.

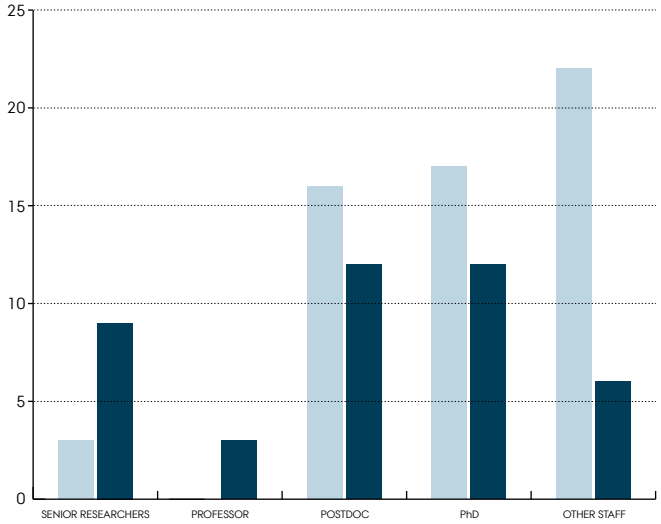


Fig. 1. Graphic representation of personnel employed and affiliated during 2015 grouped by appointment category and gender.

COUNT AND PERCENTAGES OF PERSONNEL EMPLOYED AND AFFILIATED DURING 2015 GROUPED BY APPOINTMENT CATEGORY AND GENDER

DANDRITE Personnel categories	Female	Male	Grand total	% Personnel per category
Professor	0	3	3	3
Senior Researchers	3	9	12	12
Postdoc	16	12	28	28
PhD	17	12	29	29
Other staff (Lab, Tech, Research, Assist and Administration)	22	6	28	28
Grand Totalt	58	42	100	100
% Male/Female	58	42	100	

Fig. 2. Count and percentages of personnel employed and affiliated during 2015 grouped by appointment category and gender.

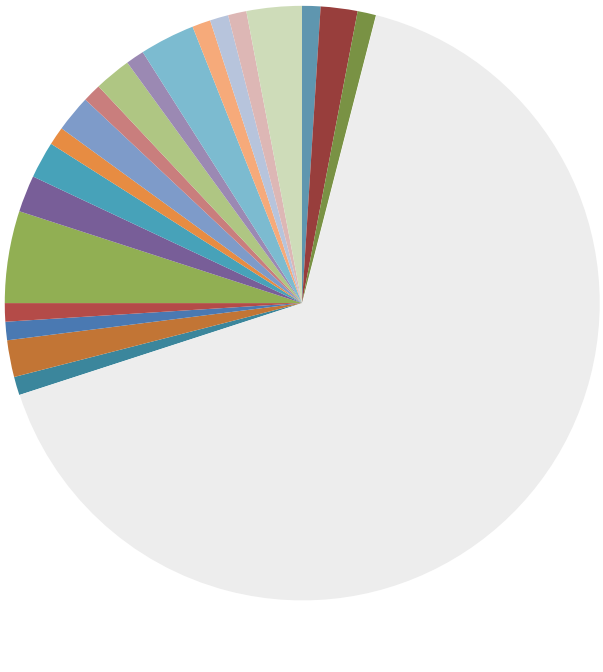


Fig. 3. Graphic representation of all employees and affiliated members during 2015 grouped by nationality.

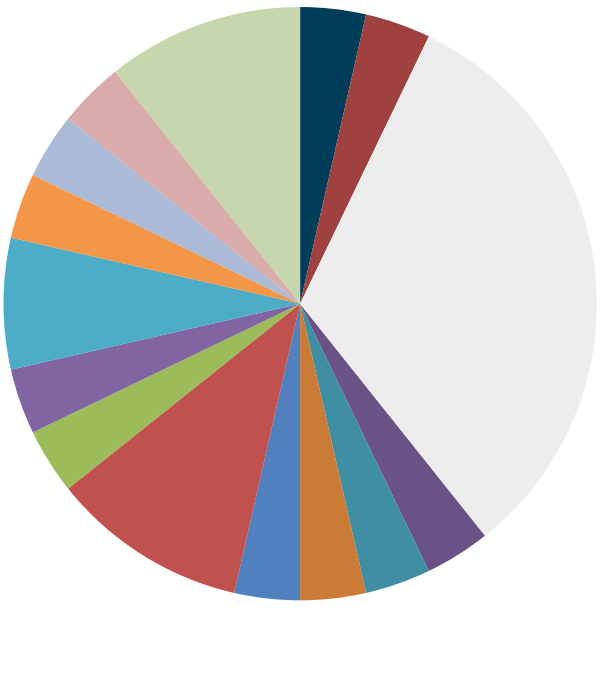


Fig. 4. Graphic representation of employees in the five young Group Leader's groups during 2015 grouped by nationality.

