LCSB

RESEARCH REPORT 2022

Luxembourg Centre for Systems Biomedicine

UNIVERSITÉ DU LUXEMBOURG

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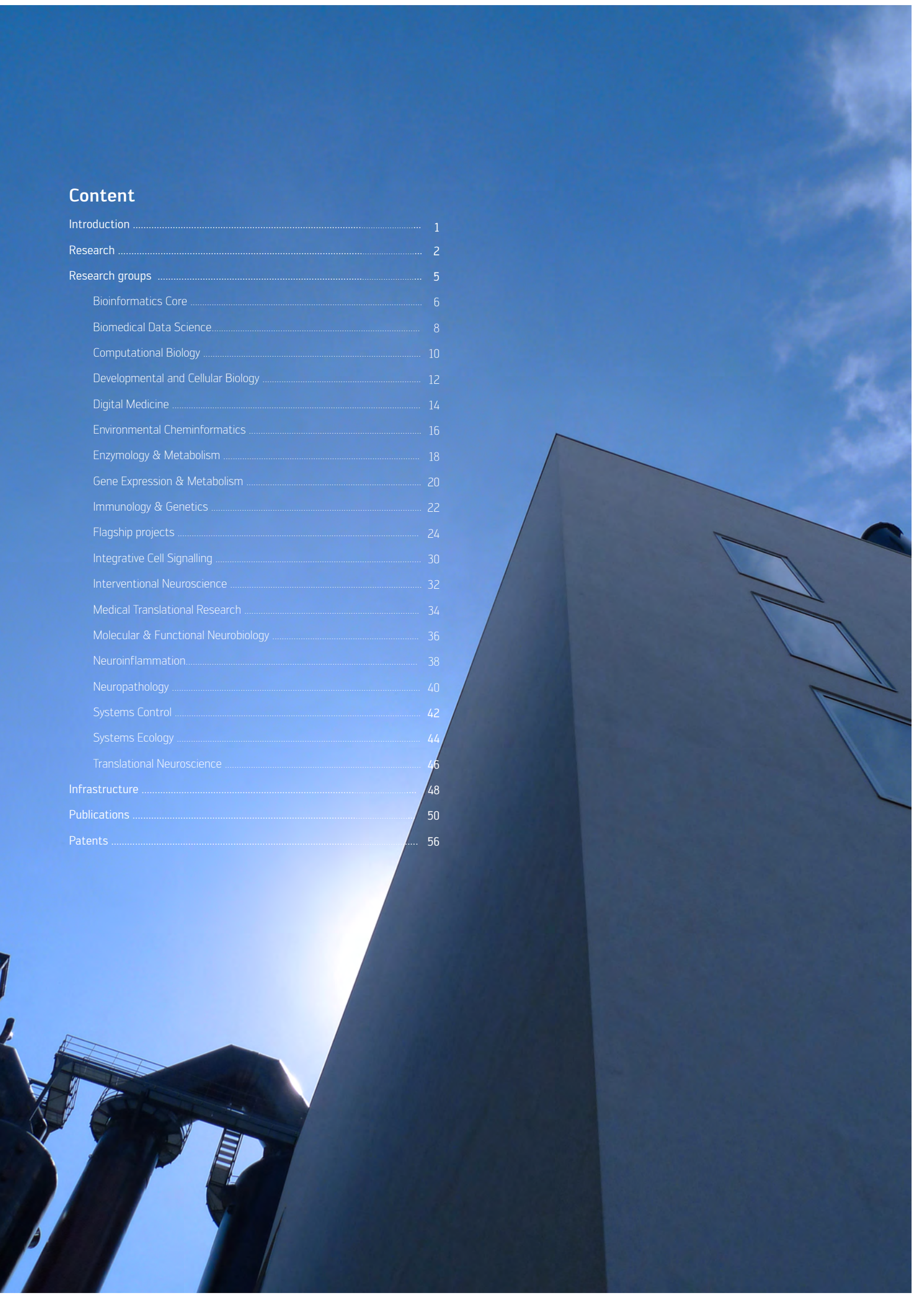


INTRODUCTION

The Luxembourg Centre for Systems Biomedicine (LCSB) is an interdisciplinary centre of the University of Luxembourg founded in 2009. It combines experimental and computational approaches to analyse complex biological systems and disease processes.

The LCSB investigates Alzheimer's, Parkinson's and other neurodegenerative disorders while also aiming to understand shared mechanisms. Its strategy is based on an interdisciplinary integrated systems approach, with core competences in the area of neurosciences, functional genomics and genetics, metabolomics, imaging, bioinformatics, computational biology and modelling, thus combining experimental molecular and cellular neurobiology, neurosciences and computational approaches. Through the establishment of research groups led by clinical scientists, the LCSB also bridges to the clinic. In addition to patients and family studies, technological platforms and models on different scales, covering *in silico*, *in vitro* and *in vivo* models, are the essential elements of the LCSB research strategy. Performing systems biomedicine on this multi-scale level is key to gaining insights into human biology and disease.

The integration of the LCSB in both the Luxembourg research landscape and the international systems biomedicine community is a driving force of the centre. The LCSB is forming strategic partnerships with internationally outstanding research institutions in order to create a powerful research network.

LCSB is also building bridges between basic research and industry. Collaborations have been initiated with various players, from small and medium enterprises to large global companies. The goal of these collaborations is to drive an output and product-oriented research in a win-win situation.

RESEARCH

Objectives

The LCSB sees itself as a basic research centre bridging discovery and clinical application. As such, the major focus is on the analysis of complex biological systems and disease processes. With the focus on systems biomedicine, the research strategy is based on the integration of four major elements: patients, experiments, computation, and technology. Major biomedical questions drive the LCSB's current and future research agenda. This strategy requires a highly interdisciplinary research environment, with a strong collaboration amongst computer scientists, engineers, mathematicians, physicists, biologists and clinical scientists. The LCSB applies these principles to the study of neurodegenerative diseases, in particular Alzheimer's and Parkinson's disease. It is the LCSB's guiding conviction that the major future challenges of the society will be based at the interface of disciplines and that their solutions will require major skills in analysing complex systems.

Vision

- Understand the mechanisms of complex biological systems and disease processes.
- Enable new ways to cure or prevent neurodegenerative diseases.

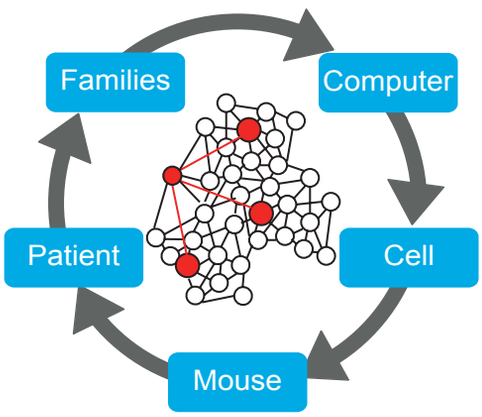
Mission

- Carry out fundamental research in the field of systems biology, biomedicine, and neurodegeneration, including the development of new models and technologies.
- Analyse the mechanisms of disease pathogenesis, with a special focus on Alzheimer's, Parkinson's and other neurological diseases.
- Identify and validate new targets for disease prevention and intervention.
- Explore opportunities for knowledge transfer from basic research into industrial applications.
- Contribute to science and society in Luxembourg.

The LCSB is collaborating with worldwide leading institutions, as well as regional and national partners. The integration of multiple disciplines and different ways of thinking is only possible in an interdisciplinary centre such as the LCSB. We have developed a culture of collaborative research and our philosophy is one of „curiosity-driven research". Leading themes are the transfer from basic research towards actual applications for patients, the building of additional bridges across disciplines to connect with other national partners, as well as the industry by creating spin-offs and valorising research results.

Research strategy

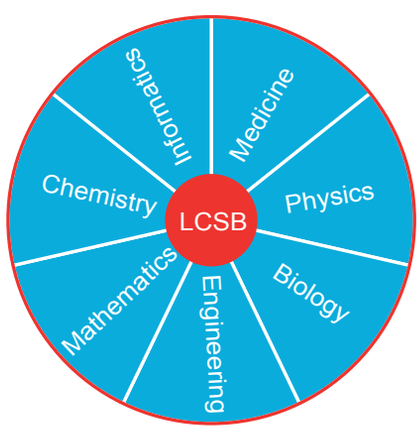
Diseases can be perceived as perturbations of networks, where genetic defects and environmental influences lead to a disturbance that cannot be compensated. Mathematical models are therefore used to describe a network on the molecular level that reflects the observations on a cellular or organism level. To gather data for a computational hypothesis generation and for the subsequent validation, the LCSB engages in a variety of different models and reaches out to the patient. We interpret "multi-scale modelling", a concept from physics and engineering in biomedicine: from computer to cells to animals to individuals to families and back. Based on different model systems, we produce feedback loops of hypothesis generation and validation, thereby jumping scales from *in vitro* models to full *in vivo* organisms like zebrafish or mouse, up to the human being and family studies of inherited diseases. For complex diseases, a multi-scale approach can give new insights and allows a transfer between different disease models, thus requiring a systems approach to unravel the underlying mechanisms. This research theme is a guidance allowing our research groups to unite in one common research goal.



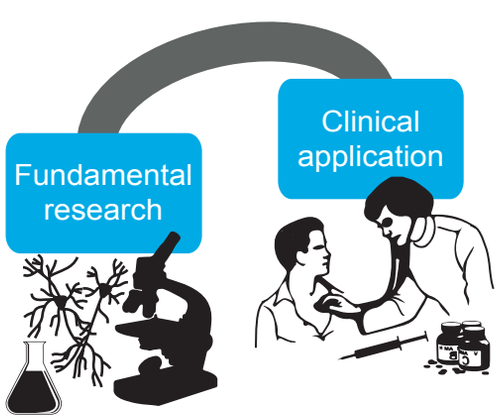
Powerful IT infrastructure
Currently, we are witnessing an explosion in the amount of data derived from biological experiments and clinical research. Furthermore, it will be very difficult for individual institutes to maintain the fast and expensive cycles of sustaining top infrastructure necessary for genomic, proteomic or bioinformatics analysis of biological data. Hence, there is a need for computational platforms provided to the scientific community by dedicated research centres. The LCSB is hosting the Luxembourg ELIXIR Node for Translational Medicine data. The goal of the LCSB is to offer bioinformatics, medical informatics and computational expertise to other research stakeholders in Luxembourg and beyond.

Mathematical and computational models to understand human diseases
Biology is becoming an extremely data-rich research discipline. In order to make sense of these vast amounts of data, the development of suitable algorithms and mathematical models is becoming more and more critical and an essential component of future research efforts. To this end, the LCSB directs major efforts towards the development of computational models, such as models of the human microbiome or models of stem cell differentiation.

State-of-the-art infrastructure
The LCSB invests in technologies that are of strategic importance for its research and that give it a competitive edge. Infrastructure and services can be used by external partners on a fee-for-service basis.



Interdisciplinarity
Research at the LCSB relies heavily on the integration of different technologies, models, disciplines, and expertise spanning from mathematical theory to medical needs in the clinic. We strive to be an interdisciplinary centre where the whole is more than the sum of the parts – we do not only pursue research in different areas but tackle questions that can only be answered in a collaborative approach involving different disciplines. Establishing a broad interdisciplinary spectrum of expertise is an explicit goal of the LCSB, and is reflected by the various professional backgrounds of the different Principal Investigators (PIs) as well as the composition of their research groups.



Bridging basic and clinical research
The integration of medicine into systems approaches is important for both parties: on one hand, medical observations in daily care can give valuable new directions to research; on the other hand, a close interaction between basic and clinical research helps to feed research results back into the clinic. The LCSB supports the training of clinical scientists and provides opportunities for medical doctors to combine research activities with patient care.

Research focus

All research programmes at the LCSB focus on biomedical questions. The application of advanced research tools, such as mathematical and computational modelling, metabolomics and imaging, as well as the development of new methodologies, aim at new findings in biomedicine while at the same time also aim at further development of the technologies and methods applied. While each research group pursues also its own research lines, all groups of the centre contribute to the central research theme: neurodegenerative diseases.

Although genetic as well as environmental factors are known to contribute to the pathogenesis of neurodegenerative diseases, a thorough understanding of the underlying disease-causing mechanisms is still missing. To elucidate mechanisms that play a role in disease origin and progression, a systems approach is needed. Therefore, the LCSB aims to look at the pathophysiological hallmarks of neurodegenerative diseases, such as mitochondrial dysfunction and neuroinflammation, from a system's point of view. Besides the genetic factors underlying diseases, the LCSB is also interested in understanding the influence of gene-environment interaction. Here, a primary focus is put on understanding the role of the gut microbiome as well as on the role of the exposome.

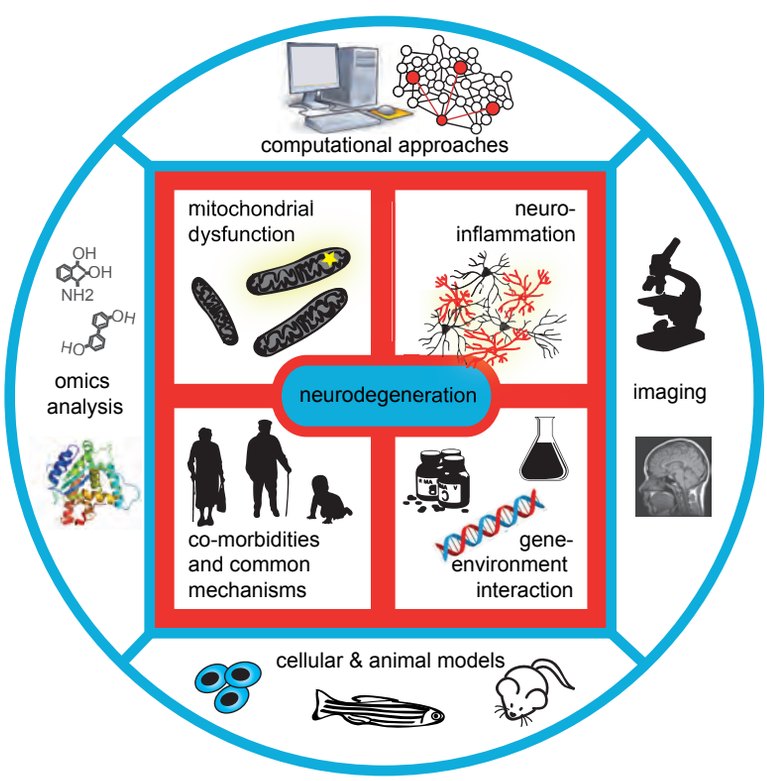


Figure: Research programmes at LCSB.

RESEARCH GROUPS

Being an interdisciplinary centre, the LCSB was founded as an entity separate from the faculties. The establishment of an autonomous structure allows a more flexible operation than is normally possible in the traditional setup of a university faculty. From a governance point of view, the LCSB chose research groups as primary unit of organisation. The groups are accompanied by research support and management structures that help them to be competitive in the international research community. Each group is led by a Principal Investigator (PI). The LCSB currently has 18 research groups, covering three areas: computational, experimental, and clinically-oriented translational groups. Even though listed distinctly below, many of the groups reach across over several disciplines, being not solely experimental or computational.

Computational focus

- **Bioinformatics Core**
- **Biomedical Data Science**
- **Computational Biology**
- **Environmental Cheminformatics**
- **Systems Control**

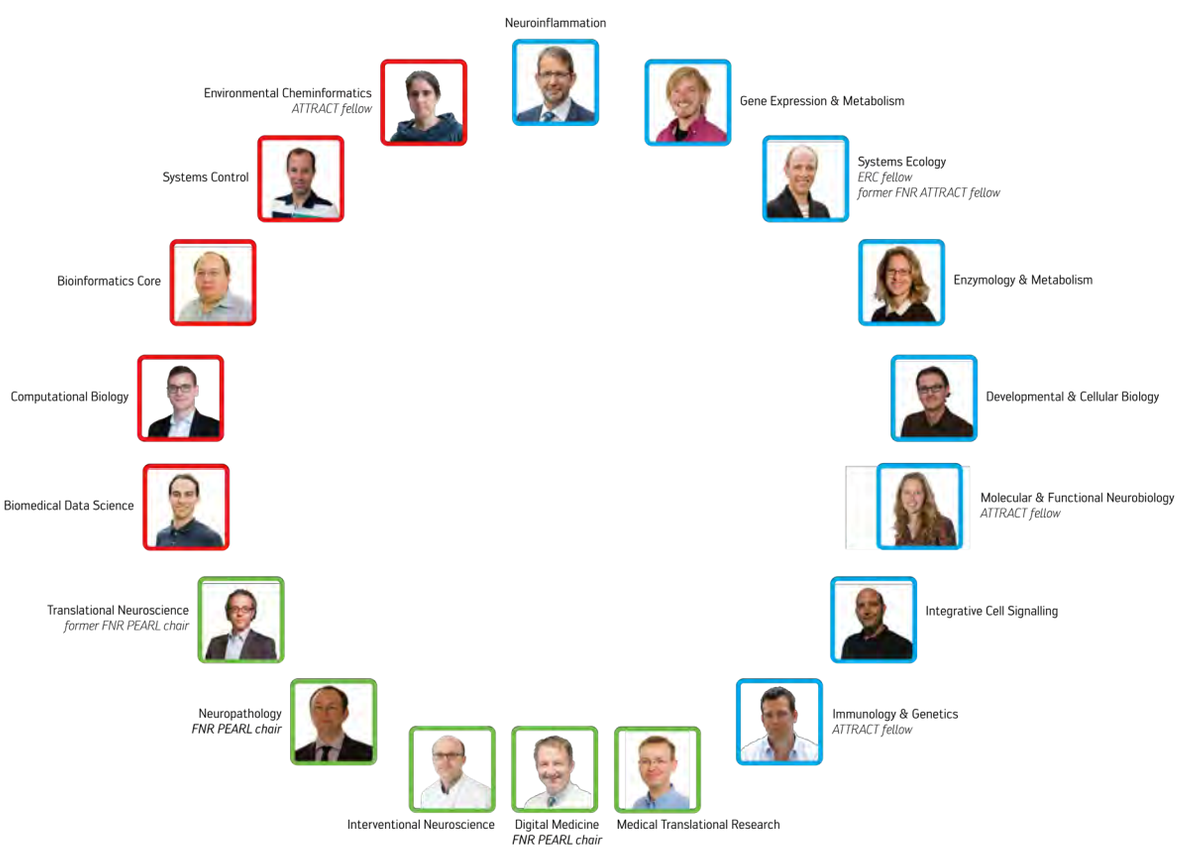
Experimental focus

- **Developmental & Cellular Biology**
- **Enzymology & Metabolism**
- **Gene Expression & Metabolism**
- **Immunology & Genetics**
- **Integrative Cell Signalling**
- **Molecular & Functional Neurobiology**
- **Neuroinflammation**
- **Systems Ecology**

Translational focus

- **Digital Medicine**
- **Interventional Neuroscience**
- **Neuropathology**
- **Medical Translational Research**
- **Translational Neuroscience**

Overlapping projects, joint personnel, and regular discussions amongst PIs ensure a close cooperation between the different groups and build bridges from artificial intelligence over experimental biology to clinical studies.



Bioinformatics Core group

Overview

Bioinformatics Core has a central role in the LCSB, as it enables the researchers to efficiently manage, analyse and interpret their data. The group ensures efficient data flow within and between experimental, theoretical-computational and medical oriented groups. The focus is on the development and deployment of (clinical) data management and storage systems as well as cost- and time-efficient automated data analysis pipelines in close collaboration with computer scientists and biologists covering a broad spectrum of disciplines. To this end, the research revolves around better accessibility and interpretation of the ever increasing data. The group develops algorithms for data mining and visualisation and works on methodologies to make data FAIR: Findable, Accessible, Interoperable and Reusable. Due to its developments around data operations and knowledge generation, the group serves as an integrator in LCSB, reflected by its key role in LCSB's cross-sectional projects like NCER-PD and the Parkinson's Disease map and its function as Luxembourg's ELIXIR node. The group also provides services for the other biomedical research stakeholders in Luxembourg and serves as an international data hub.

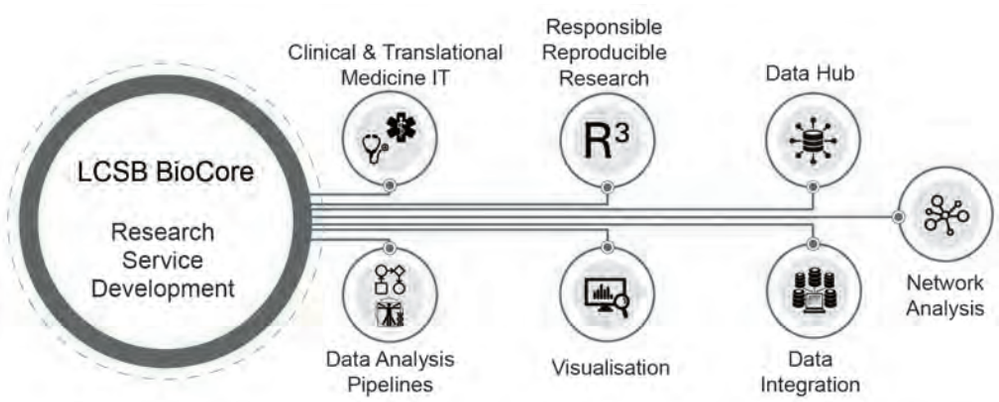


Figure: Main objectives of the Bioinformatics Core unit.

Key projects

ELIXIR Luxembourg Node: ELIXIR-LU
ELIXIR, the European infrastructure for life science information, aims to provide long-term access to bioinformatics tools and biological data. ELIXIR-LU (see Flagship projects) aims to "give life" to data for translational medicine, the combination of the clinical and experimental environment. This means optimising value gained from such data by improving usability and sustainability. On a national level, support in standardising and electronic capture of clinical data is provided together with hosting and analysis pipelines. Internationally, the group hosts translational medicine data and gives support for the curation and standardisation of datasets to improve the reusability and value of the data for the research community. ELIXIR is a pan-European initiative on governmental level that links the countries in their aim of long-term sustainability of bioinformatics resources. ELIXIR-LU is endorsed by the Ministry of Higher Education and Research in Luxembourg.

Making life science data FAIR: FAIRplus, ELIXIR-CONVERGE
Wide sharing of knowledge and data drives the progression of science and FAIRification, and reuse of existing data creates the opportunity to build large aggregated cohorts needed to detect rare signals and manage the many confounding factors in translational research. IMI FAIRplus seeks to develop the guidelines, tools and metrics needed to make data FAIR, aiming to deliver a catalogue of high quality FAIRified IMI datasets. FAIRplus comprises a coalition of Europe's leading experts in data interoperability, standards, preclinical to clinical translation and long-term sustainable data repositories, with decades of experience in making data available to a wide scientific community for reuse. ELIXIR-CONVERGE (H2020) connects ELIXIR Nodes to deliver, across Europe, distributed local support for FAIR data management and to realise a European data federation.

Clinical and translational data integration across diseases and disciplines: SYSCID, BIOMAP, Smart4Health, ImmUniverse, imSAVAR, MIRIADE, COVIRNA, EPND
The Bioinformatics Core provides clinical and translational data management and analysis for many international consortia. These EU- and FNR-funded projects cover clinical/phenotype, imaging, mobile/sensor, genomic, epigenomic,

and metagenomics data as well as a multitude of physiological factors combined with *in vivo* and *in vitro* data from model systems. The group takes care of data capture using tools such as REDCap, its standardisation, integration across species, platforms and data types for analysis as well as the visualisation in disease maps and Ada. The work includes building semantic data models and the use of machine learning and data mining approaches to gain maximum knowledge from data.

