THE MESSENGER

Newsletter No. 6

Juli 2017 — National Center of Competence in Research, RNA & Disease

NCCR
RNA & Disease

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

GOOD NEWS

We are on track and going into phase 2!

Message from the director's desk

Even if it feels as if we had only just launched our NCCR RNA & Disease, it is an undeniable fact that we have already entered the 4th and therewith last year of its first phase. NCCRs can run for three phases of four years each and each new phase needs to be applied for at the SNF with a pre-proposal and one year later with a full proposal. We are currently in the midst of this application process for phase 2 and I would like to give you some information on where we stand and where we plan to go.

During the past 3 years, the NCCR RNA & Disease grew from the 16 founding groups to a Swiss-wide research network with 23 full member groups and 20 associated groups. In the meantime, first joint publications between two or more NCCR labs came out, documenting that our efforts to foster interactions and collaborations within the network are starting to bear fruits. As pointed out by the SNF review panel at their annual site visits, our research projects overall are judged as "excellent" and "top quality". This is also reflected by the already more than 50 publications, many of which were published in the most prestigious international science journals.

Top quality research requires top quality researchers. This is the right moment to thank all of you who dedicate most of your time every day to investigate important scientific questions and overcome countless challenges, in order to develop new and smart solutions or make exciting new discoveries. We can indeed be proud of our PhD students and postdocs, whose talent and effort has also been recognized by the SNF review panel, which wrote in their 3rd year report: "The panel has been very impressed by the general enthusiasm, engagement and knowledgeability of the junior researchers." With this as the basis and a continued effort to further intensify collaborations among the NCCR labs, our research is clearly on target. We also received good marks from the review panel on our other activities regarding training and education, equal opportunities, knowledge and technology transfer (KTT), and communication.

With everything essentially on track, it came as no surprise that the SNF research council has decided that the NCCR RNA & Disease is to be continued in a phase 2. Nevertheless, this official confirmation is a big relief. What is still unknown is the financial contribution by the SNF for phase 2, which in the worst case can drop to 80% and in the best case increase to 120% of that of phase 1. This will depend on the evaluation of our full proposal and on how we are rated compared to the other NCCRs of our generation. It is our NCCR's declared goal to avoid any cuts and secure between 100 and 120%. With this ambition declared, it is needless to say that for the next 8 months the top priority of the management team is to compose a strong and convincing full proposal that incorporates the feedback of the SNF review panel on the pre-proposal in the most constructive way possible. The recent General Assembly (held in La Neuveville on June 12) was a first step in this direction. We discussed strategically important issues for phase 2 and for the full proposal and together with the support of all involved PIs, postdocs and PhD students, the management team has now begun to work towards implementing necessary adjustments.

Overall, the general directions proposed in the pre-proposal were received positively by the review panel and will be pursued. We want to continue in phase 2 with a broad and diverse research portfolio that comprises a healthy balance between "high risk – high gain" projects addressing basic problems and projects that address a concrete disease or medically relevant issue. To deliver top quality research will remain a top priority also in phase 2. Regarding our ambition of creating a rather inclusive network for all RNA research in Switzerland and to optimally support young and promising researchers in this field, we hope to be able to even grow the network a little further in phase 2.

As you can see, the goals are set. Now let's start working towards realizing them!

Oliver Mühlemann
Director NCCR RNA & Disease

Interview Prof. Thomas R. Cech

"For them, it was a weird organism doing a weird thing"

In the interview, Thomas R. Cech discusses his groundbreaking discovery regarding the catalytic properties of RNA, the RNA world hypothesis, recent developments in the field of RNA biology, his career and current research topics as well as the situation of the American research community after Trump's election.

Dr. Cech, you launched a revolution in RNA Biology by discovering the catalytic properties of self-splicing ribosomal RNA, since then the field has exploded…

…not only because of my work. I was near the beginning of that revolution; other people were working on RNA splicing, which is a fundamental process still being researched today. The splicing community thought that this was pretty cool what we were doing and supported us.

You knocked over the dogma that RNA is only the carrier of information. Can you remember an anecdote?

The RNA people were very excited in a positive way. They had been speculating much earlier about catalytic properties of RNA. In the context of the origin of life, it was an interesting hypothesis for genetic material to evolve, if it could replicate itself. This group included some of the world leaders such as Francis Crick and Leslie Orgel. Now that we had shown that RNA had catalytic activity, this fitted nicely with those people saying RNA should be able to do everything. It was just an idea, but now we had real solid evidence. The broader community was more skeptical and did not care so much, because we found this just in this little pond animal called *Tetrahymena*. So, it did not shake their tree too much at the time. For them, it was a weird organism doing a weird thing. But when there were many more examples found, then, of course, some people got more concerned about it.

There is a whole zoo of non-coding RNAs. Do we know what they are doing in the cell?

