2021

# 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 2021 annual report from DANDRITE – the Danish Research Institute of Translational Neuroscience and the Danish node of the Nordic EMBL Partnership for Molecular Medicine. DANDRITE is funded by the Lundbeck Foundation and hosted by Aarhus University at the Department of Biomedicine and the Department of Molecular Biology and Genetics.

DANDRITE follows the EMBL model and is based on EMBL type group leader programs at its core. Additionally, DANDRITE is also the host environment of several large research programs such as ERC grants and the PROMEMO Center of Excellence funded by the Danish National Research Foundation, as well as of advanced research infrastructures for e.g. imaging, electrophysiology and cryo-EM.

2021 marked important transitions in the 9th year of operations at DANDRITE. Group leaders Anne von Philipsborn and Keisuke Yonehara accepted full professorships at the University of Fribourg in Switzerland (from February 2022) and at the National Institute of Genetics in Japan (from October 2021), respectively. Furthermore, DANDRITE initiated new calls for recruitment of group leaders, and group leader Taro Kitazawa will join us from summer 2022, arriving from the FMI-Basel and University of Geneva. Also, tenure track assistant professor Gilles Vanwalleghem (AU-MBG) joined DANDRITE as a Team Leader, and Team Leader Magnus Kjærgaard was appointed associate professor at the Department of Molecular Biology and Genetics and is now an affiliated researcher at DANDRITE. Affiliated researchers as a group currently count 12 tenured researchers at Aarhus University and represent a very important resource and network of how DANDRITE integrates with Danish and international neuroscience.

Covid-19 also challenged our plans and operations in 2021, but we could maintain laboratory work on critical projects and for critical student and postdoc training programs. Despite lock-down early in the year, we managed to gather DANDRITE's community to the Annual Retreat in September at Scandic Bygholm Park in Horsens. Refreshingly, the focus of the Retreat was to restart scientific and social interactions & networking and reviving the community feeling in and around DANDRITE. 87 attended the Retreat, and it was a very happy experience.

DANDRITE organized the 2021 meeting of the Nordic EMBL Partnership for Molecular Medicine, and it was postponed from September 2021 to January 2022 with the hope of having less international travel restrictions and a physical meeting. In the end, it was transformed it into an online event, but although reduced at scale, the meeting was fruitful and well attended. The partnership had its planned rotation of the Speaker, and FIMM director Mark Daly took over the torch in 2021. Our partnership coordinator and communications assistant Annabel Robertson took a great new position in Oslo. Fortunately, Gretchen Repasky, reconnecting with FIMM, could step in as the new partnership coordinator. The Nord-Forsk infrastructure network program of the Nordic EMBL partnership continued operations in 2021 with support for science exchange visits at facilities and training courses.

DANDRITE researchers published many notable papers in 2021 in leading journals. Highlights include for example a first structure of the glycine transporter GlyT1 revealing also a new inhibitory mechanism for neurotransmitter transporters (Shahsavar et al. 2021, *Nature*), and new insights into axon terminal mechanisms for direction selectivity in retinal bipolar cells (Matsumoto et al. 2021, Neuron). Five PhD dissertations were successfully presented and conferred.

Master student Simon Arvin received the 2021 Student Research Prize at the Faculty of Health at Aarhus University, and I myself had the great honor and joy of receiving the 2021 Anders Jahre Prize for Medical Research, awarded by the University of Oslo. Also, many competitive grants were awarded to DANDRITE researchers in 2021. Team Leader/Affiliated Researcher Magnus Kjærgaard was cofounder of an Interdisciplinary Synergy Grant funded by the Novo Nordisk Foundation, Team Leader Hanne Poulsen received a Lundbeck Foundation Experiment Grant as well as an NNF-ODIN grant for research innovation. Also Mark Denham received an ODIN grant, and Sadegh Nabavi a LF-NIH collaboration grant.

Like for 2020, we hosted many online DANDRITE lectures (12 in total) and expect to continue this new tradition along with physical meetings, visits and symposia. Together with NeuroCampus Aarhus, DANDRITE took part in the Brain Awareness Week in March 2021 with an event on Parkinson's disease having more than 800 participants. Following a long tradition, we had yet again a very successful DANDRITE Encounters event in February 2021 with approx. 100 students participating to see the opportunities at DANDRITE for research projects. Although virtual, the feedback was good and researchers showed e.g. experiments and short presentations using the online format.

DANDRITE researchers also gave lectures and talks at many occasions, including several researchers presenting their work to our partnership with the Brain Research Institute at Niigata University. We had a first kick-off of a new research support center DANEMO, which is hosted in the first two years by DANDRITE and with the mission to communicate and strengthen the benefits to Denmark of the EMBL/EMBO membership. The kick-off symposium had more than 150 participants and was co-organized with the "EMBL in Denmark" initiative where EMBL gathers many of their alumni.

We hope you will spend a few moments on the following pages to learn more about our vision and activities and that will enjoy the read.

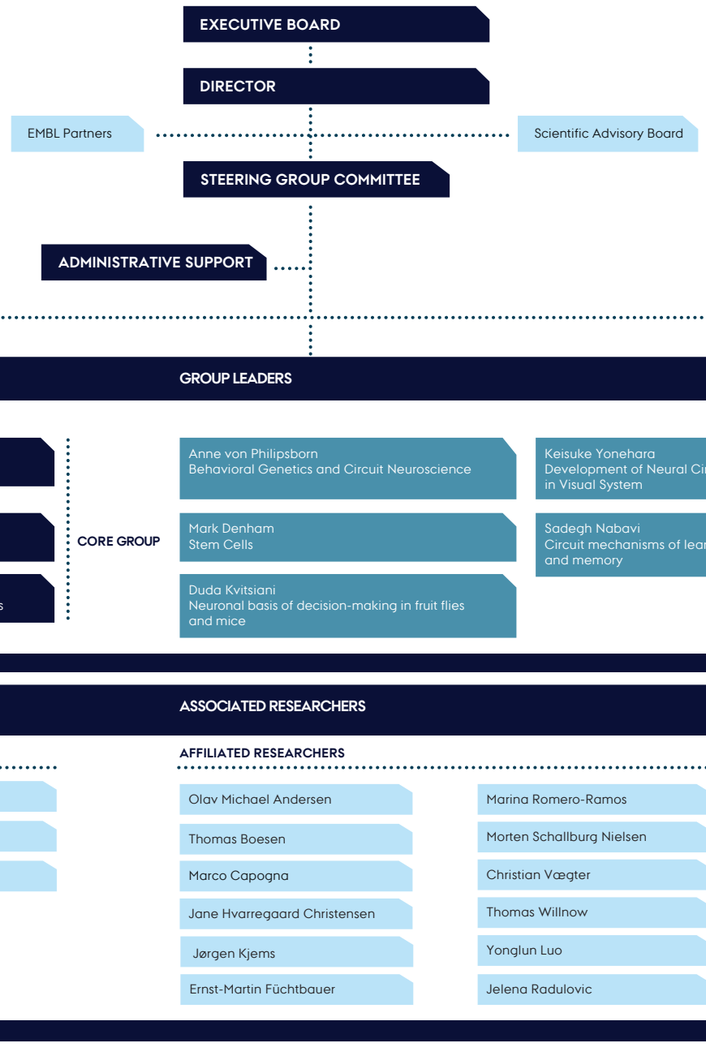
With warm regards,

Poul Nissen, Director and Core Group Leader

01

# Organization Structure

# ORGANIZATION STRUCTURE





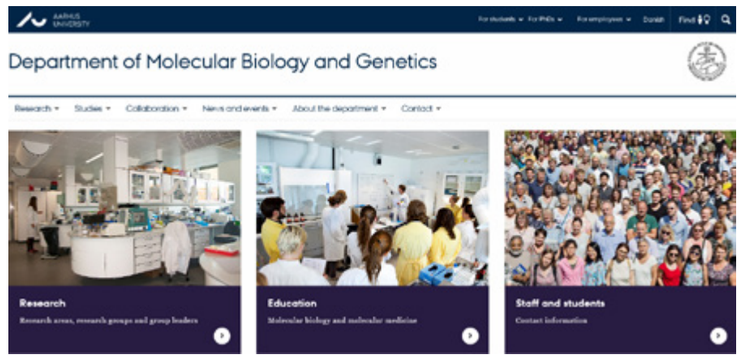

# HOSTING DEPARTMENTS

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 department 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 Dean of the faculty of Natural Sciences and the Vice-Dean of the faculty of Health, the Director, the leaders of the Core Teams, observing representatives from The Lundbeck Foundation, Heads of the two hosting departments, 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)

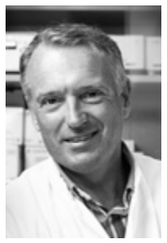
Dean **Kristian Pedersen**, Faculty of Natural Sciences, Aarhus University

Vice-Dean **Hans Erik Bøtker**, Faculty of Health Sciences, Aarhus University

Head of Department **Erik Østergaard**, Department of Molecular Biology and Genetics

Head of Department **Thomas G. Jensen**, Department of Biomedicine

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 second Monday 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 2021 consisted of the following members:

- Professor **Poul Nissen**, Director
- Professor **Anders Nykjær**
- Professor **Poul Henning Jensen**
- Group Leader **Sadegh Nabav**i
- Group Leader **Duda Kvitsiani** (took over from Mark Denham in August)
- Chief Administrative Officer, **Maria Thykær Jensen**

Furthermore, the steering committee meetings are attended by:

- Research Group Coordinator, **Astrid Munk**
- Research Group Coordinator, **Katrine Østerlund Rasmussen**
- Director PA, **Karen Bech**
- Center Administrator (PROMEMO) **Susanne Schousboe Sjøgaard**

MONTHLY EXTENDED STEERING COMMITTEE MEETING
Every other month the steering committee meets for an extended steering committee meeting. The extended committee consists of all Group Leaders and Team leaders, and spokespersons for each personnel category at DANDRITE. In 2021 the participants were:

- All DANDRITE Group Leaders
- All DANDRITE Team Leaders
- Affiliated Researcher spokesperson: **Jørgen Kjems**
- Postdoc Spokesperson: **Gergo Kovacs** (took over from Noemie Mermet-Joret in August)
- PhD student spokesperson: **Lucie Woloszczukova** (took over from Islam Faress in August)
- Technicians spokesperson: **Andreea-Cornelia Udrea** (took over from **Bjarke Thomsen** in August)

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 **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 members who will take part in the planned SAB meeting in June 2022:

- Professor **Cornelius Gross**, Interium Head of EMBL, Rome, Italy
- Professor **Peter Scheiffele**, University of Basel, Switzerland

# 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 8 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 2021, Professor Jelena Radulovic 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 2021, 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.

# 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 2021, YoDA has created a wide variety of events, such as workshops, career cafés and social events. They have been able to readjust according to the ever changing corona situation, and so, many of the events have been a hybrid format. To name a few specific events that YoDA has arranged, there has been a career café with alumni Juliane Martin, a workshop on the online tool 'Biorender' by Assistant Professor Andrea Moreno, an online career café about 'Procrastination in the workplace' by Cathie Edwards and many social activities, such as Friday bar or afternoon picnic in the University Park.

**Current members of the Young DANDRITE organizing committee:**
Meike Sieburg, Postdoc
Katia Soud, PhD student
Karen Marie Juul Sørensen, PhD student
Lucie Woloszczuková, PhD student
Mads Christensen, PhD student
Pia Boxy, Research Assistant
Ea Trond Hvid Jensen, Master student
Kristyna Safrankova, Research Assistant
Nanna Møller Jensen, PhD student

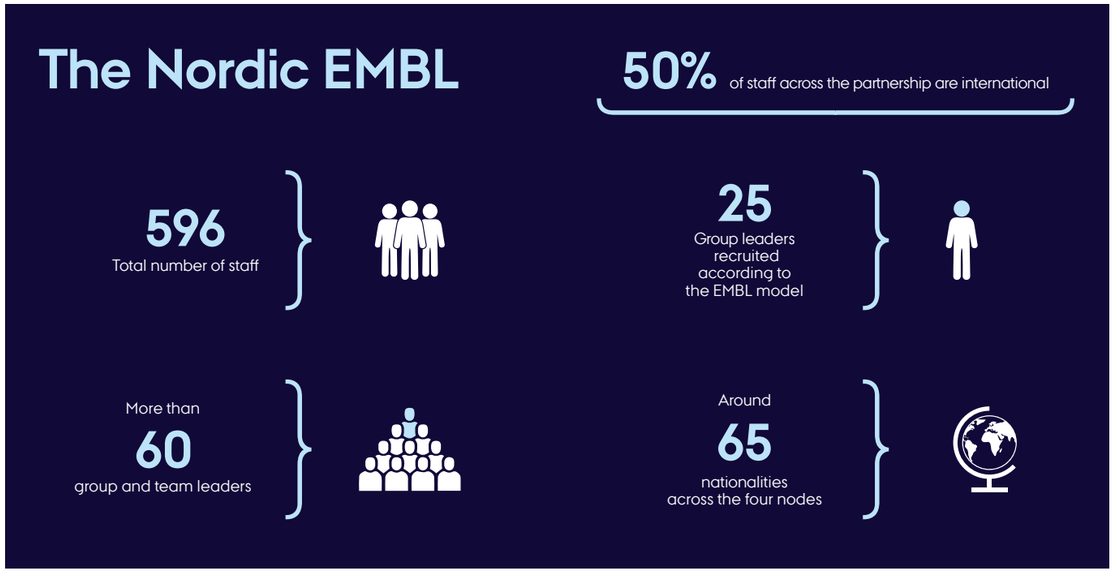
Admin. Support representative: Astrid Munk (Research Group Coordinator)

PhD representative: Lucie Woloszczukova
Postdoc representative: Gergo Kovacs


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.

# PARTNERSHIP HIGHLIGHTS DURING 2021

NordForsk

**NordForsk Infrastructure hub kickoff**
During 2021, the Nordic EMBL Partnership initiated the infrastructure hub activities funded by NordForsk. Due to strict Covid-19 travel restrictions and the pandemic, it has been very difficult to execute exchange visits within the Nordic Partnership. Instead, the partnership had to find ways to interact and collaborate in the virtual space thus, in 2021, the Hub offered five research infrastructure-related courses with more than 270 total registrants out of which162 were affiliated to the Nordic EMBL Partnership. Virtual formats of courses and meetings were a good starting point as they allowed for more attendees who could gain a theoretical knowledge. Below we highlight two courses with great attendance from all Nordic partners namely the PhD course in Molecular medicine and the Building Bridges 2021. NordForsk supported both courses via the NordForsk Research Infrastructure hub funding for the years 2021-2023. ■

Gretchen Repasky. Photo: Kalle Kallio

**New Nordic EMBL Partnership Communications Director**
As of September 2021 Gretchen Repasky joined the Nordic EMBL Partnership in the role of Communications Director. Gretchen has a background in cancer biology research, research training and teaching. She previously held Chief Operating Officer positions at the Novo Nordisk Foundation Center for Stem Cell Biology in Copenhagen, Denmark and Elevate Scientific Academy in Malmö, Sweden. Prior to these roles she was a senior researcher and research training coordinator at our sister institute, Institute for Molecular Medicine Finland for eight years, following a research and undergraduate teaching career in the United States.

As Communications Director, Gretchen will work to increase the visibility of the vibrant Nordic research environment, showcasing research and technology advances. She will also engage with scientists and staff within the Partnership to build collaborations, raise awareness of opportunities among the Nordic EMBL nodes, and promote knowledge exchange and mobility. She will also support EMBL with its wider communications objectives with particular focus on the Nordics. ■

PhD Student Alex Harvey (DANDRITE) in Oslo Science Park, Norway. Photo: Larissa Lily

**Building Bridges 2021: Technologies Advancing Molecular Medicine – Focus on Nordic Infrastructures**
The Building Bridges symposium was held on 1 December 2021 and hosted by the Partnership and FIMM. The symposium demonstrated research advances using infrastructure available in the Nordic EMBL Partnership, bridging research and technology development as well as bridging researchers across borders. With an opening and closing keynote from EMBL Heidelberg and EMBL Hamburg, the symposium highlighted research infrastructure at EMBL, as well.

Due to national and international travel and meeting restrictions, the course was converted into a hybrid format with both physical and online attendance. The course had a total of 141 participants, among these 51 from the four nodes within the Partnership. ■

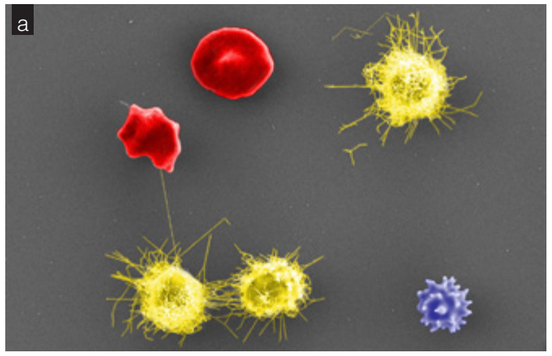
**Knowledge sharing across the Nordics: NCMM hosts national PhD course in Molecular Medicine**
During 8-19 November, NCMM hosted its annual PhD course in Molecular Medicine, strengthening scientific exchange and interactions in the Nordic countries.

38 PhD students registered for the annual intensive course hosted by the Centre for Molecular Medicine Norway (NCMM) at the University of Oslo, Norway. The course featured 44 national and international experts teaching a broad array of molecular medicine topics such as disease mechanisms and models, biobanks and registries, drug discovery, personalized and cell-based therapies, computational biology, and the timely topic of SARS-CoV-2 detection, vaccination and drug targeting. ■

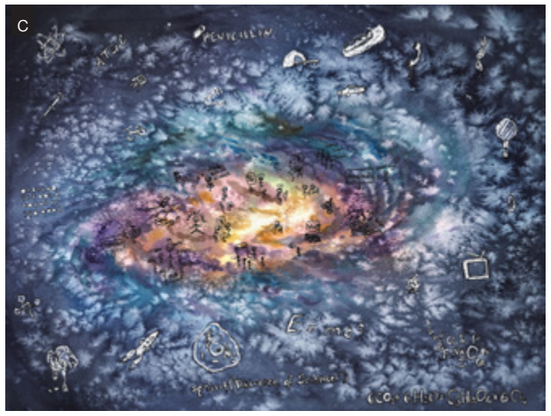


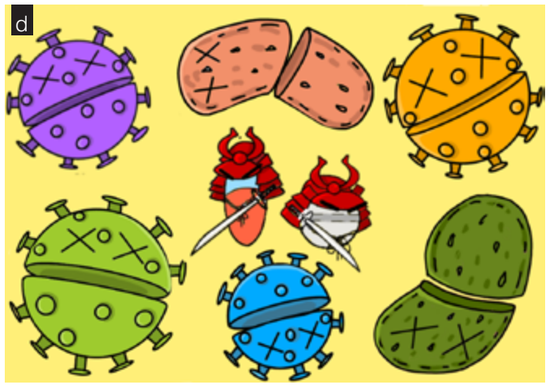
a. Tubulation of human erythrocytes — Annina Preussner (FIMM)
b. We're in this together — Aftab Nadeem (MIMS)
c. Universe of Science — Arina Tagmazian (FIMM)
d. Broad spectrum antiviral drugs fight harmful viruses — Denis Kainov (FIMM)
e. A walk to remember — Andrea Moreno (DANDRITE)
f. Take me to the candy shop — Minttu Polso (FIMM)
g. Clustering of AML Bone marrow mononuclear cells — Romika Kumari (FIMM)
h. Deep Learning Abstractionism — Arina Tagmazian (FIMM)

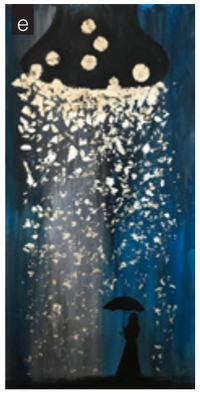
# NORDIC EMBL PARTNERSHIP SCIENCE & ART COMPETITION 2021

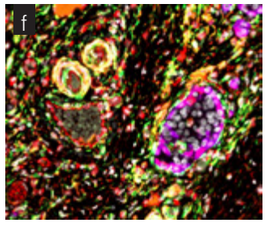




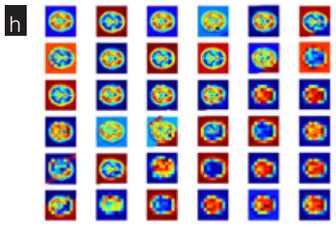






02

# Research Activities

Nissen Group

# Structural Neurobiology

PROMEMO
CENTER FOR PROTEINS IN MEMORY

Professor
**Poul Nissen**

**SELECTED PUBLICATIONS 2021**


Dieudonné T, Herrera SA, Laursen MJ, Lejeune M, Stock C, Slimani K, Jaxel C, Lyons JA, Montigny C, Pomorski TG, Nissen P*, Lenoir G* (2021). Autoinhibition and regulation by phosphoinositides of ATP8B1, a human lipid flippase associated with intrahepatic cholestatic disorder. *BioRxiv* doi: https://doi.rg/10.1101/2021.11.03.467174 – in revision

Neumann C, Rosenbæk LL, Flygaard RK, Habeck M, Karlsen JL, Wang Y, Lindorff-Larsen K, Gad HH, Hartmann R, Lyons JA, Fenton RA, Nissen P (2022). Cryo-EM structure of the human NKCC1 transporter reveals mechanisms of ion coupling and specificity. *BioRxiv* doi: https://doi.org/10.1101/2021.11.11.468215 – *in revision*

Nielsen JA, Brandt J, Boesen T, Hummelshøj T, Slaaby R, Schluckebier G, Nissen P (2022). Structural investigations of full-length insulin receptor dynamics and signalling. *J Mol Biol* 434:167458. doi: https://doi.org/10.1016/j.mb.2022.167458

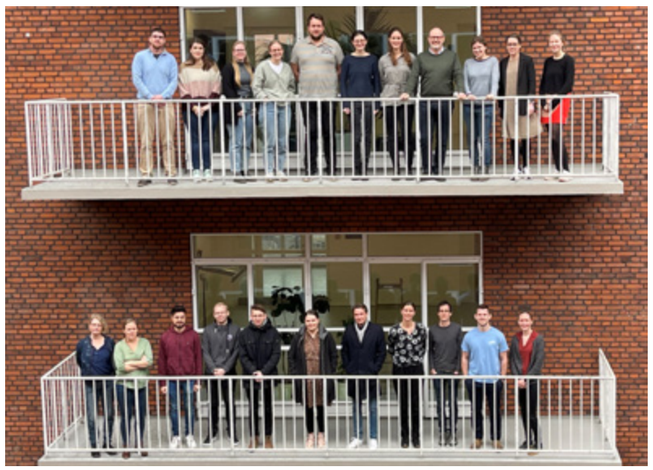
Quistgaard EM, Nissen JD, Hansen S, Nissen P (2021). Mind the Gap: Molecular Architecture of the Axon Initial Segment – From Fold Prediction to a Mechanistic Model of Function? *J Mol Biol* 433:167176 https://doi.org/10.1016/j.jmb.2021.167176


The Nissen lab focuses on the structural biology of membrane transporters and receptors in neurobiology and also neuronal membrane ultrastructure. The laboratory uses primarily cryo-electron microscopy (cryo-EM) with single-particle analysis and cryo-electron tomography. Furthermore, biochemistry/biophysics, bioinformatics, protein crystallography, and collaborative studies through e.g. molecular dynamics simulations, fluorescence microscopy, and electrophysiology are employed. New directions of research go towards super-resolution imaging and correlative light and electron microscopy (CLEM) for tomography. Main subjects include ion pumps, polyamine transporters and lipid flippases of the P-type ATPase family, Na+ dependent transporters of neurotransmitters, phosphate and and chloride, and receptors controlling trafficking and metabolism in brain. Derived activities include also structure based drug discovery. A major, long-term goal is to model higher-order networks and mechanisms in the Axon Initial Segment that integrate circuit inputs and generate action potentials (Quistgaard et al. 2021). Furthermore, synaptic structures associated with memory and learning, and molecular mechanisms underlying direction sensitivity in the visual system are being investigated.

