THE MESSENGER

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NCCR
RNA & Disease

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

Dear colleagues

I really hope we can see light at the end of this long tunnel so that we can all meet again in person for our annual retreat and the summer school in August 2021. This is now almost a year that the world in struggling with this virus and we are all more tired than usual since we cannot even enjoy the perspective of a nice Christmas vacation and family reunion. But we still need to fight for a few more months since the perspective of the massive vaccination should allow us to come back somehow to a normal life. Hopefully, we will have learned something from this crisis. One that science is important and that understanding better RNA viruses is fundamental. Two that RNA vaccines may become the fastest way to eradicate the next viruses. Three that working together instead of against each other might be the best way to achieve results.

This newsletter of course focuses on SARS-CoV-2 with a wonderful interview with Prof. Volker Thiel and the great collaborative achievements of the NCCR to better understand the virus now and in the future. Please be patient for a few more months, stay healthy and I am sure that we will all be stronger this summer and in the years to come.

On this note, I wish you all a nice end of the year rest and a good start for 2021.

Frédéric Allain
Co-Director NCCR RNA & Disease

Interview Volker Thiel

"Do what your curiosity in science drives you into. And just do it."

Interview: Dominik Theler / Veronika Herzog

In this interview, Volker Thiel, Professor in Veterinary Virology at the University of Bern and since May 2020 full member of the NCCR RNA & Disease reflects on the implication of the Corona viruses on his career, on the society, and on the relationship between science and the public.

After your studies, PhD and postdoc in Würzburg, you became a PI in St. Gallen. How was it for you to get your first PI position?
That was in 2003 and everybody told me that Coronaviruses are not really interesting and I should consider researching a virus family causing more severe human disease. It was hard to find something but luckily, they were interested in hiring me in St. Gallen and a grant application for my position to work on Coronaviruses was funded soon after. Just a week after the grant application's approval, it was discovered that a Coronavirus causes SARS. My boss in St. Gallen told me later that at that time, he feared that I would go elsewhere because suddenly Coronaviruses became interesting.

"It is impressive how the scientific community reacts to the current pandemic."

I assume that the increased interest in Coronaviruses was advantageous to you in terms of grants and publications but also resulted in increased competition?
Indeed, we can also see that right now: It is impressive how the scientific community reacts to the current pandemic. There are so many excellent studies that are being published almost daily. The competition is huge, but we have some advantages as we already have systems running in the lab and as we worked with Coronaviruses before.

Do you see this pandemic as a chance for your career?
To some extent, yes. It certainly helps that our research is interesting to a broader community now. But it will not last forever and you still have to deliver. I hope that it will make a difference for the young researchers in my lab and help advance their careers.

What was a key discovery moment in your career?
There are several such moments but one I remember very well: When I was still in Würzburg, I was trying to establish a reverse genetics system for Coronaviruses. I tried to clone the entire genome and reconstruct the virus from the cloned DNA to build a system that allows you to modify

Interview Volker Thiel

"One of my favorite moments as a scientist was when I saw the first plaque arising from what I had cloned. This was then the basis for my future work."

the virus. This was our main goal for many years, but it was very challenging at that time. One of my favorite moments as a scientist was when I saw the first plaque arising from what I had cloned. This was then the basis for my future work.

At that time, it took you years and today you can do it within weeks?
Yes, it took me essentially my entire PhD and a year after to complete it. Back then, it was quite difficult to sequence 30 kilobases. Only Sanger sequencing was available: in the beginning, we performed radioactive sequencing and then switched to capillary sequencing. You had to do about a hundred sequencing runs and purify your reactions. It took two or three days and a lot of money to sequence an entire virus genome.

What drives you in your career?
Curiosity. To see this new virus and figure out how it works. My main interest is the replication complex of Coronaviruses. Before I retire, I would like to see its structure or the replication complex synthesizing RNA in real-time. However, the techniques for that are not there yet.

According to an essay in the Horizons magazine, you think that "writing a doctorate should be a normal job". Can you elaborate?
It is at the same time normal and not normal. It should be normal in terms of working conditions and work-life balance. PhD students often suffer when experiments do not go as planned and then they put themselves under pressure. As a PI, you have the responsibility to watch out for this and see how you can help remove the pressure. You should not allow people to work day and night for a long time until they get exhausted. That is what I mean by not normal. Of course, you should not stop PhD students because they usually like to work on their project and often they do more than they formally would need to through their own motivation. It is important to give them their freedom. In this sense, it is not a normal job.

What general advice do you give to young researchers?
Do what your curiosity in science drives you into. And just do it.