Absolutely not, it will take another century. In human cells, perhaps several hundred thousands of these non-coding RNAs exist, which compares to only 20'000 messenger RNA genes. Therefore, there are a lot more different non-coding RNAs than messenger RNAs. The first question to ask is: How many of these are even functional? Some of them could be just transcriptional noise in the cell, the improper making of RNA or transcribed junk DNA that remains without function. Yes, for some of them that could be true. For other ones, it may just be the act of making the RNA in a specific region of the chromosome that helps other genes in that neighborhood to stay active; so the particular RNA itself is not important, but rather the act of making it there. Then there are those cases where the RNA product of these junk regions is not junk but it is doing something exciting, important, and maybe even medically relevant for human health. Therefore, those are the ones that people are trying to discover and focus on. We are in very early times of researching this, so it is best to be open-minded.

Interview Prof. Thomas R. Cech

"That RNA was at the origin of life is hard to prove, because it is a historical question rather than a scientific question."

Has the RNA world hypothesis now been proven?

No, that RNA was at the origin of life is hard to prove, because it is a historical question rather than a scientific question. Even if a scientist could show that you could make life from RNA today in the test tube, this would still not prove that this is how it happened.

It is hard to think of a way how you would prove it since in contrast to dinosaurs and trilobites, these RNA molecules do not leave fossil evidence. We can come up with reasonable stories, which make sense, but that does not prove that they are correct.

How did the new gene editing technologies change the field of RNA biology?

CRISPR is very easily used in human cells grown in culture and can as well be used to make mice that have precise changes in their chromosomes. This is a godsend for the RNA community because we can prevent one of these non-coding RNA from being made quite quickly and see whether that has any consequences. In many cases, researchers have found that the RNA does have a function since you see a phenotype if you knock out the RNA. Often protein coding genes stop working if you prevent the neighboring non-coding RNA from being produced. Some of these protein-coding genes are medically really important since they are involved in heart development and disease. The majority of these non-coding RNAs are involved in enhancer and promoter regions, while others work at a greater distance, and so for those, it may not be so obvious to elucidate their mechanism of action.

Can you elaborate on the role of RNA in epigenetics?

This is a fascinating topic in the context of gene silencing. At the level of proteins which condense and de-condense the chromatin, most of these epigenetic complexes bind RNA in living systems. They bind many RNAs, and this RNA binding promotes or represses their activity. Some of these complexes bind RNA promiscuously. That is what we have recently found, which is one kind of story, where the RNA binding prevents the chromatin-modifying complex from turning off a gene. Therefore, the RNA acts as an inhibitor of an inhibitor. If the RNA is being made in a particular part of the chromosome, then you want to keep this chromatin silencing complex away; so, if that is the mode of action, do you want the RNA to be very specific? No, then it would only work in one place. So you have to be general, and the chromatin modifying complex binds just any RNA it encounters. The RNA then removes it from the chromosome so that it no longer can silence that particular gene. Once there is no RNA present the complex can come and silence the gene.

What new surprises can we expect in the field of RNA biology in the next few years?

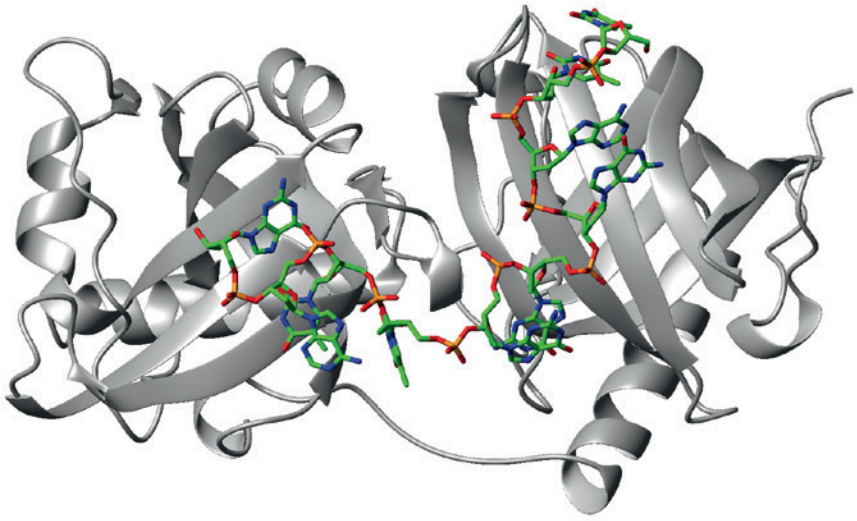
For the last 30 years, we have underestimated every time this question came up, what surprises would still come along. People thought, oh now, we are leveling off, most of the discoveries have been made, and now things will go more slowly. Instead then, for example, CRISPR or long intergenic non-coding RNAs (lincRNAs) come along, and all of a sudden open questions in the field are once again exploding. Some of the questions are: How important are lincRNAs for the brain? Are these maybe contributing to the cognitive power of primates and humans? Therefore, one can imagine, that such a thing could explode in the future; but we do not know.

