Connect the 9 dots with four straight lines without lifting the pen.

You will find the solution on the cover of this LCSB Annual Report 2013.
Building a strong network

The building up phase is over: in the last four years conceptual drawings have turned into a fully functional interdisciplinary research centre analysing the molecular networks that underlie complex diseases like Parkinson’s disease. To do so the LCSB had to build a strong research network that promotes collaborations between LCSB researchers and also with scientists from around the world. In order to foster interdisciplinarity, the LCSB had to bring in scientists from different fields of expertise, which led to an exponential growth of the LCSB staff in 2013. Now, the LCSB has reached a critical mass and is bustling with life, as around 150 employees come here every day to work on today’s burning questions in biomedicine.

To make a difference in the field of biomedicine, scientists not only have to connect among themselves but also with all the other stakeholders of the country – be it policy makers, industrial groups, students, patients or the Luxembourgish population in general. Participating in science fairs, welcoming visitors to the LCSB premises as well as the newly founded Scientee Lab for high-school students form the basis for a good relationship between LCSB and the non-scientific community in Luxembourg. We are extremely grateful for the amazing wave of interest and support that we have received in Luxembourg. It shows me that we have made our way into the heart of Luxembourg’s society.

Even though we have already chalked up the first successes, there is no time to rest or to be complacent. We need to keep up the momentum and must continue to work hard in order to »connect the dots« that bring systems biomedicine to life in Luxembourg. Besides strengthening of its relationships, it is now time to create value from this interdisciplinary network and turn its combined expertise into scientific discoveries and innovations. Only then can we bring value to Luxembourg and ultimately contribute to better health and quality of life for patients. Our high-impact publications, patents and first spin-off companies in 2013 show me that we are on the right track. In the next years it is our central task to prove that the LCSB as a whole is more than the sum of its parts.

Yours,

Rudi Balling, Director LCSB
Background

LCSB in brief

The LCSB is an interdisciplinary research centre at the University of Luxembourg. It is accelerating biomedical research by closing the link between systems biology and medical research. Collaboration between biologists, medical and computer scientists, physicists, engineers as well as mathematicians is offering new insights in complex systems like cells, organs and organisms. These findings are essential for understanding principal mechanisms of disease pathogenesis and for developing new tools in diagnostics and therapy.

Neurodegenerative diseases like Parkinson’s Disease and description of diseases as networks are in the focus of LCSB’s research. The Centre has established strategic partnerships with leading biomedical laboratories worldwide and with all major biological and medical research units in Luxembourg. The LCSB fosters collaboration with industrial partners and has founded two spin-off companies in 2013 to accelerate the translation of fundamental research results into (clinical) applications.
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Connecting the dots

Professor Balling, »Connecting the dots« sounds a lot like LCSB is connecting locations together on a map.

Prof. Dr. Rudi Balling: Well, that is basically what we are doing: we are identifying and connecting the aspects which play a role in an organism when a neurodegenerative disease is looming and then finally breaks out – like Parkinson’s disease. Until now, science has always focussed on specific aspects of the pathological process at a given time: a single protein, a metabolic pathway for example, or a certain environmental influence. Now we are gradually coming to see the interplay of these different parts as a whole network.

What has changed in the life sciences in recent years to allow this sort of network analysis?

Thanks to bioinformatics, we have been able to properly manage the large data volumes generated in laboratories for some time now. But, most recently, computational biology has also seriously taken off. We can now analyse the networks and follow their dynamics – their changes over time – better than ever. It took the integration of mathematics, physics and engineering sciences into biology for this to happen. These disciplines brought with them enormous experience in network analysis. But this integration required a »Connecting the dots« of its own. It is of no use having mathematicians, physicists and engineers sitting isolated on a science campus. They have to know what happens in the lab and they have to do research within the same centre as the medical scientists and biologists to be able to study these complex biological systems.

And you have managed that at LCSB?

(Balling laughs.) Yes, LCSB’s approach is bearing fruits. I see that with our externally funded projects. LCSB teams of biological scientists and computational biologists were well established in international projects last year, where network analysis was central. That means we did something right. Interdisciplinarity is alive at LCSB, and as the institute continues to grow, we have to keep those scientific discussions and collaborative projects between experimental and computational researchers growing as well.

The number of research groups rose in one year from seven to thirteen. Doesn’t that involve a risk of losing focus?

Too rapid growth can have such an effect. But at LCSB, we have two main focal points keeping us on track: research on Parkinson’s disease and, as already mentioned, the study of complex, biological networks. We only get involved in projects and collaborations that relate somehow to these two aspects. Evidence of our success in this can be seen from our list of publications. In 2013, we published 60 papers – and most of them fall right under our focus.
So how does research at LCSB stand with respect to Parkinson’s patients? Where do they intersect?

The points of intersection are the mechanisms that lead to Parkinson’s. It is becoming increasingly clear that there is not only one type of Parkinson’s disease. Many different factors are involved in its onset: genetic disposition, environmental influences and metabolic characteristics. But we still cannot distinguish between these factors in the clinic and administer suitably adapted drugs. We want to change that with our work. We want to understand the different causes of Parkinson’s and create the basis for more precise, personalised diagnosis and therapy.

That involves LCSB researchers getting out of their labs and making contact with the outside world.

Of course, we have a strong outreach focus in this respect. We are continually exchanging information with Luxembourg’s patient interest groups. We wish to understand what motivates people with Parkinson’s, how they live with the disease, and what they need. And we want to include them in our research, especially in the scope of patient cohorts. Such studies are extremely important for better understanding the mechanisms and processes of Parkinson’s disease. But it is also important for us to keep in touch with Luxembourg’s people. So we regularly participate in science forums and present our work. I am delighted at how interested people are in LCSB’s research activities.

