ICAR 2021 VIRTUAL CONFERENCE PROGRAM and ABSTRACTS

34th International Conference on Antiviral Research (ICAR)

ISAR

Hosted by the **International Society for Antiviral Research (ISAR)**

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THE INTERNATIONAL SOCIETY FOR ANTIVIRAL RESEARCH (ISAR)

The Society was organized in 1987 as a non-profit scientific organization for the purpose of advancing and disseminating knowledge in all areas of antiviral research. To achieve this objective, the Society organizes an annual meeting, The International Conference on Antiviral Research (ICAR). The Society, now in its 34th year of existence, has members representing 30 countries. To become an ISAR member, visit our website at **www.isar-icar.com**.

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*Supported by Gilead who provided funding. Gilead has had no input into the content of the materials used at this meeting/conference.

VIRTUAL CONFERENCE INFORMATION

How do I access the virtual Conference?

Registered attendees will receive log-in details on Monday, March 15. The ICAR2021 virtual platform will work best with the latest version of Google Chrome. Please ensure you use Google Chrome to access the platform to minimize technical problems.

ICAR 2021 Virtual Platform Link:
https://portalapp.gravesshow.eventsair.com/VirtualAttendeePortal/icar/onair/login

When will Conference content be available?

All invited, oral and poster presentations will be prerecorded and available for on-demand viewing by registered attendees on Monday, March 15, 2021, one week ahead of the live Conference sessions. The selected format will allow attendees the opportunity to view those presentations as their own schedule permits.

When will live programming take place?

All scheduled times and dates for ICAR2021 live programming are listed in Eastern Standard Time and spread across two "global golden hours" from March 22 through March 26, 2021. If you are unable to attend the live programming, recordings will be posted on demand within 24-48 hours following the live session.

How long will Conference content be available to access?

All registered attendees will be able to access on-demand content from ICAR2021 through April 25, 2021.

What is the format for the Live Q&A Sessions?

There are 10 Live Q&A Sessions which will feature invited and short oral presenters. All talks will be prerecorded and available for viewing by conference attendees starting March 15. **We highly encourage all attendees to view the talks prior to the live sessions.** For each Live Q&A Session, the session chairs will provide a brief introduction and then each speaker will present a brief summary of their presentation. After all speakers have presented their summaries, the chairs will facilitate discussion amongst speakers and attendees. Attendees will have the option to use the Q&A board to ask questions in real-time.

What will a virtual poster session look like?

Posters will be divided into two groups: Poster Session 1 and Poster Session 2. During the Conference week, each poster group will **present in TWO live sessions (A and B)**. During the live poster session, each poster presenter will have their own "room" where attendees and poster presenters will be able to speak with each other (presenter will be on video).

How do I interact with authors if I have questions?

Each presenter (invited, short oral and poster) will have a public chat message board on their page that will be monitored by the presenting author. Presenters are expected to check their chat board at least twice daily during the Conference week. We encourage attendees to leave feedback, questions, ask to be contacted for more information, or even leave a simple 'hello' to check in, so that they know you visited. The live sessions are another opportunity to interact in real-time.

Whom do I contact if I have problems?

For technical questions about accessing or using the platform:

- While in the platform, click the "Live Support" button on the top menu bar just prior to or during live sessions, or
- Contact Mike Graves at mike@gravesshow.com

For questions about registration or other Conference items, please contact ICAR Staff at info@isaricar.com.

Where can I find out more information about ICAR2021 Virtual Conference?

Please visit our website and click on the Virtual Information Frequently Asked Questions page. This page will be updated frequently with details and tips for ICAR2021 to include various training videos to help you become familiar with the virtual platform.

SPECIAL EVENTS

WOMEN IN SCIENCE ROUNDTABLE

Monday, March 22 • 12:15 – 1:15 PM ET

The Women in Science (WIS) Committee is excited to announce the 9th Annual Women in Science Roundtable. This year, our keynote speaker will be **Dr. Akiko Iwasaki, professor at Yale University** and an expert virologist and immunologist. Dr. Iwasaki is well known for her mentorship and addressing issues facing women in science, and most recently, the toll that Covid-19 has taken on women in particular. A 30-minute video presentation by Dr. Iwasaki will be available on March 15th for viewing prior to the live WIS session. This year's live roundtable will provide an opportunity to reflect on Dr. Iwasaki's presentation by participating in an important dialogue about the impact of theCOVID-19 pandemic on women in STEM. Attendees will have the opportunity to select a number of chat rooms with designated relevant topics to engage in important video chat discussions with other industry peers and professionals.

SPEED NETWORKING – TWO SESSIONS!

Monday, March 22 • 8:30 – 9:00 PM ET
Tuesday, March 23 • 11:45 AM – 12:15 PM ET

Ready to mix things up? Join us for these 30-minute sessions where you will be randomly matched with a small group of attendees for FIVE minutes for a video chat. When time is up, you will be randomly matched with a new group of individuals, giving you the chance to meet people you have never met before, and to make some new lasting connections! Do not miss this interesting opportunity to mix things up in your social world.

CAREER DEVELOPMENT INTERACTIVE WORKSHOP

Tuesday, March 23 • 1:15 – 2:15 PM ET

You belong: finding confidence in the face of self-doubt and impostor syndrome

Prof. Jen Heemstra, *Associate Professor, Emory University*

"I don't deserve to be here, and everybody knows it." This is the constant messaging of impostor syndrome – whether you're starting a new position, winning an award, or being asked to speak at a conference. While few of us talk about it, most of us experience it at some point in our careers. And, the struggles brought on by COVID-19 have only made this worse. However, with the right tools, we can fight back against impostor syndrome and help our friends and colleagues to do the same. This interactive workshop, given by Prof. Jen Heemstra, will explore the mechanisms by which thoughts of impostor syndrome can form, and how we can work to dismantle them.

PECKAKUCHA COMPETITION

Thursday, March 25 • 12:30 – 1:30 PM ET

Get ready to be entertained and informed! Join us for a fun session as seven finalists present their PechaKucha presentations. Not familiar with PechaKucha? The presenter has 15 slides, each on the screen for only 20 seconds. The slides advance automatically and the presenter has to keep up, as they won't have control. Be prepared for some humor, a few surprises and maybe something unexpected. Prizes will be awarded by a panel of judges to the top three finalists.

SCHEDULE at a GLANCE

**All times are listed in US Eastern Time.*

All prerecorded presentations are available on-demand for registered attendees starting Monday, March 15, 2021.

MONDAY, MARCH 22, 2021

11:00 AM – 12:15 PM ET	**OPENING SESSION** **Q&A Session 1: Influenza/RSV**
12:15 PM – 1:15 PM ET	**Special Event: Women in Science Roundtable**
7:30 PM – 8:30 PM ET	**Poster Session 1A**
8:30 PM – 9:00 PM ET	**Speed Networking Session 1**
9:00 PM – 10:00 PM ET	**Q&A Session 2: Pandemic Preparedness** *(dedicated to Mark Prichard)* **and Gertrude Elion Memorial Award**

TUESDAY, MARCH 23, 2021

11:00 AM – 11:45 AM ET	**Q&A Session 3: COVID-19 Vaccines**
11:45 AM – 12:15 PM ET	**Speed Networking Session 2**
12:15 PM – 1:15 PM ET	**Poster Session 2A**
1:15 PM – 2:15 PM ET	**Special Event: Career Development Interactive Workshop**
8:00 PM – 9:00 PM ET	**Q&A Session 4: COVID-19 Therapeutics and Diversity Speaker Award**
9:00 PM – 9:45 PM ET	**Q&A Session 5: Retroviruses and Herpes Viruses**

WEDNESDAY, MARCH 24, 2021

11:00 AM – 12:00 PM ET	**Poster Session 1B**
12:00 PM – 12:45 PM ET	**Q&A Session 6: Other Viruses and Women in Science Speaker Award**
12:45 PM – 1:00 PM ET	**ISAR Annual Business Meeting**
8:00 PM – 9:00 PM ET	**Poster Session 2B**
9:00 PM – 9:45 PM ET	**Q&A Session 7: Arboviruses**

THURSDAY, MARCH 25, 2021

11:00 AM – 11:45 AM ET	**Q&A Session 8: Hepatitis Viruses and William Prusoff Memorial Award**
11:45 AM – 12:30 PM ET	**Q&A Session 9: Technology and Antonín Holý Memorial Award**
12:30 PM – 1:30 PM ET	**Special Event: PechaKucha Competition**
7:00 PM – 8:45 PM ET	**Q&A Session 10: Other Respiratory Viruses** **CLOSING SESSION**

ISAR 2021 AWARDEES

GERTRUDE ELION MEMORIAL AWARDEE

William Lee, PhD

Defining innovation in the quest for treatment, prevention and cure of viral diseases

Dr. William "Bill" Lee is the Executive Vice President of Research at **Gilead Sciences**. He received his BS in Chemistry from the University of Massachusetts at Amherst and a PhD in Organic Chemistry with Teddy Traylor from the University of California San Diego. He did postdoctoral work in photocatalysis with Michael Gräzel at the EPFL in Switzerland and in bio-organic chemistry with Tom Bruice at the University of California Santa Barbara. He began his industry career at Syntex Research in Palo Alto, California and then moved to California Biotechnology where he was head of Drug Delivery. In 1991 he joined Gilead Sciences as Director of Pharmaceutical Product Development and became head of Discovery Research in 2000. During his tenure, Gilead has radically changed the paradigm for both treatment and prevention of HIV, launching multiple single-tablet regimens; discovered and developed curative antiviral regimens for HCV; and in 2020, received approval for the first antiviral drug, Veklury® against the SARS 2 virus. Dr. Lee is a co-inventor of Cellcept®, Viread® and tenofovir alafenamide, a lymphatic targeting prodrug of tenofovir, approved for the treatment and prevention of HIV in the combination products Genvoya®, Descovy®, Biktarvy®; Odefsey® and Symtuza® and as a solo product, Vemlidy® for the treatment of HBV®.

DIVERSITY SPEAKER AWARDEE

Craig Cameron, PhD

My career-long fascination with antiviral therapeutics

Craig E. Cameron is the Jeffery Houpt Distinguished Professor and Chair of the Department of Microbiology and Immunology at the **University of North Carolina School of Medicine**. He earned a Bachelor of Science degree in chemistry from Howard University in 1987. Following doctoral studies in biochemistry at Case Western Reserve University School of Medicine and post-doctoral studies in the chemistry department at Penn State, Cameron joined the faculty of biochemistry and molecular biology at Penn State in 1997. He was tenured, promoted to the rank of associate professor and appointed Louis Martarano Associate Professor in 2002. In 2005, he was promoted to the rank of professor and named the Paul Berg Professor of Biochemistry and Molecular Biology. From 2011-2012, Cameron served a two-year term as Associate Head for Research and Graduate Education. In 2013, he was named holder of the Eberly Family Chair in Biochemistry and Molecular Biology. Cameron moved to his current position in Chapel Hill in the fall of 2019. Cameron's research focuses on RNA polymerases and RNA-binding proteins required for viral replication or mitochondrial function. The goal of this work is development of novel strategies to treat and/or prevent viral infections and mitochondrial dysfunction. During his career, Dr. Cameron has received several honors, including the Howard Temin Award from the National Cancer Institute, an Established Investigator Award from the American Heart Association, a Distinguished Service Award from the Eberly College of Science Alumni Association, the Genesis Scholar Award from HBCU Digest, Fellow of the American Association for the Advancement of Science, and Fellow of the American Academy of Microbiology. Cameron currently serves as an associate editor for Journal of Biological Chemistry and Science Advances. In July 2020, Cameron became president of the American Society for Virology.

WILLIAM PRUSOFF MEMORIAL AWARDEE

David Durantel, PhD

Mid-term report on my academic journey to discover novel HBV/HDV therapeutics

David Durantel obtained his PhD in Molecular and Cellular Virology at the University of Montpellier in 1997. After three postdoctoral trainings respectively at Oxford Brookes University (with Pr Linda King and Robert Possee, UK), University of Oxford (with Pr Raymond Dwek and Dr Nicole Zitzmann, UK), and INSERM (National Institute for Health and Medical Research; with Pr Fabien Zoulim), he obtained a tenured position in 2005 at **INSERM**, then his Habilitation to direct research in 2008 from the University of Lyon (UCBL), and was finally promoted Director of Research in 2016. During all these years, he worked on numerous research projects related to drug discovery (on both Direct Acting (DAA) and Host-Targeting Agents (HTA)) in the viral hepatitis field. He currently leads a team at the **International Center for Research in Infectiology** (CIRI, *http://ciri.inserm.fr/*; Lyon), which studies HBV and HDV infections/co-infections and contributes to the R&D of novel DAAs and HTAs. He has authored/coauthored 110 PubMed-recorded articles/reviews, as well as numerous proceedings/book chapters & is an inventor in several patents. He acts as reviewers for many journals, including *Gastroenterology, Gut, Hepatology, J. Hepatol, PlosPathogen, antiviral journals, et caetera…*

Since 2014, he has been the associate editor for the Antiviral Research journal, section viral hepatitis, and, associated to this function, has co-organized several international antiviral conferences. He was recently nominated to organize the 2022 edition of the International HBV meeting.

He contributes to the French coordination on viral hepatitis research at ANRS (French Agency for AIDS and Hepatitis Research), holds seats on the boards of several ANRS "study section" and "concerted action" committees and routinely organizes excellent workshops/conferences at the National level. He was member of the executive board of the French Association for Liver Studies (AFEF) between 2015-2018, and is an active member of the European Association for the Study of the Liver (EASL).

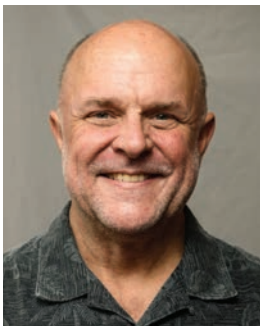
WOMEN IN SCIENCE AWARDEE

Graciela Andrei, PhD

Genetic diversity and evolution of herpesviruses

Graciela Andrei holds a PhD in Biological Sciences from the Faculty of Sciences, University of Buenos Aires, where she received a fellowship from the National Research Council (1984-1989). She undertook a post-doctoral training on antiviral chemotherapy under Prof. Eric De Clercq with focus on herpesviruses, at the Rega Institute and was recipient of a KU Leuven fellowship (1989-1996). In 1997, she performed a visiting research training at the Department of Biochemistry and Molecular Genetics, University of Alabama at Birmingham and was appointed associate researcher at the Rega Institute (1997-2005). In 2005, with her appointment as assistant professor at the Faculty of Medicine, **KU Leuven** in Belgium, she directed her research interest on chemotherapy of viral diseases, with emphasis on different herpesviruses, poxviruses, polyomaviruses and papillomaviruses. In 2008, she was promoted to Associate Professor and her research is currently directed to the investigation of the molecular mechanism of action of antiviral drug resistance and pathogenicity of viral mutants, competitive fitness of drug-resistant viruses, three-dimensional culture models for the study of viral pathogenicity and antivirals efficacy (including SARS-CoV-2), the development of novel strategies to target cancer cells and the tumor microenvironment, and the molecular mechanism of action of the anticancer activity of nucleotide analogues. In 2009, she participated to the setup of the translational research platform RegaVir for typing drug resistance among DNA viruses.

She has (co)authored more than 350 papers in international peer-reviewed journals and 6 book chapters. She has been a member of the International Society for Antiviral Research since 1989 and has served as Secretary during 2012-2019, and as member of several committees. She is part of the editorial board of *Antiviral Research, Archives of Virology, Viruses, PLoS One*, is main editor of the 'Antivirals and Vaccines' section within *Frontiers in Virology*, and serve as reviewer for various journals.



ANTONÍN HOLÝ MEMORIAL AWARDEE

Eddy Arnold, PhD

The Long and Winding Road: 35 Years of HIV reverse transcriptase structure, mechanism, and successful anti-AIDS drug design

Eddy Arnold's laboratory at the **Center for Advanced Biotechnology and Medicine (CABM) and Rutgers University** works to understand the structural and molecular basis of the chemistry underlying life, with a focus on studying human disease problems and applying the insights gained to the development of better treatments.

His research has profoundly influenced our understanding of the structure and biological function of viruses and their components. The cross-disciplinary research in Arnold's group uses a broad swath of tools and techniques from molecular biology, protein chemistry and biochemistry, biophysics, virology, crystallography, cryo-EM, and computational chemistry.

Eddy's work has illuminated fundamental molecular mechanisms of viral polymerase structure and function, infection and escape from antiviral drugs and immune surveillance, and protein-nucleic acid and protein-ligand interactions. His efforts in Michael Rossmann's laboratory culminated in elucidating the structure of a common cold virus, the first animal virus described in complete atomic detail.

Eddy's structure of HIV reverse transcriptase complexed with DNA, the first polymerase visualized with a relevant substrate, changed the landscape of the HIV/AIDS and polymerase biochemistry fields. Arnold's longstanding collaboration with Stephen Hughes has resulted in extraordinarily diverse and innovative studies of HIV reverse transcriptase structure, function, inhibition, and resistance that have helped to make this critical enzyme the most thoroughly understood of any DNA polymerase.

Arnold's efforts with legendary drug developer Dr. Paul Janssen, enabled the design and discovery of five anti-AIDS drugs that are broadly used for treating HIV-infected patients and are resilient to drug resistance. Arnold's team developed the strategic flexibility hypothesis, which postulates that structural flexibility and compactness of inhibitors can overcome resistance mutations, a concept that can be applied to any disease target. His elegant analyses of the RT inhibition mechanisms by AZT and nevirapine have likewise spawned generalizable principles. Crystallographic fragment screening efforts identified novel allosteric inhibitory sites in HIV-1 reverse transcriptase and led to new classes of antiviral inhibitors targeting influenza virus endonuclease and HIV-1 integrase. Arnold's work with Richard Ebright on multi-subunit bacterial RNA polymerase visualized aspects of transcription relevant to all living organisms and elucidated binding modes for multiple new classes of potential antibiotics.

THE 2021 CHU FAMILY FOUNDATION SCHOLARSHIP AWARDEES

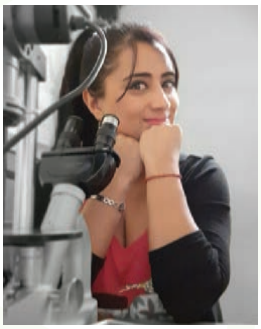
ISAR and The Chu Family Foundation (TCFF) Committee are pleased to announce the winners of the 2021 Chu Family Foundation Scholarship for Women Scientists. This scholarship supports the professional development of early career level women with the potential for significant contribution in the field of antiviral research.

2021 TCFF AWARDEES

Lorraine Bhebhe

MANCHESTER, UNITED KINGDOM

Lorraine Bhebhe is a final year PhD student in the Jones Lab in the University of Manchester. Her research focuses on the synthesis and characterization of novel biocompatible broad-spectrum virucidal antivirals. Prior to her present studies, she completed an MRes in The University of Manchester, focusing on target identification and validation in Non-small cell lung cancer. This was under the supervision of the Cancer Research UK's Manchester Drug Discovery Unit. Lorraine is also a state registered biomedical scientist with experience in the microbiology diagnostic field and more recently in the COVID testing facility at The Manchester Royal Infirmary. She is one of this year's Chu Foundation Scholarship winners and will be using the funds to travel to Switerzald to collaborate with the Supramolecular Nano-Materials and Interfaces Laboratory (SuNMIL) in the EPFL Swiss Federal Institute of Technology. During this time, she will be testing the antivirals she has synthesised against their large library of viruses including SARS-CoV-2. Lorraine has expressed her gratitude to the Chu foundation and is looking forward to gaining experience in the culture of wider repertoire of viruses, as well as being trained in characterisation techniques such as cold-spray ionization mass spectrometry. Look forward to seeing the results of her work in the next ICAR meeting!



Alejandra Castañeda Cataña

BUENOS AIRES, ARGENTINA

Mayra Alejandra Castañeda Cataña grew up in Ecuador. She is a PhD student at Universidad de Buenos Aires. Her thesis project is about design and characterization of biodegradable nanoparticles with antiviral activity. She knows there is no single antiviral approach that works for every virus, so she continues to educate herself on nanoparticle design and the up taking process of nanoparticles to provide the most complete study of how that works.

The Chu Family Foundation Scholarship will be used to develop the following project: "Studies of interaction of antiviral-loaded nanoparticles with biological macromolecules and cells". Her presence in the Group of Materials Engineering (Gemat), from the Institut Químic de Sarrià (IQS), of the Ramon Llull University (URL) Barcelona-Spain would contribute to her research and would expand her current studies to include hemorrhagic fevers viruses of great impact in South American countries. Her visit and interaction with your lab will go a long way to advance her ability to use antiviral nanoparticles against arenavirus and dengue infections.

She received her education at the University of Granada, Spain with a master's in Molecular Biology. She also holds a Biotechnology Engineer from The University of the Armed Forces- ESPE, Ecuador. Alejandra is currently working in Buenos Aires-Argentina where she does her PhD program.

Cecilia Vazquez
BUENOS AIRES, ARGENTINA

Cecilia Alejandra Vázquez was born in 1987 in Buenos Aires, Argentina. Since a very young age she has shown great interest in Science and in particular, Biology. After falling in love with Molecular Biology, she knew she wanted to become a researcher, so she graduated as a Biologist at the University of Buenos Aires and decided to pursue a PhD. Believing that it is very important to study topics that are relevant to public health, she joined the Virology Lab in the Institute of Biological Chemistry at the University of Buenos Aires under the direction of Drs. Sandra Cordo and Cybele García. There, Cecilia studies the relevance in mammarenavirus and flavivirus' replication cycle of lipid droplets and the metabolic pathways that converge in them. Her main goal is to find cellular components that can be targeted for antiviral therapies. After finding that lipid droplet depletion is a common feature of both mammarenavirus and flavivirus infection, the Chu Family Foundation Scholarship for Women Scientists will allow her to carry out a research stay in Dr. Muñoz-Fontela's lab in the Bernhard Nocht Institute for Tropical Medicine (BNITM). Focusing on Emergent diseases is an extremely urgent task and in that sense, the availability of a complete collection of pathogens and a BLS4 facility at BNITM will allow Cecilia to expand her results by including in the analysis pathogenic strains of arenaviruses, such as Junín virus, Machupo, Guanarito, Sabiá, Chaparé, Lassa, Lujo and lymphocytic choriomeningitis virus, and including Ebola virus as well. Since she hypothesizes that drugs inhibiting lipid droplets biosynthesis or their viral-mediated degradation could function as antiviral therapeutics against these viruses, she will evaluate the effect on viral replication of several inhibitor molecules of fatty acid synthesis, autophagy, lipophagy and fatty acid beta oxidation processes.

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INVITED SPEAKERS BIOGRAPHIES

Hector C. Aguilar, PhD

Emerging deadly viruses and their glycoproteins – From infection to vaccines and antivirals

Dr. Hector Aguilar-Carreno (publication name Hector C. Aguilar) is an Associate Professor in the **Department of Microbiology and Immunology at Cornell University** since July, 2017. He started his own research laboratory as an Assistant Professor at the Paul G. Allen School for Global Animal Health at Washington State University (WSU). He received a BS degree in Biochemical Engineering from Instituto Tecnologico de Tepic, Mexico. He then immigrated to the USA and obtained a MS degree in Biology from California State University, Los Angeles, and a PhD degree in Biochemistry and Molecular Biology from University of Southern California. He received post-doctoral training in Virology at University of California, Los Angeles, under the mentoring of Dr. Benhur Lee. At UCLA he helped identify the cell receptors for Nipah virus (NiV) and Hendra virus (HeV) and began to establish important tools to study NiV and HeV entry into mammalian host cells, as well as viral assembly/exit from infected cells. He is known for adopting technologies previously foreign to the field of Virology to the study of enveloped viruses, including Raman Spectroscopy, Super-resolution Microscopy, and Flow Virometry. His studies on viral entry and assembly inform novel ways to develop antivirals and vaccines. Dr. Aguilar-Carreno has served in many important scientific and diversity committees, including: Chair, WSU Immunology and Infectious Diseases Executive Committee; member, WSU CVM research committee; member, WSU Internal Governance Board for NIH T32 post-doctoral program; member, American Society for Virology Education Committee; Ad-hoc member, ~20 NIH study sections; Standing Member, VIR-A NIH study section; Chair and member, American Society of Microbiology Committee for Minority Education; Chair, Cornell College of Veterinary Medicine Diversity Committee; member, Cornell CVM Research Committee; member, Cornell presidential postdoctoral fellowship committee; Chair, 7 PhD students; member, ~30 PhD student committees; among other roles.

Ann Arvin, MD

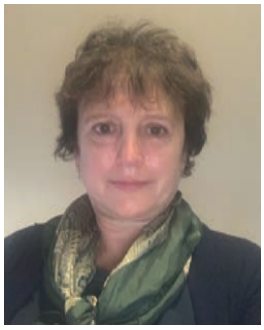
A perspective on viral vaccine immunity and the issue of disease enhancement

Ann Arvin, MD, is the Lucile Salter Packard Professor of Pediatrics and Professor of Microbiology and Immunology, **Stanford University**. Dr. Arvin's laboratory investigates the molecular virology of varicella zoster virus (VZV) pathogenesis. Her clinical research has focused on immune responses of infants and children to viral infections and vaccines, including VZV, measles and influenza vaccines, and herpes simplex virus and cytomegalovirus. She is a senior research advisor, **Vir Biotechnology**, and has consulted for several vaccine companies. Her committee service related to infectious diseases, vaccines and policy has included: NIAID Director's Advisory Council; National Vaccine Advisory Committee; NAM (IOM) Committee on the Scientific Uses of Variola Virus, Chair; WHO Steering Committee on Research Related to Measles Vaccines, Chair; NIAID Blue Ribbon Panel on Influenza; President's Council on Science and Technology Influenza Working Groups; NAS/NRC Committees on Policy and Global Affairs and Science, Technology and Law and Board on Life Sciences. She was chief of Infectious Diseases, Packard Children's Hospital (1984-2006). Dr. Arvin is a fellow of the American Academy of Arts & Sciences, the National Academy of Medicine, the American Association for the Advancement of Science, the Academy of the American Society for Microbiology, the Association of American Physicians and the American Pediatric Society. She received degrees from Brown University (AB), Brandeis University (MA), and the University of Pennsylvania (MD) and postdoctoral fellowship training at the University of California, San Francisco and Stanford University School of Medicine.

Louis Bont, MD, PhD

Treating RSV infection

Louis Bont, MD, PhD, is Pediatrician Infectiologist-Immunologist and founding chairman of ReSViNET, an international respiratory syncytial virus (RSV) research consortium. His specific research interest is RSV pathogenesis and burden of disease. His work focuses on unraveling the role of neutrophils, RSV-related mortality and long-term airway disease following RSV infection. Dr. Bont is the lead investigator of the INFORM study, a large prospective global clinical virology study to unravel the molecular epidemiology of RSV in about 4000 children. He is one of the co-leads of the RESCEU consortium aiming to define the RSV burden of disease in Europe. He is leading the RSV GOLD mortality registry funded by the Bill and Melinda Gates Foundation. His group collaborates with the World Health Organization on RSV surveillance and vaccine development. Dr. Bont's research focuses on clinical and translational mechanisms of disease and identifying targets for intervention of RSV bronchiolitis. He has been the lead author of about 200 publications in peer-reviewed medical journals. Dr. Bont is chairman of the Institutional Review Board at the **University Medical Center Utrecht, the Netherlands** and structural advisor of pharmaceutical companies. He founded the Training of Upcoming Leaders in Pediatric Science (TULIPS), a career training network for clinician scientists in the field of Child Health.



Judith Breuer, PhD

Antiviral agents for serious RNA virus infections; a personalised medicine approach

Judith Breuer is a Professor of Virology at UCL and Clinical lead for Virology at **Great Ormond Street Hospital for Children**. Her research interests include the development of high throughput pathogen sequencing directly from clinical material for the analysis of pathogen evolution and identification of pathogen genetic determinants of clinical disease. Professor Breuer has worked for many years evaluating on varicella zoster virus and its vaccine. Her work has elucidated many aspects of VZV natural history and pathogenesis. Professor Breuer's use of combined host and viral transcriptomics uncovered the requirement of VZV replication for keratinocyte differentiation and identified new epidermal signalling pathways associated with replication not only of VZV but other skin viruses. The application of enriched transcriptomics to early post mortem human trigeminal ganglia led her group to discover the canonical VZV latency transcript. More recently Professor Breuer has developed diagnostic metagenomic methods for pathogen discovery in patients with undetected infections of the brain, widening this recently to other samples. through her clinical work she has developed a pipeline for the evaluation of new and repurposed drugs, including combinations for treatment of serious viral infections particularly in immunocompromised individuals. In the absence of data from clinical trials her work has focussed on a personalised medicine approach to characterising the efficacy of novel treatments using genomics, in vitro and in vivo pharmacokinetics, pharmacodynamics measurements complemented by animal models. The methods developed have been applied to studies of antivirals used to treat SARS-CoV-2. Professor Breuer chairs the Joint Committee on Vaccines and Immunisation Varicella zoster vaccine subcommittees and the Immunocompromised Working Group. Professor Breuer is a member of the UK MHRA Expert working group on Covid vaccines, the SAGE subcommittee on Hospital Onset Covid Infection and the COG-UK steering group.

Bruno Canard, PhD

The SARS-CoV1 and 2 replication/transcription machinery and its future for drug-design

Dr. Bruno Canard of the **University of Marseille, France**, obtained his PhD in Microbiology from the University of Paris VII, at the Pasteur Institute under the guidance of Dr. Stewart T. Cole. After post-doctoral training at Harvard Medical School in 1995-1998 under the guidance of Pr. Charles C. Richardson, he started his team with an ATIPE-CNRS grant in 1998 in the laboratory of Architecture et Fonctions des Macromolécules Biologiques (UMR 7257 CNRS-Aix Marseille University). Dr. Bruno Canard is an expert in the study of emerging RNA virus enzymes and drug-design, in particular Human Immunodeficiency virus, Flavivirus (Dengue, Zika, West-Nile,...), Ebola virus, and since 2003, SARS-Coronavirus. He has trained 15 PhDs, co-ordinated the European Integrated Project project FP7 VIZIER in virology (24 partners, 12.9 M€). He is currently involved in several large scale European projects (SCORE, IMI-CARE) addressing the SARS-CoV2 virus. He has received the William Prusoff Award (2008) from the International Society for Antiviral Research. His team is supported, among others, by the Fondation pour la Recherche Médicale (2009-2011, and 2019-2021). He has published >220 peer-reviewed papers.

Kyeong-Ok Chang, DVM, MS, PhD

Development of small molecule protease inhibitors against SARS-CoV-2

Kyeong-Ok Chang received his DVM degree from Seoul National University, Seoul, KOREA and PhD degree from the Ohio State University, Columbus, OH. After post-doctoral training at NIH, he joined the **College of Veterinary Medicine, Kansas State University**, Manhattan, KS in 2005. He has over 25 years of research experience in the field of virology, specifically on viral pathogenesis and the development of therapeutic measures for important human and animal viral infections. One of his current research focuses is the identification of antiviral drug targets, development of in vitro assay systems and animal models for human coronaviruses including MERS-CoV, SARS-CoV and SARS-CoV-2. He has been actively collaborating in a multi-disciplinary team from the fields of virology, medicinal chemistry, structural biology, and drug development experts. Their major focus of the collaborative efforts is on protease inhibitors for viruses that encode 3C-like proteases (3CLpro). Through these drug development endeavors, they have identified multiple protease inhibitors including GC376 effective to multiple coronaviruses. These compounds are highly effective against human coronaviruses including SARS-CoV-2 in enzyme and cell culture and animal models.

Tomas Cihlar, PhD

Antivirals and preparedness for pandemics: what we have and what we need

Tomas Cihlar, PhD is a Vice President of Virology at **Gilead Sciences** with responsibility for coordinating preclinical antiviral research. Dr Cihlar joined Gilead after receiving his PhD in Biochemistry from the Institute of Organic Chemistry and Biochemistry in Prague, Czech Republic. While at Gilead, he has contributed to the development and regulatory approval of multiple antiviral products including the portfolio of Gilead's HIV drugs and their combinations. Together with his colleagues at Gilead, he established research programs focused on long-acting antiretrovirals, cure of HIV and chronic hepatitis B, and treatment of respiratory and emerging viral infections. For several years, Dr Cihlar served as a leader of remdesivir program at Gilead. Remdesivir has been approved by FDA in October 2020 for the treatment of hospitalized COVID-19 patients. In past, Dr Cihlar served on the Board of Directors of the International Society for Antiviral Research and is currently on the Board of Directors of Global Virus Network.

Emmie de Wit, PhD

Remdesivir treatment for emerging virus infections

Dr. Emmie de Wit is the Chief of the Molecular Pathogenesis Unit in the Laboratory of Virology of **NIAID**, where her lab focuses on emerging respiratory viruses, aiming to combine pathogenesis studies with detailed molecular analyses to identify molecular determinants of severe respiratory tract disease within the virus and the host. Dr. de Wit received her PhD in virology in 2006 from Erasmus University Rotterdam, the Netherlands. Her research there focused on the replication, pathogenesis and transmission of influenza A virus. In 2009, she moved to the Laboratory of Virology of NIAID in Hamilton, Montana to work in the biosafety level 4 laboratory there. Here, she focused on the pathogenesis of and countermeasures against Nipah virus, the Middle East Respiratory Syndrome Coronavirus and the 1918 H1N1 influenza A virus (Spanish flu). In 2014-2015, Dr. de Wit spent 4 months in a field lab in Monrovia, Liberia in charge of patient diagnostics for several Ebola Treatment Units in the area, to help contain the devastating Ebola epidemic in Liberia. Since the emergence of COVID-19, Dr. de Wit has focused her research on SARS-CoV-2, developing animal models and using those for testing of medical countermeasures and to gain a better understanding of SARS-CoV-2 pathogenesis.

Matthew Disney, PhD

Sequence-based design of small molecules targeting RNA

Dr. Matthew Disney is a Professor in the bicoastal Department of Chemistry at **The Scripps Research Institute**. He is an expert on the design, discovery, and development of small molecules that target disease-causing RNA for therapeutic benefit. Prof. Disney has developed novel strategies that provide a foundational understanding of RNA-small molecule interactions that enable design of bioactive small molecules targeting RNA in a transcriptome-wide manner and only from sequence. Indeed, his laboratory has discovered bioactive small molecules that target microRNAs involved in cancer (in situ and in vivo), addiction, and viral infections, including SARS-CoV-2 and hepatitis C virus (HCV). Collectively, his interdisciplinary and innovative approaches, which combine biochemistry, biophysics, organic synthesis, and computation, has provided expedited routes to RNA-directed chemical probes of function or lead therapeutic modalities.

In recent work, Prof. Disney has devised a method to imbue small molecules with the ability to cleave with targeted transcripts in living cells, drastically improving the activity of designer small molecules and ridding the cell of the disease-causing RNA. Dubbed ribonuclease targeting chimeras (RIBOTACs), his laboratory has shown that the small molecule hybrids can selectively cleave viral RNAs.

Prof. Disney has received various awards for his innovative work, including the National Institute of Neurological Disorders and Stroke (NINDS) Research Program Award, the National Institutes of Health (NIH) Director's Pioneer Award, Raymond and Beverly Sackler Prize in the Physical Sciences, BioFlorida's Weaver H. Gaines Entrepreneur of the Year Award, Barry Cohen Prize, awarded by the Medicinal Chemistry Section of the Israel Chemical Society and Teva Pharmaceutical Industries, Tetrahedron Young Investigator Award, and a Finalist for the Blavatnik Award for Young Scientists, among others.

Philip Dormitzer, MD, PhD

Scientific basis for the rapid development of highly effective RNA-based COVID-19 vaccines

Dr. Philip Dormitzer leads **Pfizer** viral vaccines research and development programs. These programs include the Pfizer-BioNTech RNA-based COVID-19 pandemic vaccine and influenza vaccine collaborations. The COVID-19 vaccine has been authorized for emergency use, and mass vaccination campaigns are in progress around the world. A prefusion F-based RSV vaccine to protect infants through maternal immunization has been advanced from discovery to a global phase 3 clinical trial in pregnant women. A cytomegalovirus vaccine candidate is preclinical. Before joining Pfizer, Dr. Dormitzer held positions at Novartis Vaccines that included Head of US Research. He was the founding member of the Novartis Viral Vaccine Research Center in Cambridge, MA. In 2009, his research team supported the development and licensure of three H1N1v influenza pandemic vaccines in what remains the most rapid vaccine response in history. In 2013, his team responded to the H7N9 influenza outbreak by supplying the US pre-pandemic stockpile with a vaccine generated from a synthesized virus. Before joining industry, Dr. Dormitzer was an Assistant Professor of Pediatrics at Harvard Medical School and led a structural virology laboratory, which, with collaborators, determined the structures of the rotavirus neutralization antigens. He graduated summa cum laude in Anthropology from Harvard College; conducted paleontological research in Pakistan and studied the Efe Pygmies in Zaire; obtained a Ph.D. in Cancer Biology and an MD at Stanford University; completed Internal Medicine training at Massachusetts General Hospital; and completed the Harvard Infectious Diseases Program clinical fellowship.

Rachel Fearns, PhD

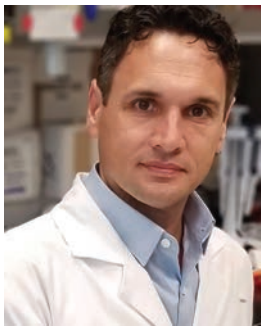
The polymerase complex of the non-segmented negative strand RNA viruses: differences in initiation mechanisms

Rachel Fearns, PhD is a Professor of Microbiology at **Boston University School of Medicine**. Her research focuses on understanding the transcription and genome replication mechanisms of respiratory syncytial virus (RSV) and other non-segmented negative strand RNA viruses. Transcription and genome replication are highly complex processes, involving multiple different steps. However, despite their complexity, both transcription and genome replication are performed by the same viral RNA dependent RNA polymerase. Her group has developed cell-based assays that allow different events in RSV transcription and RNA replication to be dissected. They also developed assays in which RNA synthesis is reconstituted in vitro using purified polymerase protein and an RNA promoter template to investigate events that occur during polymerase-promoter interactions. The development of these different assays has allowed them to elucidate RNA and protein features that enable transcription and replication initiation, mRNA capping, and mRNA and replicative RNA elongation. In addition to addressing basic research questions, because of their expertise in studying the RSV polymerase, pharmaceutical companies and academic groups have sought their collaborative support to study mechanisms of inhibition by small molecule polymerase inhibitors. In more recent work, her group has begun to extend the techniques they developed for RSV to other RNA viruses, including the pneumovirus, human metapneumovirus, the paramyxovirus, parainfluenza virus type 3 and the filovirus, Marburg virus. They are currently comparing the transcription and replication mechanisms of these different viruses. They anticipate that a detailed mechanistic understanding of their similarities and differences will help explain inhibitor specificity and identify strategies for inhibition by broad-spectrum antivirals.

Ron Fouchier, PhD

Now that we have the world's attention: Influenza!

Ron Fouchier is professor in Molecular Virology at **Erasmus MC Rotterdam**. He obtained a PhD in 1995 for HIV/AIDS research at the University of Amsterdam with Hanneke Schuitemaker and continued HIV work at the University of Pennsylvania as a postdoc with Michael Malim. Late 1998 he started a Molecular Virology research line on respiratory viruses, in particular influenza, at Erasmus MC in the department headed then by Ab Osterhaus. Ron's team contributed substantially to the identification and characterization of various "new" viruses, such as human metapneumovirus, human coronavirus NL63, SARS coronavirus, MERS coronavirus, and influenza A virus subtype H16. Currently, his research is focused on respiratory viruses of humans and animals, antigenic drift, and influenza virus zoonoses, transmission and pandemics. Fouchier is elected member of the Royal Dutch Academy of Sciences (KNAW), the Royal Holland Society of Sciences and Humanities (KHMW) and Academia Europeae. In 2006 he received the Heine-Medin award of the European Society for Clinical Virology and in 2013 the Huibregtsen award for top innovative science with societal impact. Fouchier is a web-of-science Highly Cited author.



Adam Gehring, PhD

Towards combination treatments for Chronic Hepatitis B: an immunologist's point of view

Adam Gehring received his PhD at Case Western Reserve University in Cleveland, Ohio. His training included a Postdoctoral Fellowship in the Institute of Hepatology at University College London and a position of Senior Research Fellow, and subsequently Assistant Principal Investigator, at the Singapore Institute for Clinical Sciences with Antonio Bertoletti. During his postdoctoral training Dr. Gehring was instrumental in developing TCR gene therapy for chronic HBV. His foundational work resulted in human application of engineered T cells for HBV-related HCC tumors expressing viral antigen. Dr. Gehring moved to Saint Louis University as an Assistant Professor in the Molecular Microbiology and Immunology department in March 2013 before joining the **Toronto Center for Liver Disease** as Biology Lead in February 2016.

