2020

DANDRITE ANNUAL REPORT

AARHUS UNIVERSITY

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

Words from the Director

It's with great pleasure that we welcome you to the 2020 annual report from DANDRITE – the Danish Research Institute of Translational Neuroscience funded by the Lundbeck Foundation and hosted by the Department of Biomedicine and the Department of Molecular Biology and Genetics at Aarhus University.

DANDRITE is the Danish node of the Nordic EMBL Partnership for Molecular Medicine and a proud host of five recruited EMBL type group leader programs, center-based research programs, not least to mention the PROMEMO research center, which is a Center of Excellence funded by the Danish National Research Foundation, and advanced research infrastructures.

We surprise no-one by saying that 2020 was a special year. Covid-19 affected DANDRITE just as it affected the entire world. The Danish lockdown during the spring meant that research laboratories closed down – only allowing the most critical functions, such as animal keeping and special research infrastructure. The lockdown and Covid-19 crisis has been very challenging – not only for research and educational activities, but also for the social and psychological welfare of many and in many forms. It certainly reminded us of the importance of a well-functioning and interactive research community.

However, the pandemic has also facilitated new normal by speeding up the digitalization process and new ways of working together coming forward. During 2020, DANDRITE organized 18 virtual lectures with leading international scientists. This was only possible because of the virtual format. DANDRITE Internal meetings, Business meetings and lab meetings all took place virtually - even DANDRITE's Scientific Advisory board meeting 2020.

In September, the Swedish node of the Nordic EMBL Partnership, MIMS - The laboratory for Molecular Infection Medicine - hosted the 10th Nordic EMBL Partnership conference. The conference took place online over the course of four days with great talks, panel discussions, and poster sessions. Given the circumstances, the virtual format turned into a great success and made it possible to invite several speakers from EMBL and other keynote speakers e.g. from the United States.

The Scientific Advisory board meeting was in May 2020. We had the great pleasure to be joined by our two new SAB members for the first time; Elena Cattaneo and Veerle Baekelandt. The 2020 SAB meeting was also the last meeting served by our highly valued SAB members Glenda Halliday, Matthias Wilmanns and Mart Saarma, who rotated out like Kathleen Sweadner and Moses Chao also did earlier.

The SAB discussions and feedback are of immense importance for DANDRITE, and also in relation to the process leading to DANDRITE's request for extension with the Lundbeck Foundation, which was accepted in the end of 2020. We were extremely happy to receive the message just before New Year 2020, that the Lundbeck Foundation had decided to finance DANDRITE for the period 2023-28 (the current grant runs until March 2023), and with an early start already in 2021 for the gradual recruitment of five new group leaders, one each year for the period 2021-2025 and the transition of DANDRITE from a 10 year "project" to an open-ended EMBL partnership node and talent development program in neuroscience focused on the group leader programs. We are extremely grateful and excited for this development which will ensure a dynamic structure in Danish neuroscience.

All the current group leaders have continued into their second funding period and have developed their programs brilliantly and are now disseminating their findings and preparing their steps towards new grant applications and positions. The core group leader laboratories too are in steady developments based on DANDRITE influence and activities, and have also received strong external support for new programs and research infrastructure. All group leaders are linked to international networks and communities (e.g. through international grant actions), and DANDRITE and the Nordic EMBL Partnership for Molecular Medicine have been very important examples for the new EMBL program on how outreach and collaborations with member states can be achieved through partnerships and joint missions on particular topics. Thanks to the great example of our current group leaders DANDRITE has clearly established itself as a recognized, international neuroscience community.

Several research grants and awards were awarded in 2020 to our researchers. Group Leader Keisuke Yonehara was awarded the Lundbeck Foundation Ascending Investigator grant, and Assistant Prof. Joseph Lyons was awarded the Lundbeck Foundation Fellow 2020 and is a partner of one of the large ASAP initiatives of the Michael J. Fox Foundation. Several of the young researchers achieved recognition, for example the Health Student Research prize 2020 to student Simon Arvin, the Danish Parkinson foundation's "Young Scientist Award 2020" for Postdoc Lasse Reimer, the Kjeld Marcker PhD award 2020 for PhD Milena T. Tronsgaard, and the French Biophysical Society's PhD prize for Postdoc Thibaud Diedonné.

DANDRITE also ensures the interactions with the Danish neuroscience community through appointments and renewals of so-called affiliated researchers. This is a cornerstone of the DANDRITE mission, and we maintain a commitment to NeuroCampus Aarhus, the Danish Society for Neuroscience, and the Brain Prize activities supported by the Lundbeck Foundation, and exploit vividly the many international platforms for neuroscience that we associate with, such as EMBO, EMBL, FENS (including the Danish Society for Neuroscience), and FEBS.

DANDRITE entered the eighth year of operation, and DANDRITE alumni have developed into a large and advanced community. In 2020 we have established a LinkedIn group for our alumni, enabling us all to connect, stay connected and interact. We also feature selected DANDRITE PhD graduates in this forum, and we hope you will enjoy reading about their different career paths in academia and private sector research – past, present and pointing into the future. In the coming years, DANDRITE will further develop our international alumni network to support an interspersed community of our alumni with current DANDRITE researchers, Danish neuroscience, the Nordic EMBL Partnership, and private sector enterprises. We hope to develop a strong meeting place for mutual interactions in neuroscience and research-based careers.

DANDRITE outreach activities include also the annual DANDRITE Encounters, where students at Aarhus University and also outside meet our research groups. 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. Since most of 2020 didn't allow physical meetings and events, many of our researchers contributed with virtual contributions; a format that again may point into the future.

We are pleased to invite you to spend a few moments to learn more about our activities on the following pages, and we hope you will enjoy the read.

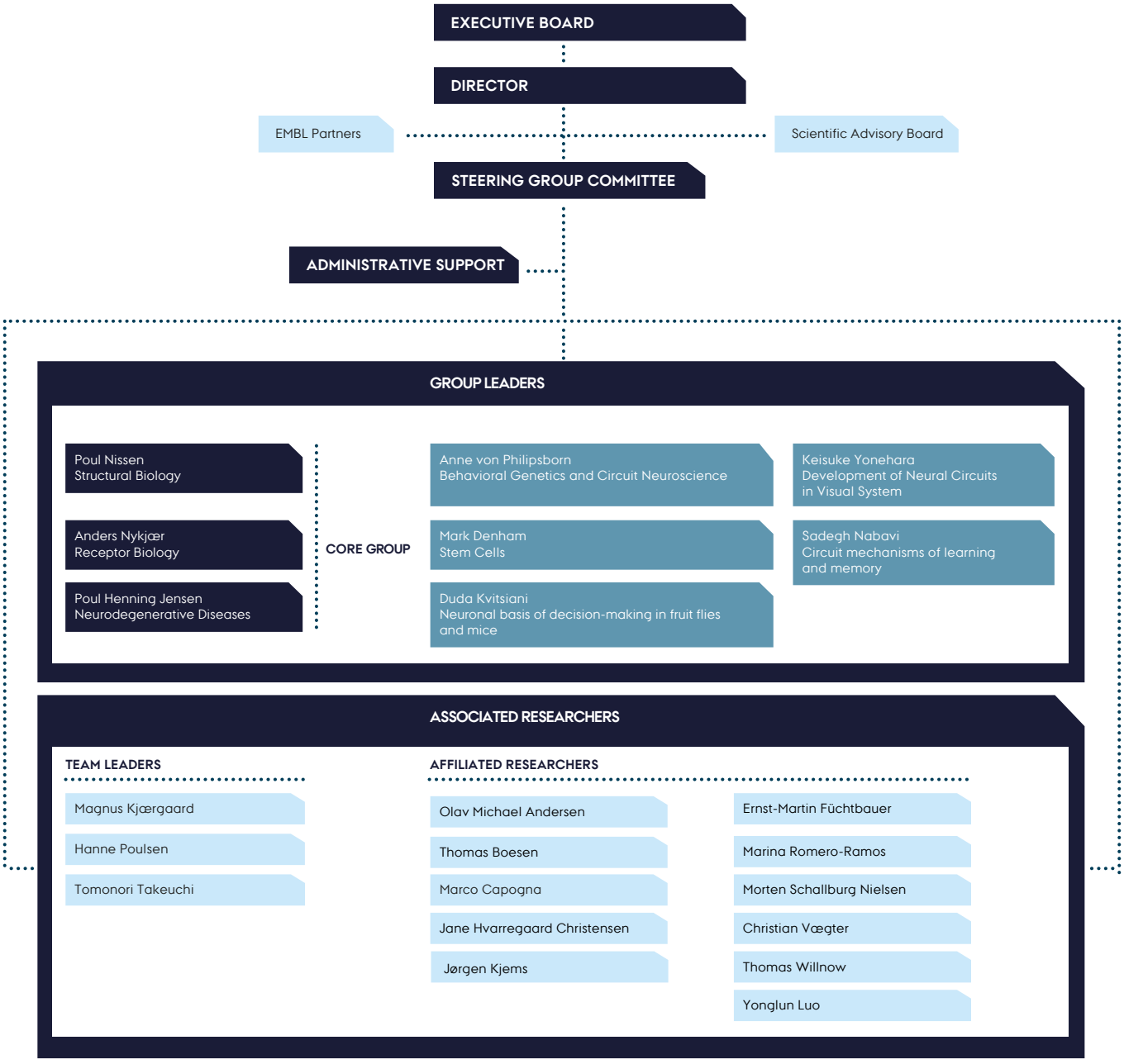
With my warmest regards,

Poul Nissen, Director and Core Group Leader

01

Organization Structure

ORGANIZATION STRUCTURE



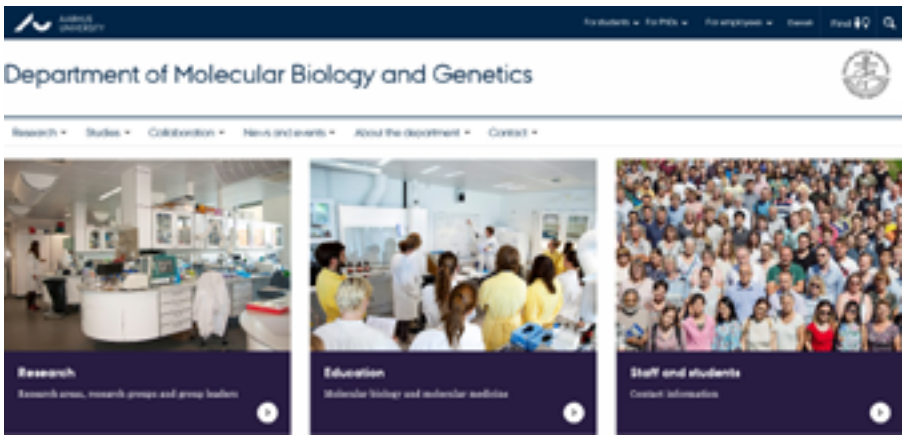
HOSTING DEPARTMENTS

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

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

→ biomed.au.dk/en

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



→ mbg.au.dk/en

EXECUTIVE BOARD

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

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

Dean **Kristian Pedersen**, Faculty of Natural Sciences, Aarhus University

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

Director & Professor **Poul Nissen**, DANDRITE

Professor **Anders Nykjær,** DANDRITE

Professor **Poul Henning Jensen**, DANDRITE

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

Lundbeckfonden Programme Manager **Lars Torup** (non-voting)

Administrative support from Chief Administrative Officer **Maria Thykær Jensen**, DANDRITE

MANAGEMENT

STEERING COMMITTEE
The steering committee meets every Monday at at 10-10.30 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 2020 consisted of the following members:

- Professor **Poul Nissen,** Director
- Professor **Anders Nykjær**
- Professor **Poul Henning Jensen**
- Group Leader **Mark Denham**
- Group Leader **Sadegh Nabavi** (took over after Anne Philipsborn in August)
- Chief Administrative Officer, **Maria Thykær Jensen**

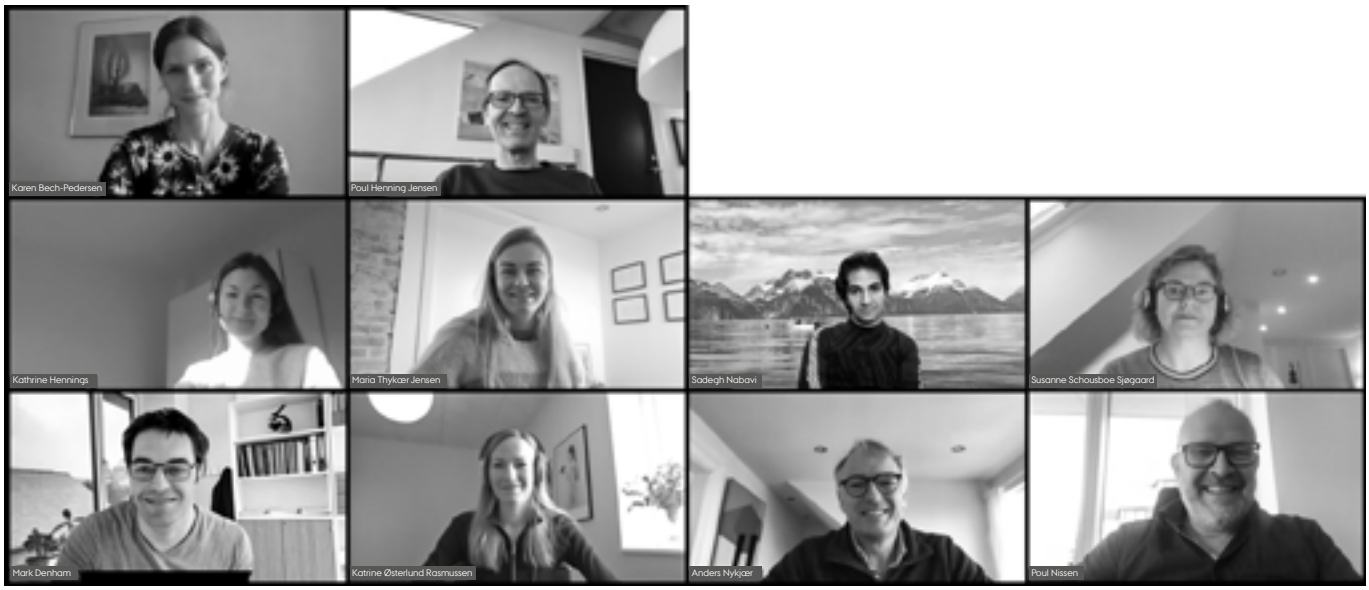
Furthermore, the steering committee meetings are attended by:

- Research Group Coordinator and Communications Officer, **Kathrine Hennings**
- Research Group Coordinator, **Katrine Østerlund Rasmussen**
- Director PA, **Karen Bech**
- Center Administrator (PROMEMO) **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 2020 the participants were:

- All DANDRITE Group Leaders
- All DANDRITE Team Leaders
- Affiliated Researcher spokesperson: **Jørgen Kjems**
- Postdoc spokesperson: **Noemie Mermet-Joret** (took over from Alena Salasova in August)
- PhD student spokesperson: **Islam Faress** (took over from Rune Rasmussen in August)
- Technician spokesperson: **Bjarke Thomsen**

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



SCIENTIFIC ADVISORY BOARD

The scientific advisory board convenes biannually and provides independent advice on scientific and strategic matters, and evaluations of achievements, ideas and strategies. SAB members are international, highly reputed researchers. The fourth DANDRITE advisory board meeting took place as a virtual event on May 26-27 2020. The current members of the DANDRITE SAB are:

- Professor and chair of DANDRITE SAB **Rüdiger Klein**, Max-Planck-Institute of Neurobiology
- Professor, **Mart Saarma**, University of Helsinki (rotating out)
- Director **Matthias Wilmanns**, EMBL Hamburg (rotating out)
- Professor **Yang Dan**, University of California, Berkeley
- Professor **Ole Kiehn**, University of Copenhagen
- Professor **Carl Petersen**, École polytechnique fédérale de Lausanne EPFL
- Professor **Elena Cattaneo**, University of Milan, Italy
- Professor **Veerle Baekelandt,** KU Leuven - Center for Molecular Medicine Belgium

New member who will take part in the planned SAB meeting in May 2022:

- Professor **Cornelius Gross**, Interium Head of EMBL, Rome, Italy
- N.N. to be appointed

ASSOCIATED RESEARCHERS

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

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

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

In 2020, Professor Thomas Willnow and Associated Professor Yonglun Luo joined as Affiliated Researchers to DANDRITE.

ADMINISTRATIVE SUPPORT TEAM

The Support Team aims at ensuring a cohesive, efficient and professional administration and research support for employees and students connected to DANDRITE. The Support Team strives for providing the framework needed for the single DANDRITE researcher to reach their full potential. As DANDRITE is an interfaculty unit, an important task for the support team is to bridge different administrative procedures among various entities and cultures and the work is done in tight collaboration with colleagues in the two hosting departments.

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

In 2020, the support team has been working from home most of the year due to Covid-19, and like most, the team had to adapt and develop new ways to collaborate, communicate and execute e.g. adjusting events and lectures to the virtual format and creating new ways to welcome new staff and students.

In 2020, the admin support team held their weekly coordination meetings online via Zoom from their home workstations.

Young DANDRITE

– The PhD & Postdoc association at DANDRITE

Young DANDRITE aim to facilitate interaction and unity among PhD students and Postdocs at DANDRITE, and support professional development of young researchers. The organizing committee meets every month to arrange both social and scientific events throughout the year.

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

In 2020, many events were cancelled and postponed due to Covid-19 which also applied to YoDa's events however, in the end of 2020 YoDa adapted to the situation and arranged their first virtual career café. The subject was stress and the mediator was Bodil Øster, certified GROW2 coach and PhD alumni from AU health.

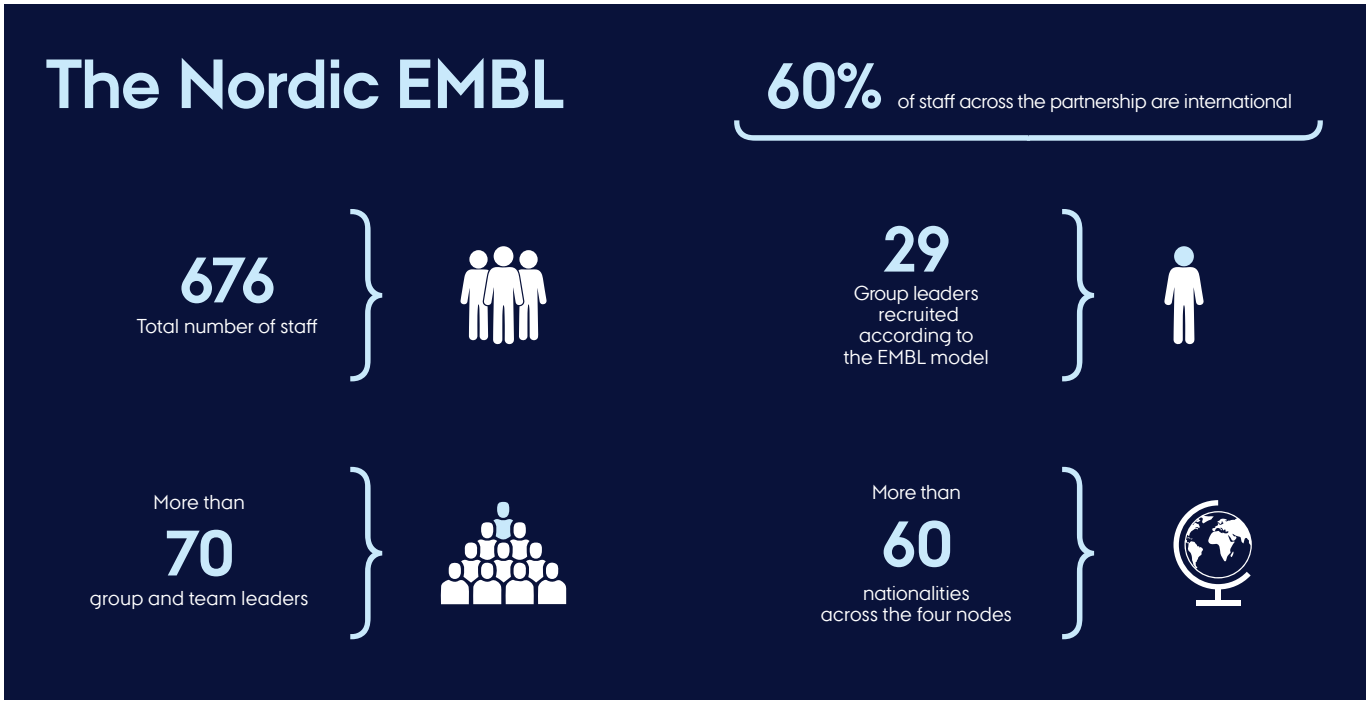
Current members of the Young DANDRITE organizing committee:
Katia Soud, PhD student
Karen Marie Juul Sørensen, PhD student
Lucie Woloszczuková, PhD student
Lixiang Jiang, PhD student
Meike Sieburg, Postdoc
Mads Christensen, PhD student
Pia Boxy, Research Assistant

Admin. Support representative: Kathrine Hennings (Research Group Coordinator & Communications Officer)

PhD representative: Islam Faress
Postdoc representative: Noemie Mermet-Joret

YoDa.
Illustration by
Sophie Seidenbecher, PhD

THE NORDIC EMBL PARTNERSHIP FOR MOLECULAR MEDICINE



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

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

Concurrently with a renewed partnership agreement with EMBL in 2013, the Nordic EMBL Partnership was expanded by a fourth node, the Danish Research Institute of Translational Neuroscience (DANDRITE, www.dandrite.au.dk). Today, the four nodes in the Partnership support over 600 staff members and house about 60 different nationalities of staff and researchers.

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

EMBL PARTNESHIP HIGHLIGHTS DURING 2020

Nordic EMBL partnership directors met with EMBL director general and other stakeholders
On behalf of the Nordic EMBL Partnership, DANDRITE Director and Partnership speaker Poul Nissen hosted a strategic meeting with EMBL Director General Edith Heard, the Nordic EMBL Partnership directors and other EMBL representatives in February 2020 in Copenhagen. In addition, key stakeholders from the Nordic region, including the Nordic EMBL Council delegates and representatives from the European spallation Source, attended the meeting. The aim of the meeting was to bring together key players in the Nordic research environment for strategic discussions about the unique strengths and opportunities within the region and to explore the alignment with EMBL and its future programme.

Nordic EMBL partnership awarded 2.5 NOK by NordForsk in 2020
The Nordic EMBL Partnership for Molecular Medicine was awarded 2.5 million NOK by NordForsk as part of their 'Nordic Research Infrastructure Hubs' initiative. The decision came after review by an international expert panel, who rated the Nordic EMBL Partnership's application as "outstanding".

A Nordic Research Infrastructure (RI) Hub is a long-term partnership between Nordic universities, universities of applied sciences, university colleges and research institutes in a consortium that provides a framework for enhancing and/or expanding RI cooperation in the Nordic region.

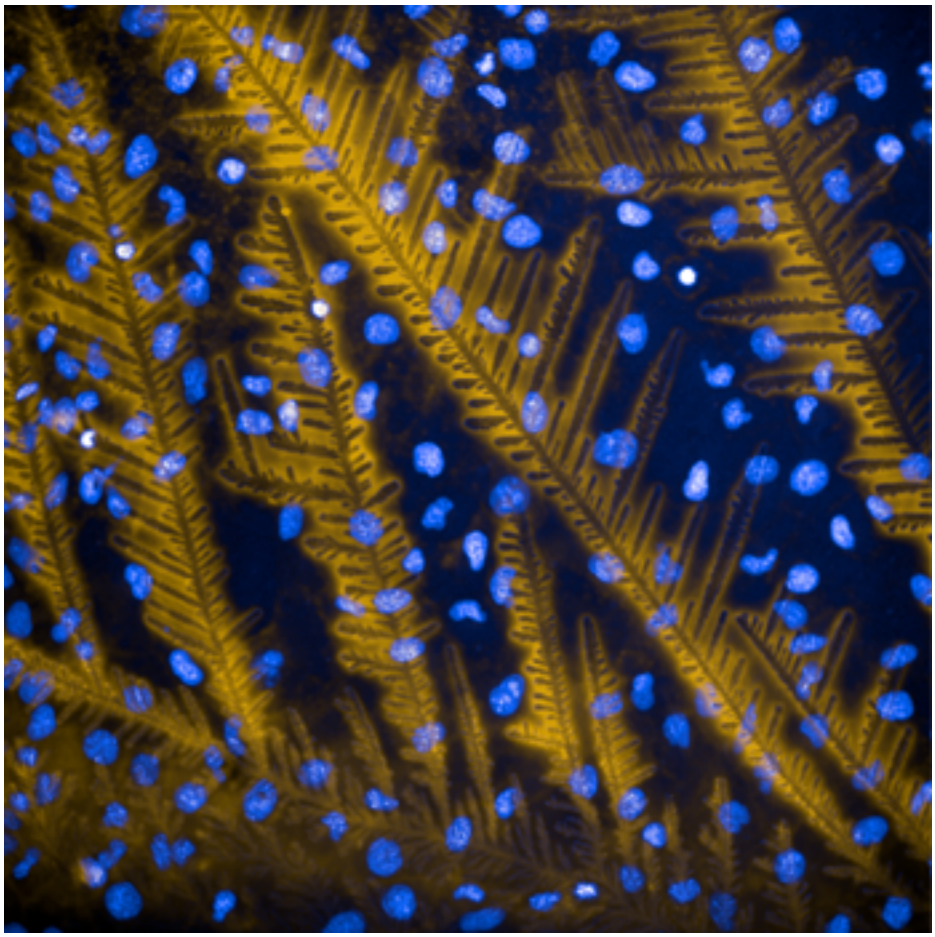
The overall aim of the Nordic RI Hub is to strengthen international competitiveness and facilitate the development of world-leading Nordic RI environments based on relevant research and research infrastructure priorities.

The grant will mean a further strengthening of molecular medicine in the Nordic countries through the Nordic EMBL Partnership. It will also enable the Partnership to better exploit its distributed infrastructures, whilst improving their accessibility and facilitating better knowledge exchange to ensure contemporary approaches in molecular medicine. The funding period is running from 2021 throughout 2023.

Former MIMS group leader, Emmanuelle Charpentier, awarded the Nopbel Prize for Chemistry
The Nordic EMBL Partnership congratulates Emmanuelle Charpentier, and collaborator Jennifer A. Doudna, on receiving the Nobel Prize for Chemistry 2020 for the groundbreaking work on the CRISPR-Cas9 gene editing technology. Emmanuelle Charpentier was one of the first group leaders recruited to MIMS according to the 'EMBL model'.

