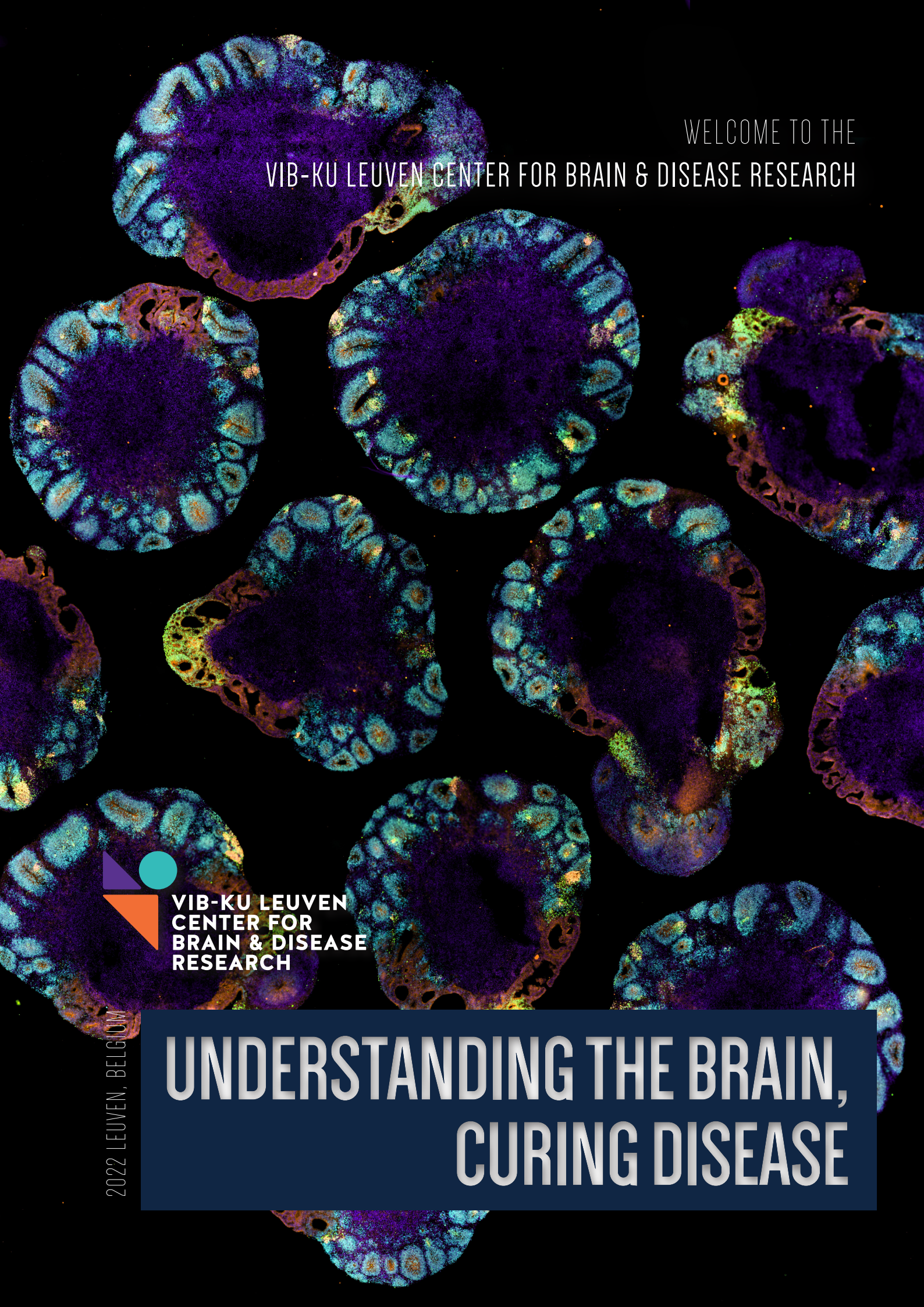

WELCOME TO THE

VIB-KU LEUVEN CENTER FOR BRAIN & DISEASE RESEARCH

VIB-KU LEUVEN
CENTER FOR
BRAIN & DISEASE
RESEARCH

UNDERSTANDING THE BRAIN, CURING DISEASE

2022 LEUVEN, BELGIUM

Our director and vice-director, Patrik Verstreken & Joris de Wit, together with our director of administration Hilde Govaert

Understanding the brain, curing disease

At the Center for Brain & Disease Research we believe that understanding how our brain is shaped to control thought and behavior—and how it loses these abilities in disease—is one of the most urgent and pressing challenges of this century. It is a valiant goal, but our teams are making immense progress taking multidisciplinary approaches to unlock the secrets of the brain and mind.

We explore how the brain develops, ages and performs, we study its remarkable resilience but also how it falls to dementia, psychiatric disability and movement disorders. Our different research groups are bridging disciplines, from artificial intelligence, microelectronics and nanoscience, to microfluidics, single cell analysis and chimeric animal models.

The journey doesn't stop there. Through partnerships across the globe, we disseminate our ideas and our findings, securing important new investments. Located at Europe's number one innovative university, KU Leuven, our Center is among the most exciting locations worldwide to pursue original ideas. We have created a biotech ecosystem including several new startups and millions in investments in the past few years. This shows that the strongest basic science propels discovery and innovation.

A hub for research talent

To achieve our goals, we invite the best minds to pursue their ideas with us. Diverse talents, who share their expertise, creativity and drive. If you share our mission, please refer to the ample opportunities, or reach out spontaneously to one of our groups.

We work hard every day to create a collaborative and inclusive environment, where everyone can bring their best ideas and work to the table. Through excellent research facilities, and by offering a wide array of opportunities for training and professional development, both research and researchers thrive.

When communities come together, extraordinary things are possible. While the past years have been challenging, flexibility, resilience and broad care and support have been the differentiating factors in our day-to-day activities, not only in our labs, but also in our expertise units.

We look forward to what's in store for the next months and years.

Patrik Verstreken, Hilde Govaert & Joris de Wit

Explore all opportunities at jobs.cbd.vib.be

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LEUVEN, BELGIUM

Our hometown has a rich history and perhaps an even richer future. Home to one of the oldest universities in Europe (and to Stella Artois), it has been consistently recognized as one of the most innovative and open-minded cities in Europe.

FIVE COMMON THEMES SPAN OUR RESEARCH QUESTIONS

NEURONAL AND NEURODEGENERATIVE DISEASE

We explore new molecular mechanisms in the context of Alzheimer's disease, Parkinson's disease, ALS, frontotemporal dementia, but also autism, epilepsy and intellectual disability. Together with our tech transfer team, we translate our findings into therapeutic avenues.
The brain poses specific challenges for drug delivery as it is shielded by a blood-brain barrier. That is why we are also developing innovative tools to ensure that drugs for brain diseases can effectively reach their target.

Tracking memories in the Drosophila brain (Joana Dopp, Liu lab)

SYNAPSES, CONNECTIONS AND BEHAVIOR

We elucidate how trillions of synaptic connections are established and what determines their specificity, stability, plasticity and function. How does glial support play its crucial role? How does sensory input regulate behavioral output? What is the role of sleep? How can we correct synaptic defects that result in disease? We also exploit our knowledge of brain wiring to create induced human neuronal circuits on purpose designed multielectrode arrays, even in 3D, allowing us to study how neuronal computation is affected in human (neurodegenerative) disease.

BRAIN DEVELOPMENT AND REPAIR

We study the developmental processes that define brain size and glial and neuronal identity. We look for human-specific processes that have resulted in the unique cognitive abilities of our species, from the fundamentals of cell-type specificity, to delineating the code of neuronal wiring and the formation of synapses. By differentiating and transplantating human brain cells, we aim to develop better models for human brain disease, and ultimately, to explore the possibility of brain repair.

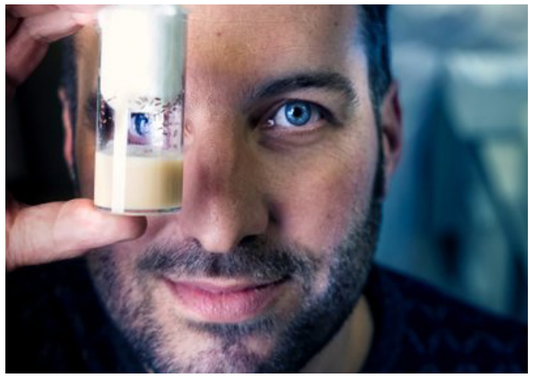
TOXIC PROTEIN ASSEMBLIES

The biophysical properties of certain proteins allow them to sometimes separate in droplets in the cytoplasm (phase separation) or even aggregate in an insoluble mass. We study how such protein assemblies form, and what the functional consequences are.
Some of our scientists are flipping things around and exploit the fact that many proteins have the intrinsic propensity to aggregate: they developed the technology to induce protein aggregation in 'unwanted cells', such as antibiotic-resistant bacteria or cancer cells, to induce their death.

