X-Letter 34

Focus on medicine

How systems biology is changing medical research

Contents

4

8

22

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Cover: Scientist viewing a DNA sequence film depicting human genetic information.
Photo: Andrew Brookes / Getty Images.

"Technological advances in biotech are being applied more and more to the study of human biology."

Photo: © David Schweizer

Today's biology is an increasingly broad field encompassing many subdisciplines. Beside the study of microorganisms, plants and animals, technological advances in molecular biology and biotechnology have spawned a host of new specializations. These technologies are being applied more and more to the study of human biology, from which it's just a stone's throw to the traditionally separate field of medicine.

As early as 2008, when the second call for proposals was published, the SystemsX.ch boards agreed to encourage researchers to submit medically relevant project proposals. In 2014, SystemsX.ch went further and created a new project category for Medical Research and Development Projects, to promote the systems approach in medical and clinical research. Nine projects were approved and granted with a total of more than CHF 18 million. Each of these projects is presented in this magazine, exhibiting a wide palette of research themes. The articles illustrate the ever-deeper levels of understanding of the human body that we are now able to achieve.

Alongside the medical projects, we have as usual portrayed other types of projects, including an ERASysAPP Project, an Interdisciplinary PhD as well as a Transition Postdoc Fellowship. As an example of what has become of a former SystemsX.ch young researcher, we have an interview with Christoph Zechner.

A film presenting an overview of some of the SystemsX.ch projects is currently being produced to bring systems biology to a wider audience. The SystemsX.ch film will be premiered on the first evening of the 3rd International SystemsX.ch Conference, and a touch book, covering more detail on the projects, will also be published.

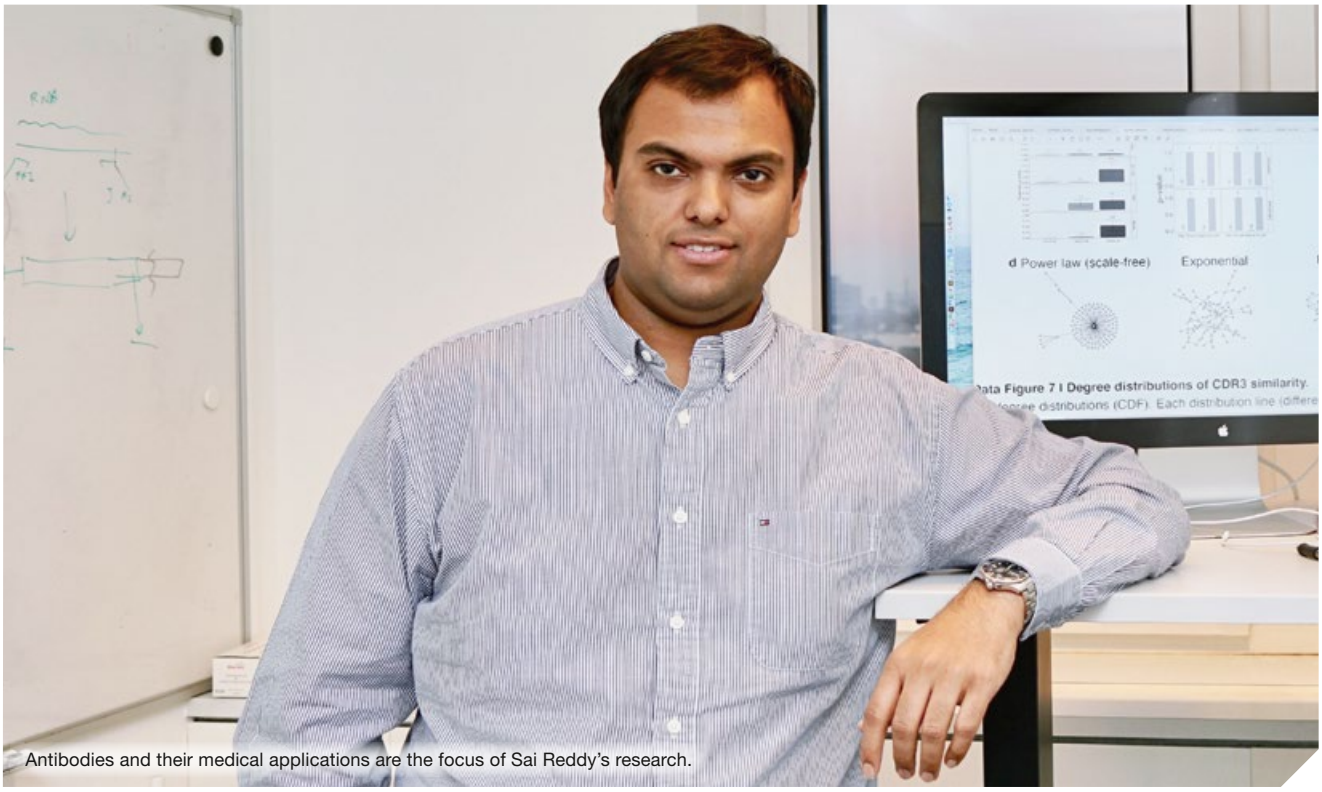
I look forward to welcoming you to our final conference in Zurich in September and wish you an interesting read.

Daniel Vonder Mühll
Managing Director SystemsX.ch

Systems biology of humoral immunity (AntibodyX)

Exploring the antibody repertoire in acute and chronic infections

Worldwide, scientists are exploring new ways of using potent antibodies for disease prevention and the treatment of acute and chronic infections, and even against cancer. Sai Reddy and his team are developing their own analytical methods to do just this and are applying them in order to understand the immune response to pathogens in detail.



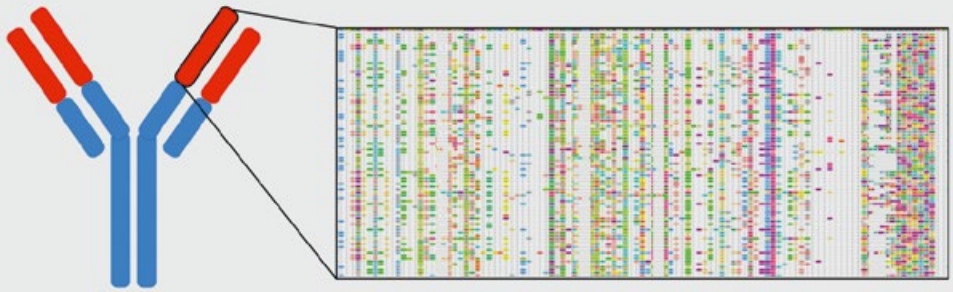
Antibodies and their medical applications are the focus of Sai Reddy's research.

Every antigen contact leaves a trace on the host organism, at least on an immunological level. "The main goal of our project is to be able to determine the antibody pattern of a given organism," says Sai Reddy, principle investigator of the Research, Technology and Development (RTD) Project AntibodyX. An extremely complex task, since there are millions of these plasma proteins within a single organism. The AntibodyX team is not only looking to find out which antibodies are present in a blood or tissue sample. They also want to be able to measure them quantitatively. But that's easier said than done. The methods enabling such analysis with high throughput and precision didn't even exist at the start of the RTD Project. "Thanks to AntibodyX, we've managed to make great progress in this area," explains the bioengineer Reddy. The team has succeeded in optimizing existing methods for the measurement of antibodies to meet even their own high requirements. "We've also developed several analytical tools to help us quickly filter out the information we're looking for from the enormous amounts of generated data," says Reddy. These methods incorporate novel concepts from the areas of mathematical ecology, statistical genetics, machine learning and network theory.

Looking for a needle in a haystack

"The search for a particular antibody in a blood or tissue sample was initially rather like looking for a needle in a haystack," says Sai Reddy. In order to make this search easier, and therefore more feasible in practice, the scientists exploited the fact that antibodies can be identified by particular genetic sequences. "The advantage of this method is that the distribution pattern of these sequences serves as a marker, allowing us to determine the immunological health of an organism," explains Reddy. In other words, the more of a particular antibody an individual has, the more efficient its body's defenses against the corresponding antigen are.

But that's not all. Every filtered-out antibody can be characterized in detail thanks to the team's new customized biochemical methods. "For example, we can also ascertain which of an antigen's molecular structures the antibody can dock onto," explains the researcher – information that the AntibodyX team needs in order to address further interesting problems. Among these is the question of why, after infection, the course of the disease can vary widely from patient to patient.



High-throughput sequencing of antibodies is providing new insight into immune responses and enabling the discovery of new vaccines and immunotherapies. © Sai Reddy

Super-antibodies as therapy

"After an HIV infection, a small number of patients exhibit a low concentration of the virus in their blood over a long time," describes Reddy. The clinical symptoms are also correspondingly milder. These patients are known as super controllers. They possess antibodies that can efficiently neutralize different strains of the HIV pathogen. "Thanks to spontaneous mutations, antibodies that are particularly effective against a particular pathogen can arise, which increase the survival chances of the affected individual," explains the researcher. The benefit of these findings is clear: "Such super-antibodies could be used for therapy or prevention." Two examples demonstrate just how promising this approach is.

Scientists at the Rockefeller University in New York have managed to extract some of these highly effective antibodies from super controller patients and synthesize them millions of times over. They then administered them to other HIV patients with considerable success. In some of the subjects a reduction in viral replication was observed over a certain period of time. Experts believe that a combination of different super-antibodies would significantly increase the effect. This hypothesis was given weight by experiences from the latest Ebola epidemic in humans, where treatment with the ZMAPP preparation was trialed. This therapeutic agent contained three types of Ebola-neutralizing antibodies. These plasma proteins were obtained from infected mice, which had produced the super-antibodies through spontaneous mutations. The success of this trial gained worldwide attention, as all of the patients treated with this method survived. "The administered antibodies kept the virus in check until the body was able to build its own immune response," Sai Reddy explains. Conversely, the Ebola pathogen damaged the bodies of untreated patients so severely within a matter of days that their immune systems were no longer able to build a defensive strategy.

Tailor-made vaccinations

The possible uses of such tailor-made vaccinations spur Sai Reddy and his team on. "Another goal of our RTD Project is to use the methods we've developed to explore the evolution of an antibody repertoire in both acute and chronic infections in detail." In order to reach this goal as quickly as possible, three groups within the AntibodyX team are investigating different problems. While the group led by Alexandra Trkola is focusing on the immune response of people with HIV, the research in Lars Hangartner's group concerns defenses against the influenza virus, and Annette Oxenius is examining the immune response to infection with the lymphocytic choriomeningitis virus (LCMV) in mice. The overarching goal of this research is to analyze the immunological processes that occur during acute and chronic infection in the hope of finding potential new vaccines. Sai Reddy can also imagine another promising use for these findings: "The application of neutralizing antibodies could also lead to a breakthrough in cancer therapy."