In 2021, many cryo-EM projects from the past years reached final stages for dissemination, and in part also based on important new infrastructures for protein production in mammalian cells.

New insights on Na+ dependent and potentially Cl- sensory regulation of SLC12 NKCC/KCC chloride transporters were obtained through a combination of cryo-EM structure determination of full-length human NKCC1, mechanistic studies with mutant forms in cellular uptake assays, and MD simulations of the intracellular ion release mechanism (Neumann et al. 2021).

Cryo-EM studies and biochemical studies also provided a detailed insight into the structure and autoinhibitory mechanism of the human flippase ATP8B1 in complex with its chaperone CDC50A (Dieudonné et al. 2021). The autoinhibitory function of the N- and C-terminal tails, and the activation by regulatory phosphoinositide lipids (PIP, PIP2 and PIP3), N- and C-terminal truncations, C-terminal phosphorylation, and peptide-based inhibition mimicking the C-terminal tail reveal many new potential target sites of intervention for both inhibition and activation of this important lipid flippase system.



Nissen group members

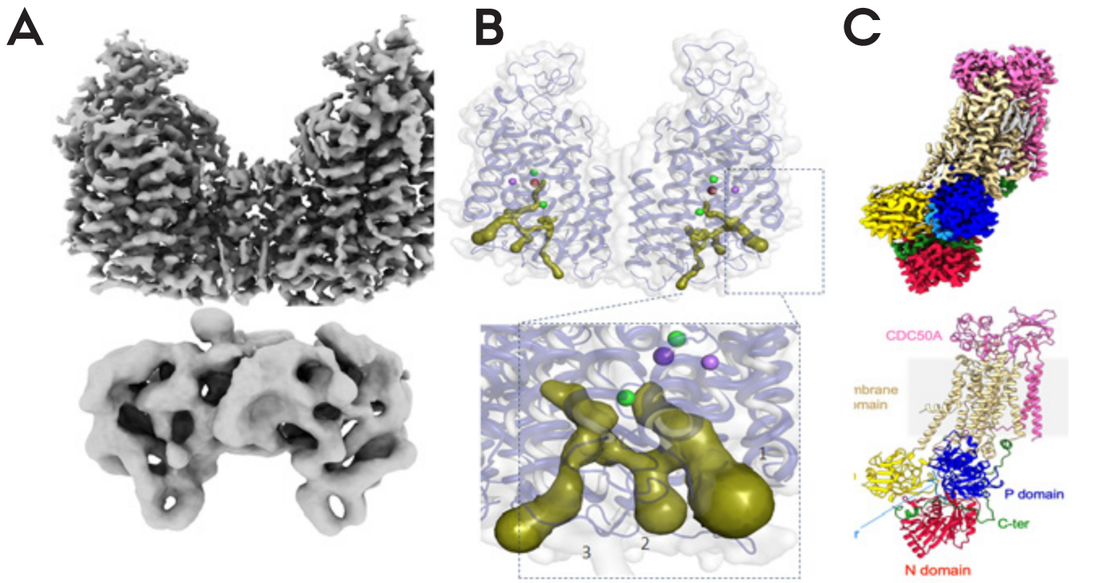



**Figure 1:** Cryo-EM structures from the Nissen group 2021.

**A.** Human NKCC1 dimer showing a well-defined structure for the transmembrane domain (top, about 2.6 Å resolution), and a flexible, low-resolution structure for the cytoplasmic domains (bottom, about 8 Å resolution).

**B.** Ion binding sites and cytoplasmic solvent and ion release pathways of hNKCC1 (*green*: Cl- sites 1 and 2, *deep purple*: K+, *light purple*: Na+, *olive green*: 3 solvent pathways leading to the cytoplasmic environment).

**C.** The human lipid flippase ATP8B1-CDC50 (multiple colors for subunits/domains, *cyan*: autoregulatory N-terminal tail, *green*: autoregulatory C-terminal tail). Solvent pathways and interaction sites of autoregulatory elements shown in panels B and C represent attractive target sites for modulatory compounds in drug discovery. Panels A and B were kindly provided by Drs. Caroline Neumann and Rasmus K. Flygaard, and panel C by master student Michelle Laursen and MSC fellow Thibaud Dieudonné.

Furthermore, we completed a cryo-EM study and functional studies of the full-length human insulin receptor and its activation at physiological levels of insulin yielding dynamic, highly asymmetric structures with 3 and 2 insulins bound to the receptor dimer (Nielsen et al. 2022).

TRANSLATIONAL STUDIES

The new insights into NKCC1 and ATP8B1 function and mechanisms invite new translational studies in drug discovery targeting the allosteric sites of regulation. Chloride gradients defined by e.g. NKCC1 function are of key importance for regulation of the membrane potential and the activity of Cl- conducting GABA/Glycine receptors. Furthermore, we investigate ATP8B1 phosphorylation as a biomarker in relation to liver diseases (PFIC) and neurodegenerative disorders implicating lipid flippase activity. Finally, the new insights into highly asymmetric insulin receptor complexes invoke many new studies of coreceptor complexes and how they may interfere with insulin signaling and direct it to specific cellular localizations.

**PERSONNEL LIST NISSEN GROUP**

Assistant Professor **Esben Quistgaard**
Assistant Professor **Azadeh Shahsavar**
Assistant Professor **Michael Habeck**
Guest researcher **Antoni Kowalski**
Postdoc **Charlott Stock**
Postdoc **Rasmus Kock Flygaard**
Postdoc **Thibaud Louis Dieudonné**
Postdoc **Louise Laursen**
Postdoc **Ronja Driller**
Postdoc **Sigrid Thirup Larsen**
Postdoc **Joao Carlos Moreno Ramos**
Postdoc **Samuel John Hjorth-Jensen**
Postdoc **Caroline Marie Teresa Neumann**
Industriel PhD Student **Jeppe Achton Nielsen**
PhD Student **Clara Nautrup Pedersen**
PhD Student **Alex Cameron Harvey**
PhD Student **Jonathan Juhl**
PhD Student **Josephine Dannersø Nissen**
PhD Student **Line Marie Christiansen**
PhD Student **Mads Eskesen Christensen**
PhD Student **Marlene Uglebjerg Fruergaard**
PhD Student **Sara Basse Hansen**
PhD Student **Sofia Trampari**
PhD Student **Sean Hansen**
PhD Student **Tomáš Heger**
Research Assistant **Christine Juul Fælled Nielsen**
Research Assistant **Gülberk Bayraktar**
Research Assistant **Kirstine Agnethe Hansen**
Research Assistant **Michelle Juknaviciute Laursen**
Laboratory Technician **Anna Marie Nielsen**
Laboratory Technician **Tanja Klymchuk**
Laboratory Technician **Bente Andersen**
Laboratory Technician **Dorthe Strandbygård**
Laboratory Trainee **Mikkel Juul Thomsen**
Laboratory Trainee **Mads Benjamin Nielsen**
Laboratory Trainee **Sofie Møller Bonde Larsen**
Academic employee **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**

**PERSONNEL LIST JENSEN GROUP**
Assistant Professor **Nelson Ferreira**
Postdoc **Asad Jan**
Postdoc **Lasse Reimer**
Postdoc **Gergo Kovacs**
PhD Student **Emil Gregersen**
PhD student **Hjalte Gram**
PhD student **Nanna Møller Jensen**
Bioanalyst **Jette Bank Lauridsen**
Lab technician **Benedicte Vestergaard**
M. Sc student **Marina Lopez Incera** (Maastricht University)
M. Sc. Student **Vasilis Theologidis** (Democritus University of Thrace)
M. Sc. Student **Anna Fabing Philina**, (University of Salzburg)
Group Leader, Professor **Poul Henning Jensen**

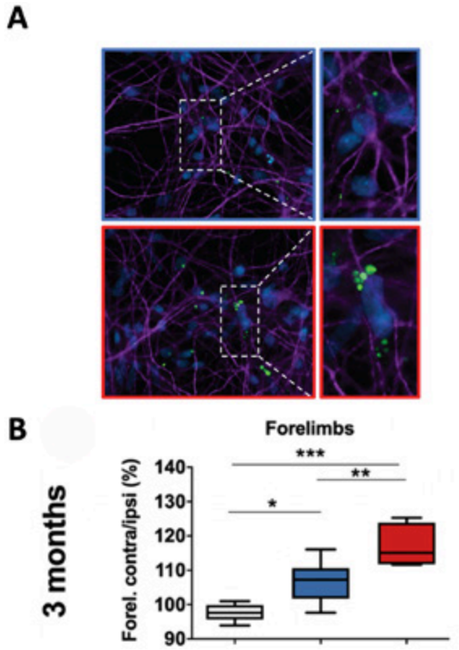
The Jensen group is studying how alpha-synuclein contributes to the neurodegenerative processes in Parkinson's disease, Lewy body dementia and multiple systems atrophy, which are hallmarked by prion-like spreading of intracellular aggregates of the protein alpha-synuclein in the nervous system. This 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. The group is diverse with Danish and international members ranging from lab technicians, postdocs, ph.d. students, research assistants, master-, bachelor-, and exchange-students. Projects are often conducted in national and international collaborations.

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 with a particular focus on calcium signalling and endoplasmic reticulum. This project is partly funded by the Lundbeck Foundation.
- Investigation of the endoplasmic reticulum calcium pump SERCA as a preclinical drug target in Parkinson's disease and other synucleinopathies. This project is conducted in collaboration with Novo Nordic Foundation Distinguished Innovator Claus E. Olesen and tests drug leads in cell and in vivo models.
- How disease-, cell- and environmental factors are contributing to the generation of specific folding strains of alpha-synuclein aggregates and how the different strains contribute to cell and tissue dysfunctions. We are both working with engineered prototype strains and novel human patient-derived alpha-synuclein strains. These projects are partly funded by the Michael J. Fox Foundation and the collaborative EU funded Joint Programme in Neurodegenerative Diseases "OligoFIT".
- Collaborative project with prof. Per Borghammer, Aarhus University Hospital on developing and applying methods to amplify alpha-synuclein strains directly from clinical biosamples.
- New antibody-based methods developed with the aim of identifying, quantifying and characterizing novel alpha-synuclein-based pathology in cells, brain tissue and biofluids from human patients and in vivo models. These projects are partly funded by the Michael J. Fox Foundation.

Jensen group members





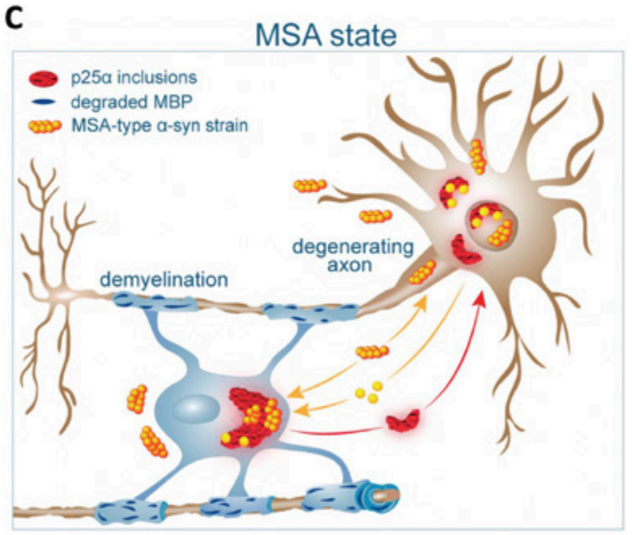




**Figure 1: Alpha-synuclein aggregates exerts strains specific functional impacts on cells and animal models. C)** We hypothesised the oligodendroglial protein p25α facilitates formation of a toxic alpha-synuclein aggregate associated to the severe disease multiple systems atrophy (MSA). Model was made by assistant professor Mette Richter, Aarhus University. **A)** Treatment of human dopamine producing neurons with control (blue) and p25α-induced aggregates (red) resulted in generation of different cellular alpha-synuclein aggregate inclusions. The human neurons were cultivated by prof. Morten Meyer, University of Southern Denmark. **B)** Injection of the two types of aggregates into the striatum of wild type mice resulted in a more severe motoric phenotype in those receiving p25α-induced aggregates (red) compared to the control (blue) injected mice. Controls injected with monomer alpha-synuclein is presented in white. The in vivo study was conducted in collaboration with assoc. professor Marina Romero-Ramos, Aarhus University. All figures are from Ferreira et al., Acta Neuropatholocica, 14:87-115

**SELECTED PUBLICATIONS**

Cui H, Kilpeläinen T, Zouzoula L, Auno S, Trontti K, Kurvonen S, Norrbacka S, Hovatta I, Jensen PH, Myöhänen TT. (2021) Prolyl oligopeptidase inhibition reduces alpha-synuclein aggregation in a cellular model of multiple system atrophy. *J Cell Mol Med.* 25(20):9634-9646. doi: 10.1111/jcmm.16910. Epub 2021 Sep 5. PMID: 34486218; PMCID: PMC8505845.

Sara Elfarrash, Nanna Møller Jensen, Nelson Ferreira, Sissel Ida Schmidt, Emil Gregersen, Marie Vibeke Vestergaard, Sadegh Nabavi, Morten Meyer, Poul Henning Jensen (2021) Polo-like kinase 2 inhibition reduces serine-129 phosphorylation of physiological nuclear alpha-synuclein but not of the aggregated alpha-synuclein. *PlosOne*, 16(10): e0252635

Laura M. Vecchio, Emil Gregersen, Amy Dunn, Shababa Masoud, M. Kristel Bermejo, Marija Milenkovic, Rong Hu, Nikhil Urs, Reza Nazari, Amy Ramsey, Gary W. Miller, Poul Henning Jensen, Ali Salahpour (2021) Enhanced tyrosine hydroxylase activity induces oxidative stress, causes accumulation of autotoxic catecholamine metabolites, and augments amphetamine effects in vivo *J. Neurochem.* 158(4):960-979. doi: 10.1111/jnc.15432

Emil Gregersen, Cristine Betzer, Woojin S. Kim, Gergo Kovacs, Lasse Reimer, Glenda M. Halliday, Steffen Thiel and Poul Henning Jensen (2021) Alpha-synuclein activates the classical complement pathway and mediates complement-dependent cell toxicity *Journal of Neuroinflammation*, 16;18(1):177. doi: 10.1186/s12974-021-02225-9

Alberto Delaidelli; Mette Richner; Lixiang Jiang; Amelia van der Laan; Ida Bergholdt Jul Christiansen; Nelson Ferreira; Jens R Nyengaard; Christian B Vægter; Poul H Jensen; Ian R Mackenzie; Poul H Sorensen; Asad Jan (2021) α-Synuclein pathology in Parkinson disease activates homeostatic NRF2 anti-oxidant response. *Acta Neuropathologica Communications*, 9(1):105

Van Den Berge N, Ferreira N, Mikkelsen TW, Alstrup AKO, Tamgüney G, Karlsson P, Terkelsen AJ, Nyengaard JR, Jensen PH, Borghammer P. (2021) Ageing promotes pathological alpha-synuclein propagation and autonomic dysfunction in wild-type rats. *Brain*. awab061. doi: 10.1093/brain/awab061.

Nelson Ferreira, Hjalte Gram, Zachary A. Sorrentino, Emil Gregersen, Sissel Ida Schmidt, Cristine Betzer, Clara Perez-Gozalbo, Marjo Beltoja, Madhu Nagaraj, Jie Wang, Jan S. Nowak,Mingdong Dong, Kaare Bjerregaard-Andersen, Daniel E. Otzen, Ümit Akbey, Morten Meyer, Benoit I. Giasson, Marina Romero-Ramos, Poul Henning Jensen (2021) Multiple system atrophy-associated oligodendroglial protein p25α stimulates formation of novel α-synuclein strain with enhanced neurodegenerative potential. *Acta Neuropatholocica*, 142(1):87-115

Nelson Ferreira, Mette Richner, Amelia van der Laan, Ida Bergholdt Jul Christiansen, Christian B. Vægter, Jens R. Nyengaard, Glenda M. Halliday, Joachim Weiss, Benoit I. Giasson, Ian R. Mackenzie, Poul H. Jensen, Asad Jan (2021) Prodromal neuroinvasion of pathological A-synuclein in brainstem reticular nuclei and white matter lesions in a model of α-synucleinopathy. *Brain Communications*, fcab104, https://doi.org/10.1093/braincomms/fcab104

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*, 9(1):31

Nykjær Group

PROMEMO
CENTER FOR PROTEINS IN MEMORY

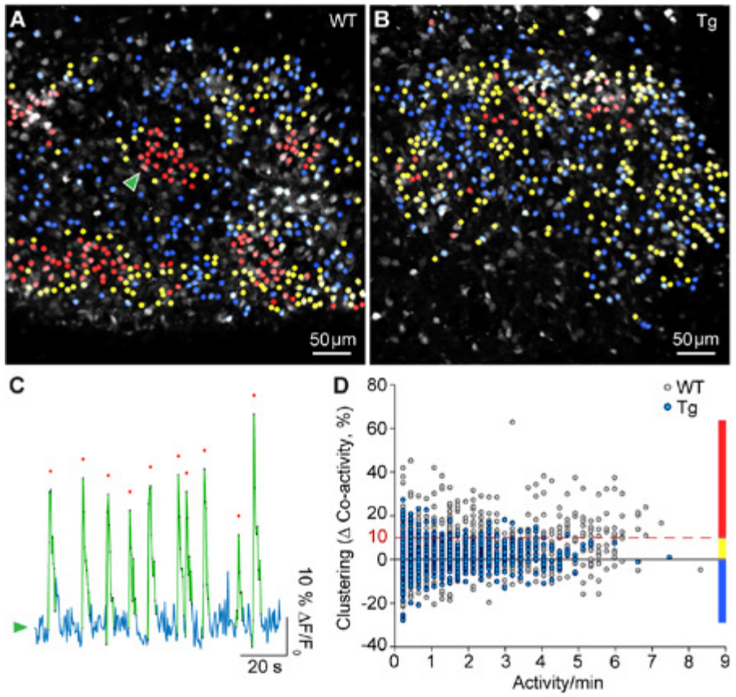
# Receptors in mental disorders and memory

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 engage in cellular trafficking and signaling of a number of ligands including neurotrophins, receptor tyrosine kinases, morphogens, amyloid precursor protein, progranulin, and neurotransmitter receptors. Accordingly, sortilin receptors have surfaced as risk genes in both psychiatric, neurological, and metabolic diseases.

We aim to understand the molecular mechanism by which the receptors control neurodevelopment, neuronal integrity, 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, mouse behavioral testing, calcium imaging to study neuronal network activity, electrophysiology, transcriptomics and proteomics, cell biology and imaging techniques. Through collaborations, our studies also incorporate human genetics.




Activity patterns of granule cells in mouse hippocampus. Granule cells in wild-type hippocampus **(A)** are significantly more co-active with their neighbors than in slices from transgenic **(B)** mice. **(C)** Automated detection of calcium spikes in a granule cell loaded with OGB-1 AM. **(D)** Co-activity differences between neighboring and distal granule cells as measure of clustered activation. 95% of transgenic granule cells exhibited less than 10% difference in co-activity (n = 1394 cells (WT), n = 1063 cells (Tg)).

Memory is the single most important brain process that determines our personality. Some experiences we remember strongly whereas other instances rapidly fades. 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 SorCS1 and -3 were 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 the SorCS receptors govern memory formation and their possible role(s) in the emotional control via the dopaminergic system.

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 recognized. Recently, sortilin receptors were identified as top-risk genes shared across several psychiatric disorders but the underlying molecular mechanisms remain far from understood. Previously we reported that SorCS2 controls dopaminergic development and most recently we found using single-unit recordings of the ventral tegmental area, 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.



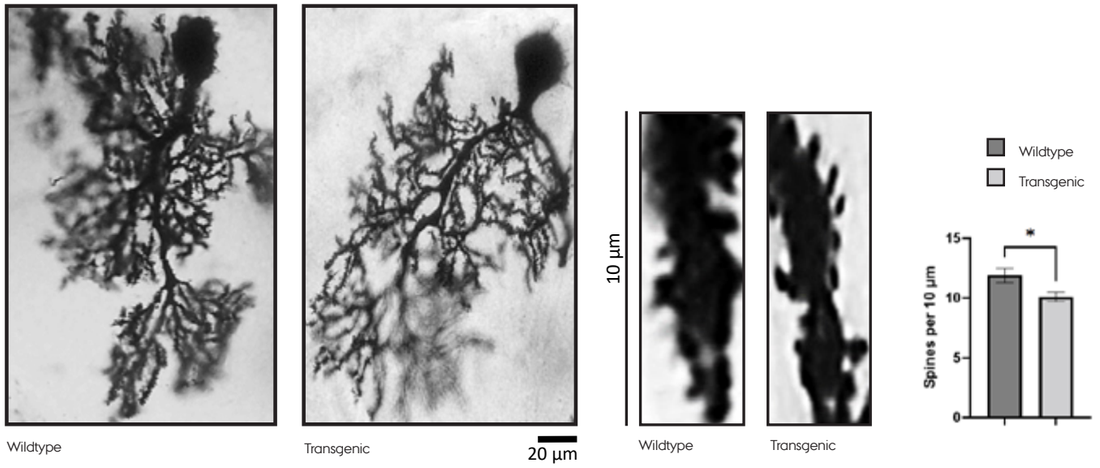



**Fig: SorCS2 single-chain reduces Purkinje cell spine density. A.** Representative images of cerebellar Purkinje neurons and spines of wildtype and transgenic SorCS2 single-chain mice using Golgi-Cox staining. **B.** Quantification of dendritic spine density. 10 neurons were counted per animal (N = 9) per genotype. Data are represented as mean ± SEM. *p < 0.05.

Nykjær group members.

**SELECTED PUBLICATIONS**

Ditte Olsen, Niels Wellner, Mathias Kaas, Inge E. M. de Jong, Florence Sotty, Michael Didriksen, Simon Glerup, Anders Nykjaer. Altered dopaminergic firing pattern and novelty response underlie ADHD-like behavior of SorCS2-deficient mice. *Transl. Psych.*, 2021 Jan 25; 11(1):74.