THE BRAIN AT SINGLE CELL RESOLUTION

The brain is the most complex organ in our body, consisting of many different cell types. We map the cellular changes that occur during disease and aging, but also specific behaviors such as sleeping and learning. We develop the next generation of technology to measure cellular function at much higher resolution and to maintain spatial information on the location of each individual brain cell.
Researchers in our Center produced the first complete map of all the cells of the entire fruit fly, and mapped the changes that occur during aging, while others have defined the types of glial support cells (astrocytes) at unprecedented resolution.

MEET OUR GROUP LEADERS



STEIN **AERTS**
LABORATORY OF COMPUTATIONAL BIOLOGY

We are interested in decoding the genomic regulatory code and understanding how genomic regulatory programs drive dynamic changes in cellular states, both in normal and disease processes.

WIM **ANNAERT**
LABORATORY FOR MEMBRANE TRAFFICKING

Our laboratory is focused on understanding the molecular biology of membrane transport in a disease-related context covering Alzheimer's and Lewy Body diseases.

LUCÍA **CHÁVEZ-GUTIÉRREZ**
LABORATORY OF PROTEOLYTIC MECHANISMS MEDIATING NEURODEGENERATION

We want to generate a quantitative understanding of the molecular mechanisms underlying Alzheimer's disease pathogenicity, more specifically the biochemical function of the molecules involved in familial Alzheimer's disease.

SANDRINE **DA CRUZ**
LABORATORY OF NEURODEGENERATIVE DISORDERS AND NEUROPHYSIOLOGY

Our lab studies the role of local axonal translation in neurodegeneration in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), as well as the spreading of RNA binding proteins, including FUS and TDP-43, in ALS. The team also focuses on muscle innervation and the development of new therapeutic targets to treat neuromuscular disorders including ALS.

BART **DE STROOPER**
LABORATORY FOR THE RESEARCH OF NEURODEGENERATIVE DISEASES

We investigate the basic mechanisms causing Alzheimer's disease starting from the genetic forms of the disorder.
We study the complex cellular phase of Alzheimer's disease using single cell, genome wide transcription profiling with spatial and temporal resolution.

JORIS **DE WIT**
LABORATORY OF SYNAPSE BIOLOGY

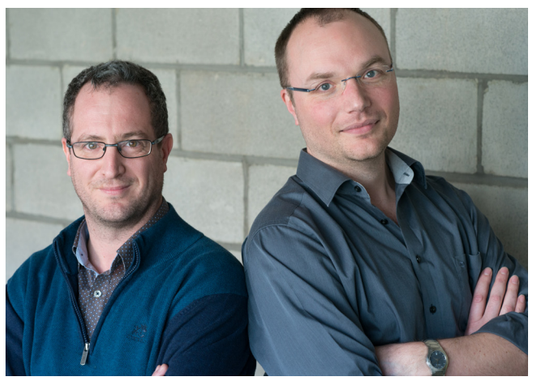
Our brain is made up of billions of neurons that are precisely connected into neural circuits, forming an immensely complex network that encodes our thoughts, memories and personalities. Our lab aims to unravel the molecular mechanisms that control neuronal connectivity in developing circuits, and determine how perturbations in this process affect cognitive function.

LYNETTE **LIM**
LABORATORY OF INTERNEURON DEVELOPMENTAL DYNAMICS

Information processing in the brain depends on specialized circuits that are formed by distinct types of neurons. We study the metabolic and transcriptomic programmes that shape neuronal diversity and circuit assembly in the developing mammalian cortex.

SHA **LIU**
LABORATORY OF SLEEP AND SYNAPTIC PLASTICITY

Sleep is a fundamental and evolutionarily conserved behavior, and the only major behavior for which the function remains unknown. The goal of our lab is to understand the synaptic and circuit mechanisms underlying sleep and its function in the brain.



FREDERIC **ROUSSEAU** & JOOST **SCHYMKOWITZ**
SWITCH LAB

We study the mechanisms gearing protein folding and misfolding and their relation to human disease. In particular, we investigate how protein aggregation affects the interactome by suppressing native interactions but also by introducing novel aggregation-specific interactions.

LUDO **VAN DEN BOSCH**
LABORATORY OF NEUROBIOLOGY

Our research focuses on the mechanisms of acute and chronic axonal and neuronal degeneration and regeneration. We aim to contribute to the development of new therapeutic strategies for neurodegenerative disorders, such as motor neuron diseases (ALS and hereditary motor neuropathies), frontotemporal dementia (FTD) and stroke.

PIERRE **VANDERHAEGHEN**
STEM CELL AND DEVELOPMENTAL NEUROBIOLOGY LABORATORY

The major research goal in our laboratory is to understand the molecular and cellular mechanisms underlying the development and evolution of the cerebral cortex, from stem cells to neuronal circuits, from mouse to man, in health and disease.

PATRIK **VERSTREKEN**
LABORATORY OF NEURONAL COMMUNICATION

The earliest stages of neurodegenerative diseases such as dementia and Parkinson's disease are characterized by synaptic problems. We probe into the diverse molecular mechanisms at the basis of neuronal degeneration and synaptic dysfunction, and how we can reverse this process. Our work uses patient-derived iPS cells and human microcircuits, rodents and powerful fruit fly genetics.

THOMAS **VOETS**
LABORATORY OF ION CHANNEL RESEARCH

We focus on a superfamily of cation channels, the transient receptor potential (TRP) channels, which includes 27 human members. There is a striking diversity in the stimuli that can regulate the gating of the TRP channels, which include physical stimuli such as temperature and voltage, as well as various endogenous and exogenous chemical ligands.

WE ALSO HOST TWO VISITING PIs

MATTHEW **HOLT**

VISITING PI 2022 // I3S, UNIVERSITY OF PORTO

Astrocytes are the most abundant glial cell in the mammalian central nervous system. The goal of our group is to understand the molecular mechanisms that control astrocyte development and function in vivo. We are particularly interested in the role of astrocyte-neuron interactions and how they shape activity in both the healthy and diseased brain.

FRANCK **POLLEUX**

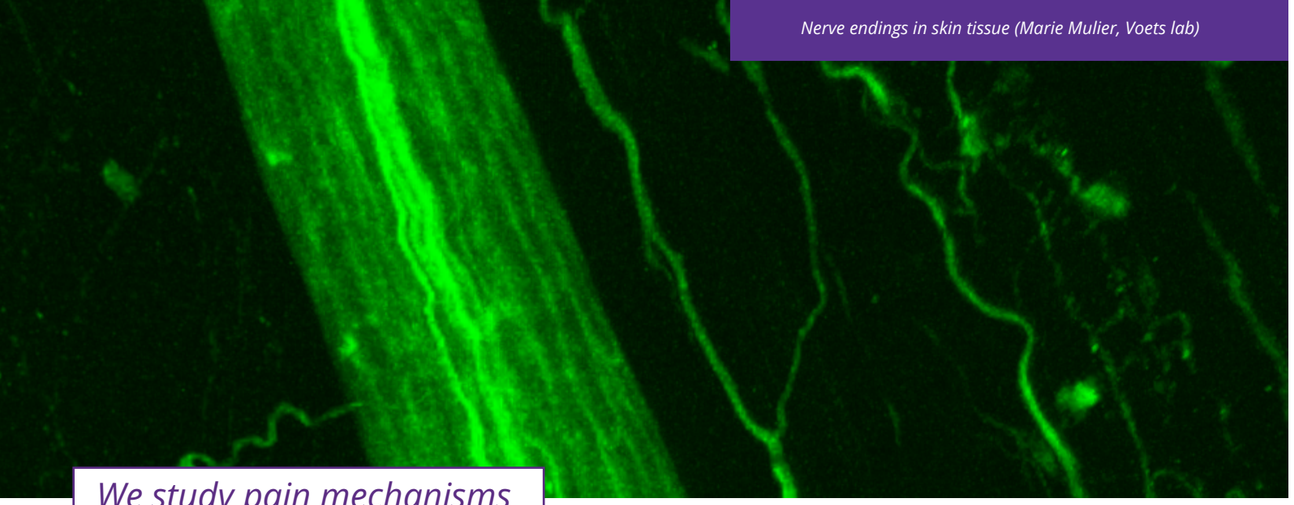
VISITING PI // COLUMBIA UNIVERSITY

Our research provides new insights into the cellular and molecular mechanisms underlying the establishment and maintenance of brain connectivity and has significant implications for our understanding of the pathophysiological mechanisms underlying socially-devastating neurodevelopmental disorders and neurodegenerative diseases.

