

THE MESSENGER

Newsletter No. 4

December 2016 — National Center of Competence in Research, RNA & Disease



**NCCR
RNA & Disease**

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

Dear colleagues

I am glad to see how well by now our Newsletter has established itself as a source of valuable information for both the NCCR researchers and people generally interested in our work. In continuing along these lines, this issue provides insights into the history, the different applications and future potential of oligonucleotides as drugs. Jonathan Hall shares with us his vast knowledge, experience and opinions regarding the use of oligonucleotide to treat diseases.

Working abroad, building a worldwide professional network and getting inspiration from scientifically thriving places is an integral part of every scientific career and the SNF mobility grants that can be applied for through the NCCR offers exactly these opportunities. Mobility grant awardee Melanie Jambeau told us her experience of conducting a part of her PhD at the Massachusetts General Hospital in Boston.

*The core business of our NCCR is and remains innovative and high quality research, and in this context it is gratifying to follow the constant stream of publications emerging from our labs. Two of the recent publications are featured in this issue of The Messenger. The first is from the lab of Mariusz Nowacki reporting in *Cell* about a ciliate species that uses a genetic code lacking stop codons, which raises the question how the position of translation termination is defined on mRNAs in this organism. The second is from the lab of Markus Stoffel reporting in *Nature Communications* how vigilin promotes fat release from the liver by enhancing the translation of the mRNA encoding ApoB.*



I hope that these teasers triggered your appetite – enjoy your reading!

Oliver Mühlemann
Director NCCR RNA & Disease

Interview with Prof. Jonathan Hall

Exciting developments in the field of oligonucleotide drugs

Jonathan Hall shares his perspective on the history of oligonucleotide drugs, collaborations with industry, Knowledge & Technology Transfer and describes his career path.

Oligonucleotide drugs have a relatively young history compared to small molecule drugs and antibodies. Could you give us a short overview of the history and the milestones of oligonucleotide drugs from your perspective?

The history of oligonucleotide drugs begins in the late seventies, early eighties. It was recognized, that oligonucleotides bind to complementary RNAs with a fantastic selectivity and very high affinities. That made it possible to consider RNA as a potential new class of therapeutics. To drive this forward, a lot of work was carried out in a small number of groups in academia and biotech and at the same time real advances in the oligonucleotide synthesis on the solid phase were starting to take off. Although it was clear that these types of reagents could work very well *in vitro* (cell culture), the step towards *in vivo* use of oligonucleotides was going to involve really big challenges; On the side of the chemistry, on the pharmacology, but also on the side of disease biology. These challenges were met stepwise, working in parallel, and it was helped along by the launch of a handful of oligonucleotide therapeutic companies: Companies like Ionis Pharmaceuticals [formerly Isis Pharmaceuticals; for the rest of the interview the name Ionis is used], Gilead Sciences or Hybridon, to name a few. The discovery that phosphorothioated RNAs circumvent-

ed some of the pharmacokinetic problems was certainly a milestone of oligonucleotide drug discovery and development. Another was the discovery of the RNase H mechanism, whereby it was recognized that most oligonucleotides working in cells and also *in vivo* actually induced enzyme-mediated degradation of the mRNA. The approval of the first drug in 1998, Fomivirsen [trade name Vitravene®], which was injected directly into the eyes of AIDS patients suffering from cytomegalovirus [CMV] infections, was an important milestone. Although the drug had non-specific effects and it was a commercial failure, its approval forced the regulatory authorities to consider oligonucleotides as a new class of drugs. The molecule was withdrawn as other conventional antiviral drugs came on the market, which were more effective and orally available. The field then had to wait a further 15 years before the approval of the first good antisense drug, called Mipomersen [trade name Kynamro®]. In those intervening years the field made a lot of progress, particularly in the field of medicinal chemistry. Large pharma companies have played a significant role in the development of this field as they supported some of the early antisense companies with substantial research and development collaborations. However, by the time the first drug was approved, most of large pharma had actually stepped back, mainly because of the slow rate of progress. It has always been tempting to compare the rate of development in oligonucleotide therapeutics to that of the antibody drugs, and oligonucleotides are taking much longer to be accepted as a

Interview with Prof. Jonathan Hall

viable therapeutic. However, there is no real reason why such a comparison is valid. Other important milestones were the discovery of a new class of RNA targets in the form of microRNAs (miRNAs) and at the same time, the introduction of small interfering RNAs (siRNAs). As the most recent milestone, I would consider the results from clinical trials of the Ionis drug Nusinersen to treat children affected by Spinal Muscular Atrophy. The CEO of Ionis, Stanley T. Crooke, showed at the Oligonucleotide Therapeutics Society meeting this year a short movie of a child that was treated with the SMN2 splice-correcting oligonucleotide Nusinersen, a molecule developed with Adrian Krainer (Scientific Advisory Board Member NCCR RNA & Disease) at CSHL. The beginning of the movie showed a baby who could basically not move his head, arms or legs, but as the baby grew into a small child we saw the progress in terms of movement capabilities after drug treatment. That was powerful! That is splicing correction with oligonucleotides. Precision medicine!

