Hosted by the International Society for Antiviral Research (ISAR)

32ND International Conference on Antiviral Research (ICAR)

PROGRAM and ABSTRACTS

Baltimore
MARYLAND
USA

Hyatt Regency
BALTIMORE

May 12-15
2019

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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 Society is now in its thirty-second year of existence, and has members representing 30 countries. Membership application forms are available at our website at **www.isar-icar.com**.

CONTRIBUTORS

Confirmed Sponsors as of April 30, 2019

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WELCOME & KEYNOTE LECTURES

Sunday, May 12, 2019

CONSTELLATION AB

Measles: A Role for Virus Persistence?

Diane Griffin

Johns Hopkins University, Baltimore, MD

2:00 PM

Remdesivir (GS-5734), A Broad Spectrum Antiviral Agent

Antonín Holý Memorial Award Lecture

Richard Mackman

Gilead Sciences, Foster City, CA

2:45 PM

NETWORKING EVENTS

Sunday, May 12, 2019

Women in Science Roundtable

12:00 PM – 1:45 PM

COLUMBIA/FREDERICK

Opening Reception

5:30 PM – 7:00 PM

PISCES (15th floor)

Monday, May 13, 2019

PechaKucha Event with Introduction of First Time Attendees

4:45 PM – 6:00 PM

CONSTELLATION AB

Tuesday, May 14, 2019

Career Development Panel

12:15 PM – 1:15 PM

COLUMBIA/FREDERICK

Networking Reception

7:00 PM – 9:00 PM

BALTIMORE VISITOR CENTER

401 Light Street

(walking distance; across the street from hotel)

SCHEDULE at a GLANCE

SUNDAY, MAY 12, 2019

TIME	EVENT	LOCATION
11:00 AM – 5:30 PM	Registration	CONSTELLATION FOYER
12:00 PM – 1:45 PM	Women in Science Roundtable	COLUMBIA/FREDERICK
2:00 PM – 3:30 PM	Welcome, Keynote and Antonín Holý Award Lectures	CONSTELLATION AB
3:30 PM – 4:00 PM	Coffee Break	CONSTELLATION FOYER
4:00 PM – 5:30 PM	Influenza Symposium	CONSTELLATION AB
5:30 PM – 7:00 PM	Opening Reception *Light hors d'oeuvres served*	PISCES (15th floor)

MONDAY, MAY 13, 2019

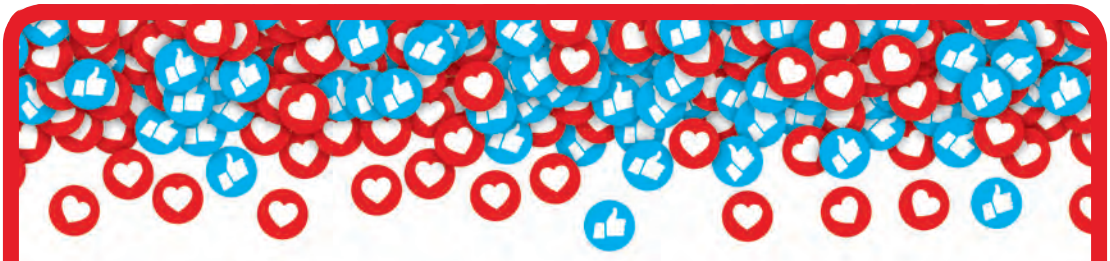
TIME	EVENT	LOCATION
8:00 AM – 5:30 PM	Registration	CONSTELLATION FOYER
8:30 AM – 9:00 AM	Women in Science Award Lecture	CONSTELLATION AB
9:00 AM – 11:00 AM	Emerging Virus Symposium	CONSTELLATION AB
11:00 AM – 11:20 AM	Coffee Break	CONSTELLATION FOYER
11:20 AM – 12:30 PM	Short Presentations 1	CONSTELLATION AB
12:30 PM – 2:30 PM	Poster Session 1 *Lunch provided*	CONSTELLATION CDEF
2:30 PM – 4:30 PM	Retrovirus Symposium *ISAR Award of Excellence Presentation*	CONSTELLATION AB
4:30 PM – 4:45 PM	Coffee Break	CONSTELLATION FOYER
4:45 PM – 6:00 PM	PechaKucha Event with Introduction of First Time Attendees	CONSTELLATION AB

TUESDAY, MAY 14, 2019

TIME	EVENT	LOCATION
8:00 AM – 5:30 PM	**Registration**	**CONSTELLATION FOYER**
8:30 AM – 10:00 AM	**What's New in Antiviral Research 1**	**CONSTELLATION AB**
10:00 AM – 10:20 AM	**Coffee Break**	**CONSTELLATION FOYER**
10:20 AM – 11:50 AM	**Short Presentations 2**	**CONSTELLATION AB**
11:50 AM – 12:00 PM	**ISAR Award for Outstanding Contributions to the Society Presentation**	**CONSTELLATION AB**
12:00 PM – 1:30 PM	**Lunch** *(on your own)*	
12:15 PM – 1:15 PM	**Career Development Panel** *Light snacks and beverages served*	**COLUMBIA/FREDERICK**
1:30 PM – 2:00 PM	**William Prusoff Young Investigator Award Lecture**	**CONSTELLATION AB**
2:00 PM – 3:30 PM	**Medicinal Chemistry Symposium**	**CONSTELLATION AB**
3:30 PM – 4:00 PM	**Coffee Break**	**CONSTELLATION FOYER**
4:00 PM – 5:00 PM	**Short Presentations 3**	**CONSTELLATION AB**
5:00 PM – 7:00 PM	**Poster Session 2** *Light hors d'oeuvres served*	**CONSTELLATION CDEF**
7:00 PM – 9:00 PM	**Networking Reception**	**BALTIMORE VISITOR CENTER** **401 Light Street** *(walking distance; across the street from hotel)*

WEDNESDAY, MAY 15, 2019

TIME	EVENT	LOCATION
8:00 AM – 3:00 PM	Registration	CONSTELLATION FOYER
8:30 AM – 9:00 AM	Gertrude Elion Memorial Award Lecture	CONSTELLATION AB
9:00 AM – 10:30 AM	What's New in Antiviral Research 2	CONSTELLATION AB
10:30 AM – 10:50 AM	Coffee Break	CONSTELLATION FOYER
10:50 AM – 12:00 PM	Shotgun Oral Presentations & Awards *(Posters and TCFF)* Recognition	CONSTELLATION AB
12:00 PM – 12:30 PM	ISAR Annual Business Meeting	CONSTELLATION AB
12:00 PM – 1:15 PM	Lunch *(on your own)*	
1:15 PM – 2:15 PM	Developing New Antiviral Therapies	CONSTELLATION AB
2:15 PM – 3:30 PM	Short Presentations 4	CONSTELLATION AB
3:30 PM	Conference Concludes	



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2019 ISAR AWARD WINNERS

32ND International Conference on Antiviral Research (ICAR)

GERTRUDE ELION MEMORIAL LECTURE AWARDEE

David Evans, PhD

David Evans is a biochemist with special interests in poxvirus recombination, antiviral drugs and genomics. He obtained his Ph.D. in 1982, performed postdoctoral studies at Berkeley and Harvard, joined the University of Guelph in 1987, then returned to the University of Alberta in 2003. He has demonstrated a longstanding commitment to research translation; the recombineering technology he devised in the late 1990's is still sold commercially as Clontech's popular InFusion® kits. More recently, his research has focused on developing oncolytic poxviruses for the treatment of bladder cancer, as well as developing applications for poxviruses assembled using gene synthesis technology. He was a long-standing member of the WHO smallpox advisory committee, and his expertise in biosafety and biosecurity has involved him in conducting international site visits for the WHO and FAO/OIE. He recently completed a term of service on the Canadian advisory committee on human pathogens and toxins. He is a Fellow of the Canadian Academy of Health Sciences and serves as Scientific Officer for the CIHR's Virology & Viral Pathogenesis grant review committee.

ANTONÍN HOLÝ MEMORIAL LECTURE AWARDEE

Richard Mackman, PhD

Richard Mackman is Vice-president of Medicinal Chemistry at Gilead Sciences, where he has spent 18 years developing novel antiviral therapies. He earned a BA in Natural Science and a PhD in the synthesis of natural products from Cambridge University. Following a postdoctoral fellowship at the University of California San Francisco, he began his industrial career in oncology, designing serine protease inhibitors. In 2001 he joined Gilead Sciences, where he has led projects and chemistry teams aimed at developing novel therapeutics against HIV, HCV, RSV, HBV, and emerging viruses such as Ebola and dengue. These programs have resulted in multiple clinical candidates, including GS-9131, a novel nucleoside phosphonate for the treatment of HIV infection; GS-9688, a selective toll-like receptor 8 agonist for the treatment of chronic hepatitis B; the respiratory syncytial virus fusion inhibitor presatovir; and remdesivir, an RNA polymerase inhibitor for the treatment of Ebola virus disease. He has published extensively in the area of nucleoside/nucleotide-based antiviral therapeutics and is named as a co-inventor on more than 40 patents. He has recently been honored by election as a Fellow of the Royal Society of Chemistry.

WILLIAM PRUSOFF YOUNG INVESTIGATOR AWARDEE

Marnix Van Loock, PhD

Marnix Van Loock is Scientific Director within the Infectious Diseases & Vaccines Discovery team of Janssen Pharmaceutica NV (Johnson & Johnson) in Beerse, Belgium). He has a leading role in flavivirus drug discovery within IDV Discovery, Global Public Health R&D. As dengue early compound development team leader, he steers the clinical development of a first-in-class small molecule for the prevention and/or treatment of dengue, tackling a major unmet medical need. He received his Ph.D. from the University of Leuven, Belgium, and also holds M.Sc. degrees in Industrial Sciences (Biochemistry) and Applied Biological Sciences. He joined the HIV entry discovery team of Tibotec BVBA (currently Janssen Pharmaceutica NV) in 2004, and subsequently joined the HIV integrase team, coordinating cell-based assay development. Beginning in 2009, he was the biology lead for the cytomegalovirus latency project, and in 2012 he became the biology lead for the dengue project within Infectious Diseases & Vaccines, reflecting roles with increasing responsibility throughout his career.

WOMEN IN SCIENCE AWARDEE

Grace Zhou, PhD

Grace Zhou is the director of the Shenzhen International Institute for Biomedical Research (SIIBR) and CEO of ImmunoVir Co., Ltd. She obtained a Ph.D. in biochemistry from the Shanghai Institute of Biochemistry, Chinese Academy of Sciencesin 1998, then began a postdoctoral fellowship at the University of Chicago, where she remained through 2013, studying gene regulation during HSV-1 lytic and latent infection and the potential use of oncolytic herpesviruses for cancer treatment. In 2013, she joined Guangzhou Medical University as a professor, and was one of the founding scientists of the SIIBR in 2015. Her current research focuses oncontrol of innate immune responses in herpesvirus-infected cells, the molecular basis of latent infection and genetic engineering of antiviral and therapeutic exosomes. In addition to basic research, she is co-founder and CEO of Immvira, which is developing a broad range of anti-cancer therapies, based on genetically engineered viruses augmented by cancer-specific immune factors or chemotherapeutic agents, that can be delivered either intra-tumorally or systemically.

ISAR AWARD FOR OUTSTANDING CONTRIBUTIONS TO THE SOCIETY

Mark Prichard, PhD

Mark N. Prichard is Professor of Pediatrics at the University of Alabama at Birmingham where he is the Director of the Molecular Diagnostic Virology Laboratory. His research focuses on the discovery of new drugs for herpesviruses, orthopoxviruses, polyomaviruses, papillomaviruses and influenza virus. He is the PI on contracts from the National Institute of Allergy and Infectious Diseases (NIAID) and helps investigators from academia and industry identify new molecules with antiviral activity and understand their mechanism of action. His laboratory also works to understand resistance to antiviral drugs and evaluates specimens from pediatric clinical trials. In 2009 he received the William Prusoff Young Investigator Award from ISAR and currently serves as co-Chair of the Program Committee. From 2007 to 2012 he served as the chairman of the ISAR Poster Award Committee; in 2009 he was elected for the Board of Directors of ISAR. From 2014- 2017 Mark served as chairman of ISAR's program committee. He is author or coauthor of more than 100 peer reviewed publications and is an editor of Antiviral Research.

ISAR AWARD OF EXCELLENCE

Robert Gallo, MD

Robert Gallo is the Homer & Martha Gudelsky Distinguished Professor of Medicine, Co-Founder & Director of the Institute of Human Virology at the University of Maryland School of Medicine and co-founder and scientific director of the Global Virus Network. He is most widely known as a co-discoverer of HIV as the cause of AIDS and developer of the first HIV blood test. His research aided colleagues in the development of HIV antiviral therapies, and his discovery that chemokines can block infection and halt the progression of AIDS has influenced thinking on how the virus works against the human immune system and led to use of chemokine antagonists or entry inhibitors in combination therapy. Prior to his work on HIV/AIDS, he was the first to identify human retroviruses and the only known leukemia-causing viruses, HTLV-1 and HTLV-2. In 1976, he and his colleagues discovered interleukin-2, a growth-regulating substance for T cells necessary to study human retroviruses. In 1986, he and his group discovered a new human herpesvirus, HHV-6, which causes roseola and is a strong suspect in the origin of some neurological diseases, including Alzheimer's.

Sunday
May 12, 2019
12:00 PM – 1:45 PM
COLUMBIA/FREDERICK

7th Annual WOMEN IN SCIENCE ROUNDTABLE

The WIS Committee is excited to announce the **7th Annual Women in Science Roundtable** at the ICAR meeting in Baltimore, Maryland. This session, the first event on the first day of ICAR, will be held on Sunday, May 12, from 12:00 – 1:45 PM. Registration will occur from noon-12:30 PM. It is open to both women and men and will feature discussions on mentoring of women in STEM.

Please join us to network with fellow scientists in industry, government, and academia who conduct all aspects of antiviral research. This roundtable will provide an opportunity to participate in an exciting exchange of ideas with our 2019 WIS Speaker Award recipient, Dr. Grace Zhou, Co-founder of ImmunoVir Co, Ltd and TheraVir Co, Ltd, as well as other antiviral research scientists.

This event is free, but space is limited. Drinks and light food will be provided.

Please go to the Registration Desk onsite or contact info@isaricar.com to RSVP for this event.

ICAR Career Development Panel

Please join us for a panel discussion about career opportunities in antiviral research at the 32nd ICAR meeting. This year we will host an excellent group of panelists who are recognized experts in various areas of antiviral research and have pursued successful careers in academia, government, or industry. As part of a moderated panel discussion, they will be ready to share their experience, answer questions, and provide feedback about career development. They will highlight the similarities and differences between different sectors of antiviral research. At the end of the formal panel discussion, you will have the opportunity to informally network with your colleagues and panelists and make new contacts.

The event is open to all ICAR attendees, but space is limited.
Please go to the Registration Desk onsite or contact info@isaricar.com to RSVP for this event.

THE 2019 CHU FAMILY FOUNDATION SCHOLARSHIP AWARDEES

ISAR and The Chu Family Foundation (TCFF) Committee are pleased to announce the winners of the 2019 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.

2019 TCFF AWARDEES

Erofili Giannakopoulou

ATHENS, GREECE

Erofili Giannakopoulou received her Pharmacy Degree (B.Sc.) from the University of Athens (NKUA) in Greece, followed by a Master's in Synthetic Pharmaceutical Chemistry in 2016. Her M.Sc. thesis focused on the synthesis of antivirals against Hepatitis C and Influenza. She currently continues her research in the field of antiviral drug discovery as a PhD candidate in the Department of Pharmaceutical Chemistry, NKUA. Her specialization is the design and synthesis of novel metal-chelating agents which are evaluated for their ability to inhibit proliferation of HBV, HCV and Flaviviruses. Being really intrigued by the medicinal applications of the antiviral agents, she also works as a visiting researcher at the Molecular Virology Laboratory of the Hellenic Pasteur Institute. She is highly interested in further improving her PhD research project and, to this end, she will use the TCFF award to acquire specialized training, such as in vitro enzymatic binding and structural assays, at the laboratory of Dr. Bruno Canard at "Architecture et Fonction des Macromolécules Biologiques" (AFMB) in Marseille, France.

Megan Gribble Lloyd

SYRACUSE, NY, USA

Megan Gribble Lloyd, PhD, is currently a postdoctoral associate in the lab of Jennifer Moffat, PhD, at SUNY Upstate Medical University in Syracuse, NY. Megan is motivated to help others, and she finds purpose through her study of antimicrobials and antivirals. Megan completed her PhD at Upstate in 2017 in Jennifer's lab, collaborating with Chris Nomura, PhD, at the SUNY College of Environmental Science and Forestry in Syracuse. Her thesis work focused on identifying a novel target for antibiotic development in Pseudomonas aeruginosa. Currently, Megan's research is focused on developing a new system to study HCMV growth kinetics and antiviral effects using skin tissue and SCID-hu mouse models. She has presented her work on this new HCMV model system at several international conferences and is looking forward to presenting this work at the CMV2019 meeting in Birmingham, AL and at ICAR in Baltimore, MD this spring. As part of Jennifer's lab, Megan also studies VZV and is working to improve the lab's model system for evaluation of VZV antivirals. Megan will be using funds from The Chu Family Foundation Scholarship to attend the CMV2019 meeting and visit the lab of Dr. Mark Prichard to experience the full spectrum of HCMV research at UAB, from bench to bedside.

Mary Yates

BALTIMORE, MD, USA

Mary Yates is a PhD candidate at the University of Maryland, Baltimore County, USA, studying under the mentorship of Professor Kathie Seley-Radtke. Mary graduated from McDaniel College in 2015 with a B.A. in ACS Chemistry and Biochemistry. In her research at UMBC, she synthesizes modified nucleoside and nucleotide analogues for potential antiviral therapeutics. Mary has used the Chu Family Foundation Early Career Scholarship to study under the mentorship of Dr. Mike Flint at the Center for Disease Control in Atlanta, Georgia, where she learned about cell culture techniques and how to run assays to determine antiviral activity of her nucleoside analogues. Mary hopes to continue in the field of small-molecule drug design after graduate school, working for a governmental agency.

Bo Kyeong Yoon

SINGAPORE, SINGAPORE

Dr. Bo Kyeong Yoon is currently a Research Fellow in the Engineering in Translational Science group at Nanyang Technological University in Singapore. She is interested in developing nano-formulations of antimicrobial lipids to inhibit membrane-enclosed pathogens, including enveloped viruses. Dr. Yoon received a joint PhD degree from Nanyang Technological University and the University of Natural Resources and Life Sciences (BOKU) in Austria, where she studied Materials Science and Engineering along with Food Chemistry and Biotechnology. Her scientific work has been published in over 20 peer-reviewed publications, including *Nature Materials, Nature Protocols, Chemical Communications, Langmuir* and *Analytical Chemistry*.

Timothy Block, PhD

Timothy Block is President and Co-founder of the Hepatitis B Foundation; of its research arm, the Baruch S. Blumberg Institute; and of the Pennsylvania Biotechnology Center. With Barry Blumberg and Raymond Dwek, he began pursuit of antivirals against hepatitis B virus, targeting the HBs antigen in the 1990s, which helped to determine the role of glycan processing in HBs protein folding. More recently, he and colleagues identified small-molecule inhibitors of HBV, some of which are now in clinical-phase human testing by Arbutus Biopharma. He is the scientific co-founder of several life sciences companies, co-inventor on 20 issued patents and 23 applications, and co-author of more than 240 scholarly papers and was elected to the US National Academy of Inventors (2018). In 2017 he was named a "Visionary in Hepatitis" by the World Hepatitis Alliance in 2017.

Andrea Brancale, PhD

Andrea Brancale is a professor of medicinal chemistry at Cardiff University. He undertook his PhD and postdoctoral work in synthetic medicinal chemistry under Professor Chris McGuigan, focusing on the design and synthesis of novel nucleosides and nucleotides analogues as antiviral drugs. With his appointment as lecturer in the WSP he strategically directed his research interests to focus on the use of computer-aided techniques to design and discover novel anti-viral and anti-cancer compounds. He was promoted to Professor in 2017, and he continues to establish his reputation as an internationally recognised drug design expert in the antiviral and anticancer field. He is author of more than 130 peer-reviewed papers and actively collaborates with several academic groups in the UK and the rest of the world. He is a member of the ISAR Board of Directors, has been chair of the ISAR website committee since 2008 and he is a member of the membership and program committees. He received the William Prusoff Young Investigator Award in 2013. He is the Editor-in-Chief of Antiviral Chemistry and Chemotherapy.