Dr. Gehring runs a translational HBV immunology research lab focused on liver pathogenesis and sex-based differences in disease progression. His primary interest lies in defining the mechanisms driving liver inflammation during HBV-related flares using functional and transcriptomic approaches in liver biopsies. He has established an internal immune monitoring core within his lab to process and analyze immune responses in Phase 2 clinical studies for HBV.

Dr. Gehring is currently Co-Chair for the Immune Monitoring Workgroup of the HBV Forum. He is Co-Chair for the International HBV Meeting being organized in Toronto in September, 2021.

James Gern, MD

The ABCs of rhinovirus infections and asthma

James E. Gern, MD FAAAAI is a Professor of Pediatrics and Medicine at the **University of Wisconsin School of Medicine and Public Health** in Madison. Dr. Gern earned his MD degree from the University of South Florida and completed pediatrics training at the State University of New York in Syracuse and at Tufts University in Boston. After serving as a general pediatrician in the US Navy for three years, he completed an Allergy/Immunology Fellowship at Johns Hopkins University in 1992, and then joined the faculty at the UW-Madison. He is currently the Chief of the Allergy, Immunology and Rheumatology Division, and the Vice Chair for Research in the Department of Pediatrics. Dr. Gern's research focuses on identifying how viral respiratory infections and other environmental and host factors promote the development of childhood asthma and acute exacerbations of this disease.

Mark Heise, PhD

New strategies for modeling and treating emerging viral pathogens

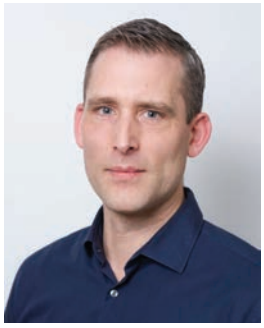
Dr. Mark Heise is a Professor in the Departments of Genetics and Microbiology and Immunology within the **University of North Carolina School of Medicine**. Dr. Heise received his BA in Biology from St. Olaf College in 1991 and his PhD in Immunology from Washington University in St. Louis in 1996. He conducted post-graduate research at the University of North Carolina in Chapel Hill on viral pathogenesis from 1997 to 2000, prior to joining the faculty at UNC.

The Heise laboratory uses molecular virology, immunology, biochemical, and quantitative genetics methodologies to understand the biology and pathogenesis of emerging alphaviruses, coronaviruses, and influenza viruses, with the goal of using this information to facilitate the development of safer and more effective vaccines and antiviral therapies against these pathogens. Dr. Heise's group has also been at the forefront of developing animal models of virus-induced disease and then using those models to develop and test antivirals and vaccines against emerging alphaviruses and coronaviruses. His laboratory has also been a leader in the use of systems genetics methods to identify and study polymorphic host genes that regulate susceptibility to viruses such as chikungunya virus and influenza A virus.

Christine Johnston, MD, MPH

HSV-1 and Alzheimer's Disease: causation or association? Understanding the biologic plausibility

Dr. Christine Johnston is an Associate Professor in the Division of Allergy and Infectious Diseases, Department of Medicine at **University of Washington**. She is an infectious diseases physician who performs clinical studies of herpes simplex virus (HSV) infection focusing on the intersection between viral pathogenesis and host immune responses, with the ultimate goal of developing successful vaccines and medications to prevent and treat HSV infections. Dr. Johnston's prior research has focused on HSV infections in the genital tract, utilizing daily genital swabs to identify localized anatomic regions of viral shedding and to perform biopsies at these sites to characterize the immune response to asymptomatic HSV-2 shedding. She has also conducted a prospective study of the natural history of genital HSV-1 infection. In addition, she is pursuing studies to understand associations between HSV-1 and Alzheimer's Disease. She is also the Medical Director of the University of Washington STD Prevention Training Center, which is part of the CDC-funded National Network of STD Clinical Prevention Training Centers (NNPTC) and the Associate Program Director for the University of Washington Infectious Disease Fellowship Training Program.



Jeroen Kortekaas, PhD

Four-segmented Rift Valley fever virus as a novel live-attenuated vaccine for animal and human use

Jeroen Kortekaas is affiliated with **Wageningen Bioveterinary Research (WBVR)**, Lelystad, the Netherlands. His research focuses on Rift Valley fever virus (RVFV) and other members of the order Bunyavirales, with an additional interest in zoonotic arboviruses of the families *Togaviridae* and *Flaviviridae*. He collaborates with several universities and research institutes around the world (Germany, US, South Africa, China). He has (co)authored more than 60 publications in peer-reviewed scientific journals and 6 patent applications. Apart from his involvement in vaccine development and fundamental studies on arboviruses, he is an ad hoc member of several Rift Valley fever expert panels. He is currently coordinator of two large, international projects, focused on the development of veterinary and human RVF vaccines. The latter LARISSA project (https://www.larissa.online/) is funded by the Coalition for Epidemic Preparedness Innovations (CEPI). In 2017, he became CSO of BunyaVax (www.bunyavax.com), a company that develops vaccines using proprietary platform technologies. In the same year, he was appointed special professor of the Laboratory of Virology of Wageningen University. He is also member of the Netherlands Commission on Genetic Modification (COGEM) and member of the board of the Virology Division of the Royal Dutch Society for Microbiology.

Florian Krammer, PhD

Antibody responses to the SARS-CoV-2 spike protein

Florian Krammer, PhD, graduated from the University of Natural Resources and Life Sciences, Vienna (Austria) in 2010. He received his postdoctoral training in the laboratory of Dr. Peter Palese at the Icahn School of Medicine at Mount Sinai, New York working on hemagglutinin stalk-based immunity and universal influenza virus vaccines. In 2014 he became an independent principal investigator and is currently Mount Sinai Professor of Vaccinology at the **Icahn School of Medicine at Mount Sinai**. Dr. Krammer's work focuses on understanding the mechanisms of interactions between antibodies and viral surface glycoproteins and on translating this work into novel, broadly protective vaccines and therapeutics. The main target is influenza virus but he is also working on coronaviruses, flaviviruses, hantaviruses, filoviruses, and arenaviruses.

Jenny Low, MBBS, MRCP, MPH

Biologics as therapeutics for rapid outbreak response – can we get there fast enough?

Associate Professor Jenny Low is a Board-Certified senior consultant with the Department of Infectious Diseases in Singapore General Hospital and faculty at the Programme in Emerging Infectious Diseases, **Duke-NUS Medical School**. Concurrently, she is the co-director of the Viral Research and Experimental Medicine Centre@ **SingHealth** Duke-NUS (ViREMiCS) in the SingHealth Duke NUS AMC and deputy clinical director at the SingHealth Investigational Medicine Unit (IMU). She led the early dengue infection and outcome (EDEN) study in Singapore that detailed, in several publications, clinical dengue in adults. She was the lead clinical investigator in the first proof-of-concept clinical trial on the use of Celgosivir as an anti-dengue drug (CELADEN) in Singapore. She was also the lead PI in an investigator led trial which tested the role of pre-existing cross-reactive antibodies and authenticated antibody dependent enhancement and in flaviviral infections in a human experimental study using 2 different flaviviral vaccines. Her current research focus is on early phase adaptive clinical trials of viral therapeutics and vaccine development for rapid response as well as the role of the innate immune response in modulating the outcome of infection or vaccination thereby improving therapeutic interventional strategies for infectious diseases. She has conducted several novel monoclonal antibodies phase 1 trials against viruses including Zika, Yellow fever and SARS-COV2 viruses. She is twice awarded the National Clinician Scientist Award by the Ministry of Health, Singapore in 2016 and 2019 for her to study these urgent unmet clinical needs.

Chris Meier, PhD

Design of nucleotide prodrugs for antiviral chemotherapy – the TriPPPro-Approach

Chris Meier obtained a diploma and a doctorate (PhD) in Chemistry from the University of Marburg, Germany for a thesis on the synthesis of ultimate carcinogens involved in the induction of the chemical carcinogenesis. He joined the Organic Chemistry Department at the Pasteur-Institute in Paris, France as a Post-Doc and started working on antivirally active nucleosides and prodrugs. In 1996 he received the *Habilitation* in Organic Chemistry from the University of Frankfurt/Main, Germany under the mentorship of Prof. J. Engels. He was appointed as associate professor at the University of Würzburg, Germany, and in 1999 he joined **Universität Hamburg, Germany** as a full professor. He is the current past-president of the International Society on Nucleoside, Nucleotides and Nucleic Acids (IS3NA) and is the Scientific Director of the Centre for Structural Systems Biology (CSSB) in Hamburg. He received the Prusoff-Award in 2007 and the Antonín Holy-Award in 2018 from the International Society on Antiviral Research (ISAR). He was awarded as a Zhiquiang-guest professor from Shanghai University. Chris's research covers pronucleotide development (*cyclo*Sal-, Di*PP*ro- and Tri*PPP*ro-approaches for the delivery of nucleotide analogues), general nucleoside chemistry, small molecule antivirals to target host cell factor to combat against Bunya viridae and hemorrhagic fever viruses, synthesis of membrane permeable and/or photocaged nucleotides, e.g. second messengers. He has published more than 250 scientific publications and is the inventor of 10 issued patents.

Johan Neyts, PhD

Pan-serotype dengue virus inhibitor that blocks the NS3-NS4B interaction and exhibits unprecedented in vivo potency

Johan Neyts is full professor of Virology at the **University of Leuven, Belgium**. He teaches virology at the medical school and at the school of dentistry. The lab has a long-standing expertise in the development of antivirals strategies and drugs against emerging and neglected viral infections such as dengue and other flaviviruses, Chikungunya and other alphaviruses, enteroviruses, noroviruses, HEV and rabies and is intensively involved in the search for antiviral strategies against SARS-CoV2. A second focus of the lab is the development of a novel vaccine technology platform technology based on the yellow fever virus vaccine as a vector; this include among others vaccines against rabies and SARS-CoV2. His team is also developing a technology, the PLLAV (Plasmid Launched Live Attenuated Virus); which allows to rapidly engineer highly thermostable vaccines against multiple viral pathogens. Johan is past-president of the International Society for Antiviral Research (www.isar-icar.com). Four classes of antivirals discovered in his laboratory have been licensed to major pharmaceutical companies (two on HCV, one on dengue and one on rhino/enteroviruses). He published >500 papers in peer reviewed journals and has given >240 invited lectures and a large number of lay-press interviews.

Christoph Nitsche, PhD

Targeting the proteases of SARS-CoV-2 and other RNA viruses

Christoph Nitsche studied chemistry and business administration. He obtained his PhD in 2014 from Heidelberg University, where his fascination for antiviral drug discovery began. In 2015, the German Chemical Society awarded him the PhD prize for medicinal chemistry for his work on inhibitors of the dengue virus protease. He worked as a Feodor Lynen Fellow (Alexander von Humboldt Foundation) at the Australian National University (2015–2018) and as a Rising Star Fellow at the Free University of Berlin (2018–2019). In 2019, he received a Discovery Early Career Research Award from the Australian Research Council to start his independent career at the **ANU**, where he was appointed Senior Lecturer in 2020. His research targets proteases from RNA viruses with a focus on dengue, West Nile, Zika, Chikungunya and SARS-CoV-2. His research operates at the interface between synthetic chemistry and biochemistry, designing selective probes and inhibitors that help to characterize and validate proteases as antiviral drug targets and develop lead compounds for drug discovery campaigns.

Maria Rosenthal, PhD

Understanding the multiple functions of the bunyavirus polymerase protein

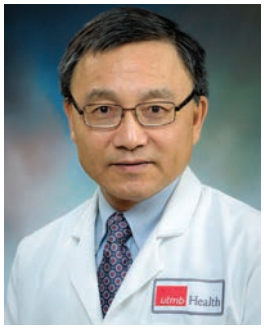
Maria Rosenthal is leading a junior research group at the **Bernhard Nocht Institute for Tropical Medicine** in Hamburg, Germany, where her team uses structural biology, virology, biochemistry and molecular biology techniques to understand the genome replication and trancription of bunyaviruses, an important group of emerging RNA viruses. After studying human biology in Marburg with a focus on infection biology she obtained her PhD in virology and biochemistry from the University of Bremen. She solved several structures of bunyavirus polymerase protein domains by X-ray crystallography substantially contributing to the understanding of bunyavirus cap-snatching mechanism. In highly collaborative projects her group currently also applies cryo-EM single particle analysis in order to solve structures of full-length bunyavirus polymerase proteins. Additionally they use biochemical assays to investigate the different functions of bunyavirus polymerase. A profound structural and functional understanding of viral genome replication and transcription should ultimately lead to the identification of suitable targets for potentially broad-spectrum antivirals against the diverse group of bunyaviruses.

Hanneke Schuitemaker, PhD

Janssen's effort in the development of an Ad26 based COVID-19 vaccine

Hanneke Schuitemaker, PhD, is the Head of Viral Vaccine Discovery and Translational Medicine and Disease Area Stronghold Leader for Viral Vaccines at **Janssen Vaccines & Prevention B.V.** She has been in these roles since 2010 and oversees Janssen's viral vaccine programs including investigational vaccine candidates for HIV, respiratory syncytial virus (RSV), Ebola, Zika, SARS-CoV-2 and HPV. In addition, she is a Professor of Virology at the Amsterdam University Medical Center.

Hanneke Schuitemaker is a medical biologist by training, received her PhD in Medicine in 1992 at the University of Amsterdam and worked for more than 20 years on HIV-1 pathogenesis, first at Sanquin (1989-2007), the blood supply foundation in the Netherlands, where she was the Chair of the department of Clinical Viro-Immunology (1998-2007), and then at the Amsterdam University Medical Center (2008-2010), where she was the Chair of the Department of Experimental Immunology and a member of the Research Council. From mid-2003 to mid-2004, she worked as a visiting scientist at The Scripps Research Institute in La Jolla, California. She successfully trained more than 30 PhD students and co-authored more than 300 peer-reviewed scientific articles.



Pei-Yong Shi, PhD

SARS-CoV-2 biology and countermeasure development

Pei-Yong Shi is John Sealy Distinguished Chair in Innovations in Molecular Biology at **University of Texas Medical Branch**. He works on RNA virus replication, drug discovery, and vaccine research. His unique expertise in public health laboratory (New York State Department of Health), pharmaceutical companies (Novartis and Bristol-Myers Squibb), and academia (University of Texas Medical Branch, Yale, and other universities) allows his team to work on both basic and translational research. He has published over 300 peer-reviewed papers in leading journals, including Nature, Science, and Cell. In response to the COVID pandemic, his team published the first peer-reviewed infectious clone and reporter virus for SARS-CoV-2; these reagents have been shared around the world to fight COVID pandemic. Many of his technologies have been used in leading pharmaceutical companies for diagnostic and countermeasure development. A recent example is his reporter neutralization assay that has enabled the rapid development of Pfizer's COVID-19 vaccine, the first vaccine with 95% efficacy in humans

Robert Siliciano, MD, PhD

Barriers to curing HIV infection

Robert Siliciano is a Professor of Medicine at the **Johns Hopkins University School of Medicine**. He is an immunologist and virologist recognized for his work on the treatment of HIV infection. He is known particularly for identifying and characterizing the latent reservoir for HIV in resting CD4+ T cells. This reservoir is the major barrier to curing HIV infection and the subject of an intense international research effort. Siliciano was born in Rochester, New York and grew up in Elmira, New York. He graduated from Princeton University with a degree in chemistry and then received an MD and a PhD in immunology from the Johns Hopkins University School of Medicine. After a postdoctoral fellowship in immunology at Harvard Medical School, he joined the faculty of the Johns Hopkins University School of Medicine in 1988. He is a member of the Howard Hughes Medical Institute and has been elected to the National Academy of Medicine, the National Academy of Sciences, and the American Academy of Arts and Sciences. For 16 years, he directed the Hopkins MD-PhD Program at Johns Hopkins.

Robert Siliciano and his wife Janet Siliciano lead a laboratory that is focused in finding a cure for HIV infection. Following the lab's discovery in 1995 of a latent reservoir for HIV, they demonstrated that latently infected cells persist indefinitely even in patients on prolonged antiretroviral therapy (ART). These studies indicated that eradication of HIV-1 infection with ART alone would never be possible. The lab is now focused on understanding the in vivo dynamics of this reservoir, specifically the factors that account for the remarkable stability of the reservoir. The lab is also working to identify drugs that will reactivate latent HIV so that it can be targeted by the immune system, and to develop accurate, scalable assays that can be used to evaluate curative interventions. In addition, the lab has studied theoretical aspects of the pharmacodynamics of antiretroviral drugs in an effort to understand the remarkable ability of these drugs to block HIV replication.

Jean-Pierre Sommadossi, PhD

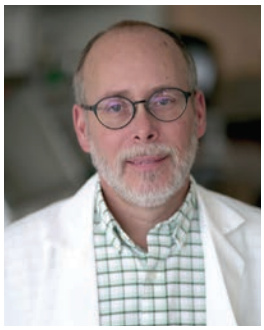
AT-527, a double prodrug of a guanosine nucleotide analog, is a potent inhibitor of SARS-CoV-2 in vitro and a promising oral antiviral for treatment of COVID-19

Jean-Pierre Sommadossi is the founder of **Atea Pharmaceuticals (NASDAQ: AVIR)**, where he currently serves as the Chairman & CEO. Jean-Pierre has over 30 years of scientific, operational, strategic and management experience in the biotech industry. Previously Jean-Pierre was the Principal Founder of Idenix Pharmaceuticals, Inc. (NASDAQ: IDIX) and a Co-Founder of Pharmasset, Inc. (NASDAQ: VRUS). Both of these companies were acquired; Idenix by Merck for $3.85 billion in 2014 and Pharmasset by Gilead for $11 billion in 2012. Jean-Pierre held a number of key executive positions at Idenix, including Chairman of the Board of Directors, Executive President and Chief Scientific Officer from 1998 to 2000, and then as Chairman and Chief Executive Officer from 2000 to 2010. During Jean-Pierre's tenure, Idenix discovered, co-developed and co-launched telbivudine (Tyzeka™/ Sebivo®) for the treatment of hepatitis B, and established a major clinical pipeline of antiviral therapeutics for the treatment of hepatitis C and HIV/AIDS. Jean-Pierre is a member of the Harvard Medical School Discovery Council, Chairman, Kezar Life Sciences, Inc. (NASDAQ: KZR), Chairman of PegaOne, Chairman, Panchrest, Inc., and a member of the Board of The BioExec Institute, as well. Prior to his entrepreneurial career, Jean-Pierre was on the faculty of the University of Alabama at Birmingham School of Medicine since March 1985. Jean-Pierre served as a Professor of Pharmacology, Toxicology and Clinical Pharmacology from June 1992 to November 2000. He has authored over 180 peer-reviewed publications and holds more than 60 U.S. patents associated with cancer and antiviral therapeutics. Jean-Pierre holds a PharmD and PhD in Pharmacology from the University of Marseilles, France.

Eike Steinmann, PhD

Principles of Hepatitis E virus replication, persistence and antiviral strategies

Prof. Eike Steinmann studied Biology at the Leibniz University Hannover and at the Northeastern University, Boston, USA. He graduated in 2004 at the Institute for Molecular Virology at University Heidelberg in the lab of Prof. Bartenschlager. Afterwards he worked as a postdoctoral fellow and junior group leader in the Department for Experimental Virology of the TWINCORE – Centre for Experimental and Clinical Infection Research. In 2012, Eike habilitated for Experimental Virology at Hannover Medical School and in 2014 he became group leader of the Virus Transmission team at the Institute for Experimental Virology at the TWINCORE – Centre for Experimental and Clinical Infection Research. Eike became extracurricular professor at the Hannover Medical School in 2016 and was then appointed to the **Ruhr University Bochum**, where he is head of the Department for Molecular & Medical Virology since April 2018.



John Tavis, PhD

Towards combination treatments for chronic hepatitis B: A virologist point of view

John Tavis, PhD, is a Professor of Molecular Virology at the **Saint Louis University School of Medicine** and Director of the **Saint Louis University Institute for Drug and Biotherapeutic Innovation**. He received his doctorate in molecular biology from Penn State University in 1990 and did postdoctoral studies into the molecular virology of Hepatitis B Virus at the University of California – San Francisco. He is the Chairman of the Scientific Advisory Council for the annual International Hepatitis B Virus Meeting, Incoming Chair of the International Coalition to Eliminate HBV (ICE-HBV), and a member of the Scientific and Medical Advisory Board for the Hepatitis B Foundation and Baruch S. Blumberg Institute. He is on the editorial boards of the *Journal of Virology and Antiviral Research*. He is the recipient of the 2013 Naomi Judd Award for his efforts to control HBV. His longstanding efforts on behalf of the American Cancer Society led to receipt of the Society's Mission Hero Award in 2018. He has studied the HBV replication mechanism, HBV reverse transcriptase's metabolism and non-catalytic roles in the cell, and biochemistry of viral reverse transcription since 1992. He has authored approximately 100 scientific papers and is an inventor on 10 awarded or pending patent applications. His current work focuses on the basic biochemistry of the HBV ribonuclease H and developing drugs to suppress HBV replication that target this essential enzyme.

Christiane Wobus, PhD

Investigating enterotropic virus infections in human intestinal organoids

Dr. Christiane Wobus is an associate professor in the Department of Microbiology and Immunology at the **University of Michigan Medical School** in Ann Arbor, MI, USA. In 1997, she received her MS from Michigan State University, East Lansing, MI, USA, and her PhD from the University of Heidelberg, Germany, in 2000. She returned to the USA to perform her postdoctoral work at Washington University in St. Louis, MO, where she co-discovered murine norovirus and her interest in enteric viruses was ignited. In 2007, she joined the University of Michigan as an assistant professor and was promoted to associate professor in 2014. Today her laboratory investigates different aspects of noroviruses and astroviruses, major causes of gastroenteritis worldwide, using a combination of transformed cell culture systems, non-transformed intestinal organoids and mouse models. After the start of the COVID-19 pandemic, she has also applied her expertise to better understand SARS-CoV-2 biology and identify therapeutics. The long-term goal of her research program is to gain a better understanding of enteric viruses and identify conserved features that may lead to the development of effective prevention and control strategies for viral causes of gastroenteritis.

Tal Zaks, MD, PhD

Overview of Moderna COVID-19 vaccine: safety, immunogenicity and efficacy

Tal Zaks, Chief Medical Officer, oversees clinical development and regulatory affairs across Moderna. Prior to joining **Moderna**, Dr. Zaks was senior vice president and head of Global Oncology at Sanofi, where he was responsible for all aspects of oncology drug discovery, development and commercialization. Dr. Zaks began his industry career at GlaxoSmithKline in the genetics research group, where he built the oncology translational medicine team and led translational research on lapatinib as well as the in-licensing and clinical development of foretinib. In addition to his industry work, Dr. Zaks is associate professor of medicine at the University of Pennsylvania, and has served as a volunteer physician at the Philadelphia Veterans Administration Medical Center, treating patients with genitourinary cancers. Dr. Zaks received his M.D. and Ph.D. from the Ben Gurion University in Israel and conducted post-doctoral research at the U.S. National Institutes of Health. He completed his clinical training in internal medicine at Temple University Hospital followed by a fellowship in medical oncology at the University of Pennsylvania. Dr. Zaks serves on the Board of Directors of Adaptimmune Therapeutics plc.

Jennifer R. Zhang, MS

Lenacapavir: A first-in-class phase 2/3 HIV capsid inhibitor with potential for twice yearly dosing

Jennifer R. Zhang joined **Gilead Sciences** as a medicinal chemist in 2003 after working for 5 years at Sugen, Inc. Over the past 17 years, she has worked on multiple programs including the discovery of GS-9669, a non-nucleoside inhibitor of the hepatitis C NS5B RNA polymerase. More recently, she has contributed to HIV projects such as the discovery of the first-in-class HIV capsid inhibitor, lenacapvir. Jennifer received MS and BS degrees in chemistry from Peking University, China.

PROGRAM SCHEDULE

All presentations will be available for on-demand viewing starting March 15, 2021. Live sessions will take place starting March 22, 2021. All on-demand content and live sessions may be accessed via the ICAR2021 Conference Portal.

MONDAY, MARCH 22, 2021

11:00 AM – 12:15 PM ET

Opening Session

Kara Carter and Kathie Seley-Radtke

Q&A Session 1: Influenza/RSV

Chaired by

María-Jesús Pérez-Pérez and Johan Neyts

1. Treating RSV infection

Louis Bont, M.D., Ph.D.[1]

[1]*University Medical Center Utrecht, Utrecht, Netherlands*

2. The Polymerase Complex of the Non-Segmented Negative Strand RNA Viruses: Differences in Initiation Mechanisms

Afzaal Shareef, B.S.[1], Tessa Cressey, Ph.D.[1], Victoria Kleiner, B.S.[1], Sarah Noton, Ph.D.[1], **Rachel Fearns, Ph.D.**[1]

[1]*Boston University School of Medicine*

3. Now that we have the world's attention: Influenza!

Ron Fouchier, Ph.D.[1]

[1]*Erasmus MC Rotterdam, Dept Viroscience, Rotterdam, Netherlands*

4. The flavonoid cyanidin shows antiviral and immunomodulatory properties against RSV, in vitro and in vivo

Carlos Bueno, Ph.D.[1], Benedetti Martina, B.S.[2], Luciana Vázquez, B.S.[3], María Virginia Gentilini, Ph.D.[4], Mercedes Soledad Nabaes Jodar, B.S.[5], Mariana Viegas, Ph.D.[5], Laura Alché, Ph.D.[6]

[1]*Universidad de Buenos Aires, FCEN, Depto de Qca Biológica-IQUIBICEN, Lab de Virología, Argentina;* [2]*Universidad de Buenos Aires, FCEN, Departamento de Química Biológica, Lab de Virología, Argentina;* [3]*UOCCB – Administración Nacional de Laboratorios e Institutos de Salud (ANLIS), Argentina;* [4]*IMETTYB-CONICET, Buenos Aires, Argentina;* [5]*Laboratorio de Virología, Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina;* [6]*Universidad de Buenos Aires, FCEN, Depto de Qca Biológica, Lab de Virología, Argentina*

6. Antagonism by a Baloxavir and Oseltamivir Drug Combination Against Baloxavir-Resistant, but Not Against Oseltamivir-Resistant Influenza A Virus Infections in Mice

Scott Gibson, B.S.[1], Ashley Sheesley, B.S.[1], Justin Moscon, B.S.[1], Brett Hurst, Ph.D.[1], E. Bart Tarbet, Ph.D.[1]

[1]*Utah State University, Logan, Utah, United States of America*

7. A single-dose live-attenuated YF17D-vectored SARS-CoV-2 vaccine candidate

Lorena Sanchez-Felipe, Ph.D.[1], Thomas Vercruysse, Ph.D.[1], Sapna Sharma, Ph.D.[1], Ji Ma, B.S.[1], Viktor Lemmens, M.S.[1], Dominique Van Looveren, Ph.D.[1], Mahadesh Prasad Arkalagud Javarappa, Ph.D.[1], Robbert Boudewijns, M.S.[1], Bert Malengier-Devlies, M.S.[1], Laurens Liesenborghs, M.D., Ph.D.[1], Suzanne J.F. Kaptein, Ph.D.[1], Carolien De Keyzer, B.S.[1], Lindsey Bervoets, B.S.[1], Sarah Debaveye, B.S.[1], Madina Rasulova, Ph.D.[1], Laura Seldeslachts, Ph.D.[2], Li-Hsin Li, B.S.[1], Sander Jansen, M.S.[1], Michael Bright Yakass, M.S.[1], Babs Verstrepen, Ph.D.[3], Kinga Böszörményi, B.S.[3], Gwendoline Kiemenyi-Kayere, B.S.[3], Nikki van Driel, B.S.[3], Osbourne Quaye, Ph.D.[4], Xin Z Zhang, B.S.[1], Sebastiaan ter Host, M.S.[1], Niraj Mishra, Ph.D.[1], Ward Deboutte, B.S.[1], Jelle Matthijnssens, Ph.D.[1], Lotte Coelmont, Ph.D.[1], Corinne Vandermeulen, M.D., Ph.D.[5], Elisabeth Heylen, Ph.D.[1], Valentijn Vergote, M.S.[1], Dominique Schols, Ph.D.[1], Zhongde Wang, Ph.D.[6], Willy Bogers, Ph.D.[7], Thijs Kuiken, Ph.D.[8], Ernst Verschoor, Ph.D.[7], Christopher Cawthorne, Ph.D.[9], Koen Van Laere, M.D., Ph.D.[9], Ghislain Opdenakker, Ph.D.[1], Greetje Vande Velde, Ph.D.[9], Birgit Weynard, M.D., Ph.D.[10], Dirk E. Teuwen, M.S.[1], Patrick Matthys, Ph.D.[1], Johan Neyts, Ph.D.[1], Hendrik Jan Thibaut, Ph.D.[1], Kai Dallmeier, Ph.D.[1]

[1]KU Leuven (Rega Institute), Leuven, Belgium; [2]KU Leuven Department of Imaging and Pathology, Biomedical MRI and MoSAIC, Leuven; [3]Department of Virology, Biomedical Primate Research Centre (BPRC), Rijswijk, Netherlands; [4]West African Centre for Cell Biology of Infectious Pathogens (WACCBIP), University of Ghana, Accra, Ghana; [5]Leuven University Vaccinology Center (LUVAC), Leuven, Belgium; [6]Department of Animal, Dairy, and Veterinary Sciences, Utah State University, Logan, Utah, United States of America; [7]Department of Virology, Biomedical Primate Research Centre (BPRC), Rjswijk, Netherlands; [8]Department of Viroscience, Erasmus University Medical Center, Rotterdam, Netherlands; [9]KU Leuven Department of Imaging and Pathology, Biomedical MRI and MoSAIC, Leuven, Belgium; [10]KU Leuven Department of Imaging and Pathology, Translational Cell and Tissue Research, Leuven, Belgium

12:15 PM – 1:15 PM ET

Special Event: Women in Science Roundtable

7:30 PM – 8:30 PM ET

Poster Session 1A

All posters are listed in numerical order starting on page 41.

8:30 PM – 9:00 PM ET

Speed Networking Session 1

9:00 PM – 10:00 PM ET

Q&A Session 2: Pandemic Preparedness *(dedicated to Mark Prichard)* and Gertrude Elion Memorial Award

Chaired by
Pei-Yong Shi and Rich Whitley

20. **2021 Gertrude Elion Memorial Award Recipient**

Defining Innovation in the Quest for Treatment, Prevention and Cure of Viral Diseases

William Lee, Ph.D.[1]
[1]*Gilead Sciences Inc., Foster City, California*

21. **Antivirals and Preparedness for Pandemics: What We Have and What We Need**

Tomas Cihlar, Ph.D.[1]
[1]*Gilead Sciences, Inc., California, United States of America*

22. **Scientific Basis for the Rapid Development of Highly Effective RNA-Based COVID-19 Vaccines**

Philip Dormitzer, M.D., Ph.D.[1]
[1]*Pfizer, Pearl River, New York, United States of America*

23. **SARS-CoV-2 Biology and Countermeasure Development**

Pei-Yong Shi, Ph.D.[1]
[1]*University of Texas Medical Branch at Galveston, Texas, United States of America*

24. **EIDD-2749, a Broadly Active Ribonucleoside Analog that is Highly Efficacious in Animal Models of Arenaviral Disease**

Brian Gowen, Ph.D.[1], Jonna Westover, Ph.D.[1], Kie-Hoon Jung, Ph.D.[1], Ashley Dagley, M.S.[1], Eric Sefing, M.S.[1], Kevin Bailey, B.S.[1], Nicole Anderson, B.S.[1], Craig Day, Ph.D.[1], Manohar Saindane, Ph.D.[2], George Painter, Ph.D.[2], Alexander Kolykhalov, Ph.D.[2], Gregory Bluemling, Ph.D.[2]
[1]*Utah State University;* [2]*Emory University*

25. **Crystal Structure of Alphavirus nsP4 RNA Polymerase**

Dahai Luo, Ph.D.[1], Yaw Bia Tan, B.S.[1], Sainan Wang, B.S.[2], Andres Merits, Ph.D.[2], Jie Zheng, Ph.D.[3]
[1]*Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore;* [2]*Institute of Technology, University of Tartu, Tartu, Estonia.;* [3]*Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China*

26. **Inhibition of human norovirus replication in cell culture and zebrafish larvae by a novel class of protease inhibitors**

Jana Van Dycke, Ph.D.[1], Wanhao Dai, M.S.[2], Zoe Stylianidou, M.S.[1], Jian Li, M.S.[2], Arno Cuvry, M.S.[1], Bingqian Li, M.S.[2], Nanci Santos-Ferreira, M.S.[1], Lindsey Bervoets, B.S.[1], Jasper Rymenants, B.S.[1], Peter de Witte, Ph.D.[3], Hong Liu, Ph.D.[2], Johan Neyts, Ph.D.[1], Joana Rocha-Pereira, Ph.D.[1]
[1]*KU Leuven, Rega Institute for Medical Research, Laboratory of Virology & Chemotherapy;* [2]*Chinese Academy of Sciences Shanghai Institute of Materia Medica, China Pharmaceutical University;* [3]*KU Leuven, Laboratory for Molecular Biodiscovery*

TUESDAY, MARCH 23, 2021

11:00 AM – 11:45 AM ET

Q&A Session 3: COVID-19 Vaccines

Chaired by
Rhonda Cardin and Kara Carter

30. **A perspective on viral vaccine immunity and the issue of disease enhancement**
Ann Arvin, M.D.[1]
[1]*Stanford University, Vir Biotechnology, California, United States of America*

31. **Antibody responses to the SARS-CoV-2 spike protein**
Florian Krammer, Ph.D.[1]
[1]*Icahn School of Medicine at Mount Sinai, New York, New York, United States of America*

32. **Janssen's Effort in the Development of an Ad26 Based COVID-19 Vaccine**
Hanneke Schuitemaker, Ph.D.[1]
[1]*Janssen Vaccines & Prevention, a Janssen Pharmaceutical Company of Johnson & Johnson, Leiden, Netherlands*

33. **Overview of Moderna COVID-19 Vaccine: Safety, Immunogenicity and Efficacy**
Tal Zaks, M.D., Ph.D.[1]
[1]*Moderna, Boston, Massachusetts, United States of America*

11:45 AM – 12:15 PM ET

Speed Networking Session 2

12:15 PM – 1:15 PM ET

Poster Session 2A

All posters are listed in numerical order starting on page 46.

1:15 – 2:15 PM ET

Special Event: Career Development Interactive Workshop

Chaired by
Leen Delang

Prof. Jen Heemstra, PhD
Associate Professor, Emory University

This talk will not be available on-demand. The live session will be recorded and available for viewing afterwards.

8:00 PM – 9:00 PM ET

Q&A Session 4: COVID-19 Therapeutics and Diversity Speaker Award

Chaired by

Luis Schang and Kathie Seley-Radtke

40. 2021 Diversity Speaker Award Recipient

My Career-long Fascination with Antiviral Therapeutics

Craig Cameron, Ph.D.[1]

[1]*University of North Carolina School of Medicine, Chapel Hill, North Carolina, United States of America*

41. The SARS-CoV1 and 2 replication/transcription machinery and its future for drug-design

Ashleigh Shannon[1], Véronique Fattorini[1], Barbara Selisko[1], Camille Falcou[1], Pierre Gauffre[1], Bhawna Sama[1], Priscila El Kazzi[1], Etienne Decroly[1], Karine Alvarez[1], Cécilia Eydoux[1], Jean-Claude Guillemot[1], Johanna Huchting[2], Chris Meier[2], Franck Touret[3], Bruno Coutard[3], Steven S. Good[4], Adel Moussa[4], Kai Lin[4], Jean-Pierre Sommadossi[4], Olve Peersen[5], François Ferron[1], **Bruno Canard, Ph.D.**[1]

[1]*CNRS and Aix-Marseille University, AFMB, Viral Replicases: Structure, Mechanisms, and Drug-Design, Marseille, France;* [2]*University of Hamburg, Faculty of Sciences, Department of Chemistry, Organic Chemistry, Hamburg, Germany;* [3]*Unité des Virus Émergents, Aix-Marseille Université – IRD 190 – Inserm 1207 – IHU Méditerranée Infection), Marseille, France;* [4]*Atea Pharmaceuticals, Inc., Boston, Massachusetts, United States of America;* [5]*Biochemistry and Molecular Biology Dept, Colorado State University, Fort Collins, Colorado, United States of America*

42. Development of small molecule protease inhibitors against SARS-CoV-2

Kyeong-Ok Chang, D.V.M., Ph.D.[1]

[1]*Kansas State University*

43. Targeting the Proteases of SARS-CoV-2 and Other RNA Viruses

Christoph Nitsche, Ph.D.[1]

[1]*Australian National University, Canberra, Australia*

44. AT-527, a double prodrug of a guanosine nucleotide analog, is a potent inhibitor of SARS-CoV-2 in vitro and a promising oral antiviral for treatment of COVID-19

Jean-Pierre Sommadossi, Ph.D.[1]

[1]*Atea Pharmaceuticals, Inc., Boston, Massachusetts, United States of America*

45. Multidisciplinary approaches identify compounds as potential new therapeutics for SARS-CoV-2

Christopher Day, Ph.D.[1], **Benjamin Bailly, Ph.D.**[1], Patrice Guillon, Ph.D.[1], Larissa Dirr, Ph.D.[1], Freda Jen, Ph.D.[1], Belinda Spillings, Ph.D.[1], Johnson Mak, Ph.D.[1], Mark Von Itzstein, Ph.D.[1], Thomas Haselhorst, Ph.D.[1], Michael Jennings, Ph.D.[1]

[1]*Institute for Glycomics, Griffith University*

47. Targeting host and viral protease to combat COVID-19

Yanmei Hu, M.S.[1], Chunlong Ma, Ph.D.[1], Jun Wang, Ph.D.[1]

[1]*The University of Arizona*

9:00 PM – 9:45 PM ET

Q&A Session 5: Retroviruses and Herpes Viruses

Chaired by
Galit Alter and Tomas Cihlar

50. HSV-1 and Alzheimer's Disease: causation or association? Understanding the biologic plausibility

Christine Johnston, M.D.[1]
[1]*University of Washington, Seattle, Washington, United States of America*

51. Barriers to Curing HIV Infection

Robert Siliciano, M.D., Ph.D.[1]
[1]*Johns Hopkins Univesity School of Medicine, Baltimore, Maryland, United States of America*

52. Lenacapavir: A First-in-Class Phase 2/3 HIV Capsid Inhibitor with Potential for Twice Yearly Dosing

Jennifer Zhang, M.S.[1]
[1]*Gilead Sciences, Inc, Foster City, California, United States of America*

53. New helicase-primase drug candidates with sufficient target tissue exposure affect latent neural herpes simplex virus infections

Gerald Kleymann, Ph.D.[1], Klaus Hamprecht, Ph.D.[2], Nadja Uhlig, M.S.[3], Christian Gege, Ph.D.[1], Fernando Bravo, Ph.D.[4], Thomas Grunwald, Ph.D.[3], David Bernstein, Ph.D.[4]
[1]*Innovative Molecules GmbH, Bad Salzuflen, NRW, Germany;* [2]*University Hospital of Tübingen UKT, Tübingen, BW, Germany;* [3]*Fraunhofer IZI, Leipzig, SN, Germany;* [4]*Children's Hospital Medical Center CCHMC, Cincinnati, Ohio, United States of America*

54. The Molecularly Engineered H84T BanLec has Broad Spectrum Antiviral Activity Against Human Herpesviruses

Megan Lloyd, Ph.D.[1], Dongmei Liu, M.S.[1], Maureen Legendre, B.S.[2], David Markovitz, M.D.[2], Jennifer Moffat, Ph.D.[1]
[1]*SUNY Upstate Medical University, Syracuse;* [2]*University of Michigan, Ann Arbor, Michigan, United States of America*

55. Oral USC-373, an HPMPC Prodrug, Prevents Varicella Zoster Virus Replication in a Mouse Model

Dongmei Liu, M.S.[1], Jinglei Lyu, Ph.D.[2], Megan Lloyd, Ph.D.[1], Jiajun Fan, Ph.D.[2], Justin Overhulse, B.S.[2], Boris Kashemirov, Ph.D.[2], **Jennifer Moffat, Ph.D.**[1], Charles McKenna, Ph.D.[2]
[1]*SUNY Upstate Medical University, Syracuse;* [2]*University of Southern California, Los Angeles, California, United States of America*

WEDNESDAY, MARCH 24, 2021

11:00 AM – 12:00 PM ET

Poster Session 1B

All posters are listed in numerical order starting on page 41.

