EXPLORING UNCHARTED TERRITORIES

As I joined the LCSB quite recently, this editorial won’t be an overview of the past year but rather a reminder of the many strengths of our research centre and a glance over what the future holds for us. I also want to take this opportunity to tip my hat to the LCSB team: in just over a decade, they have built together an internationally renowned centre for research into neurodegenerative diseases. Chapeau! I am looking forward to delving into unexplored scientific questions with all of them.

As the new director, I have to analyse where the LCSB is at and draw conclusions for further development so that we can continue to broaden our understanding of neurodegenerative diseases. In my view, the two main pillars at the LCSB – computational and experimental research – constitute very strong foundations that we can build upon. Our bioinformaticians bring their skills in data management and analysis to many projects, representing the LCSB in leading international research networks. Innovative work in computational biology and computer-based modelling also allows us to develop new research approaches. In the laboratory, LCSB scientists investigate the molecular and cellular processes of neurodegenerative diseases from small molecules to organoids. They are also at the forefront when it comes to new methods such as metaproteomics and cheminformatics. All these research efforts often result in publications in top scientific journals.

Clinical and translational research has always been a big part of who we are as well. In a way, this is the third pillar that makes the LCSB whole. During the pandemic, our expertise in the field has proved useful, allowing Luxembourg to rapidly set up large studies on COVID-19, and we will keep building it up in the coming years. A new research group focusing on Digital Medicine will help translate research results into relevant medical applications and long-term clinical studies on Parkinson’s disease will further our knowledge on risk factors and neurodegenerative mechanisms. As experimental validation is a crucial part of the scientific process, we will also further develop research with animal models, using our state-of-the-art rodent and zebrafish facilities to test assumptions from computer models in organisms.

Strengthening the multidisciplinary approach at the LCSB will lead to a virtuous cycle where data and analyses enable us to identify therapeutic targets and to generate better hypotheses. This is how scientific knowledge progresses. This is how we will contribute to mapping uncharted territories in the biomedical field. And this is how the LCSB’s research findings will find their way into clinical application for diagnosis and treatment.

The new annual report of the LCSB shows you how far we have come on this path. I wish you an interesting read full of exciting discoveries.

Michael Heneka
Together with the University’s Gender Equality Office, the LCSB conducted a survey on how female researchers feel about their work environment. Results have shown that there are still challenges faced by women concerned about being left behind compared to male colleagues. A primary concern is that female researchers no longer have access to laboratories during their pregnancy, owing to national biosafety rules. For these women, this means their research is put on hold, regardless of whether they directly handle hazardous substances or not. Beside existing support measures, the LCSB would like to strengthen short term solutions by hiring R&D specialists who perform the experimental work on behalf of pregnant and breastfeeding researchers.

Dr Lisa Smits, LCSB fundraiser and advocate for gender equality, initiated this survey and is eager to go further: “I will work on finding funds to help make this type of support possible in the long term and to compensate for any disadvantages that female researchers may face. As a scientific community, we need to work on making science and family planning compatible, without fearing that pregnancy will derail a woman’s career in research. In short, we need to empower women in science.”

Dr Lisa Smits
Together, we will identify which scientific challenges are of interest and how we can find some answers.

I say research – as usual for everyone. With some anticipation of course. After saying goodbye to Rudi in style, I think the whole team was looking forward to starting a new chapter.

Prof. Heneka, you’ve been the director of the LCSB since January 2022. When did the centre first get your attention? Heneka: Back in 2017 and I was already impressed by what was happening here. So much so that, when a colleague asked me where was a good place to do research in the region, I recommended the LCSB. The centre was still relatively young at the time, barely seven years old, but it had already made a very good name for itself in neurodegenerative disease research, even far beyond the borders of Luxembourg. Seven years is a very short time to establish a research centre the way Rudi Balling managed to do with the LCSB. I hope we will do as brilliantly in the coming years.

As a physician, you have always worked in a clinical setting. What made you come to the LCSB which is quite a different environment? Heneka: Throughout my career, there has always been a combination of clinical practice and laboratory work. Patient care has always been very important to me. However, when it comes to treating neurodegenerative diseases, in my opinion, we are falling behind. No new drug has been approved for treating Alzheimer’s disease in the last twenty years, for example. There is still no causal therapy that gets to the root of the disease rather than merely alleviating symptoms. Ultimately, this is what motivated me to devote myself entirely to clinically oriented research. The LCSB feels like the right place to do this, with its interdisciplinary backdrop and its close ties with the hospitals here in Luxembourg.

Prof. Schneider, what has it been like at the LCSB since Prof. Heneka was announced as the new head? Schneider: My impression is that there is an atmosphere of anticipation and excitement. I think the LCSB members are ready for new things and that getting new leadership is already giving our team a boost. For example, most researchers welcome the possibility to strengthen relations with hospitals, given that Michael is a physician, and see interesting new perspectives in relation to his expertise on Alzheimer’s disease.

Heneka: I am happy to bring my own know-how to the LCSB but I wouldn’t want to overstate this aspect. It is easy to label each of us – physician, natural scientist, computer scientist – although ultimately, it isn’t that important. What we want to do is good science, this is what I would like to be measured by and what I hope to achieve by bringing together the old and the new and using the full potential of the whole LCSB.

Let’s talk about your plans for the LCSB. Heneka: We want to find good answers to relevant scientific questions. To get started, I will discuss ideas with many people at the LCSB in the coming months and also reach out to other institutions within the R&D ecosystem in Luxembourg and abroad. Together, we will identify which scientific challenges are of interest and how we can find some answers. I don’t intend to restart from scratch as there is plenty to build from at the LCSB. We will reinforce everything that helps us to find these key answers. We will also reshape some things that are less relevant now or even change our orientation in some cases, in order to deliver better results.

Can you already name some of the scientific challenges that need to be tackled in the field of neurodegenerative diseases? Heneka: In neurological research in particular, we have to get better at the scientific cycle – collecting data, evaluating data, generating a hypothesis and finally collecting new data to test the hypothesis. I don’t know of any practical example where this has been done consistently and has led to better treatments. This might be linked to the fact that we are not yet able to make the most of all the data collected in the lab or in the clinic.

Schneider: As computer scientists, we often notice that the data collected during experiments don’t cover all aspects and, as a result, we cannot fully take advantage of the information we have. To really maximise our results, it will be important to raise awareness about this issue and to pay even more attention to the design of experiments at the LCSB.

Heneka: We definitely have to work on that. What excites me most about the LCSB is the wide range of disciplines that are working together here. If we succeed in better combining data collection and data evaluation, I see a great opportunity for improving our understanding of neurodegenerative processes.
Prof. Klucken’s main interest is research on Parkinson’s disease and one of the things that played a major role in his decision to come to Luxembourg was the National Centre of Excellence in Research on Parkinson’s Disease (NCER-PD). Over the past years, NCER-PD has helped establish Luxembourg’s international reputation as an important stakeholder in the field of Parkinson’s disease. Furthermore, the patient cohort in NCER-PD is an ideal resource to research digital options for the medical care of people with Parkinson’s disease. The motor symptoms experienced by the patients have a major impact on their quality of life and are therefore the main target of current treatments. This is where new digital applications could both help the patients in their daily life and assist the doctors in making treatment decisions – one example being sensor-based gait analysis.

Changes in the way Parkinson’s patients walk serve as indicators of how the disease is progressing and can signal that an aggravation of the symptoms may be imminent. “We want to use digital tools to monitor such changes,” says Klucken. “We are already testing an app that patients can use to regularly check for any changes in gait and transmit the data to their attending physician.” The data capture itself is the easy bit, Klucken explains: “It doesn’t take all that long for computer scientists and data scientists to program the necessary algorithms. The real challenge is designing the app for maximum usability so that it will be accepted and actually used by patients and doctors.” Can the patients find their way around the app? Is it user-friendly? Does the doctor receive the right data in a format that is quick and easy to understand? These are questions that Prof. Klucken and his team are looking to answer.

While Parkinson’s research is Jochen Klucken’s personal field, the Digital Medicine group will not exclusively focus on this disease. Other conditions are also of interest to the team as the digital transformation of medicine affects all fields. For that reason, Prof. Klucken works not only at the LCSB but also at the Centre Hospitalier de Luxembourg (CHL) and at the Luxembourg Institute of Health (LIH). “In this way, we ensure great thematic diversity and interdisciplinarity,” he says, adding that, alongside Parkinson’s researchers, the team also collaborates with data analysts at the LCSB, clinician scientists and study nurses at the CHL, as well as health economists and social scientists at LIH.

The work of Prof. Klucken is funded through the PEARL programme of the Luxembourg National Research Fund (FNR). This joint research programme involves the LCSB, LIH and the CHL.

The recent pandemic demonstrated that digital medicine is becoming an essential part of patient care. There are countless ideas on what this innovative field involves and how it could work. However, many of the existing solutions are still too academic: they are not yet fully developed or cannot be easily used by doctors and patients. Not to mention that, in some cases, the medical benefits are still unproven. Prof. Jochen Klucken and his team are working to change all this. In March 2021, the neurologist settled in Luxembourg as FNR PEARL Chair for Digital Medicine and head of the Digital Medicine group at the LCSB.