Rhonda Cardin, PhD

Rhonda Cardin has extensive experience in viral pathogenesis, immunology, and antiviral drug evaluation in small animal models of herpesvirus disease, and is an expert on cytomegalovirus. Her research efforts are aimed at characterizing host and viral genes required for CMV pathogenesis and latency. After receiving her A.B from Washington University in St. Louis and her PhD in microbiology from Louisiana State University, she began her career in cytomegalovirus research as a postdoc in Ed Mocarski's laboratory at Stanford. In 1994, she moved to Memphis, TN to join the laboratory of Peter Doherty at St. Jude Children's Research Hospital, studying murine gammaherpesvirus pathogenesis and immunology, as a model for the human gammaherpesviruses, EBV and KSHV. After working for several years for Parke-Davis and Pfizer, she returned to academia in 2003 and joined the faculty of the Cincinnati Children's Hospital Medical Center. In 2016, she moved to the LSU School of Veterinary Medicine in Baton Rouge, where she continues her CMV research and is Associate Dean for Research and Advanced Studies. She is a co-PI on a NIH contract for evaluating novel antivirals and vaccines in CMV and HSV animal models.

Marina Caskey, MD

Marina Caskey received her medical degree from the Federal University of Sergipe, Brazil in 1998, and following ID specialty training at Weill Cornell Medical Center in New York, she joined the Clinical Scholars Program at the Rockefeller University in 2006. Working in Dr. Ralph Steinman's Laboratory, she characterized the immune response induced by an HIV vaccine which targets HIV antigens directly to dendritic cells. Her current work focuses on the development and clinical evaluation of novel immunotherapeutic strategies against infectious diseases, with a special emphasis on HIV-1. Over the last 5 years, she has led a series of first-in-humans studies with two of the most promising broadly neutralizing anti-HIV-1 antibodies, 3BNC117 and 10-1074, which were isolated in the laboratory of Michel Nussenzweig. They are being developed for potential roles in HIV-1 prevention and therapy, and for their effects on the HIV-1 reservoir and on host immune responses, when given alone or in combination with latency-reversing agents or immune-modulatory molecules.

Marc S. Collett, PhD

Marc S. Collett received undergraduate, graduate, and postgraduate training in molecular biology and virology at the universities of Michigan, Minnesota, and Colorado and held faculty positions at the U of Minnesota. He has been a corporate officer in several biotech/pharma companies (Molecular Genetics, MedImmune, Pathogenesis, Acambis) and was a co-founder of ViroPharma and founder of ViroDefense, his current position. ViroDefense is assisting the Global Polio Eradication Initiative by developing antivirals against polioviruses. The effort is orchestrated by the Poliovirus Antiviral Initiative, a consortium managed by the Task Force for Global Health and comprised of the WHO, CDC, Rotary International, CBER/FDA, NIAID, the Bill & Melinda Gates Foundation and ViroDefense. The goal is to develop a treatment that eliminates poliovirus excretion by immunodeficient individuals chronically infected with vaccine-derived viruses (iVDPV), who pose a threat to eradication. Toward this end, ViroDefense now has two drug candidates in clinical trials.

Howard Gendelman, MD

Howard Gendelman is the Margaret R. Larson Professor of Internal Medicine and Infectious Diseases and Chairman of the Department of Pharmacology and Experimental Neuroscience at the University of Nebraska Medical Center. He is credited with unraveling the pathways by which functional alterations in brain immunity induce metabolic changes and ultimately lead to neural cell damage in a broad range of infectious and neurodegenerative disorders, and for demonstrating that AIDS dementia is a reversible metabolic encephalopathy. These discoveries have led to pre-clinical and clinically realized therapeutics aimed at preventing, slowing or reversing a broad range maladies. He developed the Nebraska Nanomedicine Production Plant, devoted to GLP and cGMP manufacture of novel long-acting antiviral medicines for phase I and II testing. He obtained a Bachelor's degree i from Muhlenberg College, his M.D. from the Pennsylvania State University-Hershey Medical Center. He did further training and has held faculty appointments at the Albert Einstein College of Medicine, the Johns Hopkins Medical Center and the National Institute of Allergy and Infectious Diseases.

Nesya Goris, PhD

Nesya Goris is co-founder and Chief Development Officer of ViroVet, a Belgian biotech company active in research on animal health. She has extensive experience in veterinary vaccinology and antiviral drug development. She obtained a MS degree in biological sciences from Leuven University and a PhD in veterinary sciences from the University of Ghent in 2008. One of her major research targets has been the development of small-molecule antiviral drugs against feline viruses such as FHV, FCV and FIV, two of which she brought from the bench into clinical field trials. Her current research focuses on the potential of antiviral prophylaxis and therapy for controlling RNA viral infections of livestock. Since 2015, she has performed research on applying plasmid-launched live-attenuated vaccine technology to infectious diseases of livestock. She is an editor for Antiviral Research.

Diane Griffin, PhD

Diane Griffin is University Distinguished Service Professor and former Chairof the W. Harry Feinstone Department of Molecular Microbiology and Immunologyat the Johns Hopkins Bloomberg School of Public Health. She earned her BA in Biology at Augustana College and her MD and PhD at Stanford University School of Medicine. Her research interests focus on the pathogenesis of viral diseases, particularly measles and arboviral encephalitis. Her studies address issues related to virulence, RNA virus persistence and the role of immune responses in protection from infection and in clearance of infection. She has more than 400 publications and has served on multiple advisory and editorial boards. She is the US Chair of the US-Japan Cooperative Medical Sciences Program and past president of the American Society for Virology and the American Society for Microbiology (ASM). She is a member of the National Academy of Medicine, the Association of American Physicians and the American Philosophical Society. She is the Vice President of the US National Academy of Sciences.

Emily Gurley, PhD

Emily Gurley is an infectious disease epidemiologist and Associate Scientist at the Johns Hopkins School of Public Health who has been involved in research on Nipah virus since 2004. Her work is multi-disciplinary, drawing on perspectives and methods from applied and academic epidemiology, anthropology, microbiology, and ecology. She earned an MPH from Emory University in 2002 and a PhD in epidemiology from Johns Hopkins University in 2012. She spent 12 years working at the International Centre for Diarrhoeal Diseases Research, Bangladesh in Dhaka. She currently leads investigations of Nipah virus transmission and works on the development of behavioral and pharmaceutical interventions to prevent its spread. She is the PI for the Bangladesh component of the PREEMPT project, which aims to predict bat shedding of henipaviruses to prevent spillover events, and serves on the WHO Nipah Virus Taskforce for the development of medical countermeasures.

Frederick Hayden, PhD

Frederick Hayden is Stuart S. Richardson Professor Emeritus of Clinical Virology and Professor Emeritus of Medicine at the University of Virginia School of Medicine, Charlottesville. He received his medical degree from Stanford University School of Medicine in 1973 and completed training in internal medicine and infectious diseases at Strong Memorial Hospital, University of Rochester, New York. His research has focused on respiratory viral infections, principally the development and application of antiviral agents and other therapeutics. He has published over 400 peer-reviewed articles, chapters, and reviews, and co-edits the ASM textbook *Clinical Virology*. During 2006-2008 he served as a medical officer in the Global Influenza Programme at the WHO and during 2008-2012 as influenza research coordinator within International Activities at the Wellcome Trust. He continues to serve as a WHO consultant on respiratory and emerging viral infections.

Michael Jacobs, PhD

Michael Jacobs is Clinical Director of Infection at the Royal Free Hospital in London. He trained at Oxford and London universities before completing a PhD in virology. He is interested in all aspects of clinical infectious diseases, with a special interest in serious viral infections and medical countermeasures. He is director of the UK High Level Isolation Unit and is a member of the UK Advisory Committee on Dangerous Pathogens. He worked at the centre of the UK response to the West Africa Ebola epidemc, and serves on several national and international Ebola advisory committees. He was NHS England Programme Director for High Consequence Infectious Diseases. He was knighted in 2016 for services to the prevention and treatment of infectious diseases.

Anthony Keefe, PhD

Anthony Keefe joined X-Chem Pharmaceuticals at its establishment in 2010, and is the Vice President of Discovery Technology. He oversees the application of the X-Chem encoded library deck to a range of collaboration and internal projects. X-Chem operates a proprietary DNA-encoded chemistry platform that comprises over 220 billion encoded compounds and has resulted in more than 50 licensed therapeutic programs. This platform has been successfully applied to a wide range of target classes and therapy areas for both internal and collaboration programs, and includes sub-libraries of both reversible and covalent irreversible encoded compounds. Currently active X-Chem collaborations include Astra-Zeneca, Abbvie, Almirall, Astellas, BMS, Bayer, Gilead, Janssen, Otsuka, Taiho and Vertex. Anthony received his BSc in chemistry from the University of Exeter, UK, in 1985 and his PhD in chemistry from the University of Birmingham, UK, in 1989. He has over 20 years of experience working with a range of encoded library platforms and affinity-mediated discovery techniques, including mRNA-display and aptamers.

Florian Krammer, PhD

Florian Krammer received his PhD degree from the University of Natural Resources and Life Sciences, Vienna, Austria. He performed postdoctoral training in the laboratory of Peter Palese at the Icahn School of Medicine at Mount Sinai, New York, working on influenza hemagglutinin stalk-based immunity and universal influenza vaccines. He has remained at the Icahn School, and in 2013 he became an independent principal investigator and is currently an associate professor. His 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 Zika virus, hantaviruses, filoviruses and arenaviruses.

Victoria Olson, PhD

Victoria Olson is Chief of the Poxvirus and Rabies Branch at the US Centers for Disease Control and Prevention in Atlanta. She obtained a BS degree in biochemistry from Michigan State University in 1994 and a PhD from the University of Wisconsin-Madison in 2001, then joined the CDC in 2002 as a postdoctoral fellow. Her research has focused on poxviruses and their interactions with their hosts, including studies of the causative agent of smallpox, variola virus. She leads the WHO Collaborating Center on smallpox and other poxviruses at the CDC, as well as one of the the WHO Collaborating Centers on rabies. The Poxvirus and Rabies Branch consists of more than 70 scientists who provide diagnostic support, both domestically and internationally, for poxvirus and rabies infections, as well as research to develop medical countermeasures and guidance on their use in public health interventions.

María-Jesús Pérez-Pérez, PhD

María-Jesús Pérez-Pérez is Research Professor at the Medicinal Chemistry Institute of the Spanish National Research Council in Madrid. Her research is principally devoted to antiviral and antitumor chemotherapy, from a medicinal chemistry perspective. She has also worked to develop selective inhibitors against therapeutically relevant nucleoside processing enzymes, such as thymidine phosphorylase and nucleoside kinases, as well as the identification and optimization of antivirals against HIV, enteroviruses and alphaviruses. One of her current projects involves the study of heterocyclic compounds that interfere with the alphavirus capping process, particularly for chikungunya virus. She has been Head of Department and Director of the Medicinal Chemistry Institute, and is also the coordinator of the Spanish network for antivirals against arboviral diseases (Rearbovir).

Izzat Raheem, PhD

Izzat Raheem joined Merck in West Point, PA in 2007, and is Director of Discovery Chemistry. He has participated in numerous successful drug discovery programs in the neuroscience and infectious disease therapeutic areas, and has contributed directly to multiple small-molecule candidates progressing through early- and late-stage clinical trials, across a range of indications. In addition to leading multiple on-going drug discovery programs, he oversees discovery prodrug efforts, enabling collaborative projects across numerous therapeutic areas. He also serves as chemistry lead for several vaccine efforts, including mRNA-based vaccine delivery, LNP and subunit vaccine conjugates, and novel adjuvants. He received a BS degree from Carnegie Mellon University and a PhD from Harvard University. He is an author on over 40 peer-reviewed publications and patents.

Amadou Sall, PhD

Amadou Sall is the scientific director of the Pasteur Institute in Dakar, Senegal, part of the Institut Pasteur International Network. He is a virologist with a PhD in public health, and his research focuses primarily on diagnostics, pathogenesis, ecology and evolution of arboviral diseases and viral hemorrhagic fever. During the past few years he has been an author on reseach reports on many emerging viruses in Africa, including Ebola, monkeypox, yellow fever, chikungunya, dengue and West Nile virus. He is a member of several expert committees for the World Health Organization and the OIE and vice chair of the Global Outbreak Alert and Response Network steering committee. He is a member of the Senegal National Academy of Science and Technology and has been recipient of the Senegal Presidential Award for Science in 2011 and the UNESCO Prize for Research in Life science in 2015.

Kathie Seley-Radtke, PhD

Kathie Seley-Radtke is the University of Maryland, Baltimore County (UMBC) Presidential Research Professor for Research, and the University of Maryland's System-wide Regents Professor for Research. Her research involves using a synthetic organic/medicinal chemistry approach to nucleos(t)ide and heterocyclic antiviral drug discovery and development. Current projects include the investigation of flexible nucleosides/nucleotides known as "fleximers", for use against SARS, MERS-CoV, Ebola, Zika, dengue and yellow fever viruses, among other infectious diseases. In addition, she has developed a series of heterocyclic anticancer drugs that are currently in preclinical animal studies. She is currently the Secretary of IS3NA, our sister nucleoside society, and prior to that, she served as President. She is also a board member of the International Society for Antiviral Research, as well as an associate editor for *Antiviral Chemistry & Chemotherapy, Molecules,* and *Current Protocols in Chemical Biology*.

Jeffery Taubenberger, MD, PhD

Jeffery Taubenberger is Chief of the Viral Pathogenesis and Evolution Section, and Deputy Chief of the Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, NIH. Before coming to NIAID in 2006, he served as Chair of the Department of Molecular Pathology at the Armed Forces Institute of Pathology (AFIP) in Washington, DC, a position he held since 1994. He received a B.S. in Biology from George Mason University in 1982, and his medical degree in 1986 and Ph.D. in 1987 from the Medical College of Virginia. His research interests include influenza virus biology, pathophysiology, characterization of clinical influenza, and development of a universal influenza vaccine. Among his key contributions to the field has been the characterization of the virus responsible for the 1918 influenza pandemic. He has published over 235 papers and 14 book chapters.

Maria Van Kerkhove, PhD

Maria Van Kerkhove is an infectious disease epidemiologist specializing in outbreaks of emerging and re-emerging pathogens. She completed her undergraduate degree at Cornell University, her MS at Stanford and her PhD at the London School of Hygiene and Tropical Medicine. Her research interests include avian influenza, MERS-coronavirus, Ebola, Marburg and Zika virus, investigating factors associated with transmission between animals and humans, and ensuring that research directly informs public health policy for action. She is currently the MERS-CoV Technical Lead in the High Threat Pathogens Unit of the Health Emergency Program. She previously headed the outbreak investigation task force at the Institut Pasteur's Center for Global Health, and was earlier employed by Imperial College London in the MRC Center for Outbreak Analysis and Modelling, where she worked closely with WHO investigators on influenza, yellow fever, meningitis, MERS-CoV and Ebola virus disease.

Subhash Vasudevan, PhD

Subhash Vasudevan is a Professor and Principal Investigator in the Signature Program for Emerging Infectious Diseases at Duke-National University of Singapore (Duke-NUS) Medical School. He obtained his PhD at the Australian National University in 1989 and performed postdoctoral training at the Max Planck Institute for Biophysics and Research School of Chemistry. He first established an independent research laboratory when he became a lecturer in biochemistry and molecular biology at the James Cook University in 1993. He moved to Singapore in 2003 to establish the Dengue Research Unit at the Novartis Institute for Tropical Diseases, and has been at Duke-NUS since 2007. His major research interests are in antiviral drug discovery against dengue and related flaviviruses, such as Zika. He is an editor for Antiviral Research and a member of the editorial board of the Journal of Virology.

Yan-Yi Wang, PhD

Yan-Yi Wang is the Director of the Wuhan Institute of Virology, one of the leading institutes in the Chinese Academy of Sciences. She received a BS degree in biological sciences from Peking University, an MS in immunology from the University of Colorado Health Sciences Center and a PhD in microbiology from Wuhan University. For the past 15 years, her research interests have focused on virus-host interactions, extending from antiviral innate immunity to viral strategies of immune evasion. She has identified multiple key players in these processes, and her publications have been cited more than 2200 times. The Wuhan Institute of Virology performs a range of basic and applied research on infectious pathogens, with an emphasis on highly pathogenic viruses. It includes the first operational BSL-4 laboratory in China.

Scott Weaver, PhD

Scott Weaver holds the John Sealy Distinguished University Chair in Human Infections and Immunity, chairs the Department of Microbiology and Immunology at the UTMB Galveston, and is the Scientific Director of the Galveston National Laboratory. He studies arthropod-borne viruses, their transmission by mosquitoes and the development of vaccines. His research encompasses the ecology and epidemiology of enzootic arbovirus transmission cycles, virus-mosquito interactions, pathogenesis, and emergence mechanisms of epidemic strains. Recently he has focused on Zika and chikungunya and viruses, and his chikungunya vaccine, licensed to Takeda Pharmaceuticals, is in late preclinical development. He received the Walter Reed Medal from the American Society for Tropical Medicine and Hygiene for distinguished accomplishment in tropical medicine, and the Robert C. Gallo Award for Scientific Excellence from the Global Virus Network. He chairs/co-chairs the GVN Chikungunya and Zika Task Forces, and serves as PI for the CDC-funded Western Gulf Center of Excellence for Vector-borne Diseases.

SUNDAY, MAY 12, 2019

Welcome, Keynote and Antonín Holý Award Lectures

CONSTELLATION AB

2:00 PM – 3:30 PM

(Abstract Number)

2:00 PM **126.** **Measles: A Role for Virus Persistence?**

Diane Griffin, Ph.D.[1]

[1]*Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America*

Antonín Holý Memorial Award Lecture

2:45 PM **127.** **Remdesivir (RDV, GS-5734), a Broad Spectrum Antiviral Agent**

Richard Mackman, Ph.D.[1]

[1]*Gilead Sciences, Foster City, California, United States of America*

Coffee Break

CONSTELLATION FOYER

3:30 PM – 4:00 PM

Influenza Symposium

CONSTELLATION AB

4:00 PM – 5:30 PM

4:00 PM **128.** **101 Years of Influenza: Lessons from the 1918 Pandemic**

Jeffery Taubenberger, M.D., Ph.D.[1]

[1]*NIAID, NIH, Bethesda, Maryland, United States of America*

4:30 PM **96.** **Influenza Antivirals: Recent Developments**

Frederick Hayden, M.D.[1]

[1]*University of Virginia School of Medicine, Charlottesville, Virginia, United States of America*

5:00 PM **130.** **A Hemagglutinin Stalk-based Universal Influenza Virus Vaccine**

Florian Krammer, Ph.D.[1]

[1]*Icahn School of Medicine at Mount Sinai, New York, New York, United States of America*

Opening Reception

PISCES (15TH FLOOR)

5:30 PM – 7:00 PM

MONDAY, MAY 13, 2019

Women in Science Award Lecture

CONSTELLATION AB

8:30 AM – 9:00 AM

8:30 AM **70. Function, Activation and Control of Innate Immune Networks to HSV Infection**

Grace Zhou, Ph.D.[1]

[1]*Shenzhen International Institute for Biomedical Research, Shenzhen, China*

Emerging Virus Symposium

CONSTELLATION AB

9:00 AM – 11:00 AM

9:00 AM **131. Research for Preparedness for Arboviruses and Hemorrhagic Fever Viruses in Subsaharan Africa**

Amadou Sall, Ph.D.[1]

[1]*Pasteur Institute, Dakar, Senegal*

9:30 AM **132. WHO's Global Program on MERS: Improving Global Preparedness and Response to High Threat Emerging Respiratory Pathogens with Significant Public Health and Economic Consequences**

Maria Van Kerkhove, Ph.D.[1]

[1]*MERS-CoV Technical Lead, World Health Organization, Geneva, Switzerland*

10:00 AM **181. Development of Medical Countermeasures against Nipah Virus: A Field Perspective**

Emily Gurley, Ph.D.[1]

[1]*Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America*

10:30 AM **134. Can We Predict Arbovirus Epidemics?**

Scott Weaver, Ph.D.[1]

[1]*Emerging Viruses and Arboviruses and Department of Microbiology and Immunology, University of Texas Medical Branch, Galveston, Texas, United States of America*

Coffee Break

CONSTELLATION FOYER

11:00 AM – 11:20 AM

Short Presentations 1 – DNA, Respiratory, and Other Viruses

CONSTELLATION AB

11:20 AM – 12:30 PM

11:20 AM **135. Human Intravenous Immunoglobulin Provides Protection Against Enterovirus 71 Infection in a Mouse Model**

Christopher Peterson, M.S.[1], Brett Hurst, Ph.D.[1], **E. Bart Tarbet, Ph.D.**[1]

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

11:30 AM **136. A Novel Human Skin Tissue Model to Study HCMV and Evaluate Antiviral Drugs *In Vivo***

Megan Lloyd, Ph.D.[1], Rebecca Harris, B.S.[1], Michael Tighe, B.S.[2], Prashant Upadhyaya, M.D.[1], Eain Murphy, Ph.D.[3], Jennifer Moffat, Ph.D.[1]

[1]SUNY Upstate Medical University, Syracuse, New York, United States of America; [2]Trudeau Institute, Saranac Lake, New York; [3]Forge Life Science, Doylestown, Pennsylvania, United States of America

11:40 AM **137. Exploring Small Molecule Synthetic Inhibitors of HSV-1 Infectivity**

Jody Cameron, B.S.[1], Furkat Mukhtarov, M.S.[1], Nargess Hosseini, Ph.D.[2], Devon Schatz, B.S.[2], Consuelo Correa-Sierra, M.D.[1], Frederick West, Ph.D.[2], **Luis Schang, D.V.M., Ph.D.**[1]

[1]Cornell University, Ithaca, New York, United States of America; [2]University of Alberta, Edmonton, AB, Canada

11:50 AM **138. Disrupting Transcriptional Feedback Yields an Escape-Resistant Antiviral**

Sonali Chaturvedi[1], Leor Weinberger, Ph.D.[1]

[1]Gladstone Institutes, San Francisco, California, United States of America

12:00 PM **139. Inhibition of DNA Viruses by Ribosylindole Nucleosides**

Scott James, M.D.[1], Caroll Hartline, M.S.[1], Emma Harden, B.S.[1], Leroy Townsend, Ph.D.[2], John Drach, Ph.D.[2], Brian Gentry, Ph.D.[3], Mark Prichard, Ph.D.[1]

[1]University of Alabama at Birmingham, Birmingham, Alabama, United States of America; [2]University of Michigan, Ann Arbor, Michigan, United States of America; [3]Drake University, Des Moines, Iowa, United States of America

12:10 PM **140. Neuraminidase-Targeted Immunotherapy of Influenza: Repurposing Zanamivir as a Targeting Ligand for Delivery of an Attached Immunogenic Hapten to Virus/Virus-Infected Cells**

Xin Liu, B.S.[1], Boning Zhang, B.S.[1], Philip Low, Ph.D.[1]

[1]Department of Chemistry and Institute for Drug Discovery, Purdue University, West Lafayette, Indiana, United States of America

12:20 PM **141. Validating Enterovirus D68 -2Apro as an Antiviral Drug Target and the Discovery of Telaprevir as a Potent D68-2Apro Inhibitor**

Rami Musharrafieh, B.S.[1], Chunlong Ma, Ph.D.[1], **Jun Wang, Ph.D.**[1]

[1]University of Arizona

Poster Session 1

CONSTELLATION CDEF

12:30 PM –2:30 PM

12:30- 1:30 PM **ODD numbered poster presentations**

1:30 – 2:30 PM **EVEN numbered poster presentations**

All posters are listed in numerical order starting on page 37.

