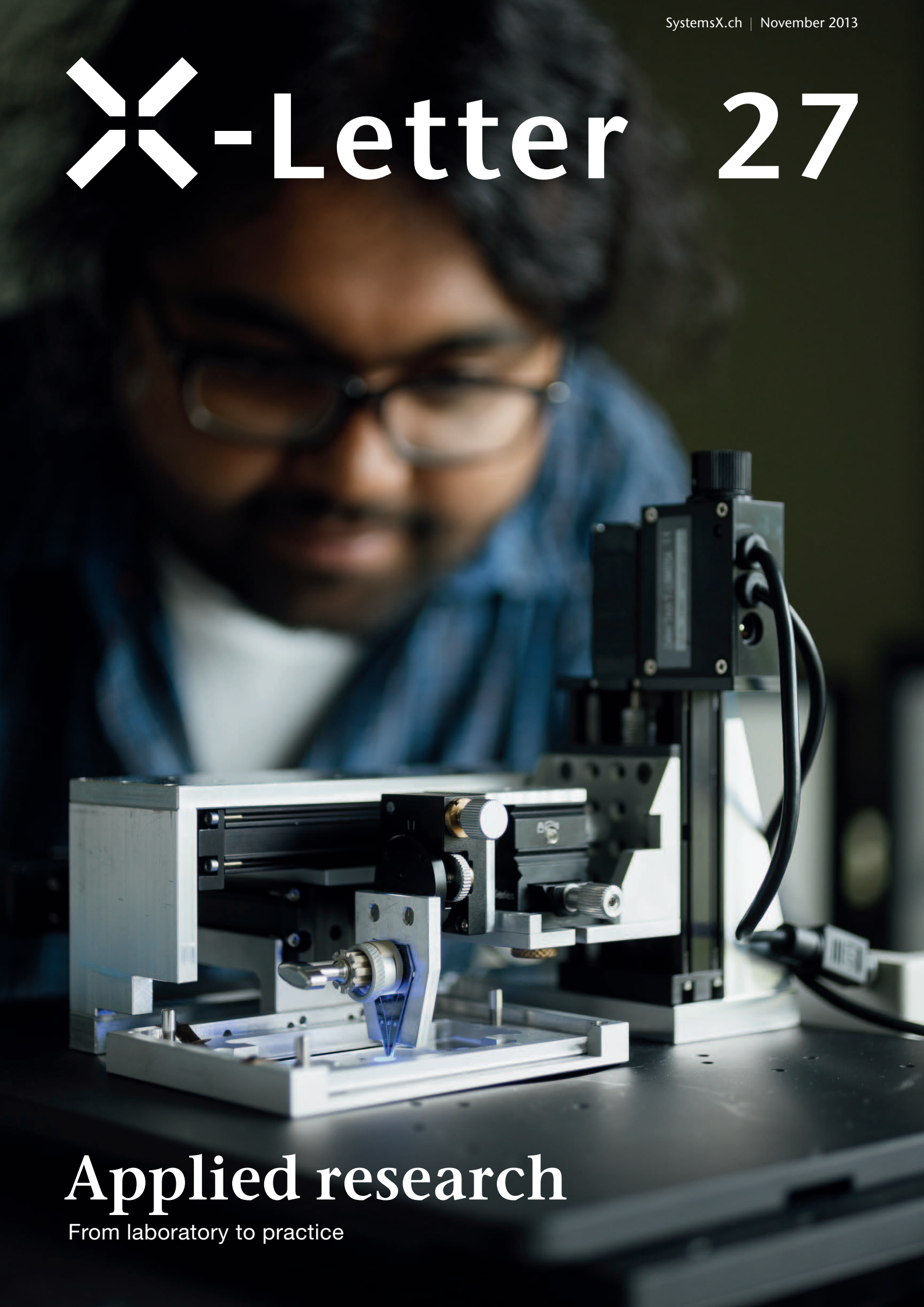
X-Letter 27

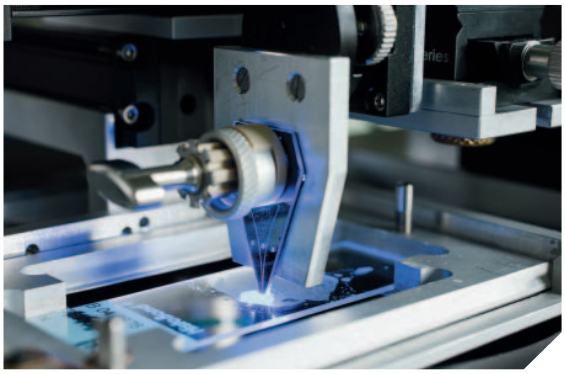


Applied research

From laboratory to practice

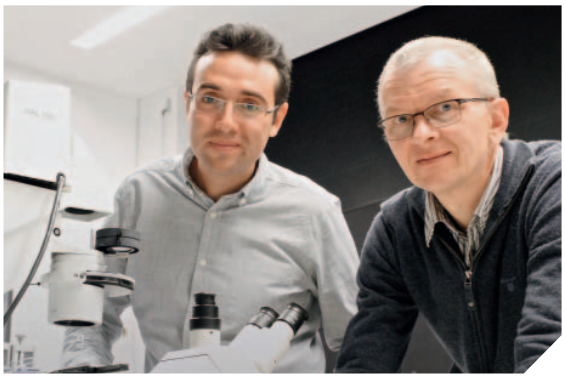
Contents

10



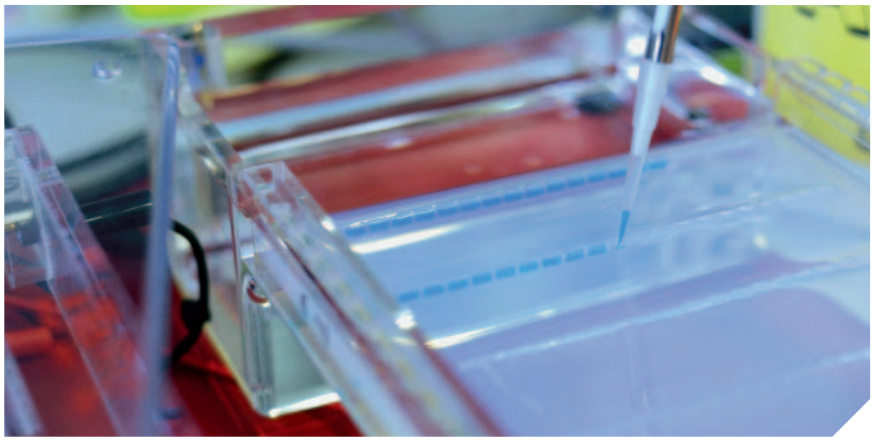
13

14



SystemsX.ch
The Swiss Initiative in Systems Biology

Cover: In the context of the µFluidX Transfer Project, Aditya Kashyap will apply the new IBM technology at the University Hospital Zurich starting in January 2014. Photo: Martin Stollenwerk



"We need to find a 'common language' or, more precisely, to build a common scientific understanding."

Within interdisciplinary teams, commonly found in systems biology research, knowledge exchange is not always easy. Being a physician, I encounter the same situation when talking to systems biologists. Each field tackles a given question applying its own logic and considers a given problem from its own field-specific perspective.

In a small way, I had already come across this phenomenon during my studies: when I started medical school, we attended lectures in physics, chemistry, then physiology, anatomy, histology and biochemistry, before finally entering the world of pathology. The most important and interesting aspect was the connecting of the various fields, so as to be able to understand the relationship between structure and function. The presence of diseases modifies these parameters and affords us further insight into processes at the cell, organ or organism levels.

For me, as a student, understanding a disease was a challenge, as the different fields applied their own logic when classifying and describing it. A good example is the classification of a glomerular kidney disease. For the clinician, an accumulation of fluid in the tissue is decisive. The pathologist pays particular attention to the histology, whereas the immunologist will describe the same disease based on the various autoantibody concentrations.

In the absence of a close collaboration between specialists, a consensus in such a situation is not possible. The same is true in clinical research: if further progress is to be achieved, a close collaboration is essential. We therefore need to find a "common language" or, more precisely, to build a common scientific understanding.

These days, the complexity of clinical research goes hand in hand with the refinement of the existing technology. We have started classifying diseases into subgroups and sub-subgroups and are moving more and more towards what is called "personalized medicine". The novel technologies yield huge amounts of data, the analysis of which requires "intelligent" computers and the appropriate specialists to interpret the information and to use it to the patient's benefit. A close collaboration between physicians and systems biologists is therefore all-important.