What are you working on right now?

My lab mainly works on telomerase and an epigenetic silencing complex. Joachim Lingner, who is now a professor at EPF Lausanne , discovered that telomerase is a reverse transcriptase, which was the first example of such an enzymatic activity in eukaryotic cells. This discovery caused an explosion in that field with currently 1000 publications published every year about telomerase, which is a medically very important protein, but about this, we had no idea at the time of that discovery.

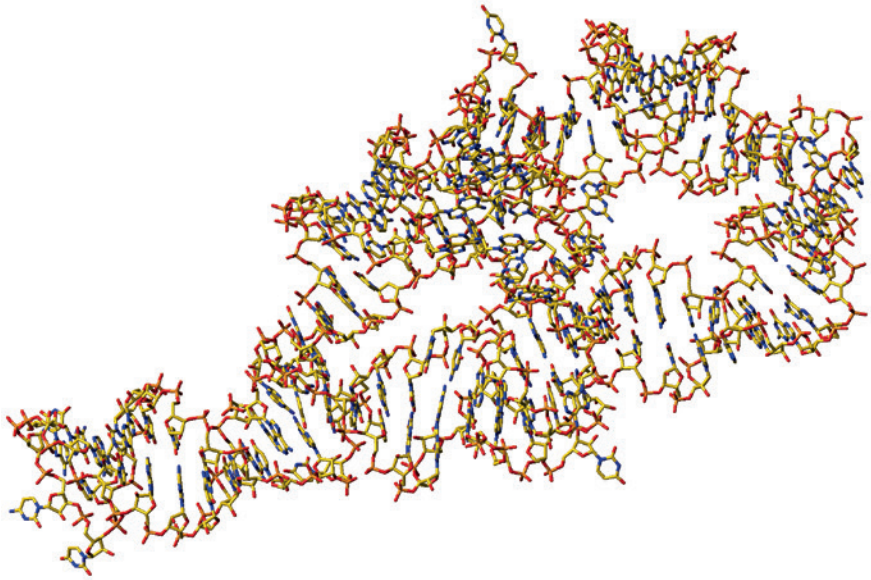
How does telomerase work?

It builds out the ends of our chromosomes. In the absence of telomerase, the chromosome ends get a little bit shorter with each cell division. Once these ends get too short, this sends a signal to the cell to quit dividing; this is a good thing for most of the cells in our body. If one did not have this process, we would be enormous now, because all of the cells in our body would continue dividing. However, cancer cells find a way to reactivate the telomerase enzyme so that they can keep dividing and this is not a good thing for us. On the other hand, there are the stem cells in our body, which are essential for tissue regeneration and have to continue dividing at a modest rate. Therefore, they need to have telomerase activity, and there are quite some human diseases occurring when stem cells do not have enough telomerase activity. This leads to problems with the body's blood supply, lungs, skin, and early aging symptoms. This is an uncomfortable situation, where we have a telomerase activity as a critical biological component: Having too much of it is like having one foot in the door for cancer, having too little of it, you get into early aging. Thus, it has to be kept under accurate control, and that is why



Depiction of the structure of the N-terminal half of the human POT1 (protection of telomeres 1) protein bound to a telomere derived DNA sequence (PDB entry: 1XJV), Lei M. et al. (2004) Nature Structural & Molecular Biology 11, 1223–1229.

Interview Prof. Thomas R. Cech



Depiction of the structure of the P4-P6 domain of a group 1 ribozyme (PDB entry: 1GID), Cate J.H. et al. (1996) Science 273 (5282).

you go one direction or the other when the control sometimes goes bad. We are trying to understand how that works.

Can this knowledge be used to develop new cancer drugs?

There are many companies and academic laboratories working on telomerase inhibitors; that could be a useful anti-cancer approach. In the clinics currently, it is more being used diagnostically, since you sometimes have mutations in the reverse transcriptase subunit that activate the telomerase. Patients that have these mutations in the regulatory promoter region do very badly regarding cancer progression. Medical doctors are using this diagnostic information regarding telomerase mutations to decide whether to apply a harsher chemotherapy or not. Telomerase mutations are not the only marker for aggressiveness of a given cancer, but it is helpful. In 70% of all melanoma samples, you detect these mutations.

RNA medicine is a buzzword, where does it stand now?

For a long time, it was just a good idea. However, there were not many examples of success. Just last year the FDA (Food and Drug Administration) approved a new treatment for SMA (Spinal Muscular Atrophy), which is an antisense RNA drug directed against an RNA process, which was developed by Ionis together with Biogen. It worked well enough that they had to stop the clinical trial early because they saw so much success with the kids that were getting the drug. This treatment is life-saving for these children, but we do not yet know whether it will allow them to live healthy lives, but it is very promising. To me as a non-expert, the drug seems to be quite specific and therefore relatively safe. It is a costly treatment.

"We are in very early times of researching non-coding RNAs, so it is best to be open-minded."