Can you give us some more insights into the different chemistries of oligonucleotides?

In the early days of oligonucleotide therapeutics much of the research was devoted to dealing with the major pharmacokinetics challenges. The problem with natural oligonucleotides is that they are degraded in vivo by nucleases extremely quickly. The challenge for medicinal chemists was therefore to find a means to protect them against nucleases, while maintaining their Watson Crick recognition properties, their ability to activate RNase H, their suitability for solid phase synthesis and keeping the structure sufficiently simple to permit large scale manufacture. Besides the phosphorothioate modification, very few chemical modifications satisfy all these criteria. Nevertheless, a handful from literally hundreds of modifications tested made it through to clinical studies. Around the mid-nineties the methoxyethyl modification was developed by the Novartis (former Ciba-Geigy) group. It was subsequently licensed by Ionis pharmaceuticals and became the mainstay of all their clinical programs. Around 2000 there was the invention of the locked nucleic acid (LNA) simultaneously by Danish and Japanese groups. This particular modification also made it as far as clinical trials. A chemical modification, which remained rather secret for a long time with respect to its structure and properties, was the morpholino modification, appearing in the mid-nineties. It has rather an innovative structure, and does not activate RNase H but still found much use as tools to be used in model organisms. It has proved valuable in a

class of oligonucleotides that work by a special mechanism, so called splice switching oligonucleotides (SSOs). Exciting developments continue to be seen: one is the introduction of chiral phosphorothioate oligonucleotides, as all oligonucleotides in clinical development are currently mixtures of diastereoisomers. The second is the so-called GalNAc conjugates, relatively large oligosaccharide ligands introduced into siRNAs, tremendously increasing delivery to the liver. The delivery of oligonucleotides is still seen as a main hurdle for this technology and it is true that oligonucleotides to date can only be used in a relatively small number of tissues, particularly liver, kidney and the central nervous system. Thus, today, a lot of academic research is devoted to the use of so called sophisticated targeting molecules to broaden the scope of the technology.

How does the chemistry of oligonucleotides affect their delivery and stability?

Oligonucleotide drugs will probably never be orally bioavailable with acceptable efficiency. They can be delivered typically intravenously or with subcutaneous injections. When phosphorothioate drugs are delivered systemically, the phosphorothioates in the molecule cause them to associate with proteins in the blood. This turned out to be a very useful property because it actually kept them in the body such that they distribute rather broadly to almost all tissues and organs. Without this protein binding they would be excreted rather quickly. The second and third generation modification chemistries make the single stranded oligonucleotide drugs rather stable against

Prof. Jonathan Hall Biography



Jonathan Hall is full professor for Pharmaceutical Chemistry at the Institute of Pharmaceutical Sciences at ETH Zürich since 2007. He serves as the delegate for Knowledge and Technology transfer (KTT) of the NCCR RNA & Disease, in which he also is a principal investigator investigating the drugability of RNA. The group of Jonathan Hall runs the RNA synthesis platform of the NCCR RNA & Disease.

Jonathan Hall obtained his bachelor and PhD (supervisor: Edward Smith) degrees from the Imperial College in London. He continued his research career with postdoctoral stays in the laboratories of Jean-Marie Lehn and later Yoshito Kishi. Before joining ETH Zurich Jonathan Hall worked as a researcher and group head for fifteen years first at the Ciba-Geigy Central Research Laboratories and subsequently at the Novartis Institute for Biomedical Research. There he began to work on the chemistry of nucleic acid synthesis and their applications as therapeutics and screening tools.



MerMade oligonucleotide synthesizer

Interview with Prof. Jonathan Hall

metabolic degradation compared to the first generation. The methoxyethyl modification in single stranded oligonucleotides is basically a rock. I am not aware of any reports in the literature where accumulation of these drugs in vivo has caused any problems. They are of course metabolically degraded and secreted as truncated versions of the original sequence. There is some concern that some of the modifications, particularly those in siRNAs, may lead to some long-term toxicity, as modified nucleotides are incorporated into natural polynucleotides in the body. But again, to my knowledge there is no evidence that this has actually been observed.