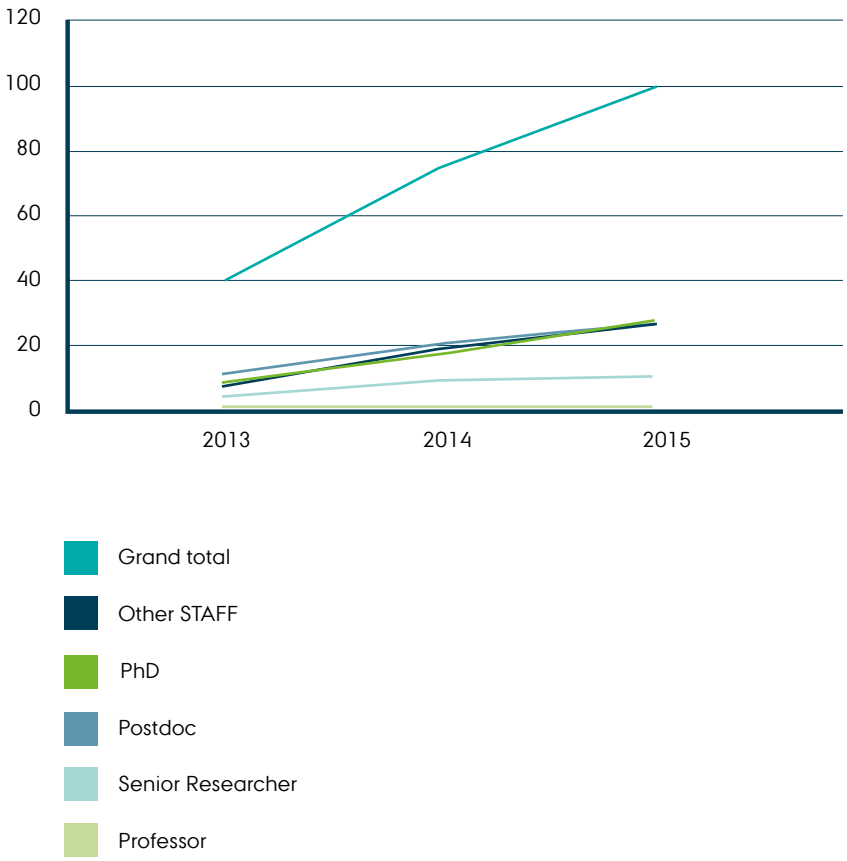


Fig. 5. Graphic representation of personnel progression 2013 to 2015 for all appointment categories summarized, for PhD students, Postdocs, Senior Researchers, Professors, and other respectively.

Personnel List Administration

- Chief Administrative officer Else Magård
- Student Assistant Eeva-Liisa Johansen
- Communications Assistant, PA Karen Bech
- Research Coordinator, PA Susanne Schousboe Sjøgaard

Awards

Professor **Poul Nissen** awarded *Gregori Aminoff Prize in Crystallography 2016*

PhD student **Sigrid Thirup Larsen** awarded *Best Presentation award* at The iNANO Autumn School, Aarhus University

Group Leader **Keisuke Yonehara** awarded *Young Investigator Award*, by the Japan Neuroscience Society.

Grants for Aarhus University Hosted Research Activities

Group Leader **Sadegh Nabavi**: ERC Starting Grant, *"Synaptic tagging and capture: From synapses to behavior"* EUR 1.5 million, Horizon 2020, The European Research Council.

Team Leader **Hanne Poulsen**: Lundbeck Foundation Fellowship, *"The sodium-potassium pump and transient receptor potential (TRP) channels"* DKK 10 million, The Lundbeck Foundation.

Affiliated Researcher **Simon Glerup**: DFF-Starting Grant, *"Novel PCSK9 regulatory proteins in the liver and brain"* DKK 6.6 million, Danish Council for Independent Research.

Professor **Poul Nissen**: Equipment grant, *Direct Electron Detector (DDD) Camera for CryoEM.* DKK 2.5 mio, Carlsberg Foundation.

Affiliated Researcher **Christian Vægter**: DFF-Research Project Grant, *"Satellite Glial cells in Nerve Injury – Modulators of Neurotrophic Signaling following Nerve Injury"* DKK 2.5 mio, Danish Council for Independent Research.

Postdoc **Louise B. Lassen**: 3 year Postdoctoral Fellowship *"Modeling a-synuclein aggregation and age-dependent dysfunction in neurodegenerative models"* DKK 2.1 million, The Lundbeck Foundation.