Emmanuelle Charpentier. Image: Hallbauer&Fioretti

NORDIC EMBL PARTNERSHIP SCIENCE ART COMPETITION 20202 winners



The overall winner:
Minttu Polso, FIMM, with her image '**SNOWDROPS ON PALM TREES**'.

The image was created whilst setting up a new high-throughput pipeline for a Laser Microdissection Microscope. This is one of Minttu's older slides, which she uses for demo purposes or when adjusting settings. Originally, the slide contained live cells, stained with blue for nuclei and orange for cytoplasm. However, when the slide dried-up, the orange coloring turned the salt crystals visible and created this wintery scene.

The runners up were:
Mette Richner, DANDRITE, with her image **'THE DELICATE BALANCE OF NEUROTRANSMISSION'**

Karolina Spustova, from the Gözen Group at NCMM with the image, **'LIPID EMBL – RUPTURE PATTERNS FORMING IN BIOMEMBRANES'.**

02 Research Activities

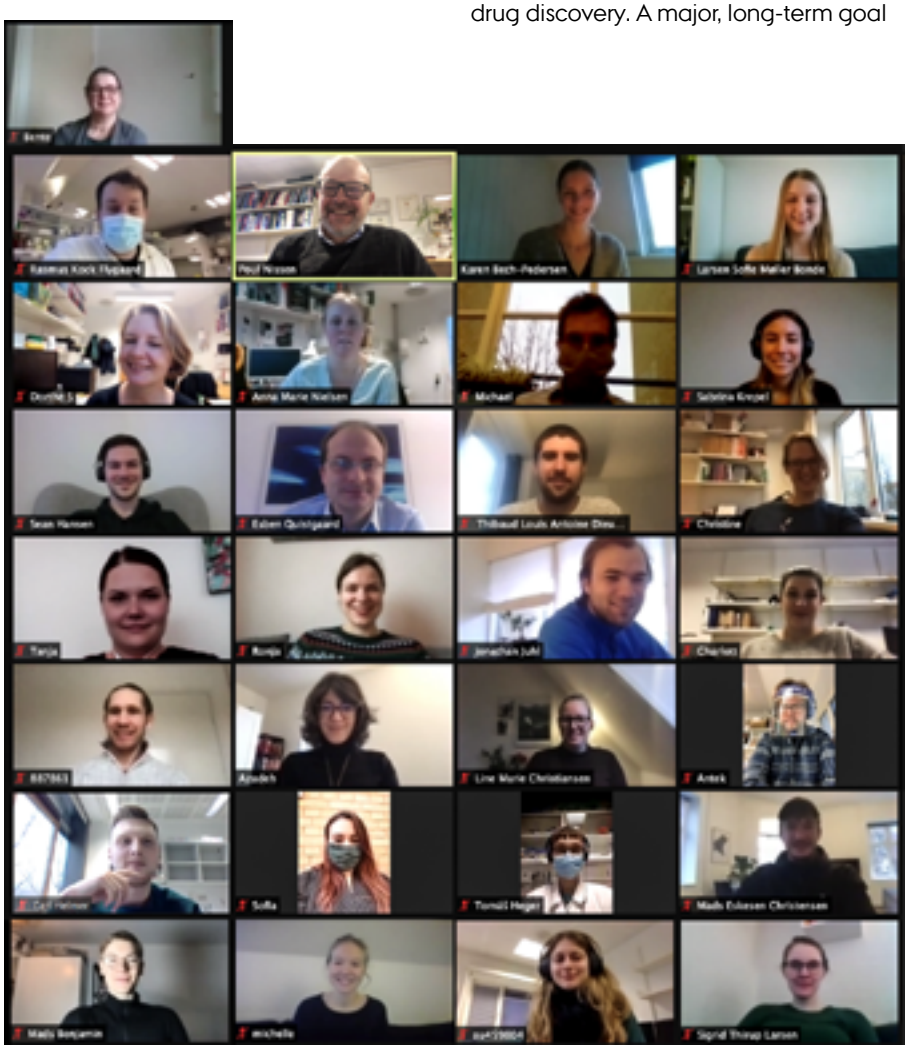
Nissen Group

Structural Neurobiology

PROMEMO
CENTER FOR PROTEINS IN MEMORY

Professor
Poul Nissen

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



A major result was the structure determination of the glycine transporter GlyT1 showing unique, new mechanisms of neurotransmitter transporter inhibition (Shahsavar et al. 2021, figure) and including also a synthetic antibody. The future perspectives of this study are to identify new inhibitors that can be used as selective glycine reuptake inhibitors in brain.

Studies of the amino acid transporter MhsT of the same transporter family as GlyT1 (and e.g. serotonin and dopamine transporters) provided also important clues to mechanisms of broader substrate specificity ranging in MhsT from valine to tryptophan (Focht, Neumann, Lyons et al. 2021).

Continuing studies of the structure and mechanism of inhibitor-bound complexes of the sarco-endoplasmic reticulum Ca2+ATPase (SERCA), the investigation of cell death pathways associated with SERCA inhibition (Lindner et al. 2020) shed light on the therapeutic potential and mechanisms of SERCA inhibitors that are of interest in cancer treatment and neurodegenerative disorders. This project has been a dual degree PhD program with NCMM in Oslo of the Nordic EMBL Partnership for Molecular Medicine.

TRANSLATIONAL STUDIES
The work on GlyT1 pointed to important new opportunities in drug design exploiting selective glycine reuptake inhibitors for the treatment of schizophrenia and other psychiatric/cognitive disorders. The SERCA studies point also towards applications in neurodegenerative disorders (see also Poul Henning Jensen's program).

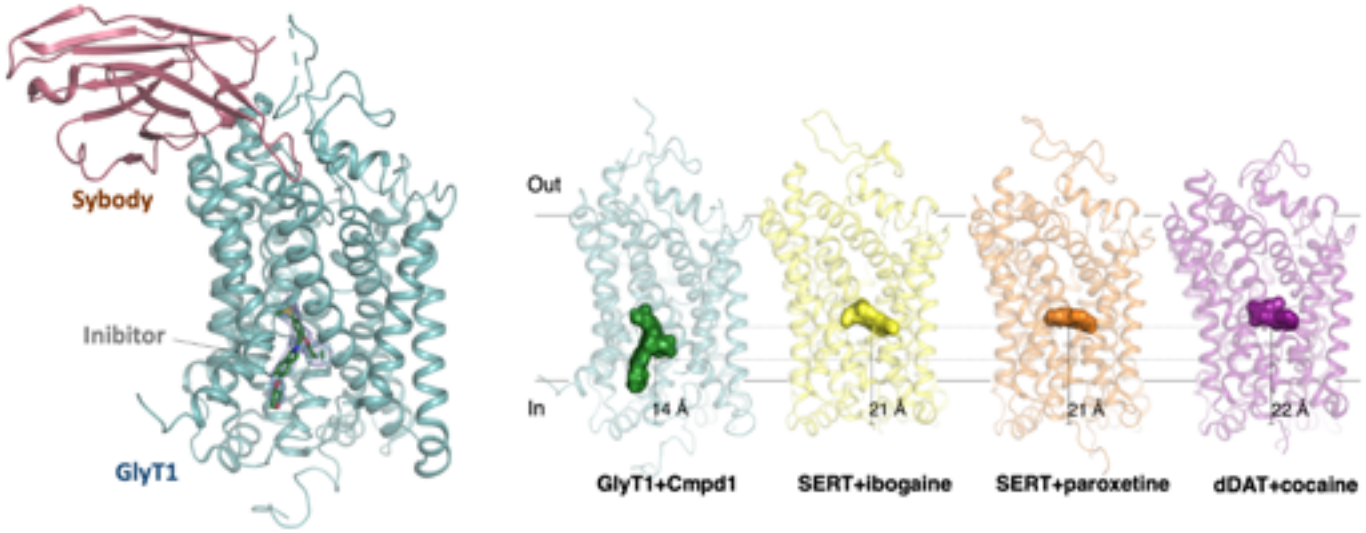


Figure 1: Crystal structure of the human glycine transporter GlyT1. Left: overall cartoon representation with GlyT1 in blue and a synthetic single-domain antibody in red (sybody, Linkster Therapeutics). The bound inhibitor (from Roche) is shown in stick representation with an overlay of the corresponding electron density map. Right: Comparison of four neurotransmitter transporters with bound inhibitors (shown as surface representations): GlyT1 with the Roche inhibitor, the serotonin transporter with psychoactive ibogaine and the antidepressant paroxetine, and the dopamine transporter with cocaine. The GlyT1 inhibition mechanism and binding site show distinct features compared to the other, previously known examples.

SELECTED PUBLICATIONS 2020

Shahsavar A, Stohler P, Bourenkov G, Zimmermann I, Siegrist M, Guba W, Pinard E, Sinning S, Seeger MA, Schneider TR, Dawson RJP, Nissen P (2021). Structural insights into glycine reuptake inhibition. *Nature*, 03.03.2021.

Focht D, Neumann C, Lyons JA, Bilbao AE, Blunck R, Malinauskaite L, Schwarz IO, Javitch JA, Quick M, Nissen P (2020). Role of transmembrane helix 6 in substrate recognition of the amino acid transporter MhsT. *EMBO J* 6:e105164

Lindner P, Christensen SB, Nissen P, Møller JV, Engedal N (2020). Cell death induced by the ER stressor thapsigargin involves death receptor 5, a non-autophagic function of MAP1LC3B, and distinct contributions from unfolded protein response components. *Cell Commun Signal* **18**:12

PERSONNEL LIST NISSEN GROUP

Senior Researcher **Thomas Lykke-Møller Sørensen**
Assistant Professor **Esben Quistgaard**
Assistant Professor **Joseph Lyons**
Assistant Professor **Michael Voldsgaard Clausen**
Assistant Professor **Azadeh Shahsavar**
Guest researcher **Antoni Kowalski**
Postdoc **Charlott Stock**
Postdoc **Rasmus Kock Flygaard**
Postdoc **Thibaud Louis Dieudonné**
Postdoc **Michael Habeck**
Postdoc **Milena Timcenko Tronsgaard**
Postdoc **Ronja Driller**
Postdoc **Sigrid Thirup Larsen**
Industriel PhD Student **Jeppe Achton Nielsen**
PhD Student **Samuel John Hjorth-Jensen**
PhD Student **Caroline Marie Teresa Neumann**
PhD Student **Jonathan Juhl**
PhD Student **Josephine Nissen**
PhD Student **Line Marie Christiansen**
PhD Student **Mads Eskesen Christensen**
PhD Student **Marlene Uglebjerg Fruergaard**
PhD Student **Paula Maria Lindner**
PhD Student **Sofia Sitsel**
PhD student **Aljona Kotsubei**
Laboratory Technician **Anna Marie Nielsen**
Laboratory Technician **Tanja Klymchuk**
Laboratory Technician **Bente Andersen**
Laboratory Technician **Dorthe Strandbygård**
Laboratory Trainee **Mikkel Juul Thomsen**
Research Assistant **Christine Juul Fælled Nielsen**
Student Assistant **Søren Brag**
Student Assistant **Jonathan Søholm-Boesen**
Scientific computing **Jesper Lykkegaard Karlsen**
Personal Assistant **Karen Bech-Pedersen**
Group Leader, Professor **Poul Nissen**

Jensen Group

Neurodegenerative Diseases

Professor
Poul Henning Jensen

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

FOCUS AREAS ARE:

- How the early phase with progressive build-up of the alpha-synuclein aggregates sculpts the degenerative process in and between neurons thereby contributing to patients' symptomatology. Investigations probe the molecular structure of alpha-synuclein aggregates generated in cells and brains, how they impact on cellular signalling pathways and how the aggregate pathology is passed between cells. Mechanism-based disease interventions are conducted in cellular and in vivo models and a project was completed on how alpha-synuclein aggregates in peripheral nerves contributes to pain.
- The impact of intracellular alpha-synuclein aggregates on calcium homeostasis and endoplasmic reticulum dysfunction is investigated in cell and animal models focussing on disease modifying strategies. A collaborative project was initiated with Novo Nordic Foundation Distinguished Innovator Claus E. Olesen focusing on generating and testing drug leads targeting the alpha-synuclein aggregate-activated SERCA pump in disease models.
- How cell- and environmental factors are contributing to the generation of specific folding strains of alpha-synuclein aggregates that displays different toxic properties. A project on how the protein p25alpha generates a more toxic strain of potential significance for the disease multiple system atrophy was completed and a new collaborative EU funded Joint Programme in Neurodegenerative Diseases "OligoFIT" initiated.
- New antibody-based methods developed with the aim of identifying and characterizing novel alpha-synuclein-based pathology in brain tissue from human patients and in vivo models are used in clinical and preclinical investigations.

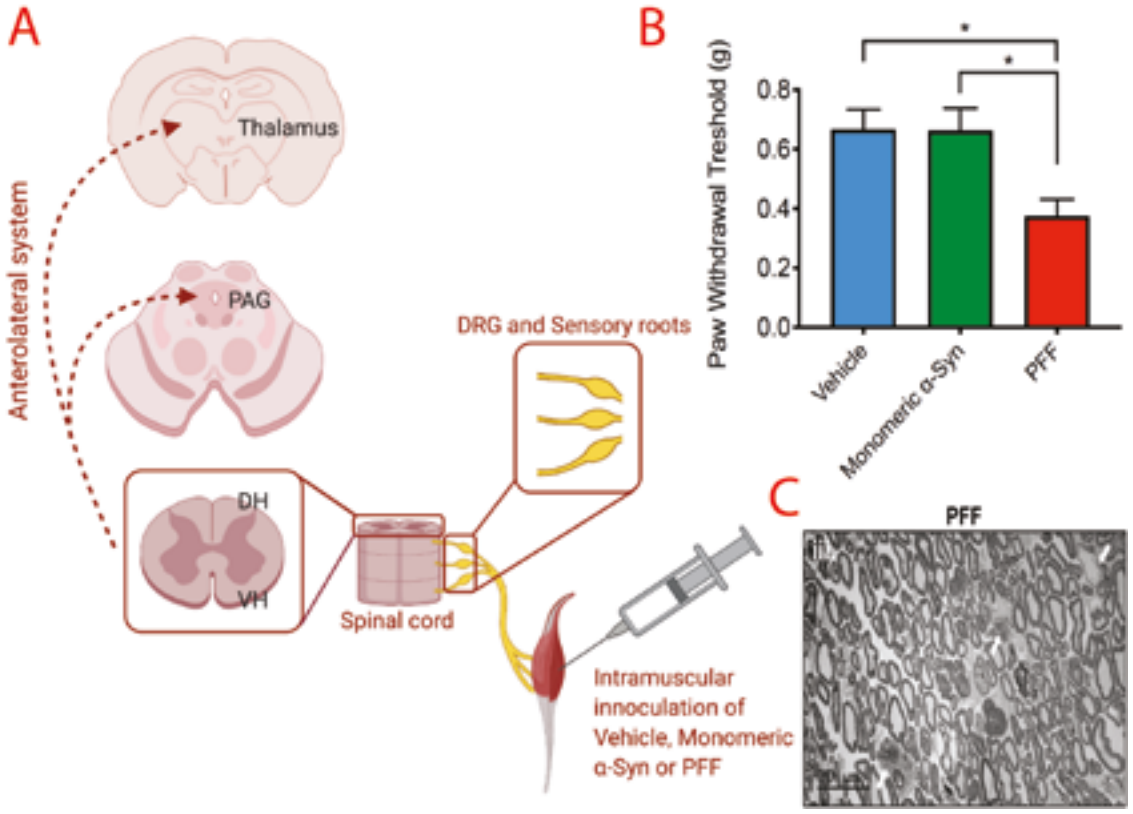


Figure 1: Alpha-synuclein aggregation in the peripheral and central nervous system induces pain that is a common non-motor symptom in Parkinson's disease patients. A) The model rely on triggering progressive alpha-synuclein pathology in an a-synuclein transgenic mouse model by injecting preformed aggregates in the hind limb. B) Mechanical allodynia (hypersensitivity of the paw to light touch) developed when pathology was induced by preformed aggregates (PFF) as compared to controls. C) Electronmicroscopic analysis of the sensory roots projecting from dorsal root ganglion (DRG) neurons demonstrates aggregate-dependent degeneration of both axons and myelin. The development is modifiable by molecules targeting the signalling pathway activated by aggregate-dependent stimulation of the calcium pump SERCA (data not shown). Data are from Ferreira et al. (2021) that was produced in collaboration with the groups of Christian B. Vægter at Dept. Biomedicine, AU and Simin Mohseni at Linköping University.

SELECTED HIGHTLIGST 2020 PUBLICATIONS

Kristian Juul-Madsen, Per Qvist, Kirstine L. Bendtsen, Annette E. Langkilde, Bente Vestergaard, Kenneth A. Howard, Martxel Dehesa-Etxebeste, Søren R. Paludan, Gregers Rom Andersen, Poul Henning Jensen, Daniel E. Otzen, Marina Romero-Ramos and Thomas Vorup-Jensen (2020) Size-Selective Phagocytic Clearance of Fibrillar α-Synuclein through Conformational Activation of Complement Receptor 4, J. *Immunology* 2020; ji1900494. doi:10.4049/jimmunol.1900494

Lasse Reimer, Cristine Betzer, Rikke H Kofoed, Christiane Volbracht, Karina Fog, Chaitanya Kurhade, Emma Nilsson, Anna K Överby, Poul Henning Jensen (2020) Direct role of PKR in the regulation of tau expression and Alzheimer's Disease-related tau phosphorylation, *Brain Pathology*, doi:10.1111/bpa.12883

Farhang Aliakbari, Hossein Mohammad-Beigi, Shahsanam, Abbasi, Nasrollah Rezaei-Ghaleh, Frederik Lermyte, Soha, Parsafar, Stefan Becker, Azita Parvaneh Tafreshi, Peter B., O'Connor, Joanna F. Collingwood, Gunna Christiansen, Duncan S. Sutherland, Poul Henning Jensen, Dina Morshedi, and Daniel E. Otzen (2020) Multiple Protective Roles of Nanoliposome-Incorporated Baicalein against Alpha-Synuclein Aggregates. *Adv. Funct. Mater.*, DOI: 10.1002/adfm.202007765

Majken B Thomsen, Sara A Ferreira, Anna C Schacht, Jan Jacobsen, Mette Simonsen, Cristine Betzer, Poul H Jensen, David J Brooks, Anne M Landau, Marina Romero-Ramos (2020) PET imaging reveals early and progressive dopaminergic deficits after intra-striatal injection of preformed alpha-synuclein fibrils in rats. *Neurobiol Disease, in press*

Nelson Ferreira, Nádia Pereira Gonçalves, Asad Jan, Nanna Møller Jensen, Amelia Van Der Laan, Simin Mohseni, Christian Bjerggaard Vægter, Poul Henning Jensen (2021) Trans-synaptic spreading of alpha-synuclein pathology through sensory afferents leads to sensory nerve degeneration and neuropathic pain. *Acta Neuropathologica Communications, in press*

PERSONNEL LIST JENSEN GROUP

Assistant Professor **Cristine Betzer**
Assistant professor **Nelson Ferreira**
Postdoc **Asad Jan**
Postdoc **Lasse Reimer**
PhD Student **Emil Gregersen**
PhD Student **Lixiang Jiang**
PhD student **Hjalte Gram**
PhD student **Nanna Møller Jensen**
Bioanalyst **Jette Bank Lauridsen**
MSc student **Helene Tallaksen**
Med. Student **Janne Schwab**
MSc student Marina **Lopez Incera** (Maastricht University)
Group Leader, Professor **Poul Henning Jensen**

Nykjær Group

Receptor Biology

PROMEMO
CENTER FOR PROTEINS IN MEMORY

Professor
Anders Nykjær

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

The receptors are multifunctional as they can bind a vast number of ligands including neurotrophins, receptor tyrosine kinases, morphogens, 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 receptors of this family control neuronal survival and development, circuitry formation, and synaptic plasticity, and what may go wrong in patients with psychiatric disorders and memory impairments. To achieve this, we take advantage of a broad repertoire of techniques including transgenic animal models, neuroembryology, transcriptomics and proteomics, cell biology, electrophysiology, mouse behavioral testing, and confocal and high-resolution imaging. Through collaborations our studies also incorporate human genetics.

Mental disorders represent one of the largest health challenges in the Western world. A complex genetic makeup is considered critical but causative mutations in several genes have also been identified. Recently, the sortilin receptor family has been identified as top-risk genes associated with psychiatric diseases but the underlying molecular mechanisms remain far from understood. Best understood is the functional link between SorCS2 and risk of ADHD. Previously we reported that SorCS2 controls dopaminergic development and most recently we found using single-unit recordings of the VTA, that neuronal firing is substantially perturbed in knockout mice due to an imbalance between the activity of the dopaminergic receptors DR1 and DR2. Given a strong genetic association of sortilin receptors with neurodevelopmental disorders, current effort is directed towards understanding their underpinnings in brain morphogenesis, in particular of the dopaminergic system.

Memory is the single most important brain process that determines our personality. Some experiences we remember strongly whereas other instances rapidly faint. A major aim of the group is to understand the molecular mechanisms that govern consolidation and recall of a memory and its selectivity. The expression of SorCS receptors was recently shown to increase by up to 200-fold in engram cells - the neurons that encode a particular memory – upon induction of a long-lasting memory trace. There are incidences that we recall with clarity decades later. These experiences typically are associated with emotional arousal as a consequence of modulation by the dopaminergic system. A major effort of our research is to understand how tSorCS1, -2, and -3 control formation of emotional memory traces.

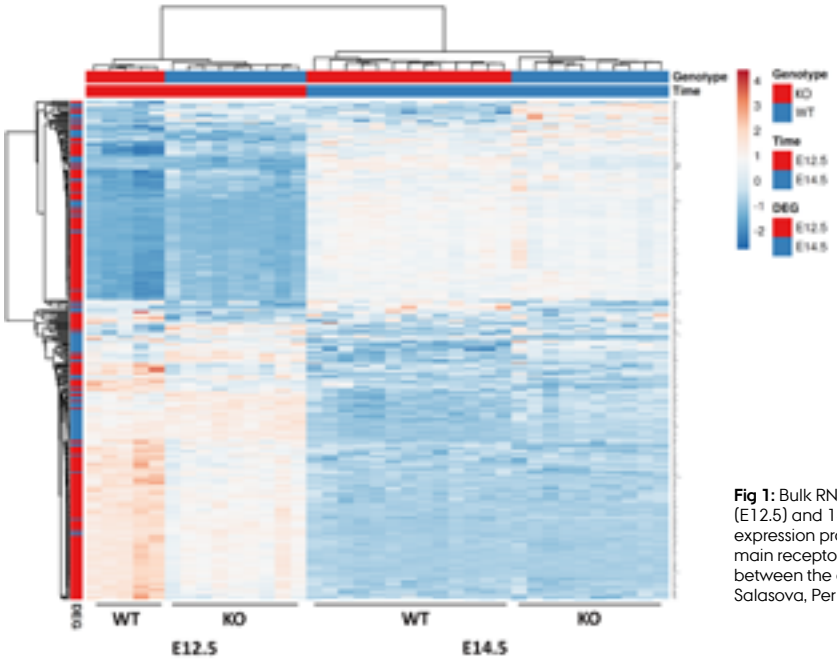


Fig 1: Bulk RNA sequencing analysis of developing embryonic brain from 12 days (E12.5) and 14 days (E14.5) old mouse embryos. The figure displays the gene expression profiles of biological replicates from wild-type (WT) and a Vps10p-domain receptor knock-out (KO) line. Transcriptional changes observed not only between the developmental stages but also between genotypes. Credits: Alena Salasova, Per Qvist.

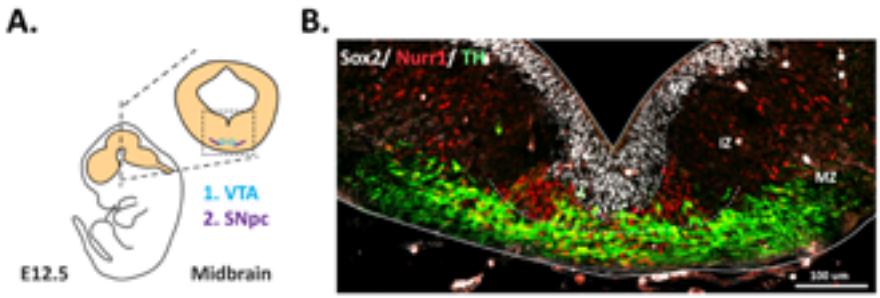


Fig 2: Tracing dopaminergic lineage cell fate using immunofluorescence. A) Illustration of a mouse embryo at E12.5 indicating areas that will develop into substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA), two major populations of dopaminergic neurons. B) Confocal microscopy image of dopaminergic progenitors (Sox2+), dopaminergic neuroblasts (Nurr1+), and immature dopaminergic neurons (Nurr1+, Th+). Credit: Alena Salasova.

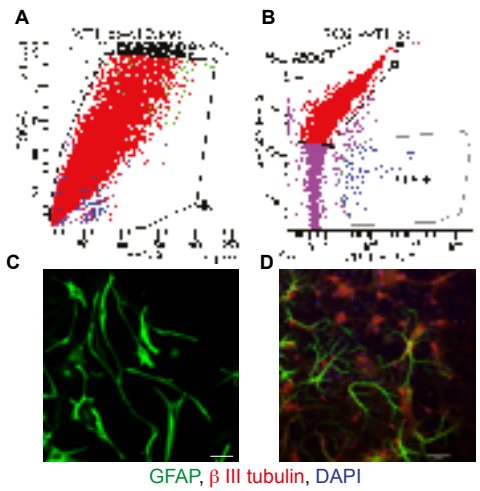


Fig 3: Fluorescein-activated cell sorting (FACS) and cultures of mouse astrocytes.
A) Forward and side scatter plot of total events: gate excludes dead cells present in the population.
B) Anti-ASCA2 and anti-CD40 were used to select only astrocytes.
C-D) Astrocytes cultured alone (C) or together with neurons (D). Scale bar: 50 mm.

