

THE MESSENGER

Newsletter No. 11

July 2019 — National Center of Competence in Research, RNA & Disease



**NCCR
RNA & Disease**

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

Message from the director's desk

Phase 2 Contract Signed: Outcome & Outlook

Oliver Mühlemann, Director NCCR RNA & Disease

It is now almost 2 years ago when I could announce in "The Messenger" the decision of the Swiss National Science Foundation (SNSF) to grant a second 4-year phase for our NCCR. Meanwhile, namely on May 1st 2018, this second funding phase has started and the transition was so smooth that most of our members probably barely noticed it. The management and the steering committee, however, were a bit nervous to start this second funding phase without knowing what the exact budget for the coming four years will be. The feeling was like being in the middle of building a house – having to decide on many details regarding bath, kitchen and roof – without yet knowing how much mortgage the bank is going to give you. The decision on the funding level was dependent on the SNSF's comparative evaluation of all 8 NCCRs of the 4th series, which was finished only in December 2018.

Our nervousness turned into relief and happiness, when just before Christmas we were informed that the NCCR RNA & Disease was one of the three top-ranked NCCRs that would receive a 7.5% increase in the SNSF contribution. Making things even better, the University of Bern thereupon decided to also increase their contribution by 7.5%. Our network had grown so much during the first phase that we were preparing for substantial financial cuts on many of our activities (as outlined in our full proposal for phase 2), but thanks to the unexpected additional money, the extent of these cuts will now be more moderate and essentially all planned projects can be implemented.

Another positive consequence of the improved funding situation is that we could integrate into our NCCR as a full member Jacob Corn, the new professor of genome biology at the ETH (since Oct 2018) and an

internationally renowned expert in genome editing. His profile and research interests match perfectly with our NCCR's mission and we are looking forward for fruitful collaborations with his team in the future.

While our various research projects are making steady progress and the past year has seen many first publications originating from collaborative research initiated among different NCCR member groups, a description of these projects here would go beyond the scope of this brief summary about the state of the network. Nevertheless, I want to reiterate that I judge these collaborations to be the most important achievement and biggest added-value of the NCCR RNA & Disease.

In terms of our networking activities, the undisputed recent highlight was the joint retreat between our NCCR and the Vienna RNA community near Salzburg in February (see page 5 in this Newsletter), and the next highlight is just around the corner: in August, the third NCCR RNA & Disease Summer School "RNA Regulation in Health and Disease" will take place in Saas-Fee and the organisers (Constance Ciaudo, Ana Marques and Raffaella Santoro) have put together a great program with an amazing list of teachers. When looking at the program, I wish I could be a PhD student again.

A topic that we have discussed on several occasions in the past was that we should try to improve our efforts in developing our research findings towards medical applications or into products that have the potential for commercialization. In order to incentivize all our members and associate members to propose and develop such projects, we made two calls for postdoctoral fellowships ([consult the KTT section of the NCCR's website](#)), one of them requiring a collaboration with clinicians at the Inselspital Bern, and the

other requesting a succinct plan on how to convert a research finding into a product or a concrete medical application. The application deadline for both calls has meanwhile past and the evaluation of the proposals has been initiated. I am very curious to find out who in our network will be able to develop the most promising translational research projects.

Last but not least, a group of people led by our communication delegate David Gatfield and the scientific officers has worked intensively, but thus far mostly behind the scene, to substantially boost and professionalize our communication activities. The harvest of all these preparative efforts has yet to come, but we can already look forward to the soon launch of a new webpage addressed to the lay public with the main goal of getting kids and young adults interested in life science. Ideas for entertaining and educational content for this website are highly welcome and should be forwarded to [David, Larissa and Dominik](#).

That's all for now, enjoy reading this issue of "The Messenger"!



Oliver Mühlemann signs the contract for Phase 2 of the NCCR RNA & Disease.

Interview with Matthias Hentze

“The field as such was not looking for such types of RNA-binding proteins.”

Interview: Dominik Theler

In this interview Matthias Hentze gives his perspective on pursuing an academic career and tells us about the discovery of “non-canonical” RNA binding proteins and the “Riboregulation” concept.

Where do you see the European research landscape standing, also in comparison to China and the USA?

There are many challenges. Europe is currently struggling more than maybe it was a few years ago. I hope it finds out of that phase. Regarding research, there are potential synergies that we should make use of but are not. In a lot of places in Europe, there is fantastic science going on, so on a small scale it is working well, but we are not obtaining a commensurate more structured and strategic benefit at the national or even continental level.

US research, I think, is currently going through a crisis. I hope it will recover soon, and I do not have any pleasure from a competitive viewpoint that now, by comparison, we are doing better because they have problems. I think the opposite is the case: The better the science in the US, the more exciting it is for European scientists to be part of that global community.

