X-Letter 26

Academia and industry

What are the prerequisites for successful collaboration?

Small things in a big way

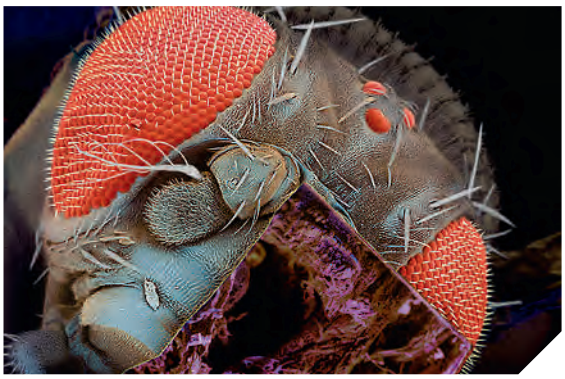
In the area of nanoanalysis, CINA is ahead of the rest

Minus 80 °C

The centerpiece of the new EvolutionX Transfer Project lies in a freezer

Contents

6



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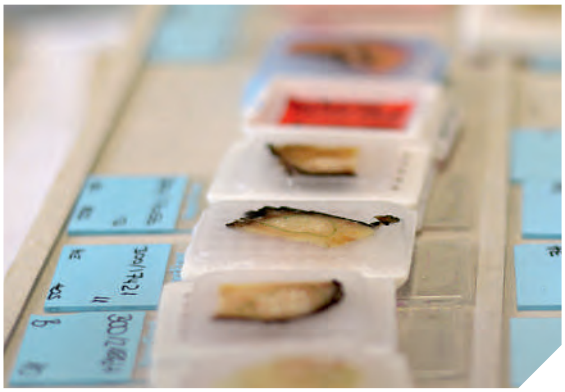

16

SystemsX.ch
The Swiss Initiative in Systems Biology

Cover: Henning Stahlberg (left) and Thomas Braun in front of the “Titan” electron microscope – CINA’s centerpiece. Photo: Heiner H. Schmitt Jr.

"Biology students are currently not sufficiently trained to use systems biology approaches."

As systems biology matures, we can observe that this field is increasingly becoming a valuable addition to the already existing strengths of a wide variety of biological sub-disciplines, going hand in hand with more classical research approaches in biology. A major measure of success of SystemsX.ch will be the fruitful integration of this domain in most biology research labs across Switzerland, and the acceptance of this field as a sub-discipline that scientists routinely use in parts of their projects.

One of the biggest challenges in this integration process will be to educate the new generation of biology researchers. Students are currently not trained well enough to use systems biology tools. Particularly the task of making them aware of the power of computation for analyzing data, mining datasets, and modeling and simulating biological systems will be essential. I specifically stress that this should be taught to biology students, and not only to students from other disciplines. Most importantly, students should be aware that this is an integrative part of the biology curriculum and a defining skill for becoming a successful researcher, no matter which sub-discipline they specialize in. Being able to program in Matlab or other computer languages will be as important as, and perhaps quickly more important than, being able to cast a gel and load a sample.

While SystemsX.ch cannot actively define curricula, I hope that the effect of systems biology integration and consolidation across biological sub-disciplines will add up to a redefinition of biology curricula. When SystemsX.ch comes to an end in 2016, this effect should be visible. Only then will we have secured a true integration and consolidation of systems biology approaches in Switzerland, and only then can we rest assured that our new generation will be well prepared to press ahead with this science.

Lucas Pelkmans
Chairman Scientific Executive Board (SEB)

Hans Widmer is actively seeking projects suitable for collaboration between academia and industry.

Hans Widmer, Novartis Institutes for BioMedical Research (NIBR)

Matthias Scholer

"We need champions"

At the Novartis Institutes for BioMedical Research (NIBR), Hans Widmer is in charge of the advancement of scientific exchange with universities. He is convinced that owing to an increased orientation towards medically relevant projects, SystemsX.ch will become more attractive for industry and that systems biology research as a whole will benefit from this situation.

With regard to potential collaborations, what type of academic research work are you interested in?

The main focus is on projects that contribute to the discovery of new drugs. This particularly includes research aimed at developing new technologies and methods leading to improved understanding of disease mechanisms and therapies.

How do you proceed? Do you search the Internet and publications using certain keywords?

We basically start with the scientific problems that arise in our projects. The best ideas usually come up during discussions. Every so often someone has knowledge of a relevant publication or, at a conference, hears of recent research that might contribute new impulses to active substance research. In this way, my colleagues and I collect ideas on how methods in systems biology might be applied to NIBR projects.

To what extent do arguments such as market size of a potential therapeutic agent influence your choices?

At NIBR, we concentrate on the medically most urgent drug discovery projects for which the understanding of the disease mechanisms is the highest. We pursue a scientific rather than a market-oriented approach. Our main duty is to prove the effectiveness of innovative therapies in the clinical context. We call this "proof of concept".

Is research in the university environment different from research in industry?

Oftentimes, the scientific questions we ask ourselves are not very different from the biological-chemical research performed in academia. The approaches are often very similar. The much cited cultural difference between academic and industrial research is hardly a topic these days. The difference much rather lies in the objectives. For an academic partner, scientific results and their publication are the primary aim, whereas for us they are a means to achieve our goals. When a hypothesis for a therapeutic approach proves wrong, we either modify the project based on these findings or abandon it, notwithstanding the fact that, from a scientific point of view, continued investigations would be of interest. In our view, this is not a failure but rather an opportunity to try something new.

Is it possible to reconcile the varying objectives of industry and academia?

Yes. A successful collaboration merely requires a sufficient overlap regarding the problems to be addressed. These need not be identical in all points. It is however essential to agree beforehand on the specific goals that one wishes to pursue together.

What else is required for a successful collaboration?

We basically believe that we need champions, professionally speaking as well as on the human level! We are always confronted with ambitious projects and problems often arise. It is only possible to overcome such situations providing the chemistry between all involved is right. The personal components are equally a very important factor. "Organically grown" collaborations work best. The partners must also be driven by scientific interest. A project should not create financial dependence or be viewed as work performed on order.

What are the benefits for an academic partner working with Novartis?

On the one hand, we provide our expertise as well as biologically relevant questions. Being focused on application and the development of new therapies, we can contribute experience and aspects which are equally relevant to basic research. This includes methods and materials, such as new active substances, which might not be available to the academic partner.

On the other hand, we can increase the significance of results by giving them broader support and by further developing them towards a clinical application.

Can you elaborate on this?

We can for example examine whether results obtained in connection with a particular disease model can be applied to other diseases, or whether results obtained in the test tube are also valid in higher systems. Ultimately, we want to understand diseases, starting at the molecular level and ending at the level of the entire human organism, and examine the significance of various patient genotypes. These questions are extremely interesting in the context of systems biology as well.

What course of action should academic scientists striving to collaborate with industry follow?

I recommend making use of personal networks or contacting someone like myself, a person involved in the promotion of collaborations with universities. Given the fact that we do not publish all our research work, personal contacts are an advantage. A conversation can also help identify a common objective.