12:00 PM – 12:45 PM ET

Q&A Session 6: Other Viruses and Women in Science Speaker Award

Chaired by
Chris Meier and Joana Rocha-Pereira

60. **2021 Women in Science Speaker Award Recipient**
Genetic Diversity and Evolution of Herpesviruses
Graciela Andrei, Ph.D.[1]
[1]*Rega Institute for Medical Research, Leuven, Belgium*

61. **Antiviral agents for serious RNA virus infections; a personalised medicine approach**
Judith Breuer, M.D.[1]
[1]*Professor of Virology Institute Child Health UCL, london*

62. **Four-segmented Rift Valley fever virus as a novel live-attenuated vaccine for animal and human use**
Paul Wichgers Schreur, Ph.D.[1], Nadia Oreshkova, Ph.D.[1], Lucien Van Keulen, D.V.M.[1], Jet Kant, B.S.[1], Sandra Van de Water, B.S.[1], Pál Soós, D.V.M.[2], Yves Dehon, Ph.D.[2], Anna Kolár, Ph.D.[2], Zoltán Pénzes, Ph.D.[2], **Jeroen Kortekaas, Ph.D.**[1]
[1]*Wageningen Bioveterinary Research;* [2]*Ceva Animal Health*

63. **Understanding the multiple functions of the bunyavirus polymerase protein**
Dominik Vogel, Ph.D.[1], Sigurdur Thorkelsson, M.S.[2], Emmanuelle Quemin, Ph.D.[2], Kristina Meier, M.S.[1], Tomas Kouba, Ph.D.[3], Harry Williams, Ph.D.[1], Sophia Reindl, Ph.D.[1], Stephan Günther, M.D.[1], Kay Grünewald, Ph.D.[2], Stephen Cusack, Ph.D.[3], **Maria Rosenthal, Ph.D.**[1]
[1]*Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany;* [2]*Centre for Structural Systems Biology, Heinrich-Pette-Institute, University of Hamburg, Hamburg, Germany;* [3]*European Molecular Biology Laboratory Grenoble, Grenoble, France*

64. **Rational modifications and biological evaluation of novel non-nucleoside agents with antiviral activity against norovirus**
Salvatore Ferla, Ph.D.[1], William Knight, B.S.[1], Giulio Nannetti, Ph.D.[2], Fabiana Saporito, M.S.[2], Beatrice Tropea, M.S.[2], Nanci Dos Santos Ferreira, Ph.D.[3], Johan Neyts, Ph.D.[3], Joana Rocha-Pereira, Ph.D.[3], Andrea Brancale, Ph.D.[2], Marcella Bassetto, Ph.D.[1]
[1]*Swansea University;* [2]*Cardiff University;* [3]*KU Leuven*

65. **Metabolic Stabilization of a Novel Inhibitor of human Dihydroorotate Dehydrogenase (hDHODH) with Potent Broad Spectrum Antiviral Activity**
Nora Fohrmann, M.S.[1], Lisa Oestereich, Ph.D.[2], Katharina Pfaff, Ph.D.[1], Gilles Querat, Ph.D.[3], Chris Meier, Ph.D.[1]
[1]*University of Hamburg, Hamburg, Germany;* [2]*Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany;* [3]*Aix-Marseille Université, Marseille, France*

66. **Small molecules from the diketo acid class engage and inhibit the endonuclease domain of a panel of bunyaviruses and interfere with viral replication in vitro**

Sebastiaan ter Horst, B.S.[1], Yaiza Fernández-García, Ph.D.[2], Marcella Bassetto, Ph.D.[3], Andrea Brancale, Ph.D.[4], Dominga Rogolino, Ph.D.[5], Mario Sechi, Ph.D.[6], Mauro Carcelli, Ph.D.[5], Stephan Günther, Ph.D.[2], Johan Neyts, Ph.D.[1], Joana Rocha-Pereira, Ph.D.[1]

[1]KU Leuven, Rega Institute for Medical Research, Belgium; [2]Department of Virology, Bernhard-Nocht-Institute for Tropical Medicine, Hamburg, Germany; [3]Department of Chemistry, College of Science, Swansea University, United Kingdom of Great Britain and Northern Ireland; [4]Cardiff School of Pharmacy and Pharmaceutical Sciences, Cardiff University, United Kingdom of Great Britain and Northern Ireland; [5]Dept. of Chemistry, Life Sciences & Environmental Sustainability, University of Parma, Parco Area Delle Scienze, Parma, Italy; [6]Dept. of Chemistry and Pharmacy, Laboratory of Drug Design & Nanomedicine, University of Sassari, Italy

12:45 PM – 1:00 PM ET

ISAR Annual Business Meeting

Kara Carter, Jinhong Chang and Brian Gowen

8:00 PM – 9:00 PM ET

Poster Session 2B

All posters are listed in numerical order starting on page 46.

9:00 PM – 9:45 PM ET

Q&A Session 7: Arboviruses

Chaired by
Justin Julander and Subhash Vasudevan

70. **New Strategies for Modeling and Treating Emerging Viral Pathogens**

Mark Heise, Ph.D.[1]

[1]The University of North Carolina, Chapel Hill

71. **Biologics as Therapeutics for Rapid Response- can we get there fast enough?**

Jenny Low, M.D., MPH[1]

[1]Singapore General Hospital, Singapore, Singapore

72. **Pan-serotype dengue virus inhibitor that blocks the NS3-NS4B interaction and exhibits unprecedented in vivo potency**

Suzanne J.F. Kaptein[1], Olivia G. M. Goethals[2], Dominik Kiemel[3], Arnaud Marchand[4], Bart Kesteleyn[5], Jean-François Bonfanti[6], Dorothée Bardiot[4], Bart Stoops[7], Tim H.M. Jonckers[8], Kai Dallmeier[1], Laurent Chatel-Chaix[9], Max Münster[9], Gilles Querat[10], Franck Touret[10], Xavier de Lamballerie[10], Pierre Raboisson[8], Kenny Simmen[11], Patrick Chaltin[12], Ralf Bartenschlager[13], Marnix Van Loock[2], **Johan Neyts, Ph.D.**[1]

[1]KU Leuven, Department of Microbiology, Immunology and Transplantation, Rega Institute for Medical Research, Laboratory of Virology and Chemotherapy, Leuven, Belgium; [2]Global Public Health Research and Development, Janssen Pharmaceutica NV, Beerse, Belgium; [3]Department of Infectious Diseases, Molecular Virology, Heidelberg University, Heidelberg, Germany; [4]Cistim Leuven vzw, Leuven, Belgium; [5]Janssen Pharmaceutica NV, Beerse, Belgium; [6]Janssen Infectious Diseases Discovery, Val de Reuil, France; [7]DMPK, Discovery Sciences, Janssen Pharmaceutica NV, Beerse, Belgium; [8]Discovery Chemistry EU, Discovery Sciences, Janssen Pharmaceutica NV, Beerse, Belgium; [9]Department of Infectious Diseases, Molecular Virology, Heidelberg University, Heidelberg, Germany; [10]Unité des Virus Émergents (UVE: Aix-Marseille Univ–IRD 190–Inserm 1207–IHU

Méditerranée Infection), Marseille, France; [11]Janssen Research and Development, Buckinghamshire, United Kingdom of Great Britain and Northern Ireland; [12]Cistim Leuven vzw; Centre for Drug Design and Discovery (CD3), Leuven, Belgium; [13]Department of Infectious Diseases, Molecular Virology, Heidelberg University; German Center for Infection Research, Heidelberg, Germany

73. **The Integrity of Yellow Fever Virus Replication Complex maintained by Nonstructural 4B protein and Targeted by a Small Molecule Antiviral Agent**

Zhao Gao, Ph.D.[1], Xuexiang Zhang, B.S.[1], Lin Zhang, M.S.[1], Julia Ma, M.S.[1], Yanming Du, Ph.D.[1], Ju-Tao Guo, M.D.[1], **Jinhong Chang, M.D., Ph.D.**[1]

[1]Baruch S. Blumberg Institute

74. **The ribonucleoside analog EIDD-2749 is broadly active in the treatment of Eastern Equine Encephalitis and Chikungunya viral infections**

Justin Julander, Ph.D.[1], Manohar Saindane, Ph.D.[2], Kevin Bailey, B.S.[1], Ashley Dagley, M.S.[3], Alexander Kolykhalov, Ph.D.[4], George Painter, Ph.D.[5], Gregory Bluemling, Ph.D.[4]

[1]Institute for Antiviral Research, Utah State University, Logan, Utah, United States of America; [2]Emory Institute for Drug Development (EIDD), Atlanta, Georgia, United States of America; [3]Utah State University, Logan, Utah, United States of America; [4]Emory Institute for Drug Development (EIDD); Drug Innovation Ventures at Emory (DRIVE), Atlanta, Georgia, United States of America; [5]Department of Pharmacology and Chemical Biology, Emory University; EIDD; DRIVE, Atlanta, Georgia, United States of America

75. **Development of a novel dengue protease inhibitor**

Gerry Rassias, Ph.D.[1], Vasiliki Zogali, M.S.[1], Dimitris Kiousis, M.S.[1], Minos-Timotheos Matsoukas, Ph.D.[1], Kitti Wing Ki Chan, Ph.D.[2], Crystall Swarbrick, Ph.D.[3], Sai Wang, Ph.D.[2], Chin Piaw Gwee, M.S.[2], Subahash Vasudevan, Ph.D.[4]

[1]University of Patras, Department of Chemistry, Patra, Greece; [2]Duke-NUS Singapore, Singapore, Singapore; [3]University, Institute for Glycomics, Australia; [4]Duke-NUS Singapore, Griffith University, Singapore

THURSDAY, MARCH 25, 2021

11:00 AM – 11:45 AM ET

Q&A Session 8: Hepatitis Viruses and William Prusoff Memorial Award

Chaired by

Jerome Deval and David Durantel

80. **2021 William Prusoff Memorial Award Recipient**

Mid-term report on my academic journey to discover novel HBV/HDV therapeutics

David Durantel, Ph.D.[1]

[1]INSERM U1111, Lyon, France

81. **Towards combination treatments for Chronic Hepatitis B: an immunologist's point of view**

Adam Gehring, Ph.D.[1]

[1]Toronto Centre for Liver Disease, University Health Network, Toronto, Ontario, Canada

82. **Principles of Hepatitis E virus replication, persistence and antiviral strategies**

Eike Steinmann, Ph.D.[1]

[1]Ruhr University Bochum, Bochum, Germany

83. **Towards combination treatments for chronic hepatitis B: A virologist point of view**
John Tavis, Ph.D.[1]
[1]*Saint Louis University School of Medicine, Saint Louis, Missouri, United States of America*

84. **CD40 agonists boost IFN-induced signaling pathway and subsequent anti-HBV response *in vitro* and *in vivo***
Antoine Alam, Ph.D.[1], Xavier Marniquet, M.S.[1], Marion Dajon, Ph.D.[1], Julie Montegut, B.S.[1], Virginie Archimbeaud, B.S.[1], Halim Guerraoui, B.S.[1], Gregory Neveu, Ph.D.[1], Charlotte Blanc, M.S.[1], Christelle Marcou, B.S.[1], Juliette Lavaux, Ph.D.[1], Hugh Watson, Ph.D.[1], Kara Carter, Ph.D.[2]
[1]*Evotec ID Lyon, Lyon, France;* [2]*Dewpoint Therapeutics, Boston, Massachusetts, United States of America*

85. **Efficient Inhibition of Hepatitis B Virus cccDNA and Pregenomic RNA by HBV ribonuclease H Inhibitors During Infection of HepG2-NTCP Cells**
Ranjit Chauhan, Ph.D.[1], Qilan Li, Ph.D.[1], John Tavis, Ph.D.[1]
[1]*St Louis University, St Louis, Missouri, United States of America*

86. **Farnesoid X receptor alpha ligands inhibit hepatitis delta virus replication and propagation in physiologic cell culture models**
Benoît Lacombe, Ph.D.[1], **Julie Lucifora, Ph.D.**[1], Anne-Flore Legrand, M.S.[1], Camille Ménard, M.S.[1], Maud Michelet, M.S.[1], Adrien Foca, Ph.D.[1], Pauline Abrial, B.S.[1], Anna Salvetti, Ph.D.[1], David Durantel, Ph.D.[1], Patrice André, M.D., Ph.D.[1], Christophe Ramière, M.D., Ph.D.[1]
[1]*INSERM U1111, CIRI, Lyon, France*

11:45 AM – 12:30 PM ET

Q&A Session 9: Technology and Antonín Holý Memorial Award

Chaired by
Andrea Brancale and Jennifer Moffat

90. **2021 Antonín Holý Memorial Award Recipient**
The Long and Winding Road: 35 Years of HIV Reverse Transcriptase Structure, Mechanism, and Successful Anti-AIDS Drug Design
Eddy Arnold, Ph.D.[1]
[1]*Center for Advanced Biotechnology and Medicine (CABM), and Department of Chemistry and Chemical Biology, Rutgers University*

91. **Sequence-Based Design of Small Molecules Targeting RNA**
Matthew Disney, Ph.D.[1]
[1]*The Scripps Research Institute, Jupiter, United States of America*

92. **Design of Nucleotide Prodrugs for Antiviral Chemotherapy – the Tri*PPP*ro-Approach**
Chris Meier, Ph.D.[1]
[1]*Organic Chemistry, Department of Chemistry, Hamburg University, Hamburg, Germany*

93. **Investigating enterotropic virus infections in human intestinal organoids**
Christiane Wobus, Ph.D.[1]
[1]*University of Michigan, Ann Arbor*

12:30 PM – 1:30 PM ET

Special Event: PechaKucha Competition

7:00 PM – 8:45 PM ET

Q&A Session 10: Other Respiratory Viruses

Chaired by
Mike Lo and Robert Jordan

10. **Emerging deadly viruses and their glycoproteins – From infection to vaccines and antivirals**
Hector Aguilar-Carreno, Ph.D.[1]
[1]*Cornell University, Ithaca, New York, United States of America*

11. **Remdesivir treatment for emerging virus infections**
Emmie de Wit, Ph.D.[1]
[1]*NIAID, NIH*

12. **The ABCs of Rhinovirus Infections and Asthma**
James Gern, M.D.[1]
[1]*University of Wisconsin-Madison*

13. **Roles of PNKP and CDK1 in Zika virus replication and pathogenesis**
Malgorzata Rychlowska, Ph.D.[1], Michael Weinfeld, Ph.D.[2], Luis Schang, D.V.M., Ph.D.[3]
[1]*Baker Institute for Animal Health, College of Veterinary Medicine, Cornell University, USA, Ithaca, New York;* [2]*Faculty of Medicine & Dentistry, Oncology Department, University of Alberta, Canada, Alberta, Canada*

14. **Plant Lectin Urtica Dioica Agglutinins (UDA) is a Potential Inhibitor Against Rabies Virus in a Muscle Model**
Xinyu Wang, M.S.[1], Ashley Banyard, Ph.D.[2], Lisanne Terrie, M.S.[3], Els Van Damme, Ph.D.[4], Lieven Thorrez, Ph.D.[3], Anthony Fooks, Ph.D.[2], Johan Neyts, Ph.D.[1], Dirk Jochmans, Ph.D.[1]
[1]*Rega Institute, Laboratory of Virology and Chemotherapy, KU Leuven, Leuven, Belgium;* [2]*Wildlife Zoonoses and Vector Bourne Disease Research Group, Animal and Plant Health Agency, United Kingdom of Great Britain and Northern Ireland;* [3]*Department of Development and Regeneration, KU Leuven;* [4]*Faculty of Bioscience Engineering, Ghent University, Belgium*

15. **Arbovirus infectivity is significantly reduced by components of the bacterial cell wall**
Lana Langendries, M.S.[1], Rana Abdelnabi, Ph.D.[1], Sofie Jacobs, M.S.[1], Sam Verwimp, B.S.[1], Suzanne Kaptein, Ph.D.[1], Pieter Baatsen, Ph.D.[2], Lieve Van Mellaert, Ph.D.[1], Leen Delang, Ph.D.[1]
[1]*Rega Institute for Medical Research, KU Leuven, Leuven, Belgium;* [2]*VIB-KU Leuven*

Closing Session

Kara Carter, Kathie Seley-Radtke and Brian Gentry

Recognition and announcement of all award winners and closing remarks.

POSTER SESSION 1A & 1B

6. Antagonism by a Baloxavir and Oseltamivir Drug Combination Against Baloxavir-Resistant, but Not Against Oseltamivir-Resistant Influenza A Virus Infections in Mice

Scott Gibson, B.S.[1], Ashley Sheesley, B.S.[1], Justin Moscon, B.S.[1], Brett Hurst, Ph.D.[1], E. Bart Tarbet, Ph.D.[1]
[1]Utah State University, Logan, Utah, United States of America

47. Targeting host and viral protease to combat COVID-19

Yanmei Hu, M.S.[1], Chunlong Ma, Ph.D.[1], Jun Wang, Ph.D.[1]
[1]The University of Arizona

101. Clinical evaluation of Lassa fever antiviral LHF-535 in a 14-day repeat dose study in healthy volunteers

Sean Amberg, Ph.D.[1], Portia Vliet-Gregg, B.S.[1], Alison Heald, M.D.[2], Eric Tarcha, Ph.D.[1], Jeff Posakony, Ph.D.[1]
[1]Kineta, Seattle, Washington, United States of America; [2]Alison Heald Consulting, LLC, Seattle, Washington, United States of America

102. Inhibition of Hepatitis Delta Virus (HDV) replication and decrease of HDV particles specific infectivity by inducers of the NF-κB pathways

Julie Lucifora, Ph.D.[1], Maud Michelet, M.S.[1], Dulce Alfaiate, M.D., Ph.D.[2], Brieux Chardès, Ph.D.[1], Suzanne Faure-Dupuy, Ph.D.[3], Rayan Fahrat, Ph.D.[1], Caroline Pons, M.S.[1], Tobias Riedl, M.S.[3], Anne-Flore Legrand, M.S.[1], Michel Rivoire, M.D., Ph.D.[4], Thomas Engleitner, Ph.D.[5], Fabien Zoulim, M.D., Ph.D.[6], Mathias Heikenwälder, Ph.D.[3], Anna Salvetti, Ph.D.[1], David Durantel, Ph.D.[1]
[1]INSERM U1111, CIRI, Lyon, France; [2]Hôpital de la Croix Rousse, Hospice Civil de Lyon, Lyon, France; [3]DKFZ, Heidelberg, Heidelberg, Germany; [4]INSERM U1032, Centre Léon Bérard (CLB), Lyon, France, Lyon, France; [5]TU Muenchen, Munich, Germany; [6]INSERM U1052, CRCL, Lyon, France

103. Effects of troponoids on mitochondrial function

Austin O'Dea, M.S.[1], Daniel Bradley, B.S.[1], Alaina Knier, B.S.[1], Bruce Rodgers, Ph.D.[2], Ryan Murelli, Ph.D.[3], John Tavis, Ph.D.[1]
[1]Saint Louis University, St. Louis, Missouri, United States of America; [2]Casterbridge pharmaceuticals, Woburn, Massachusetts, United States of America; [3]City University of New York, New York, New York, United States of America

105. General lipoperoxidators are not selective antiviral agents

Consuelo Correa-Sierra, M.D., Ph.D.[1], Luis Schang, D.V.M., Ph.D.[1]
[1]Cornell University, Ithaca, New York, United States of America

106. Chromatin dynamics and the transcriptional competence of HSV-1 genomes during lytic infections

Esteban Flores Cortes, B.S.[1], MiYao Hu, B.S.[2], Daniel Depledge, Ph.D.[3], Judith Breuer, M.D., Ph.D.[4], Luis Schang, D.V.M., Ph.D.[1]
[1]Cornell University, Ithaca, United States of America; [2]Cornell University and University of Alberta, Edmonton, Alberta, Canada; [3]New York University School of Medicine, New York, New York, United States of America; [4]University College London, London, United Kingdom of Great Britain and Northern Ireland

107. Evaluating the therapeutic potential of metformin against dengue

Nicholas Cheang, B.S.[1]
[1]*National University of Singapore, Singapore, Singapore*

108. G-quadruplex stabilising ligands like Braco-19, TMPyP4 elicit new strategies for viral drug targeting

Prativa Majee, M.S.[1], Amit Kumar, Ph.D.[2], Debasis Nayak, Ph.D.[2]
[1]*Phd Scholar, Indian Insititute of Technology, Indore, India, Indore, India;* [2]*Associate Professor, Indian Insititute of Technology, Indore, Indore, India*

109. Identification of novel dissociative inhibitors targeting the replication complex of dengue virus

Giulio Nannetti, Ph.D.[1], Beatrice Mercorelli, Ph.D.[2], Salvatore Ferla, Ph.D.[1], Marta Celegato, Ph.D.[2], Giorgio Palù, M.D.[2], Arianna Loregian, Ph.D.[2], Andrea Brancale, Ph.D.[1]
[1]*School of Pharmacy & Pharmaceutical Sciences, Cardiff, United Kingdom of Great Britain and Northern Ireland;* [2]*Department of Molecular Medicine, University of Padua, Padua, Italy*

110. Sulfonated Compounds Inhibit More Viruses Than Expected

Valeria Cagno, Ph.D.[1], Matteo Gasbarri, M.S.[2], Samuel Jones, Ph.D.[3], Francesco Stellacci, Ph.D.[2], Caroline Tapparel, Ph.D.[4]
[1]*University of Geneva, University Hospital of Lausanne, Geneva, Switzerland;* [2]*EPFL, Lausanne, Switzerland;* [3]*University of Manchester, Manchester, United Kingdom of Great Britain and Northern Ireland;* [4]*University of Geneva, Switzerland*

111. Synthesis of acyclic-phosphonate-diphosphate Prodrugs

Giuliano Kullik, M.S.[1], Dominique Schols, Ph.D.[2], Chris Meier, Ph.D.[1]
[1]*University of Hamburg, Hamburg, Germany;* [2]*KU Leuven, Leuven, Belgium*

113. Synthesis and Biological Evaluation of Flex-Acyclovir Analogues Against SARS-CoV-2

Joy Thames, B.S.[1], Consuelo Correa-Sierra, Ph.D.[2], Rodrigo Santos, Ph.D.[2], Apurv Rege, M.S.[1], Shuaishuai Liu, M.S.[1], Charles Bieberich, Ph.D.[1], Luis Schang, D.V.M., Ph.D.[2], Katherine Seley-Radtke, Ph.D.[1]
[1]*University of Maryland, Baltimore County, Baltimore, Maryland, United States of America;* [2]*Cornell University, College of Veterinary Medicine, Ithaca, New York, United States of America*

114. STAT2 signaling restricts viral dissemination but drives severe pneumonia in SARS-CoV-2 infected hamsters

Robbert Boudewijns, M.S.[1]
[1]*KU Leuven Department of Microbiology and Immunology, Rega Institute, Leuven, Belgium, Leuven, Belgium*

115. CRISPR genome-wide screening identifies host factors for SARS-CoV-2 and common cold coronavirus replication

Jim Baggen, Ph.D.[1], Leentje Persoons, M.S.[1], Sander Jansen, M.S.[1], Maarten Jacquemyn, M.S.[1], Els Vanstreels, Ph.D.[1], Dirk Jochmans, Ph.D.[1], Johan Neyts, Ph.D.[1], Kai Dallmeier, Ph.D.[1], Piet Maes, Ph.D.[2], Dirk Daelemans, Ph.D.[1]
[1]*KU Leuven, Laboratory of Virology and Chemotherapy, Rega Institute, Leuven, Belgium;* [2]*KU Leuven, Laboratory of Clinical and Epidemiological Virology, Rega Institute*

116. Polynuclear platinum complexes exhibit broad spectrum antiviral activity

Mary Zoepfl, B.S.[1]
[1]*Virginia Commonwealth University, Richmond, Virginia*

117. Viral Fitness of Herpes Simplex Virus 1 (HSV-1) Mutants Isolated From a Hematopoietic Stem Cell Transplant (HSCT) Recipient

Hanna Schalkwijk, M.S.[1], Sarah Gillemot, M.S.[1], Robert Snoeck, M.D., Ph.D.[1], Marijke Reynders, M.D., Ph.D.[2], Dominik Selleslag, M.D., Ph.D.[3], Graciela Andrei, Ph.D.[1]
[1]*Laboratory of Virology and Chemotherapy, Rega Institute, KU Leuven, Leuven, Vlaams-Brabant, Belgium;* [2]*Department of laboratory medicine, AZ Sint-Jan Brugge, Brugge, West-Vlaanderen, Belgium;* [3]*Department of internal medicine, AZ Sint-Jan Brugge, Brugge, West-Vlaanderen, Belgium*

118. Polyamine analog diethylnorspermidine restricts Coxsackievirus B3 and is overcome by 2A protease mutation

Bridget Hulsebosch, B.S.[1], Bryan Mounce, Ph.D.[1]
[1]*Stritch School of Medicine, Loyola University Chicago, Maywood, Illinois*

119. Therapeutic delivery of defective interfering particles protects hamsters from lethal Nipah virus disease

Stephen Welch, Ph.D.[1], Jessica Spengler, D.V.M., Ph.D.[1], Jessica Harmon, M.S.[1], JoAnn Coleman-McCray, B.S.[1], Florine Scholte, Ph.D.[1], Joel Montgomery, Ph.D.[1], Stuart Nichol, Ph.D.[1], Christina Spiropoulou, Ph.D.[1]
[1]*Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America*

120. Two host poly(A) polymerases PAPD5 and PAPD7 provide redundant but distinct mechanisms to protect hepatitis B virus RNA integrity and stability

Fei Liu, Ph.D.[1], Amy Lee, M.S.[2], Fang Guo, M.D., Ph.D.[2], Andrew Kondratowicz, Ph.D.[2], Holly Steuer, B.S.[1], Angela Miller, Ph.D.[2], Lauren Bailey, Ph.D.[2], Xiaohe Wang, M.D.[1], Shuai Chen, Ph.D.[1], Steven Kultgen, Ph.D.[1], Andrea Cuconati, Ph.D.[1], Andrew Cole, Ph.D.[1], Dimitar Gotchev, Ph.D.[1], Bruce Dorsey, Ph.D.[1], Rene Rijnbrand, Ph.D.[2], Angela Lam, Ph.D.[1], Michael Sofia, Ph.D.[1], Min Gao, Ph.D.[1]
[1]*Arbutus Biopharma, Warminster;* [2]*Was Arbutus employee at the time of data generation*

121. Nipamovir: synthesis and preclinical evaluation of an anti-HIV thiobenzamide prodrug

Marco Robello, Ph.D.[1], Herman Nikolayevskiy, Ph.D.[1], Michael Scerba, Ph.D.[1], Rogers Alberto Nahui Palomino, Ph.D.[2], Vincenzo Mercurio, Ph.D.[2], Tracy Hartman, M.S.[3], Robert Buckheit, Jr., Ph.D.[3], Leonid Margolis, Ph.D.[2], Daniel Appella, Ph.D.[1]
[1]*Synthetic Bioactive Molecules Section, LBC, NIDDK, NIH, Bethesda, Maryland, United States of America;*
[2]*Section on Intercellular Interactions, NICHD, NIH, Bethesda, Maryland, United States of America;*
[3]*ImQuest Biosciences, Frederick, Maryland, United States of America*

122. Design, Synthesis and Biological Evaluation of 2-(4-(phenylsulfonyl)piperazine-1-yl) pyrimidine analogues as Novel Inhibitors of Chikungunya Virus

Verena Battisti, M.S.[1], Julia Moesslacher, Ph.D.[2], Rana Abdelnabi, Ph.D.[3], Leen Delang, Ph.D.[3], Johan Neyts, Ph.D.[3], Ernst Urban, Ph.D.[1], Thierry Langer, Ph.D.[1]
[1]*University of Vienna, Department of Pharmaceutical Chemistry, Vienna, Austria;* [2]*CURA Marketing GmbH, Innsbruck, Austria;*
[3]*KU Leuven, Rega Institute for Medical Research, Leuven, Belgium*

123. Molnupiravir (EIDD-2801) inhibits SARS-CoV2 replication in Syrian hamsters model

Rana Abdelnabi, Ph.D.[1], Caroline S. Foo, Ph.D.[1], Suzanne J.F. Kaptein, Ph.D.[1], Xin Zhang, M.S.[1], Lana Langendries, M.S.[1], Laura Vangeel, Ph.D.[1], Valentijn Vergote, Ph.D.[1], Elisabeth Heylen, Ph.D.[1], Kai Dallmeier, Ph.D.[1], Arnab Chatterjee, Ph.D.[2], Steven De jonghe, Ph.D.[1], Birgit Weynand, Ph.D.[3], Johan Neyts, Ph.D.[1]

[1]Rega Institute KU Leuven, Leuven, Belgium; [2]Calibr at Scripps Research, La Jolla, CA, USA; [3]KU Leuven

124. Swellable Hydrogel Microneedles Backed by a Drug Reservoir Patch for Treatment and Prevention of the Flu

Marquicia Pierce, Ph.D.[1], Ian Bejster, B.S.[1], Aaron Chadderdon, M.S.[1], Cheryl Harteg, B.S.[1], Dawn Reyna, B.S.[1], Jonna Westover, Ph.D.[2], Bart Tarbet, Ph.D.[2], Kaley Hanrahan, M.S.[3], Ashely Brown, Ph.D.[3], George Drusano, Ph.D.[3], Lalit Vora, M.S.[4], Ryan Donnelly, Ph.D.[4], Elke Lipka, Ph.D.[1]

[1]TSRL, Inc., Ann Arbor, Michigan, United States of America; [2]Utah State University, Logan, Utah, United States of America; [4]University of Florida, United States of America; [4]Queen's University Belfast, United Kingdom of Great Britain and Northern Ireland

125. SARS-CoV-2 induce lytic reactivation of Kaposi's sarcoma-associated herpesvirus

Jungang Chen, Ph.D.[1], Lindsey Barrett, B.S.[1], Lu Dai, M.D.[1], Steven R. Post[1], **Zhiqiang Qin**[1]

[1]University of Arkansas for Medical Sciences

126. Consecutive Alternating Administration of Double Combinations and Drug Sensitivity of Coxsackievirus B3 Infection

WITHDRAWN

127. NPP-669: A Novel Broad-Spectrum Antiviral Therapeutic with Excellent Cellular Uptake, Antiviral Potency, Oral Bioavailability, Preclinical Efficacy, and a Promising Safety Margin

Elke Lipka, Ph.D.[1], Aaron Chadderdon, M.S.[1], Cheryl Harteg, B.S.[1], Dawn Reyna, B.S.[1], Eric Simon, Ph.D.[2], Matthew Doherty, Ph.D.[2], Kim Hutchings, Ph.D.[3], Xinmin Gan, B.S.[3], Andy White, Ph.D.[3], Caroll Hartline, B.S.[4], Emma Harden, B.S.[4], Kathy Keith, B.S.[4], Mark Prichard, Ph.D.[4], Scott James, M.D.[4], Rhonda Cardin, Ph.D. [5], David Bernstein, M.D.[6], Ann Tollefson, Ph.D.[7], William Wold, Ph.D.[7], Karoly Toth, D.V.M.[7]

[1]TSRL, Inc., Ann Arbor, Michigan, United States of America; [2]Depression Center, University of Michigan, Ann Arbor, Michigan, United States of America; [3]College of Pharmacy, University of Michigan, Ann Arbor, Michigan, United States of America; [4]Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama, United States of America; [5]School of Veterinary Medicine, Louisiana State University, Baton Rouge, Louisiana, United States of America; [6]Cincinnati Children's Hospital, University of Cincinnati, Cincinnati, Ohio, United States of America; [7]School of Medicine, Saint Louis University, St. Louis, Missouri, United States of America

128. Phase 1/2 Antiviral and Clinical Efficacy Primary Results With REGEN-COV (Casirivimab With Imdevimab), a Cocktail of Two Antibodies Against SARS-CoV-2 Virus, in the Outpatient Setting

Sumathi Sivapalasingam, M.D.[1], **Thomas Norton, M.D.**[1], Shazia Ali, Pharm.D.[1], Haitao Gao, Ph.D.[1], Rafia Bhore, Ph.D.[1], Andrea Hooper, Ph.D.[1], Jennifer Hamilton, Ph.D.[1], Bret Musser, Ph.D.[1], Yuhwen Soo, Ph.D.[1], Diana Rofail, Ph.D.[1], Joseph Im, B.S.[1], Christina Perry, M.B.A.[1], Cynthia Pan, B.Pharm.[1], Romana Hosain, M.D., MPH[1], Adnan Mahmood, M.D.[1], John Davis, Ph.D.[1], Kenneth Turner, Ph.D.[1], Alina Baum, Ph.D.[1], Christos Kyratsous, Ph.D.[1], Yunji Kim, Pharm.D.[1], Amanda Cook, B.S., Dip.Reg.Aff.[1], Wendy Kampman, M.D.[1], Ximena Graber, M.D.[2], Gerard Acloque, M.D.[3], Yessica Sachdeva, M.D.[4], Joseph Bocchini, M.D.[5], Anita Kohli, M.D.[4], Bari Kowal, M.S.[1], Thomas DiCioccio, Ph.D.[1], Neil Stahl, Ph.D.[1], Leah Lipsich, Ph.D.[1], Ned Braunstein, M.D.[1], Gary Herman, M.D.[1], George Yancopoulos, M.D., Ph.D.[1], David Weinreich, M.D.[1]

[1]Regeneron Pharmaceuticals, Inc.; [2]AGA Clinical Trials; [3]Universal Medical and Research Center, LLC; [4]Arizona Liver Health; [5]Willis-Knighton Physician Network

129. Fatty acid beta oxidation as a target for antiviral therapy against Junín virus

Cecilia Vazquez, M.S.[1], Cybele García, Ph.D.[1], Sandra Cordo, Ph.D.[1]

[1]IQUIBICEN (UBA-CONICET), Buenos Aires, Argentina

130. Discovery of Novel Pyrimidine Based Inhibitors of Respiratory Syncytial Virus Fusion Protein

James Good, Ph.D.[1], Matthew Barrett, Ph.D.[1], Alexandre Bedernjak, Ph.D.[1], Morgan Gilman, Ph.D.[2], John Ludes-Meyers, Ph.D.[2], Claire Scott, Ph.D.[1], Rebecca Dowey, B.S.[1], Elaine Thomas, Ph.D.[1], Jason McLellan, Ph.D.[2], Stuart Cockerill, Ph.D.[1]

[1]ReViral Ltd, Stevenage, Hertfordshire, United Kingdom of Great Britain and Northern Ireland; [2]Department of Molecular Biosciences, The University of Texas, Austin, Texas, United States of America

131. Introduction of a Cyano Group at the 2-Position of 3-Hydroxy-2-(phosphonomethoxy)propyl (HPMP) Nucleosides Elicits Potent Anti-HBV Activity

Shuai Tan, M.S.[1], Elisabetta Groaz, Ph.D.[1], Christophe Pannecouque, Ph.D.[2], Steven De Jonghe, Ph.D.[2], Piet Piet Herdewyn, Ph.D.[1]

[1]Medicinal Chemistry, Rega Institute for Medical Research, KU Leuven; [2]Laboratory of Virology and Chemotherapy, Rega Institute for Medical Research, KU Leuven

132. Structural Characterisation of Inactivated SARS-CoV-2 Particles for a Vaccine Preparation

L. Kozlovskaya, Ph.D.[1]; D. Bagrov, Ph.D[2]; G. Gluhov, Ph.D.[2]; M. Karlova, Ph.D.[2]; A. Moiseenko, Ph.D.[2] ; D. Litvinov, Ph.D.[2]; A. Shishova, M.S.[1]; A. Kovpak, M.S.[1]; Y. Ivin, Ph.D.[1]; A. Piniaeva, M.S.[1]; **D. Osolodkin, Ph.D.**[1]; K. Shaitan, Ph.D.[2]; O. Sokolova, Ph.D.[2]; M. Kirpichnikov, Ph.D.[2]; A. Egorov, Ph.D.[1]; A. Ishmukhametov, M.D., Ph.D.[1]

[1]Chumakov FSC R&D IBP RAS, Moscow, Russian Federation; [2]Department of Biology, Lomonosov Moscow State Universiy, Moscow, Russian Federation

133. Synthesis and antiviral evaluation of (1,4-disubstituted-1,2,3-triazol)-(E)-2-methyl-but-2-enyl nucleoside phosphonate prodrugs

Tuniyazi Abuduaini, Ph.D.[1]; Vincent Roy, Ph.D.[1]; Julien Marlet, Ph.D.[2]; Catherine Gaudy-Graffin, M.D., Ph.D.[2]; Denys Brand, Ph.D.[2]; Cecile Baronti, Ph.D.[3]; Franck Touret, Ph.D.[3]; Bruno Coutard, Ph.D.[3]; Tamara McBrayer, Ph.D.[4]; Raymond Schinazi, Ph.D.[4]; Luigi Agrofoglio, Ph.D.[1]

[1]ICOA UMR CNRS 7311 – Universite d'Orleans, Orleans, France; [2]Inserm U1259 – Universite de Tours, Tours, France; [3]Unité des Virus Emergents – Univ Aix-Marseille, Marseille, France; [4]Center for AIDS Research, Lab. Biochemical Pharmacology – Emory University, Atlanta, Georgia, United States of America

134. **Design, synthesis and biological evaluation of 2-substituted-6-[(4-substituted-1-piperidyl)methyl]-1H-benzimidazoles as inhibitors of ebola virus infection**

Maximes Bessieres, Ph.D.[1]; Elzbieta Plebanek, Ph.D.[1]; Payel Chatterjee, Ph.D.[2]; Punya Shrivastava-Ranjan, Ph.D.[2]; Mike Flint, Ph.D.[2] ; Christina Spiropoulou, Ph.D.[2]; Dawid Warszycki, Ph.D.[3]; **Vincent Roy, Ph.D.**[4]; Luigi Agrofoglio, Ph.D.[4]

[1]ICOA UMR CNRS 7311 – Université d'Orléans, Orléans, France; [2]Viral Special Pathogens Branch, CDC, Atlanta, Georgia, United States of America; [3]May Institute of Pharmacology, Polish Acazdemy of Sciences, Krakow, Poland; [4]ICOA UMR CNRS 7311, Orleans, France

135. **Novel Prodrugs as Inhibitors of SARS-Coronavirus-2**

Charles McKenna, Ph.D.[1]; Justin Overhulse, B.S.[1]; Nicholas Lentini, Ph.D.[1]; Boris Kashemirov, Ph.D.[1]; Ann Tollefson, Ph.D.[2]; Jacqueline Spencer, B.S.[2]; Karoly Toth, D.V.M.[2]; William Wold, Ph.D.[2]

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136. **The DHODH inhibitor PTC299 arrests SARS-CoV-2 replication and suppresses induction of inflammatory cytokines implicated in severe COVID-19 disease and is currently being evaluated in the FITE19 clinical trial in hospitalized patients**

Jason Graci, Ph.D.[1]; Marla Weetall, Ph.D.[1]; Joseph Colacino, Ph.D. [1]; Christopher Trotta, Ph.D.[1]; Liangxian; Cao, M.D., Ph.D.[1]; Nikolai Naryshkin, Ph.D.[1]; Lachlan Molony, Ph.D.[1]; Elizabeth Goodwin, Ph.D.[1]; Ellen Welch, Ph.D.[1]; Quintus Ngumah, Ph.D.[1]; Kylie O'Keefe, B.S.[1]; Mark Pykett, D.V.M., Ph.D.[1]; Allan Jacobson, Ph.D.[2]; Stuart Peltz. Ph.D.[1]

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15. **Arbovirus infectivity is significantly reduced by components of the bacterial cell wall**

Lana Langendries, M.S.[1], Rana Abdelnabi, Ph.D.[1], Sofie Jacobs, M.S.[1], Sam Verwimp, B.S.[1], Suzanne Kaptein, Ph.D.[1], Pieter Baatsen, Ph.D.[2], Lieve Van Mellaert, Ph.D.[1], Leen Delang, Ph.D.[1]

[1]Rega Institute for Medical Research, KU Leuven, Leuven, Belgium; [2]VIB-KU Leuven

26. **Inhibition of human norovirus replication in cell culture and zebrafish larvae by a novel class of protease inhibitors**

