X-Letter 32

Diversity in systems biology

From plant growth to tuberculosis and metal extraction

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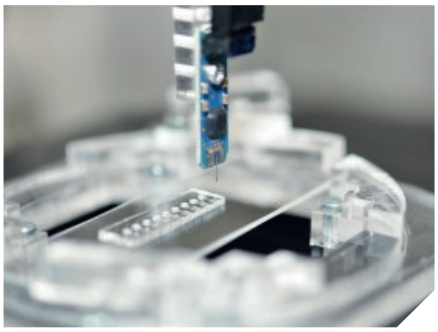

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SystemsX.ch
The Swiss Initiative in Systems Biology

Imprint

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"The interdisciplinary systems approach can now be applied to almost any scientific problem."

Photo: © David Schweizer

All SystemsX.ch projects share one thing in common: they use a systems approach to achieve an integral and comprehensive understanding of the quantitative behavior of biological systems. A central part of this type of research is mathematical modeling, which is used to simulate a system's properties *in silico* and can predict its quantitative response to internal or external perturbations. The study of biological systems in this way requires extensive interdisciplinary collaboration between biologists, medical scientists, mathematicians, physicists, computer scientists, chemists, engineers and more.

While the systems approach has been applied in other scientific fields for some time now, it is only thanks to recent technological advances, such as next-generation sequencing and mass cytometry, that it is becoming more widely used in the life sciences. This has opened up new dimensions to biological research, which means that the interdisciplinary systems approach can now be applied to almost any scientific problem.

The diversity of topics in systems biology research seems to have no limits. This X-Letter exhibits just a tiny subset of the huge range of research themes within SystemsX.ch alone. The MecanX team is using the systems approach to unravel the mystery of plant growth. In the HostPathX project, it is the key to new active agents to combat tuberculosis, and the international team from SysMetEx is employing it in their efforts to speed up copper mining by bioheap leaching.

The systems approach is to be found not only in biology, but in practically all scientific fields. A promising related area is medicine. The application of findings from basic science into clinical research has the potential to facilitate, for example, the development of new medicines and the optimization of therapies.

While SystemsX.ch slowly reaches its conclusion, a new initiative that likewise relies on the systems approach has already positioned itself on the starting blocks: a Swiss-wide initiative promoting research in personalized medicine is planned to start in 2017. You can read more about it in this X-Letter.

I wish you pleasant reading,

Daniel Vonder Mühll
Managing Director SystemsX.ch

Systems biology of mammalian forebrain development (NeuroStemX)

The key to neuron production

Brain development is guided by numerous cellular processes that determine exactly when and what types of neurons arise from neural stem cells. The RTD Project NeuroStemX is bringing these processes to light and will make its findings available in the form of a complex data set.

Verdon Taylor and his team decipher brain formation in order to provide the basis for therapies to treat neurological disorders.

When Verdon Taylor and his team publish their results, there will be no single finding, like a gold nugget, which they can hold up and say, “That’s it! We’ve found it!” The truth is much better and far-reaching. They will present an entire goldmine and say, “It is stuffed full of treasures and anyone can help themselves.”

Their goldmine is a huge data set. Several terabytes in size, it incorporates billions of RNA sequences. How the genetic code manifests itself, that is, which cell types arise from a particular stem cell, is determined at the level of RNAs and the proteins they encode. The data set potentially contains all of the RNA sequences that control the development of the cerebral cortex, providing valuable insight into these processes.

Little knowledge, fewer therapies

There has never been such a comprehensive overview. Verdon Taylor, project leader of NeuroStemX, is convinced of the significance of the data for the scientific community. “Whoever detects the right pattern in the data,” he says, “will find out which RNAs and proteins control the interactions within and also between cells, so that the right neurons form at the right point in time.” This could be the key to selectively stimulating the production of certain neurons, or even producing them in the lab.

But why is this so important? It’s best to begin with the cerebral cortex. Unbelievably powerful, it is responsible for the higher brain functions of all mammals. Thanks to the cortex, human beings are able to think, move, remember. However, it is also an exquisitely sensitive structure, and insufficient growth or the loss of certain neurons can lead to disorders including autism, Alzheimer’s and some types of epilepsy.

To date, there have been very few therapies available to tackle these developmental and neurodegenerative disorders, not least due to our limited knowledge of why and how certain neurons arise from stem cells at different points in time. How are the specific genes activated or deactivated? Taylor and his team would like to address these questions.

Simple development into a complex organ

It remains extremely time-consuming to study the roles of proteins and RNAs in the regulation of gene activation and cell fate, not to mention the complex networks involving gene expression across different cell types. “Only the most recent advances in the fields of next-generation RNA sequencing and bioinformatics allow us to specifically search for complex gene networks on a more global scale,” says Taylor.

Just how do the researchers identify the critical genes in brain development? Firstly, they take advantage of the fact that the development of the cerebral cortex follows a relatively simple process. In both mice and humans, its six layers of neurons form in

the embryo in a clear, sequential manner, one after the other. In the first step, neural stem cells produce a population of progenitor cells, which generate all neurons in layer 6, the deepest layer in the cerebral cortex. When layer 6 is complete, the neural stem cells start producing progenitor cells which go on to form the neurons in layer 5, then layer 4, and so on. This process continues, layer upon layer, until all six layers have formed.

During the formation of each of the six layers, it seems that different genes are activated and expressed for each class of cell, from the neural stem cells to progenitor cells and differentiated neurons. The different gene expression patterns seen on the RNA level control the fate of the individual cells, but also govern communication between cells and establish feedback loops to regulate the next waves of gene expression.

Correctly sorted, the data reveals its relationships

"We want to find out which genes, expressed by different types of cells at different stages of cortex formation, are connected during development," explains Taylor. "This means we have to sort the genes important for the formation of each cortical layer according to cell type." In order to achieve this, the NeuroStemX team has been studying different genetically modified mouse lines. One of these mouse lines expresses green fluorescent protein exclusively in neural stem cells, another only in its progenitor cells, and yet another in the newly formed differentiated neurons.

Since the order of events in the formation of the mouse embryo's cerebral cortex is known, it was straightforward to take samples at each stage of cortical development in each mouse line. By means of fluorescence-activated cell sorting (FACS), the researchers then isolated the neural stem cells, progenitor cells and differentiated neurons and analyzed their transcriptomes using high-throughput next-generation RNA sequencing.

"We were able to carry out the mouse work up to and including the cell sorting with two cell biology research groups here in the Department of Biomedicine of the University of Basel," says Taylor. However, for the next steps, collaboration with other research groups was of crucial importance. The sequencing was undertaken by the Genomics Facility Basel. This facility develops the state-of-the-art next-generation sequencing technology that makes such extensive analysis possible.

Treasure hunting is tough work

Lastly, two bioinformatics groups at the Biozentrum of the University of Basel and the Department of Biosystems Science and Engineering (D-BSSE) of the ETH Zurich are currently analyzing the sequence data. They are looking for clues as to which signaling pathways and transcriptional networks interact with one another and in what ways so that exactly the right neurons develop at every point during cortex development. "We have already uncovered several promising networks," says Taylor, "but whether or not these will prove helpful in the endeavor to produce particular neurons, we will have to clarify in each separate case."

This is extremely time-consuming work, as possible pathways must be subsequently verified *in vitro* or *in vivo*. "Here, with a group at the D-BSSE, we are using a microfluidics approach to test the signaling pathways previously identified in culture, analyzing the cell responses at the single-cell level in real time," says Taylor. The next step will involve studying the formation of neurons from induced pluripotent human stem cells with a view to medical applications.

Although Taylor's team is only able to pursue a few of the clues, by publishing all of the data, the researchers are making their goldmine available to other scientists. The potential for advances in the understanding of brain development is huge. However, there is much work to be done by anyone who wishes to take their share of the treasure.

NeuroStemX at a glance

Principal investigator: Prof. Verdon Taylor

Research groups:

- Prof. Verdon Taylor, Department of Biomedicine, University of Basel – Embryology and stem cell biology
- Prof. Dagmar Iber, Department of Biosystems Science and Engineering, ETH Zurich – Computational biology
- Prof. Erik van Nimwegen, Biozentrum, University of Basel – Analysis of genome-wide regulatory networks
- Prof. Suzana Atanasoski, Department of Biomedicine, University of Basel – Developmental neurobiology
- Prof. Savas Tay, Department of Biosystems Science and Engineering, ETH Zurich – Microfluidic single-cell analysis of signaling dynamics
- Dr. Christian Beisel, Genomics Facility Basel, Department of Biosystems Science and Engineering, ETH Zurich – Next-generation sequencing

Total budget (2013–2017): CHF 6.4 million, including CHF 3.0 million from SystemsX.ch

Project type: Research, Technology and Development (RTD) Project

NeuroStemX
Systems Biology of Forebrain Development

The MecanX team performs research on plant cell growth. (From left) back row: Tohnyui Ndinyanka Fabrice (IPMB, UZH), Hannes Vogler (IPMB, UZH), Chengzhi Hu (IRIS, ETHZ), Naveen Shamsudhin (IRIS, ETHZ) und Ueli Grossniklaus (IPMB, UZH); front row: Jan Burri (IRIS, ETHZ) und Gorka Santos Fernandez (IPMB, UZH)

Understanding the physics of plant growth (MecanX)

Growing under high pressure

Plant cells are surrounded by a stiff casing that withstands tremendous pressure from the cell's interior. According to current understanding of the subject, such entities should not be capable of growth, and yet grow they do. Scientists are trying to uncover their secrets in order to solve this enigma, which may help develop better crops for the future.

