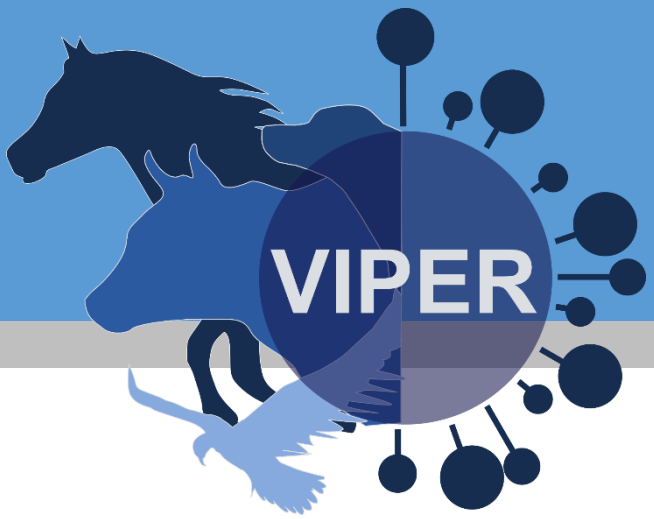
Research Training Group
Virus detection, pathogenesis and intervention (GRK 2485)



NEWSLETTER

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Volume 2 - April 2021

We are proud to release the second VIPER newsletter two years after the official start of the Research Training Group in April 2019. After introducing VIPER itself including its students and PIs in the first newsletter, the current issue will focus on the situation of the VIPER students during their second PhD year, particularly with regard to their experiences during the COVID-19 pandemic. Corona definitely had and still has an impact on scientific life, either by becoming the object of study itself or by influencing every corner of work life, especially in the lab. The second newsletter updates you on all activities that took place over the last year, the latest news and also on all new publications, showing that Covid-19 is influencing but not stopping VIPER from further achievements.

COVID-19 – How the pandemic became part of every day life and work

Let's think back one year to the time of the publication of the first newsletter, to the very beginning of the COVID-19 pandemic… At that time, no one could or wanted to foresee the far-reaching consequences of the pandemic on social life as well as on work and research. There were also many changes for the members of VIPER and the entire program of the Research Training Group. For example, social activities that were supposed to strengthen the sense of community and to lead to an exchange between the students could not be conducted during this year. All hands-on training courses had to be cancelled, en-block schools also had to be postponed and/or adjusted - sometimes very spontaneously - to online-events.

Overall, the pandemic has challenged everyone, demanding flexibility, spontaneity and creativity from all of us. On the other hand, we have gained new skills, especially in video conferencing, online meetings and were able to discover other new opportunities in the broad field of virtual working and learning. We successfully weathered the stormy times of 2020 and are now well prepared to face 2021 together with you.

Working under pandemic conditions

On the next pages, the VIPER students share their experiences with their work and COVID-19.

Shifting perspective.

By training and by project I am a wet lab biologist. I mostly do viral pseudotyping and infection experiments, the usual virology labwork I guess. However, the pandemic gave me the chance to pursue a bioinformatics project, which I had never found time to do before. So, during the first lockdown I put all my wet lab experiments on hold and started an NGS project which will hopefully be finished soon. For me personally, this very challenging time gave me the opportunity to broaden my horizon, develop new skills and even though my wet lab work was put on hold, I was able to push my PhD forward.

(André Gömer)

Actually, my work has only hardly been influenced by Corona. At first we were all a bit confused and had to sort out how to deal with the new situation. However, we got used to it very quickly and some adjustments to the working circumstances are also good and should be continued after the pandemic is over, e.g. certain hours of homeoffice. Tasks like writing or doing literature research can be accomplished much more easily when not distracted in a busy office.

In addition, I think we all found out that certain meetings do not necessarily have to be attended in person. Many online conferences and talks have taken place and I think the quality did not suffer substantially. So all in all, here in science I think we were some of the few lucky people who could go on with their work and maybe even benefit by it in a certain way.

(Franziska Geiselhardt)

Working under pandemic conditions

Due to the pandemic, our work is divided into laboratory times (practical work) and home office (e.g. result analysis, literature research) to minimize contact and avoid crowed laboratories/offices. In the first half of 2020, my colleague and me had to write an animal protocol as well as a review. Working from home during this time was very productive for me because I could concentrate better. Now most of the lectures/seminars and meetings are online. This give us the opportunity to attend in seminars of other and foreign universities which would probably not possible under "normal" conditions. However, I miss the face-to-face contact especially with my colleagues and PhD students of other institutes as well as having social events or even joint lunch breaks with them.

(Mareike Kubinski)

In the early Corona lockdown, our institute was also almost shut down. For once, it was an advantage to have experiments that all in all take around 2 months, so I was able to continue lab work even during that very critical time. I was therefore able to focus a lot on my research projects without much distraction from life. Moreover, the absence of real conferences and the reduced possibilities to spend our vacations led to an almost uninterrupted workflow. On the other hand, Corona projects quickly came along reclaiming some of our time. And since the field of Corona research is so competitive, we can never be sure if any of the work will actually be published. A PhD is a marathon and not a sprint, so now a work-life-balance is being restored after the very intense time since the first lockdown.

(Olivia Gern)

On the one hand, the pandemic in spring allowed me to focus on reading myself deeply into the topic of my thesis and resulted in a better understanding and also in the publication of a literature review. On the other hand, it slowed down my experimental progress to some extent.