If we wish to understand diseases, provide reliable prognoses and ultimately develop customized treatment strategies, we must not only retain our curiosity and fascination for complexity but also improve knowledge exchange.

Jürg A. Schifferli
Member of the SystemsX.ch Scientific Executive Board (SEB) and professor in the Department of Biomedicine of the University Hospital in Basel

Peter Meier-Abt is eagerly observing the SystemsX.ch projects.

Peter Meier-Abt, president of the Swiss Academy of Medical Sciences

"Systems biology must provide 'hard facts' "

The president of the Swiss Academy of Medical Sciences (SAMS) expects the various SystemsX.ch projects to provide valuable results that will help to promote the breakthrough of personalized medicine. But the Swiss health system as a whole could also profit from the experiences gained during the interdisciplinary and cross-institutional collaborations, as harmonization in the medical field has been difficult – to the disadvantage of the Swiss research community.

How long have you been following the SystemsX.ch activities?

As the ex-vice-rector of the University of Basel, I was involved in the foundation of the network organization, and at the time SystemsX.ch entered the second phase, it once again became the focus of my professional activities. The present emphasis on applied research in the medical field is of course of strong interest to the SAMS. Particularly projects studying indicators for certain diseases, so-called biomarkers, are meaningful for us.

Are you expecting the greatest benefit for personalized medicine in this area?

Yes, because new insights in the area of biomarkers have a direct influence on the success of therapies. The more precisely one can determine which substances have the greatest effect in a patient, by using indicators, the better the prognosis. But the analysis of single biomarkers does not suffice to determine the optimal therapy. More detailed knowledge is required regarding the role their composition and spatial arrangement plays during an illness. Therefore, these results directly influence clinical diagnostics and therapeutic decisions.

Why are you preferentially counting on systems biology research?

That is because no other discipline studies whole systems and describes relationships between the individual components of an organism to a comparable extent.

Without the iterative processes between model and experiment that are applied in systems biology, this would not be possible. This is why we expect systems biologists to provide "hard facts" facilitating the implementation of research results in a practical setting.

How do physicians acquire the knowledge needed to incorporate these findings into their therapeutic decisions?

As soon as the quality of the data has been proven and their significance for clinical medicine verified, health professionals need to be trained to handle the information. This means that the physicians need to be taught to supplement the subjectively gathered data with objective data and to draw the correct conclusions in terms of diagnosis and therapy. The professional associations have recognized the need for courses in this field.

In the long-run, however, it will be necessary to adapt the basic medical curriculum.

Matthias Scholer

How can students be prepared for work in the field of personalized medicine?

Future generations of physicians need to acquire a more thorough understanding of the handling of statistical information. But additionally, more attention must once again be paid to basic natural sciences: the better health professionals understand the biology, the better they can practice evidence-based medicine.

How long will it take to implement these measures?

Of course this cannot happen overnight. But the developments in the medical field have always required a constant adaptation of basic and continued education in this sector.

A first step in the right direction is the master's thesis which every medical graduate is required to write these days. The students are thereby compelled to intensively deal with a scientific problem for approximately half a year, and they thus gain good insight into the world of research. This will later help them to communicate with scientists and to tackle research topics.

Are there sufficient numbers of physicians willing to work in research?

Most graduates indeed prefer to take up a curative occupation. Only approximately 10 percent of all graduates opt for research. But numbers are not decisive for the outcome. The existence of a scientific community skilled at providing the basic information the practitioners need for their therapeutic decisions is much more important. Furthermore, intensive communication between these two professional groups is essential.

SystemsX.ch will be coming to an end in just a few years. Will such large research initiatives still be necessary in the future?

National as well as international networks are indispensable. The experience gained with SystemsX.ch shows us how to initiate a nationwide harmonized project that makes it possible to perform forward-looking research at this scale. The gained insight could in particular profit the medical field where a similar harmonization is urgently needed. There has been much talk about this, but its implementation has proven to be difficult.

Can you substantiate the deficiencies?

We have different problems in medicine: on the one hand, the data recording systems are not standardized. On the other hand, we are lacking a national biobank system. This is however essential, also in the area of systems biology research. In order to validate research data with clinical samples, these need to have been processed and stored under standardized conditions. If different standards prevail in each canton, a researcher has fewer samples to choose from. An appropriate harmonization is required if we wish to further perform world-class research.

The success of SystemsX.ch shows us what can be achieved thanks to collaborations reaching across regions and institutions. There is therefore good reason to hope that this will trigger a similar quantum leap and structural change in the medical field.

The SAMS in a nutshell

The Swiss Academy of Medical Sciences (SAMS) was founded in 1943 by the five Swiss medical faculties, the two veterinary medical faculties and the Swiss Medical Association FMH.

Supporting high quality medicine at different levels is one of the aims and tasks of the SAMS. Its activities include promoting the professional training of young scientists, particularly in the field of medical research, but also the early identification of new scientific developments in medicine and the quick practical implementation of validated findings.

The SAMS considers itself part of the scientific community and works in close collaboration with other academies, notably to answer questions and to perform projects in the fields of early detection, ethics and dialog with society.

More information is available at:
www.sams.ch

Matthias Scholer

The CycliX RTD Project

The end is also a new beginning

The life of an organism is based on a number of carefully concerted recurrent processes. How this synchronization is achieved and what happens at the gene level is still largely unknown. The scientists involved in the CycliX project are looking into the secrets of life's cyclic nature.

Cycles take center stage in Nouria Hernandez's research project.

The beginning was not easy. Comprehension problems and therefore disgruntlement within the team arose during the first gatherings of the various research groups. "During these meetings, all the participants reported on the progress achieved in their specific research area. In the beginning, there were situations where someone would explain something and colleagues from other disciplines would not understand what this person was trying to convey", remembers the CycliX RTD Project leader Nouria Hernandez. She is a molecular biology professor at the Center for Integrative Genomics at the University of Lausanne. This is where the said meetings take place and the laboratories in this institute are also where most of the experiments have been performed since this large-scale project was launched in 2009.

Complex subject

Nevertheless, the CycliX team very quickly found a "common language". "This was essential, as we depended on well-functioning teamwork and constructive exchange of thoughts between the various research areas. The intricacy of the subject requires this", explains the biologist. The complexity of the subject is reflected in the starting figures of the experiments: from a single sample, the scientists collect 150 million DNA pieces. The DNA sequence of each fragment is then determined before it can be assigned to one of approximately 20,000 genes. So far, the CycliX team has been able to perform this procedure on more than 200 samples, producing accordingly large amounts of data. These now need to be catalogued and made available for further analysis. "The computer specialists, mathematicians and physicists in our team are developing made-to-measure database solutions and programs that will enable us to continue our work with the available results", explains the researcher.

Liver cells as a model system

All analyses were performed on mouse liver cells. The CycliX scientists use these as a model system to study three cycles present in all higher organisms. "We wish to understand how the daylight cycle, the nutrient cycle and the cell division cycle are regulated, but also how these three cycles influence each other", says Hernandez, roughly summarizing the project objectives. Although each cycle in itself has already been examined extensively, little is known about the overall genome reactions in the cycles and the corresponding transcription regulation programs. We also know very little about how these are connected and how they influence each other.

By means of an example, Nouria Hernandez illustrates the importance of the orchestration of the cycles within an organism: "During cell division, genetic material is susceptible to damage by free radicals. As radicals are mainly produced during the oxydative phase of the metabolic cycle, organisms such as yeast shift cell division to the non-oxydative phase, during which oxygen consumption is reduced."

The CycliX team hopes to quantitatively and comprehensively define all the genome reactions and transcription programs that characterize each cycle in mammals. The researchers are

particularly interested in understanding how the transcription programs communicate via a common "core" regulation network to guarantee integration and coordination within these three cycles.

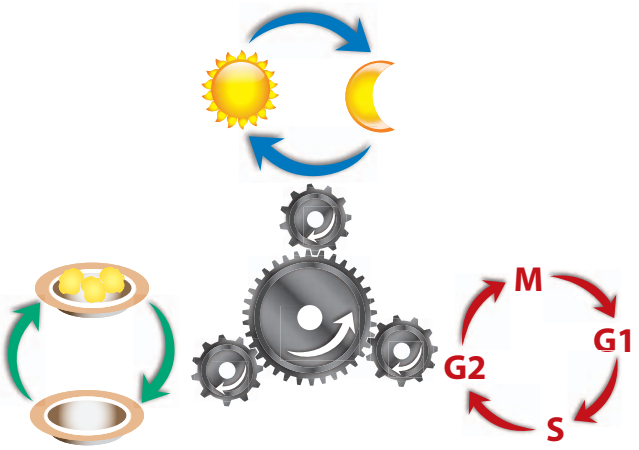
Creating different populations

In a first step, the scientists determined the gene activity for each process in each of the three cycles. This endeavor was particularly difficult as all three cycles influence each other and it is not possible to discern whether a given gene activity is related exclusively to one cycle or whether it is the result of an interaction with another cycle. How can one examine an isolated cycle? "We needed to find a way to collect liver cells in which two of the three cycles showed little or no activity", explains Nouria Hernandez. The complex task of breeding mouse populations that present a single active cycle was also tackled collaboratively by the scientists.