Retrovirus Symposium

CONSTELLATION AB

2:30 PM – 4:30 PM

2:30 PM ***ISAR Award of Excellence***

142. Human Retroviruses (HTLV-1 and HIV): Current Therapy and Prevention

Robert Gallo, M.D.[1]

[1]*Director, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, Maryland, United States of America*

3:00 PM **143. Effects of Broadly Neutralizing Antibody Combinations in HIV-1 Infection**

Marina Caskey, M.D.[1]

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

3:30 PM **144. Long Acting Antiretrovirals**

Howard Gendelman[1]

[1]*University of Nebraska Medical Center, Omaha, Nebraska, United States of America*

4:00 PM **145. The Advancement of HIV NRTTIs for Extended-duration Dosing**

Izzat Raheem, Ph.D.[1]

[1]*Merck, West Point, Pennsylvania, United States of America*

Coffee Break

CONSTELLATION FOYER

4:30 PM – 4:45 PM

PechaKucha Event with Introduction of First Time Attendees

CONSTELLATION AB

4:45 PM – 6:00 PM

TUESDAY, MAY 14, 2019

What's New in Antiviral Research 1

CONSTELLATION AB

8:30 AM – 10:00 AM

8:30 AM **147. Antiviral Treatment for Patients with Yellow Fever – a New Frontier**

Michael Jacobs, M.D., Ph.D.[1]

[1]*Royal Free London NHS Foundation Trust, London, United Kingdom*

9:00 AM **170. Novel Utilization of Smallpox Medical Countermeasures – Challenges to Vaccination Against Endemic Orthopoxvirus Disease (Monkeypox)**

Victoria Olson, Ph.D.[1]

[1]*CDC, Atlanta, Georgia, United States of America*

9:30 AM **161. Antivirals against Chikungunya Virus from a Medchem Perspective: Challenges and Lessons Learned**

María-Jesús Pérez-Pérez, Ph.D.[1]

[1]*Instituto de Química Médica (IQM, CSIC), Madrid, Spain*

Coffee Break

CONSTELLATION FOYER

10:00 AM – 10:20 AM

Short Presentations 2 – Emerging Infections

CONSTELLATION AB

10:20 AM – 11:50 AM

10:20 AM **149. Inhibition of Arenavirus Infection by a Novel Fusion Inhibitor**

Brian Gowen, Ph.D.[1], Jonna Westover, Ph.D.[1], Kie-Hoon Jung, Ph.D.[1], Vidyasagar Gantla, Ph.D.[2], Eric Brown, B.S.[2], Shibani Naik, Ph.D.[2], Brittney Downs, B.S.[1], Ashley Dagley, M.S.[1], Greg Henkel, Ph.D.[2], Ken McCormack, Ph.D.[2]

[1]*Utah State University;* [2]*Arisan Therapeutics*

10:30 AM **150. Broad-spectrum Antiviral Remdesivir Provides Superior *In Vivo* Therapeutic Efficacy against MERS-CoV Compared to a Combination of Lopinavir/Ritonavir Plus Interferon Beta**

TImothy Sheahan, Ph.D.[1], Amy Sims, Ph.D.[1], Sarah Leist, Ph.D.[1], Alexandra Schäfer, Ph.D.[1], John Won, B.S.[1], Ariane Brown, B.S.[1], Alison Hogg, Ph.D.[2], Darius Babusis, Ph.D.[2], Michael Clarke, Ph.D.[2], Jamie Spahn, Ph.D.[2], Laura Bauer, Ph.D.[2], Scott Sellers, Ph.D.[2], Danielle Porter, Ph.D.[2], Joy Feng, Ph.D.[2], Tomas Cihlar, Ph.D.[2], Robert Jordan, Ph.D.[2], Mark Denison, Ph.D.[3], Ralph Baric, Ph.D.[1]

[1]*University of North Carolina at Chapel HIll, Chapel Hill, North Carolina, United States of America;* [2]*Gilead Sciences Inc., Foster City, California, United States of America;* [3]*Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America*

10:40 AM **151. A Genome-Wide CRISPR Screen Identifies N-Acetylglucosamine-1-Phosphate Transferase as a Potential Antiviral Target for Ebola Virus**

Mike Flint, Ph.D.[1], Payel Chatterjee, B.S.[1], David Lin, Ph.D.[2], Laura McMullan, Ph.D.[1], Punya Shrivastava-Ranjan, Ph.D.[1], Eric Bergeron, Ph.D.[1], Michael Lo, Ph.D.[1], Stephen Welch, Ph.D.[1], Stuart Nichol, Ph.D.[1], Andrew Tai, M.D., Ph.D.[2], Christina Spiropoulou, Ph.D.[1]

[1]Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America; [2]University of Michigan Medical School, Ann Arbor, Michigan, United States of America

10:50 AM **152. Efficacy of a ML336 Derivative against Venezuelan and Eastern Equine Encephalitis Viruses**

Colleen Jonsson, Ph.D.[1], Xufeng Cao, Ph.D.[2], Jasper Lee, Ph.D.[1], Jon Gabbard, Ph.D.[3], Yong-Kyu Chu, Ph.D.[3], Elizabeth Fitzpatrick, Ph.D.[1], Justin Julander, Ph.D.[4], Dong-Hoon Chung, Ph.D.[3], Jennifer Stabenow, M.S.[1], Jennifer Golden, Ph.D.[5]

[1]University of Tennessee Health Science Center, Memphis, Tennessee, United States of America; [2]University of Wisconsin, Madison, Wisconsin, United States of America; [3]University of Louisville, Louisville, Kentucky, United States of America; [4]Utah State University, Logan, Utah, United States of America; [5]University of Madison, Madison, Wisconsin, United States of America

11:00 AM **153. Sofosbuvir, a Clinically Approved Antiviral Drug, Inhibits Zika Virus Replication**

Giselle Barbosa-Lima, Ph.D.[1], Carolina Sacramento, Ph.D.[1], André Ferreira, Ph.D.[1], Patricia Reis, Ph.D.[1], Camila Zaverucha-do-Valle, Ph.D.[1], Mayara Mattos, B.S.[1], Yasmine Vieira, Ph.D.[1], Caroline Freitas, M.S.[1], Milene Miranda, Ph.D.[1], Pablo Trindade, Ph.D.[2], Stevens Rehen, Ph.D.[2], Hugo Faria Neto, Ph.D.[1], Fernando Bozza, Ph.D.[1], Almicar Tanuri, Ph.D.[3], Karin Brüning, Ph.D.[4], Patricia Bozza, Ph.D.[1], Thiago Souza, Ph.D.[1]

[1]FIOCRUZ, Rio de Janeiro, Brazil; [2]IDOR; [3]UFRJ; [4]BMK Consortium: Blanver Farmoquímica Ltda; Microbiológica Química e Farmacêutica Ltda

11:10 AM **154. Single-dose Efficacy of Viral Replicon Particle Vaccines for Prevention of Lassa and Crimean-Congo Hemorrhagic Fever**

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

[1]Viral Special Pathogens Branch, Centers for Disease Control & Prevention, Atlanta, Georgia, United States of America

11:20 AM **155. A Novel Class of Small Molecule Inhibitors Targeting the Chikungunya Virus Capping Machinery with a High Barrier to Resistance**

Rana Abdelnabi, Ph.D.[1], Kristina Kovacikova, M.S.[2], Julia Kirchebner, Ph.D.[3], Pieter Leyssen, Ph.D.[1], Arnaud Marchand, M.S.[4], Patrick Chaltin, Ph.D.[4], Gerhard Pürstinger, Ph.D.[3], Thierry Langer, Ph.D.[5], Gilles Quérat, Ph.D.[6], Bruno Coutard, Ph.D.[6], Martijn van Hemert, Ph.D.[2], Johan Neyts, Ph.D.[1], **Leen Delang, Ph.D.**[1]

[1]KU Leuven, Rega Institute for Medical Research, Leuven, Belgium., Leuven, Belgium; [2]Molecular Virology Laboratory, Department of Medical Microbiology, Leiden University Medical Center, Leiden, Netherlands; [3]Department of Pharmaceutical Chemistry, University of Innsbruck, Innsbruck, Austria, Innsbruck, Austria; [4]Centre for Drug Design and Discovery , KU Leuven, Leuven, Belgium; [5]University of Vienna, Department of Pharmaceutical Chemistry, Vienna, Austria, Vienna, Austria; [6]Aix Marseille Université, CNRS, AFMB UMR7257, Marseille, France, Marseille, France

11:30 AM **156. Development of a Nucleoside Analog for Norovirus**

Randall Lanier, Ph.D.[1], Maggie Anderson, B.S.[1], Mark Mullin, B.S.[1], Marion Morrison, M.D.[1], John Dunn, Ph.D.[1], Karoly Toth, D.V.M.[2], Jacqueline Spencer, B.S.[2], Baoling Ying, M.D.[2], Dean Selleseth, B.S.[1], Myra Hosmillo, Ph.D.[3], Komal Nayak, M.S.[3], Andrew Bae, B.S.[1], Sarah Gurley, M.S.[1], Tim Tippin, Ph.D.[1], Heidi Colton, M.S.[1], Matthias Zilbauer, M.D., Ph.D.[3], Ian Goodfellow, Ph.D.[3], Brent Korba, Ph.D.[4], Phiroze Sethna, Ph.D.[1], Dennis Walling, M.D.[1], Odin Naderer, Ph.D.[1]

[1]Chimerix; [2]St Louis University; [3]University of Cambridge; [4]Georgetown University

11:40 AM **157. Rottlerin, a Small Bioactive Compound, Inhibits La Crosse Virus (LACV)-induced Neuronal Damage by Limiting Virus Release from the Golgi**

Durbadal Ohja[1], Vidon Nair, Ph.D.[2], Karin Peterson, Ph.D.[3]

[1]NIAID, Hamilton, Montana, United States of America; [2]Staff Scientist, Hamilton, Montana, United States of America; [3]Senior Investigator, Hamilton, Montana, United States of America

ISAR Award for Outstanding Contributions to the Society Presentation

Mark Prichard, Ph.D.

CONSTELLATION AB

11:50 AM – 12:00 PM

Lunch *(on your own)*

12:00 PM – 1:30 PM

Career Development Panel

COLUMBIA/FREDERICK

12:15 PM – 1:15 PM

William Prusoff Young Investigator Award Lecture

CONSTELLATION AB

1:30 PM – 2:00 PM

1:30 PM **158. An Industry Perspective on Developing Dengue Antiviral Small Molecules**

Marnix Van Loock, Ph.D.[1]

[1]Janssen Pharmaceutica NV (J&J), Global Public Health Research & Development, Beerse, Belgium

Medicinal Chemistry Symposium

CONSTELLATION AB

2:00 PM – 3:30 PM

2:00 PM **159. Rational (and Sometimes Irrational!) Strategies in Nucleoside Drug Design**

Kathie Seley-Radtke, Ph.D.[1]

[1]University of Maryland, Baltimore County (UMBC), Baltimore, Maryland, United States of America

2:30 PM **160. In Search of Novel Antivirals using Structure-based Drug Design Approaches**

Andrea Brancale, Ph.D.[1]

[1]Cardiff University, United Kingdom

3:00 PM **162. Drug Discovery using DNA-Encoded Chemical Libraries**
Anthony Keefe, Ph.D.[1]
[1]*X-Chem Pharmaceuticals, Waltham, Massachusetts, United States of America*

Coffee Break
CONSTELLATION FOYER
3:30 PM – 4:00 PM

Short Presentations 3 – Medicinal Chemistry
CONSTELLATION AB
4:00 PM – 5:00 PM

4:00 PM **163. Novel ProTide Prodrugs of Tenofovir and Their Antiviral Properties**
Filip Kalčic, M.S.[1], Ondřej Baszczyňski, Ph.D.[2], Jan Weber, Ph.D.[3], Michala Zgarbová, M.S.[3], Jan Hodek, Ph.D.[3], Zlatko Janeba, Ph.D.[3]
[1]*Institute of Organic Chemistry and Biochemistry CAS; Charles University, Department of Organic Chemistry;* [2]*Charles University, Faculty of Science, Department of Organic Chemistry;* [3]*Institute of Organic Chemistry and Biochemistry CAS*

4:10 PM **164. Cell-type Dependence of Metabolic Products and Antiviral Potency for T-705 and T-1105**
Johanna Huchting, Ph.D.[1], Evelien Vanderlinden, Ph.D.[2], Chris Meier, Ph.D.[3], Lieve Naesens, Ph.D.[2]
[1]*University of Hamburg, Chemistry Department; KU Leuven, Rega Institute for Medical Research;* [2]*KU Leuven, Rega Institute for Medical Research;* [3]*University of Hamburg, Chemistry Department*

4:20 PM **165. Development of Novel hDHODH Inhibitors as Potent Broad Spectrum Antiviral Agents**
Nora Constanze Fohrmann, M.S.[1], Katharina Pfaff, M.S.[1], Matthias Winkler, M.S.[1], Johannes Kirchmair, Ph.D.[2], Gilles Querat, Ph.D.[3], Chris Meier, Ph.D.[1]
[1]*University of Hamburg, Department of Chemistry, Hamburg, Germany;* [2]*University of Hamburg, Center for Bioinformatics, Hamburg, Germany;* [3]*Aix-Marseille University, Faculty of Medicine, Marseille, France*

4:30 PM **166. Optimizing Diarylbenzopyrimidines as HIV-1 Non-nucleoside Reverse Transcriptase Inhibitors for Superior Antiviral and Improved Drug Resistance Profile**
Sheng Han, M.S.[1], Erik De Clercq, Ph.D.[2], Christophe Pannecouque, Ph.D.[2], **Ge Meng, Ph.D.**[1], Fener Chen, Ph.D.[1]
[1]*Fudan University, Shanghai, Shanghai, China;* [2]*Leuven University, Leuven, Belgium*

4:40 PM **167. Structure-Based Design of Nucleoside Triphosphate Mimics and Their Broader Implications for Discovery of Viral DNA and RNA Polymerase Inhibitors**
Sergio Martinez, Ph.D.[1], Weijie Gu, B.S.[1], Brent De Wijngaert, B.S.[1], Shrinivas Dumbre, Ph.D.[2], Hans Vanbuel, B.S.[1], Piet Herdewyn, Ph.D.[2], Steven De Jonghe, Ph.D.[1], Kalyan Das, Ph.D.[1]
[1]*Division of Virology and Chemotherapy, Rega Institute for Medical Research, KU Leuven, Leuven, Vlaams-Brabant, Belgium;* [2]*Rega Institute for Medical Research, Department of Medicinal Chemistry, KU Leuven, Leuven, Vlaams-Brabant, Belgium*

4:50 PM **168. Potent Peptidomimetic Inhibitors of NS2B-NS3 Protease from Dengue and Zika Viruses**

Dahai Luo, Ph.D.[1], Jun Ping Quek, B.S.[1], Torsten Steinmetzer Steinmetzer, Ph.D.[2]
[1]Lee Kong Chian School of Medicine, Nanyang Technological University, EMB 03-07, 59 Nanyang Drive, Singapore 636921, Singapore, Singapore; [2]Institute of Pharmaceutical Chemistry, Philipps University, Marbacher Weg 6, 35032 Marburg, Germany.

Poster Session 2

CONSTELLATION CDEF

5:00 PM –7:00 PM

5:00 – 6:00 PM **EVEN numbered poster presentations**

6:00 – 7:00 PM **ODD numbered poster presentations**

All posters are listed in numerical order starting on page 37.

Networking Reception

BALTIMORE VISITOR CENTER

401 Light Street

7:00 PM – 9:00 PM

Walking distance; across the street from the hotel

WEDNESDAY, MAY 15, 2019

Gertrude Elion Memorial Award Lecture

CONSTELLATION AB

8:30 AM – 9:00 AM

8:30 AM **169. The Challenge of Developing Antivirals to Treat Eradicated Disease**

David Evans, Ph.D.[1]

[1]*Li Ka Shing Institute of Virology, University of Alberta, Canada*

What's New in Antiviral Research 2

CONSTELLATION AB

9:00 AM – 10:30 AM

9:00 AM **148. Small Molecules for Big Problems in Large Animals**

Nesya Goris, Ph.D.[1]

[1]*ViroVet, Leuven, Belgium*

9:30 AM **171. Polio Eradication: Need for Antivirals and Progress to Date**

Marc Collett, Ph.D.[1]

[1]*ViroDefense, Inc., Rockville, Maryland, United States of America*

10:00 AM **172. Update and Challenges in Research and Development of Dengue and Zika Antivirals**

Subhash Vasudevan, Ph.D.[1]

[1]*Duke NUS Medical School, Singapore, Singapore*

Coffee Break

CONSTELLATION FOYER

10:30 AM – 10:50 AM

Shotgun Oral Presentations & Awards (Posters and TCFF) Recognition

CONSTELLATION AB

10:50 AM – 12:00 PM

ISAR Annual Business Meeting

CONSTELLATION AB

12:00 PM – 12:30 PM

President: **Johan Neyts, PhD**

Treasurer: **Brian Gowen, PhD**

Secretary: **Graciela Andrei, PhD**

Lunch *(on your own)*

12:00 PM – 1:15 PM

Developing New Antiviral Therapies

CONSTELLATION AB

1:15 PM – 2:15 PM

1:15 PM **174. Therapeutic Strategies to Combat Cytomegalovirus Infection**

Rhonda Cardin, Ph.D.[1]

[1]*Louisiana State University School of Veterinary Medicine, Baton Rouge, Louisiana, United States of America*

1:45 PM **173. Investigational Therapies for Chronic Hepatitis B: *Does Anything Really Work?***

Tim Block, Ph.D.[1]

[1]*Baruch S. Blumberg Institute, Doylestown, Pennsylvania, United States of America*

Short Presentations 4 – Hepatitis Viruses and Retroviruses; Clinical Evaluations, etc.