When did you start working on oligonucleotide chemistry?

I first started to work on nucleic acids in 1992 when I started at the Central Research Laboratories at Ciba-Geigy. I had never worked with nucleic acids before, but this type of chemistry, especially in terms of the molecular recognition of oligonucleotides, was extremely attractive for a chemist. At that time at Ciba-Geigy, which became Novartis in 1995, all of the scientists working in the area were chemists. In 1996 the management decided to move resources more towards the biology, particularly the disease biology in house. The fundamental make-up of the group then changed and most of the chemists were replaced by people working more on the biological applications side. Then we had a long phase through the second half of the nineties trying to find the best use of this particular technology among the various therapeutic areas in the company, e.g. neuroscience, transplantation, oncology and respiratory diseases. Around 2000, the sequence of the human genome was starting

to become available and our focus switched from therapeutic applications of oligonucleotides to their use in large libraries as tools to help functionalize newly discovered genes emerging from the sequencing programs. We only really went back to the therapeutics with data that was emerging from the Novartis group in London working on neuropathic pain and when it became clear that oligonucleotides were showing exciting data for the treatment of neuropathic pain through spinal cord delivery.

How did you experience the uncertainty not knowing what the company decides to do next?

All large companies go through reorganizations from time to time and then scientists in the research organization ask themselves how the reorganization will affect them. It is particularly concerning when you are working in an area progressing relatively slowly and when there is still quite a lot of skepticism from the more conservative members of management about the potential for success of this class of drugs. Ciba was a company that was very supportive of the technology compared to other companies. Many large companies had activities in this area initially, but most of them do not have dedicated groups doing the fundamental research any more. New technologies have a natural lifetime and usually often follow such paths. In the beginning, a company will dedicate a lot of research to advance a technology in order to find out how it works best for them, and after it becomes routine then basically disband the dedicated group and use it when needed. In the case of oligonucleotides, these activities were basically shut down at large companies before the technology was

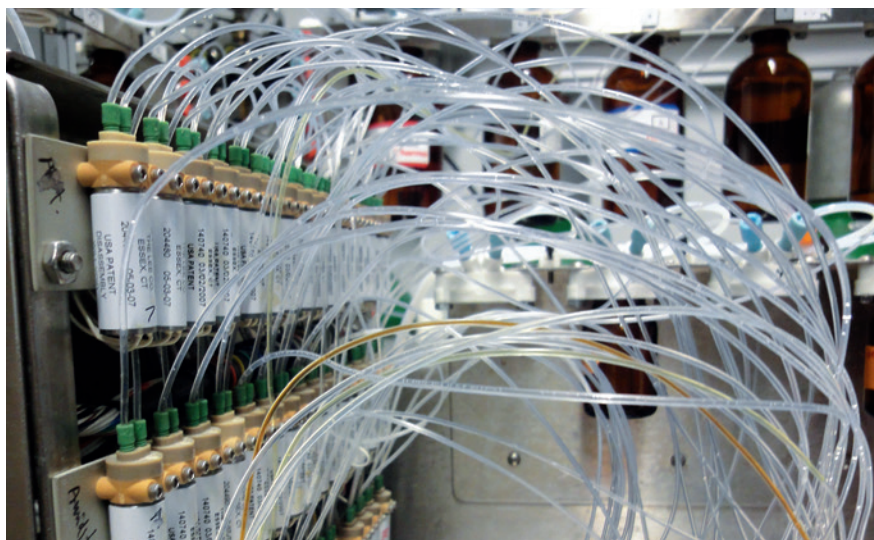
validated on the market. With new approvals, which will come in the next 2–3 years, I am confident that once again interest will be triggered at the larger companies

Why does it seem that in the end small companies were more successful than the large ones in the oligonucleotide therapeutics field?