Important milestone has been reached

And now, almost four years later, the CycliX team has reached an important milestone. Very pleased, Hernandez says: "We have succeeded in collecting tissue samples from the various mouse populations. Now we can determine the activity status of 20,000 genes at any given point in time during a cycle." Thanks to these data, the scientists now possess a multitude of genome activity snapshots in chronological order. These not only indicate when and where modifications of the genetic material take place, they also enable the researchers to determine which genes promote a cycle and where interfaces between the systems are to be found.

Even though the CycliX RTD Project, partially financed by SystemsX.ch, is slowly coming to an end, the research work in this field will certainly not be discontinued. Confidently looking ahead, Nouria Hernandez says "a follow-up project has already been submitted". Here, as in any cycle, the end of one thing is also the beginning of another.



The CycliX team is investigating how three common cycles in an organism attune to each other. Illustration: © CycliX

CycliX at a glance

Principal Investigator: Prof. Nouria Hernandez

Research groups:

- Prof. Nouria Hernandez, Center for Integrative Genomics, University of Lausanne – Regulation of Gene Expression
- Dr. Mauro Delorenzi, Center for Integrative Genomics, University of Lausanne – Computational Biology, Models and Statistical Data Analysis
- Prof. Bart Deplancke, Institute of Bioengineering, EPF Lausanne – Systems Biology, Gene Regulatory Code
- Prof. Béatrice Desvergne, Center for Integrative Genomics, University of Lausanne – Lipid Metabolism and Homeostasis in Mammals
- Dr. Nicolas Guex, Vital-IT, University of Lausanne – Computational Biology
- Prof. Winship Herr, Center for Integrative Genomics, University of Lausanne – Regulation of Mammalian Cell Proliferation, Cell Division Cycle
- Prof. Felix Naef, Institute of Bioengineering, School of Life Sciences, EPF Lausanne – Computational Systems Biology, Biological Rhythms
- Dr. Jacques Rougemont, Bioinformatics and Biostatistics Core Facility, EPF Lausanne – Computational Biology, Biostatistics
- Prof. Ueli Schibler, Department of Molecular Biology, University of Geneva – Mammalian Circadian System, Biological Rhythms

Total budget (2009–2013): CHF 9.717 million, including CHF 4.478 million from SystemsX.ch

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

CycliX
Transcription
Regulatory Networks
of three Interacting Cycles

8th Call for proposals

SystemsX.ch to support eleven new projects

Out of the 31 research proposals submitted as a result of the 8th call for proposals, the Swiss National Science Foundation (SNSF) has decided this October to support nine Research, Technology and Development Projects (RTD Projects) and two Transfer Projects. The eleven projects will be granted a total of 24.6 million Swiss francs.

Within the 8th call for proposals, 25 applications for RTD Projects and six for Transfer Projects were submitted by the end of June. All in all, the RTD consortia involved 146 research groups, and close to one quarter of the group leaders work in a faculty of medicine. The increased participation of physicians results from the efforts made by SystemsX.ch to shift the focus of future projects towards medically and clinically relevant topics.

For the first time, the RTD proposals also included seven research groups working at the Università della Svizzera Italiana (USI).

Project evaluation and selection

All RTD and Transfer Project proposals were evaluated by the SystemsX.ch Scientific Executive Board (SEB) as well as the Swiss National Science Foundation (SNSF) Review Panel. The SEB especially ascertained that the project proposals' focus was on questions related to systems biology. "Scientific quality" and "contribution to and value for systems biology" were the two criteria of importance to the Review Panel. A close collaboration on equal terms and based on a partnership was an additional requirement for the approval of a Transfer Project.

A total of eleven projects convinced the SNSF Review Panel which took into account the recommendations issued by the SEB and selected nine RTD and two Transfer Projects (see tables 1 and 2). In October 2013, the SNSF Presiding Board ratified this decision. SystemsX.ch will support the RTDs during four and the Transfer Projects during two years. Work on the first projects will begin in January of 2014.

The RTD Project focus is on medicine

A good half of the supported RTD Projects will examine medical issues: cancer is the focus of the *MERIC* and *SignalX* projects. The *TbX* and *HostPathX* RTD Projects address research questions re-

Table 1: Nine RTD Projects were approved in 2013. Support funds for all projects combined will exceed 24 million Swiss francs.

RTD Projects approved in 2013	Principal investigator	Involved institutions	Number of groups
MERIC – Mechanisms of Evasive Resistance in Cancer	Beerenwinkel, Niko	ETHZ, UniBas, UniBas-USB	5
TbX: Systems Biology of Drug-resistant Tuberculosis in the Field	Gagneux, Sebastien	UniBas, ETHZ	7
SignalX: Model-driven experimental design towards a model of TOR signaling	Sauer, Uwe	ETHZ, UniGE	6
MicroScapesX: Design and Systems Biology of Functional Microbial Landscapes	van der Meer, Jan Roelof	UniL, EPFL, ETHZ	5
Morphogenetix	Brunner, Damian	UZH, UniBas, MPI Köln (D)	5
AgingX: a cross-species, systems genetics approach to the biology of aging	Deplancke, Bart	EPFL, UniL, UniL-CHUV	4
MalarX: Development of system-level metabolic modeling for the liver stage malaria for drug target identification against Plasmodium vivax relapsing	Hatzimanikatis, Vassily	EPFL, UniGE, UniBE	4
HostPathX	Soldati, Thierry	UniGE, ETHZ, UniGE-HUG, SIB, LMU Munich/D	5
TargetInfectX – Multi-Pronged Perturbation of Pathogen Infection in Human Cells*	Dehio, Christoph	UniBas, ETHZ, UZH	6

*) This project has been approved for one year. It will then be reevaluated and a decision will be taken regarding further support.

garding the infectious disease tuberculosis, the tropical disease malaria takes center stage in *MalarX* and *TargetInfectX* will examine infectious processes.

All consortia are cross-institutional and consist of four to seven research groups. Two of the successful applicants (Dehio and Sauer) were already in charge of an RTD Project in the first phase of the SystemsX.ch initiative. For the *TargetInfectX* follow-up project (Dehio), the SNSF has formulated objectives which the consortium must achieve within a year. The SNSF will then reevaluate the project and decide whether additional funds will be rewarded.

Cancer research is the focus of the Transfer Projects

The six applications for Transfer Projects involve six academic and eight private sector research groups. The SNSF has only selected two projects in this category. Both projects deal with active ingredients for the treatment of cancer and both consist of an academic research group working in Zurich (ETH Zurich, University of Zurich) and a large company located in Basel (Novartis, Roche).

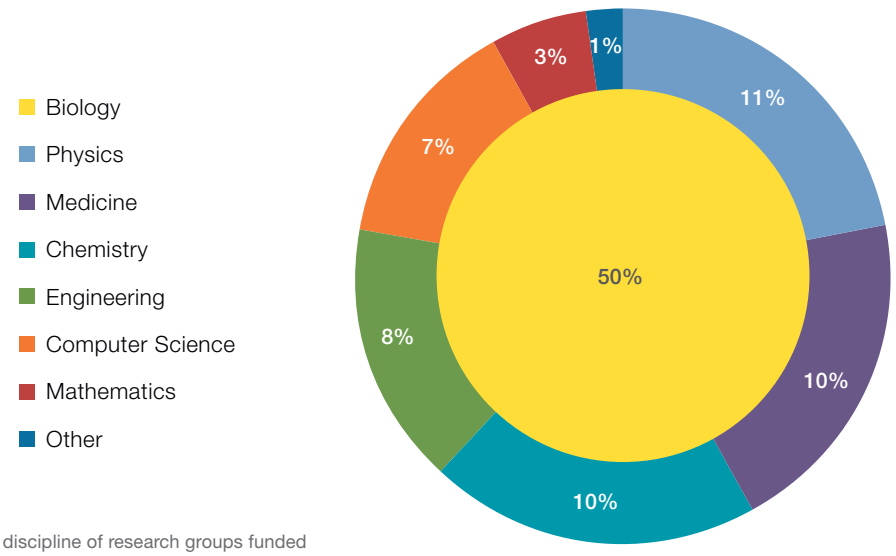
The Transfer Projects will receive funds for two years, but the project leaders can apply for funds for an additional year after the first eighteen months.