Another important connection is to young students. This year, we founded the »Scienteens Lab«, a project where high school students are invited to do experiments at the LCSB for a day. We want to show young students in particular what biomedical research entails, and that it is an extremely exciting field to work in.
Dr. Ronan Fleming has dedicated himself to this task. Since spring of 2013, he has headed the research group »Systems Biochemistry« at LCSB. Fleming’s goal is to model and simulate dopaminergic cells on the computer. »Engineers these days are able to simulate the interaction of billions of transistors on the computer as they develop new computer chips,« the veterinarian, mathematician and systems biologist says. »We need to develop similar techniques for simulating the processes of cells in the substantia nigra in a computer.«

He is most interested in the biochemical reactions taking place within these nerve cells: »Every biological process is based on biochemistry but we still barely understand how the countless reactions in the cells and in the body are correlated and how they affect one another. Only once we understand and can describe this network will we truly be on the trail of the causes of diseases like Parkinson’s,« Fleming argues.

**Every biological process is based on biochemistry**

Ronan Fleming and his group are currently following two paths: »Firstly, we are developing fundamental methods and techniques, that is algorithms and other bioinformatics tools that are important for systems biochemistry as a whole.« This takes up about half of Fleming’s group’s time and is not limited to Parkinson’s disease alone. The U.S. Department of Energy and the National Institutes of Health (NIH) considers the expansion of systems biochemistry so important and Fleming’s approach so promising that they granted him substantial funding.

Yet Fleming considers understanding Parkinson’s and other neurodegenerative diseases just as important as establishing fundamental bioinformatics tools for systems biochemistry. His group is currently compiling an up-to-date knowledge base on the biochemical reactions inside dopaminergic cells. This involves reading through literature, and then more reading through literature. While there are already technical methods for analysing scientific publications by
automated means, »if you are opening up a new area, as we are doing now, then a human reader’s capacity for interpretation is still unbeatable,« Fleming asserts.

Working from the knowledge and data collected by his team over the next few months, Fleming’s group will be running computer models and calculating the paths taken by specific biochemical molecules in dopaminergic cells — in healthy people and in Parkinson’s patients. To verify the resulting hypotheses, Fleming’s team will be collaborating with other researchers focussed more on experimental lab work, such as Karsten Hiller’s LCSB Metabolomics Group, who can actually follow the paths of metabolic products in real cells.

»Here and in many other areas, LCSB has built up vast knowledge and scientific excellence,« Fleming says. »But that is only one thing that makes researching at LCSB so good. The other is that LCSB scientists are genuinely interested in the methods and progress of their colleagues, and that a true exchange takes place here. It is interdisciplinarity for real. That is absolutely crucial if we hope to understand such complex systems as the biochemistry of Parkinson’s disease, so that we can actually help patients.«
After years of medication, many Parkinson’s sufferers are left with one last resort for relieving the symptoms of their disease: deep brain stimulation. This is a neurosurgical procedure where tiny microelectrodes are implanted into the brain. Controlled by a pacemaker placed under the collarbone, the electrodes continually give off electrical signals that block the abnormal nerve signals in the brain. The treatment is highly effective; symptoms such as tremor, rigidity or involuntary movements decrease significantly in most patients.

While the procedure is one of the established treatments for Parkinson’s today, each operation is a surgical feat in its own right: the surgeon’s target is the subthalamic nucleus (STN) of the brain. In order to reach this 0.13 square-centimetre region, the surgeons must work their way about eight centimetres through the brain starting from a small opening in the top of the skull. Then they have to place the electrodes in tiny subregions of the subthalamic nucleus.

»The targets are about four to five millimetres in size,« explains Frank Hertel, who performs such operations at the Centre Hospitalier de Luxembourg. »It is important that we reach these regions precisely for the treatment to be successful and for no side-effects to occur.«
Every operation is therefore planned in extreme detail beforehand. Using Magnetic Resonance Imaging (MRI) scans of the brain, the target coordinates are specified to the best possible accuracy. Yet, manual analysis of these scans is complicated and prone to error. More difficulties are then faced during the operation. Upon opening the top of the skull, the brain shifts very slightly, meaning the previously calculated »paths« are no longer perfectly accurate.

This is where the scientists of the research group Machine Learning at LCSB come in. Their research should help make the operation safer and plannable with greater certainty. A start has been made with a doctoral project involving close cooperation between bench and bedside. Its aim is to automatically create a patient-specific 3D model of the brain based on the MRI data obtained before the first operation. This will allow greater precision in the planning of the surgical procedure and path of the electrodes to the target points.

Avoiding risks for the patient

To create such a model, a so-called segmentation method is employed where the brain scans are broken down into non-overlapping segments. This separates relevant from irrelevant information. Theoretically, this can be done manually, but it is extremely complicated and hardly realistic in clinical practice. At LCSB, the researchers are therefore looking to develop a computer-based segmentation method specifically for those areas of the brain relevant to deep brain stimulation.

»By using computerised segmentation methods, we want to identify the relevant structures for deep brain stimulation in the patients’ brains,« explains Dr. Nikos Vlassis, head of the Machine Learning group at the LCSB. »The whole idea behind it is to personalise the operation, to make it safer for the patient and to avoid risks.«

Computerisation methods improve the patient’s safety even during the operation and lighten the surgeon’s workload. One example is continuous analysis of electrophysiological data obtained during the operation. The surgeons push their way through the brain with the help of so-called microablation electrodes. These record the cell activity in individual regions of the brain. Because different brain structures put out different signals, analysing the discharge patterns gives the surgeon his current location. Surgeons have so far had to analyse these electrophysiological signals by themselves.

