22

DANDRITE ANNUAL REPORT

AARHUS UNIVERSITY

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

Frontpage figure from:
Seeler, Sabine; Andersen, Maria Schertz; Sztanka-Toth, Tamas et al, 'A Circular RNA Expressed from the FAT3 Locus Regulates Neural Development', Molecular Neurobiology, Vol 60, 06.2023, pp. 3239–3260.

Words from the Director

It's with great pleasure to present the 2022 annual report from DANDRITE – the Danish Research Institute of Translational Neuroscience and the Danish node of the Nordic EMBL Partnership for Molecular Medicine.

2022 marked DANDRITE's 10th year of operations, and thus, we are now slowly moving towards the teenage years of our research center – and at the same time into the transition with group leaders from the first cohort leaving and new ones arriving creating a new generation of DANDRITE group leaders. Group leader Taro Kitazawa joined us in August 2022, and he is currently building up his lab and hiring staff members. Furthermore, during 2022 DANDRITE recruited another two group leaders who started with us in early 2023: Thomas Kim arriving from Johns Hopkins University, USA, and Chao Sun arriving from Max Planck Institute for Brain Research in Frankfurt, Germany. All three bring strong, inspiring research programs and new ideas and spirit. Two more group leaders will come in 2024-2025 completing our core structure of five group leader programs. We look very much forward to continuing to develop the research community at and around DANDRITE. Having established the organization and lived through the first decade, now is also the opportunity to re-evaluate, refine and improve it. Looking ahead we would like to stimulate further the integration of translation and innovation in our research. By pursuing innovation and clinical translation our discoveries disseminate also to people around us in the most effective way, and it creates jobs and developments in biotech and excellent career opportunities for students and postdocs who seek careers in neuroscience research, be that basic or applied.

We are also initiating new actions on joint research core facilities and staff in collaboration with our host departments – the Dept. Molecular Biology & Genetics at the Science Faculty and the Dept. Biomedicine at the Health Faculty. We hope that these structures and how they operate will develop into good models for the research communities at Aarhus University as a whole to contribute to high-end research equipment and scientific staff on e.g. imaging, animal facilities, and "omics" technologies.

In June, the DANDRITE's fifth Scientific Advisory Board meeting was held at Sandbjerg Manor where we welcomed Cornelius Gross and Peter Scheiffele for their first turn as DANDRITE Scientific Advisory members. With the rotation principle, we also said goodbye to two other members of the Scientific Advisory Board, namely Carl Petersen and Rüdiger Klein, who have been of immense help and support throughout their term on SAB. With the rotation principle and model for the SAB we strive to ensure a good balance of continuity and dynamics to the gradually changing profiles and focus of the group leader programs. Based on advice from SAB we have invited Prof. Jelena Radulovic on the senior management starting from 2023 to expand our international basis and our expertise in neuroscience. We are very grateful to Jelena that she immediately accepted and joined our discussions and actions while also having many important responsibilities in Aarhus and New York.

We have also been working on equity, diversity, and inclusion at DANDRITE, both in day-to-day business and for example calls for recruitment. Further, we are planning a new initiative to tap from the valuable knowledge and experience of our staff and students that we have called the DANDRITE Diversity Task Force. With this, we wish to gain knowledge from the good things and challenges that our community has been experiencing or witnessing when going to work. In a series of meetings, we will work to define tangible challenges and develop solutions, together with our staff and students. In line with Aarhus University 'Action plan for gender equality, diversity, and inclusion 2023-2025, we believe the DANDRITE Diversity Task Force can support the goal of creating an inclusive workplace culture while eliminating unfair barriers toward scientific advancement and creating a safe and diverse workspace for everyone.

In December 2022, we lost our close friend and affiliated researcher and professor Marco Capogna. His spirit and soul in neuroscience was a tremendous inspiration to us all and his passing is an immense loss to his family, friends, and colleagues. He is still with us in our thoughts, memories and research, and scientific visions, and he will never be forgotten but always be missed. In his honor and memory, we wish to commemorate him with a text piece in this year's report – we look forward to 8 November 2023 when a symposium will be held in his honor.

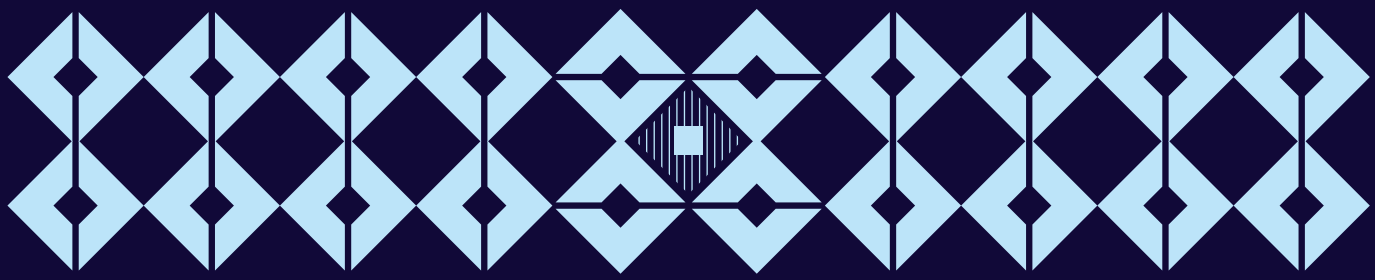
In the report, you can explore the many great events that DANDRITE hosted throughout 2022, find stats on our personnel of 2022, and dive into the list of published papers and grants received. Group leader Taro Kitazawa was awarded the ERC starting grant of EUR 1,5M, and senior group leader Poul Henning Jensen received DKK 20M from the Lundbeck Foundation's Collaborative Projects programme to shed new light on Parkinson's disease – just to mention a few highlights.

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

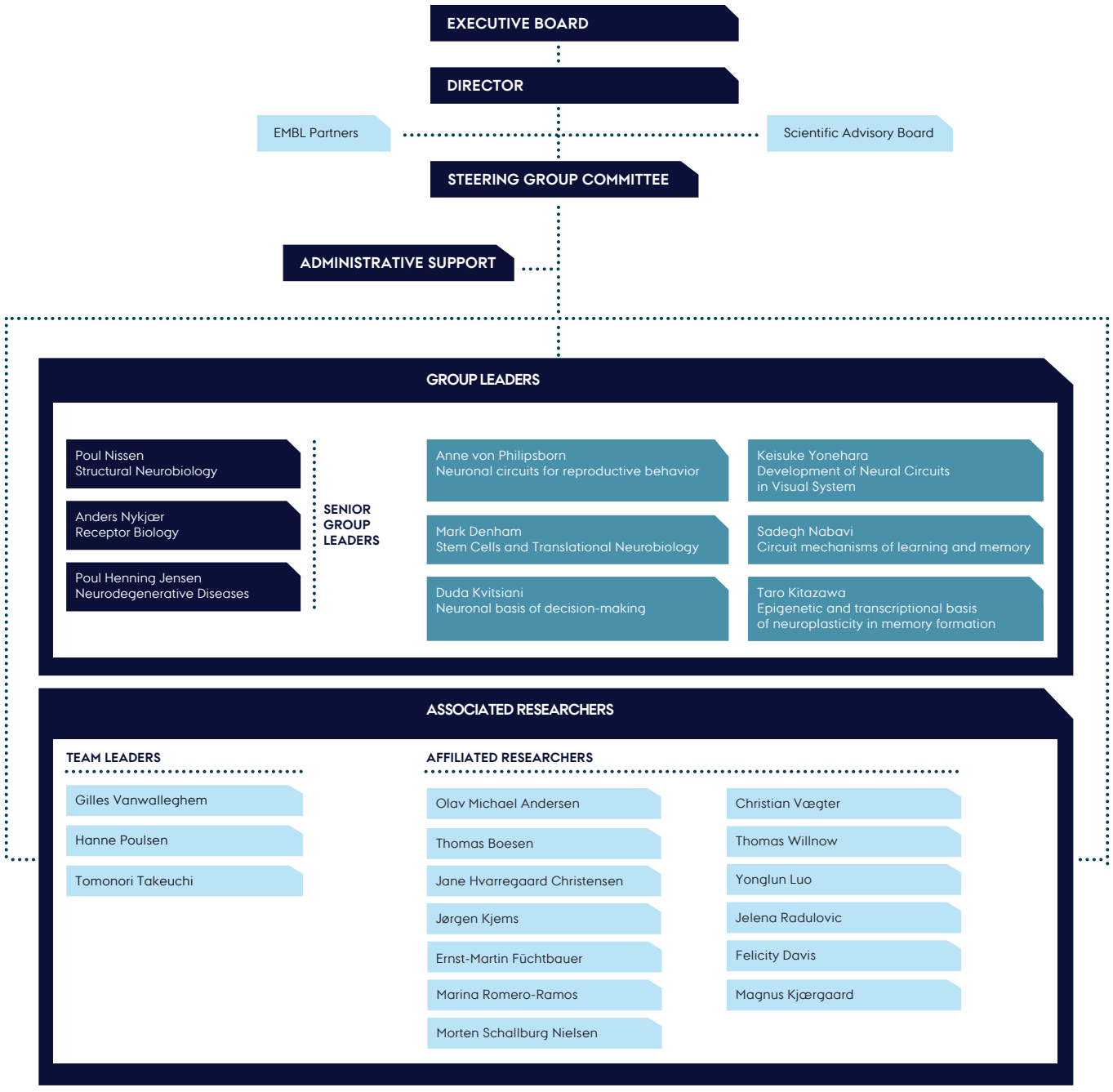
With warm regards,

Poul Nissen, Director and Senior Group Leader

01 Organization Structure



ORGANIZATION STRUCTURE



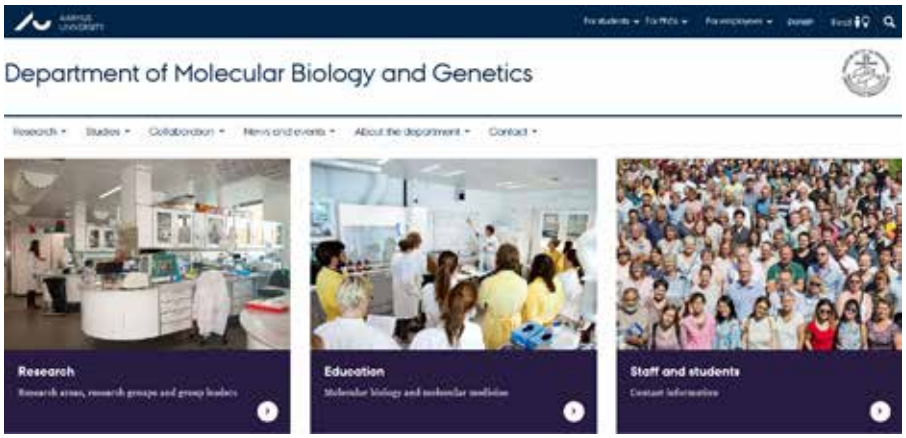
HOSTING DEPARTMENTS

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 the Department of Biomedicine bridges the divide between natural science and clinical medicine, and the results are used to improve the 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 the Department of Molecular Biology and Genetics spans from basic to applied research within molecular biology and genetics. Several focus areas at the departments are involved in neuroscience research – specifically Structural Biology, Gene Expression, and Gene Medicine.



→ mbg.au.dk/en

EXECUTIVE BOARD

The Executive Board meets twice a year and consists of the Chairman, the Deans of the two founding faculties, the Director, the leaders of the Core Teams, observing representatives from The Lundbeck Foundation, 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)

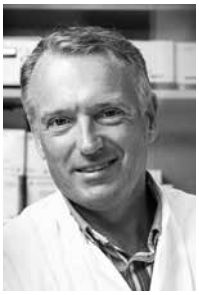
Dean **Kristian Pedersen**, Faculty of Natural Sciences, Aarhus University

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 senior 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 the running budget. The steering committee will also be overseeing public dissemination and outreach of DANDRITE research and activities. The committee in 2022 consisted of the following members:

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

Furthermore, the steering committee meetings are attended by:

- Research Group Coordinator, **Astrid Munk**
- Research Group Coordinator, **Rikke Skovgaard Lindhard**
- Director PA, **Karen Bech-Pedersen**
- 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, Team leaders, and spokespersons for each personnel category at DANDRITE. In 2022 the participants were:

- All DANDRITE Group Leaders
- All DANDRITE Team Leaders
- Affiliated Researcher spokesperson: **Yonglun Lou**
- Postdoc Spokesperson: **Rachel Kelly**
- PhD student spokesperson: **Pia Boxy**
- Technicians spokesperson: **Anne Katrine Vestergaard**

MONTHLY COORDINATION MEETING
Monthly the DANDRITE core Group Leaders and Chief Administrator meet with the heads of the two hosting departments (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 fifth DANDRITE advisory board meeting took place as on 2-3 June 2022. The current members of the DANDRITE SAB are:

1. Professor and chair of DANDRITE SAB **Rüdiger Klein**, Max-Planck-Institute of Neurobiology (rotating out)
2. Professor **Yang Dan**, University of California, Berkeley
3. Professor **Ole Kiehn,** University of Copenhagen
4. Professor **Carl Petersen**, École polytechnique fédérale de Lausanne EPFL (Rotating out)
5. Professor **Elena Cattaneo**, University of Milan, Italy
6. Professor **Veerle Baekelandt**, KU Leuven - Center for Molecular Medicine, Belgium
7. Professor **Cornelius Gross**, Interium Head of EMBL, Rome, Italy
8. Professor **Peter Scheiffele**, University of Basel, Switzerland

New members who will take part in the planned SAB meeting in 2024:

9. Professor **Ryohei Yasuda**, Max Planck Florida Institute for Neuroscience
10. Professor **Volker Haucke**, FMP, Berlin

ASSOCIATED RESEARCHERS

Associate Membership serves as a strategic tool for the further development of DANDRITE's research focus areas and must be of mutual benefit. The 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 a possible extension for a total of a maximum of 8 years.

An affiliated researcher is typically, an Aarhus University researcher with a permanent position that is tightly associated with 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 positions at associated professor level or higher.

In 2022, Associate Professor Felicity Mae Davis joined as Affiliated Researcher to DANDRITE.

ADMINISTRATIVE SUPPORT TEAM

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

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

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

In 2022 we welcomed a new member to our administrative team namely Rikke Skovgaard Lindhard who started as research group coordinator in August.

Throughout the year 2022, the team continued to develop and improve procedures and services e.g., improved onboarding procedures, expanded DANDRITE's presence on the social media platform LinkedIn, and created more video content. Further, we have worked with equality, diversity, and inclusion in connection with preparing an action plan for the next GL recruitment round, and we have even taken steps towards establishing a DANDRITE task force for equality, diversity, and inclusion.

Young DANDRITE

– The PhD & Postdoc association at DANDRITE

Young DANDRITE aims to facilitate interaction and unity among PhD students and Postdocs at DANDRITE and support the 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 of Young DANDRITE are highly valued and their engagement in DANDRITE events is crucial to the innovation and unity of DANDRITE.

In 2022, YoDa has organized a variety of scientific and social events for young researchers in DANDRITE. They are engaged with career advancement, methods on how to get ahead, and active steps they themselves can take toward advancing their careers. To support this, YoDA arranged together with the HR department a presentation of 'Opportunities in academia – rules and reality', where the participants gained insight into the system in Danish universities. Especially the international researchers found this useful, as the system can be difficult to navigate. YoDA also invited one of the DANDRITE Affiliated Researchers, Associate Professor Marina Romero-Ramos to give an inspiring talk about her career path, balanced with family life, and how she ended up where she is today.

Members of the Young DANDRITE organizing committee during 2022
Katia Soud, PhD student, Takeuchi lab
Karen Marie Juul Sørensen, PhD student , Nykjær lab
Lucie Woloszczuková, PhD student, Nykjær lab
Mads Christensen, PhD student, Nissen lab
Pia Boxy, Research Assistant, Nykjær lab
Ea Trond Hvid Jensen, Master student, Nykjær lab
Kristyna Safrankova, Research Assistant, Nykjær lab
Nanna Møller Jensen, PhD student, Jensen lab
Rachel Kelly, Postdoc, Denham lab
Sean Hansen, PhD student, Nissen lab

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

PhD representative: Pia Boxy
Postdoc representative: Rachel Kelly

YoDa.
Illustration by:
Sophie Seidenbecher, PhD

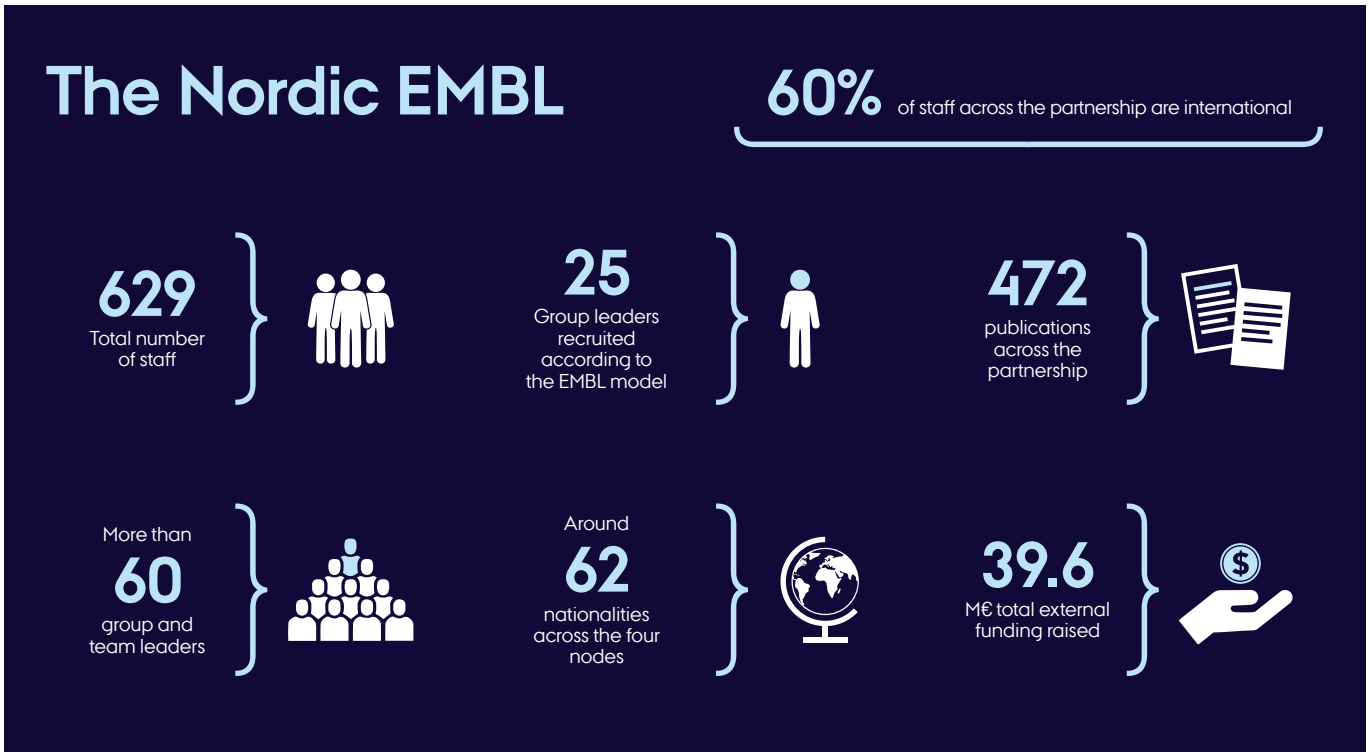
THE NORDIC EMBL PARTNERSHIP FOR MOLECULAR MEDICINE

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 open international collaboration in translational molecular medicine research and shares 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, DANDRITE expanded the partnership as the fourth node representing Denmark.

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 2022

New EMBL Program 2022-2026
In 2022, EMBL launched its new research program, "Molecules to Ecosystems." The program will run for the next five years and aims to expand EMBL's scope of study to include the molecular basis of life in changing environments. The goal is to bridge the gap between molecular biology and other disciplines such as ecology, epidemiology, engineering, and mathematics. With this new program, EMBL is working to address some of the major challenges facing life on Earth today, such as the spread of infectious diseases, loss of biodiversity, environmental degradation, and climate change. ■

EVENTS

The 4th EMBL Partnership Conference in Heidelberg
In September 2022, 28 researchers from DANDRITE attended a three-day conference in Heidelberg to exchange knowledge and collaborate with researchers from around the world. The conference was divided into three different topics: stem cells and development, neurobiology, and genomics and disease. This allowed more young researchers to present their research projects and it fostered discussions among the attendees. Over 10 young DANDRITE researchers participated in the poster session, and Ph.D. Lucie Wolosczcukova from the Nykjær Group won one of the five poster prizes with her poster "Exploring SorCS3 signaling during zebrafish, mouse, and human brain development." ■

DANEMO Symposium
In November 2022, the Danish support and Communications platform, DANEMO, held a successful symposium with speakers and participants from across Europe. The aim of the symposium was to raise awareness of the new EMBL program "Molecules to Ecosystems" and to increase knowledge about EMBL and EMBO among students and researchers in Denmark. The event brought together around 120 participants from Denmark and different EMBL sites and inspired discussions about new collaborations and scientific services. ■

KNOWLEDGE SHARING

Opening of a new EMBL Imaging Center
On June 30th, 2022, a new EMBL Imaging Center officially opened at the EMBL headquarters in Heidelberg. The center offers the highest resolution EM and LM technologies and allows researchers from Europe and beyond to carry out groundbreaking research. It will also serve as a training facility for the latest microscopy technologies and support research in all areas of life sciences. ■

DANDRITE hosted a six-day PhD-course in neural organization
In May 2022, DANDRITE Group Leader Sadegh Nabavi taught a six-day PhD course on the neural design of the brain. The aim of the course was to provide a deep understanding of the nervous system, its design, efficiency, and power. The course was partially funded by the NordForsk Research Infrastructure hub, and 7 PhD students from Denmark and the Nordic Partnership attended. The course will be offered again in June 2023. ■

PERSONNEL

New Director and Communications Officer of the Nordic Partnership

As of January 1st, 2023, Professor Oliver Billker from Molecular Infection Medicine Sweden (MIMS) at Umea University assumed the role of the new speaker of the Nordic Partnership. He replaces the Professor of genetics and director of the Institute for Molecular Medicine Finland (FIMM) Mark Daly.

Oliver Billker studies the molecular basis of infection, primarily focusing on malaria parasites. He will hold the position of speaker of the Nordic Partnership for the next four years.

With the start of 2023, the Communications Officer of the Partnership has changed. Gretchen Repasky, who has served as the Communications Director since 2021, has taken on a new role as Operating Officer at the Danish Diabetes Academy. Nora Lehotai, who was previously the acting Communications Officer at the Swedish node, MIMS, has taken over as Communications Officer. She holds a Ph.D. in plant science and brings a scientific background to the role.

Together with Oliver Billker, the new Director and Communications Officer of the Nordic Partnership, Nora will lead the effort to increase visibility and awareness of opportunities across the four Nordic EMBL nodes. ■

Oliver Billker,
Photo by Mattias Petterson

Nora Lehotai,
Photo by Niklas Mähler

02 Research Activities

Kitazawa Group

Epigenetic and transcriptional basis of neuroplasticity in memory formation

Photo of
Taro Kitazawa
By L. Heilesen

Neuroplasticity serves as the foundation of learning and memory formation, which are indispensable to our lives. Its deficits give rise to an array of disorders, including dementia and post-traumatic stress disorder (PTSD). We will tackle on fundamental questions regarding the epigenetic and transcriptional underpinning of memory-encoding neuronal ensemble formation. To this end, we will employ a multidisciplinary approach that encompasses genomics, mouse genetics, circuit analysis, and bioinformatics.

Our laboratory is built upon two main pillars. First, we will leverage high-end epigenomics and genomics sequencing technologies to uncover the molecular basis of memory-encoding neuronal ensemble formation. We will employ gene knock-down and/or overexpression, as well as optogenetics technologies, to evaluate the functional relevance of our findings based on genomics profiles. Second, we will develop novel high-throughput sequencing technologies, such as whole genome history tracing, which will overcome the critical limitations of existing snapshot-type technologies. These advanced methodologies will enable us to gain insights into how heterogeneity of neuronal ensemble is generated.

FUTURE PLANS

EPIGENETICS AND MEMORY FORMATION

Memory representation has been described as a memory trace or memory engram ensemble. Engram cells are defined as neurons that are activated and transiently express immediate early genes (IEGs) during a learning experience and have undergone physical and/or chemical changes that can be preferentially reactivated by recall experience (Figure 1). Uncovering the molecular basis of neuroplasticity in engram cell formation is considered a crucial issue in memory research.

We will tackle on this issue from the perspective of epigenetic chromatin and transcriptional analysis. Epigenetics is the study of how cells control gene activity without altering the DNA sequence. This includes the chemical modification of DNA, the post-translational modification of histone tails, chromatin accessibility, and the three-dimensional organization of chromatin in the nucleus. While a large body of literature has shown the relevance of epigenetic and transcriptional regulation in memory formation, its role in engram ensemble has been elusive this far.

EPIGENETIC AND TRANSCRIPTIONAL ANALYSIS OF NEURONAL ENSEMBLE

In a recent study, we revealed a novel epigenetic and transcriptional mechanism regulating the activation of IEGs during sensory neuron maturation (Kitazawa et al., Nature Genetics 2021, Figure 2). We found that in sensory neurons, IEGs are embedded in a unique 'bipartite' Polycomb

chromatin signature at the pre-sensory stage. This is a novel epigenetic chromatin mechanism regulating the rapidity and amplitude of the transcriptional response of IEGs at pre-sensory stages.

In the DANDRITE, our group will leverage this research expertise to investigate how neuronal activity-dependent epigenetic and transcriptional regulation underlies memory engram ensemble plasticity. First, we will carry out epigenetic and transcriptional profiling of engram cells using state- of-the-art high-throughput sequencing genomics technologies (e.g., single-cell and bulk RNA-seq, ATAC-seq, ChIP-seq, 3C-seq). Second, after identifying relevant factors, we will carry out functional analysis by gene knocking-down/overexpression and optogenetics to assess the recent and remote memory phenotypes at the levels of molecular signatures, morphologies, and behavior.