CONSTELLATION AB

2:15 PM – 3:30 PM

2:15 PM **175. A Small Molecule Human STING Agonist that Induces Antiviral Cytokine Response and Stimulates the T Lymphocyte Activation**

Xiaohui Zhang, M.D., Ph.D.[1], Bowei Liu, M.D.[1], Liudi Tang, B.S.[2], Julia Ma, B.S.[1], Qing Su, Ph.D.[1], Nicky Hwang, B.S.[1], Mohit Sehgal, Ph.D.[1], Junjun Cheng, Ph.D.[1], Xuexiang Zhang, M.S.[1], Yinfei Tan, Ph.D.[3], Yan Zhou, Ph.D.[3], Zhongping Duan, M.D.[4], Victor DeFilippis, Ph.D.[5], Usha Viswanathan, Ph.D.[1], John Kulp, Ph.D.[1], Yanming Du, Ph.D.[1], Ju-Tao Guo, M.D.[1], **Jinhong Chang, M.D., Ph.D.**[1]

[1]*Baruch S. Blumberg Institute;* [2]*Drexel University College of Medicine;* [3]*Fox Chase Cancer Center;* [4]*Youan Hospital;* [5]*Oregon Health and Science University*

2:25 PM **176. Antiviral Properties and Liver Specific Delivery of a TLR1/2 Ligand in HBV and/or HDV Infected Models**

Julie Lucifora, Ph.D.[1], Brieux Chardès, M.S.[1], Myriam Lamrayah, M.S.[2], Manon Desmares, M.S.[1], Rayan Farhat, Ph.D.[1], Laura Dimier, B.S.[1], Capucine Phelip, M.S.[2], Floriane Fusil, Ph.D.[3], François Loïc Cosset, Ph.D.[3], Fabien Zoulim, M.D., Ph.D.[1], Anna Salvetti, Ph.D.[1], Bernard Verrier, Ph.D.[2], **David Durantel, Ph.D.**[1]

[1]*CRCL - INSERM U1052, Lyon, France;* [2]*IBCP, Lyon, France;* [3]*CIRI - INSERM U111, Lyon, France*

2:35 PM **177. SMCHD1 and PML Mediate IFN-α Suppression of Hepadnaviral cccDNA Transcription**

Junjun Chen, Ph.D.[1], Jinhong Chang, Ph.D.[1], **Ju-Tao Guo, M.D.**[1]

[1]*Baruch S. Blumberg Institute*

2:45 PM **178. Advances in HBV Ribonuclease H Drug Development**

Tiffany Edwards, M.S.[1], Qilan Li, Ph.D.[1], Nathan Ponzar, B.S.[1], Austin O'Dea, M.S.[1], Cassandra Kukla, B.S.[1], Mufuza Akter, Ph.D.[1], Grigoris Zoidis, Ph.D.[2], Marvin Meyers, Ph.D.[1], Ryan Murelli, Ph.D.[3], John Tavis, Ph.D.[1]

[1]*Saint Louis University, St. Louis, Missouri, United States of America;* [2]*University of Athens, Athens, Greece;* [3]*City University of New York, New York, New York, United States of America*

2:55 PM **179. Discovery and Mechanistic Studies of Novel Suppressors of Tat-mediated HIV Expression**

Jenn Yi, B.S.[1], **Cole Schonhofer, M.S.**[1], Brandon Razooky, Ph.D.[2], Jeanne Chiaravalli, B.S.[3], Brittiny Dhital, B.S.[3], Marianne Harris, B.S.[4], Fraser Glickman, Ph.D.[3], Zabrina Brumme, Ph.D.[5], Charles Rice, Ph.D.[2], ian Tietjen, Ph.D.[1]

[1]Simon Fraser University, Burnaby, BC, Canada; [2]Laboratory of Virology and Infectious Disease, The Rockefeller University, New York, New York, United States of America; [3]High-Throughput and Spectroscopy Resource Center (HTSRC), The Rockefeller University, New York, New York, United States of America; [4]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada; [5]Simon Fraser University; British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

3:30 PM **182. Viral Compartmentalization and Rapid Evolution of Drug-resistant Herpes Simplex Virus (HSV-1) Infection in a Hematopoietic Stem Cell Transplantation (HSCT) Patient**

Hanna Schalkwijk, M.S.[1], Sarah Gillemot, M.S.[1], Robert Snoeck, M.D., Ph.D.[1], Marijke Reynders, M.D.[2], Dominik Selleslag, M.D.[3], Graciela Andrei, Ph.D.[1]

[1]Laboratory of Virology and Chemotherapy, Rega Institute for Medical Research, KU Leuven, Leuven, Belgium, Leuven, Vlaams-Brabant, Belgium; [2]Laboratory of Microbiology, AZ Sint-Jan Brugge, Brugge, Belgium, Brugge, West-Vlaanderen, Belgium; [3]Department of Internal Medicine, AZ Sint-Jan Brugge, Brugge, Belgium, Brugge, West-Vlaanderen, Belgium

3:40 PM **183. *In Vitro* and Clinical Resistance Profile of RV521, a Small Molecule Respiratory Syncytial Virus Fusion Inhibitor in Clinical Development**

Elaine Thomas, Ph.D.[1], Daniel Brookes, Ph.D.[1], Claire Scott, Ph.D.[1], John DeVincenzo, M.D.[2], Young-In Kim-Hoehamer, Ph.D.[2], Neil Mathews, Ph.D.[1], Alex Bedernjak, Ph.D.[1], Stuart Cockerill, Ph.D.[1], Rachel Harland, Ph.D.[1], Ken Powell, Ph.D.[1], Eddy Littler, Ph.D.[1]

[1]ReViral Ltd, United Kingdom of Great Britain and Northern Ireland; [2]U Tennessee Center for Health Sciences, Children's Foundation Research Institute at LeBonheur Children's Hospital

Closing Remarks

3:30 PM

1. Cidofovir and (S)-HPMPA Tyrosinamide Prodrugs: Tuning LogD by Heteratom Insertion in the Long-chain Alkyl Substructure

Jiajun Fan, B.S.[1], Jinglei Lyu, M.S.[1], Boris Kashemirov, Ph.D.[1], Caroll Hartline, Ph.D.[2], Emma Harden, Ph.D.[2], Mark Prichard, Ph.D.[2], Charles McKenna, Ph.D.[1]

[1]University of Southern California, Los Angeles, California, United States of America; [2]University of Alabama, Birmingham, Alabama, United States of America

2. Identification of Dihydrofuro[3,4-d]pyrimidine Derivatives as Novel HIV-1 Non-nucleoside Reverse Transcriptase Inhibitors with Promising Antiviral Activities and Desirable Physicochemical Properties

Zhan Peng, Ph.D.[1], Xinyong Liu, Ph.D.[2]

[1]Shandong University; [2]Shandong University

3. Chikungunya Virus is Susceptible to Sofosbuvir Both *In Vitro* and *In Vivo*

Carolina Sacramento, Ph.D.[1], Andre Ferreira, Ph.D.[1], Patrícia Reis, Ph.D.[1], Caroline de Freitas, M.S.[1], Lucas Hoelz, Ph.D.[1], Mayara Mattos, B.S.[1], Isaclaudia Quintanilha, Ph.D.[1], Natasha Rocha, M.S.[1], Giselle Barbosa-Lima, Ph.D.[1], Yasmine Vieira, Ph.D.[1], Pablo Trindade, Ph.D.[2], Stevens Rehen, Ph.D.[2], Fernando Bozza, Ph.D.[3], Patricia Bozza, Ph.D.[1], Nubia Boechat, Ph.D.[1], Thiago Souza, Ph.D.[1]

[1]FIOCRUZ, Rio de Janeiro, Rio de Janeiro, Brazil; [2]UFRJ; [3]IDOR

4. Liver-Targeted Glycyrrhetinic Acid-Chitosan Conjugated Lamivudine Nanoparticle for Effective Treatment of Chronic Hepatitis B Virus Infection

Akhilesh Singh, Ph.D.[1], Lila Nath, Ph.D.[2]

[1]Dibrugarh University, Dibrugarh, Assam, India; [2]Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, Assam, India

5. Neuraminidase Inhibitor Susceptibility Surveillance of Influenza Viruses Circulating in Rawalpindi, Pakistan

Irum Perveen, Ph.D.[1], Iqbal Memon, M.D., MPH[1]

[1]Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, Pakistan

6. Acute West-Nile Viremia and Malaria Co-infection amongst Febrile Infected HIV Participants attending a Tertiary Hospital in Abuja, Nigeria

Kehinde Aina, M.S.[1], Olajide Agbede, Ph.D.[2]

[1]Department of Medical Microbiology and Parasitology (Virology Unit) Unilorin, Nigeria, Ilorin, Northern, Nigeria; [2]Department of Medical Microbiology and Parasitology (Virology Unit), University of Ilorin, Ilorin, Nigeria

7. 3-Deaza and 3-Deaza-3-bromo L-Neplanocin Analogues: Synthesis and Antiviral Property

Alexander Smith, B.S.[1], Qi Chen, Ph.D.[1]

[1]Slippery Rock University, Slippery Rock, Pennsylvania

8. Enzymatic Removal of a Butyl-Ether Moiety by Adenosine Deaminase-Like Protein 1, a Necessary Step in the Mechanism of Action of MBX-2168

Kathryn Vollmer, B.S.[1], Anna Burns, B.S.[1], Hannah Sauer, M.S.[1], John Williams, Ph.D.[2], Gloria Komazin-Meredith, Ph.D.[2], Marc Busch, Ph.D.[3], Terry Bowlin, Ph.D.[2], Brian Gentry, Ph.D.[1]
[1]Drake University College of Pharmacy and Health Sciences; [2]Microbiotix Inc.; [3]Drake University College of Arts & Sciences Department of Biology

9. Discovery of a Novel Inhibitor of the Drug-Resistant Influenza A M2 (S31N) Viroporin

Maggie Duncan, B.S.[1], Ibuki Kihara, B.S.[1], Maya Naidu, B.S.[1], David Williams, Ph.D.[2], Aruna Balgi, Ph.D.[2], Kerstin Andrae-Marobela, Ph.D.[3], Michel Roberge, Ph.D.[2], Raymond Anderson, Ph.D.[2], Fidele Ntie-Kang, Ph.D.[4], Masahiro Niikura, Ph.D.[1], Ian Tietjen, Ph.D.[1]
[1]Simon Fraser University, Burnaby, British Columbia, Canada; [2]University of British Columbia, Vancouver, British Columbia, Canada; [3]University of Botswana, Gaborone, Botswana; [4]Martin Luther University Halle-Wittenberg, Halle, Germany

10. Heme Oxygenase-1 Mediates the Induction of Interferon Response and Suppression of Influenza A Virus Infection by Rupestonic Acid Derivative YZH-106

Yuhuan Li, Ph.D.[1], Linlin Ma, Ph.D.[1], Peng Zhang, M.S.[1], Huiqiang Wang, M.S.[1], Haji Akber Aisa, Ph.D.[2], Jiandong Jiang, Ph.D.[1]
[1]Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China; [2]Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Urumqi, Xinjiang, China

11. Predictors of HIV Status Disclosure to Sexual Partners Among PLHIV in Nigeria

Dr Abiola Adepoju, M.D.[1], Johnson Okolie, M.D.[2]
[1]KNCV Tuberculosis Foundation, Birnin Kebbi, Birnin Kebbi, Nigeria; [2]Mangement Science for Health, Birnin Kebbi, Kebbi, Nigeria

12. A Survey of Awareness and Willingness to Use HIV Self-testing Among PWID in Nigeria

Victor Adepoju, M.D.[1], Jude Inegbeboh, M.D.[2]
[1]KNCV Tuberculosis Foundation, Lagos, Lagos, Nigeria; [2]United Nations, Birnin Kebbi, Birnin Kebbi, Nigeria

13. Activity of Double Combinations of Newly Synthesized Diaryl Ethers Against Coxsackievirus B1

Adelina Stoyanova, M.S.[1], Luchia Mukova, B.S.[1], Georgi Dobrikov, Ph.D.[2], Stefan Philipov, Ph.D.[2], Vadim Makarov, Ph.D.[3], Angel Galabov, M.D., Ph.D.[1]
[1]The Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, Sofia Bulgaria; [2]Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria; [3]Bach Institute of Biochemistry, Moscow, Russian Federation

14. Structural Investigation on the Effect of Pyrimidine Functional Groups of Fleximer Analogues on Antiviral Activity

Mary Yates, B.S.[1], Katherine Seley-Radtke, Ph.D.[1]
[1]University of Maryland Baltimore County

15. Perylene Derivatives as Broad-spectrum Antivirals

Alexey Chistov, M.S.[1], Evgeny Khvatov, M.S.[2], Ksenia Sapozhnikova, M.S.[1], Nikita Slesarchuk, B.S.[1], Yury Dokukin, B.S.[3], Alexey Ustinov, Ph.D.[1], Liubov Kozlovskaya, Ph.D.[2], Dmitry Osolodkin, Ph.D.[2], Vladimir Korshun, Ph.D.[1]

[1]Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry RAS, Moscow, Russian Federation; [2]Institute of Poliomyelitis and Viral Encephalitides, FSBSI Chumakov FSC R&D IBP RAS, Moscow, Russian Federation; [3]Higher Chemical College RAS, Mendeleev University of Chemical Technology of Russia, Moscow, Russian Federation

16. Optimization of N-Substituted Oseltamivir Derivatives as Potent Influenza A Neuraminidases Inhibitors

Xinyong Liu, Ph.D.[1]

[1]School of Pharmaceutical Sciences, Shandong University

17. TAK-632 Analogues as Novel Necroptosis Inhibitors: Synthesis, Structure-Activity Relationships and *In Vivo* Efficacy

Chunlin Zhuang, Ph.D.[1], Fener Chen, Ph.D.[1]

[1]Fudan University, Shanghai, China

18. Effect of Double Combinations Applied via Consecutive Alternating Administration in Coxsackievirus B3 Infection

Adelina Stoyanova, M.S.[1], Stefan Philipov, Ph.D.[2], Gerhard Pürstinger, Ph.D.[3], Vadim Makarov, Ph.D.[4], Angel Galabov, M.D., Ph.D.[1]

[1]The Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, Sofia, Bulgaria; [2]Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria; [3]Institute of Pharmacy, University of Innsbruck, Innsbruck, Austria; [4]Bach Institute of Biochemistry, Moscow, Russian Federation

19. Therapeutic Treatment of Zika Virus Infection Using a Brain-penetrating Antiviral Peptide

Nam-Joon Cho, Ph.D.[1]

[1]Nanyang Associate Professor, School of Materials Science and Engineering, Nanyang Technological University, Singapore

20. Structure-Based Virtual Screening for the Identification of Novel Anti-Dengue Compounds Disrupting the Viral Replication Complex

Giulio Nannetti, Ph.D.[1], Salvatore Ferla, Ph.D.[1], Beatrice Mercorelli, 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 University, Cardiff, United Kingdom of Great Britain and Northern Ireland; [2]Department of Molecular Medicine, University of Padua, Padua, Italy

21. Pentostatin Antagonizes the Anti-Viral Activity of MBX-2168 by Inhibiting the Biosynthesis of Active Compound

Natalie Hagen, B.S.[1], Hannah Sauer, Ph.D.[1], Marie Nguyen, Ph.D.[2], Terry Bowlin, Ph.D.[3], Brian Gentry, Ph.D.[1]

[1]Drake University College of Pharmacy and Health Sciences, Des Moines, Iowa, United States of America; [2]Des Moines University Department of Microbiology and Immunology, Des Moines, Iowa, United States of America; [3]Microbiotix Inc., Worcester, Massachusetts, United States of America

22. Ursolic Acid Acts as an Antiviral Agent in Rotavirus Infection *In Vitro* by Interfering with Viroplasm Formation

María Julieta Tohmé, B.S.[1], María Cecilia Gimenez, B.S.[1], María Isabel Colombo, Ph.D.[1], Laura Ruth Delgui, Ph.D.[1]

[1]Instituto de Histología y Embriología de Mendoza (IHEM)- CONICET

23. Preliminary *In Vitro* Antiretroviral Activity of a *Nigella sativa* Seed Formulation (A-zam) against HIV-1

Olufunmilayo Oyero, Ph.D.[1], Adekunle Onifade, Ph.D.[1], Masanori Baba, M.D.[2]
[1]*University of Ibadan, Ibadan, Nigeria;* [2]*Kagoshima University, Kagoshima, Japan*

24. Targeting at Glu224 and Trp229 in the Non-nucleoside Binding Pocket of HIV-1 Reverse Transcriptase

Ge Meng, Ph.D.[1], Erik De Clercq, Ph.D.[2], Fener Chen, Ph.D.[1]
[1]*Fudan University, Shanghai, China;* [2]*Leuven University, Leuven, Belgium*

25. Transcriptomic and Proteomic Profiles of Human Cells Following Exposure to a Host-targeted Antiviral

Lisa Evans DeWald, Ph.D.[1], Chloe Starr, B.S.[1], Andrea Harris, Ph.D.[1], Michael Lacy, Ph.D.[1], Anthony Treston, Ph.D.[1], Kelly Warfield, Ph.D.[1]
[1]*Emergent BioSolutions Inc, Gaithersburg, Maryland*

26. A Population Study of HBV Genome Diversity: Implications for Rational Drug Design

Guangdi Li, Ph.D.[1], Samad Amini-Bavil-Olyaee, Ph.D.[2], Marijn Thijssen, M.S.[3], Philippe Lemey, Ph.D.[3], Marc Van Ranst, Ph.D.[3], Mahmoud Reza Pourkarim, Ph.D.[3]
[1]*Department of Public Health, Central South University, Changsha, Hunan, China, Changsha, Hunan, China;* [2]*Cellular Sciences Department, Amgen Inc., One Amgen Center Drive, CA 91320, USA, Thousand Oaks, California, United States of America;* [3]*KU Leuven, Department of Microbiology and Immunology, 3000 Leuven, Belgium, Leuven, Leuven, Belgium*

27. Antiviral Activity Assessment of Polyoxometalates with a Focus on Zika Virus

Rachele Francese, M.S.[1], Andrea Civra, Ph.D.[1], Massimo Rittà, M.D., Ph.D.[1], Manuela Donalisio, Ph.D.[1], Monica Argenziano, Ph.D.[2], Roberta Cavalli, Ph.D.[2], Ali Mougharbel, M.S.[3], Ulrich Kortz, Ph.D.[3], David Lembo, Ph.D.[1]
[1]*Dept. of Clinical and Biological Sciences; Lab. of Molecular Virology and Antiviral Research; University of Turin, Turin;* [2]*Dept. of Drug Science and Technology; University of Turin;* [3]*Department of Life Sciences and Chemistry, Jacobs University, Bremen, Germany*

28. Discovery of Phenylalanine Derivatives as Potent HIV-1 Capsid Inhibitors from Click Chemistry-based Compound Library

Gaochan Wu, M.S.[1]
[1]*School of Pharmaceutical Sciences, Shandong University*

29. Viral RNA-dependent RNA Polymerase Inhibitor 7-Deaza-2´-C-methyladenosine Prevents Death in a Mouse Model of West Nile Virus Infection

Ludek Eyer, Ph.D.[1], Martina Fojtikova, M.S.[1], Radim Nencka, Ph.D.[2], Ivo Rudolf, Ph.D.[3], Zdenek Hubalek, Ph.D.[3], Daniel Ruzek, Ph.D.[1]
[1]*Department of Virology, Veterinary Research Institute, Brno, Czechia;* [2]*Institute of Organic Chemistry and Biochemistry, The Czech Academy of Sciences, Prague, Czechia;* [3]*Institute of Vertebrate Biology, The Czech Academy of Sciences, Brno, Czechia*

30. Identification of RUVBL1 and RUVBL2 as Novel Cellular Interactors of Ebola Virus Nucleoprotein

M. Jane Morwitzer, B.S.[1], Sina Bavari, Ph.D.[2], St Patrick Reid, Ph.D.[1]
[1]*Department of Pathology & Microbiology, University of Nebraska Medical Center, Omaha, Nebraska, United States of America;* [2]*United States Army Medical Research Institute of Infectious Diseases, Frederick, MD, Maryland, United States of America*

31. HBc Nuclear Interactome Reveals Multiple Roles of RNA-binding Proteins in Viral Replication and Provides Insights for the Development of Novel Host-Targeting Agents