Most of the small companies that started out have gone. They have gone for a number of reasons: because their programs failed or they lost out in battles over intellectual property. The companies working on single stranded oligonucleotide drugs that have remained are basically Ionis and Santaris, which was recently bought by Roche. What distinguishes these companies from other companies has been actually the quality of their science more than anything else. They have made substantial progress on the important challenges in the field. This is also true for small interfering RNAs; the largest company working in this area being Alnylam Pharmaceuticals. I personally believe that we all underestimated the challenges associated with bringing this new pharmacology to the point where it is validated and is used on suitable drug targets for the right diseases. It is correct to say that oligonucleotides can basically target almost any RNA in the body, but only very few RNAs actually represent truly useful targets for disease indications. Being able to select those has not been so easy and thinking has evolved. In the early stages of the field, these were viral RNAs and targets involved in cancer. Now, the focus is on targets that are expressed in the liver, particularly those that have some kind of genetic validation associated with them. For commercial reasons, targets need to be free of competition from small molecules and antibodies.

Were there similar fierce patent disputes in the oligonucleotide field as there are currently taking place around the CRISPR/Cas9 technology?

Yes, in particular in the early days of the technology a large number of key patents were filed and issued: Key patents around the use of phosphorothioates, phosphoramidite reagents, the dimethoxytrityl group and oligonucleotides, which work by RNase H mechanisms. All these patent applications were filed and were fiercely defended by the companies that held them. This was also the case with small interfering RNAs. The original patents were argued over for many years. And in my view this has, more than anything else, held up developments in the field. Certainly larger companies were reluctant to enter an area where difficult intellec-



Close up view of a MerMade oligonucleotide synthesizer.

Interview with Prof. Jonathan Hall

tual property issues existed. Constraining the number of companies that can actually work in a particular area generally slows down the progress in the field. Paradoxically, this affects even those who hold the key patents.

What made you become a scientist and were there any scientists that inspired you?

It was probably my high school teacher Mr. Hawkins, who had a very aggressive character, and he said: “*Hall you will do chemistry*” and so I did. I was always more interested in science than in languages or humanities. My PhD mentor (Edward Smith) was also somebody who inspired me. He maintained a very small group at Imperial College and put a lot of attention on the PhD students. He was a fantastic person to guide me through the PhD. Somebody who also had a positive effect was Professor Jean Marie Lehn at the University of Strasbourg who was my first postdoc supervisor. He is a tremendous scientist, Nobel laureate, and is able to motivate scientists in numerous ways. He was so interested in the projects and so useful when things were going badly. I think more than anything else he kept me in chemistry and in science because of the way he was, and still is.

What made you move from academic to industrial research?

At the time it was quite difficult to actually get an academic position. In those days you applied for all positions that were advertised, and academic positions were rare. I was successful in getting job offers from three large pharma companies. The science in Basel with the nucleic acids and the new head of this department, who was a truly motivating person to interact with, made that position really appealing. It was not a difficult decision to leave academia and move into industry. It was much simpler than that. I was confronted with a project and an area of research that was just extremely attractive. It also helped at the time that Ciba Central Research Laboratories was quite a well-known organization for doing high-risk, forward-looking research. It was a large department with its own budget which was protected from the more conservative company management. We were actually judged on how we published our work, we were encouraged to go to meetings and we rarely faced hold ups because of patenting issues or typical large company traits.

What triggered your move back to academic research?

It was not one single event. My current position was open at the ETH and after in-

vestigating, it became quickly clear that to start again with a new research group at this institute was truly a fantastic and wonderful opportunity. It also came at a time when I was seeing less and less of the projects being done in the Novartis labs.

What are differences between research in academia and big pharma companies?

I spoke with several professors before moving from Novartis to here. One told me that what I would really enjoy and profit from the ETH environment because I would have the opportunity to take the time to set up the research to the highest scientific standards, setting my own timelines and priorities. That meant that I could truly focus on doing careful science in a way that one can simply not do in large pharma. The pressures of the short term deadlines preclude a lot of the types of experiments that we perform here, trying to fully understand our molecules before progressing to the next step. This is a fundamental difference. The other really large difference comes down to the people you actually interact with. In pharma we hired scientists that had already proven track records. In the academic environment we are actually training these people.

How did you interact with academia during your time in the pharmaceutical industry?

We had a lot of interactions and our own budget for collaborations, which we could use almost as we wanted. One did not have to endlessly justify collaborations to research management, nor how we set them up. These days it seems to me that it is much more difficult for the scientists in large pharma to interact with academia. The decisions to engage in even relatively small-scale collaborations seem to require a lot of discussions and signatures on various levels in the hierarchy. This tends to slow down and even prevent potential good collaborations from starting.

What are the chances and pitfalls regarding collaborations with big pharma?