PERSONNEL LIST NYKJÆR GROUP

Assistant Professor **Lilian Kisiswa**
Assistant Professor **Hande Login**
Postdoc **Alena Salasova**
Postdoc **Dongik Park**
Postdoc **Mikhail Paveliev**
Postdoc **Peter Breining**
Postdoc **Peter Lund Ovesen**
Postdoc **Pernille Thomasen**
Research Assistant **Pia Boxy**
PhD Student **Lucie Woloszczuková**
PhD Student Karen Marie **Juul Sørensen**
Laboratory Manager **Stella Solveig Nolte**
Laboratory Technician **Anne Kerstine Glintborg Jensen**
Laboratory Technician **Andreea-Cornelia Udrea**
Academic Employee **Ulrik Bølcho**
PA **Katrine Østerlund Rasmussen**
Center Manager – PROMEMO **Susanne Schousboe Sjøgaard**
Group Leader, Director of PROMEMO, Professor **Anders Nykjær**

Denham Group

Stem Cells and Translational Neurobiology

Group Leader
Mark Denham

The Denham lab works with pluripotent stem cells and is interested in understanding how the human nervous system develops. They study signalling pathways and transcriptional regulators that control the neuronal differentiation of pluripotent stem cells. They are particularly interested in what factors influence the differentiation of pluripotent stem cells through the specific progenitor states to a mesencephalic dopaminergic neuron. They aim to apply this knowledge to the development of novel therapies for Parkinson's disease (PD). Additionally, they are using patient-specific induced pluripotent stem cells (iPSCs) to generate diseased neurons. To examine early pathological changes, they are combining *in vitro* neuronal activity analysis with next-generation sequencing. The goal is to identify new disease mechanisms that may be used in the development of novel drugs for treating PD and other neurodegenerative disorders.

REGIONAL SPECIFICATION OF NEURONS FROM IPSCS

We are investigating the processes involved in the differentiation of iPSCs into subtype-specific neurons. Neurological disorders such as PD affect specific neuronal subtypes; therefore, being able to control the differentiation of iPSCs into specific neurons will allow us to examine subtype-specific phenotypes. In our lab, we developed a direct conversion method that generates subtype specific neurons. It combines both differentiation and direct conversion together. Firstly, we pattern the cells to a specific neural progenitor and, subsequently, convert them into regional-specific neurons (Chen et al., 2020). Using this approach, we can generate distinct neuronal subtypes that correspond to the forebrain, midbrain and hindbrain regions of the CNS (Figure 1). Overall, determining the factors that regulate cell fate and how the interplay between extrinsic and intrinsic factors is regulated is crucial for understanding developmental processes and will allow us to generate pure neuronal populations for disease modelling.

PUBLICATIONS

Chen M, Maimaitili M, Habekost M, Gill KP, Mermet-Joret N, Nabavi S, Febbraro F, Denham M. (2020). Rapid Generation of Regionally Specified CNS Neurons by Sequential Patterning and Conversion of Human Induced Pluripotent *Stem Cells. Stem Cell Research.* https://doi.org/10.1016/j.scr.2020.101945

Habekost M, Jørgensen AL, Qvist P, Denham M. (2020). MicroRNAs and Ascl1 facilitate direct conversion of porcine fibroblasts into induced neurons. *Stem Cell Research.* https://doi.org/10.1016/j.scr.2020.101984

Chen M, Maimaitili M, Buchholdt SH, Jensen UB, Febbraro F, Denham M. (2020). Generation of an induced pluripotent stem cell line (DANi-011A) from a Parkinson's disease patient with a LRRK2 p.G2019S mutation. *Stem Cell Research.* Mar 29;45:101781. https://doi.org/10.1016/j.scr.2020.101781

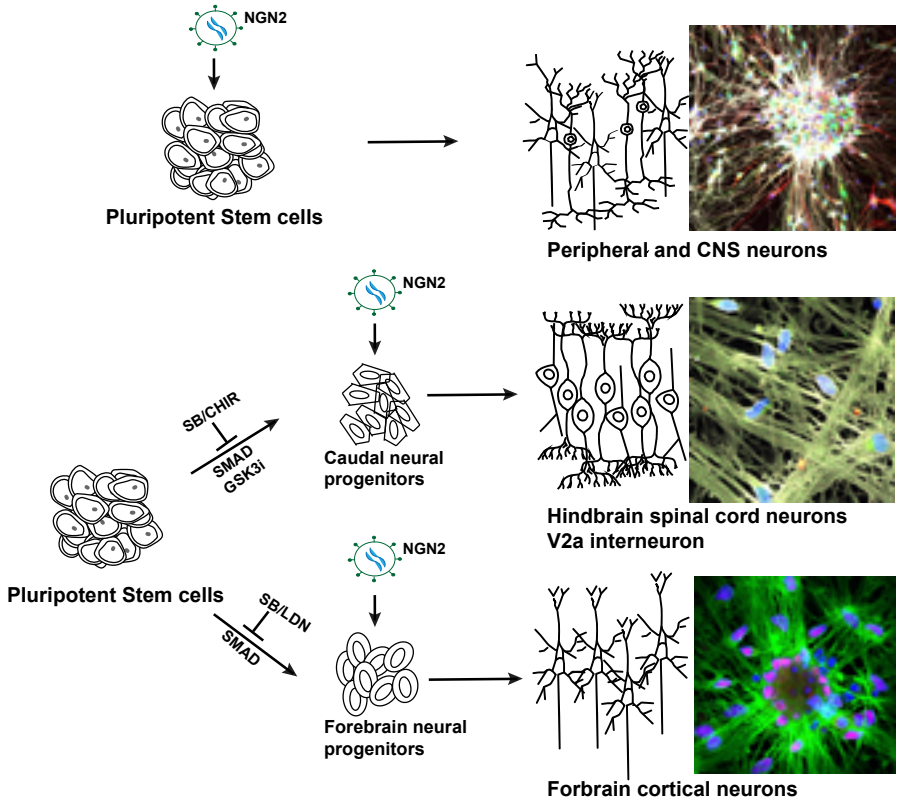
Gill, K.P., Denham, M. (2020). Optimized Transgene Delivery Using Third-Generation Lentiviruses. *Curr. Protoc. Mol.* Biol. 133, 1–21. https://doi.org/10.1002/cpmb.125

PERSONNEL LIST DENHAM GROUP

Assistant Professor **Muwan Chen**
Postdoc **Katherine Gill**
PhD Student **Mette Habekost**
PhD Student **Muyesier Maimaitili**
Laboratory Technician **Susanne Hvolbøl Buchholdt**
Group Leader **Mark Denham**

MOLECULAR MECHANISMS CONTROLLING PARKINSON'S DISEASE SUSCEPTIBILITY

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



Direct neuronal conversion of pluripotent stem cells with a single factor NGN2 yielded a mixed neuronal culture containing peripheral and CNS neurons. By combining an early patterning event of a differentiation protocol with the direct conversion approach, we can produce regional-specific neurons along the rostral caudal axis, which results in a more defined population of neurons. This approach can be used for investigating a broad range of neurological disorders.

Kvitsiani Group

Neuronal basis of decision-making in fruit flies and mice

Group Leader
Duda Kvitsiani

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

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

MAJOR ACHIEVEMENTS

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

In mice and humans using probabilistic reward foraging task (Fig.2) we discovered that animals rely both on their past reward and choice history to make decisions. Using normative framework we show that choice history integration into decision-making process is optimal and computational models that incorporate choice history effects outperform existing models that ignore choices history effects.

In parallel to behavioral studies, we also carried out single unit recordings to understand how decision variable are computed by cortical neurons. We could demonstrate that individual neurons in medial prefrontal cortex (mPFC) in a reward foraging task (Fig.2) represent state variables, like previous choices and rewards. Our work further shows that mPFC encodes task invariant variables and not subjective values as suggested by previous studies.

FUTURE PLANS

In order to understand cortical computations and the role of single spikes in decision making process we have developed the real-time spike sorting

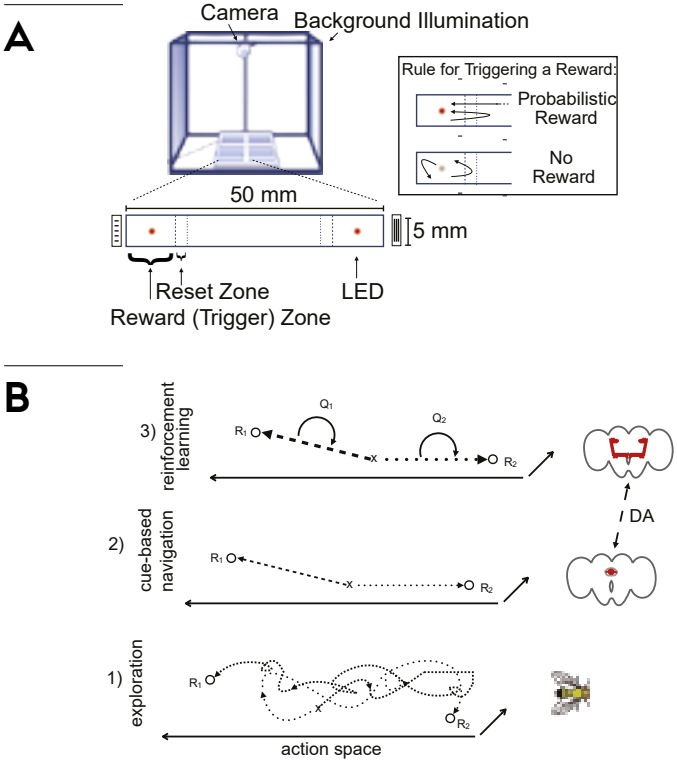


Figure 1:

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

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

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

feedback system that allows us to trigger an arbitrary stimulus when a single spike is detected from a well isolated single unit. We plan to use this method to provide millisecond time scale feedback in the form of optogenetic stimulation to cortical neurons to strengthen or weaken the existing neural ensemble activity. The method will allow us for the first time to probe how neural population activity forms stable neural representations.

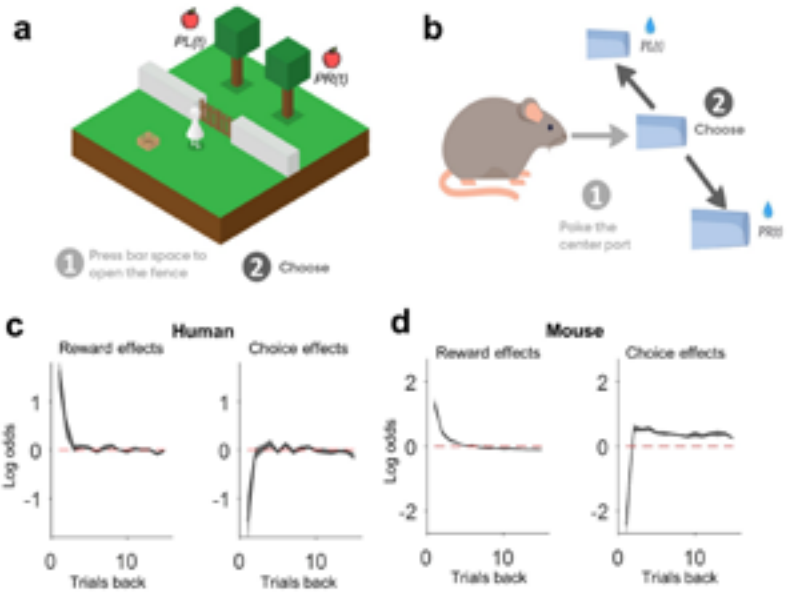


Figure 2: A Snapshot of the computer game played by the human participants. The subjects had to wait between 0s and 5s after opening a virtual fence by pressing on a keyboard before making the decision to press on the left or right key. **B** The scheme of the task adapted for mice. The rodents had to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

SELECTED PUBLICATIONS

Seidenbecher, SE, Sanders JI, von Philipsborn AC, Kvitsiani D. Reward foraging task and model-based analysis reveal how fruit flies learn value of available options. *PloS one*. October 2, 2020.

Hulme OJ, Kvitsiani D. Extending models of "How Foraging Works": Uncertainty, controllability, and survivability. *Behav. Brain Sci.* 2019 Jan;42:e43.

S Shuvaev, S Starosta, D Kvitsiani, A Kepecs, A Koulakov.R. Learning in actor-critic model offers a biologically relevant mechanism for sequential decision-making. Advances in Neural Information Processing Systems. 2020; 33.

JS Lopez-Yepez, J Martin, O Hulme, D Kvitsiani. A normative account of choice history effects in mice and humans. *BioRxiv* July 24, 2020.

Belkhiri M, Kvitsiani D. "D.sort: template based automatic spike sorting tool". *BioRxiv*. September 23, 2018.

PERSONNEL LIST KVITSIANI GROUP

Postdoctoral fellow **Jesper Hagelskjær**
Postdoctoral fellow **Maria Møller Moltesen**
Student assistant **Anna Barta**
Research assistant **Tsz Fung Woo**
Group Leader, Associate Professor **Duda Kvitsiani**

Nabavi Group

PROMEMO
CENTER FOR PROTEINS IN MEMORY

Circuit mechanisms of learning and memory

Group Leader
Sadegh Nabavi

Synaptic plasticity remains an (almost) indisputable candidate for learning and memory. For this reason, a large body of works is devoted to the mechanisms underlying plasticity, with the majority of these works take in vitro preparation as their working model. However, many behavioral phenomena either cannot be studied in slice preparation or are inconsistent with the findings. The main theme of our research is to understand the rules that govern synaptic plasticity in vivo, in respect to associative learning. We will give a particular emphasize to the types of associative learnings (and forgetting!) that cannot be reconciled with the currents models that are inspired by in vitro studies

MAJOR ACHIEVEMENTS

- **Mapping the neural circuit for an innate fear behavior:** Fears are either innate (fear of snakes) or learned (fear of a gun). It is widely accepted that the expression of learned fears relies on the amygdala activity. Using genetically irreversible and reversible inactivation and calcium imaging we found that the integrity of the amygdala is also required for the expression of an innate fear. This raises a dilemma: how the amygdala harbors two qualitatively different fears, learned vs innate. Currently, we are testing the hypothesis that the thalamic regions upstream of the amygdala may pass the signal for both innate and learned fear response. This is based on our recent observation on the behavioral consequence of thalamic lesion. We are hoping these investigations lead us to a better understanding of the processing underlying innately aversive signals at the synaptic level. The main techniques in this project are brain circuits mapping and manipulation, optogenetics, and miniaturized microscopy.
- **Tracing the plasticity for behaviorally realistic associative learning:** A fundamental, yet unresolved question in the field of learning and memory is how the brain associates events that are separated in time by seconds or more. This requires the brain to maintain the trace of the first event until the arrival of the next one and yet synaptic plasticity runs on the scale of milliseconds. To investigate associative plasticity on a behavioral timescale at the cellular/synaptic level, we have recorded cellular activity in freely moving mice during a trace fear conditioning, an associative learning wherein two events- the tone and shock- are separated by many seconds. Thus far, we were able to identify putative monosynaptic connections and monitor short- and long-term changes in synaptic strength during learning. Our next steps are to build a model based on our observations and then test it by manipulating neuronal activity during learning. On this project, we work closely with Duda Kvitsiani".
- **Synaptic Mechanisms Underlying Memory Decay** It is well known that synapses are malleable, and this ability (i.e., plasticity) is the base of learning and memory formation. However, how are changes in synaptic strength related to memory decay is still not well understood. In this project, we aim to follow the synaptic strength modification associated to a memory trace in time, and describe what happens at both synaptic and behavioral levels while a memory is forgotten. To do this, we use a variety of techniques that include optogenetics, behavioral tests, in vivo electrophysiology, and pharmacology. Recently, we have developed a precise behavioral protocol using aversive conditioning that allows us to create an optogenetically-tagged memory that decays in a short period of time. Currently we are in the process of observing the synaptic strength correlate of this forgetting process, by implanting mice with microelectrodes for in vivo recording throughout the behavioral task.
- **Synaptic Tagging and Capture: From Synapses to Behavior.** The synaptic tagging and capture hypothesis (STC) is a prominent theory of memory consolidation that hasn't been directly tested on the behavioral level. To validate the STC, we developed a behavioral model that allows investigation of heterosynaptic modulation of a conditioned response in mice. To this end an optically-induced aversive conditioning protocol was tailored to decay within 24 hours. Its mouldability was confirmed by the means of an optically induced homosynaptic high-frequency stimulation (HFS), making it longer lasting and of higher magnitude. In order to test heterosynaptic HFS, independent dual optical activation of convergent inputs was established and verified by optical- in vivo electrophysiology. Finally, the heterosynaptic HFS was tested and yielded similar effects to those of homosynaptic HFS.

- **Independent optical excitation of two neural populations.** A major unmet need in optogenetic toolbox is the ability to activate independently two distinct but intermingled populations of neurons. The fundamental challenge to this is that all opsins, in addition to their own excitation spectra, are activated by blue light. We hypothesized that pairing a red-shifted channelrhodopsin with a blue light-sensitive anion channel of appropriately matching kinetics shall render neurons responsive to a red but not blue light. To achieve this, we used a semi-rational mutagenesis strategy to optimize the kinetics and light spectrum of a chloride channelrhodopsin. By pairing an optimized blue light-sensitive anion channel with a fast red-shifted channelrhodopsin, we created a system in which red light derives precise and faithful action potentials of high frequencies, while blue light, through shunting inhibition, nullifies the effects of ChR2. Thus, simply by alternating between red and blue lights, one can effectively excite or inhibit the activity of the same neurons.

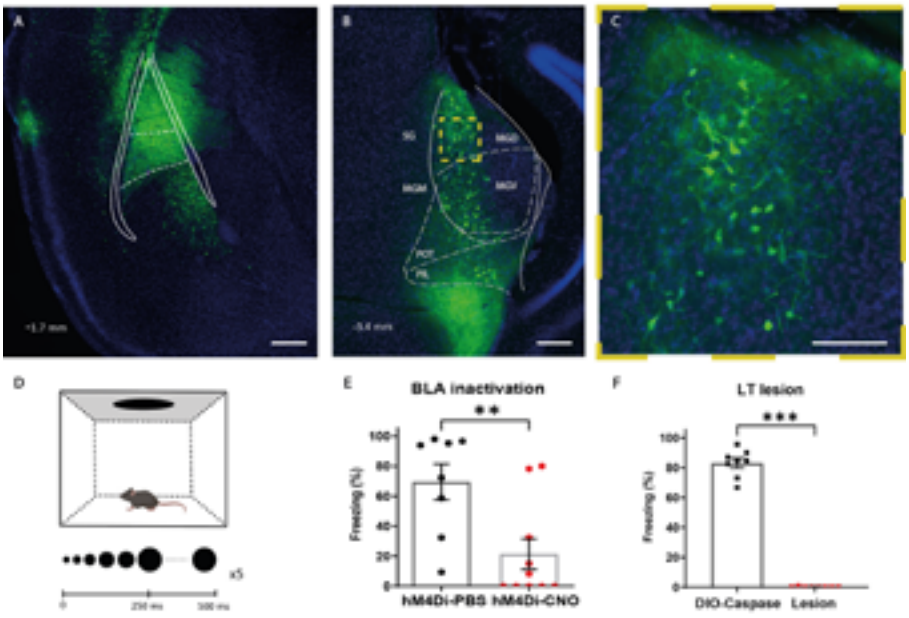


Figure 1: BLA and LT are required for looming-evoked defensive behavior A) AAV2-retro-Cre mixed with AAV2-retro-DIO-GFP injection restricted to the BLA. B) Retrogradely labelled BLA-projecting neurons (GFP+) are present in the SG, MGM, PIL; collectively referred to as LT. C) A zoomed-in view of the outlined region. D) Schematic representation of the looming stimulus setup: an arena with a monitor place on the top. The monitor delivers the looming stimulus that consist in a black expanding disk. E) BLA inactivation: chemogenetic silencing of the BLA caused a reduction in the looming stimulus-evoked response in hM4Di-CNO group compare to the control group (hM4Di-PBS n=8; hM4Di-CNO n=10; Unpaired t-test p=0.0070). F) LT lesion: lesion of the thalamic region abolished the looming stimulus-evoked response in the lesion group compared to the control group (DIO-Caspase n=8; Lesion n=8; Mann-Whitney test p=0.0002). Scale bar, 250 µm. Results are reported as mean ±S.E.M. **, p<0.001; ***, p<0.0001. BLA, basolateral amygdala; LT, lateral thalamus. Mouse created from BIORENDER

PERSONNEL LIST NABAVI GROUP

Postdoc **Andrea Moreno**
Postdoc **João Lima**
Postdoc **Noëmie Mermet-Joret**
PhD Student **Islam Moustafa Galal Faress**
PhD Student **Mariam Gamaleldin**
PhD Student **Niels Andersen**
PhD Student **Valentina Khalil**
Laboratory Technician **Anne-Katrine Vestergaard**
Laboratory Technician **Kathrine Meinecke Christensen**
Laboratory Assistant **Randi Hald Melsen**
Trainee **Alejo Mosqueira**
Group Leader **Sadegh Nabavi**

Philipsborn Group

Neuronal circuits for reproductive behavior

Group Leader
Anne von Philipsborn

2020 PUBLICATIONS

A.C. von Philipsborn (2020); Neuroscience: The female art of saying no. (Dispatch) *Current Biology*, 30 (19): R1080-R1083. DOI: 10.1016/j.cub.2020.08.023

P. Kerwin and A.C. von Philipsborn (2020); Copulation Song in Drosophila: Do Females Sing to Change Male Ejaculate Allocation and Incite Postcopulatory Mate Choice? *BioEssays*, 42 (11). DOI: 10.1002/bies.202000109

P. Kerwin, J. Yuan and A.C. von Philipsborn (2020); Female copulation song is modulated by seminal fluid. *Nature Communications*, 11, 1430. DOI: 10.1038/s41467-020-15260-6

S.E. Seidenbecher, J.I. Sanders, A.C. von Philipsborn, D. Kvitsiani (2020); Reward foraging task and model-based analysis reveal how fruit flies learn value of available options. *PLOS ONE*, 15 (10): e0239616. DOI: 10.1371/journal.pone.0239616

PERSONNEL LIST PHILIPSBORN GROUP

PhD student **Peter James Kerwin**
PhD Student **Bijayalaxmi Swain**
IT Employee **Per Rosing Mogensen**
Laboratory Technician **Anna Prudnikova**
Guest researcher **Kawtar Cherkaoui**
Student assistant **Sophie Röhling**
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. Furthermore, we are also interested in the communication between nervous system and the rest of the body. We address inter-organ signaling in the context of sexual behavior during copulation and aim at understanding how sensing of seminal fluid impacts female sexual behavior and how female signals affect male seminal fluid allocation.

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 discovered that not only males, but also females produce acoustic signals during reproduction, which depend on the receipt of seminal fluid (Kerwin et al. 2020). Current efforts are directed at understanding proximate and ultimate causes of this new female behavior, and at exploring differences in neuronal control of male and female song.

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 function and employ mass spectrometry to identify behaviorally relevant seminal fluid components.

MECHANISMS OF SEX SPECIFIC MOTOR PATTERN GENERATION DURING ACOUSTIC COMMUNICATION
How do dimorphisms in gene expression shape nervous system anatomy and physiology, explaining dimorphisms in behaviour?

Drosophila acoustic communication during mating is an excellent system to study this question. Male flies produce a precisely structured courtship song by wing vibration. Recent work in the Philipsborn lab has dissected the motor neuron control system for male song and its multifunctional use in flight control (O'Sullivan et al. 2018). Motor neurons are present in both sexes. In contrast, interneurons for motor patterning and action selection develop sex-specific cell fates, morphologies and physiological characteristics under the control of the transcription factors Fruitless and/or Doublesex. So far, the circuits for courtship song have been studied under the assumption that only male flies sing. We discovered that female flies also produce a song, which is distinct from its male counterpart and occurs during copulation (Kerwin et al. 2020). This finding redefines the functional interpretation of dimorphic circuit development and provides a starting point for identifying new genetic and neuronal motifs underlying acoustic communication. We aim at investigating to which extent the neuronal substrate for acoustic signalling overlaps in both sexes and how differences in male and female singing behaviour can be explained on the level of gene expression, physiology and circuit architecture (Figure 1).

BEHAVIORAL HIERARCHY AND COORDINATION- STATE DEPENDENT ACTION SELECTION

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

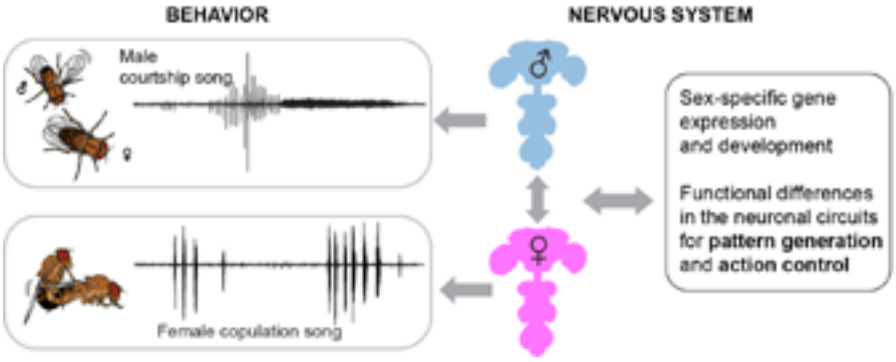
COMMUNICATION BETWEEN THE NERVOUS SYSTEM AND REPRODUCTIVE ORGANS: GENES, PATHWAYS AND CIRCUITS FOR SENSING AND ALLOCATING EJACULATE COMPONENTS

In animals with internal fertilization, seminal fluid strongly influences the physiological requirements for reproduction. Active components and signalling molecules transferred together with sperm and impact sperm storage and viability, ovulation, female immunity, susceptibility to infection, the female nervous system and her behaviour.

We found that specific components of seminal fluid incite acoustic signalling of female Drosophila during copulation (Kerwin et al. 2020). Our data indicates that female copulation song influences in turn male ejaculate allocation and biases the outcome of paternity shares under reproductive competition. These findings suggest that 1) females can rapidly sense and behaviourally react to seminal fluid and 2) males have evolved mechanisms to adjust seminal fluid quality and transfer in response to acoustic signals from the female.

Our current work is directed at finding which seminal fluid protein/peptide and respective receptor trigger female copulation song. We are also investigating the neuronal control mechanisms of male plastic ejaculate allocation in response to female song (Figure 2).
By this research, we aim at a general understanding of the female and male neuronal circuits mediating communication between the nervous system and the reproductive organs. We are interested how this signalling axis is modulated by sensory input and physiological conditions known to impact reproductive decisions (aging, nutritional state, infection, mating history and social exposure) (Figure 3).

