

# THE MESSENGER

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**NCCR  
RNA & Disease**

National Center of Competence in Research  
The role of RNA in disease mechanisms

## Dear colleagues

Training and Education has always been a main pillar of the NCCR RNA & Disease. Some activities in that area have preceded the actual research activities. The NCCR RNA & Disease officially started its activities in May 2014 and concomitantly the new NCCR PhD program in "RNA Biology" was born. Such a kick-start was only possible due to the strong dedication of many NCCR colleagues to indeed reach our professed education goal which is to "set up a Swiss RNA research network & attract students with an interest in RNA biology and its applicability in medicine". Now, at the end of the first phase of NCCR RNA & Disease more than 30 PhD students are enrolled in the PhD program. This is however by far not the only activity in training & education. Other highlights are the RNA biology lecture series, research seminars by invited speakers, and the summer schools. In fact, we just had our second summer school in August 2017 which was, such as the first one two years ago, a big success on all fronts. It is of note that we are constantly developing further measures, such as the most recently launched PreDoc program. This program allows motivated master students to rotate for one year through different NCCR labs before actually starting a PhD project. Thus the NCCR training & education program is up and running since the very beginning of our network and contributes significantly to the success of the NCCR RNA & Disease.



**Norbert Polacek**  
Delegate Training and  
Education NCCR RNA &  
Disease

## Interview Juan Valcárcel

"RNA should in a way be  
an icon of  
our culture."

**Juan Valcárcel tells us about his career, alternative splicing research including its relation to cancer and his view on research networks.**

*What made you become a scientist?*

As a child, I was very curious about the nature and composition of things. When I was twelve years old, I got interested in chemistry and with thirteen I learned about the genetic material. This convinced me that I wanted to understand how DNA ended up producing living organisms.

*Do you have scientific role models?*

Charles Darwin for example. As a child, Fleming looked to me as the ultimate scientist because he looked like a normal human being, forgetting about plates for months and not keeping the most pristine bench. What he made out of a simple observation, which initiated a whole field, was amazing. For me, Seymour Benzer was also someone that I admired because he showed how by just doing very simple experiments with bacteriophages he was able to infer the nature and structure of the genetic material.

*Can you tell us more about Fleming's discovery of antibiotics?*

I have become very interested in this story and I believe that I have read every book that has been published about this and recently also visited the Fleming lab museum in London. There were two schools at the time: one wanting to help the organism to fight infections and the other advocating the use of chemicals. Fleming was working in the group of Sir

Almroth Wright, who belonged to the school promoting the natural defense. Fleming's first main discovery was the enzyme lysozyme, which fights microbes in a natural way. The observation of the antibiotic phenomenon was like treason to his school. Nevertheless, he followed up on this observation, because this could bring essential advances to fighting infectious diseases, which was his research focus. There are many interesting sidewalks to this story, such that he named the compound but never isolated it. The compound's isolation was done more than ten years later by chemists in Oxford.

*Coming back to Darwin, can you comment on Craig Venter's reenactment of Darwin's voyage with the Beagle applying genomics techniques?*

This is great and has produced a lot of interesting information about the genomics of ecosystems. There is a nice metaphor because, in fact, Venter is now looking for weird organisms traveling the world. But I would argue that today's equivalent attitude of the naturalists in the 19th century of going into expeditions to find other organisms and how life looks like elsewhere, is looking via the computer into the databases. In these, you have the sequences of thousands of species. So for me the naturalist today is the person who sits in front of the screen and looks into the huge vast unknown that is behind these sequences. If you are smart enough to come up with exploration tools you can make discoveries that are tremendous without getting out of your living room. This allows exploration of the natural world.

## Interview Juan Valcárcel

*Given the importance of high throughput methods and the need for tools to analyze these large datasets, would you decide today to first obtain a degree in informatics or statistics before going into life sciences?*

I do not know if this would be first, but this is an absolute need not only if you are working in science but almost for anything. I have seen that these tools are as essential as any basic experimental tool. This is a crucial aspect to take into consideration when thinking about training our students. From the first year of university they should be able to be literate in computational analysis, especially bioinformatics. Without that, you are totally handicapped not only regarding the basic understanding of programs and operations that you can do in terms of computational biology, but also regarding your mind frame. Our textbooks are full of pathway schemes such as the flow of metabolites that look like linear pathways with some cycles present. Today it is apparent that we have to look at the unity of the genome and the organism. The processes are talking to each other in fascinating ways. These networks of interactions between components at any level are essential. When we do a knockdown of a gene, what we are in fact doing is perturbing many other genes, and this is a nuisance if you want because then these linear pathways are no longer going to be there. However this is reflecting a very profound reality of how living organisms are built. Everything they do is based on these networks of interactions at the gene, protein, organelle level and also between the cells forming an organism. We have to be able to understand systems from a systems perspective, and without that, we are going to be very limited.

