2018

DANDRITE ANNUAL REPORT

AARHUS UNIVERSITY

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

Words from the Director

Photo by the Novo Nordisk Foundation, Denmark

It is with great pleasure I welcome you to our 2018 annual report from DANDRITE – the Danish Research Institute of Translational Neuroscience funded by the Lundbeck Foundation, and at the same time the Danish node of the Nordic EMBL Partnership for Molecular Medicine.

In 2018, we entered DANDRITE's second 5-year funding period, and with that also new thoughts and discussions of future research directions and strategies in neuroscience. Group leaders Mark Denham, Anne von Philipsborn, and Duda Kvitsiani all successfully completed their contract extensions in 2018. DANDRITE research community continue to grow and exceeds now 130 researchers alone in the DANDRITE group leader and team leader laboratories. Our affiliated researchers also take advantage of joint initiatives to expand on neuroscience initiatives and bold new research questions. With the EMBL-inspired group leader research program and the Nordic EMBL Partnership to support it, DANDRITE has sprouted in many different, yet coherent directions and forms an expanding and dedicated community that allows interdisciplinary and innovative ideas to unfold and flourish – both within and around DANDRITE.

DANDRITE is devoted to a mission of introducing new, original lines and methods of research in Danish neuroscience and strengthen those that already are. Three two-photon imaging platforms are established for live imaging of neuronal activity, and other advanced imaging platforms are in the pipeline. In collaboration with the Department of Engineering, at Aarhus University we see exciting developments of light wave modulation for deep brain photoactivation at a single neuron level. Gaming, the use of machine learning, and other AI approaches have entered our quantitative modeling of behavior and extraction of complex patterns and correlations from large data sets and in images. The EMBION proposal for a national cryo-electron microscopy infrastructure was approved and will place a new high-end electron microscope in Aarhus to expand our capacity for e.g. single-particle and tomographic studies of molecular and cellular structures in brain. Behavior, neuronal circuits, genetics, and molecular interactions are approached with the aim of understanding mechanisms of brain and brain diseases at multiple, connecting scales.

The Nordic EMBL Partnership welcomed new directors at FIMM, MIMS and NCMM during 2018, and as the DANDRITE director, I took over the Speaker assignment for the partnership. We hope to expand on partnership activities through funded research programs.

Several publications of 2018 report on exciting discoveries in basic and translational neuroscience, and several features of DANDRITE research and the Nordic EMBL Partnership appeared in public radio, journals and magazines. Many new research grants were awarded to our research programs including for example two Lundbeck Foundation/NIH BRAIN initiative grants for Sadegh Nabavi and Keisuke Yonehara, the Novo Nordisk Foundation Young Investigator grant for Team Leader Tomonori Takeuchi, and grants from the Michael J. Fox Foundation for core Group Leader Poul Henning Jensen and Affiliated Researcher Marina Romero-Ramos. We were also very grateful for a joint initiative by the Novo Nordisk Foundation and the Wallenberg Foundation supporting a Danish-Swedish cryo-EM network that includes also the cryo-EM facilities in Umeå associated with MIMS.

Also in 2018, talented young researchers attracted numerous fellowships such as the Marie Sklodowska-Curie fellowship to Michael Habeck, the Lundbeck Foundation fellowship to Andrea Moreno, the Boehringer Ingelheim Fonds PhD stipend to Sara Basse, the Graduate School of Health full PhD fellowship to Lixiang Jiang, and numerous travel awards and bursaries. I personally had the great honor of receiving the 2018 Carlsberg Foundation Research Prize.

DANDRITE also reached out to Danish neuroscience through new appointments of affiliated researchers, which form a cornerstone of the DANDRITE mission, and we continue our deep commitments to NeuroCampus Aarhus, the Danish Society for Neuroscience, and the Brain Prize activities supported by the Lundbeck Foundation, as well as through many international collaborations.

DANDRITE outreach activities included the annual DANDRITE Encounters where students meet our research groups, and co-organization of the Neuroscience Day and Brain Prize outreach activities. Every year DANDRITE has a grand display at the Festival of Research "Forskningens Døgn", and engage year-round in public outreach lectures and social media outlets. We have increased our presence also through small YouTube videos, featuring for example important research papers, research groups, and DANDRITE overall.

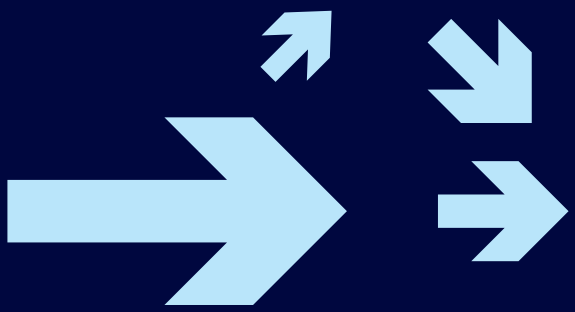
We invite you to spend a few moments to learn more about our activities on the following pages.

With my warmest regards,

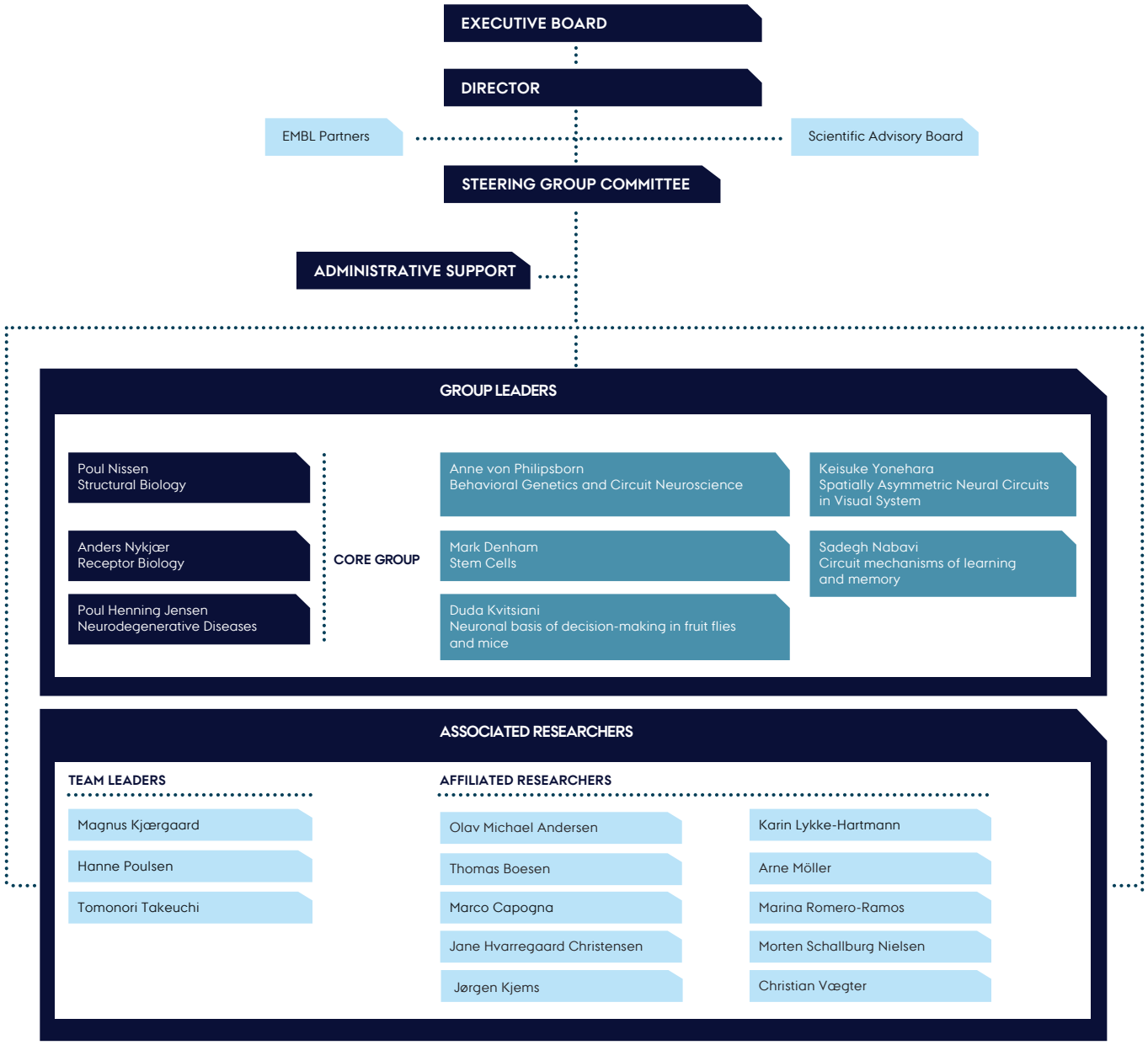
Poul Nissen, Director and Core Group Leader

01

Organization Structure



Organization Structure



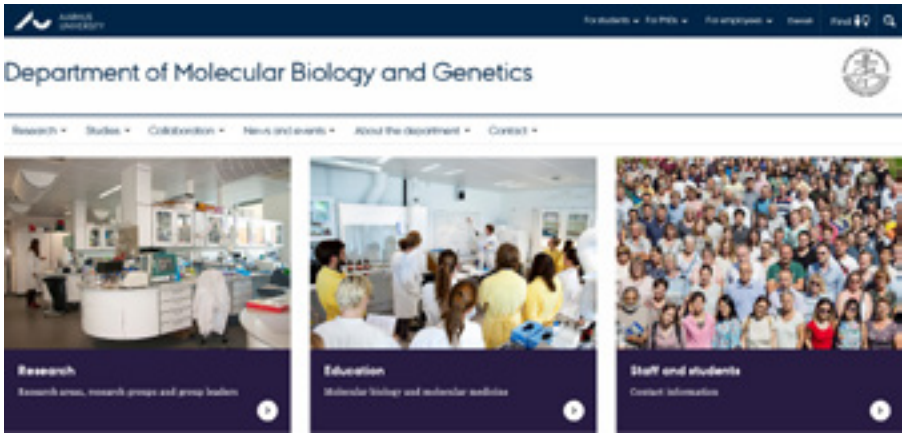
Hosting Departments

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

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

→ biomed.au.dk/en

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



→ mbg.au.dk/en

Executive Board

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

Dean **Niels Christian Nielsen**, The Faculty of Science and Technology (from February 2019, Dean Lars Henrik Andersen is interim at Science and Technology)

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

Director Professor **Poul Nissen**, DANDRITE

Professor **Anders Nykjær,** DANDRITE

Professor **Poul Henning Jensen**, DANDRITE

Director of Research **Anne-Marie Engel**, Lundbeckfonden (until mid-2018: non-voting)

Programme Manager **Lars Torup** (from mid-2018: non-voting)

Administrative support by Chief Administrative Officer **Else Magård**, DANDRITE

Management

STEERING COMMITTEE
The steering committee meets every Monday at 10-11 AM and consists of the director, the core group leaders and two representatives of the group leaders (internally elected for two-year terms). DANDRITE's administrative personnel also attends the meetings. The steering committee is responsible for strategic developments and implementation of research, the planning and coordination of activities, and the distribution of running budget. The steering committee will also be overseeing public dissemination and outreach of DANDRITE research and activities. The committee in 2018 consisted of the following members:

- Professor **Poul Nissen**, Director
- Professor **Anders Nykjær**
- Professor **Poul Henning Jensen**
- Group Leader **Duda Kvitsiani**
- Group Leader **Anne von Philipsborn** (took over in August after Keisuke Yonehara)
- Chief Administrative Officer, **Else Magård**

Furthermore, the steering committee meetings are attended by:

- Communications Assistant & Director PA, **Karen Bech**
- Research Group Coordinator and Communications Assistant, **Maria Thykær Jensen**
- Center Administrator (PROMEMO) & Professor 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. The extended committee consists of all Group Leaders and Team leaders, and spokespersons for each personnel category at DANDRITE. In 2018 the participants were:

- All DANDRITE Group Leaders
- All DANDRITE Team Leaders
- Affiliated Researcher spokesperson: **Marco Capogna** (first half year)
- Affiliated Researcher spokesperson: J**ane Hvarregaard Christensen** (second half year)
- Postdoc spokesperson: **Mette Richner** (first four months)
- Postdoc spokesperson: **Alena Salasova** (from May)
- PhD student spokesperson: **Rikke Hahn Kofoed** (first two months)
- PhD student spokesperson: **Sophie Seidenbecher** (from March)
- Technician spokesperson: **Benedicte Vestergaard** (first half year)
- Technician spokesperson: **Anne-Katrine Vestergaard** (second half year)

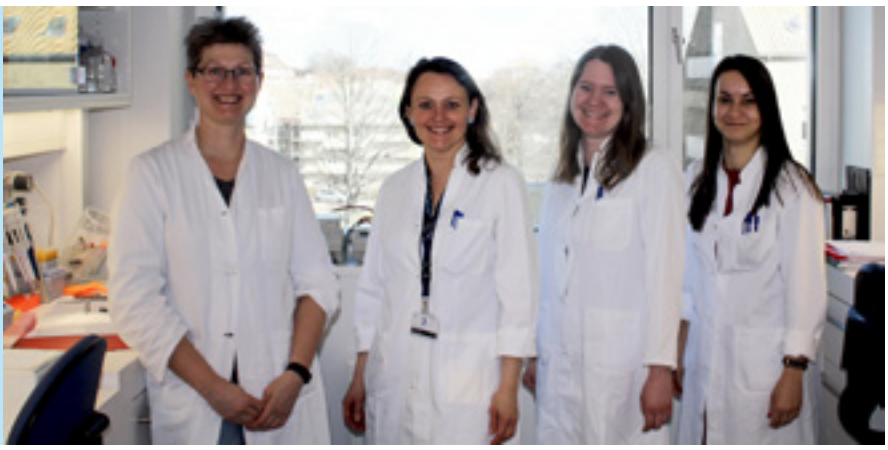
MONTHLY COORDINATION MEETING
Monthly the DANDRITE core Group Leaders and chief administrator meet with the heads of the two hosting department (Thomas G. Jensen, Department of Biomedicine and Erik Østergaard Jensen, Department of Molecular Biology and Genetics) for coordination of activities, teaching,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

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

Being small, the team still includes four academic employees and one part-time student assistant. Therefor each member of the team has responsibility for specific tasks while at the same time the team works closely together on a daily basis.

ADMINISTRATIVE SUPPORT TEAM'S TASK-MATRIX

Who to contact? / Subject	Maria T. Jensen	Karen Bech-Pedersen	Susanne S. Sjøgaard	Else Magård
Research Group support e.g. visitors, events, contact person for new group members	• Group support: Nabavi, von Philipsborn, Kvitsiani, Yonehara, Denham, Jensen, and Takeuchi	• Group support: Nissen, Poulsen, Kjærgaard • Personal assistant for Nissen	• Center Administrator PROMEMO • Personal assistant for Nykjær	
Communication	• News & events on web • Internal comm. & meetings • Nordic EMBL Partnership • SoMe / Video	• News & events on web • Web design • Newsletter • Graphic designs	• News & events on web PROMEMO & NeuroCampus related communication	
Events	• Event assistant • Lectures & seminars	• Event assistant	• Event assistant • Neuroscience Day	• Event coordinator
HR e.g. employments, extensions	• HR for Groups: Yonehara, Denham, Jensen, Nykjær, Takeuchi	• HR for Groups: Nabavi, von Philipsborn, Kvitsiani, Nissen, Poulsen, Kjærgaard	• PROMEMO related HR	
Management support				• Budgets • Reports • Strategy & coordination • Business & Board meetings • Annual wheel



Four Nykjær lab members. From left: Academic technician Karen Marie Pedersen, Laboratory Staff member Benedicte Vestergaard, Lab technician Anne Kerstine Jensen, and trainee Andreea-Cornelia Udrea

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

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

TECHNICIAN NETWORK

The laboratory technicians from all research groups affiliated with DANDRITE meet 2-3 times per year, to facilitate exchange and alignment of know-how, administrative and regulatory procedures, practical information, and for informal networking. The speaker for the extended steering committee is elected by the network and communicates matters raised or discussed in the technician network or at the extended steering committee.

DANRITE Christmas get-together 2018 – with many of the true young DANDRITEs having a blast with our very own Santa (postdoc Michael Clausen)

Young DANDRITE

– The PhD & Postdoc association at DANDRITE

The PhD & Postdoc Association at DANDRITE, "Young DANDRITE" (recently renamed to YoDa), facilitates interaction and unity among the PhD students and postdocs at DANDRITE.

The association meets several times a year for meetings and events, and ad hoc activities.
Also, Young DANDRITE are adding to DANDRITE's general social life by organizing evening get-togethers, nights out in town and by arranging entertainments and tournaments at festive occasions.

Current Young DANDRITE coordinators:
- PhD student Emil Gregersen
- Postdoc Juliane Martin
- PhD student Nathalie Krauth

YoDa.
Illustration by: PhD student Sophie Seidenbecher

Scientific Advisory Board

The scientific advisory board convenes biannually and provides independent advice on scientific and strategic matters, and evaluations of achievements, ideas and strategies. SAB members are international, highly reputed researchers. The third DANDRITE advisory board meeting took place May 13-15, 2018 and was combined with the yearly retreat. The meeting took place at the conference center Sandbjerg Manor and the 2018 SAB meeting was attended by:

- Professor **Mart Saarma**, University of Helsinki (chair)
- Director **Matthias Wilmanns**, EMBL Hamburg
- Professor **Yang Dan**, University of California, Berkeley
- Professor **Moses Chao**, New York University (NYU)
- Professor **Kathleen Sweadner**, Harvard Medical School
- Professor **Glenda Halliday**, Neuroscience Research Australia (NeuRA)
- Professor **Ole Kiehn**, Univeristy of Copenhagen
- Professor **Rüdiger Klein**, Max-Planck-Institute of Neurobiology
- Professor **Carl Petersen**, École polytechnique fédérale de Lausanne EPFL

Associated Researchers

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

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

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

In 2018 Team Leader Tomonori Takeuchi was drawn to Aarhus and associated to DANDRITE as he received the Novo Nordisk Foundation's prestigious Young Investigator Award which comes with DKK 20.0 million. Tomonori Takeuchi came from the Centre for Discovery Brain Sciences at the University of Edinburgh, where he has been a Postdoctoral Research Fellow since moving there from Japan.

In 2018 Professor Jørgen Kjems joined as Affiliated Researcher to DANDRITE. An association that comes natural as Kjems has active project collaborations with several group leaders at DANDRITE: Denham and Nykjær.

DANDRITE Affiliated Researchers

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

JØRGEN KJEMS

Nanomedicine
The Kjems lab investigates the function and biomarker potential of non-coding RNA in brain and peripheral nervous system. In particular, they study the role of microRNA and circular RNA in neuronal development and their potential function in neuronal diseases including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and temporal lobe epilepsy. The lab also develops methods for delivery of RNA and protein drugs across the blood brain barrier using multivalent self-assembled scaffold and exosomes.

Highlights for 2018:
- Patent issued: Circular RNA for inhibition of microRNA, Patent WO/2014/082644.
- Patent application filed: LNA BASED NAN ODEVICE PatentWO/2019/007930
- Spin-off company started: http://omiics.com/: Next Generation Sequencing (NGS) service

JANE HVARREGAARD CHRISTENSEN

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

Highlights for 2018:
- Discovery of the first genome wide significant loci in nocturnal enuresis
- Publication of study: Qvist P, Eskildsen SF, Hansen B, Baragji M, Ringgaard S, Roovers J, Paternoster V, Molgaard S, Corydon TJ, Stødkilde-Jørgensen H, Glerup S, Mors O, Wegener G, Nyengaard JR, Børglum AD, **Christensen JH** (2018) Brain volumetric alterations accompanied with loss of striatal medium-sized spiny neurons and cortical parvalbumin expressing interneurons in Brd1+/- mice. *Scientific Reports*, Vol. 8, No. 1
- Contributed to study: Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression published in *Nature Genetics*
- Entered the program group for Diseases and brain injuries within the "Human First" initiative

KARIN LYKKE-HARTMANN

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

Highlights for 2018:
- Publication of study: Toth AE, Siupka P, Augustine TJP, Venø ST, Thomsen LB, Moos T, Lohi HT, Madsen P, **Lykke-Hartmann K**, Nielsen MS (2018) The Endo-Lysosomal System of Brain Endothelial Cells Is Influenced by Astrocytes In Vitro. *Mol Neurobiol.* Vol. 55, No. 11, p. 8522-8537
- Publication of study: Staehr C, Hangaard L, Bouzinova EV, Kim S, Rajanathan R, Boegh Jessen P, Luque N, Xie Z, **Lykke-Hartmann K**, Sandow SL, Aalkjaer C, Matchkov VV (2018) Smooth muscle Ca2+ sensitization causes hypercontractility of middle cerebral arteries in mice bearing the familial hemiplegic migraine type 2 associated mutation. *J Cereb Blood Flow Metab.* No. 271678X18761712

- Former PhD student Toke Jost Isaksen receives Aarhus University Research Foundation PhD Award. Using mice tests Isaksen has localised a defect in the sodium-potassium pump found in brain cells. The discovery may affect future treatment of neurological disorders....

