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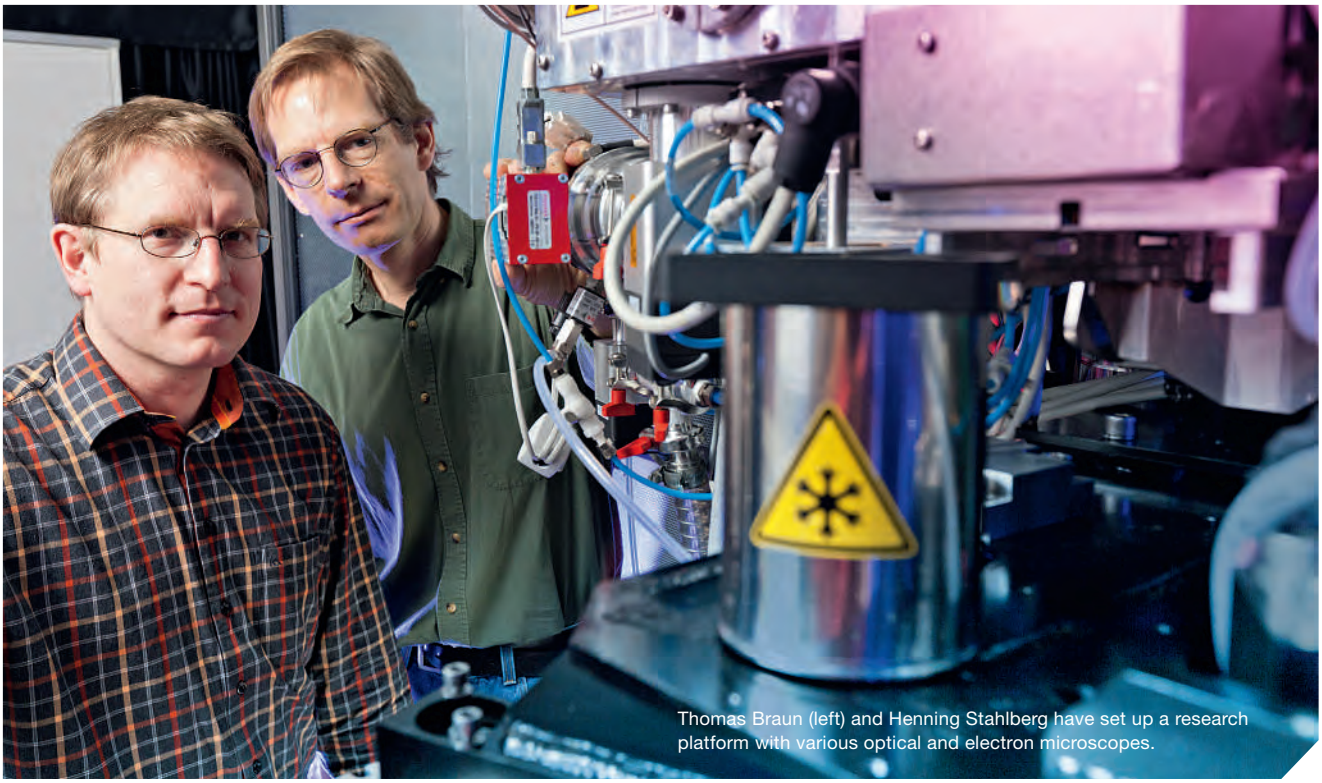
The CINA RTD Project