Every spring, grasses push their way up out of the ground, foliage sprouts from flowerbeds and buds come into bloom to form a collage of color, all within the space of a few days. In order to manage this rapid growth, plants employ a trick. In the previous year, they assemble many of the cells that go on to form the blossom, leaf or stem in miniature. When spring comes, all they have to do is enlarge these cells. But how the cells manage this without bursting or collapsing still remains mysterious.

Ueli Grossniklaus, professor in the Department of Plant and Microbial Biology at the University of Zurich, is trying to unravel these mysteries together with a highly interdisciplinary team of collaborators. As a start, he wants to measure the stiffness of the cell wall. This is the first step in an extensive research project with the aim of conclusively understanding the physics of plant growth. "There are so many theories floating about, but we don't have much concrete knowledge on the subject," says Grossniklaus.

A green cage

A plant cell's rigid cell wall can be likened to a cardboard box. Such structures are very sturdy, although when subject to external forces, they collapse easily. To counteract this, a plant cell has a large vacuole. This is like a big water balloon that fills the cell's interior, exerting high pressure – up to 10 bars – on the cell wall. This construction provides the plant cell with stability. "With this building system, plants are able to grow huge structures. For example, woodless tropical ferns can grow up to several meters long and are still very stable," says Grossniklaus.

The drawback of this approach is that in order for a cell to expand, the cell wall must be weakened in one or more places so that it can stretch out and new material can fill the gaps. This can be likened to trying to enlarge a house by opening up its outer walls, pulling them apart and then pouring fresh concrete in to fill the holes.

High pressure

In theory, a plant cell would have to reduce the pressure from the inside to avoid the cell exploding as a result of the instabilities in its wall during expansion. Yet the pressure evidently stays high. If this were not the case, all the leaves in your garden would constantly hang limp.

In order to get to the bottom of this paradox, the MecanX team is performing various measurements on pollen tubes from lilies, which are about 16 micrometers in diameter, and also much smaller ones from *Arabidopsis,* which are only 5 micrometers in diameter. These tubes grow out of pollen grains that have landed on the flower's stigma. Each tube is made up of a single cell and grows to several centimeters in length.

Measuring the stiffness of the pollen tube cell wall requires an appropriately fine sensor, which the researchers first had to develop. In essence, this force sensor is a silicon probe with a tungsten tip, much finer than a human hair (see picture, page 7). The probe is lowered perpendicularly onto the pollen tube's surface, indenting it. The depth of the indentation depends on the cell wall's stiffness and the applied force.

Measurements via capacitor

To quantify this resilience, or stiffness, the researchers attached the probe to a tiny capacitor. The capacitor is etched from a silicon wafer, a common process in computer chip production.

Capacitors store energy by separating charge, a bit like a battery. They are made up of two conducting surfaces separated by some distance. When the distance between these two plates decreases, the charge on the capacitor increases, and these changes in capacitance are measurable.

When the probe meets resilience from the cell wall, the resistive force causes the plates in the capacitor to be pushed closer together. The resulting change in capacitance is a measure of the force applied and, along with the indentation depth, is used to calculate the stiffness of the cell wall by way of a computer model. The model is based on the finite element method often used in mechanical engineering, and is simultaneously used to calculate the turgor pressure within the cell.

Silicone channels

That's in theory. In practice, measuring the stiffness of the cell wall poses still another technical challenge. Pollen tubes are somewhat difficult to work with. For example, when pollen grains are placed on a microscope slide, they germinate and the pollen tubes grow messily in all directions. It's not an ideal set-up for taking a large number of precise measurements.

The MecanX team had to find a way of restoring order to this chaos. The solution is a sort of micro-canal system for pollen tubes, a structure a bit like a computer chip and only a few millimeters across. It is, however, made of the optically transparent silicone polydimethylsiloxane (PDMS).

On this PDMS chip there is a row of channels emanating from a central basin. This is where the researcher places a few dozen pollen grains. After germination, the pollen tubes have no choice but to grow through the channels, where they can be easily probed and measured.

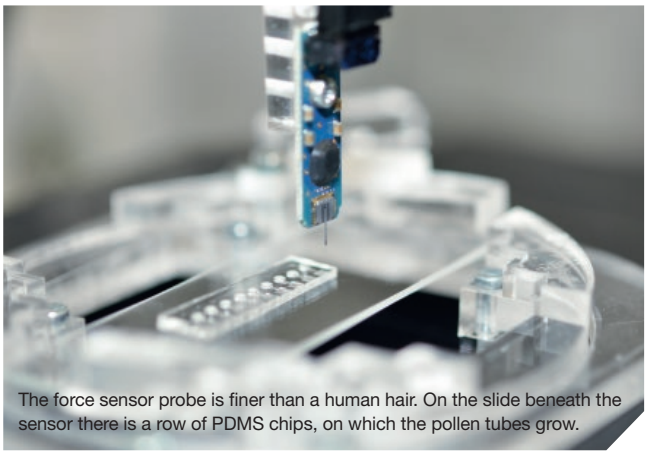
The team has developed an efficient way of producing these chips. First, they etch the negative of the chip into a silicon wafer. Liquid PDMS is then poured over this negative, and later the hardened chip is simply cut out and removed with tweezers.

Better crops

Initial results show that the pressure within lily pollen tubes amounts to about 3 bars, which is in agreement with measurements from other researchers using invasive methods. However, the stiffness of the tube casing has been measured to be roughly equal to that of rubber. A surprise, since it was previously thought to be much stiffer.

In order to solve the puzzle of plant cell growth, the MecanX team is turning to the tip of the pollen tube for answers. Until now, there have been no reliable measurements made at this location. Yet it is the most dynamic part of the pollen tube, since it is here that forward growth takes place.

The results might one day influence the development of new crop plants with improved cell wall properties. Even today there are forage maize varieties whose cell walls have a reduced lignin content. This makes them less stable, but at the same time makes the product much easier for cows to digest, leading to a 20 percent increase in milk production.



The force sensor probe is finer than a human hair. On the slide beneath the sensor there is a row of PDMS chips, on which the pollen tubes grow.

MecanX at a glance

Principal investigator: Prof. Ueli Grossniklaus

Research groups:

- Prof. Ueli Grossniklaus, Department of Plant and Microbial Biology (IPMB), University of Zurich – Biology, growth mechanics and physiology of pollen tubes
- Prof. Christoph Ringli, Department of Plant and Microbial Biology (IPMB), University of Zurich – Biology, biochemical composition of pollen tube cell walls
- Prof. Bradley Nelson, Institute of Robotics and Intelligent Systems (IRIS), ETH Zurich – Engineering, real-time cellular force microscopy, force sensors, control software, lab-on-a-chip devices
- Prof. Hans Jürgen Herrmann, Institute for Building Materials, ETH Zurich – Engineering, mathematical modeling of pollen tubes
- Dr. Abu Sebastian, IBM Research – Zurich – Engineering, applications of atomic force microscopy to pollen tubes, lab-on-a-chip devices
- Dr. Felix Beyeler, FemtoTools AG – Engineering, 2-D force sensors

Total budget (2013–2017): CHF 4.4 million, including CHF 1.9 million from SystemsX.ch

Project type: Research, Technology and Development (RTD) Project

MecanX
Understanding Physics of Plant Growth

Modeling and manipulating the phagocyte-mycobacteria interface (HostPathX)

Finding new ways of fighting tuberculosis

The battle against tuberculosis has arrived at a dead end. The pathogen causing the disease is becoming resistant to more and more classical antibiotics. The search for new ones is laborious and does not promise long-term success. As an alternative, the researchers from the SystemsX.ch project HostPathX are currently investigating the effects of 'anti-infectives', agents which directly target the infection. Amoebae are proving to be very helpful in this endeavor.

Thierry Soldati researches the effects of new agents on tuberculosis.

"Tuberculosis is THE major killer," says Thierry Soldati, professor in the Biochemistry Department at the University of Geneva and project leader of the RTD Project HostPathX. "About 30 percent of the world's population are infected, and around 1.7 million people die of it every year." At the moment, antibiotics are the only option in treating the disease. At the same time, many multi- and totally-resistant strains exist. Even when the strain in question is not resistant, it still takes half a year to treat an infection.

One reason that tuberculosis (TB) bacteria are so resilient and successful is their survival strategy in the human body. Once the airborne bacteria reach the lungs, they are taken up by macrophages. These scavenger cells, which make up part of the immune system, roam the body and eliminate intruders by phagocytosis, that is, by engulfing and killing them.

However, the TB bacteria are not simply digested like other intruders. They manipulate the macrophages to block the function of the phagolysosomes – the macrophages' digestive organelles – whose dedicated function is to kill and degrade bacterial intruders. The bacteria are then able to lodge themselves inside these manipulated compartments. So ensconced in their niches, they survive, reorganizing their metabolism.

Learning to understand the interaction between host and pathogen

With this picture in mind, it is not surprising that new antibiotic candidates selected against the bare bacteria are often unsuccessful when it comes to combating the disease in the host. Either they completely fail to reach the bacteria in their intracellular niches, or they target metabolic pathways specific to the bacteria in their environment outside the host and are therefore ineffective against the intracellular bacteria during infection.