MORTEN SCHALLBURG NIELSEN

Receptor mediated drug delivery to the brain
We are focusing on receptor trafficking in brain endothelial cells, to find effective ways to deliver drug from the blood to the brain. We are using highly advanced Blood-Brain-Barrier in vitro models base on primary endothelial cells, astrocytes and pericytes from pig and rats. In combination with high content screening systems and spinning disk confocal imaging we are mapping how recycling and retrograde transported receptors are internalized and traffics in the subcellular vesicles in the endothelial cells. The aim is to identify receptors that are optimal for transcytosis of drugs.

Highlights for 2018:
- Publication of study: Toth AE, Siupka P, P Augustine TJ, Venø ST, Thomsen LB, Moos T, Lohi HT, Madsen P, Lykke-Hartmann K, **Nielsen MS** (2018) The Endo-Lysosomal System of Brain Endothelial Cells Is Influenced by Astrocytes In Vitro. *Mol Neurobiol.* Vol. 55, No. 11, p. 8522-8537
- Extension of Lundbeck grant supporting Research initiative on Blood Brain and Drug Delivery (RIBBDD)
- New Horizon 2020 IMI2 grant on advanced BBB stem cell models

MARINA ROMERO-RAMOS

CNS Disease Modelling Group & NEURODIN: Study and Characterization of the neurodegenerative event in Parkinson's Disease and the associated immune response
My lab works on understanding the progressive changes related to the neurodegenerative process of α-synucleinopathies, such as Parkinson's Disease. We study early pathological changes induced by the mishandling of α-synuclein using in vivo modeling of the disease, behavioral tests, PET imaging, followed by anatomical analysis of brain pathology and the different cell populations relevant in disease using histological techniques. We also investigate the potential of novel neuroprotective strategies in different animal models of the disease.

During the last eight years our lab has investigated the immune response and the role of immune cells, both in brain but also in the periphery, in the disease progression. For this, besides the techniques mentioned, we also use cytometry to analyze immune cell populations. We perform rodent studies as well as analysis of human derived samples. Our main focus is to further understand, the different cell populations as well as the proteins involved in the neuroinflammatory process of these diseases with an ultimate focus on describing novel targets for therapy and define disease biomarkers.

Highlights for 2018:
- Dr. Romero-Ramos' interest for the immune response in Parkinson's Disease has resulted in a review article focused on role of α-synuclein in the neuro-inflammatory event occurring in the disease (Ferreira & Romero-Ramos, 2018).
- During the last year, the lab has shown that disease modified α-synuclein in periphery induces immune response that will affect both peripheral immune cells, but also microglia in brain, thus highlighting the interplay periphery-brain in Parkinson's Disease (Olesen et al., 2018).
- In collaboration with Dr. Stefanova at Innsbruck Univ. we have shown that early and maintained microglia activation is related to the neurodegenerative event occurring in a model of multiple system atrophy where α-synuclein overexpress in oligodendrocytes (Refolo et al., 2018).
- Dr. Romero-Ramos has been invited to become a Senior Editor of the journal Brain Research (Elsevier).

OLAV MICHAEL ANDERSEN

Transport receptors in neurodevelopment and degeneration (TREND)
We study the SORL1 gene and its translation product, SORLA during neurogenesis and neurodegeneration. SORL1 is associated with Alzheimer's disease, and we try to learn how genetic variations affect gene function, including alternative splicing and transcription, and why SORLA is downregulated in brain areas of patients with dementia.
We develop new animal models to determine the physiological function of SORL1/SORLA, including a role during eye development and synaptic function in the neuroretina.

Highlights for 2018:
- Member of the program commitee for the Brain Prize meeting on Alzheimers disease
- Published the first paper on a SORL1 splice isoform
- Patent: Olav M. Andersen, Yonglun Luo, and Charlotte B. Sørensen (2018) Genet-

ically modified SORL1 pig as a model of Alzheimer's disease (EP Application No. 18199331.2; TECH-2018-631-120)

THOMAS BOESEN

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

Highlights for 2018:
- Structure determination of LeuT in new inward facing conformation

MARCO CAPOGNA

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

Highlights for 2018:
- Setting up of electrophysiological investigation of human cortical sections at AU
- Characterization of the action of mGlu receptors at human cortical synapses (published in Frontiers in Cellular Neuroscience 2019)
- Discovery of nitric oxide-expressing GABAergic neurons of the rodent amygdala activation by sleep

ARNE MÖLLER

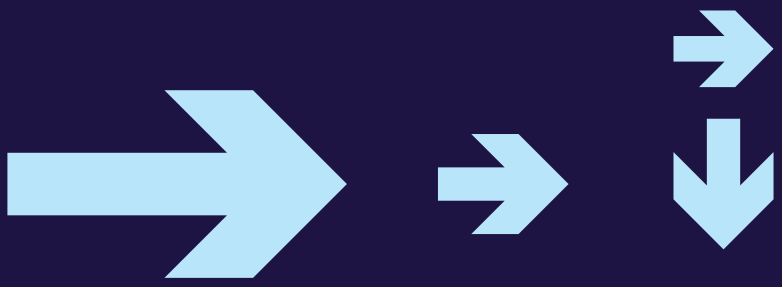
Structural characterisation of membrane protein complexes
We use cryoEM to characterize 3D structures of membrane proteins. We set our focus on the analysis of the dynamics of trans-membrane transporters that actively translocate substrates through the lipid bilayer and neuronal surface receptors that are involved in trafficking and signaling. We are also pursuing methods development to improve EM-imaging and optimize the sample.

CHRISTIAN VÆGTER

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

Highlights for 2018:
- Publication of study: Peripheral Glial Cells in the Development of Diabetic Neuropathy in *Frontiers in Neurology* (Gonçalves et al., 2018)
- Publication of study: An alternative transcript of the Alzheimer's disease risk gene SORL1 encodes a truncated receptor in *Neurobiology of Aging* (Blechingberg et al., 2018)
- External funding attracted: PhD student Alana Pinhiero received fellowship from Lundbeckfonden
- External funding attracted: Vægter is partner on project funded by Innovation Fund Denmark: "Modulation of neuropathic pain by glial targeting - Grand Challenge"

02 Research Activities



Nissen Group

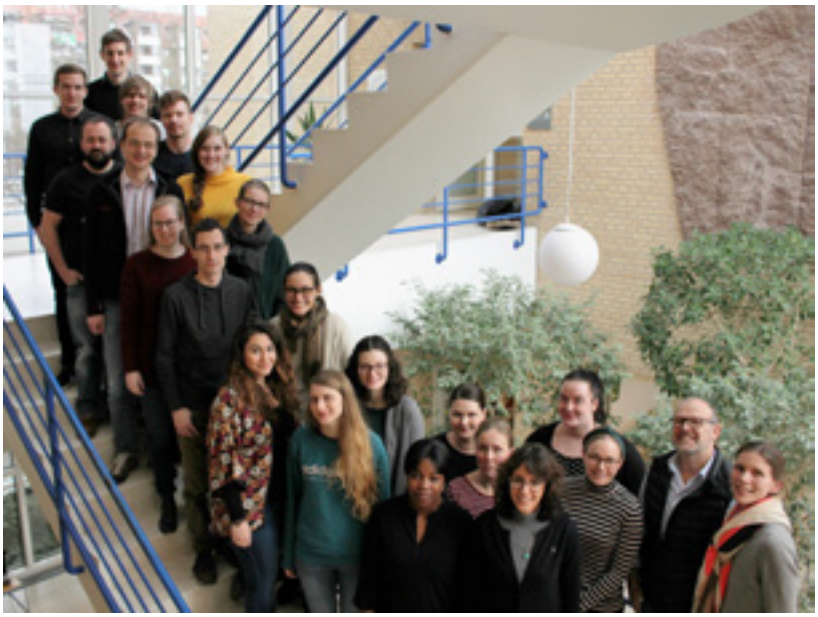
Structural and Functional Studies of Membrane Transporters in Brain

Professor
Poul Nissen

The Nissen lab investigates molecular mechanisms of membrane transport processes and higher-order structures of neuronal membranes. Activities are mainly focused on cryo-electron microscopy, protein crystallography, biochemistry and biophysics, and include also collaborative studies through e.g. small-angle X-ray scattering, molecular dynamics simulations, super resolution microscopy, and electrophysiology. Main subjects of research focus on P-type ATPase ion pumps and lipid flippases, Na+ dependent transporters of neurotransmitters and chloride, and transmembrane Tyrosine kinase associated receptors. Derived activities include also structure based drug discovery. A major, long-term goal is to investigate and model higher-order networks in the Axon Initial Segment that integrates circuit inputs and generates the action potentials in firing neurons, and also synaptic structures associated with memory and the molecular mechanism underlying direction-selective function in the visual system.

The P-type ATPase ion and lipid pumps consume more than 50% of ATP in the brain and maintain constantly the vital lipid distributions and ion and lipid gradients that potentiate e.g. ion channels, secondary transporters, membrane dynamics, and regulation of cell volume, ion homeostasis and pH control. Structural studies of Na,K-ATPase and Ca2+-ATPase reveal basic mechanisms of function and disease-mutations, ligand-induced inhibition, and of regulation by post-translational modifications. Modelling of Cu(I)-ATase in complex lipid membranes revealed a role for specific lipids on transport function.

TRANSLATIONAL STUDIES
Effects and possible circumvention of neurological disease-related mutations of Na,K-ATPase are being approached as are interactions of Na,K-ATPase and Ca2+-ATPases with pathological fibrils/aggregates in neurodegenerative disorders. Studies of dysfunctional ATP7B in Wilson's disease takes place in collaboration with the Danish Wilson's Disease Center at Aarhus University Hospital. Structures of the mechanism of action of dimethyl fumarate on RSK/MSK kinases revealed new strategies for drug intervention on signalling pathways associated with e.g. multiple sclerosis.



Nissen group members in stairs in the lab building.
Photo by Magnus Kjærgaard

Figure 1: Schematic diagram showing a mechanism of action of dimethyl fumarate (DMF in yellow), a potent drug used in the treatment of multiple sclerosis and psoriasis. A high-resolution crystal structure revealed the binding site of DMF on the RSK2 kinase, where it forms a covalent binding to a reactive cysteine at an allosteric site. This reaction blocks the activity of the kinase Figure: Andersen et al. 2018

Selected publications 2018

Andersen JL, Gesser B, Funder ED, **Nielsen CJF**, Gotfred-Rasmussen H, Rasmussen MK, Toth R, Gothelf KV, Arthur JSC, Iversen L, **Nissen P** (2018). Dimethyl fumarate is an allosteric covalent inhibitor of the p90 ribosomal S6 kinases. Nat *Commun* **9**:4344

Autzen HE, Koldsø H, Stansfeld PJ, Gourdon P, Sansom MSP, Nissen P (2018). Interactions of a Bacterial Cu(I)-ATPase with a Complex Lipid Environment. *Biochemistry* **57**, 4063-4073

Midtgaard SR, Darwish TA, Pedersen MC, Huda P, Larsen AH, Jensen GV, Kynde SAR, Skar-Gislinge N, Nielsen AJZ, Olesen C, Blaise M, Dorosz JJ, Thorsen TS, Venskutonytė R, Krintel C, Møller JV, Frieling-haus H, Gilbert EP, Martel A, Kastrup JS, Jensen PE, Nissen P, Arleth L (2018). Invisible detergents for structure determination of membrane proteins by small-angle neutron scattering. *FEBS J* **285**, 357-371

Personnel List Nissen Group

Senior Researcher **Thomas Lykke-Møller Sørensen**
Assistant Professor **Esben Quistgaard**
Assistant Professor **Joseph Lyons**
Assistant Professor **Michael Voldsgaard Clausen**
Postdoc **Antoni Kowalski**
Postdoc **Henriette Autzen**
Postdoc **Michael Habeck**
Postdoc **Montana Caballero Bermejo**
PhD Student **Aljona Kotsubei Sitsel**
PhD Student **Caroline Marie Teresa Neumann**
PhD Student **Jakob Ulstrup**
PhD Student **Jeppe Achton Nielsen**
PhD Student **Jonathan Juhl**
PhD Student **Josephine Nissen**
PhD Student **Lars Sørensen**
PhD Student **Marlene Uglebjerg Fruergaard**
PhD Student **Milena Milena Timcenko Tronsgaard**
PhD Student **Paula Szalai**
PhD Student **Samuel Hjorth-Jensen**
PhD Student **Sigrid Thirup Larsen**
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Group Leader, Professor **Poul Nissen**

Jensen Group

Neurodegenerative Disease

Professor
Poul Henning Jensen

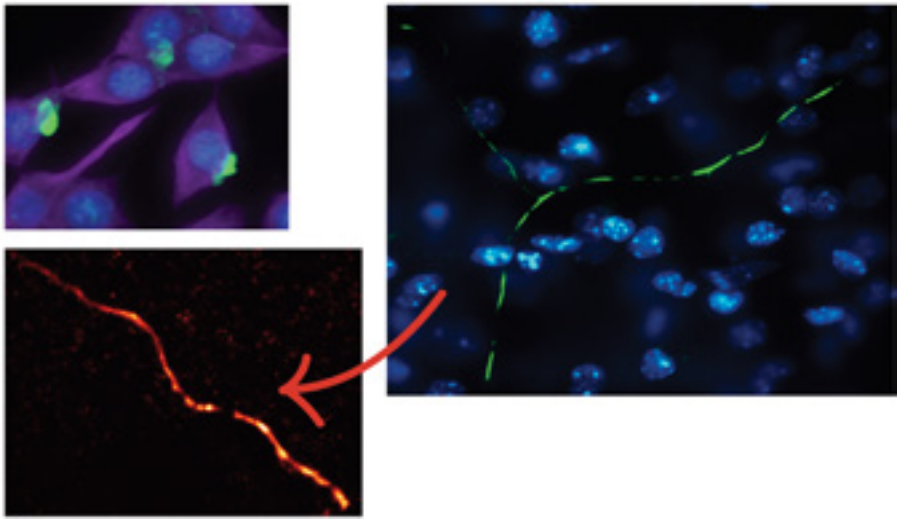
The Jensen group is studying how α-synuclein contributes to the neurodegenerative processes in Parkinson's disease, Lewy body dementia and multiple systems atrophy, which are hallmarked by prion-like spreading of intracellular aggregates of α-synuclein in the nervous system.

This is investigated in studies of α-synuclein aggregates in vitro, in cell models, transgenic animals and human tissue and involves development of new tools and methods.

Focus areas are:
1) How the early phase of the α-synuclein aggregate build-up sculpts the degenerative process in and between neurons thereby contributing to patients' symptomatology by dysfunctional but still living neurons that offset normal circuitries. Investigations penetrate the molecular structure of α-synuclein aggregates generated in cells and brains with the aim of establishing structure-function relations.

2) How cell- and environmental-factors are contributing to the folding of specific "strains" of α-synuclein aggregates that displays different properties with respect to cellular effects and in vivo propagation and toxicity. The structure of the individual strains is also subject to structural analyses with the aim of generating specific binders.

3) The expression level of brain α-synuclein represents a clinical risk factor. We study how different kinases and environmental stress factors regulates expression of α-synuclein.



Examples of induction of intracellular aggregation of endogenous α-synuclein by seeding with exogenous preformed α-synuclein fibrils.
Top left) Development of intracellular phospho-Ser129 positive α-synuclein inclusions (green) in rat glia cells expressing human α-synuclein upon treatment with exogenous preformed phosphorylation-incompetent Ser129Ala mutant α-synuclein fibrils. Tubulin is labeled in cyan. Photo: PhD student Emil Gregersen
Top right panel) Axonal phospho-Ser129 positive α-synuclein Lewy neurite-like aggregates (green) in mouse brain tissue treated with preformed α-synuclein fibrils as in top left panel. Nuclei are labeled in blue using DAPI. Photo: PhD student Sara El-Farrash and M.Sc. student Nanna Møller Jensen.
Lower left panel) Super-resolution microscopic imaging of the axonal phospho-Ser129 positive α-synuclein aggregates (orange color) using STORM microscopy. Photo: Jervis Vermal Thevathasan and Jonas Ries, EMBL Heidelberg.

Jensen group members at the project day when Denmark played 1:1 against Australia in the World Cup.
Photo by PH Jensen

Selected highligts 2018

A decreased cytosolic calcium concentration as an early decisive effect of cellular α-synuclein aggregate stress due to SERCA calcium pump activation
(Betzer et al., EMBO Report)

A novel ELISA assays to quantify pathological α-synuclein oligomers
(Lassen et al., PlosOne)

Inflammation kinase PKR phosphorylating α-synuclein and contributing to its cytotoxicity
(Reimer et al., Neurobiol. Dis.)

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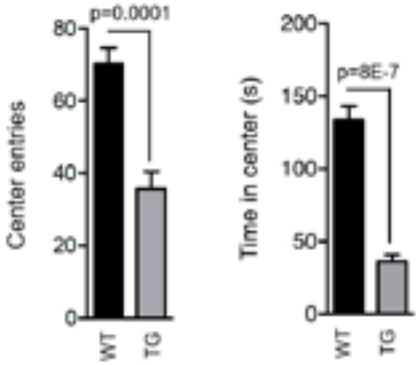
Postdoc **Fikret Emre Kapucu**
Postdoc **Nelson Ferreira**
PhD Student **Emil Gregersen**
PhD Student **Lasse Reimer**
PhD Student **Lixiang Jiang**
PhD Student **Rikke Hahn Kofoed**
PhD Student **Sara Elfarrash**
Bioanalyst **Jette Bank Lauridsen**
Laboratory Technician **Golshah Ayoubi**
Research Assistant **Hjalte Gram**
Group Leader, Professor **Poul Henning Jensen**

Nykjær Group

Receptor Biology

PROMEMO
CENTER FOR PROTEINS IN MEMORY

Professor
Anders Nykjær



Increased anxiety in a transgenic mouse model. Illustration by Dongik Park

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 are most highly expressed in neurons but are also present in some specialized cell types outside the nervous system.

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

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

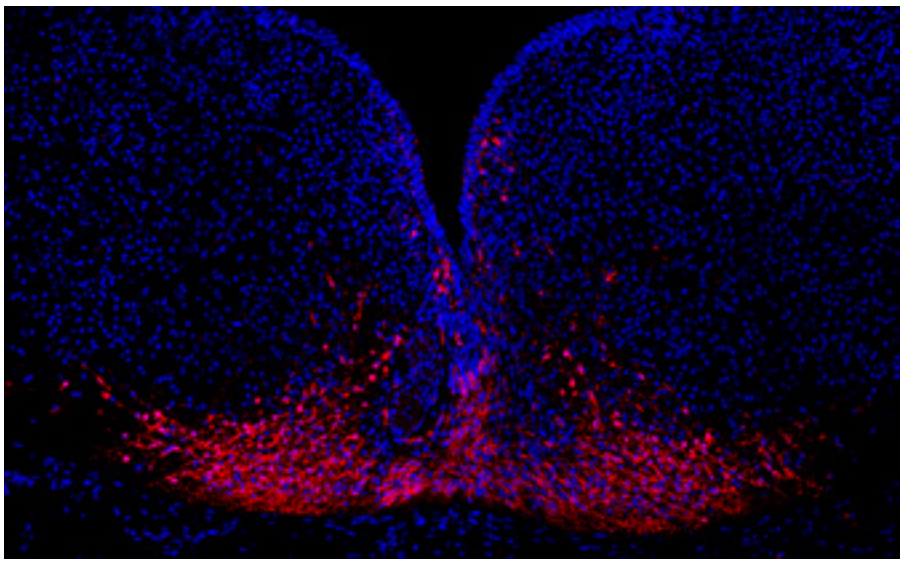
Cessation of alcohol abuse is hindered by affective and physiological components including epilepsy resulting from alcohol withdrawal. While in some populations these symptoms are particularly severe, other ethnic groups are less afflicted suggesting that the genetic makeup plays a key role in the susceptibility. In collaboration with geneticists at Yale University, we identified SORCS2 as a risk gene for development of withdrawal symptoms among European-Americans. In accordance with stress playing a detrimental role on the relapse frequency, we found a causal relationship between stress hormone levels and expression of SorCS2.