(Michael Wißing)

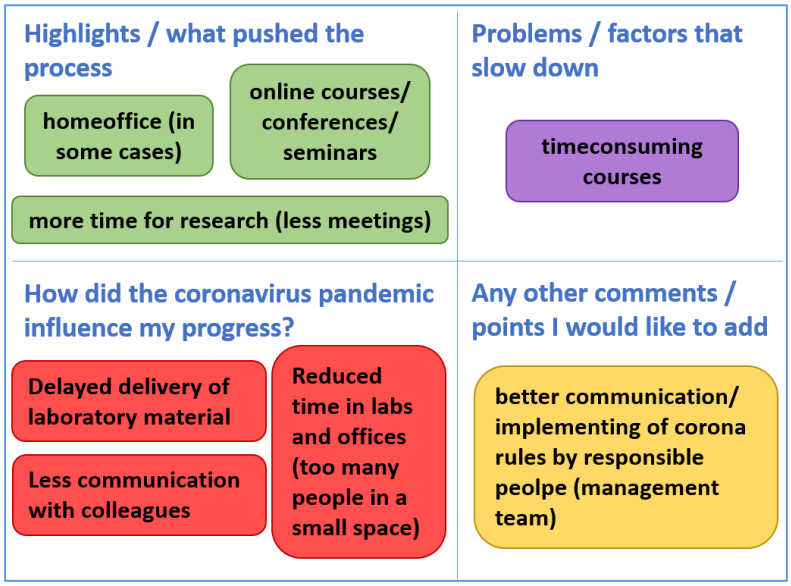
Working under pandemic conditions

Fortunately, we were able in our institute to change the room conditions so that we have only one to two people in one office. Additionally we can work in home office. In the laboratory my work is also continuing quite normal, we follow the safety instructions, keep distance – of course – and go on with our research. The biggest effects the pandemic has on the participation on workshops, lectures and congresses, so the contact and exchange with other scientists is missing.

(Nele Gremmel)

Looking back at the academic year 2019/2020 - Process evaluation by KHN

In order to keep the VIPER training programme and the entire organisation of the Research Training Group at a high level and to keep improving, the programme is evaluated once a year by an external quality management agency. For this purpose, the VIPER students had two virtual meetings with the KHN (Kompetenz-zentrum Hoch-schuldidaktik Niedersachsen) in November 2020 to discuss the good and weak points of the programme. In addition, their personal experiences of work and research with regard to the challenging pandemic situation were discussed. Afterwards, the PIs were informed by an anonymous report so that they can adapt their work in the future.



En-block schools

Junior class (05.-09.10.2020)

Due to the current situation, the junior class in October could not take place as planned. However, we made the best of the situation and moved the event to the internet and also adapted the topic. Researchers from different continents and also different research fields shared their views on SARS-CoV-2 with the students.

Monday	Tuesday	Wednesday	Thursday	Friday
Klaus Jung (Institute for Animal Breeding and Genetics, TiHo): Epidemiological compartmental models in R	**Guus Rimmelzwaan** (Research Center for Emerging Infections and Zoonoses, TiHo): Protective immunity against pandemic viruses	**Eike Steinmann** (Department for Molecular & Medical Virology, Ruhr-University Bochum): Stability and Inactivation of SARS-CoV-2	**Nadine Krüger** (German Primate Center (DPZ) Göttingen): SARS-CoV-2 in domestic animals and livestock	**Byron Martina** (Artemis One Health Research Foundation): Refocussing and potentiating the antibody response to COVID-19
Terry Jones (Institute of Virology, Charité Berlin): Challenges in making sense of COVID-19 viral load data	**A. D. M. E. Osterhaus** (Research Center for Emerging Infections and Zoonoses, TiHo): From zoonosis to pandemic – Coronaviruses as an example	**Stephanie Pfänder** (Department for Molecular & Medical Virology, Ruhr-University Bochum): LY6E impairs coronavirus fusion and confers immune control of viral disease	**Maria Schröder** (Department of Intensive Care Medicine, UKE Hamburg): Treatment of COVID-19 at ICU	**Asisa Volz** (Institute of Virology, TiHo): New vaccines against emerging zoonotic infections: From animal models to clinical evaluation
Colin Russel (Department of Medical Microbiology, University of Amsterdam): Modelling the evolutionary dynamics of influenza viruses	**Gisa Gerold** (Institute for Biochemistry, TiHo): SARS-CoV-2 host factors and their pharmacological perturbation	**Brice Wilfried Bicaba** (Ministry of Health, Burkina Faso) : COVID-19 in Burkina Faso	**Gülsah Gabriel** (Department of Viral Zoonoses – One Heath, HPI Hamburg, TiHo): SARS-CoV-2 pathogenesis in small animal models	**Maren von Köckritz-Blickwede** (Research Center for Emerging Infections and Zoonoses, TiHo): Neutrophil extracellular traps as potential risk factor that triggers COVID-19-severity

Students' opinions on the Junior class

In regard of the current situation it was inevitable to do the Junior Class online. But honestly, I was very positively surprised since there were so many good and interesting talks and lively discussions despite each one of us sitting in front of a computer. I also think it was a good idea to focus on one topic only, i.e. Coronavirus, and to look at it a little more in depth. And thirdly, it was nice to still have half of the day left for lab work!