Jana Van Dycke, Ph.D.[1], Wanhao Dai, M.S.[2], Zoe Stylianidou, M.S.[1], Jian Li, M.S.[2], Arno Cuvry, M.S.[1], Bingqian Li, M.S.[2], Nanci Santos-Ferreira, M.S.[1], Lindsey Bervoets, B.S.[1], Jasper Rymenants, B.S.[1], Peter de Witte, Ph.D.[3], Hong Liu, Ph.D.[2], Johan Neyts, Ph.D.[1], Joana Rocha-Pereira, Ph.D.[1]

[1]KU Leuven, Rega Institute for Medical Research, Laboratory of Virology & Chemotherapy; [2]Chinese Academy of Sciences Shanghai Institute of Materia Medica, China Pharmaceutical University; [3]KU Leuven, Laboratory for Molecular Biodiscovery

65. **Metabolic Stabilization of a Novel Inhibitor of human Dihydroorotate Dehydrogenase (hDHODH) with Potent Broad Spectrum Antiviral Activity**

Nora Fohrmann, M.S.[1], Lisa Oestereich, Ph.D.[2], Katharina Pfaff, Ph.D.[1], Gilles Querat, Ph.D.[3], Chris Meier, Ph.D.[1]

[1]University of Hamburg, Hamburg, Germany; [2]Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany; [3]Aix-Marseille Université, Marseille, France

201. Two synthetic steroidal analogues with antiviral and anti inflammatory activities against the infection caused by Human Respiratory Syncytial Virus

Flavia Michelini, Ph.D.[1], Maximiliano Salinas, B.S.[1], Carlos Bueno, Ph.D.[1], Luciana Vázquez, B.S.[2], Laura Alché, Ph.D.[1]

[1]CONICET – Instituto de Química Biológica – Facultad de Ciencias Exactas y Naturales – UBA, Ciudad de Buenos Aires, Buenos Aires, Argentina; [2]Unidad Operativa Centro de Contención Biológica, Instituto DR. Carlos G. Malbrán, ANLIS, Ciudad de Buenos Aires, Buenos Aires, Argentina

202. *In Vitro* Antiviral Activity of Chloroquine, interferon Beta-1a, Lopinavir, Favipiravir and Remdesivir Against Seasonal and Pathogenic Coronaviruses

Brett Hurst, Ph.D.[1], Ashley Sheesley, B.S.[1], Rebecca Strong, B.S.[1], Kie-hoon Jung, Ph.D.[1], Ernest Tarbet, Ph.D.[1]

[1]Institute for Antiviral Research, Utah State University, Logan, Utah, United States of America

203. Recent African strains of Zika virus display higher transmissibility and fetal pathogenicity than Asian strains

Maïlis Darmuzey, M.S.[1], Fabien Aubry, Ph.D.[2], Sofie Jacobs, M.S.[1], Sebastian Lequime, Ph.D.[3], Leen Delang, Ph.D.[1], Albin Fontaine, Ph.D.[4], Natapong Jupatanakul, Ph.D.[2], Elliott Miot, Ph.D.[2], Stéphanie Dabo, Ph.D.[2], Caroline Manet, Ph.D.[5], Xavier Montagutelli, Ph.D.[5], Artem Baidaliuk, Ph.D.[6], Fabiana Gambaro, Ph.D.[6], Etienne Simon-Lorière, Ph.D.[6], Maxime Gilsoul, M.S.[7], Claudia Romero-Vivas, Ph.D.[8], Van-Mai Cao-Lormeau, Ph.D.[9], Richard Jarman, Ph.D.[10], Cheikh Diagne, Ph.D.[11], Oumar Faye, Ph.D.[11], Ousmane Faye, Ph.D.[11], Amadou Sall, Ph.D.[11], Johan Neyts, Ph.D.[1], Laurent Nguyen, Ph.D.[7], Suzanne Kaptein, Ph.D.[1], Louis Lambrechts, Ph.D.[2]

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204. The Role of N-linked Glycosylation in Dengue Virus (DENV) Fitness and Virulence

Donald Heng Rong Ting, B.S.[1]

[1]Department of Microbiology and Immunology, National University of Singapore

205. An efficient workflow to identify broad spectrum antiviral compounds active against SARS CoV-2 in culture and in vivo

Consuelo Correa-Sierra, M.D., Ph.D.[1], Jody Cameron, B.S.[1], Rodrigo Santos, Ph.D.[1], Seyedeh Hosseini, Ph.D.[2], Devon Schatz, B.S.[2], James Donnelly, B.S.[2], Frederick West, Ph.D.[2], Luis Schang, D.V.M., Ph.D.[1]

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206. Analyzing Infection by Multiple Flavivirus in Real-Time in a One-Well Multiplex Format Using Multi-Color High Content Imaging for the Purpose of Antiviral Screening

Li-Hsin Li, M.S.[1], Winston Chiu, M.S.[1], Thomas Vercruysse, Ph.D.[2], Hendrik Thibaut, Ph.D.[2], Pieter Leyssen, Ph.D.[1], Johan Neyts, Ph.D.[1], Suzanne Kaptein, Ph.D.[1], Kai Dallmeier, Ph.D.[1]

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207. Structure-based macrocyclization of substrate analog NS2B-NS3 protease inhibitors of Zika, West Nile and Dengue viruses

Jun Ping Quek, B.S.[1], Dahai Luo, Ph.D.[1]
[1]*Lee Kong Chian School of Medicine, NTU, Singapore*

209. Novel Carbocyclic-Substituted Hydantoin Derivatives with Broad Antiviral Activity

Efseveia Frakolaki, Ph.D.[1], Vasileios Siozos, B.S.[1], Giorgos Niotis, B.S.[1], Erofili Giannakopoulou, M.S.[2], Vasiliki Pardali, M.S.[2], Marc Windisch, Ph.D.[3], Ralf Bartenschlager, Ph.D.[4], Nicolas Papageorgiou, Ph.D.[5], Bruno Canard, Ph.D.[5], Grigoris Zoidis, Ph.D.[2], Niki Vassilaki, Ph.D.[1]
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210. Mitochondrial Stresses in Patients With Chronic Hepatitis B and Advanced Fibrosis

Dimitri Loureiro, Ph.D.[1], Abdellah Mansouri, Ph.D.[1], Stephanie Narguet, M.S.[1], Issam Tout, Ph.D.[1], Boyer Nathalie, M.D., Ph.D.[1], Dzamitika Simplice, Ph.D.[1], Morgane Roinard, M.S.[1], Patrick Marcellin, M.D., Ph.D.[1], Valerie Paradis, M.D., Ph.D.[1], Tarik Asselah, M.D., Ph.D.[1]
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211. Novel organic supramolecular compounds as broad-spectrum viral inhibitors with a virucidal mechanism

Matteo Gasbarri, M.S.[1], Valeria Cagno, Ph.D.[2], Caroline Tapparel, Ph.D.[2], Francesco Stellacci[1]
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212. Selective modulation of the MASP-2 serine protease: a potential broad-spectrum approach for present and future coronavirus infections.

Paige Mitchell, B.S.[1], Giulio Nannetti, Ph.D.[2], Meike Heurich, Ph.D.[2], Andrea Brancale, Ph.D.[2], Salvatore Ferla, Ph.D.[1], Marcella Bassetto, Ph.D.[1]
[1]*Swansea University;* [2]*Cardiff University*

213. Developing Glycan-Based Antiviral Prophylactics to Prevent Coronavirus Infection

Emmanuelle LeBlanc, M.S.[1], Youjin Kim, B.S.[1], Daniel Whalen, B.S.[2], Chantelle Capicciotti, Ph.D.[3], Che Colpitts, Ph.D.[1]
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214. In Depth Study of the Carbohydrate-Binding Agents HHA, GNA and UDA as Potent Inhibitors of Influenza A and B Virus Replication

Evelien Vanderlinden, Ph.D.[1], Nathalie Van Winkel, B.S.[1], Lieve Naesens, Ph.D.[1], Els Van Damme, Ph.D.[2], Leentje Persoons, M.S.[1], Dominique Schols, Ph.D.[1]
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215. In Vitro Selection of Herpes Simplex Virus 1 (HSV-1) Drug-resistance Under Combination Therapy

Hanna Schalkwijk, M.S.[1], Graciela Andrei, Ph.D.[1], Robert Snoeck, M.D., Ph.D.[1]
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216. Synergistic effects of combination treatment using anidulafungin and T1105 against the Zika virus

Yi-Jung Ho, Ph.D.[1], Jeng-Wei Lu, Ph.D.[2], Yen-Chen Chen, B.S.[1], Chin-Kai Huang, B.S.[1]
[1]School of Pharmacy, National Defense Medical Center, Taipei; [2]Department of Biological Sciences, National University of Singapore, Singapore, Singapore

217. Colloidal Systems for Antiviral Drugs Encapsulation for Neglected Diseases

Mayra Alejandra Castañeda Cataña, M.S.[1], Carlucci Josefina, Ph.D.[1], Martín Dodes Traian, Ph.D.[1], Oscar Pérez, Ph.D.[1], Claudia Sepúlveda, Ph.D.[1], Margarita Sánchez Domínguez, Ph.D.[2]
[1]Universidad de Buenos Aires, Buenos Aires, Buenos Aires, Argentina; [2]Centro de Investigación en Materiales Avanzados S.C. (CIMAV), Unidad Monterrey, Monterrey

218. HBV ribonuclease H inhibitors are less toxic in primary human hepatocytes than in hepatoma cell lines

Molly Woodson, M.S.[1], Daniel Bradley, B.S.[1], Qilan Li, Ph.D.[1], John Tavis, Ph.D.[1]
[1]Saint Louis University School of Medicine Department of Molecular Microbiology and Immunology, St Louis, Missouri

220. Influence of 4′-substitution on the activity of gemcitabine and its ProTide against VZV and SARS-CoV-2

Zihua Zheng, M.S.[1], Elisabetta Groaz, Ph.D.[1], Robert Snoeck, Ph.D.[1], Steven De Jonghe, Ph.D.[1], Piet Herdewijn, Ph.D.[1], Graciela Andrei, Ph.D.[1]
[1]Rega Institute for Medical Research, KU Leuven, Leuven, Belgium

221. Cidofovir and (S)-HPMPA serinamide and homoserinamide prodrugs potently inhibit DNA viruses in cell culture

Jinglei Lyu, Ph.D.[1], Caroll Hartline, B.S.[2], Kathy Keith, M.S.[2], Emma Harden, B.S.[2], Jessica Eagar, M.S.[2], **Samantha Riemann, B.S.**[1], Richard Whitley, M.D.[2], William Britt, M.D.[2], Mark Prichard, Ph.D.[2], Boris Kashemirov, Ph.D.[1], Charles McKenna, Ph.D.[1]
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222. Targeting Polyamines Inhibits Coronavirus Infection by Reducing Cellular Attachment and Entry

Mason Firpo, B.S.[1], Bryan Mounce, Ph.D.[1]
[1]Department of Microbiology and Immunology, Stritch School of Medicine, Loyola University Chicago

223. Targeting cyclophilins to disrupt innate immune evasion by positive-sense RNA viruses

John Mamatis, B.S.[1], Yilun Huang, B.S.[2], Shan Cen, Ph.D.[3], Che Colpitts, Ph.D.[1]
[1]Queen's University, Kingston, ON, Canada; [2]Queen's University, Chinese Academy of Medical Sciences, Kingston, ON, Canada; [3]Chinese Academy of Medical Sciences, Beijing, China

224. Double combinations against the in vitro replication of Coxsackievirus B1

WITHDRAWN

225. Oral USC-093, a novel homoserinamide prodrug of (S)-HPMPA shows equivalent efficacy to USC-087 in preventing mortality against lethal hAdV-C6 challenge in a permissive immunosuppressed Syrian hamster model

Karoly Toth, D.V.M.[1], Jinglei Lyu, Ph.D.[2], Jacqueline Spencer, B.S.[1], Ann Tollefson, Ph.D.[1], Baoling Ying, M.D.[1], Samantha Riemann, B.S.[2], Nathan Dupper, Ph.D.[2], Boris Kashemirov, Ph.D.[2], Mark Prichard, M.D., Ph.D.[3], William Wold, Ph.D.[1], Charles McKenna, Ph.D.[2]

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226. Development of guinea pig disease models of Lassa fever for genetically diverse virus strains and use in vaccine efficacy studies

Jessica Spengler, D.V.M., Ph.D.[1], Markus Kainulainen, Ph.D.[1], Stephen Welch, Ph.D.[1], JoAnn Coleman-McCray, B.S.[1], Jessica Harmon, M.S.[1], Jillian Condrey, D.V.M., Ph.D.[2], Florine Scholte, Ph.D.[1], Stuart Nichol, Ph.D.[1], Joel Montgomery, Ph.D.[1], Christina Spiropoulou, Ph.D.[1]

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227. Hantavirus infection is inhibited by griffithsin in cell culture

Punya Shrivastava-Ranjan, Ph.D.[1], Michael Lo, Ph.D.[1], Payel Chatterjee, M.S.[1], Mike Flint, Ph.D.[1], Stuart Nichol, Ph.D.[1], Joel Montgomery, Ph.D.[1], Barry O'Keefe, Ph.D.[2], Christina Spiropoulou, Ph.D.[1]

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228. Discovery of a nucleotide mono-phosphate prodrug inhibitor of dengue RNA-dependent RNA polymerase

Fumiaki Yokokawa, Ph.D.[1]

[1]Novartis Institute for Tropical Diseases, Emeryville, California, United States of America

229. Identification of Imidazo[1,2-*a*]pyrimidines as Novel Inhibitors Targeting Influenza A Virus Group 2 Hemagglutinins.

Irina Gaisina, Ph.D.[1], Ruikin Du, Ph.D.[2], Pin Zhang, Ph.D.[3], Norton Peet, Ph.D.[3], Lijun Rong, Ph.D.[1]

[1]University of Illinois at Chicago and Chicago BioSolutions, Inc., Chicago; [2]University of Illinois at Chicago, Chicago; [3]Chicago BioSolutions, Inc., Chicago

231. Discovery of the FDA-approved drugs bexarotene, cetilistat, diiodohydroxyquinoline, and abiraterone as potential COVID-19 treatments with a robust two-tier screening system

Shuofeng Yuan, Ph.D.[1]; Hin Chu, Ph.D.[1]; Jasper Fuk-Woo, Chan, M.D.[1]

[1]The University of Hong Kong

232. A Tunable Approach en route to C-Linked Analogues of Glycosamines

Tuniyazi Abuduaini, Ph.D.[1]; Vincent Roy, Ph.D.[1]; Luigi Agrofoglio, Ph.D.[1]; Olivier Martin, Ph.D.[1]; Cyril Nicolas, Ph.D.[1]

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233. Ribavirin-Imprinted Polymers as pulmonary Drug Delivery System

Mohamed Ayari, Ph.D.[1]; Patrick Favetta, Ph.D.[1]; Pierre Degardin, M.S.[1]; Virginie Vasseur, Ph.D.[2]; Mustapha Si Tahar, Ph.D.[2]; **Luigi Agrofoglio, Ph.D.**[1]

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234. Nelfinavir markedly improves lung pathology in SARS-CoV-2-infected Syrian hamsters despite lack of an antiviral effect

Caroline Foo, Ph.D.[1]; Rana Abdelnabi, Ph.D. [1]; Suzanne Kaptein, Ph.D. [1]; Xin Zhang, M.S. [1]; Sebastiaan ter Horst, M.S. [1]; Raf Mols, Ph.D. [1]; Leen Delang, Ph.D. [1]; Joana Rocha-Pereira, Ph.D. [1]; Lotte Coelmont, Ph.D. [1]; Pieter Leyssen, Ph.D. [1]; Kai Dallmeier, Ph.D. [1]; Valentijn Vergote, M.S. [1]; Elisabeth Heylen, Ph.D. [1]; Laura Vangeel, Ph.D. [1]; Arnab Chatterjee, Ph.D. [2]; Pieter Annaert, Ph.D. [1]; Patrick Augustijns, Ph.D. [1]; Steven De Jonghe, Ph.D. [1]; Dirk Jochmans, Ph.D. [1]; Birgit Weynand, Ph.D. [3]; Johan Neyts, Ph.D. [1]

[1]KU Leuven; [2]Calibr Scripps Research; [3]UZ Leuven

235. Potent inhibitors of SARS-CoV-2 3C-like protease derived from Niclosamide

Subodh Samrat, Ph.D.[1]; Jimin Xu, Ph.D.[2]; Zhong Li, M.S.[1]; Pei-Yong Shi, Ph.D.[2]; Jia Zhou, Ph.D.[2]; Hongmin Li, Ph.D.[1]

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1. Treating RSV infection

Louis Bont, M.D., Ph.D.[1]
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RSV is a single-stranded RNA virus causing wheezing illness (bronchiolitis) during infancy. Additionally, RSV infection is an important cause of morbidity and mortality in older adults. Currently, there is no safe and effective specific treatment for RSV infection. Supportive care, including invasive and non-invasive ventilation, is lifesaving for infants with severe RSV infection in developed countries. In developing countries, often without sufficient intensive care capacity, not all children with severe RSV infection can be saved. In this lecture, the considerable development of antivirals during the past decade using RSV human challenge models will be discussed. First, fusion inhibitors or RSV F-targeting drugs, often small molecules, have made progress in clinical development, though not always successfully. Second, nucleoside analogues have been developed as an alternative strategy, they may have higher threshold to resistance. Third, nanobodies against RSV F have been developed to treat infants with RSV bronchiolitis. For none of the antiviral strategies the clinical utility is fully clear. In line with the short time window of oseltamivir for the treatment of influenza, it is not yet clear until how long after onset of symptoms the outcome can be improved using antivirals. Undoubtedly, part of the symptoms is explained by the antiviral immune response. The possibility of immunomodulation under an umbrella of antivirals will be discussed. At the end of the lecture, the audience will understand state-of-the-art treatment as well as novel treatment strategies to improve the outcome patients with severe of RSV infection.

2. The Polymerase Complex of the Non-Segmented Negative Strand RNA Viruses: Differences in Initiation Mechanisms

Afzaal Shareef, B.S.[1], Tessa Cressey, Ph.D.[1], Victoria Kleiner, B.S.[1], Sarah Noton, Ph.D.[1], **Rachel Fearns, Ph.D.**[1]
[1]*Boston University School of Medicine*

The non-segmented negative strand RNA viruses (nsNSVs) encompass a number of significant human pathogens including respiratory syncytial virus (RSV), parainfluenza viruses, rabies and Ebola viruses, amongst others. These viruses possess an RNA dependent RNA polymerase that is capable of transcribing and replicating the viral genome. The viral polymerase is a remarkable protein capable of RNA polymerization, mRNA capping and methylation. We are interested in identifying similarities and differences in polymerases across the nsNSVs to better understand their potential as targets for broad spectrum antivirals. Regarding transcription and genome replication initiation, we have previously shown that the RSV polymerase initiates RNA synthesis from two sites on its promoter: position 1U to begin RNA replication, and position 3C to begin transcription. Initiation from 3C is highly dominant compared to initiation at 1U. Here we show that in a biochemical assay, the human parainfluenza virus type 3 (HPIV-3) polymerase could only initiate RNA synthesis at position 1U of its own promoter, indicating a different transcription initiation strategy from RSV. Although the HPIV-3 polymerase could initiate at positions 1U and 3C on an RSV promoter sequence, initiation at 1U was significantly more efficient than in the case of the RSV polymerase. We also identified amino acid residues in the RSV initiation complex that differentially affected initiation at the 1U and 3C sites. Together, these findings reveal that the RSV and HPIV-3 polymerases differ in features that control RNA synthesis initiation. These findings will be discussed in relation to recently-described nsNSV polymerase structures.

3. Now that we have the world's attention: Influenza!

Ron Fouchier, Ph.D.[1]
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The Covid-19 pandemic has reminded us once again that there is a continuous threat of emerging respiratory viruses in humans. Despite clear warning signs in 2003 (SARS) and since 2012 (MERS), the world was still poorly prepared for SARS-CoV-2. We are equally poorly prepared for members of other RNA virus families, despite the repeated warning signals from – for example – henipavirus zoonoses. Outbreaks of influenza in animals are detected frequently around the globe, in particular in poultry, pigs, horses, dogs, and marine mammals. Four influenza pandemics in the last century alone were caused by such animal influenza viruses and we have seen thousands of zoonotic influenza virus infections in the last decades. But are we prepared for the next pandemic? Probably not. For pandemic preparedness, it is crucial to understand which of all the viruses in the animal kingdom represent potential pandemic threats and why. Our next level of pandemic preparedness must clearly be based on thorough, evidence-based risk assessments and predesigned flexible countermeasures. This requires a profound understanding of what is out there and relentless pandemic preparation efforts using the most innovative technologies available. I will present some of our own ongoing research on influenza to identify high-risk viruses among a diverse virus family and to design broadly active vaccine candidates for these viruses. I will discuss key topics for a forward-looking pandemic preparedness research agenda, including basic research, enhanced surveillance and reporting, broad-acting therapeutics, broad-acting vaccines and non-pharmaceutical interventions.

4. The flavonoid cyanidin shows antiviral and immunomodulatory properties against RSV, in vitro and in vivo

Carlos Bueno, Ph.D.[1], Benedetti Martina, B.S.[2], Luciana Vázquez, B.S.[3], María Virginia Gentilini, Ph.D.[4], Mercedes Soledad Nabaes Jodar, B.S.[5], Mariana Viegas, Ph.D.[5], Laura Alché, Ph.D.[6]
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Respiratory syncytial virus (RSV) has the ability to modulate cytokine and chemokine signaling networks, such as NF–κB and AP-1 signaling pathways, interfere with immune cell function and antibody response. Consequently, the modulation of the immune response induced by the virus represents a potential therapeutic strategy. Cyanidin, a key flavonoid that is present in red berries and other fruits, attenuates the development of several diseases through its anti-inflammatory effects. Regarding the molecular basis of cyanidin action, it inhibits signaling by the proinflammatory cytokine IL-17A, and, besides, it modulates NF-κB and AP-1 activation in different cell types and conditions. Importantly, these signaling pathways are involved in RSV-induced lung disease. Furthermore, plant extracts which contain cyanidin have antiviral activity against numerous viruses.

In this study, we demonstrate that cyanidin has virucidal and antiviral activities against RSV line 19 and A2 strains in HEp-2 and A549 cells, as well as NF-ŒB and cytokine modulating activities in RSV infected epithelial cells (HEp-2 and A549) and macrophages (J774A.1 cells), *in vitro*. Besides, in a murine model of pulmonary RSV infection, cyanidin treatment improves the course of acute disease, evidenced by decreased weight loss, reduced RSV lung titers, and attenuated airway inflammation.

Thus, our data demonstrate that cyanidin restrains RSV disease through antiviral and immunomodulatory effect. Consequently, cyanidin represents a promising therapeutic alternative against RSV infection, and may inform the development of novel therapeutic targets to control RSV pathogenesis.

6. Antagonism by a Baloxavir and Oseltamivir Drug Combination Against Baloxavir-Resistant, but Not Against Oseltamivir-Resistant Influenza A Virus Infections in Mice

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Influenza virus drug resistance remains a problem worldwide and combination drug treatment may help decrease the emergence of these drug resistant strains. A baloxavir marboxil (baloxavir)-resistant influenza A/CA/04/2009 (H1N1pdm) virus was generated in the presence of baloxavir using MDCK cells. Baloxavir, an inhibitor of influenza cap-dependent endonuclease, and oseltamivir, an influenza neuraminidase inhibitor, were evaluated alone and in combination against baloxavir-resistant pandemic influenza A/California/04/2009 (H1N1) and oseltamivir-resistant highly pathogenic avian influenza (HPAI) A/Taiwan/1/2017 (H7N9) virus infections in mice. Infected mice were treated twice daily for 5 days starting 4 hours after virus challenge. Monotherapy with oseltamivir provided 100%, 90%, and 90% protection against lethal baloxavir-resistant infection following administration of 30, 10, and 3 mg/kg/day, respectively. Baloxavir monotherapy was limited to 10% protection for the 30 and 300 mg/kg/day doses. Combination therapy decreased the protection observed by oseltamivir monotherapy in 8 out of 12 combinations tested against the baloxavir-resistant virus infection. Three-dimensional analysis of drug interactions using the MacSynergy method indicates strong antagonism for these drug combinations when used to treat a baloxavir-resistant virus infection. The reason for antagonistic effects of baloxavir on oseltamivir is not clear, as the mechanism of action for both drugs are very different. However, these results demonstrate that treatment of baloxavir-resistant influenza A/CA/04/2009 (H1N1pdm) virus with a combination of baloxavir and oseltamivir was not protective in mice. In contrast, combination therapy against oseltamivir-resistant influenza A/Taiwan/1/2017 (H7N9) was protective when compared to oseltamivir monotherapy. *[Supported by Contract HHSN272201700041I from the Respiratory Diseases Branch, DMID, NIAID, NIH]*

7. A single-dose live-attenuated YF17D-vectored SARS-CoV-2 vaccine candidate

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The explosively expanding COVID-19 pandemic urges the development of safe, efficacious and fast-acting vaccines. Several vaccine platforms are leveraged for a rapid emergency response[1]. We describe the discovery of a live virus-vectored SARS-CoV-2 vaccine candidate using the yellow fever 17D (YF17D) vaccine as vector to express a non-cleavable prefusion form of the SARS-CoV-2 Spike antigen. We assess vaccine safety, immunogenicity and efficacy in

several animal models. Vaccine candidate YF-S0 has an outstanding safety profile and induces high levels of SARS-CoV-2 neutralizing antibodies in hamsters, mice and cynomolgus macaques and concomitantly a protective immunity against YFV. Humoral immunity is complemented by a favourable Th1 cell-mediated immune response as profiled in mice. In a stringent hamster model[2] as well as in non-human primates, YF-S0 prevents infection with SARS-CoV-2. Moreover, in hamsters, a single dose confers protection from lung disease in most vaccinated animals within 10 days. Taken together, the quality of immune responses triggered and the rapid kinetics by which protective immunity can be mounted already after a single dose warrant further development this potent SARS-CoV-2 vaccine candidate.

10. Emerging deadly viruses and their glycoproteins – From infection to vaccines and antivirals

Hector Aguilar-Carreno, Ph.D.[1]

[1]*Cornell University, Ithaca, New York, United States of America*

The current COVID-19 pandemic is a perfect example of why we should focus our research on emerging viruses that can cause future pandemics. The Aguilar laboratory has been focused on studying such viruses for the last ~20 years. His talk will discuss his studies on viruses studied at biosafety levels 3 and 4, such as Nipah, Hendra, Ebola, Influenza, and SARS-CoV-2, which originate in wild-life, primarily in bats. He will discuss how these viruses use their glycoproteins to enter and infect cells and assemble new virions. He will also discuss how this knowledge can be used to create vaccines and discover therapeutic drugs against these viruses. His multidisciplinary research program combines novel Engineering technologies with classical and molecular virology, as well as animal studies.

11. Remdesivir treatment for emerging virus infections

Emmie de Wit, Ph.D.[1]

[1]*NIAID, NIH*

The COVID-19 pandemic has once again underlined the need for effective, broad-acting antivirals. Remdesivir (GS-5734) is a nucleotide analog prodrug with broad-spectrum antiviral activity that was shown to inhibit filovirus, coronavirus and paramyxovirus replication in vitro. Here, I will provide an overview of preclinical testing in nonhuman primates to show the antiviral efficacy of remdesivir against Nipah virus, MERS-CoV, and SARS-CoV-2.

12. The ABCs of Rhinovirus Infections and Asthma

James Gern, M.D.[1]

[1]*University of Wisconsin-Madison*

Rhinovirus infections are closely related to the development of asthma and wheezing illnesses in all age groups. In young children, wheezing illnesses are nearly always caused by respiratory viruses, and rhinoviruses are the most common etiology in children over age one. These illnesses are associated with an increased risk for developing childhood asthma. For children with asthma, rhinovirus infections remain important triggers for acute wheezing episodes known as asthma exacerbations. Risk factors for more severe illnesses with rhinoviruses have been identified and are related to personal factors, environmental exposures and viral characteristics. The rhinovirus-C species (RV-C) is closely associated with wheezing illnesses in young children. Individual risk factors for RV-C infections include polymorphisms in the viral receptor, CDHR3. Further, children who develop early signs of allergic inflammation are more likely to have recurrent wheezing illnesses with rhinoviruses. Environmental exposures that increase the risk for more severe illnesses include overgrowth of bacterial pathogens in the airways following acute viral infection. The combination of viral infection and bacterial pathogen overgrowth increases the risk for more severe illness and exacerbation. The large number of viral types along with species-specific differences in viral biology have hampered efforts to develop antiviral medications or vaccines. More recently, new technologies have renewed hope for the development of vaccines to induce cross-neutralizing antibodies or multiplexed vaccines to induce broad-based responses. Practical and effective treatments to prevent more severe rhinovirus infections could also reduce the subsequent development of childhood asthma.

13. Roles of PNKP and CDK1 in Zika virus replication and pathogenesis

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The molecular mechanism of Zika virus (ZIKV)-induced congenital microcephaly, including direct cytotoxicity to neural stem and cells (NSC), placental insufficiency, and immune responses, remain largely unknown. Embryonic neuronal stem cells (NSCs) divide rapidly, resulting in increased sensitivity to DNA lesions and higher dependence on DNA damage repair. Polynucleotide 5′-kinase 3′-phosphatase (PNKP) is a critical DNA damage repair enzyme, restoring the 3′-OH and 5′-P DNA termini at DNA breaks. PNKP mutations produce (rare) recessive syndromes characterized by congenital microcephaly with seizures (MCSZ).

Using iPSC-derived human NSCs (hNSC) we found PNKP relocalized from the nucleus to the cytoplasm, together with ZIKV NS1. The PNKP inhibitor A12B4C3 inhibited ZIKV replication. ZIKV also induced gross morphological nuclear abnormalities, consistent with mitotic catastrophe (MC), and accumulation of DNA damage. MC results from entering mitosis in the presence of DNA damage or unfinished genome replication. ZIKV-induced MC and viral replication were suppressed by the CDK1 inhibitor roscovitine, even at late times of infection. Roscovitine inhibited the formation of ZIKV replication compartments (RCs), suggesting that CDK1 plays a key role in RCs morphogenesis. ZIKV also induced cytoplasmic accumulation of active CDK1/CycA, which we propose triggers the membrane rearrangements to assemble the RCs. DNA damage normally activates the checkpoints that prevent the activation of CDK1, blocking mitosis until DNA is repaired whereas ZIKV induces abnormal CDK1 activity.

ZIKV-infected hNSCs undergo unscheduled CDK1 activation and mitotic catastrophe and ZIKV replication and MC induction are inhibited by existing inhibitors of PNKP or CDK1.

14. Plant Lectin Urtica Dioica Agglutinins (UDA) is a Potential Inhibitor Against Rabies Virus in a Muscle Model

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[3]*Department of Development and Regeneration, KU Leuven;* [4]*Faculty of Bioscience Engineering, Ghent University, Belgium*

Rabies virus (RABV) infection causes fatal encephalitis and paralysis in humans and animals. The current strategy of post-exposure prophylaxis (PEP) treatment, a combination of vaccines and anti-rabies immunoglobulins, provides effective protection, however, the high cost of rabies disease treatment becomes a large economic burden worldwide. Furthermore, when patients develop clinical symptoms the mortality is nearly 100%, as no antiviral strategy is available to cure for the RABV disease.

From a screening of a lectins library, we discovered an N-acetyl-D-glucosamine (GlcNAc)-specific agglutinin, Urtica Dioica Agglutinins (UDA), as a potential antiviral against RABV with EC50 at 8.2 μg/mL and CC50 at 57 μg/ml in vitro. A time-of-drug-addition assay indicated that UDA inhibits RABV infection via blocking virus entry upon binding with the target cells. Furthermore, UDA can also inhibit RABV infection in a novel muscle model, which was established based on the swine skeletal muscles.

Taken together, this study demonstrates that UDA inhibits RABV infection in vitro and in a muscle model, suggesting UDA as a potential therapeutic agent for rabies and providing novel ideas about antiviral drug discovery.

15. Arbovirus infectivity is significantly reduced by components of the bacterial cell wall

Lana Langendries, M.S.[1], Rana Abdelnabi, Ph.D.[1], Sofie Jacobs, M.S.[1], Sam Verwimp, B.S.[1], Suzanne Kaptein, Ph.D.[1], Pieter Baatsen, Ph.D.[2], Lieve Van Mellaert, Ph.D.[1], Leen Delang, Ph.D.[1]
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Little information is currently available on the impact of the host microbiome on arboviruses, i.e. viruses transmitted through bites of arthropods such as mosquitoes. In contrast, interactions of enteric viruses with gastrointestinal microbiota have been documented extensively. The first site of arbovirus infection is the mosquito bite site at the skin, which is colonized by a complex microbial community.

We demonstrated that incubation of arboviruses with bacterial cell wall components, including lipopolysaccharides (LPS) of Gram-negative bacteria, and lipoteichoic acids and peptidoglycans of Gram-positive bacteria, significantly reduced arbovirus infectivity *in vitro*. This inhibitory effect was observed for arboviruses of different families [chikungunya virus, Mayaro virus, Zika virus] and in different cell types, showing that this is a broad phenomenon. Interestingly, LPS from different bacterial species showed major differences in inhibition potency, ranging from no inhibition (e.g. LPS *E. coli*) to complete inhibition (e.g. LPS *K. pneumoniae*). A modest inhibitory effect was observed following incubation with heat-inactivated bacteria, including skin bacteria. On the other hand, pre-incubation of cells with LPS did not reduce arbovirus infectivity. A virucidal effect of LPS on virus particles was confirmed by electron microscopy, suggesting that the main inhibitory mechanism is due to a direct effect on the virus particles.

Together, our results indicate that certain bacteria decrease the infectivity of arboviruses. *In vivo* experiments are currently ongoing and will contribute to a better understanding of the early stages of arbovirus infection in the skin, which may enable the search for new strategies to fight arbovirus infections.

20. Defining Innovation in the Quest for Treatment, Prevention and Cure of Viral Diseases

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In the last 30 years, our understanding of viruses and viral pathogenesis has advanced exponentially. This is due in great part to new sequencing technologies and tissue culture methods that have allowed us to dissect the viral lifecycle, revealing novel targets for therapeutic intervention. These advances in technology and the insights they revealed have led to a remarkable ability to prevent, to treat and even to cure chronic viral diseases. The drug products that have made this possible are the result of intense academic, governmental and pharmaceutical company efforts and are true examples of "Innovation". In this presentation, I will attempt to define innovation and exemplify many of the "innovative" steps involved in the discovery, optimization and evolution of selected drug products for the treatment of HIV, HCV and coronavirus.

21. Antivirals and Preparedness for Pandemics: What We Have and What We Need

Tomas Cihlar, Ph.D.[1]
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Over the past several decades we have experienced many devastating viral outbreaks that involved emerging viruses such as SARS and MERS coronaviruses, Zika, Nipah or Ebola. Despite large number of successfully developed antivirals, the availability of effective drugs against emerging viruses is still limited. In addition to behavioral measures, quick diagnostics, robust contact tracing, and highly effective vaccines, the clinically tested antivirals to both prevent viral transmission and treat symptomatic disease are among the most critical components of any successful outbreak response. The current COVID-19 global pandemic with its unprecedented global impact triggered intense search aimed at the identification of new coronavirus antivirals. While extensive efforts have been focused on screening libraries of existing drugs for anti-SARS-CoV-2 activity and potential quick repurposing against COVID-19, the fastest progression through clinical trials has been made with antivirals that had coronavirus activity and prior clinical experience already established. Ideally, clinical stage drugs against viral pathogens with high outbreak potential should be available and ready for rapid deployment if needed. To achieve such degree of preparedness, extensive preemptive efforts focused on the discovery and development of effective antivirals against prioritized virus families with high pandemic risk need to be planned and initiated well ahead of actual outbreaks. This approach requires close partnerships and coordination across government, academic, non-profit as well as private sectors supported by appropriate funding, infrastructure and defined regulatory path to enable full scale drug discovery and development process.

22. Scientific Basis for the Rapid Development of Highly Effective RNA-Based COVID-19 Vaccines

Philip Dormitzer, M.D., Ph.D.[1]
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Less than a year after SARS-CoV-2 was identified as the COVID-19 causative agent and the virus' sequence was posted on GISAID, the Pfizer-BioNTech mRNA vaccine, BNT162b2, was shown to be ~95% effective against COVID-19 and was authorized for emergency use in adults 16 years of age and older. This rapid and effective vaccine response built on many years of scientific discovery and industrial application. In 2008, the ability of nucleoside modified RNA to evade innate immune responses associated with reactogenicity and host cell shutdown and to increase in vivo expression of an encoded protein was reported. In the aftermath of the 2009 H1N1 influenza pandemic, the need for a synthetic path to develop nucleic acid-based vaccines rapidly became apparent. Elements of such a system were deployed in response to the 2013 H7N9 pre-pandemic influenza outbreak in Shanghai. The ability of structure-based design to optimize the conformation of viral fusion glycoproteins for eliciting neutralizing antibodies was piloted with respiratory syncytial virus (RSV) in 2013 and applied to the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2017. The innovative clinical trial design implemented in a very large first in human trial of a prefusion F-based RSV vaccine, a study that tested multiple hypotheses in parallel, was the precursor to the phase 1/2/3 COVID-19 vaccine trial design that supported the authorization of BNT162b2. As we now counter the emergence of SARS-CoV-2 variants, vaccine approaches developed to prepare for the possibility of a highly pathogenic H5N1 avian origin influenza pandemic are providing a roadmap.

23. SARS-CoV-2 Biology and Countermeasure Development

Pei-Yong Shi, Ph.D.[1]
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I will present the development of reverse genetic systems for SARS-CoV-2, particularly our newly developed infection system that can potentially be performed at biosafety level-2 (BSL2). I will then present on how these systems have been used for COVID-19 diagnosis, drug discovery, and vaccine development, as well as for studying the new viral variants.

24. EIDD-2749, a Broadly Active Ribonucleoside Analog that is Highly Efficacious in Animal Models of Arenaviral Disease

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Infection by pathogenic New World arenaviruses (NWAs) can cause often-fatal viral hemorrhagic fever. These viruses are classified as priority pathogens and pose a significant public health risk in the absence of licensed countermeasures. Here, we report on a novel, broadly active ribonucleoside analog, EIDD-2749, discovered at the EIDD with potent antiviral activity against multiple arenaviruses, including Junin virus (JUNV), the etiologic agent of Argentine hemorrhagic fever. In cell culture-based virus yield reduction assays, EIDD-2749 had nanomolar range potency against NWAs with selectivity indices (SI_{90}) exceeding 1000 for Tacaribe virus (TCRV) and JUNV. EIDD-2749 is orally available with dose-dependent pharmacokinetics and broad distribution into organs, where it is rapidly converted into its active 5′-triphosphate supporting once-daily dosing. In a lethal model of TCRV-challenged mice, EIDD-2749 treatments provided complete protection against disease and mortality even when initiating therapy one week after challenge with doses as low as 0.5 mg/kg/day. In advanced studies in the guinea pig model of JUNV infection, prophylactic dosing regimens of 10, 3 or 1 mg/kg/day, beginning one hour before JUNV challenge, all resulted in undetectable viremia and no signs of disease. Remarkably, therapeutic dosing of 10 mg/kg/day initiated one week after JUNV challenge completely protected guinea pigs from lethal disease, and 71% of animals responded to therapy started 11 days after infection, well beyond the onset of clinical disease. Collectively, the data support the continued development of EIDD-2749 for the treatment of severe arenaviral infections. *Supported by the NIH (HHSN272201700041I, HHSN272201100019I and HHSN272201500008C) and DTRA (HDTRA1-15-C-0075)*

25. Crystal Structure of Alphavirus nsP4 RNA Polymerase

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Many alphaviruses such as Chikungunya virus (CHIKV) and Ross River virus (RRV) are transmitted to humans through mosquitoes and cause human infection and diseases. They are positive-sense RNA viruses. The replication process of alphavirus is mediated by four viral nonstructural proteins (nsPs 1-4). Nonstructural protein 4 (nsP4) possesses RNA dependent RNA polymerase (RdRp) activity that is essential for viral RNA replication and transcription. The structure and function of the alphavirus nsP4 have not been extensively studied. Here, we report the crystal structure of the first alphavirus nsP4 polymerase. Overall, the nsP4 adopted a typical right-hand shape common to many viral RdRps. We have also performed structure-based mutagenesis, RNA polymerase activity assay, and virology experiments to further understand the structure and function of the nsP4. Our work provides valuable knowledge about alphavirus replication and assists antiviral development targeting the viral RNA polymerase.