Postdoc **Ana Oliveira**: 3 year Postdoctoral Fellowship "Dissecting neuronal circuits underlying visually-guided behaviors" DKK 2.1 million, The Lundbeck Foundation. The grant was respectfully declined.

Postdoc **Ana Oliveira**: 2 year DFF-MOBILEX Mobility Fellowship *"Dissecting neuronal circuits underlying visually-guided behaviors"* Grant offered: DKK 1.9 million, Grant agreed (20 month): DKK 1.1 million, Danish Council for Independent Research.

Postdoc **Ana Oliveira**: 2 year Marie Skłodowska-Curie Individual Fellowships *"Dissecting neuronal circuits underlying visually-guided behaviors"* DKK 1.4 million, The European Research Council.

Team Leader **Magnus Kjærgaard**: 3 year AIAS-COFUND Marie Curie Fellowships, *"Can a cooked noodle store information? The mechanisms of disordered proteins in synaptic plasticity"* DKK 1.7 million, Aarhus Institute of Advanced Studies (AIAS).

Group Leader **Duda Kvitsiani** (in collaboration with Professor Søren Rud Keiding, Department of Chemistry, AU): PhD Fellowship Grant *"Developing patterned light stimulation and imaging system for behaving rodents"* DKK 1.6 million, The Lundbeck Foundation.

Professor **Poul Nissen** (in collaboration with Researcher Kim Nikolai Engedal, Center for Molecular Medicine Norway (NCMM), University of Oslo): PhD Fellowship Grant *"Combining cellular and in vitro studies to understand the function of sarco/endoplasmic reticulum Ca2+-ATPase in cell death and autophagy"* DKK 1.6 million, The Lundbeck Foundation.

Affiliated Researcher **Christian Vægter**: AUFF-Starting Grant *"Nerve Pathology in Type 2 diabetes"* DKK 1.5 million, Aarhus University Research Foundation (AUFF).

Postdoc **Muwan Chen**: 2 year Postdoctoral Fellowship *"Combining Stem Cells and Novel Bioactive Scaffolds to Develop new Parkinson Disease Therapies"* DKK 1.4 million, The Lundbeck Foundation.

Group Leader **Keisuke Yonehara**: Research Project Grant *"Function and Dysfunction of optokinetic circuits in mice"* DKK 1.2 million, The Lundbeck Foundation.

Group Leader **Duda Kvitsiani**: AUFF NOVA Grant *"Next generation tools to record fine temporal and spatial activity of neurons in freely behaving animals"* DKK 1.2 million, Aarhus University Research Foundation (AUFF).

Professor **Poul Nissen**: Infrastructure Grant, establishment support of *Direct Electron Detector (DDD) Camera for CryoEM DKK 1.0 million, The Novo Nordisk Foundation.*

PhD student **Aljona Kotsubei** (Cotutelle collaborative project with UK Leuven, Dr. Peter Vangheluwe): IWT Doctoral Grant DKK 1.6 million, Flanders Agency for Innovation & Entrepreneurship (IWT).

Postdoc **Joseph Lyons**: Research Project Grant *"Structure and Functions of P5 ATPases"* DKK 0.7 million, The Lundbeck Foundation.

Postdoc **Azadeh Shahsavar**: 3 year EIPOD Fellowship, hosted by Thomas Schneider, EMBL Hamburg, collaboration with Janet Thornton, EMBL - European Bioinformatics Institute and Professor Poul Nissen DKK 1.7 million, EMBL Cofund-EI3POD-program.

Professor **Poul Nissen:** EU H2020 Fellowship Grant (EU iNEXT program) DKK 0.6 million, The European Research Council.

Professor **Poul Nissen** & Team Leader **Hanne Poulsen**: AUFF Guest Researcher Grant, 5 months research visit of Professor Rikard Blunck DKK 88.000, Aarhus University Research Foundation (AUFF).

Professor **Poul Nissen:** Research Group Meeting Grant "DANDRITE 2015 Retreat" DKK 70.000, Aarhus University Research Foundation (AUFF).

Grants to Pursue Career after Aarhus University

Postdoc **Oleg Sitsel:** 2 year Long Term Fellowship, hosted by Simon Newstead, University of Oxford DKK 1.4 million, EMBO Excellence in Life Sciences.

Short Term Travel Grants

- Professor **Anders Nykjær:** Travel Funding. DKK 400.000, Vera og Carl Johan Michaelsens Legat.
- PhD student **Angela O'Sullivan**: Travel Funding DKK 30.000, Graduate School of Science and Technology, Aarhus University.
- PhD student **Angela O'Sullivan**: Travel Funding DKK 28.000, The Boehringer Ingelheim Fond.
- PhD student **Angela O'Sullivan:** Travel Funding DKK 4.000, International Brain Research Organization (IBRO).
- PhD student **Dorota Focht**: Travel Funding DKK 23.000, Boehringer Ingelheim Fonds.
- Postdoc **Joseph Lyons**: Travel Funding DKK 10.000, COST CM1306.
- Postdoc **Azadeh Shahsavar:** Travel Funding DKK 10.000, COST CM1306.