Both for US and for European research the way that science is tackled these days in Asia, you specifically mentioned China, poses a challenge. I think we have become in many parts of the west a bit complacent about our work habits. They have become a little less driven than at least I felt they were a couple

“Interdisciplinary has become something you can almost not do without.”

of decades ago. In China, I see a lot of appetite to tackle things and to progress. Unless we somehow find a way to address that, we will fall behind.

I do not know how it is here, but at institutions like EMBL, that should be exemplary, that provide an amazing infrastructure and people with a key to work anytime 24/7 when they choose to, you are a bit surprised by how few people you meet if you enter labs on a Friday afternoon after five.

“I know, times have changed and this was a very lucky strike.”

Being a researcher at EMBL provides you the environment and resources to put it in soccer terms to play at the Champions League level research-wise, but doing so still requires personal commitment.

That is right: it requires personal commitment and also dedication. You do not play Champions League in soccer or Grand Slam finals in tennis if you are not passionate about it at every given moment, even on a Saturday or on a Sunday. That sounds very old fashioned, I know. I realize that not being in the lab does not mean that you are not working on your research, particularly now that data analysis has become a much larger part of experimental progress. There is a lot of data analysis that one can do in the comfort of home rather than in a lab where you have centrifuges running in the background. I realize that, but I still think that everyone who decides for a career in science should think about it similarly to entering a professional sports career: commit from day one, sweat it out, win when possible and enjoy.

You are a marathon runner: What are the parallels between running a marathon and

research besides the endurance that both of them require?

Patience. I would certainly not be able to finish a marathon without it. You come to points where you wish it is over soon, and if you still have 15 kilometers to go, you have this urge to accelerate and get it done and over with quickly. If you do this with 15 kilometers still ahead of you, you are not going to make it to the finish line. There is a lot of this in science as well: you need the right patience and strategy to make it along a long distance.

I think the comradery and then the collegiality in sports is also very fitting to science. I have been in marathon races where somebody was pushed in a wheelchair and runners were taking turns to push the wheelchair forward. I think this is wonderful at the hobby runners' level and also when it happens in science: being ambitious for yourself but not against but together with others is a fantastic parallel not just between marathon running and science, but sports and science.

How did you become a basic scientist after studying medicine?

I started medical school because I wanted to treat patients, I finished medical school and I still wanted to treat patients. I then wanted to combine it with science becoming a physician-scientist in the area of gastroenterology and hepatology. I felt well prepared for the

“I think we should not only be judging outcomes but also paths.”

clinical part but ill prepared for the scientific part. Before starting with the clinical training, I decided to enter for two years into scientific training for which I went to the NIH, joining the lab of Rick Klausner.

Interview with Matthias Hentze

I worked on a project investigating a human genetic disease, hereditary hemochromatosis, which failed miserably. However, in the process, I cloned a human gene called ferritin. That was in the mid-eighties, and I saw a paper from the mid-seventies that suggested that ferritin protein expression was regulated in a very unusual way. There were big changes in the amount of ferritin protein made when iron levels went up and down, but no change at the mRNA level. In the mid-eighties, it was totally exotic that you would have translational control.

That was the claim of the paper, and since I cloned the gene, I could actually test this directly and there were indeed big differences in protein output without any change in mRNA levels. Then I could stepwise identify the responsible regulatory element which turned out to be the iron-responsive element in ferritin mRNA. At the time, this was the first element in a mature mRNA shown to be regulating gene expression in a physiological-relevant way.

To cut a long story short, I then contributed to four 'Science' papers in two years: Two as a first author and two as a second author. Rick strongly encouraged me to pursue a scientific career, but I insisted on wanting to practice medicine. He then suggested that I

"I thought 'wow' if this is a general principle that would be quite amazing."

go to EMBL to give a talk. I gave a talk and without even applying, I was offered a group leader position to my total surprise and I took it. I know, times have changed and this was a very lucky strike. And while this career change was totally unplanned and opportunity-driven, it turned out to be one of the best professional decisions that I ever made.

Would you still study medicine before entering a basic research career in the life sciences?

I would say, it did not hurt me, and even if people have an interest in biomedical science, I would advise them to consider studying medicine rather than biology, genetics or biochemistry. The reason is that only when you study medicine, you really have the chance to learn what medicine is about. This knowledge is very hard to acquire for a non-medic because non-medics do not have

the same environment. When you are a medical doctor and you lack some fundamental scientific knowledge, and I have to admit that my chemistry knowledge still today leaves much to be desired, you are constantly in an environment with experts who can help and advise, while you contribute your medical knowledge.

"If you make it is wonderful but if not that choice of a career path might retaliate."

What were the biggest changes you witnessed over your career how science is done and the scientific environment?

I think there is a scientific answer and a cultural answer to that. Scientifically speaking, of course, the 'omics'. I used to be a reductionist biochemist and now the omics and systems biology have a big impact, and one is even asking mechanistic questions in a totally different way. Also, the emphasis on physiological experimental conditions has changed dramatically. Those would be the two components of my scientific answer.