The VIB Neuroscience group leader community at a joint retreat in June 2022 to discuss new collaborative projects

WE ARE PART OF AN EXCEPTIONALLY RICH NEUROSCIENCE COMMUNITY

Leuven and Flanders are home to a diverse neuroscience scene, including our VIB-KU Leuven Center for Brain & Disease Research, NeuroElectronics Research Flanders (NERF) and the VIB-UAntwerp Center for Molecular Neurology. Furthermore, there is an exciting and broad group of neuroscience faculty at the KU Leuven across departments and faculties, at the university hospitals in Leuven and at the nearby institute for microelectronics, imec. The exceptionally rich neuroscience community in Leuven comes together under the umbrella of the Leuven Brain Institute, and we are part of numerous international collaborative networks, including CURE-ND.



Nerve endings in skin tissue (Marie Mulier, Voets lab)

We study pain mechanisms

INFLAMMATION SETS OFF SENSORY ALARMS

The research team of **Thomas Voets** uncovers how the upregulation of an ion channel called TRPM3 causes hypersensitivity in inflamed tissue. The new findings, published in eLife, suggest new therapeutic avenues to help patients suffering from chronic pain.

Whenever you touch a hot pan, you withdraw your hand within a fraction of a second. Likely, you will also immediately feel a burning pain. This acute pain is actually a good thing—it functions as an alarm signal, warning you that high temperatures can cause dangerous and potentially life-threatening injuries. Sometimes this alarm system can become deregulated, for example upon tissue inflammation or injury. Nerve impulses can then be initiated at temperatures that are normally non-painful, and as a result, you may experience burning pain when taking a shower or walking in the sun, or, in the worst case, all the time. Thomas Voets and his team try to understand the mechanisms that underlie this type of hypersensitivity and how it may lead to chronic pain, in the hopes to ultimately find novel pain treatments for patients.

Temperature sensors and inflammation

Voets and his team have a particular interest in so-called TRP ion channels—proteins that allow the flow of charged ions across membranes to induce electrical signals. He explains why: “From earlier research, we knew that three such TRP ion channels act as the temperature sensors that initiate an acute pain response to heat. To better understand the mechanisms behind hypersensitivity, we wanted to know whether these three TRP channels, known as TRPM3, TRPA1 and TRPV1, become deregulated in inflamed tissue.”

The researchers used a mouse model to study local inflammation of the hind paw. “For one of the ion channels, TRPM3, we found differences in gene expression between the inflamed and the unaffected paw,” explains Marie Mulier, a PhD student in Thomas Voets’ lab and first author on the study. “TRPM3 expression was higher in the sensory neurons that innervate the inflamed hind paw compared to the other, unaffected paw.”

Reducing hypersensitivity

By measuring the activity of the sensory neurons, both in the fine endings in the skin and in their cell bodies close to the spinal cord, the researchers found that all three heat-activated TRP channels become hyperactivated in neurons that innervate the inflamed paw, explaining the increased heat sensitivity. But interestingly, a compound that inhibits the function of TRPM3 restored the sensitivity of the sensory neurons to normal levels.

“Our findings suggest that increased levels of TRPM3 in sensory neurons represent an important driver of inflammatory hypersensitivity to heat,” says Voets. “Therefore, drugs that dampen TRPM3 activity may become a viable therapy to reduce pain and hypersensitivity in patients.”

Upregulation of TRPM3 in nociceptors innervating inflamed tissue
Mulier et al. 2020 eLife

We study what causes neurodegenerative disease

SOME FORMS OF ALZHEIMER’S DISEASE HIT EARLY IN LIFE, CAN WE PREDICT WHEN?

Familial Alzheimer's usually hits relatively early in life, affecting people in their forties or fifties, or sometimes even earlier. The research team of **Lucía Chávez-Gutiérrez** has uncovered a direct relationship between changes in the amyloid-beta fragments that accumulate in the brain tissue of Alzheimer’s patients, and the age at which symptoms first arise. The researchers hope we can use these insights not only to predict but eventually also to delay disease onset.

When do Alzheimer’s symptoms first appear?

In most cases, Alzheimer’s disease is not inherited and starts to manifest after the age of 65. In rare cases, however, Alzheimer’s can be passed on in families and this familial form typically also manifests much earlier in life, affecting people in their forties or fifties, or sometimes even already in their twenties or thirties. Although familial Alzheimer's is rare, close to 400 different mutations have been identified in families with early-onset Alzheimer’s around the globe.
They can all be traced back to the same small set of genes encoding the molecular machinery that generates amyloid beta fragments in the brain.

“Interestingly, the age at which clinical symptoms first manifest is relatively consistent within families and between carriers of the same mutations, but differs markedly between mutations,” says Lucía Chávez-Gutiérrez.
“It is important to understand the mechanisms by which some mutations cause symptoms to manifest decades earlier than others,” she says. “Not only because of the practical importance for families affected by familial Alzheimer’s, but also to understand how we could conceive to halt or at least delay disease.”

A linear correlation

Chávez-Gutiérrez’ team analyzed the amyloid-beta fragments generated by 25 different mutations discovered in families presenting with Alzheimer’s symptoms at ages varying from 25 to 60 years.
“We found that changes in the molecular composition of amyloid-beta correlated linearly with the age at disease onset,” says dr. Dieter Petit, a recently graduated PhD student in the lab. “Clearly, longer amyloid-beta fragments are more abundantly present in mutant amyloid-beta profiles linked to earlier symptom onsets.”

“In collaboration with our clinical partners, we were also able to use this linear correlation for the experimental assessment of age at disease onset of mutations for which there had been limited family history or a complex clinical picture,” adds Sara Gutiérrez Fernández, another PhD student closely involved in the study.

From biochemistry to therapy?

While the study involves mutations linked to rare familial forms of Alzheimer’s, all Alzheimer’s cases are characterized by amyloid-beta deposition in the brain, and clearly common pathways eventually result in the development of the same collection of symptoms.

Chávez-Gutiérrez: “Our ultimate question is: can we shift the molecular composition of brain amyloid profiles in such a way that we can delay symptom onset? This is a fundamental question, that we cannot answer in a definitive way today, but our results do support exploring the therapeutic potential of compounds that could tweak amyloid-beta production with the aim of generating shorter fragments.”
She stresses that even today, being able to predict the age of disease onset based on amyloid-beta profiles, could be really helpful in clinical settings: “Information on how a certain mutation affects amyloid processing, together with the clinical picture of a patient, can help us determine whether the mutation is indeed causative. We have already been able to clarify this for multiple mutations, which means families can receive adequate genetic counseling and gain access to clinical trials.”

Abeta profiles generated by Alzheimer's disease-causing PSEN1 variants determine the pathogenicity of the mutation and predict age at disease onset
Petit, Gutiérrez Fernández et al. 2022 Mol Psychiatry

We study protein aggregation

PROTEINS OF A FEATHER FLOCK TOGETHER

Researchers from the Switch lab, led by **Joost Schymkowitz** and **Frederic Rousseau**, predict how highly similar proteins speed up or halt protein aggregation in Alzheimer's and other brain diseases.

Different neurodegenerative diseases such as Alzheimer's and Parkinson's have one thing in common: one particular protein clumps together, first in one part of the brain, later spreading across other regions, causing increasingly severe symptoms. A research team led by Joost Schymkowitz and Frederic Rousseau has now uncovered how highly similar protein segments can speed up—or more interestingly—thwart this aggregation process, potentially explaining the specific vulnerability of certain brain regions and hinting at potential new ways to develop improved therapeutics.

Protein aggregates as the common thread

What neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, ALS and a whole range of others have in common, is the fact that the brains of deceased patients are riddled with protein inclusions.

The identity of the proteins differs, but the sequence of events is similar. Certain proteins become structurally abnormal. Often the culprit proteins fail to fold into their normal configuration; and in this misfolded state, the proteins wreak havoc or lose their normal function, either way disrupting the normal function of brain cells or tissues. The end result: degeneration of certain brain tissues, leading to the diverse disease symptoms featured by neurodegenerative disorders.

Why some protein aggregation starts in a specific brain region—like the region important for memory in Alzheimer's or the region involved in steering movements in Parkinson's disease—remains unclear.