Additional call for proposals

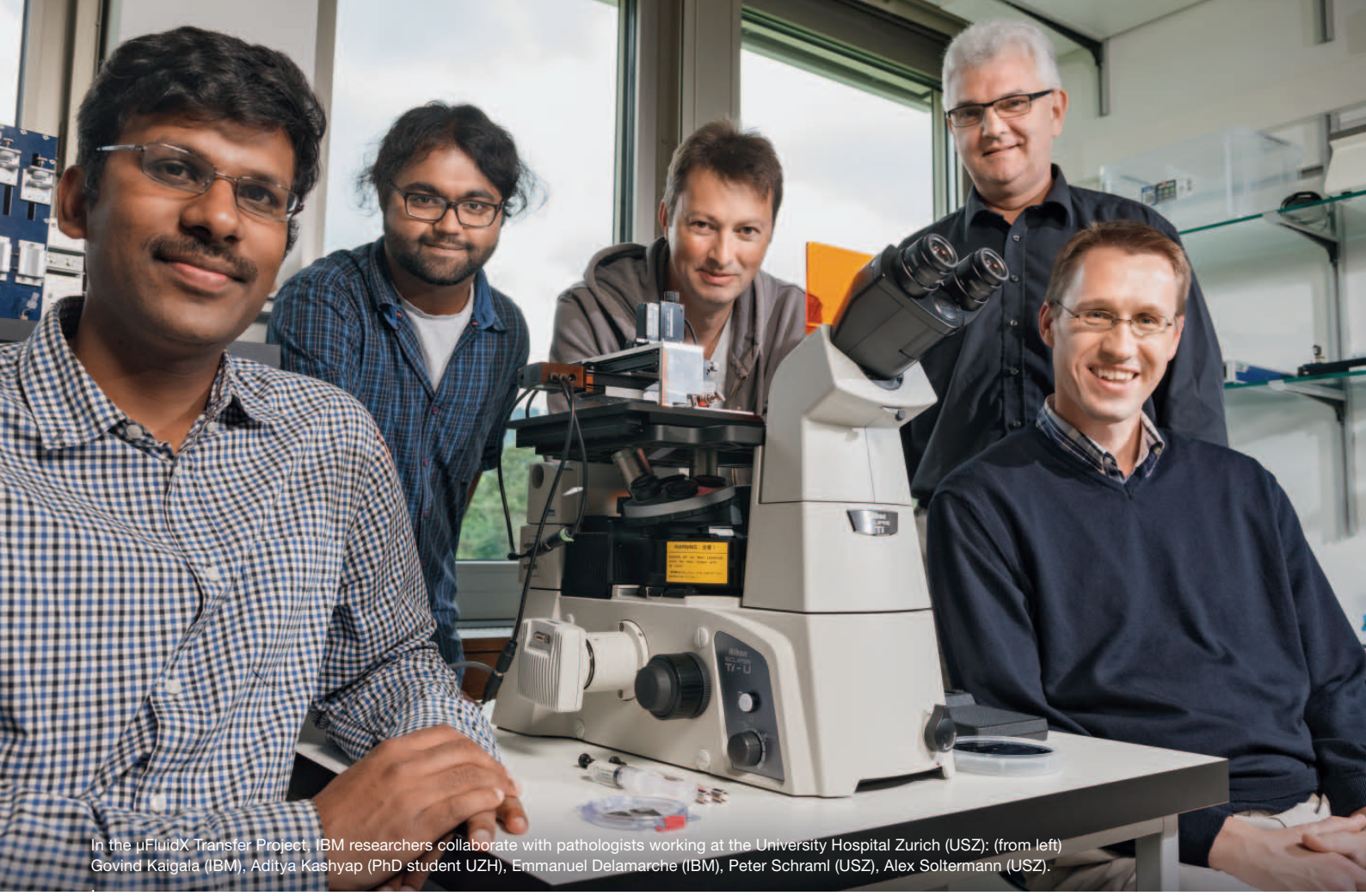
For the eleven projects approved in the context of the 8th call for proposals, the SNSF has granted the total sum of 24.6 million francs. SystemsX.ch had however reserved 30 million francs for this purpose. The remaining funds will therefore be set aside, on the one hand in case the *TargetInfectX* project is positively evaluated, and on the other hand for an additional call for proposals dedicated especially to medical and clinical projects (see page 13).

Table 2: Two Transfer Projects with a total investment volume of 432,000 Swiss francs will begin in 2014.

Transfer Projects approved in 2013	Principal investigator	Collaboration between
Foes or Friends? Reprogramming Tumor-Associated Macrophages to Fight Cancer by Targeted Signaling Network Modulation	Bodenmiller, Bernd	UZH and Roche
Mechanisms of cancer drug resistance	Gstaiger, Matthias	ETHZ and Novartis (NIBR)



Breakdown by discipline of research groups funded by SystemsX.ch (2008–2013).



In the µFluidX Transfer Project, IBM researchers collaborate with pathologists working at the University Hospital Zurich (USZ): (from left) Govind Kaigala (IBM), Aditya Kashyap (PhD student UZH), Emmanuel Delamarche (IBM), Peter Schraml (USZ), Alex Soltermann (USZ).

The µFluidX Transfer Project

Not all tumors are created equal

A world premiere is happening at the University Hospital Zurich. Within the scope of the µFluidX Transfer Project, an IBM innovation aimed at investigating cancer can now be validated under clinical conditions. In the long run, not only the scientists working at both institutions but also patients will profit from this technology.

October 2011, University Hospital Zurich. The diagnosis amounted to a death sentence: lung cancer with multiple metastases. It was estimated that the patient would live only a few months longer. Surgery to remove the tumor was not an option as the disease was already in an advanced stage. Three cycles of a standard chemotherapy were initiated, so as to grant the 76-year-old patient some time. To no avail.

The experts therefore decided to look for genetic alterations in the cells present in the malignant tissue. “This enables us to type cancerous modifications more precisely”, explains Professor Alex Soltermann.

Soltermann is a senior physician in the Institute of Surgical Pathology at the University Hospital Zurich. “The patient was very lucky”, remembers the pathologist. “We found the same genetic modification in more than 95 percent of the examined cells.” He was fortunate because the oncologists were able to resort to an inhibitor of these mutations that has recently become available in Switzerland. These inhibitors are substances that specifically suppress molecular events of central importance to cell malignancy.

The results of the medical examinations performed just a few weeks after the application surprised even the experienced experts: “The tumor and its metastases had regressed completely.” And to this day, two years after the treatment, the patient has not had a relapse.

Major individual differences

“This is a prime example of the therapeutic success that can be achieved thanks to personalized medicine”, says Soltermann. Not all tumors are created equal. One can distinguish between different forms of cancer, not only in terms of the cell type the tumors are derived from. “When similar tumors found in different patients are examined at the genetic level, major individual differences are revealed”, explains the physician. Providing the specialists are able to pinpoint these variations and to inactivate the affected gene, at least tumor growth can, in most cases, be considerably slowed down. In numbers this means that approximately 70 percent of all tumors respond to personalized therapy. In contrast, only 20 to 30 percent are receptive to standard chemotherapy.

Matthias Scholer Martin Stollenwerk

Revolutionary diagnostic technique

But considering the high success rate, why are such patient-specific inhibitors not applied more often? Professor Soltermann gives two reasons: “On the one hand, the inhibitors available on the market are currently approved only for so-called ‘second-line-therapy’, as their potential side effects are not yet known. On the other hand, we are still at the very beginning of the technical development of these diagnostic possibilities.” In order to be able to type a tumor cell down to the molecular level, adequate methods are necessary. This is the starting point for the new SystemsX.ch Transfer Project which the University Hospital Zurich (USZ) will launch at the beginning of 2014 in collaboration with the IBM research laboratory in Rüschlikon.

Soltermann, the academia representative in this project, enthusiastically says: “IBM has developed a new technology that has the potential to revolutionize the diagnostic possibilities for cancer tissues”. This device enables the scientists to scan the tissue sample and to examine cells in any given minute site. The researchers can also apply several technologies in a single experiment: It is possible to stain sample material, to localize cellular modifications and to extract DNA for further investigation.