To what extent is a national research initiative such as SystemsX.ch of interest to private companies?

Basically, such organizations offer access to a whole network of potential academic partners. The questions addressed in basic and applied research are increasingly complex. Therefore, interdisciplinary collaborations involving several different institutions are a necessity. And that is why it makes sense to bring together industry and academia. Single laboratories would be utterly unable to handle projects at this scale.

SystemsX.ch has managed to maintain the administrative obstacles linked to the submission of research proposals at a moderate level. Additionally, decisions are taken rapidly. These advantages for the participants increase the attractiveness of the initiative.

Should more such research initiatives instead of many individual projects be launched?

SystemsX.ch is certainly a forward-looking model. Nevertheless, such initiatives cannot replace individual national projects. But in both cases the same tactic is called for: collaborations between institutions and interdisciplinary research projects are the right way to go.

Even so, for SystemsX.ch the number of collaborations with industry is rather small after the first half …

In my view, this is due to the fact that during the first SystemsX.ch phase the focus was on the development of model systems and technologies. It is now possible to build on this, hence rendering the program more attractive for industry. But systems biology as a whole will also benefit, once new biomedical perspectives start setting the tone.

SystemsX.ch and Novartis – already four successful collaborations

Project title: Statistical Reverse Engineering of the Signaling Network involved in Cachexia

Applicants: Prof. Heinz Wolfgang Koeppl (ETHZ), Prof. Ruedi Aebersold (ETHZ)

Industry partner: Dr. Carsten Jacobi, Novartis Institutes for BioMedical Research

Duration: 2013–2015

Project title: System-wide Identification of Novel MALT1 Substrates

Applicant: Dr. Ulrich Auf dem Keller (ETHZ)

Industry partner: Dr. Samu Melkko, Novartis Institutes for BioMedical Research

Duration: 2012–2013

Project title: Development of Kinetic Models of RNA-dependent Silencing

Applicant: Prof. Mihaela Zavolan (UniBas)

Industry partner: Dr. Nicole Meisner, Novartis Institutes for BioMedical Research

Duration: 2011–2012

Project title: Rule-based Models for Drug-Target Identification: the TOR Pathway as a Case Study

Applicant: Dr. Heinz Wolfgang Koeppl (EPFL)

Industry partner: Dr. Peter Grass and Dr. Stefan Wetzel, Novartis Institutes for BioMedical Research

Duration: 2010–2011

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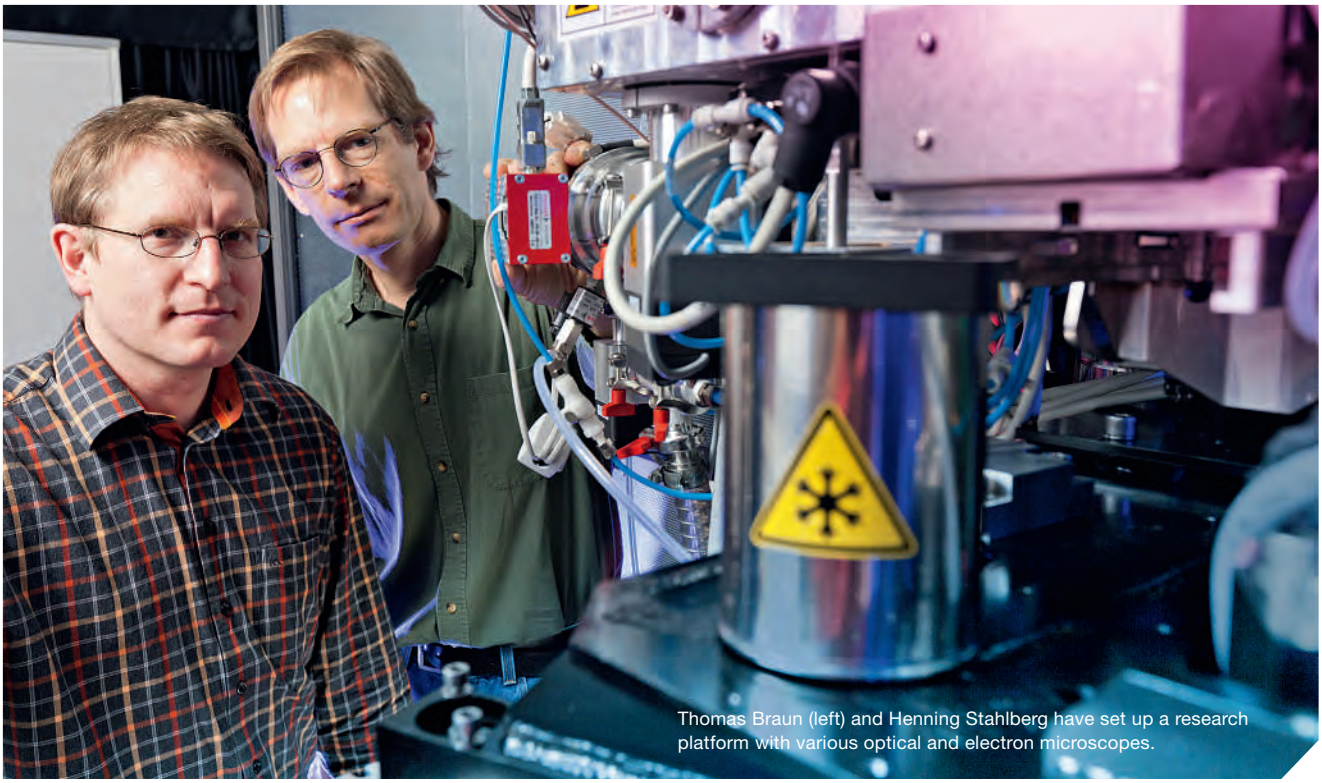
Matthias Scholer Heiner H. Schmitt Jr.

The CINA RTD Project

Small things in a big way

To date, many developments achieved by CINA have only been published in scientific journals. Yet the involved investigators are already willingly providing information regarding their innovations. And the research team need not fear competition: in the area of nanoanalysis they are ahead of the rest.



Thomas Braun (left) and Henning Stahlberg have set up a research platform with various optical and electron microscopes.

Time to descend into the basement: two floors down by elevator, along a neon-lit hallway and down a flight of stairs to where "Titan" stands in a darkened room. This giant is genuinely worthy of its name. Standing almost five meters tall, all other objects in the room seem tiny. "This is our highest resolution electron microscope", introduces Professor Stahlberg. The physicist opens Titan's double doors and reveals the giant's bowels: countless wires, blinking lights, tubes and pressure gauges. "This microscope is exclusively computer-controlled, allowing for best quality pictures, even in the nanometer range", explains Henning Stahlberg, adding that "Titan is CINA's centerpiece."

CINA stands for Cellular Imaging and NanoAnalytics, a large-scale project approved by SystemsX.ch in 2009. "Through this project, we strived to achieve two primary objectives: on the one hand the setting-up of a so-called 'Imaging Platform' and on the other hand the development of 'Visual Proteomics Technology'", explains Stahlberg, principal investigator for this RTD Project.