Hélène Chabrolles, Ph.D.[1], Héloise Auclair, Ph.D.[1], Thomas Lahlali, Ph.D.[1], Serena Vegna, Ph.D.[1], Yohann Couté, Ph.D.[2], Lucid Belmudes, Ph.D.[2], Christophe Combet, Ph.D.[1], Fabien Zoulim, M.D., Ph.D.[1], David Grierson, Ph.D.[3], Benoit Chabot, Ph.D.[4], Julie Lucifora, Ph.D.[1], **David Durantel, Ph.D.**[1], Anna Salvetti, Ph.D.[1]

[1]CRCL - INSERM U1052, Lyon, France; [2]INSERM U1038 - CEA Grenoble, Grenoble, France; [3]University of British Columbia, Vancouver, Canada; [4]Sherbrooke University, Sherbrooke, Canada;

32. Antibody Coated Liposomes for Transmucosal Vaccination

Saurabh Bhargava, M.D., MPH[1], Vishal Bhargava, Ph.D.[2]

[1]United Institute of Pharmacy, Allahabad, India; [2]GTB Hospital, Kanpur, India

33. Evaluation of the Concentration-Dependent Emergence of Antiviral Resistance in Venezuelan Equine Encephalitis Virus to ML336 using Next Generation Sequencing

Jasper Lee, B.S.[1], Jennifer Golden, Ph.D.[2], Colleen Jonsson, Ph.D.[1]

[1]University of Tennessee Health Science Center, Memphis, Tennessee, United States of America; [2]University of Wisconsin-Madison, Madison, Wisconsin, United States of America

34. HTS and Bioassay-guided Fractionation Identified Hopanetriol Analogs from *Aschersonia* Extract with Anti-flavivirus Activity

Julia Ma, B.S.[1], Fang Guo, M.D., Ph.D.[1], Xuexiang Zhang, M.S.[2], Lin Zhang, M.S.[1], Zhao Gao, Ph.D.[1], Michael Goetz, Ph.D.[3], Anne Dombrowski, Ph.D.[1], Timothy Block, Ph.D.[1], Ju-Tao Guo, M.D.[1], Sung Ryeol Park, Ph.D.[1], Matthew Todd, Ph.D.[1], Jason Clement, Ph.D.[1], Jinhong Chang, M.D., Ph.D.[1]

[1]Baruch S. Blumberg Institute; [2]Fang Guo <guofang1972@gmail.com>; [3]Baruch S. Blumberg.org

35. Studies Towards Pan-Flaviviral Protease Inhibitors

Crystall Swarbrick, Ph.D.[1], Gerasimos Rassias, Ph.D.[2], Vasiliki Zogali, M.S.[2], Kitti Chan, M.S.[1], Subhash Vasudevan, Ph.D.[1]

[1]Program in Emerging Infectious Diseases, Duke-NUS Medical School, Singapore; [2]Department of Chemistry, University of Patras, Greece

36. Development of a Complete Set of Antibodies for Yellow Fever Virus and Their Application in Antiviral Drug and Vaccine Development

Zhao Gao, Ph.D.[1], Lin Zhang, M.S.[1], Julia Ma, B.S.[1], Alexander Ball, Ph.D.[2], Ju-Tao Guo, M.D.[1], Jinhong Chang, M.D., Ph.D.[1]

[1]Baruch S. Blumberg Institute; [2]GeneTex, Inc.

37. Hepatotoxicity and Nephrotoxicity in *Plasmodium berghei*-Infected Mice Treated with Lopinavir/Ritonavir plus Amodiaquine or Artesunate - A Consequence of Drug/Drug Interactions

Tolulope Oke, M.S.[1], Oyindamola Abiodun, Ph.D.[1]

[1]Department of Pharmacology and Therapeutics, College of Medicine, University of Ibadan, Ibadan, Nigeria., Ibadan, Oyo, Nigeria

38. A Cell-based Luminescence Assay for High-throughput Screening of Potential Mayaro Virus Antivirals

Aline Tolardo, M.S.[1], Jyothi Parvathareddy, B.S.[2], Jo Davisson, Ph.D.[3], Aaron Lindstrom, Ph.D.[3], Gene Ananiev, Ph.D.[4], Colleen Jonsson, Ph.D.[2], Luiz Tadeu Figueiredo, M.D., Ph.D.[1]
[1]Ribeirão Preto Medical School, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil; [2]Department of Microbiology, Immunology, and Biochemistry, University of Tennessee Health Science Center, Memphis, Memphis, Tennessee, United States of America; [3]Purdue University, West Lafayette, Indiana, United States of America; [4]Small Molecule Screening & Synthesis Facility (SMSF),University of Wisconsin (Madison), Madison, Wisconsin, United States of America

39. Airway Proteases as Antiviral Drug Target for Influenza Virus and Possibly Other Respiratory Viruses

Manon Laporte, M.S.[1], Mohammed Benkheil, Ph.D.[1], Annelies Stevaert, Ph.D.[1], Lieve Naesens, Ph.D.[1]
[1]Rega Institute for Medical Research, KU Leuven, Leuven, Belgium

40. Micropatterned Viral Membrane Clusters for Antiviral Drug Evaluation

Soohyun Park, B.S.[1], Joshua Jackman, Ph.D.[2], Xiaobin Xu, Ph.D.[3], Paul Weiss, Ph.D.[4], Nam-Joon Cho, Ph.D.[1]
[1]School of Materials Science and Engineering, Nanyang Technological University, Singapore, Singapore, Singapore; [2]School of Chemical Engineering, SungKyunKwan University (SKKU), Suwon, Korea (Republic of); [3]School of Materials Science and Engineering, Tongji University; [4]California NanoSystems Institute, University of California, Los Angeles

41. Benzoannulenes Derivatives as Antiviral Agents with the Focus on Alphaviruses and Flaviviruses

Syed Ahmed, Ph.D.[1], Nicole Haese, Ph.D.[2], Vibha Pathak, M.S.[1], Jaden Cowan, B.S.[1], Nicholas May, Ph.D.[3], Corinne Augelli-Szafran, Ph.D.[1], Mark Suto, Ph.D.[1], Victor DeFilippis, Ph.D.[2], Thomas Morrison, Ph.D.[3], Mark Heise, Ph.D.[4], Daniel Streblow, Ph.D.[2], Ashish Pathak, Ph.D.[1]
[1]Southern Research, Birmingham, Alabama, United States of America; [2]Vaccine and Gene Therapy Institute, Oregon Health & Science University, Beaverton, Oregon, United States of America; [3]University of Colorado School of Medicine, Aurora, Colorado, United States of America; [4]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America

42. Discovery of Broad-spectrum Influenza Antivirals with a High *In Vitro* Genetic Barrier to Drug Resistance by Targeting the Influenza Polymerase PA-PB1 Subunit Interactions

Jiantao Zhang, Ph.D.[1], Yanmei Hu, M.S.[1], **Jun Wang, Ph.D.**[1]
[1]University of Arizona

43. Quinolinone Compounds Potently Inhibit Venezuelan Equine Encephalitis Virus Replication

Nicole Haese, Ph.D.[1], Nicholas May, B.S.[2], Sharon Taft-Benz, Ph.D.[3], Shuklendu Karyakrate, Ph.D.[4], Omar Moukha-Chafiq, Ph.D.[4], Lynn Rasmussen, M.S.[4], Robert Bostwick, Ph.D.[4], Corinne Augelli-Szafran, Ph.D.[4], Mark Suto, Ph.D.[4], Nathaniel Moorman, Ph.D.[3], Victor DeFilippis, Ph.D.[1], Mark Heise, Ph.D.[3], Ashish Pathak, Ph.D.[4], Daniel Streblow, Ph.D.[1], Thomas Morrison, Ph.D.[2]
[1]Vaccine and Gene Therapy Institute, Oregon Health & Science University; [2]University of Colorado School of Medicine; [3]University of North Carolina School of Medicine; [4]Southern Research

44. Development of Well-characterized Animal Models of Zaire Ebolavirus Infection for Licensure by Animal Rule

Malen Link, Ph.D.[1], Chia-Wei Tsai, Ph.D.[1]
[1]U.S. Department of Health and Human Services, Office of Assistant Secretary for Preparedness and Response, BARDA, Washington, District of Columbia, United States of America

45. A Dengue Fluorescent Reporter Virus Combined with an Automated Robotic System for High Content Image-Based Antivirals Screening

Li-Hsin Li, M.S.[1], Suzanne Kaptein, Ph.D.[1], Johan Neyts, Ph.D.[1], Pieter Leyssen, Ph.D.[1], Kai Dallmeier, Ph.D.[1]
[1]Rega Institute for Medical Research, KU Leuven, Leuven, Belgium

46. Studying Host Lipid Rafts in Early Phases of Influenza A Virus (IAV) Life Cycle for Identification of Hemagglutinin Interacting Host Raft Proteins

Dileep Verma, Ph.D.[1], Dinesh Gupta, Ph.D.[1], Sunil Lal, Ph.D.[2]
[1]International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi, Delhi, New Delhi, India; [3]School of Science, Monash University, Malaysia, Malaysia

47. ProTide Activation Pathway: Trapping the Reactive Cyclic Phosphorus Intermediates

Eliska Prochazkova, Ph.D.[1], Rafael Navrátil, M.S.[2], Zlatko Janeba, Ph.D.[1], Jana Roithova, Ph.D.[3], **Ondřej Baszczyňski, Ph.D**.[4]
[1]Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Flemingovo nám. 2, Prague 6, 166 10,, Prague, Czechia; [2]Department of Organic Chemistry, Faculty of Science, Charles University, Hlavova 2030/8, Prague 2, 128 43,, Prague, Czechia; [3]Institute for Molecules and Materials, Radboud University Nijmegen, Heyendaalseweg 135, 6525 AJ Nijmegen, Nijmegen, Netherlands; [4]Department of Organic Chemistry, Faculty of Science, Charles University, Hlavova 2030/8, Prague 2, 128 43, Prague, Czechia

48. Simvastatin Suppresses Ebola Virus-mediated Inflammation in Human Monocyte-derived Macrophages

Punya Shrivastava-Ranjan, Ph.D.[1], Anita McElroy, M.D., Ph.D.[2], Jessica Harmon, M.S.[1], Stuart Nichol, Ph.D.[1], Christina Spiropoulou, Ph.D.[1]
[1]VSPB, DHCPP, NCEZID, CDC, Atlanta, GA-30329, Atlanta, Georgia, United States of America; [2]University of Pittsburgh, Pennsylvania and Centre for Disease Control and Prevention, Atlanta, Pittburgh, Pennsylvania, United States of America

50. Characterizing the Therapeutic Potential of Nipah Virus Defective Interfering Particles

Stephen Welch, Ph.D.[1], Natasha Tilston, Ph.D.[2], Shannon Whitmer, Ph.D.[1], Jessica Spengler, D.V.M., Ph.D.[1], Markus Kainulainen, Ph.D.[1], Michael Lo, Ph.D.[1], Linda Rennick, Ph.D.[2], Stuart Nichol, Ph.D.[1], W Paul Duprex, Ph.D.[2], Christina Spiropoulou, Ph.D.[1]
[1]Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America; [2]Center for Vaccine Research, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States of America

51. The Aryl Hydrocarbon Receptor Inhibition Blocks Dengue and Zika Flaviviruses Infection

María Florencia Torti, B.S.[1], Federico Giovannoni, Ph.D.[1], Elsa Damonte, Ph.D.[1], Francisco Quintana, Ph.D.[2], Cybele Garcia, Ph.D.[1]
[1]Lab. of Antiviral Strategies, Biochem. Dept.,FSc., University of Buenos Aires- IQUIBICEN- CONICET, Buenos Aires, , Buenos Aires, Argentina; [4]Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard MedicalSchool, USA, Boston, Massachusetts, United States of America

52. Identification and Characterization of Inhibitors of Hepatitis E Virus Replication

Ila Nimgaonkar, B.S.[1], Qiang Ding, Ph.D.[1], Mohammad Shahrad, B.S.[1], Nicholas Archer, B.S.[1], Hahn Kim, Ph.D.[1], Alexander Ploss, Ph.D.[1]
[1]Princeton University, Princeton, New Jersey, United States of America

53. Nucleotide Prodrug Remdesivir (GS-5734) Protects African Green Monkeys from Lethal Nipah Virus Bangladesh Challenge

Michael Lo, Ph.D.[1], Friederike Feldmann, Ph.D.[2], Joy Gary, D.V.M.[1], Robert Jordan, Ph.D.[3], Roy Bannister, Ph.D.[3], Jacqueline Cronin, Ph.D.[4], Nishi Patel, M.S.[1], John Klena, Ph.D.[1], Stuart Nichol, Ph.D.[1], Tomas Cihlar, Ph.D.[3], Sherif Zaki, M.D., Ph.D.[1], Heinz Feldmann, M.D., Ph.D.[4], Christina Spiropoulou, Ph.D.[1], Emmie De wit, Ph.D.[4]

[1]Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America; [2]Rocky Mountain Veterinary Branch, National Institutes of Health, Hamilton, Montana, United States of America; [3]Gilead Sciences, Foster City, California, United States of America; [4]Laboratory of Virology, National Institutes of Health, Hamilton, Montana, United States of America

54. Heme Oxygenase-1 Inhibits Influenza A Virus via the Induction of Interferon Response

Peng Zhang, Ph.D.[1], Linlin Ma, Ph.D.[1], Huiqiang Wang, Ph.D.[1], Haiyan Yan, Ph.D.[1], Sheng Tang, Ph.D.[1], Danqing Song, Ph.D.[1], Jiandong Jiang, Ph.D.[1], Yuhuan Li, Ph.D.[1]

[1]Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College

55. Inhibition of Human Norovirus Replication by a Novel Class of Indolylarylsulfones *In Vitro* and in Zebrafish Larvae

Jana Van Dycke, M.S.[1], Valentina Naccarato, M.S.[2], Giuseppe La Regina, Ph.D.[2], Eloise Mastrangelo, Ph.D.[3], Delia Tarantino, Ph.D.[3], Johan Neyts, Ph.D.[1], Romano Silvestri, Ph.D.[2], **Joana Rocha-Pereira, Ph.D.**[1]

[1]Rega Institute, KU Leuven, Leuven; [2]Sapienza University of Rome, Rome, Italy; [3]Università degli Studi di Milano, Milan, Italy

56. Creation of a Potent Long Acting Emtricitabine

Dhruvkumar Soni, M.S.[1], Aditya Bade, Ph.D.[2], Nagsen Gautam, Ph.D.[3], Jonathan Herskovitz, B.S.[4], Ibrahim Ibrahim, M.D.[4], Nathan Smith, B.S.[4], Yazen Alnouti, Ph.D.[5], JoEllyn McMillan, Ph.D.[5], Howard Gendelman, M.D.[6], Benson Edagwa, Ph.D.[7]

[1]Graduate research assistant, University of Nebraska Medical Center, Omaha, Nebraska, United States of America; [2]Instructor, Omaha, Nebraska, United States of America; [3]Research Assistant Professor, Omaha, Nebraska, United States of America; [4]Graduate research assistant, Omaha, Nebraska, United States of America; [5]Associate Professor, Omaha, Nebraska, United States of America; [6]Chairman, Department of Pharmacology and Experimental Neuroscience., Omaha, Nebraska, United States of America; [7]Assistant Professor, Omaha, Nebraska, United States of America

57. Discovery of a Novel Series of Compounds that Target the Chikungunya Virus (CHIKV) nsP4 RNA-Dependent RNA Polymerase

Jodie Hamrick, B.S.[1], Guo-Hua Chu, Ph.D.[1], Charlotte Bowsher, B.S.[1], Rose Langsjoen, Ph.D.[2], Scott Weaver, Ph.D.[3], Dan Pevear, Ph.D.[1], **Glen Coburn, Ph.D**.[1]

[1]VenatoRx Pharmaceuticals, Inc., Malvern, Pennsylvania, United States of America; [2]Human Pathophysiology and Translational Medicine, University of Texas Medical Branch, Galveston, Texas, United States of America; [3]Health Institute for Human Infections and Immunity, University of Texas Medical Branch, Galveston, Texas, United States of America

58. 1,5-Dicaffeoylquinic Acid Blocks EBOV Replication Counteracting the IFN-beta Production Inhibition by the VP35 Ebola Virus Protein

Angela Corona, Ph.D.[1], Elisa Fanunza, M.S.[1], Cristiano Salata, Ph.D.[2], St. Patrick Reid, Ph.D.[3], Simona Distinto, Ph.D.[1], Cinzia Sanna, Ph.D.[1], Jane Morwitzer, M.S.[3], Aldo Frau, Ph.D.[1], Daniela Rigano, Ph.D.[4], Gian Luca Daino, Ph.D.[1], Giuseppina Chianese, Ph.D.[4], Carmen Formisano, Ph.D.[4], Orazio Taglialatela Scalfati, Ph.D.[4], Alì Mirazimi, Ph.D.[5], Enzo Tramontano, Ph.D.[6]

[1]Department of Life and Environmental Sciences University of Cagliari, Cagliari, CA, Italy; [2]Department of Molecular Medicine, University of Padova, Italy. Public Health Agency of Sweden, Sweden, Padova, PA, Italy; [3]Department of Pathology and Microbiology, 985900 Nebraska Medical Center1, Omaha, Nebraska, United States of America; [4]Department of Pharmacy, University of Naples Federico II,, Naples, NA, Italy; [5]Public Health Agency of Sweden; Karolinska University Hospital; National Veterinary Institute., Uppsala, Sweden; [6]Department of Life and Environmental Sciences University of Cagliari; IRGB, CNR., Cagliari, CA, Italy

59. Erythrosin B Protects Mice from Lethal Challenge of Zika Virus

Yuekun Lang, Ph.D.[1], Zhong Li, Ph.D.[1]
[1]*Wadsworth Center, NYSDOH, Albany, New York, United States of America*

60. Developing Pan-Bunyavirus Antivirals by Targeting the Conserved Viral Endonuclease Domain

Sebastiaan ter Horst, M.S.[1], Marcella Bassetto, Ph.D.[2], Andrea Brancale, Ph.D.[2], Johan Neyts, Ph.D.[1], Joana Rocha-Pereira, Ph.D.[1]
[1]*Rega Institute for Medical Research, KU Leuven, Leuven, Belgium;* [2]*Cardiff School of Pharmacy and Pharmaceutical Sciences, Cardiff, United Kingdom of Great Britain and Northern Ireland*

62. Anti-Adenoviral Activity of Exopolysaccharides Produced by Lactic Acid Bacteria

Liubov Biliavska, Ph.D.[1], Yulia Pankivska, Ph.D.[1], Olga Povnitsa, Ph.D.[1], Svitlana Zagorodnya, Ph.D.[1]
[1]*Zabolotny Institute of Microbiology and Virology, NAS of Ukraine, Kyiv, Ukraine*

63. *In Silico* Evaluation of the Affinity of Antivirals Against HCV NS5 Protein in Dengue Virus

Laura Mahecha, B.S.[1], Gian Pietro Miscione, Ph.D.[2], Miguel Parra, Ph.D.[1], Karina Salvatierra, Ph.D.[3]
[1]*Science faculty, Biological sciences department, Universidad de los Andes, Bogotá, Colombia., Bogotá, Colombia;*
[2]*Computational Bio-Chemistry group (COBO). Universidad de los Andes, Bogotá, Colombia., Bogotá, Colombia;*
[3]*Grupo de Investigación en Genética Aplicada (GIGA)-IBS-CONICET, UNaM, Posadas, Misiones, Argentina., Misiones, Argentina*

64. Bicyclic Carboxamides as Hepatitis B Virus (HBV) Core Protein Assembly Modulators

Yanming Du, Ph.D.[1], Nicky Hwang, B.S.[1], Matthew Campagna, B.S.[1], Shuo Wu, Ph.D.[1], Ju-Tao Guo, M.D.[1]
[1]*Baruch S. Blumberg Institute, Doylestown, Pennsylvania, United States of America*

65. HIV-1 Non-B Subtype Infected Patients Progress Faster than Subtype B Patients; Determined by Higher Genetic Stability of Non-B Following Korean Red Ginseng Treatment

Jung-Eun Kim, M.S.[1]
[1]*University of Ulsan College of Medicine, SEOUL, Korea (Republic of)*

66. Novel Piperazine Derivatives as Capsid Assembly Modulators for the Hepatitis B Virus

Huixin Luo, Ph.D.[1], Shuo Wu, Ph.D.[1], Qiong Zhao, Ph.D.[1], Junjun Chen, Ph.D.[1], Haiqun Ban, Ph.D.[1], Ju-Tao Guo, Ph.D.[1], Yanming Du, Ph.D.[1]
[1]*Baruch S. Blumberg Institute*