HETEROGENEITY OF NEURONAL ENSEMBLES AND DEVELOPMENT OF NEW GENOMICS TECHNOLOGIES

Heterogeneity of engram cells is emerging as a hot topic. Recent advance-

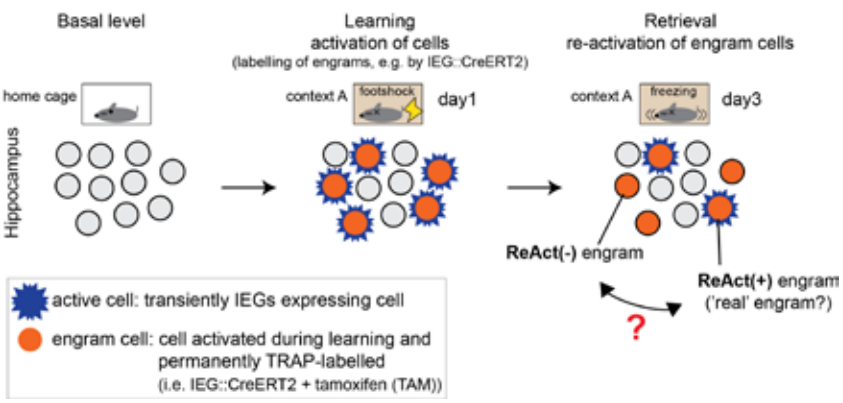


Figure 1: Memory engram cell formation in contextual fear conditioning.
During learning, (footshock in context-A, middle), sparse ensemble of hippocampal neurons are activated and express IEGs. These neurons are then labeled as an engram ensemble by IEG::CreERT2 (e.g., TRAP system). Upon re-exposure to conditioning stimulus (context-A, right), engram cells preferentially get reactivated and re-express IEGs, resulting in memory retrieval (freezing). Indeed, it remains a conundrum why only a subset of engram cells are reactivated (ReAct(+)) upon memory retrieval. By T. Kitazawa.

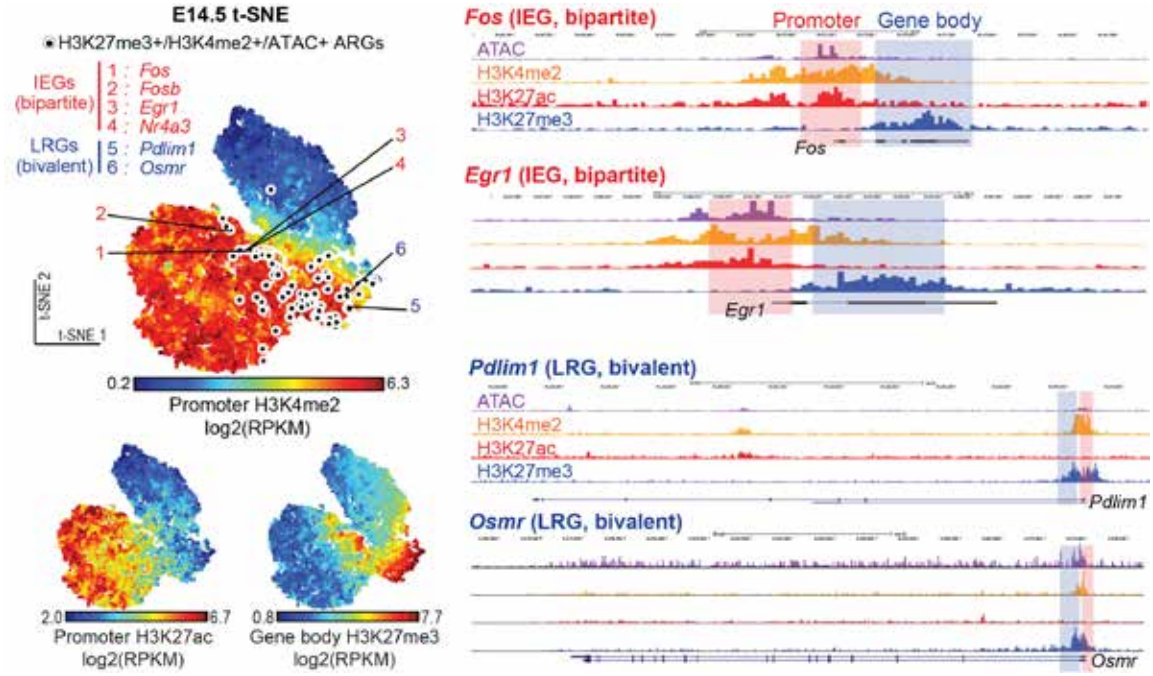


Figure 2: Epigenetic and transcriptional mechanism regulating IEG inducibility in sensory neurons.
t-SNE representation (left) and genome browser view (right) of epigenetic chromatin organization in neuronal activity-response genes at pre-sensory stage (E14.5). In sensory neurons, prior to sensory activity-dependent induction, IEGs (e.g., Fos, Egr1) are embedded into a unique 'bipartite' Polycomb chromatin signature. Namely, IEGs carry an active H3K27ac mark on promoters, but a repressive Polycomb-H3K27me3 mark on gene bodies, which is clearly distinct from the classic Polycomb bivalent organization found in activity late-response genes (LRGs). By T. Kitazawa.

ments in single-cell technologies have started to reveal that neurons belonging to the same engram ensemble that represents a specific memory are composed of a heterogeneous subpopulation of cells carrying distinct molecular signatures, circuit-specificity, and/or functional outputs. With respect to this, it remains as a conundrum why only a limited fraction (10-40%) of engram cells can be reactivated upon memory retrieval. In other words, an ensemble of neurons called engram cells can be subdivided into cells that get reactivated (ReAct(+)) and not get reactivated (ReAct(-)) upon natural recall (Figure 1, right). It is hypothesized that ReAct(+) engram cells may be functionally more relevant in learning and/or retrieval as compared with ReAct(-) cells and may consist of the "real" engram ensemble.

At DANDRITE, we aim to reveal the dynamic processes of ReAct(+) vs. ReAct(-) engram cell identity specification at the molecular level and reveal the functional relevance of these subpopulations. To this end, we will develop a novel retrospective history tracing genomics technology and apply this to overcomethe bottlenecks of existing snapshot-type approaches.

Kitazawa Group members

PERSONNEL LIST 2022

Sofie Winther Andersen: Lab technician
Kathrine Meinecke Christensen: Lab technician
Valentina Khalil: Postdoc researcher
Taro Kitazawa: Group Leader, Associate Professor

HIGHLIGHTS 2022

ERC-StG 'MemoPlasticGenomics'

Epigenetic and Transcriptional Regulation of Spontaneous and Sensory Activity Dependent Programs During Neuronal Circuit Development (https://www.frontiersin.org/articles/10.3389/fncir.2022.911023/full)

Different Ectopic Hoxa2 Expression Levels in Mouse Cranial Neural Crest Cells Result in Distinct Craniofacial Anomalies and Homeotic Phenotypes (https://www.mdpi.com/2221-3759/10/1/9)

Denham Group

Stem Cells and Translational Neurobiology

Group Leader
Mark Denham

The Denham lab works with pluripotent stem cells and uses these to understand how the human nervous system develops, with a specific interest in the differentiation of pluripotent stem cells into dopaminergic (DA) neurons for the treatment of Parkinson's disease (PD). The lab is exploring two primary approaches: a cell replacement therapy for Parkinson's disease and in vitro disease modeling.

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.

CELL REPLACEMENT THERAPY FOR PARKINSON'S DISEASE WITH LINEAGE RESTRICTING STEM CELLS.
Parkinson's disease is caused by the gradual loss of the mesencephalic dopaminergic neurons, and a potential cell therapy involves transplanting dopaminergic progenitors into the striatum to replace the lost neurons. However, the current state-of-the-art differentiation protocols result in only a minor percentage of the transplanted cells becoming dopaminergic neurons. To address this, the lab has developed a novel approach that genetically restricts the stem cell's ability to differentiate down non-dopaminergic lineages.

HIGHLIGHTS 2022

Bergmann T, Liu Y, Skov J, Mogus L, Lee J, Pfisterer U, Handfield LF, Asenjo-Martinez A, Lisa Vargas I, Seemann SE, Lee JTH, Patikas N, Kornum BR, **Denham M**, Hyttel P, Witter MP, Gorodkin J, Pers TH, Hemberg M, Khodosevich K, Hall VJ (2022) Production of human entorhinal stellate cell-like cells by forward programming shows an important role of Foxp1 in reprogramming Front. Cell Dev. Biol. https://doi.org/10.3389/fcell.2022.976549

Maimaitili M, **Chen M**, Febbraro F, Mermet-Joret N, Lauritsen J, **Ucuncu E**, Klæstrup IH, Qvist P, Nabavi S, Romero-Ramos M, **Denham M**. Enhanced Production of Mesencephalic Dopaminergic Neurons from Lineage-Restricted Human Undifferentiated Stem Cells. bioRxiv 2021.09.28.462222 https://doi.org/10.1101/2021.09.28.462222

Seeler S, Andersen MS, Sztanka-Toth T, Rybiczka-Tešulov M, van den Munkhof MH, Chang CC, Maimaitili M, Venø MT, Hansen TB, Pasterkamp RJ, Rybak-Wolf A, **Denham M**, Rajewsky N, Kristensen LS, Kjems J. A Circular RNA Expressed from the FAT3 Locus Regulates Neural Development. Mol Neurobiol. 2023 Feb 25. doi: 10.1007/s12035-023-03253-7. Online ahead of print.

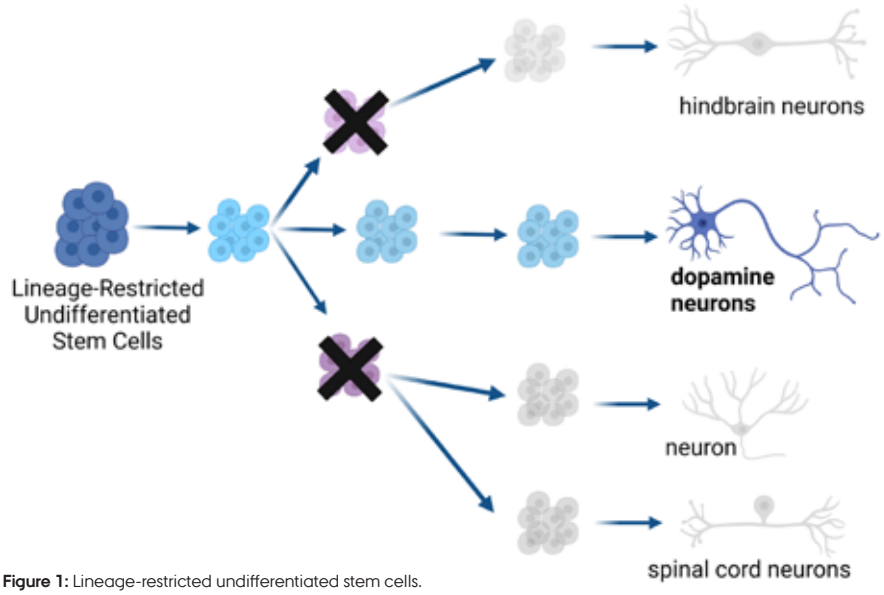


Figure 1: Lineage-restricted undifferentiated stem cells.

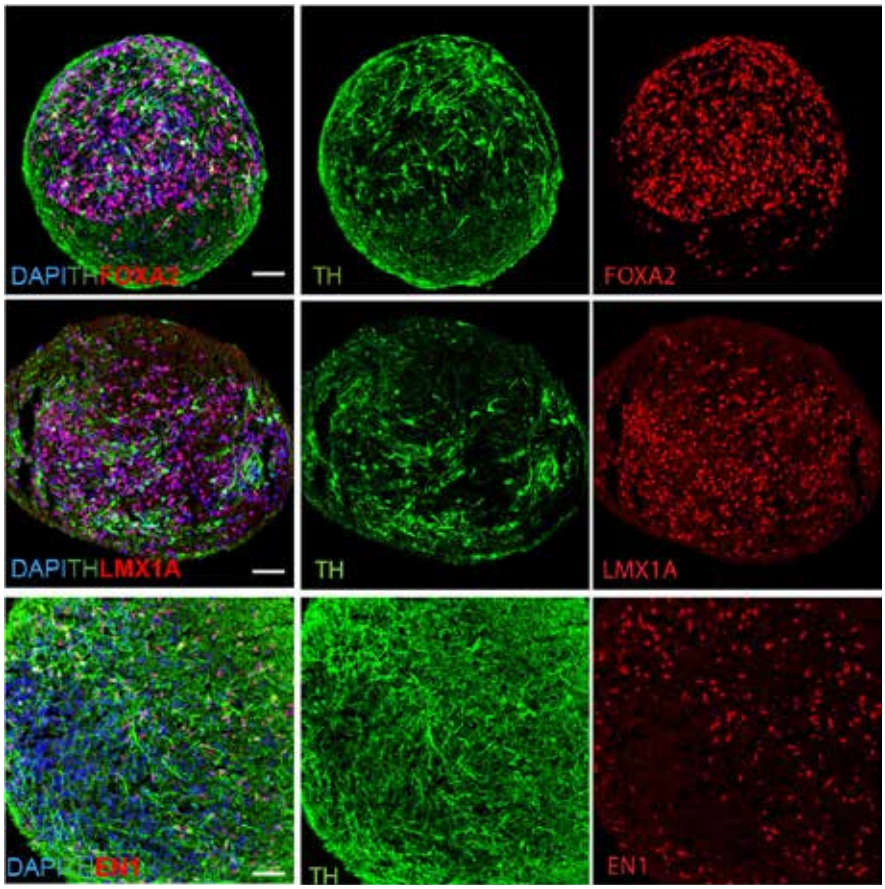


Figure 2: Miniaturized human midbrain organoids. (A) Midbrain organoids are stained with dopaminergic neuronal markers FOXA2/TH, LMX1A/TH, EN1/TH..

Denham group members.

They achieve this by knocking out transcriptional regulators critical for specifying alternate lineages. They call these lineage-restricted undifferentiated stem cells (LR-USCs). LR-USCs robustly generate mesencephalic dopaminergic neurons under a broad range of differentiation conditions, making them ideal for large-scale production. The lab is also applying this approach to create other relevant cell types for various diseases.

MINIATURISED CONTROLLED ORGANOIDS (MICOS) FOR DISEASE MODELING

Another important area of research in the lab is the development of miniaturized controlled organoids (MiCOs) that provide a more accurate and reproducible model for studying neurological disorders. Traditional organoids are large and demonstrate inter-organoid structural and cellular variation, which makes them unsuitable for high-throughput disease modeling and drug screening. By starting with regionally patterned neural progenitors and miniaturizing the organoids, the lab can generate organoids with higher reproducibility in their neuronal composition. The lab is also working to enhance the maturation and mimic in vivo cellular diversity by adding astrocytes and microglia progenitors into the organoids.

In collaboration with the stem cell team at Novo Nordisk they are comparing human neurons derived from organoids with in vivo mature human stem cell-derived neurons. This comparison will help us understand how long it takes for in vitro neurons to become mature and what factors and supporting cell types are required. Overall, the MiCO platform will aid in developing new drug compounds for treating a broad range of neurological disorders. For more information on this project, visit: https://projects.au.dk/odin/scientificscope/funded-odin-projects/mico-platform/

PERSONNEL LIST DENHAM GROUP 2022

Group leader: **Mark Denham**
Assistant Professor: **Muwan Chen**
Postdoc: **Rachel Kelly**
Laboratory Technician: **Susanne Hvolbøl Buchholdt**
Laboratory Technician: **Sanne Nordestgaard Andersen**
Erasmus Student: **Macrina Milani Capialbi**
Erasmus Student: **Gennaro Di Bonito**

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 a 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 the 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 tasks (Fig.1) we discovered that animals rely both on their past reward and choice history to optimize the reward harvesting efficiency.

KEY PUBLICATIONS

JS Lopez-Yepez, A Barta, M Moltesen, J Martin, TF Woo, O Hulme, D Kvitsiani. "Representation of senori-motor states in mouse medial prefrontal cortex". Research Square. February 17, 2023

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. Choice history effects improve reward harvesting efficiency in mice and humans. Plos.Com. Biol. October 4, 2021.

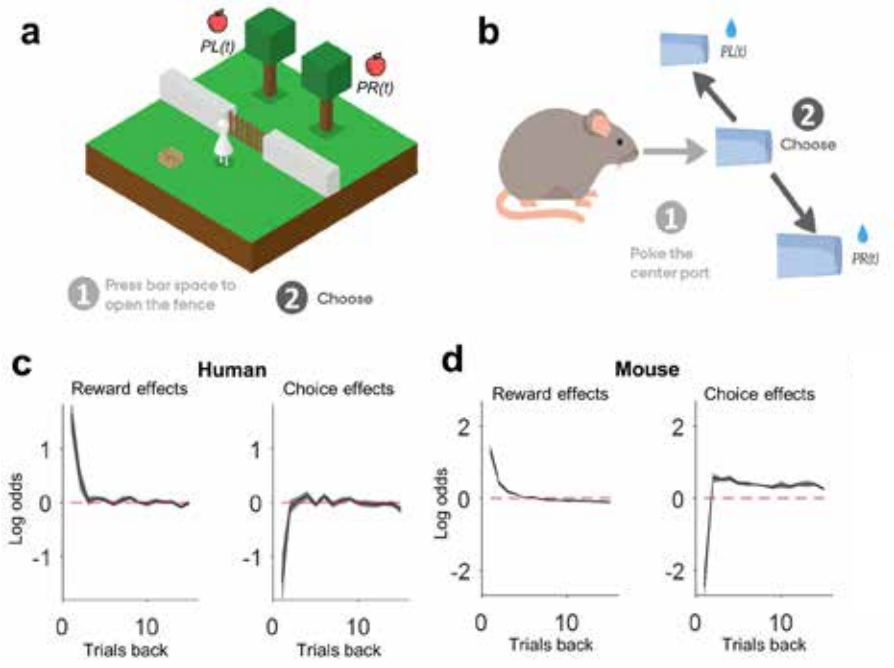


Figure 1. Choice and reward history effects in a reward foraging task.
a. Snapshot of the computer game played by the human participants. The subjects had to wait between 0s and 5s after opening a virtual fence by pressing on a keyboard before making the decision to press on the left or right key. **b.** 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.**

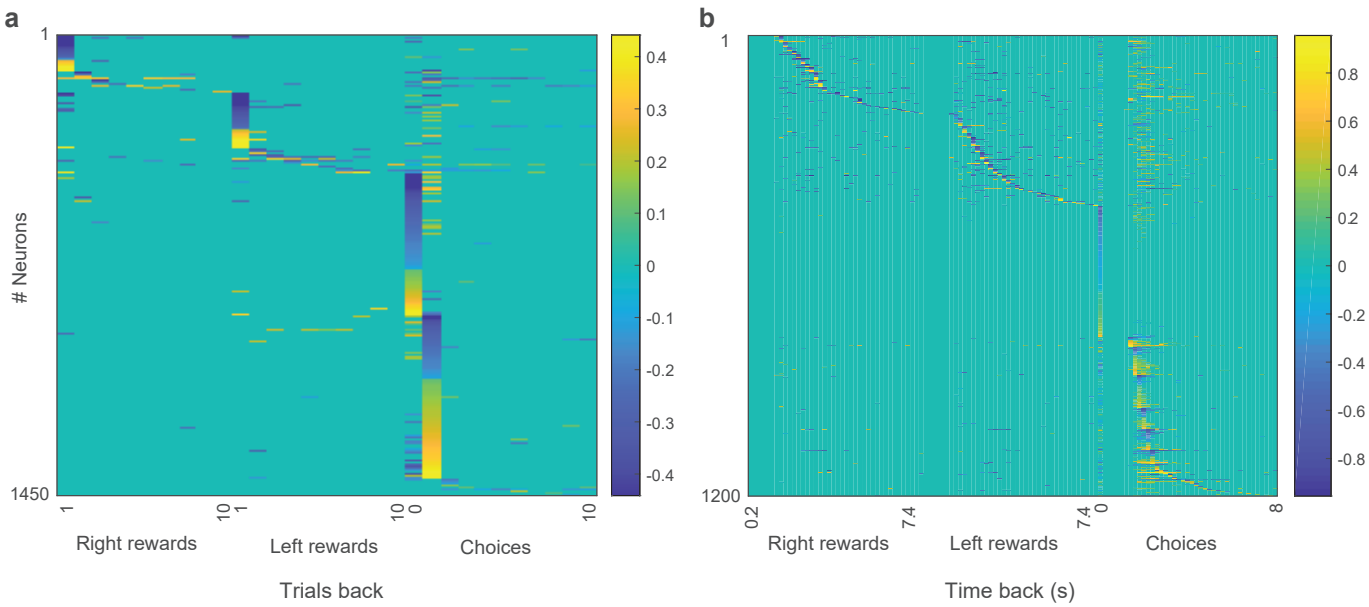
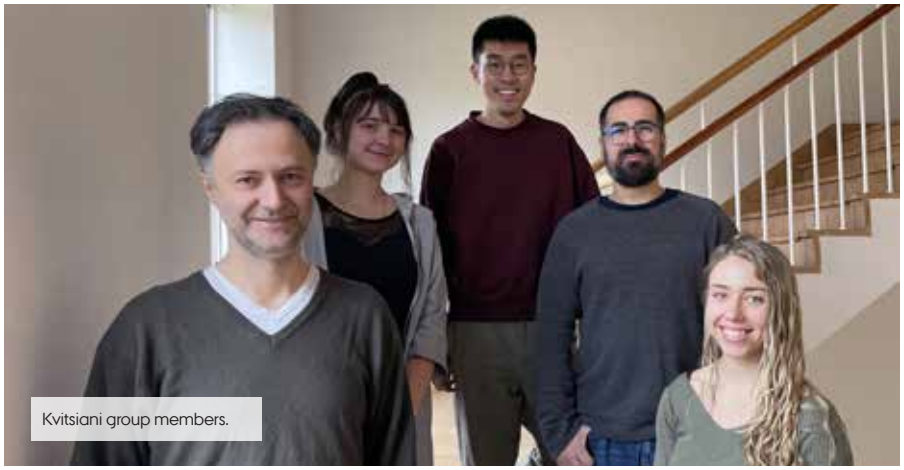


Figure 2. Reward and choice history representations in a reward foraging task.
Firing rate of electrophysiologically recorded single units in mPFC was regressed against past rewards, past and current choices. We only show neurons that passed significance threshold ($p < 0.0001$) in multiple comparison 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.

Using a normative framework we show that choice history integration into the decision-making process is optimal and computational models that incorporate choice history effects outperform existing models that ignore choice 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 the 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 are tied to the predictability of those events (Fig.2). The temporal map indicates when past rewards and choices happen with respect to the current moment. The manuscript that describes these findings is currently under review in the journal Nature Communications.

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 2022

Technical assistant **Anna Barta**
Ph.D. student **Tsz Fung Woo**
Master student **Klaudia Anna Tokarska**
Erasmus student **Alfredo di Fiore**
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 emphasis to the types of associative learnings that cannot be reconciled with the current models that are inspired by in vitro studies.

MAJOR ACHIEVEMENTS
Distinct representations of innate and learned threats within the thalamic-amygdala pathway: Behavioral flexibility and timely reactions to salient stimuli are essential for survival. The subcortical thalamic-basolateral amygdala (BLA) pathway serves as a shortcut for salient stimuli ensuring rapid processing. Here, we show that BLA neuronal and thalamic axonal activity mirror the defensive behavior evoked by an innate visual threat as well as an auditory learned threat.

Importantly, perturbing this pathway compromises defensive responses to both forms of threats, in that animals fail to switch from exploratory to defensive behavior. Despite the shared pathway between the two forms of threat processing, we observed noticeable differences. Blocking beta- adrenergic receptors impair the defensive response to the innate but not the learned threats. This reduced defensive response, surprisingly, is reflected in the suppression of the activity exclusively in the BLA, as the thalamic input response remains intact. Our side-by-side examination highlights the similarities and differences between innate and learned threat processing, thus providing new fundamental insights.

Temporal rules for homo- and heterosynaptic uncovering of memories: Hebbian plasticity is widely considered to be the cellular mechanism for learning and memory. Under the rules of Hebbian plasticity, the strength of a memory can be modified only by a tight temporal co-activation of pre- and postsynaptic inputs encoding that particular memory. Here we demonstrate that a form of plasticity modifies the strength of a memory effectively, despite deviating from Hebbian rules. To this end, we devised a learning paradigm wherein the mapping between synaptic manipulation, synaptic strength, and behavior is well defined, permitting a rigorous evaluation of synaptic basis underlying the memory. In an associative conditioning task, temporally pairing a mild foot shock with optical activation of the thalamic input (Th-I) targeting the amygdala produces no detectable memory. However, a long-term potentiation (LTP) stimulus on the same input (homoLTP), delivered minutes before or after, or even 24 hours later activates the memory of the shock. Equally important, an LTP stimulus delivered to an independent input (heteroLTP) minutes after the associative conditioning also produces a long-lasting memory accompanied by the synaptic

Nabavi group members.

