Dear colleagues

It’s happened, Daniel Schümperli has officially retired. Daniel’s research contributions have spanned nearly four decades and advanced many areas of RNA biology including histone 3’ end formation, U7 snRNP biology, roles for RNA processing in disease, and development of U7 snRNA for redirected splicing. Daniel’s career shows the ideal trajectory from basic science to the application of knowledge gained for therapeutic approaches. In addition to Daniel’s legacy of discovery, he has the legacy of having trained the next generation of scientists. Daniel is also an outstanding leader who provides a calm “on target” perspective from which the organization benefits. As researcher, mentor, and leader, Daniel’s impact on individuals and institutions continues. In this regard it is highly appropriate that Daniel’s retirement presents an excellent opportunity to bring in a prominent RNA biologist to contribute to the long-term growth of the NCCR.

Interview with Prof. Daniel Schümperli

“The field has kept on providing surprises and interesting things that nobody ever believed possible.”

Daniel Schümperli looks back on 40 years of RNA biology and gives insights into his career as a Professor in the field of RNA: He talks about the fascination of the breaks in the central dogma, the importance of teachers and role models, the Swiss RNA community, and the impact of science communication among peers and beyond.

Were you interested in Science as a young person?

During my childhood I liked to read adventure stories, especially ones about explorations in foreign countries. However my interest in science was mainly stimulated by a primary school teacher. I was about 10 years old when this teacher took over our class. He was so much interested in biology that he kept beetles and fish in the classroom and organized an exhibition of mushrooms, which we had collected in the forest. Infected by his enthusiasm for nature, I kept an aquarium and raised various caterpillars at home.

Initially you were trained as a veterinarian. What made you decide to transition to research in biology?

I was interested in animals and nature and initially thought of studying zoology. But then the veterinarian who treated our dog influenced me to go to vet school. Eventually, what made me move into experimental biology were two professors I had during my veterinary studies. In the first year, we had zoology courses with Ernst Hadorn, one of the pioneers of developmental biology in Switzerland. He gave excellent lectures on genetics and developmental biology that fascinated me. Maybe an even more important influence was a very young lecturer by the name of Roland von Fellenberg, who was teaching us biochemistry and immunology. What most stimulated my interest was a lecture about the recent discovery of retroviruses and reverse transcriptase. Being able to reverse the flow of genetic information seemed so interesting that I asked to do a practicum in the biochemistry lab during the summer break. Soon afterwards this activity turned into a veterinary thesis, which I completed almost simultaneously with my final exams in veterinary medicine. By then it was clear to me that I wanted to work in experimental biology, to look at genes and DNA, DNA replication or something in this direction.

And then you went on to study RNA processing. Why did you choose to work on RNA?

I was interested in molecular biology, and RNA is part of it. After three years in a veterinary virology institute, I found an excellent postdoctoral position at the National Institutes of Health in Bethesda Maryland with an excellent molecular biologist, Marty Rosenberg. I took over a project to develop a readout system for promoters and terminators in mammalian cells. I made reporter constructs, which was quite something new. Later I got a position in Zürich as an Oberassistent of Max Birnstiel. One of the topics in the Birnstiel lab were...
histone genes, and I thought I would use my system to study promoters and terminators of histone genes. However, it turned out that the promoters were already very well studied by Birnstiel’s students and postdocs. So I decided to look at 3' end formation. Together with a PhD student in the lab we could show that this 3' end, which looked like a bacterial terminator, was actually not a terminator but a 3' end processing site. This was when RNA processing came into the story. I had already been fascinated by RNA processing for several years - the discovery of splicing, of capping and polyadenylation, the first in vitro systems. I had read about all of that, but now, all of a sudden, I was in the middle of it. And then with my first PhD student we started to look at the cell cycle regulation of histone genes and again discovered that 3' end formation was important for this regulation. So that’s how we got into the RNA field and followed up this lead.