Research partner rather than service provider

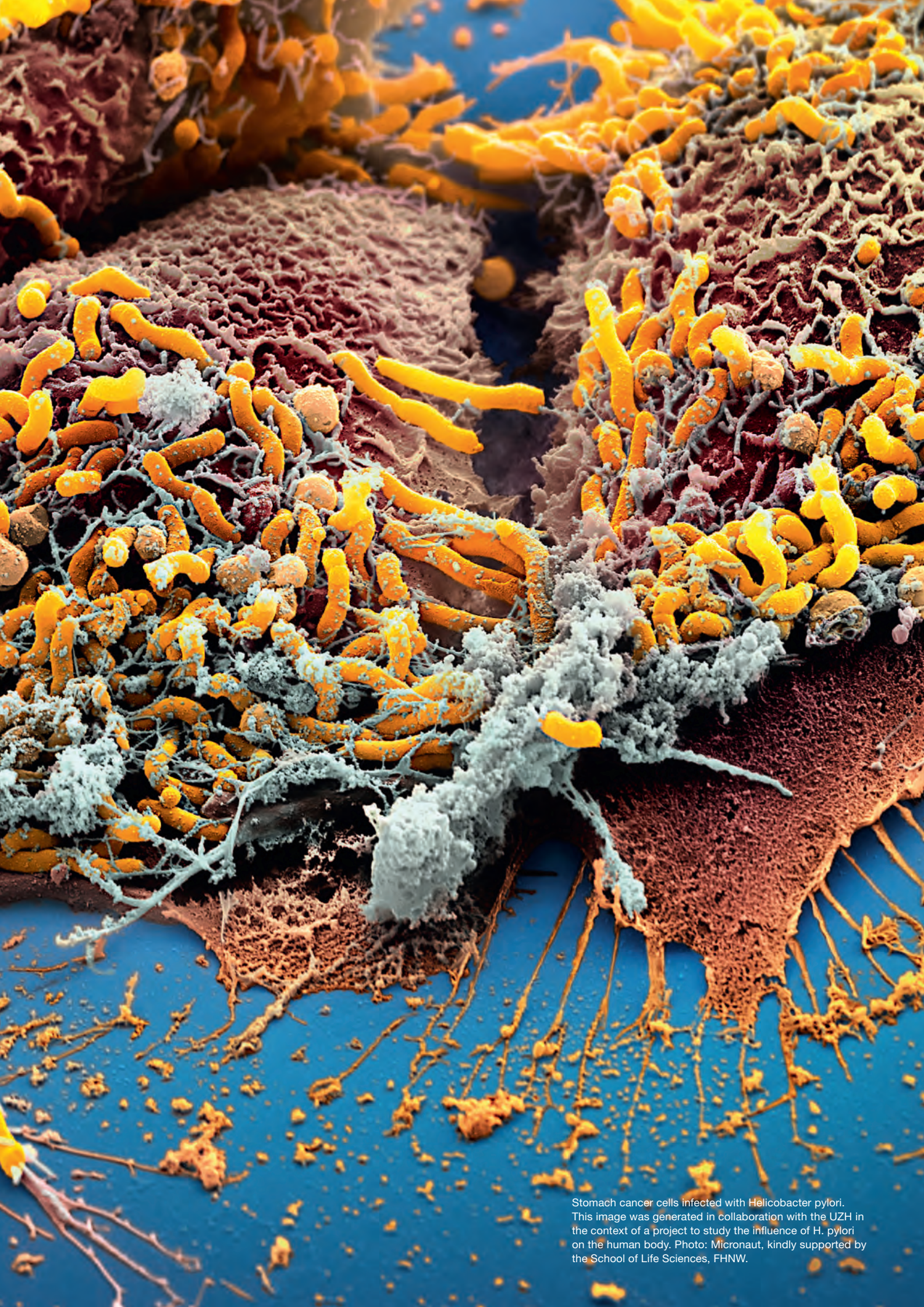
The "Imaging Platform" is a research platform uniting different types of optical and electron microscopes which allows scientists to produce two- and three-dimensional images of samples of various sizes. Basically any external research group can use the CINA platform. But Stahlberg emphasizes: "We are not a service provider. We perform research." For this reason, clear-cut conditions apply: "Collaboration is possible only if a project depends on high-resolution images or the generation of such images in another institution is not feasible within six months."

The utilization of the various instruments and the know-how of Stahlberg's team is then free of charge for the scientists. However, in return for this service, the results of the work are usually published jointly. The impressive number of collaborations and published papers show that this course of action is successful. In the past year, CINA researchers were listed as co-authors in a total of 31 publications. Ten more were added to this enumeration solely during the first two months of this year.

"Most of the collaborations are to be found in the systems biology field. Besides six SystemsX.ch RTD Projects, these include an increasing number of projects initiated by research divisions from private companies", says the scientist.

From science fiction to reality

The second CINA subproject is also running out in a few months, despite the fact that Henning Stahlberg had initially doubted its feasibility. "I must confess that when my predecessor, Andreas Engel, introduced me to the idea behind this project, I thought it



Stomach cancer cells infected with Helicobacter pylori. This image was generated in collaboration with the UZH in the context of a project to study the influence of H. pylori on the human body. Photo: Micronaut, kindly supported by the School of Life Sciences, FHNW.

was in the realm of science fiction and not realizable", remembers Professor Stahlberg. But within four years, this unconventional idea has turned into a functional method termed "Visual Proteomics Technology" which has mainly been promoted by Thomas Braun, the senior scientist in the CINA group.

Braun and his team have developed a groundbreaking method. Not only are these scientists capable of opening a cell in such a way that the tiny cell components survive the procedure unharmed. They can also prepare the cell content for visualization in record time and with hardly any loss.

Draw in, spit out

At the beginning of the process, a single cell is subjected to 1000 volts for a few microseconds. The membrane breaks up, leading to the spilling-out of the entire contents of the cell which are then immediately sucked up using an extremely fine needle. The machine then sends the material to be analyzed from workstation to workstation, stabilizing the proteins and adding dyes in the process. Finally, the entire cell contents are deposited in a snaking line on a grid.

Yet, the CINA scientists are already taking the procedure a step further. They now load the fine needle used to suck up the cell contents with antibodies, in order to pull specific macromolecules out of a sea of cell components. The researcher explains: "This not only allows us to visualize specific proteins in a single cell, but also to quantify them."