Loof Møller, P., Rohde, P. D., Winther, S., Breining, P., Nissen, L., Nykjaer, A., Bøttcher, M., Nyegaard, M., & Kjolby, M. (2021). Sortilin as a Biomarker for Cardiovascular Disease Revisited. *Frontiers in Cardiovascular Medicine*. 16 April 2021.

Monti G, Kjolby M, Jensen AMG, Allen M, Reiche J, Møller PL, Comaposada-Baró R, Zolkowski BE, Vieira C, Jørgensen MM, Holm IE, Valdmanis PN, Wellner N, Vægter CB, Lincoln SJ, Nykjær A, Ertekin-Taner N, Young JE, Nyegaard M, Andersen OM. Expression of an alternatively spliced variant of SORL1 in neuronal dendrites is decreased in patients with Alzheimer's disease. *Acta Neuropathol Commun.* 2021 Mar 16;9(1):43.

Niels Sanderhoff Degn, Alena Salašová, Niels Kjærsgaard Madsen, Mikhail Paveliev, Lucie Woloszczuková, Peter Lund Olesen, Mads Fuglsang Kjølby, Kristian Skipper Alsberg, Sune Skeldal, Saray López Benito, Anne Kathrine Aalling Sørensen, Islam Faress, Sadegh Nabavi, Juan Carlos Arévalo, Ulrik Bølcho, Anders Nykjaer. SorCS2 modifies Huntington's disease by regulating striatal BDNF signaling and plasticity. *BioRxiv*, online 16 November 2021.

**PERSONNEL LIST NYKJÆR GROUP**

Assistant Professor **Dongik Park**
Assistant Professor **Lilian Kisiswa**
Postdoc **Alena Salašová**
Postdoc **Dragos Niculescu**
Postdoc **Peter Breining**
Postdoc **Sérgio Eduardo Costa Almeida**
Postdoc **Mikhail Paveliev**
Research Assistant **Kristýna Šafránková**
PhD student **Karen Marie Juul Sørensen**
PhD student **Lucie Woloszczuková**
PhD student **Pia Boxy**
MSc student **Ea Trond Hvid Jensen**
BSc student **Katharina Wolther**
ERASMUS Intern **Tim-Simon Burmeister**
Lab Manager **Stella Solveig Nolte**
Laboratory Technician **Andreea-Cornelia Udrea**
Laboratory Technician **Anne Kerstine Glintborg Jensen**
Academic Employee **Ulrik Bølcho**
Center Manager PROMEMO & PA **Susanne Schousboe Sjøgaard**
Group Leader, Director of PROMEMO, Professor **Anders Nykjær**

Denham Group

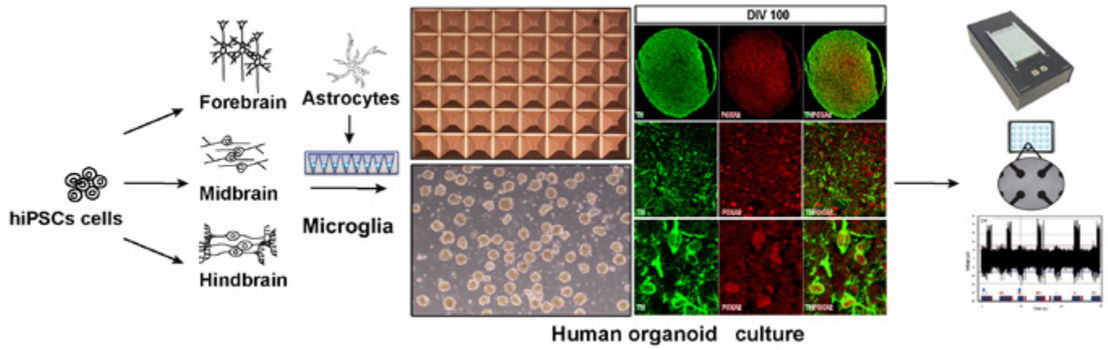
# Stem Cells and Translational Neurobiology

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 differentiation of pluripotent stem cells. They are particularly interested in what factors influence the differentiation of pluripotent stem cells to dopaminergic progenitors and mesencephalic dopaminergic (mDA) neurons. They aim to apply this knowledge to develop novel therapies for Parkinson's disease (PD). Additionally, they are developing a multi-brain region organoid system to overcome the limitations of 2D cultures and provide an enhanced model that recapitulates human development and the complex cellular interplay reflective of the *in vivo* human CNS. The goal is to use this to identify new disease mechanisms or novel drugs for treating PD and other neurodegenerative disorders.

ENGINEERING STEM CELLS TO GENERATE DOPAMINERGIC NEURONS.
We investigate the developmental processes involved in the differentiation of iPSCs into mDA neurons. A robust method for generating mDA neurons from pluripotent stem cells has the potential to be scaled up and used in a cell replacement therapy for PD patients providing a much-needed alternative to current treatments. However, current protocols for generating dopaminergic neurons from iPSCs produce a surprisingly low number – less than 10% – of DA neurons. To address this, our lab has developed a novel method for generating mDA neurons. Using a knockout approach, we delete genes involved in the specification of nondopaminergic lineages; this results in the embryonic stem cells being restricted in the types of cells they can differentiate into, blocking their differentiation down unwanted lineages. We call these lineage-restricted undifferentiated stem cells (LR-USCs). LR-USCs are significantly more efficient at generating DA neurons (Maimaitili et al., 2021). Our laboratory is also applying this to create other cell types relevant to other diseases.

Denham group members.




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 an MEA.

MINIATURISED CONTROLLED ORGANOIDS (MICOS)
Within our lab, we are developing a multi-brain region organoid platform to support the investigation of a broad range of neurological disorders. Traditional organoids are large, develop necrotic centers, and demonstrate inter-organoid structural and cellular variation, which restrains their capacity to be used in a high throughput manner for disease modelling and drug screening. We are developing miniaturised controlled organoids (MiCOs) tailored for a screening platform. Specifically, by miniaturising the organoids and starting with regionally patterned neural progenitors, we can generate organoids with higher reproducibly in their neuronal composition (Figure 1).

Furthermore, we aim to enhance the maturation and mimic *in vivo* cellular diversity by adding astrocytes and microglia progenitors into the organoids. Once formed, the organoids can be kept in vitro for over 100 days. In collaboration with the stem cell team at Novo Nordisk we are comparing *in vitro* derived organoids with *in vivo* mature stem cell-derived 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). Overall, this system will aid in the development of new drug compounds for the treatment of a broad range of neurological disorders. To read more about this project, visit: https://projects.au.dk/odin/scientificscope/funded-odin-projects/mico-platform/

**PUBLICATIONS**

Febbraro, F., Chen, M., and Denham, M. (2021). "Generation of Human iPSCs by Episomal Reprogramming of Skin Fibroblasts and Peripheral Blood Mononuclear Cells," in, 135–151.

Habekost, M., Qvist, P., Denham, M., Holm, I. E., and Jørgensen, A. L. (2021). Directly Reprogrammed Neurons Express MAPT and APP Splice Variants Pertinent to Ageing and Neurodegeneration. Mol. Neurobiol.

Maimaitili, M., Chen, M., Febbraro, F., Mermet-Joret, N., Lauritsen, J., Ucuncu, E., et al. (2021). Enhanced Production of Mesencephalic Dopaminergic Neurons from Lineage-Restricted Human Undifferentiated Stem Cells. bioRxiv, 2021.09.28.462222.

**PERSONNEL LIST DENHAM GROUP**

Group leader **Mark Denham**
Assistant Professor **Muwan Chen**
Postdoc **Ekin Ucuncu**
PhD student **Muyesier Maimaitili**
Laboratory Technician S**usanne Hvolbøl Buchholdt**
Laboratory Technician **Sanne Nordestgaard Andersen**
Erasmus Student **Ilaria Rossomanno**
Erasmus Student **Namarta Tolani Wadhwani**

Kvitsiani Group

# Neuronal basis of decision-making

Group Leader
**Duda Kvitsiani**

We investigate the neural circuit mechanisms of foraging decisions in flies, mice and humans. The methods we use include, psychophysics, behavioral electrophysiology, optogenetics and computational modeling.

To characterize behavior we build predictive and quantitative models that help us capture key decision variables. In flies we design trial based psychophysics tasks to understand how flies forage in probabilistic environment. Using extracellular electrophysiology and cell-type specific recordings we investigate how neural circuits in prefrontal areas represent decision variables in reward foraging tasks in rodents.

MAJOR ACHIEVEMENTS
In the past, we have studied probabilistic reward foraging decisions in fruit flies using closed loop optogenetic reward delivery system. Using this system in combination with reinforcement learning models we discovered that flies forget value of unchosen options and combine navigation strategies with learned values of available options. This work was published in PLOS One.

In mice and humans using probabilistic reward foraging task (Fig.1) we discovered that animals rely both on their past reward and choice history to optimize the reward harvesting efficiency. Using normative framework we

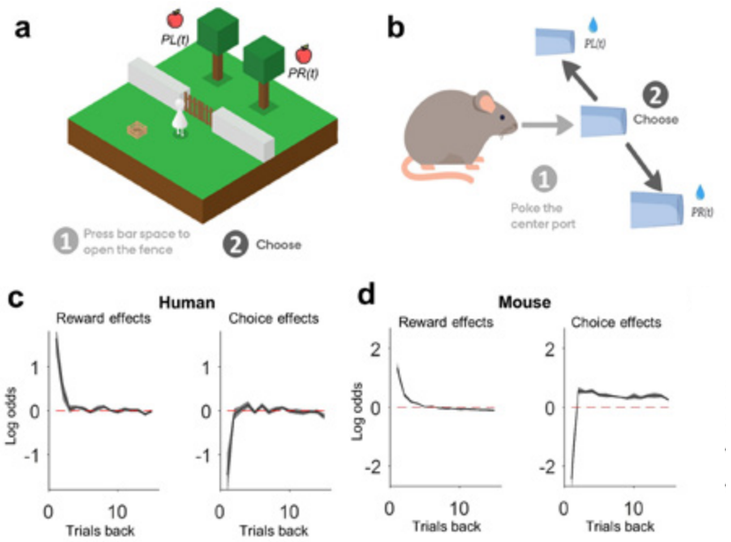



**Figure 1. Choice and reward history effects in a reward foraging task.**
**a**. Snapshot of the computer game played by the human participants. The subjects had to wait between 0s and 5s after opening a virtual fence by pressing on a keyboard before making the decision to press on the left or right 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 (a) and (b), the reinforcements are assigned probabilistically to the options independent of whether or not an animal visits that option in the given trial, and it remains to be collected until choice is made to that option. The influence of past rewards and choices on the current choice for humans c and mice **d.**

**KEY 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.



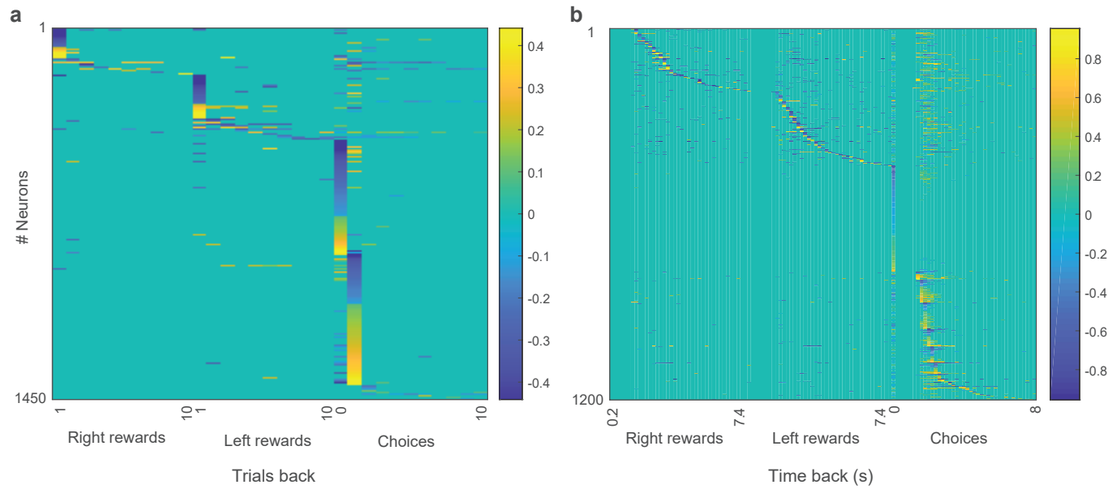



**Figure 2. Reward and choice history representations in a reward foraging task.**
Firing rate of electrophysiologically recorded single units in mPFC was regressed against past rewards, past and current choices. We only show neurons that passed significance threshold ($p < 0.0001$) in multiple comparison test to avoid false positives. **a.** Shows regression coefficients for past right rewards, past left rewards, current choice (indicated by 0) and past choices for each trial back in history. **b.** Shows the regression coefficients for past rewards and choices separated by time bins of 0.2 seconds. Hot colors indicate positive and cold colors indicate negative regression coefficients. Regression coefficients stay significant for > 2 trials back in history and up to 8 seconds for events in the past.

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. This work was published in PLOS Computational Biology.

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.1) represent perceptual and motoric events (rewards and choices), but not values. We further show that individual neurons encode temporal map of events that is tied to the predictability of those events (Fig.2). The temporal map indicates when past rewards and choices happen with respect to current moment.

FUTURE PLANS, PROJECTS & GOALS
In order to understand cortical computations and the role of single spikes in decision making process we have developed the real-time spike sorting 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.


Kvitsiani group members.

**PERSONNEL LIST KVITSIANI GROUP**

Postdoctoral fellow **Maria Møller Moltesen**
Postdoc **Jesper Hagelskjær**
Postdoc **Junior Samuel López Yépez**
Student assistant **Anna Barta**
Ph.D. student **Tsz Fung Woo**
Group Leader **Duda Kvitsiani**

Nabavi Group

# Circuit mechanisms of learning and memory

PROMEMO
CENTER FOR PROTEINS IN MEMORY

Group Leader
**Sadegh Nabavi**

RESEARCH VISION

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 give a particular emphasize to the types of associative learnings that cannot be reconciled with the currents models that are inspired by in vitro studies.

MAJOR ACHIEVEMENTS

**Memory-producing synaptic plasticity influenced by spatially and temporally removed synaptic plasticity**. Numerous forms of synaptic plasticity have been described but their relation to memory is poorly understood. Here we show that the stability of a memory produced by synaptic plasticity at one input can be influenced by plasticity occurring several minutes later at an independent input. By pairing a weak foot-shock with stimulation of a thalamic input to the amygdala, we produced an associative fear memory that decayed within 24hr. However, this memory decay was prevented if 15 minutes after thalamic conditioning, a high frequency stimulus (HFS) was delivered to cortical inputs targeting the same set of amygdala neurons.
Interestingly, the cross-synaptic effect was not exclusive to an associative form of memory as a mere foot-shock produced a long-lasting aversive response to a thalamic input if followed by HFS of a cortical input. In vivo electrophysiological recordings confirmed corroborated our behavioral findings. Thus, our studies indicate that the plasticity of synapses controlling memories can be influenced by plasticity at synapses that are spatially and temporally removed.

**Innate and Learned Fear within the thalamic-amygdala pathway:** The main purpose of the brain is not learning, but to predict; learning is just one mean to that end. The case in point is our sense of detecting dangers. The brain can predict a danger either by learning (fire smoke) or innately (the sight of a snake). Learning is done through synaptic plasticity. Detecting an innate threat, on the other hand, requires no plasticity but an already hard-wired circuit. This difference in design seems to preclude the coexistence of the two types of circuits within the same brain region.

Contradicting this view, our data show that the circuit for innate fear response to a looming overhead in part relies on the neuronal activity within the thalamic- amygdala pathway, a brain region that has been known for many decades as the hub for learning fear. This raises a number of intriguing questions: For example, how do two pieces of qualitatively different information, one signaling a neutral stimulus such as a tone, the other a predator, activate the same pathway, and yet cause the animal to response appropriately.

Personnel List Nabavi Group

Lab manager **Kathrine Meinecke Christensen**
Lab manager **Anne-Katrine Vestergaard**
Lab manager **Randi Hald Melsen**
Postdoc **João Lima**
Postdoc **Noëmie Mermet-Joret**
Postdoc **Andrea Moreno**
postdoc **Milad Nazari**
PhD student **Islam Moustafa Galal Faress**
PhD student **Valentina Khalil**
PhD student **Mariam Gamaleldin**
Visiting M.Sc. student **Alejo Mosqueira**
Traniee **Leonardo Mani**
Traniee **Sanaz Ansarifar**
Group Leader **Sadegh Nabavi**



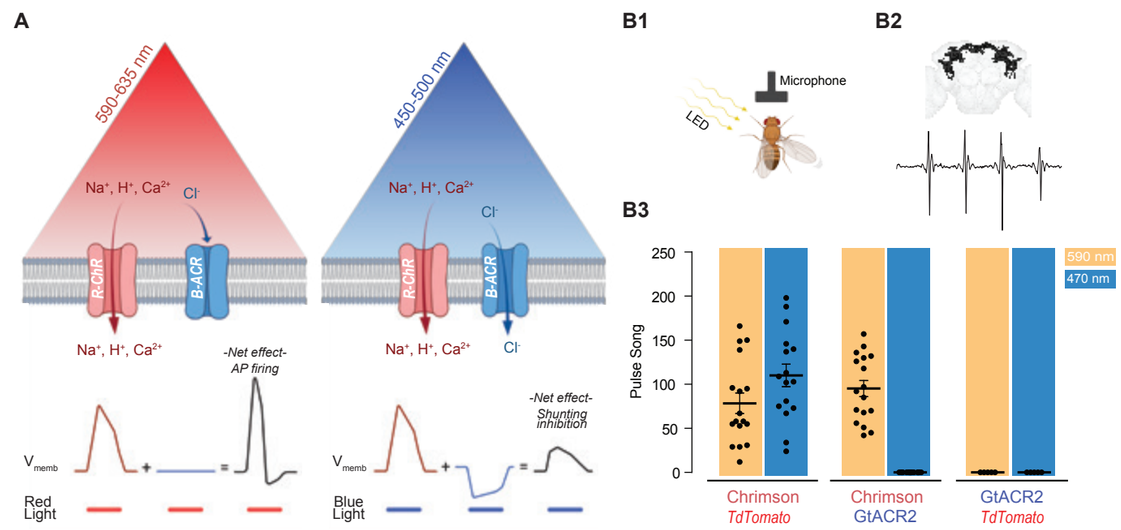



**Figure 1:** Reducing blue-light mediated excitation by red-shifted channelrhodopsins- Proof of concept. (A) Schematic representation of the approach. A red-shifted channelrhodopsin (R-ChR) is co-expressed with a blue-shifted anion channel (B-ACR). When red light is ON, there is an overall excitation of the cell due to the more dominant R-ChR response. When blue-light is ON, the shunting inhibitory effect of B-ACR reduces the excitation induced by R-ChR to blue light. (B) Validation of the approach in flies expressing Chrimson, Chrimson and GtACR2, or GtACR2 alone. (B1) Experimental setup to record the courtship song of solitary male flies. (B2) Top, Example of a reconstructed neuronal arborization of P1 neurons, Bottom, example of a courtship song induced by LED pulses. (B3) Courtship song production of the solitary male flies during 10-sec of constant illumination with 590 nm (amber) or 470 nm (blue) light. Each dot represents an individual (mean ± SEM). **Source:** Mermet-Joret, N., Moreno, A., Zbela, A., Eyjólfsson Ellendersen, B., Krauth, N., von Philipsborn, A., Piriz, J., Lin, J.Y., Nabavi, S. (2021). Dual-Color Optical Activation and Suppression of Neurons with High Temporal Precision. bioRxiv 2021.05.05.442824

We complement this by using single cell calcium imaging in freely moving mice in the amygdala to monitor neuronal activity during innate and learned defensive response. This should reveal whether the two qualitative defensive responses are encoded by distinct or overlapping neuronal populations.

**Tracing the Plasticity of Associative Learning on a Behavioral Timescale.** A fundamental, yet unresolved question in the field of learning is how the brain associates events separated in time. This requires the brain to maintain the trace of the first event until the arrival of the next event, seconds later; and yet synaptic plasticity runs on the scale of milliseconds. We are performing in vivo electrophysiology in mice undergoing trace fear conditioning, an associative learning wherein two events- the tone and shock- are separated by many seconds.

To monitor synaptic changes that may mediate the formation as well as the recall of the memory, we (i) identify putative mono-synaptic connections and measure short-term and long-term changes in synaptic strength, and (ii) study learning-induced changes in time-locked neuronal activity to task-relevant stimuli (neuronal representation).

We complement our *in vivo* electrophysiology with large-scale, single-cell calcium imaging. In one hand, *in vivo* electrophysiology detects firing rates and reveals mono-synaptic connections; on the other hand, single-cell calcium imaging can capture the activity of a large number of neurons for a long period of time.

**Synaptic Mechanisms Underlying Memory Decay.** In this project we test the hypothesis that synaptic depotentiation may underly some forms of memory decay. For this purpose, we established a protocol for an associative form of fear memory which decays within a week (measured by animals' freezing response to a cue). We argued, if synaptic depotentiation is the cause of the memory decay, LTP induction on the corresponding synapses should recover the memory.

This is indeed what we have observed. Mice tested 24hrs after the fear conditioning show a robust freezing response, which decays within a week. Subsequent LTP induction in these mice restores the freezing response which is immediate s well as lasting (at least until the next day).

To correlate the behavior with synaptic strength, currently we are doing in vivo electrophysiology in freely moving mice.

Submitted work: Dual-Color Optical Activation and Suppression of Neurons with High Temporal Precision

Philipsborn Group

# Neuronal circuits for reproductive behavior

Group Leader
**Anne von Philipsborn**

Philipsborn group members.

**2020 PUBLICATIONS**

B, Swain and A.C. von Philipsborn (2021); Sound production in Drosophila melanogaster: Behaviour and neurobiology, Advances in Insect Physiology 61, 141-187. https://doi.org/10.1016/bs.aiip.2021.08.001

N. Mermet-Joret, A. Moreno, A, Zbela, B. E. Ellendersen, N. Krauth, A. von Philipsborn, J. Piriz, J. Y. Lin, S. Nabavi, Dual-color optical activation and suppression of neurons with high temporal precision, bioRxiv 2021.05.05.442824. https://doi.org/10.1101/2021.05.05.442824

**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**
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. Brains interact with the rest of the body, and animals communicate and coordinate their behavior, especially during reproduction.

We study sexual behavior in *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. Both male and female flies generate a variety of signals by vibrating their wings, reacting to external stimuli and communicating their internal state (Figure 1, reviewed in: Swain and von Philipsborn 2021). 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 (Figure 2). 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.