Invited Talks

DECEMBER

Poul Nissen: *Structural biology - from snapshots towards molecular movies.* Annual DAPSOC Symposium 2015, The University of Southern Denmark, Denmark.

Poul Nissen: *Snapshots of the transport cycle of P-type ATPases.* Symposium on Structural Biology and Membrane Complexes, Pasteur Institute, Paris, France.

Team Leader Hanne Poulsen: *Somatic mutations in ATP1A1 and CACNA1D underlie a common subtype of adrenal hypertension.* CNRS, Paris, France.

NOVEMBER

Mark Denham: *Modelling Parkinson's disease with Stem Cells.* NeuroD2 symposium, Mechanisms in Neurodevelopment and Neurodegeneration — From Molecules to Medicine, Aarhus University, Denmark.

Poul Henning Jensen: *Toxic mechanisms in synucleinopathies – a group of putative prion-like disorders.* NeuroD2 symposium, Mechanisms in Neurodevelopment and Neurodegeneration — From Molecules to Medicine, Aarhus University, Denmark.

Poul Nissen: *Structure and mechanism of ion pumps and secondary transporters.* Montreal Structural Biology Symposium (GRASP), McGill University, Montreal, Canada.

Poul Nissen: *Structure and function of Na+ dependent transporters.* GEPROM Center, University of Montreal, Canada.

Postdoc Niels Wellner: *SorCS1 and Diabetes.* Annual Day, Danish Diabetes Academy, Nyborg, Denmark.

Poul Nissen: *A biological view of neutrons.* Annual Niels Bohr Institute International Academy Workshop on ESS Science, University of Copenhagen, Denmark.

OCTOBER

Poul Henning Jensen: *MJF-14, a novel conformation dependent alpha-synuclein antibody.* Investigating Synuclein Consortium Meeting, The Michael J. Fox Foundation. New York, USA.

Keisuke Yonehara: *Motion-sensitive circuits in the retina.* Istanbul Technical University, Turkey.

Anders Nykjær: *SorCS1 – a new principle for the treatment of type 2 diabetes?* Danish Society for Pharmacology, Toxicology and Medicinal Chemistry (DSFTM), Sandbjerg Manor, Denmark.

Team Leader Arne Möller: *A direct view on macromolecular machines.* Frankfurt University and The Max Planck Institute in Frankfurt, Germany.

Anders Nykjær: *Sortilin – A new target for treatment of neuropathic pain?* XVI Congress of SINS, Cagliari, Italy

Poul Nissen: *P-type ATPases on the move – structure, mechanism and dynamics.* Frontiers in Integral Membrane Protein Structural Biology symposium, University of Oxford, UK.

Anne von Philipsborn: *Multifunctional wing control in fly song and flight.* Institute of Zoology, University of Regensburg, Germany.

SEPTEMBER

Poul Henning Jensen: *Early intracellular alpha-synuclein aggregation - consequences and speculations of its significance.* Biomedical Research Foundation, Academy of Athens, Center for neuroscience, Greece.

Team Leader Hanne Poulsen: *Somatic mutations in ATP1A1 and CACNA1D underlie a common subtype of adrenal hypertension.* Annual Society of the Scandinavian Society of Physiology, Aarhus, Denmark.

Poul Nissen: *The mission and aim of the Danish EMBL node of neuroscience.* EMBL Alumni Meeting in Denmark 2015, University of Copenhagen, Denmark.

AUGUST

Poul Nissen: *Crystallographic Snapshots of Membrane Transport.* Benzon Symposium No. 61 - Structural Biology on the Move, Copenhagen, Denmark.

Poul Nissen: *P-type ATPases as drug targets.* BioMedical Transporters Conference 2015, Lugano, Switzerland.

JULY

Keisuke Yonehara: *Spatially asymmetric neuronal connectivity in motion-sensitive circuits.* RIKEN CDB, Kobe, Japan.

Keisuke Yonehara: *Spatially asymmetric neuronal connectivity in motion-sensitive circuits.* National Institute for Genetics, Mishima, Japan.

Poul Nissen (session chair): *Structure and mechanism of Na+ dependent transporters.* 40th FEBS Congress 2015, Berlin, Germany.

Anne von Philipsborn: *Multifunctional wing control in fly song and flight.* EMBO workshop: Neural circuits and behaviour of Drosophila, Kolympari, Greece.

Anne von Philipsborn: *Neural circuits and behaviour of Drosophila.* Neural circuits and behaviour of Drosophila workshop, Kolympari, Greece.