And when did the U7 snRNP come into play? That was early in the Birnstiel lab. As I said before, there were students looking at histone promoters. And there was this one student looking at 3' end formation with whom I could show that this was a processing and not a termination event. Another person in the lab was fractionating sea urchin extracts to trace down an activity that complemented the deficient 3' end formation of a sea urchin histone gene in the heterologous Xenopus oocyte system. It was initially thought that the active principle would be a protein. But then, soon after people in the lab tried to clone a cDNA for it, they discovered that polyadenylated RNAs couldn’t do the job but a non-polyadenylated short RNA did rescue the 3' end formation. That’s what led to the discovery of U7 snRNA. We could show that it is involved in this processing reaction. A few years later, when I was actually studying the cell cycle regulation of the histone genes, one of my own PhD students and myself started to search for the mammalian U7 RNA. We were able to determine its sequence and publish it almost simultaneously with two other labs which were on the same track. After that, we started to study the U7 snRNA in more detail in the mammalian system.

Initially, the U7 snRNP was central in your studies on histone pre-mRNA 3' end processing. Later on, you developed and used it as an antisense tool to correct aberrant splicing in beta-Thalassemia, Spinal Muscular Atrophy (SMA) and later also Erythropoietic Protoporphyria (EPP). How did the idea come up to use a modified version of the U7 snRNA as a splicing modulator?

That was an interesting story. I was already in Bern, and we had just characterized the assembly of the U7 snRNP. We had identified the Sm binding site, a sequence in the RNA that recruits proteins and that is important for making this ribonucleoprotein particle and importing it into the cell nucleus, also determined the abundance of the U7 snRNA. It was not a very efficient assembly, and we could show that, if we changed the sequence of this Sm binding site into a sequence resembling the Sm binding sites of the major snRNPs involved in splicing, then we would boost the assembly. However we produced a U7 snRNA that was no longer functional in histone RNA processing. After publishing these findings, I went to one of the RNA meetings in the US and, after the meeting, flew to North Carolina to visit my competitor Bill Marzluff. He invited me for dinner and brought along a colleague, Ryszard Kole. Ryszard told me about work he was doing with antisense oligonucleotides to correct splicing. After the dinner, I returned to my hotel room and had the idea that this U7 snRNA, which was no longer functional in histone RNA processing, could be an ideal tool to express antisense sequences in the cell nucleus. The next morning I was scheduled to have a scientific discussion with Ryszard Kole, and I told him: “well I think I have a RNA that could do exactly what your oligonucleotides are doing”. We decided to start a joint project. I sent a new PhD student to North Carolina to learn the necessary techniques in Ryszard’s lab. Later I also did a sabbatical there, and we got this project going. It was really the two different observations coming together at this dinner table that had generated a new project, a new idea.

Over 20 years have passed since you did the first experiments with the U7 snRNA as a splicing modulator. Where does the research stand today? It has been used by a number of people, including us of course. Usually it’s been successful in cell culture but it has not been applied a lot in animal models or in patients.

“By then it was clear to me that I wanted to work in experimental biology ...”
There are a few success stories in animal models. A group in France has done successful studies on mouse and dog models for Duchenne Muscular Dystrophy (DMD). We on the other hand, have had some success recently with a mouse model for SMA, where we can show that the mice, which otherwise die within 1 or 2 weeks after birth, survive for a long time and have very moderate SMA symptoms. Otherwise, I am not aware that it has been used a lot in vivo, be it in animal models or in human beings. I think one of the problems is that industry is shying away from gene therapy. There have been unwanted side effects in some gene therapy trials. Insertional mutagenesis may lead to cancer, and in one case, where adenovirus vectors were used, inflammations occurred which caused the death of a patient. On the other hand, certain gene therapies seem to be successful and start to being used. But the field has been very slow. In part, this is due to a resistance or resilience of the industry to get into the field.

Do you see a way to overcome this resistance?