AntibodyX at a glance

AntibodyX
Systems Biology of Humoral Immunity

Principal investigator: Prof. Sai Reddy

Research groups:

- Prof. Sai Reddy, Laboratory for Systems and Synthetic Immunology, D-BSSE, ETH Zurich – Experimental and computational methods
- Prof. Lars Hangartner, Institute of Medical Virology, University of Zurich – Immunology, virology
- Dr. Roland Regoes, Institute of Integrative Biology, ETH Zurich – Bioinformatics, computational biology
- Prof. Alexandra Trkola, Institute of Medical Virology, University of Zurich – Immunology, virology
- Prof. Annette Oxenius, Institute of Microbiology, ETH Zurich – Immunology, virology

Total budget (2013–2017): CHF 2.9 million, including CHF 1.4 million from SystemsX.ch

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

Julia Vorholt investigates methylotrophic bacteria.

Systems biology of bacterial methylotrophy for biotechnological products from methanol (MetApp)

Methanol as bacteria fuel

Plastics, paints, antibiotics. These and many other everyday products use chemicals, whose biotechnological manufacture requires huge quantities of crude oil or plant-based raw materials. In future, methane or methanol could increasingly be used for this purpose. However, the bacteria in the bioreactors first need to learn how to convert this new energy source into the desired products.

It's a persuasive idea: methane could be used for the production of fine and basic chemicals. This would be a sensible way of using up this abundant, climate-damaging gas. "Methane not only occurs naturally in large quantities, but is also a by-product in oil production, sewage treatment and waste disposal sites," says Julia Vorholt, Swiss research partner on the ERASysAPP Project MetApp. "Methane is a largely untapped resource and has great potential for the production of useful chemicals without the need to sacrifice valuable agricultural land," adds the biochemist.

Only specialized organisms use methane or methanol as an energy source

However, what sounds so simple in theory is in practice a complex undertaking. Methane forms a highly explosive mixture with air. Although it can be used to power bioreactors, an alternative is to convert methane into methanol, a simple alcohol compound. Some specialized microorganisms are able to use this as a substrate. "Most microorganisms lack the necessary enzymes to do this, and some become damaged by the toxic compounds that arise throughout the metabolic cycle," explains Julia Vorholt. This is because methane and methanol are single-carbon (C1) compounds. These are organic compounds that do not contain carbon-carbon bonds, such as those found in oil or sugars like sucrose and cellulose.

There are, however, a few microorganisms that have found ways to use C1 compounds for growth, and they are known as methylotrophs. Two such bacteria, *Methylobacterium extorquens* and *Bacillus methanolicus,* are the focus of the MetApp project. Vorholt summarizes the two main objectives of the project: "First, we want to comprehensively understand and model the metabolism of methylotrophic bacteria, and second, we're looking for ways of applying this knowledge to the production of fine and basic chemicals."

Examining the bigger picture

The scientists working on the MetApp project are not scrutinizing every involved enzyme in detail. Instead, they want to understand the metabolism as a whole, from the genes all the way to the metabolic products. "We want to find out which elements are essential for the growth of microorganisms from C1 compounds," specifies Vorholt. This is why the team has decided to study *Methylobacterium extorquens* and *Bacillus methanolicus* in particular. Both of these microorganisms have decisive advantages. Firstly, they are able to use C1 compounds as well as sugars or organic acids as

an energy source. “This enables us to analyze the metabolic pathways for each nutrient substrate in the same microorganism, and therefore to determine which specific cellular elements are crucial for the metabolism of methanol,” explains the biochemist. Secondly, the part of the genome responsible for the C1 metabolism differs in the two organisms, and different genes mean different metabolic pathways. “The two bacteria have developed separate strategies for making use of C1 compounds,” says Vorholt.

In a subproject, researchers are manipulating individual gene sequences to see how the bacteria react. But the MetApp team is going further and transplanting this genetic material into other organisms that are as yet only able to metabolize carbon-carbon compounds. Amongst these is *Escherichia coli,* an organism that has long been used in the biotechnology industry. “Thanks to experiments such as these, we’re able to learn a great deal about C1 metabolic pathways, and will hopefully be able to make these established organisms available for industrial methanol conversion,” enthuses Julia Vorholt.

The initial results of the MetApp project are promising. The researchers have so far managed to confirm the involvement of genes thought to be responsible for C1 metabolism. Furthermore, they have identified many new genes that are also involved. And although the precise role of these DNA pieces has not yet been clarified in detail, the findings give the scientists important clues, which they are now investigating.

Europe-wide collaboration

In order to make efficient progress, each research group involved in the MetApp project is concentrating on solving one part of the puzzle. While Trygve Brautaset’s team in Norway is studying the *Bacillus methanolicus* bacteria in depth, the team based in Toulouse is constructing mathematical models. The scientists in Bielefeld, Germany, are developing the required omics methods for the experimental work and are also looking for ways to optimize the use of methylotrophic bacteria in chemical production. “Our team in Zurich is mainly studying *Methylobacterium extorquens,*” adds Vorholt, who has many years of experience working with this particular microorganism.

Since not all conventional analytical methods can be used for the investigation of methylotrophic organisms, Julia Vorholt and her team will need to develop existing technologies further – a challenge that the researcher is happy to rise to. Thanks to the Europe-wide network of research groups pursuing a shared goal, it is feasible that in the near future, bacteria will be able to utilize methanol in place of sugars to produce valuable chemicals. This project is the first step on the way to a C1 economy with tangible ecological benefits.

More information on MetApp:
www.sintef.no > projectweb > metapp
More info on ERASysAPP: **www.erasysapp.eu**

Bioreactor with *Methylobacterium extorquens.* Photo: Jethro Hemmann

MetApp at a glance

Research groups:

- Prof. Trygve Brautaset, Department of Biotechnology and Food Sciences, Norwegian University of Science and Technology, SINTEF Materials and Chemistry, Trondheim, Norway – Molecular biology, biotechnology
- Prof. Julia Vorholt, Institute of Microbiology, ETH Zurich – Microbiology, biochemistry
- Prof. Volker F. Wendisch, Center for Biotechnology (CeBiTec), Bielefeld University, Germany – Genetics, biotechnology
- Prof. Jean-Charles Portais, INSA Toulouse, France – Modelling

Total budget (2015–2018): EUR 1.5 million, including EUR 400,000 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.

Photo: © Martin Stollenwerk

Medical Research and Development Projects

Systems biology approach in medical research

In 2015, nine Medical Research and Development (MRD) Projects were launched. These are large, interdisciplinary medical projects with close ties to clinical application and a duration of three years. For the researchers involved, from mathematicians to medical doctors, it's a chance to carry out unique projects that bridge the gap between traditionally separate disciplines.

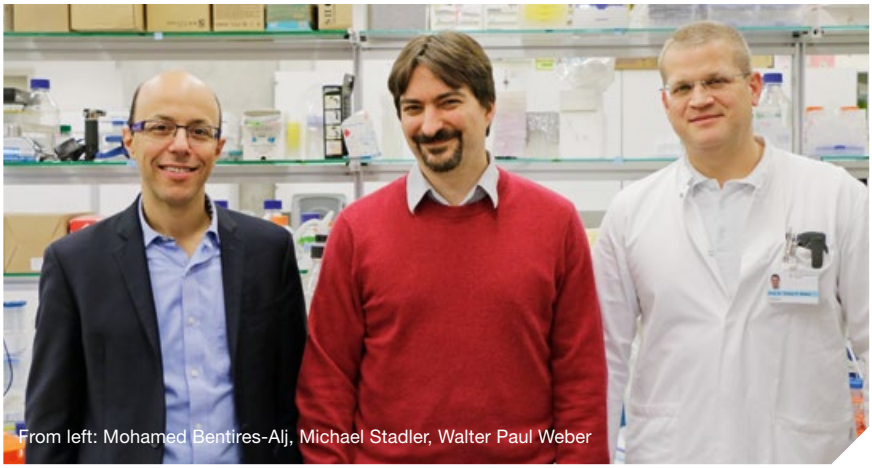
There have been huge advances in medicine over the past few decades, in diagnostics as well as treatment. Nevertheless, many of the biological processes that trigger disease remain unexplored. The systems biology approach to medical research aims to provide new insight into the causes of disease in order to better identify the risks and offer improved prediction strategies for disease prognosis. It is also steering clinical research towards personalized medicine by investigating the relationships between disease patterns and individual differences on the level of proteins and the genome.

In this report, the nine SystemsX.ch MRD Projects are presented. They cover a broad range of approaches and research questions in systems medicine, with some employing large-scale high-throughput technologies while others closely examine the interactions between a small number of molecules. A central aspect of all of the projects is the quantitative analysis or modeling of biological processes, necessitating the collaboration between hospitals and basic research groups. The diversity of topics addressed by the MRD Projects extends from cancer research to viruses to the bacteria that reside in the human gut. For the medical researchers involved, these projects present a unique opportunity to access resources that would otherwise be financially unviable. SystemsX.ch is proud to promote systems biology research within a medical and clinical setting, and hopes to contribute to the next quantum leap in medical understanding and progress.

Marc Mouci

1. MetastasiX – Cellular analysis of breast cancer

The incidence of breast cancer is on the rise all over the world. In Switzerland, over 5,000 women contract the disease every year. Thanks to progress in therapy and diagnostics, around 80% of these patients survive. However, for a fifth of the affected women, the disease is still fatal. In their cases, either the therapy is ineffective or resistance emerges. In the end, metastases are the predominant cause of death.



From left: Mohamed Bentires-Alj, Michael Stadler, Walter Paul Weber

Walter Paul Weber, professor and Head of Breast Surgery at the University Hospital Basel, leads the MRD Project MetastasiX. Together with his research colleagues involved in the project, he aims to understand the pathogenesis of fatal cases. "Some breast cancer cells roam around the body, entering the bones, liver, lungs, brain and skin. We want to find out which tumor cells do this and what gives them the ability to spread into other organs and grow again," says Weber.

The scientists working on the MetastasiX project are using a systems approach to determine the cellular and molecular factors contributing to the growth, resistance and metastasis of breast cancers. The mechanisms and dynamics behind these processes have so far hardly been investigated.

Mohamed Bentires-Alj, professor in the Department of Biomedicine at the University of Basel and co-PI on the project, describes the group's approach as follows: "What we do is single cell analysis to understand tumor heterogeneity. We examine how a particular cell differs from the others within the primary tumor, then within the metastases, and then we look at what happens during the progression from primary tumor to metastases. This is a new approach; before now, scientists hadn't analyzed breast cancer at the single cell level. With these results, we will have expression profiles of single tumor cells and will be able to look for proteins or other factors that might be responsible for seeding metastases."

This novel approach should enable the researchers to identify the cellular and molecular factors in breast metastasis, which would not only make it easier to estimate a patient's risk of developing metastases at an early stage of the disease, but in the best case would also help treat patients with existing metastases.

The interdisciplinary collaboration across institutional boundaries is new for most of the involved researchers. Michael Stadler, co-PI and Head of Computational Biology at the Friedrich Miescher Institute in Basel, summarizes: "Since we all come from very different disciplines, we first had to find a common language. But the collaboration is very exciting, as it allows us to carry out research with much more relevance to clinical applications than usual."

In the first half of the project, the scientists were able to discern some interesting differences between the tumor cells and the metastases. A closer examination and classification of the collected data will be carried out in the second part. For Weber, the way forward is clear: "In the field of medicine, we need to make a progression from diagnosis toward prediction, and the systems biology approach plays a huge role in achieving this."