In terms of culture, interdisciplinary has become something you can almost not do without, which means that a single person and sometimes even a single lab can achieve much less. Therefore, there is less autonomy of individual labs than there used to be, but in turn, there are far more collaborations that are exciting and yield profound insights.

Is an academic career still as attractive as when you started your group?

You would have to ask the younger people this question. I think yes. It depends on what you want from your professional life. I think there is not a small fraction of people who would like to have a secure job ideally before the time they start their families, which is totally understandable. I think that academia the way we still practice it today, does not offer that. This situation deters talented young people because they prefer to take a track that is more predictable in terms of career outcome. One of the big disadvantages of an academic career, today in particular, is that if you make it is wonderful but if not that choice of a career path might retaliate. You may struggle, at least for some time, before you find your bearings in an alternative career. In that sense, academic jobs have become less attractive.

The situation may be somewhat different in areas where meaningful, high-quality start-up companies are active and recruit well-trained scientists. However, too few centers in Europe are currently successful in creating such environments. When I go to Boston or the Bay area, I see much more of that. I would say in those areas pursuing an academic career is potentially more attractive because you have great science, but you also have great alternative options.

Is going from an academic career to an industrial career perceived as a failure?

For somebody in Heidelberg today, if they go to a company setting, I would not at all say that this would be looked at as a failure. I would definitely say that 15-20 years ago, it would have been looked at as your plan B, but nowadays not.

I would like to comment on how to judge failure: I think we should not only be judging outcomes but also paths. Somebody can take a very good path, learn a lot along that path, but the outcome is unsuccessful: that person has had a great learning experience, which could be useful for many things and just because the outcome was not successful, it should not be held against that person.

What advice would you give to young researchers?

Make up your mind about what you want and what would be your dream - and then try to pursue it with all that you have. Do not limit yourself by what you think would give you greater chances in the future based on probabilities, because these things change and your best guarantee to have a successful career is to work in something that you are truly passionate about. I am not recommending to be a dreamer, but to realize what your dream is and to pursue it in a strategic way.

Your group developed the RNA interactome capture method and applying it identified numerous novel RNA binding proteins: Were you surprised how many there were?

Absolutely. We actually did not develop the RNA interactome capture method as a way to discover or describe the RNA binding proteome as a whole. I simply wanted to know whether other metabolic enzymes could bind RNA. "My first protein", iron regulatory protein 1, which is identical to cytosolic aconitase, was an example of an RNA-binding protein, which is at the same time an enzyme, and where metabolic changes introduce switching between the RNA binding and the metabolic function.

I thought "wow" if this is a general principle that would be quite amazing. We need to connect cellular metabolism with cellular gene expression programs, and that would

Interview with Matthias Hentze

be a wonderful, potentially general way of how this could happen. There were papers reporting on a few other examples, like GAPDH and enolase, being RNA-binding proteins. I just wanted to know if this could be more a general principle.

So we thought of the RNA interactome capture method and Markus Landthaler's group - for different reasons - developed the same technique independently in parallel. Then we had the outcome and I was delighted to see how closely ours and Markus' data agreed with each other and that there were seventy or so enzymes. Far more than we bargained for, giving us more than enough to work on.

"You need the right patience and strategy to make it along a long distance."

However, there were all these other proteins, and initially, when I saw them, they made me worry. How can that be? These proteins had nothing to do with RNA, as far as we knew. Do I expect them all to moonlight and have a second function or is something wrong with the technique? Do we have many false positives for some reason? I was really struggling with that for a while.

Until I had the thought that these findings connected well with the RNA world hypothesis and the origins of life. The role that RNA might have played very early in evolution was to regulate protein functions. Therefore, these proteins might not bind RNA to regulate RNA expression as trans-acting factors, for example splicing or RNA stability, but some proteins could be bound by RNA to be regulated by RNA, which we now call Riboregulation.

A reversal of roles?

Exactly, suddenly we realized that RNA-protein interactions could potentially exert the same type of regulatory functions that we are accustomed to from protein-protein interactions. From SELEX-derived aptamers we know that RNAs can evolve to bind to nearly any surface, including protein surfaces. So RNAs could have evolved to binding to proteins that lack recognizable RNA binding domains. This concept of 'Riboregulation' is what we are very excited about right now, and which we intensively investigate further.

Why was the RNA binding capability of these proteins not discovered before?

In my opinion, about 30 years of RNA biology were mostly driven by looking for trans-acting factors that regulate RNAs. Researchers performed affinity purifications using RNA regulatory elements and looking for RNA-binding factors; or screening genetically for factors that influence RNA fate. So RNA-binding proteins that bind to RNA and regulate RNA were found: this outcome was inherent to the way they were looked for. Now we have what is commonly referred to as 'unbiased' approaches. And we not only 'rediscovered' these classical trans-acting factors, but also found those that would not likely have been found before, because they do not have those roles, and are instead regulated by RNA. The field as such was not looking for such types of RNA-binding proteins.