26. Inhibition of human norovirus replication in cell culture and zebrafish larvae by a novel class of protease inhibitors

Jana Van Dycke, Ph.D.[1], Wanhao Dai, M.S.[2], Zoe Stylianidou, M.S.[1], Jian Li, M.S.[2], Arno Cuvry, M.S.[1], Bingqian Li, M.S.[2], Nanci Santos-Ferreira, M.S.[1], Lindsey Bervoets, B.S.[1], Jasper Rymenants, B.S.[1], Peter de Witte, Ph.D.[3], Hong Liu, Ph.D.[2], Johan Neyts, Ph.D.[1], Joana Rocha-Pereira, Ph.D.[1]
[1]KU Leuven, Rega Institute for Medical Research, Laboratory of Virology & Chemotherapy; [2]Chinese Academy of Sciences Shanghai Institute of Materia Medica, China Pharmaceutical University; [3]KU Leuven, Laboratory for Molecular Biodiscovery

Human noroviruses (HuNoVs) are the most common cause of viral gastroenteritis resulting annually in ~219,000 deaths and a societal cost of ~$60 billion. There are no antivirals or vaccines available. We showed previously that rupintrivir inhibits norovirus replication, highlighting the norovirus protease as an attractive antiviral target. A series of related peptidomimetic aldehydes were synthetised. The early analogue, DC40_1806, inhibited murine norovirus replication (EC_{50}:0.71±0.24 μM) and the HuNoV GI.1 replicon (EC_{50}:1.21±0.58 μM) *in vitro*, without adverse effects on the host cells. Moreover, DC40_1806 cleared the HuNoV GI.1 replicon from the host cells after merely two passages of 3 days each (10 μM). After 3 months of selective pressure, a DC40_1806-resistant GI.1 replicon variant was generated, conferring a low yield of resistance against both DC40_1806 and rupintrivir. The resistant variant carries a mutation (I111V) in a conserved region of the viral protease. The direct activity of DC40_1806 on the GI, GII and GV protease was confirmed with a cell-based FRET-sensor approach. After further modifications, DC40_2267 was identified to be ~100-fold more potent in cell culture. The antiviral effect of both derivatives is currently being evaluated against HuNoV GII.4 using human intestinal enteroids. Moreover, DC40_2267 could inhibit HuNoV GII.4 replication in infected zebrafish larvae with a 0.6 log_{10} reduction in viral RNA, after a single treatment by injection in the pericardial cavity. Molecular docking indicated that the aldehyde group binds with the Cys139 in the HuNoV 3CL protease by a covalent linkage. Finally, these compounds also exhibited good PK properties in mice.

30. A perspective on viral vaccine immunity and the issue of disease enhancement

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Questions about possible immune enhancement of viral infections by vaccines and the mechanisms by which enhancement might occur are pertinent for the development of any vaccine, including those for SARS-CoV2. These questions arise because some mechanisms of humoral and cellular immunity that protect against viruses have a theoretical potential to enhance illness when an individual with pre-existing immunity encounters the pathogen. Antibody-dependent enhancement of disease and cellular immunopathology have been described as possible mechanisms. Nevertheless, clinical evidence of enhancement has been very rare despite the long history of vaccines and passive antibodies. Two instances are severe dengue associated with cross-reactive antibodies against another serotype and severe respiratory disease after formalin-inactivated RSV and measles vaccines in the 1960s. As expected from their protective functions, the clinical risks of antibody or T cell enhancement in people cannot predicted from in vitro systems, which show antibody-mediated uptake by many viruses not linked to ADE of disease and triggering of T cell inflammatory responses, or from animal models, where species differences limit infection by human viruses and consequences that mimic human disease. Animal models can reveal protective mechanisms, but models of immune enhancement depend on observations of such events in people and has been difficult to achieve even then. Most importantly, a severe infection and enhanced disease due to pre-existing immunity cannot be differentiated by clinical signs or biomarkers. These considerations underscore requirement for rigorous clinical trials of antiviral immune interventions to compare disease severity in placebo and treated groups and post-license surveillance.

31. Antibody responses to the SARS-CoV-2 spike protein

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32. Janssen's Effort in the Development of an Ad26 Based COVID-19 Vaccine

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In response to the COVID-19 pandemic, multiple vaccine candidates are being developed. Janssen is developing an Ad26-vector based COVID-19 vaccine candidate. The lead candidate Ad26.COV2.S, encoding a stabilized SARS-CoV-2 Spike (S) protein, was selected based on its high S protein expression, manufacturability, immunogenicity (binding and neutralizing antibodies, Th1 skewed cellular immunity) in mice, rabbits, hamsters and non-human primates (NHP) and on its ability to elicit protective immunity in SARS-CoV-2 pre-clinical challenge models in hamsters and NHP. These data lead to the start of a phase 1/2a first-in-human clinical trial on July 22, 2020, to assess safety, tolerability, and humoral and cellular immunogenicity of Ad26.COV2.S in healthy adults (age 18-55) and adults >65 years of age. Interim analysis after a single vaccination showed a favorable safety profile and humoral immune responses in >90% of participants by day 29, increasing to 100% by day 56, with further increasing neutralizing titers that were maintained until at least day 85, giving a first indication of durability of immune responses. Based on the overall safety and immunogenicity profile, two currently ongoing phase 3 clinical trials test the protective efficacy of a single- and a two-dose regimen of our Ad26.COV2.S vaccine candidate. First data on potential efficacy are expected by end of January 2021.

33. Overview of Moderna COVID-19 Vaccine: Safety, Immunogenicity and Efficacy

Tal Zaks, M.D., Ph.D.[1]

[1]*Moderna, Boston, Massachusetts, United States of America*

Moderna has developed an investigational mRNA vaccine to prevent COVID-19. In phase 1-2 trials, the vaccine induced neutralizing antibody in 100% of subjects after dose 2. GMTs (at a dose of 100μg or higher) were comparable to a pool of convalescent sera. In a large-scale, double-blind, placebo-controlled phase 3 trial involving 30,420 adults randomized to 100 μg vaccine or placebo, local and systemic reactions were transient. Serious adverse events occurred at a similar rate in vaccine and placebo recipients and were rare. The vaccine was 94.1% efficacious in the prevention of symptomatic COVID-19 (185 confirmed cases in placebo recipients, 11 in vaccine recipients) and 100% efficacious in the prevention of severe disease (30 cases in placebo recipients, 0 in vaccine recipients). Secondary analyses showed that the efficacy of the vaccine was 86.4% in persons 65 and older and 90.9% in persons with comorbidities.

The vaccine was authorized under an Emergency Use Authorization in the US and conditionally authorized in several other countries. It is currently being used to vaccinate adults to help prevent the significant morbidity and mortality associated with COVID-19, while further evaluation of the safety and efficacy of the vaccine continues.

The recent emergence of variants of concern (e.g., B.1.351) which may require higher titers for neutralization than those elicited by prior strain vaccines or infections, has prompted Moderna to start the evaluation of a strain-matched vaccine.

40. My Career-long Fascination with Antiviral Therapeutics

Craig Cameron, Ph.D.[1]

[1]*University of North Carolina School of Medicine, Chapel Hill, North Carolina, United States of America*

I entered graduate school at the beginning of the race for development of therapeutics to treat HIV. Since that time, I have contributed in one small way or another to the discovery of targets, off-targets, and/or mechanisms for antivirals developed over the past 25 years. In my talk, I will share some of the highlights of my career, lessons learned, and pay homage to the many, many mentors and collaborators that I have encountered along the way. I will also share some of the most recent data from the laboratory that reveal the impact of analyzing the efficacy of antivirals on viral infection dynamics one cell at a time.

41. The SARS-CoV1 and 2 replication/transcription machinery and its future for drug-design

Ashleigh Shannon[1], Véronique Fattorini[1], Barbara Selisko[1], Camille Falcou[1], Pierre Gauffre[1], Bhawna Sama[1], Priscila El Kazzi[1], Etienne Decroly[1], Karine Alvarez[1], Cécilia Eydoux[1], Jean-Claude Guillemot[1], Johanna Huchting[2], Chris Meier[2], Franck Touret[3], Bruno Coutard[3], Steven S. Good[4], Adel Moussa[4], Kai Lin[4], Jean-Pierre Sommadossi[4], Olve Peersen[5], François Ferron[1], **Bruno Canard, Ph.D.**[1]

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Viral polymerase inhibitors have been used for decades to successfully treat several viral diseases. The ongoing pandemic, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emphasizes an urgent need for vaccines and antiviral therapeutics. However, the genetic diversity generated by the viral RNA-dependent-RNA-polymerase (RdRp) during replication is challenging our current countermeasures to control the associated COVID-19 morbidity and mortality. The replication/transcription complex is a promising target for nucleotide analogues (NAs), but the presence of nsp14, an associated RNA-proofreading exonuclease (ExoN), dampens inhibitor efficiency. Beside its subunit composition and activities, the SARS-CoV RdRp complex is endowed with unusual properties relative to other viral RdRps. The RTC is at least 10-fold more active than any other viral RdRp known. It possesses both unusually high nucleotide incorporation rates and high-error rates allowing facile insertion of base-modified NAs such as Favipiravir into viral RNA, provoking C-to-U and G-to-A transitions in the already low cytosine content SARS-CoV-2 genome. 2′-Ribose-modified NAs are surprisingly more discriminated relative to other (eg., Flavivirus) polymerases, and neither 1′-cyano nor 2′-F, 2′-Methyl modifications significantly decrease their removal by nsp14-ExoN.

Understanding the specifics of RTC fidelity, NA incorporation and removal should guide the synthesis of much awaited orally available, wide spectrum drugs finding their use in prophylaxis and therapeutics against COVID-19.

42. Development of small molecule protease inhibitors against SARS-CoV-2

Kyeong-Ok Chang, D.V.M., Ph.D.[1]

[1]Kansas State University

Pathogenic coronaviruses are a major threat to global public health, as exemplified by Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and the newly emerged SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19). The 3C-like protease (3CLpro) is a virus protease encoded by coronaviruses including SARS-CoV-2, which is essential for virus replication. We previously described a series of dipeptidyl 3CLpro inhibitors (including GC376) with activities against multiple coronaviruses, including SARS-CoV, MERS-CoV and SARS-CoV-2. GC376 was recently demonstrated in clinical trials to have efficacy against a fatal feline coronavirus infection, feline infectious peritonitis (FIP) and is currently in clinical development for treating FIP in cats. We further optimized compounds more effective against multiple human coronaviruses using the enzyme assay and cell-based assays. The antiviral effects of selected compounds were examined in the animal models with MERS-CoV or SARS-CoV-2 infections. For SARS-CoV-2, the K18-hACE2 mice which develop mild to lethal infection commensurate with SARS-CoV-2 challenge doses were used. Treatment of the mice at 24 hr post infection with selected compounds resulted in increased survival of mice compared to vehicle-treated mice. Lung virus titers were decreased, and histopathological changes were ameliorated in compound-treated mice compared to vehicle-treated mice. Structural investigation using high-resolution crystallography illuminated binding interactions of 3CLpro of SARS-CoV-2 and SARS-CoV with multiple compounds. Our results suggest that the dipeptidyl compound series can serve as a platform suitable for the structure-guided design of one or more inhibitors against highly virulent human coronaviruses.

43. Targeting the Proteases of SARS-CoV-2 and Other RNA Viruses

Christoph Nitsche, Ph.D.[1]
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Viral infectious diseases are a serious global health threat. For many viruses, safe vaccines and specific antiviral treatments are yet unavailable. Our initial work focused on rather neglected arboviruses like dengue, West Nile, Zika and Chikungunya, annually infecting hundreds of millions of people. Lately, we have commenced work on coronaviruses with a strong focus on SARS-CoV-2. We target viral proteases as the Achilles heel of viral replication, aiming to provide broad-spectrum antiviral agents that may also be effective against newly emerging viruses. Because proteases recognise and cleave polypeptide substrates, peptides are appealing starting points to target them. We have explored different strategies how peptides with noncanonical modifications can selectively inhibit and probe viral proteases, ranging from genetically encoded peptide libraries to new synthetic methodologies that allow for direct peptide modification in biochemical assays. The presentation will highlight recent progress from our lab targeting the main protease of SARS-CoV-2 and the protease NS2B-NS3 from Zika and related flaviviruses.

44. AT-527, a double prodrug of a guanosine nucleotide analog, is a potent inhibitor of SARS-CoV-2 in vitro and a promising oral antiviral for treatment of COVID-19

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The impact of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of COVID-19, is global and unprecedented. Although remdesivir has recently been approved by the FDA to treat SARS-CoV-2 infection, no oral antiviral is available for outpatient treatment. AT-527, an orally administered double prodrug of a guanosine nucleotide analog, was previously shown to be highly efficacious and well tolerated in HCV-infected subjects. Herein is reported the potent *in vitro* activity of AT-511, the free base of AT-527, against several coronaviruses, including SARS-CoV-2. In normal human airway epithelial cells, the concentration of AT-511 required to inhibit replication of SARS-CoV-2 by 90% (EC_{90}) was 0.47 μM, very similar to its EC_{90} against HCoV-229E, HCoV-OC43 and SARS-CoV in Huh-7 cells. The active triphosphate (TP) metabolite inhibited both Nidovirus RdRP-Associated Nucleotidyltransferase (NiRAN) and RNA-dependent RNA polymerase (RdRp) domains of the SARS-CoV RNA polymerase. Substantial levels of the TP were formed in normal primary human bronchial and nasal epithelial cells incubated with 10 μM AT-511 (698 ± 15 and 236 ± 14 μM, respectively), with a half-life of at least 38 hours. Results from non-human primate tissues as well as pharmacokinetic data from normal volunteers given daily oral doses of AT-527, predict that twice daily oral doses of 550 mg AT-527 will produce TP trough concentrations in human lung that exceed the EC_{90} value against SARS-CoV-2 replication. AT-527 is currently being evaluated in Phase 2 clinical studies as an early treatment option for COVID-19.

45. Multidisciplinary approaches identify compounds as potential new therapeutics for SARS-CoV-2

Christopher Day, Ph.D.[1], **Benjamin Bailly, Ph.D.**[1], Patrice Guillon, Ph.D.[1], Larissa Dirr, Ph.D.[1], Freda Jen, Ph.D.[1], Belinda Spillings, Ph.D.[1], Johnson Mak, Ph.D.[1], Mark Von Itzstein, Ph.D.[1], Thomas Haselhorst, Ph.D.[1], Michael Jennings, Ph.D.[1]
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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a recently emerged virus that causes coronavirus infectious disease 2019 (COVID-19). SARS-CoV-2 has caused more than 60 million cases world-wide with almost 1.5 million deaths as of November 2020. SARS-CoV-2 spike protein, like SARS-CoV-1, uses the angiotensin converting enzyme 2 (ACE2) as a cellular receptor to initiate infection. Compounds that interfere with the SARS-CoV-2 spike protein receptor binding domain protein (RBD) - ACE2 receptor interaction may function as entry inhibitors.

Repurposing existing drugs is the most rapid path to clinical intervention for emerging diseases. Herein, we used a dual strategy of in silico screen of 57,641 compounds and biophysical screen of 3,141 compounds by surface plasmon resonance (SPR) to identify those that bind to human ACE2 or SARS-CoV-2 Spike protein receptor binding domain (RBD). These combined screens identified compounds from these libraries that bind at K_D <3 μM affinity to their respective targets; 17 for ACE2 and 6 for SARS-CoV-2 RBD. Three of these compounds demonstrated dose-dependent antiviral *in vitro* potency. Three of the identified compounds were found to inhibit viral replication in a Vero-E6 cell-based SARS-CoV-2 infection assay and may have utility as repurposed therapeutics.

Currently we test our top hits in the *ex vivo* human airway epithelial model and utilize X-ray crystallography to investigate identified scaffolds that bind to SARS-CoV-2 Spike RBD for the development of new chemical entities for treatment of COVID-19.

47. Targeting host and viral protease to combat COVID-19

Yanmei Hu, M.S.[1], Chunlong Ma, Ph.D.[1], Jun Wang, Ph.D.[1]
[1]*The University of Arizona*

We recently discovered four SARS-CoV-2 main protease (Mpro) inhibitors including boceprevir, calpain inhibitors II and XII and GC-376 with potent antiviral activity against infectious SARS-CoV-2 in cell culture. Despite the weaker enzymatic inhibition of calpain inhibitors II and XII against Mpro compared to GC-376, calpain inhibitors II and XII had more potent cellular antiviral activity. This observation promoted us to hypothesize that the cellular antiviral activity of calpain inhibitors II and XII might also involve the inhibition of cathepsin L in addition to Mpro. To test this hypothesis, we tested calpain inhibitors II and XII in the SARS-CoV-2 pseudovirus neutralization assay in Vero E6 cells and found that both compounds significantly decreased pseudoviral particle entry into cells, indicating their role in inhibiting cathepsin L. The involvement of cathepsin L was further confirmed in the drug time-of-addition experiment. In addition, we found that these four compounds not only inhibit SARS-CoV-2, but also SARS-CoV, MERS-CoV, as well as human coronaviruses (CoVs) 229E, OC43, and NL63. The mechanism of action is through targeting the viral Mpro, which was supported by the thermal shift binding assay and enzymatic FRET assay. We further showed that these four compounds have additive antiviral effect when combined with remdesivir. Altogether, these results suggest that boceprevir, calpain inhibitors II and XII, and GC-376 are not only promising antiviral drug candidates against existing human coronaviruses, but also might work against future emerging CoVs.

50. HSV-1 and Alzheimer's Disease: causation or association? Understanding the biologic plausibility

Christine Johnston, M.D.[1]
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Alzheimer's Disease (AD) is a slowly progressive degenerative neurologic illness of aging that affects nearly 6 million Americans. Increasing age and genetic variants, such as the ApoE-ϵ4 allele, are known risk factors. Although hallmark pathologic findings such as accumulation of β-amyloid and phosphorylated tau protein in the temporal region of the brain are well described, interventions targeting these pathways have not altered the natural history of AD. Novel approaches to understanding and disrupting AD are urgently needed.

Infections have long been hypothesized to be a co-factor in development of AD. In particular, viruses that cause lifelong neurotropic infections, such as herpes simplex virus type 1 (HSV-1), have been implicated, and compelling data have shown associations between HSV-1, ApoE-ϵ4 and AD, and HSV-1 co-localized with amyloid plaques in animal models and in human neuropathologic studies. However, determining how a highly prevalent infection contributes to AD is challenging. Many have resisted the viral infection theory by thinking in the traditional sense that "pathogen" leads to "disease state". In contrast, in a complex disease with genetic and environmental cofactors such as AD, HSV-1 and other pathogens are more likely to act as contributing factors that accelerate disease progression. Recent studies extending observational and epidemiologic associations between HSV-1 and AD will be reviewed, with a focus on CNS inflammation and the potential role of HSV-1 reactivation to cause chronic, low-grade inflammatory changes that may contribute to AD progression over time. Design of future studies to understand the HSV-1/AD association development will be discussed.

51. Barriers to Curing HIV Infection

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The major barrier to curing HIV infection is a reservoir of latent proviruses residing in resting CD4+ T cells. This talk will review recent issues associated with the latent reservoir and efforts to cure HIV infection. Accurate measurement of the reservoir is critical to evaluating curative interventions, and therefore recent advances in reservoir measurement will be reviewed. Recent work also suggests that most of the reservoir is actually generated by proliferation of previously infected cells rather than by de novo infection. Thus the reservoir is composed of clones of infected CD4+ T cells that are expanding and contracting on a time scale of months to years, with the total number of latently infected cells declining only very slowly. The proliferation is largely driven by exposure to cognate antigens rather than homeostatic cytokines or effects related to the site of integration, a finding that greatly complicates the problem of eradication. One recent optimistic finding is that a substantial but variable fraction of viruses in the reservoir are neutralized by low concentrations of autologous IgG. The implications of this finding will be discussed.

52. Lenacapavir: A First-in-Class Phase 2/3 HIV Capsid Inhibitor with Potential for Twice Yearly Dosing

Jennifer Zhang, M.S.[1]
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Current standard of care for HIV antiretroviral therapy consists of oral agents that are highly efficacious and well tolerated but need to be taken daily and require faithful adherence. Long acting therapy may overcome adherence challenges and prove advantageous for some patient populations. Here we describe the discovery of lenacapavir (LEN). LEN misdirects the protein-protein interactions of HIV capsid subunits and represents a first-in-class selective inhibitor of HIV capsid function. The uniquely potent antiviral activity, high metabolic stability, and physicochemical properties of LEN signify a favorable profile for a long acting injectable agent. We will share a perspective on our medicinal chemistry program that incorporated structure guided design and intensive pharmacokinetic optimization in the discovery of highly metabolically stable and highly potent compounds on the pathway to the identification of LEN. Clinical pharmacokinetic, antiviral, and therapeutic efficacy results will also be presented.

53. New helicase-primase drug candidates with sufficient target tissue exposure affect latent neural herpes simplex virus infections

Gerald Kleymann, Ph.D.[1], Klaus Hamprecht, Ph.D.[2], Nadja Uhlig, M.S.[3], Christian Gege, Ph.D.[1], Fernando Bravo, Ph.D.[4], Thomas Grunwald, Ph.D.[3], David Bernstein, Ph.D.[4]
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HSV is a sexually transmitted infection causing widespread genital or oropharyngeal herpes. Less often, HSV infections cause encephalitis (HSVE), sight impairing keratitis, neonatal or disseminated herpes. An unmet medical need exits for more effective therapies especially CNS infections, resistant viruses and ultimately a cure. Currently HSV infections are treated predominantly with valacyclovir, acyclovir or famciclovir. Second line therapy of nucleoside-resistant HSV with foscavir is less tolerable.

In a drug discovery program a proprietary new compound class of HPIs was discovered and profiled.

The drug candidate IM-250 is active against HSV *in vitro* with an IC_{50} of 20-30 nM including nucleoside-resistant HSV due to its different mechanism of action. *In vivo* it prevents herpes encephalitis in mice treated once daily for 5 consecutive days with an ED_{50} of ~0.5 mg/kg. Early therapy of genital herpes in guinea pigs significantly reduces primary disease, vaginal virus replication, viral load in ganglia and prevents subsequent recurrent disease at 3 mg/kg (BID for 4 days). Importantly, treatment of recurrent infections reduces frequency of recurrences, viral shedding and unlike nucleosidic drugs, IM-250 remains effective for a time after cessation of treatment. The pharmacokinetic enables once daily dosing in humans. No prohibitive findings were detected in safety studies to date. Based on its superior efficacy in animal models compared to nucleosides and its different mechanism of action further development is warranted. The GMP material has been produced for GLP safety and toxicity studies and potential clinical trials to prove the concept in patients are being discussed.

54. The Molecularly Engineered H84T BanLec has Broad Spectrum Antiviral Activity Against Human Herpesviruses

Megan Lloyd, Ph.D.[1], Dongmei Liu, M.S.[1], Maureen Legendre, B.S.[2], David Markovitz, M.D.[2], Jennifer Moffat, Ph.D.[1]

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H84T BanLec is a molecularly engineered lectin cloned from bananas with broad-spectrum antiviral activity against several RNA viruses. H84T dimers bind glycoproteins containing high-mannose N-glycans on the virion envelope, blocking attachment, entry, uncoating, and spread. It was unknown whether H84T is effective against the human herpesviruses varicella-zoster virus (VZV), human cytomegalovirus (HCMV), and herpes simplex virus 1 (HSV-1). These viruses all express high-mannose N-linked glycoproteins on their envelope. Thus, we evaluated H84T against them in cells, skin organ culture (SOC), and mice using VZV-ORF57-Luc, TB40/E HCMV-fLuc-eGFP, and HSV-1 R8411. The H84T EC_{50} was 0.025 μM for VZV (SI_{50}=4000) and 0.227 μM for HCMV (SI_{50}=441) in HFFs, and 0.325 μM for HSV-1 (SI_{50}=308) in Vero cells. Human skin was obtained from reduction mammoplasties and prepared for culture. Skin was infected with virus and cultured up to 14 days. H84T prevented VZV, HCMV and HSV-1 spread in skin at 10 μM in the culture medium, and also exhibited dose-dependent antiviral effects. Surprisingly, H84T also arrested virus spread when treatment was delayed. Histopathology of HCMV-infected skin showed no overt toxicity when H84T was present in the media. Adult skin implants were placed subcutaneously in athymic nude mice (NuSkin mice). After engraftment, the implants were inoculated with VZV-ORF57-Luc and virus spread was monitored by bioluminescence imaging. In the NuSkin mouse model, H84T effectively reduced VZV spread when administered subcutaneously prior to inoculation. This is the first demonstration of H84T effectiveness against DNA viruses. H84T may have additional unexplored activity against such enveloped viruses.

55. Oral USC-373, an HPMPC Prodrug, Prevents Varicella Zoster Virus Replication in a Mouse Model

Dongmei Liu, M.S.[1], Jinglei Lyu, Ph.D.[2], Megan Lloyd, Ph.D.[1], Jiajun Fan, Ph.D.[2], Justin Overhulse, B.S.[2], Boris Kashemirov, Ph.D.[2], **Jennifer Moffat, Ph.D.**[1], Charles McKenna, Ph.D.[2]

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USC-373 is an *N*-C_{18} alkenyl tyrosinamide phosphonate ester prodrug of (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine (HPMPC, cidofovir) with broad spectrum activity against DNA viruses. USC-373 is potent against varicella zoster virus (VZV) in cultured cells (EC_{50} 0.004 μM, CC_{50} 0.2 μM) and against a thymidine kinase-deficient strain. We investigated its efficacy against VZV-ORF57-Luc in skin organ culture and in SCID-Hu skin mice. In skin organ culture, USC-373 (1.2%) topical was more effective than equimolar HPMPC (0.5%) and was nontoxic to skin. USC-373 was formulated in Cremophor-DMSO-saline (1:1:8) for *in vivo* assays. Mice were treated with 10 mg/kg, QD, orally or subcutaneous, on Days 3-9 post infection. In a separate assay, mice were treated with 10, 3, or 1 mg/kg, QD, subcutaneous. USC-373 10 mg/kg orally or subcutaneous was as effective or better than HPMPC (10 mg/kg i.p.). Efficacy was dose dependent, with the 3 mg/kg dose preventing VZV spread as well as HPMPC. 1 mg/kg USC-373 was not effective on Day 10, yet it was effective on Day 14 after a 4-day rebound. VZV increased substantially from Day 10-14 in mice treated with vehicle or HPMPC. VZV did not rebound in mice treated with USC-373. USC-373 was well tolerated; mice did not lose weight. Overall, USC-373 was highly effective against VZV in skin models at 3 mg/kg (molar equivalent of 1.2 mg/kg HPMPC). USC-373 is more potent, better tolerated, and longer-lasting than the parent drug. These characteristics, together with its broad-spectrum activity and bypass of TK phosphorylation make USC-373 a promising lead compound.

60. Genetic Diversity and Evolution of Herpesviruses

Graciela Andrei, Ph.D.[1]
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RNA viruses, due to the lack of proofreading activity by most RNA-dependent polymerases (pols), are inherently variable in contrast to stable DNA viruses. However, thanks to our translational research platform RegaVir for typing drug-resistance among DNA viruses, we have shown diversity and rapid evolution of herpesviruses as well as the utility of rapid genotyping and/or phenotyping for therapy adjustment. Besides, identification of novel drug-resistant mutations and natural genetic polymorphisms, higher risk for developing (multi)drug-resistance in immune-privileged sites, compartmentalization of (multi)drug-resistance, simultaneous and concomitant herpesvirus infections, and advantage of next-generation sequencing (NGS) to detect minor viral populations and emergence of drug-resistance were demonstrated by this platform.

Both diversity and evolution of herpesviruses are impacted by different mechanisms other than the usual consideration of DNA pol fidelity. Our laboratory is interested in investigating a novel mechanism that may contribute to herpesvirus genetic diversity, i.e. mutations in DNA pols affecting DNA replication fidelity. Substitutions in the 3′€5′ exonuclease region of DNA pols may result in decreased proofreading capacity inducing high frequency of spontaneous mutations (i.e. mutator phenotypes). We identified two novel amino acid changes [C297W (3′-5′ exonuclease domain) and C981Y (thumb domain)] in murine gammaherpesvirus 68 (MHV-68) DNApol related to a mutator phenotype. The association of the C297W with a mutator phenotype was validated by CRISPR/Cas9 genome editing. Competitive fitness of MHV-68 mutator phenotype viruses w/wo antivirals was significantly impaired as evaluated following population evolution by NGS. We are currently using this approach to determine the dynamics of herpesvirus populations in clinical samples.

61. Antiviral agents for serious RNA virus infections; a personalised medicine approach

Judith Breuer, M.D.[1]
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Viruses belonging to the RNA viral kingdom are characterised by genomes comprising ribosomal nucleic acid (RNA) which encodes an RNA dependent RNA polymerase (RdRp) that is used to transcribe the viral genome into mRNA and to replicate the genome. RNA viruses are responsible for most human epidemics and pandemics. Although many RNA viruses cause short-lived infections, some, including the coronaviruses SARS, MERS and SARS-CoV-2 and Ebolavirus cause mortality in naïve populations, while established epidemic and pandemic RNA viruses, including influenza, respiratory syncytial virus and norovirus, cause excess mortality and morbidity in the young and elderly. Even RNA viruses that are normally innocuous can be fatal in subjects with compromised immune symptoms. Where vaccines do not exist, antiviral treatments are a desirable option for management of serious RNA virus infections.

Several new and repurposed drugs have been described to have broad spectrum *in vitro* activity against the RdRp of many RNA viruses. For a few there are limited data from randomised clinical trials. These are generally disappointing with evidence of limited efficacy *in vivo*. Here through detailed studies in patients with severe infections, we have identified potential causes of drug failure *in vivo* and identified possible avenues for research into optimising existing drugs to achieve better outcomes for the treatment of RNA viruses.

62. Four-segmented Rift Valley fever virus as a novel live-attenuated vaccine for animal and human use

Paul Wichgers Schreur, Ph.D.[1], Nadia Oreshkova, Ph.D.[1], Lucien Van Keulen, D.V.M.[1], Jet Kant, B.S.[1], Sandra Van de Water, B.S.[1], Pál Soós, D.V.M.[2], Yves Dehon, Ph.D.[2], Anna Kolár, Ph.D.[2], Zoltán Pénzes, Ph.D.[2], **Jeroen Kortekaas, Ph.D.**[1]

[1]Wageningen Bioveterinary Research; [2]Ceva Animal Health

Rift Valley fever virus (RVFV) is a mosquito-borne bunyavirus that causes severe and recurrent outbreaks on the African continent and the Arabian Peninsula and continues to expand its habitat. RVFV induces severe disease in newborns and abortion in pregnant ruminants. The viral genome consists of a small (S), medium (M) and large (L) RNA segment of negative polarity. The M segment encodes a glycoprotein precursor protein that is co-translationally cleaved into the two structural glycoproteins Gn and Gc, which are involved in receptor attachment and cell entry. We previously constructed a four-segmented RVFV (RVFV-4s) by splitting the M genome segment into two M-type segments encoding either Gn or Gc. RVFV-4s replicates efficiently in cell culture but was shown to be completely avirulent in mice, lambs and pregnant ewes. We now report that RVFV-4s does not disseminate in vaccinated animals, is not shed or spread to the environment and does not revert to virulence. Furthermore, a single vaccination of lambs, goat kids and calves was shown to induce protective immunity against a homologous challenge. Finally, the vaccine was shown to provide full protection against a genetically distinct RVFV strain. Altogether, we demonstrate that RVFV-4s optimally combines efficacy with safety, holding great promise as a next-generation RVF vaccine for both animal and human use.

63. Understanding the multiple functions of the bunyavirus polymerase protein

Dominik Vogel, Ph.D.[1], Sigurdur Thorkelsson, M.S.[2], Emmanuelle Quemin, Ph.D.[2], Kristina Meier, M.S.[1], Tomas Kouba, Ph.D.[3], Harry Williams, Ph.D.[1], Sophia Reindl, Ph.D.[1], Stephan Günther, M.D.[1], Kay Grünewald, Ph.D.[2], Stephen Cusack, Ph.D.[3], **Maria Rosenthal, Ph.D.**[1]

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The order of *Bunyavirales*, which was established in 2018, accommodates a diverse group of neglected viruses formerly separated into *Arena-* and *Bunyaviridae* families and contains important human pathogens such as Lassa virus (LASV) and Rift Valley fever virus (RVFV). The lack of medical countermeasures, such as vaccines and antivirals, is a limiting factor for the containment of any virus outbreak. To develop such antivirals a profound understanding of the viral replication process is essential. The L protein of bunyaviruses is a multi-functional and multi-domain protein containing the viral RNA-dependent RNA polymerase and performing both viral transcription and genome replication. Therefore, the L protein seems to be an ideal drug target. However, even though our knowledge of its structure and functions has increased over the past years, the L protein remains a challenging target due to its size, flexibility and diversity among bunyaviruses. We combine biochemistry, structural biology and virology methods to enhance our understanding of bunyavirus L protein structure and functions. By solving structures of a C-terminal domain using X-ray crystallography we identified a cap-binding domain essential for viral transcription. Furthermore, we established expression and purification procedures for full-length L proteins to investigate their structure using single-particle cryo-EM and characterize the diverse functions in biochemical assays. Our results and data published by other groups demonstrate functional and structural similarities and differences of the L protein within bunyaviruses and in comparison to influenza polymerase complex supporting targeted drug development strategies against bunyaviruses.

64. Rational modifications and biological evaluation of novel non-nucleoside agents with antiviral activity against norovirus

Salvatore Ferla, Ph.D.[1], William Knight, B.S.[1], Giulio Nannetti, Ph.D.[2], Fabiana Saporito, M.S.[2], Beatrice Tropea, M.S.[2], Nanci Dos Santos Ferreira, Ph.D.[3], Johan Neyts, Ph.D.[3], Joana Rocha-Pereira, Ph.D.[3], Andrea Brancale, Ph.D.[2], Marcella Bassetto, Ph.D.[1]
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Norovirus is the major responsible for food-borne illness worldwide: infection with this virus leads to extensive outbreaks of gastroenteritis, which represents a life-threatening condition in the developing countries and in debilitated patients. In the UK alone, norovirus is a major cause for the closure of hospital wards, with an estimated cost to the health service of £81 million per year. No vaccines or specific antivirals are currently available for this viral infection, therefore the development of antiviral treatments represents an unmet medical need.

Starting from a series of computer-aided studies, both structure-based and ligand-based, we have recently identified two novel molecular scaffolds, which are moderate inhibitors of the human norovirus polymerase (HuNoV RdRp) activity. Most importantly, our new compounds reduce murine norovirus (MNV)-induced cytopathic effect. These molecules also inhibit HuNoV replication in a human norovirus replicon assay harbouring a genogroup GI, with EC_{50} values in the low micromolar range, and no significant cytotoxicity.

In this presentation, the rational design of diverse new structural modifications of the two hit molecules will be discussed, along with their synthetic preparation, and their biological evaluation in different *in vitro* assays. In addition, further *in silico* studies will be disclosed, which indicate preliminary structure-activity relationships, and provide the basis for further optimisation of these novel antiviral agents.

65. Metabolic Stabilization of a Novel Inhibitor of human Dihydroorotate Dehydrogenase (hDHODH) with Potent Broad Spectrum Antiviral Activity

Nora Fohrmann, M.S.[1], Lisa Oestereich, Ph.D.[2], Katharina Pfaff, Ph.D.[1], Gilles Querat, Ph.D.[3], Chris Meier, Ph.D.[1]
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Recently, we identified a novel series of compounds with strong antiviral activity against a panel of RNA virus species including prominent examples of emerging viruses (e. g. Bunya, Lassa and Ebola viruses). This broad range antiviral activity results from an inhibition of human Dihydroorotate Dehydrogenase (hDHODH), a cellular enzyme that is involved in the *de novo* biosynthesis of pyrimidine nucleotides and thus crucial for viral RNA replication. One highly potent analogue with antiviral activity in low nanomolar range and an enzymatic activity of 17 nM (IC50) emerged from this series as a lead structure. Its *in vitro* metabolic stability was determined to 22% by one hour incubation in liver S9 fraction from rat.

Here we report on our recent work in improving the metabolic stability by lead optimization with regard to future *in vivo* applications. We identified the lead compound's main metabolite via LC-MS and stabilized the site of metabolism via rational derivatization. To support rational design, the x-ray structure of the lead compound in complex with hDHODH was determined and used as template for molecular design of stabilized structures as well as receptor grid for docking. These designed structures were synthesized and biologically evaluated regarding their metabolic stability and enzymatic inhibition. Two compounds showed improved metabolic stabilities as well as comparably strong inhibitory activities. A second cycle of metabolite identification, rational design and synthesis of further stabilized derivatives resulted in two promising analogues with nanomolar enzymatic inhibition and antiviral activities as well as high metabolic stabilities of around 70%.

66. Small molecules from the diketo acid class engage and inhibit the endonuclease domain of a panel of bunyaviruses and interfere with viral replication in vitro

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Many species of the order *Bunyavirales* contain potentially fatal viruses that lack effective medical countermeasures and are therefore collectively a major public health threat. Their segmented single-stranded RNA genome with either negative or ambisense polarity requires 5€capped extensions derived from the host mRNA to initiate transcription. These are obtained through a cap-snatch mechanism initially described for influenza viruses. The responsible metal dependent endonuclease domain is a constant feature throughout the bunyaviruses. Structural studies of the domain support the idea that the chelating agent class of diketo acids could serve as starting point for the creation of broad acting drug-like candidates.

We performed a thermal shift assay and a fluorescence resonance energy transfer (FRET)-based nuclease monitoring assay to show that catalytic activity of a panel of bunyavirus cap-snatching endonucleases. To further study their interaction a docking simulation using GlideSP was performed. Next, we evaluated the *in vitro* antiviral effect of diketo acids in a cell based assay using a Bunyamwera virus expressing mCherry upon viral replication. L-742,001 and derivatives exhibited EC_{50} values between 5.6 and 6.9 µM, whereas the first-in-class FDA approved diketo acid based Influenza drug baloxivir showed replication inhibition with an EC_{50} of 0.7 µM. Lastly we show that using baloxavir in combination ribavirin yields a synergistic antiviral effect *in vitro*.

Our results demonstrate that the cap-snatching endonuclease domain is a valid target for the development of broad-spectrum bunyavirus-targeting antivirals and that the class of diketo acid compounds contains chemical features worth exploring in the design of novel inhibitors.

70. New Strategies for Modeling and Treating Emerging Viral Pathogens

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Chikungunya virus (CHIKV) is a significant public health threat due to its capacity to cause massive epidemics of debilitating acute and chronic arthritis in infected humans. CHIKV exhibits tropism for joint and muscle tissues, with the subsequent induction of a pathologic inflammatory response that contributes to disease pathogenesis. Therefore, therapeutic strategies or combination therapies are needed that will effectively suppress virus replication, while dampening pathologic, but not beneficial aspects of the host inflammatory response. However, we currently have an incomplete understanding of the factors that regulate CHIKV disease severity, and this lack of knowledge has hindered the development of effective CHIKV treatment strategies. Furthermore, existing models of CHIKV disease do not reproduce the full range of CHIKV disease phenotypes seen in humans, which hinders the pre-clinical testing of both antiviral and anti-inflammatory strategies. With these challenges in mind, our team has been using the Collaborative Cross (CC), a genetically diverse mouse genetic reference population, to develop new models of CHIKV-induced disease and identify host inflammatory pathways and genes networks that regulate CHIKV disease severity. CHIKV infection of CC mouse strains results in a broader range of disease outcome than is observed in standard inbred mouse strains, and we have taken advantage of this variation to identify candidate pathways that can be targeted for treating CHIKV induced disease. We will discuss these results while also illustrating how the CC and related resources can be used for the development and testing of therapeutic strategies against other emerging viral pathogens.

71. Biologics as Therapeutics for Rapid Response- can we get there fast enough?

Jenny Low, M.D., MPH[1]
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The traditional development of biologics for chronic diseases is both lengthy and costly. Whereas in infectious disease outbreaks, which can cause massive number of deaths within a short period, timely intervention with an effective therapeutic is critical in order to reduce morbidity and mortality. Novel approaches and new technology platforms have now shifted the paradigm of using biologics against emerging pathogens through the rapid production of safe and effective biologics for human trials. In this talk I will discuss the role of monoclonal antibodies as prophylaxis and treatment during infectious disease outbreaks such as Zika, yellow fever and SARS CoV-2.