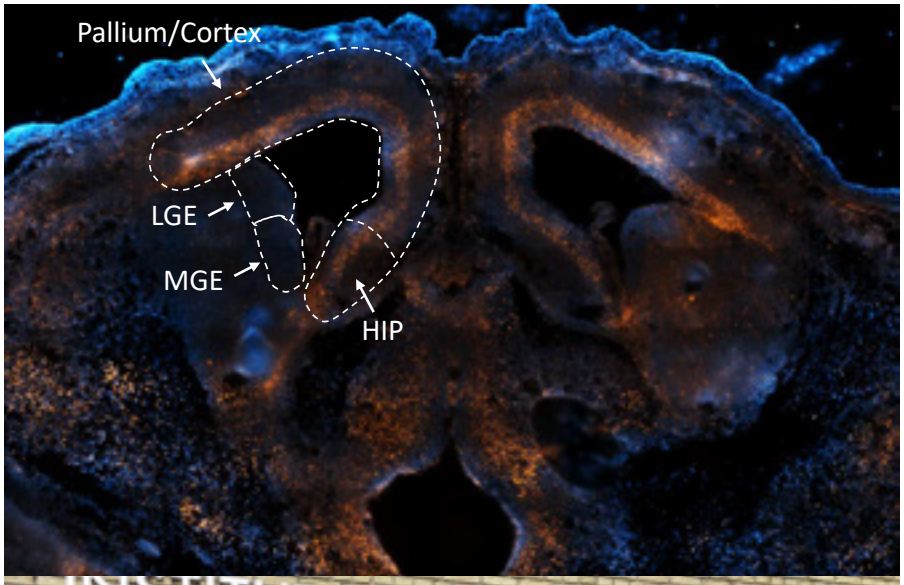
An important consequence of alcohol withdrawal is oxidative stress, which is considered implicated in some of the key symptoms including seizure. Together with scientists at Max-Delbrück-Center for Molecular Medicine, Berlin, we found that SorCS2 is protective against oxidative stress by translocating a transporter for the amino acid cysteine to the cell surface of neurons.

The gene encoding SorLA is genetically associated with risk of Alzheimer's Disease by regulating the production of the peptide amyloid-beta, which damages neurons and leads to their degeneration. We identified a new and shorter variant of SorLA that is predicted not to regulate the production of the pathogenic peptide. This suggest that SorLA may exhibit functions that go beyond regulating neuronal cell fate.

Frontotemporal lobar degeneration is after Alzheimer's Disease the second most common cause of senility in the western world. In collaboration with a genetic consortium led by scientists at the Mayo Clinic, Florida, we found that GFR-alpha2, a receptor for a neuronal growth factor, modifies disease risk and age of onset in patients with frontotemporal lobar dementia.

Visualization of dopaminergic neurons at E14.5 during mouse embryogenesis. Illustration by Alena Salasova





In situ hybridization of a receptor in sections of embryonic mouse brain. Specific brain regions are indicated. Illustration by Peter Lund Ovesen

Nykjaer group members
Photo by Else Magård

Selected highligts 2018

In 2018, the Center of Excellence, PROMEMO, was inaugurated, financed by the Danish National Research Foundation and led by Anders Nykjær. The center, which is a spin-off of DANDRITE, aims to understand the proteins and circuits that are critical for consolidation of memories.

Selected publications 2018

Smith AH, Ovesen PL, Skeldal S, Yeo S, Jensen KP, Olsen D, Diazgranados N, Zhao H, Farrer LA, Goldman D, Glerup S, Kranzler HR, Nykjaer A, Gelernter J. (2018) Risk Locus Identification Ties Alcohol Withdrawal Symptoms to SORCS2. Alcohol Clin Exp Res. 42(12):2337-2348

Blechingberg J, Poulsen ASA, Kjølby M, Monti G, Allen M, Ivarsen AK, Lincoln SJ, Thotakura G, Vægter CB, Ertekin-Taner N, Nykjær A, Andersen OM. (2018) An alternative transcript of the Alzheimer's disease risk gene SORL1 encodes a truncated receptor. Neurobiol Aging. 71:266.e11-266.e24

Pottier C, Zhou X, Perkerson RB 3rd, ..., Noel Sabbagh M, Kjolby M, Nykjaer A, Karydas AM, ..., Dickson DW, Biernacka JM, Rademakers R. (2018) Potential genetic modifiers of disease risk and age at onset in patients with frontotemporal lobar degeneration and GRN mutations: a genome-wide association study. Lancet Neurol. 17(6):548-558

Malik AR, Szydlowska K, Nizinska K, Asaro A, van Vliet EA, Popp O, Dittmar G, Fritsche-Guenther R, Kirwan JA, Nykjaer A, Lukasiuk K, Aronica E, Willnow TE. (2019) SorCS2 Controls Functional Expression of Amino Acid Transporter EAAT3 and Protects Neurons from Oxidative Stress and Epilepsy-Induced Pathology. Cell Rep. 26(10):2792-2804. In press 2018

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Group Leader, Center Director, Professor **Anders Nykjær**

Denham Group

Stem Cells

Group Leader
Mark Denham

We study how the human nervous system develops and the processes involved in neurodegeneration. To do this, we use human pluripotent stem cells, which have the unique ability to give rise to all cell types of the body, and by differentiating them into particular neuronal lineages, we investigate developmental or disease processes, in a human context. Specifically, our laboratory is interested in understanding how mesencephalic dopaminergic (mesDA) neurons develop, the cells that are predominantly affected in Parkinson's disease patients.

Furthermore, we are using patient-specific induced pluripotent stem cells (iPSCs) to generate diseased neurons, and by combining in vitro neuronal activity analysis with next-generation sequencing, we aim to detect early pathological gene-expression changes. The overall goals are to identify new disease mechanisms that may be used in the development of novel drug targets for treating Parkinson's disease and other neurodegenerative disorders.

MOLECULAR MECHANISMS CONTROLLING PARKINSON'S DISEASE SUSCEPTIBILITY

Within our lab, we have generated a bank of Parkinson's diseased iPSC lines reprogrammed from a diverse range of familial Parkinsonian patient skin samples (Fig1). With these cell lines, we are investigating genetic mechanisms that contribute to disease susceptibility. In particular, we are interested in the glucocerebrosidase (GBA) heterozygous mutation, a mutation that results in a compromised lysosomal/autophagic pathway. GBAhet mutations are the most common risk factor for developing PD, and the pathology is similar to idiopathic PD. However, not all GBAhet carriers develop the disorder, and the reason for the variability in penetrance is unknown, as such we are investigating what mechanisms in addition to GBA regulate disease severity.

To date, we have successfully generated GBAhet derived-neurons from iPSCs and developed a culture system whereby we can detect deficits in synaptic activity using a multi-electrode array (Fig2). Furthermore, by performing RNA sequencing, we have identified an RNA binding protein that is dysregulated in GBAhet neurons and shown that this imbalance can lead to an increase in Alpha-synuclein, the principal protein that is misfolded and aggregated in PD. Using ATAC sequencing, we are now further investigating what mechanism is responsible for this dysregulated expression. Overall, understanding the genetic mechanisms that contribute to the risk of developing PD is highly relevant for sporadic cases and can lead to new therapeutic targets.

REGULATION OF NEURAL PROGENITOR CELL FATES

We are investigating the processes involved in the differentiation of stem cells into neuronal subtypes, specifically the factors involved in the specification of mesDA neurons. Numerous transcription factors are known to be involved in dictating cell fate; however, the regulatory mechanism that controls transcription factor expression is poorly understood. Our laboratory is interested in understanding the contribution of both coding and non-coding RNA in mesDA neuron development. Recently we mapped the transcriptome from pluripotency to a mesDA neuronal identity and identified over two hundred circRNAs and over eighty miRNAs that are highly variable in expression across the developmental stages. Currently, we are characterising two miRNAs that may be involved in regulating floor plate differentiation. Specifically, we are examining what genes the miRNAs target and what effect this has during development. Additionally, in collaboration with Jøgen Kjems' laboratory, we are studying the involvement of circRNA. Overall, determining how gene expression is regulated during development by coding and non-coding RNA and how this interplay influences cell identity is crucial not only for understanding developmental processes but also for understanding how a cell maintains cellular homeostasis.

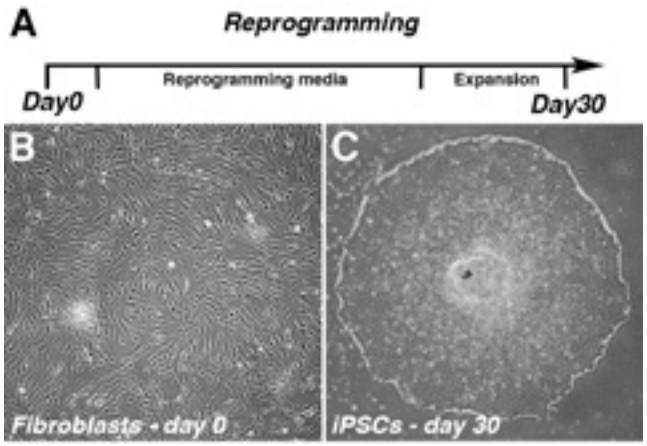


Fig 1: (A) 30 day sendai virus reprogramming protocol used to convert human patient fibroblast cells into induced pluripotent stem cells in defined media. (B) Image shows human fibroblast cells prior to reprogramming, (C) and right image shows a successfully reprogrammed iPSC colony. Illustration by Susanne Buchholdt.

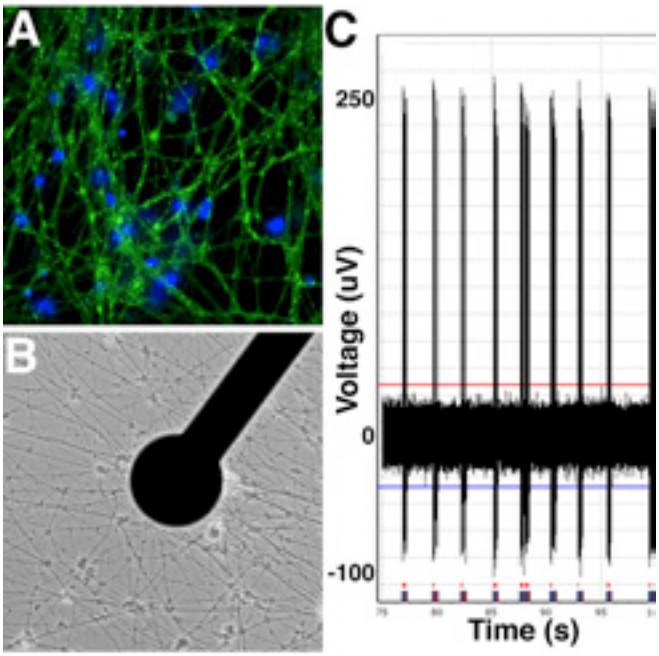
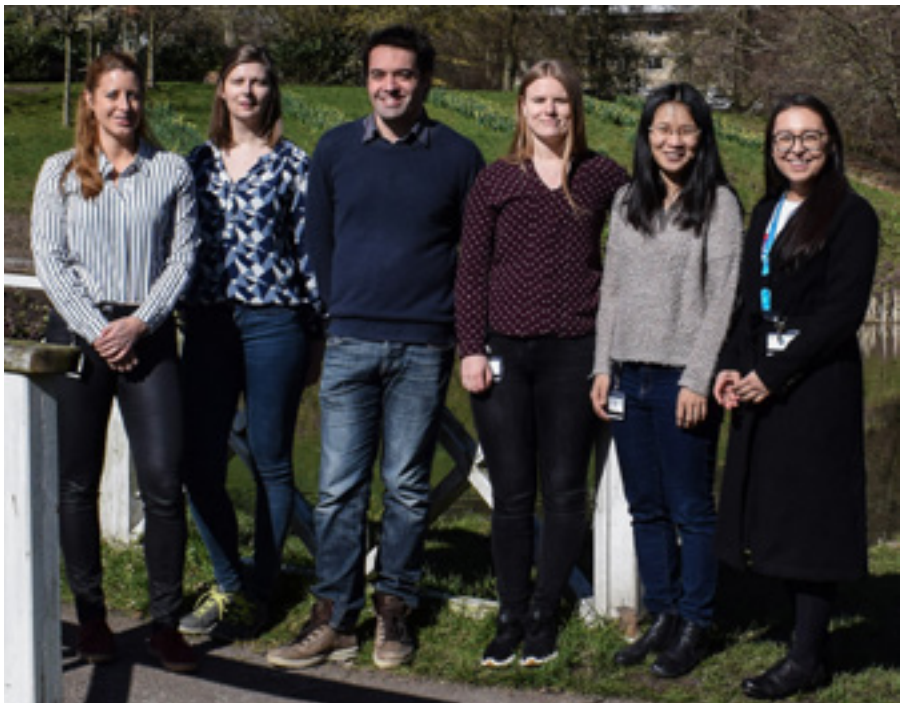


Fig 2: (A) Neurons derived from patient iPSCs. (B) Neurons cultured on multi-electrode array. (C) MEA recording of neurons. Illustration by Muwan Chen and Katherine Gill



Denham group members in the campus park at Aarhus University. Photo by: Laboratory Technician Susanne Hvolbøl Buchholdt

Publications 2018

Chen M, Laursen SH, Habekost M, Knudsen CH, Buchholdt SH, Huang J, Xu F, Liu X, Bolund L, Luo Y, Nissen P, Febbraro F, **Denham M** (2018) Central and Peripheral Nervous System Progenitors Derived from Human Pluripotent Stem Cells Reveal a Unique Temporal and Cell-Type Specific Expression of PMCAs. *Frontiers in Cell and Developmental Biology*

Knudsen C, Ásgrímsdóttir ES, Rahimi K, Gill KP, Frandsen S, Buchholdt SH, Chen M, Kjems J, Febbraro F, **Denham M** (2018) A modified monomeric red fluorescent protein reporter for assessing CRISPR activity. *Frontiers in Cell and Developmental Biology*

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Student assistant **Sofie Husted Laursen**
Group Leader **Mark Denham**

Kvitsiani Group

Neuronal basis of decision-making in fruit flies and mice

Group Leader
Duda Kvitsiani

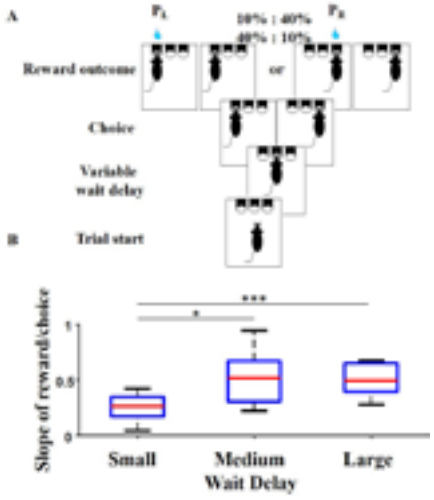


Fig. 1: a). Probabilistic reward foraging task. Mice start the trial by poking their noses into the center port, waiting different amounts of and making choices to the left or right side. Rewards come in a probabilistic way in those ports, and these probabilities change in blocks
b) X axis shows different delays and Y axis – slope of Reward/Choice ratio from multiple sessions. The ratio is calculated by linear fit of a line to sum of Rewards divided by sum of Choices for a sliding window of 20 trials in a given session.
Illustration by Duda Kvitsiani

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

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

MAJOR ACHIEVEMENTS
In the past we have studied probabilistic reward foraging decisions in fruit flies using closed loop optogenetic reward delivery system. This system allows us to study on a trial-by-trial basis how flies integrate reward history into their choices. Using behavioral data from individual flies we built predictive and generative computational models that extract hidden decision variables from observed behavior. Our analysis can demonstrate that flies comply with simple forms of reinforcement learning models and update option values dynamically as they forage in probabilistic environment.

In mice we have set up similar reward foraging task (Fig.1a) to examine how effort is integrated into choices. In this task animals initiate trial by poking into the center port, waiting variable amount of time (effort manipulation) and choosing left or right side to collect probabilistic rewards. Reward probabilities change in blocks and the task of the animal is to adjust it is choices to maximize the reward outcome. Our behavioral analysis showed that animals can adjust their choices according to reward probabilities. We can show that animals integrate delay effort into their choices by making more consecutive choices for previously rewarded side in long delay periods (Fig.1b).We also carry out single unit recordings in the behaving animals to understand how ensemble dynamics encodes reward and choice history.

FUTURE PLANS / PROJECTS / GOALS
In the future, we aim to dissect the contribution of single neurons to decision making and learning in behaving animals. For this, we are developing single cell stimulation tool to manipulate activity of individual neurons. We are developing the patterned light stimulation tool using multimode optical fibers to activate individual neurons in behaving animals. This is a collaborative project and includes groups at Hungarian Academy of Science (Zoltan Somogyvari and Balazs Hangya's labs) in Budapest. Our set up (Fig.2) is able to deliver phase-modulated wavefront of light in living brain tissue together with the high-density electrophysiological recording system.

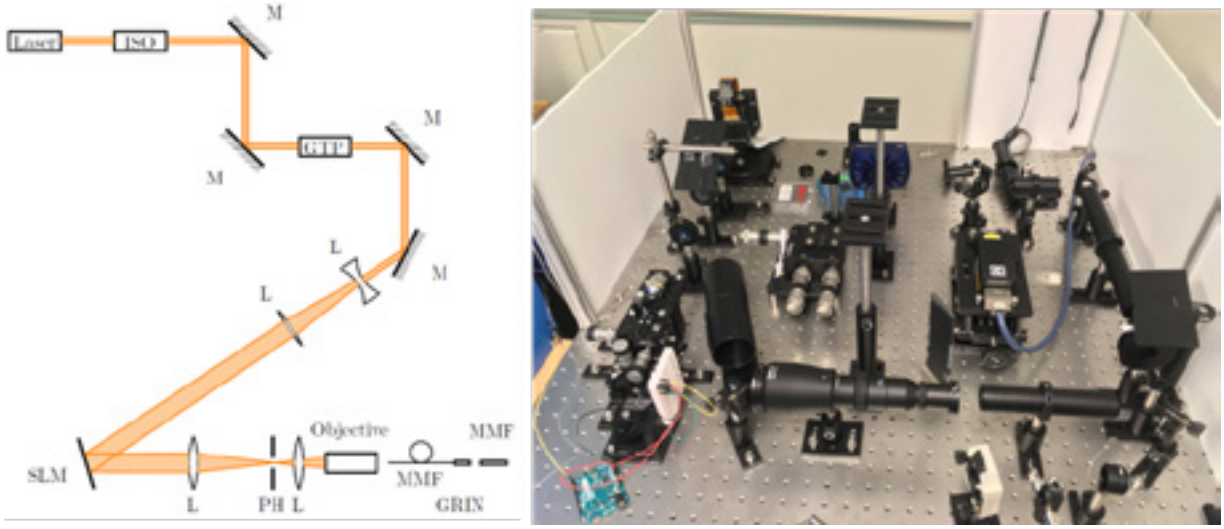
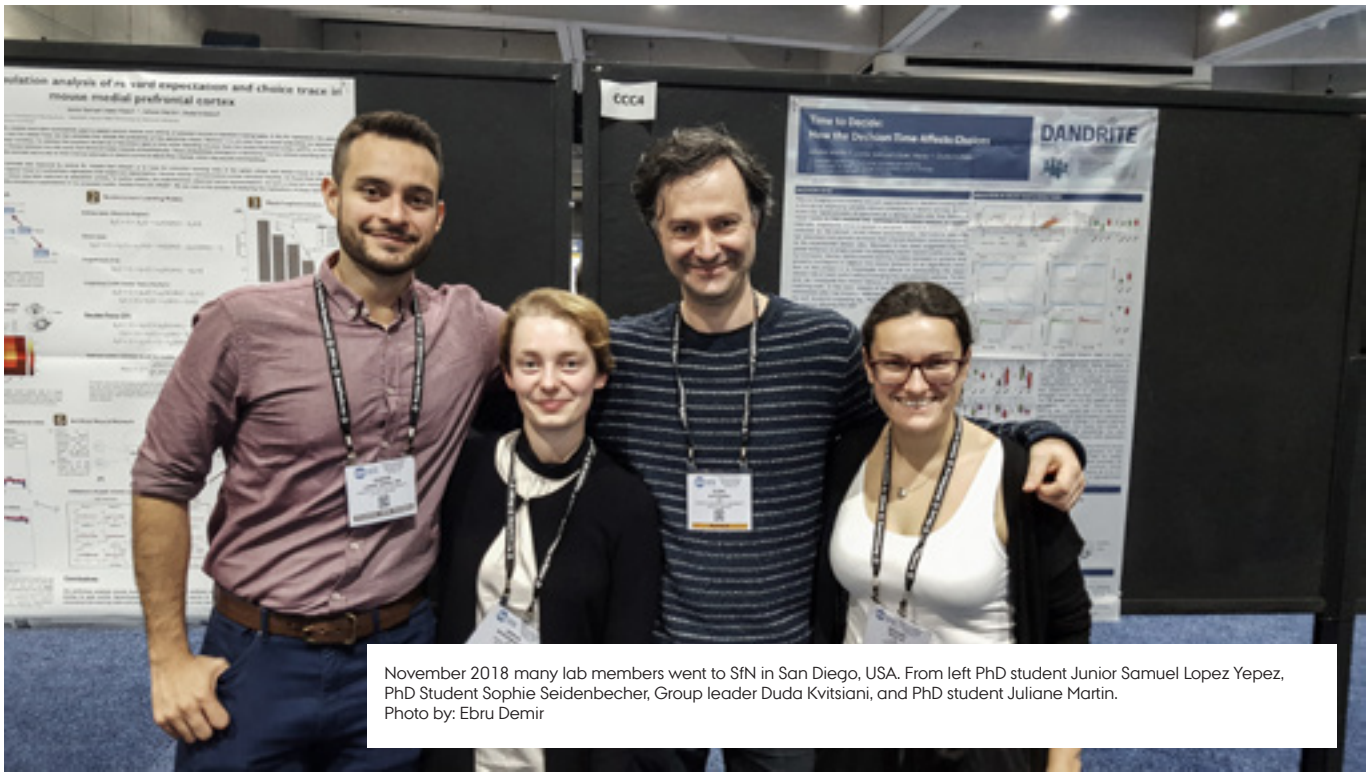


Fig. 2: Generating focus using the SLM- spatial light modulator and CCD camera. Left panel, schematics of experimental setup consisting of laser, ISO-otical isolator, GTP-light polarizer, M-mirror, L lenses for beam expansion, SLM, PH-pinhole, Objective- focusing light onto the MMF- multimode fiber. Right panel – view of the optical set up. Photo Jesper Hagelskjær



November 2018 many lab members went to SfN in San Diego, USA. From left PhD student Junior Samuel Lopez Yepez, PhD Student Sophie Seidenbecher, Group leader Duda Kvitsiani, and PhD student Juliane Martin.
Photo by: Ebru Demir

Key publication

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* June 20; 498(7454):363-6.