MetastasiX at a glance

Principal investigator: Prof. Walter Paul Weber, Head of Breast Surgery, Tumor Center, University Hospital Basel

Research groups:

- Prof. Gerhard Christofori, Department of Biomedicine, University of Basel
- Prof. Bernd Bodenmiller, Institute of Molecular Life Sciences, University of Zurich
- Dr. Michael Stadler, Friedrich Miescher Institute, Basel
- Dr. Maria Rodriguez Martinez, IBM Zurich Research Laboratory
- Prof. Mohamed Bentires-Alj, Department of Biomedicine, University of Basel

Approved SystemsX.ch funds (2015–2018): CHF 2.212 million

MetastasiX
Systems Biology of Breast Cancer

2. StemSysMed – When mutated blood cells begin to multiply uncontrollably

Blood-forming cells multiply often, with mutations occurring relatively frequently. Despite this, blood cancer is a comparatively rare disease in humans. The MRD Project StemSysMed aims to find out why some mutated blood cells suddenly start to proliferate uncontrollably.


Radek Skoda

Blood cells are formed from stem cells and progenitor cells. “Every year, a person produces around 70 kg of blood in this way,” says Radek Skoda, PI of the MRD Project and professor at the University of Basel. The high rate of cell division leads to many mutations. The fact that these do not necessarily lead to blood cancer is attributed to a finely tuned control system.

Blood-forming stem cells rarely divide – it is the progenitor cells that produce most new blood cells. These progenitor cells have a short lifespan, which limits the chance of mutations being passed on. Mutations in stem cells, however, are potentially more dangerous. The offspring of a mutated stem cell carrying the same mutation are called clones. Many of these remain harmless, but malignant clones can lead to the development of blood cancer. “Stem cells are forced to divide more frequently with increasing age,” says Skoda. “And since life expectancy is always increasing, we can expect to see a sharp rise in the number of blood cancer cases.”

The StemSysMed team wants to gather quantitative data on factors influencing the occurrence of mutations as well as those determining the early stages of these clones in order to model them. To do this, the scientists are comparing blood samples from healthy individuals with those from patients with stem cell transplantations. Furthermore, using a systems biology approach, the scientists will examine how myeloproliferative neoplasm, where mutated blood cells multiply uncontrollably, develops in a mouse model as well as in primary cells of affected patients. Their questions include: Can the development of myeloproliferative neoplasm be explained solely by the occurrence of a crucial cancer-inducing mutation in a stem cell? Or do such mutations occur relatively frequently, but only lead to blood cancer under the influence of additional external factors? The scientists will employ mathematical models to test these hypotheses.

As with the other MRD Projects, interdisciplinarity plays a central role here. Researchers from five different institutes are working together on StemSysMed. “This is extraordinary and would not have been possible without SystemsX.ch,” emphasizes Skoda. “It enables mathematicians to address biological problems, and biologists to incorporate mathematics into their research. We also have extensive access to omics methods. Such a project would have otherwise been almost impossible to assemble and finance.”

StemSysMed at a glance

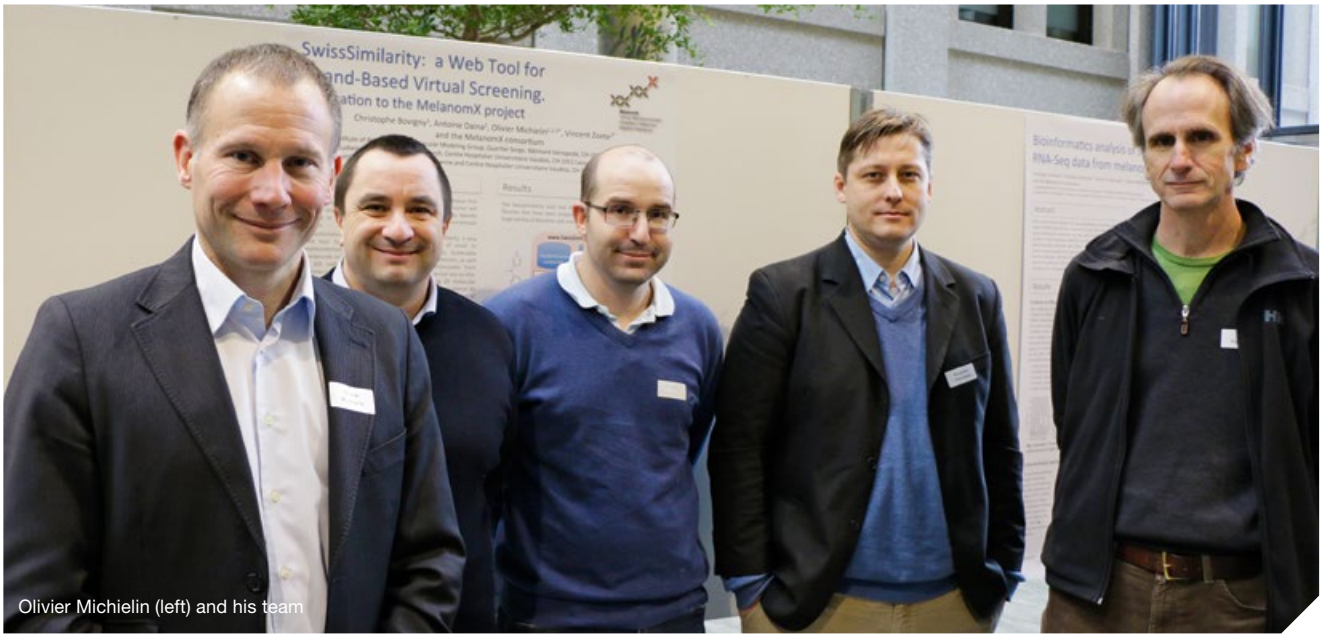
Principal investigator: Prof. Dr. med. Radek Skoda, Department of Biomedicine, University Hospital Basel and University of Basel

Research groups:

- Prof. Markus Gabriel Manz, Hematology, University Hospital Zurich
- Prof. Timm Schröder, Department of Biosystems and Engineering, ETH Zurich
- Prof. Ivan Martin, Department of Biomedicine, University of Basel
- Prof. Sebastian Bonhoeffer, Department of Environmental Systems Science, ETH Zurich

Approved SystemsX.ch funds (2015–2018): CHF 2.373 million

StemSysMed
Systems Approach to Hematopoietic Stem Cell Diseases



Olivier Michielin (left) and his team

3. MelanomX – Deciphering the mechanisms of resistance

As with other types of cancer, significant progress has been made in the treatment of melanoma over the past few years. Unfortunately, all affected patients experience resistance to the drugs after some time. The MelanomX project is searching for the cause of this resistance.

The successful use of drugs to inhibit the BRAF-oncogene was one of the most significant victories in the treatment of advanced melanoma. In spite of this, patients are still experiencing the development of resistance after about six months. Olivier Michielin, professor at University of Lausanne, and his team working on the MelanomX project are examining the mechanisms employed by cancer cells in order to develop better therapies.

Using a systems biology approach, the researchers want to decipher the resistance to BRAF inhibition (BRAF is a protein that promotes tumor growth) on the single-cell level. The researchers have developed a way of determining the complete mutational landscape of thousands of single cells from metastatic melanomas. They are studying samples taken from patients before and during BRAF inhibition, as well as patients whose therapy failed or led to disease progression. In this way, the scientists want to interpret the dynamics of resistance.

"In order to carry out this study, we first had to improve our technical equipment so that only single cells were examined, as opposed to several cells at once, which would cloud the results," says Michielin. The researchers also noticed that the frozen cancer cells they studied yielded far inferior results than the fresh samples. "We have discovered that these cancer cells are very temperature sensitive. Fresh samples are of much better quality, meaning that we have had to adjust our whole workflow. The process has become more complicated, as everything has to be done much faster," reports Michielin. After analyzing thousands of single cells, the team has managed to describe the cellular composition of melanoma in great detail and has already identified a number of potential targets for therapy.

"In the next step, we will test a number of different molecules that work to block various mechanisms within the cancer cells," explains Michielin. This could be the first step towards the development of new medication, and therefore to a sustainable treatment for melanoma.

MelanomX at a glance

Principal investigator: Prof. Dr. med. Olivier Michielin, University of Lausanne and SIB Swiss Institute of Bioinformatics, Lausanne

Research groups:

- Dr. Vincent Zoete, SIB Swiss Institute of Bioinformatics, Lausanne
- Dr. David Gfeller, Ludwig Center for Cancer Research, University of Lausanne
- Prof. Douglas Hanahan, ISREC – Swiss Institute for Experimental Cancer Research, EPF Lausanne
- Dr. Keith Harshman, Center for Integrative Genomics, University of Lausanne

Approved SystemsX.ch funds (2015–2018): CHF 2.124 million

MelanomX
Tumour Microenvironment Crosstalk in Melanoma Adaptive Resistance

4. HIV-X – Understanding the latent viral reservoir

In Switzerland, around 15,000 people are estimated to live with a diagnosis of HIV. Highly effective combination therapies prevent replication of the virus, but fail to eliminate it completely. This is because the virus integrates its own genome into the human genome and establishes long-lived viral reservoirs. If treatment is stopped, the virus begins to multiply again. The MRD Project HIV-X therefore wants to learn more about this latent viral reservoir.


Huldrych Günthard

"We know that the size of the latent viral reservoir varies from patient to patient, but after an initial drop upon initiation of treatment, it generally stays constant over time," says Huldrych Günthard, professor at the University Hospital Zurich. "With the HIV-X project, we want to find out what causes these size differences between patients. We still don't know how to reduce or eliminate these reservoirs either." The HIV-X research team is therefore looking to identify the host and viral factors that play a role in a reservoir's mechanisms. On the basis of these results, the researchers aim to develop models which could be used to predict how a patient responds to a particular treatment. In doing so, the scientists also hope to contribute to the development of more effective treatments that might eliminate the reservoirs for good.

Thanks to the Swiss HIV Cohort Study (SHCS), which has collected clinical data as well as cell and plasma samples from more than half of those registered with HIV in Switzerland since 1988, the scientists have access to a unique and considerable data set. The researchers are examining samples from around 1,200 patients who have received antiretroviral therapy for at least five years, and whose blood virus levels were below the limit of detection over this period. They are analyzing the extent of the viral reservoir, as well as the genomes of both host and virus, for each patient in this group.

"The amount of data collected during this project is immense, and we would never be able to cope with it alone. This is why we're dependent on close collaboration with other institutes," says Günthard. The team wants to use their results to find factors in the patients or virus that have an effect on the size of the viral reservoir.

"This project is our opportunity to do something big. So far, no other research groups have carried out such a comprehensive study." If it turns out that the reservoirs of particular genotypes respond differently to certain drugs, the therapy could be tailored accordingly. "This would be a step in the direction of personalized medicine in the field of HIV treatment," says the infectious diseases specialist. "I myself am very pleased that SystemsX.ch launched the MRD Projects, which promote clinical research with a systems approach."