72. Pan-serotype dengue virus inhibitor that blocks the NS3-NS4B interaction and exhibits unprecedented in vivo potency

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Dengue virus (DENV) causes ~96 million symptomatic infections annually, manifesting as dengue (hemorrhagic) fever or occasionally as dengue shock syndrome. There are no antivirals available to prevent or treat DENV infections. Here, we describe a potent DENV inhibitor (JNJ-A07) that exerts pico- to nanomolar activity against a panel of 21 clinical isolates, representing the natural genetic diversity of known geno- and serotypes. JNJ-A07 exhibits a high barrier to resistance and blocks viral replication by preventing the complex formation between two viral proteins, NS3 and NS4B, thus unveiling an entirely novel mechanism of antiviral action. JNJ-A07 has a favorable pharmacokinetic profile and shows excellent efficacy against a lethal DENV-2 challenge in mice. Delaying start of treatment until day 6 post-infection still results in an instant and significant reduction in viral load. An analogue of JNJ-A07 is undergoing further development.

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73. The Integrity of Yellow Fever Virus Replication Complex maintained by Nonstructural 4B protein and Targeted by a Small Molecule Antiviral Agent

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Flavivirus replication complex (RC) is formed by invagination of the endoplasmic reticulum membrane, which protects viral genomic RNA from cellular innate immune recognition. Among host factors and viral nonstructural (NS) proteins, available evidence suggests a prominent role of NS4B protein in the formation of RC and evasion of innate immune activation. We previously reported a benzodiazepine compound BDAA that inhibits yellow fever virus (YFV) in vitro and in hamsters, with resistant mutation mapped to P219 of NS4B. In our effort to elucidate the mode-of-action, we discovered that upon short term treatment with BDAA, double-stranded RNAs (dsRNAs), the hall markers of replication intermediates, became exposed from the intact digitonin-resistant RC in YFV-infected cells, in a time- and dose-dependent manner. Furthermore, under the experimental condition that dsRNAs were exposed by BDAA treatment, a broad range of innate immune response was also activated, as demonstrated by RNAseq analysis. Using CRISPR/Cas9 knockout cells, we demonstrated that both RIG-I and MAD5 pathways are involved in BDAA induced cytokine response. However, in MAVS knockout cells in absence of innate immune activation, the antiviral effect of BDAA was not affected suggesting that inhibition of viral replication can be independent of immune activation. Using BDAA resistant viruses with NS4B mutation, we demonstrated that BDAA's dual effect on YFV replication and innate immune activation both depend on interaction with NS4B. Our findings thus support a model that by targeting NS4B, BDAA may disrupt its function in maintaining YFV RC integrity which simultaneously inhibits viral replication and breaks immune evasion.

74. The ribonucleoside analog EIDD-2749 is broadly active in the treatment of Eastern Equine Encephalitis and Chikungunya viral infections

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Eastern equine encephalitis virus (EEEV) infection continues to cause periodic outbreaks of disease and case numbers have sharply increased over the last 20 years. Chikungunya virus (CHIKV), an arthritogenic alphavirus, re-emerged in 2006 and continues to cause periodic outbreaks worldwide. No antivirals are approved for the treatment of either virus. The ribonucleoside EIDD-2749 was discovered at the EIDD and currently under development by DRIVE. This compound has broad in vitro antiviral activity against a host of viruses, including EEEV and CHIKV, from various ribovirus families without significant cytotoxicity. The studies reported here were designed to determine the prophylactic and therapeutic efficacy of EIDD-2749 against EEEV and CHIKV in animal models. In non-infected C57BL/6 mice, weight loss and mortality were observed at a dose of 30 mg/kg/d administered orally for 7 days, while doses of 15, 10, or 3 mg/kg/d were well tolerated. In a non-lethal mouse model of CHIKV, footpad swelling and viremia were significantly reduced after EIDD-2749 treatment with doses as low as 3 mg/kg/d. In a lethal model of EEEV disease, mice were significantly protected from lethality at doses as low as 1.5 mg/kg/d. Viremia and virus titers in the brain were significantly reduced with EIDD-2749 treatment. Significant protection was observed when treatment with 15 mg/kg/d was delayed up to 48 h after virus challenge. EIDD-2749 was highly effective in mouse models of EEEV and CHIKV and further development is warranted. [supported in part by contract HHSN272201700041I, Task A11 and HHSN272201500008C, NIAID, NIH and by HDTRA1-15-C-0075, DTRA]

75. Development of a novel dengue protease inhibitor

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The flavivirus genus contains more than 50 members including Dengue and Zika viruses which affect approximately 40% of the world's population across 100 countries in the tropical and subtropical regions. Recent outbreaks and increased infections in the US and Europe have led WHO to designate these diseases as Serious Threat and unmet medical needs as there no antiviral drugs or safe vaccines available. Concerted efforts towards the development of antiviral drugs have focused on the viral proteins, particularly the protease and the polymerase which have been exemplified as the most promising and validated targets. Regarding DENV and ZIKV NS2BNS3 protease inhibitors, thousands of molecules have been evaluated but generally suffer from poor potency, cytotoxicity and cellular inefficacy. We recently disclosed our efforts culminating in novel carbazole derivatives, one of which demonstrated one of the best ZIKVpro inhibitor profile in the literature. Following on from this work, switching the amidine pharmacophore for its amidoxime prodrugs, followed by extended SAR studies we identified novel analogue SP-471P (EC_{50} 1.10 μM, CC_{50}>100 μM). SP-471P inhibits viral RNA replication and abolishes infective virus particle production even when administered six hours post-infection, which renders it one of the most potent, non-cytotoxic and cell-active DENVpro inhibitors described to date. SP-471P appears to inhibit both trans and, the more critical for virus replication, cis cleavages performed by the protease. We have developed a gram-scale synthesis of SP-471P without chromatography that has enabled the preparation of further analogues and material requirements to fund preclinical studies.

80. Mid-term report on my academic journey to discover novel HBV/HDV therapeutics

David Durantel, Ph.D.[1]

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Chronic infections with the hepatitis B virus (HBV), and resulting chronic hepatitis (CHB), are major medical burdens, with around 250 millions individuals being concerned worldwide, and only less than 5-10% of them aware of their condition. Complications of CHB include end-stage liver diseases, such as cirrhosis and hepatocellular carcinoma, which are responsible for around 1 million death/year. Current treatments, which are given to only few % of infected individuals, rely on several nucleos(t)ide analogues (NAs) and/or pegylated interferon alpha (Peg-IFN). NAs are direct acting agents (DAAs), whereas Peg-IFN is a good example of host targeting agents (HTAs). If NAs do induce a prolonged virosuppression (viremia < LOD) under continuous pressure (long-life treatment), they have little impact on cccDNA decline and HBsAg loss; the later being the novel accepted clinical end-point to define a so-called *functional cure*. Peg-IFN, in some patients, does better than NAs in a finite-duration-regimen on HBsAg loss rate, but is too toxic and outcompeted by NAs in patient's will for treatment. Novel assets and combinations are necessary to have "curative and finite" regimens.

A huge effort to develop more potent DAAs and new HTAs is on going. The role of academic researcher is to identify novel antiviral targets and contribute to the R&D of DAAs, but also and mostly HTAs, which are more difficult to move forward mainly because of poorer toxicologic profile. In this Prusoff award lecture, I will summarize my up-to-date contributions to the field and indicate what are future directions...

81. Towards combination treatments for Chronic Hepatitis B: an immunologist's point of view

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A coordinated immune response is required for clearance of Hepatitis B virus (HBV) infection. However, HBV-specific T and B cell immunity display a profile of profound exhaustion in chronic hepatitis B (CHB) patients. Immunotherapeutic drugs being developed for chronic hepatitis B target both innate and adaptive immunity. These include therapeutic vaccines, checkpoint inhibitors, and small molecules targeting host pattern recognition receptors. Therapeutic vaccines have the longest history for immunotherapeutic intervention in chronic HBV infection but have thus far proven ineffective. Checkpoint inhibitors are gaining traction, with increasing data on side effects and safety profiles from cancer patients but have only entered small pilot studies. Innate immunomodulators targeting pattern recognition receptors have demonstrated target engagement but have shown only modest impact on viral replication as monotherapy. The expectation is that combination therapy will be required to achieve hepatitis B cure. This combination will likely include directing acting antivirals, in combination with immunomodulatory drugs inducing complementary mechanisms of action to facilitate antiviral immunity in the liver. This presentation will cover the immunological status of CHB patients, the current stage of immunotherapeutic options for chronic hepatitis B and rational combinations, including direct acting antivirals covered by Dr. Tavis, to induce a coordinated immune response.

82. Principles of Hepatitis E virus replication, persistence and antiviral strategies

Eike Steinmann, Ph.D.[1]

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The Hepatitis E Virus (HEV) is the causative agent of Hepatitis E and thereby the leading cause for acute viral hepatitis involving approximately 20 million individuals, with 3.3 million symptomatic infections and 44 000–70 000 deaths per year. Although HEV is usually a self-limiting disease, immunocompromised individuals are at risk to develop a chronic course of infection with rapid progression to fibrosis, cirrhosis or even the development of liver failure. The current therapy options are limited to the unspecific antivirals ribavirin (RBV) and pegylated Interferon-α (pegIFN-α). RBV leads to viral clearance in only 80% of chronically infected patients, however, it has not been evaluated in acutely infected patients and is contraindicated in the major risk group of pregnant women, emphasizing the urgency of new therapy options. In this presentation, I will first recapitulate the knowledge in HEV molecular virology, clinical course of infection and current therapeutic options and then provide an overview of the ongoing developments in antiviral strategies against HEV.

83. Towards combination treatments for chronic hepatitis B: A virologist point of view

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Curative therapies for hepatitis B virus infections will almost certainly require combinations of multiple drugs acting by complementary mechanisms. A very wide variety of treatment strategies are under development, but it is unclear which combination(s) of them hold the best promise for achieving a functional cure in the highly diverse hepatitis B patient population. Major classes of drug strategies being explored include direct acting agents that interrupt production and/or intracellular maintenance of HBV, host targeting approaches that suppress HBV by interrupting cellular mechanisms, and immune enhancing approaches that exploit the power of the adaptive immune response against HBV. This presentation will briefly review HBV's replication cycle, give an ideal target product profile for a curative therapy, and provide a short overview of the major classes of direct-acting drugs under development. Opportunities for rational combinations of complementary virus- and host-targeting drug strategies will be evaluated in context of HBV's replication cycle. Finally, it will foreshadow the likely need for immune stimulating approaches to be included in curative combination therapies. A companion presentation in this virtual workshop given by Dr. Adam Gehring will address the role of immune-targeting approaches in future treatments.

84. CD40 agonists boost IFN-induced signaling pathway and subsequent anti-HBV response *in vitro* and *in vivo*

Antoine Alam, Ph.D.[1], Xavier Marniquet, M.S.[1], Marion Dajon, Ph.D.[1], Julie Montegut, B.S.[1], Virginie Archimbeaud, B.S.[1], Halim Guerraoui, B.S.[1], Gregory Neveu, Ph.D.[1], Charlotte Blanc, M.S.[1], Christelle Marcou, B.S.[1], Juliette Lavaux, Ph.D.[1], Hugh Watson, Ph.D.[1], Kara Carter, Ph.D.[2]

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There is a continued need for improved therapeutics for chronic hepatitis B. In this light, the combination of CD40 agonism and IFN-I stimulation was explored on HBV infection both *in vitro* and *in vivo*. *In vitro* CD40L boosts the anti-viral effect of IFN-I on HBV-infected primary human hepatocytes with a decrease of HBeAg and pgRNA. This combination also increased the release of the IFN-responsive protein CXCL10, but not the inflammatory protein IL-8. The combination boosted other Interferon Stimulating Genes, such as CXCL9, CXCL11 or ISG20, a key player in innate anti-viral immunity. Furthermore, in comparison to single agents, the co-administration of CD40L and IFNb to AAV/HBV-infected mice led to a significant reduction of viral parameters including circulating HBV DNA, HBeAg and HBsAg as well as pgRNA and HBV DNA in the liver. Importantly, *ex vivo* treatment of either human or murine whole blood cells with CD40L and IFN-I did not significantly induce inflammatory markers. Together, these results show the combination of CD40L and IFN-I has a potent anti-HBV activity *in vitro* and *in vivo* with minimal inflammation. Such a combination may have an important therapeutic effect in chronic hepatitis B patients.

85. Efficient Inhibition of Hepatitis B Virus cccDNA and Pregenomic RNA by HBV ribonuclease H Inhibitors During Infection of HepG2-NTCP Cells

Ranjit Chauhan, Ph.D.[1], Qilan Li, Ph.D.[1], John Tavis, Ph.D.[1]

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Introduction: Establishment of HBV cccDNA early after HBV infection through recircularization of viral replicative intermediates contributes to HBV persistence. The viral ribonuclease H (RNaseH) is a promising drug target, but it is unknown how its inhibition impacts cccDNA formation. Methods: Three RNaseH inhibitors from different chemotypes with efficacy against intracellular HBV DNA accumulation in inducible replication systems, 1133 (N-hydroxypyridinedione, EC50 = 0.11 μM), 110 (€hydroxytropolone EC50 = 0.30 μM), and 1073 (N-hydroxynapthyridinone, EC50 = 1.5 μM), were tested for effects on HBV product formation in infected HepG2-NTCP cells. Cells were infected with 500 *vge* HBV for 12 hours and compounds were added immediately following infection at 0.05 μM, 0.5 μM and 5 μM. Total intracellular HBV DNA, cccDNA, pregenomic RNA and total HBV RNA accumulation were measured seven days post infection. Results: Inhibition of total intracellular HBV DNA was dose-responsive, with ~99% inhibition compared to vehicle control by all compounds at 0.5 μM. All compounds inhibited cccDNA formation by 75-95% at 0.5 μM. Effects on inhibition of cccDNA were reflected in suppression of pregenomic RNA levels, with inhibition of >90% for 1133 and 110 and >50% for 1073. Similar inhibition was detected for all HBV RNAs using primers targeting the HBx region. Conclusions: HBV RNaseH inhibitors can efficiently suppress cccDNA formation. Efficacy was more efficient than predicted by EC50s in stably-transfected cells, presumably due to suppression of cccDNA amplification. These data support progression of RNaseH inhibitors as a therapeutic candidates for treatment of chronic hepatitis B.

86. Farnesoid X receptor alpha ligands inhibit hepatitis delta virus replication and propagation in physiologic cell culture models

Benoît Lacombe, Ph.D.[1], **Julie Lucifora, Ph.D.**[1], Anne-Flore Legrand, M.S.[1], Camille Ménard, M.S.[1], Maud Michelet, M.S.[1], Adrien Foca, Ph.D.[1], Pauline Abrial, B.S.[1], Anna Salvetti, Ph.D.[1], David Durantel, Ph.D.[1], Patrice André, M.D., Ph.D.[1], Christophe Ramière, M.D., Ph.D.[1]

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Hepatitis delta virus (HDV) is a satellite of hepatitis B virus (HBV), both using the human Sodium Taurocholate Co-Transporting Polypeptide (hNTCP), the main transporter of bile acids (BA) in the liver, to enter hepatocytes. Links between BA and HBV infection are not limited to the entry step as we previously showed that the farnesoid X receptor alpha (FXR), the nuclear receptor of BA, was a proviral factor for HBV and that FXR ligands acted as inhibitors of HBV replication. As putative links between BA metabolism and HDV replication have not been explored, we aimed at determining whether FXR-alpha also played a role in HDV life cycle.

In HDV/HBV co- or super-infection differentiated HepaRG cells and primary human hepatocytes, treatments with FXR ligands such as GW4064, ECDCA or tropifexor significantly decreased the levels of total intracellular HDV RNAs. The effect was reverted in FXR loss-of-function experiments, confirming the specificity of action. Immunofluorescent staining and western blot analyses of infected cells showed that FXR ligands also decreased the amount of intracellular delta antigens. The antiviral effect was very strong on viral progeny, with a > 98% loss of infectivity assessed by reinfection of Huh7.5-hNTCP cells.

FXR ligands potently inhibit HDV replication and propagation *in vitro*, independently of their effect on HBV. The antiviral effect was found far superior to that obtained with IFN-a, the current standard of care for chronic HDV patients. FXR represent an attractive target for HDV antiviral therapy, and FXR agonists should be urgently tested in these patients.

90. The Long and Winding Road: 35 Years of HIV Reverse Transcriptase Structure, Mechanism, and Successful Anti-AIDS Drug Design

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I am deeply humbled to be recognized by this prestigious award, and to have a connection with Antonín Holý, a phenomenally creative and prolific chemist. Professor Holý invented key nucleotide drugs for treating viral diseases, including tenofovir, adefovir, and cidofovir. These nucleotide drugs contain the stable phosphonate moiety as a monophosphate equivalent, allowing for efficient cellular activation to triphosphate equivalents by bypassing the often rate-limiting initial phosphorylation step.

Since 1986 I have been pursuing structures of HIV-1 reverse transcriptase (RT) with dual goals of understanding the chemistry of this marvelous molecular machine at the atomic level, while at the same time facilitating the process of developing novel therapeutic agents targeting this enzyme. Among the most important events in my research efforts on HIV-1 RT were fortuitous meetings with Dr. Stephen Hughes and Dr. Paul Janssen, both amazing scientists and people, who became very close friends of mine. As a postdoctoral researcher with Professor Michael Rossmann at Purdue University, I had been a central contributor to an effort that used crystallography to solve the three-dimensional structure of the first animal virus in atomic detail - human rhinovirus 14, a common cold virus. At the time HIV infection was a death sentence, and I was looking to help solve this disease problem by using structural biology and crystallography to unlock some of the virus' secrets and to guide the design of effective drugs targeting this deadly agent. In 1986 I met the gifted retrovirologist and molecular biologist Dr. Hughes, who had cloned HIV-1 RT and provided my entry to the field and enabled our crystallographic effort by providing purified protein and many ingenious constructs, ideas, and experiments. After working together for the past 35 years to solve many crystal structures of HIV-1 RT, we still collaborate on multiple aspects of research. In 1990 I was fortunate to initiate a collaboration with the magical Dr. Paul Janssen, who was the inventor of 80 drugs and the all-time grandmaster of drug discovery. Dr. Paul and I teamed up to develop drugs targeting HIV-1 RT that would have high potency, resilience to resistance, were simple to make and formulate, and would have favorable pharmacological properties that could enable once-daily dosing. In a structure-guided design effort driven by my laboratory's crystallographic structures and coordinated by Dr. Paul at his Janssen Center for Molecular Design, and Tibotec/Janssen in Belgium, we succeeded in developing two non-nucleoside drugs, rilpivirine and etravirine, that have since been incorporated into six licensed medications for treating HIV/AIDS. Rilpivirine in particular has many advantageous features and recently was approved the first long-acting anti-HIV treatment (together with cabotegravir, an integrase inhibitor), as the injectable Cabenuva, requiring only once-monthly dosing. The journey has been highly rewarding and enjoyable and I am extremely grateful to my laboratory's many gifted members whose dedicated efforts have made our work possible, and the many other colleagues who contributed to these efforts.

91. Sequence-Based Design of Small Molecules Targeting RNA

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Selective recognition of RNA targets by small molecules holds much promise for understanding biology and for the development of therapeutics. We have taken an unconventional approach to define small molecules that selectively bind RNA folds, using a high throughput selection strategy dubbed two-dimensional combinatorial screening (2DCS). In 2DCS, a small molecule library selects its preferred 3D folds from an RNA library, affording annotated library of druggable RNA motifs and the small molecules that drug them. These data are mined against the human transcriptome to identify disease-causing RNAs with 3D folds that are bound by small molecules, a computational lead identification strategy we named Inforna. Inforna has defined precise small molecules that target a host of RNAs involved in various incurable or difficult-to-treat diseases and have helped to demonstrate that RNA is indeed druggable with small molecules. Furthermore, these studies show that a lead medicine can be quickly designed for a disease-causing biomolecule using solely its sequence, or sequence-based design of structure-specific ligands. In this talk, I describe these strategies and others which resulted in the design of small molecules that facilitate elimination of disease-causing RNAs, including targeted degradation via chemically induced proximity.

92. Design of Nucleotide Prodrugs for Antiviral Chemotherapy – the Tri*PPP*ro-Approach

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A variety of nucleoside analogues is clinically used in antiviral chemotherapy. Often the antiviral potency of nucleoside analogues is limited due to lack of intracellular phosphorylation into their triphosphates by cellular kinases. This problem cannot be solved by using the phosphorylated nucleosides due to their high polarity. To overcome this hurdle lipophilic precursors of nucleotides, which are able to pass the cell membrane and deliver the nucleotides intracellularly were developed, e.g. nucleoside mono- (*cyclo*Sal-system) and nucleoside diphosphate prodrug approaches (Di*PP*ro-approach) and most recently nucleoside triphosphate (NTP) prodrugs. In our work, d4TTP prodrugs with different aliphatic masking units have been synthesized by phosphoramidite or *H*-phosphonate chemistry. Our triphosphate delivery system is comprised of enzymatically cleavable masking groups (acyloxybenzyl-moieties) which are attached to the gamma-phosphate . Chemical and esterase hydrolysis, enzymatic cleavage in CEM/0 cell extract, primer extension assays, whole-cell incubations and antiviral HIV tests will be presented which proved the successful delivery of NTPs. Next, a prodrug approach in which the gamma-phosphate of NTPs was modified by two different groups was developed. One of these groups represents a cleavable acyloxybenzyl masking group while the other is a non-cleavable alkyl residue. These compounds offered very high stability towards dephosphorylation as compared to d4TTP in cell extracts. These compounds were highly potent against HIV-1 and HIV-2 in thymidine kinase-deficient $CD4^+$ T-cells. Primer extension assays using HIV's reverse transcriptase and different human DNA-polymerases showed that the new compounds acted as substrates for RT but were found to be non-substrates for DNA-polymerases beta and gamma.

93. Investigating enterotropic virus infections in human intestinal organoids

Christiane Wobus, Ph.D.[1]

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The gastrointestinal mucosa is organized into villi and crypts and comprised of a layer of epithelial cells, the lamina propria containing immune cells and a layer of smooth muscle cells. Recent developments in biomimetic human models of enteric disease are opening new possibilities for studying human-specific host-microbe interactions. Wide application of these models hold promise for revealing new knowledge about the complex interplay between pathogen, host, and commensals and the development of effective disease prevention and control measures for enteric diseases.

Human intestinal organoids are derived from stem cells isolated from intestinal biopsy tissues or from induced pluripotent stem cells. Most laboratories use human intestinal enteroids (HIE), which are epithelium-only intestinal organoids derived biopsy-derived stem cells. HIE have been successfully used to culture a range of enterotropic pathogens, including human norovirus and human rotavirus. We recently established HIE as a culture system for human astrovirus and demonstrated its superiority over traditional transformed intestinal cell lines. HIEs also support robust SARS-CoV-2 infection. Therefore, we have used HIE and addition to organoids of other tissues as a validation platform for antiviral drug testing. However, a key limitation for studying virus-host interactions using the current epithelium-only HIE system is the lack of immune cells and microbes, which are important players in intestinal homeostasis and critical drivers for enteric diseases. Thus, efforts are underway in the field for further innovations to improve these models and enhance their complexity.

101. Clinical evaluation of Lassa fever antiviral LHF-535 in a 14-day repeat dose study in healthy volunteers

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Lassa fever is a viral hemorrhagic disease endemic in West Africa. LHF-535 is a small molecule antiviral currently under development as a therapeutic option to treat Lassa fever and other viral hemorrhagic fevers of arenavirus origin. The human safety and pharmacokinetics of LHF-535 was evaluated in a Phase 1b trial in healthy volunteers, using a 14-day oral dosing regimen. A total of 24 healthy participants were enrolled into 3 sequential dose escalation cohorts of 8 participants each, such that 6 were randomized to 14 daily oral doses of LHF-535 (450, 900, or 1125 mg) and 2 were randomized to matching placebo. The third cohort (1125 mg/day) utilized a loading dose (2250 mg) on the first day to correspond to what might be used therapeutically and to accelerate the time to reach steady state. LHF-535 was safe and well-tolerated at all doses studied. The frequency of participants experiencing at least one treatment emergent adverse event (TEAE) was similar between LHF-535 (72%) and placebo (83%) participants, and the frequency of treatment-related TEAEs was higher in participants treated with placebo (50%) than LHF-535 (17%) participants. There were no serious adverse events. Pharmacokinetic evaluation determined that exposures exceeded those predicted to be therapeutically efficacious, supporting the continued clinical development of LHF-535 in a patient population.

102. Inhibition of Hepatitis Delta Virus (HDV) replication and decrease of HDV particles specific infectivity by inducers of the NF-κB pathways

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Hepatitis Delta Virus (HDV) super-infection of chronically Hepatitis B Virus (HBV)-infected patients is the most aggressive forms of chronic viral hepatitis, with an accelerated progression towards fibrosis/cirrhosis and an increased risk of liver failure, hepatocellular carcinoma, and death. At least 25 million of people would be co-infected with both viruses, ranking this co-infection as one of the most prevalent and most clinically challenging worldwide. While HDV infection is not susceptible to available direct anti-HBV drugs, suboptimal responses are obtained with IFN-€based therapies, and the number of investigational drugs remains limited. We recently established *in vitro* models of HDV super/co-infection of HBV-infected cells based on primary human hepatocytes (PHH) and the HepaRG cell line that are relevant to explore new therapeutics, including immune therapeutics.

Using those models, we analyzed the effect of several innate immune-stimulators on HDV replication in chronically infected cells. We further characterized the anti-HDV effects of Pam3CSK4, an agonist of TLR1/2 and BS1, an agonist of the Lymphotoxin Beta Receptor (LTbR) that both induced dose dependent reductions of total intracellular HDV RNAs, as well as HDV proteins levels. Off-drug rebound experiments revealed a long-lasting antiviral activity suggesting an irreversible effect on HDV replication and transcription templates. Both molecules negatively affect HDV progeny release and dramatically decrease their specific infectivity.

In conclusion, immune-modulators inducing NF-€B pathways in hepatocytes can strongly inhibit HDV replication, and could be further developed as efficient therapeutic approaches for HBV/HDV chronically infected patients.

103. Effects of troponoids on mitochondrial function

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The troponoids include both tropolones and α-hydroxytropolones (α-HT) defined by the presence of hydroxyl groups at one (tropolone) or both (α-HT) α positions on the conjugated seven-membered tropone ring. These compounds are effective against a variety of viruses, bacteria, and fungi, including Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), *S. aureus*, and *C. neoformans*. We have seen activity against the HBV RNaseH protein with low micromolar activity; however, troponoids can suffer from cytotoxicity *in vitro* evident in assays that measure mitochondrial function. While the mechanism of cytotoxicity has not been determined, early studies suggest that troponoids can disrupt the mitochondrial electron transport chain (ETC). Using the Seahorse XFp Flux Analyzer we tested the effect of 35 troponoids on the ETC and the glycolytic pathway in Huh7 cells at 50 μM. Troponoids, as a class, did not suppress the ETC. However, some troponoids did impact cellular respiration by suppressing the upstream glycolytic pathway. The effect on glycolysis was limited to a subset of tropolones with an acyl group on the secondary α position of the tropolone. Three of the six α-acyltropolones ablated the glycolytic reserve of the cells, which subsequently inhibited activity of the ETC. Therefore, while certain troponoids can impact cellular respiration through inhibition of glycolysis, most compounds had no significant effects on either the ETC or glycolysis. This includes all α-HT compounds tested here for which our lab has found substantial activity against HBV RNaseH protein.

105. General lipoperoxidators are not selective antiviral agents

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Only 11 of the many medically relevant enveloped viruses are targeted by specific antivirals, which each tends to be specific for one or a few viruses. We are interested in broad spectrum antivirals against enveloped viruses. Several broad-spectrum antiviral compounds targeting virion envelope lipids have been developed starting in 2007 with the RAFIs. Some lipid targeting antivirals have been proposed to act by inducing lipoperoxidation under a model in which the metabolically inert virions would not repair lipid damage, thus being more sensitivity than cells. However, the high envelope protein content may well inhibit the lipoperoxidation chain reaction.

We tested whether virions are particularly sensitive to lipoperoxidation, using well-characterized water- and lipid-soluble lipoperoxidators, AAPH and AMVN, respectively and two different probes, C11-Bodipy and Liperfluo. The effects of the lipophilic AMVN on cell death and virion viability directly correlated with the extent of membrane lipoperoxidation, whereas the hydrophilic AAPH induced cell death and virion inactivation at lower concentrations than lipoperoxidation. Virion inactivation and lipoperoxidation were only about 5-fold more sensitive to AMVN than cell death or lipoperoxidation. Virion inactivation by incubation in aerobic conditions or exposure to presumed lipoperoxidant molecules was equally inhibited by vitamin E, cholesterol, or the BSA carrier, indicating that protection does not depend on antioxidant activity. The hydrophilic antioxidant vitamin C protected against aerobic conditions and known lipoperoxidators, but not against presumed ones.

In conclusion, HSV-1 virions are not particularly sensitive to lipoperoxidation, indicating that general lipoperoxidators do not show good antiviral potential.

106. Chromatin dynamics and the transcriptional competence of HSV-1 genomes during lytic infections

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No antiherpesviral drug cures latency or prevents reactivation. New approaches are thus needed. Epigenetics have been proposed to regulate HSV-1 replication, latency, and reactivation, and epigenetic inhibitors have been evaluated as potential antiherpesvirals. Tranylcypromine, pargyline, OG-L002, dimethyloxalylglycine, ML324, 5′-deoxy-5′methylthioadenosine, GSK126, GSK343, and UNC1999 inhibited HSV-1 replication or reactivation. However, they inhibited the expected cellular epigenetic modifications, too, and were tested under models postulating the same epigenetic regulation for HSV-1 and cellular chromatin. It is thus difficult to envision epigenetic drugs as HSV-1 antivirals. HSV-1 and cellular chromatin may well be different, though. If so, any unique viral epigenetics may be druggable.

We used nuclease protection followed by chromatin fractionation and deep sequencing to probe for differences between HSV-1 and cellular chromatin. Like cellular DNA, HSV-1 DNA was protected to mono- to polynucleosome sizes in nucleoprotein complexes with the ratios of cellular mono- to polynucleosomes, in which it interacted with histones. However, HSV-1 and cellular chromatin were differentially accessible. Whereas most cellular DNA was in intermediately accessible chromatin, HSV-1 DNA was depleted in this chromatin and enriched in the most and least accessible. All HSV-1 genes were equally accessible regardless of transcription levels. HSV-1 chromatin dynamics were similar to those of the cellular chromatin when there was not much viral transcription.

We propose that the most dynamic HSV-1 chromatin is transcriptionally competent and the least, silenced. We are characterizing the mechanisms modulating dynamics and transcriptional competence of HSV-1 chromatin to address whether viral epigenetics may be druggable targets in antiviral therapy.

107. Evaluating the therapeutic potential of metformin against dengue

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Dengue, caused by dengue virus (DENV), is a prevalent mosquito-borne viral disease in the tropical and sub-tropical regions. Its potential to progress into severe, life-threatening conditions, has fueled research to develop an effective treatment. However, as of today, none has been approved for human use and the clinical pipeline is going dry. A couple of earlier studies have suggested that metformin (MET), a popular anti-diabetic drug, displays antiviral activity against DENV, providing the idea that MET could represent a safe and cheap medication against dengue. In this study, we evaluated the antiviral effect of MET against the four serotypes of DENV both i*n vitro* and *in vivo*. Our results showed that MET inhibited DENV replication with poor efficacy in Huh7, C6/36, and BHK-21 cells, but enhanced viral replication in Vero cells. AMPK activation resulting from MET treatment correlated with the antiviral activity in Huh7 and BHK-21 cells, but not with the antiviral and pro-viral activity in C6/36 and Vero cells respectively. Furthermore, the relative contribution of AMPK-dependent effects on the overall effect of MET on DENV replication was then examined via *in vitro* treatment with Compound 991, a direct AMPK activator. *In vivo*, using asymptomatic transient viremia models, MET therapeutic treatment did not result in significant reduction in viremia titers. Neither MET treatment protected DENV2-infected IFNAR$^{-/-}$ mice from symptomatic disease. Instead, poorer survival and increased disease severity, accompanied with higher viremia titers and systemic inflammation were observed. Collectively, these results suggest that MET may not represent a promising anti-DENV therapeutic.

108. G-quadruplex stabilising ligands like Braco-19, TMPyP4 elicit new strategies for viral drug targeting

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Viral diseases caused by deadly viruses like Zika, Nipah, SARS-CoV-2, etc. have created a global menace and demands urgent attention. The viral genomes are unique in their genomic compositions, having either RNA or DNA as the genetic material. In this aspect, nucleic acid secondary structures specifically, Guanine-rich sequences folding into G-quadruplex (GQ) structures hold the affirmative scope to act as ligand binding sites and have immensely gained attention in the field of drug discovery. We have identified and explored the potential of these GQ forming sequences in Zika virus and Nipah virus. Further, studies with known GQ structure-binding and stabilizing small molecules such as Braco-19 and TMPyP4 showed their stable interaction with the viral GQ structures. Moreover, these ligands in cell culture media led to significant inhibition of infectious Zika virus yield as well as reduced viral genome replication and viral protein production. Overall, the results showcase that the viral replication can be inhibited by GQ structure binding and stabilizing compounds and suggest a new strategy for targeting such viral diseases.

109. Identification of novel dissociative inhibitors targeting the replication complex of dengue virus

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Dengue virus (DENV) is responsible for approximately 390 million infections worldwide that may progress to a severe, life-threatening dengue. To date, no licensed drugs are available to treat DENV infection, highlighting the urgent need for developing innovative antiviral strategies against dengue virus. A promising strategy to develop anti-dengue drugs is to target the protein-protein interaction between NS3 and NS5, as this binding plays a crucial role in the formation and coordination of the DENV replication complex and its interface is highly conserved in DENV. After the generation of a protein-protein model of the DENV NS3/NS5 dimer, we identified two potential druggable binding sites at the interaction interface on both proteins and performed two virtual screening of commercially available compounds in order to identify dissociative inhibitors of NS3-NS5 interaction. The ability of the selected hits to interfere with such interaction were then tested in a developed ELISA-based NS3/NS5 interaction assay able to measure this interaction in vitro, using E.coli-expressed viral proteins. Among the selected hits, some compounds were able to disrupt the physical interaction between NS3 and NS5 in a dose-dependent manner. In addition, the most promising compounds efficiently inhibited the replication of DENV in plaque reduction assays, at non-cytotoxic concentrations. In conclusion, we are reporting on the identification of novel chemical scaffolds that represent a promising starting point in the development of a novel family of DENV inhibitors.

110. Sulfonated Compounds Inhibit More Viruses Than Expected

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Heparan sulfate proteoglycans (HSPG) are receptors widely expressed on eukaryotic cells, they are involved in many biological activities, but due to the high degree of sulfation they are used as well by a range of viruses to attach to the host surface. In the past years we developed nontoxic, broad-spectrum virucidal gold nanoparticles and cyclodextrins mimicking HSPG by exposing sulfonates and proved their activity in vitro, ex vivo and in vivo. However, the same materials are active as well against non HSPG dependent viruses, in particular against Influenza virus and VSV. We investigated the mechanism of action of our compounds proving a virucidal activity against the former and a virustatic activity against the latter, although the compounds, also in this case, are able to interfere with the viral attachment. Recently we tested our nanomaterials against SARS CoV2, for which HSPG dependency has been documented by a number of papers and preprints. However, we observe only a virustatic activity of our compounds and no activity of other commercial sulfated compounds. The lack of virucidal activity against VSV and SARS CoV2 suggest that our materials are able to establish weak interactions also with non-specific domains on the viruses and thus inhibit viral attachment. Further investigation is needed to understand how to increase the affinity and therefore reach the virucidal activity also for viruses not binding HSPG.

111. Synthesis of acyclic-phosphonate-diphosphate Prodrugs

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In the 1980s, Holý and co-workers synthesized the first acyclic nucleoside phosphonates (ANP). In contrast to nucleoside analogues, these compounds act as nucleotide analogues, and they showed high anti(retro)viral activity, low toxicity, and a high barrier towards resistance development. Since the phosphonates carry at least one negative charge, they need to be applied as prodrugs to pass the cell membrane. Unlike nucleoside analogues, ANPs need two host enzyme-mediated phosphorylation steps to form the antivirally active metabolite. While different prodrugs of PMPA (TDF, TAF) and PMEA (adefovir dipivoxil) became highly successful drugs, in these prodrugs only mask the phosphonate is masked to enhance its bioavailability; of the higher phosphorylated, active form no prodrugs have yet been reported.

Our aim is to fill this gap and based on our previous work on nucleoside triphosphate prodrugs, we report on the application of our Tri*PPP*ro-approach to PMPA-diphosphate, hence generating the first example of prodrugs of the ultimately active form of PMPA. Furthermore, we aimed to enhance catabolic stability of these phosphonate-diphosphates by attaching a stable modification at the g-phosphate.

First studies confirmed that our prodrugs exhibited sufficient chemical stability and were efficiently enzymatically activated and thus released active nucleoside analogue phosphonate-diphosphates or the respective g -modified analogue. Importantly, antiviral potency against HIV-1 and HIV-2 of our Tri*PPP*ro-PMPA-compounds was up to 13-fold higher compared to our previous prepared *cyclo*Sal-analogues and up to 23-fold higher than the parent PMPA, suggesting that our new compounds are able to penetrate the cell membrane and release the active component.

113. Synthesis and Biological Evaluation of Flex-Acyclovir Analogues Against SARS-CoV-2

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Over the past year, the world has been devastated by the SARS-CoV-2 pandemic. As the pandemic continues to spread, the search for direct acting antiviral drugs has intensified. In that regard, nucleos(t)ide analogues have a rich history of use as antivirals, and one modification in nucleoside drug design that has proven successful, is the use of an acyclic sugar, such as that found in Acyclovir (ACV), an FDA-approved drug for herpes simplex virus. Acyclic nucleosides lack the 2′ and 3′ hydroxyl groups of the sugar moiety found in the naturally occurring nucleosides. For many years research in the Seley-Radtke group has focused on the development of novel nucleos(t)ide analogues known as "fleximers". The fleximers feature a "split" purine nucleobase, where a carbon-carbon single bond connects the pyrimidine and imidazole rings, thus introducing flexibility to the nucleobase scaffold. This flexibility endows the analogues with potent activity not seen for the corresponding rigid analogue. In that regard, combining the flex-nucleobase with the acyclic sugar of ACV produced the doubly flexible Flex-ACV analogues. These novel analogues have exhibited low micromolar to nanomolar levels of activity against coronaviruses (CoVs) such as SARS, MERS and human CoVs, as well as Ebola, Yellow Fever, Dengue and tickborne encephalitis, while ACV has no activity against those viruses. Following these observations, Flex-ACV analogues HP-083, HP-083-OAc, and HP-083-McG have now been screened against SARS-CoV-2 and COVID-19 in vitro and in vivo, as well as MTD and other pharmacokinetic studies. The results of those efforts are described herein.

114. STAT2 signaling restricts viral dissemination but drives severe pneumonia in SARS-CoV-2 infected hamsters

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Emergence of SARS-CoV-2 causing COVID-19 has resulted in hundreds of thousands of deaths. In search for key targets of effective therapeutics, robust animal models mimicking COVID-19 in humans are urgently needed. Here, we show that Syrian hamsters, in contrast to mice, are highly permissive to SARS-CoV-2 and develop bronchopneumonia and strong inflammatory responses in the lungs, confirmed as consolidations visualized by micro-CT, which allows to conveniently monitor the effect of therapeutic strategies and to test the preclinical efficacy of vaccine candidates. Moreover, we identify an exuberant innate immune response as key player in pathogenesis, in which STAT2 signaling plays a dual role, driving severe lung injury on the one hand, yet restricting systemic virus dissemination on the other. Our results reveal the importance of STAT2-dependent interferon responses in the pathogenesis and virus control during SARS-CoV-2 infection and may help rationalizing new strategies for the treatment of COVID-19 patients.

115. CRISPR genome-wide screening identifies host factors for SARS-CoV-2 and common cold coronavirus replication

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Common cold human coronaviruses cause only mild upper respiratory tract illness, but SARS-CoV, MERS-CoV and the recently emerged SARS-CoV-2, are highly pathogenic and can cause severe, potentially lethal respiratory infections. These viruses likely all emerged as zoonosis from bats, mice or domestic animals, which can sometimes quickly reach devastating proportions as exemplified by the recent COVID-19 pandemic. Despite this risk and its great economic and social impact, our options to prevent or treat coronavirus infections remain very limited. Hence, the development of broad-spectrum antiviral drugs against coronaviruses could help not only to address the current high medical need, but also to quickly combat and contain zoonotic events in the future. Common cellular host factors, essential for replication of multiple viruses, may represent attractive targets for such broad-spectrum antiviral drugs.