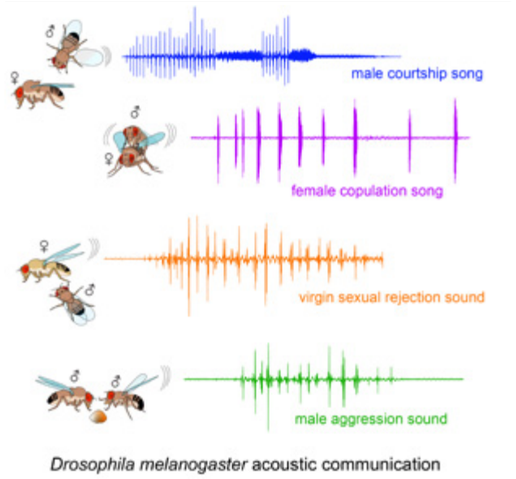



**Figure 1: Acoustic communication in *Drosophila*.**
Male and female flies generate different acoustic signals during reproduction. (modified from Swain and von Philipsborn, Advances in Insect Physiology 2021)

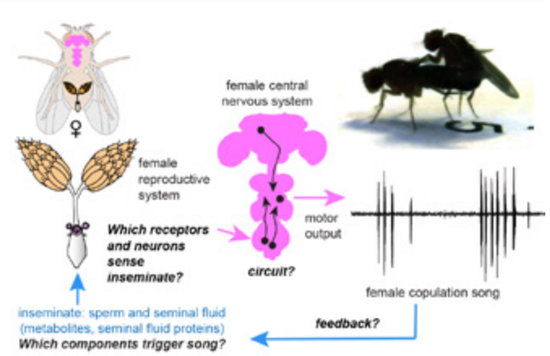



**Figure 2: Female copulation song in *Drosophila*: a new behavior raising many new questions.**
Female song depends on male seminal fluid and is hypothesized to modulate male inseminate allocation. We aim at identifying molecular players and circuit motifs mediating the communication between male and female during copulation. (part of the figure modified from Kerwin and von Philipsborn, BioEssays 2020)

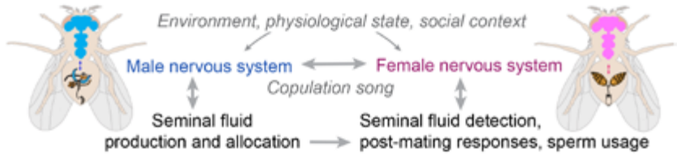



**Figure 3: Communication between the nervous system and reproductive organs**
Female copulation song provides a window into multiple pathways of information exchange between male and female, as well as between nervous system and reproductive system, and the influence of environmental stimuli, internal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

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.

For optogenetic tool development, we collaborate with the team of DANDRITE group leader Sadegh Navabi, providing a proof-of principle testing platform in Drosophila (Mermet-Joret et al. 2021).

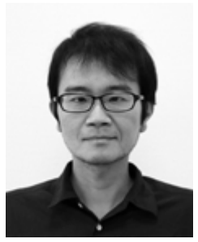
COMMUNICATION BETWEEN THE NERVOUS SYSTEM AND REPRODUCTIVE ORGANS: GENES, PATHWAYS AND CIRCUITS FOR SENSING AND ALLOCATING EJACULATE COMPONENTS
In animals with internal fertilization, seminal fluid strongly influences the physiological requirements for reproduction. Seminal fluid proteins, pheromones and metabolites 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 (Figure 2). 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.

Currently, we aim at elucidatinf which seminal fluid protein/peptide and respective receptor trigger female copulation song. Together with the laboratory of Prof. J. Enghild at Aarhus University, we are conducting mass spectrometry analysis of male inseminate and the female reproductive tract. 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).

Yonehara Group

# Function and Development of Neural Circuits in Visual System



Group Leader
**Keisuke Yonehara**

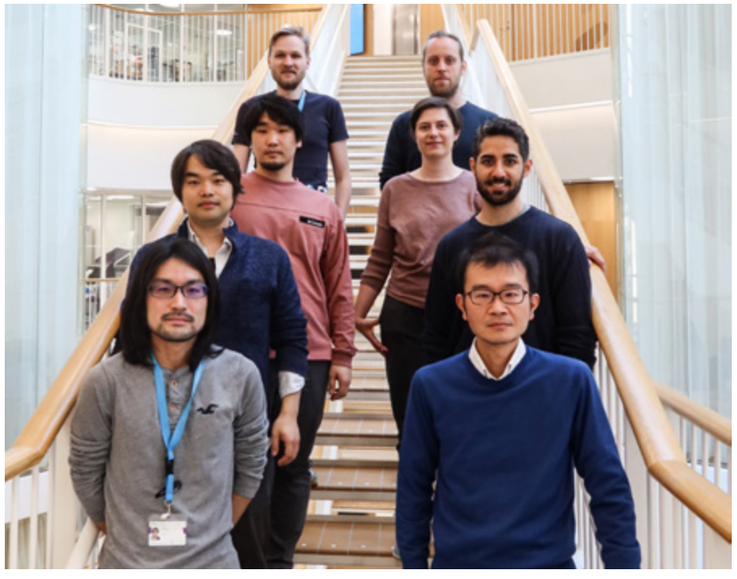
The Yonehara group investigates how cell types in the central nervous system are organized into neural circuits for extracting sensory information and how specific connectivity in the neural circuits arises during development using mouse visual system as a model.

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

RETINAL PROCESSING OF VISUAL MOTION
Inferring the direction of image motion is critical to the survival of animals. The direction of visual motion is first extracted by retinal direction-selective circuits. In 2021, we found that visual motion direction is first computed at the axon terminals of retinal bipolar cells before it is processed at the dendrites of direction-selective cells, demonstrating a novel mechanism of motion computation (Matsumoto et al., Neuron 2021). Furthermore, we identified a fast, non-synaptic form of neurotransmission mediated by acetylcholine from amacrine cells to direction-selective cells by employing two-photon acetylcholine imaging. We showed that this mechanism plays a critical role in dendritic computation of visual motion (Sethuramanujam and Matsumoto et al., Nat Commun 2021). These works together provided insights into how excitatory mechanisms contribute to visual motion processing and revealed fundamental subcellular mechanisms underlying neuronal processing.

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 optic flow-sensitive cells across visual cortical areas and suggested a logic for how retinal motion inputs from left and right eyes are combined at different cortical areas to produce distinct sensitivity to rotational and translational optic flow patterns (Rasmussen et al., Curr Biol 2021). In the next years we aim to understand how the identified motion processing stream 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.



Yonehara group members.

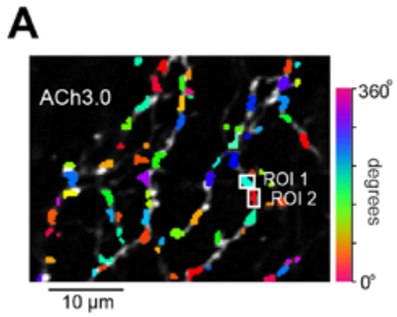



**Fig. 1:** (A) Two-photon imaging from axon terminals of mouse retinal bipolar cells revealed directional selectivity in glutamate release from axon terminal synapses. Upper panel: intensity of selectivity. Bottom: Preferred direction. (B) Directional selectivity is formed by acetylcholine and GABA signals input to axon terminals. A new concept of neural computation by axon terminals has been proposed. Figure panels from Matsumoto et al., 2021, Neuron.

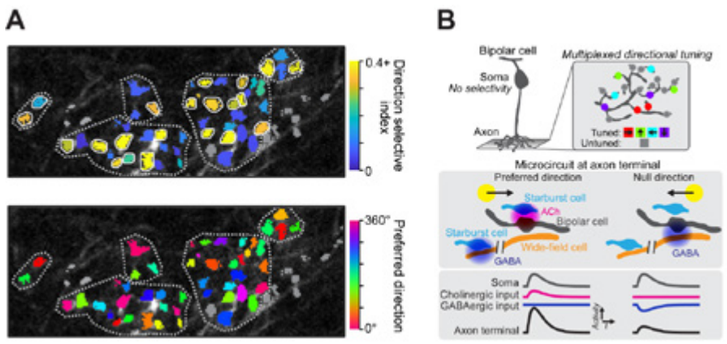



**Fig. 2:** (A) Left, two-photon acetylcholine imaging from the dendrites of retinal direction-selective cells revealed multi-directed dendritic microsegments. Right, polar plot of preferred directions of each dendritic segment show that total cholinergic input per cell is not directionally selective. Figure panels from Sethuramanujam and Matsumoto et al., 2021, Nature Communications.

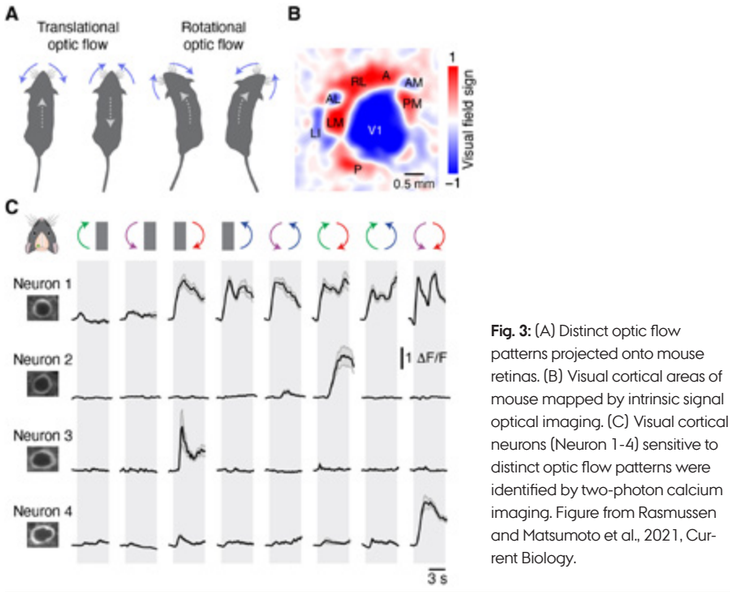



**Fig. 3:** (A) Distinct optic flow patterns projected onto mouse retinas. (B) Visual cortical areas of mouse mapped by intrinsic signal optical imaging. (C) Visual cortical neurons (Neuron 1-4) sensitive to distinct optic flow patterns were identified by two-photon calcium imaging. Figure from Rasmussen and Matsumoto et al., 2021, Current Biology.

**KEY PUBLICATIONS 2021**

Matsumoto A, Agbariah W, Nolte SS, Andrawos R, Levi H, Sabbah S, Yonehara K. (2021) Direction selectivity in retinal bipolar cell axon terminals. *Neuron* 109: 2928-2942.e8.

Sethuramanujam S§, Matsumoto A§, McIntosh JM, Jing M, Li Y, Berson D, Yonehara K*, Awatramani GB*. (2021) Rapid ´multi-directed´ cholinergic transmission at central synapses. *Nat Commun* 12: 1374. § equally contributed. *shared-corresponding authors.

Rasmussen RN§, Matsumoto A§, Arvin S, Yonehara K. (2021) Binocular integration of retinal motion information underlies optic flow processing by the cortex. *Curr Biol* 31: 1165-1174. § equally contributed.

**PERSONNEL LIST YONEHARA GROUP**

Postdoc **Akihiro Matsumoto**
Postdoc **Haruko Yamamoto**
Postdoc **Kota Takuoka**
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**
Student Assistant **Celine Thiesen**
Student Assistant **Esther Helga Klemenzerdóttir**
Group Leader **Keisuke Yonehara**

Kjærgaard Team

# Synaptic Plasticity and Intra-cellular Signaling Complexes in Memory

PROMEMO
CENTER FOR PROTEINS IN MEMORY

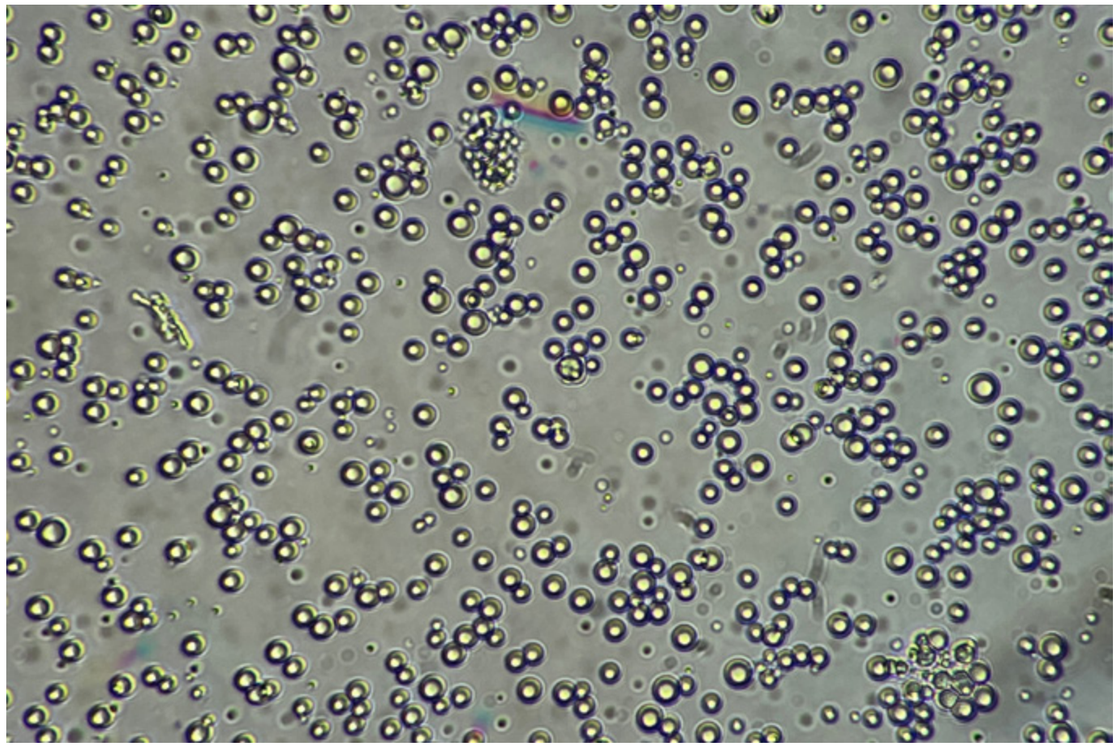
Team Leader
**Magnus Kjærgaard**

We are interested in understanding how proteins in the post-synaptic density modulate signalling pathways involved in synaptic plasticity, and how the nano-scale 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 and biochemical techniques including NMR spectroscopy and single molecule FRET spectroscopy to answer mechanistic questions about brain proteins.

Subcellular context is crucial for determining the output of signalling pathways. Activation of a kinase such as e.g. protein kinase A, leads to widely different outputs depending on where in the cell it is activated. This difference arises because the kinase is spatially restricted to a local environment, and thus only phosphorylate substrate in its vicinity. Which substrates a kinase encounters is determined by the signalling complex it is part of typically via binding to scaffolding proteins. However, we are lacking a theoretical framework for interpreting how signalling complex architecture affects phosphorylation reactions. Last year, my group developed the first quantitative model for how the structure of a signalling complex affects single-turnover kinase reactions (Dyla & Kjaergaard, 2020, PNAS). However, this only accounts for intra-molecular phosphorylations and very high affinity complex. This year, we have expanded this work to also cover the much more general care of transiently docked kinases (Dyla et al. 2022). We show that for each enzyme:substrate pair the docking interactions have a distinct optimum interaction strength and derive equations that predicts the dependence of this optimum based in enzyme kinetic parameters and the signalling complex architecture. This work reveals the design principles for making new synthetic signalling scaffolds and provides a framework for interpreting clinical mutations in scaffolding proteins.

Recently, it was discovered that cells contain a range of structures that are collectively called membrane-less organelles. These organelles create sub-cellular areas of the cell with distinct functional properties without being bounded by a membrane. Membrane-less organelles are formed by spontaneous condensation of biological macromolecules such as proteins and RNA. As the process is spontaneous similar structures called biomolecular condensates are formed in vitro from purified components (Fig. 1). We are investigating how membrane-less organelles affect signalling pathways using the post-synaptic density as a model. We hope that this will provide a new lens for understanding targeting of proteins to synapses and will reveal principles that can be applied in biotechnology.

Kjærgaard group members.



Protein droplets formed by liquid-liquid phase separation mimics the formation of membrane-less organelles such as the post-synaptic density.

**KEY PUBLICATIONS 2021**


Kjaergaard, M. (2022) Estimation of Effective Concentrations Enforced by Complex Linker Architectures from Conformational Ensembles. *Biochemistry* 2022, 61, 3, 171–182

Dyla, M. and Kjaergaard, M. (2021) Intrinsic disorder in protein kinase A anchoring proteins signaling complexes. Prog. Mol. Biol. Trans. Sci. 183:271-294

Basse Hansen, S, Dyla, M., Neumann, C., Lauwring Andersen, J., Kjaergaard, M. and Nissen, P. (2021) The crystal structure of the Ca2+-ATPase 1 from Listeria monocytogenes reveals a pump primed for dephosphorylation. J Mol Biol. 433(16):167015

Jendroszek, A. and Kjaergaard, M. (2021) Nanoscale spatial dependence of avidity in an IgG1 antibody. Sci Rep. 11(1):12663

Kjaergaard, M., Glavina, J. And Chemes, L.C. (2021) Predicting the effect of disordered linkers on effective concentratiosn and avidity with the "Ceff calculator" app. Met. Enzym. 647:145-171

Warnet, X. L., Bakke Krog, H., Sevillano-Quispe, O. G., Poulsen, H. & Kjaergaard, M. (2021) The C-terminal domains of the NMDA receptor: How intrinsically disordered tails affect signalling, plasticity, and disease. Eur. J. Neurosci. 54(8):6713-6739.


**PERSONNEL LIST KJÆRGAARD TEAM**

Postdoc **Nicolas S Gonzalez Foutel**
Postdoc **Sujata Mahapatra**
Postdoc **Macarena Gomez de Salazar**
PhD student **Emily C. Pheasant**
PhD student **Sara Basse**
PhD student **Victoria Twiddy**
PhD student **Alex Harvey**
PhD student **Nathalie Wyss**
Team Leader **Magnus Kjærgaard**

Poulsen Team

# Electrophysiology of Electrogenic Transporters and Ion Channels

PROMEMO
CENTER FOR PROTEINS IN MEMORY

Team Leader
**Hanne Poulsen**

GROUP PRESENTATION
In the group, we are two research assistants, three PhD students, and a post doc. We collaborate tightly with several DANDRITE groups, as well as with other researchers and industry. With an overall focus on membrane transport, we employ primarily electrophysiology and mouse models to understand neurological physiology and pathophysiology.

ELABORATE /DETAILS GROUP
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 ACHIEVEM} ENTS AND FUTURE PLANS, 2021
The Na,K-ATPase establishes the sodium and potassium gradients across animal cell membranes. During each catalytic cycle, it transports two potassium ions into the cell and three sodium ions out at the expense of one ATP. In the brain, these gradients lay the foundation for neuronal signaling, and the Na,K-ATPase is estimated to account for at least 2/3 of the brain's energy consumption. There are four different isoforms expressed in mammals, Na,K-ATPase alpha1-4. Mutations within the gene encoding the neuron-specific alpha3 is linked directly to several different diseases. It is still unknown why some mutations cause one disease, while other mutations in the same genes cause a different disease, and we continue the efforts to shed light on why that may be.

We find it especially intriguing that a single mutation in the gene encoding alpha3 causes deafblindness in the CAPOS (Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy, Sensorineural hearing loss) syndrome, and we are characterizing a mouse model of CAPOS in collaboration with Professor Karen Steel (King's College London). In patients, symptoms typically start after a severe fever in childhood. Surprisingly, induction strategies failed in the mice, but they do spontaneously and progressively develop both the sensory and motor phenotypes observed in patients. This mouse model will thus enable cellular, network, and physiological characterization of the disease.

At the molecular level, a focus is the NMDA receptor (NMDAR). The NMDARs are calcium-permeable channels that are activated by glutamate and glycine or D-serine in the post-synapse (see figure), and they are believed to be essential for learning and memory. They are also important drug targets with roles in e.g. pain and depression. 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 several variants that we are characterizing. To this end, there is fortunately an extensive toolbox of positive and negative allosteric modulators available whose modes of action are affected by the tails. Our studies provide novel insight into the molecular mechanism and regulation of one of the key players in synaptic plasticity and offer important insight into the mechanisms of allosteric modulation which may prove therapeutically useful.

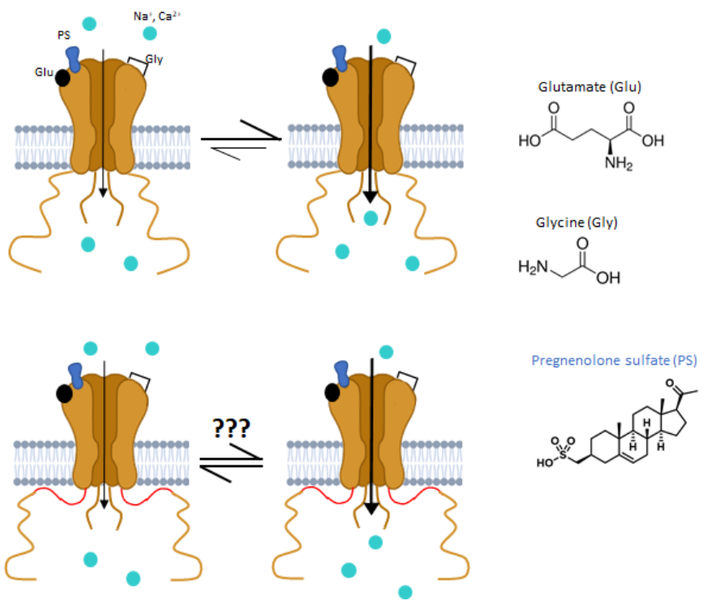



**Figure 1**
**Top:** At the synapse, glutamate and glycine can open the calcium-permeable NMDA receptors. These receptors are tetrameric ion channels with two GluN1 subunits and two other, e.g. Glun2A or GluN2B, which have long intrinsically disordered C-termini. Allosteric modulators like pregnanolone sulfate can alter the channel activity.
**Bottom:** To assess the role of the intrinsically disordered domains, we study the effect on the allosteric modulation of inserting a linker between the receptor and the disordered C-termini.
(Made with BioRender by research assistant Kirstine Hansen).

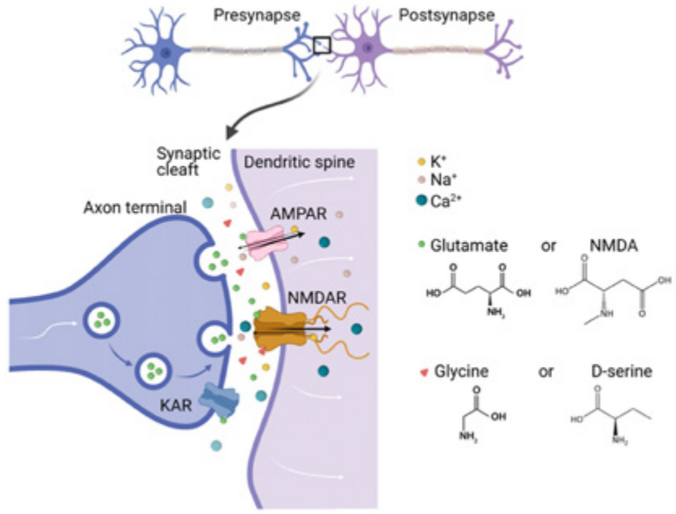



**Figure 2**
Synaptic signalling. Glutamate released from the presynapse opens cation channels AMPA receptors and NMDA receptors in the postsynapse. The NMDA receptor is regulated by intrinsically disordered vC-termini. (Made with BioRender by research assistant Kirstine Hansen).