Team Leader Arne Möller: *Conformational Spectrum of ABC transporters MSBA and P-gp.* FEBS Berlin, Germany.

Anne von Philipsborn: *Concepts in Animal Behaviour, Behavioural genetics and circuit neuroscience in Drosophila.* Warsaw University, Chlem/Poleski National Park, Poland.

JUNE

Poul Nissen: *Structure, function and mechanism of Na+ dependent transporters.* 4th International Workshop on Expression, Structure and Function of Membrane Proteins, Florence, Italy.

Anders Nykjær: *Sortilin receptors: from structure and function to drug development.* XXVI Paulo Foundation Symposium "From Atomic Structures to Disease Mechanisms", Helsinki, Finland.

Poul Henning Jensen: *Alpha-Synuclein Aggregates in Parkinson's disease, any Prospect for Therapeutic Targets?* Nordic neuroscience 2015, Trondheim, Norway.

Poul Nissen: *Structure and Mechanism of Neurotransmitter Transporters.* Nordic Neuroscience Conference 2015, Trondheim, Norway.

Poul Nissen: *The structural basis of calcium and copper transport.* NIH Membrane Protein Interest Group (MPIG), National Institute of Health (NIH), Bethesda, USA.

Poul Nissen: *Structure and mechanism of Na+ dependent transporters.* National Institute of Neurological diseases and Stroke (NINDS-NIH), Bethesda, USA.

MAY

Poul Nissen: *Visions for Studies of Biomolecules at ESS.* ESS colloquium on neutron science, Royal Institute for Technology (KTH), Stockholm, Sweden.

Mark Denham: *Generation of peripheral and central nervous system cell types.* Danish Society for Neuroscience (DSfN) Annual Meeting, Nyborg, Denmark

APRIL

Anders Nykjær: *Sortilin receptors in regulation of cholesterol and glucose metabolism.* Keystone Symposia on Molecular and Cellular Biology, The Crossroads of Lipid Metabolism and Diabetes, Copenhagen, Denmark.

Poul Nissen: *Structural biology for cancer drugs.* Sanofi Oncology Tour d'Europe, Aarhus University Hospital, Denmark

Anne von Philipsborn: *Deciphering neural circuits controlling Drosophila courtship song.* Danish Society for Neuroscience Spring meeting, Aarhus University.

Mark Denham: *Human embryonic stem cells and Parkinson's disease.* Danish Society for Neuroscience Spring meeting, Aarhus University.

Poul Nissen: *Structure and mechanism of sodium dependent transporters.* Membrane Protein Structure Meeting, Argonne National Laboratory, Chicago, US.

MARCH

Affiliated Researcher Olav Michael Andersen: *Mechanisms by which retromer transports APP via sorLA.* ADPD 2015, Nice, France.

Keisuke Yonehara: *Frmd7 is necessary for establishing horizontal motion sensitivity in the retina.* Friedrich Miescher Institute, Basel Switzerland.

FEBRUARY

Poul Henning Jensen: *Misfolded a-synuclein species – which forms exist in biological samples, can we detect them and can they do harm?* Neuroscience Research, Department Mayo Clinic Jacksonville, USA.

Poul Henning Jensen: *Multiple system atrophy, Preclinical target discovery.* Alpha-Synuclein: The Gateway to Parkinsonism, Innsbruck University, Austria.

Mark Denham: *Modelling Human Neural Development and Disease with Stem Cells.* DANDRITE encounters 2015, Aarhus University, Denmark.

Anne von Philipsborn: *Circuit neuroscience and behavioural genetics in Drosophila.* DANDRITE encounters 2015, Aarhus University, Denmark.

Keisuke Yonehara: *Function and dysfunction of motion-sensitive circuits in the visual system.* DANDRITE encounters 2015, Aarhus University, Denmark.