There are 150 ongoing clinical trials with RNA therapeutics. Which ones are the most promising?

The CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) technology requires RNA, and these are probably right now the most talked about RNA therapeutics. The development of the antisense approach being usable as a drug took a long time. RNA itself is not that great of a drug, because it is a large molecule with many negative charges on it, making delivery into cells challenging and by itself is not stable at all. Those problems have been overcome better and better over the years through chemical modifications introduced into the RNA.

Your former lab member Jennifer Doudna was one of the leading scientists in developing the CRISPR technology for genome engineering.

Jennifer Doudna was a postdoctoral fellow in the mid-90s at the same time as Joachim Lingner was in the lab. This was an exciting and fruitful time when she determined the 3-D-structure of a non-coding RNA. We knew that this RNA could act like an enzyme and therefore imagined that it must have a particular shape, but we only had a vague idea of what it might look like. She was able to determine its structure at the atomic level. It was fascinating for us to see the architecture of this RNA. Once this happened, there was a revolution in RNA structural biology, including the ribosome and the spliceosome structures. This pushed people! Jennifer Doudna was very famous already before CRISPR: She got elected to the US National Academy of Sciences at an extremely young age and promoted to full professor at Yale in record time, which she left to become a full professor at Berkeley. She was a winner from the beginning. It is now maybe not even so unexpected that she made another big discovery. I do not know if I can keep up with her (laughs).

You were president of the HHMI, why did you step down after nine years?

I enjoy teaching and love training students how to become scientists. At the HHMI (Howard Hughes Medical Institute) I was an administrator of a huge organization and would mostly talk to lawyers, finance and investment people. I was quite removed from the action of doing science and teaching. After a decade, I felt it was time to step down even though I loved it.

Today, you are still heading a lab at age 69?

You think I should retire (laughs)? I know that in Switzerland, I would be retired for four years. There is no perfect system; in the US system, there can be people that are very old, not at the height of their talent anymore, who still stick around and absorb money that younger people could use.

How did you get hooked on science?

I knew I am going to be a scientist from second grade, because my parents saved everything I ever wrote. I wrote about being a scientist at that age. The reason was genetic in my case, probably inherited from my father who was a medical doctor, but always wished he could be a physicist. In fact, his hero was Albert Einstein, and he would have loved coming to Berne to see the Einstein house.

In College, you first chose to study the humanities. Why did you then switch to chemistry?

Interview Prof. Thomas R. Cech

It is wonderful as a young person to have a broad education, because it sets you up for your life, to be a good citizen, a good parent. When it comes to making a living, I could not see doing this by reading the great books. So for a profession, I always knew, it would be science. Currently, I am reading a new translation of Dante's Inferno. I am about halfway through, and things are getting bad going down towards hell.

"I knew I am going to be a scientist from second grade."

What was your reaction when Trump got elected?

That was very surprising to many of us! A similar surprise as in the UK with the Brexit vote. Many of us had underestimated how much dissatisfaction and even anger there was in large parts of the population. They were ready for a major change. I must say though; I come to Europe quite often, there is an undercurrent of similar thinking in many European countries. Many people that are anti-immigration, who are suspicious of people with a different background, who are thinking the economy is not helping them. I think these things could happen in Europe as well as many of the manufacturing jobs have gone to Asia. The second idea I had: maybe some of Trump's ideas are pretty good such as reducing the size of the government.

Wait, wait! Trump is so much anti-science, anti-vaccine, anti-climate change.

Oh yes, this is very worrisome. The vaccine part is particularly disturbing: because of all of the medical advances in the 20th century, it is the single one that made the most difference regarding lives saved. Antibiotics would rank very high, but only second to vaccines. In our parent's generation, polio was such a devastating disease. Kids would go to school in the morning, have a fever at night and might be dead or paralyzed the next day. People have forgotten how quickly the vaccines turned this around. The irony is that those vaccines were not safe by today's standards. Vaccines have an extremely high bar for being approved because you are going to give them to a large number of small children who are healthy. Therefore, if there is any chance that they are harmful, they will not be approved. Despite the very rigorous approval process, these people just make up this stuff. In fact, the original worry turned out to be fraudulent, but on the internet, this stuff persists. There are always some parents whose kids get autism, and since we do not understand the cause of autism, they say: maybe it is the vaccine. So maybe it is one of a hundred other things, too; it is very disturbing.

Will there be a brain drain in the US?

I think it is possible that many of our students who come from Asia or the Middle East are feeling unwelcome because they are subjected to so much negative scrutiny. So I am afraid that we may lose many of our talented graduate students as well. However, I am an optimistic person and think, we can turn this around, but of course, I am concerned about it at this time.

Do you fear cuts in the National Institute of Health's budget?