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



Figur1:Male courtship song and female copulation song in Drosophila.
We aim at understanding how sex-specific gene expression and circuit architecture explains the differences in the two behaviors, regarding motor pattern generation and action control and coordination. (part of the figure modified from Kerwin and von Philipsborn, BioEssays 2020)

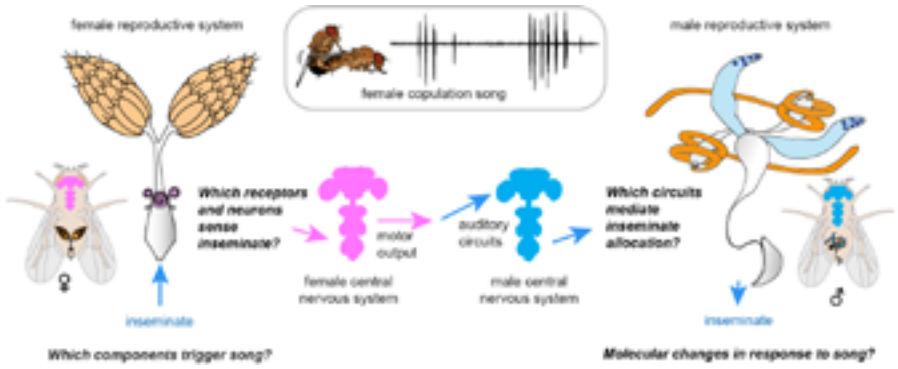


Figure: Female copulation song in Drosophila: a new behavior raising many new questions.
Female song depends on male seminal fluid and is hypothesized to modulate male inseminate allocation. We aim at identifying molecular players and circuit motifs mediating the communication between male and female during copulation. (part of the figure modified from Kerwin and von Philipsborn, BioEssays 2020)

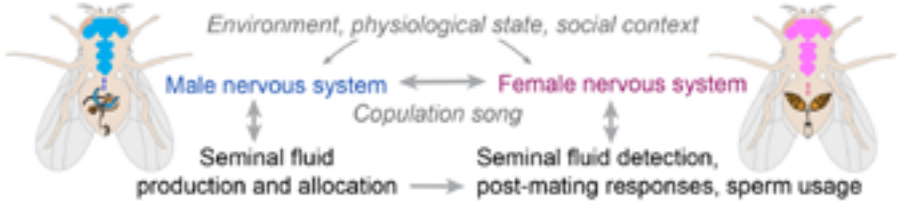
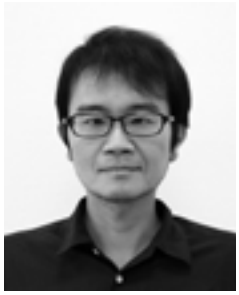


Figure 3: Communication between the nervous system and reproductive organs
Female copulation song provides a window into multiple pathways of information exchange between male and female, as well as between nervous system and reproductive system, and the influence of environmental stimuli, internal state and social context on reproductive strategies.

Yonehara Group

Function and Development of Neural Circuits in Visual System



Group Leade
Keisuke Yonehara

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

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

DYNAMIC INTEGRATION OF SYNAPTIC INPUTS FOR COMPUTING VISUAL MOTION

The direction of visual motion is first extracted by retinal direction-selective circuits. In the retina, we identified a new circuit mechanism for computing the direction and speed of visual motion in the mammalian retina by combining two-photon glutamate imaging, patch-clamp recordings, and 3D electron microscopy (Matsumoto et al., *Curr Biol* 2019). We found that slow-sustained and fast-transient excitatory inputs from bipolar cells to direction-selective cells are spatially segregated, embodying a "space-time wiring". Our modeling indicates that this space-time wiring creates the sensitivity to the direction and speed of visual motion in the direction-selective cells.

CORTICAL PROCESSING OF VISUAL MOTION SIGNALS

Motion signals transmitted from retinal direction-selective cells are further processed in downstream areas such as thalamus or visual cortex. In the visual cortex, we identified a segregated processing stream for signaling originated from retinal direction-selective cells by in vivo intrinsic signal optical imaging (Fig. 1), two-photon calcium imaging (Fig. 2), and genetic manipulation of retinal computation (Rasmussen et al., *Nature Communications* 2020; *Curr Biol* 2020). In the next years we aim to understand how the identified motion processing stream (Fig. 3) contributes to the animal's behaviors.

MOLECULAR MECHANISMS UNDERLYING THE SPATIALLY ASYMMETRIC NEURONAL CONNECTIVITY

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

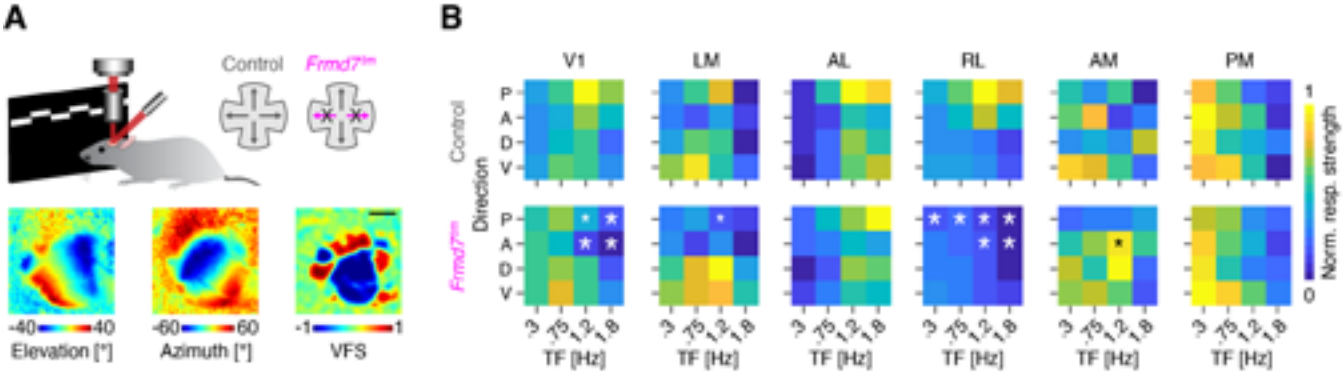


Fig. 1: (A) Intrinsic signal optical imaging of visual cortical areas in control and Frmd7tm mice. (B) Response strength as a function of motion direction (anterior [A], posterior [P], dorsal [D], and ventral [V]) and temporal frequency. White and black asterisks: significantly decreased and increased responses, respectively. Figure panels from Rasmussen et al., 2020, Nature Communications.

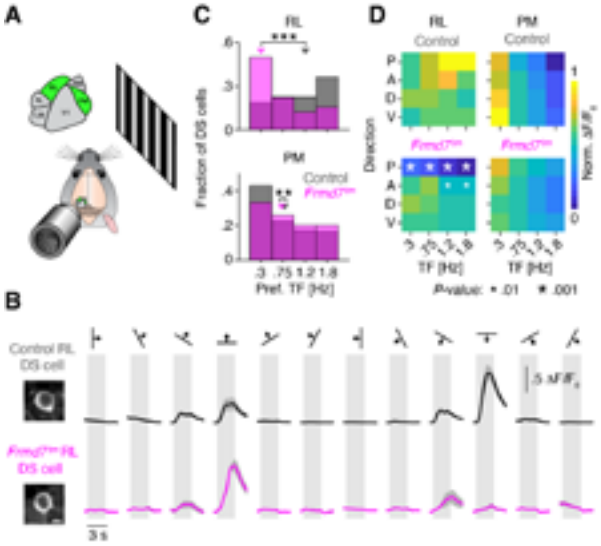


Fig. 2: (A) Two-photon calcium imaging from layer 2/3 in areas RL and PM of control and *Frmd7*^{tm} mice. **(B)** Example control and *Frmd7*^{tm} rostrolateral (RL) and posteromedial (PM) neurons expressing GCaMP6f (scale bar, 5 µm) and trial-averaged fluorescence (F/F_0) time courses for the same neurons. Shading indicates SEM. (C) Preferred temporal frequency for direction-selective cells in RL and PM. (D) Response amplitude as a function of motion direction and temporal frequency for RL and PM direction-selective cells. White asterisks: significantly decreased response amplitude in *Frmd7*^{tm} mice. Figure panels from Rasmussen et al., 2020, Nature Communications.

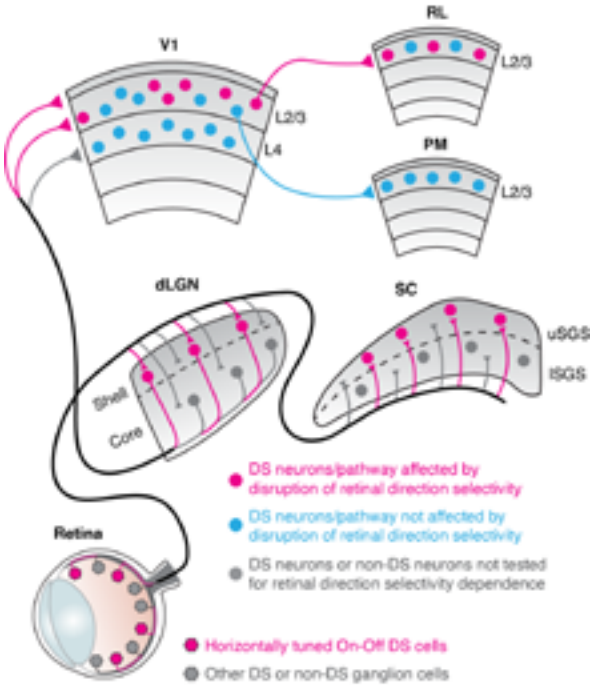
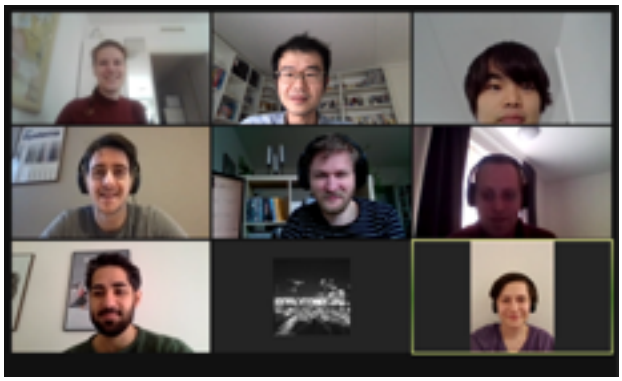


Fig. 3: Schematic diagram of the neuronal circuit linking horizontal motion tuned On-Off DS cells to DS cells in the central visual areas. Figure from Rasmussen et al., 2020, Current Biology.



SELECTED PUBLICATIONS 2020

Rasmussen R.*, Matsumoto A.*, Dahlstrup Sietam M, Yonehara K. (2020) A segregated cortical stream for retinal direction selectivity. *Nat Commun* 11: 831. *equally contributed.

Rasmussen R, Yonehara K (2020) Contributions of retinal direction selectivity to central visual processing. *Curr Biol* 30: R897-R903.

PERSONNEL LIST YONEHARA GROUP

Postdoc **Akihiro Matsumoto**
PhD Student **Monica Dahlstrup Sietam**
PhD Student **Ole Søndergaard Schwartz**
PhD Student **Rune Rasmussen**
Laboratory Technician **Bjarke Thomsen**
Laboratory Assistant **Misugi Yonehara**
Student Assistant **Simon Arvin**
Student Assistant **Allice Nyborg Rosenkrans Lind**
Group Leader **Keisuke Yonehara**

Kjærgaard Team

PROMEMO
CENTER FOR PROTEINS IN MEMORY

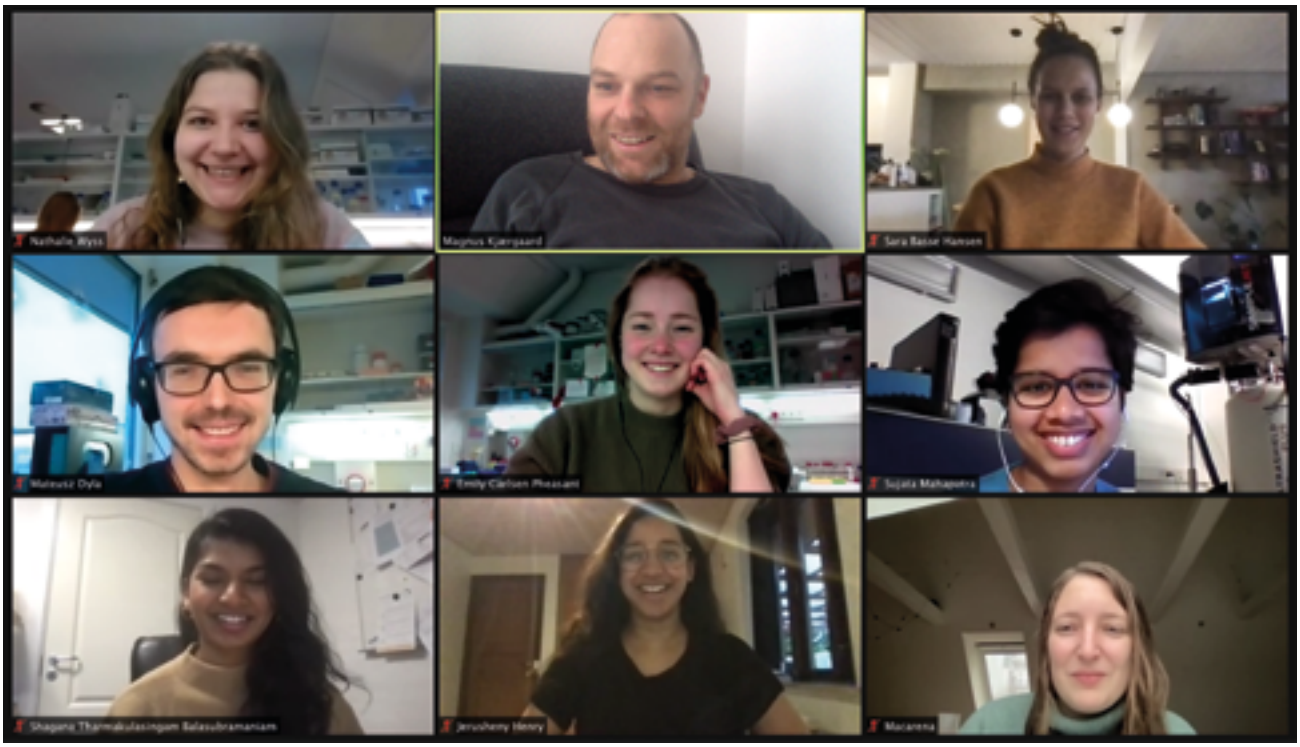
Synaptic Plasticity and Intra-cellular Signaling Complexes in Memory

Team Leader
Magnus Kjærgaard

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

Receptor activation leads to different downstream events depending on the cellular context, e.g. which other signaling pathways are active. Many steps of signalling pathways occur inside large flexible molecular assemblies called signalling complexes, that are organized by scaffolding proteins. However, little is known about how the dynamic structure of the signalling complex affect the signalling steps. We have developed the first quantitative model for how the structure of a signalling complex affects kinase reactions (Dyla & Kjaergaard, 2020, PNAS). We derive and validate a new equation that describes the speed of kinase reactions inside complexes. This equation provides a basis for understanding how signalling complex architecture can regulate phosphorylation cascades. We are currently expanding the scope of this work to be able to describe other types of intra-complex signalling steps.

Synaptic plasticity requires recruitment of newly synthesized proteins to specific synapses. This process is believed to occur via a process called synaptic-tagging-and-capture, where synaptic activity sets a tag that subsequently binds to new proteins. The molecular nature of this system is still unclear. Backed by an "Lundbeck Foundation Experiment grant", we are pioneering a new strategy to understand synaptic-tagging-and-capture. Instead of trying to identify the tag, we are trying to reverse engineer a minimal system that can function as a synaptic-tagging-and-capture system. This will allow us to explore which properties such a system should have, and possibly answer whether there are several parallel systems operating in parallel.



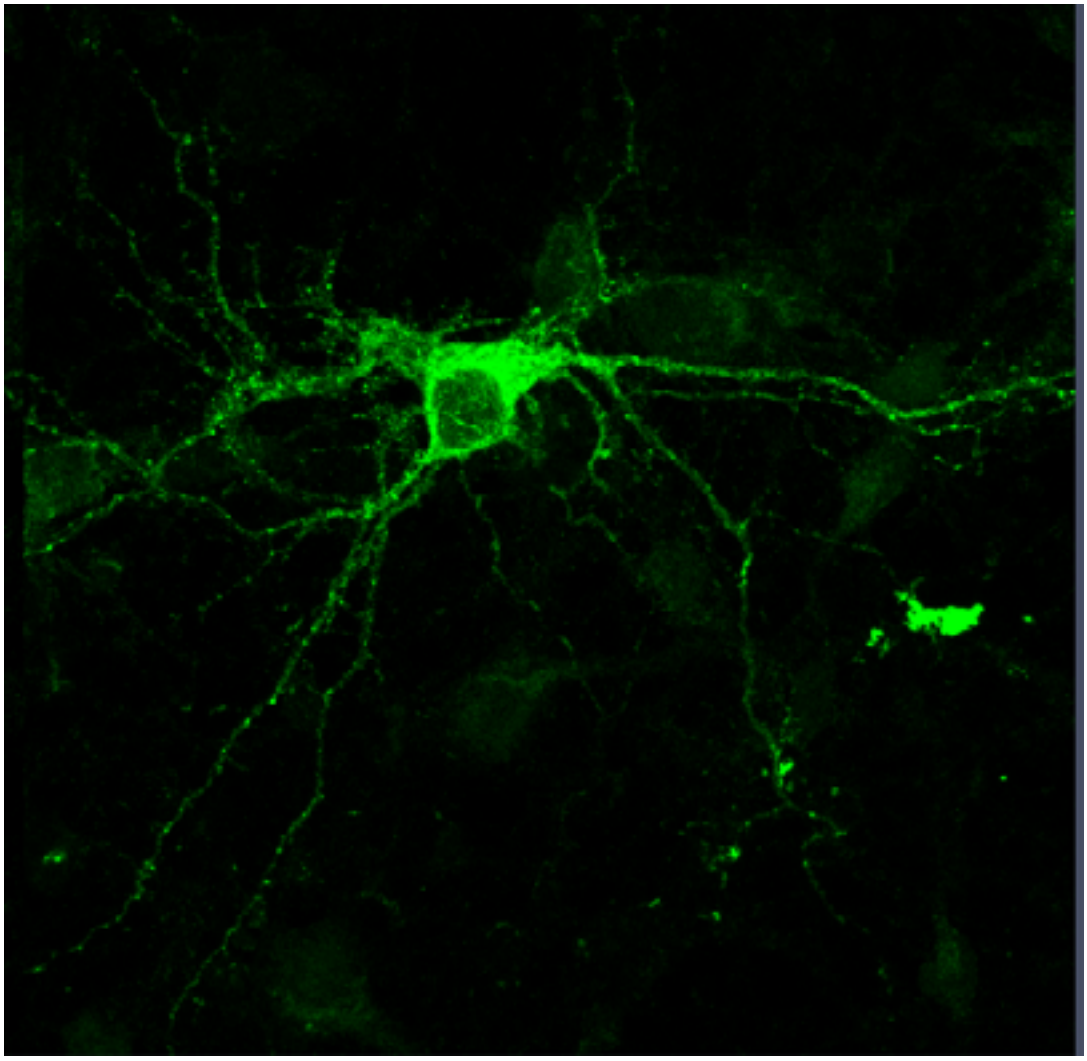


Fig 1: Hippocampal neurons expressing a syntetic synaptic tag labelled with a fluorescent protein.
Credit: Macarena Gomez de Salazar.

KEY PUBLICATIONS 2020

Kjaergaard, M., Glavina, J. And Chemes, L.C. Predicting the effect of disordered linkers on effective concentratiosn and avidity with the "Ceff calculator" app. *Met. Enzym* 647:145-171

Dyla, M. and Kjaergaard, M. Intrinsically disordered linkers control tethered kinases via effective concentration. *PNAS* 117 (35) 21413-21419

Warnet, X. L., Bakke Krog, H., Sevillano-Quispe, O. G., Poulsen, H. & Kjaergaard, M.@ (2020) The C terminal domains of the NMDA receptor: How intrinsically disordered tails affect signalling, plasticity, and disease. *Eur. J. Neuroscience* (Epub ahead of print)

Sørensen, C.S. and Kjaergaard, M. Measuring Effective Concentrations Enforced by Intrinsically Disordered Linkers. *Methods Mol. Biol.* 2141:505-518

Dear, A.J., Meisl, G., Šarić, A., Michaels, T.C.T., Kjaergaard, M., Linse, S. & Knowles, T.P.J. Identification of on- and off-pathway oligomers in amyloid fibril formation. *Chem. Sci.* 11:6236-6247

Dyla, M., Kjaergaard, M., Poulsen, H. and Nissen, P. Structure and Mechanism of P-Type ATPase Ion Pumps. Annu. *Rev. Biochem.* 89:583-603

PERSONNEL LIST KJÆRGAARD TEAM

Postdoc **Mateusz Dyla**
Postdoc **Xavier Warnet**
Postdoc **Sujata Mahapatra**
Postdoc **Macarena Gomez de Salazar**
PhD Student **Sara Basse**
Team Leader **Magnus Kjærgaard**

Poulsen Team

PROMEMO
CENTER FOR PROTEINS IN MEMORY

Electrophysiology of Electrogenic Transporters and Ion Channels

Team Leader
Hanne Poulsen

TEAM

We study ion channels and transporters to elucidate their roles in health and disease. Neuronal communication depends on efficient signaling, and a very rapid means is opening of an ion channel, typically selective for sodium, potassium, calcium, or chloride. Afterwards, transporters re-distribute the signaling molecules, both the ions and the channel agonists.

Our main methodologies include electrophysiology, fluorometry, and transgenic mice, and we use these techniques to study the NMDA receptors, the Na,K-ATPase, and the GABA transporter GAT-1. Our aim is to gain insight into the molecular determinants of the given protein's basic function, and to understand its role in larger contexts on cellular, network, and organismal levels. To this end, it has been exceedingly useful to study the molecular functional consequences of disease-causing mutations in the genes encoding the proteins. Why does a specific amino acid change cause the observed pathophysiological symptoms? What does that tell us about the protein's basic molecular mechanism and how that can be disturbed? Are other proteins affected? Does the insight provide suggestions to how the imbalance could be corrected to alleviate the symptoms in patients? With two-electrode voltage-clamping of oocytes from the frog Xenopus laevis, and patch-clamping of smaller cells, we can measure the currents generated by electrogenic membrane proteins inserted into membranes, thereby getting a direct measure of their activity, and by incorporating a fluorescent tag, we can furthermore monitor the movement of a specific position in real-time. Using pharmacology and co-expression of potential regulatory interaction partners, we can also start to delineate the effects of the cellular context.

MAJOR ACHIEVEMENTS & FUTURE PLANS

The NMDARs are calcium-permeable channels that are activated by glutamate and glycine or D-serine in the post-synapse, and they are believed to be essential for learning and memory. Their extracellular and transmembrane regions are well-described structurally, but they have huge intracellular, intrinsically disordered domains that are not nearly as well-studied. The intracellular domains interact with numerous cytoplasmic factors, and they contain several regulatory phosphorylation sites. To understand how these tails interact with and modulate the channel properties, we have made a number of variants that we are characterizing. To this end, there are fortunately an extensive toolbox of positive and negative allosteric modulators available whose mode of action are affected by the tails. Furthermore, we can label the tails with the unnatural amino acid Anap, which has an intrinsic, environmentally sensitive fluorescence, enabling us to monitor if the specific position changes position with millisecond resolution, e.g. upon channel activation. We hope that these studies will provide novel insight into the molecular mechanism and regulation of one of the key players in synaptic plasticity.

At the organismal level, we are characterizing a mouse model of the syndrome CAPOS (Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy, Sensorineural hearing loss), which is caused by a heterozygous mutation in the Na,K-ATPase gene ATP1A3 that causes E818K. This gene is highly conserved between man and mouse, and it is essential for maintaining the sodium and potassium gradients in neurons. Other distinct neurological diseases are caused by mutations in the same gene, but unique to this one position is that it also causes loss of sight and hearing. In patients, a severe fever in childhood is believed to trigger the disease, and we have not observed a similar episode in the mice, but we do see that they develop a spontaneous motor phenotype. Simple heating does not appear to be a trigger, so we are currently exploring if induction of inflammation can be. We will characterize the mutation molecularly, monitor motor, visual, and auditory phenotypes in the mouse, and characterize the visual and auditory pathways with histology. Our long-term goal is that the mouse can serve as a disease model to test potential treatments (pharmacological or genetic) for the condition.