FROM ALGORITHM TO MARKET – BRINGING MEDICAL APPLICATIONS TO LIFE

The sensitive nature of digital medicine is another reason why interdisciplinarity is needed. “Data protection and the responsible handling of patients’ data are extremely important and must be considered from the very beginning,” emphasises Klucken. Moreover, once the perfect digital application has been programmed and tailored for patients and therapists, it doesn’t end there. “Without market analysis, market access and proof of medical efficacy or positive care effects, nothing works,” details Klucken. “We want to investigate the entire development chain, from the algorithm to the marketable application, and to develop methods so that the digital products can actually get into medical practice, demonstrably help patients and healthcare providers, and ultimately be covered by third-party schemes such as health insurance.”

Prof. Klucken sees Luxembourg as an ideal environment for this research: “Things are developing rapidly here and Luxembourg is not only thinking of its own market. Solutions are being developed with Europe in mind. This is of great importance, especially in digital medicine.”
The Bioinformatics Core is committed to improving data sharing. Together with others in the research community, the LCSB scientists have taken on this mission as part of ELIXIR – the European Infrastructure for Life Science Information. Data sharing is by no means an easy feat. Legal concerns and uncertainty often outweigh scientific interest. As a result, in many cases, the wealth of data collected during a project cannot reach researchers all over Europe. A missed opportunity for science, one that is now being tackled by a specific team within the LCSB.

When it comes to sensitive patient data, utmost care is needed to keep the data secure and to ensure that they are handled in compliance with the regulatory framework. But that is no reason to stop sharing data within the academic community. A team at the Bioinformatics Core of the LCSB has been established to support researchers in relation to the General Data Protection Regulation (GDPR), providing guidance and developing useful tools.

“The GDPR is quite generic and not primarily aimed at research,” explains Dr Regina Becker. This means it is open to interpretation when trying to apply it in this context, giving rise to many questions, starting with: How do these rules aimed primarily at eCommerce relate to research? Dr Becker has been working on the answers since the introduction of the GDPR. She and her colleagues have developed in-depth expertise on ethical, legal, and social issues (ELSI) linked with data sharing.

“Instead of looking at the law from an academic point of view, we are taking a practical approach to the GDPR,” Becker explains. “We aim to find concrete solutions.” Colleagues at the LCSB and within the University of Luxembourg are already benefiting from the ELSI team’s efforts. At the LCSB, for example, “data stewards”, data management professionals specially trained in matters of data governance, assist researchers in complying with legal requirements. Jointly with Dr Becker and her team, they translate legal provisions into practical concepts and develop customised tools.

“Scrutinising the law while being positioned within a bioinformatics group is ideal – we couldn’t do this kind of work anywhere else,” Regina Becker notes.

Their skills are now also benefiting partners elsewhere in Europe. Being able to share data for research and innovation is vital for the economy and the European Commission has recognised the need to create an environment where data can be utilised efficiently. A flagship project in the EU data strategy is the European initiative “1+ Million Genomes” launched in 2018. Governments of 22 European countries aim to provide cross-border access to the genomes of at least one million people and use the resulting data to develop new, better and individually adapted therapies.

This is a huge challenge. “People are providing us with intimate health data. In return, we must assure them that these data will be handled confidentially,” says Regina Becker. “And people have a right to be informed about what is happening with their data.”

Becker’s mission is to help create the basis for this. The researcher heads the ELSI working group within the framework of the EU genome initiative. As such, she is responsible for ensuring that the implementation of the initiative meets ethical and legal requirements. And it is a tough job. “Every country has its own rules and ideology about data protection,” Becker says. But she is convinced that persevering to reconcile their differences is worthwhile – for the good of the scientists as well as the people who are supporting research with their data.

The team’s combined knowledge and experience in ELSI compliant management of sensitive personal data is becoming well known. Most recently, they have joined two particularly far-reaching projects. One of these is the European Platform for Neurodegenerative Diseases, an IMI project funded by the European Commission, which is building a platform for sharing biological samples and data on diseases such as Alzheimer’s, epilepsy and Parkinson’s. The other, HealthyCloud (H2020), aims to allow seamless sharing of health data for research and innovation in Europe. In both projects, secure, confidential and legally compliant data handling is at the heart of the activities.

“My bioinformatics colleagues often roll their eyes when I get excited about digging into yet another riddle of the GDPR,” laughs Regina Becker. But everyone in the Bioinformatics Core and ELIXIR-LU understands the importance of these aspects. Moreover, the findings are directly translated into LCSB’s data management, promoting best practice for responsible research. Becker smiles: this is yet another example of interdisciplinarity in action at the LCSB.
Could it be that the seed for developing Parkinson’s disease later in life is already planted in the embryonic stages of development? A team of researchers at the LCSB is following up on this hypothesis. They are working primarily with organoids – organ-like models grown in the laboratory from patient-derived cells.

“The number of Parkinson’s patients is continuously increasing. Worldwide, more than six million people are affected by this – still incurable – disease. Many biological processes that lead to its onset and promote its progression are still unknown. Scientists at the LCSB are studying different aspects of the disease. For example, in the Developmental and Cellular Biology group headed by Prof. Jens Schwamborn, around 20 researchers are focusing on a possible connection between processes that occur in the early stages of brain formation and an increased susceptibility to developing Parkinson’s disease. “It has long been known that Parkinson’s is characterised by a loss of neurons that secrete dopamine – a molecule involved in the communication between the neurons in the brain,” explains Schwamborn. “But in recent years, scientists have come to realise that there is also a strong developmental aspect to this neurodegenerative disease.” This means that dysfunctional processes during embryonic development might already lay the foundation for the disease to develop later in life.

To investigate this hypothesis, Dr Silvia Bolognin, a senior member of Prof. Schwamborn’s team, is using human stem cells. “These cells are at the centre of our research approaches,” says Bolognin. “We use them to create advanced disease models that can be studied in the laboratory.” One particularly promising type of model is three-dimensional organoids: artificially grown collections of cells that self-organise into organ-like formations. “Organoids resemble a real organ in their structure and function,” Bolognin explains. “Therefore, they make it possible to trace back and study metabolic or growth processes in a natural setting.”

For example, Bolognin and her colleagues at the LCSB are creating organoids of the midbrain, the area of the brain mainly affected by Parkinson’s disease. These “mini-brains” are grown from human stem cells that mature – scientists say they differentiate – under special conditions into multiple types of cells. Thus, these cultures produce not only neurons but also astrocytes: cells that partly make up the connective tissue between the neurons in the brain.

The researchers at the LCSB are using such brain models to investigate cellular and molecular processes that lead to the onset and progression of Parkinson’s disease. The team published new findings in the scientific journal *Cell Reports* in 2021. They aimed to identify peculiarities in the formation of certain brain structures that could increase the risk of Parkinson’s disease later in life. For this purpose, the scientists used stem cells from patients with a familial form of Parkinson’s disease. “In this case, the genetic cause can be traced back to a specific mutation in the gene LRRK2,” explains Bolognin.

With the help of automated image analysis and single cell RNA sequencing, the biologists were able to demonstrate, among other things, that this mutation significantly impairs the initial phase of neuronal differentiation during brain development. “We have identified several molecular effects that point to a link between early neuronal cell development and a predisposition to Parkinson’s disease,” Bolognin reports.

For the biologist, this new experimental finding is an important step towards a better understanding of the disease. And further steps are to follow. For example, the team next wants to find out whether and how the effect of the mutation can be influenced. The researchers hope that this could eventually help prevent the onset of the disease.
COVALux, a new initiative led by Research Luxembourg in collaboration with a consortium of national players, including the LCSB, is taking on these challenges. It will rely on the expertise of academic and healthcare institutions for the collection, integration and analysis of various health and socio-economic data.

The public research institutes of the Grand Duchy have come together to form the COVALux consortium. “The pandemic has shown how important speed and flexibility are. Not only for treating individual people but also for protecting society as a whole,” says Prof. Paul Wilmes, co-spokesperson of the consortium and head of the Systems Ecology group at the LCSB. “With this programme, we are combining our knowledge and capacities to support the national effort in fighting the pandemic and its consequences.”

For the next three years, the project partners will concentrate on two main topics. One revolves around the symptoms, frequency, risk factors and socioeconomic consequences of long COVID. “As over 25,000 individuals are estimated to be affected in Luxembourg, these are crucial questions,” says Paul Wilmes. Children and young adults are an important focus group in their own right, he adds: “They are the part of the population who will have to live the longest with any consequences of the disease.”

The scientists are certain that, with the data and insights gained through COVALux, they will be able to help improve the prevention, diagnosis, prognosis and treatment of long COVID.

The microorganisms living in and on our body are a good place to start investigating. “Our microbiome is extremely important for our health,” explains Prof. Wilmes, who has a long-standing expertise in the field. “Due to COVID-19, the microbiome becomes severely disrupted on multiple levels. Therefore, in order to understand the long-term effects of the disease, we have to study the changes in the microbiome within the Luxembourg population.”

TOGETHER AGAINST THE VIRUS AND ITS CONSEQUENCES

The COVID-19 pandemic is highly dynamic and science is facing major challenges: a rapidly mutating virus and the need for innovative approaches in vaccine development for example. Continually providing new insights into the longer-term effects on those afflicted and on society is also crucial.

COVALux builds on previous national studies such as PrediCOVID and CON-VINCE, the researchers already have some datasets. “We have for example investigated the reasons why people decide not to be vaccinated and have gathered demographic data on this,” says Paul Wilmes. “Also, we have presented the government with our initial results from simulations regarding booster vaccinations and the spread of Omicron in Luxembourg.” And he concludes: “Our goal is to close knowledge gaps in relation to the virus and to provide scientific data to politicians to support the decision-making process. In this way, we hope to be well prepared for the future.”