Might there be even more RNA-binding proteins that were missed by the interactome capture method?

How many have we still missed? I do not know. We currently estimate the number for mammalian systems to be somewhere between 1500 and 2000, and interactome capture has been devised to be low on false positives while accepting false negatives. False negatives can arise because UV cross-linking is very inefficient, and there might be circumstances when a facultative RNA-binding protein is not active in RNA binding; for example, it might only bind RNA in mitosis or under stress. Therefore, there are plenty of reasons for why we might still be missing some.

You discovered these metabolic enzymes binding RNA: On how many of these were follow up studies performed to reveal the mechanistic details?

Not many at all at this point and the exploration is just beginning. Cytosolic aconitase was there before and inspired the work. We have published a paper on a mitochondrial dehydrogenase, HSD17B10, but this is quite limited work. I have heard that around the globe, some groups are picking up some of these enzymes and study their RNA binding in more detail. However, I must also say that I am slightly disappointed. Our paper and that from Markus Landthaler were published in 2012, and if you had asked back then how much will we know in 2019, I would have expected more. I hope that this is still coming. We will definitely try to make our contributions and we are currently tackling several additional enzymes; however, this takes time.

What has been your impression of the NCCR RNA & Disease during your visit?

This is not a political statement: I think it is great. There is a good number of outstanding



Matthias Hentze
Biography

After completing his medical studies at the University of Münster Matthias Hentze joined the lab of Rick Klausner at the NIH Bethesda in 1985. In 1989, he became group leader at the EMBL Heidelberg. In 1990, he obtained his habilitation from the University of Heidelberg and in 1998 was promoted to senior scientist at the EMBL Heidelberg. From 2005–2013 he served as associate director of the EMBL Heidelberg and in 2013 became its director. Since 2002, he is the co-director of the "Molecular Medicine Partnership Unit" of the EMBL and the University of Heidelberg. In 2011, he was awarded an ERC Advanced Grant entitled "Exploring the interface between cell metabolism and gene regulation: from mRNA interactomes to "REM Networks"".

[Hentze Lab Website](#)

RNA scientists in Switzerland and the NCCR RNA & Disease brings them together. But it not only brings together the principal investigators but also the students. After speaking to them both in Bern and Zurich, I can say that they are really happy that the NCCR connects them.

In Zurich, some students remarked that, in their view, there was limited connectivity of PhD students between different departments, but that those who are in the NCCR-run RNA Biology PhD program feel privileged because it provides a way that connects them creating a community that exchanges and benefits from each other. I cannot evaluate this statement, but I found it a very genuine statement. So from that angle, this program is providing fantastic glue towards not only connecting PIs but connecting communities and fulfilling a very important training purpose for the involved students.

Networking across borders

Austrian Swiss RNA Meeting

This year's annual retreat of the NCCR RNA & Disease took place in form of a special edition as a joint meeting with the [Vienna RNA Biology Network](#).

Over 200 scientists from more than 60 Swiss and Austrian laboratories met in the beautiful area of Fuschlsee near Salzburg, Austria, from January 30–February 3, 2019. 5 days of intensive scientific interactions including excellent oral and poster presentations by the participants stimulated scientific exchange and aimed at initiating and fostering collaborations between established and junior scientists from the Vienna and Swiss RNA commu-

“Everyone I talked to said it was their favorite retreat they had ever been to, myself included.”



Participants attending the opening session



Discussions during coffee break

Networking across borders

nities. The meeting covered a broad spectrum of topics related to bacterial RNA networks, non-coding RNAs, RNAs in gene regulation, RNA processing, RNA modification and trans-

“A joint meeting with another RNA network was really interesting and stimulating.”

lational regulation. The researchers benefited from the opportunity to present their work to an audience of peers and established principal investigators in their field. The format of the meeting provided plenty of opportunities for networking and discussions.

We would like to thank the Austrian and Swiss organizers and all participants for contributing to such a successful and inspiring

“Really nice atmosphere, notably during poster sessions, which allowed open and interesting discussions.”

event! A special thank goes to the Scientific Advisory Board Members Sarah Woodson, Witold Filipowicz, Jørgen Kjems and Robert J. Schneider for their continuous support and joining us at Fuschlsee.