*Could you share with us a defining moment in your career?*

My PhD thesis project was supposed to be a search for genes in the influenza genome that are important for the generation of variability. This was a fascinating topic for me, but I was doing this side project trying to express a gene from the virus, which is alternatively spliced. When I did that expression through the genome of another virus, I realized that the pattern of alternative splicing was changed entirely. This was for me the first time that I had discovered something that was not in a textbook and nobody had seen before. I then started to look into the process of alternative splicing and learned that there was almost nothing known about it. What was known at the time was that alternative splicing was happening in different tissues in different ways. There was such a disconnect between the very little that was known and the perspectives that were opened by the possibility of modifying the

readout of genes. I thought it could be fantastic to learn how splicing is regulated and I was very keen to move into this field. This was the most defining moment in my whole career, because I am still obsessed researching the splicing machinery and how it works.

*You have been working in the splicing field for over three decades: What future developments do you expect given the developments in the last decades?*

So to be honest, I feel pretty much the same that I was feeling that day when I realized that there was so little known about splicing and that there was so much to explore. We have nowadays much better technologies, knowledge and have identified the components of the machinery which we think are part of it. However, we are still almost unable to predict how tissue-specific splicing is established and are lacking even basic concepts about how this works. Even for the best studied alternative splicing factors, such as hnRNP proteins or SR proteins, we only have a basic understanding of their

mode of action. The process of exon definition is not understood at all. Noncoding RNAs could be involved in this process, and I dream of a time when maybe there will be noncoding RNAs that will bring the splice sites together by base pairing bringing a simple explanation for alternative splicing. I know that most likely this idea is wrong, but we have not ruled out that such a mechanism exists. Also, the coupling of splicing with other gene expression processes is only starting to be understood. The latest data suggest that splicing can take place a few nucleotides after the RNA gets out of the polymerase. So the two machineries are in very close contact, and we do not understand their interactions. Then the possibility to modulate the process through understanding its mechanisms would open up an entirely new way to ask about the functions of genes or to correct the malfunction of genes, such as the recent developments with antisense oligonucleotides or small molecules to modulate splicing.



## Interview Juan Valcárcel

*Your group researches the splicing of exon 6 of the FAS gene. Would it be enough to kill a cancer cell by switching the splicing outcome to the pro-apoptotic protein isoform?*

Well in some context it may contribute. The gene that I think is most involved in killing cancer cells, which is alternatively spliced, to yield pro- and anti-apoptotic isoforms, is Mcl-1. When we look at alternative splicing changes after treatment with a cytostatic drug, for most such drugs the most affected alternative splicing event is in Mcl-1. So I think this is a critical one to study. There are several others like Bcl-x and FAS. Overall, there might be a program of apoptosis mediated alternative splicing that could be exploited for treatment. Another fundamental question that is not solved is why cancer cells are more susceptible to splicing modifying drugs? Why do they change their splicing much more in response to these drugs than other cells? Is it a matter of membrane permeability or how their splicing machinery is affected? Related to that, there is a very interesting concept called synthetic lethality. It appears that very often cancer cells change their alternative splicing because of for example accumulation of mutations in the splicing machinery components. This gives a cancer cell a particular advantage. For example, mutations in SF3B1, which is one of the core components of the machinery, activate the use of cryptic 3' splice sites located a bit upstream of the canonical 3' splice sites. It has been shown that these splicing changes advance tumor progression. But at the same time, this same mutation causes quite a lot of trouble because of other alterations in splicing accompanying this mutation. This makes these cells particularly sensitive to splicing inhibiting drugs. So you have a sort of synthetic lethality of this mutation with splicing inhibitory drugs, which cause in normal cells

a certain amount of disarray, but much less than in cancer cells. So, what has provided an advantage is at the same time sort of an Achilles' heel for the cancer cell. This phenomenon was observed in several different types of cancer. Another interesting case is in melanoma: Initially, melanoma can be treated quite effectively with drugs like Vemurafenib, which is a B-Raf inhibitor. The problem is that after some time the tumors become resistant and in some cases, it has been shown that there occurs an activation of a cryptic splice site in B-Raf that removes the region of interaction with the drug. The tumor cells had to relax its splicing in a way to generate this variant, which is perfectly good for the tumor to progress, but at the same time, this makes the cell more sensitive to splicing inhibiting drugs. This is another example of the concept of synthetic lethality. There are clinical trials underway with drugs that should be particularly effective when there are mutations in spliceosome components present.

*Do you have interactions with clinicians?*

Not for the drug-related projects, which are still pre-clinical, but we do for using alternative splicing as a diagnostic marker. In breast cancer studies, which we have done together with the Hospital del Mar in Barcelona and the Institute Curie in Paris, we could correlate the response to chemotherapy with the particular isoform ratios in specific oncogenes.

*What is your general view on translational research?*

This is a very important aspect of research, which has to be cultured and nurtured, but this does not mean that all research should be translational. This would make no sense at all, but there is no harm in following up the translation angle of a basic research finding whenever possible. The majority of the leads from basic research are never going to result in a translational application, therefore the more leads one explores, the better.

*What do you consider the most significant recent findings in the field of RNA Biology?*

I think that almost everybody would agree that the potential of the CRISPR system to edit the genome was a finding that has given spectacular results and has amazing potential. Closer to the field of splicing were the therapeutic effects found in clinical trials with antisense oligonucleotides to treat Spinal Muscular Atrophy. This is fantastic news for science in general and for the field in particular, because it shows that modulation of RNA metabolism has therapeutic value, which was long believed to be an utopia. We will probably see much more of this in the future, and maybe in 10 years, the picture is going to be

very different regarding therapies and applications. This is very exciting!