I believe that your best chance to have a meaningful collaboration with industry these days is if you have a unique technology or drug target that they are uniquely interested in. In this way companies are much more direct and selective these days. I do not know about the pitfalls, but it seems to me that the legal aspects of collaborations also tend to make them much more difficult to set up. It takes forever to sort out legal agreements and often by the time that an agreement is actually signed, the motivation to actually do the project may have diminished. It seems to me also, that large companies are a lot less



willing to fund academic research in a general sense, which is a shame because they lose the chance to make contacts with their future employees.

Can you comment on the importance of Knowledge and Technology Transfer (KTT) for the NCCR RNA & Disease?

The KTT aspects of the NCCR are really important. We do have a large responsibility to show Swiss society and taxpayers that we are spending their money well. Furthermore, KTT offers an opportunity to help our younger generation of researchers because one of our objectives is to stimulate the growth of companies. KTT in biomedical research is quite difficult because our progress is naturally slow compared to perhaps an engineering discipline, where one can have an idea and potentially form a company quite quickly.

What advice would you give NCCR RNA & Disease researchers regarding KTT?

We should sensitize everybody that receives funding from our NCCR to the importance of showing the value of our research to the outside world. My advice to colleagues would be to try to think about your projects in this context and search high and low for possibilities to actually bring new applications and discoveries of practical use out of your research.

Further Reading:

“RNA therapeutics: beyond RNA interference and antisense oligonucleotides”

Ryszard Kole, Adrian R. Krainer and Sidney Altman (2012)

Nature Reviews Drug Discovery, 11(2):125–40

[Link to Pubmed](#)

(PMC Free Full Text Available)

Interview: Larissa Grolimund and Dominik Theler

Research highlights

Research highlights from NCCR laboratories

Roland Fischer

Stop does not always mean stop

The genetic code is believed to be strongly conserved through evolution – from the earliest bacteria until today. Now Estienne Swart et al. from the group of Mariusz Nowacki, Institute of Cell Biology of the University of Bern, have found two ciliate species where nature seems to be in the midst of experimenting with the meaning of the stop codon.

We all know language is ambiguous. One word can have several meanings, and different words can sound the same. Still communication between humans is not a perfect mess – we have found ways to determine the meaning of ambiguous words reliably, by interpreting context. What is more, language is a fluent, ever changing system – words can shift their meaning, human languages are always evolving.

For the language of biology this does not seem to be the case – experts usually refer to

it as ‘frozen’. The genetic code is exceptionally robust: since it has been developed some maybe 4 billion years ago, it does not seem to have undergone any evolutionary changes. Each codon stands for a specific amino acid (or for ‘stop’) – the biological ‘words’ have very clear meanings. There are no ambiguities.

At least that is how it is written in the biological textbooks. But it is a common fate of textbook dogmas: sooner or later they are proven wrong. Now researchers from the Institute of Cell Biology of the University of Bern have for the first time found codons with multiple meanings.

Ciliates, complex protozoans with two nuclei, are known to translate RNA transcripts in unorthodox ways, not always following the classical codon protocol. Now Nowacki and his team have discovered that two ciliate species found in the Marine Mi-

crobial Eukaryote Transcriptome Sequencing Project (MMETSP), *Condyllostoma magnum* and an unclassified *Parduczia* species, have gone even further, reassigning the traditional ‘stop’ codons (UGA, UAA, and UAG) to amino acids. On a first impression it looked like there was ‘stop’ codons spread all over the code, so the researchers quickly considered the option that the codons were used in other ways. But where are the stops, then? “It didn’t make sense in the beginning,” says Nowacki. “Nobody would expect that there would be a stopless genetic code.”

To their big surprise the researchers found that sometimes these same codons have indeed conserved their ‘stop’ meaning, transmitting very efficiently and reliably the signal to the ribosomes to finish their job. This was found studying the transcripts of the ciliates’ histone proteins as their sequences



Research highlights

are highly conserved across all eukaryotes. Using protein mass spectrometry and ribosome profiling, the group determined that in the *Parduzia* species UAA and UAG had no 'stop' meaning whatsoever and are always interpreted as glutamine codons, but UGA can be read as a tryptophan codon in some cases and as a stop codon in other cases. Even stranger, the analysis showed that in *C. magnum* all three traditional stop codons function as either a stop or an amino acid signal.