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Student Assistant **Eske Hoy Nielsen**
Student Assistant **Maris Sala**
Group Leader, Associate Professor **Duda Kvitsiani**

Nabavi Group

Circuit mechanisms of learning and memory

Group Leader
Sadegh Nabavi

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

FUTURE PLANS / PROJECTS / GOALS

- SYNAPTIC MECHANISMS UNDERLYING MEMORY DECAY. The mechanisms underlying memory decay have been largely neglected, in part due to the technical difficulties as the process occurs in a much slower time scale. We test the hypothesis of whether synaptic depotentiation is a substrate for weakening memories. This is based on our previous works, where we demonstrated: A) induction of LTD weakens a memory; B) beta-amyloid, a causative agent in Alzheimer's disease, induces synaptic depression through a mechanism similar to LTD; C) pre-synaptic release of glutamate can induce an NMDAr-dependent LTD if the calcium influx through the receptor is blocked. We test our hypothesis using optogenetic viral approaches combined with pharmacological manipulation and in vivo electrophysiology in behaving animals
- TRACING THE SYNAPTIC PLASTICITY OF ASSOCIATIVE LEARNING ON A BEHAVIORAL TIMESCALE. The core component of Hebbian plasticity is contiguity, that is the activation of pre- and postsynaptic neurons should temporally coincide. To form an association, Hebbian plasticity requires two events to occur no more than a couple of milliseconds apart. This is in direct contrast to most of our day-to-day learning where we effortlessly associate events that are many seconds to minutes apart. As a first step to investigate the underlying mechanisms for the associative learning with longer timescale, we will use trace fear conditioning, an associative learning in which the two events are separated by many seconds. In this project, we aim to: I) Identify the ensemble regions forming the circuit for the trace condition¬ing. II) Identify the neuronal population encoding the memory trace.

MAJOR ACHIEVEMENTS

- IDENTIFYING PLASTICITY-RELATED PROTEINS: It is believed that during the formation of a memory or in¬duction of long-term potentiation (LTP), a group of proteins (plasticity-related proteins or PRPs) are synthesized. These proteins, it has been proposed, are essential for stabilization of memories and LTP. To identify these proteins, we used a novel biochemical technique that can specifically label newly synthesized proteins. We induced LTP in slices as well as in anesthetized animals. We confirmed the LTP expression biochemically or electro-physiologically. The proteins extracted from the LTP experiments will be characterized using mass spectrometry in the lab of Dr. Yates (UCSD).
- INDEPENDENT OPTICAL EXCITATION OF OVERLAPPING NEURAL POPULATIONS: A fundamental challenge in the field of optogenetics is that all opsins, in addition to their own excitation spectra, are activated by blue light, a problem known as bleed-through. We are tackling this problem by combining excitatory and inhibitory opsins. Using this approach, we developed a system for dual optical excitation in vivo. In this system, neurons expressing a red-shifted channelrhodopsin are activated by red but not blue light (figure 1).
- FUNCTIONAL MAPPING OF BRAIN CIRCUITS USING ACTIVITY-DEPENDENT RETROGRADE TRACING. Any given brain region receives many inputs from highly diverse origins. To understand the contribution of a region to a particular task one must know which of those inputs are activated. To achieve this, current approaches rely on the candidate regions that have been preselected based on previous data. We developed an unbiased approach, which combines activi¬ty-dependent promoters with virus-mediated retrograde labelling. With this approach, we will be able to identify and tag projecting neurons of unknown origins which are active only during a defined period of time. As a proof of concept, we validated our system in circuits that are known to receive defined sensory inputs during a task, including those responsible for processing aversive stimuli (figure 2).

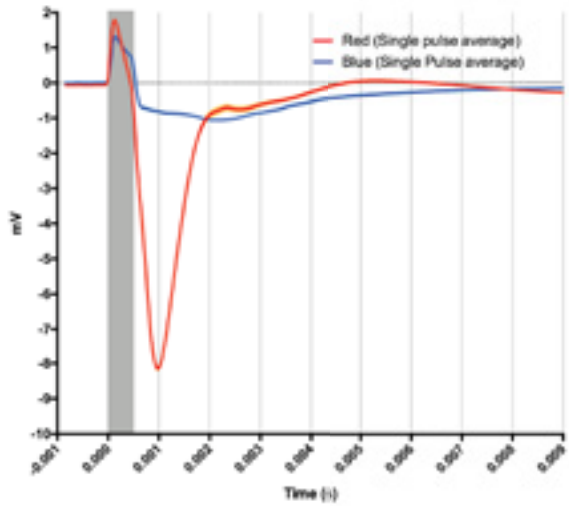
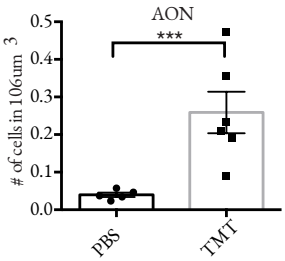
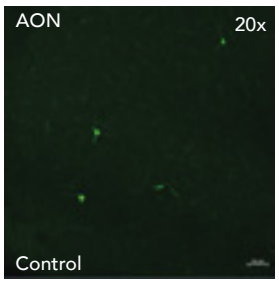


Figure 1: In vivo recording from neurons co-expressing inhibitory opsins. Example of responses to 5 ms of blue and red light (blue and red traces respectively). Note a near 80% reduction in peak response to a blue light. Figure credit: Postdoc Andrea Moreno





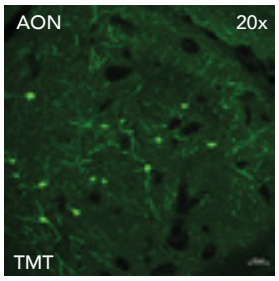


Figure 2: Exposure to an innately aversive odor induces activity-dependent tracing from the cortical amygdala (CoA) to the anterior olfactory nucleus (AON). After TMT exposure, retrograde labeling shows anterior olfactory nucleus as an active input.
Figure credit: PhD students Nathalie Krauth and Valentina Khalil

Nabavi group members in the campus park at Aarhus University.
Photo by Susanne Schousboe Sjøgaard, DANDRITE

Key publication

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

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Laboratory Technician **Kathrine Meinecke Christensen**
Research Assistant **Nehal Hassan**
Scholar student **Pardis Zarifkar**
Group Leader **Sadegh Nabavi**

Philipsborn Group

Behavioral Genetics and Circuit Neuroscience

Group Leader
Anne von Philipsborn

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

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

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

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

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

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

BEHAVIORAL HIERARCHY AND COORDINATION- STATE DEPENDENT ACTION SELECTION
How do different behaviors interact and influence each other on a circuit level? During courtship, some behavioral elements are combined and others exclude each other or occur in a preferred

Publications 2018

A. O'Sullivan, T. Lindsay, **A. Prudnikova**, B. Erdi, M. Dickinson, and **A.C. von Philipsborn** (2018). Multifunctional Wing Motor Control of Song and Flight. *Current Biology*, 28 (17): 2705-2717.

A.C. von Philipsborn; Neurobiology. (Book chapter) in: Insect Behaviour, *From Mechanisms to Ecological and Evolutionary Consequences.* Editors: Cordobar-Aguilar, Gonzalez-Tokman and Gonzalez-Santoyo, Oxford University Press 2018.

Personnel List Philipsborn Group

Postdoc **Bárður Eyjófsson Ellendersen**
Postdoc **Machteld Verzijden**
Postdoc **Stella Nolte**
PhD Student **Angela O'Sullivan**
PhD Student **Peter James Kerwin**
Laboratory Technician **Anna Prudnikova**
Laboratory Technician (Maternity cover) **Markéta Kaderávková**
IT employee **Per Rosing Mogensen**
Research Assistant **Astrid Lauridsen**
Student Assistant **Lasse Østerhaab Sell**
Student Assistant **Tatiana Adamiec**
Group Leader **Anne von Philipsborn**

Philipsborn group members in the old library.
Photo by Maria Thykær Jensen, DANDRITE

sequence. We discovered that dependent on the state of the animal and the behavior 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 state dependent action selection, aiming at identifying circuits and neuromodulators for behavioral hierarchy and coordination. Our findings highlight inhibition as an important mechanism for structuring behavioral sequences, ensuring appropriate, context dependent response to sensory stimuli.

SEX SPECIFIC MOTOR CIRCUITS FOR COMMUNICATION

We discovered that during reproduction, not only male, but also female flies use rhythmic acoustic signals for communication. We find indication that female sound production is correlated with male ejaculate quantity and/or quality, i.e. reproductive potential. Our research indicates that this newly discovered female behavior impacts sperm competition. Females lack most of the male's song neurons and show differential gene expression, which might explain striking differences in the motor output shaped to produce sex-specific sound patterns.

MOLECULAR AND CELLULAR MODELS FOR NEUROLOGICAL DISEASE IN DROSOPHILA

Fundamental mechanisms of nervous system function on the molecular, cellular and circuit level are conserved and shared across vertebrates and invertebrates. Drosophila is a convenient and genetically accessible in vivo model for analyzing the effect of pathological mutations on neuronal physiology. Together with the Kvitsiani group, we harness the potential of genetic screens in Drosophila to study genes, molecules and neurons for reward processing and foraging strategies in an operant behavior task, which will give insight into circuits for motivation, addiction and decision making. Furthermore, we are currently collaborating with Hanne Poulsen at DANDRITE to study disease causing mutations of ATP1A3 in a Drosophila model system and with Poul Henning Jensen to explore calcium dynamics during alpha-synuclein mediated neurodegeneration.

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

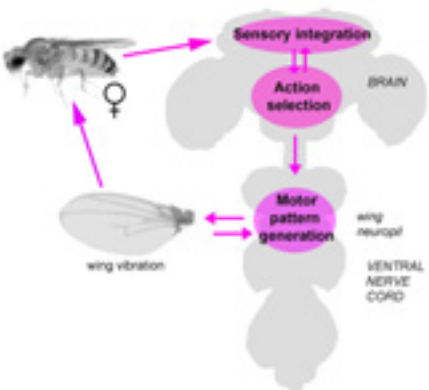


Fig. 2: Schematic of the neuronal circuits for courtship song. Illustration by Anne von Philipsborn

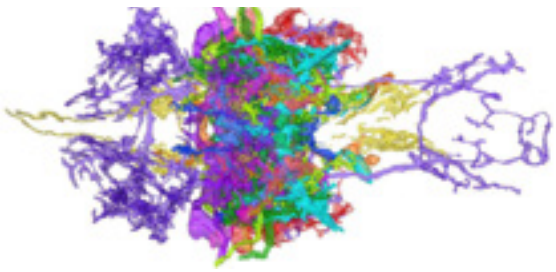
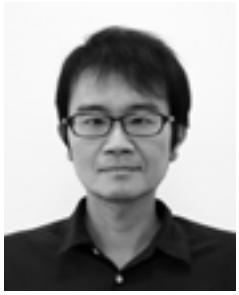


Fig. 3: Reconstruction of 3D arborization patterns of wing motor and premotor interneurons contributing to the patterning of wing movements. Illustration by Anne von Philipsborn

Yonehara Group

Spatially Asymmetric Neural Circuits in Visual System



Team Leader
Keisuke Yonehara

The Yonehara group investigates how spatial asymmetry in the neuronal circuits arises during development and support neural computation in adults using mouse visual system as a model.

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

DYNAMIC INTEGRATION OF SYNAPTIC INPUTS FOR COMPUTING VISUAL MOTION

The direction of visual motion is first extracted by retinal direction-selective circuits and further processed in downstream areas such as thalamus or visual cortex. In the retina, we identified novel spatio-temporally asymmetric circuit motifs that support velocity and direction selectivity of retinal neurons by combining two-photon glutamate imaging (Fig. 1), patch-clamp recordings, and 3D electron microscopy. In the visual cortex, we identified an area, which represent visual motion signals originated from retinal motion-sensitive neurons by in vivo two-photon calcium imaging (Fig. 2) and genetic manipulation of retinal computation. In the next years, we aim to understand the temporal dynamics of circuit components involved in those circuitries and how they are wired together during development.

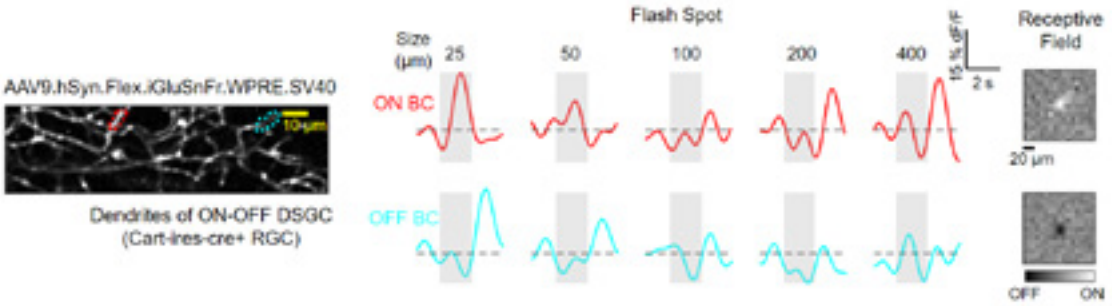


Fig. 1: Exo vivo 2-photon glutamate imaging of the dendrites of retinal DSGCs labeled with iGluSnFr in response to flash spot. Receptive fields of individual bipolar cell (BC) input are mapped by reverse correlation method. Illustration by Akihiro Matsumoto

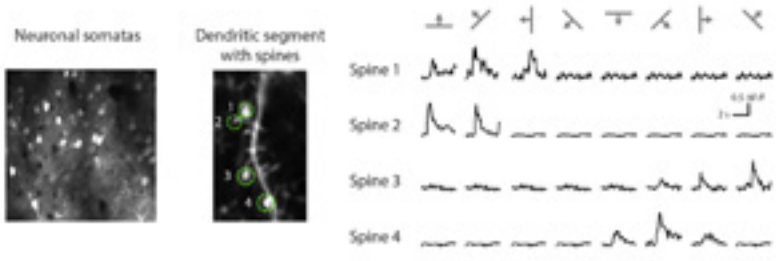
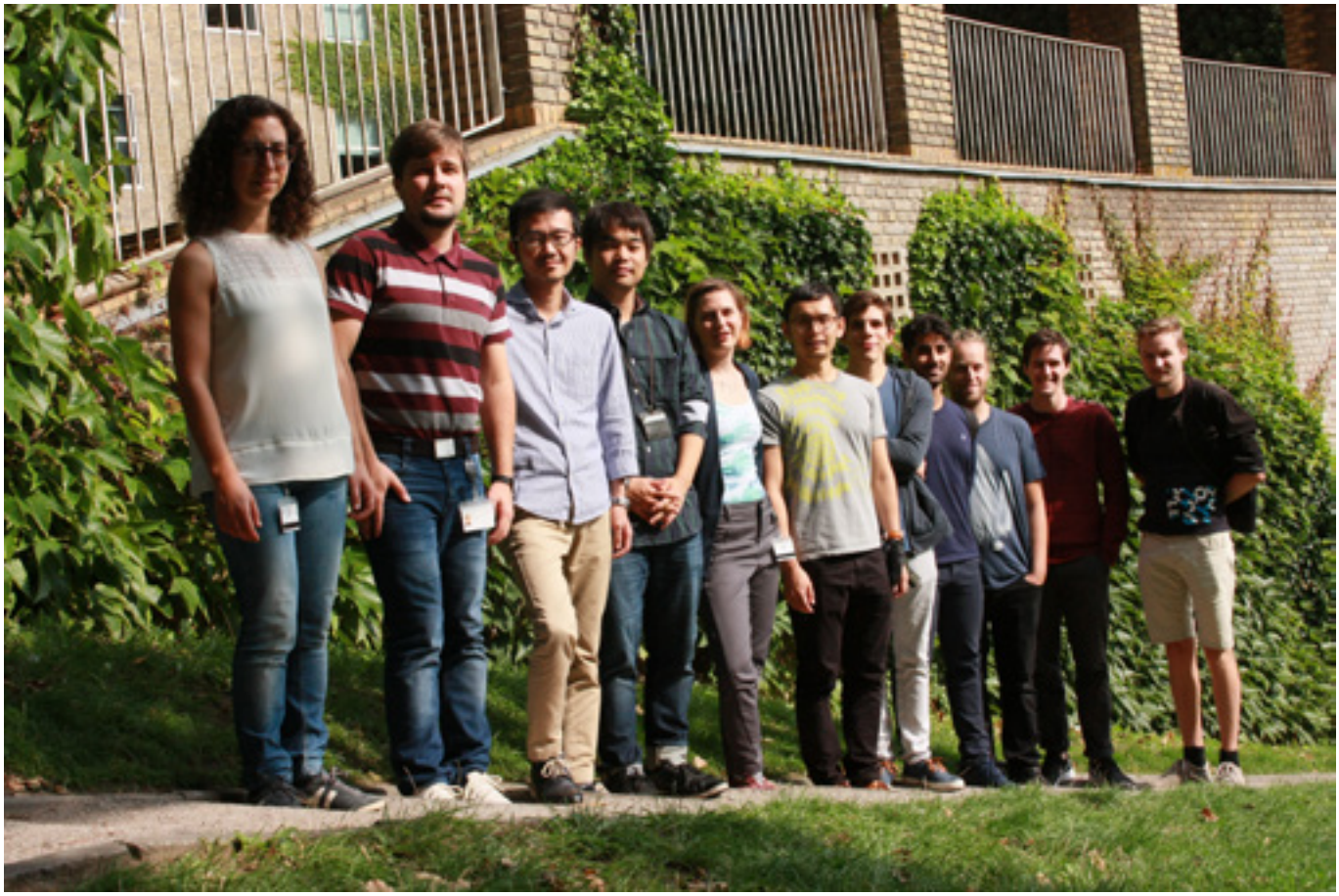


Fig. 2: In vivo 2-photon calcium imaging of neuronal somatas and dendritic spines labeled with calcium indicator GCaMP6 in an anaesthetized head-fixed mouse. Illustration by Rune Rasmussen



Yonehara lab photo taken August 2018.
Photo by Szilard Sajgo.