What were the biggest changes you witnessed in virology or science in general during your career?
The current work on the new Coronavirus is a good example: many people enter the field and bring with them all these new technologies. All sorts of "omics", for instance, where you as a "simple scientist" do not understand in detail anymore what they are doing. It is often a black box. You have to deal with massive datasets and you have to think more globally. So, it is a different kind of work nowadays. The times are gone when you have a small little project on a simple mRNA and try to do your simple experiment. It is a bit sad because that is how I grew up. I think that having these novel technologies is a big change in science.

What do we currently know about the origins of SARS-CoV-2?
It is quite clear that there are similar viruses in bats. However, it is not clear how the virus transmitted from bats to humans – whether there was an intermediate host in between or not. So far, we have not yet found this exact virus in bats but only its close relatives that are too distantly related to be the virus that was transmitted.

Would you discard the idea that SARS-CoV-2 escaped from a lab?
I would certainly discard the thesis that SARS-CoV-2 was created in a lab. I also do not think that it escaped from a lab. From what I know, the Wuhan lab was not working with live SARS viruses. Research with SARS-CoV was not allowed in China because there was a lab accident in 2004. They became cautious regarding permissions for experiments with viruses.

Why are MERS-CoV, SARS-CoV and SARS-CoV-2 so much more virulent for humans compared to other Coronaviruses?
SARS-CoV and MERS seem not to be well adapted to humans. This is often the case when viruses transmit from animals to humans. They are suddenly in a new host, on which they depend for replication and transmission. They have to adapt and optimize every mechanism that is needed to survive. What makes SARS-CoV and MERS-CoV dangerous in humans is that, for some reason, they induce a lot of inflammation, which results in severe disease and even lethal infections.

Picture kindly provided by Volker Thiel.

Volker Thiel

Biography

Volker Thiel obtained his PhD from the University of Würzburg, Germany, in 1998, where he also conducted his postdoctoral research. In 2003, he moved to Switzerland and joined the Institute of Immunobiology in St. Gallen as a group leader. Since 2014, he is Professor in Veterinary Virology at the Vetsuisse Faculty of the University of Bern and head of Virology at the Institute of Virology and Immunology in Mittelhäusern. He serves as a member of the Swiss National COVID-19 Science Task Force.

Website Thiel Lab

In the case of MERS-CoV, the original hosts, the camels, do not really suffer from severe disease when infected.
Exactly, MERS-CoV just causes a common cold in camels. While for humans, a MERS-CoV infection can cause lethal disease, for camels, it is just a "childhood disease", which they get during the first two years of their life and only causes a running nose.

Why could the spread of SARS-CoV-2 not be stopped earlier like SARS-CoV and MERS?
I think one of the main reason are the asymptomatic carriers. We know that MERS-CoV is not transmitting very well from human to human. SARS-CoV transmitted reasonably well but only when people were already having symptoms. It was relatively easy to isolate these persons and stop the chains of transmission. But with SARS-CoV-2, you do not know that you are infectious because in the beginning you do not have symptoms.

Interview Volker Thiel

Do you think that it is realistic to find a vaccine against SARS-2 that is protective without compromises on safety within a very short time?
There are some basic rules and requirements for vaccines. Everybody is aware that if we mess this up, we get into trouble. We must have the necessary safety precautions in place and I believe that this is granted at least in the developed world. People are now willing to speed up the development and they are very careful not to weaken the safety.

Based on the current knowledge regarding the mutation rate, do you expect that new vaccines will need to be developed regularly, like for Influenza?
The mutation rate of SARS-CoV-2 is not comparable to what we see with Influenza. The virus is quite stable so far. In contrast to Influenza, there are not many different strains for which the antigenicity is different and would require adapted vaccines. That is not something we expect for this new Coronavirus.

Would it help to stop SARS-CoV-2 if technologies were developed that enable testing at home?
Yes, this is under discussion. It has been proposed that if we have a cheap test, we could test ourselves by spitting on the test stripe every morning before we drink our coffee. The test should be fast and give a result within as little as 10 minutes. If you get a negative result, you go to work. If the test is positive, then you stay home and consult with your doctor. Such tests do exist already, either based on isothermal amplification or simple antigen detection. They are not as sensitive as the PCR assay but are sensitive enough to detect people that have high virus loads.

Now we have talked about diagnostics and vaccines. How fast do you think there will be new drugs available?
I do not know. Millions of compounds are being screened, but developing a new drug will take several years. If a drug can be repurposed, then we may have it very soon.

Why was there no antiviral drug developed against SARS-CoV or MERS-CoV that could now be applied to treat SARS-CoV-2?
Many people worked for a long time on drugs for Coronaviruses with different approaches, for instance, by purifying the polymerase or protease and subsequently performing binding and inhibition studies. This resulted in discovering some compounds, but they were never further developed into a product because there was no market. SARS-CoV was luckily eliminated from the human population after it had infected only a few thousand humans and for MERS-CoV, there were and are not that many cases.