67. Cidofovir and (S)-HPMPA Tyrosinamide Prodrugs with an Alkenyl Modification in the Long-chain N-alkyl Modifier are Potent Inhibitors of HSV-1, CMV and BKPyV

Jinglei Lyu, M.S.[1], Jiajun Fan, B.S.[1], Boris Kashemirov, Ph.D.[1], Caroll Hartline, Ph.D.[2], Emma Harden, Ph.D.[2], Mark Prichard, Ph.D.[2], Charles McKenna, Ph.D.[1]
[1]*University of Southern California, Los Angeles, California, United States of America;* [2]*University of Alabama, Birmingham, Alabama, United States of America*

68. Nipah Virus Attachment Glycoprotein (NiV-G) Counteracts the Antiviral Effector Protein Tetherin

Bom Nae Rin Lee, M.S.[1], Haewon Byun, M.S.[1], Hector Aguilar-Carreno, Ph.D.[1]
[1]*Cornell University, Ithaca, New York, United States of America*

69. Development and Characterization of Oral Combination Vaccine against Hepatitis B & Influenza

Prakash Gosain, M.D., MPH[1], Saurabh Jain, Ph.D.[1], Mani Bhargava, M.D., MPH[2]
[1]*Himalayan University, India;* [2]*ICFAI University, India*

71. Novel NNRTIs with Bicyclic Cores – Attempts to Improve Solubility and Resistance Profile

Ladislav Prener, B.S.[1], Ondřej Baszczyňski, Ph.D.[2], Martin Dračínský, Ph.D.[3], Jan Weber, Ph.D.[3], Michala Zgarbová, M.S.[3], Eric Hu, Ph.D.[4], Eric Landson, Ph.D.[4], Petr Jansa, Ph.D.[4], Zlatko Janeba, Ph.D.[3]
[1]*Institute of Organic Chemistry and Biochemistry, CAS and University of Chemistry and Technology, Prague, Prague, Czechia;* [2]*Institute of Organic Chemistry and Biochemistry, CAS and Dept. of Organic Chemistry, Charles University, Prague, Czechia;* [3]*Institute of Organic Chemistry and Biochemistry, CAS, Prague, Czechia;* [4]*Gilead Sciences Inc., Foster City, California, United States of America*

72. Development of Bipolymer based Novel Nanoparticles in Microsphere System as Vaccine Adjuvant

Nikhil Kapoor, M.D., MPH[1], Varun Bhargava, M.D., MPH[2], Saurabh Bhargava, M.D., MPH[3]
[1]*Manav Bharti University;* [2]*GTB Hospital, India;* [3]*United Institute of Pharmacy, India*

73. Biological Evaluation of Novel Small-molecule Antiviral Agents versus Tick Borne Encephalitis Virus

Paola Zanetta, M.S.[1], Friederike Hucke, D.V.M.[1], Friese Daniela, B.S.[1], Marcella Bassetto, Ph.D.[2], Andrea Brancale, Ph.D.[2], Joachim Bugert, M.D., Ph.D.[1]
[1]*Bundeswehr Institute of Microbiology, Virology, Munich, Germany;* [2]*School of Pharmacy, MedChem, Cardiff, United Kingdom of Great Britain and Northern Ireland*

74. Ultra-diluted Extract of *Atropa belladonna* Restrict Japanese Encephalitis Virus Infection through Modulation of Type-I Interferon in Chorioallantoic Membrane of Chick

Mousumi Chakravarty, M.S.[1], Urmita Chakraborty, Ph.D.[2], Arghyadeep Bhattacharjee, M.S.[1], Satadal Das, M.D.[2]
[1]*Regional Research Institute For Homoeopathy, Kolkata, West Bengal, India, India;* [2] *Regional Research Institute For Homoeopathy, Kolkata, West Bengal, India.*

75. Prediction of Biological Activity of Fluorinated Derivatives of Triazoles

Krystyna Naumenko, Ph.D.[1], Svitlana Zagorodnya, Ph.D.[1], Ganna Gudz, Ph.D.[2], Yurii Shermolovich, M.D., Ph.D.[2]
[1]*Zabolotny Institute of Microbiology and Virology NAS of Ukraine, Kyiv, Ukraine;* [2]*Institute of Organic Chemistry NAS of Ukraine, Kyiv, Ukraine*

76. Development and Characterization of an Aerodynamic System for Pulmonary Delivery of Influenza Vaccine

Saurabh Bhargava, M.D., MPH[1], **Priyanka Gosain, M.D., MPH**[2], Varun Bhargava, M.S.[2]
[1]*United Institute of Pharmacy, India;* [2]*GTB Hospital, India*

77. Tackling Chikungunya via Repurposing

Ashok Kumar Patel, Ph.D.[1], **Praveen Kumar Tripathi**[1]
[1]*KSBS, Indian Institute of Technology Delhi, Delhi, India*

78. Computer-aided Design, Synthesis and Evaluation of Novel Non-nucleoside Inhibitors of the Viral Polymerase as Antiviral Agents Against Norovirus

Gilda Giancotti, Ph.D.[1], Salvatore Ferla, Ph.D.[1], Ilaria Rigo, M.S.[1], Valentina Naccarato, M.S.[2], Romano Silvestri, Ph.D.[2], Johan Neyts, Ph.D.[3], Andrea Brancale, Ph.D.[1], Joana Rocha-Pereira, Ph.D.[3], **Marcella Bassetto, Ph.D.**[1]
[1]Cardiff University; [2]Sapienza University of Rome; [3]Rega Institute for Medical Research

79. Systematic Design and Synthesis of Novel Small Molecule Inhibitors of Chikungunya Virus

Verena Battisti, M.S.[1]
[1]University of Vienna, Vienna, Austria

80. An Imidazopyridine (BSBI252-C4) that Affects HBV Subviral Particle Antigenicity, and Interferes with its Assembly

Liren Sun, M.S.[1], Fanny Zhang, Ph.D.[2], John Kulp, Ph.D.[3], Timothy Block, Ph.D.[4], TianLun Zhou, M.D., Ph.D.[5]
[1]liren.sun@bblumberg.org, doylestown, Pennsylvania, United States of America; [2]Fanny.zhang@bblumberg.org, Pennsylvania, United States of America; [3]John.Kulp@bblumberg.org, Pennsylvania, United States of America; [4]Timothy.Block@bblumberg.org, Doylestown, Pennsylvania, United States of America; [5]Tianlun.zhou@bblumberg.org, Doylestown, Pennsylvania, United States of America

81. Biological Evaluation of Antiviral Agents versus Encephalitis Viruses Using Live Cell Microscopy: Optimization of Parameters for a Model of the Blood Brain Barrier

Lisa Hurler, M.S.[1], Paola Zanetta, M.S.[2], Rohan Narayan, M.S.[3], Daniela Friese, B.S.[1], Joachim Bugert, M.D., Ph.D.[1]
[1]Bundeswehr Institute of Microbiology (IMB), Munich, Germany; [2]ERASMUS program – Università degli Studi Milano Bicocca, Milan, Italy; [3]Cardiff School of Pharmacy and Pharmaceutical Sciences, Cardiff, United Kingdom of Great Britain and Northern Ireland

82. *In Vitro* Evaluation of the Role of Alcoholic Preparation of *Eupatorium perfoliatum* Plant and *Crotalus horridus* Venom against Dengue Virus Infection

Moonmoon Sinha, M.S.[1], Urmita Chakraborty, Ph.D.[1], Arghyadeep Bhattyacharjee, M.S.[1], Mousumi Chakravarty, M.S.[1], Debabrata Sarkar, M.D.[1], Satadal Das, M.D.[1]
[1]DACRRI, Kolkata, under Ministry of AYUSH, Govt. Of India, Kolkata, India

83. Design and Evaluation of Amidine and Non-Amidine Encephalitic Alphavirus Inhibitors With Prophylactic and Therapeutic Efficacy In Infectious Murine Models

Jennifer Golden, Ph.D.[1], Donghoon Chung, Ph.D.[2], Colleen Jonsson, Ph.D.
[1]University of Wisconsin-Madison, Madison, Wisconsin, United States of America; [2]University of Louisville, Louisville, Kentucky, United States of America; [3]University of Tennessee Health Science Center, Memphis, Tennessee, United States of America

84. Down Regulation of IL1 Beta Gene by Quercetin ; An Important Cytokine Marker Responsible for Determining Complications in Dengue Fever

Moonmoon Sinha, M.S.[1], Urmita Chakraborty, Ph.D.[1], Arghyadeep Bhattyacharjee, M.S.[1], Mousumi Chakravarty, M.S.[1], Debabrata Sarkar, M.D.[1], Satadal Das, M.D.[1]
[1]DACRRI, Kolkata under Ministry of AYUSH, Govt.of India, Kolkata, India

85. Fetal Protection against Zika Virus Using a Vesicular Stomatitis Virus Vectored Vaccine

Justin Julander, Ph.D.[1], Bose Sayantan, Ph.D.[2], Ashley Dagley, M.S.[1], Sean Whelan, Ph.D.[2]
[1]Institute for Antiviral Research, Utah State University, Logan, Utah, United States of America; [2]Department of Microbiology, Harvard Medical School, Boston, Massachusetts, United States of America

86. Towards the Development of Novel Anti-HBV Agents: Design, Synthesis and Biological Evaluation of *N*-hydroxyimides as RNaseH Inhibitors

Vasiliki Pardali, M.S.[1], Erofili Giannakopoulou, M.S.[1], Tiffany Edwards, M.S.[2], John Tavis, Ph.D.[2], Grigoris Zoidis, Ph.D.[1]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Athens, Athens, Greece; [2]Saint Louis University School of Medicine, Saint Louis, Missouri, United States of America

87. Metal Chelating Agents with Improved Inhibitory Activity against Hepatitis C Virus

Erofili Giannakopoulou, M.S.[1], Vasiliki Pardali, M.S.[1], Efseveia Frakolaki, M.S.[2], Vassilios Myrianthopoulos, Ph.D.[1], Emmanuel Mikros, Ph.D.[1], Ralf Bartenschlager, Ph.D.[3], Niki Vassilaki, Ph.D.[2], Grigoris Zoidis, Ph.D.[1]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Athens, Athens, Greece; [2]Molecular Virology Laboratory, Hellenic Pasteur Institute, Athens, Greece; [3]Department of Infectious Diseases, Molecular Virology, University of Heidelberg, Heidelberg, Germany

88. Pressurized DNA State Inside Herpes Capsids - A Novel Antiviral Drug Target

Alex Evilevitch, Ph.D.[1]

[1]University of Illinois at Urbana-Champaign, Department of Pathobiology, Urbana, Illinois

89. Identification of Sterol Regulatory Element Binding Protein-dependent Lipidomic Reprogramming as a Broad-spectrum Antiviral Target

Jasper Chan, M.D.[1], Shuofeng Yuan, Ph.D.[1], Hin Chu, Ph.D.[1], Zi-Wei Ye, Ph.D.[1], Lei Wen, M.S.[1], Bingpeng Yan, Ph.D.[1], Kelvin To, M.D.[1], Richard Kao, Ph.D.[1], Kwok-Yung Yuen, M.D.[1]

[1]State Key Laboratory of Emerging Infectious Diseases, Department of Microbiology, The University of Hong Kong, Hong Kong, Hong Kong

90. High-throughput Screening of 200K Small Molecules Identified Antiviral Compounds against Middle East Respiratory Syndrome Coronavirus

Jihye Lee, M.S.[1], Chul Min Park, Ph.D.[2], Jong Hwan Song, Ph.D.[2], Hyoung Rae Kim, Ph.D.[2], Seungtaek Kim, Ph.D.[3]

[1]Respiratory Virus Laboratory, Emerging Virus Group, Discovery Biology Department, Institut Pasteur Korea, Seongnam, Gyeonggi, Korea (Republic of); [2]Center for Convergent Research of Emerging Virus Infection, Korea Research Institute of Chemical Technology, Daejeon, Korea (Republic of); [3]Zoonotic Virus Laboratory, Emerging Virus Group, Discovery Biology Department, Institut Pasteur Korea, Seongnam, Gyeonggi, Korea (Republic of)

91. Evaluation of Sex as a Variable for Influenza Virus Infection and Treatment with Oseltamivir in Mice

Brett Hurst, Ph.D.[1], Bart Tarbet, Ph.D.[1]

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

92. Lipid Based Nanoparticulate System for Effective Vaccine Delivery

Marut Agarwal, M.D., MPH[1], Prateek Gupta, M.D., MPH[2], Saurabh Bhargava, M.D., MPH

[1]Dr. H S Gour University, India; [2]KRV Hospital, India; [3]United Institute of Pharmacy, India

94. To Identify Plant Based Potential Antiviral/s against Chikungunya Virus

Ashok Patel, Ph.D.[1]

[1]Kusuma School of Biological Sciences, IIT Delhi, India, New Delhi, India

97. Structural Analysis Kobuviral RNA Polymerase Reveals a Novel Fold of the N-terminus among Picornaviruses

Anna Dubankova, M.S.[1], **Evzen Boura, Ph.D.**[1]

[1]Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Prague

98. **Heme Oxygenase-1 Inhibits Influenza A Virus via the Induction of Interferon Response**

Peng Zhang, Ph.D.[1], Linlin Ma, Ph.D.[2], Huiqiang Wang, Ph.D.[1], Haiyan Yan, Ph.D.[1], Sheng Tang, Ph.D.[1], Danqing Song, Ph.D.[1], Jiandong Jiang, Ph.D.[1], Yuhuan Li, Ph.D.[1]

[1]Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing; [2]Shanghai University of Medicine and Health Sciences

99. **The Performance of ARCHITECT i2000SR in the Determination of HBsAg Qualitative II, Anti-HBc II and Anti-HBs Assays Utilized for Routine Laboratory Hepatitis B Testing**

Nafija Serdarevic, Ph.D.[1]

[1]Clinical Center University of Sarajevo, Department of Clinical biochemistry and Immuology, Sarajevo, Bosnia and Herzegovina

100. **Phenotypic Characterization of CMV Terminase Complex Genotypic Variants Observed in Subjects with Virologic Failure in a Phase 3 Study (P001) of Letermovir**

Juile Strizki, Ph.D.[1], Hong Wan, Ph.D.[1], Valerie Teal, Ph.D.[1], Carolee Welebob, Ph.D.[1], Cyrus Badshah, M.D.[1] Sunwen Chou, Ph.D.[2], Cameron Douglas, Ph.D.[1]

[1]Merck and Co., Inc., Kenilworth, New Jersey, United States of America; [2]Oregon Health and Sciences University and VA Medical Center, Portland, Oregon, United States of America

101. **Elevation of D-dimer is Linked to Disease Severity and Predicts Fatal Outcomes in H1N1 Infection**

Nafija Serdarevic, Ph.D.[1]

[1]Clinical center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

102. **Design, Synthesis and Biological Evaluation of Peptidomimetic Aldehydes as Anti-EV71 and Anti-MNV Inhibitors**

Wenhao Dai, M.S.[1], Joana Rocha-Pereira, Ph.D.[2], Johan Neyts, Ph.D.[3]

[1]Chinese Academy of Sciences Shanghai Institute of Materia Medica, China Pharmaceutical University; [2]KU Leuven · Rega Institute for Medical Research; [3]KU Leuven · Department of Microbiology and Immunology

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Nafija Serdarevic, M.D., Ph.D.[1]

[1]Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

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Tim Jonckers, Ph.D.[1], Abdellah Tahri, Ph.D.[1], Jean-François Bonfanti, Ph.D.[2], Pierre Raboisson, Ph.D.[1], Bart Stoops, M.S.[1], Marnix Van Loock, Ph.D.[1], Olivia Goethals, Ph.D.[1], Peggy Geluykens, B.S.[3], Edwin Gong, Ph.D.[1], Guenter Kraus, Ph.D.[1]

[1]Janssen Pharmaceutica N.V., Beerse, Antwerpen, Belgium; [2]Janssen-Cilag, Val de Reuil Cedex, Rouen, France; [3]Charles River, Beerse, Antwerpen, Belgium

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Xiangguo Qiu, M.D.[1], Logan Banadyga, Ph.D.[1], Wenguang Cao, Ph.D.[1], Shihua He, Ph.D.[1], Marie-Line Goulet, M.S.[2], Rongtuan Lin, Ph.D.[2]

[1]Special Pathogens Program, National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, Manitoba, Canada; [2]Lady Davis Institute-Jewish General Hospital, McGill University, Montreal, Quebec, Canada

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Onyisi Christiana Didamson, B.S.[1], Michelle Gordon, Ph.D.[1]
[1]*Department of Virology, University of KwaZulu Natal, Durban, KwaZulu Natal, South Africa*

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Marco Robello, Ph.D.[1], Herman Nikolayevskiy, Ph.D.[1], Michael Scerba, Ph.D.[1], Evan Pasternak, B.S.[1], Mrinmoy Saha, Ph.D.[1], Tracy Hartman, M.S.[2], Caitlin Buchholz, M.S.[2], Robert Buckheit, Jr., Ph.D.[2], Stewart Durell, Ph.D.[3], Daniel Appella, Ph.D.[1]
[1]*Synthetic Bioactive Molecules Section, LBC, NIDDK, NIH, Bethesda, Maryland, United States of America;* [2]*ImQuest Biosciences, Frederick, Maryland, United States of America;* [3]*Laboratory of Cell Biology, NCI, NIH, Bethesda, Maryland, United States of America*

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Michael Plewe, Ph.D.[1], Landon Whitby, Ph.D.[2], Eric Brown, B.S.[3], Shibani Naik, Ph.D.[3], Nadia Sokolova, Ph.D.[3], Vidyasagar Gantla, Ph.D.[3], Joanne York, B.S.[4], Jack Nunberg, Ph.D.[4], Dale Boger, Ph.D.[5], Greg Henkel, Ph.D.[3], Ken McCormack, Ph.D.[3]
[1]*Cullgen, San Diego, California, United States of America;* [2]*Vividion, San Diego, California, United States of America;* [3]*Arisan Therapeutics, San Diego, California, United States of America;* [4]*Montana Biotechnology Center, Missoula, Montana, United States of America;* [5]*Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, San Diego, California, United States of America*

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Carolina Sacramento, Ph.D.[1], Natalia Fintelman-Rodrigues, Ph.D.[1], Andressa Marttorelli, Ph.D.[1], Caroline de Freitas, M.S.[1], André Ferreira, Ph.D.[1], Cristiana Garcia, Ph.D.[1], Alexandre Machado, Ph.D.[1], Andrea Surrage, Ph.D.[1], Milene Miranda, Ph.D.[1], Maria de Lourdes Ferreira, Ph.D.[1], Luiz Pinheiro, Ph.D.[1], Nubia Boechat, Ph.D.[1], Fernando Bozza, Ph.D.[1], Thiago Souza, Ph.D.[1]
[1]*FIOCRUZ*

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Islam Hussein, Ph.D.[1], Karoly Toth, D.V.M.[2], Jennifer Brooks, M.S.[1], Ann Tollefson, Ph.D.[2], Baoling Ying, M.D.[2], Jacqueline Spencer, B.S.[2], John Morrey, Ph.D.[3], Mark Prichard, Ph.D.[4], William Wold, Ph.D.[2], Terry Bowlin, Ph.D.[1]
[1]*Microbiotix, Worcester, Massachusetts, United States of America;* [2]*Saint Louis University School of Medicine, St. Louis, Missouri, United States of America;* [3]*Utah State University, Logan, Utah, United States of America;* [4]*University of Alabama at Birmingham, Birmingham, Alabama, United States of America*

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Evelyn Franco, B.S.[1], Xun Tao, B.S.[1], Kaley Hanrahan, M.S.[1], Jieqiang Zhou, B.S.[1], Ashley Brown, Ph.D.[1]
[1]*University of Florida, Orlando, Florida, United States of America*

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Greg Henkel, Ph.D.[1], Michael Plewe, Ph.D.[1], Shibani Naik, Ph.D.[1], Eric Brown, B.S.[1], Nadia Sokolova, Ph.D.[1], Vidyasagar Gantla, Ph.D.[1], Alexandra Fetsko, M.S.[1], Younjun Shin, Ph.D.[1], Lihong Zhang, M.D.[2], Birte Kalveram, Ph.D.[2], Alex Freiberg, Ph.D.[2], **Ken McCormack, Ph.D.[1]**

[1]Arisan Therapeutics, San Diego, California, United States of America; [2]University of Texas Medical Branch, Galveston, Texas, United States of America

113. Exploring PA-PB1 Protein–Protein Interaction as a Target for Next-Generation Anti-influenza Therapeutics

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

[1]University of Arizona, Arizona, United States of America

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Consuelo Correa Sierra, M.D., Ph.D.[1], Luis Schang, D.V.M., Ph.D.[1]

[1]Baker Institute for Animal Health/ Cornell University, Ithaca, New York, United States of America

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Eric Rhoden, B.S.[1], Kimbell Hetzler, Ph.D.[2], Deborah Moore, B.S.[1], Heather Jost, M.S.[1], Naomi Dybdahl-Sissoko, M.S.[1], William Weldon, Ph.D.[1]

[1]CDC; [2]IHRC, contracting company for the CDC.