MOLECULAR MECHANISMS UNDERLYING THE SPATIALLY ASYMMETRIC NEURONAL CONNECTIVITY

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

Selected publications 2018

Oliveira AF, **Yonehara K** (2018) The Mouse Superior Colliculus as a Model System for Investigating Cell Type-Based Mechanisms of Visual Motor Transformation. *Frontiers in Neural Circuits*, Vol. 12, 59

Matsumoto A, **Yonehara K** (2018) Visual Circuits: Division of Labor Revealed. *Current Biology*, Vol. 28, No. 5, p. R208-R210

Schubert R, Trenholm S, Balint K, Kosche G, Cowan CS, Mohr MA, Munz M, Martinez-Martin D, Fläschner G, Newton R, Krol J, Scherf BG, **Yonehara K**, Wertz A, Ponti A, Ghanem A, Hillier D, Conzelmann KK, Müller DJ, Roska B (2018) Virus stamping for targeted single-cell infection in vitro and in vivo. *Nature Biotechnology*, Vol. 36, No. 1, 01.01.2018, p. 81-88.

Personnel List Yonehara Group

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

Kjærgaard Team

Synaptic Plasticity and Intra-cellular Signaling Complexes in Memory Formation

Team Leader
Magnus Kjærgaard

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

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

Receptor activation leads to different downstream events depending on the cellular context, e.g. which other signaling pathways are active. Large flexible molecular assemblies called signaling complexes organized by scaffolding proteins coordinate signaling pathways. These complexes connect receptors to enzymes and substrates. The signaling complexes act as molecular matchmakers by determining which molecules encounter each other. We would like to understand quantitatively how such signaling complexes work at the molecular level. To this end, we have developed a quantitative assay for measuring effective concentrations in signaling complexes, which is likely to be crucial to understand kinase activity in signaling complexes. Furthermore, we develop model systems for understanding the role of synaptic scaffolding proteins that coordinate the supra-molecular structure of signaling pathways.

Key Publication 2018

Kjaergaard M, Dear AJ, Kundel F, Qamar S, Meisl G, Knowles TPJ, Klenerman D (2018) Oligomer Diversity during the Aggregation of the Repeat Region of Tau. ACS *Chem Neurosci.* 9 (12), pp 3060–3071

Personnel List Kjærgaard Team

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

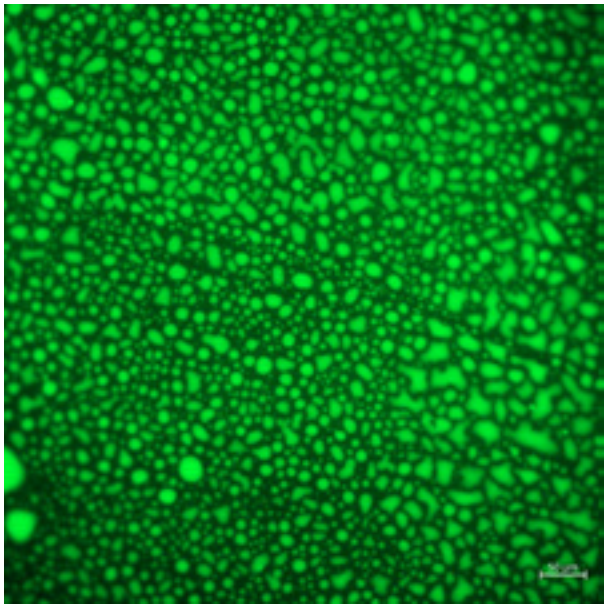
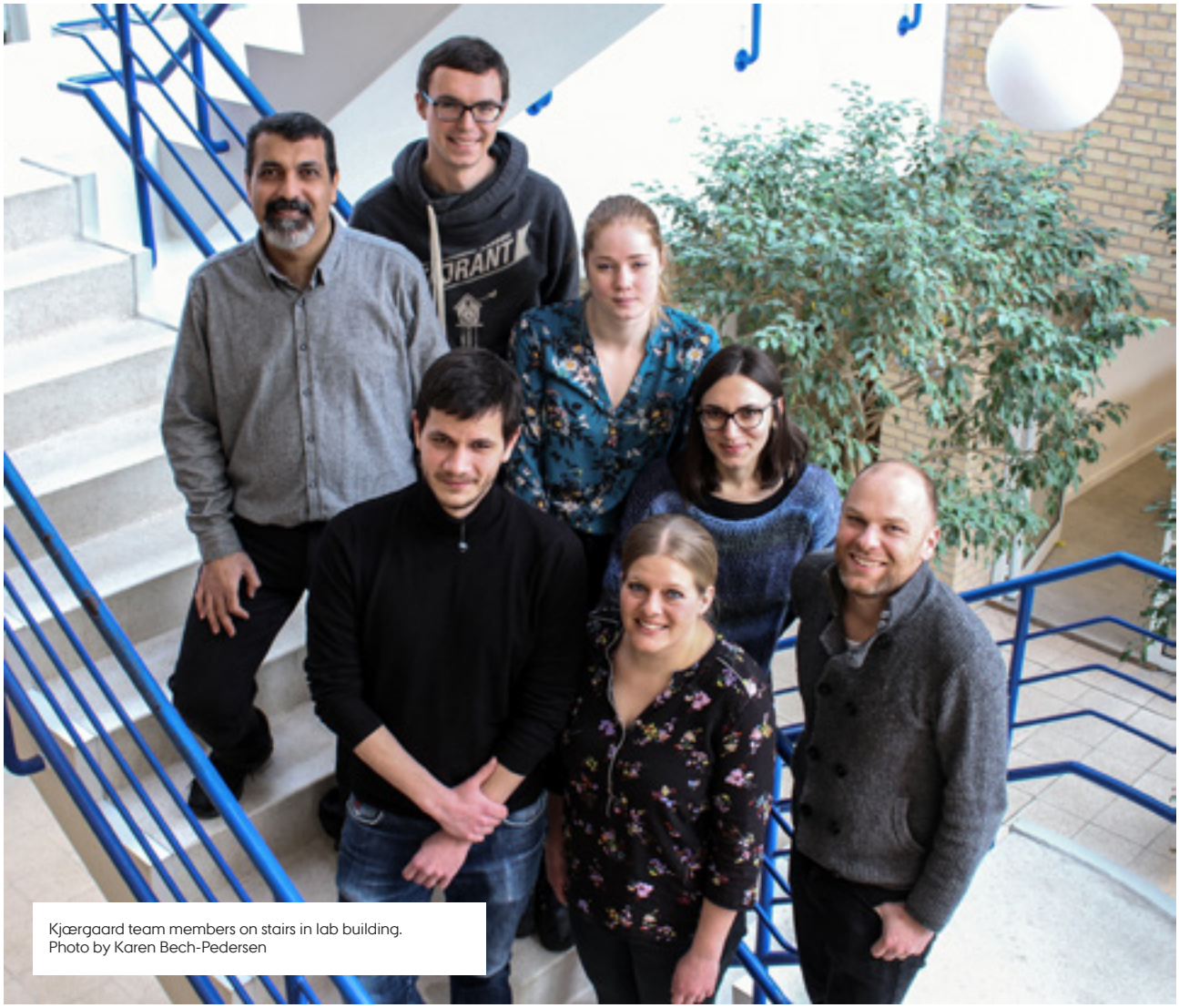


Fig 1: Liquid-liquid phase separation by synaptic scaffolding proteins.
Picture by: Postdoc Xavier Warnet

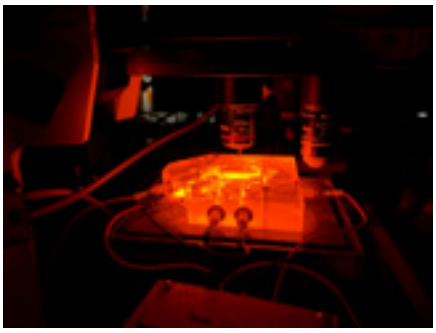


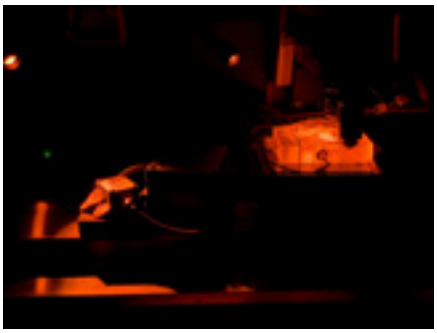
Kjærgaard team members on stairs in lab building.
Photo by Karen Bech-Pedersen

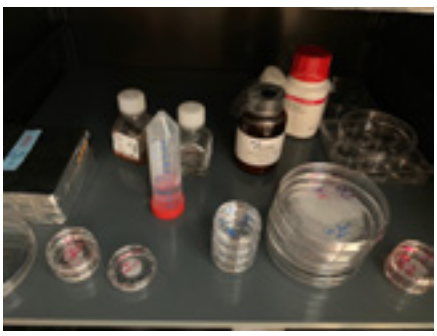
Poulsen Team

Electrophysiology of Electrogenic Transporters and Ion Channels

Team Leader
Hanne Poulsen







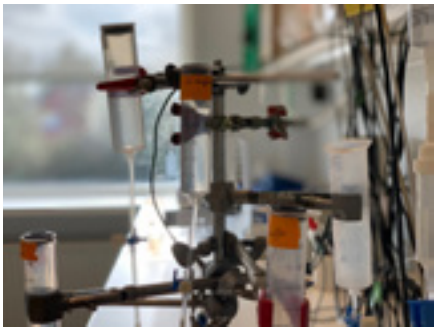
We study membrane proteins important for neuronal signaling and transport in order to understand their basic mechanisms and the pathophysiological consequences it has if they do not function optimally. We use electrophysiological methods to study membrane proteins, including voltage-clamp fluorometry (VCF), where protein movements are correlated with protein activity.

The protein of interest is labelled by replacing a specific amino acid with the fluorescent unnatural amino acid Anap. Anap's fluorescence is sensitive to the environment, so if a segment of the protein moves, this can be followed as a change in fluorescence with very fast time resolution and correlated with the activity measured simultaneously. We are studying both channels and transporters, including TRP channels, NMDA channels, the GABA transporter and the Na,K-ATPase.

ACHIEVEMENTS
Neuronal firing depends on a series of ion sluices opening and closing in the membrane, allowing in particular potassium and sodium to flow into and out of the cell. An ion pump, the Na,K-ATPase, is therefore necessary to reestablish the gradients. The brain makes several versions of the pump including α2 in glia cells and α3 in neurons. Mutations in the genes encoding the pumps are associated with several different severe neurological diseases.
In 2018, we helped characterize the functional consequences of two disease-causing mutations:
1: One was discovered by Emma Matthews (MRC, London) in a 9-year-old Brazilian boy who suffered from hypokalaemic periodic paralysis (PP), but did not show mutation in any of the previously characterized genes associated with the disease, namely a voltage-gated calcium channel and a voltage-gated sodium channel. Sequencing found a de novo mutation in one of the boy's genes encoding α2, causing S779N at the ion binding sites. This was a surprising finding, since mutations in α2 have been reported to cause hemiplegic migraine. However, none of the previously known α80 mutations were at the ion binding sites, and they generally reduce the turnover rate of the α2 pump. With S779N, we found that it has an inward leak current under physiologically relevant conditions. In addition to glia cells, α2 is also expressed in muscle, so we suggest that the hypoPP is caused by a mechanism similar to the ones known from the channels, namely an inward leak current.

2: The other is E818K in α3, which causes CAPOS (cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss). Patients with CAPOS have distinctive auditory and visual impairments, which have not been reported for two other syndromes caused by mutations in the same gene, suggesting that the mutation causing CAPOS alters protein function in a manner that has particular effects on vision and hearing. We found that the mutation alters the kinetics of particular steps in the catalytic cycle, though it remains to be determined why these changes are detrimental to the visual and auditory systems.

FUTURE PLANS / PROJECTS / GOALS
In order to understand the pathophysiology of CAPOS, we are generating a mouse with the mutation in collaboration with Karen Steel (King's College London) that we will study also with DANDRITE Group leader Yonehara. Unfortunately, the generation of the mouse line has taken almost two years, but we should receive it this year. Additionally, we are testing various mutations and conditions with electrophysiology to understand how E818K affects the basic pump function. This can further be combined with VCF studies that we will be conducting on the pump as well as on other transporters and channels.



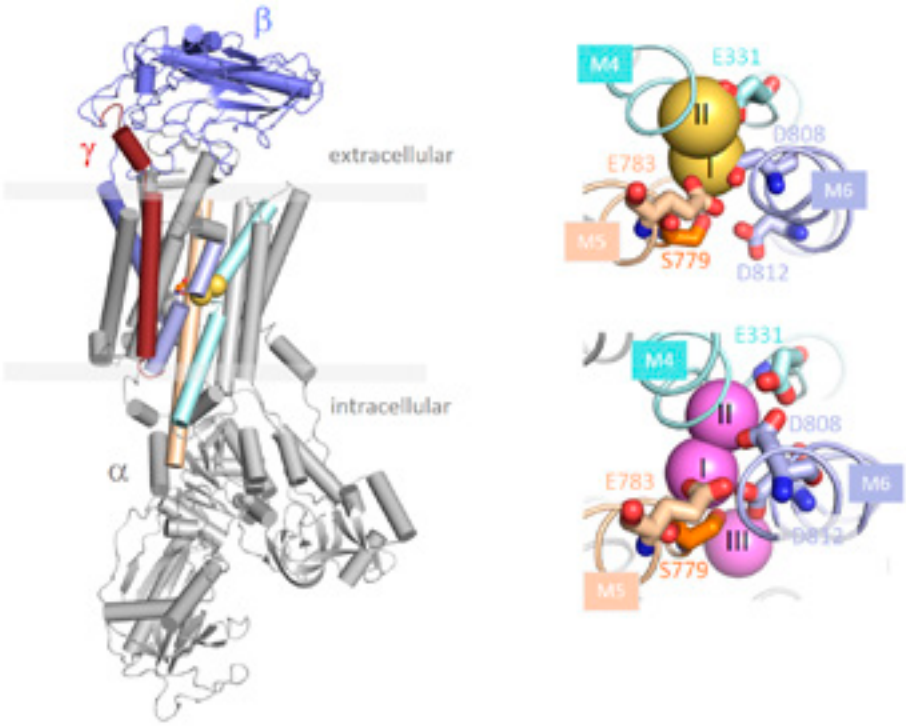


Fig 1: Structural context of S779.
Left: An overview of the Na,K-ATPase with the alpha subunit in grey, the beta subunit in blue and the gamma subunit in red. The two potassium ions are yellow spheres, S779 is in orange stick, and the ion-coordinating transmembrane helices are light cyan (M4), wheat (M5) and light blue (M6). Horizontal lines indicate the boundaries of the membrane.
Right: Close ups of the ion binding sites viewed from the extracellular side, top with two potassium ions (yellow), bottom with three sodium ions (violet). S779 is close to ion binding sites I and III. The figure was made using PDB structures 2ZXE (potassium bound) and 3WGU (sodium bound).
Graphics: Hanne Poulsen

Publications 2018

Sampedro MC, Zanoteli E, Scalco RS, Scaramuzzi V, Marques VC, Conti UR, da Silva AMS, O'Callaghan B, Phadke R, Bugiardini E, Sud R, McCall S, Hanna MG, **Poulsen H**, Männikkö R, Matthews E (2018) A novel ATP1A2 mutation in a patient with hypokalaemic periodic paralysis and CNS symptoms. *Brain: a journal of neurology*, Vol. 141, No. 12, p. 3308-3318.

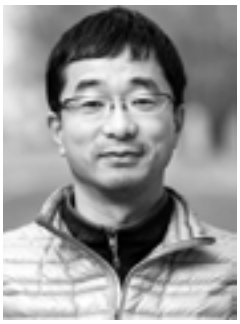
Tranebjærg L, Strenzke N, Lindholm S, Rendtorff ND, **Poulsen H**, Khandelia H, Kopec W, Lyngbye TJB, Hamel C, Delettre C, Bocquet B, Bille M, Owen HH, Bek T, Jensen H, Østergaard K, Möller C, Luxon L, Carr L, Wilson L, Rajput K, Sirimanna T, Harrop-Griffiths K, Rahman S, Vona B, Doll J, Haaf T, Bartsch O, Rosewich H, Moser T, Bitner-Glindzicz M (2018) The CAPOS mutation in ATP1A3 alters Na/K-ATPase function and results in auditory neuropathy which has implications for management. *Human Genetics*, Vol. 137, No. 2, 02.2018, p. 111-127.

Personnel List Poulsen Team

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

Takeuchi Team

Memory selectivity and knowledge updating



Team Leader
Tomonori Takeuchi

Knowledge plays a central role in human life. Indeed, we are who we are largely because of what we learn and what we remember. Our knowledge structure (called 'schema') consists of our past experiences and facts stored in our long-term memory. We use our schemas to organize current knowledge and provide a framework for future understanding. A key but poorly understood issue is "how the memories of everyday events initially stored in the hippocampus are selected and then assimilated into a relevant schema in the neocortex".

Our goal is to understand the systems-level molecular mechanisms of selective retention of trivial memory through neuromodulation and the assimilation of this retained memory into the relevant schema, applying sophisticated behavioural tests using an event arena in rats (Fig. 1) combined with cutting-edge molecular techniques.

MEMORY SELECTIVITY
Selective retention can be triggered by novelty-induced dopamine release in the hippocampus. We recently made a ground-breaking finding (Takeuchi et al., Nature, 2016): projections from the noradrenergic locus coeruleus to the hippocampus can drive the novelty-induced memory enhancement via non-canonical release of dopamine. This is a completely new concept that we will continue to explore by uncovering the molecular mechanisms of novelty detection and subsequent dopamine-dependent memory modulation.

MEMORY ASSIMILATION
Previous study showed that selected new memories can assimilate into the neocortical schema very rapidly if the relevant schema is already learned. Our follow-up study identified the neocortical area involved in the assimilation of new memory into the schema (Tse, Takeuchi et al., Science, 2011). These findings challenge the widely held view that neocortical memory stabilization is a slow process. We aim to secure definitive information about the neocortical networks and neuromodulation involved in the assimilation of new memory into the schema.

We expect to generate unprecedented outcomes: characterisation of the novelty circuits, identification of key proteins critical for novelty-induced memory enhancement, and definitive information about neural mechanisms of assimilation of new memory into neocortical schemas. Identification of proteins that enhance memory retention will have the potential to reveal new drug targets for treatment of lost memory function. Understanding the molecular mechanisms of selective retention and assimilation of new memories into schemas may lead to the development of efficient educational methods.

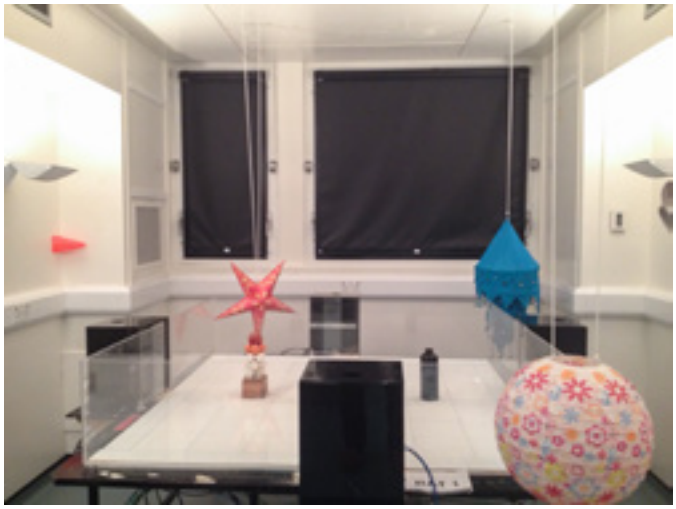


Figure 1: An event arena in rats. Photo by Tomonori Takeuchi).

Figure 2: Takeuchi team members. Photo by Kim Henningsen).