Principal Investigator
Reinhard Schneider
Start: April 2011

Construction, exploration, and analysis of Disease Maps
Disease Maps are computational and visual knowledge repositories constructed to catalogue, standardise, and model disease-related mechanisms. The Bioinformatics Core provides expertise in systems biology curation, assisted by text mining and network analysis, to build maps of different pathologies. These maps are then visualised online using our state-of-the-art web-service: the MINERVA Platform. MINERVA allows exploration of Disease Maps to the level of a protein structure, mapping experimental data, and their interpretation in the context of drug target databases. Disease Maps are seamlessly integrated into various analytical and modelling workflows using a range of converters and API endpoints. This extensive ecosystem is illustrated on the example of the recent COVID-19 Disease Map, which engages a range of tools, methods and services provided by the Bioinformatics Core.

Genomic Analysis: NCER-PD, MJFF LRRK2, Epi25K, MechEPI, TreatION, ProtectMove, ILAE Genomics, Solve-RD, MICROH-DTU, MetaPUF
Genome Analysis uses large-scale genetic data in combination with whole exome and genome sequencing to detect risk variants for rare and complex diseases and develops new methods for multi-omics microbiome studies. The studies focus mainly on neurological diseases like Parkinson's disease, epilepsy, or Alzheimer's disease. Using state-of-the-art genomic and genetic analysis pipelines, the team identifies disease-associated genetic variants that are validated by the experimental groups applying animal and cell models in projects funded through the Luxembourg National Research Fund (FNR) and the Michael J. Fox Foundation (MJFF).

Responsible and Reproducible Research (R3)
The R3 initiative aims to raise research quality and the overall reproducibility of scientific results. This ambitious goal is achieved through state-of-the-art infrastructure, GDPR compliant data processes, and high-quality research software. The classical publication workflow is standardised by structuring data, capturing lab protocols in electronic lab notebooks, source code versioning, workflow management, and freezing of project states via virtualization technologies. The R3 programme covers a broad spectrum of research needs, from the implementation of best research practice (Pathfinder), to specialized training (School), to boosting projects with strong R3 components (Accelerator). The R3 team also interacts with other institutes/domains in Luxembourg to advise on implementing R3 concepts.

Data protection compliance in data sharing: B1MG, HealthyCloud, PerMedCoE, EPND
The sharing of biosamples and personal data concerning health from patients and research subjects often faces significant ethical and legal (ELSI) barriers as it must respect the strict data protection and ethical principles governing health research. In order to enable joint research activities and the reuse of cohort data within EU-funded projects, our group assesses compliance requirements focusing on the analysis of laws, case law, interpretative guidance, research ethics policies with European-wide applications, and literature review and develops frameworks for GDPR compliance.

Key publications

1. Becker, R., et al. (2019) DAISY: A Data Information System for accountability under the General Data Protection Regulation. GigaScience, 8(12); doi: 10.1093/gigascience/giz140
2. Gu, W., et al. (2019) Data and knowledge management in translational research: implementation of the eTRIKS platform for the IMI OncoTrack consortium BMC Bioinformatics, 20(1), 164
3. Gawron, P., et al. (2016) MINERVA- a platform for visualization and curation of molecular interaction networks. npj Systems Biology and Applications 2, 16020; doi:10.1038/npjsba.2016.20
4. May, P. et al. (2018) Rare coding variants in genes encoding GABAA receptors in genetic generalised epilepsies: an xome-based case-control study. Lancet Neurol, 17(8):699-708
5. Satagopam, V., et al. (2016) Integration and Visualization of Translational Medicine Data for Better Understanding of .Human Diseases. Big Data, 4(2):97-108; doi: 10.1089/big.2015.0057

Biomedical Data Science group

Overview

The Biomedical Data Science group works on the development and application of software tools to identify diagnostic biomarker signatures, investigate pathway and network activity alterations in omics data for drug target prioritisation, and screen drug-like molecules for selected targets. Our applications focus on the analysis of biomedical omics, digital biomarkers, imaging and clinical data for neurodegenerative disorders, primarily for Parkinson's (PD) and Alzheimer's (AD) disease. We develop integrative machine learning methods for the joint analysis of multiple data modalities from patient and control subjects, by exploiting prior structured knowledge, e.g. from cellular pathways or brain atlases. Joint analyses of these information sources have the potential to provide models with increased robustness for diagnostic and prognostic. To obtain more specific models of disease mechanisms, we also investigate disease-related gender differences and apply cross-species analyses. Putative biomarker signatures and molecular drug targets derived from our analyses are then further characterized and evaluated together with experimental groups at the LCSB and external partners.

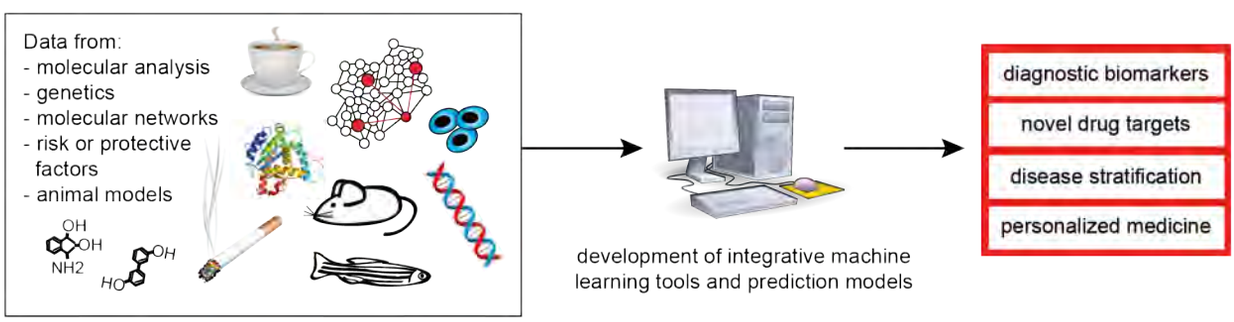


Figure: Overview of the different data sources used for integrative analyses.

Key projects

Gender differences in neurodegenerative diseases (GenderND project)

In both PD and AD, gender differences have been observed in the incidence and phenotypic manifestations of the disorder. Although these differences may result from diverse behaviours and lifestyles, previous studies suggest that the underlying causes are more complex and disease-specific, and involve hormonal and genetic influences. In the GenderND project, we investigate whether specific molecular and genetic factors contribute to the observed gender differences in neurodegenerative disorders. The analyses are supported by a grant from the Fondation Wivine Luxembourg.

For AD, we are using animal models and single-cell RNA-seq analyses to identify disease-associated molecular gender differences in tissue samples from the brain regions most susceptible to AD. Using statistical analyses and bioinformatics approaches for cellular process and gene regulatory network analysis, we determine cell-type specific alterations at the level of individual genes, pathways, and gene regulatory networks.

In our first studies in one of the most widely used AD mouse models, the Tg2576 model, we observed significant disease-associated gender differences in cellular processes related to synapse organization and reactive oxygen species metabolism, and identified a limited set of transcription factors as key regulators of many of the disease-associated and gender-dependent gene expression changes in the model. Both gender-specific and gender-dimorphic changes in upstream transcription factors and their downstream targets in this AD model were detected before the onset of overt disease. This opens a window into molecular events that could determine gender-susceptibility to AD, and uncovers tractable target candidates for potential gender-specific precision medicine for AD.

For PD, a meta-analysis of gender-linked genes using an integrated analysis of omics datasets from PD case/control studies revealed candidate genes and cellular pathways/networks, mainly associated with inflammatory and mitochondrial processes, with gender-specific changes in PD. These candidates are currently further evaluated using complementary omics data from *in vitro* and *in vivo* models for PD. The resulting information on disease-linked gender differences in the brain transcriptome could provide new insights to support the development of patient-tailored diagnostic and therapeutic approaches.

Multi-dimensional stratification of PD patients for personalized interventions (PDStrat project)

Current therapeutic approaches for Parkinson's disease (PD) can help to alleviate some of the major symptoms, but can neither halt nor slow the progression of the disease. As part of a multi-center collaborative research project, led by

Prof. Peter Heutink from the German Centre for Neurodegenerative Diseases (DZNE), we are investigating new approaches for personalised interventions against PD, hypothesising that previous clinical trials have failed for three main reasons. First, selection of potential drug targets is rarely based on robust biological evidence. Second, the disease process begins decades before clinical symptoms are observed and clinical trials on patients are therefore likely too late to reverse the neurodegeneration. Third, participants have been selected largely ignoring their underlying disease biology, phenotypic variation and their genetic risk profile, resulting in a very heterogeneous population of cases with very different progression of disease. Therefore, we are implementing a novel concept for disease mechanism-based disease onset and progression prediction. Our goals are to identify novel targets based on biological evidence with matching precision cohorts for clinical trials that will allow for personalised therapeutic interventions. For this purpose, we use a systems biology approach and have generated multi-dimensional clinical, genetic/genomic and biological risk and progression profiles for patients and at risk individuals and integrated these data into machine learning models for diagnostic and prognostic patient stratification. In the project consortium, the Biomedical Data Science group is responsible for the machine learning and network analyses of omics data and clinical records. As part of this work, we have published new machine learning methods to improve the prediction of dichotomized clinical outcomes by exploiting information from continuous outcome predictions and correlation patterns between different clinical outcomes. These approaches are applied to the omics and clinical data we are continuously collecting from multiple PD cohorts. The project has received funding support from the Luxembourg National Research Fund (FNR).

Principal Investigator
Enrico Glaab
Start: June 2015

Integrative machine learning analysis of digital biomarkers, molecular and clinical data for PD (DigiPD)
Digital biomarkers (DMs) from sensors and devices have the potential to change our understanding of Parkinson's Disease (PD) fundamentally, because they allow for a quantitative and continuous monitoring of disease symptoms, also outside clinics. This includes the possibility to monitor the response to treatment, which opens the opportunity to adapt medication pathways quickly, if necessary. The aim of this project is to evaluate, in how far DMs extracted from a mobile gait sensor system as well as recordings of voice and face movement could help for accurate disease diagnosis and treatment dependent prognosis for each individual patient. This could help to take better-informed medical decisions for each patient at the right time.
Our project brings together medical and computational experts from multiple countries in the field of PD research. Starting from pre-existing data and advanced AI methods developed by project partners in the past, we are assessing different types of DMs regarding their ability to predict different types of disease trajectories and the treatment-dependent change of disease symptoms over time. Moreover, we use statistical and AI methods to study the relation of different types of DMs to each other, to clinical outcome scores and to molecular disease mechanisms, opening the opportunity to a so far unseen level of interpretation of DMs. Finally, we provide important insights into feasible legal pathways for the future use of AI and DMs in clinical routine.
Altogether, this project is contributing to defining the technical, legal, ethical and social basis for the future use of DMs within Personalised Medicine-based PD treatment. The study is funded by the EU Horizon 2020 ERA PerMed programme.

Key publications

1. Rauschenberger, A., & Glaab, E. (2021). Predicting correlated outcomes from molecular data. Bioinformatics, 37(21), 3889-3895.
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3. Hendrickx, D. et al. (2021). A new synuclein-transgenic mouse model for early Parkinson's reveals molecular features of preclinical disease. Molecular Neurobiology, 58(2), 576-602.
4. Greuel, A. et al. (2020). GBA variants in Parkinson's disease: clinical, metabolomic, and multimodal neuroimaging phenotypes. Movement Disorders, 35(12), 2201-2210
5. Hendrickx, D. M., & Glaab, E. (2020). Comparative transcriptome analysis of Parkinson's disease and Hutchinson-Gilford progeria syndrome reveals shared susceptible cellular network processes. BMC Medical Genomics, 13(1), 1-16

Computational Biology group

Overview

The main goal of the Computational Biology Group is to develop computational models at different scales of biological organisation, including cellular, tissue and organ level, to address challenges in stem cell research and disease modelling. Among these challenges, our research focuses on improving the regenerative capacity of stem cells in old tissues, identifying lineage-specifying transcription factors involved in organ-level developmental disorders, and modulating the dysregulated hyperinflammatory response associated to various infectious and autoimmune diseases. Moreover, our computational models employ methodologies from different areas of mathematics, engineering, and physics, and integrate multiple sources of biological information (e.g. transcriptomics, epigenomics, proteomics) to study biological processes at different levels of organisation. Importantly, the development of these models aims at generating predictions to guide stem cell researchers in the design of novel regenerative medicine therapies, and to assist clinical researchers to design new therapeutic intervention strategies to revert disease phenotypes.

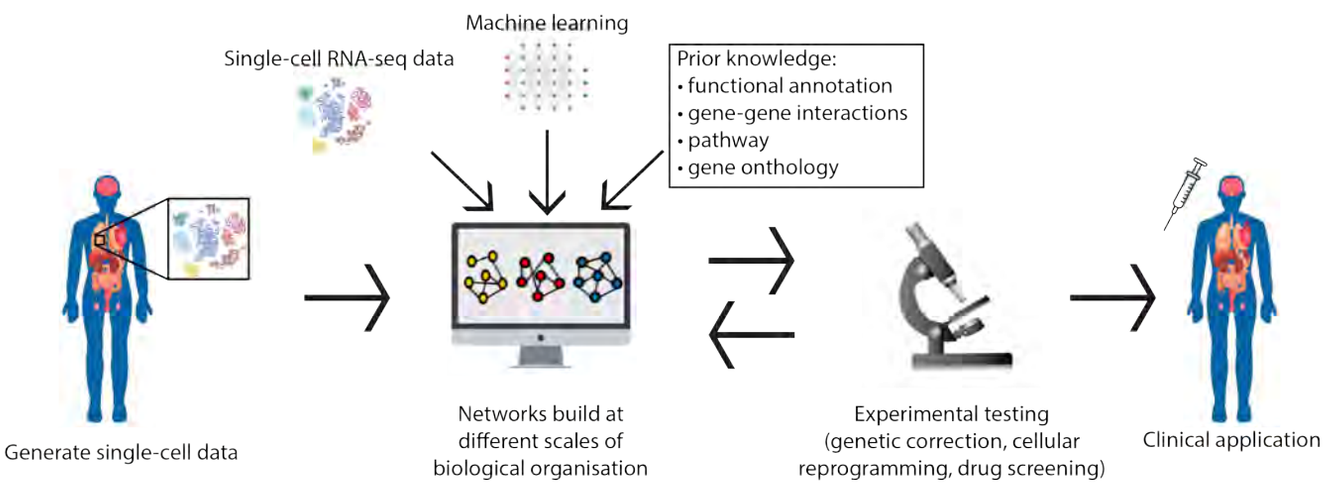

Figure: Multiscale modelling in stem cell and disease research.

Key projects

Computer-guided strategies for cellular reprogramming: clinical applications

The goal of this project is to build a computational platform that relies on gene regulatory network models to develop strategies for identifying instructive conversion factors triggering transitions between specific cell types. Importantly, it is applicable for closely related cell subtypes with similar transcriptional profiles. This platform will be applied to projects relevant to cell therapies and regenerative medicine. For example, in collaboration with Prof. Michele De Luca at the Centre for Regenerative Medicine in Modena, we intend to predict reprogramming determinants to derive corneal limbus stem cells from cultured epithelial keratinocytes. The derived experimental protocol will be further optimized and used for treating patients who have lost their corneal limbus stem cells due to injury or burn. Further, in collaboration with Prof. Mark Tuszynski at the Center for Neural Repair in San Diego, we will apply our platform to generate corticospinal tract neuron progenitors *in vitro* for transplantation in cases of spinal cord injuries. Finally, we have generated predictions for the efficient conversion of cardiac right ventricular cells into left counterparts, which are being currently validated by Prof. Deepak Srivastava at the Gladstone Institutes in San Francisco. The outcome of this project will be essential for designing strategies to treat patients with cardiovascular diseases.

Computational approach to direct cellular reprogramming into multiple dopaminergic neuron subtypes

Current reprogramming protocols are only able to reprogram one cell type into another. However, derivation of multiple cell subtypes from a single source of cells is a challenge and is of clinical interest. In this project we aim to develop a computational method that predicts instructive factors that can convert one cell type into multiple cell subtypes in a controlled way. The experimental validation will be performed in collaboration with Prof. Ernest Arenas at Karolinska Institute in Stockholm. Experiments on cultured astrocyte cell colonies will be conducted to induce cellular conversions into different

populations of dopaminergic neuron subtypes. The outcome of this project will be used in a disease model of Parkinson's disease, which will enable drug screening and drug development strategies for therapeutic intervention.

Modelling cell-cell communications for the design of novel strategies for tissue rejuvenation

In this project our goal is to model tissue-specific cell-cell communication networks to gain insights into general principles of tissue homeostasis and to design strategies to rejuvenate aged tissues. In particular, in collaboration with Prof. Pura Muñoz at the Pompeu Fabra Univeristy in Barcelona, we plan to coin a systems biology definition of tissue homeostasis. This will enable us to propose intervention strategies for the rejuvenation of old muscle tissue based on the cell-cell communication network model. Further, in collaboration with Prof. María Martínez Chantar at CIC bioGUNE in Bilbao, we plan to apply the developed methodology to the rejuvenation of old liver tissue for increasing its regenerative capacity. The validation of predicted target molecules in both projects will be conducted in *in vivo* models.

Tailored immunotherapy for pediatric SIRS (severe inflammatory response syndrome)

The systemic inflammatory response syndrome (SIRS) is a complex of nonspecific symptoms. SIRS is a life-threatening condition characterised by a mortality rate of 7-25% depending on timely recognition of the underlying disease. Currently, we lack targeted therapy for SIRS not only because triggers are often unknown, but also because host responses to triggers may vary.

In this project, we will develop a novel machine learning algorithm for integrative analysis of the multiOMICs data. Notably, the algorithm will not only predict appropriate diagnostic patterns for each cohort of patients, but also enable identification of important features and their molecular interactions that together determine the course of disease progression. In collaboration with Prof. Catharina Schütz at Technical University Dresden, experiments will be conducted to validate the predicted interactions and provide mechanistic insights into patient diagnostics and treatments.

Principal Investigator
Antonio del Sol
Start: February 2010

Key publications

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Developmental & Cellular Biology group

Overview

In recent years, it has been accepted that Parkinson's disease (PD) is a disorder which is not only characterised by a loss of dopaminergic neurons in the substantia nigra, but also has a strong neuro-developmental aspect. The aim of our research is to understand, model and treat PD. Particularly, we are interested in elucidating how developmental processes contribute to the susceptibility to suffer from PD. Human stem cells, either neural stem cells or pluripotent stem cells, are in the centre of all of our research approaches. We use these cells to generate advanced *in vitro* disease models, including three-dimensional brain organoids (so-called "mini brains"), which shall help us to understand the cellular and molecular processes underlying disease onset and progression. Concerning the molecular processes, we are particularly interested in linking the molecular function of PD-associated proteins with cell cycle progression, protein aggregation and mitochondrial/lysosomal function. By further developing these models, we will at least partially be able to replace animal experiments and to take an additional step in the direction of personalised medicine. Multiple of our projects are funded by the Luxembourg National Research Fund (FNR) and the European Commission.

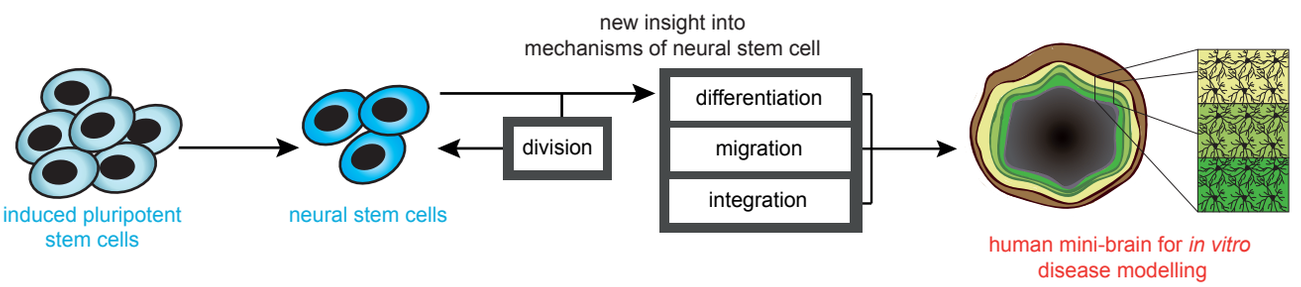

Figure: Utilisation of stem cells and mini-brain 3D cell cultures to model Parkinson's disease.

Key projects

On the way to personalised clinical trials in a dish

We use human patient specific midbrain organoids as *in vitro* disease model for PD. The primary cells for our studies are provided by PD patients that donate their skin cells (coming for instance from the Luxembourgish PD cohort). These skin cells harbor the genetic identity of the individual including the mutations that were shown to cause or increase the risk of developing PD. The skin cells are then reprogrammed into induced pluripotent stem cells (iPSCs), a cell type comparable to embryonic stem cells and able to give rise to every cell within the human body. We currently use cells with mutations in the PD associated genes *LRRK2, GBA, SNCA, VPS35, PINK1, PARKIN*, and *MIRO1*. Additionally, samples from idiopathic PD patients are used.

Using these iPSCs we mimic the neurodevelopmental process in a dish and generate complex 3D cellular structures, so called midbrain organoids - regionalised mini brains. The region we chose to produce is the midbrain, because in PD the loss of dopaminergic neurons within the midbrain is the main clinical hallmark and leads to the typical PD-associated motor symptoms such as tremor. Using these midbrain organoids, we do *in vitro* disease modelling by comparing the organoids from patients to those coming from healthy individuals. Additionally, to these healthy controls we genetically engineer midbrain organoids from iPSCs where we have introduced or gene-corrected mutations using CRISPR/Cas9 technology. As PD is a multifactorial disease and each individual has a different genetic background, this methodology helps us to differ between mechanisms and phenotypes that are disease- or mutation-dependent. The comparative analyses rely on deep cellular and molecular phenotyping and multi-omics approaches. Once the patient-specific phenotypes are established and an underlying mechanism has been discovered, different approaches can be envisioned in order to stratify the patients and find common as well as personalised differences. Phenotypes for instance can be rescued by drug/compound treatment or genetic modifications. Moreover, environmental contributions can be evaluated by the individual patient susceptibility towards external stimulants or toxins. These system manipulations allow us to discover novel potential disease modifiers as well as treatment strategies and to study their impact, leading the way to precision medicine.

Model development

The human brain is an immensely complex structure, with different anatomical and functional regions. In many aspects, iPSC-derived three-dimensional human brain organoids, collectively called mini brains, resemble the developing human brain.

They contain the most relevant cell types (neurons, astrocytes and oligodendrocytes), have functional synapses as well as axon myelination. Most importantly, they show a spatial organisation and asymmetry that resembles the developing human brain. However, they were lacking components of the immune system, such as microglia cells, and of the circulatory system, such as vasculature, which are shown to be relevant in neurodegenerative disease pathology, also in PD. Therefore, we are constantly developing our models to make them more physiologically relevant and study new roles of these cell types in the healthy and diseased context. On the other hand, PD is a complex disease, not only affecting single brain regions (like the midbrain), but the complete brain or even the complete body. By generating assembloids via merging organoids representing different brain regions, e.g. the midbrain and the striatum or the hindbrain, or different parts of the body, e.g. the brain and the intestine, we develop more complex and representative *in vitro* disease models that allow us to study not only tissues but also systems. In order to connect and culture these assembloids, we make use of both in-house and project partner-obtained microfluidic devices, inserts or chips. Interestingly, all different organoids can be derived from a single stem cell culture from any individual. Hence, they are truly personalised.