Finding the trigger(s)

Frederic Rousseau and Joost Schymkowitz have built their careers studying the biochemistry of how proteins fold and why they misfold. In two new studies, they report how thousands of proteins in our cells bear sequences that resemble the aggregation-prone regions of the culprit proteins involved in Alzheimer's disease. These 'third-party proteins' may play a meaningful part in disease progression, and—more importantly—a potential treatment.

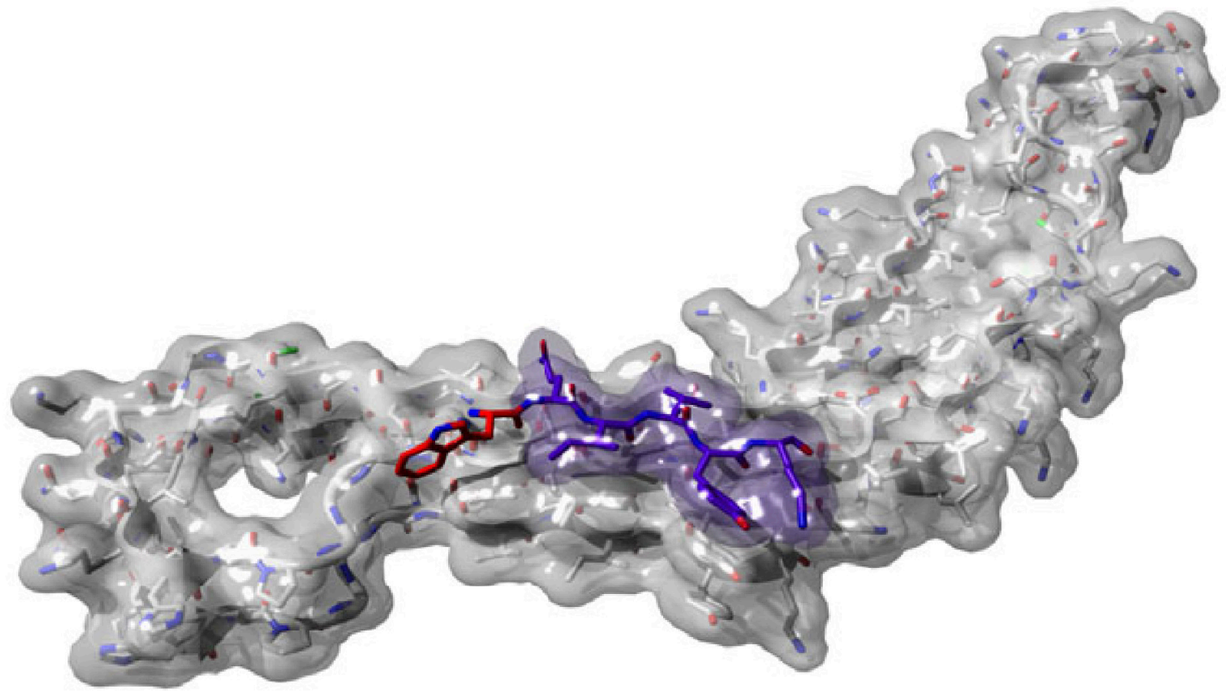
"Aggregation-prone regions are short segments with a high propensity to clump together into the sticky structures that essentially make up these disease-related aggregates," explains Rousseau. "The short segments may be part of bigger proteins, and while they typically stick to each other, we wondered whether other proteins with the same or similar regions could also set off this aggregation cascade."

"Thousands of proteins bear sequences that strongly resemble aggregation-prone regions of amyloids, allowing them to boost or halt the aggregation process."

Katerina Konstantoulea

A grammar for protein aggregation?

The team set out to look for other proteins containing similar aggregation-prone regions as those found in amyloid beta, the culprit peptide found in Alzheimer's plaques. Finding many of those, they tested 600 proteins for potential interaction with amyloid beta, explains Katerina Konstantoulea, PhD student in Schymkowitz and Rousseau's lab: "Thousands of proteins bear sequences that strongly resemble aggregation-prone regions of amyloids, allowing them to interact and either boost or halt the aggregation process."



The researchers designed a peptide and experimentally tested its capacity to inhibit tau aggregate formation

To understand why some similar proteins pushed aggregation while others slowed it down, postdoc Nikolaos Louros looked at nearly a hundred aggregation-prone regions, including those for disease-related amyloid beta, tau, and α-synuclein—which aggregate in Alzheimer's and Parkinson's disease, respectively.

Using computational methods, Louros modeled all the ways in which changes to the sequence of the aggregation-prone regions would affect their propensity to stick together. "We found that most changes reduced aggregation capacity in some way," says Louros. "Some by changing the rate of aggregation, others by hindering their spread, still others by modifying the nucleation process or the morphology of the aggregates."

Designing aggregation-blocking peptides

Using this newly gained information and with tau as an example, Louros and his colleagues tried to design a peptide that would block tau aggregation. In vitro and in cell lines, their synthetic peptide turned out to block tau aggregation and spread five-fold more effectively compared to previous designs, suggesting that this approach could indeed be promising for the development of new therapeutics.

"Our findings indicate that the proteomic background of cells and tissues can modulate the aggregation propensity of culprit proteins, which could explain—at least in part—the selective vulnerability we observe for many of these proteins and diseases," says Schymkowitz. "Importantly, we can also try to exploit this information to improve therapeutics against several of these neurodegenerative diseases."

Heterotypic amyloid β interactions facilitate amyloid assembly and modify amyloid structure
Konstantoulea et al. 2022 EMBO J

Mapping the sequence specificity of heterotypic amyloid interactions enables the identification of aggregation modifiers
Louros et al. 2022 Nature Comms

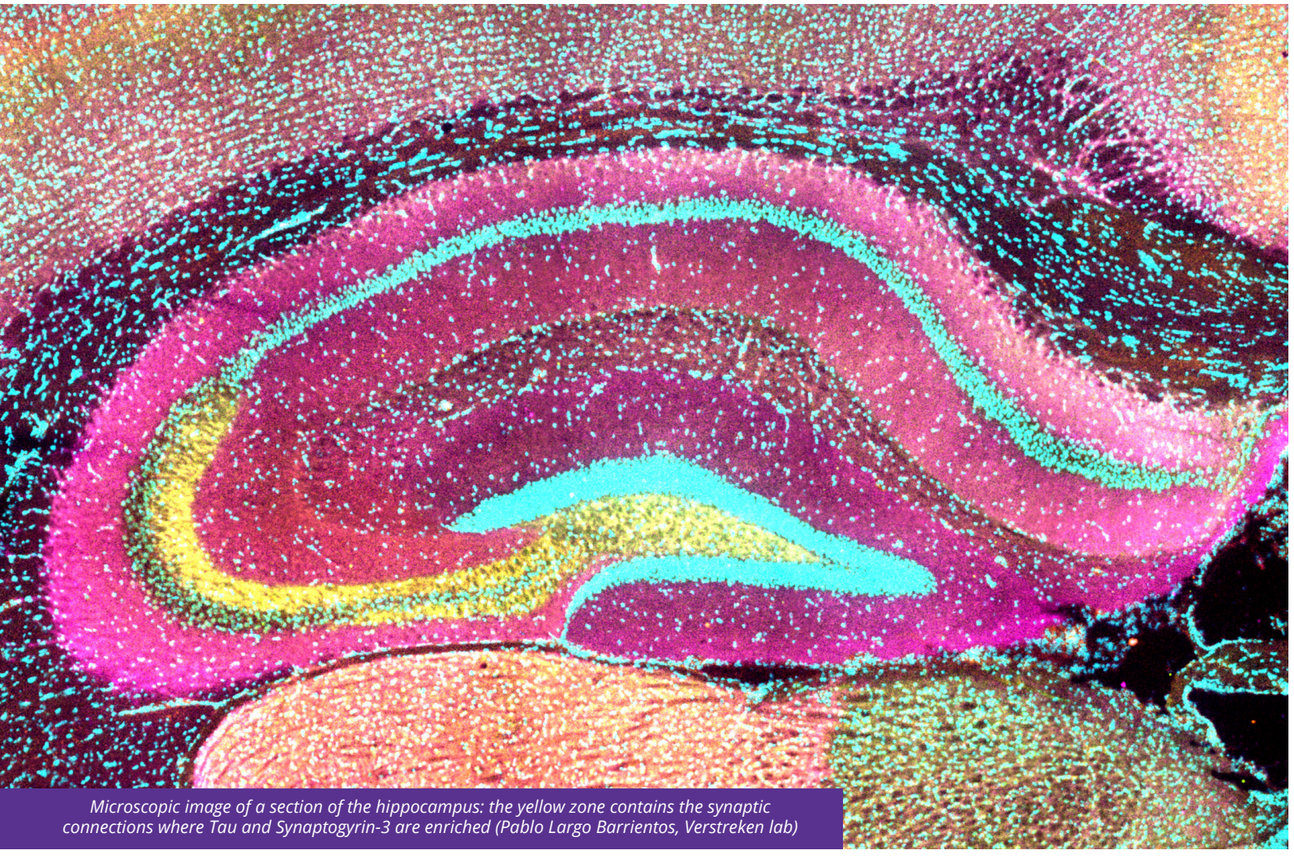
We study disease mechanisms

TARGETING TAU TO KEEP NEURONS CONNECTED

An international team of researchers led by **Patrik Verstreken** has succeeded in reversing the effects of Tau, a protein implicated in over 20 different diseases, including Alzheimer's disease. The promising findings in animal models are an important first step in the exploration of a new therapeutic avenue targeting cognitive decline.