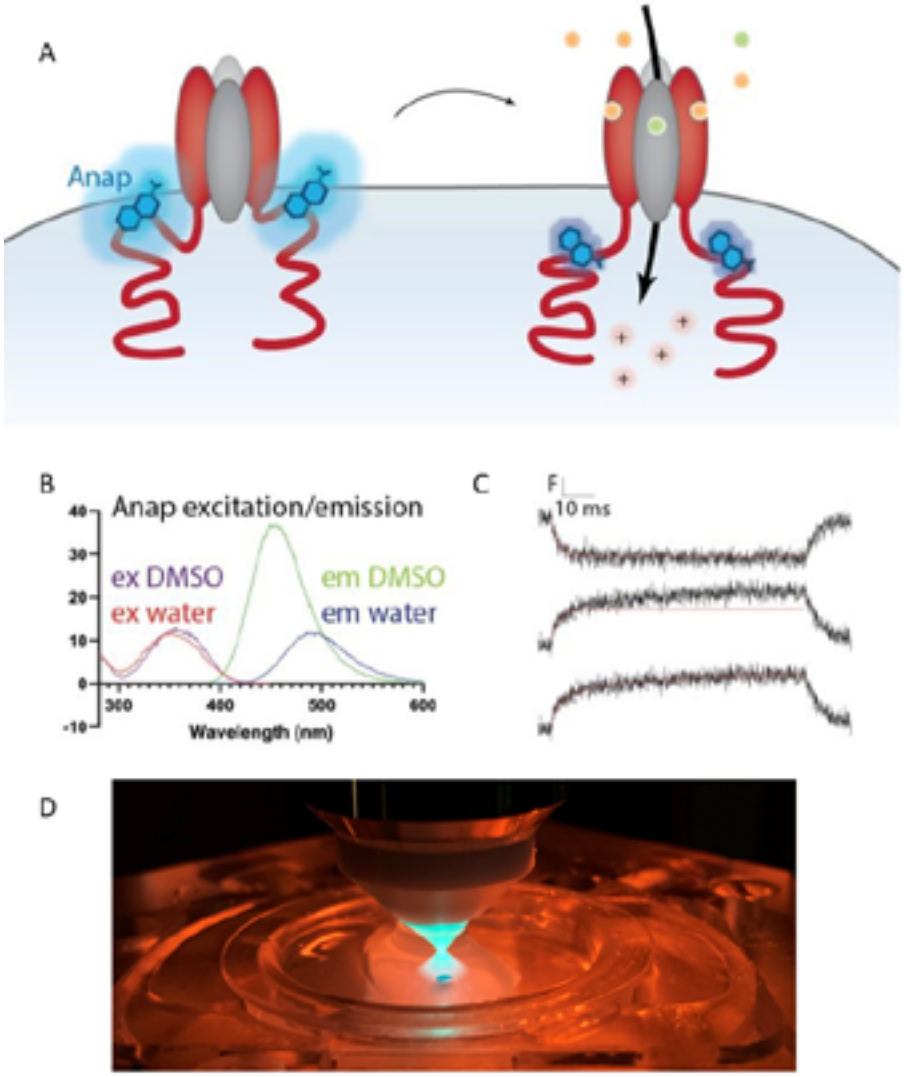


Fig 1.: Structure-function described by voltage-clamp fluorometry. A) The NMDAR is represented schematically with the large, intrinsically disordered C-terminal tails, where the fluorescent amino acid Anap (blue) is incorporated. Activation of the channel by its ligands (in orange and green) causes opening and movement of the tails. In the novel environment, Anap's fluorescence intensity has changed. B) Excitation/emission spectra for Anap in DMSO and water, showing that emission is strongly environmentally sensitive. C) Examples of fluorescence (F) changes. D) The cut-open voltage-clamp fluorometry set-up, where fluorescence and electrical changes can be measured simultaneously.

PUBLICATIONS 2020

Dyla M, Kjærgaard M, Poulsen H, Nissen P Structure and mechanism of P-type ATPase ion pumps. *Annual Review of Biochemistry*, June 20 Vol 89:583-603

Warnet XLCA, Krog HB, Quispe OGS, Poulsen H, Kjærgaard M Functions of the C-terminal domains of the NMDA receptors – How intrinsically disordered domains affect interaction networks, plasticity and disease. *European Journal of Neuroscience* May 28 Online ahead of print

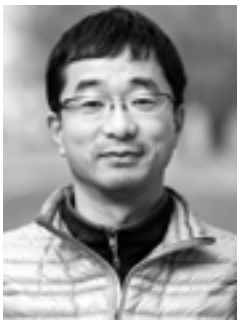
Habeck M, Poulsen H What FYXDs fix. *Journal of General Physiology*, under final review

PERSONNEL LIST POULSEN TEAM 2020

Postdoc **Helle Bakke Krog**
Postdoc **Tommi Miikael Anttonen**
PhD **Student Mette Ozol**
PhD Student **Monica Dahlstrup Sietam**
PhD Student **Oscar Gabriel Sevillano Quispe**
PhD Student **Saida Said**
MSc Student **Kirstine Hansen**
Lab Tech Student **Sofie Møller Bonde Larsen**
Team Leader **Hanne Poulsen**

Takeuchi Team

Memory selectivity and knowledge updating



Team Leader
Tomonori Takeuchi

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

The research is divided in two overall research themes

- **Novelty-induced enhancement of memory retention,** is now an established phenomenon, but the underlying molecular mechanisms remains to be elucidated. In our team, we now have the behavioral setup including the hippocampus-dependent object location task and everyday memory task in rats to investigate this subject in further detail. Further, we have an advanced fiber photometry setup, where we are able to detect novelty-induced dopamine release using a genetically encoded fluorescent sensor in free-moving rats. Finally, we are doing experiments to identify key proteins critical for novelty-induced memory enhancement. Identification of proteins that enhance memory retention will have the potential to reveal new drug targets for treatment of lost memory function.
- **Assimilation of new memory into neocortical schemas,** has been shown to be a much faster process, than initially believed. In our team, we aim to secure definitive information about the neocortical networks and neuromodulation involved in the assimilation of new memory into the neocortical schemas. Understanding the molecular- and circuit-mechanisms of assimilation of new memories into schemas may lead to the development of efficient educational methods.

MAJOR ACHIEVEMENTS 2020

First, we established a behavioral setup, the object location task, which assessed spatial recognition memory in rats. We optimized training protocols for weak and strong encoding that can produce short-term and long-term memories, respectively. Moreover, we conducted pilot experiments to determine the optimal encoding condition for novelty-induced memory enhancement. We observed a tendency for enhanced memory persistence in 24-hr test for the group of rats that had explored a novelty box 30 min after a weak encoding trial.

Second, we succeeded to develop a red-shifted fluorescent dopamine sensor, which has high selectivity for dopamine over norepinephrine (143-fold selectivity) in collaboration with National Institutes of Natural Sciences in Japan. Taking advantage of this high selectivity, we performed dual-color fluorescence live imaging using our red-dopamine sensor and the published green-norepinephrine sensor. As a result, we achieved selective detection of extracellular dopamine even in the presence of norepinephrine at a single-neuron level *in vitro*.

Furthermore, we have successfully performed in vivo fibre photometory imaging of norepinephrine in the hippocampus in freely behaving rats. Change in fluorescence intensity of green-norepinephrine sensor was observed upon norepinephrine stimulation in the hippocampus, while the response was abolished by the antagonist for the sensor.

Finally, we conducted an experiment for screening the genes that were upregulated following the application of dopamine D1/D5 receptor agonist in a primary culture of rat hippocampal neurons. This procedure allows the clear separation of newly synthesized gene products induced by initial memory consolidation from those induced by memory encoding. For the screening, transcriptome analysis using RNA sequencing was performed followed by confirmation using real-time quantitative PCR analysis. The results had pointed out three candidate genes that code plasticity-related proteins (PRPs) critical for novelty-induced memory enhancement in the hippocampus.

In addition, we tried to establish the optical experimental protocol for analyzing the function of plasticity-related protein candidates in a primary culture of rat hippocampal neurons *in vitro* in collaboration with Bordeaux University in France. Specifically, we could induce long-term potentiation (LTP) in a single spine by two-photon glutamate uncaging, and measured the change of spine volume using optical imaging techniques.

FUTURE PLANS IN 2021

First, we plan to find an optimal protocol for novelty-induced enhancement of memory persistence in the object location task in rats. We will then assess the impact of blockade of dopamine D1/D5 receptors and protein synthesis in the dorsal hippocampus during novelty exploration on novelty-induced memory boosts. Furthermore, we try to mimic a beneficial effect of novelty on memory persistence using optogenetic activation of the locus coeruleus.

Second, we try to perform imaging of dopamine and norepinephrine co-release from the locus coeruleus axons in the hippocampus in rats behaving freely using green-dopamine and red-norepinephrine biosensors combined with dual-colour fibre photometry.

Third, we will transform early-LTP into late-LTP at single spines by dopaminergic stimulation of rat hippocampal neurons and measure the change in the number of native AMPA receptors and the enlargement of the dendritic spine during LTP retention. Once establishing the protocol, we will first express the PRP candidates labelled with a fluorescent protein under a synthetic activity-dependent promoter in rat hippocampal neurons. We will track the change in fluorescence emanating from the candidates in potentiated spines following dopaminergic stimulation. This experiment will allow us to determine which PRP candidates are translocated into potentiated spines during dopamine-dependent LTP maintenance. Then, we will perform a loss-of-function analysis for the PRP candidates by expressing dominant negative forms of the PRP candidates. We will track the change of both the number of surface AMPA receptors and the morphology of the potentiated spine.

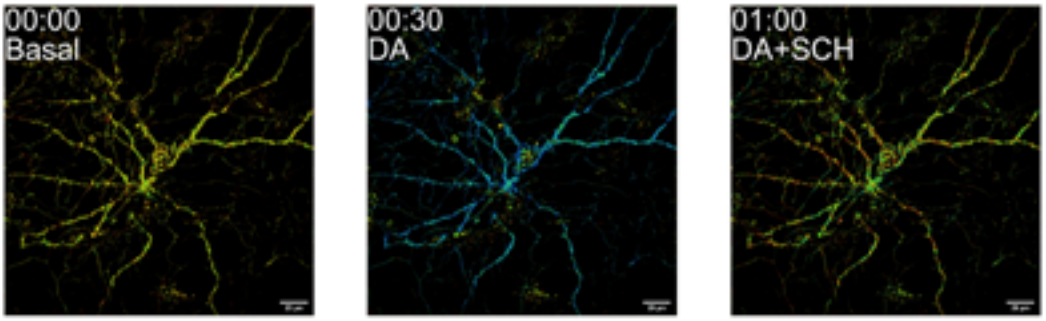


Figure 1: The image series shows a vizualization on the response to dopamine by DA1.2 sensor, expressed in a rat hippocampal neuron. DA1.2 reduces flourescence intensity upon application of dopamine, and then returns to basal level by application af dopamine receptor antagonist (sch). This work has been done in collaboration with Dr. Kazuhiro Aoki lab (@kazuhiroaokilab)

PUBLICATIONS 2020

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PERSONNEL LIST TAKEUCHI TEAM

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

DANDRITE AFFILIATED RESEARCHERS

DANDRITE is proud to enter year 2021 with 11 active affiliated researchers:

CHRISTIAN VÆGTER

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

Highlights from 2020
- Publication of study: Schwann cell p75 neurotrophin receptor modulates small fiber degeneration in diabetic neuropathy. In *Glia* (Goncalves et al, 2020).
- Publication of study: Changes in the transcriptional fingerprint of satellite glial cells following peripheral nerve injury. In *Glia* (Jager et al, 2020)
- Publication of study: A high-affinity, bivalent PDZ domain inhibitor complexes PICK1 to alleviate neuropathic pain in *EMBO Molecular Medicine* (Christensen et al, 2020)
- Partner in Open Discovery Innovation Network (ODIN) research project "oLIVER"

ERNST-MARTIN FÜCHTBAUER

Genetically modified mice
We collaborate with several DANDRITE researches in the generation of genetically modified mice and generation and differentiation of murine ES cells. In 2020, the Corona related restrictions for the animal facility postponed a number of projects, however we used the free capacity to archive and rescue a number of important mouse lines by cryopreservation and embryo transfer.

Highlights from 2020
- Our attempt to boost SorCS3 expression by an enhancer knock in seems to work.

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) and childhood incontinence in general. These genes are investigated along with genes causing rare disorders of the water balance to understand their interplay in regulating urine production, bladder activity and sleep.

Highlights from 2020
- Publication of study: Reduced Brd1 expression leads to reversible depression-like behaviors and gene-expression changes in female mice in *Translational Psychiatry* (Rajkumar et al. 2020)
- Awarded a grant from Frøknerne Anna and Dagny Hjerrilds Foundation
- Initiated genetic studies of daytime urinary and fecal incontinence in children in iPSYCH2015

JØRGEN KJEMS

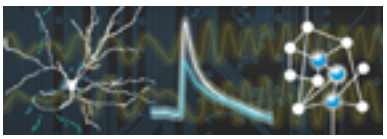
Nanomedicine
The Kjems lab investigates the function and biomarker potential of non-coding RNA in neuronal development and neurodegenerative disease (e.g. ALS, Alzheimer's disease and epilepsy). They also use organoids and CRISPR technology to test the functional role for individual circRNAs in neurogenesis. To obtain a better view of alternative spicing of linear and circular RNAs the Kjems lab is performing long-read, single DNA and RNA molecule sequencing of global RNA expression in brain and other tissues. In a different line of research, the group develops methods to deliver drugs across the blood brain barrier using multivalent nanoscaffolds and exosomes. Finally, a new project run by assistant professor Julian Valero Moreno uses nucleic acid nanotechnology to develop a new class of drugs against toxic protein aggregates in Parkinson's disease.

DANDRITE related Highlights from 2020
- Lundbeck experiment grant awarded to Julian Valero Moreno: Evolving new types of therapeutics-reshuffling old players in new ways
- EU FET-OPEN grant awarded to Jørgen Kjems: A Personalised Living Cell Synthetic Computing Circuit for Sensing and Treating Neurodegenerative Disorders

Neuro related papers published in 2020
- Venø, M.T., Reschke, C.R., Morris, G., Connolly, N.M.C., Su, J., Yan, Y., Engel, T., Jimenez-Mateos, E.M., Harder, L.M., Pultz, D., Haunsberger, S.J., Pal, A., Heller, J.P., Campbell, A., Langa, E., Brennan, G.P., Conboy, K., Richardson, A., Norwood, B.A., Costard, L.S., Neubert, V., Del Gallo, F., Salvetti, B., Vangoor, V.R., Rodriguez, A.S., Muilu, J., Fabene, P.F., Pasterkamp, R.J., Prehn, J.H.M., Schorge, S., Andersen, J.S., Rosenow, F., Bauer, S., Kjems, J., Henshall, D.C.: A systems approach delivers a functional microRNA catalog and expanded targets for seizure suppression in temporal lobe epilepsy. *Proc Natl Acad Sci.* Jul 7;117(27):15977-15988 (2020).
- Lo, IJ., Hill, J., Vilhjálmsson, B.J., Kjems, J.: Linking the association between circRNAs and Alzheimer's disease progression by multi-tissue circular RNA characterization. *RNA Biology.* Jul 3;1-9 (2020• Gonçalves NP, Yan Y, Ulrichsen M, Venø MT, Poulsen ET, Enghild JJ, Kjems J, Vægter CB.: Modulation of Small RNA Signatures in Schwann-Cell-Derived Extracellular Vesicles by the p75 Neurotrophin Receptor and Sortilin. *Biomedicines.*;8:450 (2020).

MARCO CAPOGNA

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



Highlights from 2020
- Collaboration with AUH to investigate human cortex in vitro
- Publication in collaboration with Allen Brain Institute Seattle to define cortical neuron types (Yuste et al, Nature Neurosci 2020)
- Lundbeck Foundation-NIH grant award with Ting group, Allen Seattle (3,5M DKK)
  to investigate the role of GABAergic neuron types in human cortex

Publications
- Capogna M, Castillo P.E. and Maffei A. (2020). The ins and outs of inhibitory synaptic plasticity: neuron types, molecular mechanisms and functional roles. European Journal of Neuroscience, https://doi.org/10.1111/ejn.14907
- Yuste R. et al (2020). A community-based transcriptomics classification and nomenclature of neocortical cell types. Nature Neuroscience, https://doi.org/10.1038/s41593-020-0685-8
- Krauth N., Khalil V., Jariwala M., Mermet-Joret N., Vestergaard A.K., Capogna M. and Nabavi S. (2020) TRACE: an unbiased method to permanently tag transiently activated inputs. Frontiers in Cellular Neuroscience, 12 May 2020, https://doi.org/10.3389/fncel.2020.00114

MARINA ROMERO-RAMOS

Study and Characterization of the neurodegenerative event in Parkinson's Disease and the associated immune response
During the last decade research evidence supports a relevant role for the immune system in neurodegenerative disease such as Parkinson's disease. Our lab has been studying the cells and proteins involved in the neuroinflammatory process associated to a-synuclein induced neurodegeneration. We have been particularly interested in the role of microglia but also other myeloid cells in the disease, and to define the influence of peripheral immune cells in the brain events. Our studies include both, rodent models of the disease, and analysis of human derived samples. Thus, we aim to develop translational research that can ultimately help diagnosis and treatment of patients with Parkinson and other synucleinopathies.

Highlights from 2020

- In The lab has shown that Parkinson's disease patients have a modified levels of the monocyte produced marker sCD163; these changes correlated to levels of a-synuclein and to the decline of cognition in the patients. Therefore our data supports sCD163 as a potential cognition-related biomarker in Parkinson's disease and suggest a role for monocytes in both peripheral and brain immune responses (*Nissen et al.*, 2020).
- Our collaboration with the PET imaging Center (AUH) is exemplified by our shared manuscript characterizing a novel PET ligand for the study of synaptic density in vivo using rodent models of neurodegenerative diseases (*Thomsen et al.*, 2020).
- Dr. Romero-Ramos was co-organizer of the 30th NECTAR Meeting that took place on line in Nov 2020, with over 400 participants.

MORTEN SCHALLBURG NIELSEN

Receptor mediated drug delivery to the brain
The use of receptors to deliver drug from blood to brain is the major research focus in our group. We are using advanced in vitro models of the blood brain barrier, based on human stem cells and primary brain endothelial cells, astrocytes and pericytes from pig and rodents. To succeed with receptor mediated transcytosis, we are developing monoclonal antibodies against particular Basigin and transferrin receptors.

Highlights from 2020

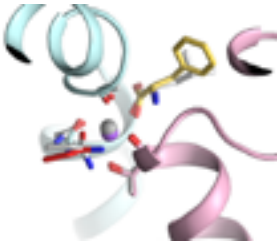
- Grant for innovation PhD together with Lundbeck
- Professorship in neuroscience
- Developing of new antibodies targeting basigin for drug delivery. Published in scientific report

OLAV MICHAEL ANDERSEN

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

Highlights from 2020

- Collaboration with Alzheimer's Association for developing a platform for SORL1variants in AD
- Invited speaker for Cold Spring Harbor Laboratory meeting on Neurodegeneration



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 EMBION-AU (embion.au.dk), I enable easy access and training on equipment and in cryo-EM and negative stain methods for DANDRITE researchers. The EMBION cryo-EM facility is an important strategic infrastructure in key DANDRITE projects.

Highlights from 2020

- Krintel C, Dorosz J, Larsen AH, Thorsen TS, Venskutonytė R, Mirza O, Gajhede M, Boesen T, Kastrup JS. Binding of a negative allosteric modulator and competitive antagonist can occur simultaneously at the ionotropic glutamate receptor GluA2. FEBS J. 2020 Jun 15. doi: 10.1111/febs.15455. Epub ahead of print. PMID: 32543078
- Gotfryd K, Boesen T, Mortensen JS, Khelashvili G, Quick M, Terry DS, Missel JW, LeVine MV, Gourdon P, Blanchard SC, Javitch JA, Weinstein H, Loland CJ, Nissen P, Gether U. X-ray structure of LeuT in an inward-facing occluded conformation reveals mechanism of substrate release. *Nat Commun.* 2020 Feb 21;11(1):1005. doi: 10.1038/s41467-020-14735-w. PMID: 32081981; PMCID: PMC7035281

THOMAS WILLNOW

Metabolism and Brain Health
We investigate the interdependency of metabolism and brain health. Using transgenic mouse and iPSC-derived human cell models we interrogate how metabolism guides development and functional integrity of the brain, and why metabolic disturbances are major causes of neurodegeneration.

Highlights from 2020

- iPSC-based disease modeling identifies ligand-induced decay of megalin as cause of Donnai-Barrow Syndrome (Flemming et al., Kidney Int. 2020)
- ApoE4 disrupts neuroprotective actions of sortilin in neuronal lipid metabolism and endocannabinoid signaling (Asaro et al., Alzheimer & Dementia, 2020)
- SorCS2 facilitates release of endostatin from astrocytes and controls post-stroke angiogenesis (Malik et al., GLIA 2020)

YONGLUN LUO

Applied Genome Technologies in Biomedical Research
Living multicellular organisms are formed by a complex hierarchy of functionally distinct cells. A long-lasting scenario in life sciences is to characterize the molecular signatures in individual cells under both health and diseased conditions. Breakthroughs in RNA and DNA sequencing now provide us with powerful tools to revisit the complex organ systems at single cell resolutions. One such organ system that our group has been focusing on is the endothelium which plays an essential role in all tissues and organs in our body. Our aim is to revisit the molecular and endothelial cellular signatures in all pathological conditions by single cell sequencing, and thus identify endothelium-targeting genes for disease diagnosis, prevention and treatment.

Highlights from 2020

- Yonglun Luo is co-awarded a Horizon 2020 FET-OPEN project grant (Circular Vision)
- Publications of study: Single-Cell RNA Sequencing Maps Endothelial Metabolic Plasticity in Pathological Angiogenesis in *Cell Metabolism (Rohlenova et al. 2020)*
- Publications of study: Single-Cell Transcriptome Atlas of Murine Endothelial Cells in *Cell (Kalucka et al. 2020)*
- Publications of study: An Integrated Gene Expression Landscape Profiling Approach to Identify Lung Tumor Endothelial Cell Heterogeneity and Angiogenic Candidates in Cancer Cell (Goveia et al. 2020)
- Publications of study: An atlas of the protein-coding genes in the human, pig, and mouse brain in *Science (Sjöstedt et al. 2020)*

Feature: Text by Group Leader Duda Kvitsiani

Workshop for building microdrives to electrophysiologically record and manipulate single neurons in behaving animals

In the following section, Group Leader Duda Kvitsiani describes the building of Microdrives – a technique several DANDRITE groups are using.

Extracellular electrophysiological recording and optogenetic manipulation of neurons in freely behaving animals offer unique opportunities to address fundamental questions in basic and translational neuroscience. By monitoring single units in behaving animals one could infer computations carried out by neural circuits. By optogenetically targeting specific classes of neurons with light addressable opsins one could causally link those computations to behavior. Furthermore, in animal models of human psychiatric disease link between aberrant neural activity and disease symptoms could be established.

To achieve these and other goals DANDRITE offers a small workshop, "JOINT" to train interested individuals in learning how to build "Microdrives" that house optical fibers and electrodes for electrophysiological recordings and optical manipulation of neurons in rodents. The workshop has station for building customized electrodes ('tetrodes'), stereo microscopes, soldering station and 3D printers (Fig.1A).

The assembled Microdrive typically houses 32 channel electrodes and one optical fiber and weights ~2grams (Fig.1B). Using open source software 'OpenEphys' (https://open-ephys.org) one could record action potentials in freely behaving mice (Fig.1C).

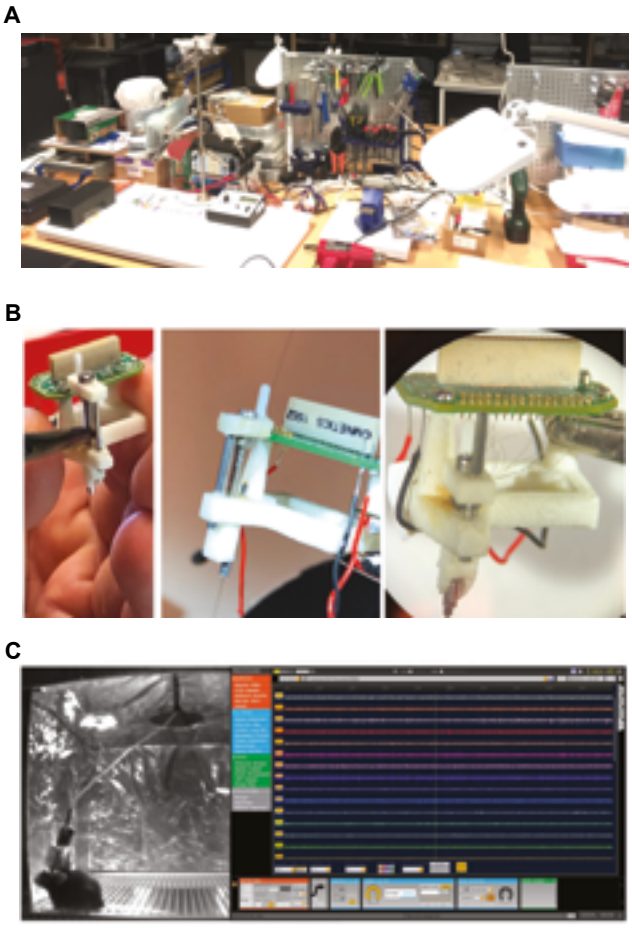
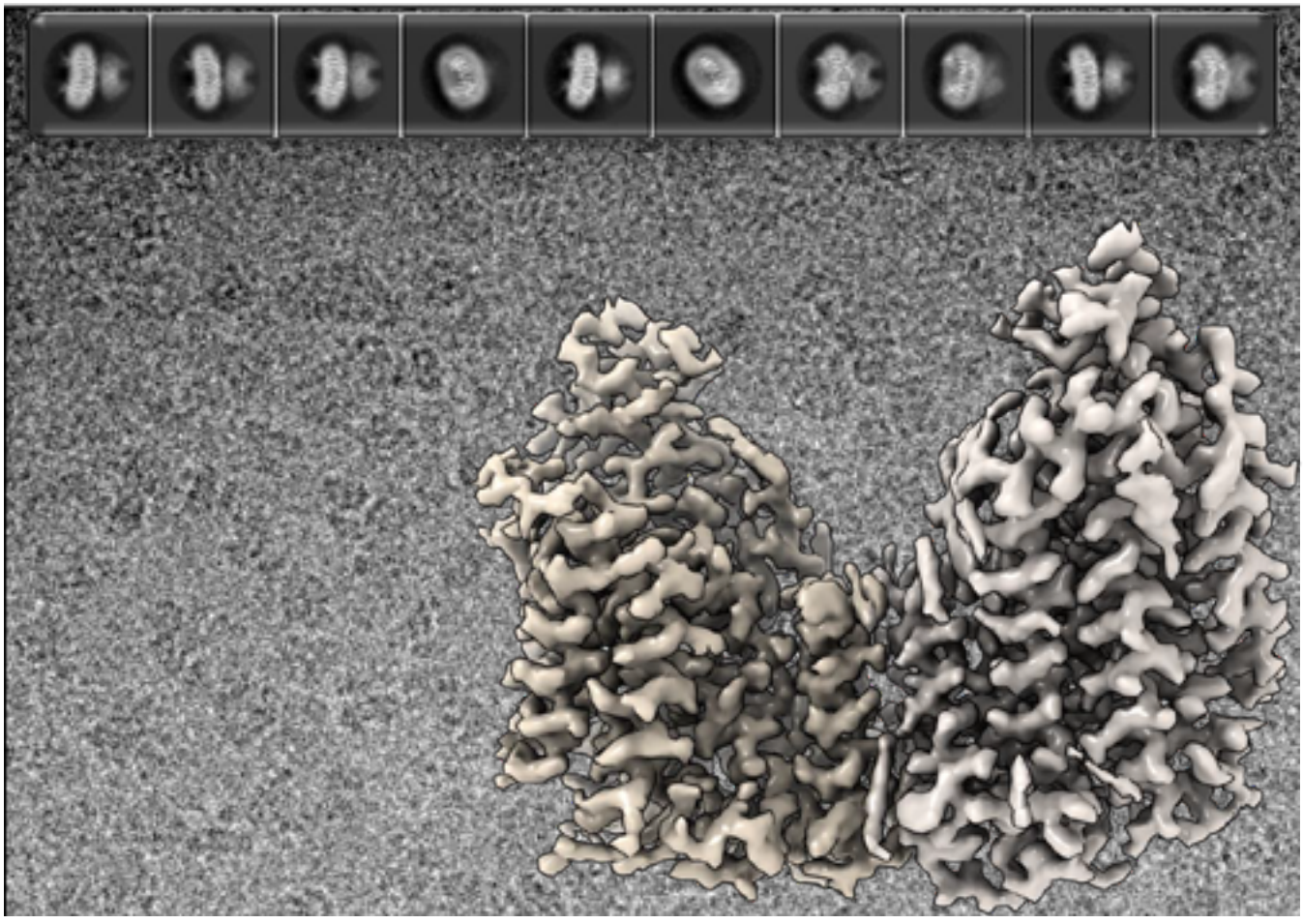


Figure 1.
A. Tetrode building station and tools.
B. Microdrive that houses 32 electrodes and optical fiber. Electrodes and optical fiber are movable using single scew.
C. Mouse that is implanted with the Microdrive (left) and electrohysiological signal aquired using OpenEphys system (rigth).