En-block schools

Students' opinions on the Junior class

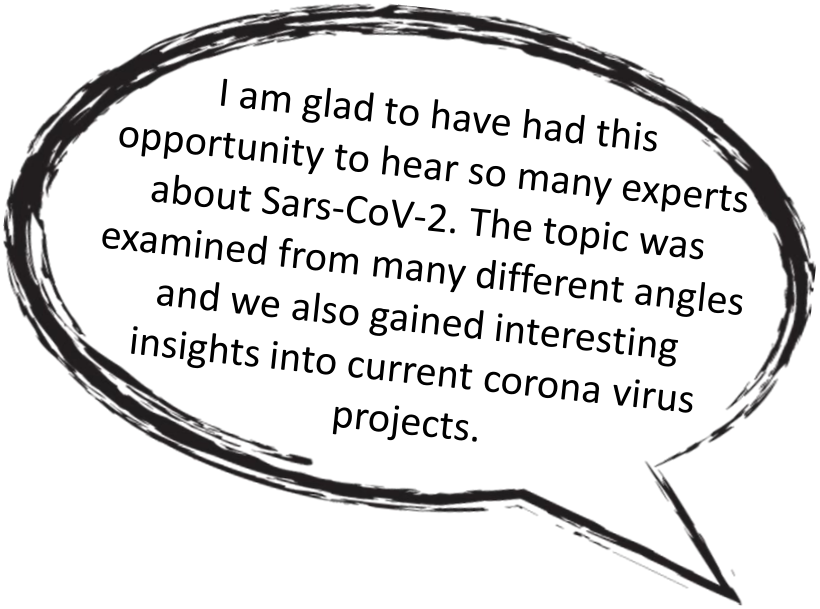
Great event, providing up-to-date information on SARS-CoV-2 and Covid-19! Nice lectures given by national and international speakers provided insights into many different areas like research, treatment strategies or pandemic crisis management.

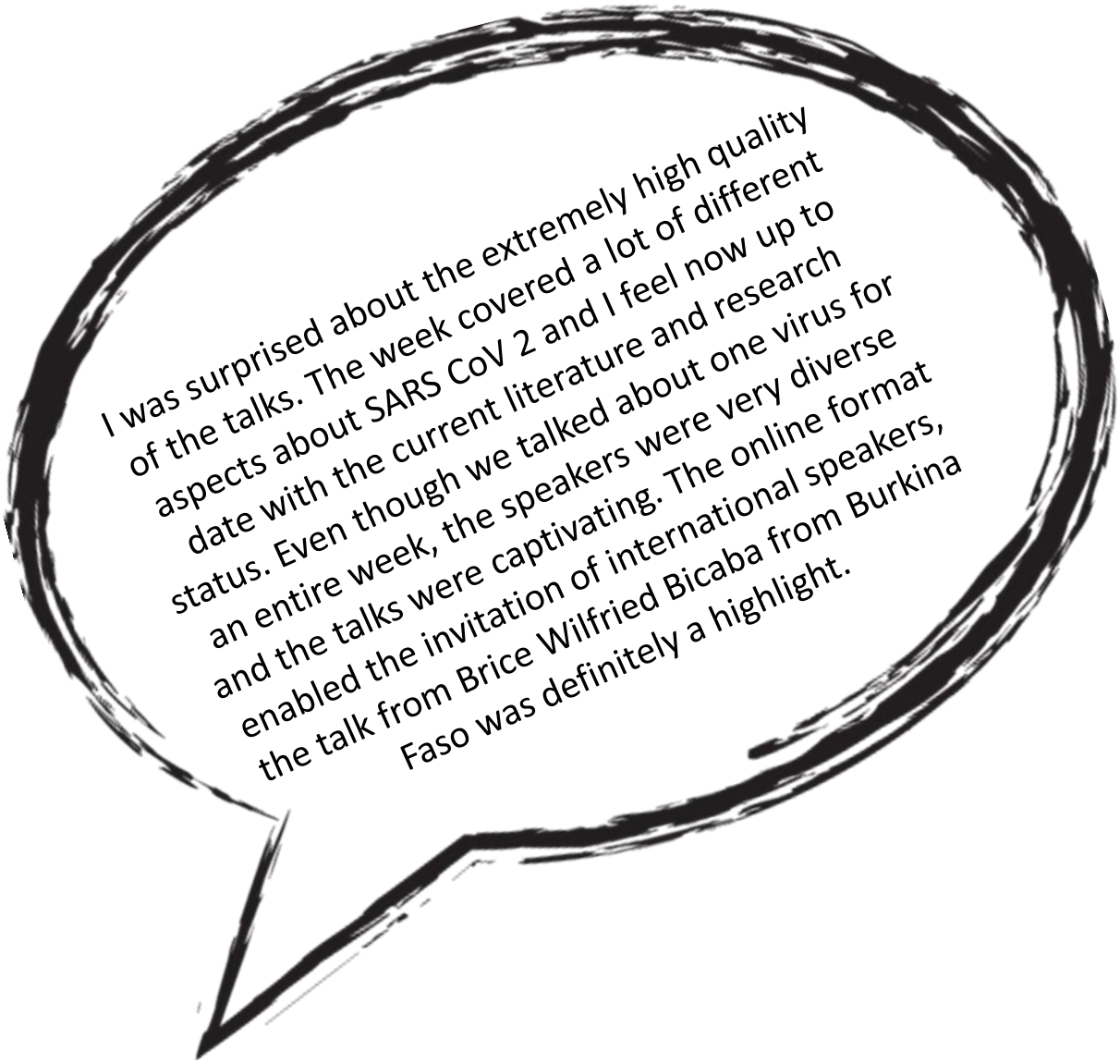
I really enjoyed the presentations about different SARS-CoV-2-related topics, which covered various aspects, e.g. treatment of COVID-19 patients in ICU or vaccine approaches. Overall, the lectures gave a nice overview about the current knowledge of SARS-CoV-2.