When did you realize that the new Coronavirus also poses a threat in Europe?
At the beginning of this year, when it became clear that what was first known as "pneumonia of unknown origin" is caused by a Coronavirus, we got, of course, very interested. However, at that time, we did not think that a pandemic could emerge from this virus. We saw that there was this outbreak on a market in Wuhan but the first announcements claimed that the virus was not transmitting between humans. It took one or two weeks, or even longer until it became clear that there must be human-to-human transmission to explain all these cases. It took quite a while until we realized that this is a massive outbreak. Even then, we did not think it would cause a pandemic given the experience of how SARS-CoV and MERS-CoV were contained. It became clear mid or end of February that this virus is different.

"It became clear mid or end of February that this virus is different."

How should the world have reacted differently to contain the virus earlier?
In the first two months, I think not too much went wrong because, as I just mentioned, nobody could really anticipate that this virus is causing so much trouble. After we realized this - I think this was in late February and in March - many countries reacted very well and took immediate measures to reduce the cases. But what went wrong is – this is now a bit political – that some countries did not take the virus seriously in the beginning. Now that they realize the severity, they try to make it too political. I think that this is not a matter of any political dimension. It is something that should go beyond parties and personal interests. It should unite people rather than putting them apart.

In research with highly pathogenic viruses, there is always the danger that you create something more dangerous, especially using reverse genetics systems or propagation experiments. How do you deal with that?
That is a serious discussion in the field, not only for Coronaviruses. There were experiments with Influenza viruses a couple of years ago where Influenza viruses were created that transmitted better between ferrets. These "gain of function" experiments were very much criticized. But we also learned a lot from these experiments, for example, which regions in certain genes to look at when assessing the risk of a new strain.

Are you in favor that these findings are published – in contrast to people who say that this information should not be publicly disseminated because of the risk of being misused?
I judge the potential that these findings are misused as relatively low because not many people have the ability to work with these viruses. Also, the previously mentioned Influenza experiments showed that these strains transmitted better, but at the same time, they lost much of their pathogenicity. It is almost impossible to create intentionally a highly transmissible virus that is also highly pathogenic.

Working at the high-security laboratory of the Institute of Virology and Immunology (IVI). © IVI

Interview Volker Thiel

Regarding the Covid-19 pandemic, do you think that the preprint server system was beneficial to accelerate the battle against the disease or did it more harm than good?
This is hard to say. There are several factors to consider: On the one hand, especially in the beginning, the press jumped on everything with a fancy title, often lacking the background to judge the merits of certain preprints and publications. On the other hand, the scientific community soon realized that there are better and worse papers. Interestingly, if you have the right network on Twitter, you can filter out most of the publications that are not that good and get the excellent papers.

Do you think that the government should build an infrastructure to be better prepared for a crisis, even if there is no profit to be made?
There are so many viruses and bacteria that it is impossible to have a vaccine or a drug for every pathogen. In Switzerland and other countries, there are good funding systems, such as the SNSF, that do not select research on the most dangerous viruses and bacteria. They provide funds for basic research and this lays the foundation that we can count on. For many years, there was good basic research on Coronaviruses that taught us a lot about the basic principles of this virus family. This knowledge can then be translated into applied research if there is the need for it. Of course, there are some viruses or bacteria that we know are dangerous. For example, the West Nile virus might come to Central Europe very soon. There are some things we can anticipate and we can prepare for it before the disease reaches us. However, in other cases, such as in the case of this new Coronavirus, it was impossible to predict the event and, thus, it is impossible to prepare for everything.

Regarding antibiotic-resistant bacteria, the numbers and the disease-burden is growing for a long time. Yet, there are not many antibiotics in development as it seems that companies cannot make enough profit. Why can new life-saving antibiotics not be priced at the same level as some other new therapy?
That is a difficult question. People are used to getting into action only when there is a danger. For a long time, and still nowadays, a couple of antibiotics work. We live in a world for 50 to 70 years, where particularly in Europe we did not have any of these widespread deadly infectious diseases. We were not really confronted with any of these diseases, and as long as we do not suffer, I fear that we will not do anything in that direction.

You said that there are now more of these outbreaks of infectious diseases; why is that?

Working at the high-security laboratory of the Institute of Virology and Immunology (IVI). © IVI

One general reason is that we are just too many people on this planet and we go more and more into areas in the wild where humans are usually not. So we get more and more in contact with wild animals that can carry viruses that are infectious to humans. And the other aspect is that we are globalized. Once there is a virus in the human population, it can quickly spread because we are so much connected not only locally but internationally.