HIV-X at a glance

Principal investigator: Prof. Dr. med. Huldrych Günthard, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich

Research groups:

- Prof. Niko Beerenwinkel, Department of Biosystems Science and Engineering, ETH Zurich
- Dr. Jasmina Bogojeska, IBM Zurich Research Laboratory
- Prof. Sebastian Bonhoeffer, Department of Environmental Systems Science, ETH Zurich
- Prof. Jacques Fellay, Global Health Institute, EPF Lausanne
- Prof. Roger Kouyos, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich
- Prof. Karin Metzner, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich
- Prof. Volker Roth, Department of Mathematics and Computer Science, University of Basel

Further information: Swiss HIV Cohort Study, www.shcs.ch

Approved SystemsX.ch funds (2015–2018): CHF 2.182 million

HIV-X
Deciphering Host-Virus Interactions to Cure HIV

5. VirX – Finding new ways of fighting viral infections

Viruses represent one of the major health threats to humans, and yet for the majority of viruses, there are no vaccines available. Antiviral drugs usually target viral proteins, and as such may quickly lose their efficacy due to mutations. The VirX project is exploring a cellular pathway that was recently identified as being employed by the influenza virus to infect human cells. This could lead the way for new approaches to combatting viruses.

"The VirX project is using a bottom-up approach," says Patrick Matthias, Senior Group Leader at the Friedrich Miescher Institute and project leader of the MRD Project. "Unlike many other systems biology projects, our starting point is not based on large-scale screenings with lots of data points. Instead, we are starting by looking at the interactions between a few cellular proteins, and investigating how these are involved in the infection of a cell by the influenza virus."

A number of cellular proteins play a role in infection by viruses such as influenza. The new cellular pathway examined in this project involves the deacetylase HDAC6, motor proteins such as dynein and myosin and also the small protein ubiquitin; together, these components form a module which helps the virus infect the cell. The virus is then able to release its genome into the cytoplasm, before it is transcribed and replicated in the cell nucleus.

The molecular interactions of these proteins form the basis of the VirX project. They are being closely investigated with the goal of developing three-dimensional and mathematical models. Yet the involvement of additional factors has not been ruled out. "It is entirely possible that other proteins also form part of this module," adds Matthias.

The team will then test a number of molecules that may interfere with the cellular pathway and thus hopefully limit the virus's entry into the cell. This could lay the foundation for new antiviral medication. Furthermore, the group is interested in whether the same cellular proteins also play a part in infections by other viruses, for example rhinoviruses – the cause of the common cold.

For Matthias, systems biology plays a key role in today's research. "This way of working enables us to adopt a truly interdisciplinary approach which is still curiosity-driven. It allows us to paint a more complete picture of complex processes, allowing scope for new discoveries and hypotheses."

VirX at a glance

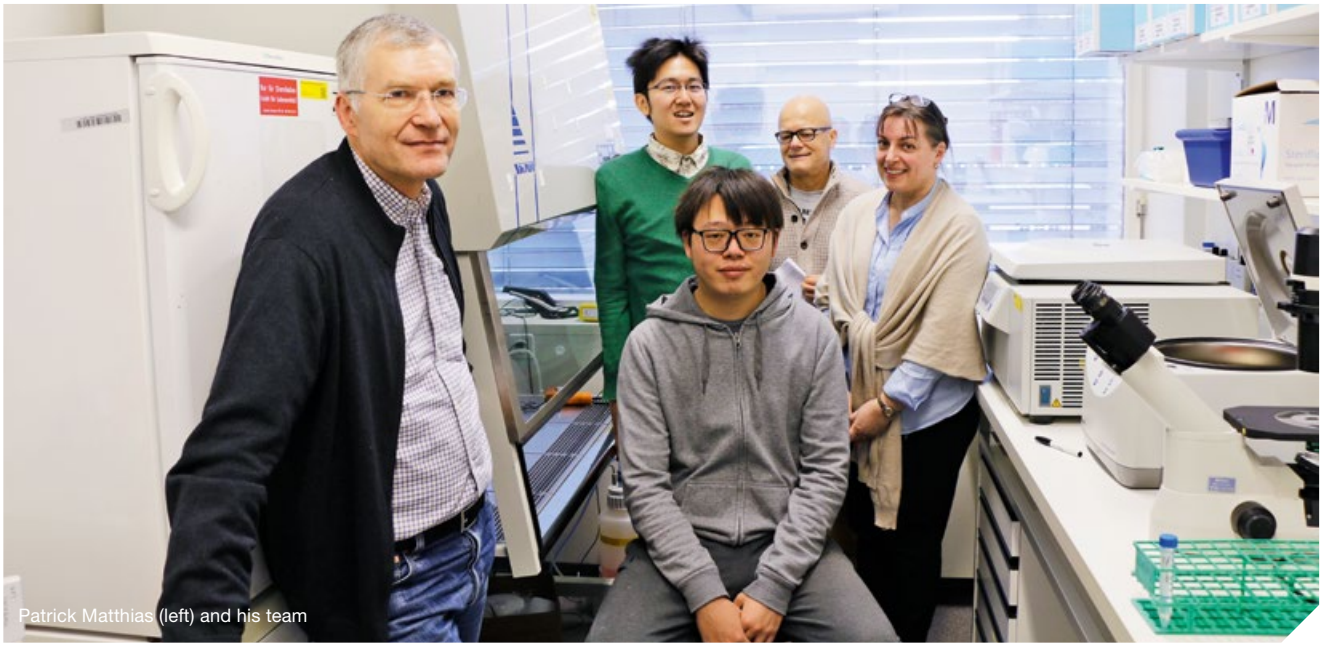
Principal investigator: Prof. Patrick Matthias, Friedrich Miescher Institute for Biomedical Research

Research groups:

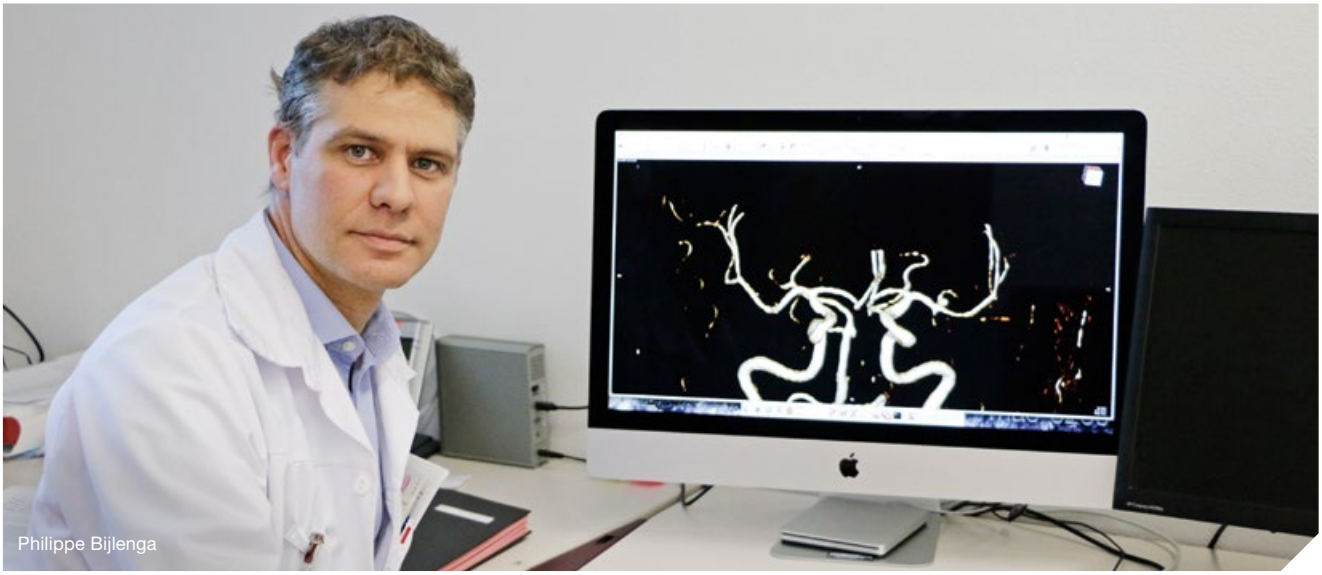
- Prof. Urs Greber, Institute of Molecular Biology, University of Zurich
- Prof. Laurent Kaiser, Clinical Virology, Geneva University Hospital
- Prof. Jörg Stelling, Department of Biosystems Science and Engineering, ETH Zurich
- Dr. Yohei Yamauchi, School of Cellular and Molecular Medicine, University of Bristol, UK
- Dr. Heinz Gut, Friedrich Miescher Institute for Biomedical Research

Approved SystemsX.ch funds (2015–2018): CHF 2.25 million

VirX
A Host-Directed Approach Against Viral Disease



Patrick Matthias (left) and his team



Philippe Bijlenga

6. AneuX – Better predictions for the treatment of aneurysms

Intracranial aneurysms are weak spots on the brain's blood vessels that swell and fill with blood. Usually, they present no symptoms and cause no discomfort. If, however, the aneurysm bursts, the consequences can be very serious. The researchers working on the MRD Project AneuX are therefore striving to develop a tool that provides a reliable prediction for an aneurysm's development.

Benign intracranial aneurysms are quite common and mostly harmless. But if the wall of the blood vessel ruptures, the subsequent brain hemorrhage leads to death in a third of cases, and in another third to severe, irreversible brain damage. Only the remaining third of patients are able to partially recover. People of all ages can be affected. "It is estimated that aneurysms occur in around 3% of the population, but the risk of brain hemorrhage cannot yet be determined," says Philippe Bijlenga, medical doctor and researcher at Geneva University Hospital, and principal investigator of the AneuX project.

There are currently no available methods by which the development of aneurysms, or the success of surgery or treatment, can safely be predicted. However, it is postulated that the shape of an aneurysm might give a clue to the disease prognosis. The team behind the MRD Project AneuX is therefore looking into the morphological characteristics of aneurysms in search of visual biomarkers. To do this, the scientists have access to a database that has been continually updated since 2006. It contains data from over 700 patients and 900 aneurysms, chronicling their development over time. The morphological data was collected by means of frequent image screenings, resulting in 3D records of a great number of different aneurysm variations at different stages of disease.

The AneuX team is pursuing two different approaches in the morphological characterization of aneurysms. "In Geneva, we're examining the biological processes, whereas researchers at the ZHAW are creating a cellular model," says Bijlenga. A model for the prediction of disease progression is to be developed based on the simulation and data from the clinical part. This model will then be tested in a clinical trial. "I am quite confident that, by the end of the project, we will have a tool that will be able to predict the potential development of an aneurysm based on its shape," declares Bijlenga. For the medical doctor, it's important that the implementation of such a tool should be as simple and straightforward as possible.