The concept of the Viper Junior Class had to be spontaneously adapted due to the corona virus situation in Germany. Some of the planned experiments and techniques could not be shown in the lab, because of the corona precautions, but they were at least presented in a seminar. The organization team tried their best to offer as much as possible, but in my opinion they could have prioritized more on technical problems and experimental planning strategies instead of sample acquisition.

En-block schools

Students' opinions on the Junior class





En-block schools

Senior class (08.-12.02.2021)

The senior class in February could not take place on site either. We again used the already established concept of the online conference. Among other things, the senior class was used to think outside the box for a break and not only to focus on the omnipresent corona research.

Monday	Tuesday	Wednesday	Thursday	Friday
Ulrich Kalinke and Andreas Pavlou (Twincore): Tissue immunity: Examples of how antigen-specific immune cells are primed in secondary lymphoid organs, how they are recruited to organs and how their function is regulated in the tissue	**Guus Rimmelzwaan** (Research Center for Emerging Infections and Zoonoses, TiHo): Antiviral immunity and ageing	**Kwang-Zin Lee** (Fraunhofer Institute for Molecular Biology and Applied Ecology (IME)): Plant protection with Insect Biotechnology	**Mark Kühnel** (Institute for Pathology, MHH): COVID-19 - Lung Pathology and beyond	**Alexander Postel** (Institute for Virology, TiHo): Prevention, intervention and control strategies for classical swine fever
	A.D.M.E. Osterhaus (Research Center for Emerging Infections and Zoonoses, TiHo): Influenza in animals and humans: from epidemics to pandemic	**Stefanie Becker** (Research Center for Emerging Infections and Zoonoses, TiHo): The most dangerous animals on earth	**Gerd Sutter** (Institute for Infectious Diseases and Zoonoses, LMU Munich): Non-clinical development of an MVA vector vaccine candidate	
Verena Haist (Boehringer Ingelheim): Clinical trials in animal vaccine development	**Paul Becher** (Institute for Virology, TiHo): African swine fever - the porcine pandemic			

Students' opinions on the Senior class

I really enjoyed the format and the content of the VIPER senior class. The lectures were captivating and designed in a way to pick up everyone from different fields of virus research and I still learnt a lot about topics I am not very familiar with. Additionally, the discussions following the talks were very interesting.

I think the senior class was a great opportunity to get a good overview on current projects in the field of Zoonoses. The experts imparted their knowledge in an authoritative and vivid way. Also the class gave me inspiration for possible later research fields after my PhD.

En-block schools

Students' opinions on the Senior class

Online format is very good as it is much easier to participate for all students. Would prefer online for talks even in normal circumstances.

The Event was streamlined and less time demanding than the usual classes and allowed for more lab work in parallel.

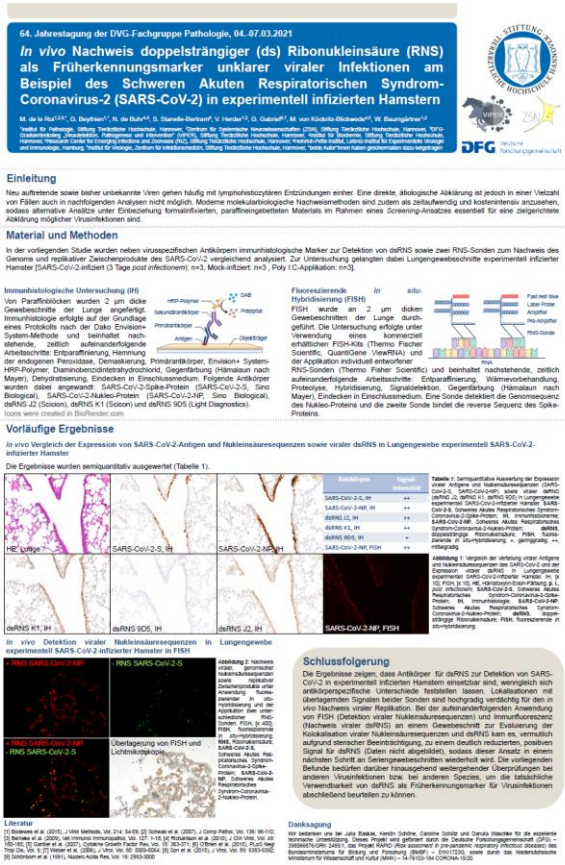
Excellent conference for learning about interdisciplinary subjects from colleagues. It was very well structured and hosted for participants to engage questions to speakers. Subjects were very interesting and speakers explained their lectures in a comprehensible manner for outsiders to understand. I am looking forward for the next conference!

I really enjoyed the senior class, the talks were given in a easy-to-follow and captivating way. Some technical issues (esp. during the talk of Kwang-Zin Lee) made it a little harder to stay concentrated and focused, but overall I learnt a lot in a fun way.