There is a proposal from the president's budget that it will be severely decreased. Initially, 25%, now the proposal is back to 5%. It turns out 5% is huge, since much of the money is already committed, so it has a much larger effect on the current year's budget. For young people who want to get started, you have to multiply by about five; we are talking a 25% decrease in a particular year that would be devastating. HHMI and the Chan-Zuckerberg Initiative (Facebook) are doing a fantastic job to find novel ways to support creative science in the biomedical area. That makes a difference, but it is hard for any private philanthropy to cover the NIH budget, which is much larger.

For the deconstruction of American science, the president can do only so much without the support of the Congress, which has to appropriate the money. There is a great deal of support for medical research in the Congress. I think the area that I am in is unlikely to be decimated, but I do worry about climate research. Two thousand scientists work in Boulder in government labs studying the climate such as NOAA (National Oceanic and Atmospheric Administration), NCAR (National Center for Atmospheric Research), and the NREL (National Renewable Energy Lab). In these areas, you can shut down with an executive order from the president certain kinds of research without the Congress being involved – I should not say this because I do not want to give anyone any idea. George W. Bush did this with stem cell research in 2001, prohibiting federal funding of research. It is a worrisome time for them; they feel like a Damocles sword hanging over them and are quite concerned.

Prof. Thomas R. Cech

Biography

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After obtaining his Ph.D. in chemistry from the University of California, Berkeley and postdoctoral research at the Massachusetts Institute of Technology, Dr. Cech joined the faculty of the University of Colorado Boulder in 1978. In 1982 Dr. Cech and his research group discovered self-splicing RNA in *Tetrahymena,* providing the first exception to the long-held belief that biological reactions are always catalyzed by proteins. Because RNA can be both an information-carrying molecule and a catalyst, perhaps a primordial self-reproducing system consisted of RNA alone. For the discovery of RNA's catalytic properties, he was awarded the 1989 Chemistry Nobel Prize together with Sidney Altman. From 2000–2009 Dr. Cech served as the president of the Howard Hughes Medical Institute, which is the largest private biomedical research organization in the USA. He is a member of the National Academy of Sciences and directs the BioFrontiers Institute at the University of Colorado Boulder.

Cech Lab Website

This interview was conducted by Nik Walter (Head science section Tages-Anzeiger) in the context of Thomas Cech's visit to Switzerland as a speaker in the NCCR RNA & Disease seminar series. Read the portrait of Thomas Cech written by Nik Walter entitled "Der Dogma-Brecher" on the Tages-Anzeiger or Bund Website. The portrait pictures were kindly provided by Adrian Moser (Chief photographer Der Bund). Depictions of the structures were generated with the program MOLMOL (Koradi R. et al. (1996) Journal of Molecular Graphics, 14(1), 51–55.

Research highlights

Research highlights from NCCR laboratories

Roland Fischer

Protein polymerization preventing pathological aggregation

There are still a lot of unanswered questions when it comes to the pathogenic effects of proteins in connection with ALS and dementia. Tariq Afroz from the Polymenidou group at the University of Zurich has now found a novel and unique higher order structure of RNA-binding proteins: the oligomerization of TDP-43, mediated by its N-terminal domain.

TDP-43 is one of the key factors when it comes to understanding the molecular mechanism of Amyotrophic lateral sclerosis (ALS) as well as a special form of dementia (Frontotemporal dementia, FTD). The protein has been shown to bind both DNA and RNA and has many functions in transcriptional repression, pre-mRNA splicing and translational regulation. A previous study by Polymenidou and colleagues revealed that thousands of RNAs are bound by TDP-43 in neurons.

A lot of work has been invested to unravel the molecular mechanisms behind the pathogenic effects of TDP-43. The protein is usually present in the cell nucleus only, but in patients with ALS and FTD it leaks out of the cell nucleus, and aggregates in the cytoplasm, thus catalysing a damaging chain of events inside the cell and causing it to die. A group around Magdalini Polymenidou from the Institute of Molecular Life Sciences, University of Zurich, and Frédéric H.T. Allain from the Institute of Molecular Biology and Biophysics of the ETH Zurich has now reported that physiological nuclear TDP-43 in mouse and human brain forms homo-oligomers that are resistant to cellular stress. The oligomerization is mediated by the N-terminal domain (NTD) of TDP-43, which can adopt dynamic, solenoid-like structures. This was revealed by a 2.1Å crystal structure in combination with nuclear magnetic resonance spectroscopy and electron microscopy. The group provides evidence that the physiological state of the protein in the nucleus is in fact oligomeric and that this oligomerization is indispensable for the functional role of the protein in RNA metabolism.

Initially the NTD of TDP-43 was thought to be unstructured. Intriguingly, while several recent studies highlighted the importance of NTD for functional TDP-43 dimerization and nucleic acid interaction, others argued that the same domain promoted pathologic aggregation and neurotoxicity. Moreover, a small fraction of TDP-43 was reported to exist as dimers in cells, so the dimers were suspected to initiate or "seed" the formation of pathologic TDP-43 aggregates.