**PUBLICATIONS 2021**

Habeck M, Poulsen H 2021 What FXYDs fix *J Gen Physiol* 153(6):e202012845

'Vores cellers saltbalance' for the Science and Technology Faculty series' Offentlige foredrag i naturvidenskab' attended by more than 800 people in Aarhus and broadcast to 312 cities

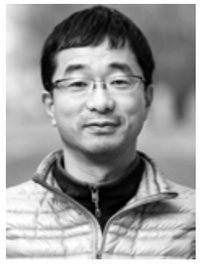
**PERSONNEL LIST POULSEN TEAM 2020**

Postdoc **Helle Bakke Krog**
PhD Student **Monica Dahlstrup Sietam**
PhD Student **Oscar Gabriel Sevillano Quispe**
PhD Student **Alex Harvey**
Research assistant **Kirstine Hansen**
Research assistant **Xingya Chang**
Lab Tech Student **Sofie Møller Bonde Larsen**
Team Leader **Hanne Poulsen**

Poulsen group members.

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 2021
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 (Bayraktar et al., J. Visualized Experiments, 2021). In addition, we have established a protocol that we observed enhanced memory persistence in 24-hr test for the group of rats that had explored a novelty box 30 min after a weak encoding.

Second, we succeeded to develop a red-shifted fluorescent dopamine sensor, which has high selectivity for dopamine over norepinephrine (66-fold selectivity) in collaboration with Dr Aoki at 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 (Nakamoto et al., Molecular Brain, 2021).

Furthermore, we have successfully performed in vivo fibre photometory imaging of dopamine or norepinephrine in the hippocampus of freely behaving rats. Change in fluorescence intensity of green-dopamine or green-norepinephrine sensors, that privided by Dr Li at Peking University in China, were observed when we optogenetically stimulated the locus coeruleus.

Third, 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 two candidate genes that code plasticity-related proteins critical for novelty-induced memory enhancement in the hippocampus.

In addition, we have established 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 Dr Nägerl at Bordeaux University in France. Specifically, we could induce long-term potentiation in a single spine by two-photon glutamate uncaging, and measured the change of spine volume using optical imaging techniques. We observed that spine surface transiently increased after glutamate uncaging, followed by back to the baseline 60-90 min after glutamate uncaging.

FUTURE PLANS IN 2021
First, we will 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 of rats ex vivo using green-dopamine or green-norepinephrine biosensors combined with two-photon microscope.

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-type glutamate 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.

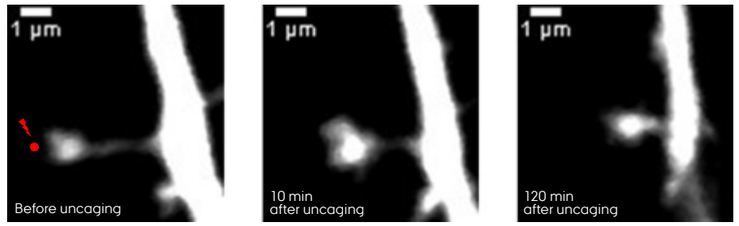
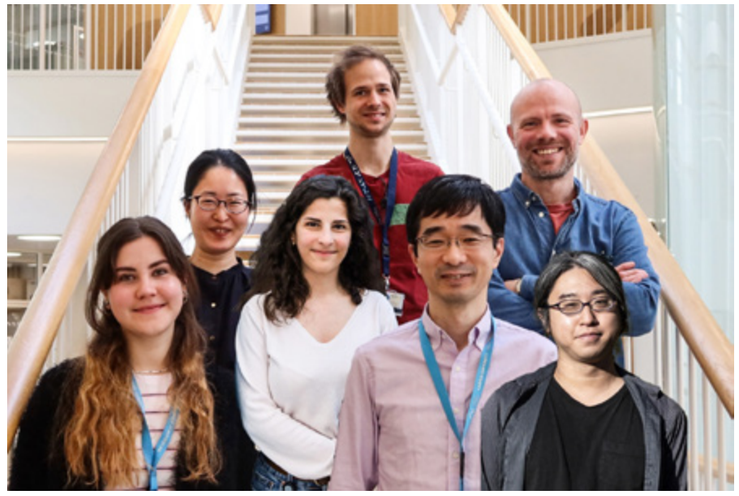



**Figure 1:** The image series shows structual plasticity in a single spine of a primary culture of rat hippocampal neurons induced by two-photon glutamate uncaging. The spine volume transiently increased after glutamate uncaging (middle), followed by back to the baseline 120 min after glutamate uncaging (right). This work has been done in collaboration with Dr Valentin Nägerl.



Takeuchi group members.

**PUBLICATIONS 2021**

Nakamoto, C.*, Goto, Y.*, Tomizawa, Y., Fukata, Y., Fukata, M., Harpsøe, K.S., Gloriam, D.E., Aoki, K.§ and Takeuchi, T.§ (2021) A novel red fluorescence dopamine biosensor selectively detects dopamine in the presence of norepinephrine in vitro. *Molecular Brain*, 14:173. https://doi.org/10.1186/s13041-021-00882-8. *Co-first author. §Co-last author.

Kjaergaard, M., Petersen, N.C., Sørensen, J.B. and Takeuchi, T. (2021) Introducing the special issue on "Proteins and Circuits in Memory". *European Journal of Neuroscience*, 54: 6691–6695. https://doi.org/10.1111/ejn.15491.

Homberg, J.R., Takeuchi, T. et. al., Genzel, L. (2021) The continued need for animals to advance brain research. *Neuron* 109: 2374–2379. https://doi.org/10.1016/j.neuron.2021.07.015

Bayraktar G.*, Højgaard K.*§, Luc Nijssen L. and Takeuchi T§ (2021) A within-subject experimental design using an object location task in rats. *Journal of Visualized Experiments*, 171: e62458, doi:10.3791/62458. *Co-first author. §Co-last author.

**PERSONNEL LIST TAKEUCHI TEAM**

Postdoc **Chihiro Nakamoto**
Postdoc **Okuda Kosuke**
PhD student **Kristoffer Højgaard**
PhD student **Katia Soud**
Intern **Bianka Szöllösi**
Lab Manager **Kim Henningsen**
Guest professor **Hiroshi Matsuno**
Team leader **Tomonori Takeuchi**

# **DANDRITE** AFFILIATED RESEARCHERS

DANDRITE is proud to enter year 2022 with 12 active affiliated researchers:

### CHRISTIAN VÆGTER

**Glia-neuron communication in health and disease**
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 2021**
- Publication: Mohr KM, Pallesen LT, Richner M, Vægter CB, Discrepancy in the Usage of GFAP as a Marker of Satellite Glial Cell Reactivity, *Biomedicines* 9(8) (2021)
- Establishing of conditional reporter mouse tagging Schwann cell-derived exosomes, a key model for future studies.
- Collaboration with Hoba Therapeutics, drug-testing HB-086 in pain models. ■

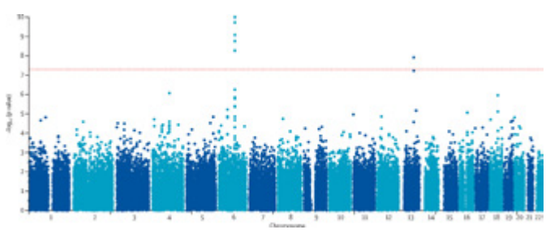
### ERNST-MARTIN FÜCHTBAUER

**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 2021, the Corona related restrictions and space limitations for the animal facility postponed a number of projects. We generated a mouse line expressing HA tag at the N-terminus of SorCS2 and started to develop an ES cell based test system for the CRISPR/Cas mediated gen. ■

### 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.

**DANDRITE related Highlights from 2021**
- Publication of first ever GWAS of bedwetting: Identification of genetic loci associated with nocturnal enuresis: a genome-wide association study in *the Lancet Child Adolescent Health* (Jørgensen et al. 2021)
- Publication of study: Inactivation of the schizophrenia-associated *BRD1* gene in brain causes failure-to-thrive, seizure susceptibility and abnormal histone H3 acetylation and N-tail clipping in *Molecular Neurobiology* (Paternoster et al. 2021)
- Novel genetic findings in bedwetting and childhood constipation/fecal incontinence using the iPSYCH2015 data
- Novel project: Genetic and epidemiological Architecture of day- and nighttime INcontinence (GAIN) in the Danish Blood Donor Study ■



### JØRGEN KJEMS

**Non-coding RNA and Nanomedicine**
The Kjems lab investigates the role for non-coding RNA in neuronal development and neurodegenerative disease (e.g. ALS, Alzheimer's disease and epilepsy). As part of the EU project PRIME, the groups studies if the accumulation of tRNA fragments seen in the central nervous system prior to the onset of epileptic seizures can be used to trigger signalling in bioimplants. In a different line of research, the Kjems group uses targeted lipid nanoparticles, multivalent nanoscaffolds and exosomes to deliver protein and RNA therapeutics across the blood brain barrier. The group also develops chemically modified RNA aptamers to target toxic protein aggregates in Parkinson's disease.

**DANDRITE related Highlights from 2021**
- Work started on the EU-supported project PRIME (A Personalised Living Cell Synthetic Computing Circuit for Sensing and Treating Neurodegenerative Disorders)
- Awarded a grant from AU's ODIN project to study biomarkers in the human psychiatric brain (BioPSYCH) in collaboration with Betina Elfving (Department of Clinical Medicine)

**Publications**
- Rahimi, K., Venø, M.T., Dupont, D.M., Kjems, J.: Nanopore sequencing of brain-derived full-length circRNAs reveals circRNA-specific exon usage, intron retention and microexons. Nat Commun. 12(1):4825 (2021)
- Lorenzi, L. et al.: The RNA Atlas expands the catalog of human non-coding RNAs. Nat Biotechnol. 39(11): 1453-1465 (2021)
- Ahmadov, U., Bendikas, M.M., Ebbesen, K.K., Sehested, A.M., Kjems, J., Broholm, H., Kristensen, L.S.: Distinct circular RNA expression profiles in pediatric ependymomas. Brain Pathol. 31(2):387-392 (2021)
- Gomes-Duarte, A., et al.: Enrichment of Circular RNA Expression Deregulation at the Transition to Recurrent Spontaneous Seizures in Experimental Temporal Lobe Epilepsy. Front Genet. 12:627907 (2021) ■

### 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. ■

### MARINA ROMERO-RAMOS

**Study and Characterization of the neurodegenerative event in Parkinson's Disease and the associated immune response**
During Parkinson's disease significant immune changes occur in parallel to the neuronal degeneration. Our lab has been studying the cells and proteins involved in the neuroinflammatory process associated to a-synuclein induced neurodegeneration. To do so we investigate the microglia response in brain, but also other myeloid cells in the periphery, in order to define the influence of the immune system 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.
- The lab has shown that prodromal Parkinson's disease patients have a modified monocyte population in blood, and that the expression of some monocytic markers correlated with inflammation and neurodegeneration in brain. This data supports a role for peripheral monocytes in the disease process and a cross-interaction between brain and periphery early in disease (PNAS, Farmen et al., 2021).
- In collaboration with Dr. PH Jensen the lab helped to show the differential pathology and degeneration induced by specific a-synuclein strains in vivo (Acta Neuropathol., Ferreira et al., 2021)
- In collaboration with the Imaging Center (AUH) the lab used PET to show progressive neurodegeneration induced by a-synuclein pathology in vivo in a rodent model of Parkinson's Disease (Thomsen et al., 2021). ■

### 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. We are developing different monoclonal antibodies, targeting trafficking receptors to maximize transport to brain parenchyma. We furthermore look in to transport of alpha-synuclein across the BBB.

**Highlights from 2021**
- Publication of Sortilin trafficking in BBB
- Cover picture in FEBS journal
- Acceptance in imaging roadmap applicationt ■

## OLAV MICHAEL ANDERSEN

**SORL1 as the fourth Alzheimer's disease gene**
Our research focuses on the role of SORL1 as an endosomal sorting receptor and how its dysfunction can lead to neurodegeneration and Alzheimer's disease. In 2021, SORL1 was included to the group of genes that when harboring pathogenic variants is considered causal of Alzheimer's disease - so SORL1 is now firmly established as the fourth AD gene. We identify novel mechanisms underlying the sorting pathways in the endolysosomal compartments, and are trying to understand whether individual SORL1 variants that have been identified in AD patients are truly pathogenic, and if so: by what mechanism(s).

### Highlights from 2021
- Publication of Monti et al., Acta Neuropath. Comms., Reporting how a novel SORL1 splice variant is decreased in neurons from Alzheimer's disease patients.
- Publication of Simoes et al., Cell Report, Reporting how SORL1 together with the retromer VPS26b subunit constitute a distinct core dedicated to endosomal recycling. ■

## THOMAS BOESEN

**Cryo-EM on membrane transporters and receptors**
I am involved in research projects with a focus on 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 with a increasing focus on in situ structural biology. 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 2021
- Aminzadeh A, Larsen CE, Boesen T, J rgensen R. High-resolution structure of native toxin A from Clostridioides difficile. EMBO Rep. 2022 Jan 5;23(1):e53597. doi: 10.15252/embr.202153597. Epub 2021Nov 24. PMID: 34817920; PMCID: PMC8728606.
- Timcenko M, Dieudonn T, Montigny C, Boesen T, Lyons JA, Lenoir G, Nissen P. Structural Basis of Substrate-Independent Phosphorylation in a P4-ATPase Lipid Flippase. J Mol Biol. 2021 Aug 6;433(16):167062. doi: 10.1016/j.jmb.2021.167062. Epub 2021 May 21. PMID: 34023399.
- Roeters SJ, Golbek TW, Bregnh j M, Drace T, Alamdari S, Roseboom W, Kramer G, Šantl-Temkiv T, FinsterK, Pfaendtner J, Woutersen S, Boesen T, Weidner T. Ice-nucleating proteins are activated by low temperatures to control the structure of interfacial water. Nat Commun. 2021 Feb 19;12(1):1183. doi:10.1038/s41467-021-21349-3. PMID: 33608518; PMCID: PMC7895962. ■
- 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. 2021 Feb;288(3):995-1007. doi: 10.1111/febs.15455. Epub 2020 Jul 8. PMID: 32543078.
- Boesen T, Nielsen LP, Schramm A. Pili for nanowires. Nat Microbiol. 2021 Nov;6(11):1347-1348. doi: 10.1038/s41564-021-00990-0. PMID: 34650249.
- Rafiq M, Ernst HA, Aduri NG, Prabhala BK, Tufail S, Rahman M, Bloch MB, Mirza N, Taylor NMI, Boesen T, Gajhede M, Mirza O. Expression, purification and characterization of human proton-coupled oligopeptide transporter 1 hPEPT1. Protein Expr Purif. 2022 Feb;190:105990. doi: 10.1016/j.pep.2021.105990. Epub 2021 Oct 9. PMID: 34637915. ■

## 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 distur-bances are major causes of neurodegeneration.

### Highlights from 2021
- Schmidt, V., Horváth, C., Dong, H., Blüher, M., Qvist, P., Wolfrum, C. and T.E. Willnow. (2021). SORLA is required for insulin-induced expansion of the adipocyte precursor pool in visceral fat. J Cell Biol. doi: 10.1083/jcb.202006058.
- Marczenke, M., Sunaga-Franze, D.Y., Popp, O., Althaus, I.W., Sauer, S., Mertins, P., Christ, A., Allen, B.L. and T.E. Willnow. (2021). GAS1 is required for Notch-dependent facilitation of SHH signaling in the ventral forebrain neuoepithelium. Development. doi: 10.1242/ dev.200080.
- Asaro, A., Sinha, R., Bakun, M., Kalnytska, O., Carlo-Spiewok, A.-S., Rubel, T., Rozeboom, A., Dadlez, M., Kaminska, B., Aronica, E., Malik, A.R. and T.E. Willnow. (2021). ApoE4 disrupts interaction of sortilin with fatty acid-binding protein 7 essential to promote lipid signaling. J Cell Sci. doi: 10.1242/jcs.258894 ■



## YONGLUN LUO

**Applied Gene and Genome Technologies in Biomedical Research**
Living multicellular organisms are formed by a complex hier¬archy 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 single cell and spatial RNA and DNA sequencing now provide us with powerful tools to revisit the complex organ systems at single cell resolutions. Based on genetic engineering tools (CRISPR-Cas9), in vitro (2D and 3D cell culture), in vivo (pig models), and human pathological samples, the aim of my research to revisit and decode the molecular and pathological signatures causing (neuro) degenerative diseases, and thus identify targeting genes for disease diagnosis, prevention and treatment.

### Highlights from 2021
- Yonglun Luo is co-founder for a CRISPR-Cas9 based cancer therapy spinout project supported by InnoExplorer supported by the Innovation Fund Denmark.
- Yonglun Luo received a project award from the Novo Nordisk Foundation to develop CRISPR and Stem cell-based therapy of Duchenne Muscular Dystrophin.
- Publication of study: Karlsson M, Zhang C, Méar L, Zhong W, Digre A, Katona B, Sjöstedt E, Butler L, Odeberg J, Dusart P, Edfors F, Oksvold P, von Feilitzen K, Zwahlen M, Arif M, Altay O, Li X, Ozcan M, Mardinoglu A, Fagerberg L, Mulder J, Luo Y, Ponten F, Uhlén M, Lindskog C. A single-cell type transcriptomics map of human tissues. Sci Adv. 2021 Jul 28;7(31):eabh2169. doi: 10.1126/sciadv.abh2169. PMID: 34321199; PMCID: PMC8318366.
- Publication of study: Xiang X, Corsi GI, Anthon C, Qu K, Pan X, Liang X, Han P, Dong Z, Liu L, Zhong J, Ma T, Wang J, Zhang X, Jiang H, Xu F, Liu X, Xu X, Wang J, Yang H, Bolund L, Church GM, Lin L, Gorodkin J, Luo Y. Enhancing CRISPR-Cas9 gRNA efficiency prediction by data integration and deep learning. Nat Commun. 2021 May 28;12(1):3238. doi: 10.1038/s41467-021-23576-0. PMID: 34050182; PMCID: PMC8163799.
- Publication of study: Xiang X, Zhao X, Pan X, Dong Z, Yu J, Li S, Liang X, Han P, Qu K, Jensen JB, Farup J, Wang F, Petersen TS, Bolund L, Teng H, Lin L, Luo Y. Efficient correction of Duchenne muscular dystrophy mutations by SpCas9 and dual gRNAs. Mol Ther Nucleic Acids. 2021 Mar 13;24:403-415. doi: 10.1016/j.omtn.2021.03.005. PMID: 33868784; PMCID: PMC8039775.
- Publication of study: Huang J, Lin L, Dong Z, Yang L, Zheng T, Gu W, Zhang Y, Yin T, Sjöstedt E, Mulder J, Uhlén M, Kristiansen K, Bolund L, Luo Y. A porcine brain-wide RNA editing landscape. Commun Biol. 2021 Jun 10;4(1):717. doi: 10.1038/s42003-021-02238-3. PMID: 34112917; PMCID: PMC8192503. ■
- Publication of study: Teuwen LA, De Rooij LPMH, Cuypers A, Rohlenova K, Dumas SJ, García-Caballero M, Meta E, Amersfoort J, Taverna F, Becker LM, Veiga N, Cantelmo AR, Geldhof V, Conchinha NV, Kalucka J, Treps L, Conradi LC, Khan S, Karakach TK, Soenen S, Vinckier S, Schoonjans L, Eelen G, Van Laere S, Dewerchin M, Dirix L, Mazzone M, Luo Y, Vermeulen P, Carmeliet P. Tumor vessel co-option probed by single-cell analysis. Cell Rep. 2021 Jun 15;35(11):109253. doi: 10.1016/j.celrep.2021.109253. PMID: 34133923. ■

## JELENA RADULOVIC

We study the molecular, cellular, and circuit mechanisms by which stressful experiences shape memory circuits and induce maladaptive behavior. We currently focus on cholinergic circuits stemming from the basal forebrain and midbrain and investigate their roles on long-term memory (Radulovic) working memory (Yamawaki), and socioaffective behavior (Tanimura). We also study the role of uncertainty in memory formation, generalization, and flexibility. Our research is performed with mouse behavioral models and include phenotypes found in patients suffering from affective disorders.