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

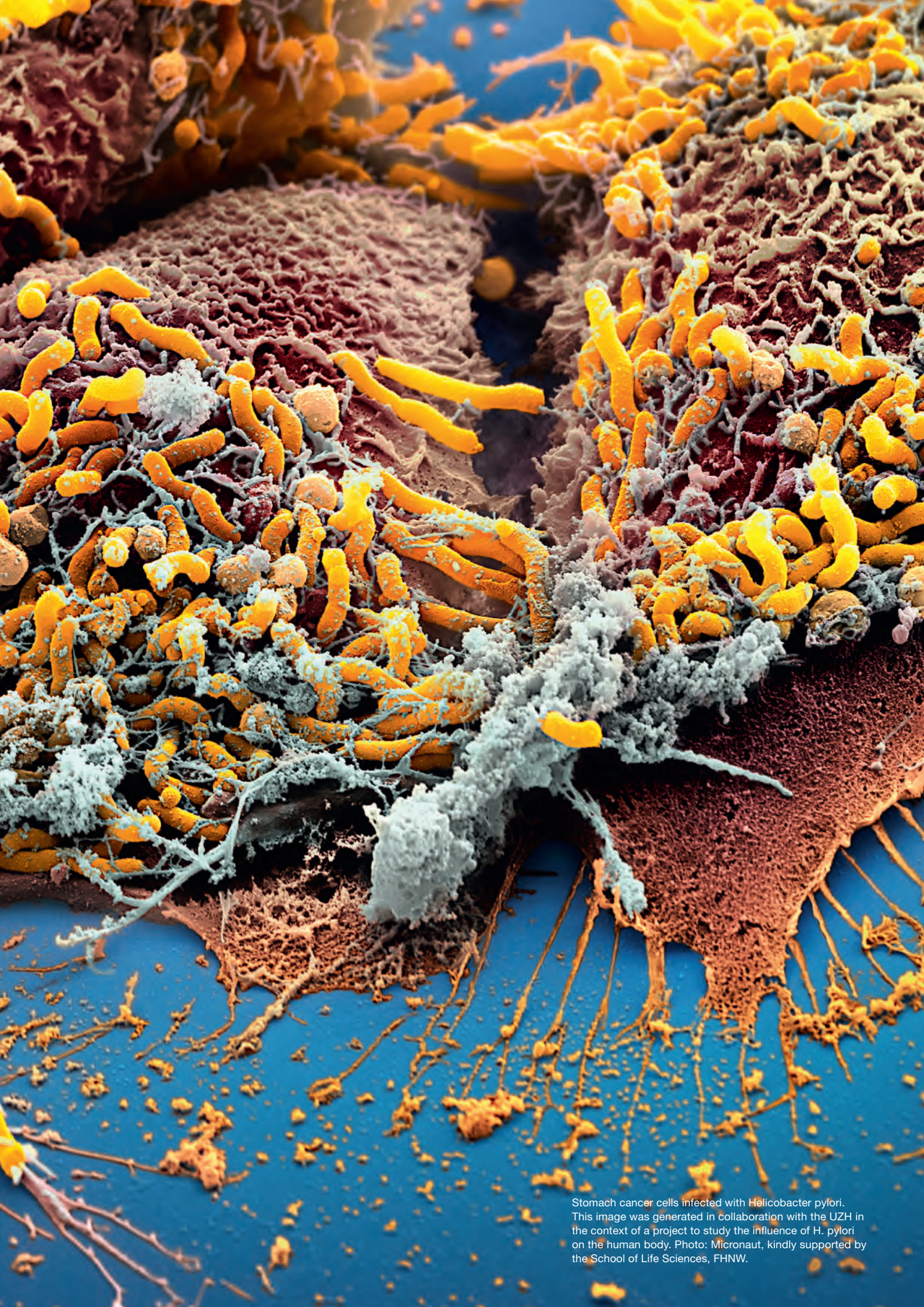
The "Imaging Platform" is a research platform uniting different types of optical and electron microscopes which allows scientists to produce two- and three-dimensional images of samples of various sizes. Basically any external research group can use the CINA platform. But Stahlberg emphasizes: "We are 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.

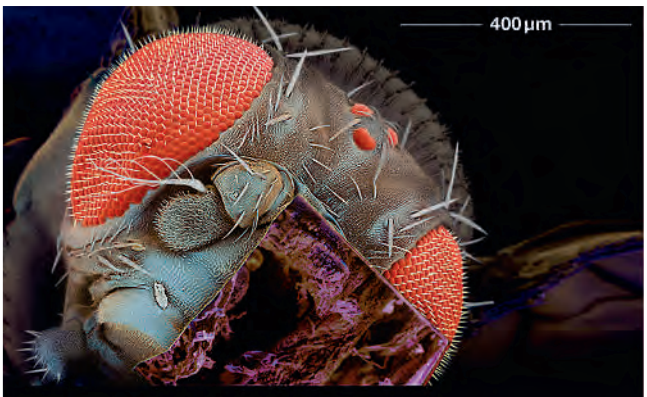
The efficacy of drugs can also be examined thanks to the CINA technologies. "When we measure the amount of a specific protein involved in a given disease before, during and after the application of a drug, we can say something about the efficacy of this medicinal product", explains the project leader.

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.

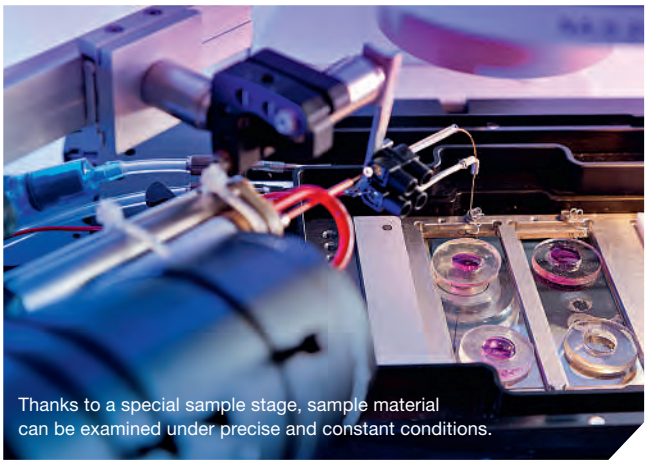
What's more: "Roche has also helped finance our Titan." The bulk of the 5.5 million Swiss francs came from the University of Basel, and SystemsX.ch funds also backed the project. But Roche equally contributed a considerable sum, amounting to approximately 1.2 million francs.

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