TDP-43 oligomerization and its mediation by NTD is novel and unique among the higher order structures described for RNA-binding proteins. This leads to a range of attractive hypotheses: First, TDP-43 binds RNA preferentially as an oligomer to increase affinity towards long contiguous UG-repeats. Moreover, TDP-43 oligomerization may act as a "recruitment platform" for specific factors involved in splicing and RNA maturation steps important for sustaining their levels. And there is another potential role of inter-molecular TDP-43 interaction that is NTD-driven: The protein has the ability to bring distal sites on RNA in close proximity, resulting in looping-out of RNA. Depending on the binding sites, this mechanism may promote inclusion or skipping of alternative exons.

One important thing remains enigmatic, though: The mechanism of transition of physiological nuclear TDP-43 to pathologic, irreversible and insoluble protein assemblies, leading to neurodegeneration. It is known that TDP-43 contains a C-terminal prion-like or low-complexity domain (LCD), mediating protein–protein interactions, and that this LCD is crucially involved in disease. So the group suggests that the transition is likely triggered by the proteolytic release of its C-terminal LCD, which harbours most of the ALS-linked mutations and indeed possesses high propensity to self-associate, phase separate, and aggregate. The collected data strongly supports the hypothesis that formation of physiological NTD-mediated, nuclear TDP-43 oligomers can counteract cytoplasmic aggregation. Any factor altering the cellular equilibrium between oligomeric and monomeric TDP-43 may trigger the initiation of cytoplasmic TDP-43 aggregation.

Afroz T. et al. (2017) Nature Communications 8, 45 (open access)

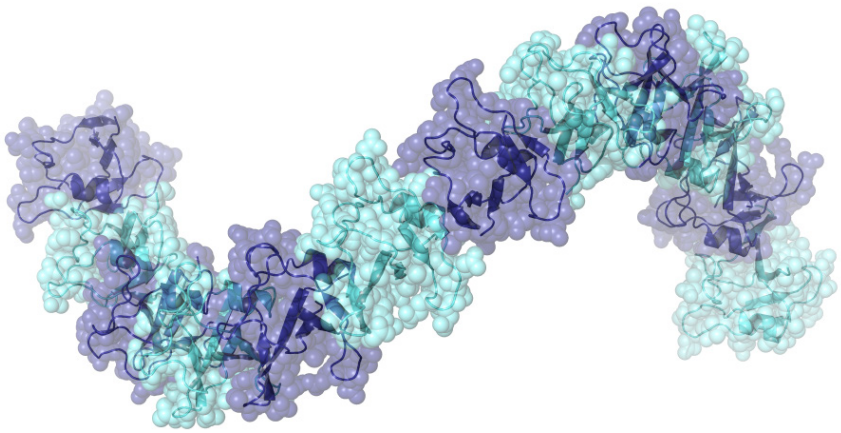


Figure kindly provided by Tariq Afroz.

Research highlights

CLIR sight on protein–RNA interactions

A new method to study protein–RNA interactions at amino acid and nucleotide resolution is proposed by Frédéric H.T. Allain, Ruedi Aebersold et al. It has been tested successfully on the complex of polypyrimidine tract binding protein 1 with a natural RNA target and is expected to be applicable to any RNP (of bigger size as well) for elucidating protein–RNA interactions and generating and refining precise structural models.

Ribonucleoproteins (RNPs) are key regulators of cellular functions such as gene expression. Even single nucleotide mutations can alter RNA–protein interactions with fatal consequences. Deciphering protein–RNA interactions at single amino acid and nucleotide resolution would therefore enable further functional characterization of RNPs, but until now, the exact positions of the proteins on the RNA have remained inaccessible. A group around Frédéric H.T. Allain from the ETH Institute of Molecular Biology and Ruedi Aebersold from the ETH Institute of Molecular Systems Biology and Biophysics led by Georg Dorn (Allain group) and Alexander Leitner (Aebersold group) has recently presented an efficient approach, termed CLIR-MS/MS, to localize protein–RNA interactions simultaneously at amino acid and nucleotide resolution.