The project partners are the Luxembourg Institute of Health, the University of Luxembourg, the Integrated Biobank of Luxembourg, the Laboratoire National de Santé, the Luxembourg Institute of Socio-Economic Research, the Luxembourg Institute of Science & Technology, the Centre Hospitalier de Luxembourg, the Centre Hospitalier NeuroPsychiatrique, the Rehazentier and Mondorf Domaine Thermal. The programme is supported by the Luxembourg Government.
HYBRID SCREENING TO FIND THE BEST ACTIVE INGREDIENTS

A team of researchers from the LCSB and the Department of Life Sciences and Medicine at the University of Luxembourg has shown that combining different computational screening methods for drug repurposing can facilitate the experimental discovery of pharmacologically active compounds.

In the fight against the disease caused by SARS-CoV-2, the development of vaccines has been accompanied from the very start by the search for drugs that can alleviate severe symptoms. A team of researchers led by Assistant Prof. Enrico Glaab has developed a methodology that can spur the repurposing of existing drugs or natural substances and provide new insights for the design of compounds with improved activity (FNR COVID-19 Fast Track)

“One goal when treating COVID-19 with pharmaceutical drugs is to reduce the viral load in severely affected patients,” explains Prof. Glaab, head of the Biomedical Data Science group at the LCSB. The first point of attack is a specific component of the virus that is essential for its replication in human body cells: the SARS-CoV-2 viral protease called 3CLPro (also known as Mpro). “Certain chemical compounds molecularly bind to this target protein and inhibit the replication of the virus,” says Glaab. “These are the ones we are looking for.”

The development of drugs against an infectious disease traditionally starts with experimental screening: testing many substances in the laboratory to find those suitable to become active pharmaceutical ingredients (APIs). It is costly and time-consuming. Enrico Glaab and his colleagues decided to take an hybrid screening approach instead. In order to identify the best virus-inhibiting APIs as quickly as possible, they combined three completely different computational methods with subsequent experimental testing.

“We chose to start with computer analyses, to filter a larger number of compounds and find those most likely to bind to the target protein and inhibit viral replication,” says Glaab. The researchers employed machine learning as well as molecular docking and ligand similarity analyses to find substances in compound databases that fit into the target protein like a key into a lock or that have similar characteristics to already known binding substances. “Next, we experimentally tested the most promising substances in the lab to confirm their inhibitory activity against the viral protein,” Glaab reports. In the end, the scientists arrived at a selection of promising compounds that have multiple drug-like characteristics: they not only have an antiviral effect but also possess the right size and chemical properties to reach the target areas in the human body – even by crossing physiological barriers like the intestinal wall.

The team’s final computational analyses also provided three dimensional models highlighting relevant chemical and structural characteristics of the selected active substances. This information is crucial to understanding how the compounds interact with Mpro and how their inhibitory effect comes about. This, in turn, makes it easier to optimise the properties of the compounds that progress to further drug development stages.

There is still a long way to go but the results already achieved constitute a relevant contribution to pharmaceutical research on COVID-19.

THE POWER OF COMPUTATIONAL MODELLING

Upon infection with SARS-CoV-2, there is one consequence that has doctors particularly concerned: a severe amplification of the immune response called hyperinflammation. The immune system releases an excess of biological messengers – called cytokines – in a feedback loop that continuously maintains the inflammation above the level needed to control the disease. It can increase the severity of the symptoms, cause organ failure and even be life-threatening.

Prof. Antonio del Sol and his team have developed a single-cell based computational approach to identify molecules of relevance to hyperinflammation in COVID-19. The team’s results were consistent with the experimental findings of an American research group, confirming a potential target for medical intervention and demonstrating the power of computational modelling for research in immunology.

When the Computational Biology group led by Prof. del Sol started this FNR-funded project, the researchers relied on single-cell data from COVID-19 patients in Wuhan, the pandemic starting point. Thanks to these data coupled with a novel computational method, they created a comprehensive map of the immune response in the lungs of the patients, detailing the interactions between ligands and receptors on the membrane of immune cells as well as the intracellular signal pathways and genetic mechanisms involved in hyperinflammation. The team was then able to identify molecules that could modulate the inflammatory response. One such molecule is the Toll-like Receptor 2 (TLR2), a protein known to play a role in the human immune response.

Shortly after the paper written by del Sol and his colleagues was released, other research groups published new experimental data on hyperinflammation. “We were excited to see how well our predictions from computational modelling matched the laboratory data,” says del Sol. There was an accordingly positive response within the scientific community, which quickly recognised the value of the theoretical work done by the LCSB researchers and was therefore interested in collaborating with the computational biologists.

The team of Dr Thirumala-Devi Kanneganti from the Department of Immunology of St Jude Children’s Research Hospital in Memphis (USA) independently obtained similar results, for instance. Their in vitro and in vivo experiments also suggested that TLR2 might act as a key modulator of COVID-19-induced hyperinflammation, highlighting how a combination of computational and experimental approaches can be relevant when it comes to research on inflammatory processes.

Considering that Antonio del Sol and his team are computational biologists rather than immunologists and tackled this problem from a different angle, the consistency of the two teams’ results is particularly meaningful. “Our results are not affected by bias,” says del Sol. “We approach the data impartially and have no preferred candidate molecules in mind. We rely purely on modelling to deliver medically relevant information.”

Increased collaboration between experimental and computational research groups seems all the more important in view of these results: “Computational studies and experimental validation are a key combination when it comes to making fundamental discoveries with therapeutic implications.” The resulting findings may in the future enable medical practitioners to respond more quickly and precisely to critical concomitant symptoms of infections.

Visualisation of a natural compound inhibitor (in purple) for the SARS-CoV-2 protease 3CLpro, docked into the binding pocket.
RESEARCHING COVID-19 THROUGH A WIDE ARRAY OF PROJECTS

How is COVID spread by people who are infected but don’t show symptoms? What are the risk factors that decide if a case will be severe? In 2020 and 2021, LCSB scientists were involved in over 15 national and international research projects all aimed at improving our understanding of the virus as fast as possible. Their results will allow for more effective responses against its propagation as well as the acute symptoms and long-term consequences of a COVID-19 infection.

During the pandemic, Research Luxembourg, a joint initiative of the main actors in Luxembourg public research, set up a COVID-19 task force with the support of the Ministry of Higher Education and Research. The goal was to promote scientific collaborations on the topic and to support the national health system with the combined expertise of researchers working in Luxembourg. Under the umbrella of this task force, several large studies came to life, such as CON-VINCE, initiated to investigate the dynamics of the epidemic in Luxembourg, and CoVaLux, a project that will explore vaccination and impacts of COVID-19 including socio-economic and environmental determinants of Long COVID.

These national studies were far from being the only research initiatives related to COVID-19. The task force was also involved in the pre-evaluation of numerous projects for the COVID-19 Fast Track Call set up by the Luxembourg National Research Fund (FNR). Adapting to the fast pace of the pandemic, the FNR funded projects through this call in 2020 and 2021, while keeping the evaluation times short. LCSB scientists were involved in several of these Fast Track projects. From operating a COVID-19 literature browser for scientific studies to studying the respiratory and intestinal microbiota of patients, from using deep learning to help diagnosis based on medical imaging to analysing phylogenomic and geographical data to better understand pathogen dynamics, they covered a wide range of topics. All these projects provide much needed additional insights, in parallel to the large-scale studies mentioned.

They will result in practicable ways of dealing with the virus and other pandemics in the future.

In addition to contributing at the national level, research groups at the LCSB are also involved in three projects supported by the European Commission, with funding totalling several million euros for all partners. In many ways, the LCSB and the whole research ecosystem in Luxembourg have been fully involved in the fight against the pandemic over the past two years. It made sense: the centre’s expertise is relevant and it was - still is - a very worthy cause.

In 2021, two events were organised to acknowledge this massive engagement. These events were held to thank sponsors for their generous support to COVID-19 research and to recognise the time and effort invested by many researchers. In November, researchers from the Luxembourg Institute of Health and the LCSB welcomed representatives from the André Lasch Foundation and the FNR to thank them for the funding they provided. Earlier that autumn, Prime Minister Xavier Bettel also visited the Belval campus together with Minister of Higher Education and Research, Claude Meisch. They met with researchers who are part of the COVID-19 Task Force and discussed milestones achieved while looking at current projects and actions to come. The event highlighted once again how science and policy collaboration helped Luxembourg navigate the COVID-19 crisis.
How is the coronavirus spreading throughout the population? How dangerous is each variant? What countermeasures work best? Who do we vaccinate first? Hundreds of questions have arisen in the course of the pandemic, none of which could be answered without the help of mathematicians and computer scientists experienced in predictive modelling.

Within the COVID-19 Task Force of Luxembourg, several researchers from different research institutions worked together to develop computer-based models and look for answers. They used their models to continuously generate projections and to create weekly reports so that policymakers could reach decisions based on the soundest facts possible. For the LCSB, Dr Atte Aalto and PhD student Françoise Kemp were key drivers of this project.