116. Characterization of a Cytomegalovirus (CMV) Cidofovir Resistant Mutant Virus by Quantitative Replication Ratio (Ro) Analysis

Edward Murray, B.S.[1], Keith Kinek, M.S.[1], Jay Grobler, Ph.D.[1], Jian Liu, Ph.D.[2], Dabbu Jaijyan, Ph.D.[2], Hua Zhu, Ph.D.[2], Philip McKenna, Ph.D.[1]

[1]Department of Infectious Diseases and Vaccines, MRL, Merck & Co., Inc., Kenilworth, New Jersey, United States of America; [2]Department of Microbiology, Biochemistry and Molecular Genetics, Rutgers – New Jersey Medical School, Newark, New Jersey, United States of America

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Timur Yarovinsky, M.D., Ph.D.[1], Stephen Mason, Ph.D.[1], Manisha Menon, Ph.D.[1], Marie Krady, Ph.D.[1], Bhaskara Madina, Ph.D.[1], Xianyong Ma, Ph.D.[1], Safiehkhatoon Moshkani, Ph.D.[2], Carolina Chiale, M.S.[2], Anasuya Chattopadhyay Pal, Ph.D.[3], Raj Kalkeri, Ph.D.[4], Kevin Walters, Ph.D.[4], Bijan Almassian, Ph.D.[1], John Rose, Ph.D.[3], Michael Robek, Ph.D.[2], Valerian Nakaar, Ph.D.[1]

[1]CaroGen Corporation, Farmington, Connecticut, United States of America; [2]Department of Immunology and Microbial Disease, Albany Medical College, Albany, New York, United States of America; [3]Department of Pathology, Yale University School of Medicine, New Haven, Connecticut, United States of America; [4]Infectious Disease Research, Drug Development Division, Southern Research, Frederick, Maryland, United States of America

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Raj Kalkeri, Ph.D.[1], Steffen Mueller, Ph.D.[2], Robert Coleman, Ph.D.[2], Zhaohui Cai, Ph.D.[1], Shuling Lin, B.S.[1], Kim Hagelin, B.S.[1], Brian Green, M.S.[1], Krista Salley, B.S.[1], Fusataka Koide, M.S.[1]

[1]Southern Research, Maryland, United States of America; [2]Codagenix, Farmingdale, New York, United States of America

121. Metabolically Improved Stem Cell Derived Hepatocyte-like Cells Support HBV Life Cycle and are a Promising Tool to Study HBV, Anti-HBV Antiviral Drugs and Drug Resistance

Tine Tricot, M.S.[1], Hendrik Jan Thibaut, Ph.D.[2], Kayvan Abbasi, M.S.[2], Ruben Boon, Ph.D.[3], Manoj Kumar, Ph.D.[1], Johan Neyts, Ph.D.[2], Catherine Verfaillie, M.D., Ph.D.[1]

[1]Stem Cell Institute, KULeuven; [2]Laboratory of Virology, Rega Institute, KULeuven; [3]Stem Cell Institute, KULeuven The Massachusetts General Hospital Cancer Center, Harvard Medical School

125. Safety, Tolerability, and Pharmacokinetics of the Iminosugar UV-4B Administered Orally as a Single Dose in Healthy Subjects

Kevin Spurgers, Ph.D.[1], Anthony Treston, Ph.D.[1], Marla Woodfolk, M.D.[2], Lisa Beth Ferstenberg, M.D.[2], Urban Ramstedt, Ph.D.[2], Kelly Warfield, Ph.D.[1], Matthew Duchars, Ph.D.[2], Mona Sharma, B.S.[1], Chandra Nimbal, Ph.D.[1], Grace Lin, M.S.[1], Mansoora Khaliq, Ph.D.[1], Brain Kaufman, B.S.[2], Preeya Lowe, M.S.[1], Aruna Sampath, Ph.D.[1], Elna van der Ryst, Ph.D.[3], Michael Callahan, M.D.[1]

[1]Emergent Biosolutions, Gaithersburg, Maryland; [2]Unither Virology; [3]TRN

180. Exploring Virus-host Cell Interactions to Battle Against Highly Pathogenic RNA Viruses

Marjo Puumalainen, Ph.D.[1]

[1]Karolinska institutet, Oncology-Pathology Department, Science for Life Laboratory, Stockholm, Sweden

1. Cidofovir and (S)-HPMPA Tyrosinamide Prodrugs: Tuning LogD by Heteratom Insertion in the Long-chain Alkyl Substructure

Jiajun Fan, B.S.[1], Jinglei Lyu, M.S.[1], Boris Kashemirov, Ph.D.[1], Caroll Hartline, Ph.D.[2], Emma Harden, Ph.D.[2], Mark Prichard, Ph.D.[2], Charles McKenna, Ph.D.[1]

[1]University of Southern California, Los Angeles, California, United States of America; [2]University of Alabama, Birmingham, Alabama, United States of America

Cidofovir ((*S*)-HPMPC) and its adenine analog (*S*)-HPMPA are acyclic nucleoside phosphonates (ANPs) with broad spectrum activity against DNA viruses. Cidofovir has low oral bioavailability and cell permeability due to its phosphonic acid group, which ionizes at physiological pH.

We have introduced a tyrosiniamide ANP ester prodrug strategy in which the ANP phosphonate equipped with a lipophilic alkyl group attached to the amido N. The modular design provides facilely variable substructures for optimizing antiviral potency and tuning other pharmacological properties. The C-16 alkyl tyrosinamide prodrugs of cidofovir and (*S*)-HPMPA (USC-505 and USC-087, respectively) show significantly enhanced potency vs a range of DNA viruses.

Here, we examine the effect on *in vitro* antiviral potency of inserting a heteroatom (O or S) into the *N*-alkyl group to adjust the logD of the resultant cidofovir or (*S*)-HPMPA prodrug to a lower value. *N*-alkoxyalkyl and *N*-alkylthioalkyl tyrosinamide prodrugs of cidofovir and (S)-HPMPA were synthesized and their logD values calculated by a standard method. All *N*-alkoxyalkyl prodrugs were more potent (EC_{50}2-4 logs lower) than the parent drugs vs CMV, HSV-1, VACV, andBKPyV *in vitro*, with CMV showing the largest increase. Introduction of a sulfur atom into the *N*-alkyl hydrocarbon chain significantly reduced the increased potency of the corresponding prodrugs. Synthesis of the prodrug analogs and an SAR analysis of the logD and antiviral results will be presented.

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2. Identification of Dihydrofuro[3,4-d]pyrimidine Derivatives as Novel HIV-1 Non-nucleoside Reverse Transcriptase Inhibitors with Promising Antiviral Activities and Desirable Physicochemical Properties

Zhan Peng, Ph.D.[1], Xinyong Liu, Ph.D.[2]

[1]Shandong University; [2]Shandong University

To address drug resistance to HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs), a series of novel diarylpyrimidine (DAPY) derivatives targeting "Tolerant Region I" and "Tolerant Region II" of the NNRTIs binding pocket (NNIBP) were designed utilizing a structure-guided scaffold-hopping strategy. The dihydrofuro[3,4-*d*]pyrimidine derivatives 13c2 and 13c4 proved to be exceptionally potent against a wide range of HIV-1 strains carrying single NNRTI-resistant mutations (EC_{50} = 0.9-8.4 nM), which were remarkably superior to that of etravirine (ETV). Meanwhile, both compounds exhibited comparable activities with ETV toward the virus with double mutations F227L+V106A and K103N+Y181C. Furthermore, the most active compound 13c2 showed favorable pharmacokinetic properties with an oral bioavailability of 30.96% and a half-life of 11.1 h, which suggested that 13c2 is worth further investigation as a novel NNRTI to circumvent drug resistance.

3. Chikungunya Virus is Susceptible to Sofosbuvir Both *In Vitro* and *In Vivo*

Carolina Sacramento, Ph.D.[1], Andre Ferreira, Ph.D.[1], Patrícia Reis, Ph.D.[1], Caroline de Freitas, M.S.[1], Lucas Hoelz, Ph.D.[1], Mayara Mattos, B.S.[1], Isaclaudia Quintanilha, Ph.D.[1], Natasha Rocha, M.S.[1], Giselle Barbosa-Lima, Ph.D.[1], Yasmine Vieira, Ph.D.[1], Pablo Trindade, Ph.D.[2], Stevens Rehen, Ph.D.[2], Fernando Bozza, Ph.D.[3], Patricia Bozza, Ph.D.[1], Nubia Boechat, Ph.D.[1], Thiago Souza, Ph.D.[1]
[1]FIOCRUZ, Rio de Janeiro, Rio de Janeiro, Brazil; [2]UFRJ; [3]IDOR

Chikungunya virus (CHIKV) causes a febrile disease associated with chronic arthralgia, which may progress to neurological impairment. Chikungunya fever (CF) is an ongoing public health problem in tropical and subtropical regions of the world, where control of the vector, Aedes mosquitos, has failed. As there is no vaccine or specific treatment for CHIKV, patients receive only palliative care to alleviate pain and arthralgia. Thus, drug repurposing is necessary to identify antivirals against CHIKV. CHIKV RNA polymerase is similar to the orthologue enzyme of other positive-sense RNA viruses, such as members of the Flaviviridae family. Among the Flaviviridae, not only is hepatitis C virus RNA polymerase susceptible to sofosbuvir, a clinically approved nucleotide analogue, but so is dengue, Zika, and yellow fever virus replication. Here, we found that sofosbuvir was three times more selective in inhibiting CHIKV production in human hepatoma cells than ribavirin, a pan-antiviral drug. Although CHIKV replication in human induced pluripotent stem cell–derived astrocytes was less susceptible to sofosbuvir compared to the hepatoma cells, sofosbuvir nevertheless impaired virus production and cell death in a multiplicity of infection–dependent manner. Sofosbuvir also exhibited antiviral activity *in vivo* by preventing CHIKV induced paw edema in adult mice at a dose of 20 mg/kg/day, and prevented mortality in a neonate mouse model at 40 and 80 mg/kg/day doses. Our data demonstrate that a prototypic alphavirus, CHIKV, is also susceptible to sofosbuvir. As sofosbuvir is a clinically approved drug, our findings could pave the way to it becoming a therapeutic option against CF.

4. Liver-Targeted Glycyrrhetinic Acid-Chitosan Conjugated Lamivudine Nanoparticle for Effective Treatment of Chronic Hepatitis B Virus Infection

Akhilesh Singh, Ph.D.[1], Lila Nath, Ph.D.[2]
[1]Dibrugarh University, Dibrugarh, Assam, India; [2]Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, Assam, India

Chronic hepatitis B is a highly prevalent disease worldwide, and one of the most common contagious disease with high infection rates. Lamivudine was found to be effective in patients with chronic hepatitis B, which lowered the HBV DNA levels and improved the serum enzyme levels and hepatic histology after long-term treatment. In this study, we attempted to develop a novel formulation of lamivudine with enhanced selectivity towards the liver. We used low molecular weight chitosan to prepare lamivudine nanoparticle using the ionic cross-linking method. It was further conjugated with glycyrrhetinic acid (GA), which has a high liver cell specificity. The synthesized conjugated nanoparticles were further characterized using FTIR, XRD, SEM and DSC techniques. The drug encapsulation efficiency and *in-vitro* drug release behaviour of lamivudine-loaded GA-CS nanoparticles (103±4 nm) were studied using UV spectroscopy and HPLC methods. The drug release kinetic study showed that lamivudine nanoparticles exhibited a biphasic pattern, initial burst release and consequently sustained release pattern. *In vitro*, cellular uptake study findings confirmed a high accumulation of lamivudine in HepaRG cells. Similarly, *In-vivo* biodistribution study suggested that GA-CS nanoparticles of lamivudine have highly targeted delivery in the liver compared to the non-conjugated nanoparticles. Our experimental findings showed that glycyrrhetinic acid and chitosan conjugated nanoparticles of lamivudine may be used as an effective treatment option for chronic hepatitis B compared to the available conventional treatment.

5. Neuraminidase Inhibitor Susceptibility Surveillance of Influenza Viruses Circulating in Rawalpindi, Pakistan

Irum Perveen, Ph.D.[1], Iqbal Memon, M.D., MPH[1]
[1]*Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, Pakistan*

Neuraminidase (NA) inhibitors (NAIs) are currently the only antivirals effective against influenza infections due to widespread resistance to M2 inhibitors. Influenza A and B viruses (n = 886) collected in Rawalpindi, Pakistan between April 2016, and September 2016, were assessed for susceptibility to two most commonly prescribed NAIs, oseltamivir and zanamivir, using the fluorescent-based NA-Fluor™ Influenza Neuraminidase Assay Kit. Out of a total of 237 influenza A (H1N1) pdm09 viruses 231 were sensitive to all NAIs, while six isolates (2.5%) with H275Y substitution, exhibited elevated IC50 s for oseltamivir and peramivir. Influenza A (H3N2) viruses (n = 357) were sensitive to all NAIs. Influenza B viruses (n = 351) were sensitive to all NAIs, except five isolates (1.3%) with H273Y substitution, exhibiting reduced susceptibility to oseltamivir and peramivir. This study summarizes NAI susceptibility of influenza viruses circulating in Rawalpindi, Pakistan during the year 2016. Despite low resistance to NAIs among tested influenza viruses, constant surveillance of influenza virus susceptibility to NAIs should be emphasized.

6. Acute West-Nile Viremia and Malaria Co-infection amongst Febrile Infected HIV Participants attending a Tertiary Hospital in Abuja, Nigeria

Kehinde Aina, M.S.[1], Olajide Agbede, Ph.D.[2]
[1]*Department of Medical Microbiology and Parasitology (Virology Unit) Unilorin, Nigeria, Ilorin, Northern, Nigeria;*
[2]*Department of Medical Microbiology and Parasitology (Virology Unit), University of Ilorin, Ilorin, Nigeria*

Malaria and West Nile fever has ubiquitous distribution in Africa. Many febrile patients are most times underdiagnosed or misdiagnosed with malaria due to striking similarities, such as fever shared by malaria and certain arboviral infections. Clinical symptoms of WNV fever often overlap with other agents of febrile illnesses. Over the years, the geographical range of WNV activity has increased and the virus has become established even in non-endemic areas where it has not been previously detected. This survey investigated the prevalence of anti-WNV IgM and Malaria among patients with febrile illnesses at Gwagwalada metropolis. Between the period of May and August 2017, a total of 171 participants attending the University of Abuja Teaching Hospital were recruited for the study. Serum samples were immediately harvested, stored and analyzed using the indirect ELISA for anti-WNV IgM antibodies using kits endorsed by the World Health Organization and also Microscopy and RDTs for Malaria. Out of the 171 febrile participants, the overall prevalence of WNV IgM antibodies was 66.1%. whereas 29.2% were positive for Plasmodium falciparum. About 31.4% were positive for both WNV virus and P. falciparum. Significant association was observed in prevalence of WNV IgM and Malaria/WNV co-infection ($p< 0.5$). Sixty two (54.9%) of WNV seropositive females and 51/113 (45.1%) seropositive males was recorded. Findings from this study necessitate the need for routine diagnosis and surveillance of WNV as possible agents of febrile illness in Nigeria. Infected patients should be closely monitored in order to detect possible associated sequelae.

7. 3-Deaza and 3-Deaza-3-bromo L-Neplanocin Analogues: Synthesis and Antiviral Property

Alexander Smith, B.S.[1], Qi Chen, Ph.D.[1]
[1]*Slippery Rock University, Slippery Rock, Pennsylvania*

Previous studies have shown that L- like carbocyclic nucleosides, such as L-isoneplanocin analogues, possess broad spectrum antiviral activities, including Ebola, norovirus, vaccinia, HBV, HCMV, measles and Dengue. Further studies have also suggested their antiviral property may be caused by inhibiting viral replication through an unknown mechanism different with their naturally occurring D-counterparts. It is noteworthy that replacing the nitrogen atom with a CH or a CBr group at the N-3 position has significant impacts on their biological properties. Our recent study has found that L-like, N-3 modified C-4′ truncated (DHCDA) (1) and 4′,6′-methanocarba (MC) (2) Neplanocin analogues are potent antiviral agents and especially effective against norovirus by adopting different conformations. Following the lead, we have designed and synthesized L-3-deazaneplanocin (3) and L-3-deaza-3-bromoneplanocin (4) with a newly developed synthetic method. Since the hydroxyl group on the C-5′ plays an essential role in inhibiting many viral RNA polymerase, 3-deaza-5′-fluoroneplanocin (5) is included in this work to further explore the antiviral mechanism for L-neplanocin analogues. Antiviral activities for the three target compounds are also included.

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8. Enzymatic Removal of a Butyl-Ether Moiety by Adenosine Deaminase-Like Protein 1, a Necessary Step in the Mechanism of Action of MBX-2168

Kathryn Vollmer, B.S.[1], Anna Burns, B.S.[1], Hannah Sauer, M.S.[1], John Williams, Ph.D.[2], Gloria Komazin-Meredith, Ph.D.[2], Marc Busch, Ph.D.[3], Terry Bowlin, Ph.D.[2], Brian Gentry, Ph.D.[1]

[1]Drake University College of Pharmacy and Health Sciences; [2]Microbiotix Inc.; [3]Drake University College of Arts & Sciences Department of Biology

Ganciclovir (GCV) is the first-line therapy option for the treatment of systemic human cytomegalovirus infections. The mechanism of action of GCV begins with monophosphorylation by the virus-encoded pUL97 protein kinase followed by phosphorylation to a triphosphate by endogenous cellular kinases. The active compound, GCV-TP, then inhibits viral DNA synthesis and replication. However, high incidences of adverse effects (neutropenia) and drug resistance limit the utility of this drug. MBX-2168, a third-generation methylenecyclopropane nucleoside analog, demonstrates broad-spectrum anti-viral activity against all members of the herpes virus family without any observable increase in adverse effects. MBX-2168 has a similar mechanism of action to GCV but differs in that MBX-2168 is in part or in whole phosphorylated by the cellular kinase TAOK3 to a monophosphate. In addition, we hypothesize that enzymatic removal of a butyl-ether moiety at the 6-position of the guanine ring by adenosine deaminase-like protein 1 (ADAL-1) is an essential step in the activation of this prodrug. Our current studies have demonstrated that pentostatin, an adenosine deaminase (ADA) and ADAL-1 inhibitor, but not EHNA (an ADA inhibitor only), antagonizes the anti-viral effect of MBX-2168. Further experimentation demonstrated conversion of MBX-2168-MP to synguanol-MP by ADAL-1 in a time-dependent manner with a K_m value of 17.5 uM, a V_{max} of 0.12 nmol/min, and a k_{cat} of 0.29 nmol/min·ug protein. In addition, ADA failed to convert MBX-2168 to synguanol. We therefore conclude that ADAL-1 catalyzes the conversion of MBX-2168-MP to synguanol-MP, a necessary step in the activation of this prodrug.