"In order to find effective substances to combat tuberculosis, we really need to understand exactly what goes on between macrophage and bacteria," explains Soldati.

Amoeba versus fish pathogen

To find out more about the interplay between the macrophages and tuberculosis bacteria, the researchers from HostPathX make use of a very simple, but no less clever, model system. Instead of macrophages and *Mycobacterium tuberculosis,* the researchers pitch the amoeba *Dictyostelium discoideum* against *Mycobacterium marinum,* a relative of *M. tuberculosis* that is not threatening to humans.

M. marinum is a disease pathogen which primarily affects cold-blooded animals such as frogs and fish. Both human macrophages and the amoeba *Dictyostelium discoideum,* commonly found in soil, share the same ancestors and therefore function similarly. Both react in the same way to mycobacteria by using phagocytosis in an attempt to disarm them.

"The model system *Dictyostelium – M. marinum* allows us to research the host-pathogen interaction simply, economically and in an ethically unproblematic way," explains Soldati. "We are able to study their battle without having to observe the strict safety precautions that would be necessary if we were to work with the highly dangerous TB bacteria, and we also don't need to work with laboratory animals."

The researchers are now probing this model system. "For example, we are interested in how the mycobacteria manipulate the amoebae by turning their usually hostile lysosomes into a bacteria-friendly environment, and how the host and pathogen recognize each other," says Soldati. "We also want to find out what happens when we use agents to directly intervene in the action."

Employing anti-infectives instead of antibiotics

The scientists are addressing this last point using about 20 agents, called anti-infectives, which were identified in a preceding project. These substances, which are distinct from antibiotics, act either as defense

Maja Schaffner

boosters in the host, strengthening resistance against the pathogen, or as anti-virulence agents, directly targeting infectious pathogens by blocking mechanisms or metabolic pathways used by the bacteria only in the course of infection. Due to the fact that these anti-infectives act so specifically during an infection, their application does not lead to the selection of resistant bacteria. Contrastingly, antibiotics attack metabolic pathways that are crucial for the survival of pathogenic mycobacteria as well as many other bacteria. The resulting pressure for selection stimulates the development of resistance.

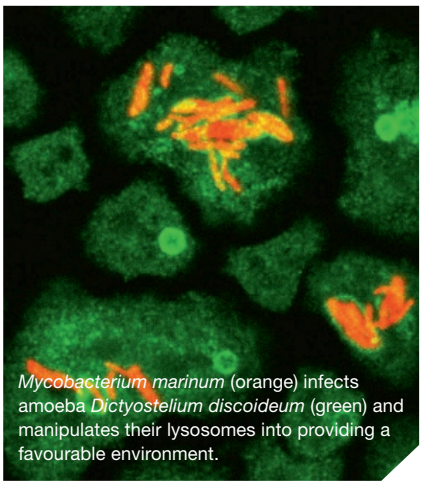
Dual profiling

One of the main goals of HostPathX is to find out exactly how and where such anti-infectives act. To investigate this, the researchers are relying on transcriptomics. "The method is high-throughput, genome-wide and cheap," says Soldati. Using this technique, the researchers are able to simultaneously profile the total RNA produced by the host and the pathogen at a particular time during infection. From the resulting transcriptomes they can infer which genes in each organism are active at a specific point in time, and which are influenced by the anti-infectives.

Genome-wide model

The researchers are integrating all of the data generated from this analysis into a newly developed genome-wide host-pathogen model. "A first!" emphasizes Soldati. In future, this model should be able to simulate the events occurring during infection, for example interactions and defensive responses.

"The goal is to use this model to make *in silico* predictions and therefore discover the best targets for preventing infection or strengthening the macrophages' defenses," explains Soldati. It should also be possible to feed virtual drugs into the model and to observe their effects on the system.



Mycobacterium marinum (orange) infects amoeba *Dictyostelium discoideum* (green) and manipulates their lysosomes into providing a favourable environment.

"Our focus at the moment is to show that it's possible to find and investigate agents that target the infection by using the model system *Dictyostelium – M. marinum*," says Soldati. "We hope that our work will contribute to long-term success in the battle against tuberculosis."

HostPathX at a glance

Principal investigator: Prof. Thierry Soldati

Research groups:

- Prof. Thierry Soldati, Biochemistry Department, University of Geneva – Molecular & cellular microbiology, host-pathogen interactions
- Prof. Hubert Hilbi, Institute of Medical Microbiology, University of Zurich – Genetic manipulation and functional phenotyping of mycobacteria
- Prof. Heinz Koeppl, Department of Electrical Engineering and Information Technology, Technische Universität Darmstadt – Design of algorithms for statistical transcriptome-based network reconstruction
- Prof. Pierre Cosson, Department of Cell Physiology and Metabolism, University of Geneva – Mechanisms of pathogen recognition and elimination by phagocytic cells
- Dr. Marco Pagni, Vital-IT group, SIB Swiss Institute of Bioinformatics – Data analysis, computational experiments and exploratory modeling

Total budget (2014–2018): CHF 6.3 million, including CHF 3.0 million from SystemsX.ch

Project type: Research, Technology and Development (RTD) Project

HostPathX
Modeling and Manipulating the Phagocyte-Mycobacteria Interface

Daniel Vonder Mühll Matthias Scholer

SystemsX.ch is winding down

New Swiss-wide research initiative

SystemsX.ch will conclude at the end of 2018. Neither an extension nor a follow-up initiative in systems biology is envisaged. The future could nevertheless hold new and exciting impulses for the field: in autumn this year, the parliament will decide on the fate of a new nationwide research initiative in personalized medicine.

Just over a year ago, the publication of the 12th and final call for proposals heralded the beginning of the winding-down phase for SystemsX.ch. With the remaining funds, amounting to CHF 2.5 million, the initiative has supported the extensions of 34 Interdisciplinary PhD Projects and Transition Postdoc Fellowships. All project funds have now been allocated and committed, meaning no more projects may be approved.

All SystemsX.ch projects must use their available funds before the end of December 2018. Any remaining amounts that have not been spent by this time must be returned and will in due course be repaid to the federal government.

2017 will be the last year of normal operation of the SystemsX.ch management office. The 3rd International SystemsX.ch Conference, which will take place from September 4–7, 2017 in Zurich, will mark the official end of the initiative.

In 2018, the last research projects will wrap up and the management office will be successively pared down. In the concluding year 2019, all final reports have to be delivered, and the repayments of unused funds will be processed.

New initiative in personalized medicine

While SystemsX.ch gradually comes to an end, a new research initiative that also embraces a systems approach is already on the starting blocks. The Federal Council's Dispatch on Education, Research and Innovation (ERI), published in February this year, includes plans for a new nationwide research initiative in the area of personalized medicine. By applying findings from basic research in clinical settings, this initiative will support the development of new drugs as well as the optimization of therapies and the detection and treatment of rare diseases.

Joining forces nationwide

In Switzerland, clinical research is carried out by the clinical and university research centers as well as the ETH Zurich and EPF Lausanne. Now it's time to combine these forces in a coordinated effort. Particular attention must be paid to data management, including the collection and processing of patient data and maintenance of biological data banks, for later use in basic as well as clinical research. This will be the initial focus of the planned initiative, titled Swiss Personalized Health Network, whose first phase is scheduled to run from 2017–2020. The joint national undertaking between universities, hospitals and funding bodies aims to secure a leading position for Switzerland in this increasingly vital healthcare sector.

The Swiss Academy of Medical Sciences (SAMS) is overseeing the initiative. Over the course of its implementation, important accompanying topics including ethics, data protection and integrity will need to be addressed. The SIB Swiss Institute of Bioinformatics will therefore need to take on a crucial role as a national data coordination center. The Swiss National Science Foundation will be responsible for publishing calls for proposals and evaluating the resulting research.

The parliament is set to vote on the new initiative, which will be financed with CHF 70 million, within the framework of the ERI Dispatch in the coming autumn. After official approval through the Swiss National Council and Upper Chamber, the national research initiative should be set to start in 2017.

A new Swiss-wide initiative promoting research in personalized medicine is planned for 2017.