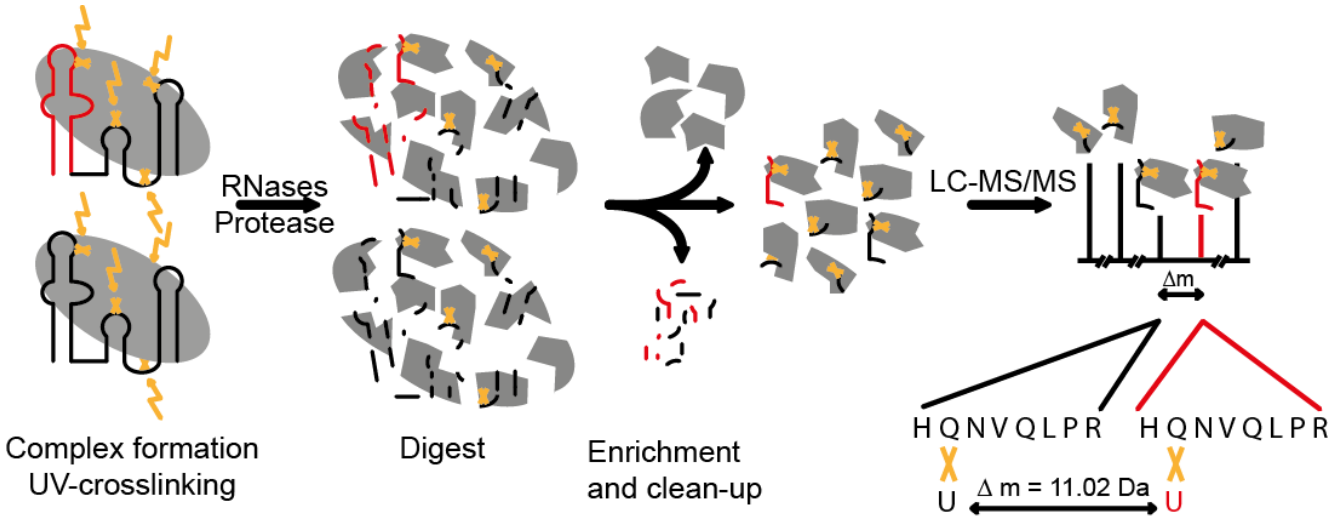
CLIR stands for "cross-linking of segmentally isotope labeled RNA". In combination with tandem mass spectrometric analysis (MS/MS), the CLIR labeling strategy uses the introduction of stable isotopes to locate the interaction site(s) between protein(s) and RNA. The group first applied the method to the complex of polypyrimidine tract binding protein 1 (PTBP1) with a natural RNA target. PTBP1 is a key alternative splicing factor and a major internal ribosomal entry site (IRES) trans-acting factor of several cellular and viral mRNAs. It was used as a model system because it is of biological relevance and has been studied in Fred Allain's group by NMR spectroscopy and other methods.

PTBP1 contains four RNA recognition motifs (RRM), whose structures in complex with a small single-stranded CUCUCU motif were determined by NMR spectroscopy. However, the recognition of guanines by PTBP1 and cooperative binding of all four RRMs to a large and structured RNA remain unexplained. The authors used MS and NMR spectroscopy to study PTBP1 in complex with a structured RNA molecule consisting of domains D–F of the IRES of encephalomyocarditis virus. This IRES part binds all four RRMs of PTBP1 and is essential for the regulatory function of PTBP1 in translation initiation.

Taking advantage of the ability of CLIR-MS/MS for high-resolution protein–RNA interaction mapping, the group used the identified crosslinks as intermolecular distance restraints (a form of spatial/distance information) for structural modelling, combined with restraints derived from available structural data of PTBP1-RRMs and from RNA structure predictions. In the context of CLIR-MS/MS, a certain amino acid and nucleotide must be close to each other in 3D space in order to be cross-linked. This "restraint" can be used in computational modelling methods to calculate the structure of protein-RNA complexes. Notably, all except one CLIR-MS/MS distance restraints were fulfilled by a single conformation for each RRM.

The authors believe that the method is applicable to any RNP of interest for elucidating protein–RNA interactions and generating and refining precise structural models of such RNPs. Furthermore the authors successfully tested the applicability of CLIR-MS/MS to larger RNPs as well – they expect that it can be used to study more complex systems such as in vitro reconstituted multicomponent RNPs. Fred Allain is convinced that the method is "a new approach that could considerably speed up the time needed to determine structures of protein-RNA complexes."

Dorn G. et al. (2017) Nature Methods 14(5), 487-490



Modified figure kindly provided by Georg Dorn. Adapted by permission from Macmillan Publishers Ltd: Nature Methods, 14 (5), 487-490 (2017)

Stefanie Jonas – New NCCR RNA & Disease Junior PI

Nuclear RNP assembly and processing machines in human cells

In August 2017, Stefanie Jonas will take up her position as an assistant professor at the Institute of Molecular Biology and Biophysics, which is part of the Department of Biology at ETH Zurich. Stefanie Jonas has throughout her scientific career applied a variety of methods to gain a mechanistic understanding of biological macromolecules, the majority of which is involved in RNA metabolism.

"Feedback on our projects and results from more senior NCCR members will undoubtedly help at this early stage of my independent research career."

In 2005, she obtained a Master of Science degree in Chemistry from the Georg-August University of Göttingen, Germany after having carried out her master's thesis research in the lab of Jennifer Doudna at the University of California Berkley, where she worked on the GTPase BMS1 involved in ribosome biogenesis. For her Ph.D., Stefanie Jonas went to the lab of Florian Hollfelder at the University of Cambridge. There, she structurally and mechanistically characterized how efficient catalytic promiscuity is achieved by enzymes of the alkaline phosphatase superfamily. In 2010, she returned to RNA Biology and Germany for her postdoctoral research in the lab of Elisa Izaurralde at the Max Planck Institute for Developmental Biology in Tübingen. During this time, she focused on complexes involved in post-transcriptional regulation and degradation of messenger RNA degradation via nonsense mediated decay, deadenylation and decapping. In 2015, she joined the lab of Ulrike Kutay at the Institute of Biochemistry at ETH Zurich characterizing complexes involved in ribosome biogenesis including the ANN complex that contains the AATF/Che-1 protein, which is required for embryonic development[1].