Speed and precision

It is wrong to think that minutes go by between the breaking-up of the cell membrane and the deposition of the cell contents on the grid. "Thomas Braun and his team have managed to connect the various steps in such a way that they are carried out within seconds. The specimens therefore remain accordingly fresh", says Henning Stahlberg. Owing to a special sample stage, incidentally partially financed by SystemsX.ch, the whole process is not only quick and precise. The ambient conditions, such as CO_2 concentration or temperature, can also be adapted and maintained, enabling the researchers to extract single live cells from cultures at given time intervals in order to analyze them (see illustration page 9). Thus, new application possibilities arise, such as the visual tracking of disease processes. Stahlberg and Braun give a specific example: "Nerve cells carrying a mutation for Parkinson's disease can be deposited next to cells free of this genetic alteration. It can then be observed whether, over time, the two cell types develop the modifications typical for this disorder." The appearance of the same alterations in cells not carrying the genetic modification would allow for conclusions regarding the infectious potential of Parkinson's disease.

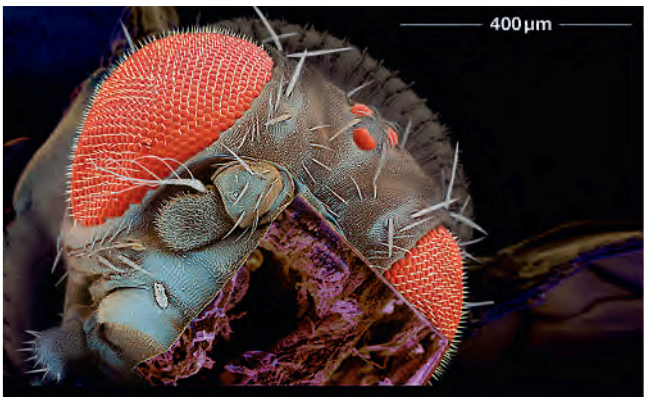
The efficacy of drugs can also be examined thanks to the CINA technologies. "When we measure the amount of a specific protein involved in a given disease before, during and after the application of a drug, we can say something about the efficacy of this medicinal product", explains the project leader.

National Geographic shows interest

Another CINA project combines science and art. During his postdoc at the University of Basel, Martin Oeggerli produced scanning electron microscope images of cancer cells. He then colored the originally black-and-white pictures on the computer. What began as a passion is today his main career track. He has received a number of awards for his work and enjoys worldwide media presence. For the production of the IMAX film "Mysteries of the Unseen World" by National Geographic, Oeggerli is now working with the CINA team and Professor Vetter's research group (University of Basel), not only to generate images of the microscopic world in unprecedented quality, but also to produce colored IMAX stereoscopic film sequences. The microscope provided by National Geographic makes it possible to cut open the bodies of the main protagonists such as flies, fleas, human cells or bacteria. The spectators can thus peer into the world of microscopic wonders.

In future, scientists in need of animated images within the scope of SystemsX.ch can also benefit from this technology.

More information on Martin Oeggerli and his work can be found at www.micronaut.ch.



Unexpected insight into the head of a fly. Photo: Micronaut and Kenneth Norman Goldie, C-CINA, 2013.

Collaborations with the pharmaceutical industry

Various joint projects with companies such as Roche, Novartis and Actelion show that the CINA developments are of interest to the pharmaceutical industry. Stahlberg's team notably entertains a lively exchange on different levels with Roche. For example, the company finances a postdoctoral fellowship in the field of Parkinson's disease, allowing for the specific encouragement of a young scientist's work over the next two years.

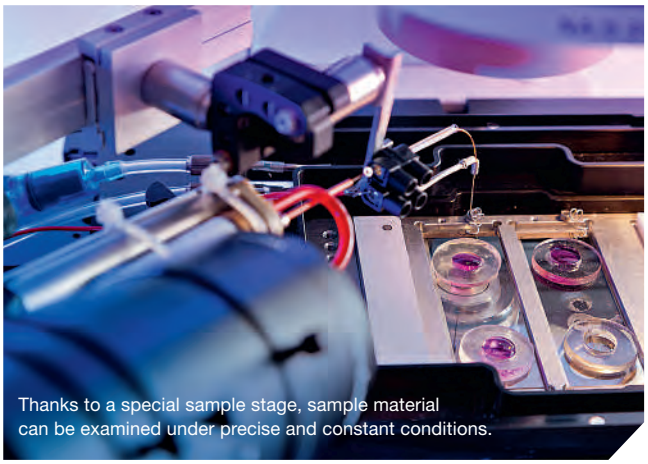
What's more: "Roche has also helped finance our Titan." The bulk of the 5.5 million Swiss francs came from the University of Basel, and SystemsX.ch funds also backed the project. But Roche equally contributed a considerable sum, amounting to approximately 1.2 million francs.

Does this tight financial connection not pose a risk of dependency or of being tempted to buy services through the back door? Henning Stahlberg answers: "No. In order to make progress in the area of systems biology, collaborations between institutions are essential. Thanks to our technology, we are in a position to offer ventures one-of-a-kind possibilities to study disease processes. In our own research, we, on the other hand, benefit from the know-how and infrastructure offered by our colleagues in the pharmaceutical field."

Applied research in the clinical field

CINA is coming to an end this fall. What will happen to all the developments and technical instruments? "In the context of the next SystemsX.ch call for proposals, we will submit a proposal for a new RTD Project", reveals Stahlberg while closing Titan's doors. "And in the future, we wish to promote applied research in the clinical field using the methods we have developed. An interdisciplinary team will focus on degenerative diseases such as Parkinson's or Alzheimer's disease."

But before the future begins, it is time to reemerge from the world of nanoparticles and enormous microscopes, at least for the time being.



Thanks to a special sample stage, sample material can be examined under precise and constant conditions.

CINA at a glance

Principal Investigator: Prof. Henning Stahlberg
Research groups:

- Prof. Henning Stahlberg, Biozentrum, University of Basel – Structural Biology
- Prof. Renato Zenobi, Laboratory of Organic Chemistry, ETH Zurich – Mass Spectrometry / Proteomics
- Prof. Andreas Hierlemann, D-BSSE, ETH Zurich – Microfluidics
- Prof. Horst Vogel, Laboratory of Physical Chemistry of Polymers and Membranes, SB, EPFL – Biophysics
- Prof. Uta Paszkowski, GRAMY, University of Lausanne – Plant Physiology
- Dr. Bernd Rinn, CISD, D-BSSE, ETH Zurich – Information Sciences and Databases
- Prof. Susan Gasser, FMI – Gene Silencing

Affiliated:

- Prof. Guy Cornelius, Biozentrum, University of Basel – Bacterial Secretion Systems
- Prof. Ari Helenius, Institute of Biochemistry, ETH Zurich – Virus/Cell Interaction
- Prof. Ruedi Aebersold, IMSB, ETH Zurich – Proteomics

Total budget (2009–2013): CHF 10.3 million, including CHF 4.06 million from SystemsX.ch

CINA
Cellular Imaging and Nanoanalytics

Since the beginning of this year, Lucas Pelkmans is the chairman of the Scientific Executive Board.

Conversation with Lucas Pelkmans

"Industry already greatly profits by SystemsX.ch"

Since the beginning of this year, the Scientific Executive Board (SEB) is chaired by Lucas Pelkmans. He is convinced that systems biology would not have established itself as rapidly in Switzerland without SystemsX.ch. But now is not the time to rest on one's laurels. Much remains to be done.