Maja Schaffner

Dedicated knowledgebase for comprehensive curated information on lipids

Project profile SwissLipids

Project goal:	The aim of SwissLipids is to develop a comprehensive reference database that supports lipidomics data interpretation, integration and exploitation. The database links lipid and lipidomic data, obtained using high-throughput mass spectrometry-based approaches, to existing knowledge of lipid structures, metabolic reactions, enzymes and interacting proteins.
Origin of project idea:	SwissLipids is a companion project to the Research, Technology and Development Project LipidX. The idea for the project came about through discussions between researchers of the LipidX project and members of the SIB Swiss Institute of Bioinformatics. By combining the expertise in lipid biology, classification and nomenclature from LipidX with the biocuration and resource development skills of SIB staff, the researchers wanted to support the exploitation of lipidomic data, which has until now been hampered to some degree by a lack of appropriate knowledge resources and tools.
Interesting facts:	In the new database, all lipids are linked to curated knowledge of known metabolic transformations, where available. This feature, which distinguishes SwissLipids from other lipid databases such as LIPID MAPS, greatly facilitates the integration of lipidomics data with information on metabolic pathways. The current version of the database includes approximately 300,000 lipid structures from over 150 lipid classes, and contains findings from around 1000 peer-reviewed publications.
Greatest highlights:	One of the major highlights was the launch of the SwissLipids website in May 2015, which allows the research community to access the database. Thanks to the expert knowledge generated during LipidX, the new database was able to provide exceptionally high coverage of both known and theoretical lipid structures as early as the launch of the website. Today, SwissLipids already has between 500 and 1000 worldwide users each month.
Biggest challenges:	One of the main challenges was finding sustainable funding. The project was created with the financial support of SystemsX.ch, LipidX, SyBIT and the SIB. Future maintenance and development of this resource will depend on new sources of funding.
Future applications:	SwissLipids is a reference database for lipid and lipidomics research with a wide range of potential applications for any project featuring lipids and their biology. The hope is that like other well-established, high-quality knowledge resources curated by experts such as UniProtKB/Swiss-Prot, SwissLipids will become an indispensable tool for life science researchers.
Research groups:	• Dr. Alan James Bridge (principal investigator), Swiss-Prot Group, SIB Swiss Institute of Bioinformatics – Knowledgebase development and biocuration • Prof. Gisou van der Goot, Laboratory of Cell and Membrane Biology, EPF Lausanne – Lipid and membrane biology • Prof. Howard Riezman, Biochemistry Department, University of Geneva – Lipid and membrane biology • Prof. Vassily Hatzimanikatis, Laboratory of Computational Systems Biotechnology, EPF Lausanne – Computational systems biology
Total budget:	CHF 1.5 million, including CHF 750,000 from SystemsX.ch (2013–2015)
Project type:	Special Opportunity Project – Highly innovative projects that promote systems biology research in the broader sense, but do not qualify for other traditional sources of funding.
Further links:	www.swisslipids.org; www.lipidx.org

A different approach to supporting young scientists

Bringing the human factor into science

Key communication skills, setting goals and priorities, or dealing with conflict: the educational events organized by SystemsX.ch promote skills that are often neglected in science. Communications expert Sašo Kočevar has led the workshops since 2012 and explains why soft skills are particularly important for researchers.

Sašo Kočevar supports researchers in their scientific careers by helping them reflect on the human aspects of science.

What gave you the idea of offering coaching in soft skills specifically to researchers?

To be honest, it wasn't a strategical choice; it just turned out that way! One of my first clients was a research institution, which is how I came into contact with this topic for the first time. After running two courses with researchers, I knew that this was exactly what I wanted to focus on. I saw what little knowledge of communication, delegation and leadership there was in science – things that are standard in other fields – and what little support and training were available in these areas.

So you discovered a gap in the market?

You could say that. But when we first started running our workshops ten years ago, academia was only just starting to take these topics seriously.

To what extent has this changed since then?

The acceptance and awareness of soft skills and their importance in science has increased significantly. The first group leaders in our courses were viewed as peculiar by their colleagues. One or two of them were surely asked why they were wasting their valuable time on workshops and coaching. Since then, it has become a lot more acceptable for scientists to address these topics. The younger generation, such as students and postdocs, even asks after these types of courses. They expect to receive training on subjects like constructive collaboration, good communication and conflict management.

Why are soft skills particularly important for researchers?

The problems that researchers endeavor to solve are very complex, which is why they depend on collaboration with other researchers. Interpersonal skills are crucial in building fruitful collaborations and achieving goals together despite differences in approaches or ways of thinking.

What are the skills promoted in your courses that encourage constructive collaboration?

The first step is to become aware of the different personalities in your team, including your own. Then it is important to realize how these differences influence the roles in a collaboration. Recognizing individualities in the people you work with, and correctly handling these differences, is crucial in constructive collaboration.

Active listening, which means really concentrating on what your collaborator has to say as well as signaling attentiveness, asking perceptive questions, or giving appropriate feedback in the right way – these are all important skills that are practiced in the workshops.

What if, despite these measures, the collaboration doesn't run smoothly?

Scientists work in an extremely competitive environment, which means conflict is inevitable. In our workshops the researchers also learn how to deal with difficult interpersonal situations. Here, active listening plays a key role too, but how to address a conflict and negotiate a solution are also important elements in overcoming difficulties, and they can be practiced.

How do you ensure the successful implementation of these concepts in practice?

We work a lot with case studies. For example, in conflict management, participants bring forward concrete cases from their own experience. The techniques learned in the workshop are then put directly into practice by means of role-play. Since the researchers receive external feedback from the coaches, they are able to correct their own behavior, further strengthening the learning experience.

You also offer training in leadership and management skills. Why do you think young researchers need these skills at their stage?

In order to achieve a research goal, you need to get people excited about your own ideas and motivate them to contribute their potential. This is really a leadership problem, even if it's not formally associated with a leadership position.

And what if I don't feel I'm a born leader? To what extent can leadership skills be developed?

Competence in leading is nothing mysterious! These skills can definitely be learned. For example, motivation and enthusiasm cannot be commanded by you as a leader. Instead, you have to understand the underlying interpersonal processes involved and include others by integrating their ideas. These are skills that can be practiced.

For me, good leadership needs both skills and awareness. This is why we guide the researchers through practical examples and techniques, as well as imparting the analytical tools to tackle difficult interpersonal situations and sharpening the focus on these issues.

What else can researchers hope to learn in your courses?

An important aspect is correctly defining one's own role. In addition to the official capacity as a researcher, further roles such as supervisor (when dealing with students) or collaborator in a diverse research group can be identified. Each of these roles involves specific responsibilities, requiring a different skill set. The researchers learn, for example, how to set goals, how to manage their own time, but also how to delegate. All of these skills are important in structuring their own research processes and making collaboration and teamwork more efficient.

This year's SystemsX.ch Retreat will focus on career development. How do your workshops support young researchers in their scientific careers?

The retreat will be all about the researchers recognizing and formulating their own competence profiles. This means understanding what abilities they can bring to the table. What skills are they developing right now during their PhD? And how can they incorporate these in a research project? The researchers will also learn how to formulate their competence profiles and present themselves well in a job interview.

In your opinion, what are the most important skills for a successful scientific career?

Organizing your own workflow, prioritizing and setting goals, as well as designing the collaborative process in the best way to achieve results are surely key ingredients. But research is not a one-way street to success. Being able to handle open questions as well as uncertainty and frustration is therefore just as important.

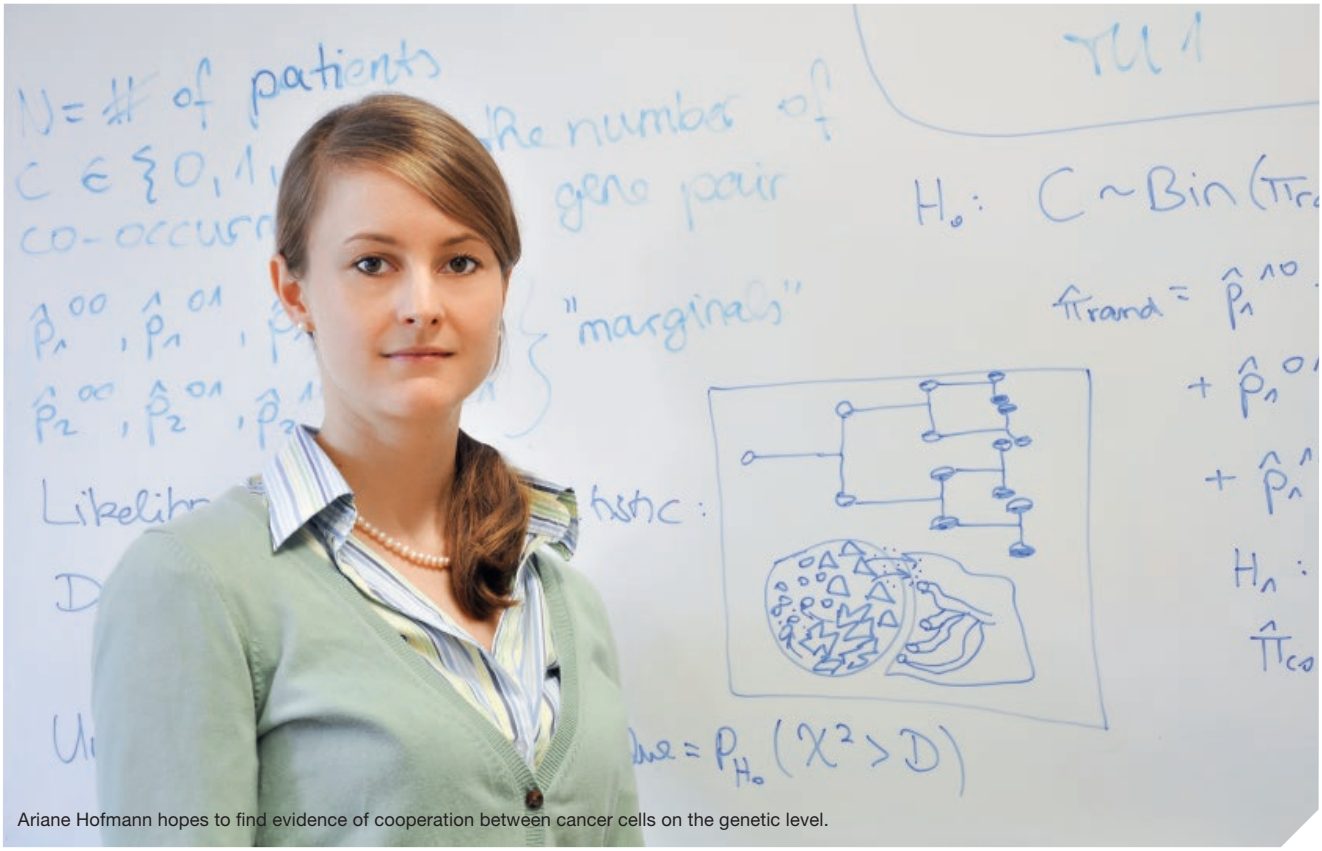
Do you perceive a difference in the participants at the end of the course?