Nissen lab

A higher resolution cryo-EM structure of the chloride transporter NKCC1



A higher resolution cryo-EM structure of the chloride transporter NKCC1. The 3D reconstruction (right side in wheat and grey) of the human NKCC1 with bound ions obtained at the EMBION cryo-EM facility at Aarhus University. The image is based on hundreds of thousands of individual observations of NKCC1 molecules in random orientations (faint features in the background micrograph) producing well-defined 2D class averages (top row of images), and the aforementioned 3D reconstruction (map at 2.6 Å resolution overall and 2 Å in core regions). Figure courtesy of PhD student Caroline Neumann and Dr. Rasmus K. Flygaard in the Nissen laboratory (on-going research).

Feature: Text by Group leader Mark Denham

Miniaturised controlled organoids (MiCOs)

In this feature, DANDRITE group Leader Mark Denham shares insight into the Open Discovery Innovation Network (ODIN) project he is a part of namely the MiCO platform - A human-stem-cell-based miniaturised controlled organoid (MiCO) platform for investigating neurological disorders.

Since the isolation and cultivation of human embryonic stem cells in 1998 and the derivation of induced pluripotent stem cells in 2006, a diverse range of methods for generating regional and neurotransmitter subtype neurons spanning all major brain lineages has been described, including glutamatergic cortical neurons (Denham et al., 2012b), midbrain dopamine neurons (Denham et al., 2012a) and hindbrain/spinal cord motor neurons (Toma et al., 2015). However, these two-dimensional (2D) in vitro cultures are difficult to maintain long-term and typically fail to acquire mature phenotypes or age-related disease states. These shortcomings are in part due to the homogeneity of advanced 2D protocols, which lack the diversity of excitatory and inhibitory neurons and glial support cells, that together in vivo constitute natural neural systems.

Neural organoids have been developed to overcome the limitations of 2D cultures and provide a model that recapitulates human development and the complex cellular interplay reflective of the in vivo human CNS (Kanton et al., 2019). These organoids can be generated for all major brain regions (Bhaduri et al., 2020; Junghyun Jo et al., 2016; Tanaka et al., 2020). However, organoids are large, develop necrotic centers and demonstrate inter-organoid structural and cellular variation due to their self-organization properties; together, this restrains their capacity to be used in a high throughput manner for disease modelling and drug screening. Indeed, to date organoid disease modelling has mainly focused on severe CNS disorders with gross anatomical changes (Junghyun Jo et al., 2016).

The goal of this ODIN project (https://projects.au.dk/odin/scientificscope/funded-odin-projects/mico-platform/) is to develop organoids into a multi-brain region platform to support the investigation of a broad range of neurological disorders. We are developing next-generation miniaturised controlled organoids (MiCOs) tailored for a screening platform. Specifically, by miniaturizing the organoids and starting with regionally patterned neural progenitors, we can generate organoids with higher reproducibly in regards to their neuronal composition (Figure 1). Furthermore, by adding in astrocytes and microglia progenitors into the organoids, we aim to enhance maturation and mimic in vivo cellular diversity. Once formed, the organoids can be kept in vitro for over 100 days.

In collaboration with the stem cell team at Novo Nordisk we will compare in vitro derived organoids with in vivo mature stem cell-derived neurons. Morten Venø from Omiics will assist in the single-cell analysis of the organoids and compare them to in vivo matured neurons. This comparison will help us to understand how long it takes in vitro for neurons to become mature and what factors and supporting cell types are required.

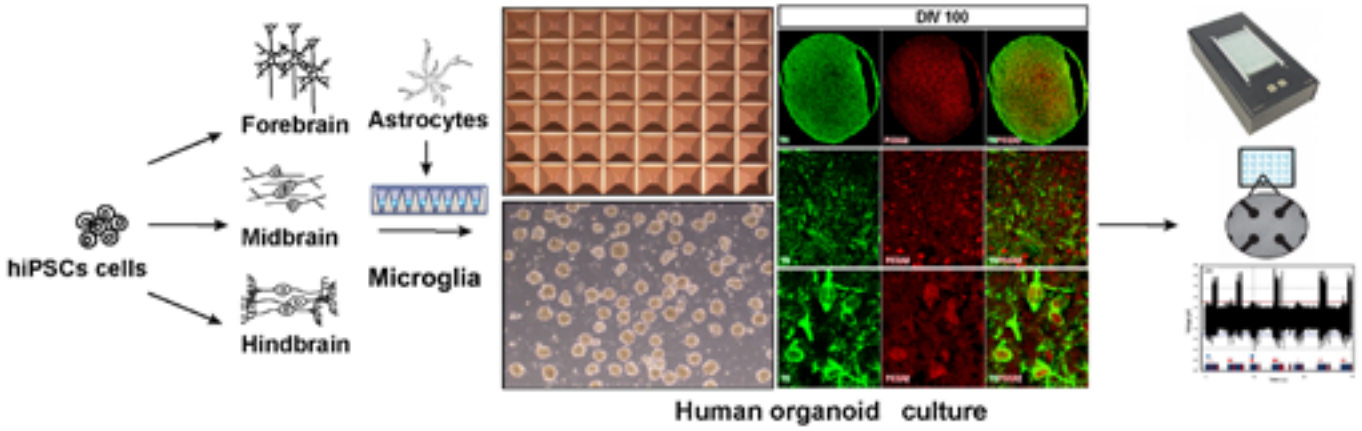
The MiCO platform will serve as a model system for drug testing. To that end, we aim to use our Parkinson's patient-derived iPSC as a genetic background for testing new drug compounds (Chen et al., 2020). In collaboration with Daniel Otzen from Aarhus University, will plan to test compounds developed in his lab that have the potential to prevent alpha-Synuclein aggregation. Overall, this system will aid in the development of new drug compounds for the treatment of a broad range of neurological disorders.

MiCO Team
The Denham lab, Aarhus University
(Mark Denham, Muwan Chen and Sanne Andersen).
Otzen lab, Aarhus University (Daniel Otzen), Novo Nordisk
(Jonathan Niclis, Josefine Rågård Christiansen and Sofia Rebekka Boldt Schmidt).
Omiics (Morten Venø).

ABOUT ODIN

The Open Discovery Innovation Network (ODIN) is an open research collaboration between Aarhus University and several international pharmaceutical companies. The ambition is to use the collective knowledge of all the participating researchers and to create long-term innovation for the benefit of patients, industry and society. The idea behind ODIN is to help the Life Sciences in Denmark improve their ability to convert research results into new products and solutions. Without the restrictive framework of patents, the ODIN collaboration boosts and uses the collective thinking and creativity of the participating university and industry researchers, enabling them to jointly refine ideas and develop projects. The Novo Nordisk Foundation has awarded a grant of DKK 54.5M to support ODIN for the period 2020-2023.

This text mirrors the description on the Novo Nordisk Foundation's website about the ODIN project, which you can find here.



Differentiation of iPSC into regionalized-neural progenitors for organoid culture. Minitauraised organoids are generated to avoid necrosis. Midbrain organoids can be cultured for over 100 days in vitro. Organoids can be assessed for maturation state and neuronal activity can be recorded using a MEA.

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03
Events of the year 2020

COVID-19 ACCELERATED DIGITALISATION – EVENTS, CONFERENCES AND MEETINGS WENT VIRTUAL

The year 2020 was one for the history books. In 2020, the outbreak of Covid-19 completely changed the everyday life on a global scale.

Denmark was among the first European countries to introduce lockdown measures, announced on 11 March. It meant that the Danish Universities closed down, staff and students were sent home, and only critical functions were allowed to continue at the University. The lockdown affected research projects, teaching, research mobility and activities such as conferences, meetings and lectures. Everyone had to find new ways in the new reality.

On the small scale, DANDRITE converted the regular seminar series into a virtual format allowing the continuation of exciting research communication. During 2020, DANDRITE hosted and organised 18 virtual lectures and seminars, which is significantly more than usual. The virtual format proved to be simple, which enabled us to have many lectures with top international researchers from nations all around the globe. The speakers included names such as Prof. Elena Cattaneo from dept. of Biosciences at the University of Milan, Prof. Veerle Baekelandt from dept. of Neuroscience at KU Leuven, Interium Head of EMBL Rome Cornelius Gross, and Professor Anthony Zador from Cold Spring Harbor Laboratory in New York.

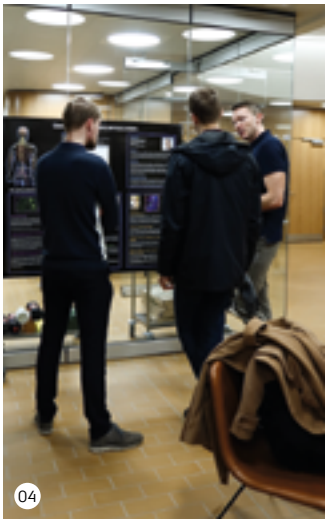
Several conferences and events were postponed or cancelled however, the DANDRITE Scientific Advisory board meeting was converted into an online format, which took place on 26 and 27 May. Despite the last minute conversion, the SAB meeting was held with great success.

In September, the annual Nordic EMBL Partnership meeting for Molecular Medicine was also held online with virtual poster sessions from 22-25 September. MIMS successfully organised and conducted the online meeting, which was full of exciting, educational, and insightful talks and sessions.

Christmas is a special time of the year. Normally, we would have had our annual DANDRITE Christmas party and be able to wish each other a merry Christmas before going on Christmas holiday. This year, we had to think of alternative ways to bring out the special Christmas spirit. The solution became a Christmas Decoration competition among the labs and teams. Moreover, virtual Christmas greeting videos were sent out among the labs and teams. Despite a global pandemic, we still managed to find a way to share the special Christmas spirit with each other.

In general, it was necessary to think outside the box in order to cope with the new and unforeseen challenges caused by coronavirus. On the positive side, 2020 has taught us a thing or two, which we can bring with us forward e.g., that it's possible to hold exciting lectures online with international top researchers on a regular basis – saving time and reducing travel activity. Despite the benefits of the virtual reality, everyone looks very much forward getting back to normal and returning to physical presence at campus.

EVENTS, VISITORS, GUESTS AND SEMINARS



JANUARY

01 SEMINAR: **DANDRITE Topical Seminar** by PhD Vladan Lucic, Max Planck Institute of Biochemistry, Germany, *"Nanoscale organization of neuronal synapses by cryo-electron tomography"* , Host: Group Leader Poul Nissen

02 SEMINAR: **DANDRITE Topical Seminar** with Professor Emeritus Emanuel E. Strehler, Mayo Clinic College of Medicine and Science, USA, *"Intrinsic disorder in the regulatory C-tail of plasma membrane calcium pump PMCA4b"*, Host: Group Leader Poul Nissen

03 EVENT: **YoDa Career Café – What do people do with a research background?** organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE")

FEBRUARY

04 EVENT: **DANDRITE Student Encounters 2020**, Aarhus University

05 SEMINAR: **Joint KJELDGAARD & DANDRITE Lecture** with Paul Saftig, Christian Albrechts University Kiel, Germany, *"The lysosome in health and disease"*

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

07 SEMINAR: **PROMEMO/DANDRITE Topical Seminar** by PhD Macarena Gomez de Salazar, Icahn School of Medicine Mount Sinai, New York, *"Role of NMDAR phosphorylation in cognitive dysfunctions"*, Host: DANDRITE Team Leader and PROMEMO PI Magnus Kjærgaard

08 EVENT: **DANDRITE/PROMEMO Writing Club**, organized by DANDRITE Team Leader and PROMEMO PI Magnus Kjærgaard

MARCH

09 SEMINAR: **Next Generation Sequencing – Methods and applications** with Affiliated DANDRITE researcher Jørgens Kjems, *"Profiling microRNA, tRNA fragments and circular RNA in human biofluids, fresh- and FFPE tissue on Illumina/Oxford Nanopore/NanoString Platforms"*

10 EVENT: **DANDRITE Spring Party**

11 ONLINE MEETING: **"Pimp my figures with PyMol"** for DANDRITE staff and students

12 ONLINE MEETING: **"Pimp my figures – Inkscape"** for DANDRITE staff and students

13 VIRTUAL EVENT: **Virtual Writing Club**, organized by DANDRITE.

APRIL

14 VIRTUAL EVENT: **Festival of Research 2020 – FASCINATING RESEARCH**. DANDRITE researchers Andrea Moreno and Emma Louise Louth recorded their presentations allowing the audience to experience a bit of the Festival of Research at home.

MAY

15 VIRTUAL LECTURE: Virtual DANDRITE Lecture with Professor Elena Cattaneo, University of Milan and National Institute of Molecular Genetics, Italy, *"Informing in vitro stem cell differentiation through single-cell RNAseq analysis of the developing human fetal striatum"*

16 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Professor Veerle Baekelandt, KU Leuven – Center for Molecular Medicine, Belgium, *"Unraveling the role of alpha-synuclein strains in Parkinson's disease and related disorders"*

17 VIRTUAL EVENT: **Virtual DANDRITE Scientific Advisory Board meeting 2020**

JUNE

18 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Professor and BRAINCITY President Leszek Kaczmarek, Nencki Institute of Experimental Biology, Warszawa, *"From c-Fos to extrasynaptic proteolysis in order to glimpse into a mind"*

19 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Head of Neurobiology of Emotions Lab and Vice-President of BRAINCITY Ewelina Knapska, Nencki Institute of Experimental Biology, Warszawa, *"Testing social behavior of mice under ecologically-relevant conditions"*
Figur 2

JULY

20 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Group Leader Hiroki Asari, EMBL Rome, *"Feedback from retinal ganglion cells to the inner retina"*
Fig 3

21 SEMINAR: **MBG FOCUS TALK** with Associate Professor Rosa L. López-Marqués, Department of Plant and Environmental Sciences, University of Copenhagen, *"Lipid specificity determinants in plant lipid flippase"*, Host: Group Leader Poul Nissen

22 **SEPTEMBER**
VIRTUAL SEMINAR: **Virtual DANDRITE Seminar** with Associate Professor Ole Kjærulff, Department of Neuroscience, University of Copenhagen, *"Drosophila Rab2 controls lysosome biogenesis and drives axonal transport of dense core vesicles and lysosomal organelles"*

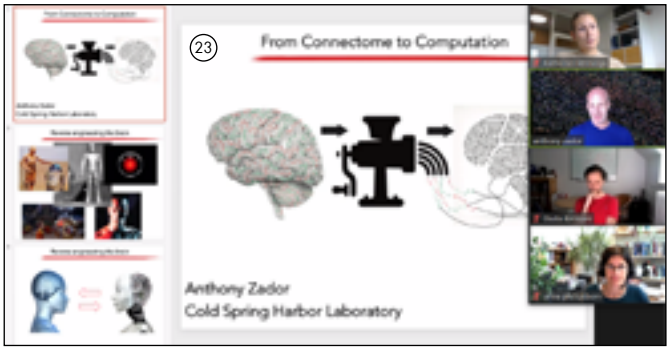
23 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Professor Anthony Zador, Cold Spring Harbor Laboratory, New York, *"From Connectome to computation"*
Fig 4

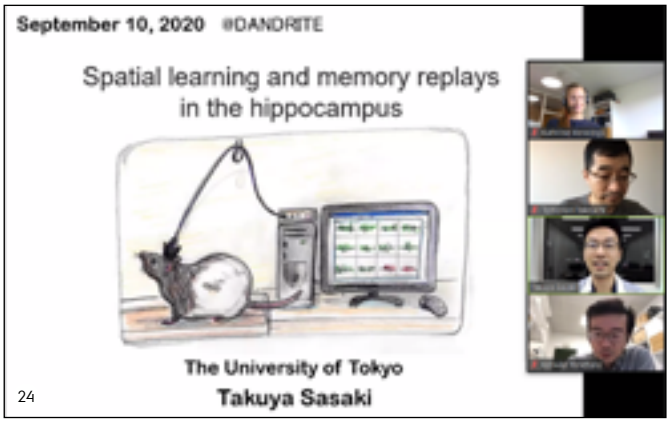
24 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Dr. Takuya Sasaki, University of Tokyo, *"Spatial learning and memory replays in the hippocampus"*
Fig 5

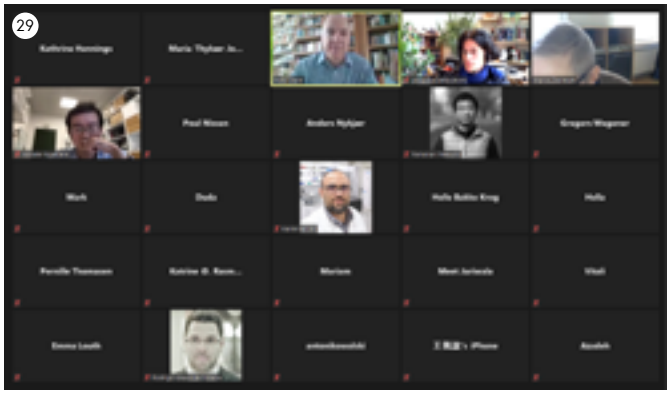
25 VIRTUAL LECTURE: **Virtual DANDRITE LECTURE** with Professor Kenneth Harris, Department of Neuromuscular Diseases, University College London, *"Learning orthogonalizes visual cortical population codes"*

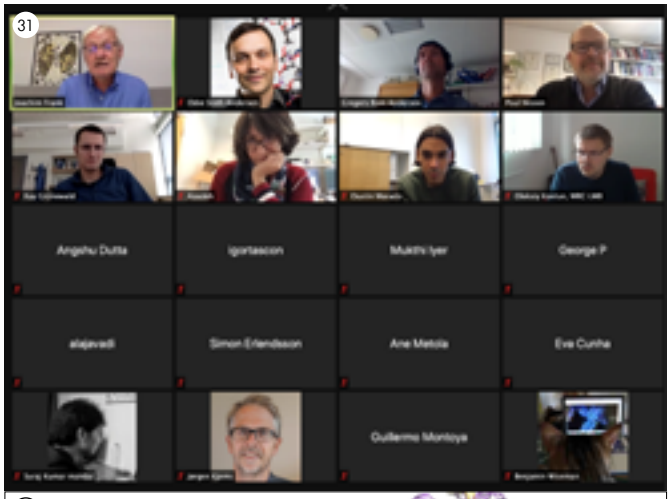
26 VIRTUAL EVENT: **Nordic EMBL Partnership Meeting 2020,** organized by the Laboratory for Molecular Infection Medicine Sweden (MIMS). Attended by DANDRITE researchers and students
Fig D

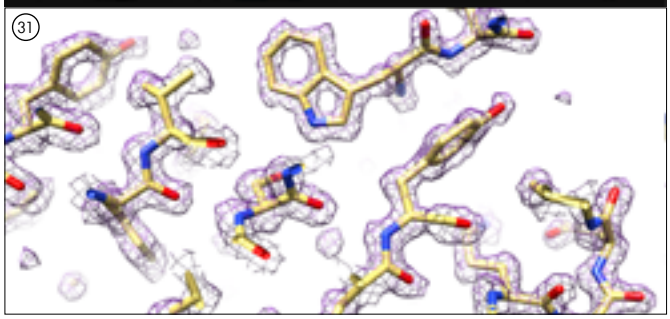
27 EVENT: **Extended Internal Meeting with DANDRITE's newly appointed Affiliated Researcher**; Professor Thomas Franz Erich Willnow
Fig F

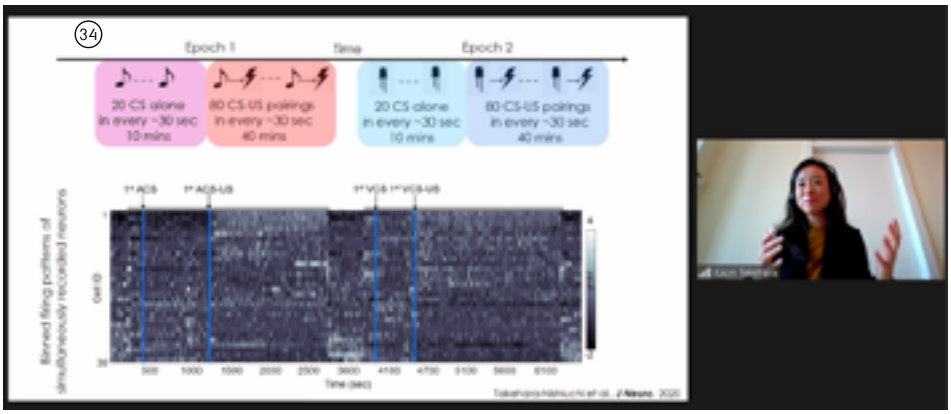












OCTOBER

28 VIRTUAL SEMINAR: **Virtual DANDRITE Seminar** with Dr Hironaka Igarashi, Center for Integrated Human Brain Science, Niigata University, *"Aquaporin4 and Hydrodynamic Pathology of the Brain"*
Fig 6

29 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Ph.D. and Senior Editor at Science, Peter Stern, *"The manuscript selection process at SCIENCE"*
Fig E

30 ONLINE EVENT: **EMBION Inauguration**. Danish National Cryo-EM Facility (EMBION) is a research collaboration led by Group Leader Poul Nissen.

31 ONLINE EVENT: **3rd CryoNET Symposium – New Directions in Cryo-EM Research** with Group Leader Poul Nissen as one of the organizers.
Fig G + Fig G2

32 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Team Leader Thomas McHugh, RIKEN Center for Brain Science, *"Memory modulation by noncanonical hippocampal-subcortical circuits"*
Fig H

33 VIRTUAL LECTURE: **Virtual DANDRITE Topical Seminar** by Postdoctoral Researcher Marc Dämgen, Stanford University, *"Hunting the open state of the glycine receptor with molecular dynamics simulations"*

November

34 VIRTUAL SEMINAR: **Virtual DANDRITE Seminar** with Associate Professor Kaori Takehara-Nishiuchi, Department of Psychology, University of Toronto, *"Detecting and integrating relevant event relationships"*
Fig 7

PUBLIC OUTREACH

35 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Dr. Sylvia Wirth, Center for Cognitive Science in Lyon, France, *"From visual space to schemas in the primate hippocampus"*

36 ONLINE EVENT: **NECTAR 2020** with DANDRITE Affiliated Researcher Jørgen Kjems as one of the keynote speakers

37 BIOMEDICIN EVENT: **Inaugural lecture** by DANDRITE's newly appointed Affiliated Researcher; Professor Thomas Franz Erich Willnow

DECEMBER

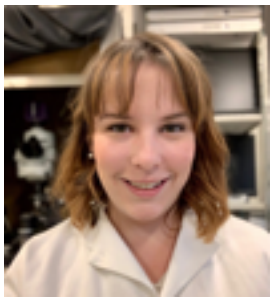
38 VIRTUAL EVENT: **Virtual YoDa Career Café** with PhD alumni from AU health, postdoc in cancer research and certified GROW2 coach Bodil Øster, organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE")

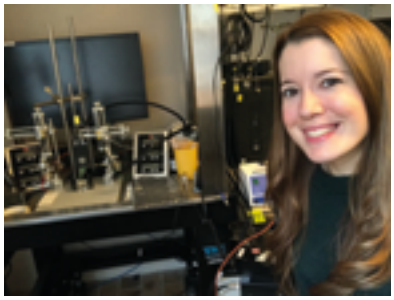
39 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Interim Head Cornelius Gross, EMBL Rome, *"Instinctive fear – sensory integration, internal state control, and adaption"*

40 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Associate Professor Atsushi Sugie, the Brain Research Institute, Niigata University, *"Elucidation of the molecular mechanisms of neural circuit maintenance via synapse"*

DANDRITE STUDENT ENCOUNTERS 2020

Just before the COVID outbreak, DANDRITE held the annual event Student ENCOUNTERS with guided lab tours for interested students. Around 80 students showed up to look for opportunities for student projects in one of DANDRITE's different research groups.





FESTIVAL OF RESEARCH 2020

Due to the COVID-19 situation, Festival of Research was unfortunately cancelled in 2020. However, four researchers from Aarhus University recorded their presentations and uploaded them online at the Aarhus University YouTube channel. Among them were two DANDRITE researchers namely Postdoc Emma Louise Louth and Postdoc Andrea Moreno. Emma presented her research within the human brain. Her virtual presentation was entitled *"Working with human brain"*. Andrea talked about how neuroscience can teach us about how to learn and forget. Her talk was entitled: *"The discovery of neuronal plasticity"*.

VIRTUAL DANDRITE SAB MEETING 2020

Due to the COVID-19 situation, DANDRITE's forth Scientific Advisory Board (SAB) meeting were held virtually via zoom on May 26 and 27. Because of the virtual format, the program was reduced and only group leaders, team leaders and DANDRITE's management attended.

The focus of this year's SAB meeting was on the research program and achievements of the Group Leaders, the future research topics of DANDRITE and on future developments and funding opportunities of DANDRITE in the context of the Lundbeck Foundation and Aarhus University.

Besides presentations by group and team leaders, the SAB also met with group leaders and team leaders in individual sessions to discuss scientific progress, future plans, and managerial issues such as mentorship and collaborations within and beyond DANDRITE.