What appeals to you in your position as chairman of the SEB?

I have been involved in SystemsX.ch projects since the very beginning of the initiative. Systems biology and quantitative cell biology are vital to my research. Therefore, it is important to me that this sector of biological research be well represented and promoted in Switzerland.

In its first phase, SystemsX.ch managed to successfully establish systems biology research. As a result, several junior scientists working mainly with systems biology methods have already begun establishing their own research groups. This change of structure now needs to be expanded and reinforced. In this respect, the SEB has the means to make a difference, and taking on an active role in this context appeals to me.

Your predecessor, Ruedi Aebersold, was a very experienced chairman. As a young scientist, how are you going about this task?

Ruedi Aebersold achieved amazing results. It is truly a challenge to follow in his footsteps. My career as a scientist is indeed shorter, but systems biology has long been a central element of my work. In my situation, as is also true for many other young scientists, systems biology has become an inherent part of research. I think this is a good prerequisite for my participation on the SEB.

What are the goals of the Executive Board during the second phase?

Within the next four years, systems biology should establish itself more firmly in Swiss universities and become an integral part of biological research. We also wish to reinforce collaboration with industry. For this reason, the SystemsX.ch projects of this second phase are more strongly focused on medical relevance.

How can systems biology contribute to medical research?

In the last ten years, systems biology has greatly contributed to the development of molecular and cell biology. I hope the same will soon be true for medical research. Quantitative measurements and high data quality are the key factors required for this to happen. Methods such as "high-throughput-imaging of single cells and quantitative image analysis" yield huge amounts of data, also highly relevant for medical research. Thanks to systems biology, it is possible to pull together these results.

Christa Smith Matthias Scholer

I also see great potential in the application of systems biology research to patients' tissue samples. Most of the important research results in the field of systems biology are based on model organisms such as yeast cells, bacteria or laboratory cell lines. From the technical point of view, we are today in a position to apply this research to patients' cells. I hope this will lead to new, fundamental discoveries of importance for the medical field.

Collaborations with industry are also a focus of the second phase. Why have only a small number of smaller collaborations been established until now?

That is a difficult question to answer. Probably, systems biology was still too busy dealing with the basics, the development of methods and the manner in which such research needs to be performed. For the past ten years, systems biology has been a fledgling science, and that is why it has been of little interest to industry. The specific encouragement of medically relevant projects will hopefully change this situation.

This of course also calls for an appropriate commitment on the part of the private sector. Thanks to the training of our young scientists, industry already greatly profits by SystemsX.ch. The pharmaceutical industry, for instance, is specifically looking for specialists in this forward-looking field.

Outstanding research is supposedly only performed in university environments, where, as opposed to the situation to be found in the private sector, the pressure to succeed is smaller and tight deadlines are less frequent …

I do not think this is always true. Some privately financed institutes that are part of a large company perform research at the highest level. But truly basic and novel discoveries are more likely to be made in the academic environment, provided the financial resources are available and the scientists are free to perform the relevant basic research. Maybe that is where this statement comes from.

SystemsX.ch is unique in Switzerland. Are there other such initiatives worldwide?

If one considers only the invested amount, which comes to approximately 400 million Swiss francs, similar initiatives are to be found in Great Britain, Germany and the United States. However, most of the comparable initiatives concentrate on a very narrow scientific theme or on a specific technology. A good example is the "1000 Genomes Project".

The fact that the initiative is not focused on a specific subject is what makes SystemsX.ch one-of-a-kind. It promotes a discipline as a whole and therefore advances a comprehensive basic research field.

SystemsX.ch will come to an end after this phase. How will Switzerland benefit from this research initiative in the long run?

Mainly thanks to the establishment of research groups in which systems biology is the primary research method. One can of course put forward the argument that this might also have been possible without SystemsX.ch. But I am convinced that in the absence of the SystemsX.ch initiative, systems biology and the "quantitative mode of thinking" in molecular and cell biology would not have gained importance as rapidly and to such an extent in Swiss universities. Now is the time to build on this momentum and to anchor this change in structure.

Which basic conditions need to be fulfilled for this to happen?

The future of systems biology research lies in computer-assisted analyses, simulations and the prediction of biological processes. This in turn calls for large quantities of high-quality data. Today, the IT infrastructure needed to process this information is mainly provided by SystemsX.ch. We must ensure that universities now continue to develop and strongly improve the appropriate infrastructure on their own. Otherwise, many research projects will come to a standstill once SystemsX.ch expires.

"I am concerned by the fact that the IT infrastructure in universities is often more outdated than in private homes."

There is a need for action in many universities, particularly with regard to the IT infrastructure. If one considers the University of Zurich, for instance, most of the floors in the buildings are fitted with an outdated rather than a fiber optic cable network. Many private households are better equipped. I am concerned by the fact that in the IT sector of all sectors the infrastructure in universities is often more outdated than in private homes. In the long run, only appropriate infrastructure will allow us to remain among the leaders in the area of systems biology research.

Mark D. Robinson, University of Zurich

Bioconductor draws the masses

Not just a statistical success

Last December, SystemsX.ch supported the yearly "Bioconductor" users' meeting in Zurich. Bioconductor, a free software add-on, contains several hundred modules used worldwide by scientists for the compilation of statistics. The surprisingly high participants numbers reveal that this development is also highly appreciated by systems biologists.

Bioconductor is now a worldwide platform for making computational and statistical tools available to the masses. In essence, Bioconductor packages are modules that extend the capabilities of the very popular and free "R" statistical programming language. Bioconductor started at the time of the explosion in the use of DNA microarrays. The number of available tools has grown steadily in many directions, such as proteomics, image processing, qPCR data, flow cytometry data and, notably, much of the new infrastructure has been developed for high-throughput sequencing data. Currently, more than 600 software packages are available, in addition to many annotation packages (e.g. genome and transcriptome annotation, platform design, gene ontology information).

Unexpectedly high number of participants in Zurich

Every year, European Bioconductor users and contributors convene for the annual European Developers' meeting, which complements the annual Developers' meeting at Bioconductor's headquarters in Seattle (Fred Hutchinson Cancer Research Center). In 2012, the European meeting took place in Zurich. The Institute of Molecular Life Sciences generously provided a seminar room and space for coffee breaks and lunches. Historically, no registration fee is charged for this meeting and thanks to the support of SystemsX.ch and other organizations we were able to maintain this tradition. We budgeted for 40 participants and to our surprise, more than 70 delegates registered. Clearly, the Bioconductor community is growing strongly!

Flashlight sessions for "young Bioconductors"

The goal of the meeting was to achieve a mixture of science and development. Many renowned guests and speakers from the USA and Europe gave updates on new methods and infrastructure developments, as well as tutorials on creating software packages in Bioconductor. Altogether, approximately 40 speakers were invited to the two-day meeting.