The LCSB researchers are working on processing these data automatically in the future and integrating them into a previously created navigation model. That way, the surgeon will be able to navigate through the brain with certainty and localise the target structures with greater precision. The project is still in its infancy. Before technological solutions can be realised at LCSB, it is essential to understand the practical problems the clinicians are faced with. Vlassis sums it up: »Close coordination between the scientists and the clinical side is therefore indispensable.«
With a little help from our »in silico« friends

Analysing a patient’s genome is an altogether colossal task. You start with a sample of cells — a biopsy taken from the skin or perhaps from a tumour, if you are looking at cancer cells. Each biopsy includes hundreds of cells. In a healthy patient, they all look pretty much the same. In a tumour, however, they can differ greatly.

Once you have extracted the DNA, you cut it into millions of pieces, multiply these pieces and then try to rearrange them back into their original pattern. Getting the pieces properly aligned in this process, known as sequencing, is crucial for correct genome analysis and is at the very heart of Sarah Killcoyne’s work.

Killcoyne is working on optimising the alignment process for cancer cells specifically. The problem with cancer cells is that, within a single tumour, the DNA can vary to an extreme degree, making the alignment process all the more difficult. Imagine trying to solve several different jigsaw puzzles at the same time when all the pieces have been mixed together into one big pile.

To cope with this incredible complexity, Killcoyne is developing a smart tool: the »in silico« patient. Working from the analyses of thousands of karyograms — photos of chromosomes — from cancer patients, she has developed statistically based computer patient models that help her to assemble all the jigsaw pieces into their proper respective pictures. Guided by the »in silico« patient models, the algorithms can find a more accurate alignment, which will ultimately help to improve our understanding of the genetics of cancer.
Great success for LCSB scientist Dr. Enrico Glaab: in November 2013 he won a public scientific challenge of the US Geoffrey Beene Foundation for a project proposal on Alzheimer’s disease. For the worldwide online vote three finalists – two from the US and one from Luxembourg – had to present their suggestions in video presentations and generally comprehensible texts on the web. The vote went to Glaab for his entirely novel research project with which he intends to find out why women are at greater risk for Alzheimer’s disease than men.

In a close finish, the LCSB came ahead of the US research elites of Harvard University. The team around Enrico Glaab now receives 50,000 US dollars from the Geoffrey Beene Foundation for its research on Alzheimer’s disease. »We are very happy about this joint success,« Enrico Glaab says.

Combining experimental data with computer-aided analyses

A success, the researcher says, that would not have been possible without the support of his colleagues at LCSB and at the University, collaboration partners and many friends: »I performed the data analysis and submitted the text for the first round of the challenge. In the second round, there were several scientists at LCSB involved in the detailed planning of the experiments – and in the end many people gave us their vote.«

Glaab’s project combines experimental data with computer-aided analyses:

Ageing is considered the most important risk factor for Alzheimer’s disease, yet elderly women are afflicted by this neurodegenerative disease much more frequently than men. Studies of the ageing human brain also show a difference in the activity of specific genes between men and women – sometimes with considerable ramifications for the risk of Alzheimer’s. Enrico Glaab has identified one such gene, called USP9. This gene is much more active in the brain of healthy men than in men with Alzheimer’s. In women the gene shows no such statistically significant differences. Whether healthy or ill, it is nearly equally active in both cases. The gene also acts as a regulator in many cellular processes associated with Alzheimer’s disease.

The research question that motivates Enrico Glaab is: Does the elevated activity of the USP9 gene in men provide protection against Alzheimer’s? With the endowment from the Geoffrey Beene Foundation, he and his team now intend to test their hypothesis – and find out whether preventive approaches against Alzheimer’s can be derived from it.
A functional »street map« of human metabolism

»We want to find out how diet influences our health.« In these concise words, FNR ATTRACT fellow Dr. Ines Thiele states the core objective of her research group Molecular Systems Physiology. But what she makes sound so simple is in fact an unimaginably complex endeavour. Countless biochemical reactions determine how food is converted into energy in our body. Genetic differences and inborn errors of metabolism influence these processes as much as the many bacteria living in our gut.

In order to map out this complexity in one big, clear picture, the scientists are simulating the entirety of human metabolism – the metabolome – on the computer. They are feeding their model with the results from more than 50 years of research in various fields such as medicine, biochemistry and bioinformatics. Most of this information is on genes and proteins, as well as the biochemical reactions and all their metabolites, i.e. the starting, intermediate and end products.

Constraint-based modelling is their method of choice, a bottom-up approach where an ever denser data network is knitted together to gradually reconstruct the biological system on the computer. A herculean task, which can only be shouldered with joint effort. Last year, an international research group led by Ines Thiele, then at the University of Iceland, published the most complete reconstruction of human metabolism to date, called Recon 2.

More than 2,600 metabolites and over 7,400 reactions have already been fed into Recon 2 – with more being added nearly every day. The model is freely accessible on the internet and is being used, commented on and thus continually expanded and refined by researchers around the world. An update of the model is released every three months.

In the research community, Recon 2 is far more than just a model of human metabolism. The model will help in making predictions on metabolic processes, such as predicting the consequences of genetic diseases or the effects of drugs. »You can imagine Recon 2 as a functional street map,« explains Ines Thiele, who has been working at LCSB since April 2013. »It tells you how to get from A to B, and even what happens if there are road works along the way.«

Understanding how diet influences our health

Thiele and her team tested the predictive power of the model by studying congenital metabolic diseases in which a specific metabolic enzyme is faulty. In the human body, for example, this leads either to omission or to excessive accumulation of certain metabolites. Such changes in metabolites can be measured in classical cell experiments. To test how closely Recon 2 models reality, the researchers then removed the faulty enzyme from their model to see how that would affect the metabolite in question in the network. They discovered that, for a total of 49 inborn errors of metabolism, Recon 2 models the changes detected in cell experiments to at least 77 percent accuracy.
Recon 2, however, is based on a kind of idealised cell whose metabolome combines the biochemical processes of entirely different cell types into one and which therefore does not exist in any cell of the body. A liver cell, for example, has to perform completely different tasks and accordingly has an entirely different metabolome from an intestinal cell. To answer specific research questions, Thiele and her colleagues are therefore working on modelling specific cell types, for instance the epithelial cells lining the small intestine. This will allow them to study the role of these cells in the enzymatic breakdown of food and absorption of nutrients in detail.