We always like to see the participants leave our courses with increased self-confidence. They gain trust in their own abilities to solve conflict situations or problems that they would previously have deemed unsolvable. Apart from that, many of them see themselves just as a researcher at the start of the course, but by the end they can identify with other roles, too. During the coaching process, they realize that leadership is not some elusive magic ingredient, and they start to feel much more comfortable and confident taking on leadership roles. Last but not least, according to testimony, the participants feel they can take home the tools they have learned for use in their private lives, as well as their professional ones.

Sašo Kočevar and his team from hfp consulting focus exclusively on training and coaching for life scientists. A further SystemsX.ch Retreat and Postdoc Workshop are planned for 2017 in order to support and encourage young researchers in their current scientific work as well as in their career development.

More information about hfp consulting is available at: **www.hfp-consulting.de**

More information on SystemsX.ch educational events can be found at: **www.systemsx.ch > Events & Education > Educational Events**



Ariane Hofmann hopes to find evidence of cooperation between cancer cells on the genetic level.

Studying the heterogeneity of renal cell carcinoma

Do cancer cells cooperate?

One reason that fighting tumors is so difficult is that they are composed of many different mutated cells. The mathematician Ariane Hofmann is studying the heterogeneity of renal cell carcinoma as part of her interdisciplinary PhD and is investigating whether it is possible to identify, on a genetic level, different mutated cancer cells that cooperate with each other.

Cancerous tissue is for the most part composed of an assembly of genetically diverse cells that have undergone different mutations. Since space and nutrients in the human body are limited, these mutated cells, which form cell lineages called subclones, compete for these resources. "The most aggressive subclones survive and multiply, whilst the others are suppressed. Novel cell lineages constantly arise as a consequence of new mutations," explains Ariane Hofmann, mathematician and PhD student at ETH Zurich.

"Studies have recently shown that these mutated cell lineages are not just in competition with each other, but may be able to cooperate," says Hofmann. This could be of great advantage to them. The mutated cells acquire all the abilities of cancer cells over the course of their development. Successive changes in specific genes ensure that the altered cells are able to provide themselves with growth signals, undergo unregulated proliferation, stimulate the production of blood vessels for their own use, or form metastases. Generally, cancer cells acquire more and more of these properties over longer periods of time.

"Now, if two subclones are in close proximity to each other, each one only possessing a subset of these properties, they can help each other out. For instance, one subclone that is able to produce its own growth factors can supply another with them, too," explains Hofmann, whose minor subject was biology. In this way, cancer cells lacking in some attributes are able to benefit from the abilities of others – together gaining full malignancy considerably faster.

First systematic investigation on the genetic level

"For the first time, we are systematically looking for genetic evidence of cooperation between different subclones," explains Hofmann. The subject of this research is renal cell carcinoma (RCC), the most common form of kidney cancer. "This type of cancer usually resists treatment by chemotherapy or radiation. Although there are a few possible treatment options for metastatic RCCs, the only really effective treatment available today for a locally confined RCC is the removal of the affected kidney," says the researcher.

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The tissue for Hofmann's analysis comes from the Institute of Surgical Pathology at the University Hospital Zurich. In the first phase of her research, the scientist is examining samples from 16 patients. Each patient provides three samples: two cancerous, and one taken from healthy kidney tissue to act as a reference. All of these samples are sequenced at the Genomics Facility Basel.

Laborious data analysis

Hofmann receives the DNA and RNA sequences of all the cells contained in each sample. But these are not yet free of errors, nor are they sorted in the correct order. Rather, the data consists of millions of disordered snippets, each around 100 bases long, which together cover the cell lineages' genomes several times over.

Then begins Hofmann's work in earnest. First, she has to restore order to the chaos. With the help of a well-chosen series of computer programs, she converts the data into the correct format for the detection of mutations. This includes removing low-quality bases resulting from sequencing errors and mapping the snippets to the correct location in the genome. "At the end of this process, I have a four- to six-gigabyte file for each sample, containing the cleaned and ordered sequences," says Hofmann.

Detecting mutations is no easy task

Once the data are fit for purpose, Hofmann inspects them for evidence of mutations such as single, erroneous base pairs or changes that arise due to the loss or insertion of whole segments.

Computer programs are available that perform exactly this task, but Hofmann has already experienced how difficult it is to choose the right one. "I tested many of these variant callers in order to uncover point mutations," she says. Rather alarmingly, they spat out very inconsistent results. "Even just the number of mutations they detected varied by up to a factor of 100," asserts Hofmann. But that wasn't the only problem. "Each one detected totally different mutations!" In order to assess their suitability and choose the best performers, the young researcher compared several variant callers based on a simulated data set.

Extremely heterogeneous renal cell carcinoma

Analysis of samples from the first 16 patients has shown that the renal cell carcinoma is especially heterogeneous. In the cancerous tissue from all 16 patients, Hofmann found an astonishing 5000 mutated genes, with very few of them appearing across different patients. The number of mutations per patient was also quite varied. While Hofmann found between 150 and 350 mutations in 15 of the patients, one patient had almost a thousand. "In addition, the great majority of mutations were only present in one of the two cancerous samples from a given patient," explains the researcher. "This tells us that even cancer tissue within the same patient is extremely heterogeneous."

The task now is to single out the genes relevant to cancer. "It's hard to determine which genes are associated with the carcinoma, since every patient has different mutations," says Hofmann. Nevertheless, she has already been able to detect some known cancer genes as well as others, which until now were not known to play a part in the development of kidney cancer. These include genes responsible for the repair of mistakes in DNA. And as hoped, the scientist has also found some mutations that clearly occur in association with each other. "We are going to look more closely at the most interesting candidates with a larger patient cohort," adds Hofmann.

The next step involves examining the cancer genomes of 100 patients using ultra deep coverage sequencing, a method that delivers much more detailed results. "This method will allow us to detect individual subclones based on their mutations," says the researcher. "Only then can we find out which subclones with which properties work together."

Results that lead to better therapies

With her research, Hofmann hopes to uncover new clues as to how cancer in general, and renal cell carcinoma in particular, functions. "We might find new links and mechanisms which could be exploited to develop new therapies to treat RCC," imagines the scientist.

"It could be that the extreme heterogeneity of RCC is the reason it's so difficult to overcome," says Hofmann. "During therapy, every single subclone must be caught. If a single one survives treatment, the cancer might return."

And what about the cooperation between subclones? "If we are able to pinpoint the occurrence of cooperation between subclones with the larger patient cohort, we will examine whether a link to treatment success and survival can be found," says Hofmann. "If it turns out that cooperation plays an important role, we'll need to find out more about it. How often it occurs, how it works exactly and, of course, how to stop it."

The project at a glance

Project title: Genomic and transcriptomic characterization of heterogeneous tumor cell populations

PhD student: Ariane Hofmann, ETH Zurich

Supervisors: Prof. Niko Beerenwinkel, ETH Zurich; Dr. Christian Beisel, ETH Zurich; Prof. Holger Moch, University Hospital Zurich

Project duration: 2012–2016

Project type: Interdisciplinary PhD Project (IPhD) – PhD students work at the interface between two systems biology-relevant fields. During their interdisciplinary doctorate, they are supervised by a mentor from each of these two distinct subject areas.

Kyle M. Douglass is working on improving super-resolution fluorescence microscopy.

Improving super-resolution microscopy techniques

Taking a closer look inside cells

Super-resolution fluorescence microscopy helps researchers closely examine the tiny structures within cells such as organelles, proteins and chromatin. The physicist Kyle M. Douglass is working on improving one such microscopy method, while at the same time employing it to study telomeres and Hox genes.

A camera, several lasers, a collection of lenses and a large, black apparatus are screwed down onto a perforated metal plate. What looks more like an experiment from an advanced home physics kit is in fact a fully functional super-resolution fluorescence microscope. Kyle M. Douglass from EPF Lausanne is working on improvements to this instrument as part of his Transition Postdoc Fellowship (TPdF), as well as using it to research chromatin.

"Super-resolution fluorescence microscopes are able to make out structures even smaller than 200 nanometers, which is something that conventional light microscopes can't do," explains Douglass. "These microscopy techniques are especially relevant for cell biology, since many of the players in a cell's interior, such as proteins or the DNA ultrastructure, fall under this limit."

Reconstructing an image from a million points of light

In order to make these nanoscopic structures visible, they are stained with photoswitchable dyes, which are activated by the laser light in the microscope. A camera captures these millions of fluorescing spots of light, scanning the sample one small area at a time. Imaging software determines the exact position of each light point, and an image of the original sample is reconstructed from the resulting data.

Douglass works with a particular "flavor", as he calls it, of super-resolution fluorescence microscopy, called stochastic optical reconstruction microscopy (STORM). This technique provides high resolution and is particularly well suited to resolving molecular locations in macromolecular assemblies, like small organelles or chromatin, in fixed samples.