Talks covered the wide range of applications that Bioconductor is known for, including microarray analysis, next generation sequencing and proteomic data. Many were presented by PhD students and postdocs in flashlight sessions (ten-minute talks with only five to ten slides), thus giving these "young Bioconductors" the opportunity to highlight a new method, package or application.

My personal highlights were, among many others, the "Gviz" package, a flexible tool for plotting data along the genome, the in-depth discussion about current RNA-sequencing counting procedures and the talk highlighting the interface of "R" with Google Maps.

For those who missed the meeting, most of the talks are now available on the Bioconductor website (see link below).

Bioconductor
OPEN SOURCE SOFTWARE FOR BIOINFORMATICS

Information on Bioconductor
www.bioconductor.org

Bioconductor European Developers' Workshop 2012 Presentations
www.bioconductor.org/help/course-materials/2012/BiocEurope2012/

The R Project for Statistical Computing
www.r-project.org

Projects in the second SystemsX.ch phase will focus more strongly on the application of research results to medicine.

Christa Smith Frederike Asaël

8th Call for Proposals

Last opportunity to submit an RTD Project

With the eighth call for proposals, the SystemsX.ch research initiative is on the lookout for new "Research, Technology and Development Projects" (RTDs) as well as "Transfer Projects". Within the next four years, the initiative will invest a total of 30 million Swiss francs in these research projects.

At the beginning of February, SystemsX.ch published the eighth call for proposals. Researchers can submit proposals for an RTD or a Transfer Project until June 30, 2013. This is the last call for RTD Projects. Proposals will be reviewed by the Swiss National Science Foundation in fall. Thereafter, the chosen projects will be funded by SystemsX.ch during four years; hence until the research initiative comes to an end.

New focus for RTD Projects

For the second SystemsX.ch phase, the project focus was adapted: scientists are requested to increase the integration of quantitative biology and the corresponding theory and model developments in their RTD Projects. Additionally, SystemsX.ch is particularly interested in projects that focus more strongly on medically relevant themes and ideally also involve hospitals or private companies in the research. Through this focus chosen for the second phase, the initiative aims to provide for the future of systems biology research in Switzerland on the one hand, and to promote collaborations with industry, SMEs and spin-off companies, on the other hand.

Lean structures

Approximately three-quarters of all SystemsX.ch funds go into the RTD Projects. Since the beginning of the initiative, approximately 107 million Swiss francs have been invested in 25 large projects. Would it have been more appropriate to support many small research projects? No, says Daniel Vonder Mühll, the managing director of SystemsX.ch. "A comparably sized research initiative bringing together scientists from various fields has never before existed in Switzerland. Yet, this interdisciplinary cooperation is the sine qua non for systems biology research. These RTD Projects create the necessary framework."

During the first SystemsX.ch phase, up to twenty different research groups could be involved in a single RTD Project. Each large-scale project was supported with up to 10 million Swiss francs during five years. For the second phase, the call is for consortia of approximately three to eight research groups. "We are seeking leaner structures so as to keep the expenses caused by coordination tasks as low as possible. For this reason, a moderate number of teams in complementary disciplines are to work together", explains Daniel Vonder Mühll.

Scientists from abroad are also invited to join a consortium. However, SystemsX.ch funds are only allocated to teams working in Swiss public institutions.

Collaborations between academia, industry and the clinical field

In the second category, called "Transfer Projects", SystemsX.ch intends to encourage cooperation between universities and the private sector (industry, SMEs, spin-offs and hospitals). A precondition is the involvement of at least one partner from each sector. Approved projects will generally receive funds for two years. If successful, funding can however be extended by an additional year.

Overview of the project categories in the 8th call:

RTD Project

Research, Technology and Development Project lasting four years.

Transfer Project

Research collaboration between academia and the private sector. Duration of the project: up to two years, with an optional one-year extension.

More information on the eighth SystemsX.ch call can be found at
www.systemsx.ch › SystemsX.ch › Calls for Proposals

StoNets RTD Project

Crunching numbers to decode biological processes

So many steps can go awry to disrupt a biological process and lead to errors. The StoNets project aims to determine how cells deal with disruptive factors and maintain stability. It combines experimental data with theory and mathematical models.

Mihaela Zavolan, professor for Computational & Systems Biology at the Biozentrum of the University of Basel, is in charge of the new StoNets RTD Project.

Whether we are trudging through the bitter cold or sitting on a sofa in a warm room – in both situations our skin cells function normally. “In a way, this is astonishing”, points out Mihaela Zavolan from the Biozentrum in Basel. Temperature has a direct influence on the processes that take place within cells. For instance, when a gene is read and transcribed into so-called mRNA, the latter takes on a different three-dimensional structure depending on the temperature. Yet, despite such changes at the molecular level, the cell as a whole manages to remain stable.

“There must be mechanisms capable of dealing with the fluctuations and preserving stability”, explains Zavolan, for there are other disruptive factors, besides temperature. Every biological process comprises a large number of steps, involving numerous molecules which need to be in the right place at the right time. There are many ways things can go awry, leading the process down a completely different track. “This is not like a maze, in which there is only one entrance and one exit”, emphasizes Zavolan.

A tiny molecule of great significance

In the StoNets RTD Project, Mihaela Zavolan aims to study the extent of the influence of disruptive factors on various biological processes and how cells deal with such situations and maintain stability.

In one of the sub-projects, the research team will closely examine the function of so-called microRNAs. These tiny molecules control the length of time an mRNA persists in a cell and consequently how often its information is translated into a protein. “MicroRNAs play a central role in controlling processes such as cell division and differentiation”, explains Mihaela Zavolan.

“Computer models help us understand biological processes that are extremely complex.”

It is not known how microRNA and mRNA find each other, what precise consequences the interaction has and or how the interplay of these molecules varies under the influence of temperature fluctuations and other factors. This is one of several biological processes that the StoNets team plans on studying during the next four years.

Different disciplines, one goal

Within the StoNets project, molecular biologists and biochemists will work closely with computer scientists and mathematicians. “The development of theories and the mathemat-

Martina Huber Matthias Scholer

ical models based on experimental data that we obtain in our labs play a central role in our work", explains Zavolan.

Interdisciplinarity begins with the project leader. Mihaela Zavolan first studied medicine. "But I quickly realized that, as a physician, I would only observe and interpret symptoms in order to treat patients. Yet I wanted to understand the causes of diseases", the scientist tells us. This is why she studied computer science after obtaining her degree in medicine. Ever since, she has strived to understand biological processes by expressing them in numbers and formulas and by developing models. "Many biological processes are so complex that we are unable to understand them without the help of computer models."

From experiment to theory

Nevertheless, computer calculations cannot replace experiments in the laboratory. Quite the opposite: a good model requires a considerable amount of accurate data. Based on this information, one can then develop a hypothesis and formulate mathematical models that will describe the relation between the various components of a biological process. "As soon as we have developed a model, we can specifically vary different values and determine how these modifications affect the process", explains the scientist. Subsequently, an experiment is performed to determine whether the behavior in the model coincides with that observed in the test tube.