It is difficult to predict. Any success in the field will influence the attitude that people have. If one of these therapies is successful, then hopefully the industry will get into it. A gene therapy is usually a relatively severe intervention depending on what the target tissue is. I can also understand from the point of view of the patients or regulatory authorities that it might be preferable to use small molecule drugs or antisense oligonucleotides. There are a few success stories with antisense oligonucleotides that have gone to the clinic and there are also promising candidate drugs that can modulate splicing. However it is not yet clear what kind of side effects these drugs will have. What works and what will eventually become state of the art in terms of correcting splicing diseases will very much depend on the success of these individual stories.

How did you experience the development in the RNA field throughout your career?

I think it was great. It was just very thrilling to see all these developments. I told you that initially what more or less got me into the field was this mention of reverse transcription. The genetic code and the discovery of translation were before my time and were very interesting. But then came all these breaks of the central dogma: the reverse transcriptase, RNA processing, RNA editing – all this happened during my lifetime, and I was part of it. Almost each new congress came with a new exciting discovery. Later there was RNA interference, microRNAs and all the non-coding RNAs. The field has kept providing surprises and interesting things that nobody ever believed possible. I think it is a great field.

Throughout your career as a group leader, you trained over 50 scientists as diploma and master students, PhD students, and postdocs. Many of them are today independent group leaders in Switzerland and abroad. What is your recipe as a successful mentor and what would you advise junior scientists to succeed in their academic careers?

My role model as a mentor was Marty Rosenberg, my supervisor during my postdoc in the US. This was a lab that functioned more or less without pressure. It was completely controlled by excitement, enthusiasm, a very collegial atmosphere, doing things together and finding that research is fun and exciting. I tried to copy this for my own group. Whether I succeeded is difficult to say. If you can provide an atmosphere where people can experience this enthusiasm and share it with others, I think that is the best you can do. People should find out what excites them, what they are really interested in, and then try to follow that lead. The best you can do is to do that for which you are highly motivated. Then you have the best chance to become good in your field and to succeed. I know that quite a number of people have suggested the same. I remember when I started my own studies that one of the older professors in Zürich had an introductory lecture and was saying exactly the same: “don’t just look at what the job market will be or where you could find chances of going, but try to find out what really interests you and then move forward”.

In the NCCR RNA & Disease you were very committed as the leader of the “RNA metabolism” work package, as the delegate

… the connectedness of the field is growing and developing, and this is a strong bonus for the future.”
Interview with Prof. Daniel Schümperli

for communication, and as member of the steering committee. How do you think the NCCR influences the Swiss RNA community and where do you see the potential of this NCCR in the future?

The Swiss RNA community was already quite well connected before the NCCR. We had the annual Swiss RNA Workshop. Also, going to the same meetings, meeting people abroad at RNA meetings – for example those of the international RNA Society – was always a good way to connect the field. What the network has brought in addition are all these common activities like summer schools, meetings between the groups, between the PI’s, but, most importantly, between students and postdocs. I can really feel in those meetings that the connectedness of the field is growing and developing, and this is a strong bonus for the future. What is a bit more difficult to predict, is the influence it will have in the broader sense: like connecting to the medical community or the private sector. Those are certainly fields where networking is much more difficult to establish but will be important. And it will be a challenge for the network to succeed in generating such connections.

You put significant effort into public outreach. How important is it to communicate the science to the public and medical community?