Regarding long noncoding RNAs, do you expect significant progress in identifying their functions or rather that it will be found that most of them are just byproducts of the transcription of nearly the entire genome?

I think that likely there will be many important discoveries made in this area. Regarding the percentage of these transcripts which have a functional role, the jury is out and is going to be out for a while. To me, it is entirely unclear at the moment what that fraction could be. One has to remember that even if the transcript itself has no function, the fact that it is being produced could have a role in transcriptional regulation. It is important to be very rigorous when assigning functions: correlations are good but just as a starting point. But proving function requires deletion and rescue experiments in simple systems that allow causality to be established.

*What is your opinion on funding large collaborative project grants potentially at the cost of less individual PI grants?*

I hate the part of "at the cost of" because both are so necessary. When I was postdoc, there was a big debate about the human genome project. There were arguments that this is going to take so much money away from basic research projects that yield mechanistic understanding that this would drag the field of biomedical research for many years. They argued that this is a disproportionate investment to be made. However who today would doubt that this was a worthwhile effort? Not only because of the outcome but also because of the technology that was developed together with that project. Today, we can sequence a genome in one afternoon at the price one million times lower than the first genome. But shall we replace all the smaller and mechanistic projects by these large projects? Of course not, because otherwise we empty the basis for understanding. One needs to have both.

*Can you comment on the role of collaborative grants such as the European Alternative Splicing Network (EURASNET)?*

They have a very important role as well. EURASNET really helped to integrate researchers in the field of alternative splicing all over Europe. It was especially important for young scientists starting their labs to be surrounded by a nurturing environment that would provide them with opportunities for collaboration, in ways that would not have been possible otherwise. The typical example is someone that would come for example with a new technology and that would all of a sudden start to establish five different

*"If you are smart enough to come up with exploration tools, you can make discoveries that are tremendous without getting out of your living room."*



## Interview Juan Valcárcel

collaborations out of a first meeting with the EURASNET consortium, which would then lead to excellent publications and sometimes long-term fruitful collaborations. It was really a very important way to integrate people to

*“What has provided an advantage is at the same time sort of an Achilles’ heel for the cancer cell.”*

ensure that they could apply complementary expertise and approaches. From people that were very interested in structural biology to people interested in medical genomics, and this allowed to bridge from the structure of a specific protein-protein interaction to patients. This was something that would have been otherwise extremely difficult to achieve. The EURASNET members were also very involved in trying to streamline procedures for example for transcriptomics. At the time, there was a big debate about microarrays, different ways of analyzing their data, RNA sequencing for transcriptomics and the transition between the two. What the consortium did was to do pilot experiments to compare results and then we could offer the members of the consortium a streamlined platform to analyze their data. This joint effort, which produced something of general value for the community would have been challenging to achieve otherwise.

*What effects of EURASNET continue to be there after it ran out?*

EURASNET, in the end, got almost 12 million Euros funding from the EU, which allowed us to integrate the field, and after it should have continued by itself and it has continued. For example we keep having meetings roughly every year and a half without EURASNET support and still the majority of former members of the consortium keep coming regularly to these meetings, because we find it is important to talk to colleagues and get to know about the latest developments in a friendly and open atmosphere. And also to maintain and start new collaborations. So this is a so far sustained effect of EURASNET, and hopefully, this will continue. I would ask the EU to reconsider to maintain, if not at the same level, some funding after the grant has ended, especially for the young people starting their groups. If they

could have some extra funds through this scheme, then this could push them to be able to really do more and to integrate themselves into this network. This would have a really important impact and would not require a massive amount of funding for them to explore things together with the consortium. Every two to three years, there could be a new generation of young people entering the network. Pushing ahead the careers of young group leaders was the most important outcome of EURASNET, and it is a pity that this is lost.

*What impression do you have so far of the NCCR RNA & Disease and from your experience as deputy-director of EURASNET, what advice would you give to the NCCR?*

Besides the meetings in the context of my visit, I know a little bit about the NCCR because my wife Fátima Gebauer is a member of its review panel. I have a lot of admiration for what you have done, and this is already having a great impact in Switzerland and is going to be great, especially for the young people. My advice would be, even if you have potentially over eight years to go, to start thinking of ways in which you can either lobby or establish structures that will keep the interest afterward. In Switzerland, you might be in an especially good position to follow this up by trying to convince the industry that there are important opportunities in RNA research. Such that the industry is aware of this and there might be jobs there but also possibilities for collaborations. Related to this, I would provide opportunities and training to young scientists, who would like to startup companies or engage in innovative activities.