"There is a brisk back-and-forth between experiment and theory, and accordingly also between scientists working in different fields", says Zavolan. When she took up her professorship at the Biozentrum in Basel, she was forced to fall back on data from other research groups for her models. But since four years she has her own small laboratory and a team of technicians and biologists. "Now we can coordinate experiments and models much more efficiently", adds a pleased Mihaela Zavolan.

Quantifying biology

According to Zavolan, molecular biology has long been a purely descriptive science, unlike physics and chemistry, fields that have since their beginnings combined theory and experiments. The reason for this is that "in chemistry, processes involving a small number of different molecules interacting with each other are typically studied." A biological system such as a cell, on the other hand, often includes up to 100,000 different molecules, most of which are only present in very small quantities.

"There is a brisk back-and-forth between experiment and theory, and accordingly also between scientists working in different fields."

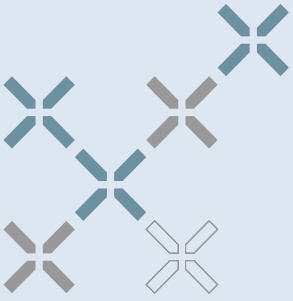
Many experiments are therefore, in a first step, aimed at determining whether or not a specific molecule is involved in a given process. Once it is known which molecule is present at which stage and in which concentration in a cell, it is possible to investigate its role in a given process thanks to mathematical models. Zavolan is convinced that "these models will allow us to take biology to a new level, turning this field into a quantitative science."

StoNets at a glance

Principal Investigator: Prof. Mihaela Zavolan
Research groups:

- Prof. Mihaela Zavolan, Biozentrum, University of Basel – Computational RNA biology
- Prof. Felix Naef, EPF Lausanne – Computational systems biology
- Prof. Erik van Nimwegen, Biozentrum, University of Basel – Computational modeling of regulatory networks
- Prof. David Gatfield, University of Lausanne – RNA biology
- Prof. Attila Becskei, Biozentrum, University of Basel – Systems biology of regulatory circuits
- Prof. Matthias Lutolf, EPF Lausanne – Stem cell bioengineering

Total budget (2013–2016): CHF 6.2 million, including CHF 3 million from SystemsX.ch



StoNets
Controlling and Exploiting Stochasticity in Gene Regulatory Networks

Marc Creus preserves the bacteria at –80 °C in a freezer.

EvolutionX Transfer Project

Giving luck a helping hand

In universities, scientists hope to publish their results in renowned journals. Companies, on the other hand, strive to protect their inventions. Despite these diverging preconditions, both parties can benefit from collaboration. Marc Creus, the biochemist who lined up the EvolutionX Transfer Project, tells us why and reveals how he found his partner in industry.

A chance encounter was the starting point for the EvolutionX Transfer Project. Last summer, the biochemist Marc Creus was invited to a symposium. During the dinner that followed, he struck up a conversation with Laurenz Kellenberger, the chief scientific officer at Basilea Pharmaceutica International Ltd.

Very rapidly, Creus realized that he and Kellenberger share various research interests. Basilea had just developed a novel antibiotic that is highly effective against Gram-negative bacteria. It is particularly also effective against bacteria resistant to carbapenem antibiotics. A combination of different characteristics brought about this feature: for example, the bacteria respond to the antibiotic more easily because the latter is linked to molecules that are similar to the ones the bacteria use to assimilate iron and other metals. In this way, the active substance employs a natural transport mechanism as a “Trojan horse”. Marc Creus, who studies the interactions of bacteria and other organisms with metals in the Department of Chemistry at the University of Basel, was immediately very interested in this approach.

After discovering that SystemsX.ch now has a new “Transfer Project” category which promotes cooperation between universities and industry, Creus seized the opportunity. He contacted the chief scientific officer at Basilea and shortly thereafter they met to develop a joint project idea – EvolutionX was born.

Planning is important

“I came well prepared to this meeting”, remembers Creus. To this end, he had studied the Basilea publications very carefully. These showed him, on the one hand, that the company is basically open to the publication of their results in the specialized press; an important criterion for Creus: “We scientists working at universities need to publish.”

On the other hand, his reading revealed the core research areas and competences of Basilea as well as the way in which his own team might complement their work. “I realized that the company does not only aim to develop and sell a product, but is also interested in understanding the mode of operation and action of their antibiotic down to the last detail”, says Creus. This includes elucidating how exactly bacteria react to the treatment and why resistances to this substance develop slowly.

Martina Huber Matthias Scholer

This is where Creus sees large potential for a joint project, for he and his team are very experienced in examining, on the molecular level, how bacteria undergo modifications and adapt to inhospitable conditions.

"We submit the microorganisms to various disruptive factors in the laboratory, collect samples of the bacteria at regular intervals and store these in a freezer", summarizes Creus. At –80 °C, the development of the bacteria comes to an immediate stop. "The microorganisms are not killed in the process. They are preserved and can be brought back to life at any given time", explains Creus. In this way, the scientists establish an archive comprising countless generations of bacteria to which they can resort as soon as the microorganisms exhibit a new behavior. Creus says: "We can compare these bacteria to their archived predecessors and find out which mutations in the genome triggered the change in behavior."

Both sides benefit

In the context of the EvolutionX project and by means of this method, one of Marc Creus' postdocs will study how bacteria react to the new Basilea antibiotic under various conditions and what mechanisms are involved. "In absence of an industrial partner, such a project would not be feasible", emphasizes Creus. Basilea not only provides the antibiotic, the bacterial strains and a lot of experience. The company also contributes part of the funds as well as essential infrastructure: safety laboratories, in which even dangerous strains of bacteria can be studied, as well as experienced personnel that will give the postdoc the needed assistance.

The scientists assume that the bacteria will manage to survive the new active substance in the laboratory tests. Experience shows that "even in the presence of the best antibiotic, the germs end up finding a way to protect themselves." The EvolutionX project will hopefully reveal the conditions under which this happens, as well as how to keep the risk of resistance development to a minimum. This knowledge, in turn, will help the industrial partner to determine the ideal dosage and the treatment duration for the drug.

Addressing conflicts of interest early on

"Both sides truly benefit from this project", says Creus. At the same time, he is aware of the fact that collaboration with an industry partner brings about certain restrictions for him and his team. "I too worked in industry for a while and I know that in this particular environment time and funds are put to use in a much more focused way than is the case in an academic context", says Creus. In an enterprise, it is not possible to endlessly work overtime or explore questions that arise once research has begun. Creus admonishes: "When working with an industrial partner, one has to stick to the focus agreed upon. The researchers in universities need to be aware of this."

The EvolutionX centerpiece: the scientists are establishing a comprehensive bacterial archive.

It is equally important to address conflicts of interest between university and industry partners early on, and to determine by contract who can publish in which journal and how the intellectual property rights are to be handled. According to Creus, "it is very wise of SystemsX.ch to have set this as a prerequisite."