### Highlighs from 2021
- We set up our new laboratory at the Department of Biomedicine, generated pilot data, and recruited several lab members.
- We reported the basic circuit regulation of two stress-related phenotypes: fear generalization (Neuropsychopharmacology) and ethanol consumption (Neurobiology of Learning and Memory).
- We published a review on the circuit regulation through long-range inhibitory pathways (Shepherd and Yamawaki 2021)
- We initiated collaborations with Poul Henning and Marina Romero-Ramos (Asami) on cholinergic modulation in Parkinson's disease and with Sadegh Nabavi and Duda Kvitsiani (Radulovic and Yamawaki) on the neurobiology of uncertainty reduction. ■

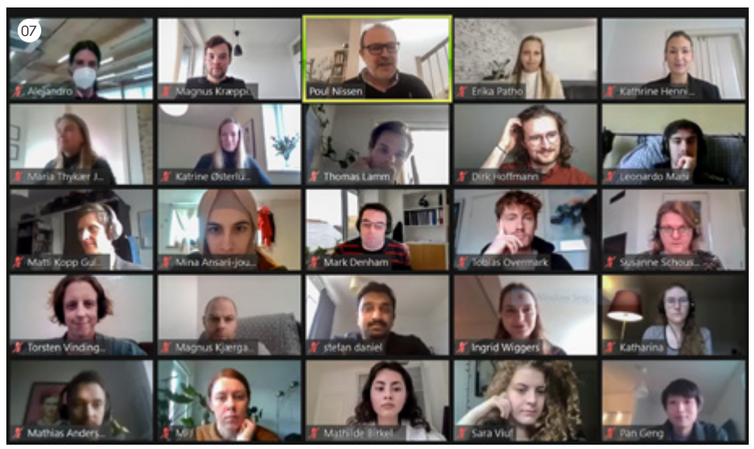
03

# Events of the year 2021

# EVENTS, VISITORS, GUESTS AND SEMINARS








**JANUARY**

01 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Associate Professor Brenda Bloodgood, University of California, San Diego, USA, *"The unexpected precision of an inducible transcription factor"*

02 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Associate Professor Sâmia Joca, Department of Biomedicine, Aarhus University, *"Cannabinoids in stress and depression: state of the art and challenges"*

03 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Professor Masaki Ueno, Niigata University, Japan, *"Rewiring of neural circuits in CNS injuries"*

**FFEBRUARY**

04 VIRTUAL LECTURE: **Virtual KJELDGAARD Lecture** with Group Leader Dario Valenzano, Max Planck Institute for Biology of Ageing in Cologne, Germany, "*African killifishes shed light on evolution and modulation of lifespan"*, Host: Group Leader Anne von Philipsborn

05 VIRTUAL TOPICAL SEMINARS: **Virtual DANDRITE Mini-symposium** on membrane transporters. Host: Group Leader Poul Nissen. Seminars by:

- Professor Jette Sandholm Kastrup, Department of Drug Design and Pharmacology, University of Copenhagen, *"Positive allosteric modulation of AMPA and kainate receptors"*
- Group Leader Gisela Brändén, University of Gothenburg, Sweden, "*XFEL – and synchrotron-based serial crystallography studies of the membrane-bound proton pump cytochrome c oxidase"*

06 VIRTUAL SEMINAR: **Virtual Neuroscience Seminar** with Associate Professor Randy Bruno, Columbia University, New York City, USA *"The Many Layers of Touch"*, Host: Group Leader Poul Henning Jensen

07 VIRTUAL EVENT: **DANDRITE Student Encounters 2021**, Aarhus University

**MARCH**

10 EVENT: **Extended Internal Meeting** with DANDRITE's newly appointed Affiliated Researcher; Professor Jelena Radulovic

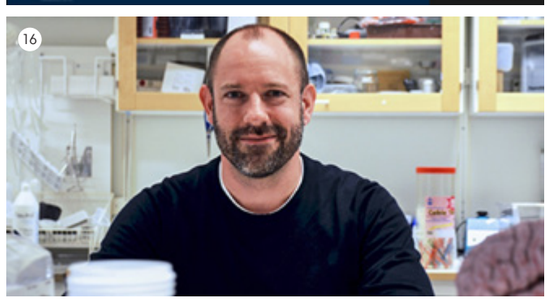
11 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Bloomberg Distinguished Professor Richard L. Huganir, Johns Hopkins University School of Medicine in Baltimore, Baltimore, MD USA, *"Regulation of Neurotransmitter Receptors in the Brain in Health and Disease"*

12 VIRTUAL OUTREACH EVENT: **Brain Awareness Week: Parkinsons sygdom – fra patientperspektiv til nyeste Forskning**, NeuroCampus Aarhus. Lectures by:

13
- DANDRITE Affiliated Researcher Marina Romero-Ramos, *"Inflammation og immunrelaterede processer ved Parkinsons-sygdom"*
- DANDRITE Group Leader Poul Henning Jensen, *"Sygdomsmekanismer i levende organismer og deres behandling"*

14 VIRTUAL EVENT: **Virtual YoDa Career Café** with DANDRITE Team Leader Magnus Kjærgaard, organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE"). Subject: Scientists on social media: Modern research dissemination or waste of time?








**APRIL**

15 VIRTUAL LECTURE: Virtual KJELDGAARD Lecture with Professor Daniel Kronauer, The Rockefeller University, New York City, USA, *"Differentiation, Communication, and Emergence in Ant Societies"*, Host: Group Leader Anne von Philipsborn

16 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Professor Christian Broberger, Stockholm University, Sweden, *"From membrane properties to behaviour: Gap junction connectivity as a determinant of paternal pup care"*

17 VIRTUAL SEMINAR: **Virtual Neuroscience Seminar** with PhD Allan-Hermann Pool, California Institute of Technology, USA, *"Mapping and re-engineering neural circuits mediating biological motivations"*, Host: Group Leader Poul Henning Jensen

18 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Assistant Professor Kazumasa Tanaka, Okinawa Institute of Science and Technology Graduate University, Japan, *"Heterogeneous Memory Traces in the Hippocampus"*

19 VIRTUAL EVENT: **Festival of Research 2021**. DANDRITE and PROMEMO researchers had signed up for the "Book a Scientist" programme and offered free, online talks.

20 VIRTUAL SEMINAR: **Virtual DANDRITE Topical Seminar** with PhD Student Louise Laursen, Uppsala University, Sweden, *"Exploring the Role of the PDZ Domain in a Supramodule"*, Host: Group Leader Poul Nissen

21 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Professor Dr. Takeshi Ikeuchi, Niigata University, Japan, *"Microglia dysfunction and new therapeutic approach in primary microgliopathy"*

**MAY**

22 VIRTUAL EVENT: Neuroscience Day 2021 - *"Flowing Neuroscience"*, NeuroCampus Aarhus

23 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Postdoctoral Fellow Alan Jung Park, Columbia University, New York City, USA, *"Brain Circuit Reset: Principle of Cognitive Enhancement in Health and Disease"*

24 VIRTUAL SEMINAR: **Virtual Neuroscience Seminar** with Dr. Sarah Melzer, Harvard Medical School, Boston, USA, *"Peptidergic modulation of cortical circuits in fear memory"*, Host: Group Leader Poul Henning Jensen

25 VIRTUAL LECTURE: **Virtual Brian Clark Biotech Lecture** with PhD and Senior Vice President Lars Fogh Iversen, Global Research Technologies, Novo Nordisk A/S, Host: Group Leader Poul Nissen

26 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Professor Johannes Letzkus, University of Freiburg, Germany, *"A thalamo-cortical top-down circuit for associative memory"*.

27 VIRTUAL SEMINAR: **MBG FOCUS TALK** with Joao Ramos, Institute Laue-Langevin, Grenoble, France and the University of Copenhagen, *"Protein and water dynamics at the atomic level using neutron crystallography"*, Host: Group Leader Poul Nissen and Associate Professor Thomas Lykke-Møller Sørensen

**JUNE**

28 EVENT: DANDRITE **Afternoon Hangout**

29 VIRTUAL EVENT: **Virtual YoDa Career Café** with professional life coach Cathie Edwards, New Zealand, organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE"). Subject: Procrastination

30 VIRTUAL EVENT: **DANDRITE Symposium**, Aarhus University. Lectures by:

- Group Leader Dr. Cordelia Imig, University of Copenhagen (UCPH), Denmark, *"Dissecting the Molecular and Structural Basis of Neurosecretion"*
- Postdoctoral Researcher Dr. Taro Kitazawa, Friedrich Miescher Institute for Biomedical Research (FMI), Basel, Switzerland, "*Epigenetic and transcriptional regulation of neuronal activity response genes during development"*
- Postdoc Dr. Winnie Wefelmeyer, Centre for Developmental Neurobiology, King's College London, UK, *"The emergence and plasticity of synapses at the axon initial segment"*
- Associate Rutgers Dr. Maxime Assous, Univ. Center for Molecular and Behavioral Neuroscience, Rutgers University, USA, *"Integration of extrinsic input by selective striatal microcircuits"*
- Research Fellow Dr. Onur Dagliyan, Harvard Medical School, Boston, MA, USA, *"Neuronal activity-dependent signaling mechanisms for transcription and splicing"*
- Postdoctoral Scientist Dr. Sarah Melzer, Sabatini Lab, Harvard Medical School, USA, *"Neuropeptidergic circuits for associative learning and memory"*
- Postdoctoral Research Associate Dr. Sarah Ruediger, Howard Hughes Medical Institute (HHMI), University of California San Francisco (UCSF), San Francisco, USA, *"Visual circuits for action – an evolutionary perspective"*

31 VIRTUAL SEMINAR: V**irtual DANDRITE Topical Seminar** with Professor David Drew, Stockholm University, Sweden, *"Elevating the molecular basis for sodium/proton exchange"*, Host: Group Leader Poul Nissen

32 VIRTUAL SEMINAR: Virtual DANDRITE Topical Seminar with PhD Daniel Gramm Kristensen, Department of Clinical Medicine, Aarhus University, *"The computational role of rod and cone photoreceptors in visual signal processing"*, Host: Group Leader Keisuke Yonehara

**JULY**

33 AU SUMMER COURSE: **AU Summer Course in Translational Psychobiology** with DANDRITE Affiliated Researcher; Professor Jelena Radulovic

**AUGUST**

34 LECTURE: **DANDRITE Lecture** with Associate Professor Kasper Bø Hansen, University of Montana, Missoula, MT, *"Structural and functional mechanisms of allosteric NMDA receptor modulation"*, Host: Team Leader Hanne Poulsen

35 EVENT: **YoDa picnic style social event**, organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE")

**SEPTEMBER**

36 ONLINE SEMINAR: **Webinar with Tecniplast**, *"Digital Ventilated Cages for mice: welfare and science"*, Host: Professor and DANDRITE Affiliated Researcher Marco Capogna

37 VIRTUAL JOINT LECTURE: Online BRI-DANDRITE Joint Lecture with Professor and Group Leader Poul Nissen, DANDRITE, Aarhus University, *"Structure and mechanism of brain transporters"*

38 HYBRID EVENT: **YoDa Hybrid Career café** with DANDRITE alumni Juliane Martin, Associate consultant at Boston Consulting Group, organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE"). Subject: My career path from science to management consulting.

39 EVENT: **DANDRITE Retreat 2021**

**OCTOBER**

40 VIRTUAL JOINT LECTURE: **Online BRI-DANDRITE Joint Lecture** with Professor and Group Leader Poul Henning Jensen, DANDRITE, Aarhus University, *"The role of patient specific alpha-synuclein aggregates in Parkinson's disease related disorders - challenge or opportunity for disease modifying therapies?"*

41 EVENT: **Extended Internal Meeting** with Professor and Group Leader Sarang S. Dalal, NEMOlab, CFIN

42 VISIT: **Delegation from the French National Centre for Scientific Research visits AU, PROMEMO and DANDRITE**

43 EVENT: **Brain States and Beyond – Reconnecting Danish Neuroscience 2021** with PhD Student Katia Soud and DANDRITE Affiliated Researcher Marco Capogna in the Programme Committee

44 HYBRID EVENT: **YoDa Hybrid Workshop Café** with senior Postdoc Andrea Moreno, DANDRITE, Aarhus University, organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE"). Subject: BioRender: How to use? Tips and tricks.

**NOVEMBER**

45 VIRTUAL JOINT LECTURE: **Online BRI-DANDRITE Joint Lecture** with Associate Professor and Group Leader Duda Kvitsiani, DANDRITE, Aarhus University, *"Dissociating value computations from the memory of events and actions in mouse anterior cingulate cortex"*

46 SEMINAR: DANDRITE **Topical Seminar** with Emmy Noether Group Leader Dr. Jan M. Ache, University of Würzburg, Germany, *"Neuronal mechanisms for sensorimotor flexibility"*, Host: Group Leader Anne von Philipsborn

47 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Assistant Professor Kei M. Igarasgi, University of California, Irvine, USA, *"Circuit mechanisms of associative memory"*, Host: Team Leader Tomonori Takeuchi

48 SEMINAR: **Animal Research 2021** with PhD Student Kristoffer Højgaard and Lab Manager Kim Henningsen, DANDRITE, Aarhus University, *"Habituation to handling. Increasing animal welfare and (perhaps) consistency of results"*

**DECEMBER**

49 EVENT: **Extended Internal Meeting** with DANDRITE's newly appointed Team Leader; Assistant Professor Gilles Claude Vanwalleghem

50 EVENT: **EMBL in Denmark 2021 – combined with DANEMO career event** with Professor and DANDRITE Director Poul Nissen

51 VIRTUAL JOINT LECTURE: **Online BRI-DANDRITE Joint Lecture** with Associate Professor and Group Leader Keisuke Yonehara, DANDRITE, Aarhus University, *"Visual motion processing from retina to visual cortical areas in mice"*



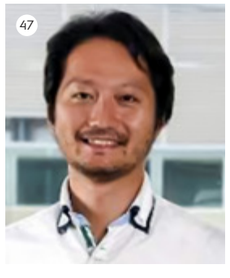

39


39


39


39


38


47


44


49

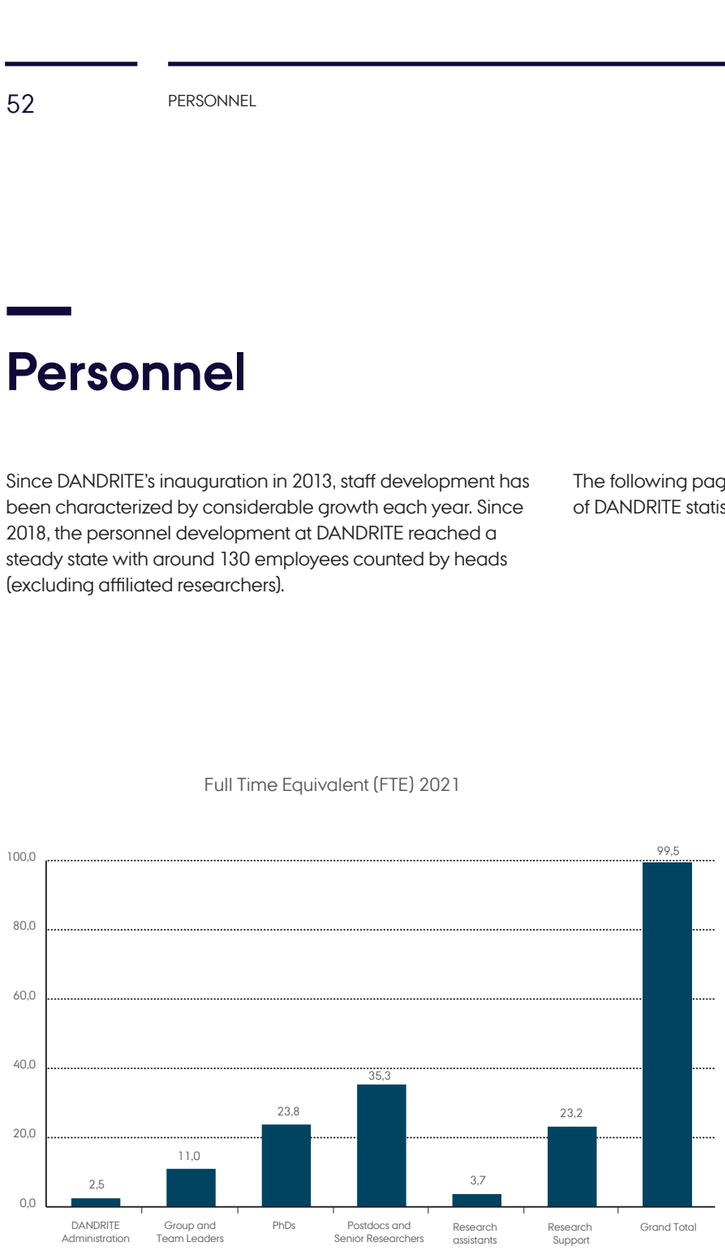
# 04
# Personnel

# 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.

Full Time Equivalent (FTE) 2021




**Personnel figure 1:**
Graphic representation of number of personnel in 2021 *counted in FTE – full time Equivalent* for appointed categories summarized: DANDRITE Administration, Group and Team Leaders, PhDs, Postdocs and Senior Researchers, and Research Support.

**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 | 2,5 |
| Group and Team Leaders | 2,0 | 9,0 | 11,0 | 11,1 |
| PhDs | 13,8 | 10,0 | 23,8 | 23,9 |
| Postdocs and Senior Researchers | 15,4 | 19,9 | 35,3 | 35,5 |
| Research assistants | 2,5 | 1,2 | 3,7 | 3,7 |
| Research Support | 18,9 | 4,3 | 23,2 | 23,3 |
| **Grand Total** | **55,2** | **44,3** | **99,5** | **100** |
| Percentage of Female/Male % | 55 | 45 | 100 | |



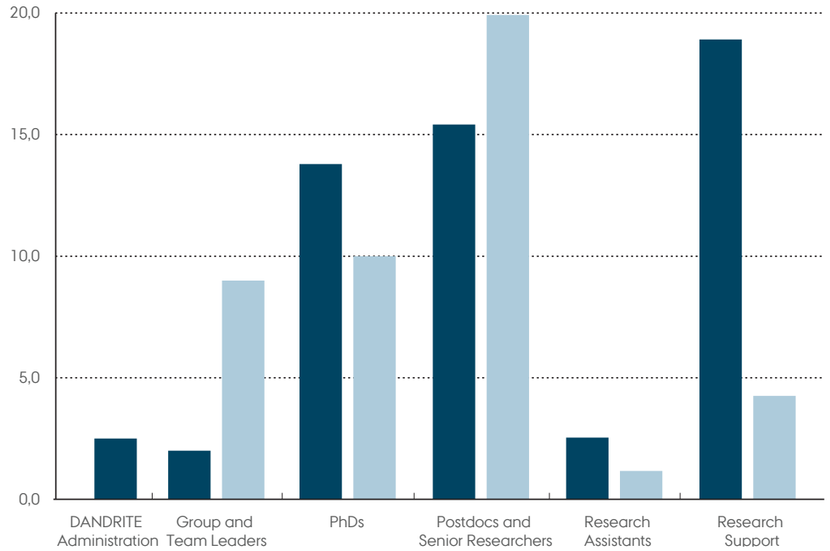



**Figure 3:**
Graphic representation of the personnel counts for 2021 (numbers grouped by appointment category and gender).

**Figure 4:**
Percentage of Female/Male

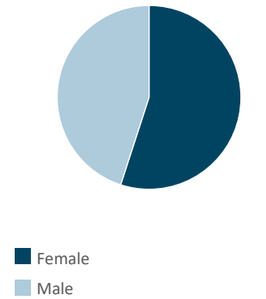



**Figure 5:**
Graphic representation of the nationality distribution of all employees. In total 31 nationalities.

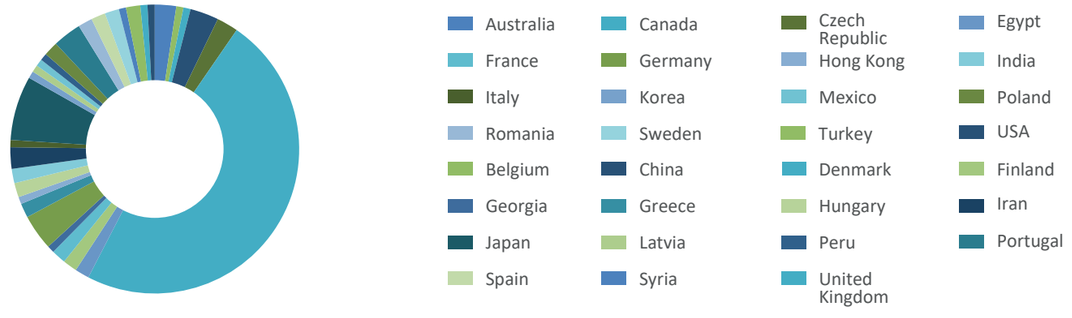
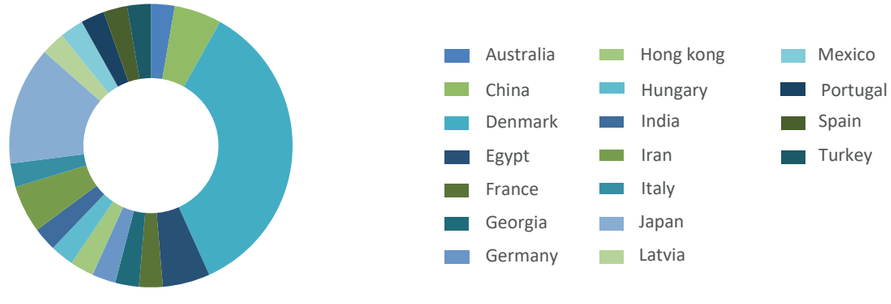



**Figure 6:**
Graphic representation of the nationality distribution of the employees in DANDRITE's five young research groups.



# DANDRITE Alumni

Following the EMBL group leader model of 5+4 years appointments, the first two DANDRITE group leaders has moved on to other positions. During 2021, GL's Anne Philipsborn and Keisuke Yonehara accepted professorship positions at the University of Fribourg in Switzerland and the National Institute of Genetics in Japan, respectively. Anne Philipsborn relocated to Switzerland in the end of January 2022. Keisuke Yonehara will continue with a partial affiliation to DANDRITE until the end of January 2024.

On the following pages, we welcome you to read an interview with Keisuke Yonehara on how experience gained at DANDRITE helped him secure a permanent professorship in Japan.

## Keisuke Yonehara:
# How experience gained at DANDRITE helped him secure a permanent professorship in Japan

**Text and photo by Annabel Robertson Darby**

Having qualified as a veterinary doctor in Japan, Dr. Yonehara became interested in molecular neurobiology and, after a PhD, took up a postdoc position in the Roksa Group at the Friedrich Miescher Institute for Biomedical Research (FMI), Basel, Switzerland. After gaining valuable experience in carrying out physiological experiments here, Dr. Yonehara accepted the role of group leader at DANDRITE in 2015 and has since worked to build up his group there.

Following the EMBL model of 5+4 years group leader appointments with a mid-term review, Dr. Yonehara accepted a new role as Professor at the National Institute of Genetics, Japan and Adjunct Professor at the Graduate University for Advanced Studies (SOKENDAI). He will now slowly wind down his activities in Aarhus from October 2021, but will continue to be partly affiliated with DANDRITE until January 2024.

Here, Dr. Yonehara describes how his time at DANDRITE has helped to shape his career as an independent PI and what he hopes for his new role in Japan.

Keisuke Yonehara is head of the Spatially Asymmetric Neural Circuits in Visual System group at DANDRITE

*What was the deciding factor in starting your group at DANDRITE/Aarhus University?*
Denmark is renowned for having a high research productivity (such as citations per publication) and an excellent quality of life. Denmark is also home to some fantastic private funding agencies, such as the Lundbeck Foundation, Novo Nordisk Foundation, Carlsberg Foundation and Velux Foundation. I think this factor has an extremely positive impact on the Danish research environment. Each of these foundations provides generous funds to researchers in basic biomedicine. I was also excited by the fact that DANDRITE is a part of the Nordic EMBL Partnership. EMBL and its outstations are seen as very prestigious centers of research excellence within Europe. I therefore wanted to join the excellent community that EMBL's research network provides to Nordic EMBL Group Leaders. Furthermore, DANDRITE provided me with an unmatched amount to start my lab up, which was far more generous than other similar job openings. This factor was important since I wanted to build a two-photon microscope facility, which is quite expensive and thus not easy to purchase with only external grants.



*How was the process of joining a newly established research Centre?*
I was the fourth group leader to start at DANDRITE, out of a total of five recruited group leaders. I was not familiar with the Danish system, which was a bit different from Switzerland where I completed my postdoc. It took a bit of time to get used to, and I had to learn about different rules and regulations over time. These included, for example, how to start animal experiments, how to buy expensive equipment, how to recruit people, and so on. Other group leaders were also involved in this learning process, so we shared our experiences, which helped. Fortunately, DANDRITE has a team of very helpful administrators who were there to support us. They helped me with my integration into DANDRITE on many different levels, from finding apartments, to recruiting members, and to renovating labs. Without their kind help, setting up my lab would have been much more difficult. Danish people are always open, fair, and kind, and so I never felt isolated in Denmark as an international researcher.