PERSONNEL LIST NABAVI GROUP

Lab manager **Anne-Katrine Vestergaard**
Lab manager **Randi Hald Melsen**
Postdoc **João Lima**
Assistant Prof. **Noëmie Mermet-Joret**
Assistant Prof. **Andrea Moreno**
Posdoc **Milad Nazari**
Research Assistant **Alejo Mosqueira**
MSc student **Andrea Thustrup Pommer**
Trainee **Sanaz Ansarifar**
Group Leader **Sadegh Nabavi**

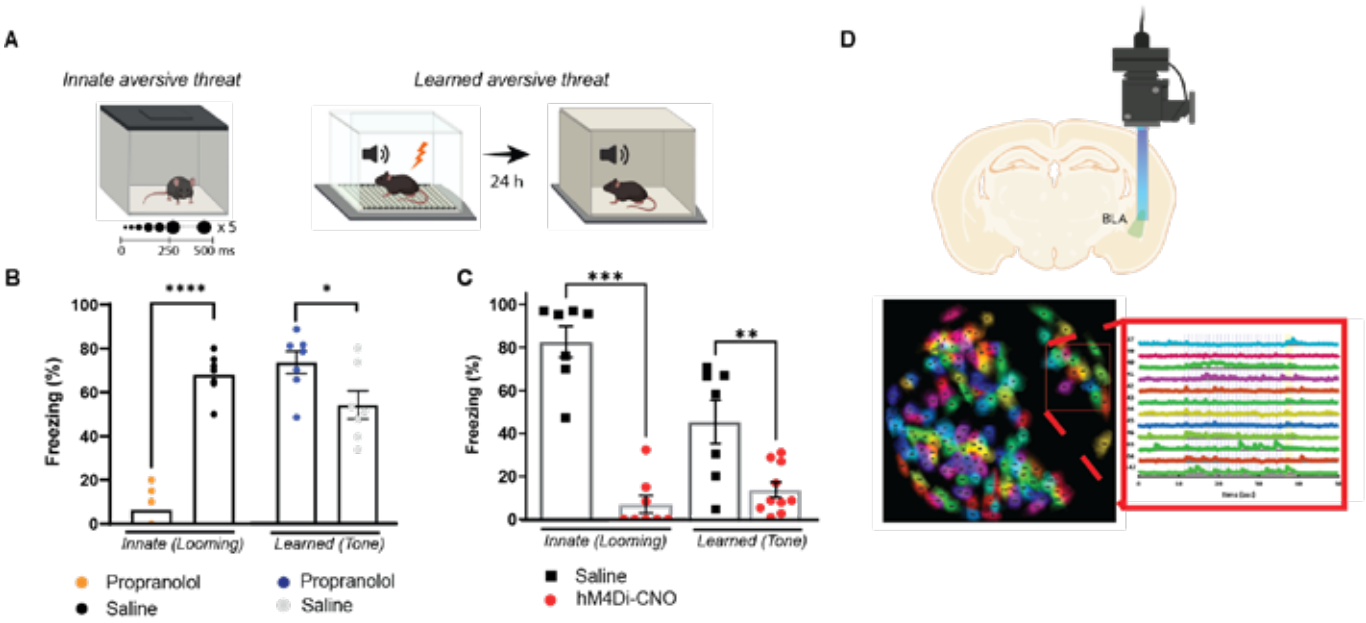


Figure 1: Preliminary data. A, Experimental approach. (Left) For the innate aversive threat, the animals are exposed to an overhead black expending disk which mimicks an aerial predator and elicits freezing in normal conditions. (Right) For the learned aversive threat, the animals are exposed to a neutral tone paired with an aversive foot-shock. Twenty-four hours later, the fear memory is tested over a recall session where only the tone, now a predictor of the threat signal, is presented. **B**, The looming stimulus-evoked freezing is significantly reduced in animals injected with propranolol compared to the re-exposure trial in which the same mice were injected with saline (n=7; Paired t-test, p****<0.0001). Conversely, the same treatment increased the freezing response to the tone over the recall session compared to control animals injected with saline (unpaired t-test, p-value= 0.4732); **C**, Silencing the principal neurons of the basolateral amygdala (BLA) using a chemogenetic approach (hM4Di) affects the defensive response (freezing) of the animals to both innate and learned threat signals (p***<0.001, p**<0,01, t-test). **D**, (Top) Sketch representing miniscope imaging within the BLA. (Bottom) Example of a field-of-view showing active cells from a recording performed in our lab in a mouse BLA. The traces on the right show the activity of individual neurons time-locked to the conditionned stimulus (tone, blue bars) and to the foot-shock (yellow bar).

potentiation of the conditioned inputs. Most surprisingly, in a non-associative conditioning paradigm, which produces neither a fear memory response nor synaptic potentiation, both heteroLTP and homoLTP uncover the aversive memory of the shock. These results indicate that synaptic plasticity can proactively as well as retroactively impact the longevity of memories of unrelated experiences, a phenomenon with computational and behavioral implications.

FUTURE PLANS

Are hardwired circuits the brain's scaffold for learning? Perhaps the greatest contrast between animals and man-made machines is our incredibly fast and efficient learning abilities. If training an artificial neuronal network requires enormous numbers of labels, animals however function and learn efficiently soon after birth, without the need of massive training datasets. What is so unique in our brains that allows such effective learning? An answer, the one we advocate, is that animals rely heavily on innate mechanisms. In this proposal, we propose that the existence of hard-wired circuits recruited for the defensive responses to innately aversive stimuli, facilitate the associative learning of an aversive signal. We will use a combination of deep-brain calcium imaging in the amygdala and genetic decoding of the neuronal populations involved in the processing and integration of innate and learned aversive signals. With this, we will test our hypothesis that hard-wired circuitry in the amygdala provides the scaffolding for rapid learning of aversive experiences.

Multi-level analysis of brain mechanisms underlying epigenetic inheritance of superb learning capabilities: How do we shape the intellectual skills of our descendants? The dominant paradigm considers hereditary (nature) and environment (nurture) as the answers. In the last two decades, a third mechanism, epigenetics, has emerged, which suggests our experiences that occur before the conception of offspring is imprinted onto our genome. The project stems from an intriguing observation by our two collaborators Dr. Barkai and Dr. Schiller, obtained when studying the mechanisms of 'rule-learning'; the ability to generalize complex rules based on learning. They found that the offspring of rats who learned complex rules are much better learners than the controls' offspring. The inheritance of superb learning capability is remarkably resilient; it is passed on to the fourth generation even if the second and third generations are not trained. Furthermore, it is not dependent on the gender of the trained parent. Accordingly, our main hypothesis is that animals learn complex rules pass on trans-generationally superb learning capabilities, with offspring of trained rats having much more "plastic" brains and needing much less training to acquire new rules. Along with the labs of Dr. Barkai and Dr. Schiller, we will apply an integrative multi-level approach by combining behavioral, electrophysiological, and advanced imaging methods. Such a new concept is bound to considerably affect our understanding of the biological bases of learning and memory and would also have significant social implications.

Submitted work: Distinct representations of innate and learned threats within the thalamic- amygdala pathway

Philipsborn Group

Neuronal circuits for reproductive behavior

Group Leader
Anne von Philipsborn

Philipsborn group members.

Latest 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 2022

PhD student **Peter James Kerwin**
PhD Student **Bijayalaxmi Swain**
IT Employee **Per Rosing Mogensen**
Laboratory **Technician Anna Prudnikova**
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 the 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

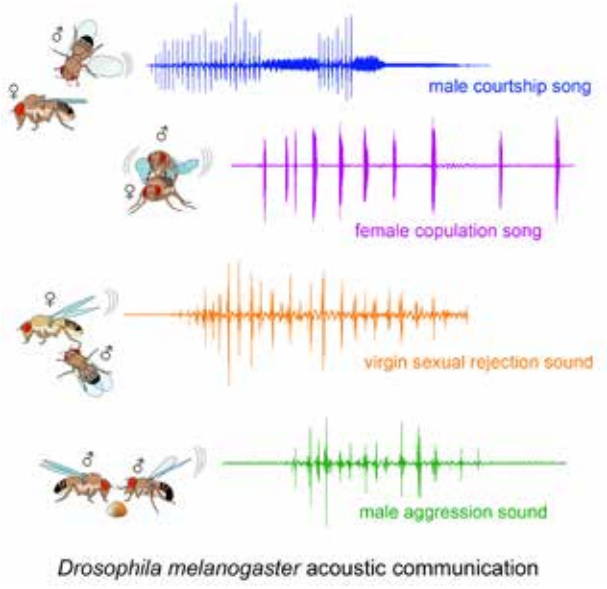


Figure 1: Acoustic communication in *Drosophila*.
Male and female flies generate different acoustic signals during reproduction. (modified from Swain and von Philipsborn, Advances in Insect Physiology 2021)

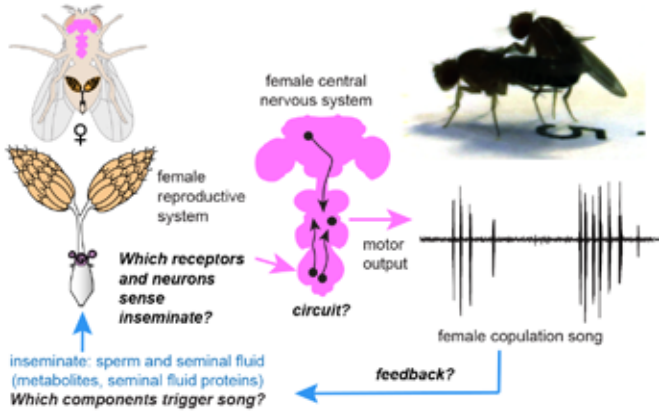


Figure 2: Female copulation song in *Drosophila*: a new behavior raising many new questions.
Female song depends on male seminal fluid and is hypothesized to modulate male inseminate allocation. We aim at identifying molecular players and circuit motifs mediating the communication between male and female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

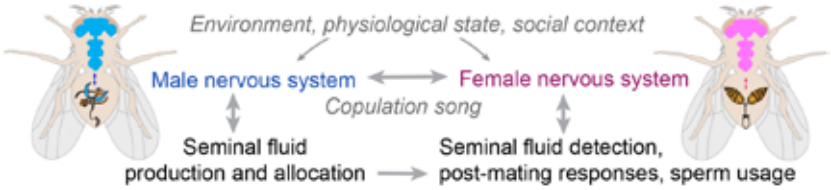


Figure 3: Communication between the nervous system and reproductive organs
Female copulation song provides a window into multiple pathways of information exchange between male and female, as well as between nervous system and reproductive system, and the influence of environmental stimuli, internal state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

singing behaviour can be explained on the level of gene expression, physiology, and circuit architecture.

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 have 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).

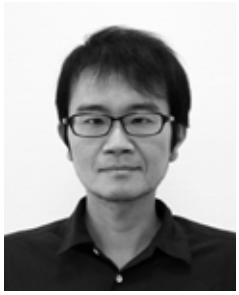
COMMUNICATION BETWEEN THE NERVOUS SYSTEM AND REPRODUCTIVE ORGANS: GENES, PATHWAYS AND CIRCUITS FOR SENSING AND ALLOCATING EJACULATE COMPONENTS
In animals with internal fertilization, seminal fluid strongly influences the physiological requirements for reproduction. Seminal fluid proteins, pheromones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

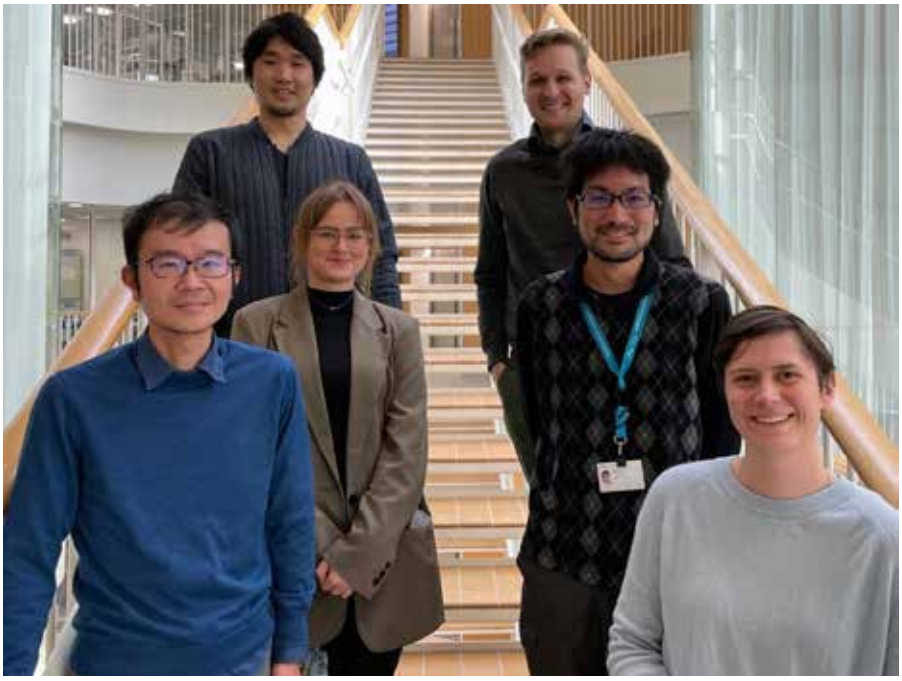
Inferring the direction of image motion is critical to the survival of animals. The direction of visual motion is first extracted by retinal direction-selective circuits. In 2021, we found that visual motion direction is first computed at the axon terminals of retinal bipolar cells before it is processed 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.

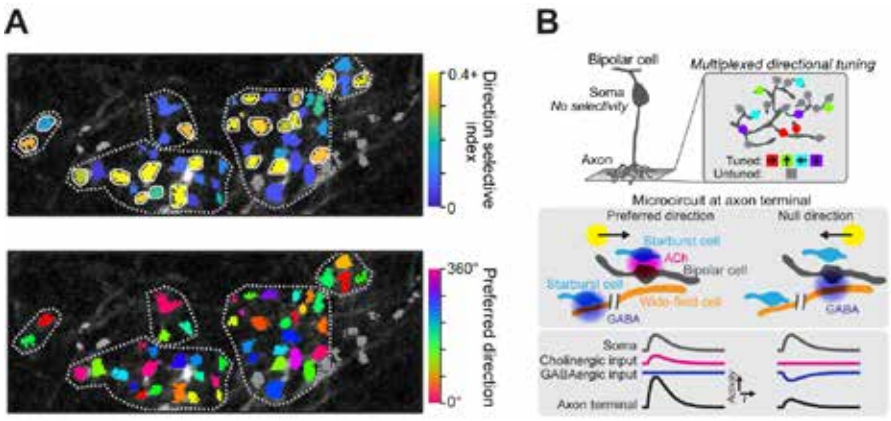


Fig. 1: (A) Two-photon imaging from axon terminals of mouse retinal bipolar cells revealed directional selectivity in glutamate release from axon terminal synapses. Upper panel: intensity of selectivity. Bottom: Preferred direction. **(B)** Directional selectivity is formed by acetylcholine and GABA 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.

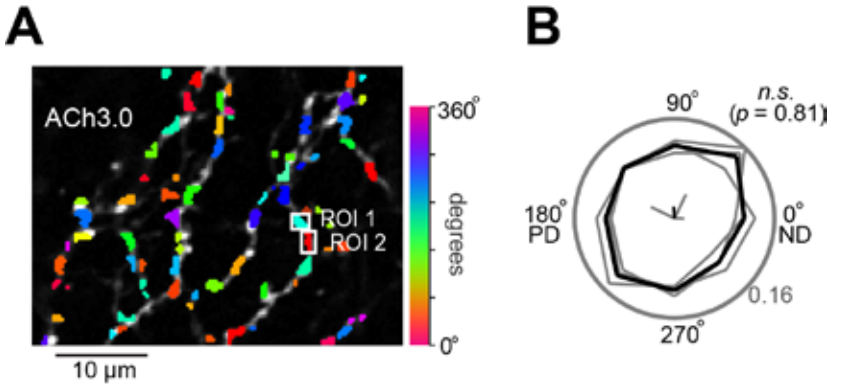


Fig. 2: (A) Left, two-photon acetylcholine imaging from the dendrites of retinal direction-selective cells revealed multi-directed dendritic microsegments. Right, polar plot of preferred directions of each dendritic segment show that total cholinergic input per cell is not directionally selective. Figure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

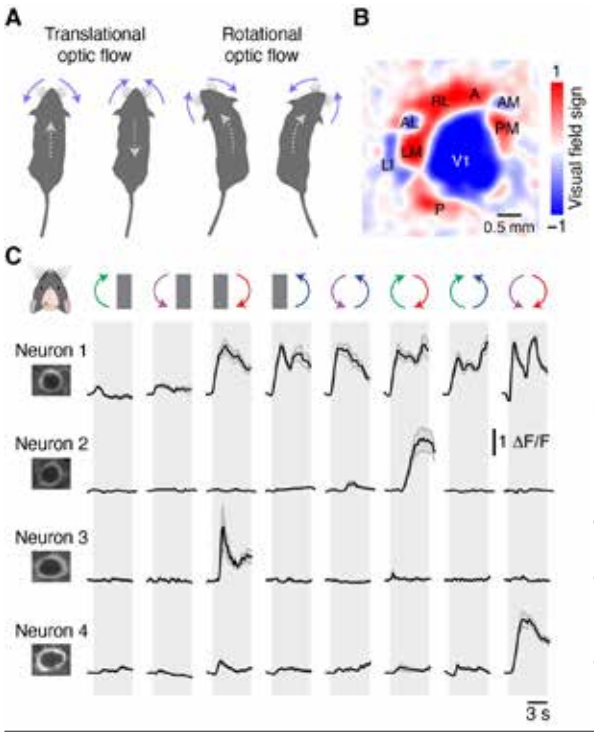


Fig. 3: (A) Distinct optic flow patterns projected onto mouse retinas. **(B)** Visual cortical areas of mouse mapped by intrinsic signal optical imaging. **(C)** Visual cortical neurons (Neuron 1-4) sensitive to distinct optic flow patterns were identified by two-photon calcium imaging. Figure from Rasmussen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

LATEST PUBLICATIONS

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.

Srivastava P, de Rosenroll G, Matsumoto A, Michaels T, Turple Z, Jain V, Sethuramanujam S, Murphy-Baum BL, Yonehara K, Awatramani GB. (2022) *Elife* 11: e81533.

Arvin S, Yonehara K, Glud AN. (2022) Therapeutic Neuromodulation toward a Critical State May Serve as a General Treatment Strategy. *Biomedicines* 10: 2317.

Arvin S, Glud AN, Yonehara K. (2022) Short- and Long-Range Connections Differentially Modulate the Dynamics and State of Small-World Networks. *Front Comput Neurosci* 15: 783474.

PERSONNEL LIST YONEHARA GROUP

Assistant Prof. **Akihiro Matsumoto**
Postdoc **Haruko Yamamoto**
Postdoc **Kota Takuoka**
PhD Student **Monica Dahlstrup Sietam**
PhD Student **Ole Søndergaard Schwartz**
Laboratory Technician **Bjarke Thomsen**
Student Assistant **Simon Arvin**
Student Assistant **Allice Nyborg Rosenkrans Lind**
Student Assistant **Celine Thiesen**
Student Assistant **Esther Helga Klemenzerdóttir**
Group Leader **Keisuke Yonehara**

Poulsen Team

Membrane transport in health and disease

PROMEMO
CENTER FOR PROTEINS IN MEMORY

Team Leader
Hanne Poulsen

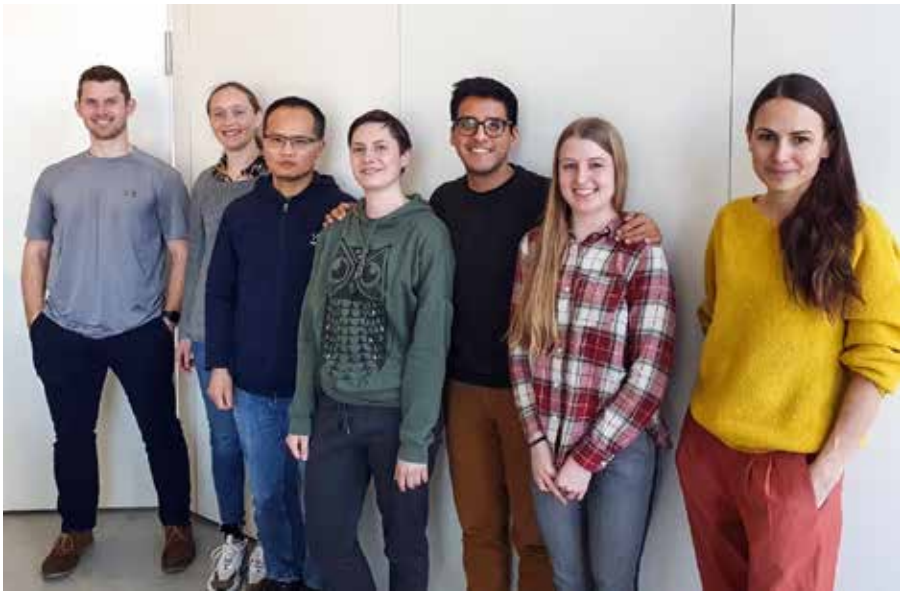
GROUP PRESENTATION
In the group, we are two bachelor students, one research assistant, two PhD students, and a post doc. To gain molecular insight into the brain's physiology and pathophysiology, we study key neuronal membrane proteins with the use of electrophysiology and mouse models. We have collaborations with several Dandrite groups as well as with other researchers and industry.

Neurons communicate across the synapse, where presynaptically released neurotransmitters act on postsynaptic receptors (figure). The most abundant excitatory neurotransmitter is glutamate, and one of the key glutamate receptors is the NMDA receptor, a calcium-permeable channel that plays crucial roles in memory and learning, and whose dysregulation is linked to neuropsychiatric disorders, especially schizophrenia. For decades, structures of the NMDA receptor have been studied with X-ray crystallography and cryo-EM, but only the extracellular and transmembrane regions have been included since the intracellular regions are highly disordered. These regions constitute up to a third of the channel subunit and are well-known to be essential for regulation and trafficking of the receptors, but little is known about their direct impact on the channel properties. We are employing electrophysiological techniques to investigate the roles of these intrinsically disordered intracellular domains on NMDA receptor function.

With two-electrode voltage-clamping of oocytes from the frog *Xenopus laevis*, and patch-clamping of smaller cells heterologously expressing the proteins of interest, we can measure the currents generated by electrogenic membrane proteins such as NMDA receptors inserted into membranes, thereby getting a direct measure of their activity. Using pharmacology and co-expression of potential regulatory interaction partners, we can also start to delineate the effects of the cellular context.

The NMDA receptors furthermore have unique regulation of their transcripts. The subunit transcript encoded by *GRIN2B* has the longest 3' untranslated region among mammalian transcripts, and it is believed to be important for the dendritic localization of the mRNA. We are determining the effects on mRNA and protein levels of mislocalizing the *GRIN2B* transcript in a mouse model where the 3' untranslated region has been modified. In parallel, with the focus on mRNA localization, we are implementing the use of the fluorescent RNA aptamer Pepper, and we are currently testing it in a pure *in vitro* system and in transfected cells.

We are thus studying aspects of the NMDA receptor that have previously received little or no attention. Our mouse model, which has reduced levels of correctly localized receptors, will serve as an important model for understanding the roles of mRNA localization and channel function for learning, memory, and neuropsychiatric diseases, and we have initiated a collaboration with a company aimed at alleviating the symptoms caused by receptor



Poulsen group members.

2022 HIGHLIGHTS

Fruergaard M et al. 2022 The Na+,K+-ATPase in complex with beryllium fluoride mimics an ATPase phosphorylated state JBC 298(9):102317

PERSONNEL LIST 2022

Postdoc **Helle Bakke Krog**
PhD Student **Oscar Gabriel Sevillano Quispe**
PhD Student **Monica Dahlstrup Sietam**
PhD Student **Alex Harvey**
Research assistant **Xingya Chang**
Team Leader **Hanne Poulsen**

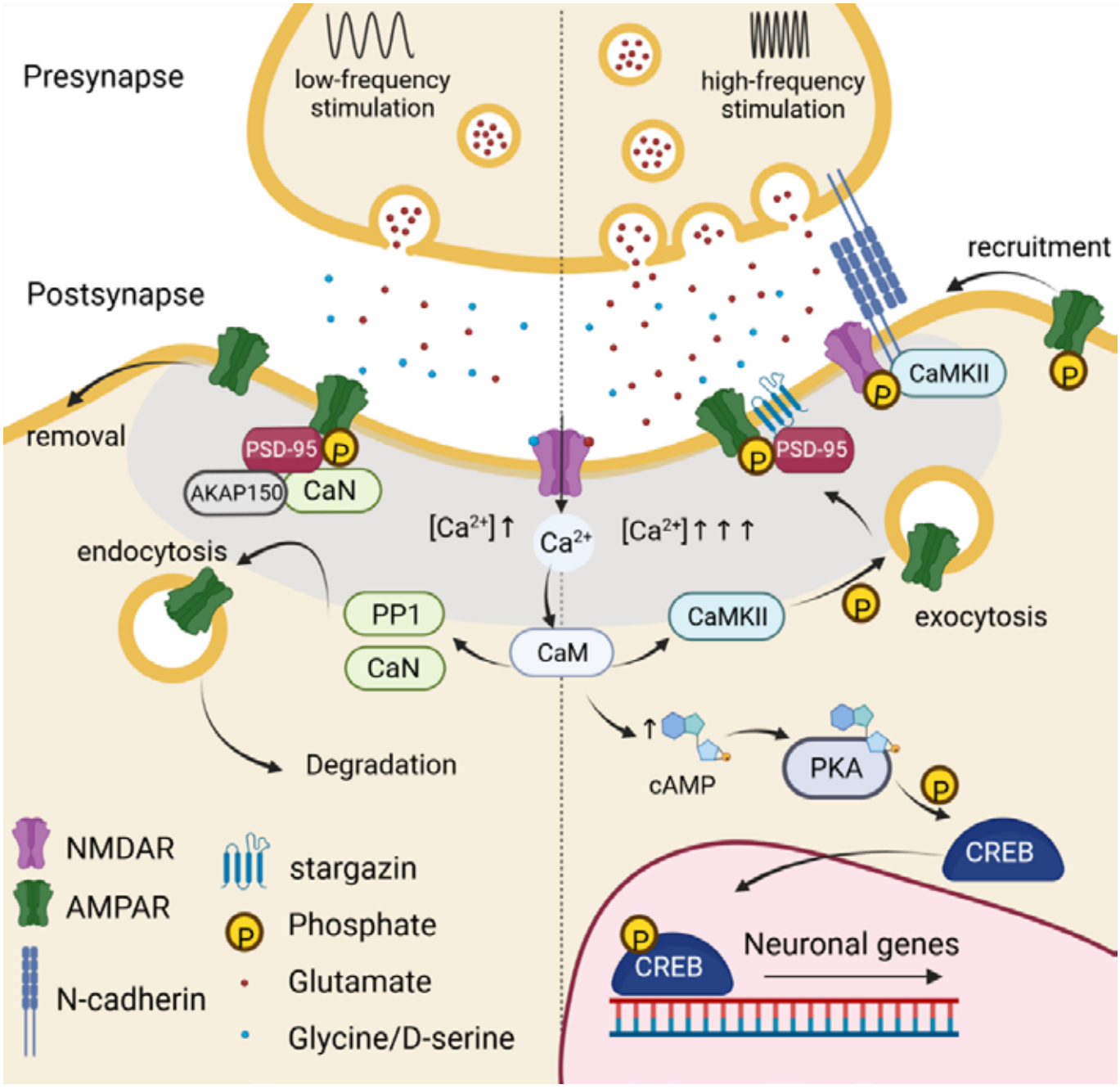
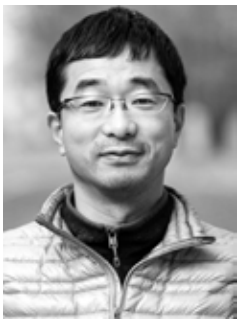


Figure: The strengthening or weakening of communication between two neurons at a synapse (long-term potentiation (right) and long-term repression (left), respectively) are regulated by Ca^{2+} influx. Stimulation frequency and entrant Ca^{2+} concentration modulate activation of different kinases, phosphatases, and signaling molecules, which will shift the dynamic balance. The NMDA receptor is a main conductor of Ca^{2+} in the postsynaptic density (indicated in gray). By Oscar Gabriel Sevillano Quispe who received his PhD degree in 2022.

misregulation. NMDA receptors have proved to be an important drug target: the channel inhibitor ketamine received FDA approval for treatment of major depression in 2019, the first drug for this disease to be approved in decades, and numerous allosteric modulators for up and down-regulation of channel activity are being tested clinically. Further underlining the receptor's importance, anti-NMDA receptor encephalitis was discovered 15 years ago, a severe neurological disease caused by autoimmune antibodies against the receptor. Understanding the molecular regulation and means of adjusting receptor activity is therefore a promising path to alleviating the broad spectrum of neurological and neuropsychiatric diseases associated with NMDA receptor dysregulation.