AneuX at a glance

Principal investigator: Dr. med. Philippe Bijlenga, Department of Clinical Neuroscience, Geneva University Hospital

Research groups:

- Prof. Sven Hirsch, Institute of Applied Simulation, ZHAW
- Prof. Niels Kuster, Foundation for Research on Information Technologies in Society (IT'IS), ETH Zurich
- Prof. Brenda Kwak, Department of Pathology and Immunology, University of Geneva
- Prof. Brigitte von Rechenberg, Center for Applied Biotechnology and Molecular Medicine, University of Zurich
- Prof. Daniel Rüfenacht, Center for Applied Biotechnology and Molecular Medicine, University of Zurich

Approved SystemsX.ch funds (2015–2018): CHF 1.875 million

AneuX
Shape as Biomarker for Aneurysm Disease

7. PrionX – Why do proteins infect other proteins?

Prions are proteins that are responsible for a number of brain diseases in humans and other mammals. So far, however, very little is known about their growth mechanisms. The PrionX project therefore seeks to learn more about these aggressive proteins.

The term *prion* stems from the words **pr**otein and infect**ion,** and refers to the virus-like properties of these types of proteins. Prion diseases gained publicity in the 1990s due to the BSE crisis. It was feared that this "mad cow disease" could be transferred to humans through the consumption of beef products. After the crisis subsided, however, the talk of these mysterious proteins once again died down.

Prion diseases, including BSE, are caused by the misfolding of proteins. The prions induce other proteins to change their shape, and these abnormal prions build up in the brain, leading to cell death. The brain's tissue becomes riddled with holes, and a spongy structure develops; a pattern that is also observed in other diseases such as Parkinson's. It is mostly the elderly who are affected, and no effective therapies exist to date. The reason for this is an incomplete understanding of the biochemical and cellular networks involved in the course of the disease.

A deeper understanding of these processes is precisely the goal of the researchers working on the MRD Project PrionX. The interdisciplinary team is planning to tackle this problem using the latest advances in genome editing (CRISPR) and microscale liquid handling. These technologies make it possible for the scientists to selectively suppress or eliminate individual genes.


Adriano Aguzzi

"The basic idea is to infect cells with prions while suppressing each gene individually in order to see what influence this has on the production of prions," explains Adriano Aguzzi, professor at the University Hospital Zurich. "And when we've made our way through the whole genome, we will be left with a picture of prion replication." Since there are around 30,000 genes in a cell, the vast extent and ambition of the study becomes evident.

A major obstacle for previous research in this area was that prions are barely active *in vitro.* Normally, when cells are infected with prions, they replicate vigorously. But *in vitro,* hardly any replication takes place. "I suspect the cells support the multiplication of the prions. This is why replication doesn't take place in a cell-free sample," speculates Aguzzi. "Once we learn more about this replication, we'll be able to tackle it therapeutically."

Aguzzi is confident that the team will find evidence of prion replication. "We're on a journey of discovery. So far, we've found a number of very interesting things that we would like to examine more closely, and which could significantly deepen our understanding of prion diseases."

PrionX at a glance

Principal investigator: Prof. Dr. med. Adriano Aguzzi, Institute of Neuropathology, University Hospital Zurich

Research groups:

- Prof. Lucas Pelkmans, Institute of Molecular Life Sciences, University of Zurich
- Dr. Vincent Zoete, SIB Swiss Institute of Bioinformatics, University of Lausanne
- Prof. Ioannis Xenarios, SIB Swiss Institute of Bioinformatics, University of Lausanne
- Dr. Tuomas Knowles, Department of Chemistry, University of Cambridge

Approved SystemsX.ch funds (2015–2018): CHF 1.347 million

PrionX
Systems Biology
of Prion Diseases

8. HDL-X – The "good" cholesterol

There is a correlation between the risk of contracting heart disease and cholesterol levels in the blood. Interestingly, this correlation is opposite for cholesterol transported in low-density lipoproteins (LDL) and high-density lipoproteins (HDL). While the causal relationship between high levels of LDL cholesterol and heart disease is generally accepted and can be successfully targeted with drugs, the causality of the association between low HDL levels and increased risk of atherosclerotic diseases and diabetes is controversial.

Cholesterol, a component of the body's cell membranes, is indispensable for the human body. But when cholesterol levels are too high, problems can arise if it is deposited in the arterial walls. Both low-density lipoproteins (LDL) and high-density lipoproteins (HDL) serve to transport cholesterol within the blood plasma. Epidemiological, genetic and intervention studies have unequivocally shown that LDL promotes atherosclerosis. By contrast, the outcomes of the same kind of studies have questioned the previously assumed protective role of HDL in the pathogenesis of atherosclerosis. Likewise, the role of low HDL cholesterol in the pathogenesis of diabetes has not been adequately demonstrated.

HDL particles exhibit manifold effects, both *in vivo* and *in vitro,* seemingly protecting the human body from harmful chemical and biological processes. However, HDL has not yet been successfully employed in the prevention or treatment of heart disease or diabetes. "Medications that increase HDL cholesterol have not revealed any positive effects on heart disease," says Arnold von Eckardstein, professor at the University Hospital Zurich and leader of the HDL-X research project.

This MRD Project is concerned with the many-facetted functions of HDL in health and disease. The aim of the project is to clarify which components of HDL are disturbed in patients with diabetes or heart disease but are relevant for the prevention of these diseases. To this end, the scientists working on the project will isolate HDL particles from the blood of healthy and affected individuals and analyze their protein and lipid composition. In addition, the researchers will examine the biological interactions of HDL with endothelial, fat and muscle cells.

With the help of mathematical analysis of the data, those components of HDL will be identified which either alone or in combination might serve as biomarkers for an increased risk of heart disease or diabetes. It is hoped that the resulting models will be able to contribute to the development of personalized treatment strategies and help monitor treatment outcomes.

"We are looking for a biomarker in HDL that can be used to assess the risk of atherosclerosis or diabetes," says von Eckardstein. "The ideal result would be the discovery of one or more lipids or proteins that are strongly related to one of these disease states and can be targeted for drug development and used to assess the risk of these diseases."

Arnold von Eckardstein

HDL-X at a glance

Principal investigator: Prof. Dr. med. Arnold von Eckardstein, Institute of Clinical Chemistry, University Hospital Zurich

Research groups:

- Prof. Jan Krützfeld, Division of Endocrinology, University Hospital Zurich
- Prof. Christian Wolfrum, Department of Health Sciences and Technology, ETH Zurich
- Prof. Bernd Wollscheid, Department of Biology, ETH Zurich
- Prof. Niko Beerenwinkel, Department of Biosystems Science and Engineering, ETH Zurich
- Prof. Manfred Claassen, Department of Biology, ETH Zurich

Approved SystemsX.ch funds (2015–2018): CHF 1.856 million

HDL-X
Systems Biology of
High Density Lipoproteins

9. GutX – The bacterial consortia

Bacteria are indispensable for our digestion, and yet more and more people are developing immune responses to these microbes. The result is chronic infection of the gut. The GutX project is investigating the interaction between humans and their resident bacteria more closely.


Andrew Macpherson

The myriad microorganisms in the large intestine, an estimated 1,000 different bacterial species making up a total population of hundreds of billions, help us to break down our food and thus provide the body with essential nutrients and vitamins. They promote the development and maintenance of the intestinal mucous membranes, as well as being involved in the body's defenses against viruses, fungi or pathogenic bacteria. Today, however, an increasing number of people are suffering from phases of acute and chronic intestinal inflammation. This is caused by immune cells in the intestine's mucous membranes that react aggressively to the body's own microorganisms.

By now, around one in a thousand suffers from chronic inflammatory bowel disease (IBD). "An increasing number of young people are becoming affected," says Andrew Macpherson, professor at the University of Bern and principal investigator of the GutX project.

The MRD Project wants to get to the bottom of this and investigate exactly what is happening in the bowels of affected patients. Until now, research in this area has mainly focused on the question of which of the thousands of possible microorganisms reside in the intestines of patients with chronic IBD. But this approach neglects to address the complex interactions that occur between the microorganisms and their host. "Our study therefore poses the question: How exactly are these bacteria interacting with one another, and to what extent does the host organism play a part in these processes?" says Macpherson.

The researchers are investigating how the metabolism of these intestinal microbes – that is, the entirety of their biochemical reactions – influences the mucous membranes and the patients' immune systems. To this end, the scientists are employing methods that simultaneously measure many of the different biochemical substances within the intestine. They then look at how these substances are passed from the bacteria to the host, and develop models that simulate these processes in a healthy and diseased organism.

The researchers have access to samples and data from the Swiss IBD Cohort Study, which encompasses over 3,000 patients. For the modeling part, they use mice, which have only 12 different kinds of intestinal bacteria. The researchers want to use this mouse model to analyze and test different bacterial consortia. The ultimate goal of the study is to vindicate microbiota manipulation as a therapy to treat IBD.

GutX at a glance

Principal investigator: Prof. Dr. med. Andrew Macpherson, Gastroenterology and Mucosal Immunology, Inselspital, University of Bern

Research groups:

- Prof. Uwe Sauer, Department of Biology, ETH Zurich
- Prof. Jörg Stelling, Department of Biosystems Science and Engineering, ETH Zurich
- Prof. Christian von Mering, Institute of Molecular Life Sciences, University of Zurich

Approved SystemsX.ch funds (2015–2018): CHF 2.369 million

GutX
Systems Biology of Inflammatory Bowel Disease

Tuncay Baubec on his Special Opportunity Project

Protein-LEGO: a scalable strategy for dissecting protein-genome interactions

Project goal:	The goal of this project is to develop a scalable system for simultaneous whole-genome binding analysis of individual DNA and chromatin reader domains. Parallel, recombination-mediated biotin tagging and sequencing (PaRBiT-seq) is based on parallel integration of multiple biotin-tagged, synthetic proteins into the mouse genome, followed by multiplexed ChIP-sequencing (Chromatin ImmunoPrecipitation, a method used to identify protein binding to specific gene regions).
Origin of project idea:	In previous studies, we have observed that mutations of chromatin reader domains can lead to drastic changes in the genome-wide binding preferences of regulatory proteins. These experiments have led us to explore in more detail how individual reader domains influence the binding specificity of regulatory factors to the genome.
Interesting facts and background:	While ChIP-based analysis of genome-wide binding preferences is a well-established method, it can currently only be applied to a single protein at a time. Recent technological developments in DNA synthesis and sequencing now allow us to efficiently produce synthetic proteins in engineered cells and to perform multiplexed ChIP experiments in a high-throughput fashion. The standardized workflow of PaRBiT-seq will not only reduce the time and effort required to screen large groups of proteins, but also facilitate the direct comparison between the analyzed proteins.
Highlights and expected milestones:	Since beginning the project, we have managed to establish efficient workflows for the generation of stable cell lines expressing various engineered proteins from synthesized DNA and test their suitability for ChIP-sequencing. This enables us to complete and scale up the PaRBiT-seq workflow in the near future and to profile a set of a hundred proteins as a benchmark.
Biggest challenges:	One of the biggest challenges is the optimization of the multiplexed ChIP-sequencing strategy. We have to fine-tune the balance between obtaining sufficient coverage for each individual protein, reducing sequencing costs, and generating bias-free sequencing results. We are currently testing various procedures to identify the most suitable approach.
Future applications:	The high-throughput nature of PaRBiT-seq can be also adopted to evaluate protein-protein or protein-RNA interactions for entire proteins and domains in parallel. Further developments, especially in combination with automation, would enable high-throughput validation of designer proteins *in vivo* and cellular localization studies. It could also potentially be used as part of a drug-screening platform for specific inhibitors that target protein interactions in the cell.
Project title:	Protein-LEGO: A high-throughput approach to dissecting protein-genome interactions by quantifying the contribution of individual domains.
Principal investigator:	SNF Prof. Tuncay Baubec, Laboratory of Systems Biology of Gene Regulation, Department of Molecular Mechanisms of Disease, University of Zurich
Total budget:	CHF 418,652 including CHF 199,652 from SystemsX.ch (2016–2017)
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 reading:	Baubec, T., et al (2013). Methylation-dependent and -independent genomic targeting principles of the MBD protein family. *Cell 153,* 480–492.
Further links:	www.baubeclab.org

Marc Mouci

Christoph Zechner is now research group leader at MPI-CBG in Dresden. Photo: © mpi-cbg.de

Interview with a former Transition Postdoc Fellow

A positive and stimulating environment is the key to successful research

He came to biology via electrical engineering and wanted to find out how living organisms perform complex calculations. Since the beginning of 2017, Christoph Zechner has been a research group leader at the Max Planck Institute for Molecular Cell Biology and Genetics in Dresden.