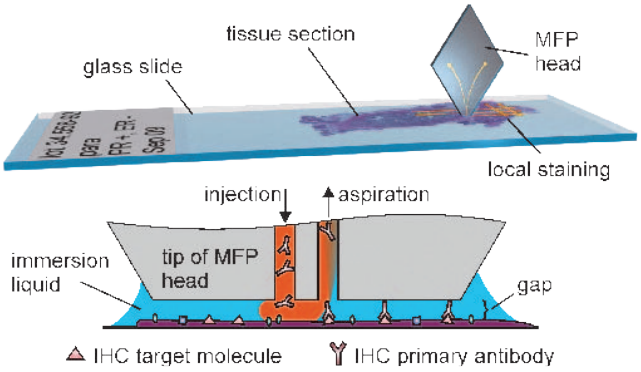
“This device enables us to scan the tissue sample and to examine cells in any given minute site.”

Furthermore, all analyses are performed using water-based methods and formalin-fixed samples. “In this way, histopathological morphology, immunohistochemistry and DNA analysis, for which several devices were necessary until now, can be performed in one step”, explains Soltermann.

An innovative micro-probe with great potential

The centerpiece of the newly developed tool is the so-called “microfluidic probe” (MFP). This is the term used for the tiny head of the apparatus, through which minute amounts of liquids, antibodies or reagents are accurately trickled onto the cells of interest. Through an additional opening, it is also possible to extract material such as DNA from the cell (see illustration).

But that is not all: “The buildup of the MFP not only allows us to work highly accurately and in a way that prevents damage to the tissues. Thanks to this method, we also require very few tumor cells for our investigations.” Therefore, during a bronchoscopy, for example, the material harvested from lymph node metastases by means of fine needle aspiration could be sufficient to perform a conclusive analysis. This is particularly important when dealing with patients suffering from cancer too advanced for surgical removal.



The diamond-shaped MFP head allows the application of various technologies. Illustration: IBM Research – Zurich

Installation is the first goal

It remains to be determined how representative of the primary tumor the cancer cells harvested on the periphery truly are.

The scientist summarizes the initial phase of the project: “In a first step, the apparatus needs to be installed at the USZ; then its functionality regarding the analysis of tissue samples from lung cancer patients must be tested and the results need to be validated”.

In this Transfer Project, SystemsX.ch not only pays the salary of the PhD student put in charge of the installation and the validation of the analysis methods, but also finances the equipment. Soltermann proudly explains: “Thanks to this project, our institute now has the opportunity to be the first institution worldwide to use this innovation for research purposes.”

A large archive is available

For the time being, the device will not be used in day-to-day clinical diagnostics. All tissue samples for the planned research work are derived from already diagnosed and closed cases. And the USZ has many samples: thinking ahead, the hospital has meticulously archived all the formalin-fixed tissue samples and apper-

taining medical records acquired over the past twelve years. "This now also profits our industrial partner: validating our new results with hundreds of retrospective patient records will markedly enhance the significance of our joint publications", emphasizes Alex Soltermann.

The beginning of a new era

This give-and-take exemplifies a new era in which technology and knowledge transfer between a private company and a public research institution is encouraged all across Switzerland. Soltermann is very pleased: "This is an exciting time for pathologists, because important cell biology models can now be validated using larger retrospective patient collectives that include the classic histopathological data such as tumor size or degree of differentiation."

Chances are that patients too will profit from this paradigm shift in the near future.

µFluidX at a glance

Project title: Multi-modal assessment of mutated predictors BRAF and DDR2 at lung carcinoma invasion fronts by topographic DNA extraction and micro-immunohistochemistry using the microfluidic probe

Applicant: Prof. Alex Soltermann, University Hospital Zurich (USZ)

Industrial partner: Dr. Govind Kaigala, IBM Research – Zurich

Duration: 2014–2016

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

µFluidX
Assessing Predictive Molecular Alterations in Tumors

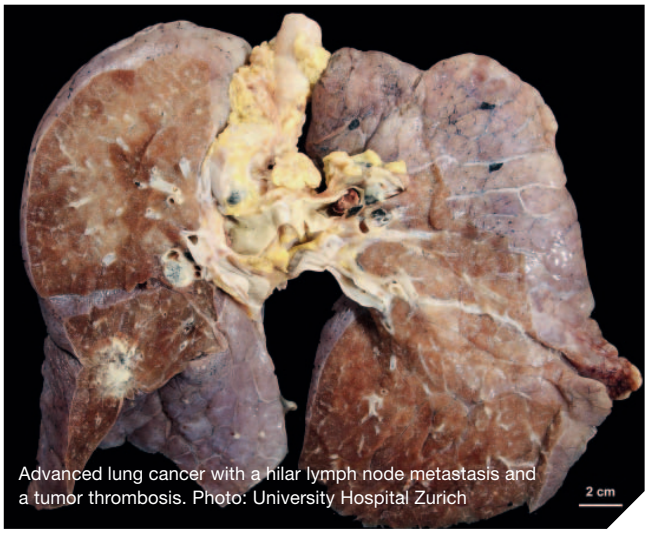
Facts and numbers about lung cancer

Each year, approximately 3800 people develop lung cancer in Switzerland. This roughly amounts to 10 percent of all cancers. According to the numbers issued by the Swiss Federal Statistical Office, lung cancer is the leading cause of death due to cancer among men and the second most frequent one among women. While incidence and mortality in men are dropping, they are increasing in women.

Lung cancer originates in the cells that line the respiratory tract. Benign lung tumors are very rare. Most lung cancer types are malignant and can be divided into two basic types: small cell and non-small cell bronchial carcinomas. The small cell carcinomas account for approximately 20 percent of all bronchial carcinomas. This form typically displays aggressive growth and a strong tendency to form metastases. The non-small cell bronchial carcinomas are divided into three subtypes according to the tissue of origin: epidermoid carcinomas, adenocarcinomas and large cell carcinomas.

Smoking as well as passive smoking are regarded as the main risk factors for lung cancer. In rare cases, the disease is caused by certain substances present in the air at the workplace or in the environment.

In most patients, lung cancer is diagnosed in an advanced stage and/or when metastases have already appeared. For these patients, recovery is to date rarely possible.



Advanced lung cancer with a hilar lymph node metastasis and a tumor thrombosis. Photo: University Hospital Zurich

Daniel Vonder Mühll Frederike Asaël

9th Call for proposals

Next call for proposals scheduled for December

Within the scope of the 9th call for proposals, SystemsX.ch will specifically support young scientists in two different project categories. In addition, the responsible panels within SystemsX.ch and the Swiss National Science Foundation (SNSF) are considering the announcement of a further call for proposals for medical and clinical projects in 2014.

The 9th call for proposals will be launched in December 2013 and is open to proposals for Transition Postdoc Fellowships (TPdF) and Interdisciplinary PhD Projects (IPhD). Interested scientists should send in their project applications by April 30, 2014. SystemsX.ch intends to support twelve TPdFs and twelve IPhDs.

Interdisciplinary PhD Projects (IPhD)

To date, SystemsX.ch has supported approximately 60 PhD students within the framework of the IPhD Projects. In this category, the focus is on interdisciplinary collaborations in fields relevant to systems biology, such as biology, computer sciences, medicine, mathematics, engineering, physics or chemistry. The application is submitted not by the doctoral candidate but by the responsible group leader, who supervises the student in a SystemsX.ch partner institute in collaboration with a co-applicant from another field.

SystemsX.ch pays the PhD student's salary during three years. A one-year prolongation is possible. The expenditures for consumables amounting to a maximum of 10,000 Swiss francs per year as well as the expenses for one international conference per PhD student are also carried by SystemsX.ch.

The feedback received until now, from the PhD students as well as from the project leaders, shows that an IPhD is more demanding than a single-discipline PhD thesis. But it also confirms the fact that incorporating a second discipline is stimulating and of great help, especially in projects geared towards practical applications.

Transition Postdoc Fellowships (TPdF)

Since first launching the Transition Postdoc Fellowships in 2012, SystemsX.ch has approved 17 TPdFs. In this project category, ambitious young scientists formulate their own interdisciplinary project application. In this context, transition means that the applicant switches from his or her original discipline to a new and complementary field. For this purpose, the researcher selects an appropriate research group in which to carry out the project and learn the ropes of the new discipline.

The time frame for a TPdF is initially limited to two years. A one-year prolongation is however possible. SystemsX.ch pays the postdoc's salary and meets the expenses for consumables amounting to a maximum of 10,000 Swiss francs per year.