*What role does the RNA society, of which you currently serve as its president, and its annual meeting play for the field?*

This was established many years ago by Tom Cech and Olke Uhlenbeck using a surplus of money they had in the bank from a meeting they had organized, and this was sort of illegal to have. So they used this money to start the RNA Society, which was a group of friends that were thinking about how to push RNA research forward. I think that this still is the spirit of this community and there are huge opportunities from the scientific point and biotech point of view. It provides a forum for people; they can meet and talk about RNA research all the way from non-coding RNAs in bacteria to oligonucleotides that will be important for the treatment of neurodegenerative disease. This forum serves to exchange information and technologies. The Society would like to serve the community of RNA researchers as much as possible, and I hope that we can

find new ways and we are always open to suggestions from members. I am currently trying to push to have a more organized mentoring system through which the young scientists can rely on experienced researchers with many years of background in the field to give them sound advice regarding the next step in their career and how they think the field will evolve. Another critical aspect is to spread the word about the beauties and opportunities of RNA research to other communities, especially the medical, biotech and pharmaceutical communities, as well as to the public. Most educated citizens know what DNA is but may be not what RNA is. Despite the fact that RNA is as important, if not even more, more interesting and more versatile than DNA. However, this has not permeated popular culture. RNA should in a way be an icon of our culture.

*Interview: Dominik Theler*

## Juan Valcárcel Biography

Juan Valcárcel obtained his PhD in 1990 from the Universidad Autónoma de Madrid under the supervision of Juan Ortín, during which he studied how the processing of the influenza virus pre-mRNA is regulated. For his postdoc, he moved to University of Massachusetts Medical Center to the lab of Michael R. Green, where he continued to work on splicing, researching the mode of action of U2AF65 and splicing regulation in *Drosophila*. From 1996 to 2002, he was a group leader in the Gene Expression Research Unit at the EMBL Heidelberg. Afterwards, he became a senior scientist at the Centre for Genomic Regulation in Barcelona and Professor at the Institució Catalana de Recerca i Estudis Avançats (ICREA). He served as the deputy coordinator of the European Alternative Splicing Network (EURASNET) and is currently the president of the RNA Society. In 2004 Juan Valcárcel was elected EMBO member and in 2014 awarded an Advanced ERC Grant for studying “Mechanisms of alternative pre-mRNA splicing regulation in cancer and pluripotent cells (MASCIP)”.

[Valcárcel Lab Website](#)

## Research highlights

# Research highlights from NCCR laboratories

Roland Fischer

## It matters how we (or RNA) are born

Eukaryotic gene expression is heavily regulated at the transcriptional and posttranscriptional levels. An additional layer of regulation occurs co-transcriptionally through processing and decay of nascent transcripts physically associated with chromatin. This process involves components of the RNA interference (RNAi) machinery and is well documented in yeast, but little is known about its conservation in mammals. Yet it is clear that control of RNA lifespan is vital for the proper functioning of our cells. Marc Bühler's group at the Friedrich Miescher Institute for Biomedical Research (FMI) in Basel has discovered a novel mechanism determining the fate of RNA in mammalian cells: two proteins of the RNAi machinery- Dgcr8 and Drosha - together with a methyltransferase, Mettl3, mark nascent RNAs for degradation right in the moment they are transcribed.

The formation, processing and degradation of RNA are all tightly regulated. This stringent control of RNA metabolism ensures that genes become active at the right time and place, making sure cell functions are always well orchestrated. In this context, control mechanisms collectively referred to as RNA interference (RNAi) has attracted a lot of attention. Commonly, RNAi leads to the fragmentation and inactivation of RNAs in the cytoplasm. Interestingly, in yeast, an active RNAi machinery can also be found in the nucleus: during RNA synthesis, while the RNA molecules still associate with the DNA, it triggers the prompt degradation of nascent RNAs.

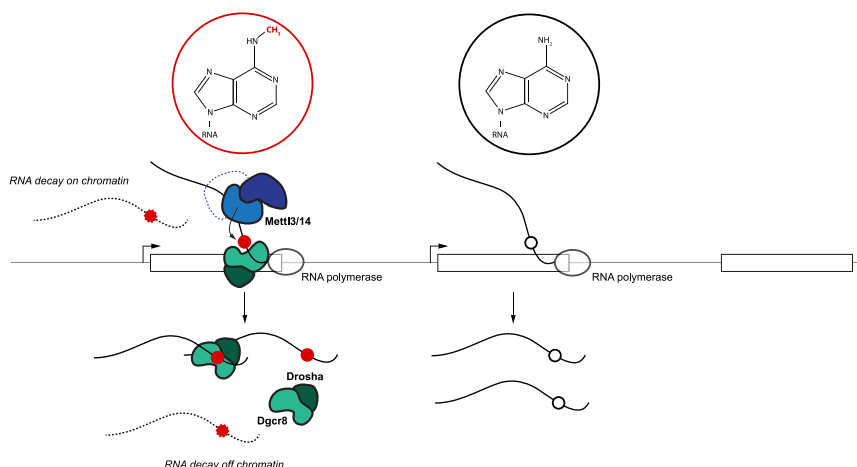
Marc Bühler and his group at the FMI used mouse embryonic stem cells to find out whether the RNAi machinery might play a similar role in mammalian cells. Bühler comments: "This is a good example of how knowledge gained in a model organism – here in fission yeast – guides our hypotheses and informs our experiments in higher organisms." His group's previous work in *S. pombe* revealed that RNAi as well as other nuclear RNA degradation pathways mediate the degradation of RNA in association with chromatin. But is such regulation evolutionarily conserved? Yes, they were indeed able to find a similar mechanism in mammals, albeit with major differences to the yeast

system. For example, Dicer does not physically associate with chromatin. Instead, their results suggest that the Microprocessor (consisting of Dgcr8 and Drosha), which does not exist in yeast, takes over this function in multicellular organisms. The FMI scientists also showed that an enzyme known as Mettl3 is involved in the degradation of nascent RNAs. Mettl3 transfers methyl groups to adenosine residues in RNA, a mark that also influences RNA stability.