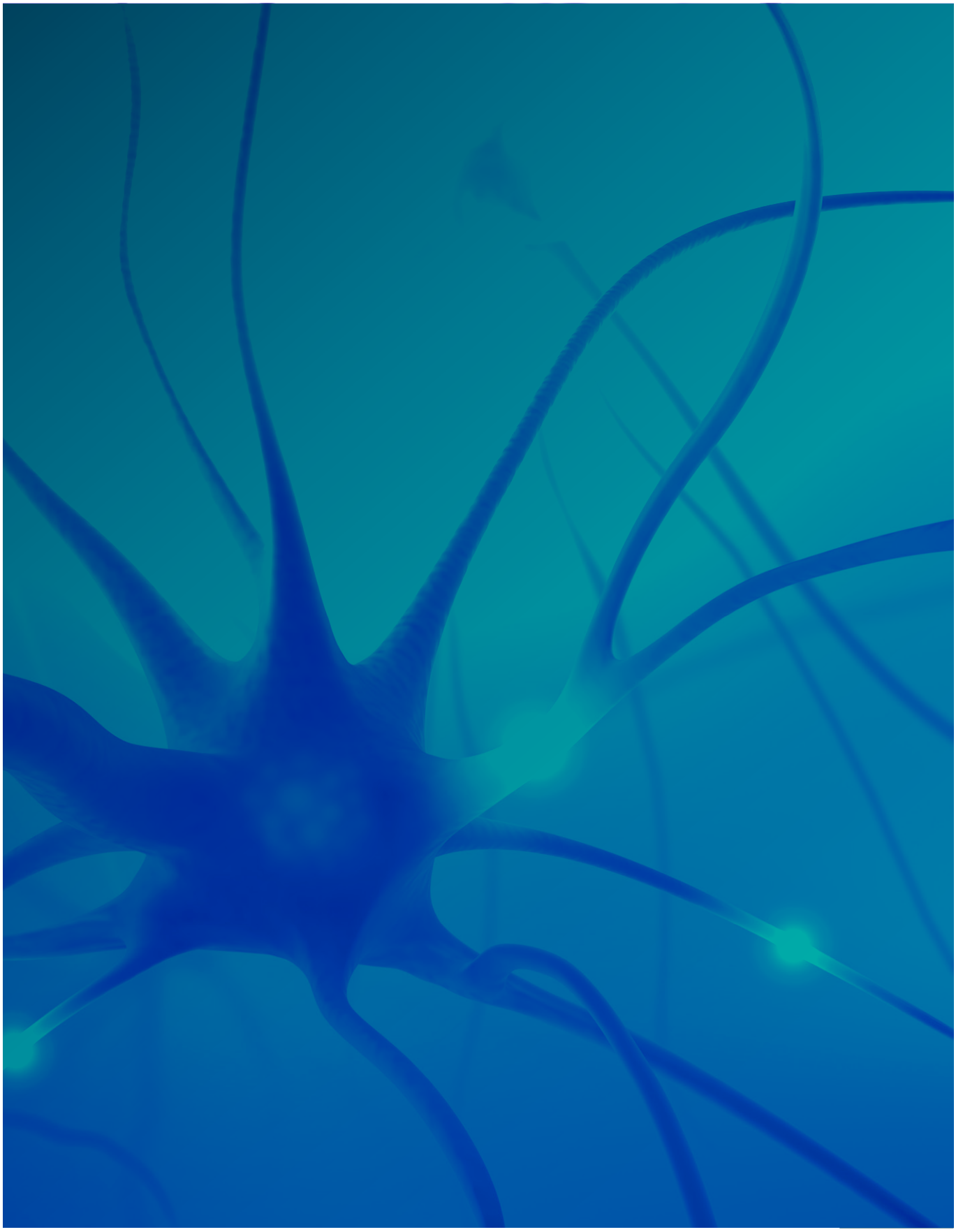
Duda Kvitsiani: *Molecular and circuit basis of effort based decision making.* DANDRITE encounters 2015, Aarhus University, Denmark.

JANUARY

Poul Henning Jensen: *Pathogenic mechanisms in multiple systems atrophy and other synucleinopathies.* Institute of Neurodegenerative Disorders, University Bordeaux, France.

Poul Nissen: *What goes in must come out - structure and function of Na+ transporters in the cell.* Radboud University Medical Center, Nijmegen, Netherlands.

Poul Nissen: *Structure and function of active transporters - research and excellence.* Inaugural Retreat of Center for Biopharmaceuticals, University of Copenhagen, Snekkersten, Denmark.



07 Publications

1. Structures and characterization of digoxin- and bufalin-bound Na+,K+-ATPase compared with the ouabain-bound complex (2015) Laursen M, Gregersen JL, Yatime L, **Nissen P**, Fedosova NU. *Proc Natl Acad Sci U S A* 112, 1755-60

2. A Sulfur-Based Transport Pathway in Cu+-ATPases (2015) Mattle D, Zhang L, Sitsel O, Pedersen LT, Moncelli MR, Tadini-Buoninsegni F, Gourdon P, Rees DC, **Nissen P**, Meloni G. *EMBO Rep* 16, 728-40

3. Structural studies of P-type ATPase-ligand complexes using an X-ray free-electron laser (2015) Bublitz M, Nass K, Drachmann ND, Markvardsen AJ, Gutmann MJ, Barends TR, Mattle D, Shoeman RL, Doak RB, Boutet S, Messerschmidt M, Seibert MM, Williams GJ, Foucar L, Reinhard L, Sitsel O, Gregersen JL, Clausen JD, **Boesen T**, Gotfryd K, Wang KT, Olesen C, Møller JV, **Nissen P**, Schlichting I. *IUCrJ* 2, 409-20