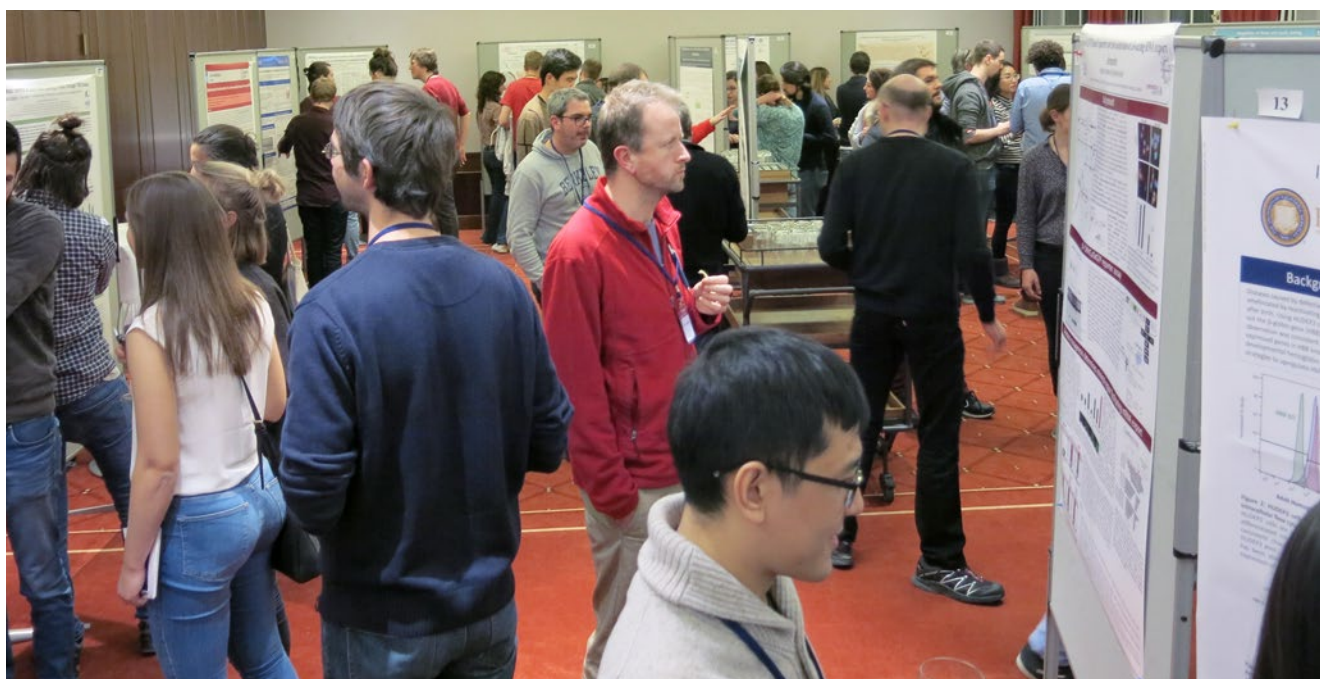
This meeting was kindly supported by Lexogen, VectorBuilder, The RNA Society, New England Biolabs and Microsynth.

Enriched with impressions and ideas collected during the Austrian Swiss RNA Meeting, we are already looking forward to the next annual retreat to be held in Kandersteg, Switzerland, from January 27.–29. 2020.

“I think mixing with another network was a great idea that could be repeated in the future. It was a very successful experience.”



Lake Fuschl



Poster viewing

Swiss RNA Workshop 2019

Bringing Together the Swiss RNA Research Community

On January 25, 2019, the 20th edition of the Swiss RNA Workshop took place at the University of Bern, which was attended by over two hundred participants.

The first edition of the workshop took place in 1995, organized by Angela Krämer and Daniel Schümperli. The workshop continues bringing together RNA researchers from Switzerland and neighboring countries for a one-day meeting.

This year's keynotes were delivered by Eric Miska (Gurdon Institute, University of Cambridge, United Kingdom) on "*An ancient machinery drives piRNA transcription in C. elegans*" and Alena Shkumatava (Curie Institute, Paris, France) on "*Dissecting the in vivo functions and mechanisms of action of lncRNAs*". Fourteen short talks were presented that were selected from submitted abstracts and fifty-nine posters presented covering a wide range of RNA research topics.

For their financial support, we would like to thank the RNA Society and the company sponsors Axonlab, Fisher Scientific, Horizon, Macherey-Nagel, Merck, Microsynth, Qiagen and Takara.

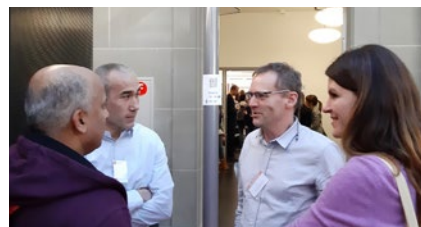
The 21st edition of the Swiss RNA Workshop will take place on Friday, January 24, 2019, in Bern.



Lunch and poster session



Keynote speaker Eric Miska (right) discussing with Rory Johnson (left)



Conversation between keynote speaker Alena Shkumatava, Oliver Mühlemann, Jeff Chao and Ramesh Pillai (right to left).



Talk session

Research highlights

Research highlights from NCCR laboratories

Roland Fischer

Still confUSED?

Fused in Sarcoma (FUS) is an RNA binding protein associated with several neurodegenerative diseases. RNA binding has been suggested to be crucial for FUS function and recent research has shown that FUS has the intrinsic ability to bind many RNAs without substantial differences in binding affinity. The actual mode of nucleic acid binding has been elusive, so what exactly determines the FUS interactome in vivo has become one of the big unanswered questions in the RNA field. Finally, Loughlin et al. from the Allain group (Institute of Molecular Biology and Biophysics, D-BIOL, ETH Zürich) managed to solve the solution structure of FUS bound to RNA, revealing a sequence-specific recognition for a GGU motif and an unusual shape recognition of a stem loop by two separate domains.