Congratulations on your new position as research group leader at the Max Planck Institute for Molecular Cell Biology and Genetics (MPI-CBG) in Dresden. You've been there since the beginning of this year. How are you settling in?

Thank you! Everyone at the institute is very friendly, open and committed to making my start here as smooth as possible. I feel very comfortable here.

Was it difficult for you to move away from Zurich?

I have a special connection to the city of Zurich, as it is the place where I "grew up", scientifically speaking. I also met some of my closest friends and colleagues there, which makes the move particularly hard. On the other hand, it's always been clear to me that I'd have to move around a bit in order to follow an academic career.

What exactly does your job in Dresden entail?

The Center for Systems Biology Dresden (CSBD) was recently established as a joint project between the MPI for Molecular Cell Biology and Genetics, the MPI for Physics of Complex Systems and TU Dresden. My job is to set up a new theory group at the CSBD, which will focus on the modeling of stochastic networks in systems biology. In molecular biology, a great many things happen randomly, and we want to understand how cells and organisms cope with this uncertainty.

Our research program is highly interdisciplinary, and we will work closely with experimental specialists at MPI-CBG and other institutes. These interdisciplinary collaborations will be strongly promoted at CSBD through specially designed PhD and postdoc programs.

"The question of how living organisms perform complex calculations fascinates me."

Photo: © mpi-cbg.de

What projects have you got in the pipeline?

I spend a lot of time talking to different collaborators, and a few projects are now taking shape. One of these is with Dora Tang and her lab. Here, we want to build artificial cells to collectively solve predefined tasks, for instance certain calculations, with the help of genetic circuits. Our hope is that we'll be able to reproduce complex behavior during tissue formation in living organisms, and thus be able to understand them better. In addition, important applications in bio- and nanotechnology could result. We've also been awarded an interdisciplinary PhD position.

What is the difference to the ETH, where you were before?

It's difficult to say, since the ETH is a whole university with many different departments and institutes, whereas the MPI-CBG is a single institute within the Max Planck society. I can only answer this based on my own experiences. At the ETH I worked in research groups with an engineering focus, during both my PhD in Heinz Koeppl's group as well as my postdoc with Mustafa Khammash. The two MPIs affiliated with the CSBD have a very strong emphasis on basic research – one in the field of molecular biology and the other in theoretical physics. So here I'm a little outside my comfort zone, so to speak, although this was a conscious decision. I think that some of the best opportunities come with new, unknown territory, and when you don't limit yourself to what you're already familiar with.

You were previously a SystemsX.ch fellow. What did you achieve in that time?

Before I started my SystemsX.ch Transition Postdoc Fellowship, I worked exclusively in systems biology and never really did any experiments. During the postdoc, I wanted to do something in the field of synthetic biology and gain experience in a wet lab. The TPdF call for proposals came just at the right time for me to make this change.

A major problem with artificial biological circuits within living cells is that they often vary widely, over time as well as from cell to cell. In my project, I wanted to find out how to systematically suppress these variations. To this end, we applied an approach that is usually used for noise reduction in signal processing. Such noise suppressors are found for example in headphones or mobile phones.

Ultimately, we were able to show theoretically as well as experimentally that very similar noise suppressors can be achieved on the molecular level, for instance with the help of DNA or proteins. Our results demonstrate that the strong variability within synthetic circuits can be considerably suppressed.

How was your experience of SystemsX.ch?

My time as a SystemsX.ch fellow was a thoroughly positive experience. I felt at ease in Mustafa Khammash's group and the project went very well. The fellowship also gave me the opportunity to spend some time at the University of Washington, USA, where I carried out the experimental part of my project. I always felt very well supported by the SystemsX.ch Management Office, and I think it's a shame that SystemsX.ch will soon come to an end.

You originally studied telematics and are now a research group leader in a completely different discipline. How did that happen? What motivated you to do your PhD in computational systems biology at the ETH?

I hear this quite often! My studies were very methodical and systems-oriented. Many of the concepts and paradigms from engineering can be applied to biology, and sometimes it doesn't matter whether you're dealing with electrical or genetic circuits. For me, this is really the basic concept behind systems biology. My interest in biology came relatively late, during my master's degree at Graz University of Technology. I was working in machine learning at the time, where many of the methods are inspired by biology (for example, artificial neural networks). The question of how living organisms perform complex calculations has fascinated me ever since.

Have you ever had doubts about your career path?

No, never. I usually go with my gut feeling when making decisions and therefore give little thought to the alternatives. However, as I was looking for a position as PI, I had to come to terms with what might happen if it didn't work out. Which makes me feel all the more fortunate to have found my current position at such a prestigious institute.

Biology has recently made great progress by embracing technological advances and informatics. In which direction do you think biology, and particularly systems biology, will develop next?

I think that systems biology can be broadly divided into two different streams. On one hand, there is the bioinformatics-inspired top-down approach, where you attempt to automatically extract and refine biological networks with the help of large datasets and algorithms. At the other end of the spectrum, there is the bottom-up approach, where you try to quantitatively and mechanically understand each individual part of a network before looking at the system as a whole. There has recently been great progress in both areas, but I believe we'll have to link the two approaches sooner or later. There's a long way to go until this happens, but I think that's where the field is going.

SystemsX.ch tries to promote interaction between different disciplines. What do you think of this?

In my opinion, it's the only way forward. You can see in the Swiss research landscape that SystemsX.ch's efforts are bearing fruit. Particularly when compared to other countries, which invested in interdisciplinary research either much later or not at all.

I believe that exchange and interaction between completely different disciplines are essential factors in modern research. As scientists, it's our job to delve deep into our own subjects, but when we do, it's all too easy to lose the bigger picture. The interaction with scientists from other fields can be hugely helpful and brings new ideas and approaches into play.

In your new job, you've suddenly found yourself in a leadership position. How do you find this?

This is a new situation for me, and I feel it's a great responsibility. As a scientist, I've already got several years' experience under my belt, but leading a group requires totally different skills. However, I am excited about taking on this new role and am interested in seeing how it unfolds over the next few years.

„Failure is a fixed and important part of a scientist's daily life."

Do you have any advice for young scientists?

In order to stay happy in research in the long term, you have to treat it like a hobby. This is important, because many of our ideas don't work straight away, and failure is a fixed and important part of a scientist's daily life. If you don't enjoy it 100%, it can become very frustrating. But if you enjoy it, it's undoubtedly the best job there is.

I would also advise potential PhD students to choose their host group very carefully. At the beginning, you're strongly dependent on the guidance and support of your colleagues and mentors, and in my experience, this phase sets the scene for the rest of the PhD, and ultimately your scientific career. A positive and stimulating environment is the key to successful research.

Christoph Zechner's SystemsX.ch project at a glance

Project title: Adaptive noise cancellation in synthetic biomolecular circuits

Fellow: Dr. Christoph Zechner, ETH Zurich

Host research group: Prof. Mustafa Khammash, Control Theory and Systems Biology Laboratory, ETH Zurich

Project duration: 2014–2016

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.

Membrane-based memory formation in bacteria

Bacteria in focus

Bacteria absorb nutrients through their membranes and are able to adapt to new food sources if their environment changes. Certain bacteria can do this very rapidly, others less so, and some not at all. Sometimes, these adaptations happen so quickly that scientists suspect the bacteria of having some sort of memory stored in their membranes. However, this memory capability must not necessarily be an advantage for these single-celled organisms.

Susan Schlegel is looking for evidence of bacteria's different memory strategies.

Bacteria live on our tongues, multiply to billions per square centimeter under our armpits, populate our foreheads in the millions, and with every handshake we exchange countless of these tiny organisms. It is estimated that we possess at least as many bacteria than there are cells in our own bodies, and that the number of those living just on our skin reaches into the billions. They are regarded as the oldest living things on earth, and it is thought that less than 5% of all bacteria have so far been identified or described. Even amongst these few, scientific research has only just scratched the surface. For Susan Schlegel, Transition Postdoc Fellow at the ETH Zurich and the Swiss Federal Institute of Aquatic Science and Technology (Eawag), this presents an exciting challenge. "Even the most simple bacteria can do unbelievable things. There is so much to discover!"

Membrane proteins form the research focus

Susan Schlegel is interested in *E. coli* bacteria, and particularly in their membrane proteins, which allow them to absorb nutrients. This topic formed a central part of her PhD thesis, which the biologist completed at the Center for Biomembrane Research at Stockholm University. Now Schlegel wants to investigate another aspect of these membrane proteins. She wants to analyze what happens to them when the bacteria are constantly confronted with new environments and therefore changing nutrients. The bacteria need to be able to adjust, otherwise they wouldn't be able to thrive. "Microorganisms have to constantly reorientate themselves. For example, our gut bacteria live on the nutrients that we provide, which change all the time."

Can bacteria have memory?

It is evident, however, that certain bacteria can adapt faster than others. What's especially interesting is that bacteria that have repeated contact with a particular nutrient are able to adapt their metabolism to it more quickly. But why? It is thought that when a bacterium comes into contact with a nutrient, a kind of signature is stored in its membrane. If bacteria are confronted with the same nutrient again, they react faster because they were already prepared for it. This signature is however not due to a change in the

genetic make-up of the bacteria, and is therefore "diluted" when cells divide, eventually disappearing completely. Some scientists describe this as history dependence, others as a memory.

"After I submitted my research proposal, an exciting study was published that showed that a bacterial population can store a memory of a nutrient," says Schlegel. Admittedly, this memory lasted for about 12 hours only. "But whereas this is a very short time for us, it is an eternity for bacteria, considering that some multiply via cell division every thirty minutes," explains Schlegel. "It is also clear that, although bacteria are part of a population, individuals can respond very differently, and not every cell responds to changes in its environment. My research therefore approaches memory from the perspective of a single bacterial cell."