There is just one thing missing to make it a completely true likeness of the human metabolome: inclusion of the gut flora. More than 1,000 species of bacteria in the human gut are indispensable for the breakdown and utilisation of food. Again, the researchers expect to gain new insights from their models: »We aim at creating metabolic models for the most important microbes in the human gut,« Ines Thiele says. »With these models we can answer questions such as: what benefits does a certain microbe offer to the host? Can bacteria possibly compensate for some genetic deficiencies of their host?« The scientists are convinced that, combined with experimental data, the models will significantly improve our understanding of how diet influences our health.
Dr. Alexander Crawford is always on the move. One day the molecular biologist will be heading the Chemical Biology group at LCSB in Luxembourg, the next managing an EU project at Leuven University in Belgium, or he will be at meetings in Saarbrücken, Germany – not to mention all the international congresses he attends. »My ›office‹ is often in trains and planes. And when I’m here at LCSB, I’m in one meeting after the other,« he says. Wherever he is, however, there is one consistent theme to his scientific work: zebrafish.

His research is about how zebrafish can help in the deciphering of genetic and molecular biological mechanisms of neurodegenerative diseases and the discovery of novel agents for treating them. Over the course of his scientific career, Crawford has become an expert in this field. He is intimately familiar with the developmental biology of these little fish, in particular the development of their nervous system; he knows how genes involved in the onset of certain diseases can be turned off in a targeted way, and knows what paths must be taken to discover possible new drugs by studying zebrafish.

Why zebrafish in particular? »These fish are genetically very similar to humans. They also develop a complex nervous system, even as tiny larvae, meaning diseases of the brain can be studied very well,« Crawford explains. Another reason why the animals make excellent model organisms is because they reproduce so effectively and are only a few millimetres in size in their embryonic and larval stages. »On top of all this, they are transparent in their early stages of development. That means changes in the activity of the nervous system can be observed very easily in live animals,« he adds. Crawford and his team are using these advantages to research hitherto untreatable human disorders, such as Parkinson’s disease and drug-resistant forms of epilepsy.

Be it Parkinson’s disease, epilepsy or neurodegenerative diseases – the Chemical Biology group’s work follows a similar approach. »First, in interdisciplinary collaboration with internal and external partners, we identify genes suspected of playing an important role in the onset of a disease,« Crawford says. The next step is to show whether this suspicion can be confirmed in the zebrafish model. To find out, the researchers create an engineered zebrafish strain in which the gene in question is deactivated.

Discovering genes – and drugs against epilepsy

Behavioural tests and other experiments on the live larvae then reveal whether and what sort of functional changes result from this. »In the positive case, these data support the hypothesis that the gene is relevant to a disease,« Crawford explains. Using these methods, as part of a European consortium, the LCSB researchers were recently instrumental in the discovery of a new epilepsy gene. This knowledge may now lead to the discovery of effective drugs against this special form of epilepsy.

The Chemical Biology group also has a strong focus on the discovery of potential therapeutics (so-called drug
leads) from nature. »Many currently marketed medicines originated in plants or microorganisms, such as the immunosuppressant drug rapamycin, which was isolated from soil bacteria on Easter Island (also known as Rapa Nui).« Crawford tells us. To find medicines in the reservoir of nature that will treat neurological diseases, he is a project manager of the EU-wide research consortium »PharmaSea«, coordinated by Leuven University in Belgium. PharmaSea aims to discover bacterial strains in the world’s oceans that produce pharmaceutically active substances. Medicinal plants used by traditional healers for the treatment of disorders of the central nervous system are also of interest to the LCSB Chemical Biology group.

»Of course, it remains quite a challenge to identify the actual active agents in complex natural substance extracts,« Crawford says. But this is exactly where the zebrafish are a big help to the researchers: Being so tiny, the fish larvae are suitable for high-throughput screening. Many different extracts can be tested in a single work step. Samples that show activity are then broken down into their individual components in an elaborate process. »We can obtain only a few micrograms of some substances in this fashion,« Crawford explains. Too little to test in mammals, but enough for testing each individual substance in the fish model. Crawford concludes: »Substances that show desirable activity here can then be structurally resolved by other colleagues, synthesised in the lab and tested for their suitability as drugs in further experiments.«
Goethe has already said »Why seek far afield when good things lie nearby?«. In this spirit, besides its international collaborations, LCSB actively fosters collaborations with research institutes, health care providers and industry partners in Luxembourg and its border countries. The map depicts collaboration partners within a radius of 200km from Campus Belval.
It was less than a year ago that Prof. Dr. Jens Schwamborn moved from University of Münster in Germany to LCSB in order to establish the research group Developmental and Cellular Biology. Despite the young history of the group, research is already in full swing. The starting conditions were good, since Schwamborn brought his entire team with him from Münster’s Center for Molecular Biology of Inflammation to the Belval campus in Luxembourg.

Schwamborn’s team is primarily interested in stem cells and their role in the symptoms of Parkinson’s disease. Stem cells are often referred to as «master cells» because they can change into any type of tissue cell, such as skin, muscle or heart cells for example. In the case of Parkinson’s disease, they could among other things serve as the starting point for generating new nerve cells. These, the theory goes, could then replace exactly those nerve cells in the brain of a Parkinson’s patient that have been destroyed in the course of the disease: the dopaminergic neurons of the substantia nigra in the midbrain.