Enlarging the field of view

In Suliana Manley's group at the Laboratory of Experimental Biophysics at EPF Lausanne, Douglass is working on further improving the STORM technique, as well as making it faster. His main goal is to considerably expand the microscope's visual field while keeping the characteristic high resolution.

"The advantage of a larger visual field is that we can cover a greater area each time," says the young researcher. "This is important, since the imaging buffer only has a lifetime of about an hour, after which its pH has to be adjusted manually. This is therefore one of the most severely limiting steps in automating the experiments." Thanks to the broader visual field, the experiments are much faster in spite of the limitation imposed by the buffer.

This faster process means that the researchers can scan a larger sample area in total, providing more context. They will be

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able to look not just at individual cells, but at whole cell populations. “This is particularly interesting, because cell biologists now know that cells influence each other very strongly, for example in which genes get transcribed,” explains Douglass.

Flattening the laser beam

In seeking to enlarge the field of view, Douglass is working on improvements to the technique on different levels, but the most important factor is the laser beam. “A laser beam’s light is brighter in the center than at the periphery,” he describes. This is why until now only the center of the beam has been used in imaging, limiting the observable area to around 25 micrometers in diameter.

“In order to make use of the entire cross-sectional area of the laser beam, which is about 100 microns across, I have to manipulate the beam so that it hits the sample with uniform intensity everywhere,” explains Douglass. In order to “flatten” the laser beam in this way, the researcher has developed a refractive element with a curved surface which bends the light as it passes through, resulting in a uniform illumination pattern.

Wrestling with big data

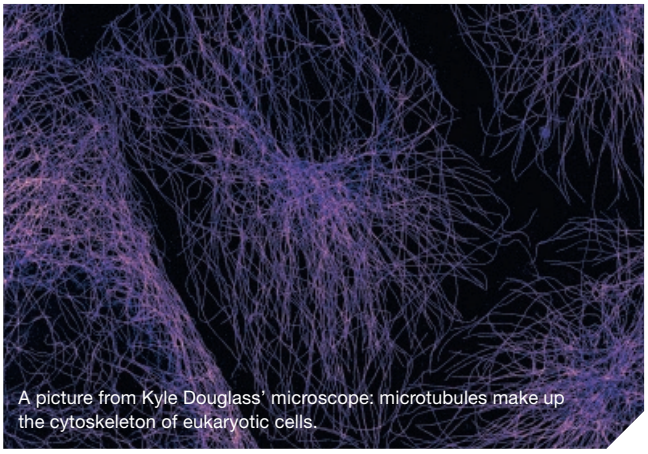
The sheer amount of imaging data that this technique generates poses further challenges. The high-throughput microscope, with Douglass’ automated workflow, produces colossal amounts of data. “The hard disc fills up within 15 minutes,” smiles Douglass. And that’s in spite of its one-terabyte capacity. “Just opening the files is a difficult task because they’re so huge!”

Processing these giant data sets is also demanding. Douglass uses a combination of off-the-shelf packages and software that he developed himself to reconstruct images from the data. In addition, he uses his own modeling software to elicit still more information from the images. “In order to control the microscope and analyze and model the data, I have had to program in a number of different languages including Python, MATLAB, C++ and Java.”

Telomeres and Hox genes

But Douglass is not only interested in the technical side of his project. He applies his technical know-how and improved microscopy techniques to problems in biology, too. In joint work with Joachim Lingner’s group at EPFL, he is investigating the architecture of telomeres, the ends of chromosomes. These are made up of repeated DNA sequences and their associated proteins. Telomeres protect the chromosomes from attaching themselves to the ends of other chromosomes, which would lead to cell death.

“Until now, it was thought that a telomere’s chromatin was very tightly packed,” says Douglass, “although no-one really knew what ‘tightly packed’ actually meant.” With the help of super-resolution fluorescence microscopy and subsequent modeling, the team was able to shed light on this problem. “We showed that telomeres are in fact not as tightly packed as was previously thought,” says the scientist. “We were able to establish an upper limit of 40 base pairs per nanometer on the packing density.”



A picture from Kyle Douglass’ microscope: microtubules make up the cytoskeleton of eukaryotic cells.

Since this compaction within telomeres can be affected by illnesses such as cancer, it is an important step to be able to quantify it. “It might be possible to use the condition of the telomeres as an indicator of cell health,” muses Douglass.

Next, in collaboration with Denis Duboule’s group from the University of Geneva, Douglass is going to turn his microscopy techniques to Hox genes. These are genes that regulate the formation of an organism along its body axis during embryo development. “I am interested in how chromatin is structured in different regions, and how its shape changes depending on its function or activity state,” states Douglass. With the help of his improved super-resolution microscope, he aims to shine a light on these topics and contribute to our understanding of chromatin.

The project at a glance

Project title: High-throughput super-resolution imaging reveals contextual effects in gene expression

Fellow: Dr. Kyle M. Douglass, EPF Lausanne

Host research group: Prof. Suliana Manley, Laboratory of Experimental Biophysics, EPF Lausanne

Project duration: 2015–2017

Project type: Transition Postdoc Fellowship (TPdF) – Young scientists formulate their own interdisciplinary project application and switch to a complementary discipline that is new to them.

Systems biology of acidophile biofilms for efficient metal extraction (SysMetEx)

Making copper flow faster

In copper mining by bio-heap leaching, microorganisms help extract the metal from rock. The international research team from ERASysAPP project SysMetEx aims to speed up this relatively slow process. The researchers are analyzing just how the colonization of the rock by these bacteria progresses.

The worldwide demand for copper is high. This metal is mainly used in the construction industry, coining, electronics and mechanical engineering. However, the remaining resources are largely present in rock only at low concentrations, and their extraction is laborious and polluting. Conventional extraction involves heating copper-containing rock to very high temperatures, which releases, amongst other substances, sulfur dioxide. This toxic gas is the cause of acid rain, which leads to soil acidification and forest dieback.

Bio-heap leaching presents a relatively environmentally friendly alternative. In this process, metals are extracted from rock with the help of acid and microorganisms. But this method, with which around 15 percent of the world's copper is currently mined, has a huge disadvantage: it's slow and therefore economically unattractive. This is especially true for mining from chalcopyrite, the most common mineral containing copper.

The international consortium of the ERASysAPP project SysMetEx, which comprises scientists from Sweden, Luxembourg, Germany and Switzerland, is now working together on the ambitious goal of speeding up bio-heap leaching. The scientists are tackling the problem by looking at the microorganisms that are used in this process and investigating whether more systematic deployment of these tiny little helpers can make the leaching process more economically viable.

Microorganisms as catalysts

In bio-heap leaching, the metal-containing rock is crushed and piled into large heaps, which are sealed from the ground with plastic sheeting. The heaps are ventilated by means of an embedded pipe system, drizzled with acid and injected with microorganisms. These act as catalysts to accelerate the chemical reaction by which the acid gradually releases the copper ions from the rock. In chalcopyrite ($CuFeS_2$), the bacteria oxidize ferrous iron, thereby turning it into ferric iron and removing sulfur compounds that accumulate on the mineral surface.

The liquid that drips from the heap and is collected in reservoirs must first reach a certain metal ion concentration before extraction by electrowinning becomes worthwhile. In the case of

In bio-heap leaching, metals are extracted from rock with the help of acid and bacteria. Photo: Talvivaara Mining Company Plc

Maja Schaffner

chalcopyrite, it can take up to a year from setting up the bio-heap until the copper trickles from the pile of rock in the required concentration.

Searching for the best bacterial cocktail

A crucial factor in determining how fast the copper is dissolved is how soon the bacteria attach themselves to the rock and form a biofilm, which is a sort of colloidal layer that is generated when bacteria adhere to the rock surface and in which these microorganisms live and multiply.

With the help of three model types of acidophilic leaching bacteria, which are introduced to interact with the surface of the rock either individually or in different combinations and sequences, the scientists investigate the bacterial films that form. Does the particular sequence in which the different types of bacteria are introduced to the rock play a role in how fast a biofilm forms? To what extent do the bacteria help each other during the formation of the biofilm? And what combination dissolves the most copper in the shortest time?

The researchers do not have their own bio-heap at their disposal; the bacteria grow under controlled conditions in flasks. The scientists analyze their activity using transcriptomic and proteomic methods. This enables them to find out how many proteins and RNAs the bacteria form and, as a result, to draw conclusions about their interactions with each other, or about metabolic changes under differing conditions. In addition, microscopy methods are being used to track the colonization of the rock surface by the various bacteria strains over time.

All of the data generated by the involved research groups is poured into models, which should in future allow predictions to be made about how to achieve optimal results in the mining of copper from chalcopyrite.

Strongly application-oriented research

The chalcopyrite samples that the scientists are using for their research is provided by a Swedish copper mining company, which will directly benefit from the results after the conclusion of the project. The Swedish firm TATAA BIOCENTER AB, a project partner of SysMetEx, will develop a kit to test whether a bio-heap accommodates a microorganism community suitable for effective leaching.

The researchers have not yet published any concrete results, but they have already shown that the sequence and combination of bacterial strains play a crucial role in bio-heap leaching. The effect is evidently so strong that the right blend of bacteria could potentially cause the opposite effect by halting unwanted leaching, which could be applied, for example, in disused mines.