On the peak of the first wave, you were interviewed on a live prime-time broadcast. How did it feel sitting in that TV studio and knowing that an afraid nation is hanging on your lips?
That reminded me of when I was a young student and had my first presentation at a big conference. I was a little nervous, but at some point, you just go there. Then you are in this bubble and do not think what others might see or think. That is my strategy to do that.

Have you experienced any difficulties with the media?
Yes, one difficulty is that sometimes your quotes will be taken out of context. When I received the interviews for approval, it was sometimes very annoying to see what they made out of what you said. And I often had the feeling that this occurred not due to a lack of knowledge but to make the story spicier.

Did people from the public reach out to you and were the reactions positive or negative?
Not a lot, but quite some. There were different reactions, and for the most, they were very positive. But some people deny that viruses exist and think you are cheating and not telling the truth.

Do you reply to them?
I try not to answer because of my experience back in 2012 with MERS. I once answered and this resulted in a big mess because they do not stop and keep arguing. You send emails back and forth and it does not bring anything in the end. You cannot convince them and they will not accept that you have another opinion.

How do you think this whole pandemic will change the relationship between science and the public?
Overall, I hope that it will change positively. It is interesting that many more people now know a little bit about virology. I also think that the public got an idea what science can tell you and what it cannot tell you - they got a feeling of where there is solid information, where it ends and where speculation starts.

"This feeling that you are restricted to this country, to your local area sometimes – that is what I will remember most."

Is there an image from this period that you will never forget?
What I will never forget again is that suddenly we were again confronted with border controls. We were used to crossing borders essentially all over Europe. And now, suddenly, you could not simply leave the country without having a reasonable explanation. This feeling that you are restricted to a country, to your local area sometimes- that is what I will remember most.

What does it mean to you to be part of the NCCR RNA & Disease? Where do you benefit from being part of the network?
In my past and current work, I have always been interested in RNA because we work with an RNA virus. We studied different mechanisms on the RNA level. Already as an associated member, I enjoyed the spectrum of methods and approaches that are present in the NCCR. It is a very broad group of people that do different things in different ways, but it all centers around RNA. That was and still is very interesting for me.

Interview conducted on July 28, 2020.

Research Highlights

Clogging the Ribosome to go Viral

Veronika Herzog

While the entire world is on alert due to the current COVID-19 pandemic, scientists are seeking to understand the molecular mechanisms underlying the virulence of SARS-CoV-2 in order to rapidly develop drugs and vaccines against COVID-19. A collaboration among three labs from the NCCR RNA & Disease network (Ban laboratory at ETH Zurich and Mühlemann and Thiel laboratories at University of Bern) has now resulted in a publication in *Nature Structural & Molecular Biology*, in which they describe how the SARS-CoV-2 virus hijacks the host cell to promote its own replication (*Schubert, Karousis et al., 2020*).

Upon host cell invasion, one of the first viral proteins translated is the "non-structural protein 1" (Nsp1). Despite its unspectacular name, Nsp1 is a major virulence factor of certain coronaviruses including SARS-CoV-1 and -2 and has been proposed to downregulate the host innate immune response to generate a virus-friendly cellular environment for viral replication. On the molecular level, Nsp1 associates with the ribosome and represses host gene expression, but the underlying molecular mechanism remained enigmatic.

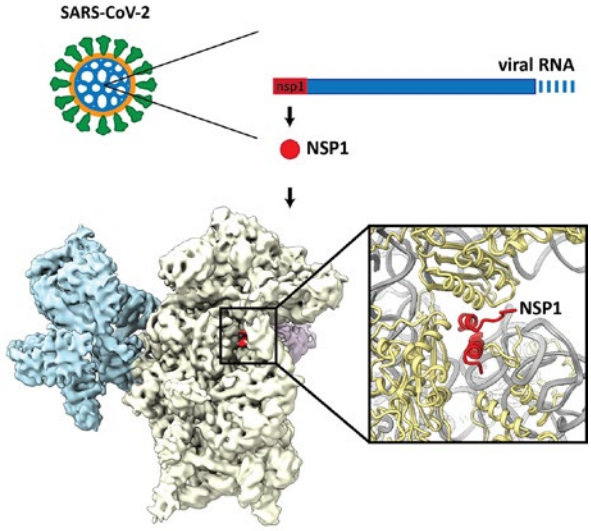
To explore the mechanism of how Nsp1 alters host translation, Schubert, Karousis and colleagues set out to solve the structure of Nsp1 interacting with the ribosomal complexes using cryo-EM. The structure already hinted towards a potential mechanism of how Nsp1 inhibits translation: Part of the Nsp1 protein binds to the site of the ribosome where mRNAs normally enter during translation initiation. Together with the fact that RNA substrates were not observed in the Nsp1-ribosome structures, this suggests that Nsp1 inhibits translation by acting as a steric roadblock for mRNAs, preventing its association with the translation machinery.