This theory is not new. A number of research groups have already used stem cells of various origins for transplantations, including stem cells from patients’ bone marrow or ones obtained from human embryos, for example. Yet there has been no resounding success so far. Schwamborn and his colleagues have instead placed their hopes in so-called induced pluripotent stem cells or iPS cells for short. These cells are obtained from already differentiated body cells – skin cells for instance. By making targeted genetic manipulations, such cells can be «rejuvenated» into pluripotent stem cells that, in a second step, will develop into the desired neurons.

iPS cells have several crucial advantages: For example, the patient’s own body cells can be put through the rejuvenation programme. That means the body will not reject the cells when subsequently transplanted. The research group at LCSB is following two strategies in their research on iPS cells.

To better understand the pathological process, the scientists turn patients’ skin cells first into iPS cells and then into neurons, and subsequently compare the development of these cells with those from healthy people in cell cultures. «We want to see what goes wrong in Parkinson’s patients compared to healthy people,» Jens Schwamborn explains. The scientists know of certain genetic changes that lead to the onset of Parkinson’s in some patients, such as changes in the Parkin, LRRK2 and PINK1 genes. In other patients, they suspect an as yet unknown genetic mutation, while in other patients still, the cause of the disease is entirely unclear.

With their cell cultures the researchers are building an entire library of cells

They already know that «the neurons of Parkinson’s patients differ greatly from healthy cells,» as Jens Schwamborn continues. «For instance, some have a completely different gene expression profile, their energy metabolism is different and the neurites grow differently.» Little by little, with their cell cultures, the researchers are building an entire library of cells of different phenotypes. Their precise characterisation helps to better connect the known dots in the aetiology and pathological progression of Parkinson. Furthermore, the researchers can test therapeutic agents on these cells.

In the second core research approach of the group, the scientists are using iPSCs for transplantation. Again, they start with skin cells. The researchers convert these to iPS cells and in turn to
dopaminergic neurons, which they then transplant directly into the brains of mouse models for Parkinson’s disease.

“It is a very promising approach,” Schwamborn says. “In the animal studies, we can successfully make the motor dysfunctions associated with Parkinson’s disappear.” One of the biggest challenges is ensuring the transplanted cells are integrated successfully into the affected area of the brain. Also, their axons, i.e. the signal-carrying nerve fibres, have to grow in the right direction. In another project, the group is researching the activity of neural stem cells in the brain itself. Contrary to a long-held belief, it is now known that neurons regrow, even in the adult brain of humans and other mammals, from adult stem cells, and that these can replenish cells to a certain extent in injured or diseased tissue. In Parkinson’s patients, according to a new hypothesis, the adult neural stem cells are instead deregulated, which impairs the growth of new neurons. This leads to abnormalities from very early on, such as olfactory problems or depressive moods, long before the appearance of the classical motor symptoms of Parkinson’s. The research group is studying how the activity of neural stem cells can be controlled, for example what genes and what regulatory factors are involved. The question behind this research is: How can we provide effective therapy that will induce adult stem cells to form new nerve cells, thus replacing those destroyed in the course of the disease?
The friendly bodyguard

To coordinate Rudi Balling’s appointments is not an easy job as Véronique Briche can credibly assure. Being Rudi’s assistant, a main challenge of her job is to always be friendly but determined at the same time. Keeping the life of the LCSB director acceptably busy - with maximum efficiency – not excluding a fair amount of time to concentrate on science – this is the challenge. Managing the queue of aspirants for an appointment in front of Rudi’s office door and taking care of all the many guests visiting LCSB is more than a full-time job.

Surrounded by her colleagues Aurelia Giovannangeli and Brigitte Melchior the secretary of the LCSB definitely works at the busiest place around. Phone calls, a noisy printer, people who meet at the secretariat by chance and start dedicated discussions, couriers delivering parcels and newcomers asking about the best place to buy a refrigerator or stamps in Luxembourg – definitely no place for the faint-hearted. But Briche is never rude. It is a complete mystery how she manages – but she does. Friendly and determined!
The LCSB prides itself on being a competitive player in biomedical research at an international level. The institute’s group leaders are experts in their field and the labs are equipped with some of the most powerful instruments currently available. It goes without saying that research at such a competitive level is very expensive: In 2013, the LCSB spent millions of Euros in operating expenses, salaries and equipment. But where does this money come from?

While the University and Ministry of Research and Education cover a large part of the LCSB’s expenses, all additional income needs to be collected through research grants from national and international funding bodies. Although many LCSB grant proposals were funded in 2013, not all of them received financial support. ”Funding agencies have a limited budget and are often faced with the challenge of choosing between numerous projects that all deserve funding“, explains Dr. Philippe Lamesch, fundraiser at the LCSB. »As a result, many ambitious and promising projects are left unfunded every year.«

With dwindling government funding and increasing international competition, researchers are forced to consider alternative funding methods. One way of bolstering research funds is through private donations. Supporters can donate to the general LCSB fund or to a specific project. Undecided donors can meet with the LCSB director to learn which projects most urgently need their support and how they can make the biggest impact with their gift. Donors can choose to make a single donation, give on a regular basis, or leave a bequest in their will.

**A voice influencing what research is carried out in Luxembourg**

Over the last two years, about a dozen foundations, clubs and private individuals have made substantial donations to the LCSB. The majority of these gifts had a specific designation. For example, the Fondation Veuve Emile Metz-Tesch made a large donation to the LCSB’s Scienteens Lab, Another major gift recently came from a Luxembourgish Parkinson’s disease patient, to support a particular research project. »By allowing individuals and foundations to support the research programme or disease area that best fits their philanthropic goals, they are truly given a voice that influences what research is carried out in Luxembourg«, notes Dr. Lamesch.