Principal Investigator
Jens C. Schwamborn
Start: June 2013

Next steps towards an advanced *in vitro* modelling of disease – Microglia & Vascularization

PD etiology is complex where many cells in the brain are implicated. Plenty evidences indicate that the immune system also plays an important role, indicating an important aspect of neuroinflammation in PD. Microglia, the main immune cells in the brain are thus a relevant target in PD pathology. The study of human microglia is rather complicated, and it is mainly done *in vivo* or from postmortem brain biopsies. Therefore, by combining iPSC and organoid technology, we aim to study the role of microglia in PD pathogenesis using patient-derived iPSC. By integrating iPSC-derived microglia into midbrain organoids, we aim to resemble the more physiological interaction between microglia and the brain. This hopefully can give us a clue on the mechanistic role of microglia in neurodegeneration.

Furthermore, our recent efforts have focused on combining midbrain and vascular assembloids. The vasculatures contain an endothelial network that could be the focus of studies related to the vasculature instability in PD and its consequences on brain physiology. By integrating microglia into midbrain-vascular assembloids, we further advance the model into an assembloid that contains all cell types in the brain. This model may recapitulate better the brain microenvironment in a 3D *in vitro* system, where it can be used to obtain more information about the disease, its molecular mechanism and possibly therapeutic targets in the future.

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Digital Medicine group

Overview

Prof. Dr. med. Jochen Klucken is the FNR-Pearl Chair of Digital medicine and head of the Digital Medicine group that works in very close collaboration with the NCER-PD project (National Centre for Excellence in Research on Parkinson's Disease) and is supported by the FNR-PEARL Programme at the LCSB (Luxembourg Center for Systems Biomedicine) of the University of Luxembourg, the LIH (Luxembourg Institute of Health) and the CHL (Centre Hospitalier de Luxembourg). The group focuses on I) shaping and innovating personalised digital healthcare solutions, and II) understanding and evaluating the new benchmarks of a new ecosystem for digital medicine. Digital medicine is a new field Medicine that aims to understand how patient-centered technology can be used in everyday medical practice, and which evidence assessment is needed to not only understand the medical benefits of healthcare technologies, but also their patient- and social acceptance and economical efficacy. Here, the major goal lies in clinical studies for healthcare technologies providing evidence for their medical, social, ethical and legal benefit as well as economic efficiency ultimately generating a concept of "clinical validation of healthcare technologies and services". The highly interdisciplinary team will closely collaborate with the academic partners from different disciplines, as well as innovative industry partners and align with the digital health strategies in Luxembourg in order to develop digital health concepts and accelerate innovative digital healthcare technologies. The overall goal is to innovate digital medicine and improve healthcare for patients, healthcare providers and society.

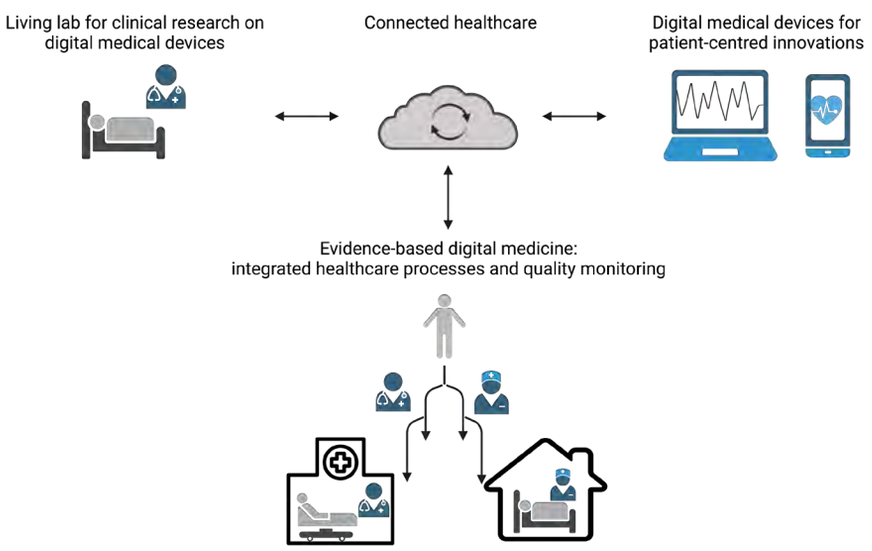

Figure: Connected healthcare.

Key projects

PEARL dHealthPD

The FNR-PEARL programme supporting the Digital Medicine group will develop digital health concepts for Luxembourg through a joint research programme involving the University of Luxembourg, the Luxembourg Centre of Systems Biomedicine (LCSB), the Luxembourg Institute of Health (LIH), and the Centre Hospitalier de Luxembourg (CHL). Parkinson's disease (PD) will serve as an optimal model disease to develop and utilise the potential of digitalisation. The novel digital health pathways will then be transferred to subsequent diseases. The emerging field of digital health technologies is the driver for digital medicine. Its success is based on an interdisciplinary understanding of digital health application development and management. To meet these challenges the Digital Medicine group is composed of experts in the field of medicine, data science, ELSA, health economy, IT-engineering and social sciences. The vision of dHealth is to create a new "ecosystem of digital medicine" by developing a "digital health triangle" consisting of a) an IT-platform supported integrated healthcare model for PD, b) new patient-centred outcome parameters by wearable devices, and c) predictive data modelling for individualised patient care.

DIGIPD

DIGIPD is a European funded project (ERA-PERMED (H2020)) with partners from Germany, France and Luxembourg. This DIGIPD project is validating digital biomarkers to improve individualised diagnosis and prognosis for Parkinson patients. To

better predict disease progression and therefore disease management, impairment of gait, voice and face movement is measured using digital technology to adapt treatment. Depending on disease progression patients can be stratified into subgroups for clinical trials to reveal new or better drugs.

EmpkinS: Visualisation of motion sequences based on a biomechanical model
The aim of this sub-project is to explore new methods and forms of representation for the visualisation of movement sequences that have been recorded with various empathokinesthetic sensors and/or for which a biomechanical simulation has been carried out. The focus is on visualisations and the extraction of features that support medical interpretation and diagnosis. In particular, the visualisation should build a bridge into medical applications and provide a quantitative assessment of physiological and disease-related data.

Mobility_APP
This project is a randomized controlled trial to determine whether gait-focused versus standard physiotherapy and home-based exercises result in greater improvement of mobility in parkinsonian disorders including PD, MSA-P and PSP-RS. With the help of the e-diary (Mobility-APP) patients are reminded to practise the home-based training.

Mobilise-D
Mobilise-D focuses on five different patient groups that together represent respiratory problems (chronic obstructive pulmonary disease – COPD), neurodegenerative conditions (Parkinson's disease – PD), neuroinflammatory problems (multiple sclerosis – MS), osteoporosis and sarcopenia (hip fracture recovery/proximal femoral fracture – PFF), and cardiac pathology (congestive heart failure – CHF). These patient groups cover a range of walking speed, mobility challenges, and potential events, such as improving versus worsening of function, falls, hospitalisation, nursing home admission, and death. Furthermore, these patient groups will be followed at 12 different sites across Europe, ensuring a good geographical representation and covering a diverse representation of healthcare organisation, such as inpatient versus outpatient care, as well as public versus private health services.

Principal Investigator
Jochen Klucken
Start: March 2021

Key publications

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Environmental Cheminformatics group

Overview

The Environmental Cheminformatics group focuses on the comprehensive identification of known and unknown chemicals in our environment to investigate their effects on health and disease. The environment and the chemicals to which we are exposed is incredibly complex, with over 180 million chemicals registered in the largest chemical registry and over 70,000 in household use alone. All detectable molecules in complex samples can now be captured using high resolution mass spectrometry (HRMS). Non-target HRMS provides a "snapshot" of all chemicals present in a sample and allows for retrospective data analysis through digital archiving. However, scientists cannot yet identify the vast majority of the tens of thousands of features in each sample, leading to critical bottlenecks in identification and data interpretation. Identifying the chemical unknowns in living organisms and our environment is essential for unravelling the causes of disease and toxicity, improving our understanding of biological processes and developing new strategies to counteract disease. For instance, the causes of Parkinson's disease (PD) are largely unidentified and hypothesized to be due to a complex combination of environmental and genetic factors. While non-target HRMS methods now provide a basis to identify unknowns, this remains extremely time-consuming and, in many cases, a matter of luck. Prioritizing efforts to find significant metabolites or potentially toxic substances responsible for observed effects is the key, which involves reconciling highly complex samples with expert knowledge and careful validation. The group pursues a fundamental shift away from single-substance assessments and develop generic approaches scalable to tens of thousands of chemicals, features and samples.

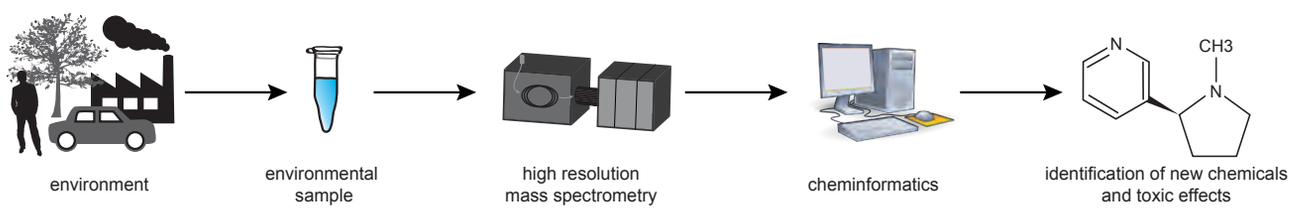

Figure: Typical workflow for identifying unknowns with environmental cheminformatics.

Key projects

Environmental Cheminformatics to Identify Unknown Chemicals and their Effects (ECHIDNA)

ECHIDNA is a five-year ATTRACT fellowship from the Luxembourg National Research Fund (FNR) starting late 2018 to build computational methods suitable for investigating and elucidating unknowns and causes of effects using HRMS of small molecules. Computational and experimental developments will improve structure elucidation, including cheminformatics approaches as well as stable and dynamic labelling of samples. New cheminformatics methods will improve our understanding of the fundamentals of HRMS and work towards the "holy grail" of a full Computer-Assisted Structure Elucidation (CASE) system for HRMS. These methods will be applied on a microbiome-PD cohort study, allowing a discovery-based prioritisation of potential neurotoxins amongst these samples, plus single cell biological systems to yield additional information on known and unknown metabolites in well-understood systems. This project involves several internal partners within the LCSB, including the Enzymology and Metabolism Group, Systems Ecology Group and the Bioinformatics Core.

Non-target Screening with High Resolution Mass Spectrometry

Analytical and computational methods for high throughput non-target high resolution mass spectrometry methods (NT-HRMS) are developed in the group, with a large focus on developing open computational methods, primarily in R. Open packages such as RMassBank will be integrated with other packages under development (ReSOLUTION, RChemMass) and connected with initiatives from the NORMAN Network (see below). MetFrag, developed in collaboration with the IPB, will form the basis for non-target identification. We collaborate with Rick Helmus at the University of Amsterdam, developer of patRoon, and actively developed Shinyscreen, led by Todor Kondic (see https://gitlab.lcsb.uni.lu/eci/).

Luxembourg Time Machine (LuxTIME)

The "Luxemburg Time Machine" (LuxTIME) project is a pilot Audacity project in the University of Luxembourg's Institute of Advanced Studies (IAS). LuxTIME will explore radically new ways for analysing and interpreting factual evidence of the past, fostering the energies and skills across two interdisciplinary centres (Luxembourg Centre for Systems Biomedicine,

Luxembourg Centre for Contemporary and Digital History) at the University in cooperation with the Luxembourg Institute of Science and Technology (LIST). LuxTIME will build an interdisciplinary framework for investigating "big data" of the past, inspired by the conceptual premises of the "European Time Machine" Flagship project. The LuxTIME digital dataset will include information from three different fields and scientific perspectives (eco-hydrology, medicine and history) and use a local showcase (i.e. the industrialisation of Belval / Minette region) as a testbed to study the impact of environmental changes on the health of the local population in a long term perspective. LuxTIME will study the past in completely new ways using evidence from eco-hydrological studies (water and pollutant sources, flow paths and transit times, topographic / geological transformations), medical records (describing disease patterns, mortality rates, social/psychological well-being), bio-chemical data (based on mass spectrometry techniques) and history (archival sources documenting economic, social, political and cultural changes. By mixing "contextual information" based on archival evidence with "scientific evidence" derived from chemical, biological, or medical investigations, the project explores new ground in interpreting "big data of the past" in a truly interdisciplinary setting.

Principal Investigator
Emma Schymanski
Start: September 2017

Open Data Exchange, the NORMAN Network and NORMAN-SLE

Ensuring the open availability of high quality data is critical to improving computational methods and the Environmental Cheminformatics group is involved in several initiatives within the NORMAN Network and beyond. We coordinate the NORMAN Suspect List Exchange, ensuring our datasets are FAIR, archived on Zenodo (https://zenodo.org/communities/norman-sle) and integrated into public resources such as PubChem and the CompTox Chemicals Dashboard. Our work with PubChem is part of the group's R3 workflows on GitLab. The NORMAN-SLE is tightly connected with unique European initiatives launched within several NORMAN working groups (Prioritization, EDA and Non-target screening) such as NormaNEWS, the NORMAN Digital Sample Freezing Platform and MassBank.EU. We gratefully acknowledge our many collaborators contributing to these Open Science initiatives, especially the PubChem, CompTox and NORMAN members working closely with us.

ZeroPM: Zero Pollution from Persistent, Mobile Substances

ZeroPM is a new 15 partner, 5 year EU project that will interlink and synergise prevention, prioritisation and removal strategies to protect the environment and human health from PM substances. Starting late 2021 and funded under the H2020 research and innovation call "Building a low-carbon, climate resilient future: Research and innovation in support of the European Green Deal: Innovative, systemic zero-pollution solutions to protect health, environment and natural resources from persistent and mobile chemicals", the project is led by the Norwegian Geotechnical Institute (NGI) with Dr Sarah Hale as the Project Coordinator and Prof. Hans Peter Arp as co-coordinator. ZeroPM will establish an evidence-based multilevel framework to guide policy, technological and market incentives to minimise use, emissions and pollution of entire groups of PM substances. The Environmental Cheminformatics group is involved in the Substance Grouping work package of ZeroPM, collaborating with Prof. Hans Peter Arp (NGI), work package lead, and Dr. Zhanyun Wang (EMPA). The Substance Grouping team will look at ways to prioritise all groups of PM substances and transformation products on the global market for prevention and remediation prioritisation, integrating this information into open resources for maximal dissemination.

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Enzymology & Metabolism group

Overview

Several observations clearly indicate that our understanding of cellular metabolic networks, and the regulation thereof, is far from being complete. A main objective of our group is to exploit genomic and post-genomic data to discover new enzyme functions relevant to human disease and ageing. Our research is currently focusing on (1) better understanding the physiological role of recently identified protein and metabolite repair mechanisms, (2) characterising poorly studied enzymes involved in rare diseases, and (3) developing strategies for accelerating enzyme function discovery. Comparative genomics-based bioinformatics tools are used for *in silico* predictions of gene functions. On the experimental level, we use gas or liquid chromatography and mass spectrometry-based (GC- or LC-MS) metabolomics methodologies, as well as the model organisms *Saccharomyces cerevisiae* and zebrafish, and human cell lines as central tools. In addition, recombinant protein expression and purification and development of enzymatic assays are important for biochemical validation and characterisation of predicted gene functions. Reverse genetic strategies are employed to study the role of enzymes of interest in the complex setting of whole cells or organisms. Yeast, zebrafish and human cell lines are also used for modelling rare metabolic diseases and performing small molecule screens to find potential drug candidates. Our research is intended to impact fields ranging from fundamental biochemistry to metabolic modelling, metabolic engineering and medicine.

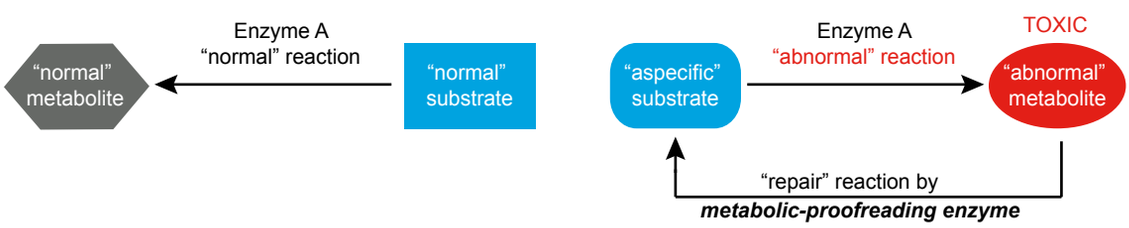

Figure: Principles of enzymatic metabolite repair mechanisms.

Key projects

Role of damaged forms of NADH and NADPH in neurodegeneration

We have discovered a widely conserved enzymatic repair mechanism for hydrated, redox-inactive forms of NADH and NADPH (designated NAD(P)HX), two central cofactors of cell metabolism. With our collaborators, we have shown that genetic defects in this repair system result in febrile-induced and eventually lethal forms of infantile neurodegeneration. We now aim to better understand how and under which circumstances NAD(P)HX is formed in the cell and what cellular functions are affected by the accumulation of NAD(P)HX. These studies include transcriptomics and metabolomics analyses, cell viability assays, and mitochondrial function studies in multiple environments. In yeast, we could already demonstrate that NAD(P)HX repair deficiency leads to a blockage of the main serine synthesis pathway and we elucidated the underlying molecular mechanism. Establishment of zebrafish and human iPSC-derived models as well as drug screens for this new infantile neurodegenerative disease are ongoing. The central roles of NAD(P)H in living cells, the conservation of the NAD(P)HX repair system across all kingdoms of life and its causal association with neurodegeneration in humans suggest that a better understanding of the NAD(P)HX repair system will reveal new fundamental aspects of cell metabolism as well as the preservation of neuronal health. This research is supported by the Luxembourg National Research Fund (FNR), the Juniclair foundation, and the Lions Club Luxembourg.

Towards small-molecule therapies for ATP13A2 deficiencies and Zellweger spectrum disorders

Mutations in ATP13A2 can lead to a variety of more or less early-onset neurodegenerative diseases, including Kufor-Rakeb syndrome and Batten disease. Zellweger spectrum disorders (ZSD) are a group of rare peroxisomal biogenesis disorders, affecting several organs (including brain, liver and kidneys), but with different degrees of severity depending on the pathogenic mutations. Efficient treatment options for these fatal diseases are currently not available. We develop yeast models, as well as human cell and zebrafish models, for ATP13A2 deficiency and ZSD to screen for small molecules with potential disease-modifying properties. In addition, these models allow us to investigate underlying disease mechanisms in the lab. Based on a greatly decreased metal toxicity resistance observed in ATP13A2-deficient yeast and zebrafish models, we recently identified two drugs that were able to rescue metal-induced defects in both models. Currently we are testing these two drugs in ATP13A2 patient-derived cells. Using fibroblasts of a patient affected by a ZSD called infantile Refsum disease, we developed a highthroughput imaging-based assay to perform drug repurposing screens and we generated a zebrafish model of Zellweger syndrome, a more severe ZSD, using CRISPR/Cas9-mediated knockout of the *PEX1* gene.

This work is supported by various funding sources including the FNR, an internal LCSB flagship grant, the ATOZ foundation, the LOSCH foundation, the Rotary Club, and private donors.

Principal Investigator
Carole Linster
Start: January 2013

2-Hydroxyglutarate metabolism and its role in disease
D-2-hydroxyglutarate (D-2HG) and L-2-hydroxyglutarate (L-2HG) are metabolites that accumulate in several types of inherited neurometabolic diseases and certain forms of cancer, such as glioblastomas and acute myeloid leukaemia. In each of these diseases, mutations in specific dehydrogenases cause 2HG accumulation. The pathways leading to 2HG formation and the roles of 2HG in disease and aging are still unclear. We recently filled a prominent gap in yeast metabolism by discovering the enzymes responsible for the formation and degradation of D-2HG in this organism. Our results show that in yeast, D-2HG metabolism links the main serine synthesis pathway to the mitochondrial respiratory chain. Ongoing experiments are designed to find additional genes involved in D-2HG metabolism and to better understand the interplay between D-2HG and epigenetic regulation. This work may lead to a better understanding of the pathophysiology of D-2HG associated diseases. This research was supported by the FNR and the University of Luxembourg.

Comparative genomics- and metabolomics-based strategies for enzyme function discovery
In collaboration with the Bioinformatics Core, we identified more than 600 and 2000 putative enzyme genes among the about 2000 and 6500 genes of unknown function in yeast and human, respectively. Prioritising putative enzyme genes with predicted roles in metabolism and/or disease, we develop, in collaboration with the Metabolomics platform and with the Environmental Cheminformatics group, targeted and non-targeted LC-MS-based approaches to compare metabolite profiles of control cells and cells with specific gene deletions. Metabolites whose levels differ significantly between these cells help to predict endogenous reactions catalysed by the enzymes of interest. Those predictions can then be validated on recombinant protein level through appropriate enzymatic assays. This approach has already allowed to identify a new eukaryotic D-ribulokinase and a new transhydrogenase activity for D-2-hydroxyglutarate degradation. With this project, we aim to address a major post-genomic challenge that can only be tackled by a community-wide effort: progress from knowing the code to understanding the message by decreasing the number of genes of unknown function. This project is supported by the FNR.

Crosstalk between a protein repair methyltransferase, cell signalling, and brain function
PCMT1 is a highly conserved repair enzyme that recognises spontaneously formed isoaspartatyl residues in proteins and, through methylation, facilitates their reconversion back into the normal aspartyl precursors. PCMT1 deficiency leads to accumulation of high levels of damaged proteins, especially in the brain, and massive seizures in a knockout mouse model. In addition, PCMT1 overexpression leads to a longer life span in worms and flies. Other studies suggest roles for PCMT1 also in neurodegenerative disease and cancer. In this project, we have established and phenotyped zebrafish and mouse hippocampal cell models with PCMT1 deficiency. Our studies indicate that PCMT1 plays an important role in supporting normal calcium signalling in the brain and our models can now be used to investigate the underlying molecular mechanisms. This project was funded by the FNR.

Key publications

1. Griffith C.M., Walvekar A.S., and Linster C.L. (2021) Approaches for completing metabolic networks through metabolite damage and repair discovery. Curr. Opin. Syst. Biol. 28. doi: 10.1016/j.coisb.2021.100379
2. Soliman R., Cordero-Maldonado M.L., Martins T.G., Moein M., Conrotte J.F., Warmack R.A., Skupin A., Crawford A.D., Clarke S.G., and Linster C.L. (2021) L-Isoaspartyl Methyltransferase Deficiency in Zebrafish Leads to Impaired Calcium Signaling in the Brain. Front. Genet. 11:612343. doi: 10.3389/fgene.2020.612343
3. Heins-Marroquin U., Jung P. P., Cordero-Maldonado M. L., Crawford A. D., and Linster C. L. (2019) Phenotypic assays in yeast and zebrafish reveal drugs that rescue ATP13A2 deficiency. Brain Communications 1, fcz019
4. Van Bergen N.J., et al. (2019) NAD(P)HX dehydratase (NAXD) deficiency: a novel neurodegenerative disorder exacerbated by febrile illnesses. Brain 142(1):50-58. doi: 10.1093/brain/awy310
5. Becker-Kettern J., et al. (2018) NAD(P)HX repair deficiency causes central metabolic perturbations in yeast and human cells. FEBS J. 285(18):3376-3401. doi: 10.1111/febs.14631

Gene Expression & Metabolism group

Overview

The Gene Expression & Metabolism group focuses on how metabolic diseases arise as a combination of interactions between differences in individuals' genetic profiles and their varying environments. In particular, we examine how changes to diet and exercise affect the development or prevention of obesity, diabetes, fatty liver disease, and how these clinical diseases are caused by long-term underlying changes at the molecular, cellular, and tissue-level. To this end, we have developed and use large-scale measurement technologies (particularly nucleotide sequencing and mass spectrometry) to measure the molecular landscapes of cells and tissues. This "multi-omics" approach is applied in genetically-diverse populations, measured over time, to determine which molecular deficits precede disease, when these deficits occur, and finally what causes their imbalance: genetic factors, environmental changes, or a combination of the two? Each of these "layers" of molecular biology – DNA, RNA, protein – yields a unique window into the aetiology of complex metabolic diseases, ultimately allowing us to define earlier biomarkers of disease development, protective and risk factors in the genome and environment, and ultimately potential treatment pathways to reverse early-stage metabolic diseases. Our research group is thus focused on the intersection of molecular biology, metabolism, data science, and bioinformatics.