Both scientists refer to themselves as applied mathematicians: “Neither of us knew how to model an epidemic,” says Dr Atte Aalto, at the time a postdoc in the Systems Control group at the LCSB. “But we did know how to make models and we quickly learned how to apply this knowledge to the pandemic.” Françoise Kemp, who is writing her PhD thesis in the Integrative Cell Signalling group, adds: “We developed a broad range of models adapted to the situation and the data available in Luxembourg. They differed greatly depending on the question we were focusing on.” With these tools, the team was soon able to make predictions on how the rate of viral spread would evolve, what hospitalisation rates could be expected and what effects certain countermeasures might have.

Initially, a large number of scientists were involved in the modelling work package of the COVID-19 Task Force. After many months of intense work, things have slowly settled down to a different pace, as Aalto describes: “We are still running models and writing weekly reports but now only six of us are still involved and we have managed to integrate this routine in our daily work.” Still, being part of this scientific endeavour was quite a unique experience and has by no means become routine for Françoise Kemp: she is now writing her PhD thesis not – as originally planned – on modelling cancer but on modelling COVID-19. “It is a very exciting topic, which makes me eager to work on it,” she says. So, as often in research, we can count on bright young minds to tackle the scientific issues of their time.

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Initially, a large number of scientists were involved in the modelling work package of the COVID-19 Task Force. After many months of intense work, things have slowly settled down to a different pace, as Aalto describes: “We are still running models and writing weekly reports but now only six of us are still involved and we have managed to integrate this routine in our daily work.” Still, being part of this scientific endeavour was quite a unique experience and has by no means become routine for Françoise Kemp: she is now writing her PhD thesis not – as originally planned – on modelling cancer but on modelling COVID-19. “It is a very exciting topic, which makes me eager to work on it,” she says. So, as often in research, we can count on bright young minds to tackle the scientific issues of their time.

Building on these results, Luxembourg has joined ORCHESTRA, a three-year international research project funded by the European Commission. Involving partners from 15 countries around the world, it aims to connect data derived from several national studies to improve prevention and treatment of COVID-19, and to ensure we are better prepared for future pandemics.

ORCHESTRA will provide an opportunity to study the long-term consequences of COVID-19, while monitoring the immune response post-vaccination and evaluating the psychosocial impact of the pandemic. Prof. Royko Krüger, coordinator of ORCHESTRA Luxembourg, director of Transversal Translational Medicine at the Luxembourg Institute of Health and head of the Translational Neuroscience group at the LCSB, explains: “The core of ORCHESTRA is a large patient cohort that makes it possible to do retrospective and prospective studies on COVID-19. With the data and information acquired from the CON-VINCE study – funded by the Luxembourg National Research Fund (FNR) and the André Losch Fondation – and our expertise on Parkinson’s disease, we can make valuable contributions, in particular as to how the coronavirus affects Parkinson’s patients.”

Indeed, additionally to most of the 1800 participants from CON-VINCE who are now enrolled in ORCHESTRA Luxembourg, this new project will also rely on the help of 150 people with Parkinson’s disease. All these volunteers will regularly fill out online questionnaires about their health, socioeconomic and psychological status and give blood or stool samples as well as nasal swabs, providing researchers with information on immune response, genetic predisposition, mental well-being and other factors.

Thanks to the data collected during CON-VINCE, the scientists have already studied the course of the pandemic very closely and followed how the virus spreads throughout the population. “As we are also observing those who are asymptomatic,” Krüger says, “we have a very detailed picture of the situation.” In June 2021, the team discovered that around 50% of the population had antibodies against SARS-CoV-2 in their blood. Most had acquired them after vaccination but around 34% had developed antibodies due to direct contact with the virus. The researchers also looked into the global effect of the pandemic, such as some forms of depression which have developed over the past two years.

Now, scientists are especially interested in examining long COVID and the vaccination effectiveness over time. CON-VINCE provided essential information that will be translated at the international level through ORCHESTRA to assess the protection conferred by the vaccine in the long run and to investigate if and how the immune system reacts to vaccination differently in people with Parkinson’s disease. “Findings from ORCHESTRA will help in redeveloping vaccines and adapting vaccination strategies so that we can properly protect vulnerable people like Parkinson’s patients and the general population alike,” says Krüger.
THE SCIENTEENS LAB LAUNCHES INTO COMPUTER SCIENCE

“Learning computer science at school will become about as important as learning to read and write,” says Dr Elisabeth John, team leader of the Scienteens Lab, an extracurricular learning centre of the University of Luxembourg. Society is indeed undergoing a rapid digital transformation and smart technologies have become part of our daily life. It is now more than ever crucial to familiarise young generations with the science behind these devices. To help tomorrow’s citizens become informed users, the Scienteens Lab has recently extended its activities to computer science. It now offers new workshops focusing on artificial intelligence (AI) and coding where teenagers can learn through hands-on activities. They can for example discover how machines learn on their own or how to train an AI to transform selfies into artworks. “These workshops offer pupils a playful introduction to computer science, introduce them to the thriving research in the field and will increase the computational literacy of youngsters in Luxembourg,” Dr John is certain.

After a successful pilot phase launched in 2021 with the support of the Royal Bank of Canada, the Scienteens Lab is now developing additional activities in collaboration with the Faculty of Science, Technology and Medicine. The implementation of an exhaustive programme in computer science over the next three years is funded by the Luxembourg National Research Fund (FNR) through its PSP-Flagship programme.

A BOOSTER FOR CELL CONVERSION

Regenerative medicine needs artificially cultivated cells. Doctors use these cells in new therapies, to replace tissues lost to disease or injury and to treat sick organs or even the immune system. Scientists can also learn a lot by studying them in the lab.

In recent years, biomedical scientists have developed methods to convert pluripotent stem cells into specific human cell types but until now these methods have not been very efficient. Improving the efficiency of cell conversions is key to enhancing the production of cells readily usable in therapeutic applications.

In collaboration with the Wyss Institute for Biologically Inspired Engineering at Harvard Medical School, Prof. Antonio del Sol, head of the Computational Biology groups at the LCSB and at CIC biogUNE in Bilbao, and his team have developed a new computer-based approach that greatly increases the efficiency of cell conversion. The new tool, called IRENE (Integrative gene Regulatory Network model), helps to boost the conversion process by giving pluripotent stem cells a more efficient set of instructions for transforming into cells of the desired type.

In principle, pluripotent stem cells can be converted into any type of cell. This process requires the presence of a defined set of gene regulatory transcription factors (TFs). Their task is to switch the genes required for conversion on and off at the right time. Researchers have therefore to define which very specific combinations of TFs should be used in lab protocols to guide the differentiation of stem cells in the right direction, rather like recipes for specific cell types. “Until now, these protocols have only been created based on the analysis of gene expression patterns in many cell types and through trial and error,” says del Sol. “Computational biologists only focused on which genes had to be switched on or off and did not take into account the effects of the epigenetic landscape on the efficiency of cellular differentiation.”

Meaning previous models did not consider how the conditions in the cells and their surrounding environment could affect the way the genes work, preventing cell conversion techniques from breaking through the efficiency limit.

IRENE not only looks at transcription factors as the gene regulators but also takes the epigenetic state of the cell into account. By incorporating these new parameters that influence which genes get turned on or off, this innovative approach covers a higher level of control for genetic activities in the cell.

“We can use this computational tool to control gene expression in a much more targeted way and pinpoint highly effective combinations of TFs,” says del Sol. The team demonstrated that their approach significantly increases the efficiency of cell conversions for a range of cell types employed in biomedical applications, such as natural killer cells used in immune therapies and mammary epithelial cells that could help with breast tissue regeneration.

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Residues of pesticides, sunscreens and antifreeze are polluting our rivers and oceans along with residues of medicines and party drugs. Prof. Emma Schymanski and her Environmental Cheminformatics group want to find out exactly what is accumulating in Luxembourg’s waters. “The number of registered chemicals has long since exceeded the hundred million mark,” the scientist says, giving us an idea of the challenge. “Our household products alone account for more than seventy thousand of them and they mostly end up in our rivers with our wastewater.”

Finding out which chemicals are accumulating in the environment and how they might be endangering our health is detective work. Emma Schymanski and her team regularly receive samples from several rivers in Luxembourg from the Water Management Authority. They examine the samples using high resolution mass spectrometers and sophisticated computer algorithms. “Every chemical substance has its own fingerprint,” reveals the chemist and environmental engineer. The mass spectrometers recognise these fingerprints and, with the help of cheminformatics, the scientists can attribute them to different substances and their degradation products. “With some chemicals we get lucky. Their fingerprint is already stored in our database,” says Schymanski. With many others, however, the researchers first have to painstakingly research what might have been the original substances that entered the water in the area where the sample was taken and how these substances typically break down. Then, they take the predicted fingerprints of the substances and compare them with those from the water sample.

Schymanski’s team examines the water samples for chemicals such as pesticide residues, drug residues and – as part of the new European H2020 ZeroPM project – persistent and mobile substances. These are substances that are very difficult or impossible to break down in nature and, at the same time, spread over long distances with water. If they are ingested by humans or animals over long time scales, they can have adverse health effects.