The Microprocessor/Mettl3 system allows the cell to react rapidly to changing growth conditions. Interestingly, Bühler's group has found that the novel mechanism helps cells to cope with heat stress. There, genetic ablation of Dgcr8 or Mettl3 leads to the accumulation of Hsp70 mRNA, elongation of its half-life, and an increase in protein levels – so they propose that acute heat stress co-transcriptionally marks Hsp70 mRNAs for subsequent RNA degradation to control the timing and magnitude of the heat-shock response. According to Bühler, both the fast stress response and the rapid clearance of heat-shock transcripts and proteins are important for cells: "The accumulation of stress response proteins is detrimental to the cell and is often observed in cancer." The new findings shed light on the important role of co-transcriptional regulation of genes, especially in such full-speed/full-stop cases. In fact, Bühler

would not be surprised if many more of such co-transcriptional markings would be found – if the RNA remembered a lot more details from the moment of its birth than is actually known.

[Knuckles P. et al. \(2017\) Nature Structural & Molecular Biology 24, 561-569](#)



Adapted by permission from Macmillan Publishers Ltd: Nature Structural and Molecular Biology, 24, 561-569 (2017)

## Research highlights

### Sending a second messenger

Since its discovery a few years ago, the CRISPR-Cas system – or rather a simplified version of it (CRISPR-Cas9) – has triggered a biotech revolution due to its use as an effective tool to modify the genomes of cells or entire organisms. By delivering the Cas9 nuclease complexed with a synthetic guide RNA into a cell, the genome can be cut at a desired location to remove existing genes and to add new ones. Originally though, CRISPR systems and their associated Cas proteins are found in bacteria, in which they function as an immune system to provide protection against genetic invaders such as viruses and plasmids. In these systems, the invaders are recognized by effector molecular complexes that use short RNA molecules as molecular guides to bind the invader's DNA or RNA and target it for destruction. The exact mechanisms of this prokaryotic immune response are still being investigated but have drawn striking parallels between prokaryotic and vertebrate innate immune systems, as reported recently by an international research team headed by Martin Jinek of the University of Zurich. So CRISPR-Cas systems not only serve as a revolutionary genome editing tool but also prove to be a fascinating field for basic microbiology research.

Jinek et al. were able to show a new CRISPR-Cas defense mechanism involving a “second messenger” that is synthesised when the bacterial immune system detects an invad-

ing virus. The mechanism was discovered in a close collaboration with the research group of Jonathan Hall from the ETH Zürich, whose expertise in the chemical synthesis and analysis of modified ribonucleic acids has made a critical contribution to the project. The team effort, facilitated by the NCCR RNA & Disease, yielded results that point to an unprecedented mechanism for regulation of CRISPR immunity.

At the heart of the mechanism is a CRISPR-associated protein known as Csm6. It had previously been shown before that the CRISPR-associated protein Csm6 contributes to invader immunity by functioning as a ribonuclease that degrades invader-derived RNAs, but the mechanism linking invader sensing to Csm6 activity was not understood. Jinek's group now shows that Csm6 proteins are activated by a cyclic RNA molecule composed of four or six adenine bases linked in a circular manner (cyclic oligoadenylates). These “second messenger” molecules are synthesised from ATP by the RNA-guided effector complex when it detects an invader RNA. The messengers in turn allosterically activate the Csm6 RNase by binding to its CRISPR-associated Rossmann fold (CARF) domain. As the synthesis of cyclic oligoadenylate is triggered by invader RNA recognition, this provides a failsafe interference mechanism in case the intrinsic DNase and RNase activities of the CRISPR system are insufficient to counteract

the invader, such as when the target gene is expressed late during viral infection.

The newly found mechanism for regulation of CRISPR interference is strikingly similar to a well-known mechanism found in mammalian innate immunity in which viral RNAs trigger the production of oligoadenylate second messengers that in turn activate a cellular ribonuclease to promote viral RNA degradation. “So bacteria, in their own way, fight viral infections in a way that is surprisingly similar to what human cells do”, Jinek says. Moreover, the study notes that other CRISPR-associated proteins that are predicted to respond to the second messengers appear to be transcription factors rather than nucleases. This raises the intriguing possibility that CRISPR-Cas systems might also use cyclic oligoadenylate signaling to activate other host genes to help fight genetic invaders.