The functional consequence of the Nsp1-ribosome interaction was further examined in an *in vitro* translation assay, which was recently developed in the Mühlemann laboratory and has recently been published in *Nature Communications* (*Karousis et al., 2020*). This *in vitro* translation system allows to monitor the ribosome occupancy on reporter mRNAs in mammalian cell lysates. With this tool in hands, the authors could validate their hypothesis that Nsp1 can effectively inhibit translation of a reporter mRNA. The detailed structure of Nsp1 allowed the design of Nsp1 mutants that are not able to bind to the 40S ribosomal subunit *in vitro*. These Nsp1 mutants could no longer inhibit translation both *in vitro* as shown in the translation assay and *in vivo* as shown in a puromycin incorporation experiment in HeLa cells.

If the virus inhibits the ribosome, how can the virus itself evade Nsp1-mediated translation inhibition to ensure the translation of its own messages? To solve this conundrum, the authors modified the reporter mRNA by replacing the 5' UTR of the reporter mRNA with the 5' UTR of the SARS-CoV-2 genomic RNA. They compared the translation efficiency of these transcripts using the *in vitro* translation assay and observed that the reporter mRNA harbouring the viral sequence is more efficiently translated than the native reporter transcript. When Nsp1 is added to the reaction, both reporter mRNAs are affected by the translation inhibition to the same extent. Oliver Mühlemann, Professor of Biochemistry at the University of Bern and one of the co-corresponding authors of the study, explains a potential mechanism of how viral mRNAs could be translated efficiently despite the global shut-down of ribosomes: *"When Nsp1 blocks the ribosomes, functional ribosomes become scarce and at the same time viral RNA can make up almost half of the total RNA in the cell. Under these conditions, the viral RNA is preferentially read from the still functional ribosomes compared to the cell's own messenger RNA."* The authors further speculate that this mechanism also suppresses host mRNAs required for innate immune responses. The combination of these effects could provide an ideal cellular environment for viral replication and contribute to the successful replication and dissemination of SARS-CoV-2.

Due to its essential role in promoting virulence to SARS-CoV-2, Nsp1 represents an attractive target for future drug and attenuated vaccine development. Nenad Ban, Professor for Molecular Biology at ETH Zurich and co-corresponding author of the study, explains the importance of the published results: *"The high-resolution structure of Nsp1 interacting with the ribosome provides important information for the design of a drug that could prevent Nsp1 from binding to the ribosome without interfering with the ribosomal function. If Nsp1 can no longer inhibit translation, we expect that the cellular defence system can be active and stop the viral replication."*

Schubert & Karousis et al. (2020) Nat Struct Mol Biol, 27(10), 959-966
Karousis et al. (2020) Nat Commun, 11(1), 4134



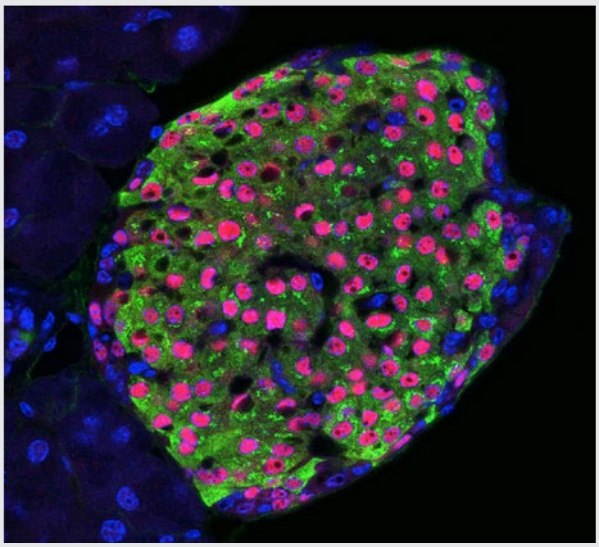
The virus protein NSP1 (red) binds to the ribosome (white and blue) and thus inhibits the production of cellular proteins. Visualization: ETH Zurich / Nenad Ban

Research Highlights

JAZF1 tips the balance in metabolic stress responses

Veronika Herzog

A tight control of blood glucose levels is essential to ensure a normal body function. The pancreatic ß-cells are key players by secreting the hormone insulin, which mediates the cellular glucose uptake and thus lowers the blood sugar levels. Pancreatic ß-cell function and the insulin secretory pathway underly an intricate transcriptional network that allows fast and coordinated responses, which are required upon changes in glucose (i.e. after a meal) or cytokine concentrations (i.e. following infection). Disturbances in the insulin secretory pathway can manifest in metabolic disorders, such as type 2 diabetes (T2D). T2D accounts for 90% of the 420 million diabetic patients worldwide and represents a complex metabolic disease ultimately causing life-threatening health complications. Thus, it is of importance to understand the mechanism underlying the transcriptional network interactions causing the disease to develop novel therapeutic strategies.