More info about SysMetEx: **www.sysmetex.eu**
More info on ERASysAPP: **www.erasysapp.eu**

The international SysMetEx team: (from left) Igor Pivkin, Emma Hermansson, Stephan Christel, Kjärstin Hagman Boström, Paul Wilmes, Mark Dopson, Olga Ilie, Ansgar Poetsch, Mario Vera, Sören Bellenberg, Antoine Buetti-Dinh, Malte Herold.

SysMetEx at a glance

Research groups:

- Prof. Mark Dopson (principal investigator), Department of Biology and Environmental Sciences, Linnaeus University, Kalmar, Sweden – Biomining, metal extraction, -omics analysis
- Prof. Wolfgang Sand, Biofilm Centre, Aquatic Biotechnology, University of Duisburg-Essen, Germany – Advanced microscopy, leaching experiments
- Prof. Paul Wilmes, Luxembourg Centre for Systems Biomedicine, University of Luxembourg – Biomolecular extraction, integrated -omics analysis, bioinformatics, data management
- Prof. Igor Pivkin, Institute of Computational Science, Faculty of Informatics, Università della Svizzera italiana – Mathematical modeling
- Dr. Ansgar Poetsch, Department of Plant Biochemistry, Ruhr University Bochum – Proteomics, bioinformatics
- Prof. Mikael Kubista, TATAA BIOCENTER AB, Gothenburg, Sweden – Industrial partner

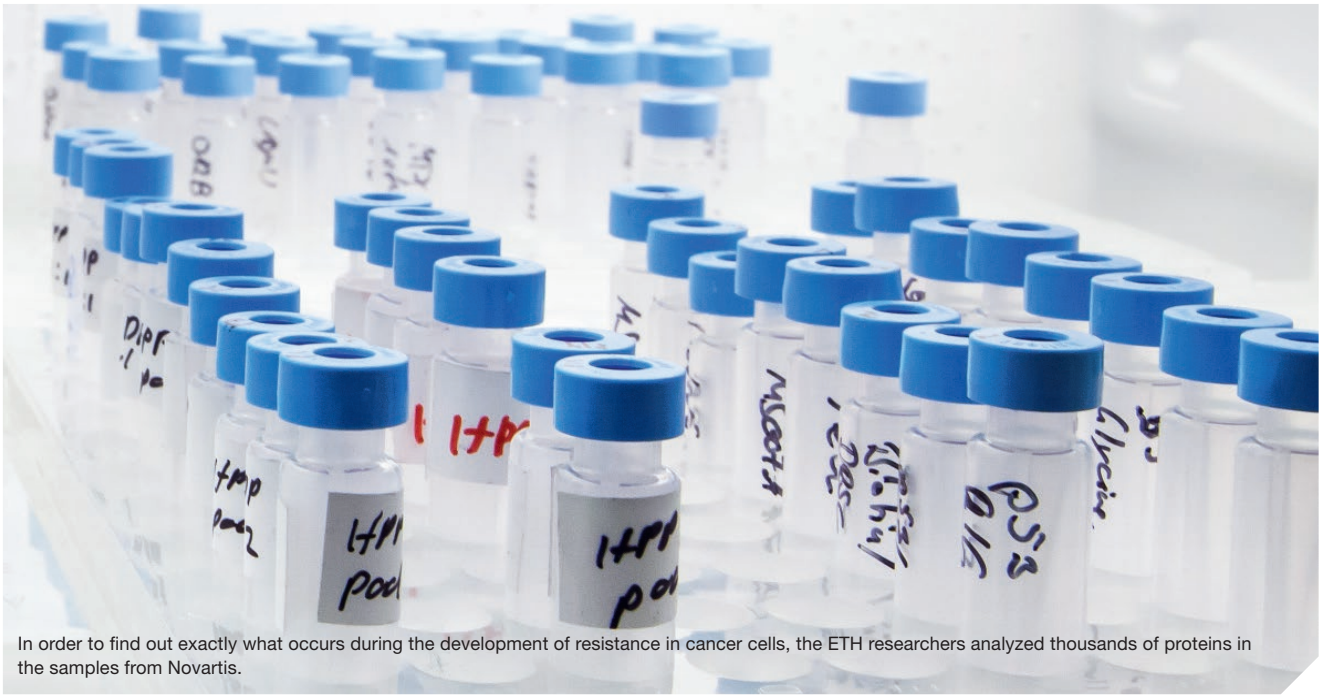
Total budget (2015–2018): CHF 2.5 million, including CHF 487,000 from SystemsX.ch

Project type: International Project – As a partner in the European research network ERASysAPP, SystemsX.ch has co-funded six international application-oriented projects in which Swiss consortium partners are involved.

Mechanisms of cancer drug resistance

Overcoming challenges in academia and industry collaboration

Researchers from Novartis and ETH Zurich got together to investigate how cancer cells form resistance against drugs. The Transfer Project demonstrates how fruitful collaboration with industry can be, but that there are hurdles to overcome.



In order to find out exactly what occurs during the development of resistance in cancer cells, the ETH researchers analyzed thousands of proteins in the samples from Novartis.

In the battle against cancer, the cancer still has the upper hand most of the time. Often the elation that comes with a newly developed, promising treatment is short-lived as the sobering truth emerges: "The cancer cells evolve and develop new ways of evading the effects of a new drug," says Matthias Gstaiger, senior scientist in the Institute of Molecular Systems Biology at ETH Zurich and project leader of the Transfer Project 'Mechanisms of cancer drug resistance'. How exactly this resistance works, however, is still only partly understood.

Collaboration between academia and industry

"As we embarked on a collaboration with Novartis to get to the bottom of this problem, we didn't have much experience of studying cancer drug resistance," says Gstaiger. "The core competence of our group is the analysis of protein alterations in cells and their future applications in personalized medicine, which was complemented very well by Novartis' practical knowledge on drug resistance." Using SWATH mass spectrometry, a technology developed in Ruedi Aebersold's group at the Institute of Molecular Systems Biology, researchers measure proteins in human cells with unprecedented completeness and accuracy, and use this information to draw conclusions about what's happening in the cells.

"This was exactly the sort of technology that we were interested in," says Francis Bitsch, senior investigator in Analytical Sciences and Imaging (ASI) at Novartis and co-PI of the Transfer Project. The researchers at Novartis had been investigating resistance to targeted cancer therapies. By augmenting their approach with the analysis of proteomic alterations occurring during resistance, they wanted to gain a deeper understanding of this complex topic and contribute to combating resistance. For both partners it was clear that only a systems approach would allow them to look at the whole range of changes occurring in the cells.

The initial plan was to examine the formation of resistance in human cancer cells in both cell cultures and cancer cells that had been implanted in mice. Novartis was to contribute the samples and know-how regarding the *in vitro* and *in vivo* cell models. "We composed a joint proposal for a SystemsX.ch Transfer Project," says Gstaiger. It was accepted. Unfortunately, the project had a bit of a rocky start, as one of the co-PIs, who had the required expertise in the mouse model and drug resistance, left Novartis. Nevertheless, the industry partner reacted swiftly to appoint a replacement to assure project continuity.

Scientific challenges

By aiming to elucidate the mechanisms of cancer drug resistance, both project partners were faced with a very complex research question. This posed a number of challenges on both scientific and technical levels. For example, the samples for the *in vivo* cell

Maja Schaffner and Christa Smith Matthias Gstaiger

models could not be generated as planned. “We had to revise the project goals, because the biology involved is sometimes unpredictable,” explains Bitsch.

There were also obstacles on the technical side, which only became evident during the course of the project. The researchers from ETH had to make adjustments to their analytical pipeline in order to effectively profile the resistant cells, and it took them longer to analyze the samples than originally envisaged.

Through intensive exchange between both partners, the scientists were able to overcome these hurdles. “In such collaborations, it’s particularly important to jointly assess the research plan critically from time to time, and to be mindful of the different timelines and objectives of each party,” summarizes Bitsch.

Differing objectives

Aside from the obstacles presented on the scientific and technical levels, Gstaiger found the changeover of personnel and the occasional fluctuation in working capacity challenging. “This aspect is one of the main reasons why I have found collaborating with industry more complicated than with academic partners,” says Gstaiger.

“The objectives of both industry and academia overlap to a great extent, but they are not identical,” Gstaiger is convinced. In academia the aim is to develop robust and sensitive analytical tools, publish scientific insights, and last but not least educate the next generation of researchers. In industry the focus lies on developing novel drugs and new therapeutic approaches for unmet medical needs, and any new methods used need to provide reproducible and conclusive results that enable this. In industrial firms, the goals of individual research projects can be subject to short-term changes, and are influenced by the company’s overarching objectives. “For example, it can happen that the resources within a company might be suddenly transferred from one project to another,” says Gstaiger of his colleagues’ experiences from other industry collaborations.

Ambitious project goals

Over the course of the project, it became apparent that the original project proposal was too ambitious. “We weren’t able to realize one part of the project at all,” says Gstaiger. The transplantation of human cancer cells into the mouse model had to be omitted, because the resistant tumor cells did not grow when transplanted into mice. In the remaining part of the project, the protein composition of breast cancer cell lines developing resistance was analyzed. “The collaboration with the Novartis team on this aspect of the project was very fruitful, and we obtained some interesting results,” emphasizes Gstaiger.

Now at the end of the two-year research project, the ETH scientists are analyzing the huge amounts of data that have been generated. They have already established that within cancer cells exposed to an inhibiting drug for an extended period, the alterations in the protein composition are very specific and reproducible. Most of these changes involve increases or decreases in the concentrations of specific proteins in the drug-resistant cancer cells.