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 into two overall research themes

- Novelty-induced enhancement of memory retention is now an established phenomenon, but the underlying molecular mechanisms remain 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 2022

First, we established a novel environment for rats suitable for enhancing the spatial memory encoded during the object location paradigm (Figure 1). The novelty-induced memory enhancement was inhibited by treatment with the dopamine D_1/D_5 receptor antagonist, SCH 23390. We then conducted an experiment for screening the genes that were upregulated in the dorsal hippocampus following the 5-min exploration of a novel environment. This procedure allows the clear separation of newly synthesized gene products induced by *initial memory consolidation* from those induced by *memory encoding*. The 5-min exploration of a novel environment upregulated *Agap3* mRNA expression, which controls AMPA-type glutamate receptor trafficking in synapses and might be involved in maintaining functional plasticity.

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

PERSONNEL LIST TAKEUCHI TEAM

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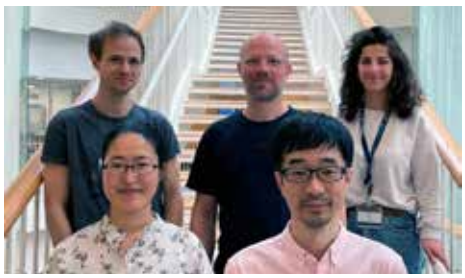
PhD student **Kristoffer Højgaard**
PhD student **Katia Soud**
Intern **Bianka Szöllösi**
Lab Manager **Kim Henningsen**
Guest professor **Hiroshi Matsuno**
Visiting Researcher **Daisaku Sawada**
Team leader **Tomonori Takeuchi**



Takeuchi group members.

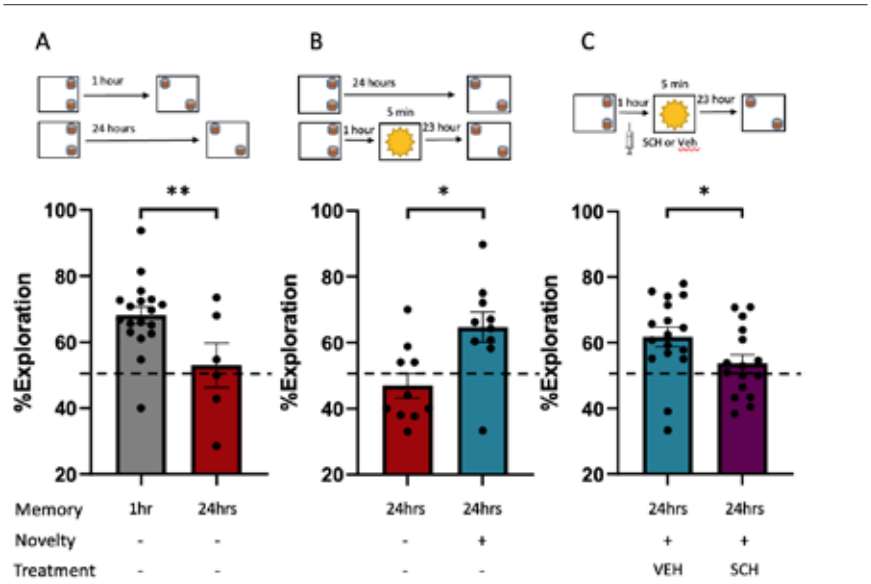


Figure 1: Novelty exploration after memory encoding enhances memory retention.
Graphs show % time exploring object in novel location. (A) 20 min encoding protocol resulted in 1 hr memory but not 24 hr. Memory significantly different between 1 hr and 24 hr ($p = 0.017$). (B) Novel context exploration improved 24 hr memory ($p = 0.007$). (C) Dopamine D_1/D_5 receptor antagonist (SCH) reduced novelty-induced memory enhancement ($p = 0.049$). Data as mean ± SEM. *$p < 0.05$, **$p < 0.01$.

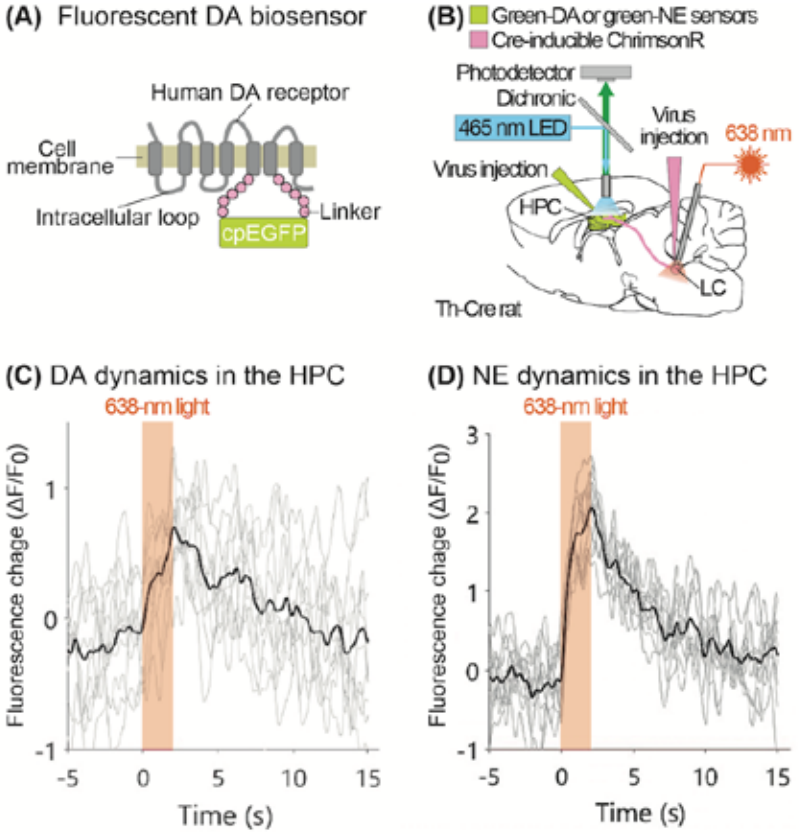


Figure 2: In vivo imaging of dopamine (DA) and norepinephrine (NE) release from locus coeruleus (LC) axons in the hippocampus (HPC) during optogenetic activation of the LC.
(A) Structure of green-DA biosensor (cpEGFP replaced by third intracellular loop of human DA receptor) that changes fluorescence upon DA binding. (B) Th-Cre rats expressing green-DA or green- NE sensors were implanted with fiber directed at dorsal HPC for *in vivo* fiber photometry. Cre-inducible virus carrying ChrimsonR, a red light-drivable optogenetic actuator, was injected into the LC, followed by implanting fiber over the LC. (C & D) Optogenetic activation of LC neurons with 638- nm laser reliably increased fluorescence of green-DA and green-NE sensors in HPC. Each trace (grey) and average trace (black) aligned to start of LC photoactivation shown.

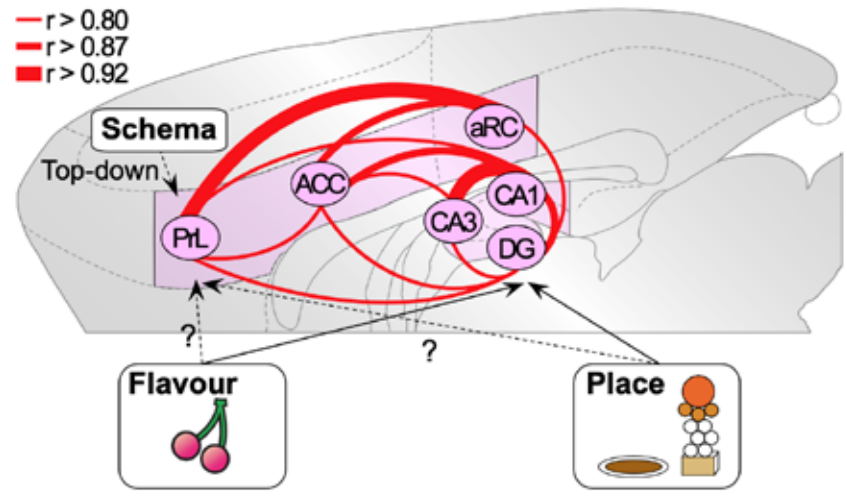


Figure 3: Network model during memory assimilation into schema.
The framework emerging from correlational and clustering analyses. Plasticity-related midline neocortical-hippocampal connectivity (Pearson's r > 0.80, 0.87 or 0.92) is strongly associated with successful memory encoding of new paired-associates against the backdrop of the schema. ACC, anterior cingulate cortex; aRC, anterior retrosplenial cortex; DG, dentate gyrus; PrL, prelimbic cortex.

HIGHLIGHTS

Duszkiewicz, A.J., Rossato, J.I., Moreno, A., Takeuchi, T., Yamasaki, M., Genzel, L., Spooner, P., Canals, S. and Morris, R.G.M. (2022) Execution of new trajectories towards a stable goal without a functional hippocampus. Hippocampus, In Press. https://doi.org/10.1002/hipo.23497. IF (2 years Journal Citation Reports Impact Factor with Journal Rank) = 3.753 [141/275 (Neurosciences)], CI (Times Cited from Scopus) = 0.

Schomaker, J., Ruitenberg, M.F.L. and Takeuchi, T. (2022) Memory's penumbra in the older or pathological brain. Trends in Cognitive Sciences, 27: 118–119. https://doi.org/10.1016/j.tics.2022.09.013. IF = 24.482 [3/275 (Neurosciences)], CI = 0.

Takeuchi, T.*[§], Tamura, M.*, Tse, D., Kajii, Y., Fernández, G. and Morris, R.G.M.[§] (2022) Brain region networks for the assimilation of new associative memory into a schema. Molecular Brain, 15:24. https://doi.org/10.1186/s13041-022-00908-9. *Co-first author. [§]Co-last author. IF = 4.399 [110/275 (Neurosciences)], CI = 0.

in a single spine by two-photon glutamate uncaging and measure 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.

Second, 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, provided by Dr. Li at Peking University in China, was observed when we optogenetically stimulated the locus coeruleus (Figure 2).

Third, we applied correlational and clustering analyses to data on the expression of immediate early gene products that were acquired in our previous study (Tse *et al.,* Science, 2011). Our main finding is that medial neocortical-hippocampal connectivity is strongly associated with successful memory encoding of new paired-associates against the backdrop of the schema, compared to both (1) unsuccessful memory encoding of new paired-associates that are not relevant to the schema, and (2) the mere retrieval of the previously learned schema. This finding suggests that the certain medial neocortical and hippocampal networks support the assimilation of newly encoded associative memories into a relevant schema (Figure 3).

Vanwalleghem Team

Neurobiology of the gut-brain axis

Group Leader
Gilles Vanwalleghem

INTRODUCTION

Our group started in 2022 and aims to untangle the gut-brain axis, to understand how visceral information from the gut, and microbiome, can affect behaviour. We use a transparent vertebrate animal model, the zebrafish larvae, and cutting-edge imaging to follow the development, and activity of the gut. We are especially interested in the 'second brain', the enteric nervous system, and the role it plays in regulating the gut microbiome.

The gut-brain axis is complex, it involves neuronal, hormonal, and immune bidirectional connections between our gut and the brain. There is a lot of interest in the gut microbiome, and how it may be involved in disease, and several mental health disorders. On the other hand, we know that gastrointestinal disorders are a common co-morbidity of mental health disorders, so the causal direction within these gut and brain interactions is unclear. We focus on the enteric nervous system, which regulates gut function, but has also been shown to be closely involved in the immune response to bacteria, as well as the regulation of the gut microenvironment and the microbiome. By using our transparent animal model (Figure 1), we will be able to study the interactions between nervous and immune systems *in vivo*. Furthermore, zebrafish are easy to manipulate,

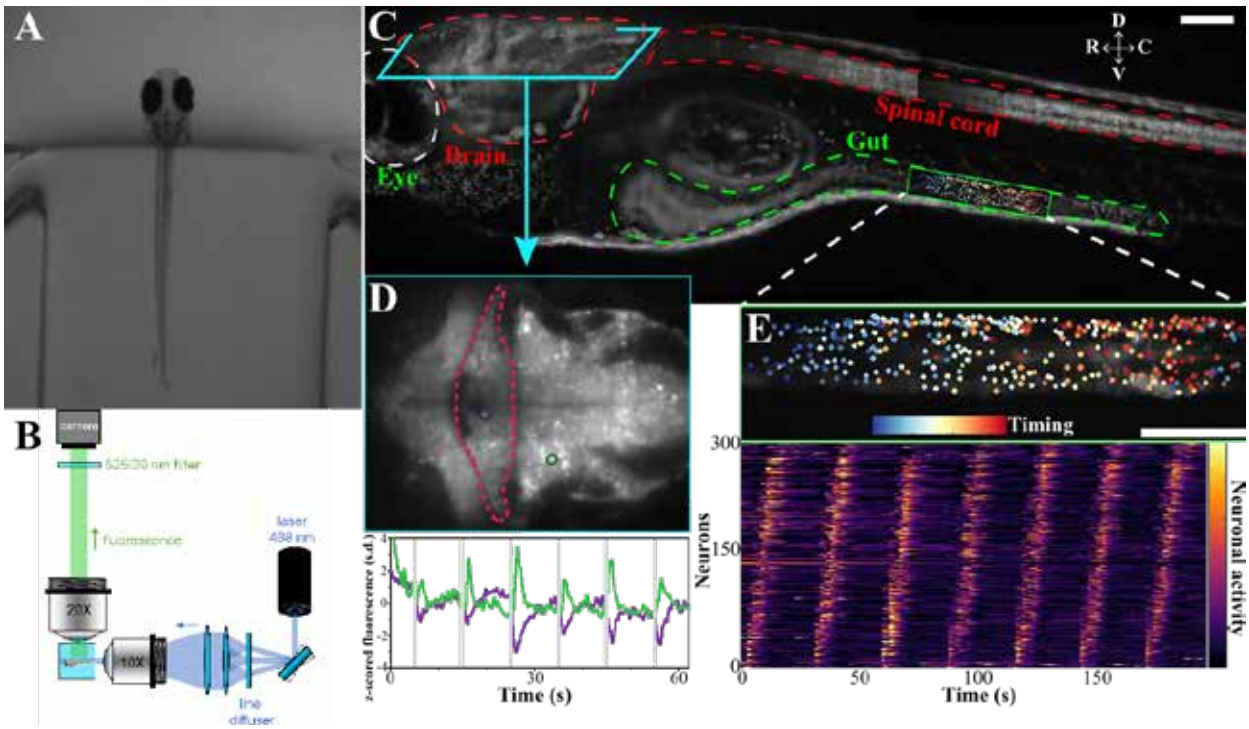


Figure 1: Functional imaging of the larval zebrafish nervous system.
(A) 6 days post fertilization larva embedded in low melting point agarose, with its tail free. **(B)** Schematic of our diffuse digitally scanned light-sheet microscope. **(C)** 6 days post fertilization larva expressing the nuclear-targeted calcium indicator GCaMP throughout its nervous system. The central nervous system is outlined in red. The enteric nervous system in the gut in green. Scale bar=100µm, Arrows indicate the rostro-caudal and dorso-ventral axes. **(D)** (Top) Individual neuron nuclei from the cerebellum (red outline) can be resolved (coloured circles) and their activity tracked across time. (Bottom) The signal from each neuron can be seen in either activated (green) or inhibited (magenta) neuron. Such data are available for thousands of cells in this plane, and tens of thousands across in the animal. **(E)** Individual neurons from the posterior gut color-coded for the timing of their firing from early (blue) to late (red), it shows thepropagation of firing driving peristalsic waves. Bottom, z-scored fluorescent traces from the 350 neurons above, ordered by their firing timing.

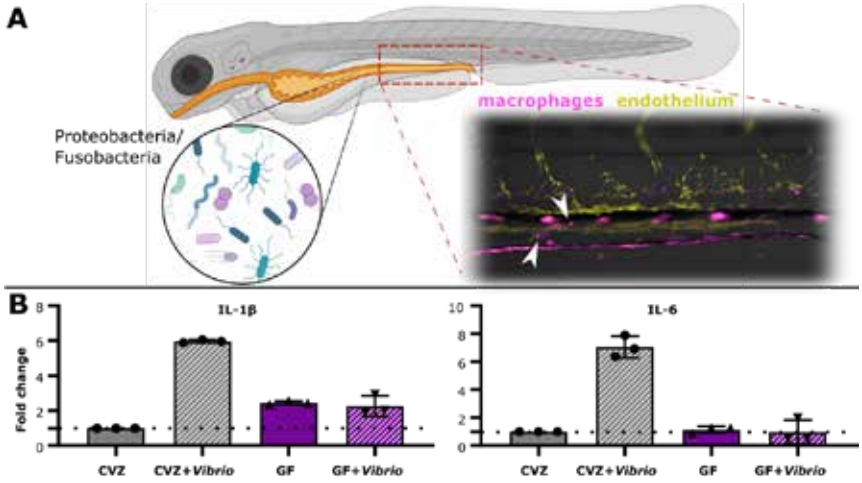


Figure 2: innate immunity of the zebrafish gut
(A) Illustration of the gut of zebrafish, and our ability to track resident gut macrophages (arrowheads). **(B)** Preliminary results on the expression of the two inflammatory cytokines IL-1β and IL-6 upon exposure to the Vibrio symbiont. CVZ are conventionalized zebrafish larvae, 4dpf, and GF are germ-free. We can measure a significant increase in inflammation upon exposure to the Vibrio symbiont in the control animals, but not in the germ free. (Figure made by Audrey Andersen-civil, with BioRender)

2022 HIGHLIGHTS

Light-sheet microscope built and functional.

Novo Nordisk Exploratory Synergy grant.

Chair of Lundbeck Foundation Investigator Network.

PERSONNEL LIST

Group Leader **Gilles Vanwalleghem**
Lab manager **Hanne Jørgensen**
Postdoc **Audrey Inge Andersen-Civil**
PhD student **Rajlakshmi Sawale**
Trainee **Esther Helga Klemenzardóttir**
Trainee **Eva Sofie Bovbjerg**

Vanwalleghem group members.

and we can change and constrain their gut microbiome as needed.

By studying the gut-brain axis in zebrafish larvae, our group hopes to gain a deeper understanding of how gut-related information and the microbiome can affect behaviour and contribute to disease.

MAJOR ACHIEVEMENTS AND FUTURE PLANS

Light-sheet microscopy and optical trapping. We assembled a custom light-sheet microscope (Figure 1B), that will be made available to DANDRITE and the department. This was the first piece of equipment needed to start answering our research questions, we will add more capabilities to this setup as our group expands. This will empower us to fully take advantage of the transparent larval zebrafish (Figure 1) and will serve as the platform on which we develop the optical trapping method described below.

We have now fully established the zebrafish model at Aarhus university, including germ-free preparation of the larvae (Fig.2). We can conventionalize the larvae by re-introducing the parent bacteria to the larvae's water, or we can colonize them with single bacteria, such as a *Vibrio* symbiont. We have shown that this *Vibrio* bacteria can elicit an inflammatory response from the animal, our plan is to link this immune activation to a special type of enteric cell, the enteroendocrine cells, which can synapse with the vagal nerve and the enteric nervous system.

Enteroendocrine cells can respond to nutrients or bacterial factors and are the main sensory input from the gut.

A major issue in studying the interactions between the gut microbiome, the immune and the nervous system, is the lack of control on where, and when bacteria contact the gut. To improve our control of the bacteria, we partnered with Professor Giovanni Volpe from The University of Gothenburg, Sweden. He is an optical physicist expert in optical trapping, that uses light to move objects. We will leverage optical tweezers, and the transparency of larval zebrafish, to move bacteria in contact with the gut of germ-free animals. Combined with our light-sheet microscope, we can image the real-time *in vivo* response of the larvae to the bacteria. This will permit us to test hypotheses about causal links between the bacteria, neuronal activation, and gut motility.

Nissen Group

Structural Neurobiology

PROMEMO
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Professor
Poul Nissen

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). Furthermore, biochemistry/biophysics, bioinformatics, protein crystallography, and collaborative studies through e.g., molecular dynamics simulations, super-resolution fluorescence microscopy, and electrophysiology are employed. New directions of research go towards cellular/tissue imaging and correlative light and electron microscopy (CLEM) with cryo-electron tomography and X-ray imaging. Main subjects include ion pumps, polyamine transporters and lipid flippases of the P-type ATPase family, Na+ dependent transporters of neurotransmitters, phosphate and chloride, and receptors controlling trafficking and metabolism in the brain. Derived activities also include structure-based drug discovery. Major, long-term goals include models for higher-order networks and mechanisms in the Axon Initial Segment that integrate circuit inputs and generate action potentials. Furthermore, synaptic structures associated with memory and learning, and molecular mechanisms underlying direction sensitivity in the visual system are being investigated.

New studies include the discovery of a new mechanism of activation of the plasma-membrane Ca2+- ATPase by the membrane-associated monomer form of alpha-synuclein (Kowalski et al. 2022), which we expect to be of particular importance for calcium homeostasis and signaling in presyn-

SELECTED PUBLICATIONS 2022

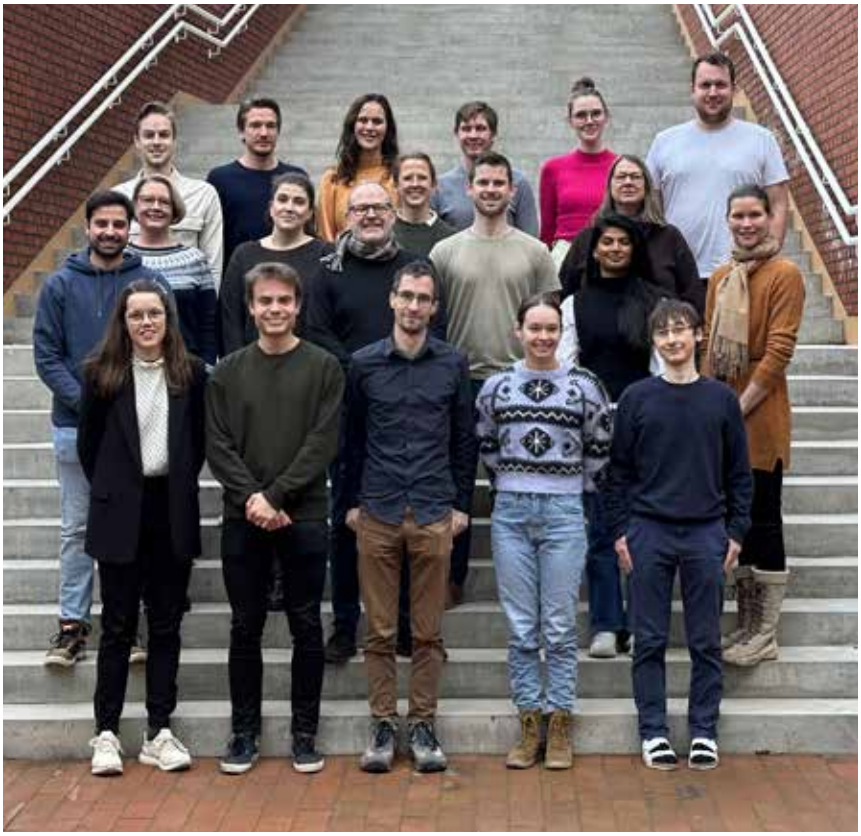
Dieudonné T, Herrera SA, Laursen MJ, Lejeune M, Stock C, Slimani K, Jaxel C, Lyons JA, Montigny C, Pomorski TG, Nissen P*, Lenoir G* (2021). Autoinhibition and regulation by phosphoinositides of ATP8B1, a human lipid flippase associated with intrahepatic cholestatic disorder. *Elife* **11**:e75272. doi: 10.7554/eLife.75272.

Fruergaard MU, Dach I, Andersen JL, Ozol M, Shahsavar A, Quistgaard EM, Poulsen H, Fedosova NU, Nissen P (2022). The Na+,K+-ATPase in complex with beryllium fluoride mimics an ATPase phosphorylated state. *J Biol Chem* **298**:102317. doi: 10.1016/j.jbc.2022.102317.

Fruergaard MU, Nielsen CJF, Kjeldsen CR, Iversen L, Andersen JL, Nissen P (2023). Activation and inhibition of the C-terminal kinase domain of p90 ribosomal S6 kinases. *Life Sci Alliance* 6:e202201425. doi: 10.26508/lsa.202201425

Kowalski A, Betzer C, Larsen ST, Gregersen E, Newcombe EA, Bermejo MC, Langkilde AE, Kragelund BB, Jensen PH, Nissen P (2022). Monomeric α-Synuclein activates the Plasma Membrane Calcium Pump. *bioRxiv* https://doi.org/10.1101/2022.02.21.481193

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. *EMBO J* **41**:e110169. doi: 10.15252/embj.2021110169



Nissen group members

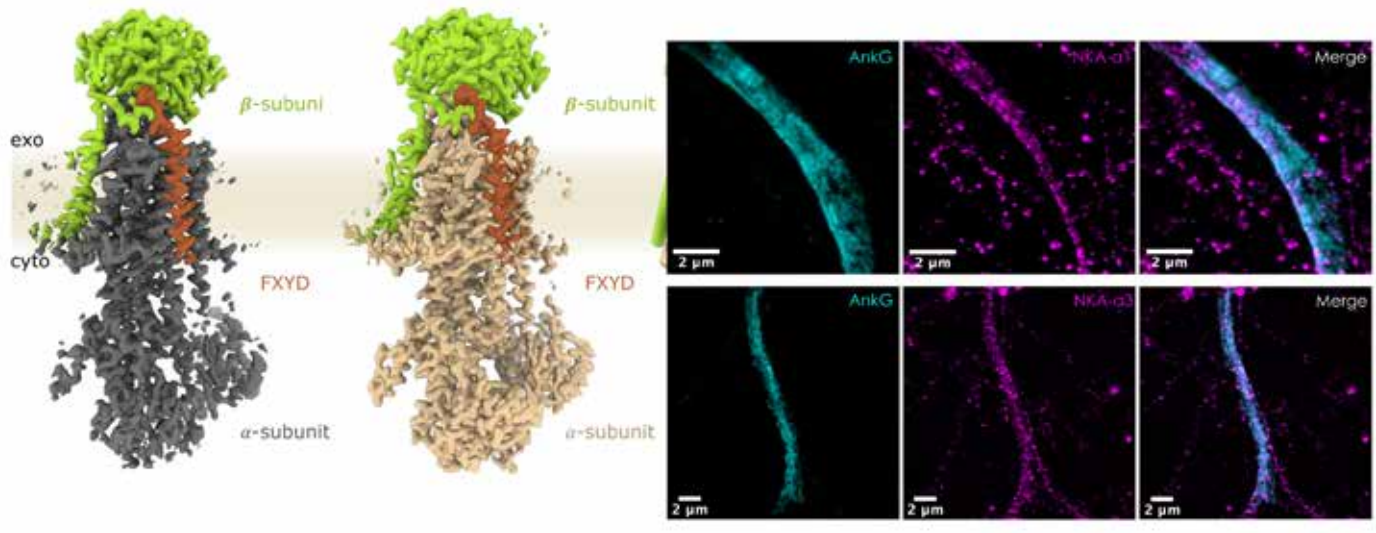


Figure 1: New Cryo-EM structures and super-resolution microscopy studies of Na,K-ATPase from the Nissen group 2022. A. Human alpha1 (left) and alpha3 (right) isoform complexes of Na,K-ATPase obtained from a yeast expression system (both about 2.6 Å resolution) showing both similarities and important differences (figure courtesy of Dr. Michael Habeck, unpublished results). B. STED microscopy studies of rat primary hippocampal neurons showing Na,K-ATPase alpha1 and alpha3 isoforms colocalized with ankyrin G, a marker of the axon initial segment in neurons (figure courtesy of Ph.D. student Gülberk Bayraktar, unpublished work obtained in collaboration with Prof. Valentin Nägerl, Univ. Bordeaux).

aptic compartments of neurons (and red blood cells). The activation depends on negatively charged lipids and complements the classical activation mechanism of PMCA by calcium-bound calmodulin. We are currently investigating the mechanism of activation that we expect to be of complex, dynamic nature at the membrane interface.