To identify host factors that support coronavirus infection, we performed CRISPR-based genome-wide functional genetic screens with SARS-CoV-2 and the common cold virus HCoV-229E. These screens identified PI3K type 3 as a potential drug target against multiple coronaviruses, which we pharmacologically validated for SARS-CoV-2, HCoV-229E, and HCoV-OC43 infection. We identified TMEM41B and TMEM106B as specific host factors for HCoV-229E and SARS-CoV-2 infection respectively. The lysosomal protein transmembrane protein TMEM106B is required for SARS-CoV-2 replication in multiple human cell lines derived from liver and lung, and is expressed in SARS-CoV-2-susceptible cells in the airways of COVID-19 patients. In conclusion, our results identify new coronavirus host factors that may potentially serve as drug targets to combat the COVID-19 pandemic or future zoonotic coronavirus outbreaks.

116. Polynuclear platinum complexes exhibit broad spectrum antiviral activity

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Broad spectrum antivirals would offer (1) treatment for viruses without specifically-targeted antivirals, (2) treatment for viruses which have developed resistance to their specifically targeted treatments, and (3) a rapidly deployable treatment option in viral epi/pandemics. A well-defined target for many viruses is heparan sulfate (HS), a highly sulfated glycosaminoglycan necessary for virion/host cell attachment. To date, HS-viral attachment inhibitors have utilized biopolymers, inorganic polymers, and cationic organic and inorganic compounds. We recently published the anti-human cytomegalovirus (HCMV) activity of substitution-inert polynuclear platinum complexes (PPCs), defined platinum compounds with high positive charges, the ability to hydrogen bond, and inability to covalently bond, decreasing their cytotoxicity. PPCs have previously been shown to bond electrostatically to HS via formation of a sulfate clamp that is analogous to phosphate clamp-mediated interactions with DNA. Thus, through this 'metalloshielding' PPCs have the ability to inhibit HS functions, including viral attachment as demonstrated with HCMV (Shoup et al., *Antiviral Research*, 184, 2020). Current efforts are directed toward further exploring the spectrum of antiviral activity. We have defined their anti-adenovirus activity and mechanistic studies are consistent with an inhibition of viral attachment and/or entry. Inhibition of pseudotyped lentivirus particle entry mediated by SARS-CoV-2 spike protein has also been demonstrated, while collaborators have recently demonstrated activity of PPCs against enterovirus 71 (EVD71) and human metapneumovirus (von Itzstein, personal communication). PPCs offer an attractive alternative to current antiviral compounds with the potential to target a broad spectrum of viruses that utilize HS for attachment and entry.

117. Viral Fitness of Herpes Simplex Virus 1 (HSV-1) Mutants Isolated From a Hematopoietic Stem Cell Transplant (HSCT) Recipient

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Introduction: HSV-1 is a widespread human pathogen that can cause severe disease in immunocompromised patients (ICs), who often require prolonged antiviral therapy, increasing the risk of drug-resistance. Therefore, it is important to study evolution of drug-resistance and its effect on viral fitness.

Objectives: The effect of mutations found in HSV-1 samples of a HSCT recipient on drug-resistance and viral fitness was evaluated.

Methods: A patient that received a HSCT was treated consecutively with Acyclovir, Foscarnet, Cidofovir, and a combination of Ganciclovir and Cidofovir. In 3 months, five HSV-1 samples were recovered and characterized genotypically [Sanger Sequencing of the viral thymidine kinase (TK) and DNA polymerase (DP)] and phenotypically (plaque reduction assay). Viral clones were isolated by serial dilution. *In vitro* dual growth competition with wild-type virus was performed under pressure of several antivirals and viral populations were quantified by Next Generation Sequencing.

Results: A rapid evolution of drug-resistance to Acyclovir and Foscarnet was observed. Two samples taken the same day from different lesions showed difference in viral populations and heterogeneity. In total, six different viral variants were isolated, including TK-, DP-, and TK/DP mutants. Except for the TK:A189V+DP:L802F double-mutant, clones showed no change of fitness compared to wild-type virus without antiviral pressure. All mutants showed significant loss of fitness under CDV pressure, even the mutant TK:T183P+DP:L778M that showed multi-drug resistance. *In vitro* dual growth competition is useful to study HSV-1 fitness and determining the effect of mutations on viral fitness may help to improve treatment of HSV-1 infections in ICs.

118. Polyamine analog diethylnorspermidine restricts Coxsackievirus B3 and is overcome by 2A protease mutation

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Enteroviruses, including Coxsackievirus B3 (CVB3), are pervasive pathogens that cause significant disease, including cardiomyopathies. Unfortunately, no treatments or vaccines are available for infected individuals. We identified the host polyamine pathway as a potential drug target, as inhibiting polyamine biosynthesis significantly reduces enterovirus replication *in vitro* and *in vivo*. Here, we show that CVB3 is sensitive to polyamine depletion through the polyamine analog diethylnorspermidine (DENSpm), which enhances polyamine catabolism through induction of polyamine acetylation. We demonstrate that CVB3 acquires resistance to DENSpm via mutation of the 2A protease, which enhances proteolytic activity in the presence of DENSpm. Resistance to DENSpm occurred via mutation of a non-catalytic site mutation and results in decreased fitness. These data demonstrate that potential for targeting polyamine catabolism as an antiviral target as well as highlight a potential mechanism of resistance.

119. Therapeutic delivery of defective interfering particles protects hamsters from lethal Nipah virus disease.

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Defective interfering (DI) genomes alter the kinetics of viral replication and propagation by directly competing with the full-length virus for resources. We previously demonstrated potent in vitro inhibition of Nipah virus (NiV) infection (>10,000-fold reduction in titer) using artificially generated DI particles based on natural DI sequences detected in serial passaging studies. To evaluate the in vivo therapeutic potential of DI particles, we investigated the effect of 4 therapeutic candidates (3 copybacks and 1 deletion DI) on clinical outcome in the lethal Syrian hamster model of NiV disease. We first evaluated intraperitoneal high-dose DI co-administration with virus; a single dose (DI:NiV ratio of 20,000:1) protected up to 80% of animals from lethal disease. Then, to more closely mimic natural exposure, we evaluated intranasal co-administration of DI with virus challenge. Intranasal DI delivery also conferred up to 80% survival, even with a 200-fold lower DI:NiV ratio than administered intraperitoneally. Additionally, we found that DI treatment reduced viral RNA levels in multiple organs during early infection, and reduced oral shedding. Overall, DI treatment reduced incidence, duration, and severity of NiV disease in hamsters. These data provide evidence that DI particles can be successfully administered therapeutically, supporting further development of DI therapeutics for NiV and for other high-consequence pathogens.

120. Two host poly(A) polymerases PAPD5 and PAPD7 provide redundant but distinct mechanisms to protect hepatitis B virus RNA integrity and stability

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Cellular noncanonical poly(A) polymerases, PAPD5 and PAPD7 (PAPD5/7), are required for HBV RNA stability. The dihydroquinolizinones chemical class, exampled by RG7834 and AB-452, has been reported to destabilize HBV RNA. AB-452 targets PAPD5/7 and inhibits their enzymatic activities, resulting in potent reduction of HBsAg in HBV replicating cell culture models with either integrated viral genome or cccDNA as the viral transcription source (EC_{50} = 1.4 to 6.8 nM), and *in vivo* using the AAV-HBV mouse model. Mechanism of action studies show that AB-452 destabilizes HBV RNA by shortening the poly(A) tail from 100-120 to 50-60 nucleotides and reduces guanosine incorporation within the poly(A) tail. Genetic analysis using PAPD5/7 single and double knock-out (DKO) cell lines revealed that (i) silencing PAPD5 or PAPD7 alone had no apparent effect on viral replication, (ii) the DKO effectively impaired viral gene expression and DNA replication, and (iii) PAPD5/7 provide redundant but distinct mechanisms in protecting HBV RNA integrity and stability. Our results indicate that HBV utilizes PAPD5 as the dominant protection mechanism to maintain the integrity of its poly(A) tail and the stability of the viral RNA. On the other hand, PAPD7 did not contribute to protecting poly(A) tail integrity but serves as a second line of protection to stabilize viral transcripts. The small-molecule DHQ compound, AB-452, disrupts viral RNA integrity and stability by inhibiting both PAPD5/7, which leads to the deprotection of viral poly(A) tails and subsequently decreased HBsAg production and DNA replication.

121. Nipamovir: synthesis and preclinical evaluation of an anti-HIV thiobenzamide prodrug.

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Human immunodeficiency virus type 1 (HIV-1) is still a major public health concern. Highly active antiretroviral therapy (HAART) is a combination of antiretroviral drugs targeting the virus at multiple stages of its replication cycle which has helped reduce new HIV infections as well as AIDS-related deaths. However, its routine application has led to multi-drug resistance and the onset of adverse side-effects that results from long-term use. It is therefore crucial to continue the development of novel antivirals, particularly those that are inexpensive, nontoxic, and which are unlikely to result in viral resistance. Thiobenzamide molecules like Amovir (Fig. 1) are chemically simple HIV inactivators targeting viral nucleocapsid protein 7 (NCp7), a 55 amino acid protein that performs essential functions during the assembly and maturation of new HIV virions. This class of molecule also shows low toxicity, and a high barrier to viral resistance. We developed Nipamovir (Fig. 1), a prodrug which protects the sulfur atom of Amovir in a similar manner to the clinically used immunosuppressant Azathioprine. Our molecule is very simple to reproducibly synthesize and has similar antiviral activity compared to Amovir and other thiobenzamides. Here we report the synthesis, in-vitro and in-vivo preclinical evaluation of Nipamovir.

122. Design, Synthesis and Biological Evaluation of 2-(4-(phenylsulfonyl)piperazine-1-yl) pyrimidine analogues as Novel Inhibitors of Chikungunya Virus

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Despite the worldwide re-emergence of the chikungunya virus (CHIKV) as an epidemic threat and the rising morbidity associated with this alphavirus, so far there are neither vaccines nor pharmacotherapy available to prevent or treat an infection.

We identified a novel compound series (2-(4-(phenylsulfonyl)piperazine-1-yl)pyrimidine analogues) with remarkable antiviral activity against this alphavirus based on a hit molecule identified by high-throughput screening. Pharmacophore based analysis and molecular docking approaches were then used for a thorough structure-activity relationship study to identify common interactive patterns and to improve the already promising antiviral activity (starting from EC_{50} of 8.68 μM resulting in a lower EC_{50} value of 3.95 μM). By carefully investigating the small variations of the molecular structures and their antiviral effect measured in the biological CPE-reduction assays a relationship between these two parameters was found and were further influencing the future molecular modelling process. Additional extensive *in silico* investigations were then performed to examine other fundamental properties such as metabolic stability, logP, and cytotoxicity of our compound series. In addition, an optimization of the established synthesis route was achieved. By changing the starting point of the synthesis route and by incorporating new protocols the reaction time was shortened from 96.5 h to 18.5 h. Moreover, the products of two of the newly introduced protocols can be taken further without any purification needed – which shortens also the synthesis time by avoiding the difficult and time-consuming purification steps and increasing the overall yield.

123. Molnupiravir (EIDD-2801) inhibits SARS-CoV2 replication in Syrian hamsters model

Rana Abdelnabi, Ph.D.[1], Caroline S. Foo, Ph.D.[1], Suzanne J.F. Kaptein, Ph.D.[1], Xin Zhang, M.S.[1], Lana Langendries, M.S.[1], Laura Vangeel, Ph.D.[1], Valentijn Vergote, Ph.D.[1], Elisabeth Heylen, Ph.D.[1], Kai Dallmeier, Ph.D.[1], Arnab Chatterjee, Ph.D.[2], Steven De Jonghe, Ph.D.[1], Birgit Weynand, Ph.D.[3], Johan Neyts, Ph.D.[1]

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Since its emergence in Wuhan, China in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide resulting in a global pandemic with >1.5 million deaths until now. In the search for small molecule inhibitors of SARS-CoV-2, drug repurposing is being extensively explored. Molnupiravir (EIDD-2801) is an orally bioavailable nucleoside analog that possesses a relatively broad-spectrum antiviral activity including against coronaviruses. We here studied the effect of EIDD-2801 in a well-established Syrian hamster SARS-CoV2 infection model. Treatment of SARS-CoV-2-infected hamsters with 200 mg/kg BID of EIDD-2801 for four consecutive days, starting from the day of infection, significantly reduced infectious virus titers and viral RNA loads in the lungs and markedly improved lung histopathology. When onset of treatment was delayed until 1 or 2 days after infection, a very modest antiviral effect was observed. The potential of EIDD-2801 for the treatment and or prevention of SARS-CoV2 deserves further attention.

124. Swellable Hydrogel Microneedles Backed by a Drug Reservoir Patch for Treatment and Prevention of the Flu

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Yearly influenza epidemics strike millions, causing up to 650,000 deaths with significant mortality, especially in the very young and the elderly. Current antiviral treatments include oseltamivir, zanamivir and baloxavir. While Zanamivir (ZAN) has a superior resistance profile compared to other products, its delivery method is currently restricted to oral dry powder inhalation.

Transdermal delivery systems offer a number of advantages over inhalation and IV administration. TSR-066 is a 2-part system, consisting of a ZAN-loaded reservoir patch that is placed on top of a hydrogel microneedle (MN) array. Upon skin penetration, MNs become hydrated and swell, creating pores for drug to diffuse through at comparatively high doses and over prolonged periods of time.

We demonstrated in a rat pharmacokinetic study that with administration of a 1 cm^2 ZAN MN patch, that ZAN directly enters the systemic circulation and reaches the target compartment for efficacy, the epithelial lung lining fluid, at levels well above its IC_{50} within 30 minutes, and sustains these levels over 72 hrs. Exposure-matched subcutaneous administration of ZAN in a lethal mouse model of influenza was assessed against an oseltamivir-resistant influenza strain (A/HongKong/2369/2009 (H1N1pdm)). We demonstrated dose-dependent increase in survival with BID dosing and with intermittent dosing regimen when ZAN was administered 4 hrs prior to the infection, and with dosing as late as 24 hrs post infection.

We have shown that efficacious plasma levels of zanamivir are achievable via microneedle-enabled transdermal delivery, and TSR-066 will now advance to pharmacokinetic and toxicology studies in pigs, and, ultimately, clinical evaluation.

125. SARS-CoV-2 induce lytic reactivation of Kaposi's sarcoma-associated herpesvirus

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An outbreak of the novel coronavirus SARS-CoV-2, the causative agent of Coronavirus Disease-2019 (COVID-19), a respiratory disease, has infected over 75,000,000 people since the end of 2019, killed over 1,600,000, and caused worldwide social and economic disruption. Because the mechanisms of SARS-CoV-2 infection of host cells and its pathogenesis remain largely unclear, there are currently no antiviral drugs with proven efficacy. Besides severe respiratory and systematic symptoms, several comorbidities increase risk of fatal disease outcome. Therefore, it is required to investigate the impacts of COVID-19 on pre-existing diseases of patients, such as cancer and other infectious diseases. Kaposi's sarcoma-associated herpesvirus (KSHV) is the etiologic agent of several human cancers, such as Kaposi's sarcoma (KS) and Primary effusion lymphoma (PEL), mostly seen in immunosuppressed patients especially people with HIV infection. In the current study, we report that SARS-CoV-2 encoded spike (S) and nucleocapsid (N) proteins and some currently used anti-COVID-19 drugs (especially Azithromycin and Nafamostat mesylate) are able to induce lytic reactivation of KSHV from virus infected normal and tumor cells, through manipulation of intracellular signaling pathways such as MAPK and NF-κB. In addition, we also found the obvious upregulation of ACE2 expression, the major receptor of SARS-CoV-2, in AIDS-KS tissue when compared to normal skin tissue, indicating the potential of increasing SARS-CoV-2 infectivity. Together, our data indicate that those KSHV+ patients especially in endemic areas exposure to COVID-19 or undergoing the treatment may have increased risks to develop some virus-associated cancers, even after they have fully recovered from COVID-19.

126. Consecutive Alternating Administration of Double Combinations and Drug Sensitivity of Coxsackievirus B3 Infection

WITHDRAWN

127. NPP-669: A Novel Broad-Spectrum Antiviral Therapeutic with Excellent Cellular Uptake, Antiviral Potency, Oral Bioavailability, Preclinical Efficacy, and a Promising Safety Margin

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DNA viruses are responsible for many diseases in humans, often exhibiting long-term persistent or latent infections. While the host's immune system generally keeps them in check, these infections can become severe and life-threatening in immunocompromised patients. Current treatments are effective, but are limited by resistance and dose-limiting toxicity. For example, Cidofovir (CDV, Vistide®) is a broad-spectrum antiviral, licensed for treatment of AIDS-related cytomegalovirus (CMV) retinitis, and is also used against other DNA virus infections including adenovirus (AdV) infections. CDV is a polar molecule with poor oral bioavailability, and must therefore be administered intravenously. Moreover, its overall clinical utility is limited by high occurrence of acute nephrotoxicity.

We have designed a series of orally available CDV analogs with excellent solubility, optimized metabolic stability, increased cellular permeability, and rapid intracellular conversion to the pharmacologically active diphosphate (CDV-PP). These compound characteristics resulted in significantly enhanced antiviral potency against a wide range of DNA viruses in infected human foreskin fibroblasts (e.g., IC_{90} against HCMV of <0.0001 μM). The increased *in vitro* prodrug stability correlated with a decrease in systemic clearance *in vivo*, and a pharmacokinetic profile that maintained plasma and target tissue levels well above the IC_{50} for 24 hrs. These data allowed us to identify a novel lead candidate, NPP-669, with improved drug-like properties, demonstrated efficacy against CMV infections in mice and AdV infections in hamsters following oral dosing, and a favorable exploratory safety profile compared to CDV. NPP-669 has been scaled up and will now advance towards GLP toxicology studies.

128. Phase 1/2 Antiviral and Clinical Efficacy Primary Results with REGEN-COV (Casirivimab With Imdevimab), a Cocktail of Two Antibodies Against SARS-CoV-2 Virus, in the Outpatient Setting

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Initial descriptive Ph1/2 results (275 patients) reported antiviral effects of casirivimab and imdevimab, neutralizing monoclonal antibodies (used together as a "cocktail" to minimize mutant escape), against SARS-CoV-2 spike protein (DOI:10.1056/NEJMoa2035002). We now describe formal hypothesis testing of efficacy from the subsequent 524/total 799 patients.

Nonhospitalized patients were randomized 1:1:1 to placebo, 2.4 g, or 8.0 g cocktail. Endpoints tested hierarchically included time-weighted-average-daily-change from baseline (TWACB) in viral load (Days 1–7) (primary) and proportion of patients with ≥1 COVID-19-related medically-attended visit (MAV: hospitalization; outpatient, urgent care, ER visit) through Day 29 (key secondary), in SARS-CoV-2 PCR-positive patients.

Differences (LS-mean) in TWACB in viral load for the combined-dose-group vs placebo were –0.73 $\log_{10}$ copies/ml/day ($p<0.0001$) among seronegative patients (undetectable baseline SARS-CoV-2 antibodies) and –0.36 $\log_{10}$ copies/ml/day ($p<0.001$) in the overall PCR-positive population; antiviral effect was greater in those with higher baseline viral load. Fewer combined-dose-group patients (2.8%;12/434) vs placebo (6.5%;15/231) reported ≥1 MAV ($p<0.05$), with greater benefit in seronegative patients. Most MAVs (18/27) were hospitalizations or ER visits. MAVs were reduced by 72% ($p<0.01$; post-hoc) in combined-dose-group patients with ≥1 risk factor for hospitalization; hospitalizations or ER visits were reduced 70% ($p<0.05$; post-hoc). Rates of hypersensitivity or infusion-related reactions and SAEs were similar between groups.

Casirivimab and imdevimab cocktail significantly decreased viral load, confirming prior results, with greatest effect in seronegative patients and/or patients with high baseline viral load. The antibodies demonstrated benefit in significantly decreasing the proportion of patients with COVID-19-related MAVs, with greatest reductions in patients with risk factors.

129. Fatty acid beta oxidation as a target for antiviral therapy against Junín virus

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Argentine Hemorrhagic Fever (AHF) is a disease caused by a member of the Arenaviridae family, Junín virus (JUNV). There is currently no chemotherapy against it, only immunotherapy with convalescent plasma. We have previously described a close relation between JUNV's replication cycle and the host cell's lipid metabolism. We found that cells infected with JUNV have fewer lipid droplets than non-infected cells. The activation of pro-viral autophagy after JUNV infection could be the mechanism behind this phenotype. Since this mechanism is accompanied by an increase in fatty acid beta oxidation, we hypothesized that the latter could be targeted to inhibit JUNV's replication. To that end, we assayed the effect on viral replication of etomoxir, a specific and irreversible inhibitor of the carnitine palmitoyltransferase I (CPT-I), a mitochondrial enzyme that catalyzes the rate limiting step in long-chain fatty acid oxidation.

To test our hypothesis, we infected human hepatoma cells, HepG2 with JUNV and treated the monolayers with 5 to 200 uM of etomoxir. 48 hours post infection, the supernatants were titrated by plaque assay. The number of infective particles produced by the cells was reduced in a dose-dependent manner, reaching an EC50 of 7.7 uM, with a CC50 of 148.2 uM and an SI of 19.2. We are currently exploring this finding in depth, via RT-PCR and immunofluorescence.

These results show for the first time that fatty acid beta oxidation is a pathway that could be targeted by an antiviral therapy against JUNV. Consequently, etomoxir and other inhibitors should be further studied.

130. Discovery of Novel Pyrimidine Based Inhibitors of Respiratory Syncytial Virus Fusion Protein

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Respiratory Syncytial Virus (RSV) causes respiratory tract infections in vulnerable patient groups including infants, immunocompromised adults and the elderly. No effective treatments are available, and consequently RSV imposes a significant burden upon patients and healthcare providers. Viral attachment and entry into the host cell is mediated by the RSV fusion (F) protein. Inhibitors of RSV F-protein have demonstrated efficacy in RSV human viral challenge studies, and several are currently under evaluation in Phase II clinical trials in patient populations, including Sisunatovir. As part of our program to identify novel inhibitors of RSV F-protein, we identified a series of pyrimidine-based inhibitors. The leading compounds in this series demonstrate potent antiviral activity in RSV fusion and plaque reduction assays against both RSV A and B subtypes. ADME properties are also favorable for developing an orally available inhibitor. A crystal structure of a lead compound from this series bound to the pre-fusion conformation of F-protein shows key binding interactions of the compound to the protein which are described herein.

131. Introduction of a Cyano Group at the 2-Position of 3-Hydroxy-2-(phosphonomethoxy)propyl (HPMP) Nucleosides Elicits Potent Anti-HBV Activity

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Clinically approved acyclic nucleoside phosphonate (ANP) drugs play a central role in the therapy of viral infections such as those caused by human cytomegalovirus (HCMV), hepatitis B virus (HBV), and human immunodeficiency virus (HIV). ANPs resulted from the replacement of the rigid sugar ring of related cyclic nucleosides with a flexible acyclic side chain. The prototypes of ANPs are 3-hydroxy-2-(phosphonomethoxy)propyl (HPMP) nucleoside analogues, which were shown to be effective inhibitors of DNA virus replication. Particularly, the cytosine congener [(*S*)-HPMPC, Cidofovir] received FDA approval on the basis of its ability to suppress the progression of CMV retinitis in immunocompromised patients. Herein, we investigated the effect of structural modification at the 2-position of HPMP-type nucleosides on their antiviral profile by synthesizing racemic 2-cyano-3-hydroxy-2-(phosphonomethoxy)propyl (CHPMP) analogues. The introduction of a 2-cyano group significantly reduced the anti-HCMV activity of (*S*)-HPMPC, while leading to a marked enhancement of the anti-HBV activity of the thymine-containing congener. CHPMPT (1) was found to be not only highly active (EC_{50} = 0.331 mM), but also a selective anti-HBV ANP. Moreover, compound 2 (CHPMPA) was endowed with significant activity against HBV (EC_{50} = 3.60 μM) and HCMV (EC_{50} = 1.09 μM), while compound 3 (CHPMPG) exhibited an EC_{50} value of 2.03 μM against HCMV. Nucleoside derivatives with potent activities against HBV are often equipotent antiretroviral agents. However, compound 1 completely lacked anti-HIV activity, representing a rare example of ANP with a substantial difference in anti-HIV and anti-HBV activity.

132. Structural Characterisation of Inactivated SARS-CoV-2 Particles for a Vaccine Preparation

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COVID-19 pandemic boosted antiviral research, and vaccines appeared to be the fastest public health response strategy. Different platforms were employed for vaccine design, among which the inactivated whole virion approach is the most conventional, being used for several decades. This approach was exploited in Chumakov FSC R&D IBP RAS for the development of a vaccine based on the SARS-CoV-2 strain AYDAR-1 (EPI ISL 428851), isolated in Russia (Int J Infect Dis. 2020;99:40-46).

Here we present a characterisation of inactivated SARS-CoV-2 particles, obtained using vaccine production pipeline with gel-permeation chromatography and via ultracentrifugation of the inactivated virus, by means of transmission electron microscopy (TEM), atomic force microscopy (AFM), and dynamic light scattering. TEM of negatively-stained concentrates revealed pleomorphic spherical particles about 90-120 nm in diameter. Both AFM and TEM revealed the spikes on the surface of the virions. The sizes of the virions measured using TEM and AFM matched perfectly, considering these methods' special aspects.

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133. Synthesis and antiviral evaluation of (1,4-disubstituted-1,2,3-triazol)-(E)-2-methyl-but-2-enyl nucleoside phosphonate prodrugs

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Acyclic nucleoside phosphonates (ANPs) are a key class of antiviral drugs (1). Recently, our group has reported a new family of ANPs based on a *trans*-but-2'-enyl phosphonate scaffold, (2,3). Herein, we report the synthesis of a series of *hitherto* unknown (1,4-disubstituted-1,2,3-triazol)-*(E)*-2-methyl-but-2-enyl nucleosides phosphonate prodrugs with 4-substituted-1,2,3-triazoles; the straight and convergent approach is based on olefin acyclic cross metathesis and CuAAC reaction as key synthetic steps. In order to improve their cell absorption, these phosphonate analogs have been designed as bis(POC), mixed HDP/POC and phosphonoamidate prodrugs. All novel compounds were evaluated for their antiviral activities against HBV, HIV and SARS-CoV-2. Data will be presented.

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134. Design, synthesis and biological evaluation of 2-substituted-6-[(4-substituted-1-piperidyl)methyl]-1H-benzimidazoles as inhibitors of ebola virus infection

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Ebola virus (EBOV) causes severe hemorrhagic fever, for which therapeutics are still needed. Even if promising results with antibody therapies have been reported, and very recently one has been approved for the treatment of EBOV infection, one important application for an anti-EBOV small molecule could be the treatment of persistently-infected patients. Some representative antifilovirus small molecules belong to several chemical classes target virus genome replication such as Remdesivir or virus entry such as toremifene and terconazole (two Niemann-Pick C1-dependent inhibitors) or the benzylpiperazine adamantane diamide-derived (3.47) which was reported to block binding of EBOV-GP to NPC1. Several of the virus entry inhibitors are sharing common moieties, such as benzimidazole, piperazine and piperidine. Based on this finding, we have designed and synthesized novel 2-substituted-6-[(4-substituted-1-piperidyl) methyl]-1H-benzimidazoles. The target compounds were screened *in vitro* for their anti-Ebola activity. Among tested molecules, two compounds exhibited an $EC_{50=}$0.93 μM (SI = 10) and $EC_{50=}$0.64 μM (SI = 20), respectively and were as potent as and more selective than Toremifene reference drug (EC_{50} = 0.38 μM, SI = 7) against cell line. Data suggests that the mechanism to block EBOV infection is through the inhibition of viral entry at the level of NPC1. Furthermore, a docking study revealed that several of the NPC1 amino acids that participate in binding to GP are involved in the binding of those two compounds. Our results could enable the development of small molecule drug capable of inhibiting Ebola virus, especially at the viral entry step.

135. Novel Prodrugs as Inhibitors of SARS-Coronavirus-2

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The unprecedented challenge to global health of the COVID-19 pandemic is spurring efforts to develop effective antiviral agents for the treatment of SARS-CoV-2 infections.

Short-term COVID-19 drug discovery has focused on repurposing FDA-approved drugs. Nucleoside and nucleotide analogues already used to treat viral infections constitute a promising category of candidates for evaluation against SARS Coronavirus-2 (SARS-CoV-2) targeting the SARS-CoV-2 RNA-dependent RNA polymerase (CoV2-RDRP). Examples range from antiviral nucleoside phosphonates known to be effective against DNA viruses, such as cidofovir, to remdesivir, a phosphoramide derivative of GS-441524, a modified nucleoside developed against other RNA viruses. The efficacy of remdesivir is not yet clearly established in ongoing clinical trials, but it is currently used as a high-dose i.v. therapy for hospitalized patients with severe COVID-19 illness.

We previously reported that oral USC-087, an *N*-hexadecylamidoamino acid hydroxy side-chain ester of the adenine cognate of cidofovir (HPMPA), inhibited multiple strains of human adenoviruses (HAdVs) in cell culture (EC50 2-35 nM). USC-087 was highly effective orally against HAdV-C6 in an immunosuppressed Syrian hamster model at the same or lower i.v. therapeutic dose of the parent drug. We report here adaption of this approach to create novel prodrugs of GS-441524. The resulting compounds were tested for potency and cytotoxicity against a clinical SARS-CoV-2 strain in Vero E6 cells, revealing EC50 enhancements of an order of magnitude relative to remdesivir as a control, with CC50 ≥ 100 μM. The results will be compared with data obtained for USC-087 and related prodrugs in the same assay.

136. The DHODH inhibitor PTC299 arrests SARS-CoV-2 replication and suppresses induction of inflammatory cytokines implicated in severe COVID-19 disease and is currently being evaluated in the FITE19 clinical trial in hospitalized patients

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SARS-CoV-2, the causative agent of COVID-19, emerged in 2019 and quickly swept across the globe, resulting in more than 100 million cases with over 2 million deaths worldwide. Infection with SARS-CoV-2 can result in a wide range of clinical outcomes. More severe cases are associated with increased production of pro-inflammatory cytokines. Simultaneous reduction of both viral replication and the hyper-inflammatory immune response is expected to mitigate the most severe symptoms of COVID-19.

PTC299 is a clinical-stage small molecule inhibitor of the cellular enzyme dihydroorotate dehydrogenase (DHODH) that reduces the de novo production of pyrimidine nucleotides. Virus infected host cells as well as rapidly proliferating lymphocytes have an increased need for pyrimidine nucleotides, resulting in a vulnerability to blockade in this pathway. PTC299 has broad-spectrum antiviral activity in cell culture, including against SARS-CoV-2. PTC299 also inhibits the production of inflammatory cytokines including IL-6, IL-17A, and IL-17F. PTC299 has promise to treat COVID-19 through the dual mechanisms of viral replication inhibition and modulation of the hyper-inflammatory immune response. Since PTC299 targets DHODH, a host enzyme, the emergence of resistant virus variants is unlikely.

Prior clinical experience with PTC299 demonstrated favorable pharmacokinetics and safety. PTC299 is being studied in the FITE19 Phase 2/3 clinical trial for treatment of COVID-19 (Clinicaltrials.gov NCT04439071). The FITE19 trial will enroll 380 patients in approximately 12 countries, with a primary endpoint of 'time from randomization to respiratory improvement'. Secondary endpoints include viral load and immune response.

201. Two synthetic steroidal analogues with antiviral and anti inflammatory activities against the infection caused by Human Respiratory Syncytial Virus

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At present, the search for antiviral agents involves not only drugs that specifically inhibit any stage of the virus replication cycle but also that may affect a cellular target needed by the virus for its propagation. In many cases, treatment of viral infections also includes the reduction of host exacerbated inflammatory response to the infection, which ends in an immunopathology. Respiratory Syncytial Virus (RSV) is a leading cause of lower respiratory tract disease and bronchiolitis in children worldwide and no vaccine or effective treatment is currently available against it. This virus provokes lung injury through its replication in the epithelial cells and also through the triggering of a cytokine storm. Steroidal analogs (22S, 23S)-22,23-dihydroxystigmast-4-en-3-one (Compound 1) and (22S,23S)-22,23-dihydroxyestigmast-1,4-dien-3-one) (Compound 2) exert antiviral activity against non-related viruses of clinical relevance, with different structures and replicative strategies, like ADV and HSV-1. In this work we describe the antiviral activity of these compounds against RSV A2 and L19 strains in vitro. The compounds are not virucidal, and they exert their inhibitory effect after virus entry to the cell, more effectively when they are added to the infected cells between 4 and 8 hours post infection. Both compounds reduce IL-6, IL-8 and TNF-€cytokines secretion in THP-1 macrophages infected with RSV. Furhermore, a concentration of 10 mg/kg of the compounds dissolved in DMSO 90% diminish lung viral load in Balb/c mice infected with RSV L19 strain, and significantly reduce lung inflammatory cell infiltration. Both are promissory drugs to ameliorate the disease caused by RSV.

202. *In Vitro* Antiviral Activity of Chloroquine, interferon Beta-1a, Lopinavir, Favipiravir and Remdesivir Against Seasonal and Pathogenic Coronaviruses

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Human coronaviruses cause a range of respiratory diseases, from a common cold to a severe and sometimes lethal disease. Coronaviruses HCoV-229E and HCoV-OC43 cause the common cold, whereas SARS-CoV, MERS-CoV, and SARS-CoV-2 can cause a more serious infection. Most recently, SARS-CoV-2, which causes coronavirus disease-2019 (COVID-19), emerged in Wuhan, China at the end of 2019 and was declared a pandemic by the WHO in March of 2020. The emergence of this new highly pathogenic coronavirus has increased the urgency to determine effective treatments against COVID-19. These studies determined the *in vitro* antiviral activities of Chloroquine, Interferon beta-1a, Lopinavir, Favipiravir and Remdesivir against HCoV-OC43, HCoV-229E, SARS-CoV, MERS-CoV, SARS-CoV-2. The *in vitro* antiviral activity of each compound was evaluated using a standard cytopathic effect assay. Of these compounds, interferon beta-1a was the most potent against all five coronaviruses with the following mean 50% effective concentrations (EC_{50}) reported in µg/ml: 0.0015 (229E), 0.0013 (OC43), 0.0013 (SARS-CoV), 0.00032 (MERS-CoV), and 0.0012 (SARS-CoV-2). Remdesivir also broadly active against all five coronaviruses with the following mean EC_{50} values reported in µg/ml: 0.032 (229E), 0.1 (OC43), 1.2 (SARS-CoV), 2.4 (MERS-CoV), and 8.3 (SARS-CoV-2). Slight activity was observed for chloroquine against MERS-CoV, SARS-CoV, and HCoV-229E, while no activity was observed for lopinavir and favipiravir. The activity of interferon-beta1a against SARS-CoV-2 was confirmed by virus yield reduction assay in a differentiated normal human bronchial epithelial cell assay with a 90% effective concentration of 0.057 µg/ml. *[Supported by Contract HHSN75N93019D00021 from the Respiratory Diseases Branch, DMID, NIAID, NIH].*

203. Recent African strains of Zika virus display higher transmissibility and fetal pathogenicity than Asian strains

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The global emergence of Zika virus (ZIKV) in the last decade revealed the unprecedented ability for a mosquito-borne virus to cause congenital birth defects such as microcephaly. A puzzling aspect of ZIKV emergence is that all human outbreaks and birth defects to date have been exclusively associated with the Asian ZIKV lineage, despite a growing body of laboratory evidence pointing towards higher transmissibility and pathogenicity of the African ZIKV lineage. Whether this apparent paradox reflects the use of relatively old African ZIKV strains in most laboratory studies is unclear. Here, we experimentally compared the transmissibility and pathogenicity of seven low-passage ZIKV strains representing the recently circulating viral genetic diversity. We found that recent African ZIKV strains largely outperformed their Asian counterparts in mosquito transmission kinetics experiments, which translated into a markedly higher epidemic potential in outbreak computer simulations. In addition, African ZIKV strains were significantly more lethal than Asian ZIKV strains in immunocompromised adult mice. Finally, prenatal infection of immunocompetent mouse embryos with an African ZIKV strain resulted in embryonic death whereas it caused microcephaly with Asian ZIKV strains. Together, our results demonstrate the high epidemic potential and pathogenicity of recent ZIKV strains from Africa. Importantly, they also imply that the African ZIKV lineage could more easily go unnoticed by public health surveillance systems than the Asian ZIKV lineage due to its propensity to cause fetal loss rather than birth defects.

204. The Role of N-linked Glycosylation in Dengue Virus (DENV) Fitness and Virulence

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Glycoproteins play important roles in infectious diseases caused by viruses or bacteria, ranging from entry, intracellular replication to immune evasion. A member of the *Flaviviridae* family, DENV poses a huge disease burden globally with an estimated 390 million infections annually. The main viral structural protein, envelope protein (E), is a promising sub-unit vaccine candidate. It is glycosylated at two asparagine (N) sites (N67 and N153) but its glycosylated variants and their biological importance have been largely overlooked.

Firstly, using high-resolution glyco-analytics, we found that high mannose glycans represent the dominant form on both N67 and N153 glycosylation sites. However, the glycan motifs on N153 are slightly more complex with a fucosylated core structure.

Secondly, using reverse genetic, we have generated partially deglycosylated DENV mutant (N153Q). The *in vitro* and *in vivo* fitness of the mutant was studied. Our data show that the N153Q mutant grown in mosquito C6/36 and mammalian BHK-21 cells was as fit as wildtype virus but was impaired in human hepatocyte Huh-7. Further mechanistic studies suggested that N153Q was impaired in post entry steps. Besides, the deglycosylated mutant was greatly attenuated in mice, as evidenced by milder clinical manifestations and lower virus titers both in circulation and specific organs (kidney and liver). Finally, removal of glycan motifs at N153 resulted in increased antibody-mediated virus neutralization.

Our findings provide further insights on the role of glycosylation in DENV pathogenesis with important implications for the development of effective therapeutic antibodies, vaccine candidates and anti-viral drugs.

205. An efficient workflow to identify broad spectrum antiviral compounds active against SARS CoV-2 in culture and in vivo

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Emerging and re-emerging viruses are challenging threats not amenable to prompt control with antivirals targeting specific viral proteins, as evidenced by SARS CoV-2. We have therefore been working on broad spectrum antivirals for over 15 years. On March 2020, we applied our expertise toward identifying broad spectrum antivirals against SARS CoV-2. We tested two groups of compounds with broad antiviral activity against several unrelated viruses, 42 gallates derivatives and 78 RAFIs, plus 72 other compounds. To this end, we developed and validated a viability screen using HCoV-OC43. The gallate derivatives included inactive compounds and compounds that inhibit the infectivity, but not the replication, of many unrelated viruses, including HCV, IAV, VSV, Ad, HSV and RV (but not that of poliovirus). We then blindly screened all pre-selected compounds. Forty-four scored as hits at low moi and 26 at high moi, as expected, and 51 were cytotoxic or cytostatic at 10 μM and 12 more at 100 μM. Twenty non cytotoxic hits were tested in burst assays to identify potency and maximum inhibition. The activity of the gallate derivatives against HCoV-OC43 was consistent with their previously identified broad spectrum antiviral activities. Active compounds were tested against SARS CoV-2 in burst assays and compounds that inhibited replication by more than 1,000-fold were identified. We have also developed a mouse model of severe (fatal) and less severe COVID-19 and are preparing to test selected hits in vivo.

206. Analyzing Infection by Multiple Flavivirus in Real-Time in a One-Well Multiplex Format Using Multi-Color High Content Imaging for the Purpose of Antiviral Screening

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Flaviviruses such as dengue (DENV), yellow fever (YFV) and Japanese Encephalitis viruses (JEV) pose a significant threat to about half of the world population urging to find potent antivirals. We developed a series of recombinant flaviviruses tagged with different fluorescent proteins (FP) to visualize infections by multiple flavivirus concomitantly in one well and real time by high content imaging (HCI). First, a spectrum of FP was evaluated by fluorescence microscopy and flow cytometry. Based on brightness and spectral properties, Azurite, GFP/Citrine and Cherry were selected for use in a panel of optically compatible reporter viruses. Second, a bias caused by particular FPs on viral replication and infectivity was ruled out by inserting individual colors in a DENV type 2 (DENV2) infectious clone. Though all DENV2 reporter viruses appeared to be slightly attenuated compared to wild type DENV2, no significant differences among the differently colored viruses could be observed. Eventually, we combined DENV2/Azurite, JEV/GFP, and YF17D/Cherry and use these for mixed infections in Vero cells that themselves constitutively expressing a far-red FP. This all-optical multi-virus infection system is amenable to imaged-based antiviral screening and can be run in an automated combined robotics-biosafety containment system. For proof of concept, a series of known pan-flavivirus small molecule inhibitors as well as virus-specific agents are evaluated by this assay. Our novel approach may provide an efficient means to find potential pan-flavivirus inhibitors to curb current and future flavivirus outbreaks.