Congress reports

64th annual meeting of the DVG-group of veterinary pathology

Once a year veterinary pathologists from all over Germany and even abroad come together for the annual conference on pathology of the German Veterinary Society (DVG). Beside histological slide seminars with special emphasis on specific organ systems and lectures from well-recognized pathologists, the congress offers all participants, including doctoral candidates as well as PhD students, the possibility to present interesting and relevant topics to the plenum. The range of contributions includes case reports about rare findings in animals as well as preliminary results of own research work covering a great variety of subjects with regard to diagnostic and/or experimental pathology. This year's conference focused on emerging infectious diseases with special emphasis on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the development of suitable animal models. Moreover, an overview of the first confirmed cases of African swine fever reported in Germany in 2020 was presented. In this context, I was given the opportunity to introduce my recent findings detailing the detection of double-stranded ribonucleic acid (dsRNA) as an early detection method in viral infections using the example of experimentally SARS-CoV-2 infected syrian hamsters to the audience. The study bases on the hypothesis, that a pre-screening of suspicious cases regarding the expression of dsRNA concomitant with the exclusion of already known viral pathogens, allows a target-orientated investigation of the presence of newly or so far unrecognized viruses. DsRNA is produced during viral replication and recognized by pattern recognition receptors, which initiate signaling pathways that result in the activation of the innate immune response to embank viral spread.



In this study, two virus-specific antibodies as well as three antibodies detecting dsRNA were analyzed comparatively in lung tissue of experimentally SARS-CoV-2 infected hamsters. By performing immunohistochemistry, targeting virus-specific spike glycoproteins and nucleoproteins, positive signals were detected in hyperplastic bronchial epithelial cells. Two of three antibodies directed against dsRNA revealed a co-localization with these viral antigens, indicating viral replication (Fig. 1).

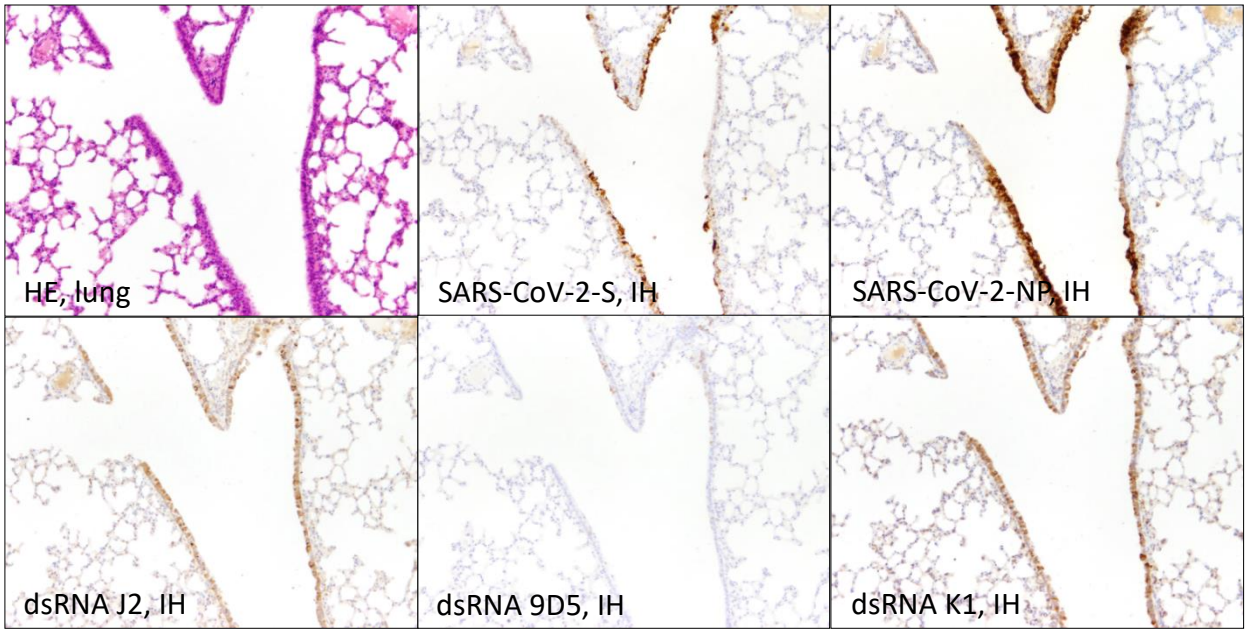


Figure 1: Comparison of SARS-Cov-2-antigen and the expression of dsRNA in SARS-CoV-2-infected, formalin-fixed and paraffin-embedded lung tissue of a hamster. IH, [x 10], FISH [x 10]. **HE**, hematoxylin and eosin; **SARS-CoV-2-S**, severe acute respiratory syndrome coronavirus 2 spike glycoprotein; **SARS-CoV-2-NP**, severe acute respiratory syndrome coronavirus 2 nucleoprotein; **IH**, immunohistochemistry; **FISH**, fluorescent in situ hybridization; **dsRNA**, double-stranded ribonucleic acid

Furthermore, we applied two differently designed RNA probes, one detecting the genome RNA of the nucleoprotein and the other one labelling the reverse sequence of the spike glycoprotein. This approach revealed areas with overlapping signals, which are highly suggestive for the *in vivo* detection of viral replication (Fig. 2).