Furthermore, ongoing studies of Na,K-ATPase highlight new directions and ambitions of our research. Cryo-EM studies comparing the different isoforms associated with brain function in humans – the ubiquitously expressed alpha1, the glia-specific alpha2, and the neuron-specific alpha3 – and investigating the effect of mutations associated with neuropsychiatric disorders have provided us with important new insights into mechanisms that also relate Na,K-ATPase function to e.g. neurodevelopment and signaling. These cryo-EM studies complement also crystallographic studies of the pig kidney enzyme that show important steps in the K+ transport process (Fruergaard et al. 2022). Furthermore, we map the distribution of alpha1 and alpha3 at the axon initial segment (AIS) of rodent primary hippocampal neurons and find strong indications of segregated localisations that point to important roles of alpha1 for general Na+ and K+ homeostasis in cooperation with voltage-gated ion channels, and of alpha3 at focal points at AIS.

Further studies include for example the final publications of the human NKCC1 including a 2.6 Å resolution cryo-EM structure, molecular dynamics simulations of the Na+,K+, 2Cl- release mechanism, and transport studies and site-directed mutagenesis in cells (Neumann et al. 2022) and of the human lipid flippase ATP8B1 including also structural and functional studies (Diedonné et al. 2022). Furthermore, we concluded a technological study on the construct design and validation of a constitutively active RSK2 kinase, downstream of the MAPK/ERK pathway (Fruergaard et al. 2023).

PERSONNEL LIST NISSEN GROUP 2022

Assistant Professor **Michael Habeck**
Assistant Professor **Esben Quistgaard**
Assistant Professor **Azadeh Shahsavar**
Postdoc **Caroline Marie Teresa Neumann**
Postdoc **Marlene Uglebjerg Fruergaard**
Postdoc **Sigrid Thirup Larsen**
Postdoc **Louise Laursen**
Postdoc **Thibaud Dieudonné**
Postdoc **Charlott Stock**
Postdoc **Michael Habeck**
Postdoc **Joao Carlos Moreno Ramos**
Postdoc **Rasmus Kock Flygaard**
Postdoc **Ronja Driller**
Postdoc **Samuel John Hjorth-Jensen**
PhD Student **Mads Eskesen Christensen**
PhD Student **Line Marie Christiansen**
PhD Student **Gülberk Bayraktar**
PhD Student **Clara Nautrup Pedersen**
PhD Student **Mariam Schani Khelifa**
PhD Student **Tomáš Heger**
PhD Student **Sean Hansen**
PhD Student **Josephine Karlsen Dannersø**
PhD Student **Michelle Juknaviciute Laursen**
Academic employee **Christine Juul Fælled Nielsen**
Laboratory Technician **Anna Marie Nielsen**
Laboratory Technician **Tanja Klymchuk**
Laboratory Technician **Bente Andersen**
Lab Assistant **Daniel Sejer Christensen**
Scientific Computing **Jesper Lykkegaard Karlsen**
Personal assistant **Karen Bech-Pedersen**
Group Leader, Professor **Poul Nissen**

Jensen Group

Neurodegenerative Diseases

Professor
Poul Henning Jensen

The Jensen group is studying how alpha-synuclein contributes to the neurodegenerative processes in Parkinson's disease, Lewy body dementia, and multiple systems atrophy, and how the disease progression can be blocked by modulating specific mechanisms. This is investigated in studies of alpha-synuclein aggregates in vitro, in cell models, transgenic animals, and human tissue and involves the 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 associate professor Marina Romero-Ramos, and tests drug leads in cell and in vivo models. This project is funded by the Novo Nordic Foundation and the Lundbeck Foundation.
- How disease-, and cellular 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 represent collaborations with assoc. prof. Thomas J. D. Jørgensen, SDU, associate professor Nathalie van den Berge, AUH, associate professor Marina Romero-Ramos, and international collaborators, and are partly funded by the Michael J. Fox Foundation, the collaborative EU-funded Joint Programme in Neurodegenerative Diseases "OligoFIT", and the Lundbeck Foundation.
- New Antibody-based methods to identify, quantify, and characterize novel alpha- synuclein-based pathology in cells, brain tissue, and biofluids from human patients and in vivo models. These international projects are partly funded by the Michael J. Fox Foundation.

SELECTED HIGHLIGHTS & PUBLICATIONS

Postdoc Lasse Reimer received a DKK 5 million grant from the Lundbeck Foundations new Frontier Grant programme to further develop the SERCA pump a preclinical drug target.

Reimer L, Haikal C, Gram H, Theologidis V, Kovacs G, Ruesink H, Baun A, Nielsen J, Otzen DE, Li JY, Jensen PH. (2022) Low dose DMSO treatment induces oligomerization and accelerates aggregation of α-synuclein. *Sci Rep.* 12(1):3737

Ghanem SS, Majbour NK, Vaikath NN, Ardah MT, Erskine D, Jensen NM, Fayyad M, Sudhakaran IP, Vasili E, Melachroinou K, Abdi IY, Poggiolini I, Santos P, Dorn A, Carloni P, Vekrellis K, Attems J, McKeith I, Outeiro TF, Jensen PH, El-Agnaf OMA. (2022) α-Synuclein phosphorylation at serine 129 occurs after initial protein deposition and inhibits seeded fibril formation and toxicity. *Proc Natl Acad Sci USA.* 119(15):e2109617119.

Lassen LB, Thomsen MS, Basso E, Füchtbauer E-M, Füchtbauer A, Outeiro TF, Jensen PH, Moos T. (2022) Mutation of Tyrosine Sites in the Human Alpha-Synuclein Gene Induces Neurotoxicity in Transgenic Mice with Soluble Alpha-Synuclein Oligomer Formation. *Cells* 11, 3673.

Reimer L, Gram H, Møller Jensen N, Betzer C, Yang L, Jin L, Shi M, Boudeffa D, Fusco G, De Simone A, Kirik D, Lashuel HA, Zhang J, Jensen PH. (2022) Protein kinase R dependent phosphorylation of α-synuclein regulates its membrane binding and aggregation. *PNAS Nexus*, Vol. 1, Issue 5, pgac259

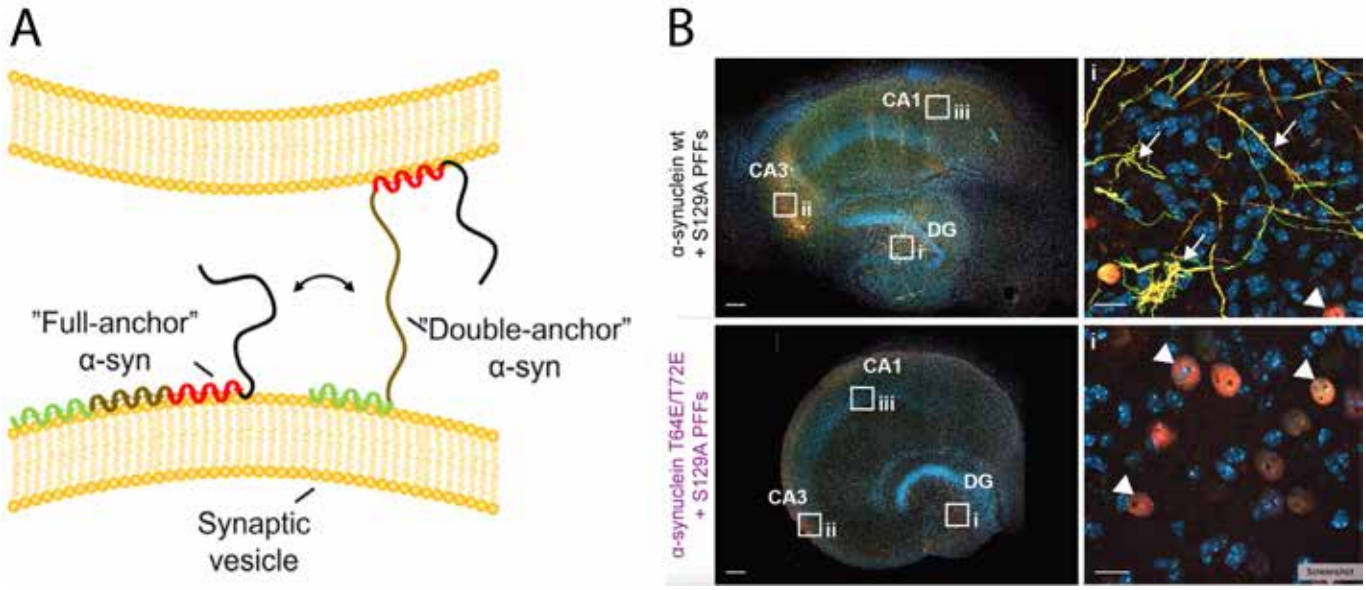


Figure: Phosphorylation of protein kinase R (PKR)-reactive Threonine 64 and 72 on alpha-synuclein facilitates "double-anchor" clustering of vesicles and blocks spreading of alpha-synuclein aggregate pathology in mouse brain tissue.
A) Illustrative representation of alpha-syn vesicle bound through the "double-anchor" mechanism. Phosphorylation of Thr 64 and 72 will loosen the membrane association of the grey segment in alpha-syn. This will allow "fully anchored" alpha-syn to adopt a "double anchor" state, that can induce vesicle clustering. This is carried out by independent membrane interactions of the N-terminal anchor (green segment) and the central region (red segment). **B)** PKR-phosphomimetic T64E/T72E alpha-syn fails to form inclusions and propagate pathology between neurons in organotypic hippocampal brain slice cultures.
Representative images of slice cultures expressing either wild type or T64E/T72E-phospho-mimetic alpha-syn, injected with S129A alpha-syn preformed fibrils and fixed 21 days post injection. Left panels shows overview of the tissue, and right panels demonstrate the area of the dentate gyrus.
Slices are stained with antibodies for aggregated alpha-syn (green), phospho-S129 α-syn (red), and nuclei (blue). Arrows indicate alpha-syn inclusions, while arrowheads indicate nuclei with high expression of nonaggregated, S129-phosphorylated alpha-syn. All figures are from Reimer et al., ***PNAS Nexus***, Vol. 1, Issue 5, pgac259

Jensen group members.

PERSONNEL LIST JENSEN GROUP 2022

Postdoc **Lasse Reimer**
PhD student **Hjalte Gram**
PhD student **Nanna Møller Jensen**
Ph.d. student **Sólveig Hlín Brynjólfsdóttir**, visitor from Dan.Canc.Soc.Research center
Postdoc **Zagorka Vitic**
Research assistant **Shubhangini Tiwari**
Research assistant **Vasilis Theologidis**
Research assistant **Sofie Metz Jansen**
Lab technician **Benedicte Vestergaard**
M. Sc. **Louise Andreassen**
B. Med. **Mia Rosa Antorini**
B. Sc. **Mariona Ridao Barceló** (Barcelona University)
Group Leader, Professor **Poul Henning Jensen**

PROMEMO
CENTER FOR PROTEINS IN MEMORY

Nykjær Group

Receptors in mental disorders and memory

Professor
Anders Nykjær

Research activities in the Nykjær lab are focusing on the functional characterization of a family of neuronal receptors denoted Vps10p-domain receptor family or sortilins. Members of this receptor family, which comprises sortilin, SorCS1, SorCS2, SorCS3, and SorLA, predominate 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 top-risk genes in both psychiatric, neurological, and metabolic diseases.

Mental disorders represent one of the largest health challenges in the Western world. A complex polygenic makeup is the most common disease cause but disruptive mutations in single genes have also been recognized. Recently, receptors of the sortilin family were identified as top-risk genes shared across several psychiatric disorders but why this is remains unexplained. Studying rare penetrant disease mutations of sortilin genes not only is a key entry point to understanding the functions of the receptors and disease biology per se, but it may also provide fundamental insight into why and how combinations of risk gene variants underlie a psychiatric disease.

We previously found that SorCS2 controls dopaminergic development, neuronal firing of the ventral tegmental area, and balances the activity of dopaminergic receptors, DR1 and DR2. In new studies, we uncovered that SorCS2 can bind the BDNF receptor TrkB and the NMDA receptor subunit GluN2B, which are both required to control neurotransmission in several brain regions. While BDNF stimulates SorCS2-TrkB complex formation to enable TrkB signaling, it disengages SorCS2 from GluN2B, leading to the enrichment of the subunit at the synapse. These findings allowed us to formulate a novel molecular concept by which SorCS2 acts as a molecular switch to control and coordinate synaptic function and strength. When SorCS2 is dysfunctional, it results in cognitive impairment and behavioral deficits that typify several psychiatric disorders.

In the future, we will define the function of the receptor family for mental health and memory from the level of the molecule to the living organism. In particular, we aim to understand the molecular underpinning by which the receptors control neurodevelopment, neuronal integrity, circuitry formation, and synaptic plasticity. This is essential to understand what may go wrong in patients with a neurodevelopmental psychiatric disorder such as ADHD, autism spectrum disorder, schizophrenia, and in conditions when memory fails. To achieve this, we will take advantage of a broad repertoire of techniques including transgenic animal models, neuroembryology, mouse behavioral testing, calcium imaging to study neuronal network activity, dopamine sensors, electrophysiology, omics, cell biology including organoids.

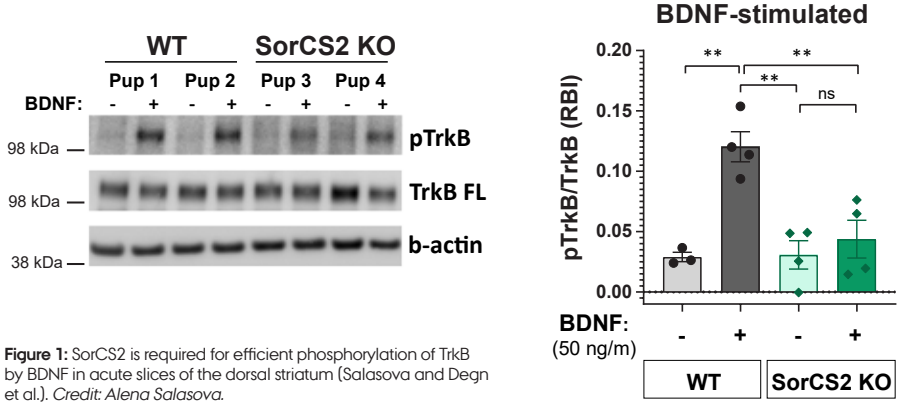


Figure 1: SorCS2 is required for efficient phosphorylation of TrkB by BDNF in acute slices of the dorsal striatum (Salasova and Degn et al.). *Credit: Alena Salasova.*

2022 HIGHLIGHTS

Salasova A, Monti G, Andersen OM, Nykjaer A. Finding memo: versatile interactions of the VPS10p-Domain receptors in Alzheimer's disease. *Mol Neurodegener.* 2022 Nov 18;17(1):74. doi: 10.1186/s13024-022-00576-2.

Anders Nykjaer appointed Bluefield Investigator of the Bluefield Research Consortium (https://www.bluefieldproject.org/consortium/).

Establishment of a method for imaging of dopamine dynamics in behaving animals using genetically encoded dopamine sensors (collaboration with Team leader Tomonori Takeuchi).

8 patents applications (4 families) filed and 3 published.

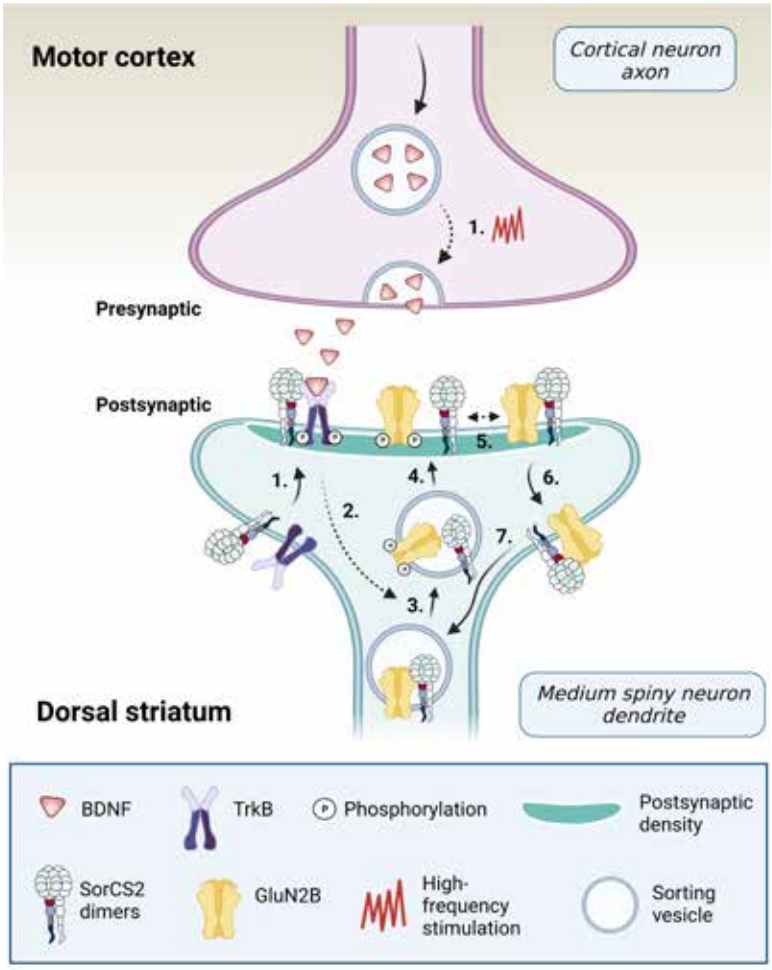


Figure 2: A schematic model depicting SorCS2 as a molecular switch that links BDNF/TrkB signaling with glutaminergic neurotransmission. *Step 1:* Upon BDNF secretion, SorCS2 associates with TrkB to enable its trafficking to postsynaptic densities. Here, TrkB becomes autophosphorylated to stimulate downstream signaling pathways. *Step 2-3:* This results in phosphorylation of GluN2B and its subsequent dissociation from SorCS2. *Step 4:* Once liberated from SorCS2, GluN2B is targeted to postsynaptic densities. *Step 5:* Upon dephosphorylation of GluN2B, it re-associates with SorCS2. *Step 6-7:* The SorCS2-GluN2B complex diffuses to the perisynapse, after which it is endocytosed into recycling vesicles and ready for reuse (Salasova and Degn et al.). Created with Biorender.com. *Credit: Alena Salasova.*

PERSONNEL LIST NYKJÆR GROUP

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

Nykjær group members.

DANDRITE AFFILIATED RESEARCHERS

In memory of Marco Capogna, Professor of Neurobiology and DANDRITE Affiliated researcher

In December 2022 we lost one of our dearest and most valued friends and colleagues, Professor Marco Capogna. Marco played a significant and important role in the DANDRITE research community throughout his seven years with us. With these words, we wish to commemorate him and honor his memory.

Marco was an eminent neuroscientist who possessed the highest academic research virtues, which he valued so highly: High ambitions, curiosity and integrity, collaboration, guidance, and teaching of younger researchers.

Marco was born in Italy where he achieved his first degrees in Experimental Psychology in Rome and in Biology in Pisa. He received his Ph.D. in Neuroscience also from the University of Pisa. After a postdoctoral fellowship at the Brain Institute at the University of Zurich in Switzerland, he took a position in 1998 as a senior scientist at the Neurophysiology Laboratory of the Novartis Institute for Medical Sciences, University College, London also including a stay at the Department of Clinical Neuropharmacology of the Max Planck Institute for Psychiatry, Munich. In 2001 he took a position as a senior group leader at the University of Oxford University and was awarded a Professorship of Cellular Neuropharmacology in 2014.

In 2015 Marco contacted us from Oxford, inquiring about the possibility to join the neuroscience community at DANDRITE and Aarhus University. He stood out as a great capacity and leader of the field and with magnificent overlaps and complements in his research interests to our neuronal micro-anatomy and circuits community. In 2016 he started a professorship at the Department of Biomedicine and in a defining role as a DANDRITE affiliated researcher.

His contribution to the neuroscience community at Aarhus University and DANDRITE has been numerous and very important. Throughout his career, he has garnered great honors and well-deserved recognition.

A major interest of his was understanding circuitry that guides emotionally dependent behaviors with a particular focus on GABAergic neurons in the hippocampus and amygdala. In this work, he also continued collaborations with many important neuroscience centers in Europe and he had a very strong, positive influence on our international neuroscience network. Through his work, he forged close collaborations with many important research institutions and universities such as Harvard, Stanford, and MIT in the US and through his close connections to the neuroscience communities in London and Oxford.

These studies, capacities, and a strong commitment to collaborations with DANDRITE scientists made him one of the instigators of the research center PROMEMO, which focuses on mechanisms underlying emotional memory.

In addition to his superior qualifications in science, he was also highly dedicated to the education and training of undergraduate and graduate students in neuroscience by developing and coordinating courses of the highest quality for medical and Ph.D. students. Furthermore, Marco mentored many successful junior scientists. He respected them as scientists, and he cared for them as individuals.

Marco has left an everlasting footprint on the neuroscience research community both in Aarhus, Denmark, and internationally and he is in its most true meaning an inspiration to us all.

He struggled for the last years with health problems, but he stayed optimistic, dedicated, and caring to the very end. We will forever have Marco Capogna in our thoughts and research - bringing up his name and example will always be a joy.

Marco leaves behind his wife Teresa and their twins.

Marco Capogna's group continue their research initiated by Marco.

One highlight from 2022 was the contribution to the discovery of a novel GABAergic neuron type of the mouse hippocampus associated with sharp wave ripples and memory, in collaboration with Ivan Soltesz' group, Stanford, published in Neuron.

DANDRITE is proud to enter year 2023 with 13 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 2022

- Elected board members of Danish Society for Neuroscience (DSfN)
- Publication: Comparative transcriptional analysis of satellite glial cell injury response, Jager et al. (2022). Wellcome Open Res, 7:156 (DOI: 10.12688/wellcomeopenres.17885.1).
- Publication: Sortilin Modulates Schwann Cell Signaling and Remak Bundle Regeneration Following Nerve Injury, Ulrichsen et al. (2022). Front. Cell. Neurosci. 16:856734 (DOI: 10.3389/fncel.2022.856734).
- Commissioned research agreement with Hoba Therapeutics, drug-testing HB-086 in pain models. ■

JANE HVARREGAARD CHRISTENSEN

Childhood incontinence – Genes and disease mechanisms

Our primary focus is to discover genetic risk factors and disease mechanisms in childhood incontinence with a special focus on aspects of impaired body-brain interactions and psychiatric comorbidities. We are mapping novel risk genes in bedwetting, daytime urinary incontinence, and fecal incontinence. We also study genetic associations between incontinence and psychiatric disorders. Risk genes are investigated along with genes causing rare disorders of the water balance to understand their interplay in the regulation and integration of urine production, bladder activity, and sleep.

DANDRITE related Highlights from 2022

- Publication of study: The psychiatric risk gene BRD1 modulates mitochondrial bioenergetics by transcriptional regulation in Translational Psychiatry (Paternoster et al. 2022)
- Novel genetic findings in daytime urinary incontinence using iPSYCH2015 data
- Validated incontinence questionnaire developed for the Danish Blood Donor Study ■

ERNST-MARTIN FÜCHTBAUER

Genetically modified mice

We collaborate with several DANDRITE researchers 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 gene activation.

Highlights from 2022

Mutation of Tyrosine Sites in the Human Alpha-Synuclein Gene Induces Neurotoxicity in Transgenic Mice with Soluble Alpha-Synuclein Oligomer Formation. Lassen LB, Thomsen MS, Basso E, Füchtbauer EM, Füchtbauer A, Outeiro TF, Jensen PH, Moos T. Cells. 2022 Nov 18;11(22):3673. doi: 10.3390/cells11223673. PMID: 3642909 ■

Photo: Simon Byrial Fischel

FELICITY DAVIS

Research focus

Mammalian cells reside within dynamic cellular societies where one cell's function or fate can be determined or altered by the actions of its neighbours. My laboratories in Denmark and Australia explore how cells transmit and decode messages. Using volumetric imaging and photo- pharmacology, we are exploring how cells in the mammary gland are connected and how they respond to maternal oxytocin signalling during lactation. By exploring how information flows between cells in the body, we are also beginning to understand how cells of the immune system shape the development of many of our internal organs and how germ cells can coordinate their behaviours.