The Tau protein is implicated in numerous neurodegenerative disorders, sometimes called 'tauopathies', including Alzheimer's disease and other types of dementia. In all these diseases, Tau causes havoc by aggregating within neurons. While such Tau aggregates are closely correlated with cognitive decline, we still don't fully understand how they cause it.

"In tauopathies, we observe inflammation and loss of neuronal connections in the brain, even before Tau aggregates start to form on a massive scale," says Patrik Verstreken. Verstreken and his team are specialized in neuronal communication and its links to disease. They teamed up with colleagues at the UK Dementia Research Institute to explore how the different aspects of the disease process lead to the cognitive symptoms induced by Tau.



Microscopic image of a section of the hippocampus: the yellow zone contains the synaptic connections where Tau and Synaptogyrin-3 are enriched (Pablo Largo Barrientos, Verstreken lab)

Partner in crime

The team turned their attention to another neuronal protein: Synaptogyrin-3. It is one of the proteins Tau interacts with, but it can only be found in the vicinity of neuronal connections, explains Pablo Largo Barrientos, PhD student in the Verstreken lab: "Since Synaptogyrin-3 is only present near neuronal connections, we interfered with its function to determine the role Tau plays specifically at this location."

By eliminating Tau's partner in crime in a mouse model, the researchers could prevent the loss of neuronal connections that Tau would normally induce. "We also found that the working memory of these mice didn't decline as we'd normally expect," adds Pablo.

Intriguingly, however, the inflammation effects remained the same. This led the researchers to propose that Tau induces inflammatory effects and loss of connectivity independently, and that the latter is a major determinant of cognitive decline.

> "We found that the working memory of these mice didn't decline as we'd normally expect."
>
> Pablo Largo Barrientos

A window of opportunity

"Our work provides the first evidence that it is possible to rescue the loss of neuronal connections and memory impairment, namely by targeting Tau specifically where neurons connect," says Patrik.

The researchers are now developing drugs that could decrease Synaptogyrin-3 levels in the brain. With those, they plan to test the therapeutic value of this approach for tauopathies, eventually in patients.

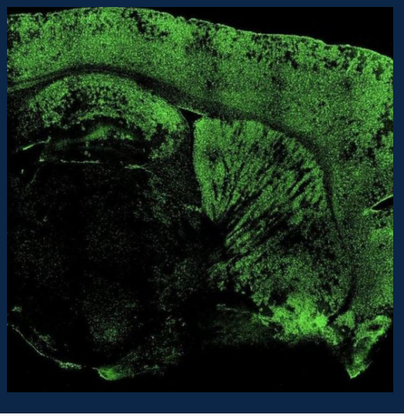
Lowering Synaptogyrin-3 expression rescues Tau-induced memory defects and synaptic loss in the presence of microglial activation
Largo Barrientos et al. 2021 Neuron

We develop new models

TRANSPLANTING HUMAN MICROGLIA

A team of scientists led by **Bart De Strooper** (VIB-KU Leuven) and **Renzo Mancuso** (VIB-UAntwerp) published a protocol to study human microglia in the context of the mouse brain.

Microglia are the immune cells of the brain, and they play a crucial role in neurodegenerative disease processes. With their protocol called MIGRATE, they provide a step-by-step workflow that includes in vitro microglia differentiation from human pluripotent stem cells, followed by transplantation into the mouse brain and subsequent quantitative analysis of the engraftment. The entire protocol takes approx. 40 days.



Stem-cell-derived human microglia transplanted into mouse brain to study human disease
Fattorelli, Martinez-Muriana et al. 2021 Nat Protocols

Katarina Stoklund Dittlau holding the microfluidic chamber

We develop new research tools

MICROFLUIDIC MODEL OF NEUROMUSCULAR JUNCTIONS SPEEDS UP ALS RESEARCH

A research team led by **Ludo Van Den Bosch** has established a versatile and reproducible in vitro model of a human motor unit to investigate the effects of ALS-causing mutations. Using their new microfluidic model, the team finds more evidence for HDAC6 inhibition as a potential therapeutic strategy for ALS.

Where nerve cells and muscle cells meet
Neuromuscular junctions ensure communication between our motor neurons and our muscles. These connections are lost in motor neuron disorders such as ALS, resulting in muscle wasting and ultimately death.

A research team led by Ludo Van Den Bosch has now established a versatile and reproducible in vitro model of this so-called 'human motor unit' to investigate the effects of ALS-causing mutations.

"We generated a co-culture of human iPSC-derived motor neurons and human primary mesangioblast-derived myotubes and grew both within a microfluidic device," explains Katarina Stoklund Dittlau, PhD student in Van Den Bosch's lab. "A gradient of growth factors facilitated the growth of the motor neuron axons through the microgrooves of the device, resulting in the formation of neuromuscular junctions upon interaction with the myotubes."

Rescuing the effects of ALS
Thanks to a close collaboration with Philip Van Damme, who also coordinates the Neuromuscular Reference Center at the University Hospitals Leuven, the model immediately proved useful to study motor neurons derived from patient material.

"We also grew motor neurons derived from the skin cells of patients with a mutation in FUS, and compared them with healthy motor neurons," says Stoklund Dittlau.

"We saw that the ALS motor neurons sent fewer axons across the channels of the microfluidic chamber and formed fewer neuromuscular junctions with the muscle cells."

"We saw that ALS motor neurons formed fewer neuromuscular junctions with the muscle cells."

Katarina Stoklund Dittlau

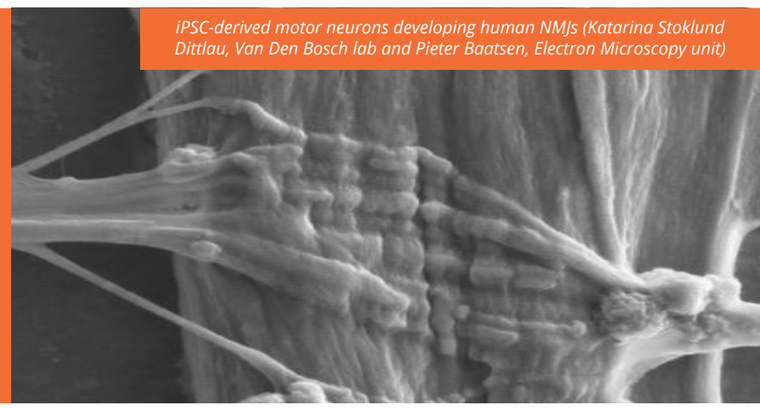
Interestingly, a selective HDAC6 inhibitor improved neurite outgrowth, regrowth and overall structure of the neuromuscular junctions in the microfluidic device. HDAC6 inhibition has been a longstanding interest of the Van Den Bosch lab, showing promising results in reversing some of the cellular and molecular signs of ALS—at least in the lab.

"We are not the first ones to culture human neuromuscular junctions on a chip," says Van Den Bosch, "We are, however, the first to do so using commercially available microfluidic chambers and a relatively simple method. This opens up new possibilities to investigate the function and dysfunction of neuromuscular junctions, not only in the context of ALS, but also for other neuromuscular disorders."

Human motor units in microfluidic devices are impaired by FUS mutations and improved by HDAC6 inhibition
Stoklund Dittlau et al. 2021 Stem Cell Reports

NEUROMUSCULAR JUNCTIONS

In addition to the Van Den Bosch lab, the Da Cruz lab also uses and develops in vitro co-culture models for functional neuromuscular junctions. These models are essential tools in the search for therapeutics that can rescue or slow down the denervation process and/or improve innervation/reinnervation in diseases such as ALS.