207. Structure-based macrocyclization of substrate analog NS2B-NS3 protease inhibitors of Zika, West Nile and Dengue viruses

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In the last decade, there have been increased and larger magnitude of *flavivirus'* outbreaks. However, there is no specific antiviral treatment for these diseases and patients can only rely on supportive therapy to manage and alleviate the symptoms. With the worsening endemic of *flavivirus* and the lack of antiviral treatments, *flavivirus* infection is becoming a major health concern.

Flavivirus' NS2B-NS3 protease is an attractive antiviral target due to its essential role in the viral polyprotein processing process. However, the progress towards designing a potent inhibitor is slow, due to the hydrophilicity and the depth of the protease active site. By means of structural based drug design approach, we will present a series of cyclic, peptidomimetics inhibitors with Ki values within nanomolar range against NS2B-NS3 protease from Zika, West Nile and Dengue Virus. Crystal structures of seven Zika protease inhibitor complexes were determined to support the inhibitor design. Biochemical assays reveal that the inhibitors are very sensitive to cyclic backbone ring size and ring variations. Other findings include the improved potency of R-enantiomer at the P1 position as well as using glycine as a linker for cyclisation. The most potent compound inhibits the Zika protease with *Ki* values < 5 nM. But, West Nile and Dengue 4 proteases are inhibited less efficiently. Nonetheless, similar structure-activity-relationships were observed for these enzymes, suggesting potential application as pan-flaviviral protease inhibitors. These novel peptidomimetics inhibitors will provide insight and guide future antiviral development with improved potency and biostability.

209. Novel Carbocyclic-Substituted Hydantoin Derivatives with Broad Antiviral Activity

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Addressing the rising need for broad-spectrum antivirals, we previously identified lipophilic carbocyclic-substituted hydantoin analogues with an acetohydroxamic acid metal-chelating group as active against hepatitis C (HCV) and dengue (DENV) viruses (Giannakopoulou et al., *MedChemComm* 2019). Preserving the 2,4-diketoimidazolidine core scaffold, we constructed new, rationally designed derivatives to improve effectiveness against *Flaviviridae* viruses (HCV, DENV, YFV, ZIKV), and examined their activity against viruses from distinct lineages (HBV, EBOV). Derivatives bearing different carbocyclic rings as spiro-substituents and methyl- or benzyl-groups at the amide nitrogen of hydantoin, were evaluated for antiviral activity (luciferase, viral protein/RNA) and cytotoxicity (ATP), in infectious and subgenomic systems and *in vitro* enzymatic assays. Methoxytetralone, phenylcyclohexane and adamantanyl-substituted compounds were the most promising, with broad effectiveness against the replication of all viruses studied. Especially for *Flaviviridae* viruses, they showed EC_{50} in low nanomolar range and high selectivity index (>100). The presence of the metal-chelating group was crucial for antiviral activity. In HCV and DENV replicon-harboring cells, the inhibitors showed a high barrier to resistance (2-fold reduction of activity), which is conferred by a mutation in NS3 helicase, as identified by NGS and site-directed mutagenesis. *In vitro* enzymatic activity of NS3 ATPase was not suppressed, suggesting a different mechanism of NS3 targeting. The implication of cellular factor(s) was excluded, after reintroduction of replicon into cured cells previously adapted to the compounds. Overall, we present novel carbocyclic-substituted hydantoin analogues, with broad antiviral activity mediated by the acetohydroxamic acid chelating moiety, that possibly target metal-dependent viral enzymes such as *Flaviviridae* NS3 helicase.

210. Mitochondrial Stresses in Patients With Chronic Hepatitis B and Advanced Fibrosis

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Background & Aims: Mitochondrial genome is particularly sensitive to oxidative stress which is increased by hepatitis B virus (HBV) in the liver. The aim of our study is to evaluate alterations of mitochondrial functions and dynamics in relation to fibrosis progression in patients with Chronic Hepatitis B (CHB).

Methods: 136 naive patients with CHB and different fibrosis stages [METAVIR score (F0-F1-F2 n=86; F3-F4 n=41)] and 17 controls were included. Hepatic mtDNA levels and deletions were determined (Slot Blot and PCR). Expression of cytochrome c oxidase subunits 1 (COX1), Parkinson juvenile disease protein 2 (PARKIN), Phosphatase and Tensin-Induced Putative Kinase-1(PINK1), Lon Peptidase 1(LonP1), HSP60 and HSP70 chaperones were investigated by RT-qPCR and Western blotting.

Results: 78% of all patients with CHB carried a mtDNA deletion ($p<0.01$) and 100% of those with advanced fibrosis exhibited either a single or multiple mtDNA deletions ($p<0.001$). Compared to patients with F0-F2 fibrosis, significant decreases were observed in patients with F3-F4 fibrosis for the relative expression of mRNAs of COX1 (1.20±0.75 vs 0.55±0.36,$p<0.001$), HSP70 (1.06±0.37 vs 0.70±0.28,$p<0.001$), HSP60 (1.10±0.44 vs 0.83±0.36,$p<0.05$), LonP1 (1.06±0.33 vs 0.83±0.22,$p<0.05$), Parkin (1.12±0.57 vs 0.45±0.26,$p<0.0001$), and Pink1 (1.06±0.26 vs 0.59±0.17,$p<0.0001$) and protein levels for COX1 (3.44±0.80 vs 2.55±0.88,$p<0.01$), HSP70 (1.20±0.77 vs 0.67±0.31,$p<0.05$), and LonP1 (0.87±0.51 vs 0.67 ± 0.31,$p<0.05$).

Conclusions: In patients CHB and advanced fibrosis, diverse mtDNA rearrangements are associated with alterations in mitochondrial function, mitochondrial unfolded protein response and mitophagy. These mitochondrial abnormalities might concomitantly play an important role in the pathophysiology of CHB and the development of fibrosis.

211. Novel organic supramolecular compounds as broad-spectrum viral inhibitors with a virucidal mechanism

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Despite the development of vaccines and antivirals, viruses are still a primary source of harm for humans. The recent outbreaks of SARS-CoV-2 or the percentages of people infected by contagious diseases such as HSV, HIV, influenza, show the urgency of different and efficient solutions against viral diseases. Our group has recently demonstrated a novel approach to fighting viruses: gold nanoparticles coated by long sulfonated ligands. These ligands present on the shell mimic heparane sulfate proteoglycans (HSPGs), exploited by different viruses for cell recognition. The nanoparticles resulted so to be an effective antiviral against a number of viruses (*i.e.* broad-spectrum activity) such as HSV-2, RSV, HPV, Dengue.

The key feature of such a compound is the capability to irreversibly inhibit the viral infection (*i.e.* virucidal mechanism) that, along with the non-toxicity of the nanomaterial, pave the way to a novel approach in fighting viral diseases. To the best of our knowledge these compounds were the first non-toxic virucidal nanomaterial with a broad-spectrum activity.

Despite the promising properties of the nanoparticles, their gold core raises concern about bio-accumulation and long-term biocompatibility.

Here, we show the design of organic supramolecular compounds with the very same antiviral properties of the gold nanoparticles (nanomolar activity against multiple viruses with a non-toxic virucidal mechanism).

The possibility to translate these novel concepts to a different system enable us to elucidate the role of key molecular features in the design of such virucidal compound with broad-spectrum activity.

212. Selective modulation of the MASP-2 serine protease: a potential broad-spectrum approach for present and future coronavirus infections.

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MASP-2 is an important serine protease which plays a central role in the lectin pathway of complement activation, therefore representing a key enzyme for immune and inflammatory processes. Recent evidence suggests that human deadly coronaviruses SARS-CoV, MERS and SARS-CoV-2 all induce an excessive immune response by hyper-activating MASP-2, through the interaction of the viral N-protein with this protease. This hyperactivation results in aggravated lung inflammation, severe pneumonia, lung injury, and high mortality rates. The MASP-2 interacting interface of the N-protein is highly conserved in different coronaviruses, including bat coronaviruses, highlighting the risk of emergence of future human coronaviral diseases with similar characteristics to COVID-19. As a consequence, the direct inhibition of MASP-2 represents a promising strategy to interfere with the serious consequences of both present and future coronaviral infections.

A docking-based virtual screening of ~5 million commercial compounds was performed on the catalytic site of MASP-2. In parallel, these compounds were counter-screened *in silico* against structurally related serine-proteases, in order to identify selective inhibitors of MASP-2. A total of ~50 potential inhibitors was selected for *in vitro* evaluations, including virtual hits identified within a drug repurposing sub-library of compounds, as a means to provide hit molecules that could be rapidly evaluated in clinical stages and may be readily used as a treatment option for current coronaviral infections.

In this presentation, the rationale behind this approach will be discussed, along with the virtual screening carried out, and the early findings obtained for our selected hits in preliminary *in vitro* assays.

213. Developing Glycan-Based Antiviral Prophylactics to Prevent Coronavirus Infection

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The COVID-19 pandemic underscores the severe health threat posed by emerging coronaviruses (CoVs). The SARS-CoV-2 outbreak marks the third emergence of highly pathogenic CoVs in the 21st century. The diversity of SARS-related coronaviruses in bats points to the potential for future spillover into human populations. In the absence of vaccines for emerging CoVs, we aim to develop broadly acting antiviral prophylactics to prevent CoV infection. Most human viruses, including CoVs, initiate attachment to cell surfaces through low affinity but high avidity interactions with abundant complex carbohydrates, called glycans. Glycan binding allows virions to concentrate on the cell surface to facilitate binding to less abundant specific receptors. Blocking initial glycan interactions with molecules that compete for virion binding is a demonstrated approach to inhibit entry of diverse viruses. As proof-of-concept, we show that the natural product epigallocatechin gallate inhibits entry of SARS-CoV-2 and other CoVs (IC_{50}, 10-25 uM), consistent with its previously described inhibition of glycan-dependent viral attachment. However, the specific glycan moieties mediating CoV attachment remain poorly defined. We are currently defining the specific glycan structures and precise epitopes necessary for attachment of SARS-CoV-2 and other CoVs through targeted glyco-engineering approaches based on enzymatic glycan cleavage and remodelling of cell-surface glycans. These findings are enabling the rational design of potent CoV attachment inhibitors through chemoenzymatic synthesis of glycan mimetics displayed on multivalent scaffolds. Through exploiting highly conserved virus-host interactions, our findings will advance the development of pan-coronavirus antivirals to address current CoV infections and to prepare for future emerging CoVs.

214. In Depth Study of the Carbohydrate-Binding Agents HHA, GNA and UDA as Potent Inhibitors of Influenza A and B Virus Replication

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Here, we report on the anti-influenza virus activity of the mannose-binding agents, *Hippeastrum* hybrid agglutinin (HHA) and *Galanthus nivalis* agglutinin (GNA), and the $(N\text{-acetylglucosamine})_n$-specific *Urtica dioica* agglutinin (UDA). These carbohydrate-binding agents (CBA) strongly inhibited various influenza A(H1N1), A(H3N2) and B viruses *in vitro*, with EC_{50} values ranging from 0.016 to 83 nM, generating selectivity indexes up to 125,000. Somewhat less activity was observed against the A/PR/8/34 and an A(H1N1)pdm09 strain. In time-of-addition experiments, these CBA lost their inhibitory activity when added 30 min p.i. Interference with virus entry processes was also evident from strong inhibition of virus-induced hemolysis at low pH. However, a direct effect on acid-induced refolding of the viral hemagglutinin (HA) was excluded by the tryptic digestion assay. Instead, HHA treatment of HA-expressing cells led to a significant reduction of plasma membrane mobility. Crosslinking of membrane glycoproteins, through interaction with HA, could also explain the inhibitory effect on the release of newly formed virions when HHA was added at 6 h p.i. These CBA presumably interact with one or more N-glycans on the globular head of HA, since their absence led to reduced activity against mutant influenza B viruses and HHA-resistant A(H1N1) viruses. The latter condition only emerged after 33 cell culture passages in the continuous presence of HHA, and the A(H3N2) virus even retained full sensitivity after 50 passages. Thus, these CBA qualify as potent inhibitors of influenza A and B viruses *in vitro* with a pleiotropic mechanism of action and a high barrier for viral resistance.

215. In Vitro Selection of Herpes Simplex Virus 1 (HSV-1) Drug-resistance Under Combination Therapy

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Introduction: In immunocompromised patients, HSV-1 infections can be severe and persistent needing prolonged antiviral therapy, which increases the risk of drug-resistance. All currently approved antivirals target the viral DNA polymerase (DP) and drug-resistance is associated with changes in the viral thymidine kinase (TK) and/or DP. The helicase-primase inhibitor Pritelivir (PTV) is currently under clinical investigation.

Objective: *In vitro* drug-resistance under pressure of mono- or combination therapy was compared to study if combination therapy targeting different HSV-1 enzymes (DP and helicase-primase) is a good approach to prevent rapid evolution to drug-resistance.

Methods: Wild-type HSV-1 was grown *in vitro* under increasing doses of antivirals, as monotherapy [Acyclovir (ACV), Ganciclovir (GCV), Foscarnet (PFA), Trifluorothymidine (TFT), Pritelivir (PTV)] or combination therapy [GCV+TFT, ACV+TFT, ACV+PTV, and PFA+PTV]. After 5 passages, virus cultures were characterized by Sanger sequencing of the HSV-1 genes UL23 (TK), UL30 (DP), and UL5 / UL52 (helicase-primase). Five viral clones were isolated and characterized per condition. Next-generation sequencing was performed after passage 2 and 5 to determine HSV-1 heterogeneity and viral evolution.

Results: Mutations conferring drug-resistance were detected at passage 5 under all treatment conditions, except for the GCV+TFT combination at high drug concentrations. TFT pressure as monotherapy resulted in mutations in the TK. Under pressure of ACV+PTV or PFA+PTV, mutations in the TK or DP emerged; however, most clones did not develop mutations in the UL5 or UL52 genes, implicating that combination therapy did slowed down evolution to PTV-resistance. Combination therapy with different antiviral classes might be effective in preventing drug-resistance.

216. Synergistic effects of combination treatment using anidulafungin and T1105 against the Zika virus

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Zika virus (ZIKV) is a mosquito-borne virus that belongs to Flavivirus, Flaviviridae. The outbreak of rash illness in Brazil in 2015 was identified as a ZIKV infection. Researchers found that ZIKV infection highly correlated with Guillain-Barré syndrome and microcephaly. Now, there is not any vaccine and effective antiviral drugs against ZIKV infection. To reduce the ZIKV titer was considered which could be a benefit to reduce the risk of microcephaly, even those drugs have the risk of pregnancy. Anidulafungin is an antifungal drug, classified into pregnancy category B+ to C. The study explored that anidulafungin could inhibit the level of RNA, protein, and virus yield of ZIKV at the concentration of 2.5μM to 10μM. In the time of addition assay, anidulafungin could suppress at the early stage of ZIKV infection and more efficiently at the full treated group. Anidulafungin revealed the inhibition at the concentration of 2.5μM to 10μM in binding and entry assay but does not affect virus replication and release. Anidulafungin also showed a significant decrease in ZIKV stability from 2.5μM to 20μM. When anidulafungin added with T1105, a viral replication inhibitor, that showed the synergistic effect in the combination. In conclusion, anidulafungin possessed the ability to against ZIKV infection via inhibiting virus entry and destroying virus stability and revealed more effective during the combination with T1105.

217. Colloidal Systems for Antiviral Drugs Encapsulation for Neglected Diseases

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The emergence of viral resistant mutants to antiviral drugs is the most important issue in current antiviral therapy, so an ideal therapeutic goal to prevent this is represented by host factors that are crucial to the viral replicative cycle. Poor pharmacokinetic profiles and resistance are the main disadvantages of the currently used antiviral agents, so they are excellent research objectives, especially in presence of viral pandemics such as DENV, ZIKV, HIV, Hepatitis. Mycophenolic acid (MPA) is a non-nucleoside and non-competitive inhibitor of inosine monophosphate dehydrogenase (IMPDH), clinically safe and usually used as an immunosuppressant for prevention of rejection of transplanted organs. To solve cytotoxicity problems, sustained drug delivery systems are required through the use of nanoparticles. Nanocarriers can provide key advantages for drugs or therapeutic molecules in vivo administration.

We have confirmed the binding interaction between MPA and bovine seroalbumin protein (BSA) by fluorescence spectroscopy with a Kd = 12.0 ± 0.7 μM. We obtained BSA-nanoparticles of 59 ± 9 nm, PLGA-nanoparticles of 65 ± 10 nm and Niosomes of 85 ± 9 nm, determined by scanning electron microscopy (SEM). The BSA-MPA formulations did not show cytotoxicity in the range of concentrations tested; however, although they were active against Junín arenavirus, their antiviral effect was not superior to free MPA.

218. HBV ribonuclease H inhibitors are less toxic in primary human hepatocytes than in hepatoma cell lines

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N-hydroxypyridinediones (HPD), *N*-hydroxynapthyridinones (HNO), and α-hydroxytropolones (α-HT) are effective against the HBV ribonuclease H and can suppress hepatitis B virus (HBV) replication at sub-micromolar concentrations. These compounds are variably cytotoxic in HepDES19 cells by MTS (mitochondrial toxicity) assays. HepDES19 is a HepG2 hepatoblastoma cell line derivative that contains a tetracycline-repressible HBV cassette. As such, cytotoxicity may deviate from that in HepG2 and Huh7 cells, as well as in primary human hepatocytes (PHH) – cells that are used as *in vitro* models to emulate the liver environment. To evaluate potential differences in cytotoxicity, MTS and LDH release (cell lysis) assays were conducted following three- and seven-day incubations with compounds. Cytotoxicity in HepG2 and Huh7 cells was comparable to that in HepDES19 cells following compound addition for three days. After seven days, relative cytotoxicity patterns were similar to results from the three-day incubation; however, more toxic compounds further decreased cell viability. Twelve compounds were tested in PHHs. Surprisingly, 100% viability was observed following a three-day incubation with all compounds. These results indicate that hepatoma cell lines are likely more sensitive to the tested compound classes than PHHs. Elevated cytotoxicity may be due to the continuous cell division of the cell lines compared to the quiescent state of the PHHs. As such, it will be imperative to monitor toxicity in rapidly dividing tissues such as bone marrow and epithelial linings as well as in the liver during *in vivo* studies.

220. Influence of 4′-substitution on the activity of gemcitabine and its ProTide against VZV and SARS-CoV-2

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In addition to its therapeutic value as chemotherapy drug, gemcitabine is of ongoing interest to the scientific community for its broad-spectrum antiviral activity. In this context, the structural modification of gemcitabine as a means to convert a life-saving antitumoral drug into selective and effective analogues for the treatment of severe viral infections represents an attractive research endeavor. In this study, we selected electron-withdrawing substituents via inductive effect, such as a methoxy group and fluorine atom, to modify the 4′-position of gemcitabine in an effort to identify compounds potentially active against selected viruses but with a reduced cell toxicity. The synthesis of 4′-methoxy and 4′-fluoro gemcitabine analogues was also accompanied by that of their corresponding prodrugs. Among these derivatives, 4′-fluoro-gemcitabine 1b proved active against varicella zoster virus (VZV, TK+ strain) with an EC_{50} of 0.042 μM, while displaying a 30-fold lower cytostatic effect than gemcitabine (CC_{50} = 0.11 μM versus 0.0036 μM for gemcitabine). Interestingly, although a decreased anti-VZV activity was observed in the case of the corresponding phosphoramidate prodrug 2b, an improved selectivity index was obtained (SI: 36). Moreover, in the screening against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), compounds 1b and 2b were 20 and 10 times more active than remdesivir, respectively. Unfortunately, the antiviral activity of these compounds was comparable or slightly lower than their cytotoxic concentration when measuring cell growth or cell morphology.

221. Cidofovir and (S)-HPMPA serinamide and homoserinamide prodrugs potently inhibit DNA viruses in cell culture

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Certain acyclic nucleoside phosphonate (ANP) drugs have broad spectrum activity against DNA viruses, including cidofovir ((S)-HPMPC), the first nucleotide antiviral approved for clinical use, and its adenine analog (S)-HPMPA. These mononucleotide analogs have low oral bioavailability and cell permeability due primarily to their phosphonic acid group, which ionizes at physiological pH. A variety of prodrug strategies have been developed to overcome this limitation.

We previously showed that USC-087, an *N*-hexadecylamido tyrosine ester of HPMPA, potently inhibits multiple strains of human adenoviruses (HAdVs) in cell culture (EC_{50} 2-35 nM) and is highly effective orally against HAdV-C6 in an immunosuppressed Syrian hamster model.

In this study, we examined the effect of changing the esterifying promoiety to amino acids having non-aromatic, hydroxyalkyl side chains (a serinamide, USC-374 and two homoserinamides, USC-150 and USC-093), to modulate the polarity, metabolic specificity and potency of the prodrugs.

All prodrugs exhibited significantly lower antiviral EC_{50} values in cell assays relative to a reference drug: herpes simplex virus 1 (HSV-1, 17–32x vs ACV); human cytomegalovirus (HCMV, 700–10,000x vs GCV); vaccinia virus (VACV, 3–50x vs BCV); BK virus (BKV 300–2000x vs CDV); human herpes virus 6B (HHV-6B, 420–1100x vs CDV); adenovirus 5 (ADV-5, 400–1500x vs CDV); adenovirus 6 (ADV-6, 800–2500x vs CDV) with CC_{50} values >1 μM in stationary HFF cells (7 d, luminescence assay). These results demonstrate the versatility and potential for future development of this unique nucleoside prodrug platform.

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222. Targeting Polyamines Inhibits Coronavirus Infection by Reducing Cellular Attachment and Entry

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The rapid emergence and spread of SARS-CoV-2 demanded the development of antivirals to treat SARS-2 infected patients. We tested the FDA approved drug DFMO, which is used to treat African trypanosomiasis, on its ability to limit SARS-2 and the mouse coronavirus MHV-A59 infection in vitro. DFMO blocks the rate limiting step of polyamine synthesis, small biomolecules that are necessary for a multitude of cellular functions and have been shown to be necessary for multiple RNA viruses. We found that DFMO was able to reduce both SARS-2 and MHV-A59 titers with multiple cell types. This antiviral effect of DFMO on MHV-A59 was due to the decreased concentration of polyamines within the cell. This lack of polyamines negatively impacted the early stages of binding and entry of both MHV-A59 and SARS-2 spike psuedovirus. Additionally, other drugs that target the polyamine pathway and downstream usage of the polyamine spermidine decreased MHV-A59 titers implicating that polyamines play a role in multiple stages of coronavirus infection.

223. Targeting cyclophilins to disrupt innate immune evasion by positive-sense RNA viruses

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Cyclophilin A (CypA) is an essential host factor for several positive-sense RNA viruses, including hepatitis C virus (HCV) and coronaviruses (CoVs). However, a clear mechanism as to how these viruses exploit cyclophilins to promote their replication has yet to be elucidated. We showed that hepatitis C virus (HCV) requires CypA in order to evade antiviral responses dependent on protein kinase R (PKR) and interferon regulatory factor 1 (IRF1), but not MAVS. Treatment of HCV-replicating human hepatoma Huh7 cells with cyclophilin inhibitors (CypI) induced expression of antiviral genes, which inhibited HCV replication and blocked formation of the membranous replication organelle. Antiviral potency of CypI against HCV replication and induction of antiviral genes was dependent on PKR and IRF1 expression. We hypothesize similar mechanisms may be involved in inhibition of CoV replication by CypI. Interestingly, a recent study showed that treatment of MERS-infected Calu-3 lung cells with the classical CypI cyclosporine A (CsA) similarly activated antiviral immunity (Sauerhering et al. 2020 Eur. Respir. J.) Using HCoV-229E and -OC43 as models, we show here that treatment of A549 and MRC5 lung cell lines with CsA inhibits CoV replication. We are currently extending these studies to non-immunosuppressive CsA derivatives. Furthermore, silencing of CypA expression resulted in a decrease in CoV replication, suggesting a specific role for CypA. Studies are ongoing to evaluate the impact of CypI treatment on cellular antiviral immune responses to CoV infection and elucidate the antiviral mechanisms. We expect these findings to open perspectives for novel therapeutic approaches against CoVs.

224. Double combinations against the in vitro replication of Coxsackievirus B1

WITHDRAWN

225. Oral USC-093, a novel homoserinamide prodrug of (S)-HPMPA shows equivalent efficacy to USC-087 in preventing mortality against lethal hAdV-C6 challenge in a permissive immunosuppressed Syrian hamster model

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Human adenoviruses (HAdVs) are small, double stranded DNA viruses that are classified into 7 species and over 100 types. Depending on the type, HAdVs cause self-resolving respiratory, gastrointestinal, eye, or bladder infections in healthy adults, but can result in life-threatening disseminated disease in immunocompromised individuals. Presently, there is no drug specifically approved to treat adenovirus infections. Cidofovir, an FDA approved acyclic nucleoside phosphonate (ANP), has broad spectrum activity against DNA viruses but it has poor bioavailability and is nephrotoxic. Prodrugs of cidofovir and its adenine analog (HPMPA) have improved oral bioavailability and permeability. In 2018, we reported the success of prodrug USC-087, a *N*-hexadecyl tyrosinamide ester of HPMPA which inhibits multiple HAdV strains *in vitro* (EC_{50} 2-35 nM) and is effective orally against HAdV-C6 in immunosuppressed Syrian hamsters. Here we report that a novel *N*-hexadecyl homoserinamide ester of HPMPA (USC-093) administered orally to Syrian hamsters infected with HAdV-C6 inhibited virus replication in the liver and prevented HAdV-induced pathology while protecting against the LD_{50} of HAdV-C6 at a lower dose concentration than intraperitoneally administered cidofovir. USC-093 has a better toxicological profile then either CDV or USC-087. Further, USC-093 prevented adenoviral pathogenesis when the administration of the drug was delayed up to 2 days post challenge, and it significantly extended the median survival time even when drug administration started at 4 days post challenge. These results demonstrate that this promising prodrug platform is not limited to tyrosine as the ANP-ester linking amino acid scaffold.

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226. Development of guinea pig disease models of Lassa fever for genetically diverse virus strains and use in vaccine efficacy studies

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Rodent-borne Lassa fever, caused by Lassa virus (LASV), occurs frequently in endemic regions of West Africa. LASV strains are classified into 6 phylogenetic clades. We previously showed that a single-dose subcutaneous (SC) vaccination with a Lassa viral replicon particle (VRP)-based vaccine, consisting of a LASV genome lacking the glycoprotein gene, conferred 100% protection against all clinical signs after homologous challenge with LASV Josiah (clade IV) in Strain 13 guinea pigs. For use in therapeutic efficacy studies, we characterized the clinical course and outcome in Strain 13 guinea pigs inoculated with diverse strains of LASV. The strains were first extensively characterized in vitro in human A549 and guinea pig GPC16 cell lines (growth kinetics, interferon sensitivity, apoptosis induction) and then selected for in vivo studies. Guinea pigs were inoculated SC with one of 5 strains of LASV representing clades II, III, and VI, and followed for up to 42 days. Only 2 animals reached end-point criteria; however, weight loss was observed in all groups, and infection with 4 of 5 strains resulted in a characteristic elevation in body temperature. Two of the newly developed models (clade II and III) were then used in vaccine studies; VRP vaccination conferred complete protection against clinical disease from heterologous infection after a single dose. These data further support the LASV VRP vaccine platform by providing critical evidence for its use against diverse virus strains, and demonstrate the value of non-lethal models for assessing therapeutic and vaccine candidates.

227. Hantavirus infection is inhibited by griffithsin in cell culture

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Andes virus (ANDV) and Sin Nombre virus (SNV), highly pathogenic hantaviruses, cause hantavirus pulmonary syndrome in the Americas. Currently no therapeutics are approved for use against these infections. Griffithsin (GRFT) is a high-mannose oligosaccharide-binding lectin currently being evaluated in phase I clinical trials as a topical microbicide for the prevention of human immunodeficiency virus (HIV-1) infection (ClinicalTrials.gov Identifiers: NCT04032717, NCT02875119) and has shown broad-spectrum in vivo activity against other viruses, including severe acute respiratory syndrome coronavirus, hepatitis C virus, Japanese encephalitis virus, and Nipah virus. In this study, we evaluated the in vitro antiviral activity of GRFT and its synthetic trimeric tandemer 3mGRFT against ANDV and SNV. Our results demonstrate that GRFT is a potent inhibitor of ANDV infection. GRFT inhibited entry of pseudo-particles typed with ANDV envelope glycoprotein into host cells, suggesting that it inhibits viral envelope protein function during entry. 3mGRFT is more potent than GRFT against ANDV and SNV infection. Our results warrant the testing of GRFT and 3mGRFT against ANDV infection in animal models.

228. Discovery of a nucleotide mono-phosphate prodrug inhibitor of dengue RNA-dependent RNA polymerase

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DENV RNA-dependent RNA polymerase (RdRp) is one of the most attractive antiviral targets, because it is essential for viral replication, has no mammalian counter part. Nucleoside DENV polymerase inhibitors are anticipated to provide an increased barrier to developing resistance and have pan-serotype activity, given that they bind to the highly conserved active site of the RdRp.

To identify a potent and selective nucleoside inhibitor of DENV RdRp, we studied SAR of a series of 2′- and/or 4′-ribose sugar modified nucleoside phosphoramidate prodrugs and their corresponding triphosphates. Their in vitro safety profile was assessed by single nucleotide incorporation rate by human mitochondrial RNA polymerase and the cell-based mitochondrial toxicity assay using human prostate cancer cell lines.

2′-Deoxy-2′-fluoro-2′-*C*-methylguanosine was chosen for designing prodrugs to deliver high level of triphosphate in peripheral blood mononuclear cells (PBMCs), which is one of the major dengue virus replication sites. We identified a cyclic phosphoramidate prodrug demonstrating well-balanced anti-dengue cellular activity and *in vitro* stability profiles. In dogs, oral administration of the prodrug resulted in high PBMC triphosphate level, exceeding TP_{50} (the intracellular triphosphate concentration at which 50% of virus replication is inhibited) at 10 mg/kg. The prodrug demonstrated 1.6- and 2.2 log viremia reduction in the dengue mouse model at 100 and 300 mg/kg twice daily, respectively. At 100 mg/kg twice daily, the terminal triphosphate concentration in PBMCs reached above TP_{50}, defining for the first time the minimum efficacious dose for a nucleos(t)ide prodrug.

229. Identification of Imidazo[1,2-*a*]pyrimidines as Novel Inhibitors Targeting Influenza A Virus Group 2 Hemagglutinins.

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Vaccination remains the principal prophylactic for controlling influenza infections although its efficacy is limited; the overall effectiveness of the flu vaccine in the 2019-20 season was only 45%. Therefore, small molecule anti-influenza therapeutics with an effective mechanism of action that are suitable for oral administration are needed for the acute treatment of influenza infections to control this virus and prevent epidemics/pandemics from developing. We have recently discovered a series of imidazo[1,2-a]pyrimidines that display excellent potency against both H3N2 and H7N1 influenza A group 2 viruses. These compounds target hemagglutinin (HA), which mediates virus entry and fusion, and show a significant inhibitory effect during the early phase of viral infection in a time-of-addition assay. Escape mutant analyses and in silico docking suggested that these imidazo[1,2-a]pyrimidines bind to a pocket in the vicinity of the fusion peptide within the HA trimer and stabilize the HA from low pH-induced conformational changes, which are required for virus-host membrane fusion. We have developed a series of inhibitors that have greatly improved potency against influenza A virus infection, with potency in the nanomolar range, and low cytotoxicity. Our lead compounds display excellent in vitro metabolic stability and druglike properties and have potential to be developed as a new class of antiviral drugs.

231. Discovery of the FDA-approved drugs bexarotene, cetilistat, diiodohydroxyquinoline, and abiraterone as potential COVID-19 treatments with a robust two-tier screening system

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Coronavirus Disease 2019 (COVID-19) caused by the emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with a crude case fatality rate of about 0.5-10 % depending on locality. A few clinically approved drugs, such as remdesivir, chloroquine, hydroxychloroquine, nafamostat, camostat, and ivermectin, exhibited anti-SARS-CoV-2 activity in vitro and/or in a small number of patients. However, their clinical use may be limited by anti-SARS-CoV-2 50 % maximal effective concentrations (EC_{50}) that exceeded their achievable peak serum concentrations (C_{max}), side effects, and/or availability. To find more immediately available COVID-19 antivirals, we established a two-tier drug screening system that combines SARS-CoV-2 enzyme-linked immunosorbent assay and cell viability assay, and applied it to screen a library consisting 1528 FDA-approved drugs. Cetilistat (anti-pancreatic lipase), diiodohydroxyquinoline (anti-parasitic), abiraterone acetate (synthetic androstane steroid), and bexarotene (antineoplastic retinoid) exhibited potent in vitro anti-SARS-CoV-2 activity (EC_{50} 1.13-2.01 μM). Bexarotene demonstrated the highest C_{max}:EC_{50} ratio (1.69) which was higher than those of chloroquine, hydroxychloroquine, and ivermectin. These results demonstrated the efficacy of the two-tier screening system and identified potential COVID-19 treatments which can achieve effective levels if given by inhalation or systemically depending on their pharmacokinetics.

232. A Tunable Approach en route to C-Linked Analogues of Glycosamines

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Carbohydrates including nucleosides are essential ubiquitous molecules involved in many fundamental biological events. Given the inherent propensity for chemical and enzymatic degradation of N- or O-linked glycosides, the most diverse forms of natural glycoconjugates, glycomimetics which carry a C-linked pseudo anomeric residue in a well-defined configuration have therefore received a great deal of attention in recent years [1]. These analogues may interfere in biochemical pathways wherein carbohydrates play key roles and are associated with pathological disorders. They function as effective glycosidase inhibitors and are *per se* much more stable towards hydrolysis than their N- and O-linked glyco congeners. Among them, glycosamine-*C*-glycosides are an important sub-class of compounds, key elements of chitin, the peptidoglycan in bacterial cell walls, of some glycoprotein hormones and sensory nerves of humans and animals. L-Imucillin H, an imino nucleoside, a powerful transition-state analog inhibitor of purine nucleoside phosphorylase, selectively inhibits human T lymphocytes

As part of our research on iminosugar-*C*-glycosides, we have reported a methodology, whereby an original stereospecific Migita-Kosugi-Stille Cross-Coupling reaction of chemically and configurationally stable 1-*C*-tributylstannyl iminosugars with aroyl and *n*-alkanoyl chlorides is feasible [2]. Taking advantage of this strategy, we report herein the Pd-mediated coupling of stannylated iminoalditols *en route* to an efficient, stereospecific and tunable preparation of glycosamine-*C*-glycosides (Scheme 1).

[1] (a) Suzuki, K. et al. *Chem. Rev.* 2018, *118*, 1495–1598; (b) Yang, Y.; Yu, B. *Chem. Rev.* 2017, *117*, 12281–12356.

[2] Li, S.; Jaszczyk, J.; Pannecoucke, X.; Poisson, T.; Martin, O. R.; Nicolas, C. *Adv. Synth. Catal.* 2021, *363*, 470–483.

233. Ribavirin-Imprinted Polymers as pulmonary Drug Delivery System

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Respiratory infections, such as influenza, are still one of the major causes of death, which have an impact on other chronic pathologies such as asthma and bronchitis. Ribavirin (l-€D-ribofuranosyl-l,2,4-triazole-3-carboxamide) has long been employed as an antiviral agent, mainly through an oral and intravenous administration. In some pulmonary viral diseases, ribavirin is known to be administered by aerosol inhalation but, unfortunately, this requires slow dosing of 12-20 hours per day of drug inhalation over at least a three-day period, all of which provides no more than a few hundred milligrams of drug. The molecular imprinting technology (MIP) has an enormous potential for creating satisfactory drug dosage forms through rate-programmed drug delivery, where drug diffusion from the system has to follow a specific rate profile.

Thus, herein, we describe the synthesis of a ribavirin-MIP (hydrogel microparticles, rigid beads) as a new drug delivery system (DDS) for sustained release of ribavirin. Some MIPs were synthetized with ribavirin as template, using various monomers (e.g., commercially acrylamide, made-home N1-acryloylthymine) and cross-linkers in different solvent. After optimization of the ratio template/monomer/cross-linker, the adsorption isotherms and the kinetics of release were determined for designed MIPs and NIPs. The releasing kinetics of ribavirin were realized in a buffer mimicking lung biofluid and were function to temperature. Some biological evaluation will be presented"

234. Nelfinavir markedly improves lung pathology in SARS-CoV-2-infected Syrian hamsters despite lack of an antiviral effect

Caroline Foo, Ph.D.[1]; Rana Abdelnabi, Ph.D. [1]; Suzanne Kaptein, Ph.D. [1]; Xin Zhang, M.S. [1]; Sebastiaan ter Horst, M.S. [1]; Raf Mols, Ph.D. [1]; Leen Delang, Ph.D. [1]; Joana Rocha-Pereira, Ph.D. [1]; Lotte Coelmont, Ph.D. [1]; Pieter Leyssen, Ph.D. [1]; Kai Dallmeier, Ph.D. [1]; Valentijn Vergote, M.S. [1]; Elisabeth Heylen, Ph.D. [1]; Laura Vangeel, Ph.D. [1]; Arnab Chatterjee, Ph.D. [2]; Pieter Annaert, Ph.D. [1]; Patrick Augustijns, Ph.D. [1]; Steven De Jonghe, Ph.D. [1]; Dirk Jochmans, Ph.D. [1]; Birgit Weynand, Ph.D. [3]; Johan Neyts, Ph.D. [1]

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In response to the ongoing COVID-19 pandemic, repurposing of drugs for the treatment of SARS-CoV-2 infections is being explored. The FDA-approved HIV protease inhibitor Nelfinavir is one of the drugs that has been reported to inhibit *in vitro* SARS-CoV2 replication. We here report on the effect of Nelfinavir in the Syrian hamster SARS-CoV-2 infection model. Although treatment of infected hamsters with either 15 mg/kg BID or 50 mg/kg BID Nelfinavir [for four consecutive days, initiated on the day of infection] does not reduce viral RNA loads nor infectious virus titres in the lungs (as compared to the vehicle control at the end of treatment) the drug reduced virus-induced lung pathology (at doses that are well tolerated) to nearly the baseline scores in healthy animals. Yet, a massive interstitial infiltration of neutrophils is observed in the lungs of treated (both infected and uninfected) animals. The protective effect of Nelfinavir on SARS-CoV-2-induced lung pathology that is unrelated to an antiviral effect warrants further exploration in the context of the treatment of COVID-19.

235. Potent inhibitors of SARS-CoV-2 3C-like protease derived from Niclosamide

Subodh Samrat, Ph.D.[1]; Jimin Xu, Ph.D.[2]; Zhong Li, M.S.[1]; Pei-Yong Shi, Ph.D.[2]; Jia Zhou, Ph.D.[2]; Hongmin Li, Ph.D.[1]

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SARS-CoV-2, like SARS-CoV and MERS-CoV, belongs to the *Betacoronavirus* genus. SARS-CoV-2 causes global pandemic of coronavirus disease 2019 (COVID-19). Several vaccines have been approved recently; however, further investigation is required to assess these vaccines› protection level. Except for remdesivir, which was approved for emergency use, there are no approved specific antiviral drugs available to combat SARS-CoV-2 infection. Besides, due to the rapid dissemination of SARS-CoV-2, several new variants have been identified. These facts highlight an urgent need to identify a new class of antiviral drugs against SARS-CoV-2. The 3C-like protease ($3CL_{pro}$) of SARS-CoV-2 hydrolyses viral polyproteins to produce functional proteins. $3CL_{pro}$ is essential for coronavirus replication, so it is considered one of the most important therapeutic targets for COVID-19. Previously our lab has found niclosamide and its derivatives as potent inhibitors for flaviviruses. In current studies, using FRET-based enzymatic assay, we have screened a small library of niclosamide derivatives and identified three molecules, JMX0286, JMX0301, JMX0941, as potent inhibitors against SARS-CoV-2 $3CL_{pro}$, with IC_{50} values like that of known covalent inhibitor boceprevir. In the cell-based assay, we have found that these inhibitors can inhibit the virus growth with EC_{50} in the range of 2-3 uM. Our experiment confirmed that these inhibitors bound at the active site of 3CLpro and worked as non-covalent competitive inhibitors. Further study is continuing to characterize the interaction at the molecular level between 3C protease and different inhibitors by co-crystallization, microscale thermophoresis (MST), Thermal shift assay, and Isothermal titration calorimetry (ITC).

AUTHOR INDEX

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