For me, it started out of a personal necessity. When I returned from my postdoctoral stay in the US, I started as an Obersassistent in Max Birnstiel’s lab, in one of the best labs in Europe or in the world. I came back to Switzerland, and there was such a negative attitude towards molecular biology, towards cloning and gene technology. Many of the people whom I interacted with, whom I loved or liked were very negative. This put me in a difficult position. I had to find ways of justifying what I was doing, and I was struggling with this. I realized that, as a scientist, one could not just pretend that these problems didn’t exist but that one had to do something about it. Later, when I had become a professor in Bern, I was asked to do something for the broader community. While others may have served on the scientific board of the Swiss National Science Foundation or have done something within science, I was asked by the Swiss Academy of Sciences to get into science communication. At this time, they set up a forum on gene technology, “Forum Genforschung”, which was more or less a reaction to criticism in the society and to a people’s initiative, the “Genschutzinitiative”, that would have forbidden quite a number of activities. I worked in the board of this forum for quite a while and later became its chairman. We tried to establish a dialogue with stakeholders in the field, such as consumer organizations, animal protection people, people in the agricultural community and politicians. I think that was really important work. Personally, I was at that time a member of the social democrat party. I joined a committee that was counseling the party’s parliament members on all kinds of issues related to education and science. Of course, gene technology was one of the hot topics there. I tried to communicate to the people what I was thinking of the field and could to some extent act as a mediator. I saw that there were lots of fears and antagonisms against this area of research. In the long run, if we want to use the money of the taxpayers, we as scientists need to provide something that is of interest to the community as a whole and we need to justify what we are doing. It is also important in terms of culture. The public knowledge of science is probably more or less at the level of the 1930s, 1940s – the time of the discovery of antibiotics. Many of the new things that have happened since the 2nd world war have not gone into general culture. One needs to do something to communicate these things and to help the society to integrate the new knowledge.

Besides your engagement in science, you were also active in merging science with music in a project with two other scientists that you called “HUGO hat Töne”. How much art do you think is needed in science?

Well, in a way you don’t need art in science, but I think that the two fields are related. Maybe people in the art field or art history field would not agree with me, but I can see parallels. On the one hand, art has always progressed with people who are avant-garde, who are outside of the mainstream and have maybe crazy ideas, do something that is not trivial. The rest of the society often neglects these people. It is a bit similar in the sciences. We are not particularly well noticed by the society and we are kind of outside, trying to develop new things and new ideas. This is the avant-garde aspect. But then there are also other aspects – how you make something completely new. In the arts a lot of it is playful, trying to combine different things, finding new techniques and finding new combinations. In some parts of the arts community, for example in music, it is also important that you can interact, that you can be part of a team, like a band or a group of musicians. I think those aspects also play a role in science. A lot of discoveries in science come from playing around, from figuring out how to make something, how to make an experiment work, how to develop a new technique. All of a sudden, with this technique, you discover something new. And a lot of it is interaction, teamwork. These are aspects that I find very similar in arts and sciences. Whether one needs the other is completely subjective. For me it was interesting, because I was also involved in experimental music and I tried to bring these two fields together. It was an interesting experience and also helped in science communication. It was a way of showing on the one hand to the people interested in modern music or art that there was something in science to be discovered, and on the other hand to people in science that there was something in modern music to be discovered.

What activities are you looking forward to after your retirement?

I will certainly stay connected to research, I will stay connected to this NCCR but I also want to develop some of my personal hobbies. Depending on how healthy I will stay, I will do more outside activities, hiking, training our dogs. Having a bit more freedom and leisure time to do things that I like, read, play music, all kinds of things.

“Any success in the field will influence the attitude that people have.”
Research highlights from NCCR laboratories

Thomas Schnyder

Major role for minor spliceosome

Dysregulation of RNA metabolism is associated with a wide range of diseases, notably cancer and several neurological disorders. A deeper understanding of how RNA-processing is regulated could not only provide insight into the pathomechanism of diseases but also lead to the identification of targets for medical treatments.

By having pinned down the mechanism of action of the RNA-binding protein Fused in Sarcoma (FUS), the groups of Marc-David Ruepp and Oliver Mühlemann now made a big step closer towards the understanding of one of the most devastating human neurological diseases, amyotrophic lateral sclerosis (ALS). Most ALS cases appear sporadically, but ALS can also be inherited (familial, fALS; ~10%) due to mutations in different genes. In 2009, mutations in the FUS gene were identified as a novel cause for ALS. FUS is a ubiquitously expressed, mainly nuclear protein of the hnRNP family. Most reported ALS-causing FUS mutations are missense mutations clustered in the C-terminal nuclear localization signal, which lead to a reduced import of FUS into the nucleus and to the formation of FUS aggregates in the cytoplasm of neurons of ALS patients. Is it the loss of FUS function in the nucleus or the gain of FUS function in the cytoplasm by which mutations the FUS gene drive the pathomechanisms in ALS?