Confocal image of a pancreatic islet from an obese, diabetic mouse stained with anti-INSULIN, anti-JAZF1 antibodies and DAPI. Picture kindly provided by Markus Stoffel.

In a recent publication in *Cell Reports,* a team from the Stoffel lab at ETH Zurich in collaboration with endocrinologists and pathologists from the University Hospital Zurich investigated the cellular functions of JAZF1, a gene previously associated with T2D susceptibility. Initial characterization of JAZF1 expression revealed that JAZF1 expression is lowered in T2D patients and it re-localizes from cytoplasm to nucleus upon stimulation with glucose in pancreatic ß-cells.

These results encouraged the authors to further seek for a better understanding of the cellular function of JAZF1 in metabolic stress conditions. By analyzing the functional consequences of JAZF1 loss in mouse and cellular models, they found that JAZF1 deficiency predisposes to ER stress, activation of the p53 pathway and ultimately results in apoptosis during metabolic stress conditions. This is accompanied by a reduction of pancreatic ß-cell mass, a phenotypic hallmark that can often be found in T2D patients.

But what is the molecular explanation of the ER stress/apoptosis susceptibility of Jazf1-deficient cells? *Kobiita and colleagues* performed various experiments on the genomic and transcriptomic scale to identify a set of target genes regulated by JAZF1, which were further characterized in follow-up assays. These experiments revealed a multilayered transcriptional regulation of JAZF1 that ensures the fidelity of translation upon metabolic stress conditions: JAZF1 is a transcriptional regulator of ribosome biogenesis and translation, regulates the expression of aminoacyl-tRNA synthetases, and directly negatively regulates the expression of insulin. *"It is challenging, but also fascinating that this factor is a positive regulator for many genes, but a negative regulator for others"*, Markus Stoffel, corresponding author of the study, states.

Concluding a wealth of generated data, the researchers propose a model for the function of JAZF1: Under normal non-glycemic conditions, JAZF1 is dispensable: It is localized to the cytoplasm and is lingering until environmental conditions change. Upon elevated glucose levels, the cell can rapidly react to the stimulus by re-localizing JAZF1. In the nucleus, JAZF1 acts as a transcriptional regulator and ensures a cellular environment that allows to cope with the increased demand for insulin production: JAZF1 controls the fidelity of ribosome biogenesis and translation to prevent ER stress and subsequent cellular damage. Under chronic stress such as in diabetes, however, the overall levels of JAZF1 drop by a yet to determined mechanism. This relieves the JAZF1-mediated transcriptional regulation, ribosomal defects accumulate and translation goes out of balance. Resulting ER stress and the activation of the p53 pathway causes apoptosis and degradation of pancreatic ß-cell mass. Markus Stoffel is excited about the therapeutic implications of the new findings: *"Re-boosting the activity of JAZF1 in diabetic ß-cells is a promising therapeutic approach that we will be following up in future."*

Kobiita et al. (2020) Cell Rep, 32(1), 107846

Lab Exchange Experience

When COVID19 hit New York City – A research stay experience of a different kind

Hasan Vatandaslar

To go in quarantine and be on pause or work on SARS-CoV-2? That was the question I needed to answer when the pandemic hit New York.

Back in February, with support of the Lab Exchange Program of the NCCR RNA & Disease, I started a research stay in the laboratory of Dr. Thomas Tuschl at the Rockefeller University in New York City. I was really looking forward to see some of my old colleagues, spend time in this scientifically highly stimulating environment and of course enjoy and absorb the energy of this incredible city.

March 1, the first confirmed case of the coronavirus is recorded in Manhattan. Two weeks and thousands of cases later NYC became the hot spot of Covid19 leading to a shutdown of the whole city including the Rockefeller University. I decided to join the group of scientists working on the virus and was granted permission to access the laboratory during the university lockdown. The city itself was dead: no traffic, empty buildings and empty sidewalks. But there was this steady sound of ambulance sirens and the long queues of sick people in front of public hospitals, later joined by refrigerated trucks to hold the bodies of the dead.