This is not only interesting on a theoretical level: FUS plays an important role in regulating genetic messengers and the interaction of different proteins. FUS mutations lead to FUS accumulations in the cytoplasm. The two neurodegenerative diseases amyotrophic lateral sclerosis (ALS) and fronto-temporal lobar degeneration (FTLD) show neuropathological protein aggregates containing FUS, and it is hypothesized that mis-regulation of RNA processing could play a major role in these diseases.

Transcriptomics studies have already indicated that FUS binds a large variety of RNA motifs, suggesting that FUS RNA binding can only be explained with a complex pattern. The findings of Loughlin et al. finally shed some light on the binding mode of FUS. With the help of colleagues from the Department of Chemistry and Biochemistry of the University of Bern (Mühlemann and Ruepp's labs) and the Institute of Molecular Life Sciences of the University of Zürich (Polymenidou's lab), the structure solved by the Allain group that revealed a bipartite binding mode of RNA via its RRM and zinc-finger (Znf) could be functionally validated in cell-based assays.

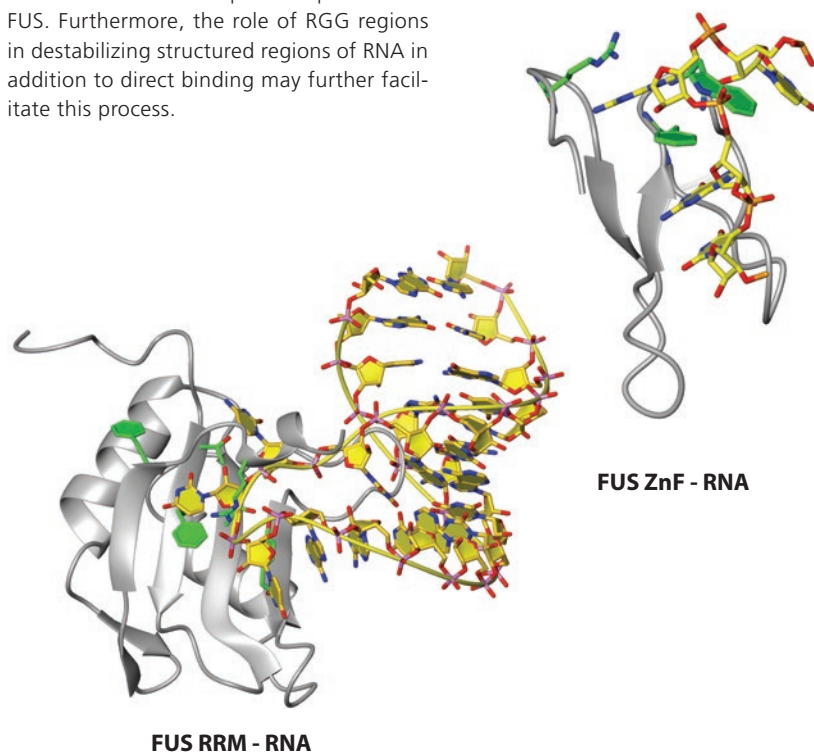
The ZnF provides sequence specificity to FUS, whereas the FUS RRM binds stem-loop RNAs in an unusual manner and with highly degenerate specificity. The structure of the FUS RRM bound to the stem-loop RNA reveals three individual binding pockets on the

betasheet surface, as expected for an RRM. However, the path taken by these nucleotides is unusual, with the three nucleotides forming a tight turn rather than a straight line. Most contacts are of non-sequence-specific nature, with hydrophobic interactions and contacts to the phosphate backbone.

RNA binding by FUS is important in facilitating efficient liquid-liquid phase separation into membrane-less compartments like liquid droplets, the aging of which could lead to aggregation of FUS in ALS and FTLD patients. The modular nature of FUS RNA binding and the weak RNA binding affinity of the folded domains shown here are perfectly consistent with the weak multivalent interactions known to facilitate phase transition. This multivalent RNA binding, together with the disordered regions of FUS, are well suited to play a role in the formation of the different phases, and the RRM and ZnF have recently been shown to contribute to RNA-mediated phase separation of FUS. Furthermore, the role of RGG regions in destabilizing structured regions of RNA in addition to direct binding may further facilitate this process.

It is a complex story, indeed. The results not only open up interesting new paths for further research, but also help understand why deciphering the RNA binding mode of FUS has been so challenging. "This was a very difficult structure to solve due to the very dynamics nature of the interaction of the RRM with the RNA. But I am glad this could be achieved, thanks to the heroic effort of Dr. Fiona Loughlin (mother of two with 120% SNF support and now back to Australia) and a great collaborative effort from four NCCR groups" said Prof. Fred Allain.