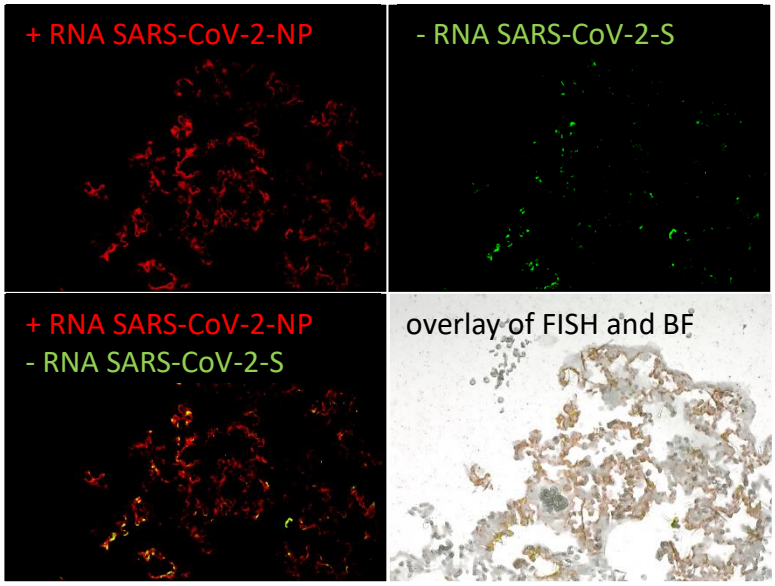


Fig. 2: Detection of SARS-CoV-2 genome RNA and replicative intermediates by performing FISH with two differently labeled probes. In situ hybridization, [x 400]. **RNA,** ribonucleic acid; **SARS-CoV-2-S**, severe acute respiratory syndrome coronavirus 2 spike glycoprotein; **SARS-CoV-2-NP**, severe acute respiratory syndrome coronavirus 2 nucleoprotein; **FISH**, fluorescent *in situ* hybridization; **BF**; bright field

An evaluation of the co-localization of the overlapping signal obtained via fluorescent *in situ* hybridization (FISH) in comparison with the expression of dsRNA will be further investigated using a multiplex-assay, combining FISH and subsequent immunofluorescence. To sum up, the preliminary results shown here need to be further investigated in other species and other virus infections to evaluate the applicability of dsRNA as an alternative approach for the detection of virus infection.

For me personally, presenting the first results of my PhD project as a poster during this event was a great experience. It allowed me to not only improve and refine my performance skills but also to discuss my scientific results with an expert audience. Moreover, I got an insight into different interesting topics and methods presented by other participants. In conclusion, I can say that I profited very much from attending this conference and I am happy that VIPER supported me with that.

(Madeleine de le Roi)

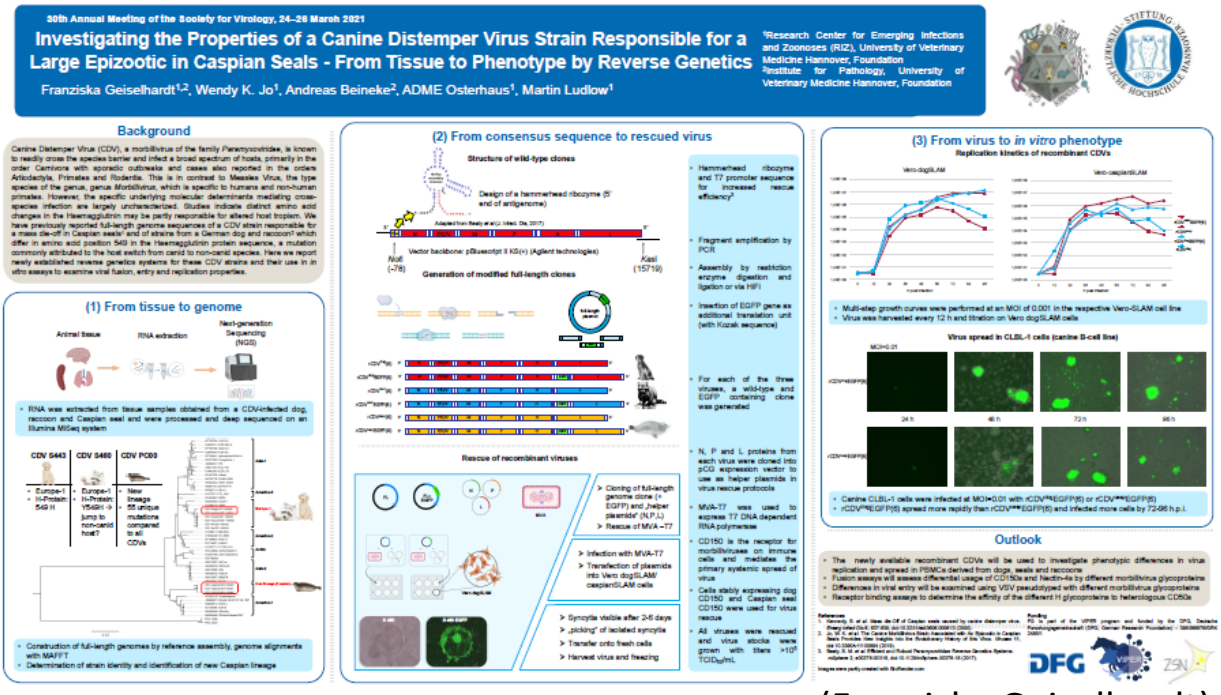
Cytokines 2020

Through VIPER support, I attended online the annual meeting of the International Cytokines and Interferon Society (ICIS), the Cytokines 2020. Major researchers from the fields of innate and adaptive immunity gave fascinating talks and insights into their ongoing research. From the field of research my PhD is about, neuroinfection, I was able to follow a talk by Robyn Klein, who is a leading group leader in the field. In her talk, I learned a lot about immune response in the brain that I wasn't aware of before. Another talk deeply impressed me: Glen Barber, the discoverer of STING, showed how infection, STING activation and tumor control can be linked.

(Olivia Luise Gern)

30th Annual Meeting of the Society for Virology

Many thanks to VIPER for funding my participation at the German Society for Virology meeting taking place from March 24-26, 2021! Although this year the conference had to take place as an online event, it was still nice to take part. I contributed a poster presenting our research on reverse genetics systems for three CDV strains to investigate differences in viral properties. It is amazing to see how many different aspects of virological research are pursued in Germany and how many young virologists there are apart from us VIPER students.