In order for a scientist to find an appropriate industrial partner, a bit of luck as well as a certain openness are a must. "It is a bit like dating", says Creus. If the idea you have of the woman of your dreams is too fixed, you will never find her. And staying at home will make it difficult to meet her. So here is Creus' advice to all researchers hoping to initiate a Transfer Project: "Keep your eyes open at conventions, conferences and other happenings and engage other people in conversation, for not everything can be planned. But it is possible to give luck a helping hand."

EvolutionX at a glance

Project title: EvolutionX – Analysing Evolution of Adaptation to a Novel Siderophore Antibiotic in Gram-negative Bacteria by Next Generation Sequencing

Applicant: Dr. Marc Creus, University of Basel

Industrial partner: Basilea Pharmaceutica International Ltd.

Duration: 2013–2015

Project type: Transfer Project

This year's Summer School partner: the CRG in Barcelona.

Christa Smith CRG

Modeling for Systems Biology

Summer School 2013 in Spain

The "Centre for Genomic Regulation" and SystemsX.ch are jointly holding this year's Summer School in Barcelona, Spain. The one week "Modeling for Systems Biology" class will be held from June 9–14 and will be supported by the newly founded "ERASysAPP" European network.

In the "Centre for Genomic Regulation (CRG)", SystemsX.ch has found a renowned research centre as an organizational partner for the Summer School 2013. The 24 participants can expect an attractive program focused on dynamic network modeling. But also the vicinity to the beach should contribute to making this year's Summer School an exciting educational event.

A mix of theory and practical exercises

The program includes lectures on basic methods as well as new techniques in systems biology research. The theoretical part will be combined with hands-on sessions during which the participants can apply and practice what they have learned. Teachers from Spain and abroad will impart their knowledge and address practical problems with the PhD and post-doctoral students.

The teachers for Summer School 2013 were chosen by the CRG and the SystemsX.ch Scientific Executive Board (see box). The selection process not only aimed to win over experienced scientists for the course. An important criterion was equally their ability to convey the subject matters on the applied level.

First Summer School supported by ERASysAPP

Since 2013, SystemsX.ch is a partner of the new European "ERASysAPP" (ERA Systems Biology Applications) network. Within this network, SystemsX.ch is responsible for "Training and Exchange" matters. Summer School 2013 is the first in a series of educational events to be organized by SystemsX.ch in collaboration with network partners: a yearly one-week Summer School on a concrete scientific theme related to a systems biologist's everyday research is planned. The course is to be organized every year in collaboration with a different European ERASysAPP partner from abroad.

Teaching team for Summer School 2013

- Fernando Amat, Janelia Farm Research Campus, Ashburn, USA
- Nicolas Buchler, Duke University, Durham, USA
- Kai Dierkes, CRG, Barcelona, Spain
- Dagmar Iber, ETH Zurich, Basel, Switzerland
- Andreea Munteanu, CRG, Barcelona, Spain
- Jordi Garcia-Ojalvo, UPF, Barcelona, Spain
- Theodore Perkins, OHRI, Ottawa, Canada

Information concerning the SystemsX.ch Summer Schools can be found at **www.systemsx.ch › Events › Educational Events**

Matthias Scholer

Finding innovative results and taking them into the market

Michael Dillhyon assists future young entrepreneurs.

An important domain SystemsX.ch wants to promote is that of public-private partnership. In 2013, SystemsX.ch has therefore launched a pilot project that identifies innovative results of SystemsX.ch projects that are worth evaluating and urging towards the market.

Entrepreneur in Residence

At the beginning of this year, SystemsX.ch mandated Michael Dillhyon in the role of "Entrepreneur in Residence (EiR)" to search out promising innovative findings and provide experienced entrepreneurial know-how to the research groups on how to approach the market in an efficient manner. Particular emphasis will be placed on identifying potential young entrepreneurs amongst the researchers and to give them support in collaboration with complementary organizations.

Entrepreneurial know-how

In today's competitive markets, the capital cost of bringing a technology onto the world stage is closely linked to the ability to efficiently satisfy demand. This is why Michael Dillhyon is particularly interested in findings that provide a novel approach to a customer's need. "I am looking for technologies which have a meaningful unique selling proposition, a significant market opportunity and are highly scalable", explains the entrepreneur.

Once Dillhyon has found innovative results that meet the criteria for marketability, his goal is to work with the team to build a sustainable growth strategy. "This strategy may include business planning, but more likely will be comprised of creating advanced channel relationships for efficient selling, a suitable marketing strategy and a potential funding scenario", specifies the Entrepreneur in Residence.

Participation of ETHZ, PSI and UZH

Currently, the ETH Zurich, the Paul Scherrer Institute (PSI) and the University of Zurich (UZH) are involved in the pilot project. However, all interested SystemsX.ch partner institutions are welcome to benefit from the service of the Entrepreneur in Residence. One important condition is that the service of the Entrepreneur in Residence is only provided where the institution's management, the respective technology transfer office and the researcher are in agreement.

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Entrepreneur in Residence at a glance

Complementary to the tasks of and in close collaboration with the transfer technology offices of the partner institutions, SystemsX.ch offers the following assistance:

- finding potentially exploitable results in SystemsX.ch projects
- supporting the scientists and corresponding technology transfer offices to bring innovative results close to market
- providing experienced entrepreneurial know-how during the development of innovative results and the process of putting them on the market

For questions concerning the "Entrepreneur in Residence" pilot project, please contact Daniel Vonder Mühll: daniel.vondermuehll@systemsx.ch, phone +41 44 632 78 88

New addition to the Management Office

Heide Marie Hess joined the SystemsX.ch Management Office in March 2013. On a 50 percent schedule, she is in charge of the SystemsX.ch work pertaining to the new "ERASysAPP" European systems biology network. The main focus of her assignment will be on the interconnecting of training and continued education in the field of systems biology at the European level, as well as the scientific exchange between the sixteen ERASysAPP partner organizations.


Heide Marie Hess is in charge of the SystemsX.ch network across Europe.

After a time-out, during which Heide Marie Hess devoted herself to her family and her two children, she has now returned to her career in this newly created SystemsX.ch position. Earlier, she worked for a Swiss health insurance company and a Swiss bank in the area of strategic project work, communication and event management.

Thanks to her studies in Cambridge with a main focus on social policy and a stint in New Jersey (USA), Heide Marie Hess, who has a degree in nutritional science and home economics, is ideally prepared for collaboration with our new international partner.

We extend a warm welcome to Heide Marie Hess, our competent new colleague in the SystemsX.ch team!

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Upcoming Events

May 13, 2013
All SystemsX.ch Day
Bern

June 3-10, 2013
International Course in Yeast Systems Biology
Gothenburg

June 9-14, 2013
Joint Summer School SystemsX.ch and CRG
Barcelona

June 12-14, 2013
International Conference on the Systems Biology of Human Disease
Heidelberg

June 23-27, 2013
Systems Biology of Infection Symposium
Ascona

August 30-September 3, 2013
International Conference on Systems Biology
Copenhagen

SystemsX.ch
The Swiss Initiative in Systems Biology

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