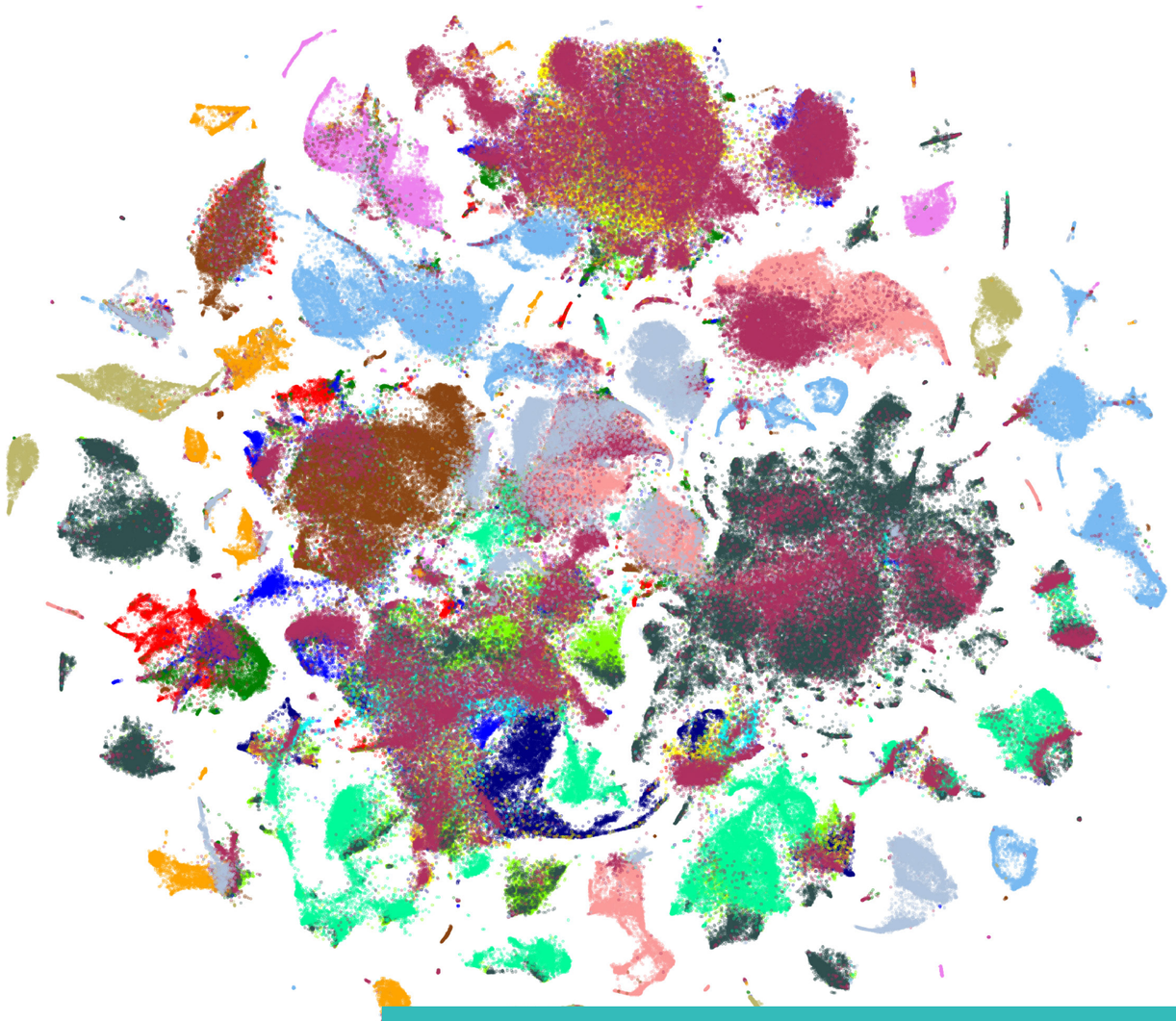


iPSC-derived motor neurons developing human NMJs (Katarina Stoklund Dittlau, Van Den Bosch lab and Pieter Baatsen, Electron Microscopy unit)

We develop new resources

THE FRUIT FLY: TINY RESEARCH HERO NOW FULLY MAPPED

A large international consortium co-lead by **Stein Aerts**, creates the first complete atlas of all fly cells. The story started back in 2017, at the first Fly Cell Atlas meeting in Leuven, Belgium.



580,000 cells were sequenced and >250 cell types were annotated

The fruit fly: a small but powerful creature

Fruit flies have played a leading role in biological research for over a century, ever since Thomas Hunt Morgan used these tiny insects to discover that genes reside on chromosomes, essentially uncovering the mechanical basis of heredity. Many scientists followed in Morgan's footsteps and several went on to win a Nobel Prize for their groundbreaking discoveries using this small model organism.

Aside from key insights into the basic workings of biological mechanisms such as genetics and developmental biology, fruit flies have played a vital role in developing treatments for cancer, immune disease and diabetes, to name just a few. That is because fruit flies are more similar to humans than their appearance suggests. Of the approximately 14,000 protein-encoding genes in the fruit fly genome, about two-thirds have a human counterpart.

The single-cell revolution

With the advent of single-cell genomic technology, scientists have been able to study tissues at unprecedented resolution, looking at the expression of all genes simultaneously in thousands of individual cells. Such fine-grained insights can help to decipher how certain cells differ from and interact with their neighbors, and how they form and function in the tissue.

With the fruit fly as popular as ever in biomedical research—small in size, easy to breed—single-cell analysis has quickly gained traction in this research community.

"Several research groups across the globe, including my own, have recently applied single-cell sequencing to different fruit fly tissues at different developmental stages," says Stein Aerts. "The problem is that these data have been generated by different laboratories on different genetic backgrounds with different protocols and sequencing platforms, which has hindered the systematic comparison of gene expression across cells and tissues."

Stein Aerts is one of the founders of the Fly Cell Atlas consortium, which grew organically after gathering specialists in the fly research community to Leuven back in December 2017. What began as wild plans forged over Belgian beers has now become a reality: after four years, many meetings, and a lot of hard work, the consortium now presents the first complete Fly Cell Atlas in Science.

Teamwork makes the dream work

"This was really a titanic piece of work," says Liqun Luo of Stanford, who co-lead the endeavor together with Aerts, and three other leading figures in the field: Stephen Quake at Stanford and the Chan Zuckerberg Biohub, Bart Deplancke at EPFL, and Norbert Perrimon at Harvard. "The entire consortium involved 158 experts from 40 different laboratories across the world."

Two early-career researchers on opposite sides of the Atlantic spearheaded the data generation and analyses: Jasper Janssens, a soon-to-graduate PhD student at the Aerts lab, and Hongjie Li, assistant professor at Baylor College of Medicine and until recently postdoc in Luo's lab at Stanford.

Jasper Janssens: "We aimed to establish a cell atlas for the entire adult fruit fly — with the same genetic background, dissociation protocol and sequencing platform. In this way, we'd be able to obtain a comprehensive categorization of cell types, integrating our single-cell transcriptome data with existing knowledge about gene expression and cell types, to systematically compare gene expression across the entire organism and between males and females. It would also allow us to identify cell type-specific markers across the entire organism."

The team took two complementary strategies to achieve their goal, adds Jasper Janssens: "We sequenced genetic material from dissected tissues so we knew the identity of the tissue source, but we also sequenced genetic material from the entire head and body to ensure that all cells were sampled."

The resulting dataset, named Tabula Drosophilae—for Drosophila melanogaster, the Latin name of the fruit fly—contains more than 580,000 cells, resulting in more than 250 distinct cell types. "Many of these cell types are characterized for the first time," says Janssens.

In service to (human) medicine

"What is particularly inspiring", says Bart Deplancke, "is how the fly community united over biological, technological and computational borders to generate this huge dataset and study all the different cell types in great detail, yielding perhaps the most highly curated cell atlas to date".

"Our Fly Cell Atlas will constitute a valuable resource for the research community as a reference for studies of gene function at single-cell resolution," says Norbert Perrimon. "This will be helpful for anyone studying biological processes in flies but also for modeling human diseases at a whole-organism level with cell-type resolution."

The consortium made all its data freely available online for further analysis through multiple portals or for custom analyses using other single-cell tools.

"I am so pleased that the CZ Biohub was able to contribute to this monumental community resource," says Stephen Quake. "We are excited that whole-organism cell atlases are now reaching fruition for a number of important organisms and are being made available to scientists across the globe."