*How has your time as Group Leader formed your research and career choice?*
My research program was gradually shaped by the interaction of my careful planning and new group members' ideas, abilities, and enthusiasms. When a new member had exciting ideas, I would approve them and we would work on them together. This meant we could shape these ideas into a form that excited both the member and me. I allowed myself to enjoy chances of coincidence, so to say. I think this helped to motivate students also make the most out of our research. As we made several findings in mouse models, I became interested in testing similar ideas in non-human primate models that are closer to humans than mice. However, this type of research is not easy to complete in Europe.

In terms of career choice, after I have deepened my experience as a group leader in conducting science, managing the lab, and publishing several milestone papers, I gained the confidence and feeling that I could do high-level research anywhere in the world. Japan is my home country and I always wanted to run a lab there, which my Japanese family also hoped for. Japan usually does not provide enough startup funding for a young PI to build an expensive lab like mine. Now that I have published some papers and gained valuable experience, I feel that I have acquired the ability and experience to be able to secure the right grants for building an expensive lab in Japan. It was also important for me that, in Japan, I can use non-human primate models. Because of these reasons, it felt like the right time to go back to Japan and so I decided to take on a new challenge.

*What do you think are the advantages of the EMBL non-tenure model (5 years with review plus 4 years' extension)?*
With the EMBL non-tenure model and the generous resources made available, it is possible to rocket-start your big research programme, and then see what kind of challenges you want to tackle next after your first 5 years. If I had taken another tenure-track position, I think I would have had to start a much smaller lab and slowly aim for a tenure contract. Since I wanted to keep the option of returning to Japan with a good research profile, the EMBL non-tenure model was very suitable for me. I do also think there should be opportunities to stay in the host university in case you wish to remain there. This can be made possible by applying for a tenured position through job openings within the university. It is obvious that the EMBL non-tenure model not only heavily contributes to Europe's research environment, but also to non-European countries by providing experienced PIs.

*Tell me about your next role; what are your plans for your group there?*
All of the professors at the National Institute of Genetics, in Mishima, Japan, where my new role is based, are also given a role as an adjunct Professor of the Graduate University for Advanced Studies (SOKENDAI). Since there are no Bachelor programs, my duty for teaching is quite minimal. This unique setting will allow me to supervise PhD students whilst also working at the research institute. This is a great environment for me since I wanted to keep focusing on conducting research. Furthermore, the National Institute of Genetics is equipped with the most advanced animal facility and transgenic mice production unit in Japan. These factors make for an ideal environment for my research program. My big goal is to establish a center of excellence for visual circuit neuroscience, by building a cutting-edge imaging system and gathering talented students and postdocs from all over the world. With such a team, I aim to reveal the mysteries of the function and structure of neural circuits that underlie our vision and visual disorders.

*What are you most looking forward to about your new role?*
Due to a non-ideal research environment for particularly young scientists, largely caused by suboptimal funding schemes, a low birthrate, and a closed mentality in terms of international researchers, Japanese basic research is weakening. I, therefore, want to contribute towards reversing this trend by preparing an ideal research environment for young scientists. I would like to internationalize the research institute by hosting students from abroad and activating international collaborations. I also want to train next-generation scientists who will keep advancing the neuroscience field and training disciplines through generations. For these tasks, I believe my experience as a group leader at DANDRITE will be very useful. I will be able to use my experiences here as a model for how to fast track and internationalize the research environment. I am also looking forward to continuous collaborations with researchers in Aarhus and Europe.

Find out more

Learn more about **the National Institute of Genetics** at www.nig.ac.jp/nig

Learn more about **The Graduate University for Advanced Studies**, SOKENDAI at: www.soken.ac.jp/en

Learn more about the **EMBL group leader model** at: https://projects.au.dk/fileadmin/ingen_mappe_valgt/EMBL_non-tenure_system_final.pdf

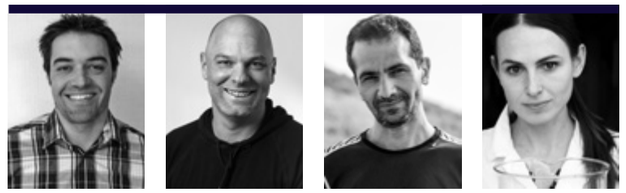
# Awards


1. **Professor and DANDRITE Director Poul Nissen** was awarded the Anders Jahre medical prize 2021. One of Scandinavia's most prestigious research honours, the Anders Jahre Medical Prize, has been conferred on Professor Poul Nissen of Aarhus University. The prize has been awarded in recognition of Professor Nissen's groundbreaking research on the structure and function of membrane proteins. His work has advanced our understanding of a variety of diseases, including cancer, cardiovascular disease and psychiatric disorders

2. **Student assistant Simon Arvin**, was awarded the health student research prize 2021 for his project titled: "EyeLoop – an open-source eye tracker for interactive brain research". The Prize is awarded to a student that Health wishes to recognize as someone who have submitted extraordinary work.



# Grants




1. PhD **Anders Breinbjerg**: Genetic architechture of childhood incontinence, DKK 50.000, Dagmar Marshalls Fond.
2. PhD **Anders Breinbjerg**: Genetic architechture of childhood incontinence, DKK 50.000, A.P. Møller Fonden.
3. PhD **Anders Breinbjerg**: Genetic architechture of childhood incontinence, DKK 10.000, Lizzi og Mogens Staal Fonden.
4. Group Leader **Mark Denham**: A Human Stem cell based miniaturised controlled organoid MiCO Platform for investigating neurological Disorders, DKK 4.889.608, ODIN.
5. Postdoc **Thibaud Dieudonné**: Structural and cellular investigation of the regulation of ATP8B1/CDC50A, a human flippase important for the hepatic function, DKK 1.633.874, EU-H2020.
6. Group Leader, **Poul Henning Jensen** (In collaboration with Magnus Kjærgaard and Peter Kristensen, AAU): Development of intracellular alpha-synuclein aggregate sensors - Part 1, Building the single chain MJF14 IgG derived binding module and in vitro validating its high avidity, DKK 826.000, M. J. Fox Foundation.
7. Group Leader, **Poul Henning Jensen**: Study of alpha-synuclein aggregate strain biology, DKK 380.000, Parkinsonforeningen.
8. Group Leader, **Poul Henning Jensen**: Testing disease modification in MSA model, DKK 320.000, MSA Coalition.
9. Group Leader, **Poul Henning Jensen**: Material and Technical Support for the BioLegend aSyn Aggregate ELISA, DKK 640.000, M. J. Fox Foundation.
10. Associate Professor **Jørgen Kjems**: BioPsych, DKK 200.000, ODIN.
11. Team Leader **Magnus Kjærgaard**: Kinase signaling in membrane-less organelles, DKK 2.600.000, Novo Nordisk Foundation – Interdisciplinary synergy.
12. Team Leader **Magnus Kjærgaard**: Phospho-specific protein interactions in synaptic tagging and capture, DKK 2.900.000, Danish Council for Independent Research (DFF - FNU).
13. Team Leader **Magnus Kjærgaard**: Instrument for Characterization of biomolecular phase transitions, DKK 1.234.240, Carlsberg Foundation.
14. PhD **Ida Klaestrup**: Vagus nerve in Parkinson: PhD fellowship, DKK 1.500.000, Health Faculty, AU.
15. Associate Professor **Yonglun Lou**: Ex vivo CRIPSPR repair and the creation of muscle stem cells for curing Dushenne muscular dystrophy (EXOCURE), DKK 2.700.000, Novo Nordisk Foundation.
16. Group Leader **Sadegh Nabavi**: Dual-color optical activation and suppression of neurons with high temporal precision, DKK 2.975.000, Lundbeck Foundation.
17. Group Leader **Poul Nissen**: Mass photometry for structural studies of complex biomolecular assemblies, DKK 1.329.070, Carlsberg Foundation.
18. Team Leader **Hanne Poulsen**: Lundbeck Foundation Experiments grant, DKK 2.000.000, Lundbeck Foundation.
19. Team Leader **Hanne Poulsen**: Industry-academia collaboration, DKK 2.250.000, ODIN.
20. Affiliated Researcher **Jelena Radulovic**: Mechanisms of Stress-Enhanced Aversive Conditioning, DKK 22.784.037, NIH/NIMH.
21. Affiliated Researcher **Marina Romero-Ramos**: Immune response in Parkinson: Running cost & salaries, DKK 4.500.000, ODIN.
22. Affiliated Researcher **Marina Romero-Ramos**: Vagus nerve in Parkinson, DKK 250.000, Danish Parkinson Foundation.
23. Postdoc **Charlott Stock**: PiT project: Postdoc fellowship, DKK 556.712, Deutsche Forshungsgemeinschaft (DFG).
24. Associate Professor **Asami Tanimura**: The role of midbrain acetylcholine signaling in chronic stress-induced degeneration of substantial nigra dopaminergic axons, DKK 22.000, Neuroscience theme, Aarhus University.
25. Postdoc **Haruka Yamamoto**: The development of cell-type-specific synaptic convergence in the mouse retina-brain pathway, DKK 2.400.000, Lundbeck Foundation.

# Invited Talks

Photos: Roar Lava Paaske and Lars Kruse

**JANUARY**
Yonglun Luo: *Overview of BrainStem related research*, BrainStem symposia, Denmark.

**FEBRUARY**
Keisuke Yonehara: *Visual motion processing: Cell types, circuits and computation*, ExCELLS retreat, Okazaki, Japan.

**MARCH**
Poul Henning Jensen: *Transporters in motion – How do we go about it?, Workshop on Strategy for future EMBL research infrastructures in the Life Sciences*, Hamburg, Germany.

**APRIL**
Lilian Kisiswa: *Formatin and maintenance of complec neuronal morphology and synaptic connectivity*, Erasmus MC, Rotterdam, Netherlands.

**MAY**
Magnus Kjærgaard: I*ntrinsically disordered linkers as regulators of tethered enzymes and multivalent interactions*, Departmental seminar, Uppsala University, Sweden.

Marina Romero-Ramos: *Immunomodulation as future therapeutic target in Parkinson's disease*, XXVI World Congress Of Parkinson's Disease and Related Disorders, Prague, Czech Republic.

**JUNE**
Magnus Kjærgaard: *Intrinsically disordered linkers as regulators of tethered enzymes and multivalent interactions*, Departmental seminar, Hebrew University, Jerusalem, Israel

Jane Hvarregaard Christensen: *Genetic studies in childhood incontinence and future plans*, Aarhus-Gehnt Incontinence Symposium, Virtual Lecture.

Anders Breinbjerg: *Genetic studies in childhood BBD*, Aarhus-Gehnt Incontinence Symposium, Virtual Lecture.

**JULY**
Jørgen Kjems: *Targeting of cells and viruses using nano-engineered ligand displays*, 1st symposium on oligonucleotide technology and thereputics, Virtual Lecture.

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

**AUGUST**
Naoki Yamawaki: *Untangling the cortico-thalamo-cortical loop: cellular pieces of a knotty circuit puzzle*, SMAC interdepartmental seminar series, University of Sydney, Australia.

Yonglun Luo: *Efficient and scalable CRISPR-Cas9 gene editing*, Aarhus University – Novo Nordisk workshop on Nulceic Acids in Life Science, Denmark.

**SEPTEMBER**
Poul Nissen: *Structural neurobiology – Ion transport*, Neuroseminar series, University of Copenhagen, Denmark.

Poul Nissen: *Structure and mechanism of brain transporters*, Brain Research Institute, Virtual Lecture.

Michael Habeck: *Cryo-EM structures of human NA,K-ATPase isoforms with a focus on lipids*, Meeting of the Scandinavian Physiological Society, Stockholm, Sweden.

Marina Romero-Ramos: *Peripheral immune changes in Parkinson's disease*, XIX Congresso Nazionale SINS, Itanial Soc For Neurosci, Virual Lecture.

**OCTOBER**
Mark Denham: *Enhanced Production of Mesencephalic Dopaminergic Neurons from Lineage-Restricted Human Undifferentiated Stem*, Novo Nordisk A/S, Copenhagen, Denmark.

Poul Nissen: *Internationalization, organization and funding*, Danish National Research Foundation, Annual Meeting, DGI byen, Denmark.

Jelena Radulovic: *Nonsynaptic mechanisms of long-term memory*, Annual meeting of the Danish Society for Neuroscience "Brain states and Beyond", Copenhagen, Denmark.

Naoki Yamawaki: *Long-range inhibitory intersection of a retrosplenial thalamocortical circuit by apical-tuft targeting CA1 neurons*, Danish Society for Neuroscience, Copenhagen, Denmark.

Yonglun Luo: *Gene and genome technologies for the development for generative medicine*, ICG-16, China.

**NOVEMBER**
Lilian Kisiswa: *Formation and maintenance of complex neuronal morphology*, University of Virginia, USA.

Duda Kvitsiani: *Dissociating value computations from the memory of events and actions in mouse anterior cingulate cortex*, Joint seminar series between DANDRITE and Brain Research Institute, Niigata University, Virtual lecture.

Mark Denham: *Investigating the role of ELAVL4 in GBA-associated Parkinson's disease*, Parkinson foreningen, Copenhagen, Denmark.

Naoki Yamawaki: *Long-range inhibitory intersection of a retrosplenial thalamocortical circuit by apical-tuft targeting CA1 neurons*, Barrels 34 – SfN Statellite meeting, Chicargo, USA.

Jørgen Kjems: *Profiling biofluids using highly parallelized RNA aptamer screens, applied to cancer, neuro- and cardiovascular diseases*, Annual meeting of the personalized medicine network AU, Aarhus, Denmark.

Marina Romero-Ramos: *Monocyte changes in Parkinson's disease*, 7th Aarhus Immunotherapy Symposium, Aarhus, Denmark

**DECEMBER**
Azadeh Shahsavar: *Unlocking the molecular mechanism of glycine reup-take inhibition*, EMBL in Denmark 2021, Copenhagen, Denmark.

Jelena Radulovic: *Translating animal bio behavioral research to human psychology and psychopathology*, International Webinar on Neurobiology of Behavior: the Challenge and the Promise for Translational Research, Virtual lecture.

Jørgen Kjems: *Targeting of cells and viruses using nano-engineered ligand displays*, DDA RNA mechanism and therapeutics in metabolic disease, Copenhagen, Denmark.

05

# Publications

# Publications


1 **Arvin S., Rasmussen R.N.** & **Yonehara K.**, 2021, 'EyeLoop: An open-source system for high-speed, closed-loop eye-tracking', *Frontiers in Cellular Neuroscience*, vol. 15.

2 **Bayraktar G.**, **Højgaard K.**, **Nijssen L.** & **Takeuchi T.**, 2021, 'A within-subject experimental design using an object location task in rats', *Journal of Visualized Experiments*, vol. 2021, no. 171, e62458.

3 Christensen S.B., Simonsen H.T., Engedal N., **Nissen P.**, Møller J.V., Denmeade S.R. & Isaacs J.T., 2021, 'From Plant to Patient: Thapsigargin, a Tool for Understanding Natural Product Chemistry, Total Syntheses, Biosynthesis, Taxonomy, ATPases, Cell Death, and Drug Development' in *Progress in the Chemistry of Organic Natural Products* . vol. 115, Springer, Cham, pp. 59-114.

4 Cui H., Kilpeläinen T., Zouzoula L., Auno S., Trontti K., Kurvonen S., Norrbacka S., Hovatta I., **Jensen P.H.** & Myöhänen T.T., 2021, 'Prolyl oligopeptidase inhibition reduces alpha-synuclein aggregation in a cellular model of multiple system atrophy', *Journal of Cellular and Molecular Medicine*, vol. 25, no. 20, pp. 9634-9646.

5 Dach I. & **Nissen P.**, 2021, 'Membrane transport | Structure of P-Type adenosine triphosphatases' in *Encyclopedia of Biological Chemistry: Third Edition*. vol. 2, Elsevier, pp. 1014-1020.

6 Delaidelli A., **Richner M.**, Jiang L., van der Laan A., Bergholdt Jul Christiansen I., **Ferreira N.**, Nyengaard J.R., **Vægter C.B.**, **Jensen P.H.**, Mackenzie I.R., Sorensen P.H. & **Jan A.**, 2021, 'α-Synuclein pathology in Parkinson disease activates homeostatic NRF2 anti-oxidant response', *Acta Neuropathologica Communications*, vol. 9, no. 1, 105.

7 Donovan L.L., **Henningsen K.**, Kristensen A.F., Wiborg O., Nieland, J.D. & Lichota J., 2021, 'Maternal Separation Followed by Chronic Mild Stress in Adulthood Is Associated with Concerted Epigenetic Regulation of AP-1 Complex Genes', *Journal of Personalized Medicine*, vol. 11, no. 3, 209.

8 **Dyla M.** & **Kjaergaard M.**, 2021, 'Intrinsic disorder in protein kinase A anchoring proteins signaling complexes'. *Dancing Protein Clouds: Intrinsically Disordered Proteins in the Norm and Pathology, Part C*. Elsevier, Amsterdam, Progress in Molecular Biology and Translational Science, vol. 183, pp. 271-294.

9 **Elfarrash S.** & **Jensen P.H.**, 2021, 'Organotypic hippocampal slices, an emerging tool to model synucleinopathies', *Neural Regeneration Research*, vol. 16, no. 5, pp. 999-1000.

10 **Elfarrash S.**, **Jensen N.M.**, **Ferreira N.**, Schmidt S.I., Gregersen E., Vestergaard M.V., Nabavi S., Meyer M. & Jensen P.H., 2021, 'Polo-like kinase 2 inhibition reduces serine-129 phosphorylation of physiological nuclear alpha-synuclein but not of the aggregated alpha-synuclein', *PLOS ONE*, vol. 16, no. 10, e0252635.

11 Farmen K., Nissen S.K., Stokholm M.G., Iranzo A., Østergaard K., Serradell M., Otto M., Svendsen K.B., Garrido A., Vilas D., Borghammer P., Santamaria J., Møller A., Gaig C., Brooks D.J., Tolosa E., Pavese N. & **Romero-Ramos M.**, 2021, 'Monocyte markers correlate with immune and neuronal brain changes in REM sleep behavior disorder', *PNAS*, vol. 118, no. 10, e2020858118.

12 Febbraro F., **Chen M.** & **Denham M.**. 2021, 'Generation of Human iPSCs by Episomal Reprogramming of Skin Fibroblasts and Peripheral Blood Mononuclear Cells' in *Nuclear reprogramming: Methods and protocols*. Humana Press, New York, Methods in Molecular Biology, vol. 2239, pp. 135-151.

13 Fedosova N., **Habeck M.** & **Nissen P.**, 2021, 'Structure and Function of Na,K-ATPase-The Sodium-Potassium Pump', *Comprehensive Physiology*, vol. 12, pp. 2659-2679.

14 **Ferreira N.**, **Gram H.**, Sorrentino Z.A., **Gregersen E.**, Schmidt S.I., **Reimer L.**, **Betzer C.**, Perez-Gozalbo C., Beltoja M., Nagaraj M., Wang J., Nowak J.S., Dong M., Willén K., Cholak E., Bjerregaard-Andersen K., Mendez N., Rabadia P., Shahnawaz M., Soto C., Otzen D.E., Meyer M., Giasson B.I., **Romero-Ramos M.** & **Jensen P.H.**, 2021, 'Multiple system atrophy-associated oligodendroglial protein p25α stimulates formation of novel α-synuclein strain with enhanced neurodegenerative potential', *Acta Neuropathologica*, vol. 142, pp. 87-115.

15 **Ferreira N.**, Gonçalves N.P., **Jan A.**, **Jensen N.M.**, van der Laan A., Mohseni S., Vægter C.B. & Jensen P.H., 2021, 'Trans-synaptic spreading of alpha-synuclein pathology through sensory afferents leads to sensory nerve degeneration and neuropathic pain', *Acta Neuropathologica Communications*, vol. 9, 31.

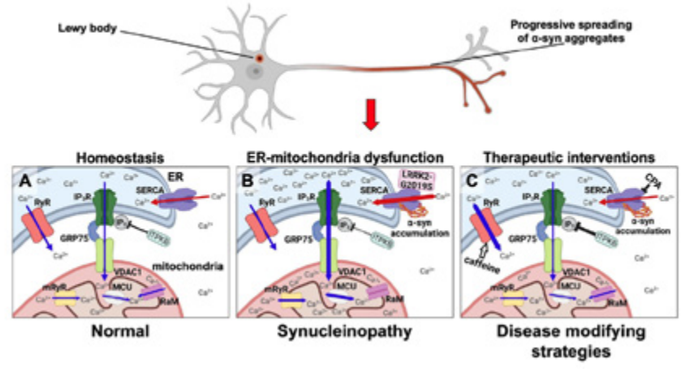
16 **Ferreira N.**, **Richner M.,** van der Laan A., Bergholdt Jul Christiansen I., **Vægter C.B.**, Nyengaard J.R., Halliday G.M., Weiss J., Giasson B.I., Mackenzie I.R., **Jensen P.H.** & **Jan A.**, 2021, 'Prodromal neuroinvasion of pathological α-synuclein in brainstem reticular nuclei and white matter lesions in a model of α-synucleinopathy', *Brain Communications*, vol. 3, no. 2, fcab104.

17 Focht D., Neumann C., **Lyons J.**, Eguskiza Bilbao A., Blunck R., Malinauskaite L., Schwarz I.O., Javitch J.A, Quick M. & **Nissen P.**, 2021, 'A non-helical region in transmembrane helix 6 of hydrophobic amino acid transporter MhsT mediates substrate recognition', *EMBO Journal*, vol. 40, no. 1, e105164.

18 **Gregersen E.**, **Betzer C.**, Kim W.S., **Kovacs G.**, **Reimer L.**, Halliday G.M., Thiel S. & **Jensen P.H.**, 2021, 'Alpha-synuclein activates the classical complement pathway and mediates complement-dependent cell toxicity', *Journal of Neuroinflammation*, vol. 18, 177.

19 Gunst J.D., Staerke N.B., Pahus M.H., Kristensen L.H., Bodilsen J., Lohse N., Dalgaard L.S., Brønnum D., Fröbert O., Hønge B., Johansen I.S.,




33


Monrad I., Erikstrup C., Rosendal R., Vilstrup E., Mariager T., Bove D.G., Offersen R., Shakar S., Cajander S., Jørgensen N.P., Sritharan S.S., **Breining P.**, Jespersen S., Mortensen K.L., Jensen M.L., Kolte L., Frattari G.S., Larsen C.S., Storgaard M., Nielsen L.P., Tolstrup M., Scædder E.A., Østergaard L.J., Ngo H.T.T., Jensen M.H., Højen J.F., **Kjolby M.** & Søgaard O.S., 2021, 'Efficacy of the TMPRSS2 inhibitor camostat mesilate in patients hospitalized with Covid-19-a double-blind randomized controlled trial.', *EClinicalMedicine*, vol. 35, 100849.

20 **Habeck M.** & **Poulsen H.**, 2021, 'What FXYDs fix', The Journal of general physiology, vol. 153, no. 6.