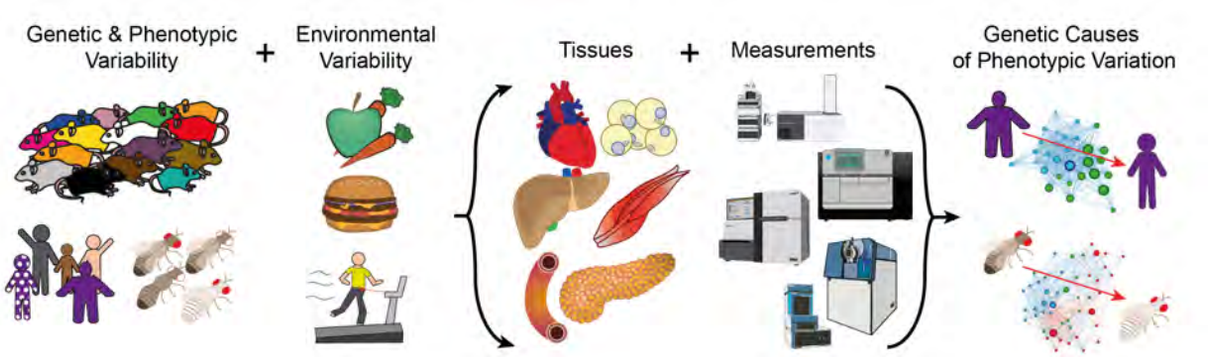

Figure: Variation in populations' genetic profiles and their differing environments leads to diverging incidence and severity of metabolic diseases.

Key projects

Quantifying the impact of genetic variation on ageing-related diseases

We have previously collected tissues and data from around 700 genetically-diverse mice which have varying diets, ages, and incidences of metabolic disease. Since moving to the LCSB in 2020, we have focused on creating and analysing molecular profiles of the tissues from these individuals to determine the development of molecular perturbations preceding overt clinical manifestation of disease. This project uses causal modelling to examine which changes in regulatory networks of gene expression are preliminary drivers of metabolic disease, and which changes are downstream biomarkers of a system that has already lost homeostasis. This technique uses a time course-based analysis to determine how and which genetic and environmental factors lead to the development of disease, and then via which genes, metabolites, and regulatory mechanisms. In this project, we develop tools that allow us to move from "correlation to causality," particularly by taking a multivariate approach where the model system is modified by multiple factors simultaneously – rather than one variable at a time as in a traditional biological approach. Candidate genes have recently been examined largely in *C. elegans*, but the laboratory plans to continue validation work in higher-order organisms now that this initial work has been published (Williams et al., 2021).

Understanding the relationship between the microbiome and host

Our intestines are colonised with some tens of trillions of bacterial cells which make up our "microbiota". These bacteria can be symbiotic, enabling us to more efficiently metabolise food and to ward off disease, but they can also be detrimental, either causing disease or locking us in a negative feedback loop and inhibiting recovery. Experiments in both humans and model organisms have shown that changing our gut microbiome can change disease phenotypes, proving that microbiota can have causal effects on the host, and highlighting their potential utility in medical

treatments. However, due to the huge diversity of the microbiome, much remains unknown about the cause and effect of specific changes in its composition. In our research, we examine how the gut microbiome in the cecum changes over the lifespan of a mouse. We can thus determine when the gut microbiome changes in response to differences in genetics, diet, and time, and by examining other tissues in the mice, we can see how the gut microbiome communicates with the host organism. This will allow us to define not only which parts of the gut microbiome are beneficial or detrimental, but also which changes in gene expression – at either the microbe or host level – are active.

Principal Investigator
Evan Williams
Start: May 2020

Exercise, Diet, Genetics, and Weight Loss

It is a common truism that exercise aids in fitness, and that certain diets have negative health effects, but there is a tremendous range in how different people respond to similar exercise and dietary regimens. We have previously examined the natural propensity of a large population of mice to the development of metabolic disease under different dietary states, and the propensity of mice to exercise when given access to suitable equipment. At the LCSB, we have started a project to merge these two prior findings. Do mice that are predisposed to obesity and diabetes, but which enjoy exercise when given the opportunity, still develop metabolic disease, and to what extent? We have just established a long-term experiment – roughly one year – where we will follow these mice over the first third of their natural lifespan, where they will eat and exercise to their own volition to determine to what extent the ability to exercise can ameliorate (or even prevent) metabolic disorders. Should these mice be able to largely mitigate the negative effects of a diet if they were living a sedentary lifestyle, we will investigate further to determine the contribution of behavioral traits (e.g. desire to exercise) versus core metabolic changes (e.g. mitochondrial morphology).

Key publications

1. Williams, E.G., Pfister, N., Roy, S., Statzer, C., Haverty, J., Ingels, J., Bohl, C., Hasan, M., Cuklina, J., Buhlmann, P., Zamboni, N., Lu, L., Ewald, C.Y., Williams, R.W., Aebersold, R. (2021). Multiomic profiling of the liver across diets and age in a diverse mouse population.
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3. Williams, E., Wu, Y., Wolski, W., Kim, J. Y., Lan, J., Hasan, M., Halter, C., Jha, P., Ryu, D., Auwerx, J., & Aebersold, R. (2018). Quantifying and Localizing the Mitochondrial Proteome Across Five Tissues in A Mouse Population. Molecular and Cellular Proteomics, 17(9), 1766-1777.
4. Williams, E., Wu, Y., Jha, P., Dubuis, S., Blattmann, P., Argmann, C. A., Houten, S. M., Amariuta, T., Wolski, W., Zamboni, N., Aebersold, R., & Auwerx, J. (2016). Systems proteomics of liver mitochondria function. Science (New York, N.Y.), 352(6291), 0189.
5. Williams, E., & Auwerx, J. (2015). The Convergence of Systems and Reductionist Approaches in Complex Trait Analysis. Cell, 162(1), 23- 32.

Immunology & Genetics group

Overview

The immune system is crucial for a healthy body to function and protects us from severe infection. However, a dysregulated immunity can cause inflammation, autoimmune diseases and cancer. Especially, the control of immune cell metabolism has emerged as a powerful way to regulate immunity. The Immunology & Genetics group investigates the metabolic regulation of the immune system and how this ensures a coordinated immune response and homeostasis. We seek to define the molecular, metabolic and cellular processes of inflammation and integrate in vitro with in vivo studies to gain a comprehensive picture of inflammation and cancer.

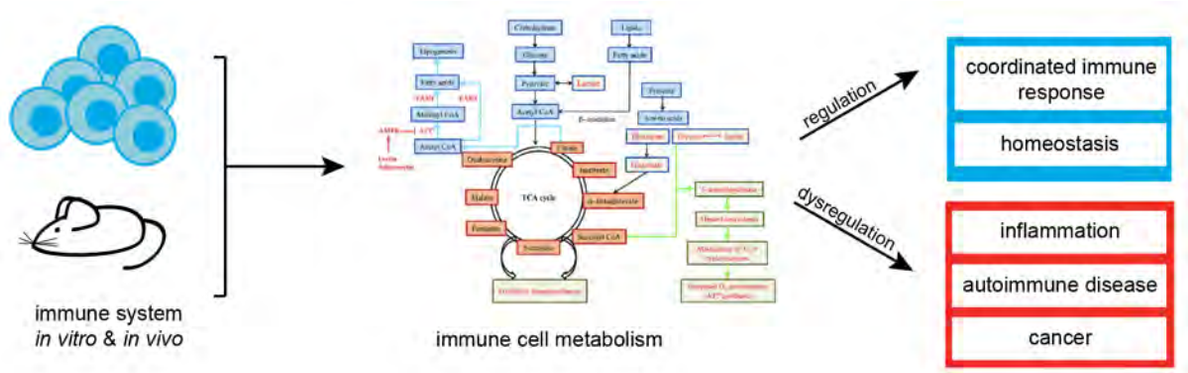

Figure: Studying the metabolic regulation of the immune system in health and disease.

Key projects

Investigating metabolic circuits in immune cells

It has become clear that the metabolic reprogramming that occurs in activated immune cells is essential for their proper functions leading to the creation of a new field of research termed "immunometabolism". Recent studies have underlined the role of cellular metabolism in the generation and maintenance of various types of immune cells. In T cells for example, distinct subsets utilise different energetic and biosynthetic pathways to sustain their activities. Naive CD4+ Th cells use oxidative phosphorylation (OXPHOS) for energy generation when in the quiescent state. Upon activation by antigen, these cells proliferate and differentiate into CD4+ T helper (Th) effector cells (Teffs), such as Th1, Th2, and/or Th17 cells and switch from OXPHOS to a highly glycolytic form of metabolism. In contrast, upon activation, regulatory T cells (Tregs) employ glycolysis at a low rate and high lipid oxidation. This divergent use of metabolic pathways can influence cell fate in various ways. For instance, fatty acid oxidation (FAO) fosters the generation of Tregs while dampening the polarisation of Teffs. Our lab therefore focuses on investigating how cellular metabolism affects cellular functions in specific contexts and various inflammatory diseases. Our analyses are not only focused on T cells, but also include innate immune cells and B cells. A key goal and focus of all our projects is to identify the metabolic checkpoints that interfere with cellular activity in the context of abnormal immune homeostasis like inflammation and cancer.

Glutathione (GSH) a major antioxidant and regulator of metabolism in the immune system

One of the major focus areas of our lab is the control of reactive oxygen species (ROS) by glutathione (GSH) in immune cells and the physiological consequences of ROS accumulation. ROS are balanced by antioxidants, which generally include molecules that are stable enough to donate electrons and thus act as ROS scavengers. The most abundant intracellular antioxidant system is GSH, a tri-peptide of γ-glutamyl-L-cysteinyl-glycine. The enzyme γ-glutamyl cysteine ligase (GCL), which is composed of a regulatory subunit (Gclm) and a catalytic subunit (Gclc), ligates glutamate and cysteine to form a di-peptide in the rate-limiting step of the synthetic pathway. This di-peptide is then covalently linked to glycine by GSH synthase (GS) to generate GSH. We investigate the function of GSH in immune cells by reversed genetic approaches *in vivo* and *in vitro*. Conditional deletion of Gclc, the rate limiting enzyme in GSH-synthesis, in immune cells impairs the production of GSH. For example, our group has identified GSH as an important regulator of T cell metabolism. We could show that the absence of GSH in conventional T cell lead to the accumulating ROS, which shuts down Teff responses. This prevents the onset of autoimmunity, but at the same time increases the susceptibility to viral infections. High ROS levels impair metabolic reprogramming in T cells by hindering proper activation of mTOR, NFAT and Myc and the establishment of T effector functions (Mak and Grusdat et al., Immunity 2017).

Interestingly, GSH exhibits subset specific functions, which we are currently investigating in detail. It seems that GSH acts as a rheostat to adjust cellular ROS concentrations to cell subset-specific threshold level that allows for productive signalling and metabolism.

Our group has recently shown that Tregs contain significantly higher cellular GSH concentrations, which renders them more resistant to increasing ROS. Conditional deletion of Gclc in murine Tregs impairs their production of GSH. These mutant Tregs consequently display increased levels of reactive oxygen species (ROS) but no apparent defects in Treg homeostasis, stability or differentiation. However, Gclc-deficient Tregs do show increased proliferation and activation and the mutant mice develop spontaneous autoimmunity. Importantly, Gclc-deficient Tregs show elevations in both their synthesis and uptake of serine. Accordingly, dietary intervention in the form of feeding the mutant mice on serine/glycine-deficient chow prevents the onset of autoimmunity. In line with this finding, dampening of serine metabolism reinstated the suppressive function of Tregs, firmly linking serine metabolism to Treg function (Kurniawan et al. Cell Metabolism 2020).

Principal Investigator
Dirk Brenner
Start: July 2020

Key publications

1. Kurniawan H, Franchina DG, Guerra L, Bonetti L, Soriano-Baguet L, Grusdat M, Schlicker L, Hunewald O, Dostert C, Merz MP, Binsfeld C, Duncan GS, Farinelle S, Ewen A, Nonnenmacher Y, Haight J, Das Gupta D, Taskesen R, Halder R, Chen Y, Jäger C, Ollert M, Wilmes P, Vasiliou V, Harris IS, Knobbe-Thomsen C, Turner JD, Mak TW, Lohoff M, Meiser J, Hiller K, Brenner D. Glutathione restricts serine metabolism to preserve regulatory T cell function. Cell Metabolism, 2020 May;31(5):920-936e7. doi: 10.1016/j.cmet.2020.03.004
2. Cox MA, Duncan GS, Lin GYH, Steinberg BE, Yu LX, Brenner D, Buckler LN, Elia AJ, Wakeham AC, Nieman B, Dominguez-Brauer C, Elford AR, Gill KT, Kubli SP, Haight J, Berger T, Ohashi PS, Tracey KJ, Olofsson PS, Mak TW. Choline acetyltransferase-expressing T cells are required to control chronic viral infection. Science, 2019 Feb 8;363(6427):639-644. doi: 10.1126/science.aau9072
3. Mak TW, Grusdat M, Duncan GS, Dostert C, Nonnenmacher Y, Cox M, Binsfeld C, Hao Z, Brüstle A, Itsumi M, Jäger C, Chen Y, Pinkenburg O, Camara B, Ollert M, Bindslev-Jensen C, Vasiliou V, Gorrini C, Lang PA, Lohoff M, Harris IS, Hiller K, Brenner D. Glutathione Primes T cell metabolism for Inflammation. Immunity, 2017 Apr 18;46(4):675-689. doi: 10.1016/j.immuni.2017.06.009
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5. Harris IS, Treloar AE, Sasaki M, Inoue S, Gorrini C, Lee KC, Yung KY, Brenner D, Knobbe CB, Adeoye , Brüstle A, Molyneux SD, Elia A, Berger T, Mason JM, Blaser H, Berman HK, Wakeham A, Khokha R, Done S, Kavanagh TJ, Lam CW, Mak TW. Glutathione and thioredoxin antioxidant pathways synergize to drive cancer initiation and progression. Cancer Cell, 2015 Feb 9;27(2):211-22. doi: 10.1016/j.ccell.2014.11.019

Flagship projects

The LCSB's flagship projects bring together several of our research groups and are highly interdisciplinary by nature. The following pages highlight important infrastructures such as the national ELIXIR Node in Luxembourg and the NCER-PD Parkinson's cohort as well as research and education endeavors such as the three Doctoral Training Units that are coordinated by the LCSB in the areas of Parkinson's disease (PD(, the microbiome and critical transitions.

National Centre of Excellence in Research on Parkinson's Disease

Programme coordinators: Rudi Balling (until 2019), Rejko Krüger

NCER-PD (www.parkinson.lu, funded by the Luxembourg National Research Fund (FNR)) unites Luxembourg's clinical, biomedical, and computational research. Within the second funding period (until 2023), the aim is to establish emerging precision medicine concepts for Parkinson's disease (PD), including earlier diagnosis, patient stratification, and personalised treatments.

NCER-PD established a nation-wide and deeply phenotyped cohort of more than 1,600 participants from Luxembourg and the Greater Region, called LuxPARK. These include patients diagnosed with PD and other forms of parkinsonism (followed-up yearly) and matching control subjects (followed-up every 4 years). This longitudinal cohort ranks amongst the 7% largest PD cohorts worldwide. Research physicians, psychologists, and study nurses routinely collect clinical and neuropsychological data, as well as biosamples such as blood, urine, stool, and saliva. These data and samples are then stored, curated, and integrated into state-of-the-art data and biobank facilities for processing within the NCER-PD programme and beyond.

During its second funding phase, NCER-PD is harvesting the collected data and exploring new avenues of biomedical research aiming to translate findings into therapies for PD. Besides sustaining the Parkinson's cohort, two at-risk cohorts are being set up. One, launched in 2021, is of people with prodromal PD defined by REM sleep behaviour disorder (RBD) to identify preclinical biomarkers preceding the clinical evolution of PD and define future strategies for treatments in early disease stages. The second is of people with GBA gene mutations – the most common genetic risk factor for PD – to identify brain imaging biomarkers for early diagnosis. Building on computational modelling, we aim to integrate functional modelling in patient-derived cellular models. The latter will be used as personalised clinical trials in a dish to validate identified biomarkers and test novel compounds using a robotic platform.

The multi-faceted nature of NCER-PD is also reflected by the expertise of major Luxembourgish research stakeholders: the LCSB, Centre Hospitalier de Luxembourg, the Luxembourg Institute of Health, the Integrated Biobank of Luxembourg, and Laboratoire National de Santé. NCER-PD is privileged to collaborate with excellent international partners in PD, including the University of Oxford and the University of Tübingen, and continues attracting complementary PD research initiatives, such as from the Michael J. Fox Foundation, European Institute of Innovation & Technology, and Genetic Epidemiology of Parkinson's Disease Consortium, besides industrial collaborations in research and clinical trials. Furthermore, NCER-PD provides momentum for innovative care and prevention concepts led by the LCSB.

Impact on care and prevention

ParkinsonNet Luxembourg (supported by the Fondation Veuve Emile Metz-Tesch) gathers different healthcare professionals and facilitates Parkinson-specific care via interdisciplinary collaboration and knowledge exchange. It aims to assure the best possible quality of life for each person with PD in Luxembourg (www.parkinsonnet.lu).

Programme Démence Prévention (pdp, funded by the Ministry of Health) aims to prevent, or at least delay the development of dementia in a target population – defined by mild or subjective cognitive impairment – by employing personalised lifestyle interventions via neuropsychologists as Memory Coaches.

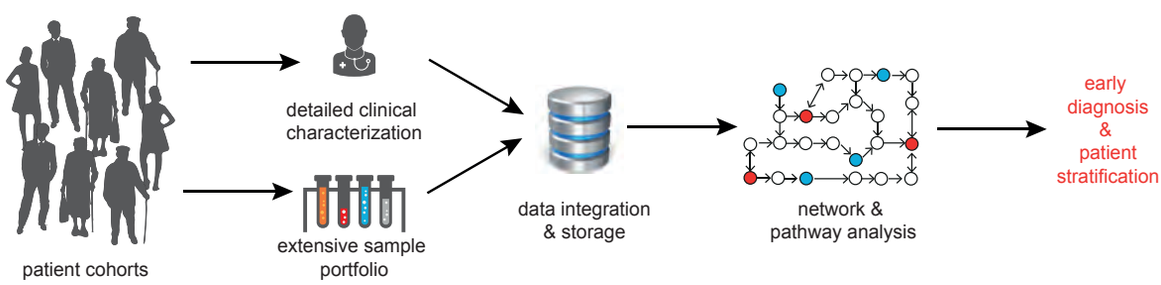


Figure: NCER-PD is an international cross-disciplinary research initiative on Parkinson's disease based in Luxembourg, combining clinical, biomedical, and computational efforts for personalised medicine.

ELIXIR Luxembourg

Head of Node: Reinhard Schneider

In research projects all over Europe, valuable data are generated but usually remain local and lack a broader use. ELIXIR, the European infrastructure for life science information, aims to provide access to this wealth of biological data as well as bioinformatics tools. ELIXIR offers the possibility to archive, integrate, analyse and exploit the large and heterogeneous data sets of modern life science research beyond the life-time of individual research projects. It has been acknowledged as one of the most strategic research infrastructures in Europe. The Luxembourg-based ELIXIR implementation is supported by the Ministry of Higher Education and Research.

Luxembourg – a data hub for Translational Medicine

ELIXIR-LU, the Luxembourg ELIXIR Node, is based at the LCSB. The Node focuses on long-term sustainability of tools and data for translational medicine. Translational medicine data integrate clinical information with molecular and cellular data for a better understanding of diseases. They bridge the gap between the molecular level, findings from the laboratory, and the clinical observations and applications. ELIXIR-LU facilitates long-term access to those research data. This allows the reuse of previously generated translational medicine data to address new research questions and dramatically save time and costs. With ELIXIR-LU we want to overcome the major hurdles in the availability of biomedical data for a wider research community: fragmentation of data types, different terminologies and the legal challenges of sharing personal data. Through suitable data management systems that collect and integrate all types of data, support in the curation and harmonisation of clinical data and secure data hosting and analysis platforms we will open up existing translational medicine data to the research community.

ELIXIR-LU promotes and further develops quality and security of data processing, data stewardship and GDPR compliance in biomedical research on the national and the international level. Activities include a national GDPR working group for scientific research and Horizon 2020-funded projects such as ELIXIR-CONVERGE, B1MG, FAIRplus, Smart4Health, HealthyCloud and BY-COVID.

ELIXIR-LU offers the following services, available for life science researchers as well as biomedical stakeholders in the EU and worldwide:

Secure storage and access management: GDPR[1] compliant data sharing

Integration of well-curated clinical and molecular data from cohorts and large consortia and giving efficient access in line with security and data protection requirements of biomedical research.

Data Catalogue: help researchers to find interesting data

A standardised registry of metadata that enables findability of data from research projects.

Disease maps: enabling better understanding of diseases

Hosting of and development support for integrative maps of molecular mechanisms related to diseases.

Tools: sharing and mining the data

Platforms and tools to facilitate the GDPR-compliant management and sharing of sensitive data as well as analysis of translational medicine data that can be applied directly on data in the ELIXIR-LU repository or used for the analysis of own data sets.

User training: proficiency in data literacy

Workshops and courses on translational medicine data management, processing, standards and structures, analytics, and visualisation as well as reproducibility in research.

[1] General Data Protection Regulation

Doctoral Training Unit: Critical Transitions in Complex Systems (DTU - CriTiCS)

Project coordinators: Jorge Gonçalves, Alexander Skupin **Start:** Autumn 2016

Catastrophic events occur in various fields and at various levels. Examples include earthquakes, stock market crashes and, for individuals, the onset of diseases such as cancer. If we could understand the critical transitions (CTs) that induce catastrophes, we would be better equipped to prevent them arising or at least to mitigate their effects. Yet, despite much multidisciplinary endeavour, current tools often lack a rigorous theoretical foundation and sometimes exhibit poor predictive power.

The research within the Doctoral Training Unit (DTU) CriTiCS confronts this problem within a range of disciplines in the areas of clinical science, immunology, biology, and finance. Diverse approaches are employed, including data collection (from new experiments and literature), statistical analysis, mathematical modelling and theory development (critics.uni.lu).