Can memory have drawbacks as well as advantages?

With her research work, the scientist is aiming to pursue a number of questions. To what extent are changes in the cell membrane as a response to different nutrients detectable? How and under which conditions do the bacteria form a memory of nutrients? Are there perhaps several possible strategies for nutrient uptake in genetically identical organisms? Could memory even be a disadvantage in certain situations? Are the cells with memory able to proliferate faster in some cases, but those without, in other cases? The possibility of using different strategies could determine the success of a population. All very interesting questions.

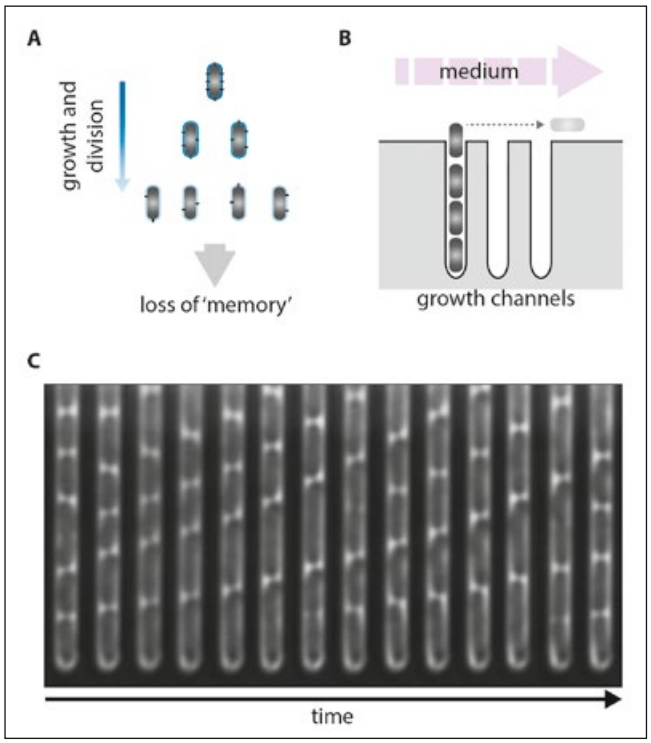
From single cells to populations

When Susan Schlegel was looking around for a postdoc opportunity after her PhD, she came across the work of Prof. Martin Ackermann at ETH Zurich/Eawag, which roused her curiosity. The group's projects were very diverse, and yet they all had one thing in common. "Their starting point is the single cell, from which they move on to look at the whole population; that was new and exciting to me," says the researcher. "In my previous work, I always started from the population perspective."

For Schlegel, statistical analysis and modeling is a very important aspect of her work. She is therefore glad that she is able to approach scientists who have the necessary theoretical background. "I am a very practical person and love working in the lab. I can carry out endless experiments and analysis, but I lack a background in modeling." She also appreciates her working environment at Eawag/ETH. "You can develop your research independently here, but you're also part of a team. That's not always a given."

Further research and experiments

Susan Schlegel would be very happy if she could demonstrate evidence for bacteria's different memory strategies. But for now, she's carrying on with her research and concentrating on finishing up her postdoc. "I've not got as far as I would like to, and would love to spend a bit more time on this project." Where the researcher will go next is still unclear. She aims to continue her research as a group leader in a laboratory. And of course, she will stay faithful to her bacteria; they continue to fascinate her, and there are still 'tons' of things to be learned.



A Memory of a nutrient could be stored as a signature in the bacterial membrane. As the bacteria grow and divide, this signature is diluted and eventually disappears, leading to a loss of memory.
B To observe single bacterial cells, they are grown in tiny channels under a microscope. The growth medium can be switched periodically, exposing bacteria to different nutrients. As the bacteria grow, the topmost cells will be pushed out of the growth channel. However, the cell at the very bottom remains and can be observed for several days.
C Montage of growing and dividing bacteria over time. Each channel represents a consecutive time point. Over time, the bacterial cells grow until they eventually divide and start again.

The project at a glance

Project title: Membrane-based memory formation in bacteria: scaling up from single-cell behavior to the dynamics of populations

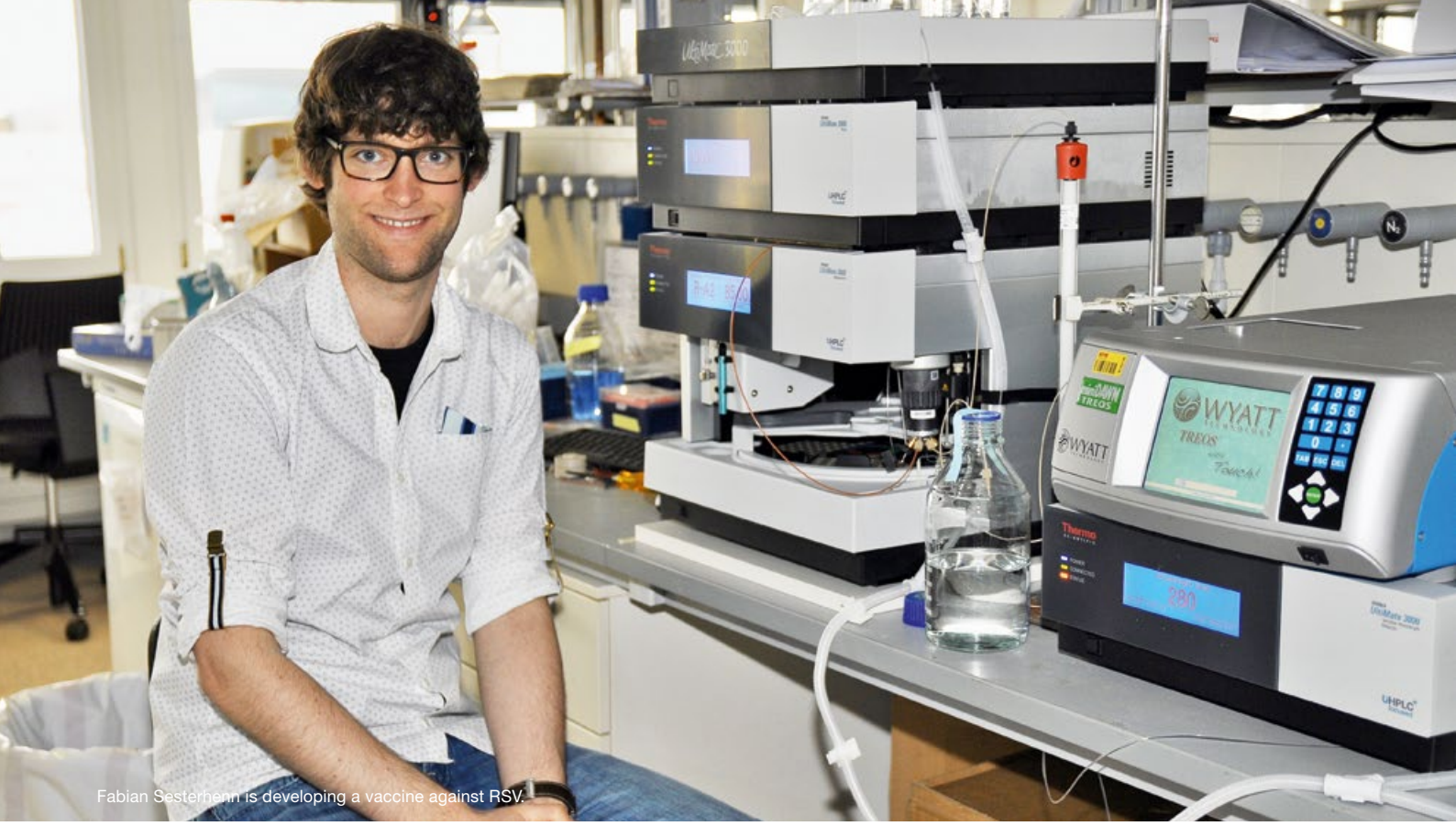
Fellow: Dr. Susan Schlegel

Host research group: Prof. Dr. Martin Ackermann, Department of Environmental Systems Sciences, ETH Zurich, and Department of Environmental Microbiology, Eawag

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.

Further reading: Lambert, G., and Kussell, E. (2014). Memory and Fitness Optimization of Bacteria Under Fluctuating Environments. *PloS Genetics* 10 (10): e1004793



Fabian Sesterhenn is developing a vaccine against RSV.

Epitope-focused vaccines

Giving the immune system a helping hand

Researchers at EPF Lausanne are developing synthetic vaccines to combat viruses that have so far been resistant to traditional vaccination strategies. Interdisciplinary PhD student Fabian Sesterhenn is working on helping the immune system produce effective antibodies. The initial vaccination trials in animal models have yielded promising results.

Vaccination is one of the most effective measures in the prevention of disease caused by infectious pathogens. But there are still many viruses for which effective vaccines don't exist. Examples of these include HIV, the Zika virus and the dengue virus. They trick the immune system and prevent the formation of potent antibodies. Fabian Sesterhenn, Interdisciplinary PhD student in Prof. Bruno Correia's group at EPFL and co-supervised by Prof. Sai Reddy at ETH Zurich, is trying to change this. He wants to give our immune systems a helping hand by showing them exactly where to target the viruses' weak spots.

The classical strategy for producing a vaccine is to first inactivate the virus or weaken it so much that it is no longer able to infect the host cells. The inactivated or attenuated virus is then injected into muscle tissue. The immune system recognizes this inactivated virus, triggering the production of many antibodies that bind to different sites on the virus's surface protein. The immune system saves this information, and with it is well equipped to tackle an active virus of the same type, should one enter the bloodstream at a later stage. "This is why vaccination is generally effective," Sesterhenn explains.

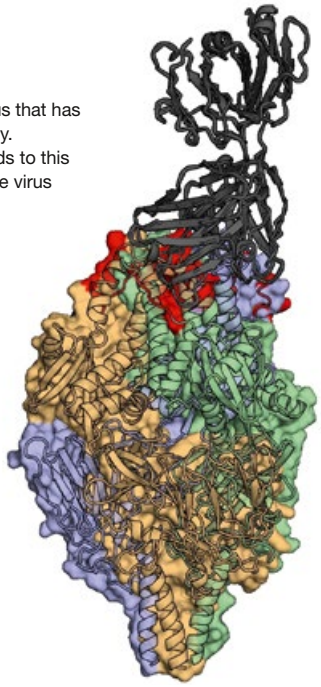
Amplification effect

"The problem is, this system unfortunately doesn't work for a whole range of diseases," explains the PhD student. "In these cases, the immune system just can't find the virus's weak spots. Worse, it can even be counterproductive." This phenomenon is known as the "disease enhancement effect". Doctors were made painfully aware of the effect in the 1960s when they used the classical method to produce a vaccine against the respiratory syncytial virus (RSV). This virus affects almost all children within the first two years of life and can cause severe airway problems.

The vaccine containing the inactivated virus was administered to children. However, instead of becoming immune, the children that were vaccinated developed much stronger symptoms of RSV when they later encountered a real RSV infection, compared to the nonvaccinated control group. Later, the researchers found out that the process of killing off the viruses caused changes in their surfaces, which led to the development of ineffective antibodies by the host. These impotent antibodies actually helped the active virus to infect the human cells, using mechanisms that are still poorly understood today.