Fly Cell Atlas: A single-nucleus transcriptomic atlas of the adult fruit fly
Li, Janssens, et al. 2022 Science

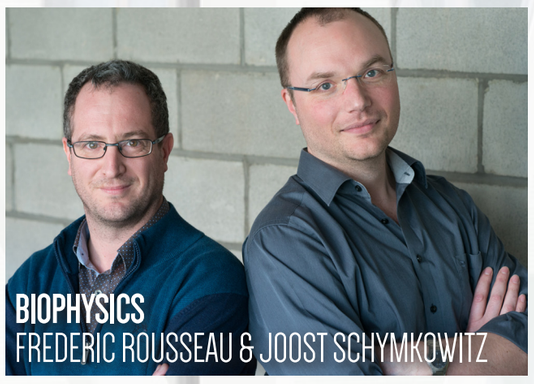
Decoding gene regulation in the fly brain
Janssens, Aibar, Ihsan Taskiran et al. 2022 Nature

MEET OUR EXPERTS

Everyone joining our research Center has access to top-notch facilities *and* the expertise to use them available at their fingertips. From biophysics to microfluidics, and from microscopy to behavioral analysis, our expertise units are hubs combining state-of-the-art services and equipment with the tailored development of new ideas, protocols and technologies. They are set up in house or in close collaboration with our two host institutes, VIB and KU Leuven.

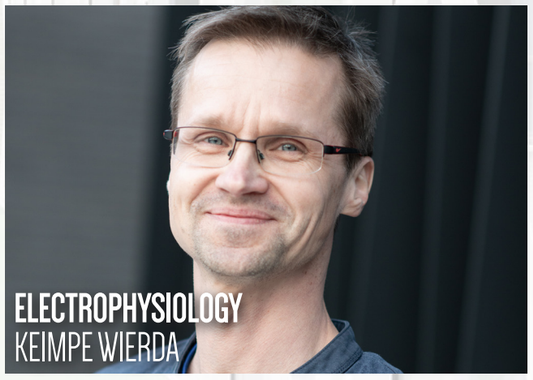
"We provide the expertise and infrastructure for cutting-edge imaging. Our support ranges from macro to super-resolution microscopy and the development of novel schemes for image analysis."

"We enable ultrastructural imaging of biological samples and provide training in scanning and transmission electron microscopy and in sample preparation. Our expertise ranges from conventional scanning and transmission electron microscopy, to immunocytochemistry and advanced 3D methods."

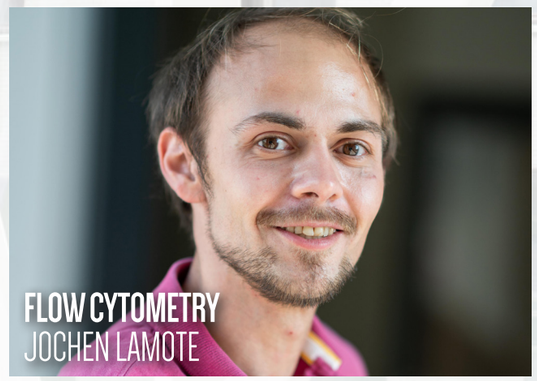


"Our expertise spans from structural bioinformatics to molecular biophysics, including protein purification, in silico modelling and studying protein conformation, structure and interactions. Get in touch if you would like to know more about the stability, folding or interactions of your protein(s) of interest."

"We are here to help lower the practical and administrative barriers of setting up collaborative, multidisciplinary research projects. We help you find local and international partners, finetune your proposal and obtain funding for your project."



"We help you design and execute electrophysiological experiments. We have several state-of-the-art whole-cell electrophysiology systems available—complemented with optogenetics and imaging equipment—for in vivo, ex vivo and in vitro preparations."



"We provide you with technical and scientific support for all your FACS-related experiments. Our platforms are high throughput and our sorting and analysis software are relatively easy-to-use. We work with you to develop downstream solutions to help your research move forward."

GENOMICS & NUCLEOMICS

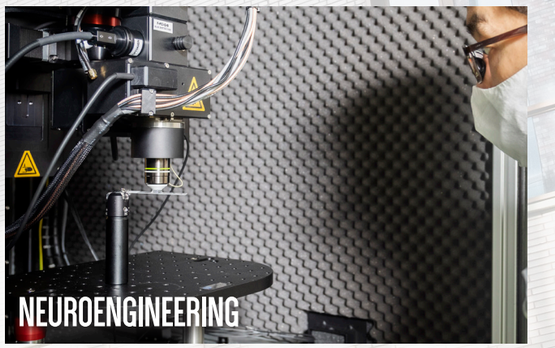
"Through both our host institutes, VIB and KU Leuven, you have access to next-generation sequencing technologies and analysis. Our personalized expert services for expression analysis, RNA and DNA sequencing, include both short (Illumina) and long read sequencing (Pacific Biosciences and Oxford Nanopore) technologies."

SINGLE CELL

"We offer a wide and continuously growing range of cutting-edge single cell technologies, including single-cell transcriptomics, epigenomics and proteomics. From low throughput plate-based techniques to high throughput, droplet-based single-cell sequencing techniques, as well as newly developed technologies such as CITEseq and Cell Hashing. From experimental design, to tailored microfluidic solutions and bioinformatic analysis, we are here to help you meet your research goals."

"We have unique expertise in tracer-based metabolomics, which can deliver crucial insights into the activity of metabolic pathways. Using state-of-the-art high resolution mass spectrometry, metabolimics, proteomics and lipidomics, the fate of labeled isotopes is followed throughout the metabolic network."

"From genome engineering to embryo services and detailed behavioral analysis, our animal facility and rodent expertise unit enable you to create and study your animal model(s), of course observing the 3R principles."



In our dedicated workshop, we design, create and build optical, electrical and mechanical instruments in collaboration with the research labs and expertise centers in support of your experimental neuroscience research. This unit is run in collaboration with NeuroElectronics Research Flanders (NERF).

"Disruptive technologies push excellent science forward. That is why VIB's Tech Watch program spots, evaluates and implements breakthrough technologies to push innovative research in our labs. With both funding and hands-on support, we help you to engage in high-gain high-risk technology projects with early-access technology providers."

MAKING AN IMPACT
FOR PATIENTS AND FOR SOCIETY

5
SPIN-OFFS LAUNCHED
OVER THE LAST 5 YEARS

16 ERC grants
OVER THE PAST 5 YEARS

26.1 M €
INTERNATIONAL GRANTS
& CHARITY FUNDING
OVER THE LAST 5 YEARS

15 M €
INDUSTRIAL INCOME
OVER THE LAST 5 YEARS

18
PATENT APPLICATIONS
OVER THE LAST 5 YEARS

BUSINESS DEVELOPMENT

Translating scientific findings into products for patients and consumers requires a wide array of skills, expertise and financial means. That is why the Business Development team looks for partnerships to achieve academia-to-industry transition for innovations.

INTELLECTUAL PROPERTY MANAGEMENT

Scientific excellence can lead to improvements in health and economic activity, provided the right intellectual property management mechanisms are in place. VIBs IP Managers make sure that our researcher's inventions are appropriately protected via a patent application.

VIB DISCOVERY SCIENCES

The VIB Discovery Sciences team initiates and guides the transformation of scientific insights into projects that could deliver novel therapeutics.

NEW VENTURES

New Ventures supports the creation of new start-ups by proactively scouting innovative inventions or platforms, that could result in new companies. They do so by incubating new technologies, building proprietary platforms, developing a business plan, identifying experienced managers to run the company and attracting national or international investors willing to invest in the start-up.

INWARD INVESTMENT

To bring economical value to the region and to boost international scientific interactions within Flanders, VIB also proactively attracts new companies to the region. For example, VIB takes a leading role in providing laboratory space and office facilities to innovative biotech companies.

When two become one

NEW VIB SPIN-OFF MUNA THERAPEUTICS LAUNCHES THROUGH MERGER, WITH THE MISSION TO STOP NEURODEGENERATIVE DISEASES

Muna Therapeutics launched in the summer of 2021 to advance novel small molecule therapeutics for neurodegenerative diseases. Muna is the result of the merger between two innovative European start-ups: K5 Therapeutics, a VIB-Droia spin-off, and Muna, an Aarhus University-Novo Holdings start-up.

Muna Therapeutics is pioneering the development of first-in-class small molecule therapeutics for neurodegenerative diseases. It combines the strengths of two innovative European start-up companies: Muna and K5 Therapeutics.