For more information on how to support the LCSB, please contact Philippe Lamesch at philippe.lamesch@uni.lu or visit www.uni.lu/lcsb/support.
Events 2013

ISB-LCSB partnership symposium

On 11-12 June 2013, LCSB and the Institute for Systems Biology (ISB) in Seattle, USA celebrated the 4-year anniversary of their collaboration with a symposium on the state of the art in systems genetics and metabolism, integration of networks, ecosystems biology and systems medicine research. Selected scientific presentations gave insights into the collaborative projects between the two institutions and other international partners. As part of the collaborative and educative efforts, several researchers from Luxembourg spent up to 2 years in Seattle. In his speech, Jeannot Krecké reminisced about the development from the first decision of the Luxembourgish government to embark on biomedical research up to the present day. He expressed his satisfaction about the unprecedented speed with which the biohealth sector in Luxembourg is growing thanks also to knowledge transfer partners like the ISB.

SYSMED 2013 summer school

Together with Systems Biology Ireland (SBI), LCSB jointly organised the SYSMED 2013 summer school which preceded the ISB-LCSB partnership symposium (see text below). During this two-day event, young researchers from around the world attended lectures and practical workshops focusing on highly relevant topics for systems medicine such as family genomics, protein design and light microscopy applications.

Workshop »Modelling Parkinson’s disease in animals: mission impossible?«

Over the last two decades many different animal models have been established to better understand Parkinson’s disease (PD). Are the current PD models in zebrafish, mice and primates adequate to meet modern biomedical research needs? Do we need improved models to study the disease? — These questions were the central topic of the workshop »Modelling Parkinson’s disease in animals: mission impossible?« held on 21 May 2013 under the lead of Dr. Manuel Buttini. Key international experts presented their latest data on animal models of PD, and debated on their limitations. The researchers concluded that although significant progress has been made in recent years, the need for models with a more pronounced PD pathology continues.


2nd International Systems Biomedicine Symposium

Systems biology approaches using high-throughput data have been applied to many diseases in recent years. During the 2nd International Systems Biomedicine Symposium on 21-22 October 2013 a list of highly acknowledged scientists presented their latest insights in systems biology, discussed recent technological developments and debated on what is needed to pave their way into clinical practice. Amongst the speakers was Nobel prize laureate Prof. Bruce Beutler from the University of Texas Southwestern Medical Center who inspired more than 200 participants with his talk on forward genetic analysis of immunity.

Workshop »Curation of Parkinson’s disease-related molecular pathways«

In December 2013, LCSB organised a satellite event of the XX World Congress on Parkinson’s Disease and related disorders in Geneva, Switzerland to curate the latest knowledge on molecular pathways associated with PD. 50 clinicians and researchers from around the world joined the workshop to learn about the PD map and contribute their expertise to this publicly available knowledge repository (http://pdmap.uni.lu). The results of this workshop were presented during the hot topics session of the conference. LCSB was also present during the expo organised for the congress, explaining its research activities and PD focus. The large touch screen attracted a lot of curious scientists to join a guided tour through the molecular landscape of the disease.
Systems biomedicine as an economic driver

Spin-offs: Theracule and Luxfold

The primary purpose of LCSB is systems biomedical research. Its aim is to find new approaches that will deliver better methods for prevention, diagnosis and therapy for people with Parkinson’s and other neurodegenerative diseases. Knowledge gained from this research naturally also carries a certain economic interest. To maximise the chance of commercial success in Luxembourg, LCSB scientists are establishing companies here, together with LCSB and the University of Luxembourg. Scientific know-how is injected directly into these spin-offs, which continue developing the knowledge to market maturity or for licensing out to large companies. Two such spin-offs were founded in 2013: Theracule and Luxfold.

The largest stake in Theracule is held by LCSB scientist Dr. Alex Crawford. His topics are epilepsy and zebrafish: »Zebrafish are ideal subjects for studying diseases like epilepsy or Parkinson’s,« he says. »The fish lay a large number of eggs; the larvae that hatch are transparent and allow a precise study of the nervous system.« Using special techniques, Crawford and his team can deactivate individual genes in the zebrafish. Like those suspected of triggering epilepsy if they fail because of a mutation, for instance. »We simulate these mutations in the zebrafish larvae by knocking out single genes,« Crawford explains. Theracule uses the zebrafish larvae to find and test potential therapeutic agents against epilepsy. The compounds come from collaboration partners with large substance libraries. »With Theracule, we hope to develop drugs especially for those people suffering from rare diseases,« Crawford says.

Luxfold is a company that is dealing with the structure of proteins. Its initiators are Paola Pozzo and Dr. Reinhard Schneider: »We have developed a method by which we can predict the three-dimensional structure of the gene product, i.e. the protein, from a gene sequence.« Until now, it has only been possible to read from a gene which components – amino acids – make up the resulting protein. What laws govern how the proteins fold after their synthesis, however, has always been one of the biggest puzzles in biology. »We have a paper in preparation in which we will reveal this secret,« says Schneider. And a patenting process will secure the knowledge so that it can be introduced into Luxfold. »We have already convinced investors of the potential of our idea at this early stage,« Reinhard Schneider continues: »Luxfold is now funded for one and a half years, so we can develop the business model concurrently with the publication and patenting process.«
From the very beginning, Prof. Dr. Rudi Balling envisaged creating a space within LCSB where Luxembourgish high school students could participate in hands-on experiments related to biomedical research. The goal was to give young students a realistic glimpse into the profession of a researcher while keeping them abreast of the evolving research landscape in Luxembourg. Recently, this vision became a reality. After a 12-month pilot project, Dr. Elisabeth John took the lead in October 2013 to officially create Luxembourg’s first student lab, named the »Scienteens Lab – De Labo fir Jonker«.