ZeroPM stands for “Zero Pollution of Persistent, Mobile Substances” and was launched as part of the European Union’s Green Deal in the final quarter of 2021 (grant agreement No 101036756). Led by the Norwegian Geotechnical Institute, 15 partner institutions will be researching innovative solutions over the next five years to prevent, prioritise and remove pollution with persistent and mobile substances, and thus protect our health, environment and natural resources. “We are part of the Substance Grouping Team. We are helping to prioritise the various groups of substances,” explains Emma Schymanski. “We make a representative selection of substances of concern which other working groups then examine more closely.” This is important because more than 180 million chemical substances are registered to date, with tens of thousands of chemicals present in the products we use or buy every day. To examine them all in detail would exceed the limits of any project. “We use our cheminformatics methods to figure out which of the many registered substances are persistent and mobile or may break down into substances with these properties as they degrade,” the researcher explains. “The other teams then use our results to test the selected substances for their toxicity or remediation potential.” A real collaborative effort to tackle pollution on a European scale! (zeropm.eu)
SUCCESSFUL ARTIFICIAL INTELLIGENCE CHALLENGE FOR LCSB TEAM

Contracting COVID-19 can result in severe lung damage. Countless images of the damage have to be taken in order to diagnose and treat the disease, and experts can only go through all of them with the help of artificial intelligence (AI). Competitions like the “COVID-19 Lung CT Lesion Segmentation Challenge” organised by the American Children’s National Hospital are helping to advance the field fast. The LCSBmedAI team, led by Dr Andreas Husch, and the Interventional Neuroscience group of Prof. Frank Hertel and Beatriz Garcia Santa Cruz from the Department of Physics, as well as the Systems Control group of Prof. Jorge Goncalves. The team was a collaboration between members of the LCSB and CRIMTYP, two new initiatives involving LCSB researchers.

The subsequent run on the test data was then a success, training data what damaged and healthy lungs look like. The scientists first fed an algorithm with images composed of seven LCSB researchers, made it into the fast. The LCSBmedAI team, led by Dr Andreas Husch, and the Interventional Neuroscience group of Prof. Frank Hertel and Beatriz Garcia Santa Cruz from the Department of Physics, as well as the Systems Control group of Prof. Jorge Goncalves. The team was a collaboration between members of the LCSB and CRIMTYP, two new initiatives involving LCSB researchers.

The Institute for Advanced Studies (IAS) at the University of Luxembourg was established in 2020 to facilitate interdisciplinary and innovative research. The IAS supports young scientists and finances particularly ambitious and promising projects – such as IDAE and CRIMTYP, two new initiatives involving LCSB researchers.

Epilepsy has researchers puzzled. The disease, which is characterised by spontaneously occurring seizures, is one of the most widespread neurological afflictions. Yet its treatment is a huge challenge: many patients do not respond to any of the available drugs and others only to a laboriously adjusted combination of multiple drugs. The causes of epilepsy are also still largely unknown. Although scientists have identified more than 500 genetic mutations that may contribute to the development of the disease, this only provides part of the explanation.

With a new research project launched in 2021, scientists from the university now hope to answers these open questions with an interdisciplinary approach oriented towards medical feasibility. The project, called IDAE (Integrative Data Analysis in Epilepsy), involves scientists from the Interdisciplinary Centre for Security, Reliability and Trust and the Department of Physics, as well as the Integrative Cell Signalling group at the LCSB led by Associate Prof. Alexander Skupin. To better understand epilepsy, the three teams are combining results from genetic research on zebrafish, realistic modelling of metabolic processes and data analyses using machine-learning algorithms. “With this approach, we hope to find new biomarkers and thus facilitate the personalisation of treatment for epilepsy patients,” explains Skupin.

Another project, which also started in 2021, shows just how broad the thematic scope of the IAS is. Its goal is to strengthen a relatively new scientific field in Luxembourg: forensic science. It focuses on modern methods of genetic sequencing, to which Dr Patrick May from the Bioinformatics Core of the LCSB is contributing his long-standing expertise. “Genetic analyses can now be used to deduce many different characteristics of the perpetrator from minute traces at the crime scene,” explains Dr May. For example, age, hair, skin and eye colour, as well as geographical origin and even behavioural characteristics can be deduced from genetic traces.

In order to find out how reliable such predictions are and to what extent they can be legally integrated into future searches for criminals, the LCSB researchers will be working closely with colleagues in the university’s Department of Law during the two-year term of the project. They also want to bring police and judicial representatives as well as private companies specialised in genetic analyses on board. A perfect example of how establishing connections between many different actors and perspectives will help tackle important societal challenges.
Metaproteomics

Proteins are an extremely diverse set of tools in the cells of all living organisms. The diversity of proteins expressed by microbial communities, such as the gut microbiome, is at the heart of the relatively young field of metaproteomics, which was further promoted in 2021 by the Systems Ecology group led by Prof. Paul Wilmes. He contributed to the emergence of the field just over a decade ago and his team recently hosted the 4th Metaproteomics Symposium in Luxembourg. The increasing interest of the international community in metaproteomics demonstrates the robustness of the methods developed over time.

“In metaproteomics, we study all the proteins expressed by microbial communities,” explains Paul Wilmes. “These macromolecules are not only vitally important in different ecosystems but also play an essential role in the stimulation of the human immune system.” The professor of Systems Ecology at the LCSB has not only worked in this field for most of his research career; it was he who brought metaproteomics to life. “I was already investigating how microbial communities function during my PhD,” he recalls. “In the world’s first metaproteomic study, my PhD supervisor, Dr Phil Bond, and I even came up with the name for this new field.” Back then, they coined the term metaproteomics for the characterisation of proteins expressed by microbial communities at a given time.

That was 15 years ago. A lot has since happened in the field, despite getting off to a slow start. “Compared to other omics approaches – such as metagenomics, the study of all genetic material from a microbial community – metaproteomics did not develop as quickly in the past,” Paul Wilmes says. “This is mainly because it can be more challenging than other research fields but now we have advanced tools and methods that have allowed the field to blossom in the last five years or so.”

Metaproteomics has thus become a powerful tool for studying functional interactions within microbial communities, as well as their interactions with for example the human host. The Systems Ecology group recently participated in a multi-laboratory comparison in metaproteomics, investigating the impact of method choice and workflow. In this study, several laboratories worldwide received two microbial samples – a simplified sample simulating the gut microbiome and a natural stool sample – and performed their own sample preparation, mass spectrometry and data analysis. Thanks to a critical evaluation of the different results obtained and as described in their article in Nature Communications, LCSB researcher Dr Benoît Kunath and colleagues were able to demonstrate the robustness of current metaproteomics research. They also provided data sets that can serve as benchmarks for future method development and will help with standardisation.

“‘To promote this innovative research, better connect scientists involved in metaproteomics worldwide and facilitate the exchange of new findings, we founded the International Metaproteomics Initiative,’” says Paul Wilmes. Since February 2021, this information hub, of which the LCSB is a founding member, has been recognised as an official initiative of the European Proteomics Association. In September, at the 4th International Metaproteomics Symposium, co-funded by the FNR and hosted in Luxembourg, Benoît Kunath was appointed administrator and Paul Wilmes scientific advisor. “For us as organisers, it was a great relief that the symposium could finally take place,” Paul Wilmes says happily. “Normandy we meet every two years. However, due to the pandemic, the metaproteomics community had to wait longer this time. But the wait was worth it: around 60 scientists met at Neumünster Abbey, while another 20 participated in the hybrid event online. Together, they listened to scientific lectures, discussed hot topics and, in the process, also generated ideas for new projects, which they hope will give metaproteomics yet another boost in the coming year. This is exactly the objective of the International Metaproteomics Initiative: disseminate information about advancements in the field through collaborative networking.”
TWO LCSB RESEARCHERS EXCELLENT THESIS AWARDS FOR
was still in its infancy and there was no midbrain-specific diseases. “When I started my PhD, the organoid technology excellent for the non-invasive study of neurodegenerative organoid. These stem cell-derived brain proxies are culture model of the human midbrain, termed midbrain During her PhD, Anna Monzel developed a novel 3D cell doctoral theses.

Dr Anna Monzel and Dr Susana Martinez, who obtained their milestone in the career of these young scientists. In 2021, every year, the University of Luxembourg presents several doctoral graduates with awards recognising the outstanding quality of their work. The “Excellent Thesis Awards” celebrate cutting-edge research and mark an important milestone in the career of these young scientists. In 2021, Dr Anna Monzel and Dr Susana Martinez, who obtained their PhDs at the LCSB, both received an award for their excellent doctoral theses. 

During her PhD, Anna Monzel developed a novel 3D cell culture model of the human midbrain, termed midbrain organoid. These stem cell-derived brain proxies are excellent for the non-invasive study of neurodegenerative diseases. “When I started my PhD, the organoid technology was still in its infancy and there was no midbrain-specific model,” explains Dr Monzel. “Now, the model I developed at the LCSB is being used to study the early steps of Parkinson’s disease pathogenesis.” 