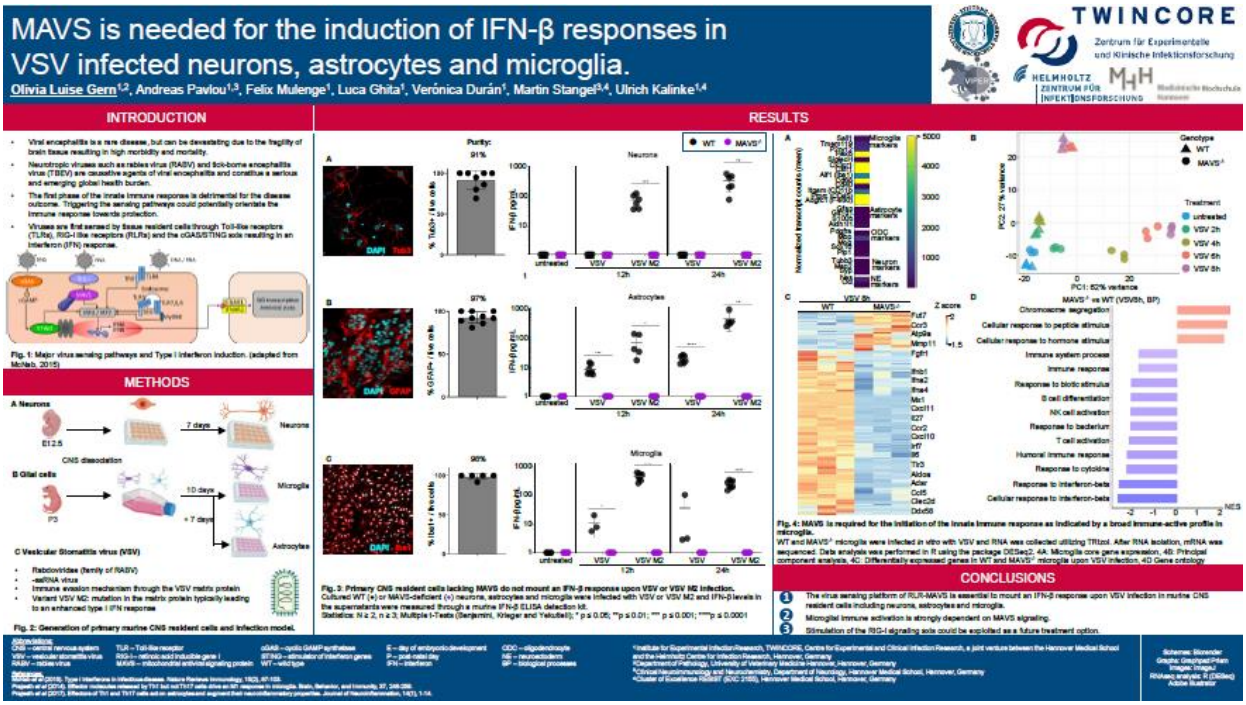


(Franziska Geiselhardt)

30th Annual Meeting of the Society for Virology

At the annual meeting of the German society of virology this year, I had for the first time the opportunity to submit a poster and poster presentation. During this conference, members of most of the virology labs in Germany present their latest research results. Additionally, also very successful international speakers are invited to share their data and hypothesis.

For me it was the second time participating in this conference, but the first time in an online format. Of course this made the organization much easier without booking of transport or hotels. The talks were of very high quality, some of them even groundbreaking. In one presentation of Benjamin tenOver from the Icahn School of Medicine at Mount Sinai we listened to the short term and long term consequences of Covid-19 reflecting in high inflammation and a Parkinson's Disease like phenotype, respectively. These very preliminary data were fascinating for me. Moreover, Marco Hain from the Chan Zuckerberg Biohub in San Francisco showed results from single cell genomics of Cytomegalovirus infected cells and could conclude that knocking out cellular proteins leads to an abortive infection of the cells, while knocking out viral genes lead to a different trajectory of the infection.



During my poster presentation, I shared the progress in one of my projects about the role of MAVS (Mitochondrial antiviral signaling protein) for the induction of Interferon responses in cells of the central nervous system, being neurons, astrocytes and microglia.

Especially in microglia MAVS was fundamental for the induction of a broad immune-active transcriptomic program. Pathways of the immune response, as well as the activation of immune cells (B cells, T cells and NK cells) and the response to cytokines were enriched in wild type microglia, but completely missing from MAVS deficient microglial cells. For me, it would have been ideal to have a poster session in presence to actually stimulate some discussions, but it was still a very helpful experience.

(Olivia Luise Gern)

Travel reports

Pseudotyping in Nottingham

For my PhD project, I am investigating how the equine hepacivirus facilitates its host cell entry using a pseudotype system. When I started my PhD, one of my supervisors mentioned that pseudotyping with the equine hepaciviral surface glycoproteins is a rather tricky task and that we might get help from a collaborator in Nottingham who was able to implement this system in his lab.

My journey started on a small propeller plane, which was quite exciting. After arriving in Nottingham, I had a day to experience the beautiful city including authentic British weather. On my first day at work, I was welcomed by Alex Tarr, who gave me a tour around the Queens Medical Centre, the campus of the University of Nottingham, and also supervised me during my stay.