Through synthesising the work undertaken within each discipline, the project as a whole is designed to enable the development of a more robust, generalised, interdisciplinary theory of CTs. Such theory may be used first to classify CTs according to their dynamics and then to provide the foundations for:

- Identifying early warning signals to enable timely and reliable predictions of catastrophes
- Developing tools to model, analyse, and detect CTs in diverse areas of application

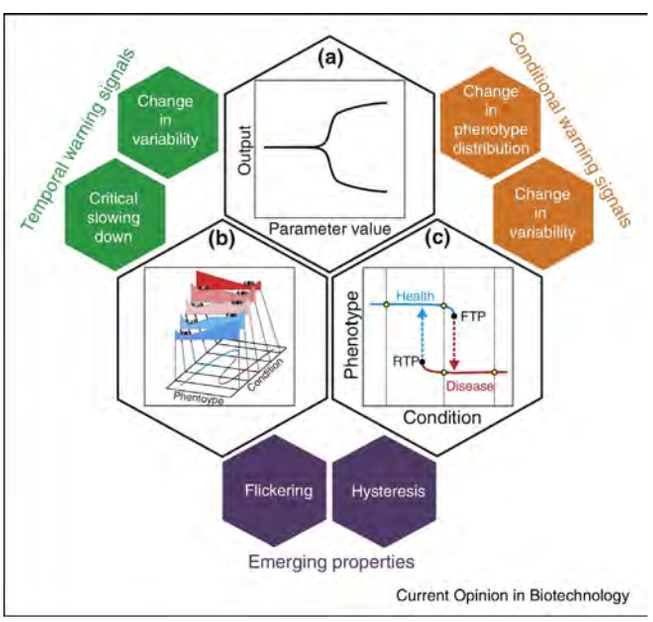
Ultimately, the goal of the project overall is two-fold: to support more advanced research of CTs within scientific disciplines and, in multiple fields, to improve society's ability to anticipate CTs to undesirable states.

The CriTiCS consortium is led by the LCSB, which hosts its two coordinators, and is comprised of 11 doctoral students, 10 supervisors, 1 postdoctoral researcher, and 3 international external researchers. The interdisciplinarity of the project is increased by the presence of supervisors from other departments of the University of Luxembourg from the Department of Physics and Materials Science, the Luxembourg School of Finance and the Department of Life Sciences and Medicine, as well as from another national partner, the Luxembourg Institute of Health. The collaboration and interaction among these partners is of great importance for the development of the project. This comes for instance from the mutual benefit from the interaction between computational/analytical partners with experimental partners having complementary approaches, but also from the interaction of partners with similar backgrounds to which the project provides interlocutors on the same ground. Regular meetings and workshops are held to enhance the interactions between the students and to allow them to present their research and to identify potential collaborations across projects.

For the students, the ambition of this project is not only to enable them to achieve more than discipline-specific expertise, but also to experience first-hand the development of integrated research that:

- Produces cross-fertilisation between disciplines,
- Synthesises empirical investigation and theoretical development, and
- Combines basic and applied scientific approaches.

This project is funded by the Luxembourg National Research Fund (FNR).



Copyright: Trefois, C., et al. (2015). Critical transitions in chronic disease: transferring concepts from ecology to systems medicine. Curr. Opin. Biotechnol. 34, 48–55. doi:10.1016/j.copbio.2014.11.020

Doctoral Training Unit: Microbiomes in One Health (DTU - MICROH)

Project coordinator: Paul Wilmes **Start:** September 2018

In a changing and interconnected world, the functions of microbiomes must be better understood in view of sustaining the health of the human population. Two important healthcare challenges of our time are linked to microbiomes in different ecosystems, notably the spread of antimicrobial resistance genes and the increasing prevalence of chronic diseases.

The field of microbiology is currently undergoing a revolution driven largely by a shift away from classical reductionist approaches towards the study of microorganisms directly in their native environments through advanced analytical methods. These approaches are allowing us to unravel the interdependencies between microbiomes associated with animals, the environment, and humans.

The concept of "One Health" as well as our Doctoral Training Unit, MICROH, recognise that human health is connected to the health of animals and the environment. MICROH is a truly interdisciplinary doctoral training programme aimed at studying the interactions within and between microbiomes in relation to human health by using systems-level approaches. We focus on two main research areas which represent frontier research topics of immediate public health relevance: (i) the spread of antimicrobial resistance genes and their acquisition by clinically relevant microorganisms, and (ii) the role of the human microbiome in chronic diseases.

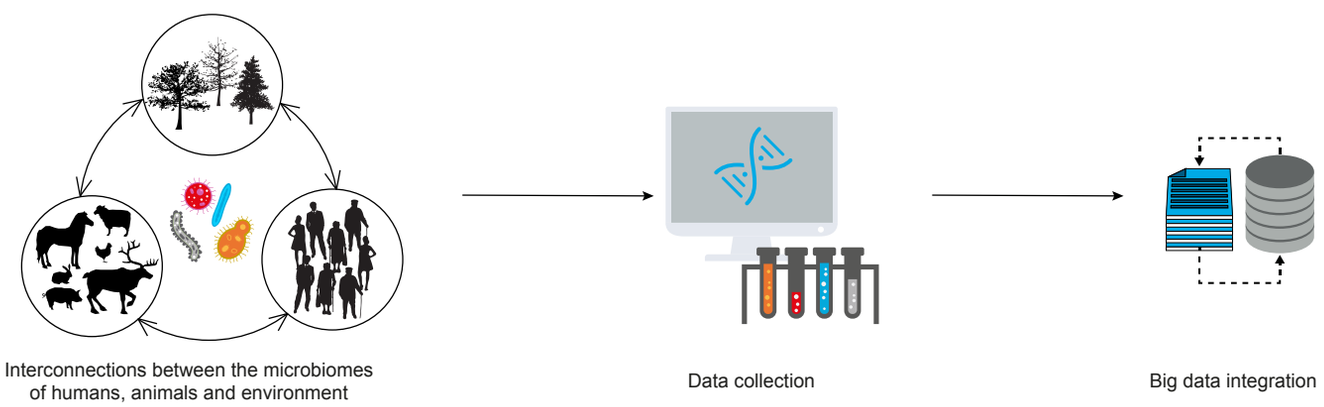


Figure: Bridging microbiology and big data analytics in an interdisciplinary doctoral training unit.

This Doctoral Training Unit (DTU) started in September 2018 and will leverage the existing world-leading expertise in microbiology and systems biology in Luxembourg. The DTU links all major national research institutions active in the field of microbiology, namely the LCSB, the Department of Life Sciences and Medicine and the Department of Physics and Materials Science of the University of Luxembourg, the Luxembourg Institute of Health, the Luxembourg Institute of Science and Technology, the Laboratoire National de Santé as well as the private company Laboratoires Réunis. By regrouping individual doctoral research projects focused around the two themes, MICROH will generate important new knowledge on how to leverage system-wide big data for the management of human health in the future. We provide an excellent, interdisciplinary research and training environment hosting 17 doctoral students and 2 postdocs/project managers, all connected via 21 supervisors, from 7 national as well as 3 international partner institutions. The learning and networking opportunities of the MICROH DTU have been extended through the FNR-funded Lecture Series "From Single Organisms to Systems Ecology and Evolution" in which world-leading experts in the microbiome field present their cutting-edge research to the MICROH students, postdocs, supervisors, and interested listeners. Overall, the DTU will facilitate the education and training of the next generation of microbiome scientists with excellent skills and knowledge essential to pursuing successful career paths in the future.

This project is funded by the Luxembourg National Research Fund (FNR).

Doctoral Training Unit: Molecular, Organellar and Cellular Quality Control in Parkinson's disease and other Neurodegenerative Diseases (DTU - PARK-QC)

Project coordinator: Jens Schwamborn **Start:** July 2018

Ageing is the most important risk factor for neurodegenerative diseases, such as Parkinson's disease (PD), and linked to a progressive decline of molecular, organellar and cellular homeostasis quality control mechanisms. As for other incurable neurodegenerative diseases, mutations in genes responsible for monogenic forms of PD have been identified, that directly interfere with quality control mechanisms that affect (i) molecular quality control, e.g. via protein misfolding and aggregation or (ii) key instances of organellar quality control, e.g. via impaired mitochondrial clearance, and (iii) cellular quality control for selective elimination of damaged cells.

To define the missing link between these functional networks, in PARK-QC we dissect mechanisms of quality control surveillance using a unique panel of advanced cellular and animal models of PD as well as other neurodegenerative diseases and applying novel computational modelling strategies for the identification of complex regulatory networks underlying dysfunctional quality control mechanisms.

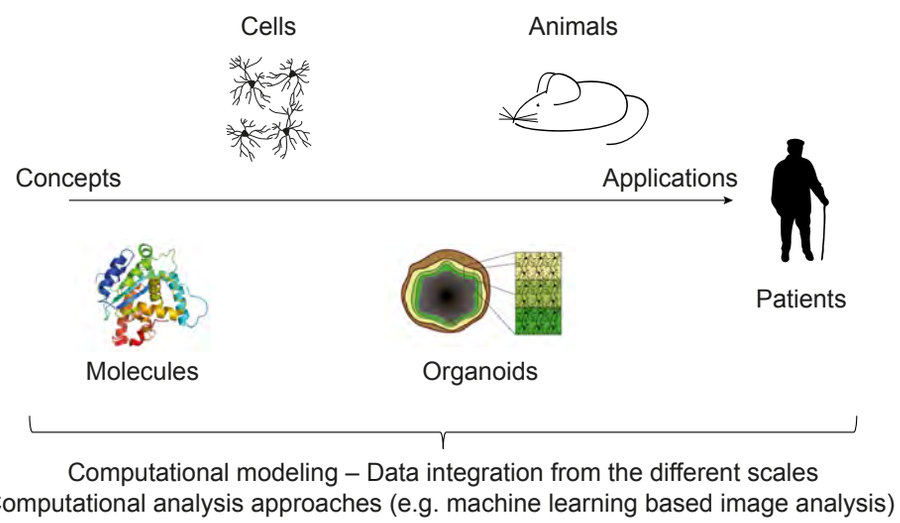


Figure: PARK-QC'S data integration from different scales

Based on these novel experimental approaches and advanced screening platforms for *in vitro* and *in vivo* models, we will use pharmacological and genetic interventions to develop novel therapeutic approaches. Our interdisciplinary approach directly synergises with current national research programmes on PD and is envisaged to translate into novel diagnostic and treatment options for neurodegenerative diseases. In total, the PARK-QC DTU has 17 PhD students with individually coherent but interconnected projects that are overseen by 12 supervisors from 3 national research institutions (LIH-IBBL, CHL and UL).

The year 2021 saw the publication of manuscripts authored by PARK-QC students with four of them as first author contribution. Moreover, a DTU retreat was organised in October with a scientific seminar session and a teamwork challenge. The students took also actively part in the NCER-PD 2021 consortium meeting. Lastly, the students were offered a tailored workshop on Neuropathology by Prof. Mittelbron at the LNS in March 2021 with hands-on training on the different techniques and uses of pathology for clinical diagnosis, in particular applied to Parkinson's disease.

This project is funded by the Luxembourg National Research Fund (FNR) under Grant PRIDE17_12244779.

In addition, the Luxembourg Centre for Systems Biomedicine participates in a number of Doctoral Training Units led by other institutions:

The **NextImmune2** Doctoral Training Unit will investigate different human diseases and disease models to study immune-metabolic crosstalk and understand how communication networks orchestrate and coordinate responses to environmental cues or immunological challenges. It focuses particularly on two aspects of immune regulation, immunometabolism and systems immunology, to broaden our global understanding of the body's immune response on the cell, organ and organism level.

Lead: Prof Dirk Brenner
Partners: Luxembourg Institute of Health (coordination), University of Luxembourg (Luxembourg Centre for Systems Biomedicine, Department of Life Sciences and Medicine)

i2TRON is a doctoral training unit with a strong focus on developing the new generation of translational scientists, who can turn observations in the laboratory, clinical setting or community into interventions that improve health of individuals via innovative diagnostics or treatments. Here we use specific non-communicable diseases (NCDs) as model diseases across auto-immunity/allergy, cancer and neurodegeneration, that are characterised by inflammation as a shared key pathogenic mechanism.

Lead: Prof Rejko Krüger
Partners: Luxembourg Institute of Health (coordination), University of Luxembourg (Luxembourg Centre for Systems Biomedicine, Department of Life Sciences and Medicine), Laboratoire National de Santé (LNS), Centre Hospitalier de Luxembourg (CHL)

The **ACTIVE** Doctoral Training Unit aims to develop and apply new concepts of active matter across biological scales to allow new perspectives on the multiscale organisation of life. Its PhD students work on molecular, cellular and population levels and their interactions using complementary approaches from quantum physics, stochastic thermodynamics, machine learning and molecular biology as detailed in PhD projects.

Lead: Prof Massimiliano Esposito, University of Luxembourg
Partners: University of Luxembourg (Luxembourg Centre for Systems Biomedicine, Department of Physics and Material Science)

The **DRIVEN** Doctoral Training Unit on Data-driven Computational Modelling and Applications trains cohorts of doctoral candidates who develop data-driven modelling approaches common to a number of applications strategic to the Luxembourgish Research Area and Luxembourg's Smart Specialisation Strategies. The DTU creates a bridge between strong methodological core competencies and application domains by training each doctoral candidate both in state-of-the-art data-driven approaches, and in the particular application domain in which these approaches are expected to lead to new discoveries: Computational Physics and Engineering, Computational Biology and Life Sciences, Computational Behavioural and Social Sciences.

Lead: Prof Andreas Zilian, University of Luxembourg
Partners: University of Luxembourg (Luxembourg Centre for Systems Biomedicine, Faculty of Humanities, Education and Social Sciences, Faculty of Science, Technology and Medicine), Luxembourg Institute of Science and Technology (LIST), Luxembourg Institute of Socio-Economic Research (LISER), Digital Lëtzebuerg

Integrative Cell Signalling group

Overview

The general approach of the group is to combine state-of-the-art imaging and single cell techniques with mechanistic modelling and bioinformatics analyses to investigate how the emergent behaviour of cells, organs and organisms originates from molecular entities. To understand the underlying cell signalling mechanisms, we focus on live cell imaging and single cell transcriptomics analyses complemented by multi-scale simulations. Our major interests are signalling pathways related to neurodegeneration and epileptogenesis with a particular focus on mitochondrial dysfunction and dynamic coupling between intercellular energy metabolism and cell signalling such as Ca^{2+} dynamics. Therefore, we use induced pluripotent stem cell (iPSC) lines, human post mortem brain samples, and zebrafish for phenotyping assays including sophisticated image analysis, bioinformatics and information theory-based methods to reveal the dynamic consequences of disease-related perturbations at single cell resolution. During the COVID-19 pandemic, the group has played a major role in the Research Luxembourg COVID-19 Taskforce by integrating mechanistically data into epidemiological models and perform statistical projections of the pandemic dynamics to advice political decision makers.

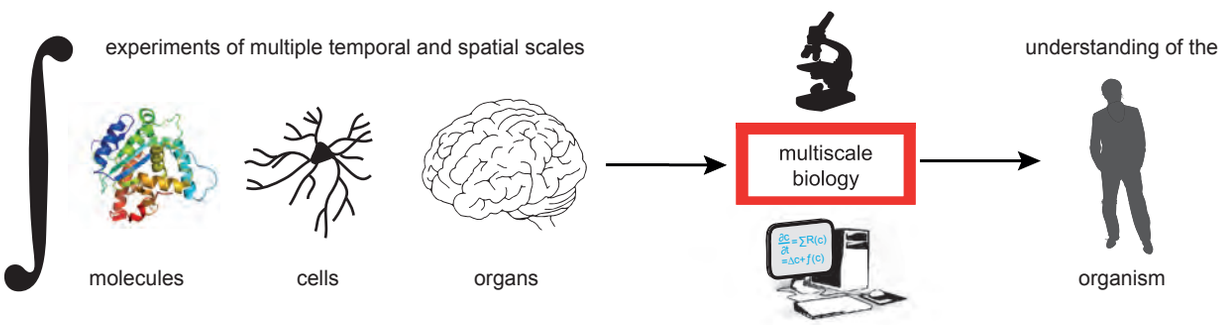


Figure: Integrative approach to understand underlying signalling mechanisms in health and disease.

Key projects

Dissecting cell population heterogeneity dynamics

Cell fate commitment is the key process for understanding how a multicellular organism's genotype gives rise to phenotypic traits including disease development and progression. To understand the role of epigenetically-induced cell heterogeneity and its importance for development and pathogenesis, we characterise population dynamics of diverse models including iPSC differentiation, human breast cancer cells and development of zebrafish brains at single cell resolution. We quantify cellular heterogeneity dynamics by combining single cell RNA sequencing approaches, microscopy and flux cytometry with advanced bioinformatics analyses. The resulting multi-scale data enables to get a comprehensive picture of cell fate dynamics and is integrated into a developmental modelling framework. The methods developed to characterise critical transitions of cell states in this project are also applied to changes of mitochondrial dynamics.

Cellular heterogeneity in neurodegeneration

The human brain is probably the most complex system in the universe and perturbations of its homeostasis are linked to severe diseases such as neurodegeneration and epilepsy. Besides neurons, glial cells like microglia and astrocytes play a critical role in the pathogenesis of neurodegenerative diseases. For example, a subfraction of microglia seems to lose their protective functions and become harmful to the brain. These subgroups of microglia engage maladaptive inflammatory or phagocytic responses that promote neuroinflammation and neuronal cell death and may contribute to the progression of Alzheimer's disease (AD). To characterise this intercellular phenomenon, we image post mortem human brain samples from AD subjects and controls, and develop an unbiased automatic image analysis pipeline. This enables to extract a wide range of cellular features from individual cells including standard morphological characteristics to more innovative graph-based features accounting different patterns of arborisation and complexity. Comparing brain tissues from patients and controls for different brain regions, we identify alterations of the potentially harmful microglia, characterise their key phenotypic features and impact on the disease. Additionally, this methodology provides new tools for the understanding of microglia, and its involvement in neurodegenerative processes and other brain alterations.

Brain energy metabolism in neurodegeneration

Brain energy metabolism is based on the fine-tuned interplay of glycolysis and mitochondrial activity, as the energy providing pathways, and intercellular energy transfer. It represents a promising unifying perspective for neurodegenerative diseases because mitochondrial dysfunction, as a common hallmark, interrelates several known pathological processes including dopamine synthesis, oxidative stress and proteostasis To account for the complex interplay of different cell types in brain energy metabolism, we combine high-resolution imaging and mechanistic spatial modelling of intra- and intercellular energy homeostasis. In collaboration with Mark Ellisman at the National Center of Microscopy and Imaging Research (NCMIR) at La Jolla, we use super-resolution 3D electron microscopy (EM) to image astrocytic morphologies and mitochondria to develop spatiotemporal in silico models of intracellular energy metabolism that allow us to investigate the dynamic consequences of potentially disease related morphological and molecular impairments.

To elucidate the underlying dynamic mechanisms of impaired brain energy metabolism, we study mitochondrial dynamics at different levels. First, we analyse the crosstalk between Ca^{2+} signalling and mitochondrial activity by live cell fluorescent imaging and dynamic modelling, and show how the coupling can increase robustness of energy homeostasis within cells. Second, we use PD-related iPS cell lines and pharmacological perturbations together with multiscale modelling to study mitochondrial transport and its impact on mitochondrial turnover. This fission- and fusion-based processes ultimately determine the energy profiles along neurites and their functionality. Finally, we develop a microscopic in silico model of mitochondria to investigate how mitochondrial morphology is affecting energy production. This project is partially funded by the FNR.

Mechanisms of epilepsy establishment

Epilepsy is characterised by a hyperexcitability of the brain that can lead to seizures. To investigate how this hyperexcitability is established within the brain and how seizures build up, we monitor epileptogenesis in zebrafish models at single cell resolution. For this purpose, we combine EEG measurements, Ca^{2+} dynamics imaging and single cell RNA sequencing experiments with machine learning algorithms and mechanistic modelling to characterise perturbation specific mechanisms of seizure dynamics and disease development. Our integrative approach identifies distinct brain cell populations for different disease causes and our advanced analysis methods allow for reliable seizure predictions. These insights may also support future translational intervention in patients..

Principal Investigator
Alexander Skupin
Start: October 2014

Key publications

1. Novak, G., Kyriakis, D., Grzyb, K., Bernini, M., Rodius, S., Dittmar, G., Finkbeiner, S., and Skupin, A. (2022). Single-cell transcriptomics of human iPSC differentiation dynamics reveal a core molecular network of Parkinson's disease. Commun. Biol. 5, 1–19.
2. Wilmes, P., Zimmer, J., Schulz, J., Glod, F., Veiber, L., Mombaerts, L., Rodrigues, B., Aalto, A., Pastore, J., and Snoeck, C.J. (2021). SARS-CoV-2 transmission risk from asymptomatic carriers: results from a mass screening programme in Luxembourg. Lancet Reg. Health-Eur. 4, 100056.
3. Tiraboschi, E., Martina, S., Ent, W., Grzyb, K., Gawel, K., Cordero-Maldonado, M.L., Poovathingal, S.K., Heintz, S., Satheesh, S.V., Brattespe, J., et al. (2020). New insights into the early mechanisms of epileptogenesis in a zebrafish model of Dravet syndrome. Epilepsia 61, 549–560.
4. Salamanca, L., Mechawar, N., Murai, K.K., Balling, R., Bouvier, D.S., and Skupin, A. (2019). MIC-MAC: An automated pipeline for high-throughput characterization and classification of three-dimensional microglia morphologies in mouse and human postmortem brain samples. Glia.
5. Komin, N., and Skupin, A. (2017). How to address cellular heterogeneity by distribution biology. Curr. Opin. Syst. Biol. 3, 154–160.

Interventional Neuroscience group

Overview

The Interventional Neuroscience group is a highly translational research unit that transfers innovative neurosurgical methods form bench to beside and back. Their main focus is applied computational science for clinical practice in neurosurgery and related fields. Researchers and clinicians develop methods that use artificial intelligence and machine learning algorithms as well as tools used in image-guided procedures and biomedical modelling in neurosurgery and systems biomedicine. Besides scientists and clinicians, PhD, MD and Master students are working hand in hand in highly interdisciplinary research projects. Collaboration partners include the Centre Hospitalier de Luxembourg (CHL), the Luxembourg Institute of Health (LIH) and the Laboratoire National de Santé (LNS). This allows to analyse results from clinical research on a highly scientific level and transfer those efficiently from the lab setting into the clinic and back. Innovations from research directly benefit patient care, and clinical observations can lead to new insights. The developed tools in the Interventional Neuroscience group offer highly innovative potential and are interesting for industrial partners.

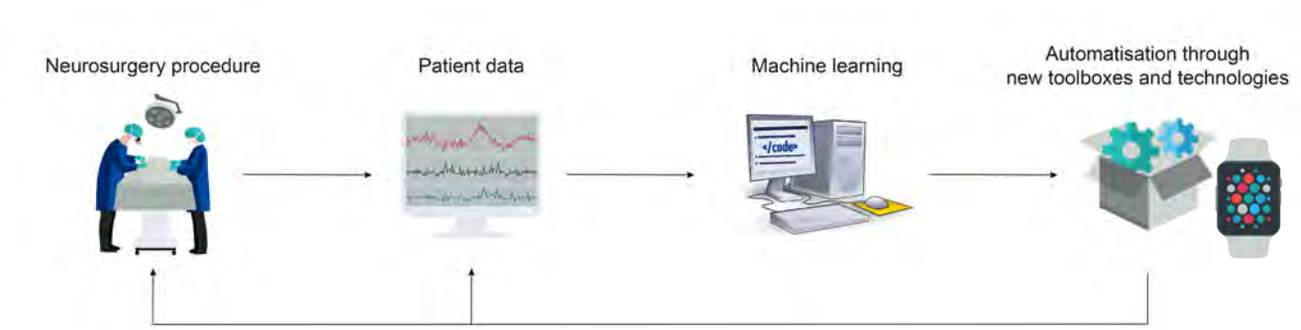


Figure: Bridging the gap between the research and patient care.