4. The 4 isoform of the Na+ ,K+ -ATPase is tuned for changing extracellular environments (2015) Voldsgaard Clausen M, **Nissen P**, **Poulsen H**. *FEBS J*

5. Regulation of the Ca(2+)-ATPase by cholesterol: A direct or indirect effect? (2015) Autzen HE, Suida I, Sonntag Y, **Nissen P***, Møller JV, and Thøgersen L. *Mol Membrane Biol* 32, 75-87

6. Structure and function of Cu(I)- and Zn(II)-ATPases (2015) Sitsel O, Gronberg C, Autzen H, Wang K, Meloni G, **Nissen P**, Gourdon P. *Biochemistry,* Vol. 54, No. 37, p. 5673-5683

7. Discovery of Tricyclic Clerodane Diterpenes as Sarco/Endoplasmic Reticulum Ca(2+)-ATPase Inhibitors and Structure-Activity Relationships (2015) De Ford C, Calderón C, Sehgal P, Fedosova NU, Murillo R, Olesen C, **Nissen P**, Møller JV, Merfort I. *J Nat Prod* 78, 1262-70

8. Against the Odds? De-novo Structure Determination of a Pilin with Two Cysteine Residues by Sulfur SAD (2015) Gorgel M, Bøggild A, Ulstrup JJ, Mueller U, Weiss MS, **Nissen P**, Boesen T. *Acta Cryst D* 71, 1095-101

9. Indications of radiation damage in ferredoxin microcrystals using high-intensity X-FEL beams (2015) Nass K, Foucar L, Barends TR, Hartmann E, Botha S, Shoeman RL, Doak RB, Alonso-Mori R, Aquila A, Bajt S, Barty A, Bean R, Beyerlein KR, Bublitz M, Drachmann N, Gregersen J, Jönsson HO, Kabsch W, Kassemeyer S, Koglin JE, Krumrey M, Mattle D, Messerschmidt M, Nissen P, Reinhard L, Sitsel O, Sokaras D, Williams GJ, Hau-Riege S, Timneanu N, Caleman C, Chapman HN, Boutet S, Schlichting I. *J Synchr Radiat* 22, 225-38

10. Targeting thapsigargin towards tumors (2015) Doan NT, Paulsen ES, Sehgal P, Møller JV, Nissen P, Denmeade SR, Isaacs JT, Dionne CA, Christensen SB. *Steroids* 97:2-7

11. On the molecular mechanism of flippase- and scramblase-mediated phospholipid transport (2015) Montigny C, Lyons J, Champeil P, Nissen P, Lenoir G. *B B A - Molecular and Cell Biology of Lipids*

12. Digesting New Elements in Peptide Transport (2015) Lyons JA, **Nissen P**. *Structure,* Vol. 23, No. 10, p. 1779-80

13. High-resolution structure of a type IV pilin from the metal-reducing bacterium Shewanella oneidensis (2015) Gorgel M, Ulstrup J, Bøggild A, Jones NC, Hoffmann SV, **Nissen P**, **Boesen T**. *BMC Structural Biology,* Vol. 15, No. 4, 2015, p. 1-17

14. Membrane proteins - do we catch up with the breathless pace of soluble protein structural biology? (2015) Pedersen BP, **Nissen P**. *B B A - Molecular and Cell Biology of Lipids,* Vol. 1850, No. 3, p. 447-8

15. Identification of Alpha-Synuclein Interacting Synaptosomal Proteins (2015) Betzer C, Movius AJ, Shi M , Zhang J, **Jensen PH**. *Plos One,* 10(2):e0116473

16. Phosphorylated -synuclein in Parkinson's disease: correlation depends on disease severity (2015) Stewart T, Sossi V, Aasly JO, Wszolek ZK, Uitti RJ, Hasegawa K, Yokoyama T, Zabetian CP, Leverenz JB, Stoessl A, Wang Y, Ginghina C, Liu C, Cain KC, Auinger P, Kang U, **Jensen PH**, Shi M, Zhang J. *Acta Neuropathol Commun.* 3:7

17. The A-B-C for SORting APP (2015) Coulson EJ, **Andersen OM**. *J Neurochem.* 135(1):1-3

18. Y682G Mutation of Amyloid Precursor Protein Promotes Endo-Lysosomal Dysfunction by Disrupting APP-SorLA Interaction (2015) La Rosa LR, Perrone L, Nielsen MS, Calissano P, **Andersen OM**, Matrone C. *Front Cell Neurosci.* 9:109