Susana Martinez’s thesis focused on the dynamics of microbiomes, more specifically the different microorganisms found in biological wastewater treatment plants. She investigated the CRISPR-Cas system, the so-called “DNA scissors”, a mechanism playing a key role in promoting adaptation and diversity within microbiomes. “The breakdown of organic substances by microorganisms is an important part of wastewater treatment,” explains Dr Martinez. “The results obtained during my PhD improve our understanding of complex interactions within microbial communities and could help us to better control these processes in the future.”
The roots of Parkinson’s disease reside in the midbrain, a relatively small area located at the top of the brain stem. There is a consensus about this among scientists but it is still largely unknown what types of cells are involved in the idiopathic forms of the disease, where the causes cannot be attributed, for example, to inherited genetic defects. “Up to now, research has focused primarily on neurons that produce the neurotransmitter dopamine,” says Prof. Anne Grünewald, head of the Molecular and Functional Neurobiology group at the LCSB. When these cells die, the lack of dopamine in the brain ultimately triggers the disease. However, when it comes to the origin of neurodegeneration, researchers cannot yet paint the whole picture. “There are clues suggesting that glial cells have a role to play in the onset of Parkinson’s,” says Grünewald. “But the molecular mechanisms involved are only poorly understood.” The team led by the LCSB researcher has now succeeded for the first time in studying the role of diverse cell types in the early stages of Parkinson’s disease at the single-cell level. Glial cells come in many kinds and fill the areas between neurons in the brain, where they ensure, among other things, that the nerve cells are physically supported and supplied with nutrients. In order to distinguish the activities of different cell types and examine them separately from each other, the researchers used a method, called single nucleus RNA sequencing, that is still quite new. It can precisely analyse the processes in individual cells and determine, for example, which genes are currently being transcribed in a given cell. This is an impressive advantage over conventional experimental techniques, which can only ever examine many, often diverse, cells together. “Until now, there has been no way to clearly attribute molecular effects to specific cell types,” says Semra Smajic, a doctoral researcher in Anne Grünewald’s team. She compares this to the challenge of distinguishing the taste of a specific fruit from a blended smoothie. By analogy, single-nucleus RNA sequencing is equivalent to tasting each single raw fruit within the mix.

“In our work, we used for the first time single-nucleus RNA sequencing on post-mortem tissue from Parkinson’s patients,” Smajic reports. The researchers compared tissue samples from patients and people who did not have Parkinson’s. In the laboratory, they analysed more than 41,000 cells from these samples, creating a unique dataset focusing on the diverse components of the human midbrain. In the process, they came across several striking and previously unknown characteristics that appear to be linked to Parkinson’s disease. “First, we discovered an unusual cluster of nerve cells in the tissue samples from people with Parkinson’s,” Smajic reports. This cluster contained around 120 cells that could not be clearly classified. “We suspect it is made up of degenerated dopaminergic neurons,” says Anne Grünewald. Inflammation of the brain tissue could have played a role in the demise of these neurons – and this is where the glial cells come in. The LCSB team studied these components of the midbrain in detail as well. “There were clear differences between sick and healthy people,” Smajic explains. “Gliaal cells were found to be much more prevalent in the tissue samples affected by Parkinson’s disease and were also more strongly activated.” The researchers speculate that this could be evidence of a pro-inflammatory effect and would thus represent a new piece of the puzzle in understanding the causes of Parkinson’s disease.

The team recently published the results of their work in the scientific journal Brain. “All in all, our findings suggest that glial cells contribute to the destruction of dopamine-producing neurons and that their activation is a crucial mechanism leading to idiopathic forms of Parkinson’s disease,” Grünewald summarises. “They highlight that inflammation is an important aspect of the disease that needs to be explored in more detail.”
### External funding for research

**THE EXPERT TOUCH OF THE GRANT OFFICERS**

A considerable part of the research done in the 17 research groups of the LCSB is financed by third-party funding. To allow the researchers to focus primarily on the scientific details when submitting their applications, the research facilitators, or grants officers, Dr Linda Ebermann, Estelle Ferreira, Dr Teresa Martins and Dr Simone Witzmann take care of the formal aspects of the process.

100 applications were submitted by the LCSB in 2021 and, on average, one in three was approved. “Sometimes the success of an application even creates an unexpected dilemma for our researchers,” smiles Linda Ebermann, who coordinates the team of grants officers. When two approvals come in for one project, for example, the researchers have to decide which funding they want to accept.

Each staff member in the Grants Office supports three to five LCSB research groups and remains in contact with the researchers throughout the entire application process. The grants officers are not only familiar with the full spectrum of third-party funding. Each of them has acquired additional specialised skills in the course of their career: Teresa Martins is particularly familiar with the European Research Council, the European Commission’s prestigious research funding programme aimed at top individual researchers and particularly competitive. Estelle Ferreira works with diverse stakeholders inside and outside the LCSB to refine the centre’s ethics guidelines for research with biomedical data and keep them constantly up to date. Simone Witzmann supports the three female principal investigators at the LCSB, an initiative meant to help the team leaders and professors whose scientific career can be impacted by maternity. She is offering guidance both as a grants officer and a project officer for diverse national, European and international projects. Lastly, Linda Ebermann is heavily involved in issues of data management and data protection which are keys in many bioinformatics projects at the LCSB. Third-party funding is highly competitive and the skills of the LCSB grants officers are an essential asset for a research centre. They help finance outstanding research and valuable equipment, all for the benefit of science.

The majority of the LCSB’s third-party funding applications relate to national and European funding programmes from the Luxembourg National Research Fund (FNR) and the European Commission. In addition, there are international grant programmes such as those of the US National Institute of Health and funding programmes from private foundations such as the Michael J. Fox Foundation for Parkinson’s research.

### RESEARCH ON BRAIN ORGANOIDS – A RISING START-UP

Breaking new ground in drug development for treating Parkinson’s disease: this is the aim of the researchers at OrganoTherapeutics – a spin-off company that emerged from the LCSB in 2019. They are using an innovative approach based on organoids, 3D tissue models aiming to mimic human organs in miniature. They hope the use of brain organoids will facilitate drug discovery and the development of personalised neuroprotective treatments for individual Parkinson’s patients.

The start-up, founded by Dr Javier Jarazo and Prof. Jens Schwamborn, head of the Developmental and Cellular Biology group at the LCSB, received a boost in April 2021 with a special award at BioVaria. This annual event is a meeting place for life scientists, biotech companies and investors, where research institutes, universities and young companies can present their projects. OrganoTherapeutics received the BioVaria Startup Award in the category “Rising”. For the impressive presentation of their business model, the jury of experienced investors picked the Luxembourg-based company over six other European start-ups.
IDENTIFYING RISK FACTORS FOR PARKINSON’S DISEASE

The earlier Parkinson’s disease is diagnosed, the better are the chances of optimally treating its symptoms and avoiding complications, which allows patients to enjoy a better quality of life in the long term. In the framework of the National Centre of Excellence in Research on Parkinson’s Disease (NCER-PD), LCSB scientists and their partners work on improving the early detection of Parkinson’s. They focus on identifying genetic and environmental risk factors as well as pinpointing early signs of the disease.

In 2021, the team led by Prof. Rejko Krüger, head of the Translational Neuroscience group at the LCSB, established a so-called risk cohort. Over several years, they will observe this group of people, who are thought to have a higher risk of developing the disease. The cohort includes people with REM sleep behaviour disorder (RBD), a disease involving abnormal behaviour during a phase of the sleep cycle. People with this disorder talk or shout in their sleep, kicking and punching as they act out their dreams – sometimes so harshly that they harm themselves or their partner.

Poor sleep quality can be associated with various conditions and following patients diagnosed with RBD over time will help the researchers to better understand the emerging link with neurodegenerative diseases such as Parkinson’s.

To establish the risk cohort, NCER-PD launched a nationwide survey on sleep quality under the patronage of the Ministry of Health, inviting all Luxembourg residents aged between 55 and 75 years to participate. Among the thousands of participants, people most likely to suffer from RBD were invited for further tests. The ones for whom the diagnosis is eventually confirmed will be able to take part in the long-term RBD study if they wish to.

By coming to the clinic for yearly follow-ups and giving biological samples – such as blood, saliva, urine or cerebrospinal fluid – they will provide researchers with an insight into the causes of RBD and how it can evolve toward the early stage of Parkinson’s. Prof. Krüger and his team will give special attention to any links with the main hallmarks of Parkinson’s disease, such as the misfolding of a protein called alpha-synuclein that impairs the function of neurons. “We want to study in which patients and in combination with which risk factors misfolding of alpha-synuclein occurs,” Krüger explains. The researchers also want to identify early biomarkers: molecules whose occurrence can indicate the onset of Parkinson’s disease and could lead to much more accurate and earlier diagnoses in the future. “Not all Parkinson’s cases are the same,” says Prof. Krüger. “If we can recognise and distinguish them at an early stage thanks to new biomarkers, then much more specific and thus better care will be possible.”

Soon Luxembourg will also join a worldwide study including more than 50 research institutions that contribute data and biological samples to one of the most robust Parkinson’s databases and specimen banks worldwide. Participants from the RBD cohort will have the opportunity to join this extensive project and take part in more clinical assessments, including imaging. “We are systematically bringing together different perspectives on Parkinson’s disease,” Prof. Krüger says. “In this way, we hope to identify more risk factors and their influence – and make advancements in early diagnosis and treatment of Parkinson’s disease.”

“We are systematically bringing together different perspectives on Parkinson’s disease.”
International exchange programme

LUXEMBOURG-JAPAN: A CONTINUOUS COLLABORATION IN THE MIDST OF THE PANDEMIC

For many years, the LCSB and the Luxembourg Institute of Health have been collaborating intensively with RIKEN, a long-established Japanese research institute. Despite the COVID-19 pandemic, scientific discussions and knowledge exchanges never stopped: not one but two symposia were organised in 2021.

Research institutions in Luxembourg have been collaborating closely with RIKEN for more than a decade, backed by grants from the Luxembourg National Research Fund (FNR). Researchers regularly visit the partner institutions and RIKEN Outpost Labs have been created in Luxembourg, allowing Japanese scientists to work together with local colleagues on long-term projects.

Since the start, annual symposia have been an integral part of this fruitful collaboration. A Kick-Off Symposium was held in Yokohama in 2017 and its counterpart was organised at the University of Luxembourg the following year.