Based on more recent data showing that FUS is present in spliceosomes and that it interacts with several splicing factors, the group of Ruepp addressed the roles of FUS in influencing pre-mRNA splicing. In collaboration with researchers from the University of Milano, the Bernese characterized the FUS interactome by mass spectrometry. They found minor spliceosome components highly enriched among the FUS-interacting proteins, and that a FUS knockout affected predominantly the removal of minor introns.

The authors confirmed that FUS is necessary for regulating the splicing of minor intron-containing mRNAs, among them voltage-gated sodium channels that are required for proper muscle function and post-natal maturation of spinal motor neurons. Moreover, an ALS-associated FUS mutation that leads to cytoplasmic aggregates fails to promote minor intron splicing and traps the minor spliceosome components U11 and U12 snRNA within these aggregates.

The paper of Reber et al. shifts the attention from the current focus of the more abundant major spliceosome to the far less abundant minor spliceosome. Due to its low abundance, the minor spliceosome is much more at risk of being functionally affected by the sequestration of U11 and U12 snRNAs into cytoplasmic FUS aggregates than the major spliceosome.

The finding that FUS plays a role in splicing of minor introns suggests a possible pathomechanism for ALS and extends the spectrum of diseases, where minor spliceosome plays a major role. It even might open a new gateway to develop and design new therapeutics.

Original article in The EMBO Journal

Expanding the genome editing toolkit

In recent years, life science research has been transformed by the emergence of genome editing technologies based on the CRISPR-Cas system. Cas9 is a CRISPR-associated DNA endonuclease that can be programmed by short guide RNA molecules to cut genomic DNA whose sequence matches the guide RNA. This can be exploited to introduce genetic modifications near Cas9-generated DNA cuts. In addition to basic research, the Cas9-mediated genome editing technology holds great promises for industrial and clinical applications, and has sparked a major bioethical debate.

The group of Martin Jinek, Department of Biochemistry, University of Zurich, uses structural biology to study the molecular mechanism of Cas9. By using x-ray crystallography, they determined the atomic structures of the Cas9 and its complex with guide RNA and target DNA molecules and elucidated the mechanisms of action by which Cas9 binds target DNA.

RNA-guided DNA binding and cleavage by Cas9 depends on the presence of a short sequence known as protospacer adjacent motif (PAM) in the target DNA. Although the PAM requirement greatly contributes to the precision of DNA cutting, it also restricts the utility of the natural Cas9 enzyme to target genomic sequences juxtaposed to the canonical PAM sequence NGG. Thanks to a method known as directed protein evolution, a new generation of Cas9 enzymes has been developed. These artificial variants, known as VQR, EQR and VRER Cas9, recognize non-canonical PAM sequences such as NGAG and NGCG.

The group of Martin Jinek and colleagues aims at contributing to the development of genome editing tools and technologies.

Original Article in Molecular Cell
New support schemes for young scientists with family care duties

Female academics are a minority because at each branch point in the academic career a higher proportion of woman than man leaves science. Despite significant efforts made in the past that for example allowed to close the gender gap at the PhD level, recent years have seen little advances in this trend and the continuous loss of female scientists as they progress in their career persists. In the EU, the number of woman full professors is still disproportionally low at around 20% (see Figure).

There are multiple reasons underlying the academia’s leaking pipeline and they are multi-faceted. This is a complex problem and is likely a consequence of obvious (maternity leave for example) and more intangible differences between man and woman. Some of the factors that have hindered women’s career progression are also likely to affect men, for example if they chose to contribute equal amounts of time to the raising of children.

The NCCR RNA & Disease Equal Opportunities work package develops activities aiming to promote diversity within our network by providing training and funding schemes to support equal opportunities.