The connection between these alterations and the cancer’s resistance mechanisms is not yet clear. “It’s too early to say,” says Gstaiger. The researchers must first find out what effects the protein alterations have on the signaling pathways, metabolism and other processes within the cell, and whether these modifications are even directly related to resistance.

“We will write a detailed report on the protein alterations in drug-resistant cancer cells,” says Gstaiger. Only additional experiments will be able to reveal the significance of the protein alterations the scientists found, and whether they might be put to use in personalized medicine as an indicator of a particular type of resistance. “The decision as to whether we will continue with the project has not yet been made,” says Bitsch. “We will first have to finish evaluating the vast amounts of data that were collected.”

A valuable experience

“Once again, we’ve learnt a lot thanks to this collaboration with academia,” says Bitsch. For Matthias Gstaiger, however, this project was his first experience working in partnership with industry. “It was interesting to see how it works there,” says Gstaiger. “Even though we were unable to implement everything as planned, the Transfer Project was a valuable experience. It has shown us where potential obstacles lie when working with industrial partners, but also that they can be overcome.”

The project at a glance

Project title: Mechanisms of cancer drug resistance

Research groups:

- Dr. Matthias Gstaiger, Institute of Molecular Systems Biology, ETH Zurich – Signaling Proteomics
- Dr. Francis Bitsch, Novartis Institutes for Biomedical Research – Analytical Sciences and Imaging
- Dr. Moriko Ito, Novartis Institutes for Biomedical Research – Oncology

Total budget (2015–2016): CHF 774 000, including CHF 232 000 from SystemsX.ch

Project type: Transfer Project (TF) – Research collaboration between academia and the private industry

Maja Schaffner

Open access

Make your research visible!

Open access consists in making scientific publications freely available electronically. To guarantee worldwide, free access to the research findings and results of its projects, SystemsX.ch urges the community to submit their publications to the Zurich Open Repository and Archive (ZORA).

Open access enables free access to research results.

Free and easy access to research results is a keystone for scientific progress. Just how important this is, is evident in the field of medicine. It is clearly in the best interest of both doctors and patients to have access to new advancements. However, not all doctors, particularly those working outside of the university hospitals, have the opportunity to access this knowledge, as research results are usually published in specialist journals. Anyone wishing to read these, including doctors and patients, must purchase the individual articles.

Benefit to researchers

One of the main arguments for open access is that publically funded research should be made publically accessible. Beside the contribution to society as a whole, those who experience the greatest benefit are the researchers themselves. "Their work becomes more visible," says Christian Fuhrer, head of the Zurich Open Repository and Archive (ZORA), as publications can be found easily via search engine.

Another very important aspect is that open access publications may also be freely made use of. This makes possible the automated search and analysis of these publications, known as text and data mining, allowing scientists to pursue their research questions more efficiently, for example by gathering all available information on a particular protein. With many conventional publications, this is not allowed, despite the fact that they may be electronically available through a subscription.

Two roads to open access

At the moment there are two ways of making one's work freely available. The first option is publishing in an open access journal from the start, which is also known as gold open access. For this method, the author must often cover any publication costs incurred. "Money is often the reason authors don't go down this gold road," explains Fuhrer. The advantage is that it allows others to make use of the works immediately.

The second option is to follow the green road to open access. Those who choose this method publish an article in a regular journal, subsequently making it open access, for example by way of a university repository. The conditions vary according to the journal that publishes the original article. In most cases, the article may be made freely available only after a defined time period has elapsed, and must be published as the final manuscript version (as accepted by the journal but lacking its layout, logos and pagination).

SystemsX.ch advocates ZORA

SystemsX.ch requires all publications written as a result of or in association with a SystemsX.ch project to be submitted to the Zurich Open Repository and Archive (ZORA). The submission form can be found at: www.sybit.net/zora_submission.

- It only takes a couple of minutes to submit your publication!
- Publications that are already registered in another institution's repository should also be submitted and can be easily linked.

If you have any questions, contact admin@systemsx.ch.

The Swiss National Science Foundation (SNSF) also supports the principle of open electronic access to scientific knowledge.
Read more: **www.snsf.ch > The SNSF > Research policies > Open Access**

New Norwegian biotechnology initiative

"Digital Life – Convergence for Innovation" is a new Norwegian research initiative in biotechnology, established as part of the BIOTEK2021 program by the Research Council of Norway. Under this initiative, biotechnologists will work closely with mathematicians, informaticians and engineers to create innovations based on biotechnology research. One objective is to transform vast amounts of genetic data into concrete applications.

Daniel Vonder Mühll, Managing Director of SystemsX.ch, was on the advisory board that helped set the initiative in motion. "I was able to pass on much of the knowledge gained throughout SystemsX.ch," he says.

As part of the Digital Life Initiative, a number of Norwegian universities and research institutes are together establishing a national competence center for biotechnology. The first six research projects to operate under this umbrella have already been selected. The topics range from aquaculture to lab-on-a-chip and brain research. Further calls are in the pipeline.

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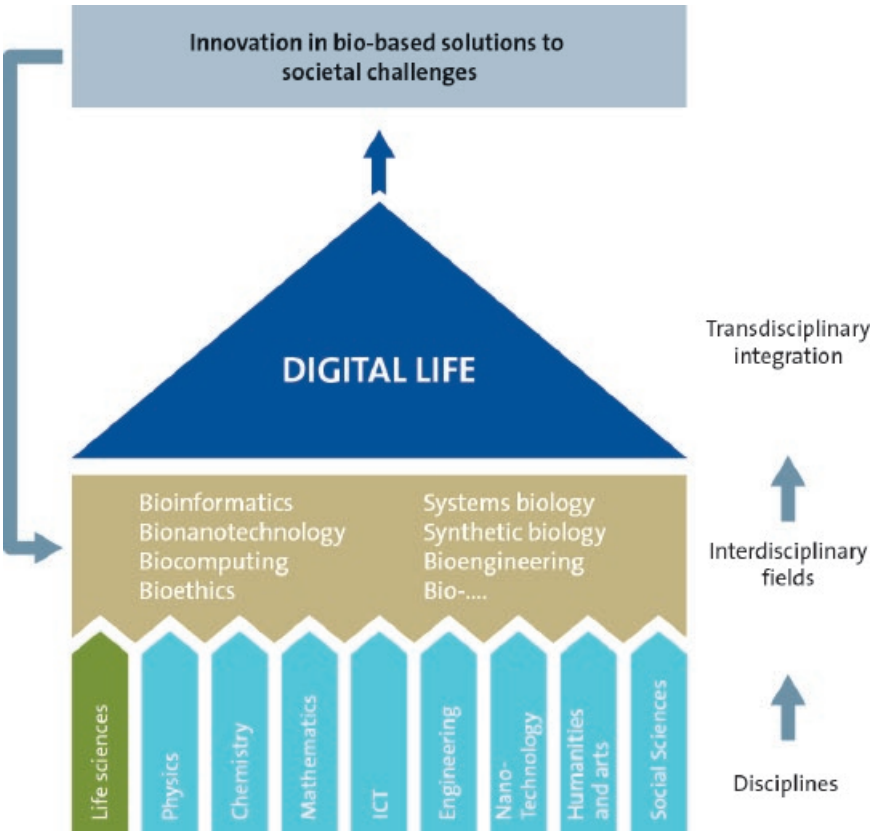

Figure: Illustration of the scope and content of "Digital Life – Convergence for Innovation".

Results of the X-Letter reader survey

After the publication of the X-Letter 31, SystemsX.ch carried out a short online survey amongst X-Letter readers. For one lucky reader, participation in the survey was particularly worthwhile: Alan Bridge from the SIB Swiss Institute of Bioinformatics won the original piece of artwork by Martin Oeggerli.

We would like to thank everyone who filled in the online questionnaire. The feedback contained many interesting suggestions and ideas for further improving the X-Letter. *csl*

The results of the survey can be found at:
www.systemsx.ch/reader-survey

All SystemsX.ch Day 2016

The All SystemsX.ch Day is set to take place at the Zentrum Paul Klee in Bern on September 1, 2016. This final event of its kind for SystemsX.ch will include talks in the areas of synthetic biology and single-cell modeling, as well as poster sessions and some new elements to increase networking opportunities for participants.

As a first, this year's event will also include lightning poster talks, which will offer presenters the chance to get up on stage and present their research to the audience in an extremely condensed format – participants only have 90 seconds to get their message across! *kp*

More information will be available soon at:
www.systemsx.ch/ASXD

Upcoming events

September 3–7, 2016
European Conference on Computational Biology (ECCB)
The Hague, Netherlands

September 1, 2016
All SystemsX.ch Day 2016
Zentrum Paul Klee
Bern, Switzerland

June 14–16, 2016
International Conference on Systems Biology of Human Disease (SBHD)
Boston, USA

September 16–20, 2016
International Conference on Systems Biology (ICSB)
Barcelona, Spain

November 12–15, 2016
EMBO Conference From Functional Genomics to Systems Biology
Heidelberg, Germany

September 25–27, 2016
EMBL Conference Big Data in Biology and Health
Heidelberg, Germany

Cover: Skin cells of a zebrafish. The small, oval openings are the outlets of mucous cells.
Picture: Magnification 8,400:1, ©Martin Oeggerli, www.micronaut.ch