While the pandemic made it difficult to travel for scientific events, it didn’t prevent the Luxembourgish and Japanese researchers from sharing recent results and developing new projects, thanks to two well-attended scientific symposia hosted online in 2021. On 16 March, a first symposium focused on how artificial intelligence could improve healthcare in the future and on neuroinflammation. Besides the main lectures, several scientists presented novel ideas to push the boundaries in fields such as immunology, neurodegenerative diseases and microbiome research.

A second symposium followed in December, dedicated this time to open science. Entitled “How to boost research collaborations through open data exchange”, it featured success stories in insulin resistance and Parkinson’s disease research as well as other presentations on current research topics and opportunities for the future. The omnipresence of the pandemic was reflected in the latter session of the symposium, when participants discussed mathematical methods used for COVID-19 prognosis and risk assessment. Remarkably in addition to scientists from the RIKEN community, many of their colleagues from the School of Medicine of Chiba University also took part, highlighting the interest in these bilateral exchanges and the potential for further collaborations.

Science outreach

SCIENCE IN THE SPOTLIGHT - OF BLOOD SAMPLES AND PARASITES

Outreach activities are an integral part of a researcher’s life: they are key to building trust in science and are a good way to learn how to share knowledge with different audiences. At the LCSB, young scientists are encouraged to hone their communication skills early on. In 2021, three doctoral researchers took up the challenge by participating in – and sometimes winning – various science communication competitions.

Kathleen Mommaerts was runner-up in the Three Minutes Thesis competition (3MT) hosted by LuxDoc, an association of young researchers in Luxembourg. At 3MT, PhD students present their doctoral thesis, or parts of it, in a three-minute oral presentation. The difficult part is making it understandable for everyone and humour can be a good option: “I am not too worried about our bank being robbed. The only thing to steal is blood and urine,” laughs Kathleen.

In her presentation, she explains why research on biospecimens is so important. Biospecimens are biological samples such as human blood or urine that are typically stored at -80°C Celsius in institutes like the Integrated Biobank of Luxembourg (IBBL). At the IBBL, Kathleen is writing her doctoral thesis on the correct preparation and storage of biospecimens and is closely cooperating with the LCSB. She considers research about how to best take care of the samples to be just as important as the research being done with those samples: “Standardised procedures for sample preparation and storage must be in place to increase the chances of having a meaningful result.” Speaking in front of an audience is not the only way researchers can share their passion for science: writing skills can also prove useful. The demodex mite is a term that most people have never heard. For his text about this microscopic animal that lives closer to humans than most people would like, Daniele Proverbio won first place in the Science Writing competition organised by the Doctoral Education in Science Communication (DESCom) project of the University of Luxembourg. A jury of science communicators was impressed by his choice of topic, the writing style and the use of humour, which all made for an entertaining read. “I deliberately chose a topic that arouses curiosity in science and is fun to read about,” says Daniele Proverbio, PhD student in the Systems Control group at the LCSB. He believes trust between scientists and the general public is important: “It is why Daniele put his writing to good use during the pandemic by developing with other researchers a glossary of terms related to the virus giving definitions and short explanations to help readers better understand the specific terminology.

Semra Smajic also feels it is important to promote mutual understanding between researchers and the public. She took part in the Science Slam organised by LuxDoc, where she had ten minutes – on stage and live – to explain her research on brain organoids in an understandable way. “While I was preparing, I had my grandma in mind,” she smiles. If her grandmother understands what Semra is working on during her doctorate, surely many others will too. “I love it when I can present a topic in a lively way that gets the audience laughing,” she says. Even better if it can inspire others: after her presentation, she was approached by a student who was keen to learn. He is now set to do an internship with her at the LCSB.
Goodbye and thank you!

After exactly 12 years, the LCSB’s founding director, Prof. Rudi Balling, said goodbye to the research centre he established. His farewell was personal, cheerful and optimistic. Exactly how he had shaped the LCSB to be. First, a scientific talk concluded a two-month-long “goodbye” lecture series that brought together internationally renowned scientists who shared their perspectives on future scientific challenges. Then the LCSB staff and Rudi’s long-time colleagues and friends had prepared a little celebration: the uniJAM band played some songs especially prepared for the occasion and Rudi received farewell gifts to accompany him in his future journeys through the world of science. Finally, he handed the symbolic key of the LCSB over to his successor, Prof. Michael Heneka. For many, a moving moment. For the LCSB, the beginning of a new era.
Highlights of 2021

1. **Full professorship for Anne Grünewald**  
   In 2021, the principal investigator of the Molecular and Functional Neurobiology group was promoted to full professor at the University of Luxembourg. Prof. Grünewald joined the LCSB as an FNR ATTRACT fellow in 2016 and now leads a team of over 10 scientists studying Parkinson’s disease to decipher its origins and identify novel targets for therapeutic intervention. Congratulations!

2. **FNR KITS grant for the BioIncubator**  
   “Biohealth Incubator”, a joint initiative by the Luxembourg Institute of Health and the LCSB Innovation and Partnering Team, was initiated by the Luxembourg “Biohealth Incubator”, a joint BioIncubator.

3. **First real LCSB Team Retreat since 2019**  
   In September, LCSB members met in Gaalgebberg park in Esch-sur-Alzette for a treasure hunt in the surrounding nature, followed by some mingling and an early dinner provided by several food trucks. This was the first non-virtual LCSB team event since the start of the pandemic. It was great to see familiar faces again and to meet new LCSB members as well!

4. **Science Festival 2021 – Outreach activities back on track!**  
   As the 2021 edition of the Science Festival went ahead despite the pandemic, the LCSB participated once again in this big outreach event organised by the FNR and the National Museum of Natural History. A group of volunteers from different LCSB teams took turns to bring to life a booth about genetics. Between classes visiting on Thursday and Friday and the general public at the weekend, hundreds of visitors discovered how to decode the information stored in our cells and extracted some DNA with the help of LCSB members!

5. **Launch of BY-COVID: A new project for pandemic preparedness**  
   BYOND-COVID (BY-COVID), a new €12 million Horizon Europe funded project, was launched in 2021. It will tackle the data challenges that can hinder effective pandemic response. The core aim of the project is to ensure that data on SARS-CoV-2 and other infectious diseases can be found and used by everyone. ELIXIR Luxembourg and the Bioinformatics Core of the LCSB participate in this ambitious European project: they will co-lead one of the use-cases focusing on the interpretation of viral variants and molecular biology data for a better understanding of the mechanisms behind variant responses.

6. **ParkinsonNet celebrates 5 years**  
   ParkinsonNet Luxembourg promotes patient-centred care by training healthcare providers to identify and address the specific Parkinson’s related needs of each patient and by facilitating communication between the different healthcare disciplines around a patient’s individualised treatment. Established 5 years ago, this national network, modelled after a similar Dutch programme, is supported by a range of partners from the private and public sectors, and facilitated by the Bioinformatics Core of the LCSB. It was a successful year for ParkinsonNet Luxembourg, hosting several virtual meetings and workshops and collaborating with the Bioinformatics Core of the LCSB to develop innovative solutions for Parkinson’s disease.

   Every year, the Rotary Clubs of Luxembourg raise money to support research on brain diseases by organising exceptional screenings in cinemas in Luxembourg. In 2021, the 9th year of “Espoir-en-Tête”, its organisers were able to collect important donations despite the cancellation of the traditional screening due to the pandemic. This 9th edition raised 88,000 euros that will support two projects involving LCSB researchers. The first project focuses on the development of a new treatment targeting the microbiome in Parkinson’s disease. It is led by Prof. Paul Wilmes, head of the Systems Ecology group at the LCSB. The second project aims at deciphering cellular signatures associated with memory decline in Alzheimer’s disease and identifying the alterations that lead to cognitive symptoms. It is led by the Neuropathology group.

8. **Prof. Heneka at the Rentrée Académique**  
   On 7 October, the University of Luxembourg started the new academic year 2021-2022 with its “Rentrée Académique”, an event combining speeches and presentations of awards for outstanding teaching and student initiatives. In his keynote speech, Prof. Michael Heneka, new director of the LCSB, addressed the topic of the delayed impact of COVID-19 on the brain. He highlighted the impact of COVID-19 on memory functions and brain morphology. He also encouraged the promotion of support centres devoted to neurocognitive studies and the search for new therapies for people affected by Long COVID.
Facts and figures

2021 LCSB income (in kEUR)
- University of Luxembourg: 564 (1.9%)
- Luxembourg National Research Fund (FNR): 963 (3.1%)
- Corporate: 896 (2.6%)
- 1,757 (6.1%)
- 7,039 (24.4%)
- 17,867 (62.8%)

2021 LCSB expenses (in kEUR)
- Wages: 599 (2%)
- Operating expenses**: 753 (3%)
- Investments: 1,161 (25%)
- Representation and registration: 580 (1.9%)
- Sub-contracting: 62 (0.2%)
- Travel: 19,574 (68%)

Cause
- Parkinson’s research: 17,847 (61.8%)
- Operating expenses**: 7,039 (24.4%)
- Investments: 1,757 (6.1%)
- Representation and registration: 696 (2.4%)
- Sub-contracting: 544 (1.9%)
- Travel: 19,574 (68%)