In December 2015 we surveyed the NCCR RNA & Disease community to assess the awareness on equal opportunities issues and identify potential areas of action. The results of this survey (that can be accessed on the NCCR RNA & Disease webpage) were presented at the NCCR retreat in January 2016 and used as the starting point for the lively group discussion that followed. We would like to thank to everyone who participated in the survey and/or the discussions for engaging in this activities and for all the feedback and suggestions. Your contributions have been invaluable to develop the Equal Opportunities activities that we will pursue in the current phase of the NCCR RNA & Disease.

In the past months we focused on the development of two new schemes that will significantly improve our support to NCCR RNA & Disease parents and parents-to-be.

Alongside the financial support for female and male researchers with family care duties (120% support grant), we are happy to announce two new schemes available as of July 2016:

**Emergency childcare**: The NCCR RNA & Disease will reimburse up to 10 hours/per year per parent for emergency childcare.

**Pregnancy and maternity leave compensation**: To reduce stalling of the project due to maternity leave, the NCCR RNA & Disease will cover the salary of a support person during the last 3 months of pregnancy to ensure appropriate training of a research assistant employed to continue the project of an expectant scientist during her maternity leave.

Both schemes are open to members of NCCR RNA & Disease laboratories and associated groups and are available until allocated funds run out. For detailed information on eligibility criteria and how to apply, please refer to the NCCR RNA & Disease webpage.

We hope this new schemes will support the careers of talented Swiss RNA scientists.

Ana Marques and Larissa Grolimund
Announcements

People

We would like to welcome Prof. Ramesh Pillai as a new full member of the NCCR. He joined the network as an associate member in 2015 and is full member since May 1st 2016. Read more about his research here.

Further, we would like to introduce Prof. Volker Thiel, Institute of Virology and Immunology, University of Bern, as a new associate member. His work focuses on RNA viruses, the mode of viral RNA synthesis, mechanisms of RNA virus gene expression, and how RNA impacts host cell response and disease.

As of May 1st 2016, Prof. Daniel Schümpeli was replaced by Prof. Mihaela Zavolan as the leader of work package 2 on “RNA metabolism” and by Prof. Oliver Mühlemann as the delegate for communication. Furthermore, Prof. Ana-Claudia Marques succeeded Prof. Mihaela Zavolan as the delegate for equal opportunities and Prof. Mariusz Nowacki took over the mandate of the delegate for the technology platforms from Prof. Marc Bühler as of May 1st 2016.

Upcoming events organized by the NCCR RNA & Disease

> NCCR RNA & Disease PI retreat: August 30–31 2016, Oberhofen

> NCCR RNA & Disease monthly seminar series at University of Bern and ETH Zürich

> Joint NCCR Workshop on “Collaboration” by the NCCRs RNA & Disease, TransCure, and Kidney.CH: November 24–26 2016, Schloss Münchnwiler

Passed events organized or supported by the NCCR RNA & Disease

> Farewell Symposium for Daniel Schümpeli “RNA Biology and beyond”: June 9–10 2016, Bern

> NCCR RNA & Disease general assembly: April 5 2016, Bern

> 2nd NCCR RNA & Disease site visit: March 22–23 2016, Bern

Jobs

PhD program in RNA biology

Find out more on our website.

Support Grants

The NCCR RNA & Disease granted a lab exchange to Dr. Sébastien Campagne (Allain lab) for a two weeks visit at the facility of electron microscopy and tomography at CEITEC Masaryk University, Brno, Czech Republic, to Dominique Furrer and Cristina Höhener (Nowacki lab) for a short stay in the laboratory of Ramesh Pillai at EMBL Grenoble, France, and Hasan Vatandaslar (Wutz lab) for a visit in the laboratory of Thomas Tuschl at the Rockefeller University, New York, USA.

Please visit our webpage for more information on the Lab exchange program, the Doctoral mobility grant and measures in equal opportunities.

Cryo-EM support

As of the beginning of May NCCR groups and associated members have access to cryo-EM support. The support includes preparation of provided samples for visualization using negative stain techniques and for cryo-electron microscopy. Upon negotiation the platform collects data for the determination of a low resolution structure from negative stained samples. Please visit our webpage for more information on the cryo-EM support.