Publications 2018

Duszkiewicz AJ, McNamara CG, **Takeuchi T,** Genzel L (2018) Novelty and Dopaminergic Modulation of Memory Persistence: A Tale of Two Systems. *Trends in Neuroscience. In press*

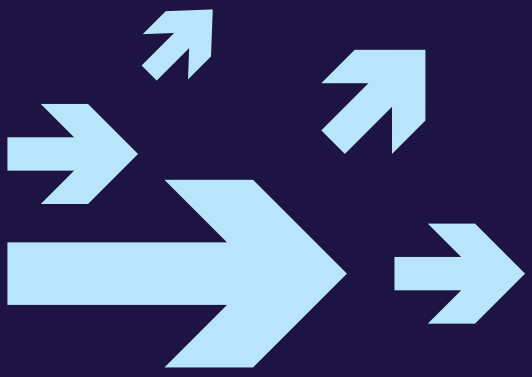
Rossato JI, Moreno A, Genzel L, Yamasaki M, **Takeuchi T**, Canals S, Morris RGM (2018) Silent learning. *Current Biology*, 28: 3508–3515

Watanabe T, **Takeuchi T,** Kubota N, Wainai T, Kataoka K, Nakaya T, Sugimoto A, Sato T, Ohira H, Tsujino I, Kumagai K, Kubota T, Hasegawa C, Tokuyama K, Ueki K, Yamauchi T, Mishina M, Kadowaki T (2018) A transgenic mutant mouse line accompanied by the complete deletion of interleukin-33 showed insulin and leptin resistances. *bioRxiv* doi:10.1101/416529

Personnel List Takeuchi Team

Postdoc **Kosuke Okuda**
Postdoc **Mai Iwasaki**
Lab Manager **Kim Henningsen**
Research Assistant **Kristoffer Højgaard**
Team leader **Tomonori Takeuchi**

03
Events, Visitors, Guests & Seminars



EVENTS, VISITORS, GUESTS & SEMINARS


03


04


05

01 **DECEMBER**
SEMINAR: **DANDRITE Topical Seminar,** PhD Student **Kota Tokuoka**, Kyoto University, *"Role of midbrain cholinergic inputs to the superficial layer of superior colliculus – Anatomical and electrophysiological studies"*, Host: Group Leader Keisuke Yonehara

02 EVENT: **DANDRITE Christmas Get-together** with spouses and children

03 SEMINAR: **AIAS Fellows' Seminar**, AIAS Fellow & Postdoc at DANDRITE **Asad Jan**, *"Protein aggregation in neurodegenerative diseases: Mechanisms of neuronal toxicity and opportunities for novel therapies"*

04 **NOVEMBER**
SEMINAR: **DANDRITE Topical Seminar**, Professor **Menno P. Witter** & Postdoc **Shinya Ohara**, Kavli Institute for Systems Neuroscience, Norway. *"How to relate neural architecture to function. The entorhinal cortex as a model"* & *"Organization of the hippocampal output circuit in the entorhinal cortex"*, Host: Team Leader Tomonori Takeuchi

05 SEMINAR: **DANDRITE Lecture**, Associate Professor **Antoine Adamantidis**, University of Bern, Switzerland, *"Thalamic dual-modulation of sleep and wakefulness"*, Host: Affiliated Researcher Marco Capogna

06 SEMINAR: **Biomedicine Seminar**, Professor & DANDRITE Group Leader **Poul Henning Jensen** *"A journey with sticky stuff – from afterbirths to Parkinson's disease brains"*

07 GUESTS: **Visit by 90 Dutch students** from the Science Honours Academy, University of Utrecht, Host: Research group of Sadegh Nabavi

08 **OCTOBER**
SEMINAR: **DANDRITE Topical Seminar**, PhD student **Kenta Hagihara**, Friedrich Miescher Institue for Biomedical Research, Basel, *"Distinct clusters of the amygdala intercalated cells bi-directionally control fear state"*, Host: Group Leader Keisuke Yonehara

09 SEMINAR: **DANDRITE Lecture**, Professor **Andreas Schaefer**, University College London & The Francis Crick Institute, *"Mammalian olfaction is a high bandwidth sense"*, Host: Young DANDRITE by PhD student **Sophie Seidenbecher**


07

10 SEMINAR: **Distinguished iNANO Lecture**, Professor **Jay T. Groves**, College of Chemistry, UC Berkeley, *"Biochemical signaling on membrane surfaces: the roles of space, force, and time"*, Host: Group Leader Poul Nissen

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

- Professor **Naoshige Uchida**, Center for Brain Science, Harvard University, *"Multiple dopamine systems: weal and woe of dopamine"*
- Deputy Head at EMBL Rome **Cornelius Gross**, EMBL-Rome, *"Do microglia really eat synapses?"*
- Associate Professor **Rune Berg**, Copenhagen University, *"Sparse network connectivity revealed from physiology: What pairwise intracellular recordings can tell us about the spinal circuitry behind movement"*
- DANDRITE Group Leader **Keisuke Yonehara**, Aarhus University, *"How does a neuron compute the direction and speed of visual motion?"*

12 EVENT: **Skou Building Inauguration**, Aarhus University Faculty of Health inaugurated Department of Biomedicine's new ultra-modern research building, named after Nobel Laureate Jens Christian Skou. Several DANDRITE research groups have moved their labs to the Skou Building.

SEPTEMBER

13 EVENT: **DANDRITE Extended Internal meeting**, inaugural presentation by DANDRITE's newly appointed Affiliated Researcher; Professor **Jørgen Kjems**

14 SEMINAR: **PROMEMO/DANDRTE Topical Seminar**, Postdoc **Beatriz Alvarez Castelao**, Max Planck Institute for Brain Research, Frankfurt, *"Neuronal proteostasis"*, Host: Affiliated Researcher **Marco Capogna**


18

15 SEMINAR: **DANDRITE Topical Seminar,** Postdoc **Erica Ehrhardt,** Janelia HHMI Research Campus & University of Cologne, *"The VNC project: generating a cell-type specific driver line library targeting ventral nerve cord of Drosophila melanogaster"*, Host: Grop Leader Anne von Philipsborn

16 EVENT: **AIAS Symposium on "Cutting Edge Technologies for Neurobiology"**, Aarhus Institute of Advanced Studies (AIAS), Aarhus University, Scientific organizers; Team Leader Tomonori Takeuchi & Group Leader **Keisuke Yonehara**
Presentation by DANDRITE researcher:
- DANDRITE Team Leader **Tomonori Takeuchi**, Aarhus University, *"Memory modulation by light"*
- DANDRITE Group Leader **Keisuke Yonehara**, *"Visual motion processing from retina to visual cortex in mice"*

17 SEMINAR: **DANDRITE Lecture**, Distinguished Professor and Director **Cheng-Chang Lien**, National Yang-Ming University, Taiwan, *"Circuit specificity in the inhibitory architecture of the dentate gyrus"*, Host: Marco Capogna, DANDRITE Affiliated Researcher

18 EVENT: **9th Annual Network Meeting of the Nordic EMBL Partnership for Molecular Medicine**, hosted by Centre for Molecular Medicine Norway (NCMM), Soria Moria Hotel, Oslo, Norway, attended by many DANDRITE students and researchers.

19 **AUGUST**
SEMINAR: **DANDRITE Topical Seminar**, Associate Professor **Tomi Rantamäki**, University of Helsinki, *"No laughing matter: understanding rapid antidepressant effects with nitrous oxide"*, Host: Affiliated Reseacher Simon Glerup

20 EVENT: **AIAS Conference on "The Thinking Machine: Interdisciplinary Perspectives on Neural Networks"**, Aarhus Institute of Advanced Studies (AIAS), Aarhus University. The five membered Scientific committee included the two AIAS Fellows and postdocs at DANDRITE: Postdoc Michael Voldsgaard Clausen and Postdoc Asad Jan.

Keynote lecturers:
- **José del R. Millán**, Swiss Federal Institute of Technology in Lausanne (EPFL), *"Brain-Machine Interfaces: A Tale of Two Learners"*
- **Patrick Jagoda**, University of Chicago, USA, *"How Video Games Can Help Us Think Through Networks"*
- **Maria Schuld**, University of KwaZulu-Natal, Durban, South Africa & Xanadu Quantum Computing Inc, Toronto, Canada, *"Quantum Neural Networks"*

Presentation by DANDRITE researcher:
- Group Leader **Duda Kvitsiani**, *"Distributed representations in cortical neural networks"*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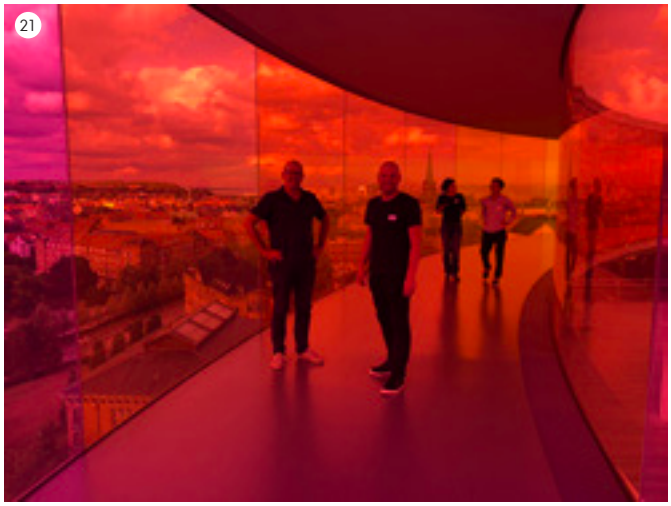
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21 EVENT: **Group Leader and Team Leader Retreat Day**, Program: Research in depth and Leadership. Venue: AROS Art Museum

22 SEMINAR: **DANDRITE Topical Seminar**, Dr. **Jan Clemens**, European Neuroscience Institute, Göttingen, *"From song to behavior in Drosophila"*, Host: Group Leader Anne von Philipsborn,

23 SEMINARS: **Joint SDC/CFIN/DANDRITE talks**, Professors **Jianyuan Sun**, Institute of Biophysics Beijing, & **Ninglong Xu,** Institute of Neuroscience, Shanghai, *"Quantal transmission at single central synapses"* & *"Neural circuit mechanisms for auditory-based perceptual decision-making"*

JULY

24 SEMINAR: **Biomedicine Seminar**, Dr. **Augustin Hrvoje**, King's College London, *"Using Drosophila to study synaptic function and development, ageing and neurological disorders"*, Hosts: Head of Dept. Thomas G. Jensen, Group Leader Anne von Philipsborn

25 **JUNE**

SEMINAR: **DANDRITE Topical Seminar**, PhD student **Sebastian S. Brøndum**, University of Copenhagen, *"Re-targeting a bacterial assassin: Engineering PlyC specifity using directed evolution"*


27

26 SEMINAR: **MBG Focus Talk**, postdoc **Matthew L. Wohlever**, University of Chicago, *"Quality Control of Mitochondrial Tail Anchored Proteins"*, Host: Group Leader Poul Nissen

27 EVENT: **Meeting for Administrators, Training, and Communication Coordinators of the Nordic EMBL Partnership for Molecular Medicine**, hosted by the DANDRITE Admin. Support Team. Attendance of admin personel from NCMM, MIMS, FIMM, and EMBL-Heidelberg.

28 SEMINAR: **MBG Focus Talk**, Professor **Todd R. Graham**, Vanderbilt University, *"Flippase-gate: Explorations Into How P4-ATPases Recognize Their Lipid Substrate"*, Host: Poul Nissen

MAY

29 EVENT: **DANDRITE Mini Symposium,** Aarhus University
Lectures by:
- Professor **Benjamin Eaton**, University of Texas Health Science Center, *"Using the fly neuron to study diet, aging, and pain"*
- Professor **Lisa Stowers**, The Scripps Research Institute, *"Leveraging olfaction to study mechanisms that drive innate behavior in the mouse"*
- DANDRITE Group Leader **Duda Kvitsiani**, Aarhus University, *"Foraging decisions in flies and mice"*

30 SEMINAR: **DANDRITE Topical Seminar** with Dr. **Santiago Rompani,** Friedrich Miescher Institute for Biomedical Research, *"Integration and modulation of visual information in the thalamus"*, Host: Keisuke Yonehara

31 SEMINAR: **DANDRITE Topical Seminar** with **Henne Holstege**, VUmc Alzheimer Center, Amsterdam, *"SORL1... The fourth autosomal dominant Alzheimer gene?"*, Affiliated Researcher Olav Andersen

32 EVENT**: DANDRITE SAB meeting & retreat 2018**, Sandbjerg Manor, Denmark

33 EVENT: **Neuroscience Day 2018: Rewarding Neuroscience**. Organized by NeuroCampus Aarhus.

APRIL

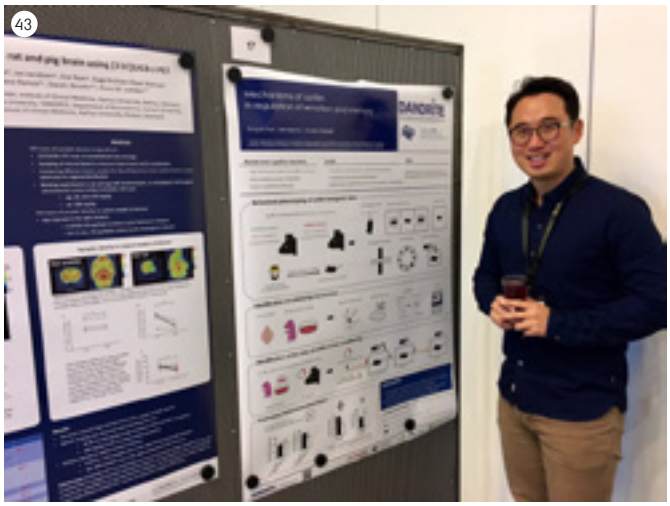
34 EVENT: **Festival of Research 2018 – FASCINATING RESEARCH**, DANDRITE research groups attending.

35 SEMINAR: **DANDRITE Lecture**, Academy Research Fellow **Petri Ala-Laurila**, University of Helsinki, *"Revealing the neural code: Linking single-photon signals to neural spikes and behavior in mice and men"*, Host: Keisuke Yonehara

36 EVENT: **Official Inauguration of PROMEMO** – Center for Proteins in Memory – a Danish National Research Foundation Center of Excellence

MARCH

37 EVENT: **DANDRITE Spring Party**



38 EVENT**: DANDRITE Extended Internal meeting**, inaugural presentation by DANDRITE's newly appointed Associated Researcher, Team Leader **Tomonori Takeuchi**

39 SEMINAR: **Biomedicine Seminar**, Group Leader **Anders Nykjær**, *"Functional characterization of the type-2 diabetes and Alzheimer's Diseases risk gene SORCS1"*

FEBRUARY

40 EVENT: **DANDRITE Student Encounters 2018**, at Department of Biomedicine, Aarhus University

JANUARY

41 SEMINAR: **DANDRITE Lecture**, Professor **Leonidas Stefanis**, University of Athens Medical School, "*Pathogenesis of Parkinson's disease: Focus on lysosomes"*, Host: Group Leader Poul Henning Jensen

42 SEMINAR: **PROMEMO / DANDRITE Topical Seminar**, Postdoc **Dongik Park**, Max Planck institute of Psychiatry, *"Molecular Pathway Delineation of the Antidepressant Treatment Response"*, Host: Group Leader Anders Nykjær

SAB MEETING & RETREAT

88 participants attended the 2018 Retreat and SAB meeting at Sandbjerg Manor in southernmost Denmark.

DANDRITE's third Scientific Advisory Board (SAB) meeting were held on Monday May 13th to15th and was combined with the yearly retreat. The meeting took place at the conference center Sandbjerg Manor.

The focus of this year's SAB meeting was on future directions, general strategy and future funding of the institute, as well as the progress and collaboration of individual Group Leaders and Team Leaders, and translational activities of the Institute. During the visit, the SAB had one-to-one meeting with Group and Team Leaders as well as closed meetings with postdocs and PhD students.

The SAB members attending in 2018 where from left back: Professor Carl Petersen, Professor Rüdiger Klein, Research Director Matthias Wilmanns, Professor Glenda Halliday, Porfessor Mart Saarma, Professor Ole Kiehn, Professor Kathleen Sweadner, Professor Yang Dan, and Professor Moses V. Chao.

THE SAB WRITES IN EVALUATION REPORT

"...DANDRITE has continued to be very successful in its mission to generate significant new knowledge in basic and translational neuroscience. Researchers continue to take innovative approaches to key scientific questions as demonstrated by their successes in publishing in top journals. ... "

... "Thus, by all measures, DANDRITE is a top contributor to Danish and European neuroscience. As stressed already previously, if the institute continues on a similar track in the following years and begins publishing breakthrough discoveries, DANDRITE can establish itself as a leading research centre in molecular, systems and translational neuroscience. ..."

... "The Institute has also attracted three Team Leaders and ten Affiliated Researchers to work at or in close connection with DANDRITE. This reflects the important role of DANDRITE as a landing pad for successful neuroscientists often at the beginning of their independent careers and with many options from which to choose. ..."

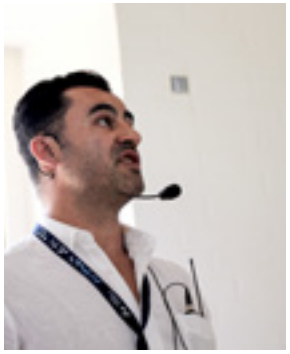
... "During the retreat the SAB met enthusiastic and intellectually very active researchers. We witnessed an excellent spirit and heard numerous successful collaborations between the groups at DANDRITE. Creating such a stimulating scientific atmosphere is challenging and we would like to congratulate director Poul Nissen and the two core Group Leaders Poul Henning and Anders Nykjær in achieving this. In a short period of time DANDRITE has brought together a unique combination of groups with top class structural, systems and cellular neuroscience. This has created a unique strength of DANDRITE: the possibility for studies from molecules to cells to organisms and back. ..."

... "The five Group Leaders have significantly enriched the intellectual and technological repertoire of DANDRITE and they are playing the key role in the development of systems neuroscience. All of them are performing exciting work, and are focusing on preparing top level publications. The SAB is confident that this strategy is successful. In the coming years, these groups are expected to publish seminal discoveries in leading journals. ... "

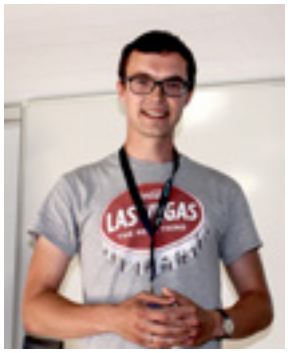
... "The SAB members had also the opportunity to listen to the presentations of several postdocs and graduate students, and as an interesting new initiative follow the preparation and presentation of student-generated collaborative subproject ideas. This event was successful and presented in a very interesting way the creativity and intellectual capability of DANDRITE graduate students. ... "














A vibrant part of the Retreat program was **The Elevator Talk Session**.
All PhD and Postdoc made a two-minutes presentation of their research.

From left top: PhD student Josephine Dannersø Nissen, PhD student Monica Dahlstrup Sietam, Postdoc Dongik Park, Postdoc Ana Oliveira, PhD student Mariam Gameleldin, Assistant Professor Nelson Ferreira, Postdoc Alena Salasova, PhD student Line Marie Christiansen, Postdoc Katherine Gill, Postdoc Mateusz Dyla, Research Year student Anne Kathrine Aalling Sørensen, PhD student Emil Gregersen, PhD student Jesper Hagelskjær, Postdoc Milena Timcenko Tronsgaard, Postdoc Andrea Moreno, and PhD student Angela O'Sullivan.

PROMEMO
CENTER FOR PROTEINS IN MEMORY

PROMEMO

April 4th was the Official inauguration of PROMEMO: Center for Proteins in Memory - a Danish National Research Foundation Center of Excellence. PROMEMO is a brilliant example of a DANDRITE spin-off activity. The core researchers of PROMEMO are all related or directly part of DANDRITE. The aim of PROMEMO is to identify and understand the function of memory associated proteins that determines the persistence of a memory. In a longer perspective, understanding memory-associated proteins may help identifying molecular targets for memory-associated disorders such as anxiety, depression, and dementia.
Read more on: **promemo.au.dk**

PROMEMO's principal researchers from left are DANDRITE Team leader Hanne Poulsen, DANDRITE Group Leader Sadegh Nabavi, DANDRITE Team Leader Magnus Kjærgaard, DANDRITE Affiliated Researcher Professor Marco Capogna, Center Leader, DANDRITE Professor Anders Nykjær, and DANDRITE Professor Poul Nissen.

Public outreach

FESTIVAL OF RESEARCH
DANDRITE researchers always take part in the annual recurring nationwide Festival of Research and not least in 2018.