Highlights from 2022

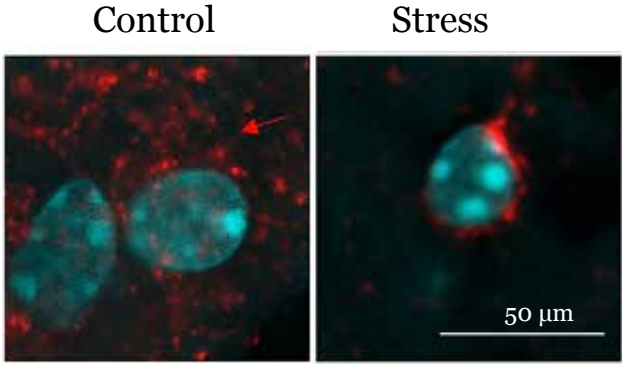
- Hosted the Emerging Concepts in Cell and Developmental Biology Meeting in Aarhus, funded by the Novo Nordisk Foundation
- Acquired infrastructure funding from the Carlsberg Foundation for two new microscopes
- Obtained a large education grant from the Novo Nordisk Foundation to improve public understanding of women's health and female biology through a multi-year museum exhibition at KØN
- Published a manuscript on diversity, equity and inclusion in academia in Nature Reviews Molecular Cell Biology. ■

JELENA RADULOVIC

Modulation of Memory Circuits by Stress
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 socio affective behavior (Tanimura). We also study the role of uncertainty in memory formation, generalization, and flexibility. Our research is performed with mouse behavioral models and includes phenotypes found in patients suffering from affective disorders.

Highlights from 2022

- We identified a cholinergic circuit triggering generalization of fear after stress (LY Ren, A Cicvaric, H Zhang, MAA Meyer, AL Guedea, P Gao, Z Petrovic, X Sun, Y Lin, J Radulovic. Stress-induced changes of the cholinergic circuitry promote retrieval-based generalization of aversive memories. Mol Psychiatry 2022, 27(9):3795-3805.)
- We demonstrated that cholinergic afferents to the hippocampus regulate the nuclear localization of the transcription factor REST (Ren LY, Cicvaric A, Zhang H, Meyer MAA, Guedea AL, Gao P, Petrovic Z, Sun X, Lin Y, Radulovic J. Nuclear exclusion of the repressor REST in the dentate gyrus after stress. Mol Psychiatry 2022, 27(9):3557.
- We offered the course "Translational Psychobiology", Aarhus University Summer University, July 11- July 29, 2022.
- We proposed a novel model by which chronic stress might lead to neurodegenerative brain disorders (Radulovic J, Ivkovic S, Adzic M. From chronic stress and anxiety to neurodegeneration: focus on neuromodulation of the axon initial segment. In: Handbook of Neurology: Neuroplasticity in Neuropsychiatric disorders. F. Ghilardi and A. Quartarone (Eds), Elsevier, Handb Clin Neurol. 2022;184:481-495.
- Radulovic gave a key note lecture on "Neurobiological Mechanisms of Stress-Related Memories", at the Center for Translational Pain Research, Northwestern University, Chicago, IL.



Nuclear localization of the transcription repressor REST in control mice (left) and its exclusion from the nucleus after stress (right). This effect is associated with enhanced activation of hippocampal neurons mediating retrieval of stress-related memories.

JØRGEN KJEMS

Non-coding RNA and Nanomedicine
The Kjems lab investigates the role of 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 group 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 nano scaffolds, 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 2022

- Differential RNA aptamer affinity profiling on plasma as a potential diagnostic tool for bladder cancer.
  Fjelstrup S, Dupont DM, Bus C, Enghild JJ, Jensen JB, Birkenkamp-Demtröder K, Dyrskjøt L, Kjems J.NAR Cancer. 2022 Aug 22;4(3):zcac025. doi: 10.1093/narcan/zcac025. eCollection 2022 Sep.
- Best practice standards for circular RNA research.
  Nielsen AF, Bindereif A, Bozzoni I, Hanan M, Hansen TB, Irimia M, Kadener S, Kristensen LS, Legnini I, Morlando M, Jarlstad Olesen MT, Pasterkamp RJ, Preibisch S, Rajewsky N, Suenkel C, Kjems J.Nat Methods. 2022 Oct;19(10):1208-1220. doi: 10.1038/s41592-022-01487-2. Epub 2022 May 26.
- Site-specific nanobody-oligonucleotide conjugation for super-resolution imaging.
  Teodori L, Omer M, Märcher A, Skaanning MK, Andersen VL, Nielsen JS, Oldenburg E, Lin Y, Gothelf KV, Kjems J.J Biol Methods. 2022 Mar 1;9(1):e159. doi: 10.14440/jbm.2022.381. eCollection 2022.
- The Role of Plasma Extracellular Vesicles in Remote Ischemic Conditioning and Exercise-Induced Ischemic Tolerance.
  Gu T, Just J, Stenz KT, Yan Y, Sieljacks P, Wang J, Groennebaek TS, Jakobsgaard JE, Rindom E, Herskind J, Gravholt A, Lassen TR, Jørgensen M, Bæk R, Gutiérrez-Jiménez E, Iversen NK, Rasmussen PM, Nyengaard JR, Jørgensen MM, de Paoli F, Bøtker HE, Kjems J, Vissing K, Drasbek KR.Int J Mol Sci. 2022 Mar 19;23(6):3334. doi: 10.3390/ijms23063334.
- Expression of Circ_Satb1 Is Decreased in Mesial Temporal Lobe Epilepsy and Regulates Dendritic Spine Morphology.
  Gomes-Duarte A, Venø MT, de Wit M, Senthilkumar K, Broekhoven MH, van den Herik J, Heeres FR, van Rossum D, Rybiczka-Tesulov M, Legnini I, van Rijen PC, van Eijsden P, Gosselaar PH, Rajewsky N, Kjems J, Vangoor VR, Pasterkamp RJ.Front Mol Neurosci. 2022 Mar 3;15:832133. doi: 10.3389/fnmol.2022.832133. eCollection 2022.
- The emerging roles of circRNAs in cancer and oncology.
  Kristensen LS, Jakobsen T, Hager H, Kjems J.Nat Rev Clin Oncol. 2022 Mar;19(3):188-206. doi: 10.1038/s41571-021-00585-y. Epub 2021 Dec 15.

MAGNUS KJÆRGAARD

Dynamic organization of signaling pathways in the post-synaptic density.
The post-synaptic density is a protein-rich compartment located at the tip of synapses, which integrates synaptic and intracellular signaling. The structure of the is important to the correct integration of signals, but is hard to understand because it is highly dynamic and heterogeneous. We aim to understand how proteins are recruited in an activity-dependent manner, and how the supra-molecular organization of protein complexes affects signaling.

Highlights from 2022

- *Setting up a new lab in the old "Aarhus Kommunehospital"*
- *Lab visit by HRH the queen of Denmark*
- *Publications:* Dyla, M.; González Foutel, N. S.; Otzen, D. E.; Kjaergaard, M. (2022) The Optimal Docking Strength for Reversibly Tethered Kinases. PNAS 119 (25) e2203098119 ■

MARINA ROMERO-RAMOS

Genetic, clinical and basic research studies support the significant role of the immune system in Parkinson's disease. This refers not only to the brain immune cell, the microglia, but also to innate and adaptive immune cells in the periphery. Our lab is studying the cells and proteins involved in the neuroinflammatory process associated with -synuclein-induced neurodegeneration. To do so we investigate rodent models of the disease, and we do parallel analysis of human-derived samples. Thus, we aim to develop translational research that can ultimately help the diagnosis and treatment of patients with Parkinson's and other synucleinopathies.

DANDRITE related Highlights from 2022

- The lab has shown that monocytes from Parkinson's disease patients are modified and these changes differ as time progress, and between sexes. These changes suggest that the higher migratory capacity of the monocytes was associated with decreased cognition (Brain, Behav & Immun, Nissen 2022).
- Dr Romero-Ramos was granted an Ascending Investigator Grant (Lundbeck Foundation) and a Synergy Grant (Novo Nordisk Foundation) in 2022
- Dr. Romero-Ramos since 2022 is a member of the AU Health faculty PhD Fellowships Committee and a member of Management Committee and a Work Package leader at the EU COST action IMMUPARKNET
- In 2022, Dr. Romero-Ramos became part of the Editorial Board of Neurobiology of Disease. ■

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 pigs and rodents. We are developing different monoclonal antibodies, targeting trafficking receptors to maximize transport to brain parenchyma. Currently, we are particularly interested in the transferrin receptor and how it can perform bidirectional trafficking across the BBB.

Highlights from 2022

- Publication in Fluids and Barriers of the CNS regarding alpha-synuclein in the BBB.
- Purchase of a light sheet confocal from Zeiss ■

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 an 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 2022

- Kobberø SD, Gajhede M, Mirza OA, Kløverpris S, Kjær TR, Mikkelsen JH, Boesen T, Oxvig C. Structure of the proteolytic enzyme PAPP-A with the endogenous inhibitor stanniocalcin-2 reveals its inhibitory mechanism. Nat Commun. 2022 Oct 18;13(1):6084. doi: 10.1038/s41467-022-33698-8. PMID: 36257932
- Hartmann S, Ling M, Dreyer LSA, Zipori A, Finster K, Grawe S, Jensen LZ, Borck S, Reicher N, Drace T, Niedermeier D, Jones NC, Hoffmann SV, Wex H, Rudich Y, Boesen T, Šantl-Temkiv T. Structure and Protein-Protein Interactions of Ice Nucleation Proteins Drive Their Activity. Front Microbiol. 2022 Jun 17;13:872306. doi: 10.3389/fmicb.2022.872306. PMID: 35783412
- Nielsen J, Brandt J, Boesen T, Hummelshøj T, Slaaby R, Schluckebier G, Nissen P. Structural Investigations of Full-Length Insulin Receptor Dynamics and Signalling. J Mol Biol. 2022 Mar 15;434(5):167458. doi: 10.1016/j.jmb.2022.167458. Epub 2022 Jan 21. PMID: 35074483.
- Aminzadeh A, Larsen CE, Boesen T, Jørgensen 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 2021 Nov 24. PMID: 34817920; PMCID: PMC8728606. ■

THOMAS WILLNOW

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

Highlights from 2022

- Shih, A.Z.L., Chen, Y.-C., Speckmann, T., Søndergaard, E., Schürmann, A., Verchere, C.B. and T.E. Willnow. (2022): SORLA mediates endocytic uptake of proIAPP and protects against islet amyloid deposition. Mol Metab. doi: 10.1016/j.molmet.2022.101585.
- Bunatyan, L., Margineanu, A., Boutin, C., Montcouquiol, M., Bachmann, S., Ilso Christensen, E., Willnow, T. and A. Christ. (2022): LRP2 contributes to planar cell polarity-dependent coordination of motile cilia function. Cell Tissue Res. doi: 10.1007/s00441-023-03757-7.
- Sandmann, C.L., Schulz, J.F., Ruiz-Orera, J., Kirchner, M., Ziem, M., Adami, E., Marczenke, M., Christ, A., Liebe, N., Greiner, J., Schoenenberger, A., Muecke, M.B., Liang, N., Moritz, R.L., Sun, Z., Deutsch, E.W., Gotthardt, M., Mudge, J.M., Prensner, J.R., Willnow, T.E., Mertins, P., v.Heesch, S. and Hubner, N. (2023): Evolutionary origins and interactomes of human young microproteins and small peptides translated from short open reading frames. Mol Cell. (in press) ■

OLAV MICHAEL ANDERSEN

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

Highlights from 2022

- Awarded the AlzheimerForsksningsFondens basic research award 2022
- Publication on our SORL1 het minipigs as a model of early AD - in Cell Rep Med
- Invited speaker for Cold Spring Harbor Laboratory meeting on Neurodegeneration ■

YONGLUN LUO

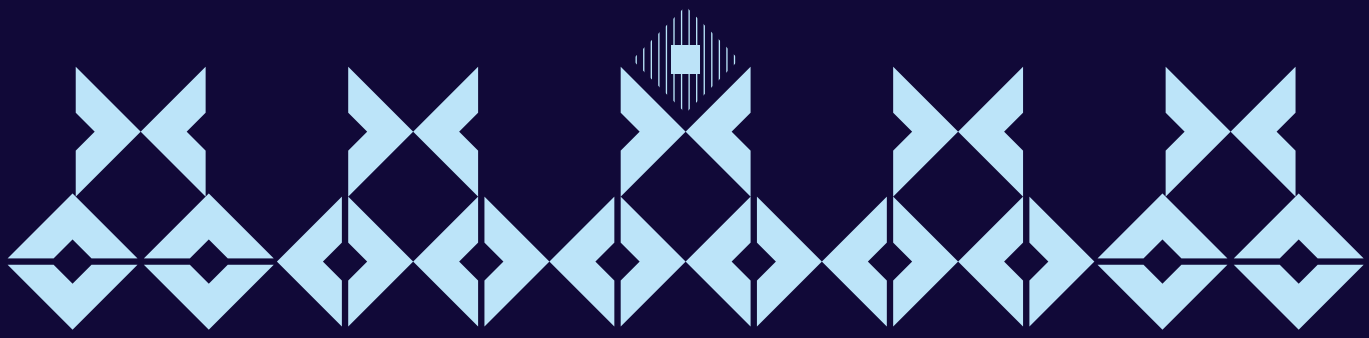
Applied Gene and Genome Technologies in Biomedical Research
Living multicellular organisms are formed by a complex hierarchy of functionally distinct cells. A long-lasting scenario in life sciences is to characterize the molecular signatures in individual cells under both health and diseased conditions. Breakthroughs in 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 is to revisit and decode the molecular and pathological signatures causing (neuro) degenerative diseases, and thus identify targeting genes for disease diagnosis, prevention, and treatment. ■

NORDIC EMBL PARTNERSHIP SCIENCE & ART COMPETITION 2022 WINNER:

'A Walk to Remember' by ***Andrea Moreno*** *from DANDRITE*

"The painting represents the spontaneous release of neurotransmitters that might be one of the causes of memory decay by synaptic depotentiation. In an allegory, by preventing the "neurotransmitter rain" to reach certain spots, the figure saves some memory traces from weakening.

03
Events of the year 2022



EVENTS, VISITORS, GUESTS AND SEMINARS

JANUARY

01 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Associate Professor **Rune W. Berg**, Dept. of Neuroscience, University of Copenhagen, Denmark, *"A new theory for the neural principles behind generation of movement"*

02 VIRTUAL EVENT: **Online 11th Nordic EMBL Partnership Meeting hosted by DANDRITE** with DANDRITE Group Leader, Mark Denham as one of the keynote speakers.

MARCH

03 EVENT: **DANDRITE Student Encounters** organized by DANDRITE

04 VIRTUAL OUTREACH EVENT: **FIMM Scientific Coffee Break** with DANDRITE Group Leader Taro Kitazawa

05 LECTURE: **Inaugural lecture** by Professor and DANDRITE Affiliated Researcher Morten Schallburg Nielsen, *"Another round – Receptor crossing in BBB"*

06 TALK: **Talk** by Professor in microbiology and Scientific Director Morten Sommer, Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark (DTU), *"Towards Advanced Microbiome Therapeutics"*, hosted by DANDRITE Affiliated Researcher Marina Romero-Ramos

07 EVENT: **YoDA - Trip To Studenterhuset**, organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE").

APRIL

08 EVENT: **DANDRITE Easter Get-together** organized by DANDRITE

09 VIRTUAL EVENT: **DANDRITE Symposium** organized by DANDRITE. Lectures by:

- Postdoctoral Fellow Dr. Pierre De Rossi, University of Zurich , Switzerland, *"Moving away from pathological hallmarks and identifying early mechanisms of neurodegenerative diseases"*
- Postdoctoral Researcher Dr. Raunak Basu, Max Planck Institute for Brain Research, Germany, *"Representation of navigational goals in the orbitofrontal cortex"*
- Postdoctoral Researcher Dr. Chie Satou, Friedrich Miescher Institute for Biomedical Research, Switzerland , *"Network hub for experience-dependent sensorymotor transformation in adult zebrafish."*
- Postdoctoral Researcher Dr. Janko Gospocis, Medical Center-University of Freiburg, Germany, *"Hormones and High Society: Control of Caste Identity in Ants"*
- Postdoctoral Research Associate Dr. Clemence Bernard, King College London, United Kingdom, *"Post-transcriptional regulation of cerebral cortex development"*
- Postdoctoral Fellow Dr. Dong Won Kim, John Hopkins University, USA, *"Leveraging – Omics to understand the molecular mechanisms of neurodevelopment and neurodegeneration"*
- Postdoc Dr. Gabriel Bosse, University of Utah, USA, *"Zebrafish as a model to study neurological disorders"*
- Postdoctoral Fellow Dr. Muriel Desbois, Seattle Children's Research Institute, USA, *"Ubiquitin Ligase activity in axon development and disease"*

10 EVENT: **YoDa Method Café** with DANDRITE-affiliated member Mette Richner, organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE"). Subject: JoVE – Journal of Visualized Experiments.

11 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Professor of Neuroscience and Group Leader Santiago Rompani, EBML Rome, Italy, *"Integration and modulation of visual information in the thalamus"*

12 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Professor and Vice Director of the International Institute of Integrative Sleep Medicine Takeshi Sakurai, University of Tsukuba, Japan, *"Role of amygdala and dopamine in the mechanism of REM sleep initiation"*

MAY

13 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Postdoctoral Fellow Dr. Chao Sun, Max Planck Institute for Brain Research, Germany, *"Synaptic Protein Synthesis and Degradation Machines"*

14 SEMINAR: **Biomedicine Seminar Series: Synthesis and delivery of RNA therapeutics** presented by DANDRITE Affiliated Researcher Jørgen Kjems

15 OUTREACH EVENT: **Matchpoint 2022 – Our Fascinating Brain** organized by Aarhus University, with lecture from DANDRITE Group Leader Poul Nissen

16 EVENT: **FEBS 2022 course** – Lost in Integration – Probing Biomolecules with Electrons, Photons, Neutrons, and Magnetic Spins organized by Prof. Poul Nissen

17 EVENT: **YoDa Career Café** with HR-supporter Jesper Madsbjerg and HR-partner Dorte D. Thomsen, organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE"). Subject: Opportunities in academia – Rules and Reality.

18 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Dr. and Scientific Director Ryohei Yasuda, Max Planck Florida Institute, USA, *"Neuronal signal transduction in synaptic plasticity"*

19 EVENT: **ODIN Knowledge Sharing Event** with talks from DANDRITE Group Leader Mark Denham and Affiliated Researcher Jørgen Kjems

JUNE

20 EVENT: **DANDRITE Sab & Retreat** organized by DANDRITE

21 SEMINAR: **DANDRITE Topical Seminar** with Assistant Professor of Biology and Pharmacology Alberto Cruz-Martin, Boston University, MA, USA, *"Neuroimmune modulation of prefrontal cortex development and early social behavior"*

22 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Professor at the Dept. of Pharmacology Yasunori Hayashi, Kyoto University Graduate School of Medicine, Japan, *"Synaptic plasticity during sleep is required for memory",*

23 EVENT: **DANDRITE Internal Meeting (Poster Session)**

24 EVENT: **YoDa Friday Beer**, organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE").

JULY

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

AUGUST

25 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Professor at the Dept. of Physiology, Anatomy and Genetics Vladyslav Vyazovskiy, University of Oxford, United Kingdom, *"Local and global aspects of sleep regulation"*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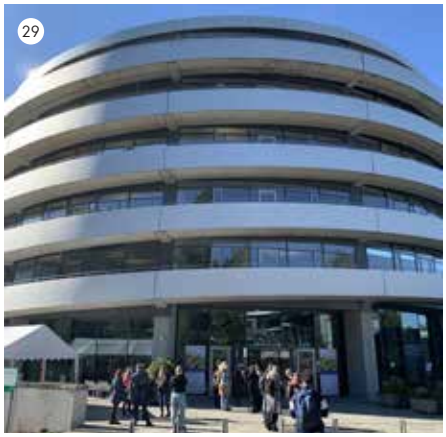
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26 SEMINAR: **DANDRITE Topical Seminar** with Dr. Kakoli Bose, Advanced Centre for Treatment, Research and Education in Cancer, Mumbai, India, *"Unraveling the conundrum of multitasking serine protease HtrA2"*

SEPTEMBER

27 EVENT: **DANDRITE Summer Party 2022** organized by DANDRITE

28 SEMINAR: **Approaches to Personalized Medicine at Health** with Affiliated Researcher Jørgen Kjems, *"RNA's many faces – in diagnostics and taylormade medicine"*

29 EVENT: **4th EMBL Partnership Conference 2022** in Heidelberg, Germany.

30 MEETING: **Emerging Concepts in Cell and Development Biology Meeting** organized by DANDRITE Affiliated Researcher Felicity Davis

31 OUTREACH EVENT: **Hearts and Minds Festival about "The Brain"** organized by Folkeuniversitetet, Aarhus. Lectures by:
- DANDRITE Group Leader Poul Henning Jensen about Parkinson's disease and dementia
- DANDRITE Group Leader Anders Nykjær, *"Få styr på hukommelsen"*

32 OUTREACH EVENT: **NCA BrainTrain: New treatment modalities in Parkinson's disease**, NeuroCampus Aarhus with lecture by Group **Leader Mark Denham**, *"Human lineage-restricted stem cells"*

OCTOBER

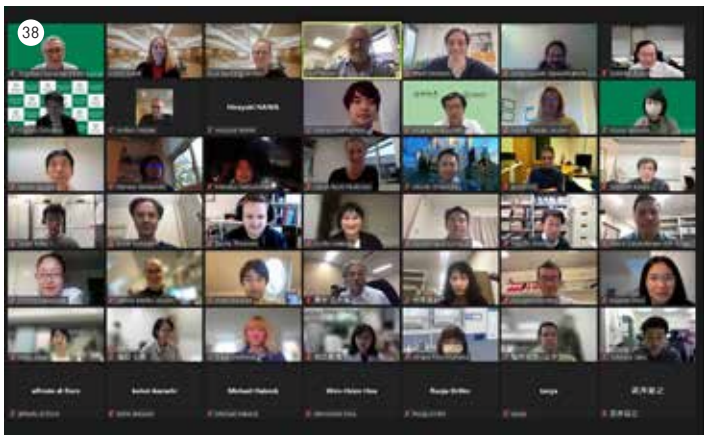
33 EVENT: **DANDRITE Tour de Lab – Building 1182** organized by DANDRITE

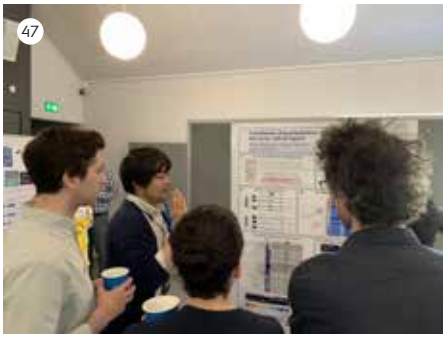
34 OUTREACH SEMINAR: **MBG Internal Seminar Series** with DANDRITE Group Leader Taro Kitazawa presenting, organized by MBG

35 JOINT LECTURE: **Joint KJELDGAARD & DANDRITE Lecture** with Professor Marco Prinz, Institute of Neuropathology, University of Freiburg, Germany, "The myeloid side of the brain" hosted by DANDRITE and Department of Molecular Biology and Genetics, Aarhus Univeristy

36 EVENT: **Mini symposium** hosted by DANDRITE Group Leader Poul Nissen, Aarhus University. Lectures by:
- Professor Wayne Hendrickson, Columbia University, USA, *"Allosteric Control of Hsp70 Protein Folding Activity"*
- Professor Inga Hänelt, University of Frankfurt, Germany, *"Potassium transporters and channels in bacteria survival"*
- Professor Michael Palmgren, University of Copenhagen, Denmark , *"Evolution of Na+/K+- and plasma membrane H+-ATPases – which pump came first? (and where did P4 ATPases come from?)."*

37 TALK: **Nobel Laurate Talk** by Edvard Moser, hosted by DANDRITE and Aarhus University





NOVEMBER

38 VIRTUAL JOINT SYMPOSIUM: **Online BRI-DANDRITE Joint Symposium** organized by DANDRITE and Brain Research Institute, Niigata University, Japan

39 SYMPOSIUM: **DANEMO Symposium: Molecular Ecosystems** organized by DANDRITE Group Leader Poul Nissen, Aarhus University, Aarhus

40 WORKSHOP: **Biophysics workshop** organized by DANDRITE Affiliated Researcher Magnus Kjærgaard, Aarhus University, Aarhus. Lecture and workshop by:

- Head of Sample Preparation and Characterization Facility Maria Garcia Alai, EMBL Hamburg, Germany, *"Biophysical characterization and quality control of integral membrane proteins and protein complexes"*
- ARISE Postdoctoral Fellow Osvaldo Burastero, EMBL Hamburg, Germany, *"eSPC – an online data analysis platform for molecular biophysics"*

41 SEMINAR: **DANDRITE Topical Seminar** with Dr. Tamir Gonen, Dept. of Biological Chemistry, David Geffen School of Medicine, University of California, Los Angeles, USA, *"MicroED: Conception, practice and future opportunities"*

42 LECTURE: **Inaugural lecture** by Professor and DANDRITE Affiliated Researcher Yonglun Lou, *"Way Towards Personalized Regenerative Medicine"*

43 VIRTUAL LECTURE: **Virtual DANDRITE Lecture** with Director at the Dept. of Neuro- and Sensory Physiology Silvio Rizzoli, University Medical Center Göttingen, Germany *"Expansion microscopy at one nanometer resolution"*

44 LECTURE: **YoDA Lecture** with PhD Student Elena Perez-Montoyo, Institute of Neuroscience, Alicante, Spain, *"Memory encoding and brain-wide functional connectivity is controlled by dentate gyrus parvalbumin interneurons"* organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE").

45 SEMINAR: **PROMEMO Seminar** with Associate Professor Kasper Hansen, University of Montana, USA, hosted by DANDRITE Team Leader Hanne Poulsen

DECEMBER

46 EVENT: **YoDA Career Café** with DANDRITE Affiliated Researcher Marina Romero-Ramos, *"Femalie perspectives on an academic career path"* organized by The PhD & Postdoc Association at DANDRITE called "YoDa" (short for "Young DANDRITE").

47 EVENT: **DANDRITE Internal Meeting (Poster Session)**

48 EVENT: **DANDRITE Christmas Get-together**

49 SYMPOSIUM: **Minisymposium: Seeing Single RNA and Protein Conformations in Solution – Application of Plasmonic Optical Tweezers and Nonospores** hosted by DANDRITE Affiliated Researcher Jørgen Kjems

DANDRITE SAB MEETING AND RETREAT 2022

DANDRITE's fifth Scientific Advisory Board (SAB) meeting was held in June combined with the yearly retreat. The meeting took place at the beautiful conference center Sandbjerg Manor located in Sønderborg.

The foci of the SAB meeting were how to support and ensure a smooth transition of a first to a second generation of Group Leaders, the future research topics, recruitment of DANDRITE, and the progress of individual Group Leaders and Team Leaders.