Their Royal Highnesses the Crown Prince Guillaume and Crown Princess Stéphanie showed their support for this project by visiting the Scienteens Lab, accompanied by the Minister for Higher Education and Research Claude Meisch. They attended a Scienteens Lab workshop, met with the students and even participated directly in some of the experiments.

Most importantly, Crown Princess Stéphanie became patroness of the student lab, creating even more motivation for many young students to attend the Scienteens Lab.

A major part of the Scienteens Lab’s success is owed to the Fondation Veuve Emile Metz-Tesch, which is supporting this educational project with substantial funding. Dr. Elisabeth John plans to expand the portfolio of classes offered in the months to come, and hopes to initiate Science Camps during school holidays in the near future.
Concentrating on dynamics

Systems Control

Prof. Dr. Jorge Gonçalves. He is currently establishing the Systems Control research group and is looking at these systems from a new angle that had not been taken before at LCSB. Gonçalves is researching their dynamics, i.e. their change in condition over time.

When explaining the importance of dynamics, Gonçalves is apt to use technological examples. Not a surprise, given the researcher’s background as an electrical engineer and computer scientist. »A modern plane is one example of a complex system. When standing on the ground, with its turbines off, we can see all its components at rest, i.e. static. As soon as the machine starts up, though, the aircraft components start interacting with one another and with the environment. The aircraft behaves dynamically. It can only be controlled if you consider the changes in its conditions – and react dynamically to them.«

Gonçalves originally worked exclusively on technological systems, their dynamics and their control: »But it dawned on me that similar laws apply to biological systems – and that they are much more interesting, at least to me.« Gonçalves accordingly started working on biological matters in his earlier scientific career. Biomedicine, and Parkinson’s disease in particular, were only added to his repertoire upon coming to LCSB. Jorge Gonçalves finds this new topic especially stimulating: »Here at LCSB, I can research the dynamics of biological systems and so hopefully contribute to identifying the causes of diseases and creating the foundation for new diagnostic and therapeutic methods. Personally, I find that a great enrichment and motivation for my work.«

An almost immeasurable number of components

Biological systems such as brain cells are made up of an almost immeasurable number of components and are incredibly complex. »We have only just identified the tip of the iceberg of this complexity,« say Gonçalves. »That is why it is so important to persist in identifying new components of the networks and to connect the individual dots. For that we require the efforts of several fields such as mathematics, engineering and physics. But, to understand how the components influence one another and what feedback loops arise as they do, we need to study how they change over time.«

So far, it has only been possible to analyse the systems dynamics within small sections of the cellular networks. Gonçalves continues: »My work consists to a large degree of developing new theoretical approaches and techniques so that we understand the
dynamics of ever larger subsystems. «One of these techniques is system identification, Gonçalves explains: »In this method, we work with data that are related to the system’s change over time. We process these data in a dynamic model, with which we can predict the behaviour of the system.« In this way, Gonçalves intends to formulate hypotheses on what processes in neurons, for example, contribute towards the onset of Parkinson’s. »We need physical proximity to the labs for this – just as we have here at LCSB. That is namely where we get the research questions and data for our models. And only there can our hypotheses be subsequently tested, confirmed or refuted.« Yet Jorge Gonçalves still has a lot to organise before everything is ready: »Our team meetings are still very orderly; there are namely only two of us at the moment. But we will be getting good reinforcements – in order to expand LCSB Systems Control to an appreciable scientific size.«
Inflammation of the brain

Feng He is from China – originally. But he moved to Europe many years ago. Before he joined LCSB he was doing research at the Helmholtz Centre for Infection Disease (HZI) in Braunschweig, Germany. There he met Rudi Balling. Following Rudi, he finally found his way to the Luxembourg Centre for Systems Biomedicine.

Feng He’s research is dedicated to the role of inflammation in the brain. This might play a significant role in neurodegenerative diseases like Parkinson’s disease. Several lines of evidence suggest that neuroinflammation and chronic activation of the immune system are associated with the pathogenesis of PD. A special type of immune cells specifically caught Feng’s attention: the regulatory T Cells or Tregs for short. Interestingly, patients suffering from neurodegenerative diseases such as PD display a Treg dysfunctional phenotype. Feng He’s research is dedicated to the molecular mechanisms underlying T cell function. Genes involved in Parkinson’s disease might also play an important role in Treg suppressor function which might contribute to the pathogenesis of this neurodegenerative disease.

Obviously there is a connection, but the details are still unclear. Hopefully Feng is on the track of a highly relevant molecular pathway. Understanding it might bring biomedicine closer to understanding Parkinson’s disease.
Facts and figures

2013 LCSB income (in kEUR)

- University of Luxembourg (UL): 6,080 (44%)
- Ministry of Research and Higher Education: 2,301 (17%)
- Fonds National de la Recherche (FNR) Grants: 4,575 (33%)
- EU grants: 573 (4%)
- Internal UL project grants: 180 (1%)
- Further grants: 142 (1%)

2013 LCSB expenses (in kEUR)

- Wages: 7,896 (59%)
- Investments: 365 (3%)
- Operating expenses: 2,917 (22%)
- Travel: 2,066 (15%)
- Representation: 98 (1%)
- Documentation: 6 (0.04%)
Staff categories LCSB 2013

- Researchers: 53%
- Technicians: 21%
- PhD students: 11%
- Management and administration: 15%

LCSB organigram

LCSB Director (R. Balling)