Picture kindly provided by H. Vatandaslar

Our mornings in the lab would usually start with studying the new numbers on the John Hopkins coronavirus map and discussions on the latest news and data regarding the virus. I would check for same day flights back to Europe, in case of getting sick. From all the bad news from our colleagues in the NY hospitals, it was clear that healthcare wasn't really guaranteed anymore. After a while we got used to the situation and I was happy to be able to still work in the laboratory. Additionally, Tom was doing his best to keep our motivation high by providing his tasty self-made ice-cream and Sake.

A part of the laboratory focused on isolating all compounds of the viral replicon and I choose to work on the RNA dependent RNA polymerase (RdRp). The exciting times started when the inactivated virus arrived and we were able to isolate its RNA to clone the sequences of our interest. I started to express and purify the RdRp (encoded by non-structural protein 12 [nsp12]) that functions as a RdRp-holoenzyme (comprising nsp7, $nsp8_2$ and nsp12). I investigated the biochemical properties of the RdRp complex, the action of inhibitory compounds like Remdesivir and also begun to set up a high-throughput drug screening to aim for new compounds. At the same time, I joined a collaboration of the labs of Elizabeth Campbell, Seth Darst, Brian Chait and Tarun Kapoor. Together we solved the structure of the SARS-CoV-2 holo-RdRp with an RNA template product in complex with two molecules of the nsp13 helicase[1]. This new structural template will be crucial for drug developers to find new compounds that can efficiently inhibit the viral replication process and gives us new insights of the replication mechanism.

Nevertheless, the happiness of our achievement was modest. The killing of George Floyd sparked heavy protests that impacted our lives in New York as strong as the virus did months before. Walking the surreal streets of the Upper East Side were the Rockefeller University is based, you could find broken windows, boarded up buildings, empty storefronts for rent and abandoned restaurants that had to give up their business.

Scientifically my stay was an intensive and exciting time working under great pressure to find something meaningful in such an important topic, even under the adversities like closed facilities or delayed orders. On a personal level it was stressful and sad, seeing many people in fear and hardship, and with a constant awareness of the thousand COVID victims around us. Or seeing friends that lost their jobs, who had to quit their apartments and move away from NYC.

For the future I hope to get the chance to visit again and see the city and the people recovered from this calamity, as I hope so for everyone in the world.

Lastly, I also want to take the opportunity to thank for the support of the NCCR RNA & Disease and Prof. Markus Stoffel that gave me a lot of security during these uncertain times. Likewise, many thanks to Tom and his laboratory that feels like a little family to me.

[1] Chen et al. (2020), Cell, 182(6), 1560-1573.e13

Events

NCCR/SIB Summer School: Computational RNA Biology

From August 23 – 28, 2020, the Computational RNA Biology Summer School organized by the NCCR RNA & Disease and the Swiss Instiute of Bioinformatics was held on-site in Schwarzenberg, which is close to Lucerne. Over thirty participants, mostly from Switzerland, were taught by nine teachers from France, Germany, Sweden and Switzerland. The program consisted of lectures and hands-on group projects on the topics of long-read RNA sequencing, ribosome-profiling, single cell RNA analysis and CLIP-seq. Participants gave a very positive feedback on the summer school. We would like to thank the teachers and Grégoire Rossier, who took care of most of the organization of the summer school.

Participants group foto *(Picture by Grégoire Rossier)*

Class room complying with social distancing rules *(Picture by Grégoire Rossier)*

Landscape around the venue *(Picture by Philipp Becker)*

Teachers:

Sarah Djebali
INSERM, Toulouse, France

Melina Klostermann & Kathi Zarnack
BMLS, Frankfurt am Main, Germany

Paulo Czarnewski & Erik Fasterius
NBIS, Stockholm, Sweden

Gert van Geest, Sebastian Leidel & Puneet Sharma
University of Bern, Switzerland

Giancarlo Russo
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Events

Digital Reputation Building in Science Seminar & Workshop

A "Digital Reputation Building in Science" Seminar and Workshop were planned to take place beginning of April in Bern. Due to the lockdown they were postponed to middle of October and only days before the planned dates the Corona quarantine travel measures prevented the speaker to travel and, thus, the events could not be carried out on site.

In line with the topic of the event, the Seminar and Workshop on Digital Reputation Building in Science had to be moved online. The Seminar and Workshop were given by Dr. Johanna Havemann from access2perspectives. The seminar took place on October 16, 2020, and covered a wide range of topics from self-marketing and online public relations to digital tools that can be used during the research and publication workflow. During two half-days on November 5 & 6, 2020, the workshop participants further deepened the topics of the seminar and discussed in smaller groups questions, strategies and experiences related to Digital Reputation Building in Science.