Nowacki: "That led us to the conclusion that these codons are read in a context-dependent manner." Further research showed that structural features at the end of the coding sequence have an influence on how the ribosome "understands" the codon, but the exact mechanism of how it reads the context

remains a bit of a mystery. What the researchers could determine is that the appearance of the ambiguous codons declined dramatically near the end of transcripts. Additionally, *C. magnum* and the *Parduzia* species had a remarkably short length of untranslated mRNA between the translated part of the transcript and the 3' poly(A) tail, compared with other eukaryotes (only around 21–23 nucleotides between a genuine stop codon and the polyadenylation poly(A) sequences, compared with more than 100 nucleotides in most other species). The team suggests that proteins coating or interacting with the poly(A) tail may act as roadblocks to translation when the ribosome bumps up against them. In yeast, poly(A)-binding proteins have been shown to play a role in translation termination.

"We have been fighting about the term 'ambiguous', actually", says Nowacki. Because the context gives clear hints how to interpret the codon, the biological language remains very clear – the cell machinery does not seem to get confused by these codons with multiple meanings.

The findings are not only interesting because they show that simple truths almost certainly prove wrong when it comes to cellular mechanisms. Nowacki thinks that they may have accidentally found a transitional stage in the evolution of this special cell mechanism, highlighting evolution "as it happens". Studying this anomaly could help biologists understand how in some species the genetic code might gradually change. Maybe the biological language is not as frozen as we thought.

A protein as a "lock keeper"

ETH researchers around Markus Stoffel have discovered that vigilin, a RNA-binding protein in liver cells, controls the synthesis and release of proteins that regulate lipid and cholesterol levels in the bloodstream. Silencing of vigilin efficiently reduces atherosclerotic plaque formation.

Eating fat or drinking alcohol in excess can take a toll on our body – one becomes overweight and diabetic, leading to a condition known as fatty liver. If eating and drinking habits are changed in time, the liver usually recovers completely from the degeneration, but in severe cases the organ becomes inflamed – a condition notoriously difficult to treat. What is more, fatty liver is also leading to elevated blood fat values. The degenerated organ seeks relief by releasing fat into the bloodstream, including "good" fat in the form of high density lipoprotein (HDL), but also "bad" fat, such as low density lipoprotein (LDL) and even more worse its precursor, very low density lipoprotein (VLDL) that serves as a carrier of triacylglycerides in the blood. Too high concentrations of LDL and VLDL in the circulation can lead to the formation of atherosclerotic plaques. When such a plaque ruptures or detaches itself, there is a real risk of a vascular blockage and a heart attack or stroke.

Now scientists from the group of Markus Stoffel, Professor of Molecular Health Sciences at ETH Zurich, have been able to show

that the RNA-binding protein (RBP) vigilin is upregulated in livers of obese mice and in patients with fatty liver disease. The protein seems to act as a kind of "lock keeper", regulating the release of fats, including VLDL, from the liver into the bloodstream. Vigilin is the largest RBP of the KH domain family. It is conserved from human to yeast and is thought to play a crucial role in diverse biological processes such as sterol metabolism, carcinogenesis, control of translation, formation of heterochromatin, nuclear export of tRNA, cytoplasmic transport of RNA and metabolism of specific mRNAs. Yet up to date, no systematic analysis has been performed and very few mRNA targets and no precise RNA recognition element have been reported in mammals.

By using in vivo, biochemical and genomic approaches, Markus Stoffel and his group showed that vigilin indeed controls VLDL secretion through the modulation of apolipoproteinB/Apob mRNA translation. Apob is responsible for exporting triglycerides from the liver. Triglycerides also promote vascular calcification when present in concentrated form in overweight people. It appears that the primary function of vigilin is to regulate transport proteins responsible for the release of fat out of the liver. But it accomplishes this not by binding directly to these transport proteins, but rather to certain points of the associated mRNA. Crosslinking studies