Besides presentations by group leaders, team leaders, and younger researchers, the SAB also met with group leaders and team leaders in individual sessions to discuss scientific progress, future plans, and managerial issues such as mentorship and collaborations within and beyond DANDRITE. Further, the SAB members had closed meetings with postdocs and PhD students.

QUOTES FROM THE EVALUATION REPORT READS:

"...DANDRITE has profited strongly through the Nordic EMBL Partnership for Molecular Medicine and through its strong support by the Lundbeck Foundation. The excellent science emanating from DANDRITE and the excellent leadership has now transformed DANDRITE into a sustainable institute with a 5-year rolling budget supported by the Lundbeck Foundation"

"The SAB is extremely impressed by the quality of oral and poster presentations by the students, their passion for science, and genuine concern for the well-being of DANDRITE."

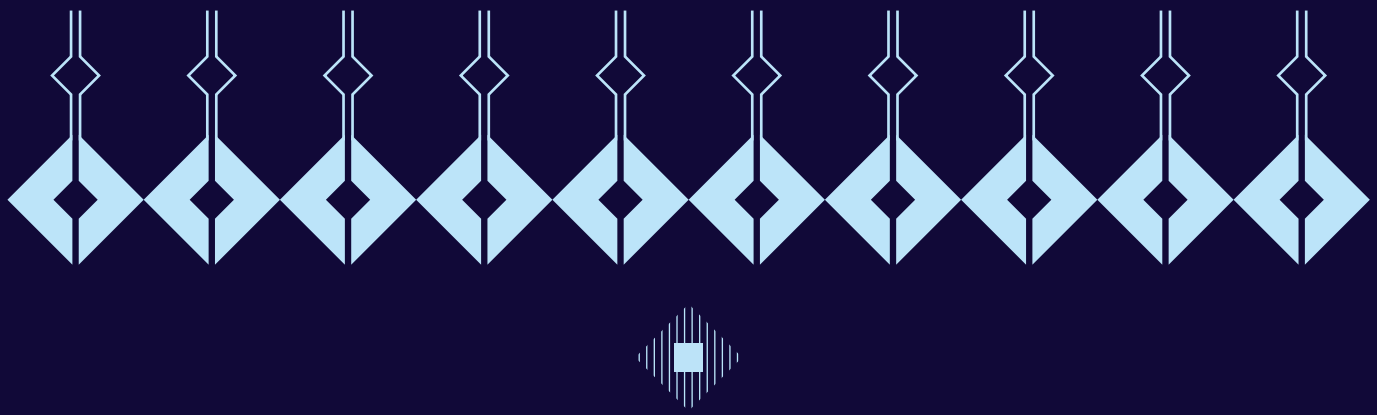
"There was as strong attendance of postdoctoral fellows from most DANDRITE labs at the retreat. They exhibited a high level of commitment and engagement for their research and projects and gave excellent well-prepared oral and poster presentations. It is clear that postdocs are essential for the excellence of the program as a whole. The SAB sensed an overall excitement for DANDRITE among the postdoctoral fellows".

DANDRITE OUTREACH

FESTIVAL OF RESEARCH
DANDRITE researchers usually take part in the annual recurring nationwide Festival of Research and not least in 2022.
At Aarhus University's campus, the festival is each year a day event where the general Danish public is invited to meet researchers firsthand. It was also in 2022 busy and enjoyable day in which students from DANDRITE demonstrated their research areas. Two labs were represented: Poul Nissen's lab about the hidden world of proteins, and Poul Henning Jensen's lab about Parkinson's disease and demonstrations of pig brains.

DANDRITE STUDENT ENCOUNTERS 2022
DANDRITE held the annual event Student ENCOUNTERS with guided lab tours for interested students. Many students showed up to look for opportunities for student projects in one of DANDRITE's different research groups.

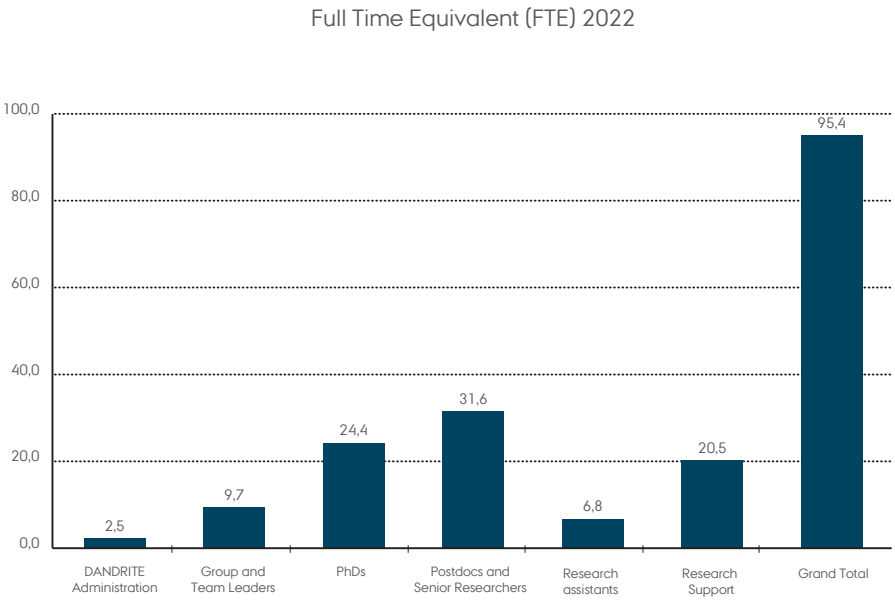
04 Personnel



Personnel

Since DANDRITE's inauguration in 2013, and until 2019, staff development has been characterized by considerable growth each year. Since 2021, the number of staff has started to decrease as the first cohort of GLs is ramping down their activities because they are finishing their contracts and preparing for the next step. In the coming years, we expect an increase in staff since the new cohort of GLs is establishing their labs and recruiting staff members.

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



Personnel figure 1:
Graphic representation of number of personnel in 2022 *counted in FTE – Full Time Equivalent* for appointed categories summarized: DANDRITE Administration, Group- and Team Leaders, PhDs, Postdocs and Senior Researchers, Research assistants, and Research Support.

FIGURE 2:
COUNT OF NUMBER AND PERCENTAGES OF PERSONNEL EMPLOYED DURING 2022 GROUPED BY APPOINTMENT CATEGORY AND GENDER. FTE COUNT.

DANDRITE Personnel categories	Female	Male	Total	%
DANDRITE Administration	2,5	0,0	2,5	2,6
Group and Team Leaders	1,1	8,6	9,7	10,1
PhDs	13,8	10,6	24,4	25,6
Postdocs and Senior Researchers	15,3	16,3	31,6	33,1
Research assistants	5,0	1,8	6,8	7,1
Research Support	16,2	4,3	20,5	21,5
Grand Total	**53,8**	**41,6**	**95,4**	**100**
Percentage of Female/Male %	56	44	100	

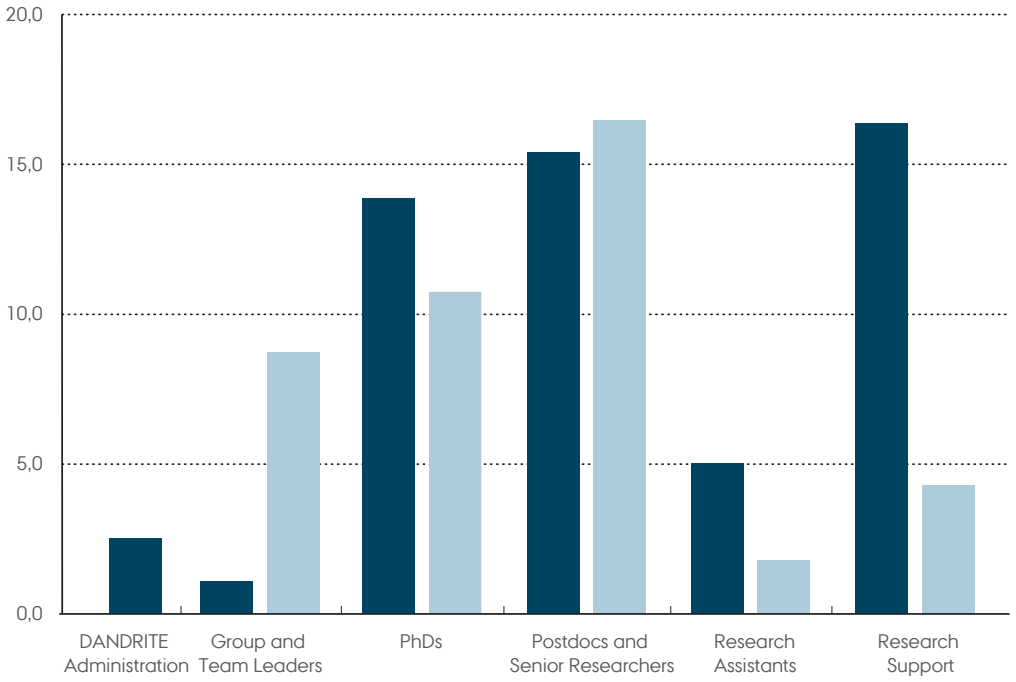


Figure 3:
Graphic representation of the personnel counts for 2022 (numbers grouped by appointment category and gender).

Figure 4:
Percentage of Female/Male

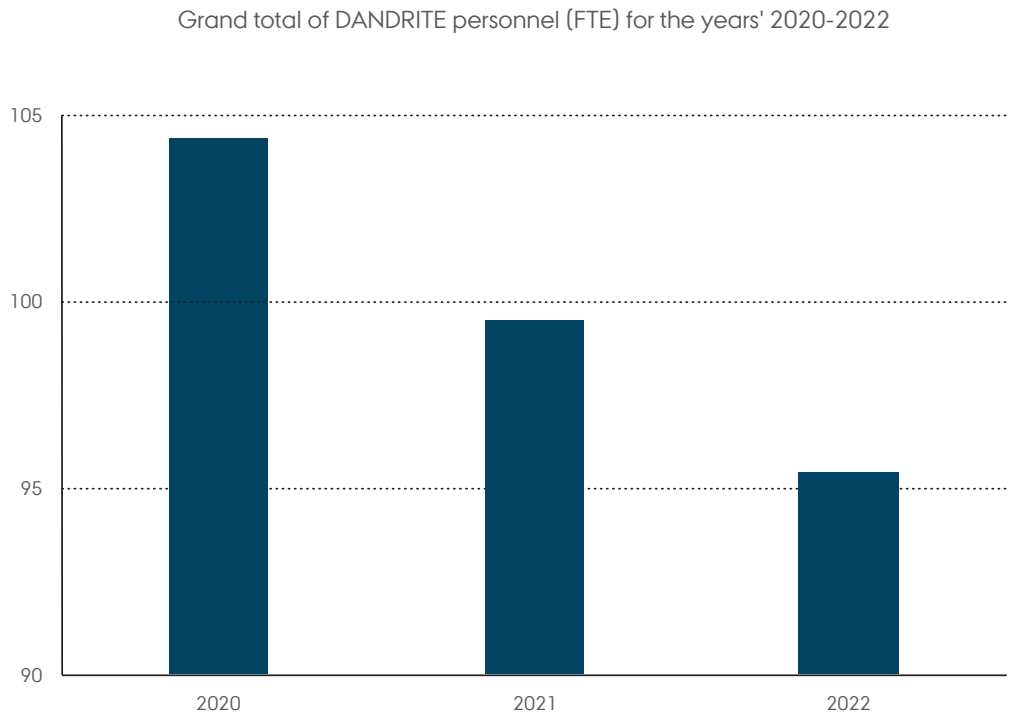


Figure 5:
Graphic representation of personnel progression from 2020 through 2022 for appointment categories (FTE count).

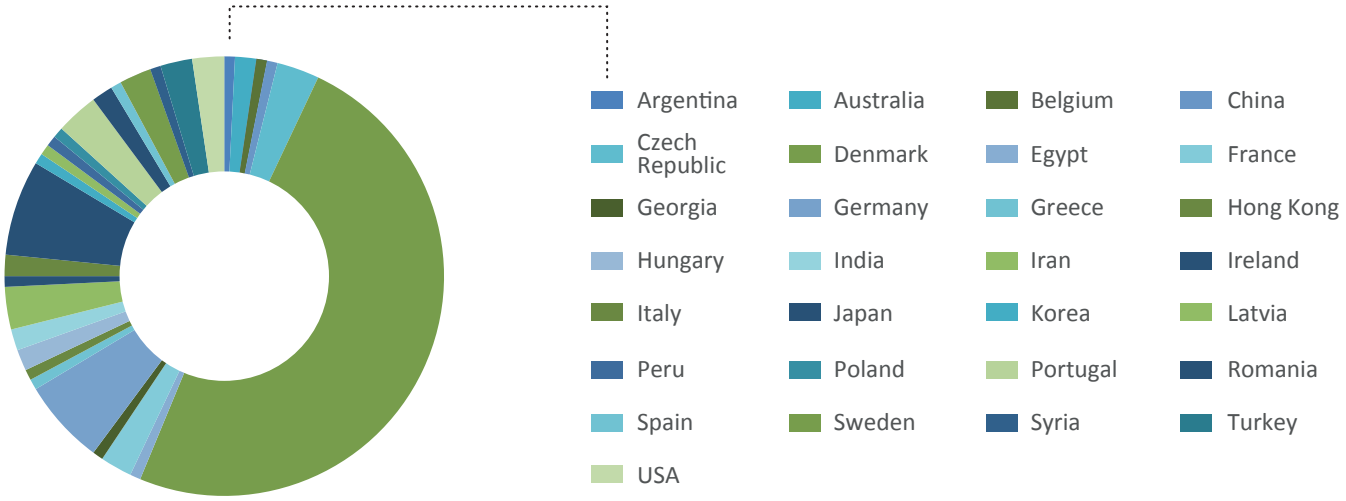


Figure 6:
Graphic representation of the nationality distribution of all employees. In total 29 nationalities.

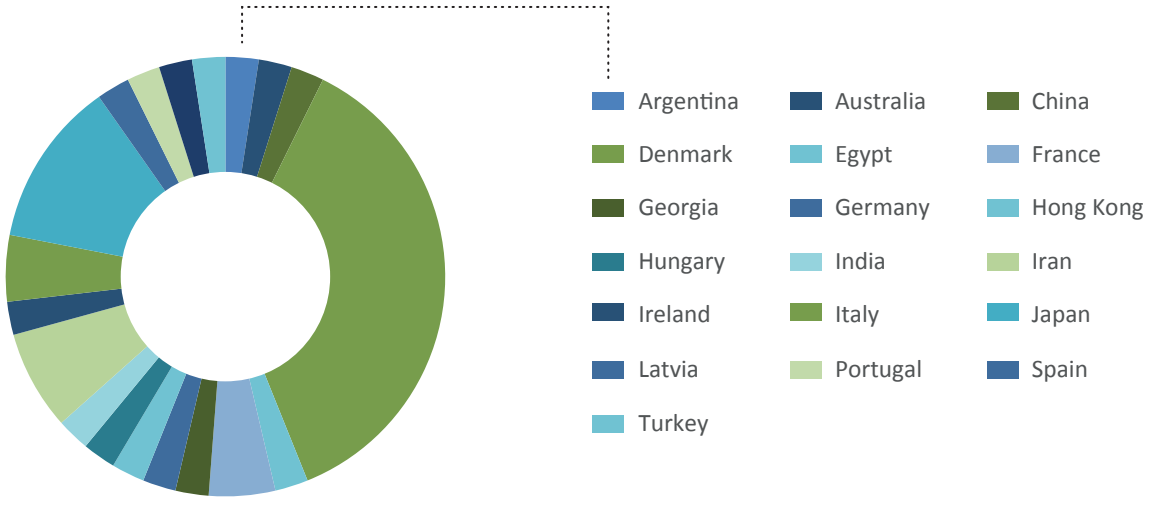
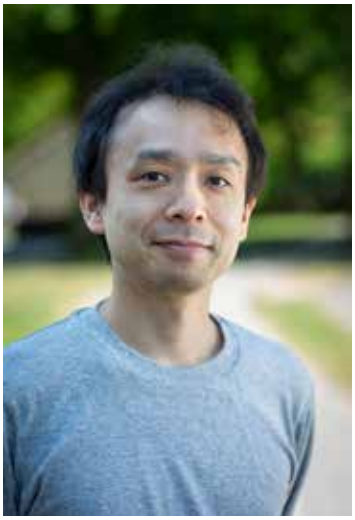


Figure 7:
Graphic representation of the nationality distribution of the employees in DANDRITE's EMBL recruited GL's research groups.

Awards and Prizes



1. DANDRITE Group Leader **Taro Kitazawa** was awarded an ERC Starting Grant of EUR 1.5M from the European Research Council for research into the molecular basis of neuroplasticity to answer the fundamental questions regarding how memory is stored in the brain.

2. DANDRITE Team leader **Gilles Vanwalleghem** was selected for The Lundbeck Foundation Investigator Network - a new initiative designed to strengthen Danish neuroscience by connecting people and disciplines. Further, Gilles is chairing the network.

Poster Prizes

Assistant professor **Alena Salasova** was awarded the 2nd prize for the best poster talk at The Precision Neuroscience Conference 2022 in Virginia.

PhD student **Lucie Woloszczukova** was awarded a Poster Prize for the poster: "Exploring SorCS3 signaling during zebrafish, mouse and human brain development" at the 4th EMBL Partnership meeting 2022, Heidelberg, Germany.

Postdoc **Mads Eskesen Christensen** was awarded a Poster Prize of EUR 200 at FEBS Advanced Course "Lost in Integration - Probing Biomolecules with Electrons, Photons, Neutrons, and Magnetic Spins" in May 2022, Spetses Island, Greece.

Postdoc **Mads Eskesen Christensen** and PhD student **Michelle J. Laursen** were awarded Poster Prizes at the P-Type ATPases in Health and Disease Conference 2022, Banff, Alberta, Canada.

PhD Student **Caroline Neumann** was awarded the Kjeld Marcker PhD Award 2022 at the Department of Molecular and Biology's Annual Meeting at Aarhus University. The prize is given to exceptional Ph.D. students who have defended their PhD studies in the past year.

Patents

Patent application: Dopaminergic neuron progenitor cells or cell derivatives thereof obtained from lineage restricted pluripotent stem cells.

Inventors **Mark Denham** and **Maimaitili Muyesier**, 2022, WO2022136306A1.

Grants


14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21


26

1. Affiliated Researcher **Olav Andersen**: Funktionel karakterisering af ny SORLA-variant som giver Alzheimer's demens, DKK 45.000, A.P. Møller Foundation

2. Affiliated Researcher **Olav Andersen**: Sammenhæng mellem SORLA phosphorylering og AD, DKK 300.000, Alzheimer-forskningsfonden

3. Affiliated Researcher **Olav Andersen**: SORLA phosphorylering of endosome recycling, DKK 2.200.000, Novo Nordisk Foundation

4. Affiliated Researcher **Thomas Boesen**: iTEAC Interdisciplinary course, DKK 2.000.000, Novo Nordisk Foundation

5. Affiliated Researcher **Felicity Davis**: Science communication and public outreach project at KØN in Aarhus, DKK 5.980.108, Novo Nordisk Foundation

6. Group Leader **Mark Denham**: A Novel Stem Cell Therapy for Parkinson's Disease/ Pioneer, DKK 1.000.000, Novo Nordisk - Pioneer Grant

7. Group Leader **Mark Denham**: Creating a novel stem cell therapy for Parknson's disease, DKK 1.500.000, Innovationsfonden – InnoExplorer

8. Research Assistant **Rosa Groth**: Cross border science and society project, DKK 170.000, HALOS

9. Senior Group Leader **Poul Henning Jensen**: Development of intracellular alpha-synuclein aggregate sensors - Part 1, DKK 826.000, M. J. Fox Foundation

10. Senior Group Leader **Poul Henning Jensen**: Assessment of 2 commercially available pS129-aSyn species and comparison to an MJF14 aSyn aggregate ELISA in rodent tissue, DKK 427.756, M. J. Fox Foundation

11. Senior Group Leader **Poul Henning Jensen**: The next level -Towards investigation of aplha-synuclein pathology, DKK 300.000, Parkinsonforeningen

12. Senior Group Leader **Poul Henning Jensen**: Industrial PhD project "Identification of early-stage pathology markers in synuclein-opathy models of Parkinson's disease", DKK 360.000, Innovationsfonden

13. Senior Group Leader **Poul Henning Jensen**: Collaborative Research project "Endoplasmic reticulum dysfunction in the pathophysiology of synucleinopathies" with prof. Fulvio Reggiori, AU and assoc. prof. Marijn Kuijpers, Radboud University, the Netherlands, DKK 20.000.000, Lundbeck Foundation

14. Research Assistant **Kaho Ito**: Scholarship, DKK 461.500, The Murata Overseas Scholarship Foundation

15. Group leader **Taro Kitazawa**: LF-NIH-Brain Initiative "Deciphering the logic of stimulus-response gene regulation by distinct kinase pathways in neurons", DKK 3.000.000, Lundbeck Foundation

16. Affiliated Researcher **Jørgen Kjems**: mRNA vaccine, DKK 2.245.769, Novo Nordisk Foundation

17. Affiliated Researcher **Jørgen Kjems**: GutBio-Mod, DKK 2.248.000, Arla Food for Health

18. Affiliated Researcher **Jørgen Kjems** circRNA composition, DKK 2.879.954, Independent Research Fund Denmark

19. Postdoc **Louise Laursen**: Marie Curie post-doc fellowship, DKK 1.800.000, EU-H2020

20. Affiliated Researcher **Yonglun Luo**: Research grant, DKK 5.054.000, Lundbeck Foundation

21. Assistant Professor **Noëmie Mermet-Joret**: LF Experiment Grant, Are hardwired circuits the brain's scaffold for learning? DKK 2.000.000, Lundbeck Foundation

22. Postdoc **Kristian Juul-Madsen**: Postdoctoral research grant, DKK 2.500.000, Lundbeck Foundation

23. Postdoc **Kristian Juul-Madsen**: Postdoctoral research grant, DKK 2.056.000, Independent Research Fund Denmark

24. Group Leader **Sadegh Nabavi**: Novo Nordisk Exploratory Interdisciplinary Synergy Program, collaborative project: Multi-level analysis of brain mechanisms underlying epigenetic inheritance of superb learning capabilities, DKK 4.998.087, Novo Nordisk Foundation

25. Team Leader **Hanne Poulsen**: Industry-academia collaboration, DKK 2.250.000, ODIN

26. Postdoc **Lasse Reimer**: Lundbeck Foundation Frontier Grant, DKK 5.000.000, Lundbeck Foundation

27. Assistant Professor **Alena Salasova**: 19th International Congress of Developmental Biology (ISDB), DKK 5.000, Danish Society for Biochemistry and Molecular Biology

28. Assistant Professor **Alena Salasova**: ISDB travel award 2021, DKK 1.500, ISDB

29. Postdoc **Charlott Stock**: Attending EMBL course on "Protein quality control for downstream processes", DKK 8.535, Nordforsk

30. Team Leader **Gilles Vanwalleghem**: Starting grant, DKK 2.000.000, AUFF

31. Team Leader **Gilles Vanwalleghem**: Starting package grant, DKK 3.000.000, Novo Nordisk Foundation

32. Team Leader **Gilles Vanwalleghem**: Novo Nordisk Exploratory Interdisciplinary Synergy Program, DKK 5.000.000, Novo Nordisk Foundation

33. PhD Student **Lucie Woloszczukova**: DMM Conference Travel Grant, DKK 5.000, Disease Models & Mechanism Journal

Invited Talks

JANUARY

Thomas Boesen: *Wired life – insights into unique enzymes from cable bacteria,* HALOS Symposium, Virtual Lecture

Anders Breinbjerg: *Genetic variants associated with Childhood Daytime Urinary Incontinence – A genome wide association study,* International Children's Continence Society, Virtual Lecture

Taro Kitazawa: *Epigenetic and transcriptional basis of neuronal activity-dependent gene regulation,* University of Tokyo, Japan

Taro Kitazawa: *Epigenetic and transcriptional regulation of neuronal activity-response genes,* RCAST, University of Tokyo, Japan

Taro Kitazawa: *Epigenetic and transcriptional regulation of neuronal activity-response genes,* National Institute of Genetics, Japan

Taro Kitazawa: *Epigenetic and transcriptional basis of neuronal activity-dependent gene regulation,* RIKEN, Japan

FEBRUARY

Mark Denham: *Modeling Neurological Disorders with Human Pluripotent Stem Cells,* Translational Neuropsychiatry Unit, Aarhus University, Denmark

Mark Denham: *Lineage-Restricted Undifferentiated Stem Cells: A Novel Cell Replacement Therapy for Parkinson's Disease,* 11th Nordic EMBL Partnership Meeting, Virtual Lecture

Michelle Laursen: *Lecture for potential student,* U-Days at Aarhus University, Denmark

Yonglun Luo: *Presentation on xenotransplantation,* The Danish Council on Ethics, Denmark

Jelena Radulovic: *Stabilization of memory circuits through inflammatory signaling,* Einstein INI monthly bi-speaker meeting, Albert Einstein College of Medicine, USA

Keisuke Yonehara: *What the eyes tell the brain,* Microsoft Project Users Forum, Virtual Lecture

MARCH

Mark Denham: *Lineage-Restricted Undifferentiated Stem Cells: A Novel Cell Replacement Therapy for Parkinson's Disease,* Wollongong University, Australia

Taro Kitazawa: *Epigenetic and transcriptional basis of neuroplasticity in memory formation,* FIMM, Finland

Poul Nissen: *Structure and Function of Autoregulatory Mechanisms of P-Type ATPases,* Gordon Research Conference on "Ligand Recognition and Molecular Gating", Italy

Jelena Radulovic: *Balancing specificity and generality in fear circuits,* Einstein INI monthly bi-speaker meeting, Albert Einstein College of Medicine, USA

APRIL

Silke Chalmers: *European Network of Breast Development and Cancer Laboratories Meeting,* Switzerland

Felicity Davis: *European Network of Breast Development and Cancer Laboratories Meeting,* Switzerland

Mark Denham: *Creating a Stem Cell Therapy for Parkinson's Disease,* Sunstone Ventures, Aarhus University TTO, Denmark

Michelle Laursen, Sara Basse Hansen: *Public outreach with stand,* Forskningens Døgn at Aarhus University, Denmark

Yonglun Luo: *Generation of oncogene eccDNA by CRISPR,* Circular Vision consortium meeting, Switzerland

Vasilis Theologidis, Mia Rosa Antorini, Louise Bruun: *Presentation of novel insights in Parkinson's disease,* Forskningens Døgn at Aarhus University, Denmark