Research

- Bioinformatics Core (R. Schneider)
- Chemical Biology (A. Crawford)
- Computational Biology (A. del Sol)
- Developmental and Cellular Biology (J. Schwamborn)
- Eco-Systems Biology (P. Wilmes)
- Enzymology and Metabolism (C. Linster)
- Experimental Neurobiology (R. Balling)
- Machine Learning (N. Vlassis)

Support

- Medical Translational Research (J. Schneider)
- Metabolomics (K. Hiller)
- Molecular Systems Physiology (I. Theile)
- Systems Biochemistry (R. Fleming)
- Systems Control (J. Gonçalves)

Central Office
- Secretary
- HR
- Infrastructure
- Finance
- IT Support
- Legal Support

Communication Office
- External & Internal communication
- Fundraising

Infrastructure
- General Laboratory Support
- IT Support
- Facility Management

Scientific Support
- Grants Office
- Project Management

Scientees Lab
## FNR grants in 2013

<table>
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<th>Project acronym</th>
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<td>HuMORS</td>
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<td>Stefania Magnusdottir</td>
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<td>MITOSYN</td>
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<td>Rudi Balling</td>
<td>RESCOM</td>
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<td>CaMeGIt</td>
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## UL grants in 2013

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<td>DopaMet</td>
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## European grants in 2013

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<td>BioCog</td>
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<td>Georg Winterer (Berlin)</td>
<td>Reinhard Schneider</td>
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<td>AETIONOMY</td>
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<td>UCB Pharma (Belgium)</td>
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<td>COURAGE-PD</td>
<td>JPND</td>
<td>Thomas Gasser (Tübingen)</td>
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## International grants in 2013

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<td>BrightFocus Foundation</td>
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<td>WGS data from LRRK2 PD families</td>
<td>Michael J Fox Foundation</td>
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<td>Jens Schwamborn</td>
<td>2013</td>
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</table>

## Interim board 2013

- **Participants 2013**
  - Ludwig Neyses: Vice-rector for Research, University of Luxembourg
  - Alfred Funk: Director of Administration, University of Luxembourg
  - Paul Heuschling: Dean of Faculty of Science, Technology and Communication (FSTC), University of Luxembourg
  - Rolf Tarrach: President, University of Luxembourg
  - Eric Tschirhart: Vice-rector for Academic Affairs, University of Luxembourg
Meetings and workshops (co)organised by the LCSB

<table>
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<tr>
<th>Date 2013</th>
<th>Event</th>
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<tbody>
<tr>
<td>11th February</td>
<td>MCISB-LCSB Workshop I on »Iron metabolism« (held in Manchester, UK)</td>
<td>Manchester Centre for Integrative Systems Biology, UK</td>
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<td>26th February</td>
<td>METU-LCSB Health Informatics Summit (held in Ankara, Turkey)</td>
<td>Middle East Technical University, Turkey</td>
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<td>12th April</td>
<td>Helmholtz-LCSB partnership day »Chemical biology meets mouse genetics«</td>
<td>Helmholtz Institute for Pharmaceutical Research, Saarland (HIPS) and Helmholtz Zentrum München, Germany</td>
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<tr>
<td>21st May</td>
<td>Conference on »Modelling PD in animals: mission impossible?«</td>
<td>-</td>
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<tr>
<td>3rd June</td>
<td>MCISB-LCSB Workshop II on »Iron metabolism«</td>
<td>Manchester Centre for Integrative Systems Biology, UK</td>
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<td>9th - 10th June</td>
<td>SYSMED 2013 summer school on »Genome analysis, protein design and image analysis«</td>
<td>Systems Biology Ireland, Ireland</td>
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<td>11th June</td>
<td>LCSB-ISB partnership symposium</td>
<td>Institute for Systems Biology (ISB), USA</td>
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<td>10th October</td>
<td>Inauguration of LuxFold (2nd LCSB Spin-off)</td>
<td>LuxFold SA, Luxembourg</td>
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<td>21st - 22nd October</td>
<td>2nd International Systems Biomedicine symposium: »From System Biology to Systems Medicine: The road ahead«</td>
<td>-</td>
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<td>5th December</td>
<td>Mini symposium on »Stochastic biology and chemical networks«</td>
<td>Physics and Material Sciences Research Unit, University of Luxembourg</td>
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<td>6th December</td>
<td>UniGR Workshop on »Big Data – challenges and opportunities«</td>
<td>UniGR partner universities</td>
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<td>8th December</td>
<td>Workshop on »Curation of PD-related molecular pathways« (satellite event during the XX World Congress on Parkinson’s Disease, Geneva, Switzerland)</td>
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Patents filed 2013

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<td>LuxFold – 3D protein structures</td>
<td>Reinhard Schneider, Paola Pozzo</td>
<td>LU92271 GB1315236.8</td>
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<tr>
<td>Irg1 – Production of itaconic acid</td>
<td>Karsten Hiller, Alessandro Michelucci, Thekla Cordes, Jenny Ghelfi</td>
<td>LU82184</td>
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<tr>
<td>Visualization of high-dimensional nucleotide sequence data</td>
<td>Paul Wilmes, Nikos Vlassis, Cédric Lazny</td>
<td>LU92276</td>
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LCSB spin-offs 2013

<table>
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<th>Date 2013</th>
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<tr>
<td>TheraCule Sàrl: »Zebrafish as a model system to develop new therapies for epilepsy«</td>
<td>Alex Crawford, Rudi Balling (LCSB), Camila Esguerra, Peter de Witte (KU Leuven)</td>
<td>March</td>
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<tr>
<td>LuxFold Sàrl: »Prediction, design and engineering of protein structures and discovery of new therapeutic targets«</td>
<td>Advent Venture Partners LLP, Alain Huriez (Advent V. P.), Reinhard Schneider (LCSB), Paola Pozzo (LCSB)</td>
<td>October</td>
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Publications 2013

Publications in refereed journals