Key projects

AI-based diagnosis of COVID-19 from imaging X-Ray and CT (AICovIX)

This project focuses on the study and development of Computer-Aid-Diagnosis solutions for X-ray and CT (computed tomography) of COVID-19 pneumonia. Currently, hospitals are using medical images such as X-ray or CT to assess potential lung damage of COVID-19 patients. Analysis of these images with artificial intelligence solutions could allow for better and faster diagnosis as well as better understanding of COVID-19 effects; in addition, it could significantly improve disease treatment and allocation of resources. To this end, both an analysis of current solutions and the development of deep learning in-house solutions are performed. Special focus is placed on model generalizability, transportability, and clinical applicability, in particular on the different sources of data-set bias that could hamper wide clinical translation. Hence, the aim of this project is not only to provide a specific solution but also to assess the complex problem of closing the gap between the current proposed solutions and its clinical application. This project received funding from the FNR COVID-19 fast track scheme.

Integrated neurosurgical perioperative imaging (INSITU® study)

This study evaluates the diagnostic accuracy of state-of-the-art laser technologies, such as Raman spectroscopy (RS) and optical coherence tomography (OCT), in the evident intraoperative tumour diagnosis. Tissue specimens taken during the surgery of tumours of the nervous system (brain, spinal cord, peripheral nerves) are examined with a novel robotised device (SOLAIS System, Synaptive, Canada). Recorded data are classified using methods of artificial intelligence/machine learning and correlated with conventional tumour diagnostic methods (histopathology, computed tomography, etc.). The aim of this project is to support a clear intraoperative tumour diagnosis, which in the future will help to perform resection control during surgery, as well as to clarify perioperatively if a tumour has been sufficiently removed or if there are still remaining parts. These new techniques may be able to replace or supplement intraoperative MRI and will help the surgeon in direct analysis of the data under the surgical microscope. Further findings will reveal new information on the tumour composition at the protein level. This could improve personalised adjunctive postsurgical treatment and could potentially close the gap between epigenetics, histopathology, imaging and biochemistry. This innovative research project, within a collaborative partnership between the National Service for Neurosurgery at the CHL, the LIH and the LNS, is funded by the Luxembourgish Cancer Foundation.

Deep brain stimulation planning and postoperative analysis with deep learning methods

Deep Brain Stimulation (DBS) is a clinically proven surgical treatment of the symptoms of Parkinson's disease and other neurological and psychiatric diseases. Patients receiving DBS have electrodes implanted into specific brain structures containing different functional areas. The trajectory for such electrode insertion has to be a straight line through the brain, without injuring brain structures or blood vessels. The post-operative reconstruction of the DBS electrodes is important for an efficient stimulation parameter tuning. A major limitation of existing DBS approaches is that they are manual or semi-automatic, and thus both time-consuming and subjective. High quality 3D images are needed to define the best path in each patient for inserting the electrodes and to decide on a precise electrode positioning. Sophisticated device programming to reach an optimal electrical stimulation for each patient after surgery is currently lacking as well. The PaCER algorithm developed in our team most accurately detects the electrode position, based on postoperative CT scans. Furthermore, we work on algorithms for automatic trajectory planning for DBS. The aim is to develop an automatic image processing pipeline offering access to high quality 3D images and guidance for planning and execution of this procedure. To define optimal electrical stimulation for each patient after surgery, we build real-time feedback loops to deliver best electrical stimulation, thus to design personalised feedback systems optimised for each patient.

Principal Investigator
Frank Hertel

Precision therapy concepts in gait and movement disorders with wearables and AI-based data analytics (MoveSenseAI study)

This project designs an AI-based motor prediction and evaluation system to objectively study the effects of therapeutics and to gain new insights on how motor impairments affect patients in everyday life. The project aims to monitor, detect, classify and predict early on gait and motor symptoms in Parkinson's disease and spinal disorders in order to analyse and restore patients' mobility. Wearable motion sensors from the INS group and a new foot pressure sensor from the IEE S.A. company, Luxembourg, are used to capture movements and annotated data of patients in a clinical setting and during daily activities at home. The project should unlock the powerful symbiosis of combining wearables and AI for the next generation of therapeutic decisions to improve clinical outcomes and reduce healthcare costs. The BRIDGE project has been selected for funding by the FNR and is conducted as a collaboration between the National Department of Neurosurgery (CHL), the Systems Control group (LCSB) and IEE S.A..

Deep learning tools for microscopical images

Automation of biological image analysis is essential to boost biomedical research. The recent advances in computer vision and deep learning outperformed other technologies becoming state-of-the-art. The project's aim is to build precise and intuitive tools for pattern recognition tasks using deep learning techniques to analyse microscopy images from quality control to disease diagnosis.

Key publications

1. Husch A., et al. (2018). Post-operative deep brain stimulation assessment: Automatic data integration and report generation. Brain Stimul. July 1;11(4):863-866. doi: 10.1016/j.brs.2018.01.031. Epub 2018 (Feb. 1).
2. Husch A., et al. (2017). PaCER - A fully automated method for electrode trajectory and contact reconstruction in deep brain stimulation. Neuroimage Clin. Oct 6;17:80-89. doi: 10.1016/j.nicl.2017.10.004. eCollection 2018.
3. Bernard F., et al. (2017) Shape-aware surface reconstruction from sparse 3D point-clouds. Medical Image Analysis 38 77–89. doi: 10.1016/j.media.2017.02.005.
4. Husch A, et al. (2015). Assessment of Electrode Displacement and Deformation with Respect to Pre-Operative Planning in Deep Brain Stimulation. H. Handels et al. (eds), Informatik aktuell. Springer Vieweg, Berlin, Heidelberg, pp: 77-82, doi 10.1007/978-3-662-46224-9_15.
5. Bremm R.P. et al. (2020). Analysis and visualisation of tremor dynamics in deep brain stimulation. Conference Paper (accepted), Biomed Eng. (Biomed Tech.) Conference, Leipzig, Germany, 29 September – 1 October 2020.

Medical Translational Research group

Overview

The motto of the Medical Translational Research group is to combine research with clinical care and clinical research. Translational research is carried out in close collaboration with the Bioinformatics Core of the LCSB. The team, moreover, provides education on disease-related and general medical knowledge within the interdisciplinary environment of the LCSB. It emphasises research activities among physicians in Luxembourg and the Greater Region consisting of Luxembourg, France and Germany. While actively providing clinical care to patients, the Medical Translational Research group forms the ideal link between bench and bedside.

Many chronic diseases often share common underlying mechanisms such as inflammation, disturbed signalling or polyclonal proliferation. The interplay between chronic disease mechanisms are currently underexplored. The Medical Translational Research group is interested in exploring the nature of these common mechanistic features by employing NGS or omics methods to sample material from cell culture, mouse models and human clinical trials. Major foci of research are metabolism disorders, microbiome, cancer, inflammation and comorbidities, in addition to sequencing both familial and nonfamilial.

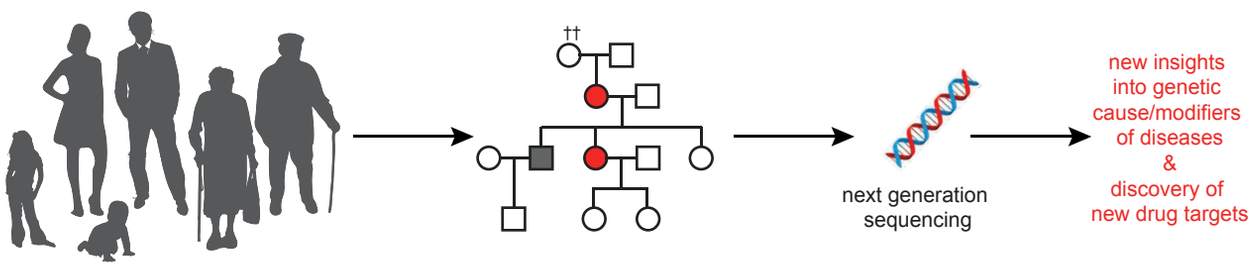


Figure: Principles of family sequencing projects.

Key projects

Metabolism disorders

Metabolic disorders include obesity, insulin resistance, diabetes and fatty liver diseases. Several clinical and experimental projects are ongoing in collaboration with several clinical partners such as the University of Magdeburg, the Saarland University Medical Center in Homburg/Saar and the University of Lorraine in Nancy. Together with Charité Berlin, we will be investigating the effects of calorie restriction/fasting on inflammation and especially rheumatoid arthritis.

Microbiome

We are interested in studying dynamic changes in the microbiome of healthy individuals and patients. Understanding microbiome-related consequences in health and disease opens a huge opportunity for designing personalised diagnostics and treatments. Together with collaborators at the LCSB and hospitals, we focus on microbiome-dependent changes in conditions such as malignant diseases or inflammation.

In the SMART (saliva microbiome and radiation therapy) clinical study, we are investigating the changes in the saliva microbiome of head and neck cancer patients undergoing radiation therapy. The microbiome signatures are expected to facilitate understanding the severity of side effects as well as to discover novel and individualised treatment options. In the MICROH-Liver project, using 3D liver models, we will be investigating the role of microbial metabolites in glucose and lipid homeostasis. Our microbiome research is supported by the University of Luxembourg and the Luxembourg National Research Fund (FNR).

Endocrinology

An ongoing effort relies in the detection of candidate genes for endocrine disorders, both in familial or sporadic settings. Together with the University of Würzburg we sequence a series of adrenal tumors and the corresponding leukocyte DNA to find the causing mutations for the onset of sporadic Cushing´s disease. Conn syndrome is another adrenal disease. It is an aldosterone-producing adenoma which may result in hypertension, muscle cramps and weaknesses as well as chronic headaches. With our partners from Alicante and Munich, we have identified a family with a suspected inherited genetic cause of Conn syndrome. We have sequenced the family to investigate the genetic causes. We are validating the results with a CRISPR/Cas gene-edited *in vitro* model. The results of the project will help identify modifiers of the disease and discover new drug targets in aldosterone regulation.

Inflammation and signalling

Inflammatory vascular disease such as atherosclerosis or vascular inflammation affect many subjects of the world population. Since vascular diseases represents a lipid-driven inflammation the pathophysiology requires a wiring of metabolism and immune system. *IRG1* is a macrophage specific gene characteristic for immune system activation and is induced by bacterial stimuli as well as oxLDL. The *IRG-1* dependent production of the substrate itaconic acid (ITA) directly interferes with cellular tricarboxylic cycle (TCA) metabolism. *IRG-1* also mediates the production of reactive oxygen species (ROS) in macrophages. These data suggest that *IRG-1* links innate immune activation with metabolism. We aim to characterise the role if *IRG-1* in inflammatory vascular disease *in vivo* and *in vitro*. This project aims at defining a novel player as potential target mechanism for inflammatory processes in the vasculature. Another molecule of interest is β3 integrin, which is shown to be involved in various pathophysiologic processes such as cancer/neoangiogenesis, platelet aggregation, inflammation, bone resorption, and vascular disease. We further elucidate the role of β3 integrin in a cell-specific fashion using Cre/Lox technology *in vivo*, in conditional β3 deletion *in vitro* models and *in silico* utilising high-throughput data acquisition followed by modelling of the signalling pathway based on the experimental data. This research has received funding from the European Union's Seventh Framework Programme.

Principal Investigator
Jochen Schneider
Start: February 2011

Comorbidities

In collaboration with Charité Berlin, providing a huge cohort of tinnitus and comorbid disorders, we are investigating the epigenome and metabolome of these patients to discover mechanistic causative factors to stratify the study population. As preparatory work, we will be collaborating with the Department of Life Sciences and Medicine, the Luxembourg Institute of Health and the Integrated Biobank of Luxembourg for the development of analytic methods.
In another study, PERMENTI, we are investigating the psychological effects, especially depression, caused by inflammatory bowel disease (IBD). Together with the Centre Hospitalier Emile Mayrich in Esch-sur-Alzette, we will investigate the effects of immunological factors in IBD patients on the mental well-being of the patients.

Shaping the biomedical landscape in Luxembourg and beyond

In addition to the research projects described above, Prof. Jochen Schneider also holds various functions impacting the biomedical landscape in Luxembourg and beyond by:

- Serving as deputy director for the first year of medical education of students at the University of Luxembourg
- Being a member of the Comité National d'Ethique de Recherche (CNER), Luxembourg
- Being a member of the Animal Experimentation Ethics Committee (AEEC)

Key publications

1. Kaysen A, et al. (2017) Integrated meta-omic analyses of the gastrointestinal tract microbiome in patients undergoing allogeneic hematopoietic stem cell transplantation. Transl Res. doi: 10.1016/j.trsl.2017.06.008. [Epub ahead of print]
2. Biemann R., et al. (2016) Serum bile acids and GLP-1 decrease following telemetric induced weight loss: results of a randomized controlled trial. Sci Rep, 25(6): 30173, doi: 10.1038/srep30173
3. Su X, et al. (2016) Antagonizing Integrin β3 Increases Immunosuppression in Cancer. Cancer Res. ;76(12):3484-95. doi: 10.1158/0008-5472.CAN-15-2663.
4. Ba Le V., et al. (2015) Platelet activation and aggregation promote lung inflammation and influenza virus pathogenesis. AJRCCM, 191(7): 804-819, doi: 10.1164/rccm.201406-1031OC
5. Elbelt U., et al. (2015) Germline and additional somatic ARMC5 mutations causing familial primary bilateral macronodular adrenal hyperplasia and Cushing´s syndroma. JCEM, 100(1): E119-28. doi: 10.1210/jc.2014-2648

Molecular & Functional Neurobiology group

Overview

The Molecular & Functional Neurobiology Group employs molecular, 'omics' and single-cell approaches to decipher the genetic and non-genetic origins of Parkinson's disease (PD). We explore the role of mitochondria in the pathogenesis of idiopathic and genetic PD using post-mortem and iPSC-derived tissues. Our work aims at the identification of novel cellular pathways, which may be targets for therapeutic intervention in the future.

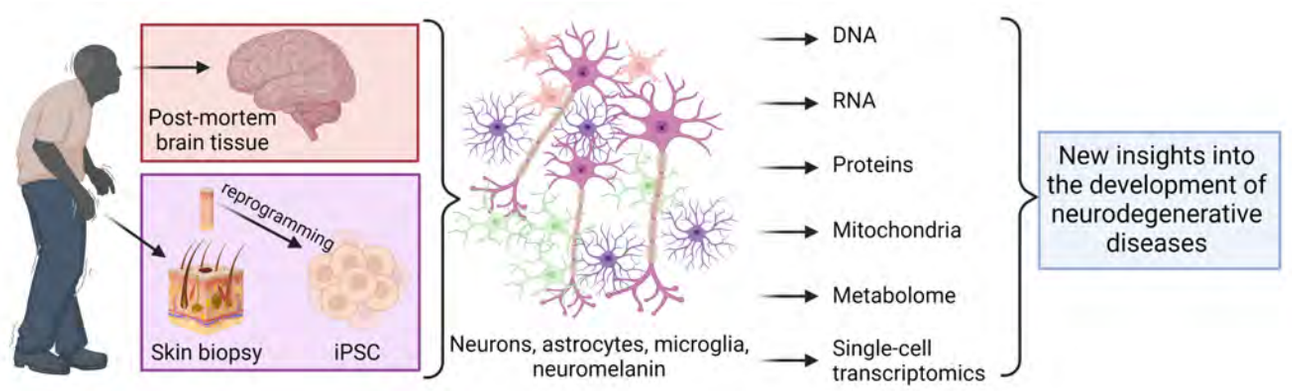


Figure: Analysis of mitochondrial phenotypes in cell culture models and post mortem tissues of neurodegenerative diseases.

Key projects

Mitochondrial-based stratification of idiopathic Parkinson's disease (IPD) patients

Idiopathic Parkinson's disease (IPD) is a complex condition, in which a genetic cause has not been defined, and thus encompasses patients with diverse underlying disease mechanisms. In this project, we are assessing the value of mitochondrial-based stratification approaches to help disentangle the complexity of PD. Our study aims to identify approaches to categorise IPD patients into homogeneous subgroups that will facilitate mechanistic studies, and drug screening ventures. In collaboration with the Biomedical Data Science group, we explored published datasets from the FOUNDIN-PD study. RNA-seq data of iPSC-derived 65d-old dopaminergic neurons show that the abundance of a gene associated to familial PD can be used to cluster IPD patients into two subgroups with distinctive mitochondrial pathway signatures. Identified altered pathways were explored in an independent cohort comprising iPSCs from seven IPD cases and four age-matched controls. We assessed parameters such as mtDNA maintenance, mitochondrial morphology and mitophagy in 2D neuronal cultures. Cluster and machine learning analyses of these results identified a subclass of IPD patients depicting aberrant mitochondrial function ("mito-IPD"). Together with the Developmental & Cellular Biology group, we investigate the implication of our findings in midbrain organoids derived from the same cohort. We are evaluating cell type dynamics and viability, neuronal development and function as well as astrocyte function. These experiments revealed possible links between mitochondrial dysfunction and astroglial activation in mito-IPD. This project (Model-IPD) is funded through the ATTRACT programme of the Luxembourg National Research Fund (FNR).

Single-cell transcriptomic analysis of midbrain tissue from IPD patients and healthy controls

To overcome the limitations of common bulk RNA analysis approaches, we performed single-cell RNA sequencing of post-mortem human midbrain tissue of five IPD patients and six age-matched controls to obtain an unbiased and global view of the cell type composition and cellular phenotypes of IPD. We identified all major known midbrain cell types including different neuronal, glia and microvasculature cells and detected differentially expressed genes in each of those cell types. Of note, we discovered an IPD-specific neuronal cluster characterised by overexpression of CADPS2 and low TH levels, which we believe to be dysfunctional dopaminergic neurons. In addition, we observed a disease-specific upregulation of microglia and astrocytes further strengthening the role of neuroinflammation in PD (Smajic et al. Brain 2021). This project is also part of the FNR ATTRACT project Model-IPD.

IPSC-derived microglia as a model to study inflammatory phenotypes in IPD

Many studies in human biosamples have shown a significant upregulation of proinflammatory cytokines and chemokines in PD patients. This includes our own work, which identified increased levels of circulating cell-free (ccf) mtDNA and an upregulation the proinflammatory cytokine IL-6 in serum from PD patients with PRKN or PINK1 mutations (Borsche et al.

Brain 2020). Inspired by these results, we sought to investigate, if IPD inflammation can be modeled in iPSC-derived microglia. Our preliminary experiments show that microglial cultures from IPD patients are indeed more responsive to LPS than control cells. Moreover, an upregulation of NLRP3 expression suggests stronger immune priming in the patient glia (Badanjak et al. Front Cell Dev Biol 2021). Alpha-synuclein is a key protein involved in idiopathic as well as genetic forms of PD, which has been associated with the release of inflammatory mediators and mitochondrial dysfunction. Using iPSC-derived microglia as well as neuron-glia co-cultures, we aim to further study the effect of alpha-synuclein on mitochondria modulation and NLRP3 inflammasome activation. This project is carried out within the framework of the FRNR CORE Junior project NeuroFlame.

Principal Investigator
Anne Grünewald
Start: January 2016

Markers and mechanisms of reduced penetrance in *LRRK2* mutation carriers of PD
So far, only few factors have emerged, which define disease penetrance or constitute signs of advanced progression in LRRK2-PD. By contrast, in fibroblasts from G2019S mutation carriers, we previously detected a correlation between mtDNA deletions and disease status (Ouzren et al. Ann Neurol 2019). Furthermore, cells from manifesting G2019S carriers had impaired complex I function as well as increased mitochondrial mass and mtDNA copy number, suggestive of impaired mitophagy. Moreover, elevated Nrf2 levels implicated ROS scavenging in the penetrance of LRRK2-PD (Delcambre et al. Front Neurol 2020). Thus, we now speculate that, in manifesting G2019S mutation carriers, increased LRRK2 kinase activity interferes with Nrf2 antioxidant signaling, which in turn (i) promotes mtDNA damage, (ii) mediates ccf-mtDNA release, and eventually (iii) triggers pro-inflammatory signaling. We are exploring this hypothesis in patient iPSC-derived neurons and microglia. Of note, G2019S-mutant iPSC-derived microglia exhibit higher levels of pS1292 LRRK2, a known pathogenic form of phosphorylated LRRK2, and this increase is accompanied by an upregulation of pRab10, a key LRRK2 target. Our findings further strengthen the role of LRRK2 kinase activity in the pathogenesis of PD. We are currently investigating the effect of kinase inhibitor treatments on glial activation in our models. This project is part of the Research Unit "ProtectMove" (www.protect-move.de), which is co-funded by the FNR and the DFG.

Impact of PD-associated alpha-synuclein mutations on astrocytic metabolism
Recently, the neurocentric view of PD has been challenged with evidences that the disrupted interaction between neurons and glia contribute to the disease progression. Notably, there is a strong body of evidence indicating that astrocytic metabolism is pivotal to ensure proper neuronal function. In light of these findings, we aim to study the neuronal-astrocytic cooperation in astrocytes derived from patients harboring mutations in SNCA, with a special focus on metabolic alterations that could exacerbated neuronal pathology. Within the framework of the FNR-funded project CAMeSyn, we are collaborating with Dr Johannes Meiser (LIH) and Prof Rejko Krüger (LCSB, LIH). Furthermore, applying a differentiation protocol developed in the group of Prof Jari Koistinaho (University of Helsinki), we are generating pure non-activated astrocyte cultures from patients and controls, which are suitable for metabolomics studies, as well as cytokine profiling in the context of neuroinflammation.

Key publications

1. Smajić S, Prada-Medina C, Landoulsi Z, Ghelfi J, Delcambre S, Dietrich C, Jarazo J, Henck J, Balachandran S, Pachchek S, Morris C, Antony P, Timmermann B, Sauer S, Pereira S, Schwamborn J, May P, Grünewald A, Spielmann M. Single-cell characterization of patient midbrain tissue reveals tissue remodeling and glial activation in Parkinson's disease. Brain 2021; 10.1093
2. Borsche M, König IR, Delcambre S, Petrucci S, Balck A, Brüggemann N, Zimprich A, Wasner K, Pereira SL, Avenali M, Deuschle C, Badanjak K, Ghelfi J, Gasser T, Kasten M, Rosenstiel P, Lohmann K, Brockmann K, Valente EM, Youle RJ, Grünewald A (shared senior author), Klein C. Mitochondrial damage-associated inflammation highlights biomarkers in PRKN/PINK1 parkinsonism. Brain 2020; 143:3041-3051
3. Badanjak K, Mulica P, Smajic S, Delcambre S, Tranchevent LC, Diederich N, Rauen T, Schwamborn J, Glaab E, Cowley S, Antony P, Pereira S, Venegas C, Grünewald A. iPSC-derived microglia as a model to study inflammation in idiopathic Parkinson's disease. Front. Cell Dev. Biol. 2021; 9:740758
4. Ouzren N, Delcambre S, Ghelfi J, Seibler P, Farrer MJ, Aasly JO, Trinh J, Klein C, Grünewald A. MtDNA deletions discriminate affected from unaffected LRRK2 mutation carriers. Ann Neurol 2019; 86:324-326
5. Delcambre S, Ghelfi J, Ouzren N, Grandmougin L, Delbrouck C, Seibler P, Wasner K, Aasly JO, Klein C, Trinh J, Pereira SL, Grünewald A. Mitochondrial Mechanisms of LRRK2 G2019S Penetrance. Front Neurol 2020; 11:881

Neuroinflammation group

Overview

The Neuroinflammation group is involved in fundamental and translational research with a focus on neurodegeneration and neuroinflammation. The latter is a hallmark of diseases such as Alzheimer's (AD) which is characterised by the accumulation of extracellular amyloid-beta (Aβ) in amyloid plaques and intracellular tau in neurofibrillary tangles (NFTs). The activation of the innate immune cells of the brain, called microglia, seems to be involved in the development and progression of the disease and it is also known to play a role in other neurodegenerative diseases. To date, the underlying mechanisms in the transition of an initially protective to a chronic and harmful neuroinflammatory response are unknown. Hence, the group aims at understanding molecular mechanisms of inflammatory regulation in neurodegenerative diseases, including AD, using novel preclinical mouse models and a variety of techniques such as transcriptome analysis and induced pluripotent stem cells (iPSCs). The group also studies the cellular interactions between microglia, neurons, astrocytes, and oligodendrocytes through tunneling nanotubes. From a translational perspective, the goal of the group is to develop new biomarkers and insights into medical interventions around various aspects of neuroinflammation involved in neurodegenerative and cerebrovascular diseases.