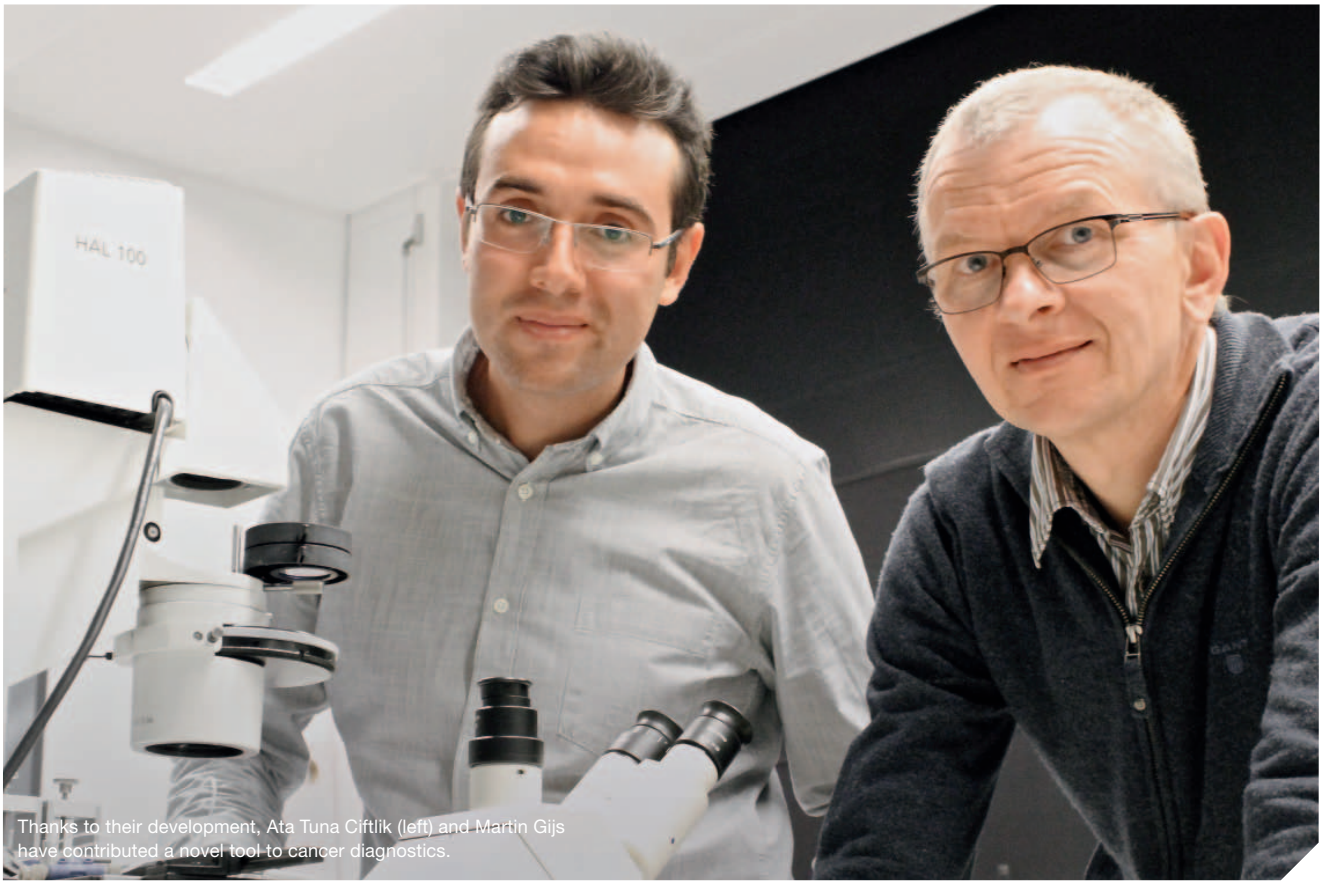
Through this project type, as is also the case with the IPhDs, SystemsX.ch aims to specifically encourage the next generation of systems biologists who impart new perspectives and impulses to future research.

Through the 9th call for proposals, SystemsX.ch will support tomorrow's young systems biologists.

Special call for proposals for medical and clinical projects

SystemsX.ch and the SNSF have agreed to support only projects that have thoroughly convinced both evaluation committees, the SEB and the SNSF Review Panel. The SEB must determine that the proposals are clearly for research projects in the field of systems biology, and the SNSF must assess that they are of high quality. Projects which fulfill only one requirement will not be authorized.

Due to this restrictive support policy, fewer projects than originally planned were authorized within the scope of several previous calls for proposals. With the remaining funds, SystemsX.ch intends to launch an additional call for proposals specifically for medical and clinical research projects. The requirements for the submission of an application have not yet been defined. All details will be published at the beginning of 2014.



Thanks to their development, Ata Tuna Ciftlik (left) and Martin Gijs have contributed a novel tool to cancer diagnostics.

Interdisciplinary PhD Project (IPhD)

From IPhD Project to start-up company

The IPhD Project of a young scientist at the EPF Lausanne has shown in an impressive way how successful applied research paired with inventive talent and practical value can be. Thanks to a device he developed, it will be possible to perform more precise cancer diagnoses in the near future.

"If there is money to be made here, he is the one who will make it", laughs Martin Gijs, pointing at Ata Tuna Ciftlik, one of his PhD students. Gijs is the director of the Laboratory of Microsystems at the EPF Lausanne, where he oversees several projects in the area of microfluidics. This is the name given to technological developments involving the targeted steering of fluids in a minute space.

One of these projects is now coming to a crowning conclusion. Gijs is convinced that "Ata Tuna Ciftlik has developed a 'microfluidic chip' which can trigger a new point of view in the field of cancer diagnosis."

Ciftlik's innovation has indeed already been patented and a prototype will shortly be put to the test in clinical diagnostic centers. "We strove to develop a device which can be integrated into the standardized processes of tumor diagnostics with only minor adaptations", adds Ciftlik. The young engineer and mathematician succeeded in developing this innovation during his four-year Interdisciplinary PhD Project, financed by SystemsX.ch.

The secret lies within

The device consists of a block the size of a fist, in the center of which can be anchored a specimen slide carrying the material to be analyzed. The microfluidic chip is located in a square plate, only a few centimeters in size, and is rather unspectacular to the naked eye. However, a magnified view of this object reveals its complexity. A large number of micro-capillaries, a thousandth of a millimeter in diameter, are arranged in the plate. "On one side there is an entry through which the system can be filled with fluids. These capillaries lead to a chamber where the liquid can be removed thanks to a separate drainage system", explains Ciftlik.

The central chamber is the heart of the device. This is where tissue samples can be examined by means of immunohistochemistry (IHC). This method, which is intensively used in biology and medicine, enables researchers to quantify single structures in cells of a tissue section. For this purpose, specific antibodies that only bind to the sought-after cellular components are added to a liquid that flows over the tissue section. These antibodies carry a fluorescent dye. The scientist sums

up the functional principle of the method as follows: “The intensity of the dye directly correlates with the number of bound antibodies.” In other words: the stronger the glow in the tissue sample, the larger the amount of the structures one is looking for. “We are thus applying a proven method. Yet, thanks to our device, even more precise measurements and consequently a more precise diagnosis are possible”, emphasizes Ciftlik.

Scientifically proven advancement

Current IHC methods regularly lead to results that cannot be clearly interpreted. Ciftlik knows the reasons therefor: “To date, a tissue sample had to be placed in an antibody bath for a long time, so as to ensure that each part of the material to be examined had been in contact with the reagent for a sufficient amount of time.” However, above average antibody binding or false linkage can occur during this long bath. “In certain cases, it is then impossible to establish a precise diagnosis using this approach”, says Ciftlik, summarizing the shortcomings of this method. These questionable samples subsequently need to undergo a costly and time-consuming gene analysis.

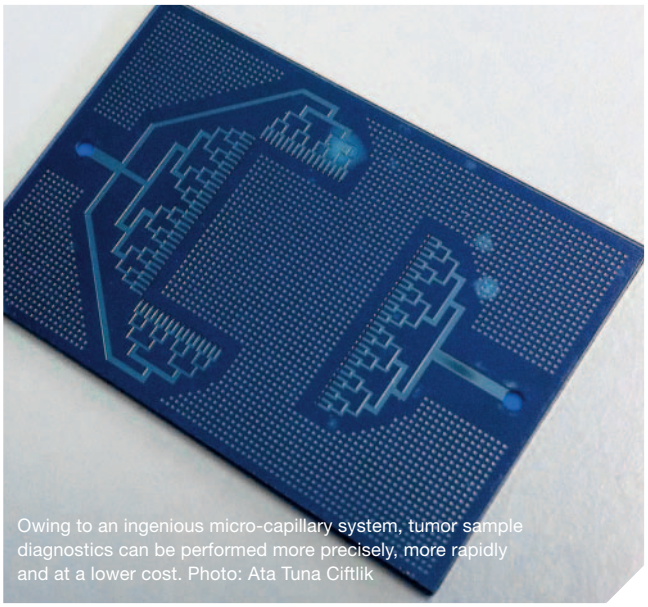
But this is not the case in Ciftlik’s innovation: “Our micro-channel system not only enables us to bring the tissue sample into contact with the reagent for a precisely defined amount of time. The layout of the channels also ensures the regular distribution of the liquid across the entire sample, including the edges and the corners.”