Team Leader Magnus Kjærgaard successfully made himself available for the "Book a Researcher" which resulted in seven lectures at seven localities in Denmark giving 500 attendances insight into the subject "The Memory's Molecules". At Aarhus University's campus, the Festival is each year a day-event where the general Danish public is invited to meet researchers first hand. It was also in 2018 busy and enjoyable day where students from DANDRITE demonstrated their research areas. Two labs were represented: Anne von Philipsborn lab and Poul Henning Jensen lab.

Festival of Research, DANDRITE student: Hjalte Gram

DANDRITE STUDENT ENCOUNTERS 2018
In 2018 we reinvented the format of the annual DANDRITE Encounter. Previous years the encounter have been based on auditorium presentation while this year we invited each of the participants on guided tours to two preselected DANDRITE labs. The new format was highly appreciated and more than 60 students showed up to look for opportunities for student projects in one of DANDRITE's different research groups.

Neuroscience Day 2018 Participants. Photo by Lars Kruse, AU Photo

NEUROSCIENCE DAY

EVENT: Neuroscience Day 2018: Rewarding Neuroscience. Organized by NeuroCampus Aarhus (NCA). NCA is a cross-disciplinary research network at Aarhus University and Aarhus University Hospital open for all interested in the brain. DANDRITE strongly supports and are involved in the NCA network in general and in the organizing of the Neuroscience Day 2018 in particular.

Keynote lecturers were:

- 2017 Brain Prize Winner Professor **Ray Dolan**, University College London, "Reward, prediction and brain dopamine"
- Dr. **Thomas Zoëga Ramsøy**, CEO and founder of Neurons Inc., "Compulsions and behavioural addictions from the lab to the store"
- Professor **Morten Kringelbach**, Center for Music in the Brain, Aarhus University & Oxford University, "Hedonia and eudaimonia: Towards whole-brain models in health and disease"

Presentations by DANDRITE researchers:

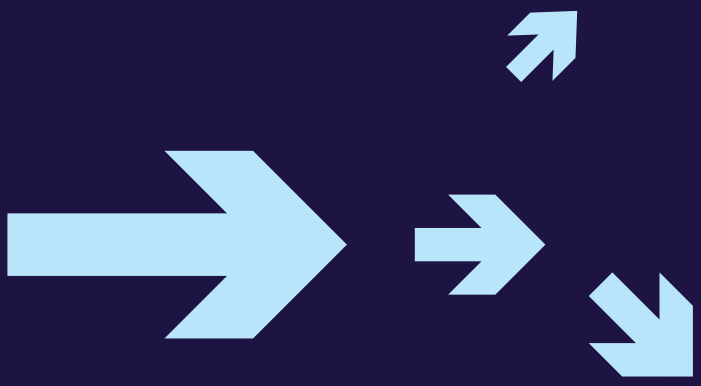
- DANDRITE Group Leader **Duda Kvitsiani**, "Foraging decisions in probabilistic environments in flies and mice"
- DANDRITE Team Leader **Tomonori Takeuchi**, "Dopaminergic memory modulation by two distinct novelty systems"

Group Leader Duda Kvitsiani "question from audience" at Neuroscience Day 2018. Photo by Lars Kruse, AU Photo

VIDEO PRODUCTIONS AND TWITTER
Our dissemination and outreach efforts have in 2018 resulted in several video productions and with lively twitter activity via our account: **twitter.com/dandrite**

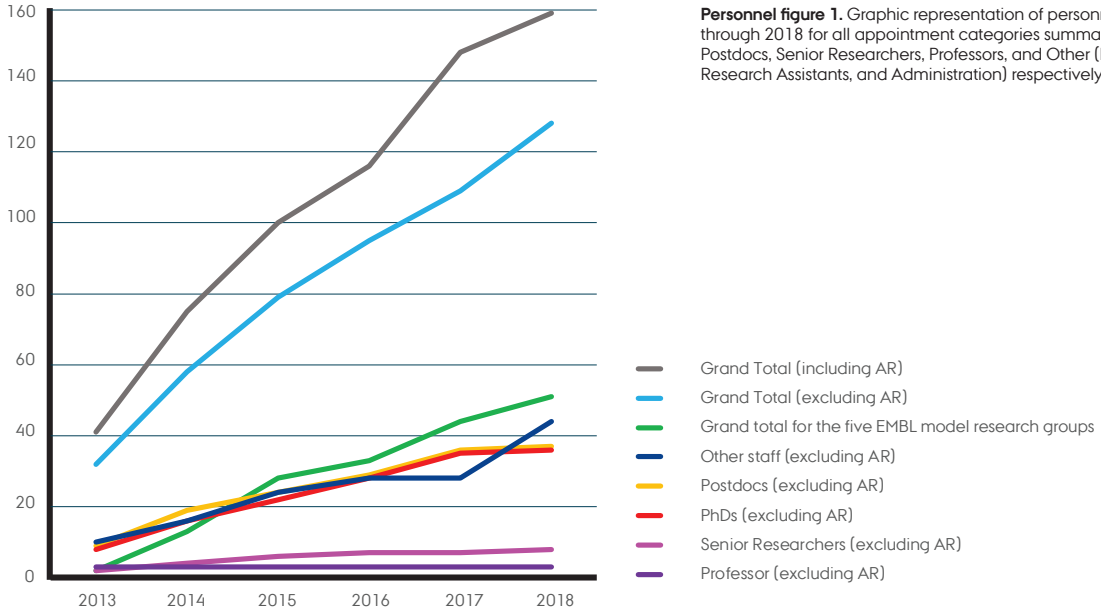
Snapshot during video production. From left Laboratory Technician Anne-Katrine Vestergaard, Group Leader Sadegh Nabavi, Aarhus University TV Producer Hans Plauborg. Photo: Maria Thykær Jensen

04
Personnel



Personnel

Each one of the five young group leaders during 2018 continued the successful establishment and build-up of their groups with students, technical support staff, and promising postdoctoral fellows. Additionally, all groups have attracted several summer students, interns, and research visitors from EU, Denmark, as well as rest of the World.



Personnel figure 1. Graphic representation of personnel progression 2013 through 2018 for all appointment categories summarized, for PhD students, Postdocs, Senior Researchers, Professors, and Other (Laboratory Technicians, Research Assistants, and Administration) respectively.

COUNT OF NUMBER AND PERCENTAGES OF PERSONNEL EMPLOYED DURING 2018 GROUPED BY APPOINTMENT CATEGORY AND GENDER. THE COUNT EXCLUDES AFFILIATED RESEARCHERS

DANDRITE Personnel categories	Female	Male	Total	%
Professors		3	3	2
Senior Researchers	2	6	8	6
Postdocs	17	20	37	29
PhDs	22	14	36	28
Other staff (Laboratory Technician, Research Assistant, and administration)	33	11	44	34
Grand Totalt	74	54	128	100
% Male/Female	58	42	100	

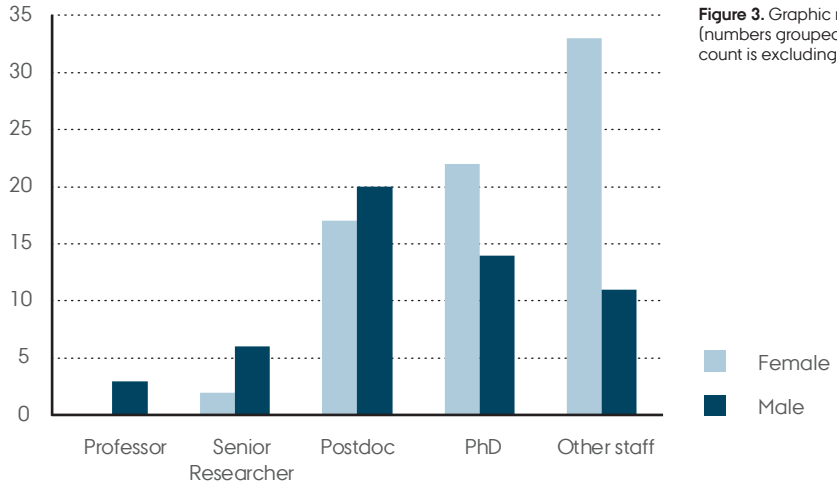


Figure 3. Graphic representation of the personnel counts for 2018 (numbers grouped by appointment category and gender). The count is excluding affiliated researchers.

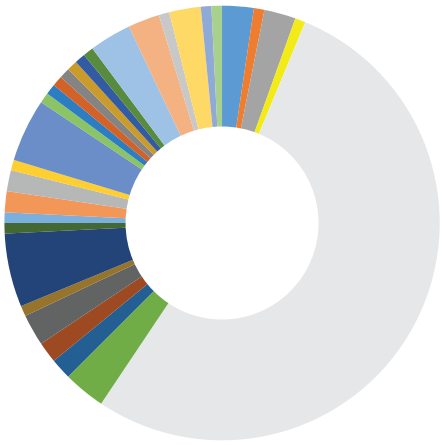


Fig 4: Graphic representation of the nationality distribution of all employees. The count is excluding affiliated researchers.

Australia
Canada
China
Czech Republic
Denmark
Egypt
Estonia
Finland
France
Georgia
Germany
Greece
India
Iran
Ireland
Italy
Japan
Korea
Latvia
Mexico
Netherland
Nigeria
Norway
Peru
Poland
Portugal
Romania
Spain
Sweden
Turkish

Fig 5: Graphic representation of the nationality distribution of the employees in DANDRITE's five young research groups

Australia
China
Czech Republic
Denmark
Egypt
Estonia
France
Georgia
Germany
Iran
Ireland
Italy
Japan
Latvia
Mexico
Netherland
Portugal
Romania
Spain

Awards

Award of the Carlsberg Foundation Research Prize 2018. From the Left Secretary-General of the Royal Danish Academy of Sciences and Letters Lars Arge, Minister of Higher Education and Science Tommy Ahlers, Prize winner Professor Tim Bollerslev, HRH Crown Princess Mary, Prize winner Professor **Poul Nissen**, Chairman of the Carlsberg Foundation Flemming Besenbacher and President of the Royal Danish Academy of Sciences and Letters Mogens Høgh Jensen (photo: Martin Juul)

Affiliated researcher **Jørgen Kjems** was awarded the Novo Nordisk Prize 2018. The Prize is awarded in recognition of his pioneering translational studies of how RNA plays a key role in the regulation of cells. The studies have a huge potential in future disease treatment. The Novo Nordisk Foundation Prize is accompanied by DKK 3.0 million.

DANDRITE Director and Group Leader **Poul Nissen** was awarded the Carlsberg Foundation Research Prize 2018. Nissen received the prize for his groundbreaking work in structural biology. The Carlsberg Foundation Research Prize is accompanied by DKK 1.0 million.

Affiliated researcher **Jane Hvarregaard Christensen** won the first prize for best research result and oral presentation at ICCS2018 (International Childrens's Continence Society) held in Rome September 2018.

PhD Student **Rune Rasmussen** won the Best Flash Talk Presentation Award at the PhD day held by Graduate School of Health, Aarhus University.

PhD student **Cecilie Siggaard Jørgensen** (from AR Jane Hvarregaard Christensen's group) was elected for giving Best Oral Presentation at Department of Clinical Medicine 2nd Annual Research Meeting 2018, Aarhus University.

Jørgen Kjems
Photo Novo Nordisk Fonden

Grants

1. Group Leader **Keisuke Yonehara**: Infrastructure grant, DKK 0.15 million, Carlsbergfondet

2. Affiliated Researcher **Olav Andersen**: DKK 38.000, New exon structure of SORL1, A.P. Møller Fonden

3. Group Leader **Anders Nykjær**: Sortilin – balancing synaptic strength and mood states, DKK 15.0 million, Lundbeckfonden

4. Team Leader **Tomonori Takeuchi**: Young Investigator Award, DKK 20.0 million, Novo Nordisk Foundation

5. Team leader **Tomonori Takeuchi**: Marie Skłodowska-Curie Fellowships, DKK 1.0 million, AIAS-COFUND with EU-H2020

6. Group Leader **Sadegh Nabavi**: Independent optical excitation of overlapping neural populations in behaving animals, DKK 2.0 million, Lundbeckfonden-NIH BRAIN Initiative

7. Team Leader **Tomonori Takeuchi**: Identification of plasticity-related proteins critical for novelty-induced memory enhancement, DKK 5.0 million, Japanese pharmaceutical company

8. Postdoc **Andrea Moreno**: Memory erasure by depotentiation: revealing the molecular basis of forgetting, DKK 2.1 million, Lundbeckfonden

9. Affiliated Researcher **Marina Romero-Ramos**: Study of CD163 receptor in Parkinson's disease, DKK 1.1 million, Michael J. Fox Foundation for Parkinson's Research

10. Affiliated Researcher **Olav Andersen**: Splice variant in AD, DKK 75.000, Jascha Foundation

11. Postdoc **Michael Habeck:** Marie Skłodowska-Curie Fellowships, DKK 1.6 million, EU-H2020

12. Affiliated Researcher **Karin Lykke-Hartmann**: Conference funding, DKK 25.000, AHC symposium

13. PhD Student **Nathalie Krauth**: Travel grant, DKK 7.600, Lundbeckfonden travel grant

14. Student **Oscar Gabriel Sevillano Quispe**: Screening grant for PhD, DKK 45.900, Graduate School Science and Technology, Aarhus University

15. Group Leader **Poul Henning Jensen**: Supplying aSyn filament-spotted membrane, DKK 65.000, Michael J. Fox Foundation for Parkinson's Research

16. Affiliated Researcher **Karin Lykke-Hartmann**: AHC prize, DKK 100.000, Alternating Hemiplegia of Childhood (AHC)

17. PhD Student **Rune Rasmussen**: Travelling stipend, DKK 5.000, Frimodt-Heineke Foundation

18. PhD Student **Rune Rasmussen**: Travelling stipend, DKK 4.000, Augustinus Foundation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19. PhD Student **Alana Miranda Pinheiro**: PhD fellowship: Satellite cells in neuropathic pain, DKK 1.6 million, , Lundbeckfonden

20. Affiliated Researcher **Olav Andersen**: Local synaptic translation of a novel splice-variant of the Alzheimer´s disease risk gene SORL1, DKK 0.5 million, Danish Alzheimers research foundation

21. PhD Student **Lixiang Jiang**: 1/1 PhD Stipend: Regulation of α-synuclein transcription by the PLK-2/GSK-3β signalling pathway – a potential modulator of Parkinson's disease risk, DKK 1.8 million, Graduate School of Health Sciences, Aarhus University

22. Affiliated Researcher **Christian Vægter**: Modulation of neuropathic pain by glial targeting, DKK 2.3 million, Innovation Fund Denmark: Grand Challenge

23. Postdoc **Kosuke Okuda**: Identification and functional classification of proteins crucial for novelty-induced memory enhancement in the hippocampus, DKK 2.1 million, Lundbeckfonden

24. Affiliated Researcher **Marina Romero-Ramos**: Microglia characterization, DKK 240.000, Dansk Parkinsonforeningen

25. Group Leader **Poul Henning Jensen**: Investigation of whether attempts to increase neurons cytosolic calcium levels protect a mouse model of progressive Parkinson's disease – Effects of SERCA inhibition and activation of calcium channels, DKK 350.000, Parkinsonforeningen

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

27. Group Leader **Poul Nissen**: EMBION - national cryoEM infrastructure, DKK 31.8 million, Danish Ministry for Research and Innovation

28. Affiliated Researcher **Jørgen Kjems**: Role of tRNA halves in Neuronal stress, DKK 1.5 million, JPND EU

29. Affiliated Researcher **Jørgen Kjems**: NanoString infrastructure, DKK 0.8 million, Carlsberg Foundation

30. Affiliated Researcher **Olav Andersen**: A fast screening protocol for pathological SORL1 gene mutations, DKK 140.000, Dansk selskab for Neurovidenskab

31. PhD Student **Rune Rasmussen**: Travelling stipend, DKK 15.000, Niels Bohr Foundation & The Royal Danish Academy of Sciences and Letters

32. Group Leader **Poul Nissen**: Project grant: Glycine transporter, DKK 1.6, Novo Nordisk Foundation

33. PhD Student **Rune Rasmussen**: Travelling stipend, DKK 3.000, Biokemisk Forening

34. Group Leader **Keisuke Yonehara:** Lundbeckfonden-NIH BRAIN Initiative, DKK 3.0 Lundbeckfonden

35. Affiliated Researcher **Marco Capogna**: Role of non-classical GABAergic cells on sleep, DKK 3.0 million, Lundbeckfonden-NIH BRAIN Initiative

36. Affiliated Researcher **Marco Capogna**: Role of nitric oxide-expressing GABAergic neurons on sleep-wake cycle, DKK 2.8 million, DFF- Independent Research Fund

Patents

Affiliated Researcher **Jørgen Kjems** (together with T.B. Hansen) obtained patent: Circular RNA for inhibition of microRNA, Patent WO/2014/082644.

Affiliated Researcher **Jørgen Kjems** (together with J.S. Nielsen and V. Andersen) filed patent: LNA BASED NANODEVICE PatentWO/2019/007930

Affiliated Researcher **Olav Andersen** (together with Yonglun Luo, and Charlotte B. Sørensen) obtained patent: Genetically modified SORL1 pig as a model of Alzheimer's disease:
EP Application No. 18199331.2; TECH-2018-631-120

Group Leader **Mark Denham** obtained patent: Development of an artificial transgene for regulating Alpha-Synuclein in vivo. Passed patentability assessment, Aarhus University: TECH-2017-631-039: (2017)

Spin-off Company

Affiliated Researcher **Jørgen Kjems** set out with the start-up company OMIICS (omiics.com). OMIICS offers the complete Next Generation Sequencing service from sample to figure.

Invited Talks

DECEMBER

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

NOVEMBER

Poul Nissen: *Presenting The Nordic EMBL Partnership and DANDRITE to incoming Director General Edith Heard*, EMBL Heidelberg, Germany

Peter Lund Ovesen: *SorCS1 regulates O-glycosylation of APP and prevents amyloid plaque formation*, The Brain Prize Meeting 2018, Hindsgavl, Denmark

Poul Nissen: *What membrane protein structures can teach us about membrane protein–lipid interactions*, Novo Nordisk Foundation Symposium – Protein–Membrane Costructures, Copenhagen, Denmark

Alena Salasova: *SorCS2 is a novel regulator of Wnt/PCP pathway and brain development*, The Brain Prize Meeting 2018, Hindsgavl, Denmark

Dongik Park: *Mechanisms of sortilin in regulation of emotion and memory*, The Brain Prize Meeting 2018, Hindsgavl, Denmark

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

Cristine Betzer: *Chronic caffeine treatment modulates disease progression in a mouse model of prion-like spreading of aggregated α-synuclein*, The Brain Prize Meeting, Hindsgavl, Denmark

Mark Denham: *Investigating GBA-associated Parkinson's disease using human IPSCs*, Lund University, Sweden

Magnus Kjærgaard: *Quantifying the functions of flexible protein linkers: Effects on catalysis and avidity*, Linderstrøm-Lang Symposium, University of Copenhagen, Denmark

Poul Nissen: J*ohn E. Walker introduction*, The Royal Danish Academy for Science and Letters, Copenhagen, Denmark

Poul Nissen: *Kjeld A. Marcker 1932 - 2018*, The Royal Danish Academy of Science and Letters, Copenhagen, Denmark

Keisuke Yonehara: *Visual motion processing from retina to visual cortical areas in mice,* UCSF, San Francisco USA

Mark Denham: *Circular RNA in Mesencephalic Dopaminergic Neurons*, Circular RNA symposium, iNANO, Aarhus University

OCTOBER

Poul Nissen: *CryoEM studies of synaptic structures*, PROMEMO annual meeting, Aarhus University, Denmark

Mark Denham: *Investigating GBA-associated Parkinson's disease using human IPSCs*, Parkinsonforeningen, Denmark

Sadegh Nabavi: *Activity-dependent retrograde labeling of brain circuits,* SAN2018, Argentina

Poul Nissen: *Krystalsymmetri og et røntgenblik på livets molekyler*, Folkeuniversitetet, Aarhus University, Denmark

Poul Nissen: *Krystalsymmetri og et røntgenblik på livets molekyler*, Folkeuniversitetet Emdrup, Denmark

Tomonori Takeuchi: *Selective retention of memory and updating schematic knowledge*, University of Oxford, United Kingdom

Tomonori Takeuchi: *Selective retention of memory and updating schematic knowledge*, University of Sussex, Falmer, United Kingdom

Poul Nissen: *Betydningen af Jens Chr Skous forskning*, Lemvig Gymnasium (high school), Denmark

Poul Nissen: *Betydningen af Jens Chr. Skous forskning i natrium-kalium-pumpen*, Folkeuniversitetet, Lemvig, Denmak

SEPTEMBER

Poul Nissen: *Structure and Dynamics of Active Transporters*, IRB/IBMB-CSIC Biomedicin seminar, Barcelona, Spain

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

Poul Nissen: *Livet på atomart niveau*, Carlsberg Foundation Research Prize lecture, The Royal Danish Academy of Science and Letters, Copenhagen, Denmark

Keisuke Yonehara: *Visual motion processing from retina to visual cortical areas in mice*, IST Vienna, Austria

Poul Nissen: *The Molecules of Life*, Danish Society for External Quality Assessment in Medical Practices, Denmark

Keisuke Yonehara: *Visual motion processing from retina to visual cortical areas in mice*, University of Oslo, Norway

Poul Nissen: *Structural studies of membrane proteins in different sample presentation modes*, EMBO Practical course mPEPC1, EMBL-Hamburg, Germany

Poul Henning Jensen: *Calcium dysregulations in Parkinson's disease Nordic EMBL Partnership Meeting 2018*, Oslo, Norway

Keisuke Yonehara: *Excitatory circuit motif for visual motion computation in the mouse retina, CSVS Symposium*, Osaka, Japan

Poul Henning Jensen: *Regulation of brain α-synuclein levels, Role of synthesis and catabolism*, Alpha-Synuclein Function Symposium and Workshop, EPFL, Lausanne, Switzerland

Anders Nykjær: *Functional characterization of the type-2 diabetes and Alzheimer's Diseases risk gene SORCS1*, Danish Diabetes Academy Summer School, Gl. Avernæs, Denmark

Poul Nissen: *Carlsberg Foundation Research Prize: award speech*, Glyptoteket, Copenhagen, Denmark

AUGUST

Katherine Gill: I*nvestigating Molecular pathways in Parkinson's disease GBA heterozygous carriers*, Brain Stem Symposium, University of Copenhagen

Duda Kvitsiani: *Distributed representations in cortical neural networks*, AIAS Conference: The Thinking Machine: Interdisciplinary Perspectives on Neural Networks, Aarhus, Denmark

Keisuke Yonehara: *Visual motion processing from retina to visual cortical areas in mice*, University of Copenhagen, Denmark

Tomonori Takeuchi: *Memory selectivity and knowledge updating*, Hiroshima University, Hiroshima, Japan

Tomonori Takeuchi: *Memory selectivity and knowledge updating*, Niigata University, Niigata, Japan

JULY

Tomonori Takeuchi: *Memory selectivity and knowledge updating*, Kobe University, Kobe, Japan.