THE SAB WRITES IN EVALUATION REPORT

"...DANDRITE has made a strong impact on neuroscience research within the local Aarhus University, such that the Department heads make use of the DANDRITE brand name to attract new faculty to AU. Being part of the four Nordic EMBL Nodes in Molecular Medicine, DANDRITE has also positively influenced the wider Danish Neuroscience community and biomedical research in Scandinavia."

"...With great satisfaction the SAB has noticed that most of our earlier recommendations have been seriously considered and implemented in DANDRITE".

"...The SAB was impressed by the development of tools and the establishment of state-of-the-art research infrastructure by DANDRITE researchers, including the constitution of the Danish national cryoEM facility network, which serves the greater Danish community and allows the expansion of structural biology research into the physiological cell biology context".

"...The SAB acknowledges the development of modern circuit neuroscience technologies combined with behavioral, genetic, cellular and molecular analyses. Novel biosensors and electrical probes are being developed with engineering groups at the university. Computational approaches, including machine learning, are being used and further developed. These are important achievements and the SAB recognizes that DANDRITE Group Leaders have played a leading role in establishing this important infrastructure".

"...Translational aspects of the research at DANDRITE are also very visible and successful. Collaborations with clinical departments at the university and Biotech or Pharmaceutical industries are visible and promising. Some of the work has matured to the point that compounds are entering clinical trials".

"...The SAB acknowledges that DANDRITE has launched a mentorship program and that the existing Group Leaders have received valuable advice on many aspects of their work. Nevertheless, we feel that there is room for additional mentoring..."

INAUGURATION OF THE DANISH NATIONAL CRYO-EM FACILITY

In recent years, advances in hardware and software have paved the way for the current growth of the application of cryogenic electron microscopy (cryo-EM). Early on, Denmark recognized and exploited the future potential of this technique on a national level with first investments in 2011 into a high-performance cryogenic Electron Microscope (first generation Titan Krios) for both materials research and structural biology, and later also with co-support from the Lundbeck Foundation and the Carlsberg Foundation into further performance enhancement.

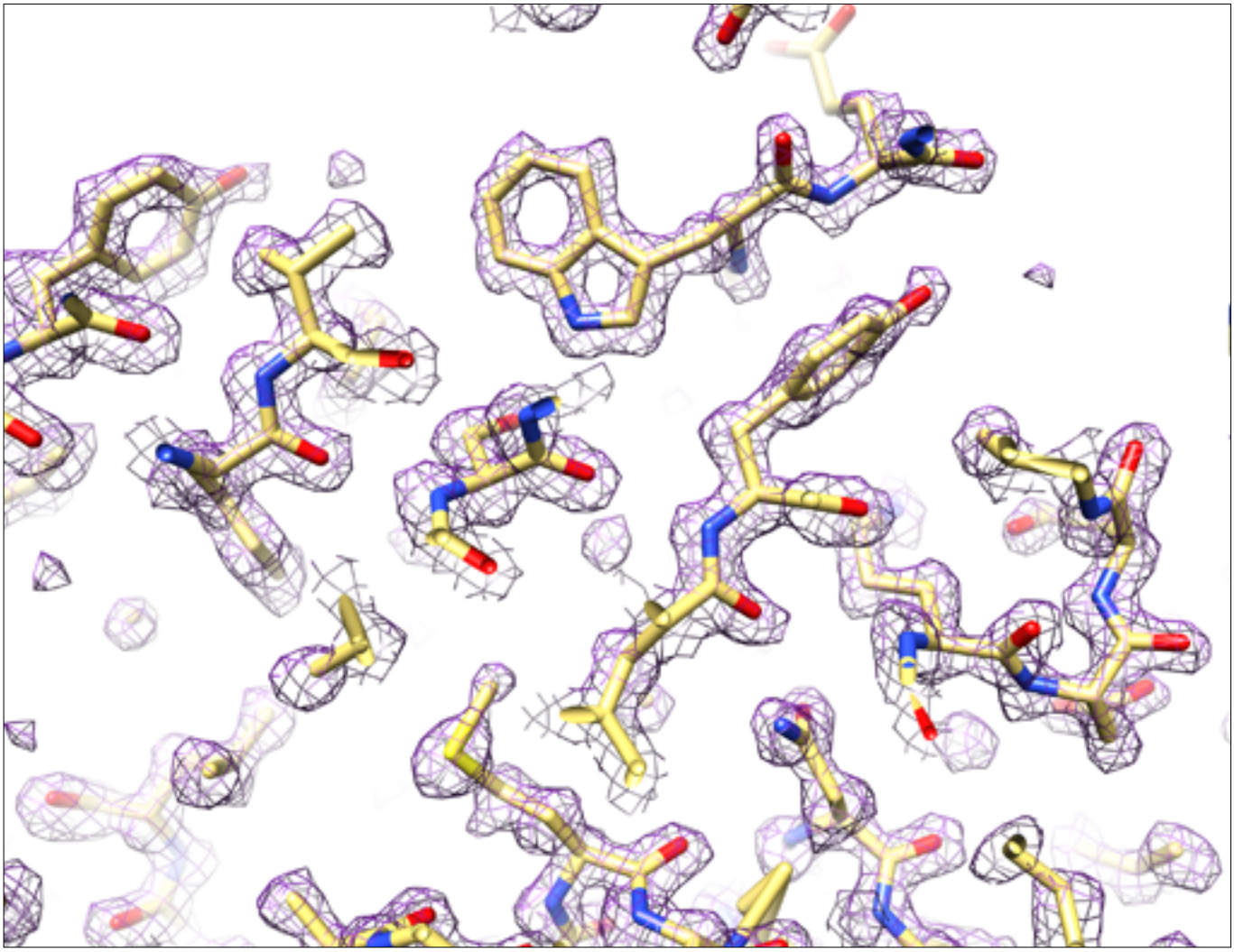
Recently, the Danish Agency for Research and Innovation awarded 4.2 million euros to a proposal for the establishment of the Danish National Cryo-EM Facilities for Biological Nanomaterials (EMBION) on the Danish national roadmap for research infrastructure for the purchase of another high-performance cryo-EM devoted to biological samples.

EMBION is a research collaboration led by EMBO Member and DANDRITE director Poul Nissen from Aarhus University, with participation from the University of Copenhagen as a co-host, as well as the University of Southern Denmark, the Statens Serum Institut, and the Technical University of Denmark as partners. Aalborg University also supports EMBION. The facilities were inaugurated in October 2020, and "...the aim of EMBION is to provide the cryo-EM technology to the Danish research community in general," explains Poul Nissen, and adds that small companies and industry also can gain access.

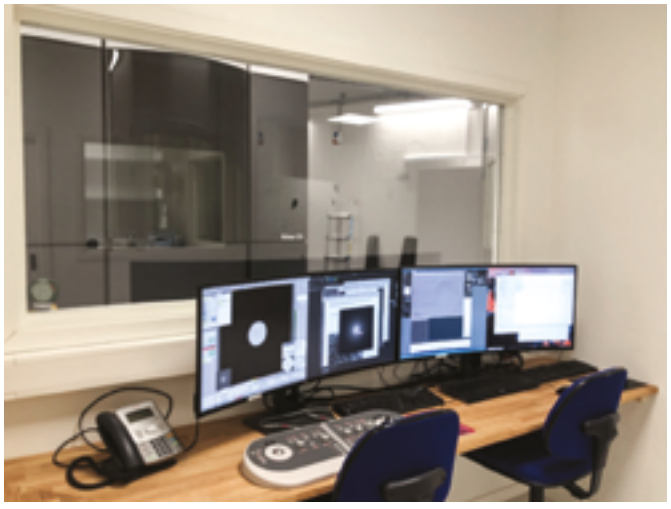
More recently strong financial support was also provided from the Novo Nordisk Foundation for cryo-electron tomography at EMBION, namely a cryogenic focused ion beam scanning electron microscope and a high-pressure freezing device for tissue and cell samples (ICE-T project).

The Novo Nordisk Foundation is also supporting the cryo-EM facilities in Copenhagen led by EMBO Member Guillermo Montoya, and a network grant (cryoNET) for the two facilities in Aarhus and Copenhagen that also encompasses the two cryo-EM facilities in Sweden at Stockholm University (led by EMBO Member Gunnar von Heijne) and Umeå University (led by EMBO Member Bernt-Eric Uhlin), both supported by the Wallenberg Foundation.

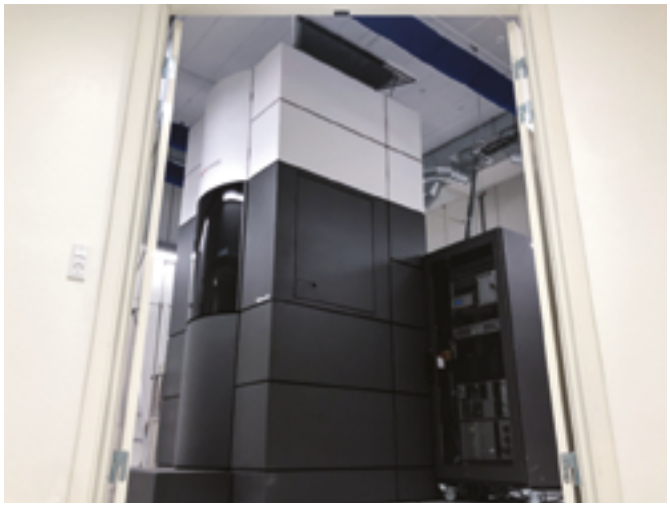
Read more: embion.au.dk



Details of 1.6Å Apoferritin map with atomic model from first benchmarking data on Titan Krios 2



Control room at Titan Krios 2



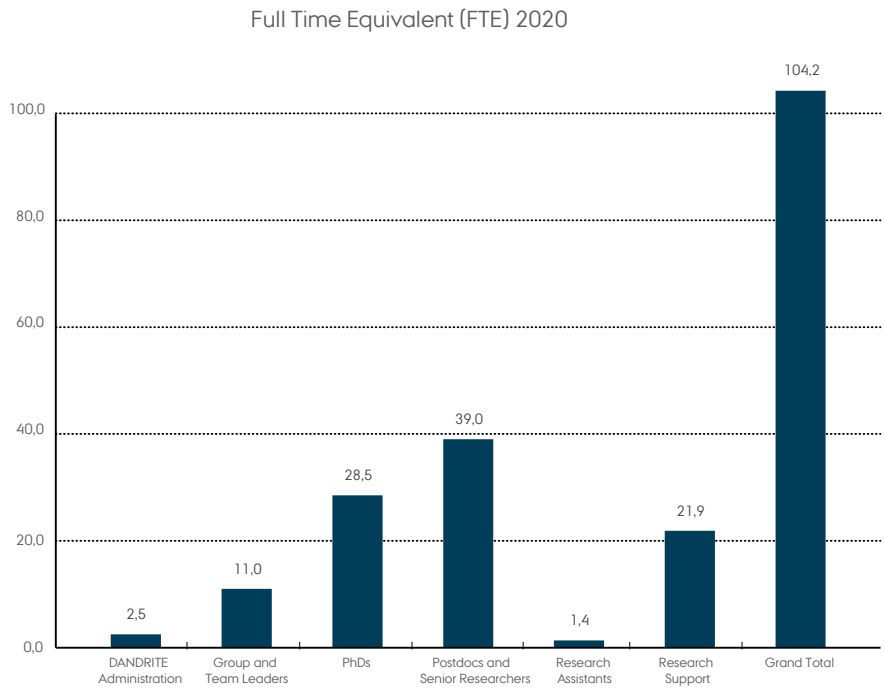
View of Titan Krios 2 (height 4 meter)

04
Personnel

Personnel

Since DANDRITE's inauguration in 2013, staff development has been characterized by considerable growth each year. Since 2018, the personnel development at DANDRITE reached a steady state with around 130 employees counted by heads (excluding affiliated researchers).

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



Personnel figure 1:
Graphic representation of number of personnel in 2020 counted in FTE – full time Equivalent for appointed categories summarized: Postdocs and Senior Researchers, Research assistants, Research Support, PhD students, Group and Team Leaders and DANDRITE Administration.

FIGURE 2:
COUNT OF NUMBER AND PERCENTAGES OF PERSONNEL EMPLOYED DURING 2020 GROUPED BY APPOINTMENT CATEGORY AND GENDER. FTE COUNT.

DANDRITE Personnel categories	Female	Male	Total	%
DANDRITE Administration	2,5	0,0	2,5	2,4
Group and Team Leaders	2,0	9,0	11,0	10,6
PhDs	16,9	11,6	28,5	27,3
Postdocs and Senior Researchers	18,9	20,1	39,0	37,4
Research assistants	1,0	0,3	1,4	1,3
Research Support	18,0	3,9	21,9	21,0
Grand Total	59,3	44,9	104,2	100
Percentage of Female/Male	57	43	100	

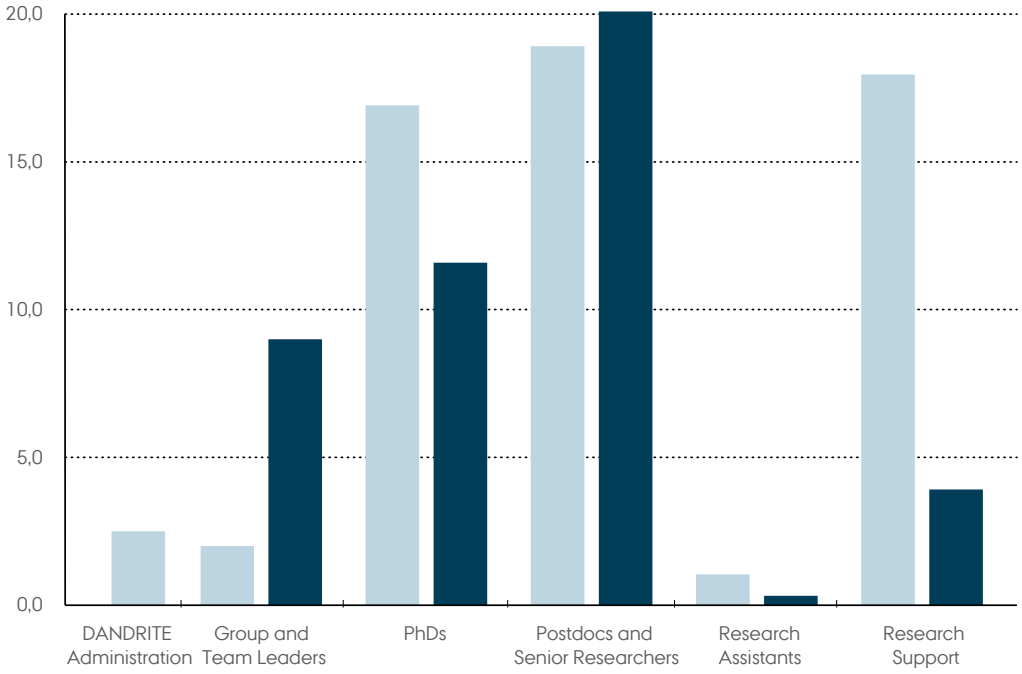


Figure 3:
Graphic representation of the personnel counts for 2020 (numbers grouped by appointment category and gender).

Figure 4: Percentage of Female/Male

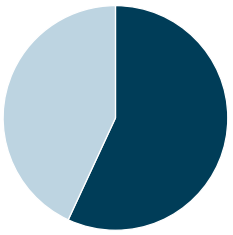


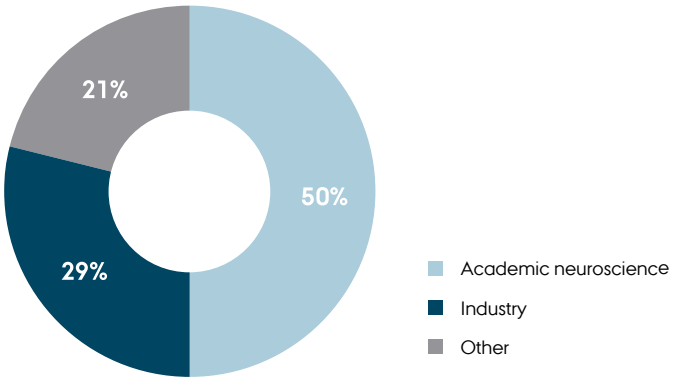
Figure 5:
Graphic representation of the nationality distribution of all employees

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

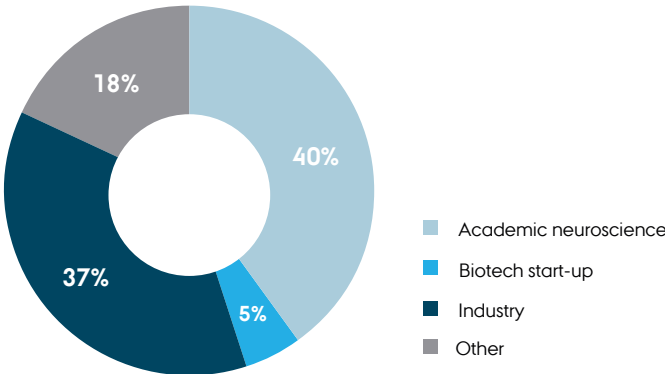
DANDRITE Alumni

In 2020, the number of Alumni continued to grow and DANDRITE created an official DANDRITE Alumni Network at LinkedIn. The network is for former employees and students as well as current DANDRITE staff. The purpose of the network is to take advantage of the growing neuroscience community around DANDRITE for the mutual benefit of active researchers at DANDRITE and DANDRITE alumni in science careers and neuroscience. The network aims at enabling the community to connect with former colleagues and other likeminded alumni. The LinkedIn group allows alumni and current staff to share relevant job postings, exciting lectures, new publications and stories from the neuroscience community.

PhD Alumni



Postdoc Alumni



Alumni figures:
Some DANDRITE alumni stay in academia others go to private sector research or consulting, and some to public sector teaching and administration. These graphics show the ratio of career paths taken by PhD and Postdoc alumni from DANDRITE research groups (excluding affiliated researchers). The statistics include alumni in the period 2013 to 2020.

Alumni Features

On the following pages, we present the different career paths of three DANDRITE PhD graduates:
Dr. **Emil Gregersen** (former PhD student in Poul Henning Jensen's group)
Dr. **Junior Samuel Lopez Yepez** (former PhD student in Duda Kvitsiani's group)
Dr. **Rune Nguyen Rasmussen** (former PhD student in Keisuke Yonehara's group)
Dr. **Sara Elfarrash** (Former PhD student in Poul Henning Jensen's group).

ALUMNI FEATURE
/ Text by Emil Gregersen.

In this feature, Emil Gregersen, PhD student from Poul Henning Jensen's group, sheds a light on the field of research of his PhD, and the skills and memorable experiences he has gained at DANDRITE, Aarhus University, and from his social engagement at DANDRITE. Finally, Emil will give his advice to someone who is considering pursuing a PhD.

In brief, tell me about your specific field of research and explain why you are interested in this particular area?
I investigated the cellular mechanism misfolding-associated protein secretion (MAPS). I wanted to determine if MAPS is involved in the secretion of pathological α-synuclein aggregates from affected cells. This is very interesting as the release of α-synuclein aggregates is believed to play a crucial role in the development and progression of Parkinson's disease, but we do not know the responsible mechanism. It makes me proud to have contributed to the understanding of the molecular pathology of Parkinson's disease with my research. Moreover, it has been very exciting to follow the development in the Parkinson's disease-field, which have made substantial advancements in the last five years.

What was most memorable to you about your experiences in your PhD program, and what was most memorable to you about your experiences at DANDRITE and Aarhus University?
Looking back, I have had many memorable experiences during my PhD. If I should highlight one, it would be attending international conferences and coursers. Here, I listened to great talks and presentations, which inspired me and helped me develop into a mature and confident researcher.

One of the unique features of DANDRITE is the different focus points of the groups albeit all within the field of neuroscience. It has been very interesting to learn about the other groups' research in the weekly meetings from which I have gained a very broad understanding of neuroscience and relevant research techniques.

Please describe your engagement in social activities at DANDRITE, and what you have gained from it?
I was involved in the development of young DANDRITE (YoDa), where I helped organizing social and scientific events. I gained a lot from both organizing and attending the events as they provided great opportunities to get to know your peers beside their research. I believe non-work-related interactions are important for creating a great work environment and will enhance collaboration between the groups.

I have also twice been part of arranging a small stand at the Festival of Research, where we presented our research to the public. This was a great exercise in communicating detailed research in a simple and clear way using props and videos. Moreover, it was motivating to feel the genuine interest in your research from people outside the field. I can highly recommend it.

What advice would you give to someone who is considering pursuing a doctorate within science?
Do not focus solely on your own project. Be curious and expand your knowledge in different areas. This will inspire you to create better research ideas and improve your research. The network you create in the process can very well help your career in the long run.

I would also recommend that during your PhD-education, you pay attention to which work tasks you enjoy and excel at. This can help you to narrow down your future career path after the PhD. Thus, if you for instance love to teach, then maybe you should engage yourself more in that activity and investigate possible career paths, where teaching are part of the job description.

Alumni Feature
/ Text by Junior Samuel Lopez Yepez

In this feature, Junior, postdoc from Kvitsiani Group, sheds a light on the field of his research, his career path, and how he has used the skills and experiences gained at DANDRITE in his subsequent positions. Finally, Junior will give his advice to someone who is considering pursuing a PhD.

In brief, tell me about your specific field of research and explain why you are interested in this particular area?

I focused my research on understanding the decision-making process under uncertain conditions. I found the development of algorithms that could mimic the complex decision-making process, and how neurons could implement them fascinating. Just imagine that we could come up with a formal framework that could explain why fundamental decisions are made and under what conditions. And not only that, how all this information is represented and used in neural circuits. In very general terms, from my perspective, understanding the decision-making process is understanding the purpose of the brain. In a very philosophical view, our purpose.

What was most memorable to you about your experiences in your PhD and postdoctoral program, and what was most memorable to you about your experiences at DANDRITE and Aarhus University?
For both questions, it is the same answer. For me it will be the people. The opportunity to meet and learn from amazing and diverse people from around the world will be the most memorable. From lab visits and conferences abroad to my regular meeting with my amazing colleagues. It helped me grow as a person and as a professional more than I could have imagined.

Can you describe your career path to us? Where are you now?
I am a biomedical engineer with a master's degree in applied physics. Before starting my PhD at DANDRITE, I did an internship on new nanodevices for bioinspired computing. I have been fascinated by the topic of how to generate intelligent agents since then. During my time at DANDRITE, I applied and gained knowledge by building new devices and analyzing neural activity and actual animal behavior. Currently, I work as an Artificial Intelligence (AI) Scientist at Thales Group's R&D institute CortAIx.

How have you used your skills and experiences gained at DANDRITE and Aarhus University in your subsequent positions?
With the experiences that DANDRITE and Aarhus University have given me, I can now discuss scientific issues more objectively. I have been able to research on cutting edge techniques. I can also plan how to develop some ideas around a very specific topic. And I must say that, inspired by the behavior of mice and humans, I learned to develop better Artificial Intelligence (AI) algorithms. In my current position, I hope to create and apply algorithms in products for artificial and augmented intelligence in areas such as defense, cybersecurity, and aerospace.

What advice would you give to someone who is considering pursuing a doctorate within science?
A PhD is a great, valuable, and amazing experience. However, it's probably not the way you're thinking right now (and it will probably take you to places you weren't expecting at all). You have to be sure that this is the path you want to take. Because a PhD comes with a lot of responsibility and several challenges (some are fun and many are not). You will probably feel ignorant like never before and will have to deal with frustration many times. And it's okay to feel that way sometimes. You will also feel great at other times. This is all part of the journey and it is worth it. Never take things related to your project too personal (trust me in this one). And above all, enjoy this welcoming institute, the city that surrounds you, the great people you will meet, and this incredible journey.

Alumni Feature
/ Text by Rune Nguyen Rasmussen

In this feature, Rune Nguyen Rasmussen, PhD student from Keisuke Yonehara's group sheds a light on the field of research of his PhD, the skills and memorable experiences he has gained at DANDRITE and Aarhus University. Finally, Rune will give his advice to someone who is considering pursuing a PhD, and tells us what his plans are after having defended his PhD.

In brief, tell me about your specific field of research and explain why you are interested in this particular area?

The overall research field of my PhD research has been the visual system (i.e., the neural circuits that give rise to the experience of sight). Specifically, in my PhD studies, I have investigated if and how motion-encoding cells residing within the retina contribute to motion processing carried out by the visual cortex of mice. I am generally fascinated by many topics and questions within the realm of neuroscience, and thus my scientific interests span many facets of brain functioning. The research question that I addressed in my PhD studies appealed to me for several reasons. For one, our causal and mechanistic understanding of how the sensory periphery subserves higher-order sensory processing carried out by the cerebral cortex is very limited. In the lab of Keisuke Yonehara, we are ideally equipped to tackle this question in the context of the visual system, and thus I was driven by genuine curiosity to explore this. Furthermore, in order to provide answers to the question at hand, I had to learn and master a suite of experimental techniques which I also find deeply motivating and fun!

What was most memorable to you about your experiences in your PhD program, and what was most memorable to you about your experiences at DANDRITE and Aarhus University?
Several things come to mind concerning this question. My PhD pursuit has taken me on a truly wonderful journey. In addition to the countless hours in front of a two-photon microscope, I have been privileged to visit a number

of inspiring scientific environments around the world (e.g., Cold Spring Harbor Laboratories, EPFL, FMI, and MPFI), which all have been rewarding and motivating experiences. I can genuinely say that I have relished these three years of PhD research, I have learned an exceptional amount — knowledge both theoretical and practical — and I have made new friends and collaborators from around the world. What probably has been most memorable for me about my experiences at DANDRITE, and at Aarhus University in general, is the tremendous helpfulness and kindness that I have met everywhere. I have always felt that no matter who I have approached for help or guidance, they always tried their very best to help me. Thus, the environment of the DANDRITE community have been such a joy to be part of — scientifically but not least collegially.

Please describe your engagement in social and work-related activities at DANDRITE, and what you have gained from it?
During my PhD study, I think it is fair to say that I have been very focused on the science and my work. Yet still I have strived to be involved in work-related activities at DANDRITE as much as I have been able to. For example, I was involved in creating video presentations for the Yonehara Group and DANDRITE, I interacted with potential future students at DANDRITE Encounters, and I have served as PhD spokesperson. All of these experiences have been very rewarding and not least fun to engage in.
What advice would you give to someone who is considering pursuing a PhD within science?