In collaboration with Hans-Anton Lehr at the Pathology Institute of the University of Lausanne, Martin Gijs and Ata Tuna Ciftlik have shown that the precision of the diagnosis increases several-fold thanks to their development. For this purpose, these scientists examined 76 tumor samples provided by their project partner, the University Hospital in Lausanne. In 27 of these samples, a clear diagnosis could not be established by means of the conventional IHC method. However, using the microfluidic chip, this was only the case in three samples. “To be on the safe side, we checked all our results a second time. All were correct”, Ciftlik happily reports and goes on to mention the next advantage of his device: “Each test takes less than five minutes and requires much smaller amounts of the expensive reagents than the commonly applied procedure.”

Broad application in the area of tumor diagnostics

Thus, quick, precise and cost-saving are also the attributes that prompted Martin Gijs and Ata Tuna Ciftlik to patent their device and to let pathologists work with the prototype in the near future. “Before the device can go into the production phase, we want the diagnostic front to give us feedback, so that we can cover the practitioner’s needs as satisfactorily as possible”, says Ciftlik, looking ahead.

To date, the device has primarily been validated using tissue samples from patients suspected of suffering from breast cancer. “In breast cancer, many indicators used to classify the tumors, so-called biomarkers, have already been singled out. Accordingly, a number of antibodies needed for identification as well as specific inhibitors used in the treatment of advanced tumors are available”, explains the scientist. Although the newly developed microfluidic chip will primarily be used in breast cancer diagnostics in a first step, the aim is to later employ it for other tumors as well. “The device and the method should work independently of the origin of the tissue. As soon as the corresponding biomarkers have been studied in more detail, it will be possible to exploit our chip for other cancer types”, believes the young scientist.



Owing to an ingenious micro-capillary system, tumor sample diagnostics can be performed more precisely, more rapidly and at a lower cost. Photo: Ata Tuna Ciftlik

If everything goes according to plan, Ata Tuna Ciftlik will soon be dealing with business plans, production facilities and markets. And then his advisor’s theory will have proven correct and the innovation will have become not only a scientific but also a commercial success.

The project at a glance

Project title: Time-resolved Luminescence Imaging of Cells and Tissue in a Lab-on-a-Chip Using Lanthanide-doped Nanoparticle Labels for Breast Cancer Detection

PhD student: Ata Tuna Ciftlik, EPF Lausanne

Advisors: Prof. Martin Gijs, EPF Lausanne;
Prof. Hans-Anton Lehr, University of Lausanne

Duration: 2009–2013

Project type: Interdisciplinary PhD Project

Additional literature:
Microfluidic processor allows rapid HER2 immunohistochemistry of breast carcinomas and significantly reduces ambiguous (2+) read-outs
See full text (PDF) at: www.pnas.org

Transition Postdoc Fellowship (TPdF)

Giving the immune system's memory a helping hand

Roger Geiger is investigating how the metabolism can be used to steer the development of human T cells. In future, his research could contribute to attaining more durable vaccine protection.

Using a mass spectrometer, Roger Geiger examines how the exact composition of human T cells changes during their development.

"I collect the cells for my research from fresh human blood", says Roger Geiger, postdoc at the Institute for Research in Biomedicine (IRB) in Bellinzona and holder of one of the SystemsX.ch Transition Postdoc Fellowships (TPdF) approved in 2012. "In this way, I can work with cells that truly exist in the healthy body."

He actually uses so-called naive T helper cells. As soon as these immune cells are exposed to a pathogen, they develop into specialized T helper cells and, in their role as important immune defense actors, contribute to eliminating the intruders. After their work is done, most of them die. Only a few long-lived memory cells remain and, as a result, the pathogen is immediately recognized and eliminated by the immune system the next time it appears.

Geiger is interested in learning what happens in the T cells when they are activated, and while they grow and develop into one of several types of cells. "To date, these relationships have mainly been examined in mice", observes the scientist. But if the results are to be applied in medicine or clinical research, more detailed knowledge regarding human cells is needed.

Elucidating metabolic pathways

The researcher is examining which metabolites, substances such as vitamins and sugars, are converted in T cells. For this purpose, he grows human T cells in incubators and takes samples at given time points. He then determines the exact composition of these using a special mass spectrometer.

Maja Schaffner

The device is located in the Swiss Federal Institute of Technology in Zurich (ETHZ) and was developed in the group of Nicola Zamboni who is a group leader at the ETHZ Institute of Molecular Systems Biology. “The mass spectrometer can simultaneously detect 650 different metabolites in any given sample and determine their relative frequency”, emphasizes Geiger.

As soon as he knows which substances and metabolites are present when and in which concentrations in the cells, he can track their involvement in the development of the T cells. “I look at whatever stands out”, explains the researcher. In so doing he can for instance prove that particularly large amounts of sugar are used in the cells at a specific point in time.

Additionally, Geiger checks the cells’ health using other methods: how many cells are still alive, for example, or which proteins and messenger substances are produced at which moment. In this way, he can also find out which cell type they develop into.

Influencing the development of T cells

However, the scientist not only observes but also takes his experiments a step further: he influences the development of the T cells by adding selected metabolites. “As the separate metabolic pathways are interrelated, the addition of a substance modifies not just one but possibly five different metabolic pathways at the same time. In the process, the relative abundance of up to 50 metabolites changes”, emphasizes Geiger.

Modifications in the concentrations of nutrients also influence the development of the T cells as a whole: “Depending on the substance we either add to the naive T cells or omit, different cell types develop”, explains Geiger.

For this reason, the young scientist is now studying how the metabolic network, an entanglement of various interdependent metabolic pathways, functions as a whole. Amongst other things, he wishes to find out what must happen in the system to turn a naive T cell into a memory cell.

Combining data to achieve new insights

On the computer, Geiger visualizes the metabolic network as a map which he then combines with the underlying model of the metabolic processes and supplements with other data. In this way, results which the scientist generates by inhibiting the production of protein at the gene level are also incorporated.

Geiger gains additional information regarding the processes in the metabolic network by feeding his model extensive data concerning all the proteins formed, modified and degraded during the development of T cells. This information is provided by Matthias Mann, professor at the Max Planck Institute of Biochemistry.

Thanks to this integrative approach, the scientist can on the one hand check whether the independently collected sets of data are compatible and on the other hand determine how they are linked to each other. In this way, he can for instance show how the abundance of a metabolite changes when larger quantities of the protein that generates it are produced.

Possible applications in medicine and clinical research

However, Geiger is not only involved in basic research. The objective of this project is clearly to apply the results in medicine and clinical research. Antonio Lanzavecchia’s research group at the IRB is the perfect setting to do so. Lanzavecchia, a physician by profession, specializes in the work with human cells and follows an holistic and application-oriented approach.

Geiger is currently taking the first step towards a practical application: he is about to launch a long-term experiment with mice, aimed at finding out whether it is possible to steer the differentiation of T cells using certain active substances. “Our first ambition is to see whether we can increase the number of memory cells in the mice’s blood by submitting them to a specific diet”, explains the scientist.

Providing this experiment succeeds, it might in future be possible to use a diet or dietary supplements to selectively influence the human body’s own defense system. According to Geiger, it might also be possible to render certain vaccines more efficient and the protection they provide more durable by concurrently administering a drug that encourages the development of memory cells.

Geiger describes his project and systems immunology, a very specialized field of research, as being “super interesting”. He feels very privileged because he can collaborate with excellent partners, who in his words are “among the best in their respective disciplines”, and thanks to whom his work is progressing very rapidly. With regard to his project, the scientist especially hopes that his work “will bring results which can later be of use to someone”.

The project at a glance

Project title: Metabolic Regulations of Human T Cell Activation and Differentiation

Applicant: Dr. Roger Geiger, ETH Zurich and Institute for Research in Biomedicine (IRB) Bellinzona

Host research groups: Prof. Antonio Lanzavecchia, ETH Zurich / Institute for Research in Biomedicine (IRB) Bellinzona and Dr. Nicola Zamboni, ETH Zurich

Duration: 2013–2015

Project type: Transition Postdoc Fellowship – young PhD graduates formulate their own interdisciplinary project application and switch to a complementary discipline that is new to them.