After work Alex and some colleagues showed me around the city, including Britain's oldest Pub, the Ye Olde Trip to Jerusalem, which is located beneath the Nottingham castle.

Thanks to the VIPER funding I was able to learn new techniques, get to know collaboration partners in Nottingham and have a lot of scientific discussion in my field which boosted my project and goes beyond lab work. Saying this, I would also like to thank the people from Nottingham who welcomed me with open arms: Alex Tarr, Barney King, Terry Akagha, Stuart Astbury and the group of Jonathan Ball.

(André Gömer)

Lab visit at the LMU in Munich

At the beginning of 2020, I spent three months at the laboratory of our collaboration partner professor Gerd Sutter at the Ludwig-Maximilians-University in Munich. His working group is specialized in the development of vaccines based on the modified Vaccinia virus Ankara (MVA). During my stay, I learned how to generate and characterize recombinant MVAs. This technique is important for my PhD project which focusses on the development and examination of novel MVA-based vaccine candidates against the tick-borne encephalitis virus (TBEV).

(Mareike Kubinski)

Further activities – Gender equality

Group coaching

In a group of about 12 participants, we had a very interesting workshop about leadership. Understanding the theoretical side of personality types and communication underlying conversations will definitely help me in many situations now and in the future. Some communication techniques can be applied in daily life and can make discussions efficient and constructive .

(Olivia Luise Gern)

Personal coaching

Through VIPER resources, I had the opportunity for funding of a personal coaching series. I have gained some insights into my own personality, my way of working and ultimately how to best deploy my character traits. The regular meetings with the trainer help me with my continuous development, each time addressing another field with room of improvement.

(Olivia Luise Gern)

Recent VIPER publications

- **Neurotrophic effects of GM1 ganglioside, NGF, and FGF2 on canine dorsal root ganglia neurons in vitro.** **S. Schwarz**, A. Lehmbecker, W. Tongtako, K. Hahn, Y. Wang, F. Felmy, I. Zdora, G. Brogden, K. Branitzki-Heinemann, M. von Köckritz-Blickwede, W. Baumgärtner & I. Gerhauser. Scientific Reports (2020).
- **Tick-Borne Encephalitis Virus: A Quest for Better Vaccines against a Virus on the Rise.** **M. Kubinski**, **J. Beicht**, T. Gerlach, A. Volz, G. Sutter & G. Rimmelzwaan. Vaccines (2020).
- **Virus–Host Cell Interplay during Hepatitis E Virus Infection.** **M. Wißing**, Y. Brüggemann, E. Steinmann, D. Todt. Trends In Microbiology (2020).
- **Measuring Reproducibility of Virus Meta-Genomics Analyses using Bootstrap Samples from FASTQ-Files.** **B. Saremi**, M. Kohls, P. Liebig, U. Siebert K. Jung. Bioinformatics (2020).
- **Adaptive Immunity to Dengue Virus: Slippery Slope or Solid Ground for Rational Vaccine Design?.** **L. Wilken**, G. Rimmelzwaan. Pathogens (2020).
- **Impact of Protein Glycosylation on the Design of Viral Vaccines.** **K. Schön**, B. Lepenies, G. Goyette-Desjardins. Advances is Biochemical Engineering / Biotechnology (2020).
- **SARS and COVID-19: New zoonotic outbreaks emerging from bat reservoirs.** **F. K. Kaiser,** A. D. M. E. Osterhaus. Berliner und Münchener Tierärztliche Wochenschrift (2021)
- **Reverse genetics systems for contemporary isolates of respiratory syncytial virus enable rapid evaluation of antibody escape mutants.** W. K. Jo, **A. Schadenhofer**, A. Habierski, **F. K. Kaiser**, G. Saletti, T. Ganzenmueller, E. Hage, S. Haid, T. Pietschmann, G. Hansen, T. F. Schulz, G. Rimmelzwaan, A. D. M. E. Osterhaus & M. Ludlow. PNAS (2021).
- **Enteric Ganglioneuritis, a Common Feature in a Subcutaneous TBEV Murine Infection Model.** M. Boelke, C. Puff, K. Becker, F. Hellhammer, **F. Gusmag**, H. Marks, K. Liebig, K. Stiasny, G. Dobler, W. Baumgärtner, C. Schulz & S. C. Becker. Microorganisms (2021).

Outlook and announcements

VIPER still is providing further training opportunities to its students. Whether and how long the upcoming classes will have to take place as online-only courses is unforeseeable so far. Until then, quarterly VIPER network meetings with all members of the RTG will be realized virtually. Students will still get the opportunity to present their progress and achievements to the VIPER community. Accordingly, there will still be lively discussions and constructive feedback on projects and results. Moreover, we were already successful in recruiting experts in the field of virology, biomedical sciences and immunology for the upcoming master class in October 2021. Therein, PhD students will be introduced to different career options, e.g. in academia, research institutes or industry as well as to funding acquisition, among other things. Whether and in what framework an informal get-together of the students can be realized remains to be seen. VIPER nevertheless wants to offer them the chance to connect and exchange their experiences, challenges, and successes during their second year within VIPER. In 2022, their official course of study will end. As closing, we are organizing a multi-day symposium for February next year.

Moreover, we are looking forward to the announcement of the projects for the second VIPER cohort, mid this year. The next group of VIPER students will start on 01.04.2022.

We keep our fingers crossed that the pandemic will slow down and that at least some planned activities can be realized. Still, flexibility is required from all of us in these times.

Until then and beyond, **Stay healthy!**

For further information about VIPER, please visit our website: www.rtg-viper.com

Impressum:

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