- **Muna** was founded in 2020 by progranulin pathway thought leaders Professor Simon Glerup and his team at Aarhus University, Denmark, with investor Novo Holdings.

- **K5 Therapeutics**, a Belgian VIB company focusing on resilience in neurodegeneration, was founded in 2020 by VIB, Droia Ventures and professor Bart De Strooper, and was operating in stealth mode.

The combined entity's innovative all-in-human target discovery and validation platform is based on proprietary insights into molecular pathways in different human brain cell types that underlie disease pathology and resilience to neurodegeneration, based on work from the De Strooper and Glerup laboratories.

Muna has built a cutting-edge small molecule drug discovery engine that leverages high-resolution target structural approaches, AI-driven computational chemistry and cell-based screening. Muna will be based in Copenhagen and Leuven and is led by seasoned pharma executives CEO Rita Balice-Gordon and COO Anders Hinsby, both entrepreneurs-in-residence of Novo Seeds.

The research of Bart De Strooper at VIB-KU Leuven is a core value driver of Muna Therapeutics. "In all parts of the scientific endeavor, partnership is key," says Bart De Strooper. "By combining the innovative strategies of both start-ups, I am convinced we can dramatically accelerate the road to small molecule therapeutics for Alzheimer's. The field has suffered some setbacks over the past decades, but I am optimistic that with proportionate investments, we will succeed in generating better treatments for patients."

We asked three of our alumni

WHY JOIN OUR RESEARCH CENTER?

Primary motor neurons expressing FUS in purple (Tessa Robberechts, Da Cruz lab)

If you are looking for good reasons to join our research center, why not talk to some of our alumni? Many of them are pursuing exciting careers, both inside and outside of academia, in different areas across the globe. We reached out to former postdocs Evgenia Salta, Luís Ribeiro and Elsa Lauwers to learn more about the latest steps in their professional journey.

Tell us a bit more about your current role and research.

Evgenia Salta: I started up my own research group at the Netherlands Institute for Neuroscience in Amsterdam in the summer of 2020. In the lab of Neurogenesis and Neurodegeneration, we explore the endogenous regenerative potential of our brain in neurodegeneration. We ask whether and how adult hippocampal neurogenesis can contribute to developing resilience to Alzheimer's dementia and be recruited to prevent or counteract pathology. In our research, we employ single-cell omics in human postmortem brain, iPSC reprogramming and Alzheimer's mouse models.

Luís Ribeiro: I'm currently Assistant Researcher at the Center for Neuroscience and Cell Biology at the University of Coimbra. Within the Synapse Biology group headed by Prof. Ana Luísa Carvalho, I am developing my independent line of research. It's a very interesting setting because it provides me with access to expertise and equipment and offers critical mass, while at the same time I am able to create my independence as a scientist.

One of the main research questions we have in the lab is to identify and characterize the molecular machinery responsible for sending neuronal cargoes to the axon. In doing so we are aiming at better understanding the molecular basis of neuronal polarity.

Elsa Lauwers: Paleo is a young Belgian start-up using precision fermentation to produce animal proteins as highly functional ingredients for meat and fish replacers. As CSO, I lead the R&D team that engineers the microbial strains, optimizes the production process and tests these proteins. We are looking at regulatory, nutritional and sensorial aspects, sometimes in collaboration with manufacturers of plant-based meat or fish mimics.

How do you look back on your time with us in Leuven?

Evgenia Salta: VIB is research heaven. I am eternally grateful for all the opportunities I was provided with to get trained, learn, collaborate and grow as a scientist. Apart from being at the forefront of research, having direct access to cutting-edge technologies and being surrounded by amazing colleagues, supporting teams and facilities, have all been instrumental for my career.

VIB, KU Leuven and, more specifically, the lab of Bart De Strooper, have been a great school and one of the most important reasons for me to be where I am today.

Luís Ribeiro: It was a very intense experience both scientifically and personally. My time as a postdoc allowed me to become a far more complete scientist than I had ever hoped for. I feel I became a better thinker, a better writer, definitely more critical, in sum a better scientist. At the VIB-KU Leuven Center for Brain & Disease Research and VIB, all the conditions are in place to get the best out of each of us; not in the least through excellent technical and admin support, which is one of the things that I have been missing the most.

Elsa Lauwers: When I meet potential partners or investors, it is clear that my experience at VIB gives me scientific credibility. My time at the VIB-KU Leuven Center for Brain & Disease Research has been an invaluable learning experience. Still today, I am inspired by many former colleagues, who probably don't realize how profoundly they have influenced me and helped me grow.

Any advice for others aspiring to become group leaders (or CSOs)?

Evgenia Salta: My advice is that there is no right advice. There is no 'one size fits all' path or recipe. I did not know exactly 'what I wanted to be'. But I did know what I love to do, and that was research. As a group leader, I get the chance to do what I love and additionally to train the next generation of young scientists, and this is all extremely rewarding.

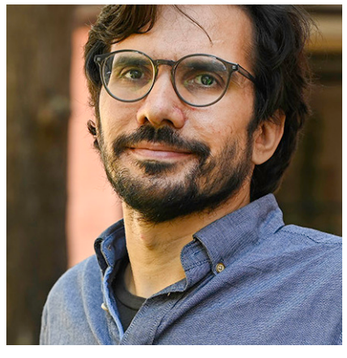
As PhDs or postdocs, we do get trained to do experiments and publish our work, yet often we do not get trained to be good team leaders and mentors. I was fortunate to have ample opportunities as a postdoc to write my own grant applications and supervise several students. I found this an invaluable experience for not drowning as a starting group leader.

Luís Ribeiro: Start applying as early as possible, and try to get your PI and other more senior colleagues involved. Ask them to read your proposals, and discuss your ideas with them. They will give you precious feedback because they went through the same process and most likely they will perceive your proposal in the same way as the reviewers.

Elsa Lauwers: Take advantage of all the knowledge around you, including all the training opportunities that VIB offers. And do keep an open mind, you never know where opportunities will come from.

Evgenia Salta
Group leader at the Netherlands Institute for Neuroscience in Amsterdam

Former postdoc at the De Strooper lab



Luís Ribeiro
Group leader at the University of Coimbra, Portugal

Former postdoc at the de Wit lab

Elsa Lauwers
Chief Scientific Officer at Paleo, Belgium

Former postdoc at the Verstreken lab and head of the Collaborative Research Expertise unit

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CURIOUS ABOUT OUR LABS? TAKE A VIRTUAL TOUR!

Marijn Kuijpers
FMP, Berlin, DE

Gaia Novarino
ISTA, AT

Rosa Cossart
Inserm, FR

Sten Linnarsson
Karolinska Institutet, SE

Benedikt Beringer
J Gutenberg University Mainz, DE
Kings College London, UK

Gero Miesenböck
Oxford, UK

Joshua Sanes
Harvard University, US

Barbara Treutlein
ETH Zurich, SW

"So great to give first in-person talk with full auditorium after pandemic! Thanks @CBD_VIB for the amazing hospitality and to the students for interesting lunch discussion! Leuven is a really nice place."

@slinnarson

Sten Linnarsson

Samantha Morris
Washington University in St. Louis, US

Michael greenberg
Harvard University, US

Aaron Gitler
Stanford, US

Elena Gracheva
Yale, US

Selina Wray
UCL, UK

Christophe Leterrier
CNRS, FR

Jaewon Ko
Daegu Gyeongbuk Institute of Science and Technology, SK

MARK YOUR CALENDAR

Leuven Protein Aggregation Meeting
September 21-23, 2022 - Leuven, Belgium

Neurotechnologies
September 27-29, 2022 - Leuven, Belgium

Brain Body Interactions
Fall, 2023 - Leuven, Belgium

Brain Mosaic
Fall, 2024 - Leuven, Belgium

More info on these & other meetings:
vibconferences.be

JOIN US

Technology experts
We are looking for a diversity of experts to help us strengthen and expand the in-house technology to support the research projects in our Center. These senior experts work in close collaboration with our group leaders, the other technology experts and all scientists across our center.

Postdoc positions
We currently have several open positions for postdocs across our different labs. Spontaneous applications are also welcome: we are continuously looking for talented researchers to join our teams.

Research technicians
Skilled scientific support staff are essential to run our research projects. Several labs are looking for junior and senior profiles.

PhD opportunities
Would you like to do a PhD in neuroscience in a diverse and international environment, with top-notch expertise and facilities at your fingertips?
Send your CV and motivation letter to our PIs.

More info & how to apply:
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Credits

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Cover: Brain organoids, PAX6 in cyan, SOX2 in orange (Franck Maurinot, Vanderhaeghen lab)