My advice to someone who is considering pursuing a PhD, in any academic field, would be to first nail down the "why" — why do you want to pursue this PhD, and what do you want to gain from it? Unquestionably, during these three years of intense studies and work, there will be times where you experience frustrations and things are not going as smoothly as you might had hoped for. In such situations, I truly feel it helps having something to anchor to, which reminds you why you embarked on this PhD in the first place and helps you to see the bigger picture.

Can you tell us about your plans after having defended your PhD?
After having defended my PhD, I am going to the lab of Professor Ole Kiehn at the University of Copenhagen where I will be a postdoctoral fellow within the field of motor neuroscience.

Alumni Feature
/ Text by Sara Elfarrash

In brief, tell me about your specific field of research and explain why you are interested in this particular area?
During my PhD, I have been studying a protein called alpha synuclein that is believed to play an important role in the pathology of different neurodegenerative diseases including Parkinson's disease. Using organotypic hippocampal slices, we have managed to introduce and validate a novel model that replicates the pathology reported in brains of Parkinson's disease patients, including aggregation of alpha synuclein protein, which is spreading between neurons and formation of Lewy pathology. This was followed by using our new model to manipulate the pathology using different compounds or drugs. This was a very exciting project and we believe that it will help improve and fasten our understanding of PD and other alpha synuclein related diseases.

What was most memorable to you about your experiences in your PhD program, and what was most memorable to you about your experiences at DANDRITE and Aarhus University?
It is quite difficult to highlight one memorable thing in doing my PhD! Doing a PhD itself is the most memorable thing I guess. It's like a roller coaster, it can be tough but in the end, most of the people will enjoy the ride. Doing my PhD in a healthy environment like DANDRTIE made things easier. The diversity at DANDRITE makes it easier to fit in. Research-wise being exposed to the different topics of neuroscience studied in different groups, either during casual discussions, attending the weekly DANDRITE meeting or lectures given by invited speakers, helped me to grow as a researcher and to expand my knowledge in the field of neuroscience. It also allowed me to gain different insights, perspectives and feedback for my own project.
Describe your career path since completing your education at Aarhus University? Where are you now?
After finishing my PhD, I was appointed Assistant Professor of Physiology at the Faculty of Medicine, Mansoura University, Egypt. I am teaching different courses related to Neuroscience and neuro physiology for medical students and for postgrads. I am also running my small research group, where we focus on Alzheimer's diseases and investigate the role of oxidative stress in the progression of the disease using mice models and brain slices.

How have you used your skills and experiences gained at DANDRITE and Aarhus University in your subsequent positions? What advice would you give to someone who is considering pursuing a PhD within science?
Because I have continued to investigate neurodegenerative diseases in my new position, I have the chance to use all the technical experience and knowledge gained during my PhD in a direct way. Other skills like building collaborations, arranging journal clubs and writing funding applications were all useful to continue my career as a more mature and independent scientist.

My advice for someone considering doing a PhD will be that they should only do it, if they believe that this is what they want to do. Also, when it comes to choosing their PhD topic, they need to choose the topic that they do not mind thinking continuously about for the next 5 years. Last but not least, I encourage them to always follow their values and not their goals.

Magnus Krøpping Andersen, student assistant, edited the features.

Awards

Group Leader **Keisuke Yonehara r**eceived Lundbeck Foundation Ascending Investigator of DKK 5 million for his neuroscientific research with the project entitled "Development and disease of spatially asymmetric circuits in the mouse retina". With this award Yonehara and his group will study how spatially asymmetric neuronal connectivity, which is one of the most basic building blocks of neuronal processing, is established during development by specific molecular mechanisms. Gained insights will be helpful for understanding and treating neurodevelopmental disorders such as congenital nystagmus.

Assistant Prof. **Joseph Lyons** was awarded the Lundbeck Foundation Fellow 2020 of DKK 10 million which enables him to establish his own research group and devote himself to research for the next five years at the Department of Molecular Biology and Genetics, Aarhus University.

Postdoc **Ronja Driller** received the highly prestigious Marie Sklodowska-Curie Individual Fellowship of DKK 1.6 million. Ronja is investigating the structure and function of human and yeast P5-ATPases.

Student assistant **Simon Arvin**, was awarded Health's Student Research Prize 2020 of DKK 11.180. The prize is awarded to a student that Health wishes to recognise as someone who have submitted extraordinary work.

Postdoc **Thibaud Diedonné** was awarded the PhD prize 2020 from the French Biophysical Society for his PhD thesis entitled "Functional and Structural characterization of lipid flippases: the yeast Drs2p/Cdc50p and the disease-related human ATP8B1/CDC50A complexes".

Postdoc **Lasse Reimer** was awarded the Danish Parkinson's foundation "Young Scientist Award 2020" for his work on posttranslational modifications of α-synuclein in relation to pathology in Parkinson's disease. Along with the award follows a grant of 12.500 DKK.

PhD **Milena T. Tronsgaard** was awarded the Kjeld Marked PhD award 2020 for her work on P4ATPases and cryo-EM studies.

Affiliated researcher **Ernst-Martin Füchtbauer** was elected president of International Society for Transgenic Technology (ISTT). The term runs until October 2023

Affiliated researcher **Jane Hvarregaard** received a scholarship from Frøknerne Anna and Dagny Hjerrilds Foundation of DKK 100.000. The scholarship has been awarded for her work to limit the use of laboratory animals in her research.

Grants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17

1. Affiliated Researcher **Olav Andersen**: SORL1 activity regulated by phosphorylation, DKK 300.000, Alzheimers forskningsfonden

2. Affiliated Researcher **Olav Andersen**: SORL1 activity regulated by phosphorylation, DKK 2.200.000, Novo Nordisk Foundation

3. Group Leader **Mark Denham**: Investigating the role of ELAVL4 in GBA-associated Parkinson's disease, DKK 133.770, Bjarne Saxhofs Foundation facilitated by the Parkinsons Association

4. Group Leader **Mark Denham**: A Human Stem cell based miniaturised controlled organoid MiCO Platform for investigating Nurological Disorders, DKK 4.889.608, ODIN

5. Assistant Professor **Nadia Goncalves:** Diabetic neuropathy, DKK 100.000, Dagmar Marshalls Fond

6. Group Leader **Poul Henning Jensen**: Establishing structural and cellular phenotypes of a-syn aggregates amplified from patient cerebrospinal fluid and validating PMCA and RT-QuIC amplified polymorphs, DKK 780.000, The Michael J Fox Foundation

7. Group Leader **Poul Henning Jensen**: Biomarkers for a-syn aggregate cytotoxicity to inform drug development, patient stratification in clinical treatment trials and determine treatment responses to disease modifying treatments, DKK 270.000, Parkinsonforeningen

8. Group Leader **Poul Henning Jensen**: Glucocerebrosidase inducers for treatment of Parkinson's disease; Innobooster, DKK 1.680.000, Innovationsfonden; Innobooster grant in collaboration with Orfazyme

9. Assistant Professor **Lilian Kisiswa** (Master Student Ea Jensen as co-applicant): Scholar stipend, DKK 140.000, DSfN-Lundbeckfonden

10. Affiliated Researcher **Jørgen Kjems**: PRIME - tRNA fragments in epilepsy, EUR 640.000, EU H2020

11. Assistant Professor **Mads Kjolby**: Lundbeck Fonden COVID19 funds, DKK 5.000.000, Lundbeckfonden

12. Assistant Professor **Mads Kjolby**: COVID19 medication Region Midt, DKK 2.500.000, Region Midt

13. Team Leader **Magnus Kjærgaard**: Novo Nordisk Fonden - Industrial Biotechnology, DKK 2.000.000, Novo Nordisk Fonden - Industrial Biotechnology

14. Team Leader **Magnus Kjærgaard**: Carlsberg instrument grant, DKK 325.000, Carlsberg Foundation

15. Assistant Professor **Julián Valero Moreno**: Evolving new types of therapeutics-reshuffling old players in new ways, DKK 2.000.000, Lundbeck Foundation

16. Group Leader **Poul Nissen**: Nordic Research Infrastructure hub funding for Nordic EMBL Partnership, DKK 1.750.000, Nordforsk

17. Group Leader **Poul Nissen**: Infrastructure for Cryo-Electron Tomography - ICE-T, DKK 13.270.779, Novo Nordisk Foundation

18. Senior Researcher **Claus Elsborg Olesen** (Prof. Poul Henning Jensen co-applicant): Targeting the SERCA transporter to increase neurons cytosolic calcium levels as a paradigm changing protection against progressive Parkinson's disease- drug lead development and validation, DKK 6.000.000, Novo Nordisk Foundation

19. Postdoc **Lasse Reimer**: OligoFIT, fund 3-year postdoc and running expenses, DKK 2.000.000, EU Joint Programme – Neurodegenerative Disease Research (JPND)

20. Postdoc **Haruka Yamamoto**: Postdoc Research Abroad Fellowship, DKK 239.720, Daiichi Sankyo Foundation of Life Science

21. Postdoc **Haruka Yamamoto**: Postdoc Research Abroad Fellowship, DKK 191.366, Uehara Memorial Foundation

22. Group Leader **Keisuke Yonehara**: International collaboration grant, DKK 18.400, Brain Research Institute, Niigata University

23. Group Leader **Keisuke Yonehara**: Heparan sulfate proteoglycan-mediated establishment of neuronal circuit asymmetry for motion processing, DKK 2.459.520, Novo Nordisk Foundation

24. Group Leader **Keisuke Yonehara**: PRESTO grant, DKK 2.397.127, Japan Science and Technology Agency (JST)

25. Group Leader **Keisuke Yonehara** (in collaboration with Clinical Prof. Toke Bek): Novo Nordisk Foundation Exploratory Interdisciplinary Synergy Programme. BIRD – Biocompatible Retinal prosthesis for restoring visual computations in blinding Diseases, DKK 4.996.374, Toke Bek

Patents

Group Leader **Anders Nykjær** (together with Anne Louise Askou, Thomas Juhl Corydon & Toke Bek) obtained patent: Inhibition of sortilin for the treatment of diabetic retinopathy, PCT/EP2020/085539

Invited Talks

JANUARY
Yonglun Luo: *Circularization of genes in human cells by CRISPR, Circular DNA in normal development and disease*, Berlin, Germany

FEBRUARY
Jørgen Kjems: *9th course on the Non-Coding Genome*, Institute Curie, Paris, France

Poul Nissen: *Structure and mechanism of P4-ATPase lipid flippases*, Department of Biochemistry and Biophysics conference, Stockholm University, Sweden

Yonglun Luo: *Single-cell transcriptome profiling of endothelial cells*, BDMR Research Conference, Bern, Switzerland

MARCH
Poul Henning Jensen: *MJFF aSyn Biomarkers Workshop-Symposium chair*, The Michael J Fox Foundation, New York, USA

APRIL
Anne von Philipsborn: *Female copulation song in Drosophila: a signal in mate choice*, Systems Neuroscience Nencki Institute, Poland (virtual lecture)

Magnus Kjærgaard: I*ntrinsically disordered linkers as regulators of tethered enzymes and multivalent interactions*, Dewpoint Tx - condensates.com (virtual lecture)

JUNE
Keisuke Yonehara: *Multiplexed axonal direction selectivity in retinal bipolar cells*, The 43rd Annual Meeting of the Japan Neuroscience Society, Graduate School of Frontier Biosciences, Osaka University, Japan

Mateusz Dyla: *Intrinsically disordered linkers control tethered kinases via effective concentration*, IDPSIG and friends Virtual Symposium (virtual lecture)

Poul Nissen: *Micromanagement of amino acid transporters*, Joint ESS – MAX IV Science Colloquia, organized European Spallation Source ERIC (virtual lecture)

JULY
Duda Kvitsiani: *Reward foraging task, and model-based analysis reveal how fruit flies learn the value of available options*, NENSKI OpenLab seminar (virtual seminar)

AUGUST
Jørgen Kjems: *Applications of aptamers and miRNA for diagnosis and treatment of neuroloigcal diseases*, (virtual meeting)

Lilian Kisiswa: I*ncreasing "healthspan" – why is it important?*, Cardiff Science café, UK, (virtual lecture)

Magnus Kjærgaard: *Intrinsically disordered linkers as regulators of tethered enzymes and multivalent interactions*, University of Melbourne - Departmental seminar (virtual seminar)

SEPTEMBER
Akihiro Matsumoto: *Multiplexed axonal direction selectivity in retinal bipolar cells*, Visual Science Forum Japan, (virtual lecture)

Anne von Philipsborn: *Female copulation song: eavesdropping on the communication between nervous system and reproductive organs*, Nordic EMBL Partnership meeting, Laboratory for Molecular Infection Medicine Sweden (virtual lecture)

Keisuke Yonehara: *Multiplexed axonal direction selectivity in retinal bipolar cells*, Nordic EMBL Partnership meeting, Laboratory for Molecular Infection Medicine Sweden (virtual lecture)

Magnus Kjærgaard: *Intrinsically disordered linkers as regulators of tethered enzymes and multivalent interactions*, University of Massachussets – Departmental seminar (virtual seminar)

Photos: Roar Lava Paaske and Lars Kruse

Mark Denham: *Identifying Genetic Risk Variants for Parkinson's Disease, Nordic EMBL Partnership meeting*, Laboratory for Molecular Infection Medicine Sweden (virtual lecture)

Poul Nissen: *Cryo-EM studies of membrane transporter systems in brain*, Nordic EMBL Partnership meeting, Laboratory for Molecular Infection Medicine Sweden (virtual lecture)

Poul Nissen: *DANDRITE and the Nordic EMBL Partnership for Molecular Medicine*, Lundbeck Foundation, Copenhagen

OCTOBER
Yonglun Luo: *CRISPR Gene Editing at Scale*, ICG-15, China

NOVEMBER
Jørgen Kjems: *IDA: Exploring bioscience – digital festival*, online meeting
Jørgen Kjems: Annual meeting, NECTAR, online meeting

Keisuke Yonehara: *Synapse-specific direction selectivity in retinal bipolar cell axon terminals*, World Wide Neuro (virtual lecture)
Magnus Kjærgaard: *Intrinsically disordered linkers as regulators of tethered enzymes and multivalent interactions*, Johns Hopkins University – Departmental seminar (virtual seminar)

Magnus Kjærgaard: *Social Media for Researchers*, Aarhus Institute of Advanced Studies (virtual lecture)

Magnus Kjærgaard: *Intrinsically disordered linkers as regulators of tethered enzymes and multivalent interactions*, Washington University St. Louis – Departmental seminar (virtual seminar)

Mark Denham: *Investigating the role of ELAVL4 in GBA-associated Parkinson's disease*, Danish Parkinson's foundation

Olav Andersen: *Endosomal trafficking is required for the normal maturation of the Alzheimer's-associated protein SORLA*, Royal Society (virtual lecture)

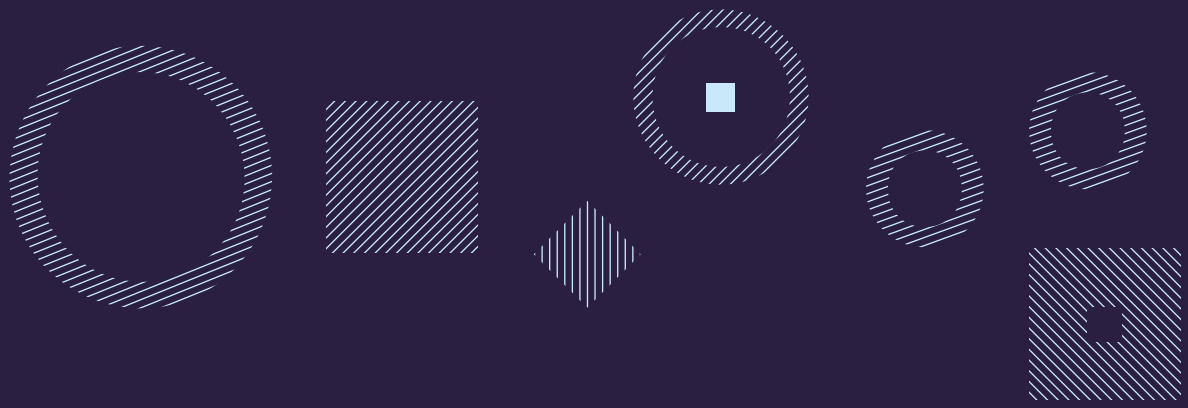
Poul Henning Jensen: *P25a function in neurodegenerative disorders*, International Workshop for Human Brain Banking & the 2nd National Human Brain Banking Continuous Education Program, Beijing, China (virtual lecture)

Poul Nissen: *Always two sides to a story – structure and function of lipid flippases*, 1st CIBSS Symposium – signalling across scales, Freiburg (virtual lecture)

DECEMBER
Magnus Kjærgaard: *Does stronger equal better for kinase anchoring proteins*, IDPSIG/IDP seminars (virtual seminar)

Olav Andersen: *A new SORL1-deficient animal model of Alzheimer's disease*, CSHL (virtual lecture)

05 Publications



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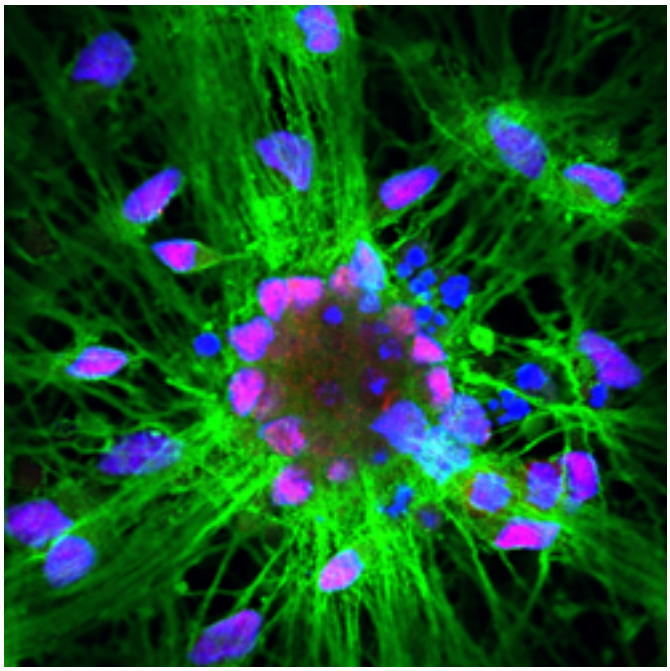

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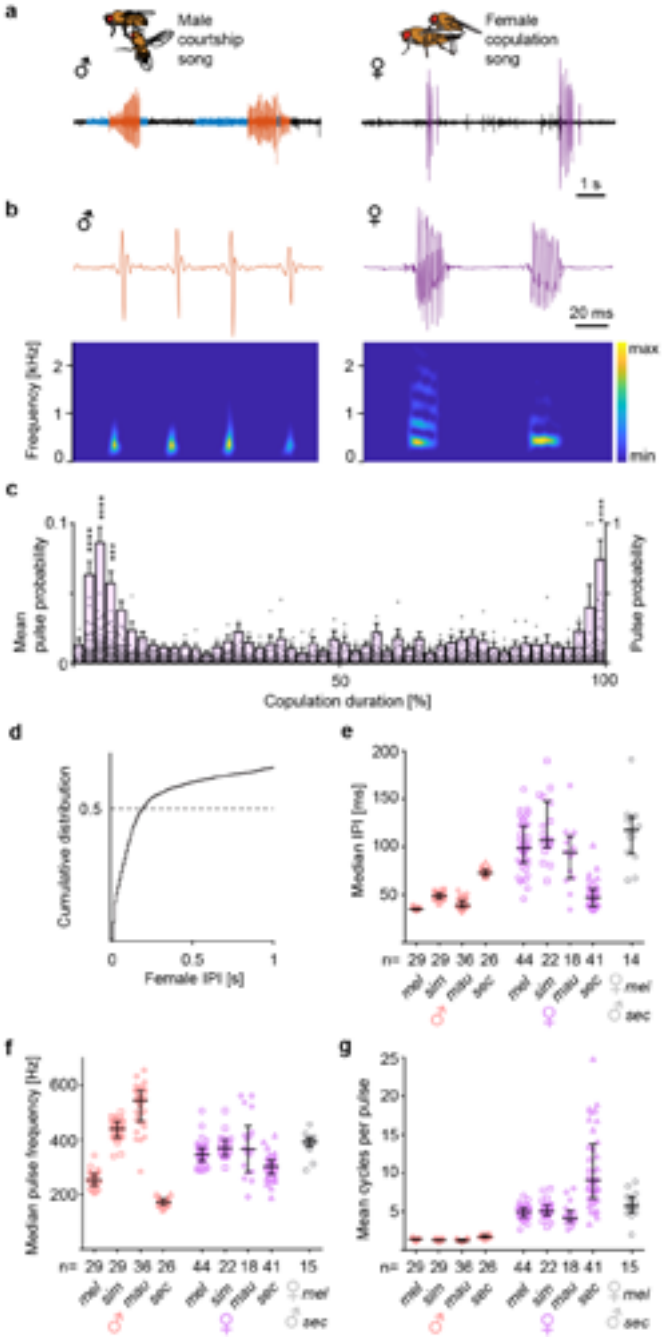

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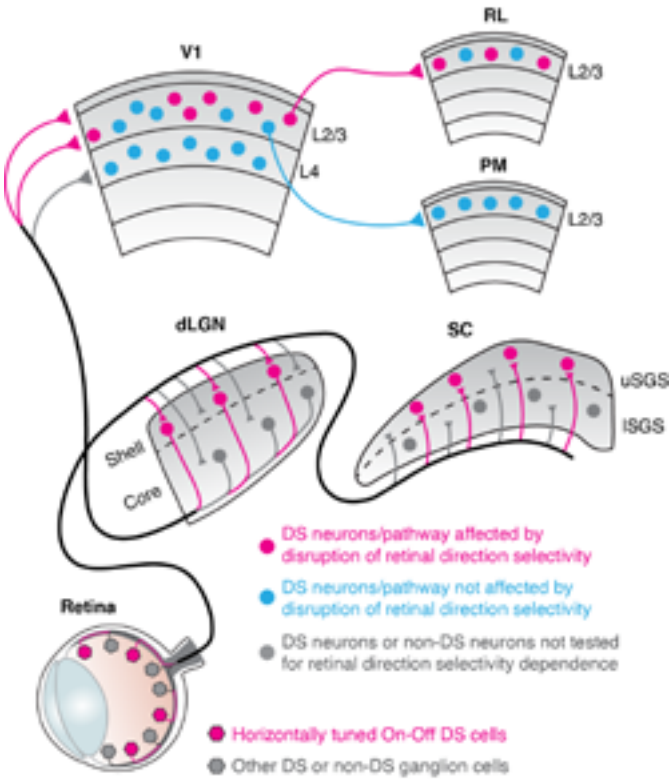

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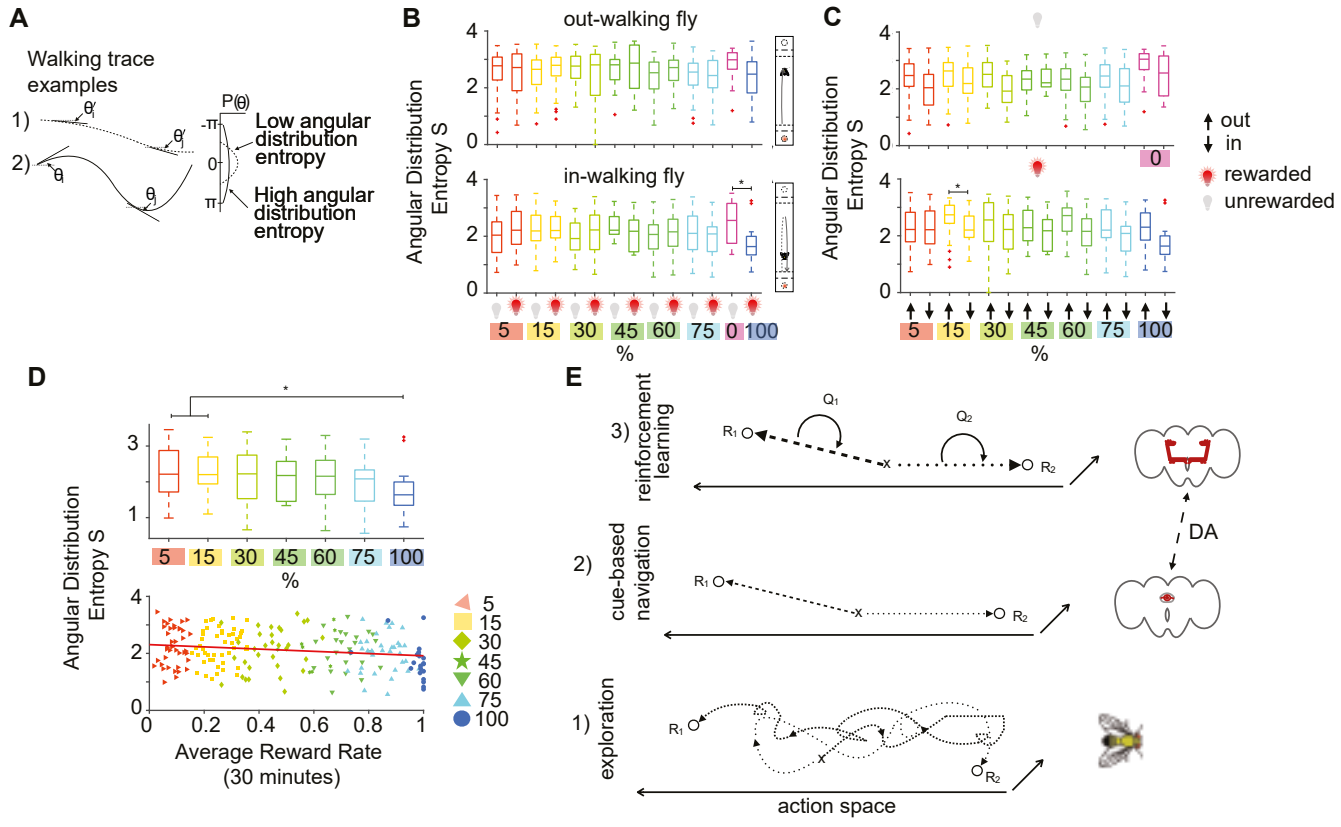

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DANDRITE is located at the following addresses at Aarhus University:

Department of Molecular Biology and Genetics
Gustav Wieds Vej 10
Building 3130
DK- 8000 Aarhus

Department of Biomedicine
Høegh-Guldbergs Gade 10
Building 1116
DK- 8000 Aarhus

www.dandrite.au.dk