Heide Hess

ERASysAPP launches a first transnational call for proposals

Extending interdisciplinary research beyond national boundaries

"ERASysAPP", the European Network for Applied Systems Biology, launched its first transnational call for proposals at the beginning of November 2013. The sixteen network partners are jointly calling for systems biology research projects involving interdisciplinary teams from various participating countries.

By means of this transnational call for proposals, ERASysAPP aims to encourage collaborations in the field of systems biology beyond national boundaries and to link scientists across Europe more efficiently. Interested researchers are invited to submit their project applications by January 31, 2014. These will subsequently be reviewed by a panel of experts consisting of renowned scientists from various fields as well as representatives of the partner countries. A decision regarding the projects to be funded will be taken in the fall of 2014.

Applied research at the heart of this call for proposals

This ERASysAPP call for proposals intends to promote systems biology projects focused on a practical application of results, in industry for instance. According to Rob Diemel, representative of the Dutch network partner, systems biology is now well established in basic research, and industry is increasingly showing interest. "It is time to determine which systems biology results might be applicable in practice", adds Diemel, who is involved in the organization of this call for proposals.

Project proposals should deal with biological or physiological processes of general interest to life sciences and biotechnology. The main focus of the planned research should be on microorganisms, plants or animals. But proposals in the health field will also be considered, providing the emphasis is placed on answering biological questions.

International consortia are to be formed

To guarantee transnational collaborations, only projects involving at least three ERASysAPP partner countries will be given financial support. The consortia should include at least three and at the most eight research groups. When describing the joint project, it is essential that the applicants adhere to the framework requirements specific to their respective countries. These conditions are detailed in the National Annex of the call for proposals. Important variations are to be expected regarding eligibility, financing and administration, depending on the regulations defined by each country.

The following rules apply for Swiss applicants: only researchers working in public institutions are qualified to receive funding. Private companies can join a consortium but will not be eligible for financial support. The amount to be allocated is also country-specific: the Swiss research team will receive a maximum of 400,000 Euros per project for a period not exceeding 36 months.

Success factors for transnational projects

The writing of the joint project proposal is not the only challenge the applicants will encounter. "Establishing intensive research collaborations beyond national boundaries will be much more demanding", believes Rob Diemel. He knows from experience that "efficient communication within the project and regular meetings for exchange purposes are important success factors."

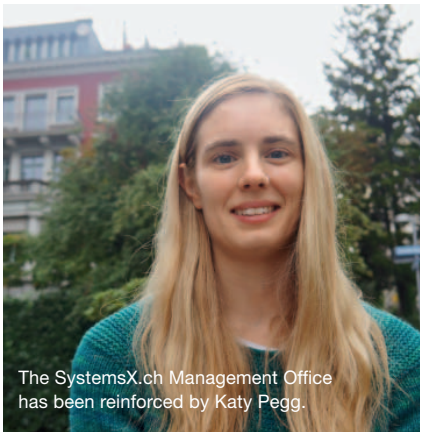
ERASysAPP
ERA-Net for Applied Systems Biology

Partner countries and institutions participating in the first transnational call for proposals:

Cyprus	Research Promotion Foundation
Germany	Federal Ministry of Education and Research (BMBF)
Latvia	Latvian Academy of Science
Luxembourg	National Research Fund
Norway	Research Council Norway
Romania	National Authority for Scientific Research
Sweden	Swedish Research Council, West Götaland County Councill
Switzerland	SystemsX.ch
The Netherlands	ZonMw – The Netherlands Organisation for Health Research and Development

Detailed information regarding the first joint transnational ERASysAPP call for proposals can be found at:
www.erasysapp.eu/open-calls

Welcoming a new SystemsX.ch colleague and an internal shift



The SystemsX.ch Management Office has been reinforced by Katy Pegg.

Katy Pegg joined the SystemsX.ch team in September. In her role as personal assistant to the managing director, Daniel Vonder Mühll, she supports him in all administrative matters and is consequently one of the main contacts in the Management Office. Katy Pegg will also organize the second International SystemsX.ch Conference, to be held in October 2014 in Lausanne.

Katy Pegg has worked for two different SystemsX.ch partner institutions: she was able to gain experience in research and academic environments during an internship at the Paul Scherrer Institut and as a research assistant at the EPF Lausanne. Prior to these positions, Katy Pegg, originally from Britain, completed her masters in mathematical physics at the University of Edinburgh and spent time abroad, completing hands-on training and working for social projects.

Thanks to this reinforcement of the team, Vanessa Deppeler, the previous assistant, can be relieved of her administrative tasks and can now concentrate on financial issues, her tasks and responsibility in this area having steadily increased over time.

The whole team is looking forward to a productive collaboration and extends a warm welcome to Katy Pegg.

vdm

Second International SystemsX.ch Conference

The second International SystemsX.ch Conference on Systems Biology is scheduled to be held October 20–23, 2014, and will take place at the Swiss Tech Convention Center in Lausanne. This event, lasting several days, will bring together leading systems biologists from Switzerland and abroad.

The conference program includes five key topics: “Quantitative Cell Biology”, “Theory and Biophysical Modeling”, “Systems Genetics and Medicine”, “Single Cell Dynamics and Stochastic Phenomena” and “Regulatory Genomics”. Noted scientists will give a subject-related talk in each of these categories. The scientific contributions will be accompanied by a large poster exhibition with awards for the best presentations.

csl

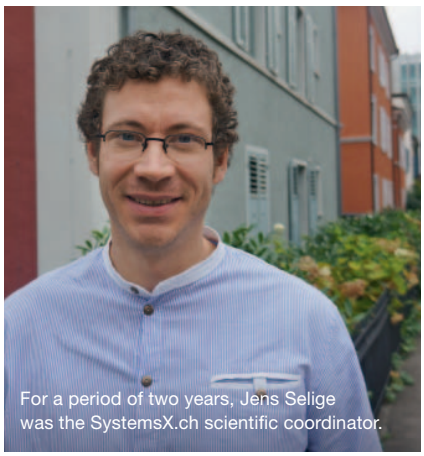
The provisional program and the confirmed speakers can be found at:
www.systemsx.ch > Events > SystemsX.ch Conferences

Jens Selige to leave SystemsX.ch

Jens Selige’s initial encounter with SystemsX.ch took place when he attended the “1st International SystemsX.ch Conference” in 2011 in Basel. This event offered him a good opportunity to gain an overview of the ongoing projects of the research initiative. In January 2012, he then began his work as the scientific coordinator for SystemsX.ch. From the very beginning, his expertise was highly appreciated, as the application for participation of SystemsX.ch in the ERASysAPP program, the European network for applied systems biology, needed to be written at that time. Jens was also in charge of postdoctoral and doctoral education and networking among young scientists. He organized the 2012 and 2013 retreats in Engelberg as well as the 2013 All SystemsX.ch Day in Bern. But Jens Selige was equally able to motivate scientists to participate in events outside the educational field: last year, two interdisciplinary SystemsX.ch running teams successfully took part in the SOLA-Stafette.

We thank Jens Selige for his contribution and wish him all the best in his further pursuits.

vdm



For a period of two years, Jens Selige was the SystemsX.ch scientific coordinator.

Upcoming Events

February 4-5, 2014
Life Sciences Switzerland (LS²) Annual Meeting
Lausanne

March 2-8, 2014
Advanced Lecture Course on Systems Biology
Innsbruck, Austria

June 17-19, 2014
International Conference on the Systems Biology of Human Disease (SBHD)
Boston, USA

June 22-27, 2014
Joint Summer School SystemsX.ch and SIB Swiss Institute of Bioinformatics
Kandersteg

September 14-18, 2014
International Systems Biology Conference (ICSB)
Melbourne, Australia

October 20-23, 2014
2nd International SystemsX.ch Conference on Systems Biology
Lausanne

SystemsX.ch
The Swiss Initiative in Systems Biology

Impressum

Publisher: SystemsX.ch, Clausiusstr. 45, CLP D 7, CH-8092 Zurich — Contact: admin@systemsx.ch, Phone +41 44 632 42 77, www.systemsx.ch — Editors: Christa Smith (csl), Matthias Scholer (msc) — Collaboration: Daniel Vonder Mühll (vdm), Heide Hess (hh) — Graphic design: Daniel Zwimpfer — Print: Sihldruck AG, Zurich — Translation: Scitrans.ch

Newsletter subscription: communications@systemsx.ch