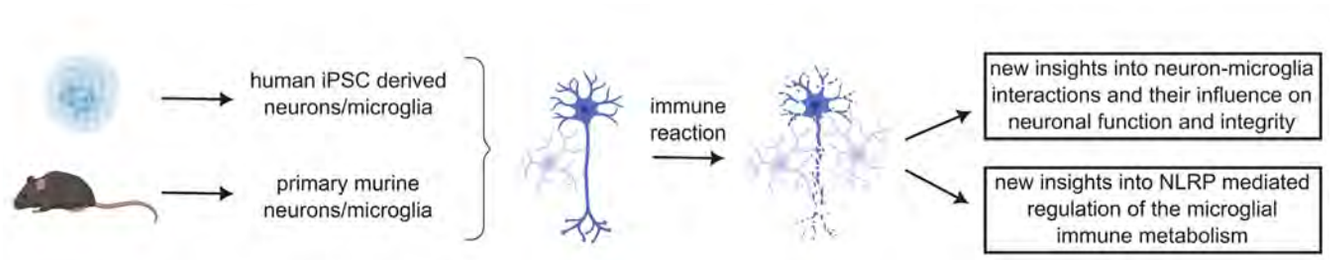


Figure: Understanding molecular mechanisms of neuroinflammation in neurodegenerative diseases.

Key projects

Identification of NLRP3 and NLRP1 mediated regulation of microglial immune metabolism in models of aging and neurodegeneration

Activation of microglia and subsequent formation of NACHT, LRR and PYD domains-containing proteins 3 and 1 have been implicated in ageing and neurodegenerative disease. Recent evidence suggests that NLRP3 and NLRP1 have gene regulatory effects that directly connect their assembly to the innate immune metabolism of microglia presumably through the regulation of key elements of the Krebs cycle. In this project, we investigate in human iPSC-derived microglia how NLRP3- and NLRP1-mediated gene regulation influences microglial transcriptomes and microglial function, which are key for maintaining synaptic integrity and neuronal plasticity. Since microglial senescence has been found to cause tau pathology, a major phenotype of the ageing and degenerating brain, we will further study how NLRP3 and NLRP1 affect microglial senescence and renewal in the respective models. This project is supported by the Luxembourg National Research Fund (FNR) through the NextImmune2 Doctoral Training Unit.

Characterisation of microglia-neuron interactions in Alzheimer's disease

Microglia respond to misfolded proteins such as α-synuclein (α-syn) fibrils through pattern recognition receptor ligation and activation of inflammatory pathways. A previous study demonstrated the establishment of an on-demand microglial network through the formation of tunnelling nanotubes (TNTs). The latter enable the intercellular transfer of α-syn assemblies from overloaded microglia to naive microglia where the cargo gets degraded, thus lowering the α-syn burden and attenuating the inflammatory profile. Recent findings suggest that TNTs are formed not only between microglia but also between neurons and microglia. In this project, we characterise the formation and the function of TNTs between microglia and neurons. We will further describe the transfer and transport of protein aggregates (α-syn, tau) between the two cell types as well as how the transfer of misfolded proteins between microglia and neurons influences neuronal function and integrity. To further characterise the regulation of TNT formation and transfer efficacy, we will unravel the molecular pathways responsible for nanotube formation and analyze the influence of immune-activation, senescence and the exposure to neurotransmitters and trophic factors on these intercellular connections.

Characterisation of the interaction of ASC and β-amyloid

The spreading of pathology within and between brain areas represents a hallmark of neurodegenerative disorders. In Alzheimer's disease, deposition of β-amyloid (Aβ) is accompanied by innate immune activation involving inflammasome-dependent ASC speck formation in microglial cells. ASC specks released by microglia undergoing pyroptosis rapidly bind to Aβ and increase Aβ oligomer and aggregate formation, acting as an inflammation-driven cross-seed for Aβ pathology. Previously, we were able to show that intrahippocampal ASC speck injection resulted in spreading of Aβ pathology in APP/PS1 mice. In contrast, APP/PS1 brain homogenates failed to induce seeding and spreading of Aβ-pathology in ASC-deficient APP/PS1 mice. These findings support the concept that inflammasome activation is connected to seeding and spreading of Aβ pathology in Alzheimer's disease through ASC speck release by pyroptotic microglia. These experiments are further strengthened by the analysis of APP/PS1xCx3Cr1-EGFPxKiASCmcherry mice by intravital two photon laser scanning microscopy, which is currently used to assess the dynamics of pyroptosis in the context of Alzheimer's disease. Experiments using Aβ labelling by systemic methoxy-x04 administration will visualise the interaction of ASC and Aβ in the living mouse brain.

Principal Investigator
Michael Heneka
Start: January 2022

Key publications

1. Scheiblich H., Dansokho C., Mercan D., Schmidt S.V., Bousset L., Wischhof L., Eikens F., Odainic A., Spitzer J., Griep A., Schwartz S., Bano D., Latz E., Melki R., Heneka M.T. (2021). Microglia jointly degrade fibrillar alpha-synuclein cargo by distribution through tunneling nanotubes. Cell 184(20), 5089-5106
2. Ising C., Venegas C., Zhang S., Scheiblich H., Schmidt S.V., Vieira-Saecker A., Schwartz S., Albasset S., McManus R., Tejera D., Griep A., Santarelli F., Brosseron F., Opitz S., Stunden J., Merten M., Kayed R., Golenbock D.T., Blum D., Latz E., Buée L., Heneka M.T. (2019). NLRP3 inflammasome activation drives tau pathology. Nature 575(7784), 669-673
3. Venegas C., Kumar S., Franklin B.S., Dierkes T., Brinkschulte R., Tejera D., Vieira-Saecker A., Schwartz S., Santarelli F., Kummer M.P., Griep A., Gelpi E., Beilharz M., Riedel D., Golenbock D.T., Geyer M., Walter J., Latz E., Heneka M.T. (2017) Microglia-derived ASC specks cross-seed amyloid-β in Alzheimer's disease. Nature 552(7685), 355-361
4. Heneka M.T., Kummer M.P., Stutz A., Delekate A., Schwartz S., Vieira-Saecker A., Griep A., Axt D., Remus A., Tzeng T.C., Gelpi E., Halle A., Korte M., Latz E., Golenbock D.T. (2013). NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature 493(7434), 674-678
5. Kummer M.P., Hermes M., Delekarte A., Hammerschmidt T., Kumar S., Terwel D., Walter J., Pape H.C., Konig S., Roeber S., Jessen F., Klockgether T., Korte M., Heneka M.T. (2011). Nitration of tyrosine 10 critically enhances amyloid beta aggregation and plaque formation. Neuron 71(5), 833-844

Neuropathology group

Overview

The Neuropathology group is a translational group linking more clinically-oriented neuropathological diagnostics and research at the Laboratoire national de Santé (LNS) with basic neurodegenerative research at the LCSB, as well as neurooncological research at the Luxembourg Institute of Health (LIH) and is supported by the PEARL Excellence Programme for Research in Luxembourg of the Luxembourg National Research Fund (FNR). The overarching goal is to translate clinico-pathological findings into cell culture- and animal-based experimental laboratory models and to validate basic research findings in patient cohorts. With this approach, we aim at deciphering the pathogenesis of neurological disorders as well as translate basic laboratory findings into diagnostic and therapeutic applications.

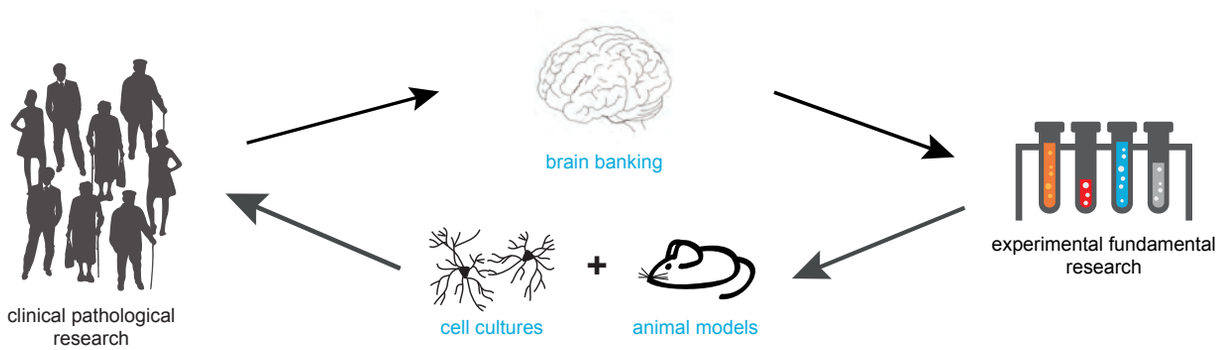


Figure: Bridging from clinical to fundamental research and back.

Key projects

Neurodegeneration (Luxembourg Centre for Systems Biomedicine)

Our aim is to understand the pathological causes and processes of Parkinson's disease (PD) with the help of mouse models. One of the advantages of mouse models is the possibility to study neurological disease in a mammalian brain that has the basic architecture and cellular composition at least partially similar to those found in the human brain.

In a first approach, PD-like disease is induced in experimental mouse models by either genetic engineering (transgenic, knockout, knockin for familial PD genes), or toxin administration (neurotoxin such as 6-Hydrxydopamine, or alpha-synuclein fibrils). Disease induction is followed up by longitudinal characterisation of pathological changes by behavioral, neuropathological, biochemical, and systems biological measurements.

Using these methods, two novel observations have been made:

(1) The earliest pathological change detected in all models is a distinctive shift in the gene expression signature of midbrain dopaminergic neurons, notably in regulatory transcription factors unique to these neurons. This change is detected months before any visible neurodegeneration is observed. Investigations are underway to determine what causes this gene signature change, and whether it can also be found in the peripheral nervous system (PNS) and could be a biomarker candidate for early PD detection.

(2) In a PD-induced model that incorporates prion-like spreading of alpha-synuclein pathology, an exceptionally strong alpha-synuclein aggregation independent microgliosis was found. Current investigations are aimed at determining what causes this microgliosis and if it is a driver of neurodegeneration.

In a second approach, a mouse genetic reference population, the Collaborative Cross (CC), is used to identify novel genetic regulators of dopaminergic neuron integrity. The demise of these neurons is responsible of the PD-typical decline in motor function. A number of mutations associated with familial PD or sporadic PD risk have been identified, yet few are known that modulate specifically PD-linked decline in motor function. The Neurodegeneration project uses the CC mouse genetic reference population, composed of mouse strains that differ in their dopaminergic function and architecture, to identify novel genetic modulators of these neurons. Neuropathology, neurochemistry, molecular genetics, cell biology, and bioinformatics approaches are used to pursue these goals. Toward the end of this project, it is projected to link the findings, by working with human geneticists, to new gene candidates that govern dopaminergic neuron function in humans.

Neurooncology (Luxembourg Institute of Health)
Glioma cells display a high degree of genetic and epigenetic alterations that frequently lead to altered metabolism. A second important feature of glioma cells is their diffuse infiltration into residual CNS tissue. Our hypothesis is that certain metabolic reprogramming in tumor cells impacts their invasive properties. We therefore aim at deciphering the metabolic signature of diffusely infiltrating cells, compared to the tumor core and normal brain tissue by utilising non-targeted metabolic analysis of different tumor- and brain regions of the established PDX models. Additionally, we aim at integrating metabolomics with proteomic- and epigenetic data for a better understanding how tumor cell migration and metabolism are interconnected in glioblastoma (GBM). The outcome of this project will be the identification of novel metabolic targets to attenuate or possibly prevent the diffuse infiltration of GBM cells.

Principal Investigator
Michel Mittelbronn
Start: January 2017

Key publications

1. Ashrafi A., Garcia P., Kollmus H., Schughart K., Del Sol A., Buttini M., Glaab E.. (2017) Absence of regulator of G-protein signaling 4 does not protect against dopamine neuron dysfunction and injury in the mouse 6-hydroxydopamine lesion model of Parkinson's disease. Neurobiol Aging., 58:30-33. doi: 10.1016/j.neurobiolaging.2017.06.008
2. Ilina E., Armento A., Garea Sanchez L., Reichlmeir M., Braun Y., Penski C., Capper D., Sahm F., Jennewein L., Harter P.N., Zukunft S., Fleming I., Schulte D., Le Guerroué F., Behrends C., Ronellenfitsch M.W., Naumann U., Mittelbronn M. (2017) Effects of soluble CPE on glioma cell migration are associated with mTOR activation and enhanced glucose flux. Oncotarget., doi: 10.18632/oncotarget.18747
3. Jaeger C., Glaab E., Michelucci A., Binz T.M., Koeglsberger S., Garcia P., Trezzi J.P., Ghelfi J., Balling R., Buttini M. (2015) The mouse brain metabolome: region-specific signatures and response to excitotoxic neuronal injury. Am J Pathol., 185(6):1699-712. doi: 10.1016/j.ajpath.2015.02.016. Epub 2015 Apr 28.
4. Jäger C., Hiller K.,Buttini M. (2016) Metabolic Profiling and Quantification of Neurotransmitters in Mouse Brain by Gas Chromatography-Mass Spectrometry. Curr Protoc Mouse Biol., 6(3):333-42. doi: 10.1002/cpmo.15
5. Jennewein L., Ronellenfitsch M.W., Antonietti P., Ilina E., Jung J., Stadel D., Flohr L.M., Zinke J., von Renesse J., Drott U., Baumgarten P., Braczynski A.K., Penski C., Burger M.C., Theurillat J.P., Steinbach J.P., Plate K.H., Dikic I., Fulda S., Brandts C., Kögel D., Behrends C., Harter P.N.,Mittelbronn M. (2016) Diagnostic and clinical relevance of the autophago-lysosomal network in human gliomas. Oncotarget., 7(15):20016-32. doi: 10.18632/oncotarget.7910

Systems Control group

Overview

The Systems Control group collaborates with biologists and clinicians to improve our understanding of diseases, with the goal to develop new therapies. The group produces theoretical and computational methods to identify how diseases arise and how they are mitigated. A key part is to build mathematical models that help pinpoint the locations and underlying mechanisms of diseases. The models capture an important feature of biological systems: the fact that they change over time in response to internal or external stimuli. Hence, the group focuses mostly on time series data. Time series data consist of snapshots of system properties at different time points, such as molecular concentrations (e.g. RNA, proteins or metabolites) or clinical data (e.g. ECGs or blood tests). While time series data is more expensive to produce than steady state data, tracing a system's transient behaviour provides essential information on how different species interact with each other and reveals causal mechanisms. With diverse backgrounds in mathematics, computational sciences, biology and medicine, members of the group engage with this overall problem from different perspectives. The group collaborates closely with biologists and clinicians to develop mathematical models with key predictive powers that are subsequently experimentally validated. This ensures that the group's research has broad-ranging applications within biology and biomedicine, including Parkinson's disease, deep brain stimulation, heart attacks and arrhythmias, mechanisms of circadian rhythms and the immune system.

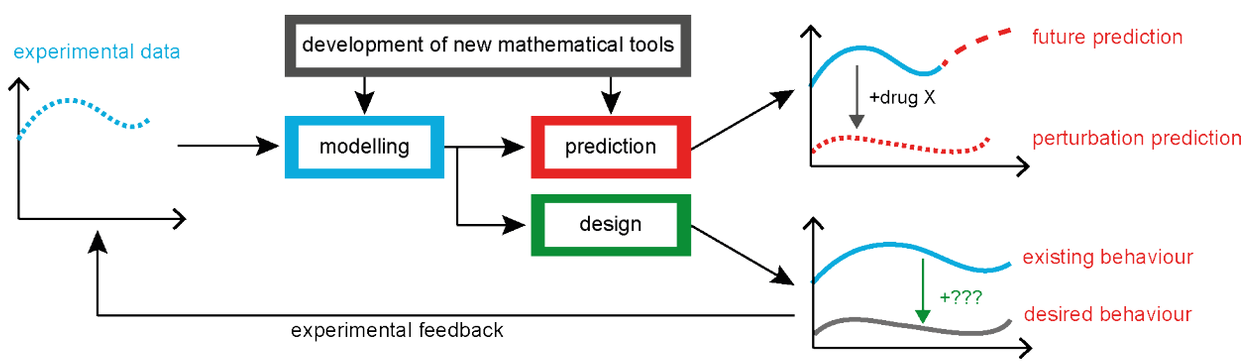


Figure: Modelling and prediction of dynamic systems from time series data.

Key projects

Real-time prediction of heart attacks and arrhythmias

The aim of this project is to detect and predict heart arrhythmias before they occur. Heart attacks and arrhythmias typically happen without noticeable warning. Predicting heart arrhythmias, such as atrial fibrillation (AF), in real-time and with enough anticipation can allow patients to seek immediate medical attention and prevent health complications. This project searches for subtle changes in heart dynamics, captured via ECG or PPG (via a smartwatch, for example), using state-of-the-art machine learning tools. The project is funded by FNR.

Network inference

The aim of this project is to understand how networks of genes and other molecules causally interact over time to produce disease related phenotypic behaviours. Reliable models of these regulatory networks allow us to simulate hypotheses that can be used to guide experimental testing, and to identify changes in biological network structures that occur when a system is perturbed in responses to stimulation, pharmacological intervention or genetic mutations. Networks are inferred from time-series or single-cell data. The project also contributes to broader theoretical research into mathematical, algorithmic and software tools for understanding causal dynamic network structures and interactions between different omics layers, such as metabolomics and transcriptomics. The developed tools have been applied to understand the mechanisms of action of circadian clocks and the immune system. This project involves collaborations with the Department of Plant Sciences at the University of Cambridge and the Institute of Biology Leiden. The project is funded by Luxembourg National Research Fund (FNR).

COVID-19 dynamical modelling

The spreading of the COVID-19 pandemic within a community changes over time. Since March 2020, our dynamical models have been assessing its severity, anticipating future evolutions and providing information to aid the Luxembourgish Government in

decision making. We explored a range of models, from simple epidemiological models to detailed individual agent-based models to simulate the effects of different confinement and deconfinement measures and vaccination policies, among others. Models included forecasts of hospital, ICU and deaths and the impact on the local economy. A quantitative model estimated the infected population from viral samples collected in wastewater, providing an alternative for an efficient and robust epidemic tracking. Finally, using critical transitions methodologies, we developed models to anticipate new waves of infections.

Principal Investigator
Jorge Gonçalves
Start: September 2013

Next generation of deep brain stimulation (DBS)
Deep Brain Stimulation (DBS) is a surgical therapy for several movement disorders (e.g. Parkinson's disease (PD) and essential tremor) and psychiatric diseases. During this procedure, an electrode is implanted into the brain, constantly delivering electrical pulses to specific regions of the brain. This project aims to considerably improve the efficiency of DBS while reducing side effects. In particular, it develops algorithms to deliver personalised stimulations that adapt to the patient's needs, and computational tools to aid physicians initialize DBS parameters. This project is funded by the JPND Research Joint EU Programme.

Predicting financial crashes
The project aims to study hidden statistical patterns in financial systems to test potential early warning signals for critical transitions in equity markets. Financial markets are known for their complexity due to the presence of many different types of agents whose actions belong to a very diverse set of strategies. This project studies the causal effect of latency delays on occurrence of mini-flash crashes. This latency delay slows down the trading while reducing price impact, and results in decreased number of mini-flash crashes. The methods studied in this project can also be applied for forecasting critical transitions in other contexts, such as the early warning of Atrial Fibrillation or in epidemic models.

Key publications

1. Aalto A., Viitasaari L., Ilmonen P., Mombaerts L., Gonçalves J. (2020). Gene regulatory network inference from sparsely sampled noisy data, Nature Communications, 11:3493.
2. Yan L., Zhang H.-T., Gonçalves J., Xiao Y., Wang M., Guo Y., Sun C., Tang X., Jing L., Zhang M., Huang X., Xiao Y, Cao H., Chen Y., Ren T., Wang F., Xiao Y., Huang S., Tan X., Huang N., Jiao B., Cheng C., Zhang Y., Luo A, Mombaerts L., Jin J., Cao Z., Li S., Xu H., Yuan Y. (2020) An interpretable mortality prediction model for COVID-19 patients, Nature Machine Intelligence.
3. Yuan Y., Tang X., Zhou W., Pan W., Li X., Zhang H.-T., Ding H., Gonçalves J. (2019). Data Driven Discovery of Cyber Physical Systems, Nature Communications, 10:4894.
4. Mombaerts L., Carignano A., Robertson F., Hearn T., Junyang J., Hayden D., Rutterford Z., Hotta C., Hubbard K., Yuan Y., Hannah M., Gonçalves J., Webb A. (2019) Dynamical Differential Expression (DyDE) Reveals the Period Control Mechanisms of the Arabidopsis Circadian Oscillator, PLoS Computational Biology.
5. Markdahl J., Thunberg J., Gonçalves J. (2018). Almost Global Consensus on the n-Sphere, IEEE Transactions on Automatic Control, Vol. 63, Issue 6, pages 1664-1675.

Systems Ecology group

Overview

The main goal of the Systems Ecology group is to obtain unprecedented understandings of mixed microbial communities (e.g., gastrointestinal microbiota), their interactions with the environment (e.g., the human host), and how certain microbial community compositions lead to certain outcomes (e.g., pathogenesis). Changes to the human microbiome (microbial dysbiosis) have been linked to several human diseases including cancer, metabolic, and neurodegenerative diseases. The group is currently involved in research projects investigating these diseases using its high-resolution molecular biology approaches. To develop the field of Microbial Systems Ecology, the group has pioneered key methodologies and technologies that allow the systematic and high-resolution study of microbial community-driven processes. These range from wet-lab techniques and microfluidics-based *in vitro* co-culture systems to downstream bioinformatic analysis methods for the integration of high-resolution molecular data ("integrated multi-omics"). The overall vision of the group is to use an integrated multi-omics approach to identify key processes governing microbial community structure, function as well as products, which may inform control strategies for microbial communities in the future, especially those within the gut.