[Loughlin F.E. et al. \(2019\) Molecular Cell 73\(3\), 490-504.e6](#)



Picture kindly provided by Antoine Cléry.

Research highlights

Turbocharger for the cell machinery

That's how we've learned the molecular-biological narrative in school, in its classic simple form: Gene-RNA-protein. DNA is transcribed into RNA and the RNA serves as a kind of punch card in the ribosomes – the proteins are assembled by the machinery according to the DNA template. In recent decades, however, biologists have realised that this scheme is far too simple, in particular with regard to the role of RNA. More and more RNA has been found bearing no code, i.e. no protein instructions. Today, it is assumed that in most living organisms the majority of RNA produced is actually "non-coding". In humans, noncoding RNA makes up an amazing 98 percent of RNA. Why is so much RNA transcribed not serving the "classical" purpose? As simple as the question is, it still offers plenty of surprising answers.

As reported in Nature Communications, Researchers from the Polacek and the Schneider groups of the University of Bern have discovered a new molecular regulatory mechanism in the unicellular parasites *Trypanosoma brucei* never described before. Trypanosomes, parasitic protozoa responsible for sleeping

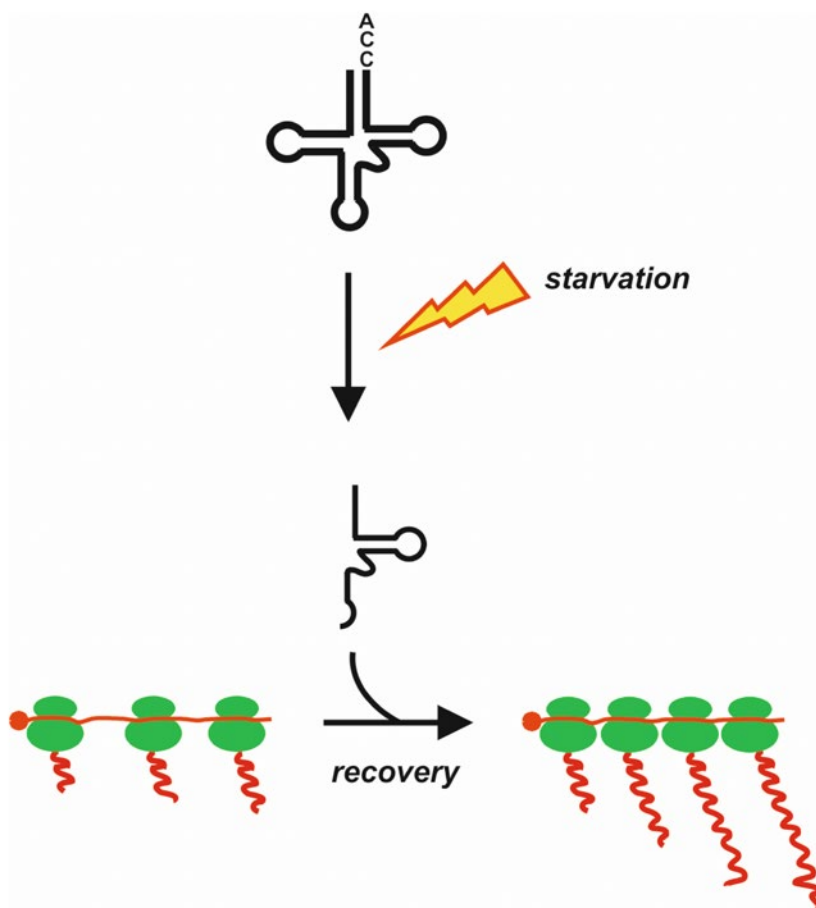
sickness, are known for their unique molecular biological apparatus. In the absence of extensive transcription control mechanisms the parasite crucially depends on translation regulation to orchestrate gene expression. However, molecular insight into regulating protein biosynthesis is sparse. The Polacek and the Schneider groups analyzed the small non-coding RNA (ncRNA) interactome of ribosomes in *T. brucei* during different growth conditions and life stages. Ribosome-associated ncRNAs have recently been recognized as unprecedented regulators of ribosome functions. The researchers have identified one especially intriguing ncRNA, the tRNA^{Thr} 3' half. It is produced during nutrient deprivation and becomes one of the most abundant tRNA-derived RNA fragments (tdRs). tRNA^{Thr} halves associate with ribosomes and polysomes and, once starvation conditions ceased, stimulate translation by facilitating mRNA loading during stress recovery.