[Niewoehner O. et al. \(2017\) Nature 548, 543-548](#)

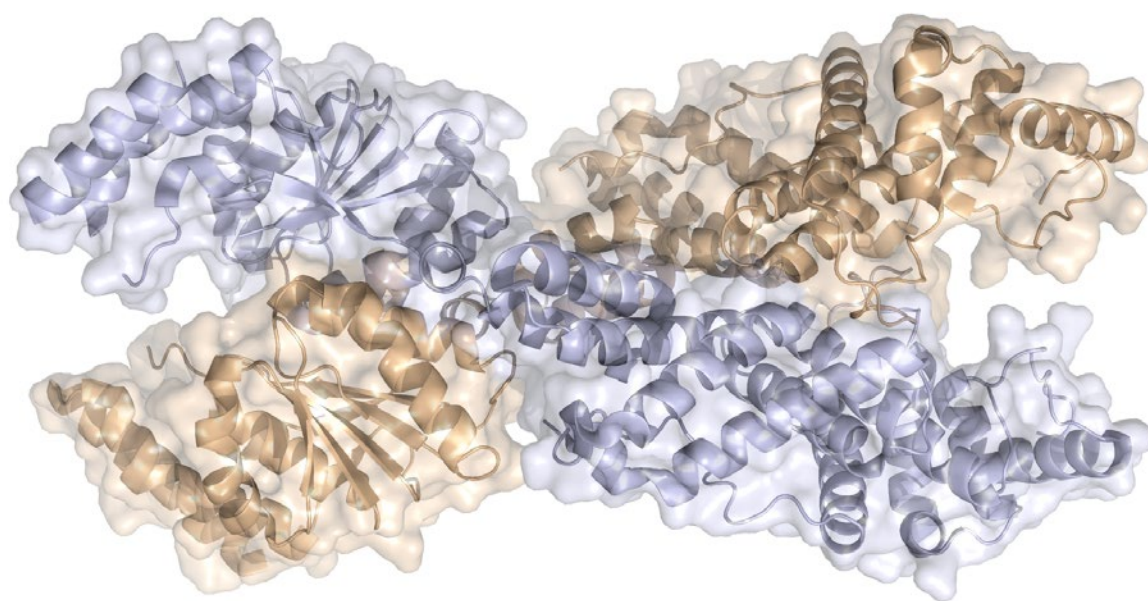


Figure of the CSM6 structure kindly provided by Ole Niewoehner  
([Niewoehner O. and Jinek M. \(2016\) RNA 22 \(3\), 318-329](#))



**2<sup>nd</sup> NCCR RNA & Disease Summer School**

# RNA & RNP architecture: from structure to function to disease

Larissa Grolimund und Norbert Polacek

From August 28th to September 1st 2017, the NCCR RNA & Disease held its second Summer School in the beautiful scenery of Saas-Fee in the heart of the Swiss Alps. The five-day Summer School “RNA & RNP architecture: from structure to function to disease” allowed students and postdoctoral researchers to expand their knowledge in the field of RNA structure and its importance in function and disease. Moreover, a one-day workshop dedicated to RNA techniques provided the unique opportunity for participants to gain deep insights into the state of the art methodologies in the field. The Summer School also provided a platform for young scientists to discuss their research and exchange ideas with leading international experts and pioneers in the field and among each other. A stunning lineup of invited speakers gave the students and postdocs an excellent overview on the multifaceted topic of RNA structural biology and beyond. Topics of the lectures included structure-based discovery of RNA functions, an integrative view of interaction networks between mRNA, tRNA and rRNA,

the power of combining structural approaches to solve structures of protein-RNA-complexes, the impact of high-throughput data in structure and interaction predictions, non-coding RNA pathways guided by microRNAs and circular RNAs, circadian RNA biology, structural and functional insights into ribosomes, miscoding-induced stalling of substrate translocation on the ribosome,

ribosome functions revealed by nucleotide analog interference, translational control in cancer, and mechanistic and biological functions of Nonsense-Mediated mRNA Decay. During the RNA techniques workshop the power, the area of applications as well as the limitations were presented in an interactive discussion for a variety of methods: Chemical tools in RNA research, Selective 2’



Participants hiking on the Ibex Trail during the free afternoon on Wednesday.



Participants of the 2<sup>nd</sup> NCCR RNA & Disease Summer School



## 2<sup>nd</sup> NCCR RNA & Disease Summer School

Hydroxyl Acylation analyzed by Primer Extension (SHAPE), RNA live cell imaging, ribosome profiling, CRISPR-Cas genome editing, structure determination of protein-RNA complexes using Mass-spectrometry, and Cryo Electron Microscopy.

Furthermore, all participants were given the opportunity to train their presentation skills in short presentations or chalk talks. During the two-hour discussion rounds with the invited speakers, an ideal setting was provided for the participants to informally discuss science with distinguished scientists in the field. The organizers would like to thank all invited guests and participants for shaping a successful, stimulating and memorable Summer School!