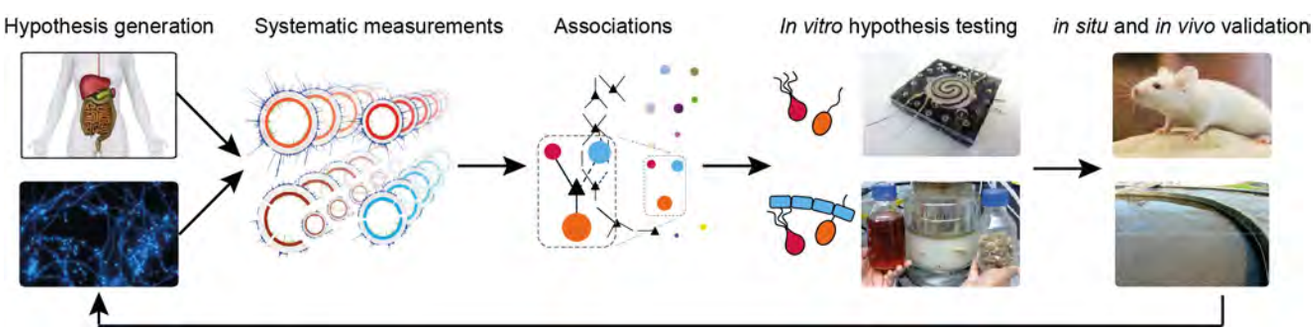


Figure: Systems biology approach to study mixed microbial communities in unprecedented detail.

Key projects

Integrated omics

High-resolution molecular biology approaches are key for comprehensively characterising microbial consortia, and for understanding the interaction of microbial communities with biotic and abiotic environmental factors. Integrated omics, comprising metagenomics, -transcriptomics, -proteomics, and -metabolomics, can reveal the links between genetic potential and functionality in a truly systematic fashion. Our recently developed methods range from comprehensive biomolecular extraction methods, yielding high-quality DNA, RNA, protein, and metabolite extracts from single, unique samples, to new bioinformatic analysis tools. This enables meaningful integration of the generated multi-omics data for downstream analysis and modelling of mixed microbial communities, including those of human-health interest. For example, we have obtained new insights into functional changes within the gut microbiota in the context of type 1 diabetes, and we have found that birth mode (caesarean section vs. vaginal delivery) affects the transfer of key functional strains from mother to infant very early, which leads to differences in immune system stimulation.

The human microbiome and its role in Parkinson's disease

Parkinson's disease (PD) is hypothesised to start in the enteric nervous system and the olfactory bulb, potentially triggered by a so far unknown pathogenic agent. Aberrations within the gastrointestinal or nasal microbiomes may play a role in the initiation of this process. Using our high-resolution molecular methods, we are investigating whether changes in microbial community structure and function in the gastrointestinal tract or in the nasal cavities accompany PD onset, its progression, and its prodromal REM sleep behavior disorder (RBD). We identified differences in PD patients' gut microbiomes, most notably in mucus foraging Akkermansia or Bacteroides species, and we revealed microbiome signatures for PD and RBD. Overall, this strengthens the importance of the gut-brain-axis in PD and contributes to our understanding of disease development.

Microfluidics-based human-microbial interaction models

Microbial dysbiosis may lead to a range of human diseases. To ascertain causal links, we have developed a representative microfluidics-based in vitro model, named HuMiX, which allows the prolonged co-culture of differentiated human epithelial cell lines and human microbiota under biomimetic conditions. The device is particularly well-suited for investigating the

nature and impact of molecular crosstalk between human and microbial contingents, how imbalances therein may be involved in disease pathogenesis, and how the diet-related food components as well as pro-, pre- and anti-biotics may affect human-microbial molecular interactions. Furthermore, we have included representative immune cell populations in the model and are working on the integration of representative neuronal cell populations. By integrating individual-derived host cells and microbial cells, HuMiX serves as our platform to create truly personalized in vitro models. Finally, we are interfacing HuMiX with a liver-on-a-chip model as well as constructing an *in vitro* model of the entire human gastrointestinal tract, termed GUT, which, among other applications, will be suited to study the pharmacokinetics of drugs.

Principal Investigator
Paul Wilmes
Start: October 2011

Towards One Earth: Systems biology of environmental microbial assemblages
To better understand how mixed microbial communities and environments affect and are affected by anthropogenic factors, we are investigating these communities occurring in the environment, and their internal as well as external interactions. Our research longitudinally follows lipid accumulating microbial (LAM) communities, which are found at the air-water interface of certain wastewater treatment plants and whose phenotypes may be harnessed for the concomitant treatment of wastewater and production of biofuel. Moreover, we study biofilms in glacier-fed streams. These biofilms exhibit important phenotypic properties, e.g., biosynthetic functionality, as well as diverse resistomes, which upon exposure and possible transfer to human/animal-relevant microorganisms could have consequences on human/animal health.

Our collaborators on these projects are Prof. Wolfgang Oertel (University of Marburg ; Germany), Prof. Brit Mollenhauer (University of Göttingen; Germany), Dr. Alexander Mosig (University Clinic Jena; Germany), Prof. Frederic Zenhausern (University of Arizona; USA), Prof. Kenya Honda (RIKEN Center for Integrative Medical Sciences; Japan), Prof. Andreas Michalsen (Charité Berlin; Germany), and Dr. Robert Hettich (Oak Ridge National Laboratory; USA). Financial support is provided by the European Commission, the Luxembourg National Research Fund (FNR), the Michael J. Fox Foundation, the Parkinson's Foundation, and the Swiss National Science Foundation.

Key publications

1. Greenhalgh K., et al. (2019). Integrated in vitro and in silico modeling delineates the molecular effects of a synbiotic regimen on colorectal-cancer-derived cells. Cell Reports 27:1621-1632.e9, doi: 10.1016/j.celrep.2019.04.001
2. Heintz-Buschart A., et al. (2018). The nasal and gut microbiome in Parkinson's disease and idiopathic REM sleep behavior disorder. Movement Disorders 33(1):88-98, doi: 10.1002/mds.27105
3. Wampach L., et al. (2018). Birth mode is associated with earliest strain-conferred gut microbiome functions and immunostimulatory potential. Nature Communications 9:5091, doi: 10.1038/s41467-018-07631-x
4. Heintz-Buschart A., et al. (2017). Integrated multi-omics of the human gut microbiome in a case study of familial type 1 diabetes. Nature Microbiology 2:16180, doi: 10.1038/nmicrobiol.2016.180
5. Narayanasamy S., et al. (2016). IMP: a reproducible pipeline for reference-independent integrated metagenomic and metatranscriptomic analyses. Genome Biology 17:260, doi: 10.1186/s13059-016-1116-8

Translational Neuroscience group

Overview

The group is bridging the gap between fundamental research and clinical care, to help citizens affected by neurodegenerative diseases via earlier diagnosis, better therapy and effective prevention in Luxembourg and beyond. Fundamental research focuses on patient-based induced pluripotent stem cells (iPSC)-derived neuronal models to elucidate the molecular and cellular alterations contributing to neurodegeneration in both familial and idiopathic Parkinson's disease (PD), Dementia with Lewy bodies, atypical parkinsonism, and in amyotrophic lateral sclerosis (ALS). Newly discovered molecular targets and disease-associated cellular phenotypes are subjected to drug screening in order to identify molecules that, after in vitro and *in vivo* validation, can be used to develop precision medicine therapeutic strategies for translation into future care.

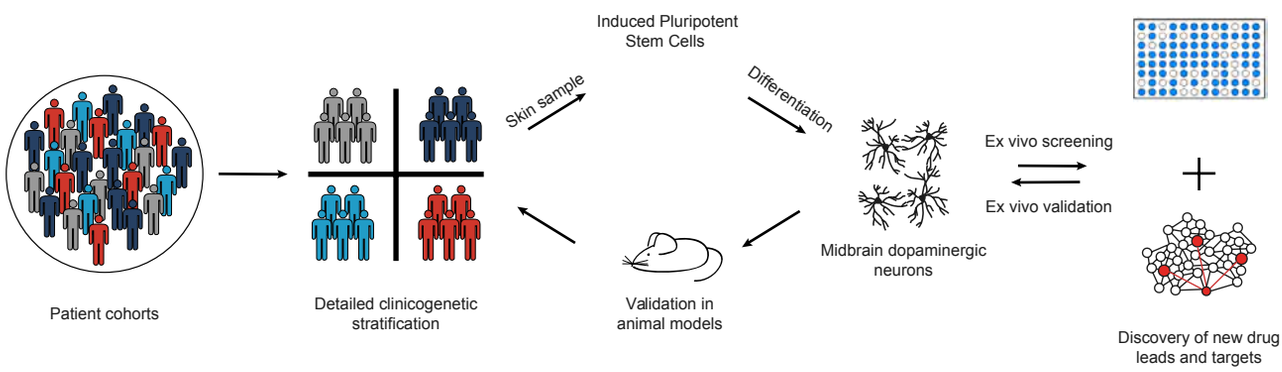


Figure: Pharmacological screening based on dopaminergic neurons from patient-derived induced pluripotent stem cells.

Key projects

I. Fundamental Research

DJ-1 for mechanism-based genetic and pharmacological treatment of PD

One of the causes of familial PD is homozygous loss-of-function mutations of DJ-1, a protein encoded by the gene PARK7, with broad biological functions including effects on mitochondrial and lysosomal homeostasis. Patient-derived iPSCs are differentiated into midbrain-specific dopaminergic (mDA) neurons to study the effect of DJ-1 loss- of-function in PD. We use cellular phenotypes are used for pharmacological library screens to detect compounds that rescue PD-associated cellular phenotypes and have developed a mechanism-based pharmacological treatment for aberrant splicing in our cellular models. This causative treatment for PD is now being tested for its in vivo efficacy in a humanized DJ-1 mouse model habouring the same mutation as the patient-derived cells.

DJ-1 in PD and glioblastoma multiforme (GBM)

The role of DJ-1 is analysed in GBM and PD to shed light on the inverse association of cancer and PD. We are studying the effect of differential DJ-1 levels in PD-patient-derived neurons and astrocytes and in GBM cells. We found that metabolism (glycolysis and TCA cycle) and immune responsiveness are DJ-1 level dependent in these models.

Pathological role of α-synuclein encoding gene (SNCA) in PD

Genetic variants in the SNCA locus are major risk factors in PD. We study isogenic pairs of iPSC-derived mDA neurons from patients with the A30P and A53T mutation to better understand the link between α-synuclein and mitochondrial dynamics and function. Related ongoing studies on neuronal autophagy and α-synuclein investigate how the interplay of mDA neurons and astrocytes can spread PD.

GBA mutations as a genetic modifier of familial PD

Mutations in the GBA gene are the most common genetic risk factors for developing PD. Fibroblasts from a PD patient carrier of a GBA mutation alongside with a PARK2 mutation to explore if GBA could modify the expression of PD on a familial PD background. These fibroblasts were reprogrammed into iPSC, which were CRISPR-Cas9 edited for GBA and differentiated into mDA neurons. Protein expression, lysosomal activity, α-synuclein metabolism and mitochondrial morphology and function can then be studied.

Genetic modifiers of LRRK2 PD

LRRK2 mutations are amongst the most frequent genetic causes for PD and penetrance is highly correlated with an individual's genetic background. Leveraging whole genome sequencing in families with a history of LRRK2 PD we identify variants segregating with earlier or later age at onset. Using cell type-specific functional genomics, we prioritise candidates

for functional validation through PD-associated phenotypes in patient iPSC derived cell cultures. Via targeted chromatin modulation we interrogate cell type-specific regulatory elements for their contribution to PD gene expression.

Principal Investigator
Rejko Krüger
Start: June 2014

Mitochondrial risk variants in PD
We use advanced computational modelling approaches to identify mitochondrial risk variants and investigate mitochondrial network perturbations in both sporadic PD and healthy controls. Patient-based cellular models from high- vs low-mitochondrial risk groups are subjected to functional characterisation to determine if such computational approaches can be used to stratify PD patients or even predict higher risk to develop PD in healthy controls. The protein Miro1 regulates mitochondrial mechanisms associated with PD pathogenesis. We identified PD patients carrying mutations in the RHOT1 gene (encoding Miro1), as cause of neurodegeneration. We demonstrated that fibroblasts from these patients and induced-pluripotent stem cells (iPSC) derived dopaminergic (DA) neurons from the R272Q patient had an impaired mitochondrial quality control mechanisms. The aim of this project is to identify disease-associated phenotypes in Miro1 mutant models *in vitro* and *in vivo* and to find novel targets to correct impaired Miro1 function PD.

Genetic identity of mDA neurons
iPSC-derived mDA neuron cell-replacement therapies have been proposed as a possible treatment for PD. Lack of accurate control of cell state and high heterogeneity in the current protocols hinder clinical progress. We study the gene regulatory program underlying mDA neuron differentiation and identity using time series epigenomic and transcriptomic data. Integration of the different datasets allowed us to identify novel regulators for the functional validation in *in vitro* system.

Diabetes and PD: the role of insulin resistance in neurodegeneration
This FNR CORE Junior project investigates the cellular alterations underlying PD and Type 2 Diabetes (T2D) pathogenesis. Evidence indicates that patients suffering from T2D have higher risk of developing PD, suggesting the existence of shared molecular alterations likely related to dysregulated insulin metabolism. We will use patient-based iPSC-derived neurons and pancreatic beta cells to characterize the molecular and metabolic alterations linking deficiency in PD-related genes to neuronal insulin resistance and pancreatic beta cell failure, respectively.

Pathogenetic mechanisms in amyotrophic lateral sclerosis (ALS)
We aim at deciphering the pathogenetic alterations underlying ALS in patient-based fibroblasts and iPSC-derived motor neurons. Isogenic gene-corrected lines from the patient have been generated and will be used to assess mitochondrial activity, neuronal metabolism, gene expression and neuronal function. Phenotypic alterations and newly identified molecular/metabolic targets will be validated in ALS mouse models.

II. Clinical Research
The National Centre of Excellence in Research on Parkinson's Disease (NCER-PD) aims to improve diagnosis and treatment of PD by developing novel disease biomarkers. PD patients and healthy subjects are recruited in Luxembourg and the Greater Region. This is a LCSB flagship project funded by the FNR (see Flagship projects).

III. Care and Prevention
The group implements two innovative care concepts for people with PD and with mild or subjective cognitive impairment (see Flagship projects).

Key publications

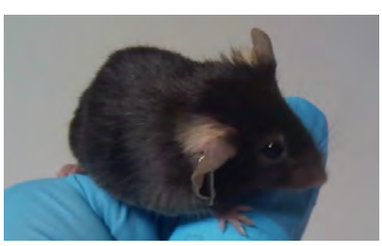
1. Hanss Z., Larsen S.B., Antony P. et al. (2021) Mitochondrial and Clearance Impairment in p.D620N VPS35 Patient-Derived Neurons Mov Disord. 36(3):704-715.
2. Boussaad et al. (2020) A patient-based model of RNA mis-splicing uncovers treatment targets in Parkinson's disease. Sci. Transl. Med. 12, eaau3960
3. Berenguer-Escuder et al. (2020) Impaired Mitochondrial-Endoplasmic Reticulum Interaction and Mitophagy in Miro1-Mutant Neurons in Parkinson's Disease. Hum Mol Genet; 29(8):1353-1364.
4. Burbulla et al. (2017) Dopamine oxidation mediates mitochondrial and lysosomal dysfunction in Parkinson's disease. Science (New York, N.Y.), 357(6357), 1255-1261.
5. Boussaad, I., Cruciani, G., Bolognin, S. et al. (2021) Integrated, automated maintenance, expansion and differentiation of 2D and 3D patient-derived cellular models for high throughput drug screening. Sci Rep. ;11(1):1439

INFRASTRUCTURE

Cutting across disciplines in systems biomedicine, the LCSB integrates different technologies, models and expertise; from mathematical theory to practical medical requirements of the clinic. This allows the centre to adapt in the best possible way to the challenges of modern biomedical research. The goal is to establish and provide access to important infrastructure that supports the key research lines of the LCSB. Larger infrastructure is established as 'central platforms' to make it easily accessible across all research groups, and to offer fee-based services at national and international level. Besides offering customised services and method development, the platforms offer trainings on new technologies, and consultations for experimental design, data processing and troubleshooting. So far, the LCSB has established the following central platforms:

Aquatic Facility

The Aquatic Platform at the LCSB has been established as a breeder, supplier and user of zebrafish (*Danio rerio*). This teleost fish is a vertebrate organism widely used to study developmental biology and to model various human diseases. The platform consists of a modern, semi-automated facility that provides husbandry and embryo production services to support biomedical research and teaching activities. The facility can house up to 30,000 adult zebrafish, offering robotic feeding, maintenance of constant micro-environmental conditions (e.g. pH, temperature and conductivity), and semi-automated cleaning systems that ensure excellent conditions for research quality and for animal welfare. Among its services, the Aquatic Platform offers the generation of zebrafish disease models using morpholino antisense technology and CRISPR/Cas9 mutagenesis, as well as pharmacological models and reporter lines using Tol2 transgenesis. In addition, the platform supports research activities by offering the possibility to perform diverse types of small-molecule screens, as well as toxicity screens for drug safety assessment and for eco-toxicological studies.



Rodent Facility

The rodent facility was established to assist researchers in the development and analysis of various *in vivo* models including humanised and germ-free animals. The facility has the capacity to house more than 100 different mouse lines in 1,500 IVC cages in the Breeding barrier under SOPF status. The Experimental barrier with a capacity for 600 mouse and 300 rat cages, is dedicated to studies on transgenic rodents and offers as well the possibility to realise BSL-2 activities and housing xenograft models. Genetically modified rodent lines can be generated by our Transgenic Core Unit and kept either as live animals or as cryopreserved sperm. The facility offers the possibility of running a broad number of experimental procedures on the premises, including stereotaxic surgical procedures and motor behavior equipment as the Catwalk. Additionally, humanised mouse models can be provided within an SPF environment. The Germ-free Unit is established within the Breeding barrier to ensure a controlled health status. For colonisation studies, germ-free mice can be inoculated with a suspension of a specific microbe (mono-colonisation), a defined finite group of microbes, or a polymicrobial mixture. This unit also employs a Sealed Positive Pressure IVC system to achieve the type of germ-controlled environment.

Sequencing Platform

The sequencing platform offers next-generation sequencing services to researchers by using a combination of a NextSeq and a MiSeq sequencer from Illumina and 2 MinION nanopore sequencers from Oxford Nanopore Technologies, to address broad sequencing possibilities. The platform offers full service, starting with advice in experimental design up to sequencing data generation. Receiving RNA or DNA samples, sample quality check, library preparation, library quality control, sequencing run, raw data generation and preliminary data quality control report is performed. Last year, the platform performed 100 Illumina sequencing runs (processed 1,238 RNA and 1,932 DNA samples), generated a combined of more than 18 Tbp of sequencing data, and supported 20 research groups. General applications of these projects included RNA sequencing, metatranscriptomics, single cell RNA sequencing, metagenomics, ChIP sequencing, ATAC sequencing and targeted gene sequencing, as well as long read DNA sequencing using Oxford Nanopore MinION sequencer. In 2021, the sequencing platform also acquired an NextSeq2000 to increase the sequencing capacity and reduce the sequencing costs.

Metabolomics and Mass Spectrometry Platform

The Metabolomics Platform offers LC-MS, GC-MS and IC-MS services, access to equipment for sample preparation and a comprehensive set of tools for reliable data analysis based on a statistical evaluation. To address the needs in this fast-changing field, the platform continuously develops new analytical and tailor-made methods to address upcoming biological and biomedical questions. This includes targeted and non-targeted analyses, semi-quantification and absolute

quantification of small molecules (metabolites) and a special focus on stable isotope-assisted metabolomics applications. The platform hosts three cutting-edge LC-MS systems (Thermo Q Exactive HF, Agilent 6560 Ion Mobility Q-TOF, Sciex Q-Trap), two Agilent GC–MS and a newly installed IC system coupled to a Thermo Q Exactive MS. Using these technologies and standardised laboratory protocols, the Metabolomics Platform strives to offer high quality mass spectrometry-based measurements of a wide range of small molecules in biologically relevant samples.

Bioinformatics Platform

The LCSB's Bioinformatics Core offers large data storage as well as bioinformatics expertise, which includes state-of-the-art workflows for data capture and data analysis using OpenStack based private cloud as well as high-performance computing (HPC) cluster of the University. Since 2016, the core facility group is the Luxembourgish Node of the European bioinformatics infrastructure ELIXIR and serves as an international data hub for clinical and translational medicine data (see Flagship projects). The bioinformatics platform further assists in the curation of existing clinical data for computational analysis, introducing international standards and performing quality control of entries. Support is given for the development of electronic data capture based on controlled vocabulary in CDISC standards and their storage in suitable tools for analysis such as tranSMART. A powerful genome analysis pipeline interprets data from exome and whole genome data while other bioinformatics tools have been developed to interpret differentially expressed genes within pathways and networks. The Bioinformatics Core further develops advanced dynamic visual analysis workflows and libraries (e.g. Fractalis) based on machine learning approaches and tools (e.g. ADA) for the integration of heterogeneous data across different data types and disciplines. Visualisation is supported by virtual and augmented reality, as well as disease map approaches, such as the Parkinson's disease map. Easy tools provided by the team allow researchers to set up and fill their own disease maps.

Bioimaging Platform (bip)

The bioimaging platform offers access to a broad palette of specialised microscopy systems: a laser scanning confocal microscope (Zeiss LSM 710) for high-resolution imaging of fixed samples, a spinning-disk confocal microscope (Zeiss Cell Observer), an inverted epifluorescence microscope (Nikon Eclipse Ti-E) for prolonged live-cell imaging equipped with a high-resolution confocal scanner (Confocal.nl RCM), a selective plane illumination microscope (SPIM) for low phototoxicity whole organ and organism imaging, as well as a high-content screening system (Perkin Elmer Opera), and a super-resolution confocal microscope with fluorescence lifetime imaging (Leica SP8 STED 3X FALCON) for live-sample studies. Platform technologies are used to analyse fixed and living cells and tissues with genetic or pharmacological perturbations. For image analysis of cell morphology, topology and cellular dynamics, the platform supports both the use of advanced commercial software and in-house developed analysis tools. Furthermore, the facility comprises of a flow cytometry branch with a cell sorter (BD FACSAriaIII) and high-speed analyser (BD LSRFortessa) allowing to quantify large cell populations at single cell resolution and to perform a variety of high-throughput assays and phenotypic selections. User trainings take place throughout the year through practical courses, seminars and workshops. Recently, a Scanning Electron Microscope (Zeiss Sigma 500) was built up in cooperation with the Laboratoire National de santé (LNS).

Disease Modeling & Screening Platform (DMSP)

The DMSP is the result of the collaboration between the Luxembourg Centre for Systems Biomedicine at the University of Luxembourg and the Luxembourg Institute of Health (LIH). The ultimate objective of the DMSP is to provide a diversity of core facilities infrastructure, disease models and expertise, to facilitate the translation of basic scientific discoveries into tangible hit (drug) candidates. The platform is physically located at the LCSB site.

Further LCSB infrastructure is available through collaborative group platforms who also offer services. Details can be found on our webpage: **https://www.uni.lu/lcsb/services**

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2022 [status August 2022]

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Patents

Title	Partners	Reference number
Method and kit for the isolation of genomic DNA, RNA, proteins and metabolites from a single biological sample	Paul Wilmes, Hugo Roume, Thekla Cordes, Karsten Hiller	WO 2013/029919
Method to predict the presence of Itaconic Acid, IRG1, and/or proteins IRG1 in a subject and pharmaceutical composition for treating or preventing inflammation	Alessandro Michelucci, Rudi Balling, Thekla Cordes, André Wegner, Jenny Ghelfi, Karsten Hiller	WO 2013/041692
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