Donors
- Private: 64%
- Foundations: 15%
- Corporate: 18%
- Associations: 33%

National grants in 2021
- AstAging: FNR CORE - Silvia Bolognani
- BIOFLCS: FNR CORE - Carole Linster
- CSB-library: FNR CORE Junior - Melanie Grudzdaet
- FIN1-ChiP@s: FNR CORE Junior - Giuseppe Arena
- careCDG: AFR PHD - Leonardo Mastrelli
- CevIR: INTER MOBILITY - Silvia Bolognani
- CUSMPD: JUMP PHC - Reijo Kröger, Ibrahim Bousbaa
- iWibiFOE-JA52: JUMP PHC - Emmanuel Ghiaia, Daniel Abankwa (FSTM)
- CRONAVAR COVID-19: Paul Wilmes, Patrick May, Leslie Gospodar (LIST)
- EIRCSacov COVID-19: Alexander Slupien
- BioHealthHub: KITS - Clemens Dostrowski, Jérémie Langlet (LIH)
- CATALYST-LU: KITS - Reijo Kröger, Pranjul Shah
- BeC5: RSP Flagship - Elisabeth John
- Science Festival 2021: Science in Society, Sabine Schmitz
- IRBMON: IAS Young Academics - Maryem Abab Abdalaziz, Andreas Hasch
- AQNA: IAS Young Academics - Alexander Slupien, Minela Pulina (FSTM), Alexandre Tsitcherkenko (FSTM)
- SUMO: IAS Young Academics - Jochen Schneider, Nina Buntic (FSHE), André Schütz (FSHE)

European grants in 2021
- EPND: IMI-JU - Venkata Satagopam, Adrian Thorogood, Reijo Kröger
- SyMPabiome Widening Fellowships - Charlotte De Rudder, Paul Wilmes
- ZeroPM Horizon 2020 European Green Deal - Emma Schymanski, Hans Peter Arp, Stiftelsen Norges Geotekniske Institutt, Norway
- BY-COVID Horizon Europe Research Infrastructures - Reinhart Schneider, Nikolai Blumberg, ELINR-Hub
- CorEUScem CDIST (FNR INTER) - Jens Schwemmer, Laura Batlle Meiner, Center for Genomic Regulation, Spain
- TeaTime CDIST (FNR INTER) - Djöj Coozer, Voothe Vokar, Helsinki Institute of Life Science, Finland
- BMFL-19 DFG Research Unit (FNR INTER) - Andreas Hasch, Florian Bernard, University of Bonn, Germany
- MechEpi-2 DFG Research Unit (FNR INTER) - Alexander Slupien, Patrick May, Roland Krause
- MERIDiex Télervé - Paul Wilmes, Elisabeth Letellier (FSTM)

International grants in 2021
- PARKdiet: Michael J Fox Foundation - Paul Wilmes, Brit Möhlenbrucher, Paracelsus Elena-Klinik Kassel, Germany
- MitoDNAdel-PD: Michael J Fox Foundation - Anne Grünewald, Julia Fritzgerald, Hertie Institute for Clinical Brain Research, University of Tübingen, Germany
- HehBA - Healthy Brain Ageing: Michael J Fox Foundation - Reijo Kröger, Venkata Satagopam, Brit Möhlenbrucher, Paracelsus Elena-Klinik Kassel, Germany

* These figures do not reflect a credit amount of 285 kEUR related to bookings
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Key performance indicators

**Personnel**
- Research groups: 17
- PEARL (active): 2
- ATTRACT (active): 2
- ERC (active): 1
- Total staff: 273
- Externally funded staff: 122
- PhD students: 64
- Nationalities: 52

**External competitive funding**
- Total: 309.9 M EUR

**Fundraising**
- Total: 6 M EUR

**Collaborations**
- Collaborative projects active in 2021: 574
- Industrial partners in active projects: 56

**Publications**
- Total publications: 168
- Publications IF=3.0: 35
- Publications in 25% best of field: 65%
- Open Access (OA) Publications: 82%
- Publications in OA journals: 52%
- Cumulative number of publications: 1,234
- Patents: 34
- Proof of concept: 9 (total 3.8 M EUR)
- Spin-offs active: 6

**Innovation**

**Publications**

**Scientific central services**
- Animal facilities Aquatics and Rodents
- Bioinformatics services & ELIXIR-LU
- Disease modelling & screening platform
- Imaging
- Metabolomics
- Sequencing

**Research Strategy**

**Research groups**
- Bioinformatics Core (R. Schneider)
- Biomedical Data Science (E. Glaab)
- Computational Biology (A. Vogler)
- Developmental & Cellular Biology (J. Schwamborn)
- Digital Medicine (J. Goncalves)
- Systems Ecology (P. Wilmes)
- Environmental Cheminformatics (E. Glaab)
- Enzymology & Metabolism (C. Linster)
- Gene Expression & Metabolism (E. Williams)
- Immunology & Genetics (G. Bronner)**
- Integrative Cell Signalling (A. Skupin)
- Interventional Neuroscience (F. Hertel***)
- Medical Translational Research (J. Schneider)
- Molecular and Functional Neurobiology (A. Grünewald)
- Neurounmology (M. Heneka)
- Neuropathology (M. Mittelbronn****)
- Translational Neuroscience (R. Krüger*)

**Operations**

**Infrastructure**

**Computational Biology**

**Medical Translational Research**

**Digital Medicine**

**Enzymology & Metabolism**

**Integrative Cell Signalling**

**Interventional Neuroscience**

**Molecular and Functional Neurobiology**

**Neurounmology**

**Neuropathology**

**Translational Neuroscience**

**Systems Control**

**Bioinformatics Core**

**Bioinformatics services & ELIXIR-LU**

**ScienCeinsLab**

**Animal facilities Aquatics and Rodents**

**Bioinformatics services & ELIXIR-LU**

**Disease modelling & screening platform**

**Research Strategy**

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**Scientific central services**
- Animal facilities Aquatics and Rodents
- Bioinformatics services & ELIXIR-LU
- Disease modelling & screening platform
- Imaging
- Metabolomics
- Sequencing

**Awards 2021**

<table>
<thead>
<tr>
<th>Award</th>
<th>Name</th>
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<tbody>
<tr>
<td>Excellent Thesis Award - University of Luxembourg</td>
<td>Anna Sophia Monzel</td>
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<tr>
<td>Excellent Thesis Award - University of Luxembourg</td>
<td>Susana Martinez Arias</td>
</tr>
<tr>
<td>COVID-19 Lung CT Lesion Segmentation Challenge - 5th place</td>
<td>Jan Stöller, Danièle Proverbio, Mehri Baraniadi, Mathias Nicolas Boose, Vanja Vison, Beatriz Garcia Santa Cruz, Andreas Roisch</td>
</tr>
<tr>
<td>BioVaria Startup Award</td>
<td>OrganTHERAPY (spin-off of the LCSB)</td>
</tr>
<tr>
<td>Science Writing Competition - University of Luxembourg - 1st place</td>
<td>Danièle Proverbio</td>
</tr>
<tr>
<td>Three Minute Thesis competition - 2nd place</td>
<td>Kathleen Mommerts (IBBL - Visiting researcher at the LCSB)</td>
</tr>
<tr>
<td>Uberflieger 2 - Winner in Luxembourg</td>
<td>BRAINS - Elisa Zuccoli (LCSB), José Ignacio Delgado Centens (SnT), Daniela Vega Gutierrez, Aiden Chung Castro and Lisa Maria Amaya Mejia (Master students)</td>
</tr>
</tbody>
</table>

° cumulative (2009-2021)
* based on WoS

*° cumulative (2009-2021)
57. Maria Pena-Chilet, Joaquin Ostaszewski, Falco, Carlos Loucera, Devrim Gunyel
152. In Genetics, 11 - 612343, 10.3389/fimmu.2020.594350
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154. Anne-Marie Hanft, Claire Pauly, Laure Pauly, Valerie E. Schröder, Maxime Hansen,
Guillerme Ramos Meyers, Anne Kaysen, Leila Hafsan, Feneka Wauters, Rejko Krüger,
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Frontiers In Neurology, 11 - 635772, 10.3389/fneur.2020.635772
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156. David G Ashbrook, Danny Anands, Pjotr Prins, Megan K Mulligan, Suheeta Roy, Evan G
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McCarty, Arthur G Centeno, Reinmar Hager, Casey J Bohl, Jesse F Ingels, Melinda S
“A Platform for Experimental Precision Medicine: The Extended BXD Mouse Family,”
157. Henry Kurniawan, Teresa G Martins, Maria Lorena Cordero-Maldonado, Teresa G Martins,
Maha M. Moein, Jean-François Coutrotte, Rejko Krüger, David G Ashbrook, Danny Arends, Pjotr
Prins, Megan K Mulligan, Suheeta Roy, Evan G Williams, Cathleen M Lutz, Alice Valenzuela,
“A Platform for Experimental Precision Medicine: The Extended BXD Mouse Family,”
158. Patrick Cahan, Davide Cacchiarelli, Sara-Jana Dunn, Martin Hemmings, Susana M Chua
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1. Tim Van Den Bossche, Mayoun O Artzuen, Dorte Bocher, Dirk Bienroder, Vincent G H
Eijpker, Celine Henri, Pratik D Jagtap, Nico Jahmich, Catherine Justa, Beneo J Kunath,
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a coordinated approach for propelling the functional characterization of microorganisms.”
Microbiome, 9 - (1) - 263, 10.1186/s40168-021-01176-w

* status in February 2022
** in bold, employees and former employees of the LCSB

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