*Impressions of the discussion rounds with invited speakers Ronald Micura, Gunter Meister, Robert Schneider, Eric Westhof, Scott Blanchard, and Kevin Weeks (from top left to lower right).*

## Lecturers of the 2<sup>nd</sup> NCCR RNA & Disease Summer School:

<b>Frédéric Allain</b>	ETH Zürich, CH
<b>Nenad Ban</b>	ETH Zürich, CH
<b>Scott Blanchard</b>	Weill Cornell Medical College NY, USA
<b>Jeffrey Chao</b>	Friedrich Miescher Institute Basel, CH
<b>David Gatfield</b>	University of Lausanne, CH
<b>Martin Jinek</b>	University of Zürich, CH
<b>Gunter Meister</b>	University of Regensburg, DE
<b>Ronald Micura</b>	University of Innsbruck, AU
<b>Oliver Mühlemann</b>	University of Bern, CH
<b>Norbert Polacek</b>	University of Bern, CH
<b>Robert Schneider</b>	NYU School of Medicine, USA
<b>Kevin Weeks</b>	University of North Carolina, USA
<b>Eric Westhof</b>	IBMC/CNRS, FR
<b>Mihaela Zavolan</b>	University of Basel, CH





## Public outreach

# Spreading scientific knowledge and passion

Larissa Grolimund and Dominik Theler



Discovering the beauty of own cells at the Nacht der Forschung (© University of Bern/Franziska Rothenbuehler)

**Communicating research activities and its relevance to the public is an important goal of the NCCR RNA & Disease. The network is committed to share its findings and passion for science beyond the scientific community.**

This summer, the NCCR RNA & Disease conveyed its scientific activities by participating in two of the most visited science exhibitions in Switzerland: At the **Scientifica** in Zürich, the NCCR gave insights into how big data reveals the roles of microRNAs, and at the **"Nacht der Forschung"** in Bern, the NCCR was represented with an interactive "RNA-Parcours".

## Small worms and big data:

This year's edition of the [Scientifica – Zurich Science Days](#), was running under the theme big data and attracted over 30'000 visitors. The NCCR RNA & Disease was present with a booth, at which visitors were taken on a journey to learn about miRNAs, the role of big data for their study and the therapeutic potential of small RNAs. Visitors were told how initial discoveries made through basic

research with the model organism *C. elegans* translate decades later into drugs undergoing clinical trials. A number of visitors were surprised to hear that the genome of these tiny worms they were looking at with microscopes contains approximately the same number of protein-coding genes as theirs. Especially the "do it yourself microscope" based on a webcam attracted a lot of attention. Visitors could create themselves "RNA drugs" with the use of a puzzle and were given instructions how to create an alignment of members of a given miRNA family with just a couple of clicks using the miRBase-database. We would like to thank the groups of Constance Ciaudo, Helge Grosshans, Jonathan Hall, Markus Stoffel and Mihaela Zavolan for their contributions. Special thanks go to Marc Duseiller and Urs Gaudenz for their support regarding the DIY microscope and to Justine Kusch from the Scientific Center for Optical and Electron Microscopy of ETH Zurich.

## A "Parcours" through the central Dogma – from DNA to RNA to Protein – and beyond:

At the ["Nacht der Forschung"](#) at the Univer-

sity of Bern, guests could explore the world of RNA by visiting the interactive NCCR RNA & Disease "Parcours". Besides a number of posters and videos illustrating our research, the visitors had the unique opportunity to directly learn from scientists and to carry out experiments on-site. Six Bernese NCCR groups with over 50 researchers represented the NCCR RNA & Disease at this event. At this occasion, the NCCR RNA & Disease management would like to thank the groups of Rory Johnson, Oliver Mühlemann, Mariusz Nowacki, Norbert Polacek, Marc –David Ruepp, and André Schneider for their invaluable contributions.

While taking a walk through the "Parcours", visitors observed their own cells under the microscope, isolated DNA from bacteria and discovered the differences between the macromolecules DNA and RNA. By playing "molecular grammar", they learned in a playful way the importance of RNA splicing, and in the "dark matter of the genome" visitors discovered that RNA molecules are produced almost from the entire genome. At the "RNA as a tool" booth, a real-time experiment visualized the effect of



## Public outreach

RNA interference under the microscope and our scientists explained the widely mentioned methodology of CRISPR-Cas. Reaching the final station of the Parours, the guests took over the task of a ribosome and translated the information of a messenger RNA by using the genetic code into the recipe for their favorite cocktail, which was then pipetted by the researchers at the molecular bar. Colorful cocktails revealed correct translation, while a black drink indicated erroneous translation. Luckily, in this case, all drinks were enjoyable - which is not always the case for translation errors in our cells!



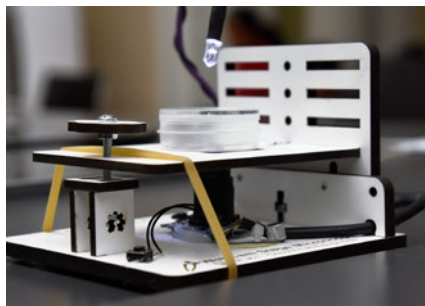
*Translating a messenger RNA into a recipe for a cocktail at the Nacht der Forschung*



*Scientifica exhibition in the Lichthof of the University of Zurich*



## Public outreach/Bridging ideas



Instructions to build such a microscope can be found on:

[https://hackteria.org/wiki/DIY\\_microscopy](https://hackteria.org/wiki/DIY_microscopy)



The Molecular Bar at the Nacht der Forschung



Extraction of DNA at the Nacht der Forschung

## CSM lab retreat

Inspired by discussions during NCCR in RNA & Disease retreats the Ciaudo, Santoro and Marques groups have recently organized a very successful joint lab retreat in the Bernese Oberland. This event gathered 21 researchers from the 3 teams for 2.5 days of fun and science in Oey. The scientific program covered ongoing projects on the roles of noncoding RNAs, RNAi proteins and epigenetic modifiers in stem cell biology and cancer. In the evening teams combining members of all groups and at different career stages had fun explor-

ing collaborative project ideas that were discussed during the last evening. Team 1 came up with a new approach to identify molecular players in chromosomal architecture. Team 2 will personalize colorectal cancer treatment and team 3 will find ways of targeting cancer cells in the G1 phase of the cell cycle.