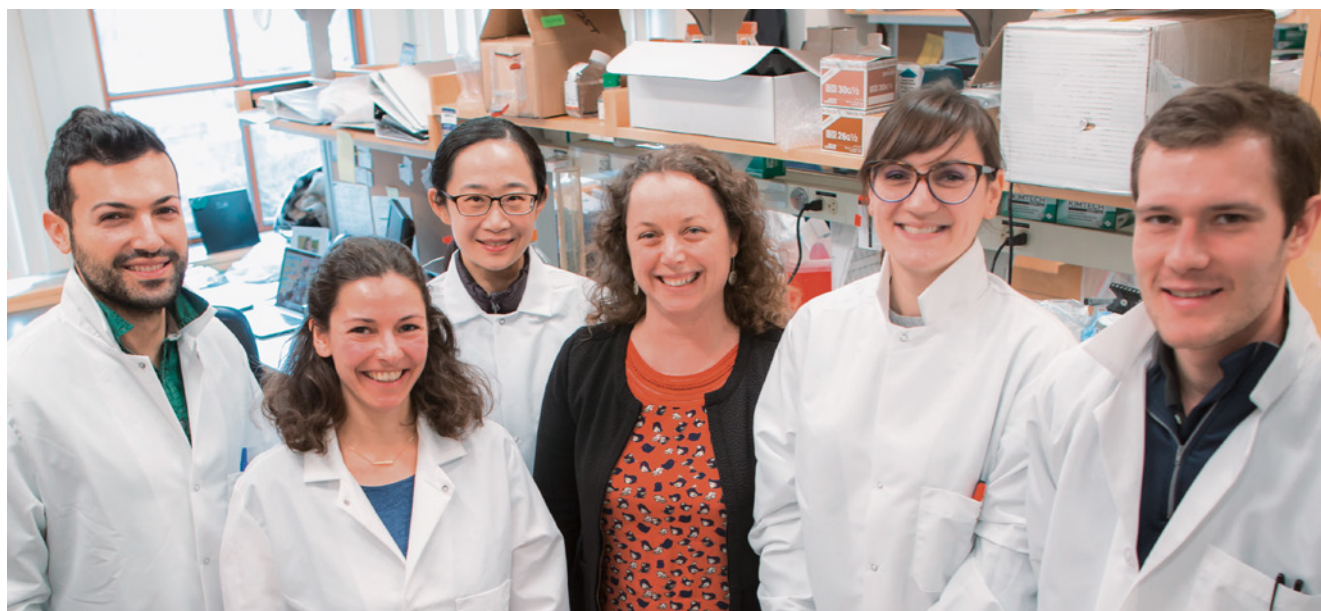
revealed that vigilin binds to CU-rich regions in the mRNA coding sequence of Apob and other proatherogenic secreted proteins, including apolipoproteinC-III/Apoc3 and fibronectin/Fn1.

Thus the researchers uncovered a primary role in lipid metabolism and hepatic steatosis in mice and humans to be mediated by an RNA-binding protein. "Vigilin intervenes at the level of gene regulation, which has barely been investigated to date," says Stoffel. Regulatory processes from DNA to mRNA are increasingly understood, but regulation of the step from mRNA to protein is something we know much less about.

The discovery that silencing of vigilin in the liver (using a new process of RNA interference) reduces the production of proteins that regulate blood lipid levels and thereby atherosclerotic plaque formation in accordingly treated mice suggests a critical role of vigilin in hepatic metabolism and a possible therapeutic approach for the prevention of cardiovascular diseases. The atomic structure of vigilin remains a mystery though - it is currently being studied by several groups around the world. The molecule has 14 different binding points - so vigilin can influence multiple proteins with a variety of possible side effects. But nonetheless the researchers believe that there is opportunity to inhibit vigilin as a pharmacological approach to treat or prevent cardiovascular diseases.

Mobility grant

A great opportunity to build international connections



Melanie Jambeau (2nd from left) with Clotilde Lagier-Tourenne (4th from left) and members of the Lagier-Tourenne laboratory at the Massachusetts General Hospital, Boston, USA.

The NCCR RNA & Disease offers mobility grants to PhD students and postdocs allowing the opportunity to conduct research in a laboratory abroad. The duration of the grant is between six and twelve months and can cover costs for travelling, living abroad, and attendance of scientific conferences. Melanie Jambeau (Polymenidou lab) was awarded a mobility grant and shares her experience with us.

My name is Melanie and I am a first year PhD student at the University of Zurich in the Polymenidou lab. I am doing a collaborative PhD at the University of Zurich and at the Massachusetts General Hospital, in the Lagier-Tourenne lab.

I have one project, two supervisors and I am part of two labs. The goal is to use complementary approaches and to join forces to better understand how amyotrophic lateral sclerosis (ALS) progresses in order to block it. Since the beginning, this project has been challenging and at the same time extremely stimulating. The PhD includes stays in Zurich, but also in Boston, an exciting and new city for me.

In December 2016, the NCCR RNA and Disease offered me a mobility grant (funded by the SNF) to support my research in the lab abroad, covering accommodation and travel expenses.