The Seminar and Workshop were a joint initiative by the NCCRs Kidney.CH, RNA & Disease and Transcure. The slides of the seminar can be accessed on Zenodo using the following link:
Slides Digital Reputation Building in Science Seminar – October 16, 2020

Snapshot of a part of the collaborative Whiteboard Tool (Miro) used during the workshop. On the bottom, the result of a survey conducted during the preceding seminar is illustrated using the Mentimeter system.

2nd bench2Biz workshop

The 2020 Bench2Biz workshop for aspiring entrepreneurs took place as a virtual event over five afternoons from November 23 to December 4, 2020. The workshop could be successfully transformed from an on-site event to a virtual event and 11 teams answered key questions regarding their business idea with the help of a team of experts with various backgrounds. The NCCR RNA & Disease is part of the bench2Biz consortium alongside six other NCCRs organizing the workshop. We would like to thank this year's lead organizers from the NCCRs Chemical Biology and PlanetS, the Swiss Institute of Intellectual Property for their generous support and all experts and team members for their efforts.

Survey from where participants joined the virtual workshop.

Announcements

People

We would like to welcome Alex Schier as a new associate member of the NCCR RNA & Disease. Alex Schier is Director and Research Group Leader at the Biozentrum, University of Basel. His lab researches vertebrate development and behavior using mainly Zebrafish as a model organism. He has a long-standing interest in RNA biology, ranging from the functions of miRNAs and lncRNAs to the identification of sequence motifs in 3' UTRs.

Grants

SNSF Funding for Research on SARS-CoV-2:
We congratulate the NCCR RNA & Disease members Sebastian Leidel, Ramesh Pillai and Volker Thiel for securing funding for a collaborative project by the SNSF special call on Covid-19 research, which is now continued under the umbrella of the NRP78 on Covid-19. We also congratulate Frédéric Allain, Steve Pascolo and Francesco Bertoni, who received funding from the NRP78 on Covid-19.

Short documentary "NO DENIAL"

The recent findings on how the SARS-CoV-2 Protein NSP1 inhibits cellular translation published by three NCCR RNA & Disease groups (Ban group at ETHZ, Mühlemann and Thiel group at University of Bern) were highlighted in a short documentary with the title "NO DENIAL" presented at the 3rd Global Science Film Festival. The movie highlights the importance of a collaboration between scientists and the media to combat misinformation. It was produced by a team of researchers from the University of Zurich, ETH Zurich and the University of Bern and can be watched online on the NCCR RNA & Disease public outreaching website molecool.ch with subtitles in English, German and French.

Support grants

Please visit our webpage for more information on the Lab exchange program, the Mobility grants and measures in Equal Opportunities.

Swiss RNA Workshop

Due to the SARS-CoV-2 pandemic the Swiss RNA Workshop 2021 was cancelled. We hope that the Swiss RNA workshop can take place again in its usual format in 2022.

Annual Retreat

The 6th NCCR RNA & Disease Annual Retreat scheduled to take place from February 1–3, 2021, in Kandersteg had to be postponed due to the SARS-CoV-2 pandemic and is now planned to take place from August 18–20, 2021 in Engelberg.

Upcoming events organized or supported by the NCCR RNA & Disease

> **NCCR Seminar Series Spring Semester 2021**
Due to the SARS-CoV-2 pandemic, no NCCR RNA & Disease seminars were organized in the autumn semester 2020. In early 2021, the following virtual seminars are scheduled:
  – Roy Parker (University of Colorado Boulder, Colorado, USA), January 25, 2021, 16:00h (CET), Zoom
  – Maria Barna (Stanford University, California, USA), February 22, 2021, 16:00h (CET), Zoom
  – Amy Pasquinelli (UC San Diego, California, USA), March 23, 2021, 16:00h (CET), Zoom

The respective Zoom invitations will be sent out prior to each seminar by the NCCR RNA & Disease office.

NCCR RNA & Disease Internal Events

> Site visit Year 7, March 30 & 31, 2021.

Jobs

Postdoctoral Position (100%) – Cryoelectron Microscopy
Jinek Lab, University of Zurich
Find out more

Postdoctoral Positions (100%) – Gene Regulation by RNA modifications
Pillai Lab, University of Geneva
Find out more

Postdoctoral Position (100%) – Mitochondrial Biogenesis in Parasitic Protozoa
Schneider Lab, University of Bern
Find out more

PhD program in RNA Biology
The next application deadline is July 1, 2021.
Find out more on the PhD program website.

Predoc program RNA & Disease Switzerland
Due to the SARS-CoV-2 pandemic, the next application deadline for the Predoc program was moved to July 1, 2021.
Find out more on the Predoc program website.

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

Join our new LinkedIn NCCR RNA & Disease Current Members & Alumni Group and follow us on LinkedIn and Twitter!

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