Keisuke Yonehara: *Function and development of motion-sensitive circuits from retina to visual centers*, Annual Meeting of Japan Neuroscience Society, Japan

Tomonori Takeuchi: *Memory selectivity and knowledge updating*, Annual meeting of the Japan Neursocience Society, Kobe, Japan

Keisuke Yonehara: *Visual motion processing from retina to downstream brain areas in mice*, Institute of Medical Science, University of Tokyo, Japan

Tomonori Takeuchi: *Dopaminergic memory boost by two distinct novelty systems,* National University of Singapore, Singapore

Keisuke Yonehara: *Visual motion processing from retina to downstream brain areas in mice*, NIG, Mishima Japan

Keisuke Yonehara: *Visual motion processing from retina to visual cortex in mice*, Niigata University, Japan

JUNE

Keisuke Yonehara: V*isual motion processing from retina to visual cortical areas in mice*, FASEB, New York USA

Anders Nykjær: *Regulated sortilin shedding balances synaptic input and mood states*, NGF Meeting, Salamanca, Spain

Poul Nissen: T*he Structure and Dynamics of P-type ATPases, COMPPAA Symposium*, Columbia University, USA

Tomonori Takeuchi: *Dopaminergic memory modulation by two distinct novelty systems*, Neuroseminar, University of Copenhagen, Denmark

Marco Capogna: *Fear and sleep: key role of amygdala GABAergic neurons and 5-HT, Innsbruck*, Department of Pharmacology

Poul Nissen: S*tructure and dynamics of P-type ATPases*, Biocenter at University of Basel, Switzerland

Poul Nissen: E*nabling structure and mechanism based drug discovery on Ca2+ pumps and SLC6 transporters*, Novartis, Basel, Switzerland

Keisuke Yonehara: V*isual motion processing in mice: cell types, circuits, and disease*, Institute of Neuroinformatics, University of Zurich/ETH, Switzerland

MAY

Mark Denham: *New Approaches to Understanding Parkinson's Disease using Human Pluripotent Stem Cells*, University of Copenhagen, Denmark

Anders Nykjær: *From Basic Research to Biotech, Science and Technology*, Aarhus University, Denmark

Poul Nissen: *Membrane Transporters of the Brain*, EMBO Conference on Molecular Neurobiology, Crete, Greece

Marco Capogna: *mGluRs mediate presynaptic inhibition in human cerebral cortex*, Department of Pharmacology, Oxford, United Kingdom

APRIL

Poul Nissen: *The Structure and Dynamics of P-type ATPases*, Dept. Biochemistry and Molecular Biology, The University of Chicago, USA

Poul Nissen: *The Structure and Dynamics of P-type ATPases*, Membrane Proteins in Health and Disease, Banff, Canada

Duda Kvitsiani: *Foraging decisions in flies and mice*, Champalimaud Centre for the Unknown, Lisbon, Portugal

Keisuke Yonehara: *Visual motion processing in mice: cell types, circuits, and disease*, Ritsumeikan University, Japan

MARCH

Keisuke Yonehara: *Visual motion processing from retina to visual cortical areas in mice*, Annual Meeting of Japan Physiology Society, Japan

Poul Henning Jensen: *Parkinson's disease mechanisms. Regulation of alpha-synuclein functions*, Institute of Medical and Clinical Biochemistry, School of Medicine, University of Belgrade, Serbia

Anders Nykjær: *Functional characterization of the type-2 diabetes and Alzheimer's disease risk gene SORCS1*, Aarhus University, Denmark

FEBRUAR

Anders Nykjær: *Den emotionelle hukommelse, den slettede hukommelse og folk der ikke glemmer*, Vartovs Videnskab, Seminar Series, Denmark

Anders Nykjær: *NeuroCampus Aarhus, The European Brain Council, Copenhagen*, Denmark

Tomonori Takeuchi: *Dopamine-dependent memory boosting by two distinct novelty systems*, National Institute for Basic Biology, Aichi, Japan

Tomonori Takeuchi: *Dopaminergic memory enhancement by two distinct novelty systems*, The BRI International Symposium 2018, Niigata University, Niigata, Japan

Poul Nissen: *Structural biology at the interface to industry and innovation*, Workshop with Danish Service Technology providers, Denmark

JANUARY

Poul Nissen: *Structure and Dynamics of Membrane Protein Complexes*, Hamburg Life science Summit

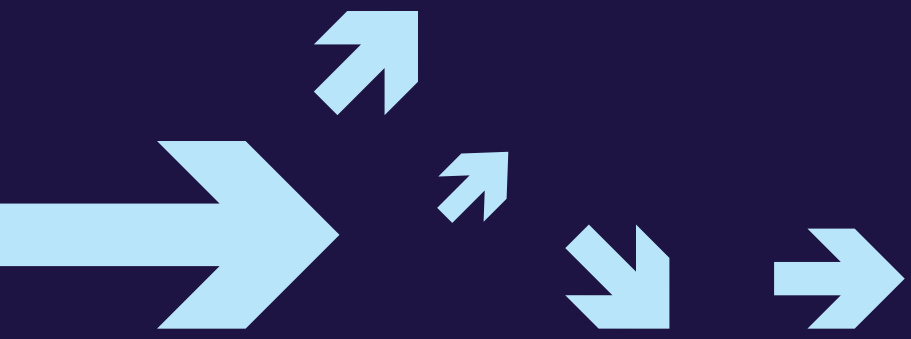
Keisuke Yonehara: *Visual motion processing in mice: cell types, circuits, and disease*, NIBB, Okazaki Japan

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

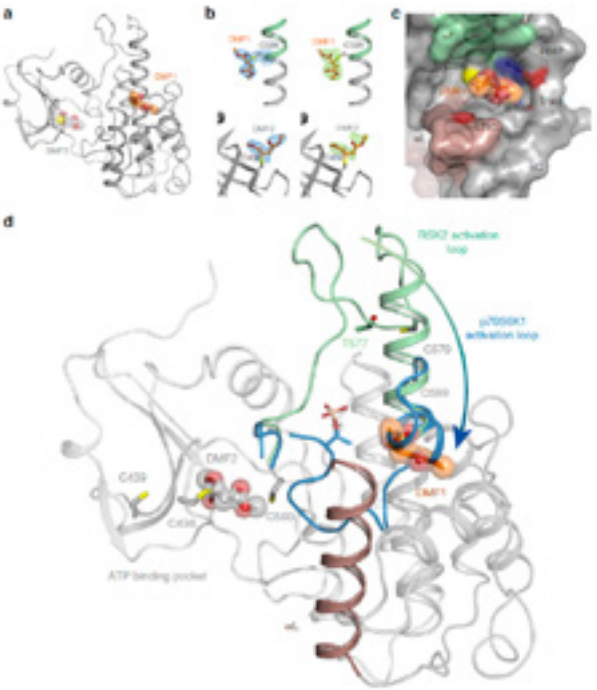
Keisuke Yonehara: *Visual motion processing in mice: cell types, circuits, and disease*, Nara Medical University, Japan

Keisuke Yonehara: *Visual motion processing in mice: cell types, circuits, and disease*, Kyoto University, Japan

05 Publications



Publications



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4 Autzen HE, Koldsø H, Stansfeld PJ, Gourdon P, Sansom MSP, **Nissen P** (2018) Interactions of a Bacterial Cu(I)-ATPase with a Complex Lipid Environment. *Biochemistry*, Vol. 57, No. 28, p. 4063-4073

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10 Buttenschøn HN, Mortensen PB, Grove J, Børglum A, Qvist P, **Christensen JH** (members of: Generation Scotland; Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium) (2018) Genome-wide interaction study of a proxy for stress-sensitivity and its prediction of major depressive disorder. *PLOS ONE*, Vol 13, No. 12

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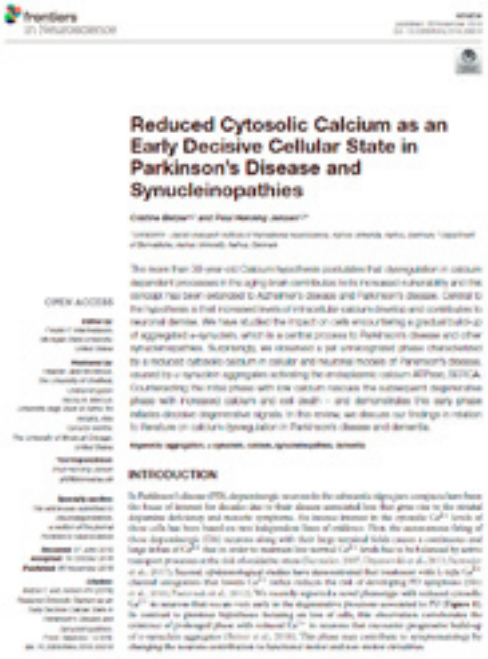
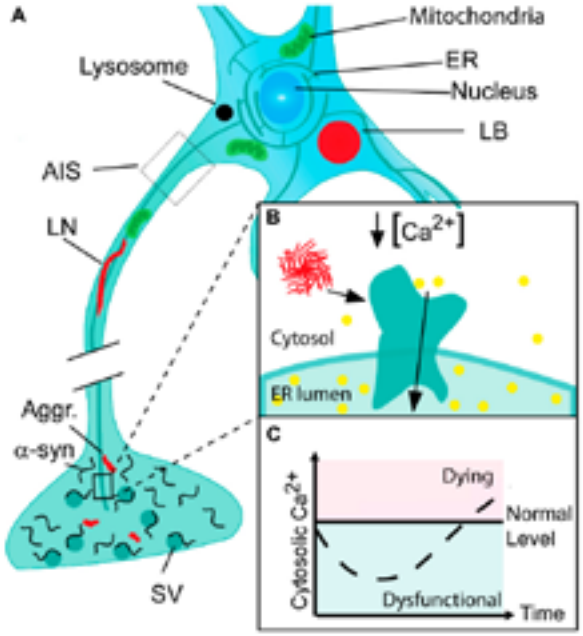
12 de Jong S; ... Breen G. **Christensen JH** (member of: Major Depressive Disorder and Bipolar Disorder Working Groups of the Psychiatric Genomics Consortium (2018) Applying polygenic risk scoring for psychiatric disorders to a large family with bipolar disorder and major depressive disorder. *Communications Biology,* Vol. 1, 163, 2018.



Reduced Cytosolic Calcium as an Early Decisive Cellular State in Parkinson's Disease and Synucleinopathies



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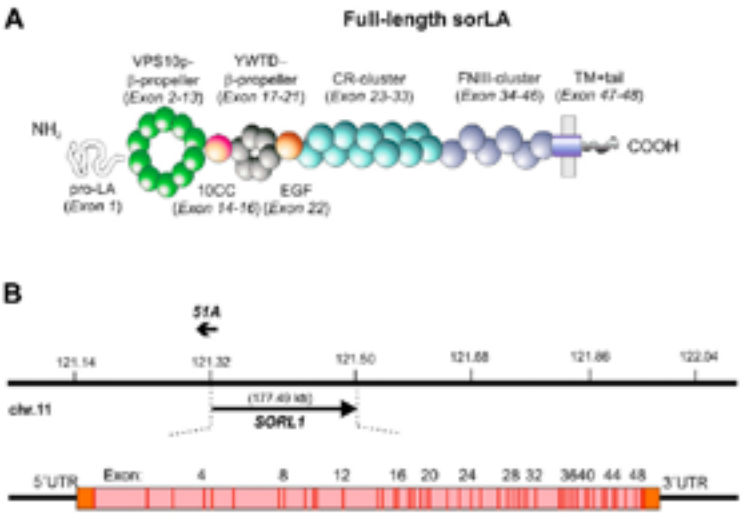
Neurobiology of Aging

An alternative transcript of the Alzheimer's disease risk gene SORL1 encodes a truncated receptor



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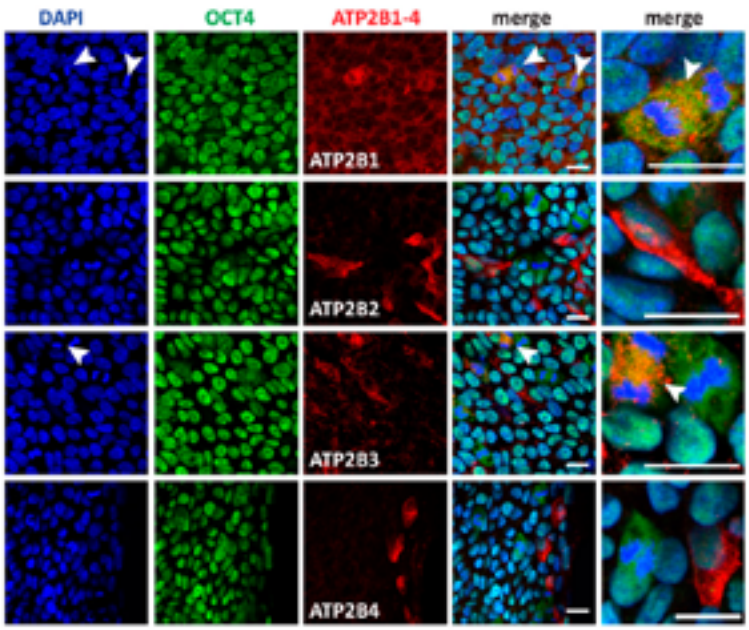
Central and Peripheral Nervous System Progenitors Derived from Human Pluripotent Stem Cells Reveal a Unique Temporal and Cell-Type Specific Expression of PMCAs



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24 Joshi S, Kvistgaard H, Kamperis K, Færch M, Hagstrøm S, Gregersen N, Rittig S, **Christensen JH** (2018) Novel and recurrent variants in AVPR2 in 19 families with X-linked congenital nephrogenic diabetes insipidus. *European Journal of Pediatrics*, Vol. 177, No. 9, 09.2018, p. 1399-1405.

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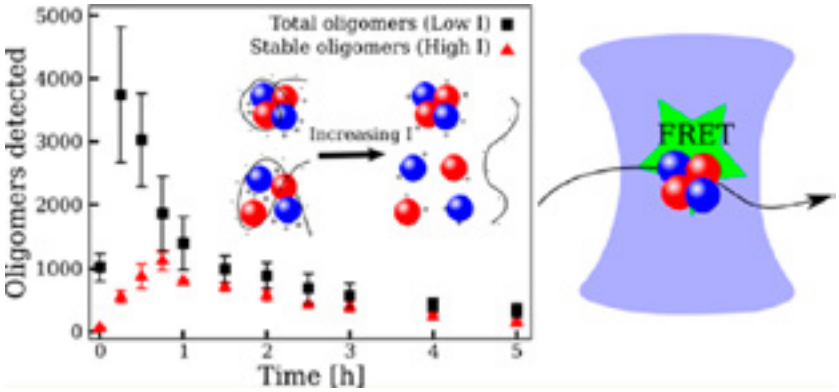
26 **Knudsen C**, **Ásgrímsdóttir ES**, **Rahimi K**, **Gill KP**, **Frandsen S, Buchholdt SH**, **Chen M, Kjems J**, **Febbraro F**, **Denham M** (2018) A modified monomeric red fluorescent protein reporter for assessing CRISPR activity. *Frontiers in Cell and Developmental Biology , Vol. 6, No. 54*

27 **Kofoed RH**, **Betzer C**, Lykke-Andersen S, Molska E, **Jensen PH** (2018) Investigation of RNA Synthesis Using 5-Bromouridine Labelling and Immunoprecipitation. Journal of *Visualized Experiments*, No. 135



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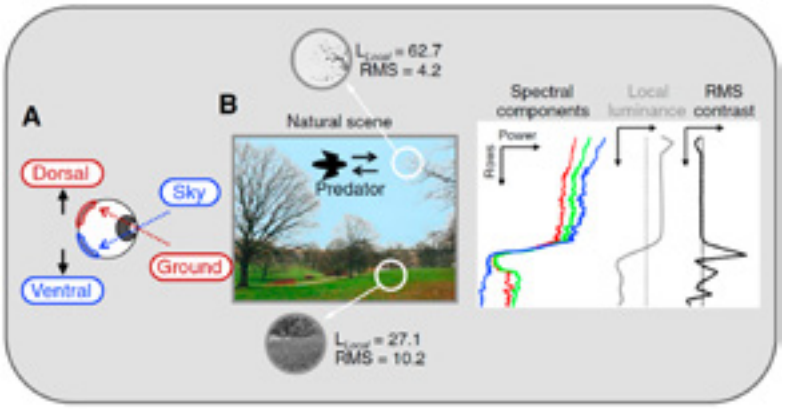
Dispatches

Visual Circuits: Division of Labor Revealed



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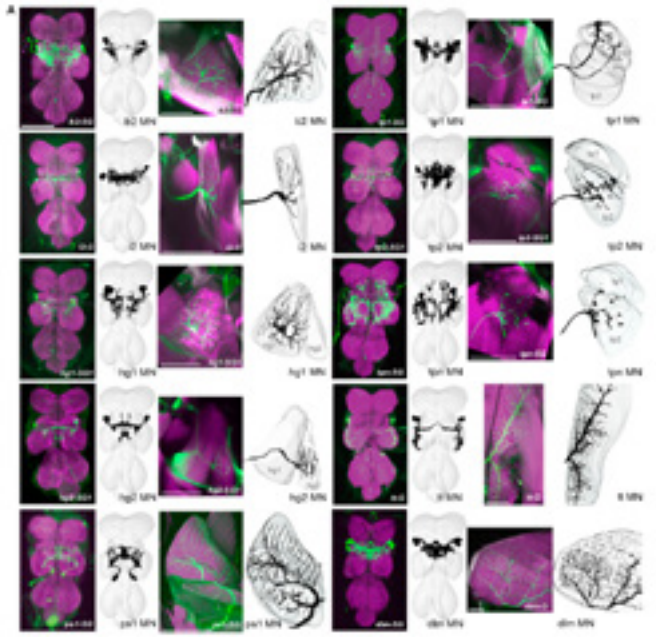
Article

Multifunctional Wing Motor Control of Song and Flight



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