During these six months in Boston I learnt new techniques, attended fascinating conferences, met brilliant scientists, was inspired by great talks and laughed and exchanged ideas with students from all over the world. Knowing that Boston counts more than 50 universities, it was exciting that science goes on pretty much around the clock. Even a subway journey could be the setting for a passionate scientific debate. I remember registering for a conference that was to take place close by on the campus on CRISPR-Cas9, thinking that it would be a small meeting and I ended up in a huge amphitheater, surrounded by hundreds of people; sitting next to me was a post-doc who had come all the way from New-Zealand to attend this conference. During three very intense days, we were able to listen to the most prominent and inspiring researchers in this field.

This NCCR mobility grant was a wonderful opportunity and one that allowed me to fully benefit from Boston's scientific environment.

These 6 months abroad helped me to better define my PhD project, which is centered on dipeptide repeat proteins, produced by RAN translation in patients suffering from the most common genetic form of ALS. We are now part of a larger collaborative project, involving four groups, which aims to understand how these toxic dipeptide repeats spread in the central nervous system and whether this could be prevented by immunotherapy. My contribution to this project is to define an RNA signature and assess the spreading abilities of each of these dipeptide repeats and to investigate the efficacy of the immunotherapy in vitro.

Going abroad gave me the opportunity to learn about new people, a different culture and to experience the way research works on the East coast of the US. This Doctoral mobility grant was a great opportunity and I would recommend it to people interested in having an enriching experience during their PhD.

I am now back in Zurich, and feel very motivated to be part of a bigger collaborative project, after this exciting start.

Melanie Jambeau

Announcements

People

We would like to welcome Prof. Rory Johnson as a Junior Principal Investigator of the NCCR RNA & Disease. Rory Johnson has taken up his position as a group leader at the Department of Clinical Research at the University of Bern in November 2016. The Johnson lab uses bioinformatics and wet lab experimental approaches to elucidate the function of long noncoding RNAs and their role in disease pathways.

Furthermore, we would like to introduce Dr. Giuseppina Carbone and Dr. Carlo Catapano from the Institute of Oncology Research in Bellinzona as new associate members of the NCCR RNA & Disease. The Carbone lab studies the role of ETS transcription factors in the pathogenesis of prostate cancer and how alterations of their functions regulate networks of noncoding RNAs.

Research in the Catapano group aims at elucidating the mechanism of transcriptional control of genes involved in cancer pathogenesis including the role of noncoding RNAs and how these mechanisms could be targeted for cancer therapy.

We would like to congratulate Prof. Ana Claudia Marques for being selected as one of the new EMBO Young Investigators and Prof. Michael Hall for being awarded an honorary doctorate by the University of Geneva.

PhD fellowships for associate member labs:

The NCCR RNA & Disease made a call for associate principal investigators to submit PhD project proposals in collaboration with NCCR principal investigators. The proposals of Dr. Silvia Monticelli, Prof. Vikram Panse, PD Raffaella Santoro and Prof. Volker Thiel have been selected for funding by the NCCR RNA & Disease.

Support Grants:

Violeta Castelo-Székely (Gatfield lab) has received a doctoral mobility grant to support a yearlong stay at the University College of London pursuing research in the groups of Profs. Jernej Ule and Nicolas Luscombe.

The requests of Dr. David Ramrath (Ban lab) and Dr. Marina Cristodero (Polacek lab) for a 120% support grant were 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

- > The **18th Swiss RNA Workshop**, January 27 2017, University of Bern
- > **NCCR seminar series** spring semester 2017 at the University of Bern and ETH Zurich. Speakers: Profs. Brenda Bass, Irene Bozzoni, Christopher Burge, Tom Cech and Juan Valcarcel.
- > **2nd NCCR RNA & Disease Summer School** "RNA & RNP architecture: from structure to function to disease", August 28–September 1 2017 Saas-Fee
- > **NCCR RNA & Disease Internal Events:**
 - 2nd NCCR RNA & Disease Retreat, January 29–31 2017, Kandersteg
 - 3rd NCCR RNA & Disease Site Visit, February 23–24 2017, Zurich

Past events organized or supported by the NCCR RNA & Disease

- > Joint NCCR **Workshop on "Collaboration"** by the NCCRs RNA & Disease and Kidney. CH: November 24–26 2016, Schloss Münchenwiler
- > **NCCR seminar series** fall semester 2016 at the University of Bern and ETH Zurich
- > **Open-door day** Department of Chemistry and Biochemistry, University of Bern, November 5 2016
- > NCCR RNA & Disease **PI retreat**: August 30–31 2016, Park Hotel Oberhofen am Thunersee

Jobs

PhD program in RNA Biology

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NCCR RNA & Disease

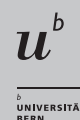
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