19. Increased serum levels of sortilin are associated with depression and correlated with BDNF and VEGF (2015) Buttenschøn HN, Demontis D, Kaas M, Elfving B, Mølgaard S, Gustafsen C, Kaerlev L, Petersen CM, Børglum AD, Mors O, **Glerup S**. *Transl Psychiatry.* 5:e677

20. SorLA complement-type repeat domains protect the amyloid precursor protein against processing (2015) Mehmedbasic A, Christensen SK, Nilsson J, Rüetschi U, Gustafsen C, Poulsen AS, Rasmussen RW, Fjorback AN, Larson G, **Andersen OM**. *J Biol Chem.* 90(6):3359-76

21. Absence of a thyroid phenotype in sortilin-deficient mice (2015) Lisi S, Madsen P, Botta R, Petersen CM, **Nykjaer A**, Latrofa F, Vitti P, Marinò M. *Endocr Pract.,* Sep;21(9):981-5

22. Identification of a multipotent neural progenitors that give rise to the central and peripheral nervous system (2015) **Denham M**, Hasagawi K, Zhang D, Hough S, Menheniott T, Leung J, Rollo B, Newgreen D, Pera M, Dottori M. *Stem Cells*

23. How to make a midbrain dopaminergic neuron (2015) Arenas E, **Denham M**, Villaescusa JC. *Development*

24. Enteric Neural Cells from Hirschsprung Disease Patients form Ganglia in Autologous Aneuronal Colon Muscle Tissue (2015) Rollo BN, Zhang D, Stamp LA, Menheniott TR, Stathopoulos L, **Denham M**, Dottori M, King SK, Hutson JM, Newgreen DF. *Cellular and Molecular Gastroenterology and Hepatology*

25. Multipotent Caudal Neural Progenitors Derived from Human Pluripotent Stem Cells that Give Rise to Lineages of the Central and Peripheral Nervous System (2015) **Denham M**, Hasegawa K, Menheniott T, Rollo B, Zhang D, Hough S, Alshawaf A, Febbraro F, Ighaniyan S, Leung J, Elliott DA, Newgreen DF, Pera MF, Dottori M. *Stem Cells,* 33:1759–1770

26. Male Drosophila melanogaster learn to prefer an arbitrary trait associated with female mating status (2015) Verzijden MN, Abbott JK., **Philipsborn A**, Loeschcke V. *Current Zoology,* Vol. 61, No. 6, p. 1036-1042

27. PRESYNAPTIC NETWORKS. Single-cell-initiated monosynaptic tracing reveals layer-specific cortical network modules (2015) Wertz A, Trenholm S, **Yonehara K**, Hillier D, Raics Z, Leinweber M, Szalay G, Ghanem A, Keller G, Rózsa B, Conzelmann KK, Roska B. *Science* 349: 70-74

28. Crystal structure of rhodopsin bound to arrestin by femtosecond X-ray laser (2015) Kang Y, Edward XZ, Gao X, He Y, Liu W, Ishchenko A, Barty A, White TA, Yefanov O, Han GW, Xu Q, Waal PW, Ke J, Tan MHE, Zhang C, **Moeller A**, West GM, et al. *Nature* 523, 561–567

29. Division of labor in transhydrogenase by alternating proton translocation and hydride transfer (2015) Leung JH, Schurig-Briccio LA., Yamaguchi M, **Moeller A.**, Speir JA., Gennis RB, Stout CD. *Science* 347 Issue 6218, 178-181

30. Distinct conformational spectrum of homologous multidrug ABC transporters (2015) **Moeller A**, Lee SC, Tao H, Speir JA, Chang G, Urbatsch IL, Potter CS, Carragher B, Zhang Q. *Structure* 23, Issue 3, 450–460

31. Conformational states of the full-length glucagon receptor (2015) Yang L, Yang D, De Graaf C, **Moeller A**, West GM, Dharmarajan V, Wang C, Siu FY, Song G, Reedtz-Runge S, Pascal BD, Wu B, Potter CS, Zhou H, Griffin PR, Carragher B, Yang H, Wang MW, Stevens RC, Jiang H. *Nature Communications,* Vol. 6, p. 1-13

32. TRIP13 is a protein-remodeling AAA+ ATPase that catalyzes MAD2 conformation switching (2015) Ye Q, Rosenberg SC, **Moeller A**, Speir JA, Su TY, Corbett KD. *eLife,* Vol. 2015, No. 4, p. 1-44

33. Corrigendum to "Long-term valproic acid exposure increases the number of neocortical neurons in the developing rat brain" [Neurosci.Lett. 580 (2014) 12–16] A possible new animal model of autism (2015) Sabers A, Bertelsen FCB, Scheel-Krüger J, Nyengaard JR, **Møller A**. *Neuroscience Letters,* Vol. 588, p. 203-7

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