Targeting the weak spots

A new type of vaccine, which Correia's group is working on, is called an "epitope-focused vaccine". The goal is for the immune system to only produce antibodies that can actually combat the virus. To this end, the researchers have to identify a virus's weak points. "The good thing is, other researchers have already done this for RSV," says Sesterhenn. "Now we just have to let the immune system know where they are."



Colored: the part of the virus that has to be visible for the antibody.
Gray: the antibody that binds to this fragment, thus rendering the virus harmless.

A particularly vulnerable region is for example the part of the virus which docks onto a host cell in order to infect it. These are small protein motifs that consist of roughly 25 amino acids. “These peptides could be easily produced in the lab,” says the researcher. In theory, the researchers could use this piece as a vaccine. “The problem is, it’s too small and is not perceived by the immune system as a threat,” Sesterhenn explains.

This is why he increases the size of this piece by grafting it on to a synthetically generated protein. This carrier protein, or scaffold, is created entirely on the computer. “We have a program that makes thousands of suggestions for how the carrier protein could look. On the one hand, it has to allow the virus’s docking site to be clearly visible, and on the other hand, it has to be stable.”

From computational model to mouse immunization

After several suitable scaffolds have been designed that effectively display the docking site, these proteins are produced in the lab. This is done by injecting the genetic information encoding the synthetic proteins into bacteria, which in turn produce the protein. At this point, it’s already clear which of the proposed proteins are unsuitable. “Some of the proteins degrade immediately because they’re unstable. Others even begin to disintegrate within the bacteria,” says Fabian Sesterhenn. “But after screening a few of the protein variants, we can easily identify the stable ones.”

In collaboration with Lucia Csepregi in Sai Reddy’s lab at ETH Zurich, Sesterhenn is working on vaccinating mice with the synthetic immunogens. Their immune systems immediately start to produce antibodies. “Some of these attack the carrier protein, but this doesn’t give rise to any negative effects, since the protein is synthetic and doesn’t resemble anything else in the body,” explains Sesterhenn.

Presented on a silver platter

Many of the antibodies target the virus segment. The immune system no longer has trouble recognizing it, since the virus’s vulnerable site is effectively presented on a silver platter. “After the mice have been immunized with the synthetic immunogens, we evaluate whether they actually created antibodies that can also recognize the native virus. If so, that usually means that one of the motifs successfully elicited antibodies against the vulnerable site on the virus, and these antibodies will be protective.”

Correia’s group has successfully immunized mice against RSV using one of these proteins. However, they still have a long way to go with this work. There are known to be two to three further weak spots on RSV, for which they also hope to develop synthetic immunogens. All of the effective proteins are to be administered together in a single vaccine. “In this way, we hope that the mouse will become completely immune to RSV infection,” says Sesterhenn. When the mouse trials are complete, the new vaccines will be tested on monkeys. If everything goes well, a human clinical study will be planned.

Unlimited potential

Correia’s team is not the only one developing new vaccines using this method. In the USA, scientists are working on a new vaccine for HIV, using molecules created on the computer screen. Another candidate for this method is the influenza virus, which triggers annual flu epidemics. “This virus changes every year, meaning you have to be vaccinated again and again,” says Sesterhenn. “However, there are sites on the surface of the virus that remain unchanged, where antibodies could dock and render the virus harmless. Unfortunately, these sites are difficult for the immune system to recognize.”

Researchers are hopeful that with the development of new vaccines, influenza and other severe viral diseases could become a thing of the past. If this new vaccination method works in humans without serious side effects, it would be a major breakthrough in the fight against viral infections of all kinds.

The project at a glance

Project title: A systems immunology-guided strategy for immunogen engineering

PhD student: Fabian Sesterhenn, Laboratory of Protein Design and Immunoengineering, Institute of Bioengineering, EPF Lausanne

Supervisors: Prof. Bruno E. Correia, Laboratory of Protein Design and Immunoengineering, Institute of Bioengineering, EPF Lausanne; Prof. Sai Reddy, Laboratory for Systems and Synthetic Immunology, Department of Biosystems Science and Engineering, ETH Zurich

Project duration: 2015–2017

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.

Further reading: Correia, B. E., et al. (2014). Proof of principle for epitope-focused vaccine design. *Nature 507 (7491):* 201–206.

Katy Pegg

Join us at the SystemsX.ch Conference in Zurich

The 3rd International SystemsX.ch Conference on Systems Biology will be the last major gathering of the SystemsX.ch community before the initiative comes to an end. This event will take place at ETH Zurich and will bring together Swiss and international systems biology researchers for four days of scientific exchange.

Following on from the previous two SystemsX.ch conferences, this third meeting will reflect the state-of-the-art in quantitative and systems approaches to the life sciences. The scientific themes cover multiple issues on a broad scale, from single molecules and cells to whole tissues and organisms. The conference is divided into five main foci:

- Synthetic biology
- Physics of living systems
- Single-cell biology
- Systems genomics
- Medical systems biology

Extensive fringe program

To kick-start the event, James Ferrell from Stanford University, USA, will give a keynote talk. This will be followed by the launch party for the new SystemsX.ch film, which is currently in production (see page 27). This will take place at the ETH Zurich's Dozentenfoyer, which offers stunning views over the city of Zurich. We will be showing the film throughout the party in the adjoining cupola of the ETH Zurich main building.

Participants will have the chance to visit Zoo Zurich on a guided tour of the Masoala Rainforest. In addition, we are organizing an informal conference dinner in the form of an open-air barbecue at the Hönggerberg campus after the day's talks on Wednesday, September 6. We hope to encourage as many participants as possible to attend, to foster networking and exchange between researchers.

The conference will conclude with the session on medical systems biology, with talks from eminent international researchers as well as scientists working in SystemsX.ch Medical Research and Development Projects. The event will be brought to a close with a keynote lecture by Chris Sander from the Dana-Farber Cancer Institute and Harvard Medical School, USA.

More information can be found on the conference website: **www.iscsb2017.com**

Call for abstracts

We would like to invite abstract submissions that broadly fall into one of the five categories, with the option to apply for a 10-minute talk at the conference. Those not wishing to give a talk are invited to present a poster in one of the dedicated poster sessions, with the chance to win one of the prestigious SystemsX.ch Best Poster Awards. **The deadline for abstracts is June 19.**

We look forward to welcoming you to Zurich for what promises to be a memorable conference!

Keynote speakers:

- James Ferrell, Stanford University, USA
- Chris Sander, Dana-Farber Cancer Institute, USA

International speakers:

- Ido Amit, Weizmann Institute of Science, Israel
- Martha Bulyk, Harvard Medical School, USA
- Peter Campbell, Sanger Institute, UK
- Raymond Goldstein, University of Cambridge, UK
- Eran Segal, Weizmann Institute of Science, Israel
- Sander Tans, FOM Institute AMOLF, Netherlands
- Barbara Treutlein, MPI Leipzig, Germany
- Kevin Verstrepen, KU Leuven, Belgium

SystemsX.ch speakers:

- Attila Becskei, University of Basel
- Damian Brunner, University of Zurich
- Manolis Dermitzakis, University of Geneva and SIB
- Zoltan Kutalik, University of Lausanne
- Matthias Lutolf, EPFL
- Karin Metzner, University Hospital Zurich
- Aleksandra Radenovic, EPFL
- Timm Schroeder, ETH Zurich
- Julia Vorholt, ETH Zurich

Film about SystemsX.ch

Over the years of the SystemsX.ch initiative, a great many interesting projects have been carried out. SystemsX.ch has decided to produce a documentary film to chronicle this wealth of research, which will be premiered at the 3rd International SystemsX.ch Conference in Zurich in September. Eavan Dorcey is overseeing the film project, in which a handful of very diverse projects will be portrayed, giving an overview of the Swiss Initiative in Systems Biology. The one-hour long film, written by the science journalist Barbara Gallavotti, is being filmed at several institutions.

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New national center for data science – Swiss Data Science Center

In February this year, ETH Zurich and EPF Lausanne launched a national center for data science. With the new data center, the two institutions want to ensure that Switzerland develops the necessary expertise to be globally competitive in data science. The importance of data science is gaining recognition worldwide as more and more scientific data is being generated. The problem is that many researchers and institutes lack the know-how necessary to deal with such large amounts of data. There is also often a divide between the researchers who generate data, computer scientists and data experts. The Swiss Data Science Center (SDSC) aims to help these different groups find a common language to facilitate effective communication between them.

Researchers at the center will be on hand to help solve everyday data-related problems, with particular emphasis on fields such as personalized health, environmental science and manufacturing. At the new center, which has locations in Zurich and Lausanne, a multidisciplinary team of 30 to 40 data specialists, computer scientists and experts from other fields will collaborate to provide assistance and online services, develop real-life applications and foster knowledge sharing.

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More information about the SDSC:
www.datascience.ch

Thank you, Heidi!

As SystemsX.ch is slowly phasing out, we must say goodbye to one of our collaborators. Heide Marie Hess joined the SystemsX.ch Management Office in March 2013. She was in charge of the "Training and Exchange" work package of the European Research Area Network ERASysAPP, and organized summer schools and educational events. She set up mobility programs and also elaborated a website for graduate programs in Europe. Since ERASysAPP ended last year, Heidi has been working on the SystemsX.ch impact analysis and prepared the final report. We wish to thank Heidi for her commitment to SystemsX.ch. It was a pleasure to work with you, Heidi!

vdm

SystemsX.ch at Scientifica

Scientifica, the Zurich Science Days, is organized by the University of Zurich and ETH Zurich and will take place from September 1–3, 2017. This year, the three-day event is devoted to the topic of "What data reveals", as nearly every branch of science is confronted with new possibilities in data processing. SystemsX.ch will be represented on a panel discussion, as well as through the documentary film about different SystemsX.ch projects.

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For more information:
www.scientifica.ch

3rd International SystemsX.ch Conference on Systems Biology

September 4 – 7, 2017
ETH Zurich, Switzerland

Keynote Speakers

James Ferrell Stanford, USA
Chris Sander Dana-Farber Institute, USA

International Speakers

Ido Amit Weizmann Institute, Israel
Martha Bulyk HMS, USA
Peter Campbell Sanger Institute, UK
Raymond Goldstein Cambridge, UK
Eran Segal Weizmann Institute, Israel
Sander Tans AMOLF, Netherlands
Barbara Treutlein MPI Leipzig, Germany
Kevin Verstrepen KU Leuven, Belgium
Aleksandra Walczak ENS, France

SUBMIT ABSTRACT

Deadline: June 19, 2017
http://www.iscsb2017.com

SystemsX.ch
The Swiss Initiative in Systems Biology

SystemsX.ch is funded by the Swiss Federation and evaluated by the SNSF.
Photo: Martin Oeggerli, supported by School of Life Sciences FHNW. Invasive Human Cancer Cell, Homo sapiens, Magnification: 4'500:1, www.micronaut.ch