Everyone came back boosted with energy and ideas and interactions between the 3 groups started to materialize. CSM retreat will be definitely repeated next autumn.

### Feedback from attendees

*"What I liked the most from the Ciaudo-Santoro-Marques retreat was the great and fruitful exchange between the three labs and the nice feedback and interactions with other colleagues working in similar research areas."*

*"The very first CSM lab retreat boasted a fabulous environment for both scientific and casual interactions among the three research groups."*

*"A relaxed atmosphere to discuss science of different but still closely related research areas, widening one's own horizon to new topics and details otherwise overlooked"*

*"This retreat was a really nice (and necessary) occasion to recall that scientific seminars can be simultaneously fun and instructive."*



Participants of the CSM retreat

## Announcements

### People

We would like to welcome Steve Pascolo and Gerhard Schratt who became associate members of the NCCR RNA & Disease.

Steve Pascolo is group leader at the Dermatology Clinic of the University Hospital Zurich and head of the URPP Translational Cancer mRNA platform. The Pascolo group researches therapeutic applications of mRNA, such as its use as a vaccine to treat cancer.

Gerhard Schratt is full professor for Systems Neuroscience at D-HEST, ETH Zurich. The Schratt laboratory investigates the functions of non-coding RNAs in neuronal development and plasticity.

We congratulate Michael N. Hall on receiving the Lasker Basic Medical Research Award 2017. Congratulations to Jeffrey Chao and Magdalini Polymenidou for having been selected as EMBO Young Investigators.

### Support Grants

Melanie Jambeau (Polymenidou lab) received a doctoral mobility grant for a second 6 months stay in the laboratory of Prof. Clotilde Lagier-Tourenne, Massachusetts General Hospital and Harvard Medical School, Boston, USA

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

### Think Swiss Research Scholarships

[Think Swiss Research Scholarships](#) financially support 2–3 months research stays in Switzerland of graduate and undergraduate students enrolled at an accredited US or Canadian university.

### Swiss Company Maker

In the context of the 2018 pre-seed workshop a [Preliminary Training on Intellectual Property](#) is offered on January 29, 2018 at the Federal Institute for Intellectual Property, Bern. The number of participants is limited and the application deadline is December 18, 2017.

The [SwissCompanyMaker Pre-seed Workshop](#) takes place on April 17, 18 & 25, 2018 at the Schloss Köniz, Bern. Application closes February 11, 2018 and the number of participating teams is limited.

### Upcoming events organized or supported by the NCCR RNA & Disease

- > [Careers in Science Symposium](#) organized by the NCCR Chemical Biology, November 28–29, 2017, Geneva

- > [NCCR Seminar Series](#): Bertrand Séraphin, December 4, University of Bern & December 5, 2017 ETH Zurich
- > The 19th [Swiss RNA Workshop](#), February 2 2018, University of Bern. Keynote speakers: Julius Brennecke, Sarah Woodson
- > [NCCR seminar series](#) spring semester 2018 at the University of Bern and ETH Zurich. Speakers: Jennifer Doudna, Fátima Gebauer, Michelle Hastings, Leemor Joshua-Tor, Gene Yeo

### NCCR RNA & Disease Internal Events

- > 3<sup>rd</sup> NCCR RNA & Disease Retreat, February 4–6 2018, Kandersteg
- > 4<sup>th</sup> NCCR RNA & Disease Site Visit, March 20–21 2018, Bern

### Past events organized or supported by the NCCR RNA & Disease

- > 2<sup>nd</sup> NCCR RNA & Disease summer school “RNA & RNP architecture: from structure to function to disease”, August 28 – September 1 2017 Saas-Fee (Registration closed)
- > [Scientifica – Zurich Science Days](#), September 2–3 2017, ETH & University of Zurich and the [Night of Research](#), September 16 2017, University of Bern
- > [2017 RiboClub Meeting](#) (co-organized by the NCCR RNA & Disease) “RNPs: the Good, the Bad and the Ugly. Insights into RNA-protein complex assembly and function in health and disease.” September 25–28, Orford, Canada
- > [Joint NCCR Workshop on “Career Development and Application Training”](#) by the NCCRs RNA & Disease, and Kidney.CH: October 4–6 2017, Bettlach

### Jobs

[PhD program in RNA Biology](#)  
[Find out more on our website.](#)

[PhD and Postdoc Positions – Gene Regulation by RNA modifications – Pillai Lab, University of Geneva](#)

[Check the jobs's section of the NCCR RNA & Disease webpage for other openings.](#)

## IMPRINT

The National Centres of Competence in Research (NCCR) are a research instrument of the Swiss National Science Foundation

### NCCR RNA & Disease

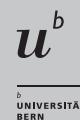
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