These findings astonished the researchers because until now only the opposite function of non-coding RNA had been known, acting as inhibitors for the cell apparatus. During

stress, ncRNA molecules attach to ribosomes, as if pushing the emergency stop button of the protein machinery. When nutrients become scarce or environmental conditions become especially challenging, the entire assembly line is shut down, saving time for the cell. ncRNA molecules are predestined for such a regulatory mechanism – they are produced within fractions of minutes and can thus trigger a fast reaction of the cell. But an acceleration of production? This irritated the researchers in two respects: Firstly, it is not immediately clear what the purpose of such a regulation might be, and secondly, it is much more difficult to come up with an intuitive mechanism for such a mode of operation. "We knew of inhibitors, which typically block important binding sites," said Norbert Polacek, the head of the research group. He believes that the ncRNA fragment has the effect of bringing the ribosomes up to full production capacity without delay as soon as, for example, sufficient nutrients are available again - Polacek calls it a "kick start" for the cell.

Blocking or depleting the endogenous tRNA^{Thr} halves mitigates this stimulatory effect both in vivo and in vitro. *T. brucei* and its close relatives lack the well-described mammalian enzymes for tRNA half processing, thus hinting at a unique tdR biogenesis in these parasites. The exact mechanism remains unclear, however, and Polacek believes this opens up an interesting field for further research. Furthermore, the findings widen the understanding of the regulatory potential of tdRs in general, as compared to other small ncRNA regulators. The researchers do not exclude the possibility that the *T. brucei* tRNA^{Thr} 3' half has additional biological roles in the parasite beyond translation control. They find it "astounding" that the "precursor" molecule of tdRs, genuine tRNA that is, has basically one major cellular role as substrate for the protein synthesis machinery, while processing products thereof are functionally so heterogeneous. Thus post-transcriptional cleavage events can generate novel regulatory molecules thereby further increasing the complexity of cellular RNomes in general and expanding tRNA biology in particular.

[Fricker R. et al. \(2019\) Nature Communications 10\(1\),118 \(open access\)](#)



Picture kindly provided by Norbert Polacek.

Announcements

People

As of the beginning of the year Jacob Corn became full principal investigator of the NCCR RNA & Disease.

We would like to welcome Christa Flück, Françoise Stutz and Karsten Weis as new associate members of the NCCR RNA & Disease. Christa Flück is the head of the endocrinology, diabetes and metabolism unit of the University Hospital of Bern Pediatrics Division and principal investigator at the Department for BioMedical Research (DBMR). Her lab's primary research interest is human steroid biology. Françoise Stutz is full professor at the University of Geneva and her lab researches several aspects of RNA metabolism including mRNA biogenesis and export as well the roles of nuclear architecture and non-coding antisense RNAs in gene expression regulation. Karsten Weis holds a full professor-ship at the ETH Zurich and research in his lab deals with intracellular macromolecular transport especially across the nuclear pore complex, mRNA degradation and the function of membrane-less organelles like P-bodies and stress granules.

We congratulate Michael Hall for receiving the 2019 Howard Taylor Ricketts Award and the 2019 Nakasone award. Congratulations to the NCCR's Scientific Advisory Board Member Adrian Krainer (Cold Spring Harbor Laboratory) for being awarded the 2019 RNA Society Lifetime Achievement Award.

NCCR RNA & Disease Chimia Issue

The May issue of the Chimia journal is a topical issue on the NCCR RNA & Disease. Member and associate member groups contributed eight review articles and the editorial was written by the co-directors.

[Link to the NCCR RNA & Disease Chimia issue.](#)

NCCR Technology Platforms

The NCCR RNA & Disease has two new bioinformatics support persons in Basel and Zurich. Dr. Michaela Schwaiger is based at the Friedrich Miescher Institute in Basel, while Dr. Markus Schröder is at the Molecular Health Sciences Platform at ETH Zurich. Dr. Julius Rabl at ETH Zurich is the new contact person for Cryo-EM support.

[Visit the technology platform website of the NCCR RNA & Disease for more information and the contact details.](#)

Support Grants

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

NCCR Bio-Inspired Women in Science Postdoctoral Fellowship

The NCCR Bio-Inspired Materials made a new call of their Women in Science Postdoctoral Fellowships. The fellowships funds research conducted in laboratories of the NCCR Bio-Inspired Materials. [Please follow this link for more information.](#)

Upcoming events organized by or involving the NCCR RNA & Disease

> [NCCR Seminar Series Autumn Semester 2019:](#)

Christine Mayr (Memorial Sloan Kettering Cancer Center, New York, USA), September 23, University of Bern & September 24, 2019, ETH Zurich

Bryan Cullen (Duke University, Durham USA) October 7, University of Bern & October 8, 2019, ETH Zurich

David Bartel (Massachusetts Institute of Technology, Cambridge, USA) October 14, University of Bern & October 15, 2019, ETH Zurich

Paul Anderson (Harvard Medical School, Cambridge, USA) October 21, University of Bern & October 22, 2019, ETH Zurich

Phil Bevilacqua (Pennsylvania State University, Pennsylvania, USA) November 18, University of Bern & November 19, 2019, ETH Zurich

Jobs

PhD program in RNA Biology

[Find out more on the PhD program website.](#)

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

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NCCR RNA & Disease

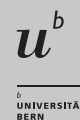
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