The Jonas laboratory aims at deciphering the structures and mechanisms of nuclear machines that process RNAs. One of its research targets is the small ribosomal subunit processome, which is a key machine involved in ribosome biogenesis. The production of ribosomes is a highly complex process requiring the coordinated interplay of many factors at different locations in the cell. To sustain their rapid growth, cancer cells depend on high rates of ribosome production and inhibiting this process might prove to be a useful approach for battling tumors, which is currently tested in clinical trials. Other examples illustrating the disease relevance of ribosome biogenesis are ribosomopathies, which form a group of human genetic diseases whose symptoms arise due to the production of faulty or lower levels of ribosomes. The Jonas lab will apply a broad array of methods ranging from structural to omics techniques to shed light on these machines and the cellular processes they are involved in, as well as how defects of those can lead to human diseases.

Stefanie Jonas is looking forward to broadening the scope of scientific questions she can address through collaborations with other laboratories of the network and emphasizes the importance of the NCCR's technology platforms for her research. Additionally, she expects that being part of the network will enhance the visibility of her research. For building up her lab, she will also rely on recruiting Ph.D. students through the RNA Biology Ph.D. program. She states that her future lab members will profit from the training possibilities offered by the NCCR RNA & Disease and she will encourage them to make the most out of these opportunities.

[1] Bammert L. et al. (2016) Nucleic Acids Research 44(20), 9803-9820

Dominik Theler

Announcements

People

We would like to welcome Prof. Lukas Jeker as a new associate member of the NCCR RNA & Disease. Lukas Jeker is an SNSF assistant professor at the Department of Biomedicine at the University of Basel. The Jeker lab studies the role of microRNAs in the regulation of the immune system.

We congratulate Jessica Willi (Polacek lab) for receiving a RNA Society Poster Award at the society's annual meeting in Prague. The poster described the findings made regarding: "How oxidation in the ribosome's active site affects translation".

Support Grants

The NCCR RNA & Disease will award fourteen travel grants to PhD students and postdocs from NCCR labs to support their attendance of the 2017 Riboclub Meeting in Orford, Canada, of which the NCCR RNA & Disease is a co-organizer.

The request of Dr. David Ramrath (Ban lab) for a 120% support grant was approved.

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

Upcoming events organized by the NCCR RNA & Disease

> Symposium for Professorship in RNA Biochemistry, August 23–24, 2017, Department of Chemistry and Biochemistry, University of Bern

> 2nd NCCR RNA & Disease Summer School "RNA & RNP architecture: from structure to function to disease", August 28 – September 1 2017 Saas-Fee (Registration closed)

> The NCCR will present parts of its research to the public in the form of stands both at the 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

> Careers in Science Symposium organized by the NCCR Chemical Biology, November 28–29 2017, Geneva

> NCCR seminar series autumn semester 2017 at the University of Bern and ETH Zurich. Speakers: Mariano Garcia-Blanco (Invited by the RNA Biology PhD program students), Chuan He and John Rinn.

> 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

> Swiss Company Maker – Pre-seed Workshop, April 17–18 & 25, 2018 in Bern

> **NCCR RNA & Disease Internal Events:**
3rd NCCR RNA & Disease Retreat, February 4–6 2018, Kandersteg
4th NCCR RNA & Disease Site Visit, March 20–21 2018, Bern

Past events organized or supported by the NCCR RNA & Disease

> First steps in computational biology for RNA Research training course, May 15–16, 2017

> General Assembly Meeting, June 12 2017, La Neuveville

Knowledge and Technology Transfer (KTT)

The KTT flyer of the NCCR RNA & Disease is now available for download.

Jobs

PhD program in RNA Biology
Find out more on our website.

Postdoctoral Positions – Oscillatory gene expression dynamics in developmental time control – Grosshans Lab, FMI Basel

Postdoc Position – Bioinformatics of Long Non-Coding RNA in Cardiac Regeneration – Johnson lab University of Bern

Check the jobs's section of the NCCR RNA & Disease webpage for other openings.

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NCCR RNA & Disease
Phone: +41 31 631 38 12
office@nccr-rna-and-disease.ch
www.nccr-rna-and-disease.ch

Office Bern
University of Bern
Departement of Chemistry and Biochemistry
Freiestrasse 3, CH-3012 Bern

Office Zürich
ETH Zürich
Institute of Molecular Biology & Biophysics
ETH-Hönggerberg, HPP L15
Otto-Stern-Weg 5, CH-8093 Zürich

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