21 **Habekost M.**, Qvist P., **Denham M.**, Holm I.E. & Jørgensen A.L., 2021, 'Directly Reprogrammed Neurons Express MAPT and APP Splice Variants Pertinent to Ageing and Neurodegeneration', Molecular Neurobiology, vol. 58, no. 5, pp. 2075-2087.

22 Han H., Round E., Schubert R., Gül Y., Makroczyová J., Meza D., Heuser P., Aepfelbacher M., Barák I., Betzel C., Fromme P., Kursula I., **Nissen P.,** Tereschenko E., Schulz J., Uetrecht C., Ulický J., Wilmanns M., Hajdu J., Lamzin V.S. & Lorenzen K., 2021, 'The XBI BioLab for life science experiments at the European XFEL', *Journal of Applied Crystallography*, vol. 54, no. Part 1, pp. 7-21.

23 **Hansen S.B.**, **Dyla M.**, **Neumann C.**, **Quistgaard E.M.H.,** Andersen J.L., **Kjaergaard M.** & **Nissen P.**, 2021, 'The Crystal Structure of the Ca2+-ATPase 1 from Listeria monocytogenes reveals a Pump Primed for Dephosphorylation', *Journal of Molecular Biology*, vol. 433, no. 16, 167015.

24 Homberg J.R., Adan R.A.H., Alenina N., Asiminas A., Bader M., Beckers T., Begg D.P., Blokland A., Burger M.E., van Dijk G., Eisel U.L.M., Elgersma Y., Englitz B., Fernandez-Ruiz A., Fitzsimons C.P., van Dam A.M., Gass P., Grandjean J., Havekes R., Henckens M.J.A.G., Herden C., Hut R.A., Jarrett W., Jeffrey K., Jezova D., Kalsbeek A., Kamermans M., Kas M.J., Kasri N.N., Kiliaan A.J., Kolk S.M., Korosi A., Korte S.M., Kozicz T., Kushner S.A., Leech K., Lesch K.P., Lesscher H., Lucassen P.J., Luthi A., Ma L., Mallien A.S., Meerlo P., Mejias J.F., Meye F.J., Mitchell A.S., Mul J.D., Olcese U., González A.O., Olivier J.D.A., Pasqualetti M., Pennartz C.M.A., Popik P., Prickaerts J., de la Prida L.M., Ribeiro S., Roozendaal B., Rossato J.I., Salari A.A., Schoemaker R.G., Smit A.B., Vanderschuren L.J.M.J., **Takeuchi T.**, van der Veen R., Smidt M.P., Vyazovskiy V.V., Wiesmann M., Wierenga C.J., Williams B., Willuhn I., Wöhr M., Wolvekamp M., van der Zee E.A. & Genzel L., 2021, 'The continued need for animals to advance brain research', *Neuron*, vol. 109, no. 15, pp. 2374-2379.

25 **Jan A.**, **Gonçalves N.P.**, **Vaegter C.B.**, **Jensen P.H.** & **Ferreira N.**, 2021, 'The Prion-Like Spreading of Alpha-Synuclein in Parkinson's Disease: Update on Models and Hypotheses', *International Journal of Molecular Sciences*, vol. 22, no. 15, 8338.

26 **Jendroszek A.** & **Kjaergaard M.**, 2021, 'Nanoscale spatial dependence of avidity in an IgG1 antibody', *Scientific Reports*, vol. 11, 12663.

27 **Junior S.L.Y.**, **Martin J.,** Hulme O. & **Kvitsiani D.**, 2021, 'Choice history effects in mice and humans improve reward harvesting efficiency', *PLOS Computational Biology*, vol. 17, no. 10, e1009452.

28 Kaushik R., Lipachev N., Matuszko G., Kochneva A., Dvoeglazova A., Becker A., **Paveliev M.** & Dityatev A., 2021, 'Fine structure analysis of perineuronal nets in the ketamine model of schizophrenia', *The European journal of neuroscience*, vol. 53, no. 12, pp. 3988-4004.

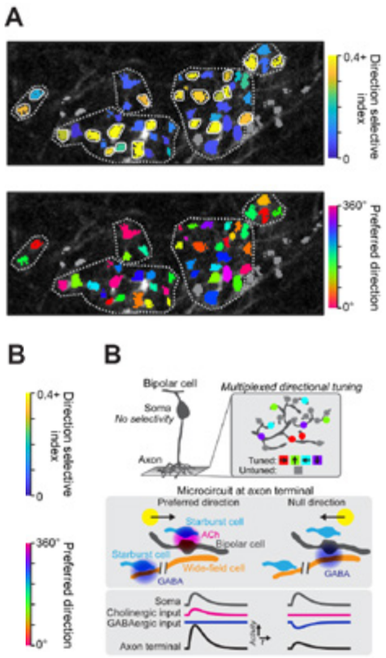
29 **Kjærgaard M.**, 2021, *Lagevrio: Hvordan virker de nye coronapiller?*, Forskerzonen.

30 **Kjaergaard M.**, Glavina J. & Chemes L.B., 2021, 'Predicting the effect of disordered linkers on effective concentrations and avidity with the "Ceff calculator" app.' in *Linkers in Biomacromolecules*. Academic Press, Methods in Enzymology, vol. 647, pp. 145-171.

31 **Kjaergaard M.**, Petersen N.C., Sørensen J.B. & **Takeuchi T.**, 2021, 'Introducing the special issue on "Proteins and Circuits in Memory"', *European Journal of Neuroscience*, vol. 54, no. 8, pp. 6691-6695.

32 **Kock Flygaard R.**, **Neumann C.**, **Anthony Lyons J.** & **Nissen P.**, 2021, 'Transport unplugged: KCCs are regulated through an N-terminal plug of the ion pathway', *EMBO Journal*, vol. 40, no. 14, e108371.

33 **Kovacs G.**, **Reimer L.** & **Jensen P.H.,** 2021, 'Endoplasmic Reticulum-Based Calcium Dysfunctions in Synucleinopathies', *Frontiers in Neurology*, vol. 12, 742625.




38


34 Lamy A., Macarini-Bruzaferro E., **Dieudonné T.**, Perálvarez-Marín A., Lenoir G., Montigny C., le Maire M. & Vázquez-Ibar J.L., 2021, 'ATP2, The essential P4-ATPase of malaria parasites, catalyzes lipid-stimulated ATP hydrolysis in complex with a Cdc50 β-subunit', *Emerging Microbes and Infections*, vol. 10, no. 1, pp. 132-147.

35 Lenoir G., D'Ambrosio J.M., **Dieudonné T.** & Čopič A., 2021, 'Transport Pathways That Contribute to the Cellular Distribution of Phosphatidylserine', *Frontiers in Cell and Developmental Biology*, vol. 9, 737907.

36 **Louth E.L.**, Jørgensen R.L., Korshoej A.R., Sørensen J.C.H. & **Capogna M.**, 2021, 'Dopaminergic Neuromodulation of Spike Timing Dependent Plasticity in Mature Adult Rodent and Human Cortical Neurons', *Frontiers in Cellular Neuroscience*, vol. 15, 668980.

37 Margetts-Smith G., Macnaghten A.I., Brebner L.S., Ziminski J.J., **Sieburg M.C.**, Grimm J.W., Crombag H.S. & Koya E., 2021, 'Acute, but not longer-term, exposure to environmental enrichment attenuates Pavlovian cue-evoked conditioned approach and Fos expression in the prefrontal cortex in mice', *European Journal of Neuroscience*, vol. 53, no. 8, pp. 2580-2591.

38 **Matsumoto A.**, Agbariah W., **Nolte S.S.**, Andrawos R., Levi H., Sabbah S. & **Yonehara K.**, 2021, 'Direction selectivity in retinal bipolar cell axon terminals', *Neuron*, vol. 109, no. 18, pp. 2928-2942.e8.

39 **Mermet-Joret N.**, **Capogna M.** & **Nabavi S.**, 2021, 'Fear Memory Relapse: The Importance of Input Associativity', *Trends in Neurosciences*, vol. 44, no. 5, pp. 337-339.

40 **Moreno A.**, 2021, 'Molecular mechanisms of forgetting', *European Journal of Neuroscience*, vol. 54, no. 8, pp. 6912-6932.

41 Møller P.L., Rohde P.D., Winther S., **Breining P.,** Nissen L., **Nykjær A.**, Böttcher M., Nyegaard M. & **Kjolby M.**, 2021, 'Sortilin as a Biomarker for Cardiovascular Disease Revisited', *Frontiers in cardiovascular medicine*, vol. 8, 652584.

42 **Nakamoto C.**, Goto Y., Tomizawa Y., Fukata Y., Fukata M., Harpsøe K., Gloriam D.E., Aoki K. & **Takeuchi T.,** 2021, 'A novel red fluorescence dopamine biosensor selectively detects dopamine in the presence of norepinephrine in vitro', *Molecular Brain*, vol. 14, no. 1, 173.

43 **Okuda K., Højgaard K.**, Privitera L., **Bayraktar G.** & **Takeuchi T.**, 2021, 'Initial memory consolidation and the synaptic tagging and capture hypothesis', *The European journal of neuroscience*, vol. 54, no. 8, pp. 6826-6849.

44 Oliveira L.M.A., Gasser T., Edwards R., Zweckstetter M., Melki R., Stefanis L., Lashuel H.A., Sulzer D., Vekrellis K., Halliday G.M., Tomlinson J.J., Schlossmacher M., **Jensen P.H.**, Schulze-Hentrich J., Riess O., Hirst W.D., El-Agnaf O., Mollenhauer B., Lansbury P. & Outeiro T.F., 2021, 'Alpha-synuclein research: defining strategic moves in the battle against Parkinson's disease', *npj Parkinson's Disease*, vol. 7, no. 1, 65.

45 Olsen D., Wellner N., Ollendorff M.K., de Jong I.E.M., Sotty F., Didriksen M., Glerup S. & **Nykjær A.**, 2021, 'Altered dopaminergic firing pattern and novelty response underlie ADHD-like behavior of SorCS2-deficient mice', *Translational Psychiatry*, vol. 11, 74.

46 **Quistgaard E.M.**, 2021, 'Erratum to 'BAP31: Physiological functions and roles in disease', *Biochimie*, vol. 189, pp. 168.

47 **Quistgaard E.M.H.**, **Nissen J.D.**, **Hansen S.** & **Nissen P.**, 2021, 'Mind the gap: molecular architecture of the axon initial segment – from fold prediction to a mechanistic model of function?', *Journal of Molecular Biology*, vol. 433, no. 20, 167176.

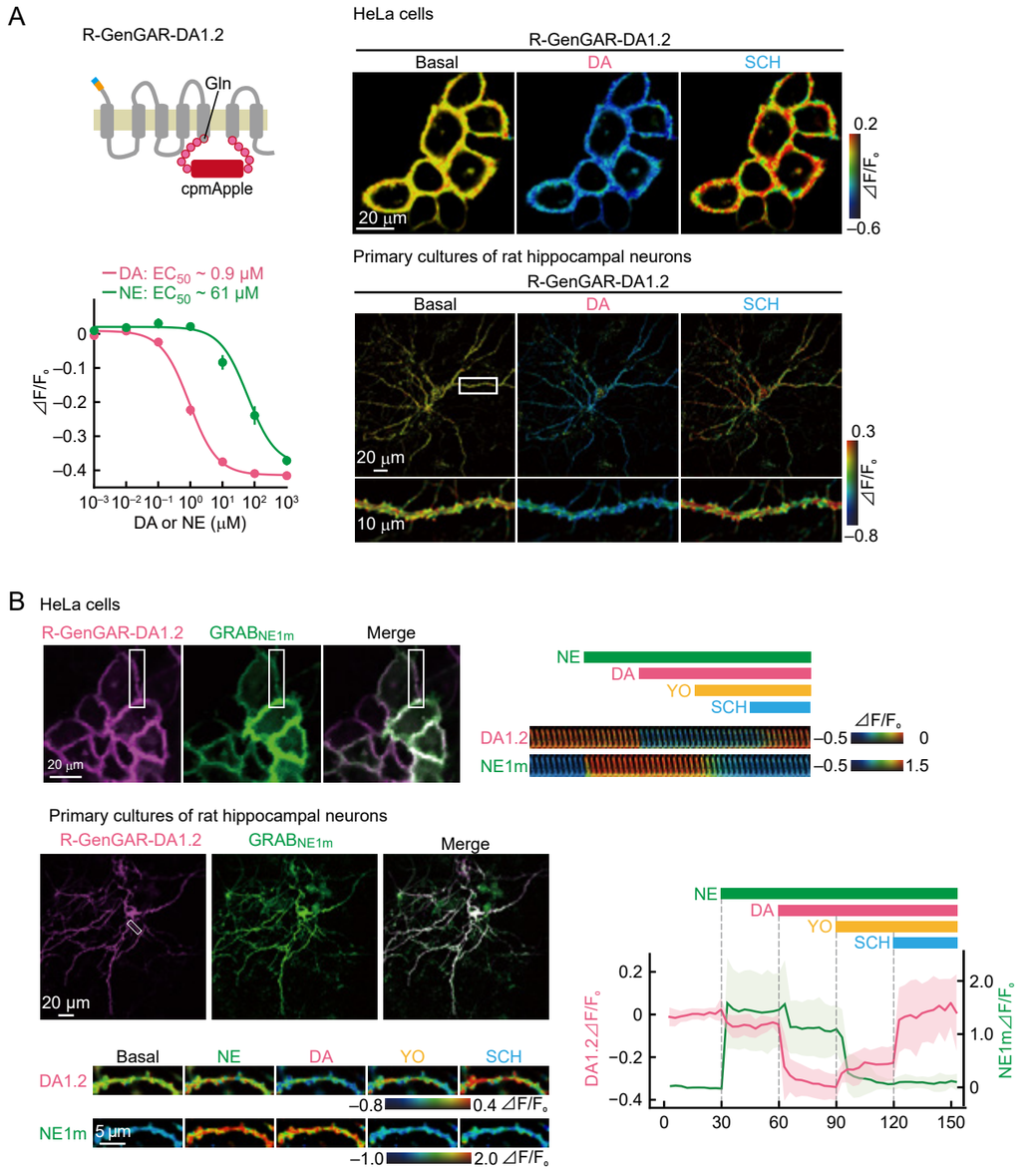
48 **Rasmussen R.N.**, **Matsumoto A.**, **Arvin S.** & **Yonehara K.**, 2021, 'Binocular integration of retinal motion information underlies optic flow processing by the cortex', *Current Biology*, vol. 31, no. 6, pp. 1165-1174.e6.

49 **Reimer L.**, **Betzer C.**, **Kofoed R.H.,** Volbracht C., Fog K., Kurhade C., Nilsson E., Överby A.K. & **Jensen P.H.,** 2021, 'PKR kinase directly regulates tau expression and Alzheimer's Disease-related tau phosphorylation', *Brain Pathology*, vol. 31, no. 1, pp.

50 Ruff T., Peters C., **Matsumoto A.**, Ihle S.J., Morales P.A., Gaitanos L., **Yonehara K.,** del Toro D. & Klein R., 2021, 'FLRT3 Marks Direction-Selective Retinal Ganglion Cells That Project to the Medial Terminal Nucleus', *Frontiers in Molecular Neuroscience*, vol. 14, 790466.

51 Sethuramanujam S., **Matsumoto A.**, deRosenroll G., Murphy-Baum B., McIntosh J.M., Jing M., Li Y., Berson D., **Yonehara K.** & Awatramani G.B., 2021, 'Rapid multi-directed cholinergic transmission in the central nervous system', *Nature Communications*, vol. 12, no. 1, 1374.

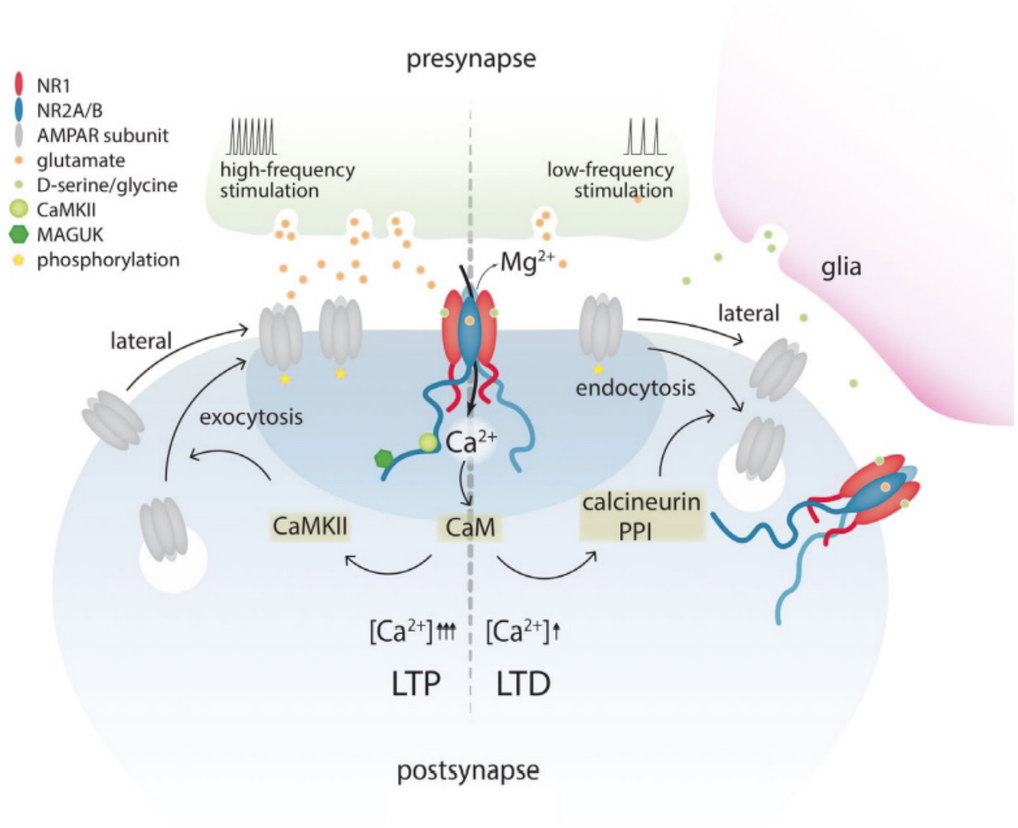



42


52 Shahsavar A., Stohler P., Bourenkov G., Zimmermann I., Siegrist M., Guba W., Pinard E., Sinning S., Seeger M.A., Schneider T.R., Dawson R.J.P. & **Nissen P.**, 2021, 'Structural insights into the inhibition of glycine reuptake', *Nature*, vol. 591, pp. 677-681.

53 Silberberg J.M., Corey R.A., Hielkema L., **Stock C.**, Stansfeld P.J., Paulino C. & Hänelt I., 2021, 'Deciphering ion transport and ATPase coupling in the intersubunit tunnel of KdpFABC', *Nature Communications*, vol. 12, no. 1, 5098.







54 Thomsen M.B., Ferreira S.A., Schacht A.C., Jacobsen J., Simonsen M., **Betzer C.**, **Jensen P.H.**, Brooks D.J., Landau A.M. & **Romero-Ramos M.**, 2021, 'PET imaging reveals early and progressive dopaminergic deficits after intra-striatal injection of preformed alpha-synuclein fibrils in rats', *Neurobiology of Disease*, vol. 149, 105229.

55 **Timcenko M.**, **Dieudonné T.**, Montigny C., **Boesen T.**, **Lyons J.A.**, Lenoir G. & **Nissen P.**, 2021, 'Structural Basis of Substrate-Independent Phosphorylation in a P4-ATPase Lipid Flippase', *Journal of Molecular Biology*, vol. 433, no. 16, 167062.

56 Trampari S., **Neumann C.M.T.**, **Hjorth-Jensen S.J.**, Shahsavar A., **Quistgaard E.M.H.** & **Nissen P.**, 2021, 'Insights into the mechanism of high lipid–detergent crystallization of membrane proteins', *Journal of Applied Crystallography*, vol. 54, no. Part 6, pp. 1775-1783.

57 Van Den Berge N., **Ferreira N.**, Mikkelsen T.W., Alstrup A.K.O., Tamgüney G., Karlsson P., Terkelsen A.J., Nyengaard J.R., **Jensen P.H.** & Borghammer P., 2021, 'Ageing promotes pathological alpha-synuclein propagation and autonomic dysfunction in wild-type rats', *Brain : a journal of neurology*, vol. 144, no. 6, pp. 1853–1868.

58 Vecchio L.M., Sullivan P., Dunn A.R., Bermejo M.K., Fu R., Masoud S.T., **Gregersen E.**, Urs N.M., Nazari R., **Jensen P.H.**, Ramsey A., Goldstein D.S., Miller G.W. & Salahpour A., 2021, 'Enhanced tyrosine hydroxylase activity induces oxidative stress, causes accumulation of autotoxic catecholamine metabolites, and augments amphetamine effects in vivo', *Journal of Neurochemistry*, vol. 158, no. 4, pp. 960-979.

59 **Warnet X.L.**, **Bakke Krog H.**, **Sevillano-Quispe O.G.**, **Poulsen H.** & **Kjaergaard M.**, 2021, 'The C-terminal domains of the NMDA receptor: How intrinsically disordered tails affect signalling, plasticity and disease', *European Journal of Neuroscience*, vol. 54, no. 8, pp. 6713-6739.




# Released preprints

1 Skoven C.S., Tomasevic L., **Kvitsiani D.**, Pakkenberg B., Dyrby T.B. & Siebner H.R., 2021, 'Profiling the transcallosal response of rat motor cortex evoked by contralateral optogenetic stimulation of glutamatergic cortical neurons' in: *bioRxiv*.

# PhD Dissertations 2021

**Gamaleldin M.**, 2021, Analysis of newly synthesized proteins and synaptic plasticity – a small step towards understanding memory. Aarhus University.

**Hjorth-Jensen S.J.**, 2021, Crystallographic investigations of the sarco/endoplasmic reticulum Ca2+-ATPase: towards neutron, time-resolved, and novel inhibitor structures. Aarhus University.

**Neumann C.M.T.**, 2021, Structural studies of LeuT-fold transporters: 1) Investigation of the binding site specificity and promiscuity of the multihydrophobic amino acid transporter, MhsT; 2) Towards a cryo-EM structure of cation:chloride co-transporters. Aarhus University.

**Rasmussen R.N.**, 2021, On the contributions of retinal direction selectivity to cortical motion processing. Aarhus University.

**Trampari S.**, 2021, Crystallization and phase behaviour of membrane transporters in lipid-detergent micelles. Aarhus University.

## DANDRITE ANNUAL REPORT 2021


**PRODUCED BY:**
DANDRITE – The Danish Research Institute of Translational Neuroscience

**EDITOR:**
Maria Thykær Jensen

**DESIGN & LAYOUT:**
Hreinn Gudlaugsson, AU Research and External Relation

**PHOTOS:**
DANDRITE, Lundbeckfonden, The Novo Nordisk Foundation, AU Communications

**PRINT:**
Fællestrykkeriet

**EDITION:**
125

**DANDRITE.AU.DK**

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**