MAY

Mark Denham: *Pruning the Genome: A Novel Cell Therapy for Parkinson's Disease,* Matchpoints 2022, Denmark

Mark Denham: *Miniaturised Controlled Organoid Platform for Disease Modeling and Drug Discovery,* ODIN – Knowledge sharing event, Virtual Lecture

Photos: Roar Lava Paaske/AU-Kommunikation and Lars Kruse/AU Kommunikation

Poul Henning Jensen: *New non-inclusion a-syn aggregate neuropathology – how to detect it, does it matter and can we counteract it?* Finpharmanet webinar, Virtual Lecture

Poul Henning Jensen: *Session chair on neurodegeneration,* Matchpoints 2022, Denmark

Taro Kitazawa: *Epigenetic and transcriptional basis of neuroplasticity,* Kumamoto University, Japan

Andrea Moreno: *Synaptic depotentiation and forgetting: understanding and manipulating memory decay,* Young Researchers Event Denmark: EBRAINS – a digital Infrastructure for next-generation basic & clinical neuroscience, Denmark

Poul Nissen: *Molecular Mechanisms of Transport and Signaling in the Brain,* Matchpoints 2022, Denmark

Anders Nykjær: *Nyeste hjerneforskning ved Aarhus Universitet – Hukommelse*, Matchpoints 2022, Denmark

Anders Nykjær: *Glemmer du, så husker jeg...,* Matchpoints 2022, Denmark

Anders Nykjær: *The Neurexin Receptor SorCS1: Another Player in Autism Spectrum Disorder?* Precision Neuroscience Conference 2022, USA

Hanne Poulsen: *CAPOS recapitulated in mouse model,* 51st Sandbjerg meeting on membrane transport, Denmark

Alena Salasova: *Proneurotrophin receptor SorCS2 interacts with Wnt receptor Ror2 to regulate embryogenesis and brain development across vertebrates,* Precision Neuroscience Conference 2022, USA

Alena Salasova: *Proneurotrophin receptor SorCS2 is a novel regulator of WNT/Planar Cell Polarity pathway during brain development,* Weill Cornell Medicine, USA

Tomonori Takeuchi: *Selective memory retention and updating knowledge structure,* Tohoku University, Japan

Tomonori Takeuchi: *Dopamine, initial memory consolidation and two distinct novelty systems in rodents,* International Conference of Cognitive Neuroscience 2020 (ICON2020), Finland

Gilles Vanwalleghem: *Imaging neuronal circuits in the Gut,* University of Gothenburg, Sweden

Keisuke Yonehara: *Linking Neural Circuit Asymmetries to Eye Movement Disorders,* Matchpoints 2022, Denmark

JUNE

Mark Denham: *Enhanced Production of Mesencephalic Dopaminergic Neurons from Lineage-Restricted Human Undifferentiated Stem Cells,* The International Society for Stem Cell Research conference, USA

Yonglun Luo: *Genetically modified pigs for organ transplantation,* Summer school "Transplantation medicine", University of Groningen, Holland

Poul Nissen, Azadeh Shahsaver: *Structure and mechanism of human NKCC1,* ITTS 2022: 2nd International Transmembrane Transporter Society Meeting, Denmark

Poul Nissen, Hanne Poulsen: *Na, K-ATPase Brain Isoforms, AHC Neurological Disease Mutant,* Gordon Research Conference on "Membrane Transport Proteins", Spain

Hanne Poulsen: *Ins and Outs of the Na, K-ATPase,* Gordon Research Conference on "Membrane Transport Proteins", Spain

Jelena Radulovic: *Primary cilia control the formation of lasting memories,* MCCS Asia, Japan

Gilles Vanwalleghem: *A window into large neuronal networks from the brain to the gut of zebrafish,* IRIBHM Seminar, Belgium

JULY

Poul Henning Jensen: *Summer school "General lecture on neurodegeneration and relation to psychiatric symptoms",* Aarhus University, Denmark

Jelena Radulovic: *Cholinergic Mechanisms of Retrieval-Based Generalization of Aversive Memories,* Japanese Neurochemistry meeting, Japan

Jelena Radulovic: *Neurobiological Mechanisms of Stress-Related Memories,* Center for Translational Pain Research, Northwestern University, USA

Gilles Vanwalleghem: *Functional connectivity of the developing enteric nervous system,* Zebrafish Brain Conference, Norway

Keisuke Yonehara: *Retinal direction selectivity specified by homeobox gene Vax2,* The 45th Annual Meeting of the Japan Neuroscience Society, Japan

AUGUST

Duda Kvitsiani: *Representation of event history and their relibility in medial prefrontal cortex,* Columbia University, USA

Yonglun Luo: *Decoding the roles of endothelial cell heterogeneity and complement system in diseases and regenerative medicine by single cell and spatially resolved transcriptome analysis,* 18th European Meeting on Complement in Human Disease (EMCHD), Switzerland

Poul Nissen: *Structure and mechanism of membrane transporters,* Integrative structural biology course 2022, Lund Universitet, Sweden

Poul Nissen: *Transporter-based drug discovery,* EMBO Workshop: Membrane transporters as essential elements of cellular function and homeostasis, Greece

Dongik Park: *Roles of Sortilin in Frontotemporal Dementia: Identification of Affected Hippocampal Pathways using Integrated Omics Analysis,* Gordon Research Conference on: "Brain Disorders", Spain

Alena Salasova: *Proneurotrophin receptor SorCS2 is a novel regulator of WNT/Planar Cell Polarity pathway during brain development,* Gordon Research Conference on: "Neural Development", USA

SEPTEMBER

Audrey Andersen-Civil: *Implications of Immune Function and the Gut Microbiota and on the Development of the Enteric Nervous System in Zebrafish models of Autism,* LBBB Meeting 2022, Germany

Line Marie Christiansen: *Structural and Functional Clues on a P4B-ATPases Suggest Autoinhibition,* P-Type ATPases in Health and Disease Conference, Canada

Poul Henning Jensen: *Parkinson's syge og demens,* Hearts & Minds Festival, Denmark

Poul Nissen: *Structures and Regulation of Membrane Transporters,* Yale University, USA

Poul Nissen: *Autoinhibition and Activation of PType ATPases,* P-Type ATPases in Health and Disease Conference, Canada

Jelena Radulovic: *Moderation of talks,* World Conference on Basic Sciences and Sustainable Development, Serbia

Jelena Radulovic: *Advancing mental health through basic science,* World Conference on Basic Sciences and Sustainable Development, Serbia

Katia Soud: *Presentation of behavioral test,* Visit from the Academy of Talented Young People, Aarhus University, Denmark

Gilles Vanwalleghem: *Whole brain imaging in a vertebrate model using light-sheet microscopy,* University of Hasselt, Belgium

Keisuke Yonehara: *Structure, development, and disease of direction-selective circuits in the mammalian retina,* The annual meeting of Vision Society of Japan, Japan

OCTOBER

Line Marie Christiansen: *Structural and functional clues on a P4B-ATPase,* 5th CryoNET Symposium 2022, Denmark

Yonglun Luo: *Generation of oncogene eccDNA by CRISPR,* Circular Vision consortium meeting, Spain

Poul Nissen: *What is the role of ATP1A3?,* AHC and ATP1A3 diseases 10-year anniversary conference and 10th Symposium on ATP1A3 in disease, Scotland

Poul Nissen: *Cryo-EM studies of membrane transporters and receptors,* ISBUC Symposium: Realizing Integration in Structural Biology, Denmark

Anders Nykjær: *Få styr på hukommelsen,* Hearts & Minds Festival, Denmark

NOVEMBER

Olav Andersen: *SORLA and AD,* Royal Society London, England

Anders Breinbjerg: *Genetic Variants associated with Childhood Daytime Urinary Incontinence – A Genome Wide Association Study,* Børn og Unge Forskningssymposium, Aarhus University Hospital, Denmark

Felicity Davis: *Single Molecule Science Club*, Wollongong University, Australia

Poul Henning Jensen: *Presentation of novel insights in Parkinson's disease and research project,* Parkinsonforeningens patientmøde, Denmark

Cecilie Siggard Jørgensen: *Pathogenesis of polyuria in children with nocturnal enuresis, Børn og Unge Forskningssymposium,* Aarhus University Hospital, Denmark

Duda Kvitsiani: *Sensorimotor state representations by medial prefrontal cortex,* JOINT seminar series between DANDRITE and Brain Research Institute, Niigata University, Virtual Lecture

Poul Nissen: *Soft Matter ESS Lighthouse(s),* Danish Lighthouse for Structural Biology with Neutrons – NEULIFE, Denmark

Poul Nissen: *Academic careers in Life Sciences,* Synapse Life Science Career Fair 2022, Aarhus University, Denmark

Keisuke Yonehara: *Structure, development, and disease of direction-selective circuits in the mammalian retina,* Hiroshima University, Japan

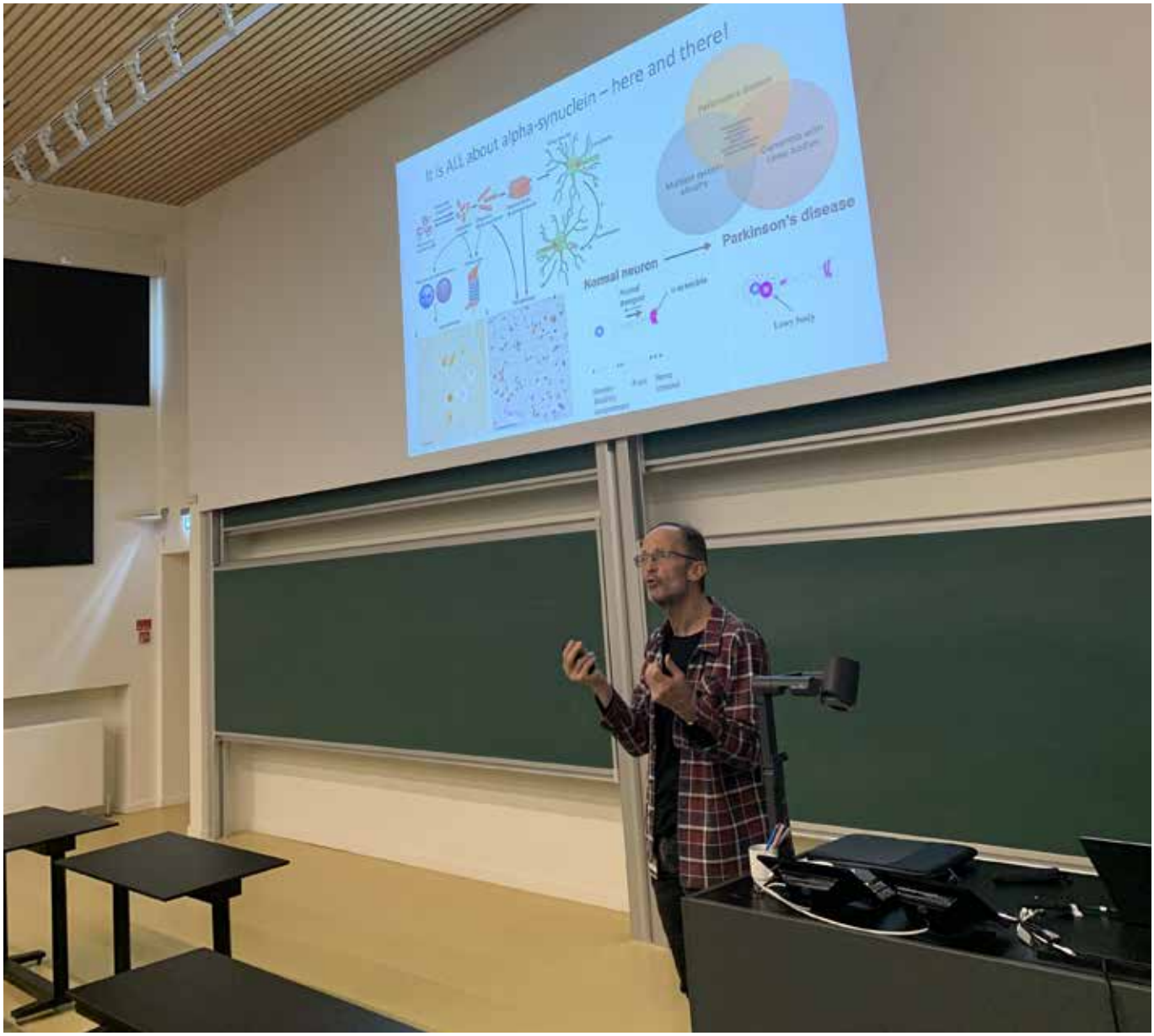
DECEMBER

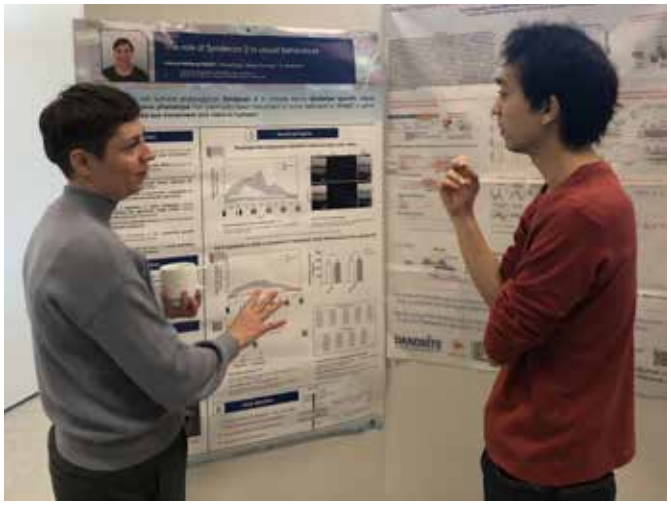
Thomas Boesen: *Shedding light on a unique cytochrome from cable bacteria,* 6th International cable bacteria workshop, Belgium

Rasmus K. Flygaard: *Struturel Neurobiologi,* Ungdommens Naturvidenskabelige Forening i Aarhus, Denmark

Cecilie Siggard Jørgensen: *Genome-wide association study of nocturnal enuresis hints at the orexin/hypocretin system to be important in the pathoetiology,* International Children's Continence Society, Virtual Lecture

Keisuke Yonehara: *Structure, development, and disease of motion-sensitive circuits in the mammalian retina,* Tsukuba University, Japan


It is ALL about alpha-synuclein – here and there!
Normal neuron
Parkinson's disease



05 Publications

Publications

1 **Andersen, OM**, Bøgh, N, Landau, AM, Pløen, GG, Jensen, AMG, Monti, G, Ulhøi, BP, Nyengaard, JR, Jacobsen, KR, Jørgensen, MM, Holm, IE, Kristensen, ML, Alstrup, AKO, Hansen, ESS, Teunissen, CE, Breidenbach, L, Droescher, M, Liu, Y, Pedersen, HS, Callesen, H, Luo, Y, Bolund, L, Brooks, DJ, Laustsen, C, Small, SA, Mikkelsen, LF, Sørensen, CB 2022, 'A genetically modified minipig model for Alzheimer's disease with SORL1 haploinsufficiency', Cell Reports Medicine, vol. 3.

2 Alam, P, Holst, MR, Lauritsen, L, Nielsen, J, Nielsen, SSE, **Jensen, PH**, Brewer, JR, Otzen, DE, **Nielsen**, **MS** 2022, 'Polarized -synuclein trafficking and transcytosis across brain endothelial cells via Rab7-decorated carriers', Fluids and Barriers of the CNS, vol. 19, no. 37

3 Aminzadeh, A, Larsen, CE, **Boesen, T**, Jørgensen, R 2022, 'High-resolution structure of native toxin A from Clostridioides difficile', EMBO Reports, vol. 23,

4 **Arvin, S, Yonehara, K** & Glud, AN 2022, 'Therapeutic Neuromodulation toward a Critical State May Serve as a General Treatment Strategy', Biomedicines, vol. 10, no. 9, 2317.

5 **Arvin, S**, Glud, AN & **Yonehara, K** 2022, 'Short- and Long-Range Connections Differentially Modulate the Dynamics and State of Small-World Networks', Frontiers in Computational Neuroscience, vol. 15, 783474.

6 Bergmann, T, Liu, Y, Skov, J, Mogus, L, Lee, J, Pfisterer, U, Handfield, LF, Asenjo-Martinez, A, Lisa-Vargas, I, Seemann, SE, Lee, JTH, Patikas, N, Kornum, BR, **Denham, M**, Hyttel, P, Witter, MP, Gorodkin, J, Pers, TH, Hemberg, M, Khodosevich, K & Hall, VJ 2022, 'Production of human entorhinal stellate cell-like cells by forward programming shows an important role of Foxp1 in reprogramming', Frontiers in Cell and Developmental Biology, vol. 10, 976549.

7 Blevins, AS, Bassett, DS, Scott, EK & **Vanwalleghem, GC** 2022, 'From calcium imaging to graph topology', Network Neuroscience, vol. 6, no. 4, pp. 1125-1147.

8 Bunatyan, L, Margineanu, A, Boutin, C, Montcouquiol, M, Bachmann, S, Christensen, EI, **Willnow, TE,** Christ, A 2022, 'LRP2 contributes to planar cell polarity-dependent coordination of motile cilia function', Cell and Tissue Research, vol. 392, no. 2.

9 Corsi, GI, Qu, K, Alkan, F, Pan, X, **Luo, Y** 2022, 'CRISPR/Cas9 gRNA activity depends on free energy changes and on the target PAM context', Nature Communications, vol. 13, no. 3006.

10 **Dieudonné, T**, Herrera, SA, **Laursen, MJ**, Lejeune, M, **Stock, C**, Slimani, K, Jaxel, C, Lyons, JA, Montigny, C, Pomorski, TG, **Nissen, P** & Lenoir, G 2022, 'Autoinhibition and regulation by phosphoinositides of ATP8B1, a human lipid flippase associated with intrahepatic cholestatic disorders', eLife, vol. 11, e75272.

11 **Dyla, M,** González Foutel, NS, Otzen, DE & **Kjaergaard, M** 2022, 'The optimal docking strength for reversibly tethered kinases', Proceedings of the National Academy of Sciences, vol. 119, no. 25, e2203098119.

12 Fjelstrup S, Dupont DM, Bus C, Enghild JJ, Jensen JB, Birkenkamp-Demtröder K, Dyrskjøt L, **Kjems J**, 2022, 'A Circular RNA Expressed from the FAT3 Locus Regulates Neural Development', NAR cancer, Vol. 4, No. 3, zcac025, 09.2022.

13 Folke, J, **Ferreira, N**, Brudek, T, Borghammer, P & Van Den Berge, N 2022, 'Passive Immunization in Alpha-Synuclein Preclinical Animal Models', Biomolecules, vol. 12, no. 2, 168.

14 Fonager, SV, Winther, G, Wittenborn, TR, Jensen, L, Fahlquist-Hagert, C, Hansen, **LA, Füchtbauer, E-M, Romero-Ramos, M** & Degn, SE 2022, 'Increased maternofoetal transfer of antibodies in a murine model of systemic lupus erythematosus, but no immune activation and neuroimmune sequelae in offspring', Journal of Neuroimmunology, vol. 370, 577927.

15 **Fruergaard, MU**, Dach, I, Andersen, JL, **Ozol, M, Shasavar, A**, Quistgaard, EMH, **Poulsen, H**, Fedosova, N & **Nissen, P** 2022, 'The Na,K-ATPase in complex with beryllium fluoride mimics an ATPase phosphorylated state.', Journal of Biological Chemistry, vol. 298, no. 9, 102317.

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19 Gomes-Duarte A, Venø MT, de Wit M, Senthilkumar K, Broekhoven MH, van den Herik J, Heeres FR, van Rossum D, Rybiczka-Tesulov M, Legnini I, van Rijen PC, van Eijsden P, Gosselaar PH, Rajewsky N, **Kjems J**, Vangoor VR, Pasterkamp RJ, 2022, 'Expression of Circ_Satb1 Is Decreased in Mesial Temporal Lobe Epilepsy and Regulates Dendritic Spine Morphology', Frontiers in Molecular Neuroscience, Vol 15, 832133, 03.2022.

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22 Hoang, T, **Kim, DW**, Appel, H, Pannullo, NA, Leavey, P, Ozawa, M, Zheng, S, Yu, M, Peachey, NS & Blackshaw, S 2022, 'Genetic loss of function of Ptbp1 does not induce glia-to-neuron conversion in retina', Cell Reports, vol. 39, no. 11, pp. 110849.

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24 Jankowski, V, Saritas, T, **Kjolby, M**, Hermann, J, Speer, T, Himmelsbach, A, Mahr, K, Heuschkel, MA, Schunk, SJ, Thirup, S, Winther, S, Bottcher, M, Nyegard, M, **Nykjaer, A**, Kramann, R, Kaesler, N, Jankowski, J, Floege, J, Marx, N & Goettsch, C 2022, 'Carbamylated sortilin associates with cardiovascular calcification in patients with chronic kidney disease', Kidney International, vol. 101, no. 3, pp. 574-584.

25 Just, MK, **Gram, H, Theologidis, V, Jensen, PH**, Nilsson, KPR, Lindgren, M, Knudsen, K, Borghammer, P & Van Den Berge, N 2022, 'Alpha-Synuclein Strain Variability in Body-First and Brain-First Synucleinopathies', Frontiers in Aging Neuroscience, vol. 14, 907293.

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27 Kim, J, **Kim, DW**, Lee, A, Mason, M, Jouroukhin, Y, Woo, H, Yolken, RH & Pletnikov, MV 2022, 'Homeostatic regulation of neuronal excitability by probiotics in male germ free mice', Journal of Neuroscience Research, vol. 100, no. 2, pp. 444-460.

28 **Kim, DW,** Place, E, Chinnaiya, K, Manning, E, Sun, C, Dai, W, Groves, I, Ohyama, K, Burbridge, S & Placzek, M 2022, 'Single-cell analysis of early chick hypothalamic development reveals that hypothalamic cells are induced from prethalamic-like progenitors', Cell Reports, vol. 38, no. 3, pp. 110251.

29 **Kim, DW**, Tu, KJ, Wei, A, Lau, AJ, Gonzalez-Gil, A, Cao, T, Braunstein, K, Ling, JP, Troncoso, JC & Wong, PC 2022, 'Amyloid-beta and tau pathologies act synergistically to induce novel disease stage-specific microglia subtypes', Molecular Neurodegeneration, vol. 17, no. 1, pp. 1-23.

30 **Kjaergaard, M** 2022, 'Estimation of Effective Concentrations Enforced by Complex Linker Architectures from Conformational Ensembles', Biochemistry, vol. 61, no. 3, pp. 171-182.

31 Klæstrup, IH, Pedersen, MKJ, Holm, KL, Alstrup, AKO, **Romero-Ramos, M**, Borghammer, P & Van Den Berge, N 2022, 'Impact of aging on animal models of Parkinson´s disease', Frontiers in Aging Neuroscience, vol. 14, 909273.

32 Krispil-Alon, M, Jovasevic, V, **Radulovic, J**, Richter-Levin, G 2022, 'Sex-specific roles of hippocampal microRNAs in stress vulnerability and resilience', Translational Psychiatry, 2022, vol. 12, no. 503.

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34 Kobberø, SD, Gajhede, M, Mirza, OA, Kløverpris, S, Kjær, TR, Mikkelsen, JH, **Boesen, T**, Oxvig, C 2022, 'Structure of the proteolytic enzyme PAPP-A with the endogenous inhibitor stanniocalcin-2 reveals its inhibitory mechanism', Nature Communications, vol. 13, no. 6084.

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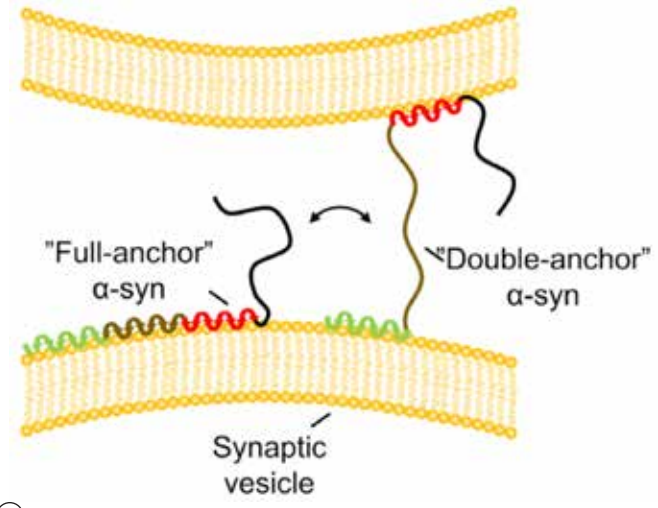

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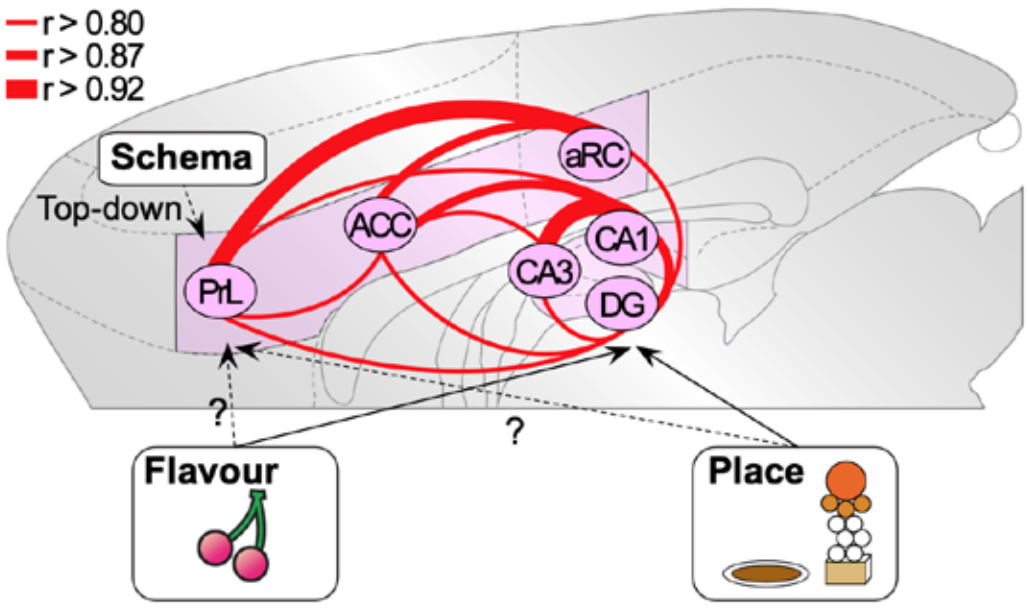

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Quispe, OGS 2022, Studies on the C-terminal domain of the NMDA receptor subunit GluN1: Allosteric modulation and channel properties. Aarhus University.

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