9. Discovery of a Novel Inhibitor of the Drug-Resistant Influenza A M2 (S31N) Viroporin

Maggie Duncan, B.S.[1], Ibuki Kihara, B.S.[1], Maya Naidu, B.S.[1], David Williams, Ph.D.[2], Aruna Balgi, Ph.D.[2], Kerstin Andrae-Marobela, Ph.D.[3], Michel Roberge, Ph.D.[2], Raymond Anderson, Ph.D.[2], Fidele Ntie-Kang, Ph.D.[4], Masahiro Niikura, Ph.D.[1], Ian Tietjen, Ph.D.[1]

[1]Simon Fraser University, Burnaby, British Columbia, Canada; [2]University of British Columbia, Vancouver, British Columbia, Canada; [3]University of Botswana, Gaborone, Botswana; [4]Martin Luther University Halle-Wittenberg, Halle, Germany

Circulating strains of influenza A are overwhelmingly resistant to licensed therapies that target the virally-encoded M2 proton channel. Widespread resistance is due primarily to a Ser31Asn (S31N) mutation in M2. As seasonal and pandemic outbreaks continue to cause substantial morbidity and mortality worldwide, antivirals that act on M2(S31N) remain urgently needed. We performed virtual screening of compound libraries derived from marine natural products and medicinal plants to identify molecules containing pharmacophores resembling those of the few known M2(S31N) inhibitors. Screening hits were assessed *in vitro* using an established yeast-based assay where inducible M2(S31N) expression inhibits growth, which in turn is restored by co-incubation with M2 inhibitors. Compounds that restored ³ 15% of growth at 25 µg/mL (comparable to 100 µM of control adamantane inhibitor M2WJ352) were tested for replication inhibition activity against A/PR/8/1934(H1N1) influenza viruses encoding M2(S31N) or M2(WT). We identified 26 virtual screening hits, of which 15 (57.8%) restored growth of M2(S31N)-expressing yeast. Of these, chebulagic acid consistently inhibited replication of influenza encoding M2(S31N) (EC_{50} = 21.3 ± 11.6 µM) with efficacy comparable to M2WJ352 (EC_{50} = 17.6 ± 11.2 µM). Chebulagic acid also inhibited M2(WT)-containing virus but with 1.7-fold reduced efficacy (EC_{50} = 36.7 ± 18.6 µM) and at substantially higher concentrations than control M2(WT) inhibitor amantadine (EC_{50} = 1.8 ± 1.7 µM). Using virtual screening and *in vitro* validation, we report chebulagic acid as a novel inhibitor of drug-resistant M2(S31N) viroporin and virus replication.

10. Heme Oxygenase-1 Mediates the Induction of Interferon Response and Suppression of Influenza A Virus Infection by Rupestonic Acid Derivative YZH-106

Yuhuan Li, Ph.D.[1], Linlin Ma, Ph.D.[1], Peng Zhang, M.S.[1], Huiqiang Wang, M.S.[1], Haji Akber Aisa, Ph.D.[2], Jiandong Jiang, Ph.D.[1]

[1]Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China; [2]Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Urumqi, Xinjiang, China

Influenza A virus (IAV) infection remains to be a global public health threat with significant morbidity and mortality. Heme oxygenase-1 (HO-1) is a cellular enzyme that can be induced by virus infections and suppresses the replication of many medically important viruses, such as HIV, HCV, HBV, EV71, IAV, RSV, DENV, ZIKV and EBOV. We reported previously that rupestonic acid derivatives exhibited a potent antiviral activity against IAV, but its mode of action remains to be determined. We report herein that YZH-106, a novel rupestonic acid derivative, exhibited a broad-spectrum antiviral activity against influenza viruses, including drug-resistant strains *in vitro* and provided partial protection of mice to lethal dose IAV infection. Mechanistic studies revealed that YZH-106 treatment induced p38 MAPK and ERK1/2 phosphorylation, which led to the activation of erythroid 2-related factor 2 (Nrf2) that up-regulated HO-1 expression in addition to other genes. We further showed that HO-1 directly interacted with IRF3 to promote its phosphorylation/nuclear translocation and subsequent activation of type I IFN expression, which, in turn, induced antiviral ISG expression and suppression of IAV replication. Interestingly, HO-1 activation of IFN response and suppression of IAV infection did not depend on its heme oxygenase activity. In conclusion, our studies clearly demonstrate that YZH-106 inhibits IAV infection by inducing a HO-1-mediated IFN response. HO-1 is thus a promising host target for antiviral therapeutics against IAV and other viral infectious diseases.

11. Predictors of HIV Status Disclosure to Sexual Partners Among PLHIV in Nigeria

Dr Abiola Adepoju, M.D.[1], Johnson Okolie, M.D.[2]

[1]KNCV Tuberculosis Foundation, Birnin Kebbi, Birnin Kebbi, Nigeria; [2]Mangement Science for Health, Birnin Kebbi, Kebbi, Nigeria

Disclosure of HIV positive sero-status to sexual partners, colleagues and family members is critical for the prevention and care of HIV. A huge number of PLHIV patients fail to disclose their status in Nigeria. Our objective was to assess the status disclosure rate and factors associated with HIV seropositive status disclosure to sexual partners among PLHIV. A multi-center, cross-sectional study was conducted in January-June 2017, including 400 selected PLHIVs at 6 government hospitals in Kebbi state, Northern Nigeria. Data were collected through a pre-tested questionnaire administered by trained data collectors. Bivariate and multivariate analyses were used to identify associated factors for disclosing their HIV seropositive status to a sexual partner. A majority (64.2%) were females, attended Arabic school (21.3%), were unemployed (51.3%), perceived HIV as a death sentence (33.6%), have disclosed their HIV status (83.3%), married (74.8%) and sero-discordant (73.8) relationship. Being married (OR2.4; 1.4-3.9,p<0.001), in seroconcordant relationship (OR 2.5; 1.4-4.6, p=0.002) and having a positive perception about HIV (OR 2.3; 1.3-3.6, p=0.002) were significantly associated with HIV status disclosure. There is a need to develop adherence messages aimed at changing negative perception of HIV particularly among PLHIV who are single and in sero-discordant relationships.

12. A Survey of Awareness and Willingness to Use HIV Self-testing Among PWID in Nigeria

Victor Adepoju, M.D.[1], Jude Inegbeboh, M.D.[2]
[1]*KNCV Tuberculosis Foundation, Lagos, Lagos, Nigeria;* [2]*United Nations, Birnin Kebbi, Birnin Kebbi, Nigeria*

HIV self-testing is an important intervention for HIV uninfected People who Inject Drugs (PWID). The study present results of survey of HIV self-testing among people who Inject Drugs in Lagos, Nigeria. Between December 2017 and January 2018 , we interviewed 100 PWID across hotspots in Lagos. The participants were recruited through respondent driven sampling (RDS) assessments. A questionnaire was adapted from University of San Francisco Center for Research among Key Population as part of the regional Key Population survey across Lagos PWID hotspots. Data were captured on socio-demographics, awareness of HIV self-testing, history of usage of self-testing kits, means of getting the self-testing kit, and willingness to use the self-testing kits. Data were entered into Microsoft Excel and later imported into SPSS version 21 for analysis. Of the total 100 participants, 80 (80%) were male and 20 (20%) were female. The mean age was 26.98 (19-77 years). Only 10 (10%) had heard about HIV self-testing, but none had administered the self-testing. Among those who have heard HIV self-testing kits, a majority (50%) obtained it from NGO. 28 (28%) of the participants stated they were willing to use HIV self-testing kits if available, 66 (66%) stated they were not willing to use the HIV testing kit while 6 (6%) were neutral. Awareness and willingness to use HIV self-testing is still low among PWID in Nigeria despite its benefits in achieving the first 90 of the 90:90:90 target. There is a need to create more awareness for the adoption of HIV self-testing among PWID in Nigeria.

13. Activity of Double Combinations of Newly Synthesized Diaryl Ethers Against Coxsackievirus B1

Adelina Stoyanova, M.S.[1], Luchia Mukova, B.S.[1], Georgi Dobrikov, Ph.D.[2], Stefan Philipov, Ph.D.[2], Vadim Makarov, Ph.D.[3], Angel Galabov, M.D., Ph.D.[1]
[1]*The Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, Sofia Bulgaria;*
[2]*Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria;*
[3]*Bach Institute of Biochemistry, Moscow, Russian Federation*

Coxsackievirus (CV) infections have worldwide distribution and causes severe morbidity and mortality, particularly in the very young. Chemotherapy is an important tool for controlling CV infections, but clinically effective anti-enteroviral drugs do not currently exist, mainly due to the development of drug resistance and serotype diversity. In the last decades many molecules that selectively inhibit CV replication have been identified and characterized. We investigated the effects based on combination of inhibitors with different mode of action and some new synthesized diethyl ethers.

Double combinations by newly synthesized diethyl ethers (derivatives of MDL-860) – SHIB 13403 and SHIB 1602 with pleconaril, guanidine hydrochloride, and oxoglaucine were tested *in vitro* on HEp-2 cells for their activity against Coxsackievirus B1 strain Connecticut-5. Antiviral combination effects due to drug–drug interaction were examined by relying on the three-dimensional model developed by Prichard and Shipman (1990) by using the program MacSynergy™ II.

The combinations of both SHIB 13602 and SHIB 13402 with pleconaril and oxoglaucine were synergistic with the exception of the additive effect with guanidine hydrochloride. The highest volume of synergy is observed when SHIB 13602 and SHIB 13402 were combined with pleconaril (175,44 mM^2% and 161,54 mM^2% respectively).

The resistance occurring after monotherapy with a certain anti-enteroviral drugs makes it reasonable to focus interest on combined administration of antivirals. The results in this study show that the combination application of tested anti-enteroviral has a protective effect in *in vitro* experiments with Coxsackievirus B1.

14. Structural Investigation on the Effect of Pyrimidine Functional Groups of Fleximer Analogues on Antiviral Activity

Mary Yates, B.S.[1], Katherine Seley-Radtke, Ph.D.[1]
[1]*University of Maryland Baltimore County*

Filoviruses, such as Ebola (EBOV), Sudan (SUDV), and Marburg (MARV) viruses, represent a severe health threat with mortality rates reaching 90% and, with the recent outbreaks of EBOV and SUDV, it is imperative that a viable and efficient treatment is developed in order to increase survival rates of these lethal diseases. While there are currently no FDA approved treatments for these viral diseases, nucleoside analogues have long served as the cornerstone for antiviral therapeutics due to their ability to inhibit viral DNA or RNA replication. In that regard, the Seley-Radtke lab has developed various types of flexible nucleoside analogues, called "fleximers", that have demonstrated the ability to increase interactions in the binding pocket of biologically relevant enzymes. Preliminary studies have shown that several acyclic Flex-analogues of the FDA-approved drug Acyclovir demonstrate potent activity against EBOV *in vitro*, however, this activity could be increased by altering functional groups on the pyrimidine scaffold. As such, a structure-activity relationship study was pursued, and the change in activity against EBOV and other filoviruses was analyzed. The results of this study are reported herein.

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15. Perylene Derivatives as Broad-spectrum Antivirals

Alexey Chistov, M.S.[1], Evgeny Khvatov, M.S.[2], Ksenia Sapozhnikova, M.S.[1], Nikita Slesarchuk, B.S.[1], Yury Dokukin, B.S.[3], Alexey Ustinov, Ph.D.[1], Liubov Kozlovskaya, Ph.D.[2], Dmitry Osolodkin, Ph.D.[2], Vladimir Korshun, Ph.D.[1]
[1]*Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry RAS, Moscow, Russian Federation;* [2]*Institute of Poliomyelitis and Viral Encephalitides, FSBSI Chumakov FSC R&D IBP RAS, Moscow, Russian Federation;* [3]*Higher Chemical College RAS, Mendeleev University of Chemical Technology of Russia, Moscow, Russian Federation*

Several enveloped viruses, e.g. influenza A virus, Ebola virus, dengue virus, Zika virus, etc., cause severe epidemic and pandemic events around the world, and others, like HCV or HIV, present a constant public health burden in many countries. As the lipid membrane bilayer is a crucial structural feature of enveloped viruses, membrane-targeting small molecule compounds inhibiting the viral entry may find their use as promising broad-spectrum antivirals. Rigid amphipathic fusion inhibitors (RAFIs),[1,2] especially perylene nucleosides dUY11 and aUY11, are potent inhibitors of enveloped viruses, HSV-1, HSV-2, influenza A, etc. Recently, anti-TBEV activity of perylene RAFIs was discovered.[3] The antiviral action of perylene compounds was postulated to be lipid membrane-targeting via a biophysical[1,2,4] or photochemical[5] mechanism.

Here we report new perylene compounds, including uracil-1-acetic acids cm1pUY11, cm1mUY11, and series of their amides with potent, in some cases subnanomolar, activities against TBEV. Studies on other enveloped viruses are in progress.

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16. Optimization of N-Substituted Oseltamivir Derivatives as Potent Influenza A Neuraminidases Inhibitors

Xinyong Liu, Ph.D.[1]
[1]*School of Pharmaceutical Sciences, Shandong University*

Based on our earlier discovery of N1-selective inhibitors, the 150-cavity of influenza virus neuraminidases (NAs) could be further exploited to yield more potent oseltamivir derivatives. Among the synthesized compounds, 15b and 15c were exceptionally active against both group-1 and -2 NAs. Especially for 09N1, N2, N6 and N9 subtypes, they showed 6.80-12.47 and 1.20-3.94 times greater activity than oseltamivir carboxylate (OSC). They also showed greater inhibitory activity than OSC towards H274Y and E119V variant. In cellular assays, they exhibited greater potency than OSC towards H5N1, H5N2, H5N6, and H5N8 viruses. 21h exhibited antiviral activities similar or better than those of oseltamivir carboxylate (OSC) against H5N1, H5N2, H5N6 and H5N8. Besides, 21h was 5- to 86-fold more potent than OSC toward N1, N8, and N1-H274Y mutant NAs in the inhibitory assays. Computational studies provided a plausible rationale for the high potency of 21h against group-1 and N1-H274Y NAs. In addition, 15b and 21h demonstrated acceptable drug-like properities, making them promising drug candidates for the treatment of influenza virus infection.

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17. TAK-632 Analogues as Novel Necroptosis Inhibitors: Synthesis, Structure-Activity Relationships and *In Vivo* Efficacy

Chunlin Zhuang, Ph.D.[1], Fener Chen, Ph.D.[1]
[1]*Fudan University, Shanghai, China*

Necroptosis is a form of programmed, caspase-independent cell death that is mediated by receptor-interacting protein kinases, RIPK1 and RIPK3, and the mixed lineage kinase domain-like (MLKL). Necroptosis contributes to the pathophysiology of infectious diseases and various inflammatory diseases. Thus, identification of small molecule inhibitors for pathologic necroptosis has broad therapeutic relevance. Herein, we identified that the pan-RAF kinase inhibitor TAK-632 is a potent inhibitor of necroptosis from an *in-house* fluorinated compound library. TAK-632 inhibits RIPK1 and RIPK3 kinase activity and thus disrupted RIPK1-RIPK3 necrosome complex formation. *In vivo*, TAK-632 alleviates TNF-induced systemic inflammatory response syndrome (SIRS). An structure activity relationship (SAR) analysis of TAK-632 analogues were performed to generate a highly-potent, selective inhibitor for RIPK1/3. Collectively, TAK-632 is an inhibitor of necroptosis and we could develop more selective and highly potent inhibitors for RIPK1/3 based on TAK-632 scaffold.

18. Effect of Double Combinations Applied via Consecutive Alternating Administration in Coxsackievirus B3 Infection

Adelina Stoyanova, M.S.[1], Stefan Philipov, Ph.D.[2], Gerhard Pürstinger, Ph.D.[3], Vadim Makarov, Ph.D.[4], Angel Galabov, M.D., Ph.D.[1]
[1]*The Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, Sofia, Bulgaria;* [2]*Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria;* [3]*Institute of Pharmacy, University of Innsbruck, Innsbruck, Austria;* [4]*Bach Institute of Biochemistry, Moscow, Russian Federation*

In our previous studies, the efficacy of consecutive alternating administration (CAA) of the triple combinations pleconaril/guanidine.HCl/oxoglaucine (PGO) and pleconaril/MDL-860/ oxoglaucine (PMO) against Coxsackievirus B1 (CVB1) infection in newborn mice was proven. It was shown that these drug combinations prevented the development of drug resistance in virus progeny.

In the present study, we test the effect of the double combinations of compounds described above on experimental infection in newborn mice infected subcutaneously with 20 MLD50 of Coxsackievirus B3 (Woodruff strain).

The results of these experiments indicate efficacy of PG, PO and PM combinations administered according to the CAA treatment schedule in CVB3 infected mice – decreased mortality rate and lengthening of the mean survival time (MST). In comparison with placebo group the monotherapeutic course with pleconaril demonstrated some independent antiviral effect. It was found that MDL-860, oxoglaucine and guanidine.HCl monotherapies were without a marked antiviral effect.

19. Therapeutic Treatment of Zika Virus Infection Using a Brain-penetrating Antiviral Peptide

Nam-Joon Cho, Ph.D.[1]
[1]Nanyang Associate Professor, School of Materials Science and Engineering, Nanyang Technological University, Singapore

Zika virus is a mosquito-borne virus that is associated with neurodegenerative diseases, including Guillain–Barré syndrome and congenital Zika syndrome. As Zika virus targets the nervous system, there is an urgent need to develop therapeutic strategies that inhibit Zika virus infection in the brain. Here, we have engineered a brain-penetrating peptide that works against Zika virus and other mosquito-borne viruses. We evaluated the therapeutic efficacy of the peptide in a lethal Zika virus mouse model exhibiting systemic and brain infection. Therapeutic treatment protected against mortality and markedly reduced clinical symptoms, viral loads and neuroinflammation, as well as mitigated microgliosis, neurodegeneration and brain damage. In addition to controlling systemic infection, the peptide crossed the blood–brain barrier to reduce viral loads in the brain and protected against Zika-virus-induced blood–brain barrier injury. Our findings demonstrate how engineering strategies can be applied to develop peptide therapeutics and support the potential of a brain-penetrating peptide to treat neurotropic viral infections.

20. Structure-Based Virtual Screening for the Identification of Novel Anti-Dengue Compounds Disrupting the Viral Replication Complex

Giulio Nannetti, Ph.D.[1], Salvatore Ferla, Ph.D.[1], Beatrice Mercorelli, 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 University, Cardiff, United Kingdom of Great Britain and Northern Ireland; [2]Department of Molecular Medicine, University of Padua, Padua, Italy

Dengue virus is a major health threat as it can cause infections that could develop into a severe dengue disease with potentially life-threatening complications. The lack of specific treatments for dengue virus infections highlights the urgent need to develop anti-dengue drugs. Since the binding between NS3 and NS5 dengue virus proteins is essential for the formation of the viral replication complex and its interaction interface is highly conserved among the four dengue virus serotypes, the disruption of such interaction may represent a promising strategy for the development of broad-spectrum anti-dengue drugs. Starting from the available structural and biological information of NS3 and NS5 proteins of dengue virus, a model of the NS3/NS5 dimer was generated using a combination of molecular modelling techniques. The resulting model allowed us to define the dynamic intermolecular interactions and identify two potential druggable binding sites at the protein-protein interface. With the aim of identifying new anti-dengue compounds targeting the NS3/NS5 binding, two distinct structure-based virtual screening approaches of commercially available compounds were performed on the selected binding sites. Starting from the purified NS3 and NS5 recombinant proteins expressed in E.coli, we are setting up an ELISA to measure the NS3/NS5 interaction specifically and to evaluate the ability of the selected hits to disrupt this binding. Active compounds will then be tested in cell-based assays to characterize their potential antiviral and cytotoxicity properties. Collectively, this study offers an innovative and multidisciplinary strategy for the discovery of novel antiviral agents against dengue virus.

21. Pentostatin Antagonizes the Anti-Viral Activity of MBX-2168 by Inhibiting the Biosynthesis of Active Compound

Natalie Hagen, B.S.[1], Hannah Sauer, Ph.D.[1], Marie Nguyen, Ph.D.[2], Terry Bowlin, Ph.D.[3], Brian Gentry, Ph.D.[1]
[1]*Drake University College of Pharmacy and Health Sciences, Des Moines, Iowa, United States of America;*
[2]*Des Moines University Department of Microbiology and Immunology, Des Moines, Iowa, United States of America;*
[3]*Microbiotix Inc., Worcester, Massachusetts, United States of America*

First-line therapy for the treatment of herpes-virus infections are acyclovir (ACV) and ganciclovir (GCV). The mechanism of action of these drugs requires viral specific monophosphorylation followed by phosphorylation by endogenous cellular kinases to a triphosphate, the active compound that inhibits the viral DNA polymerase. However, these drugs are limited by high toxicity, poor bioavailability, and/or the development of drug resistance. MBX-2168, a broad-spectrum anti-herpes agent, has a mechanism of action similar to that of ACV/GCV, but two unique steps differentiate this drug from ACV/GCV. First, MBX-2168 is, at least partially, phosphorylated by the endogenous cellular kinase TAOK3 to a monophosphate. Our current studies demonstrate that co-incubation with pentostatin (dCF), an adenosine deaminase like protein-1 (ADAL-1) inhibitor, antagonizes the anti-viral activity of MBX-2168. We therefore hypothesize that the second distinct metabolic step involves the removal of a moiety at the 6-position of MBX-2168-MP by ADAL-1 and by inhibiting this step, less active compound is produced resulting in a decrease in anti-viral effect. To test this, we examined the effect dCF has on the conversion of MBX-2168 to a triphosphate in herpes virus-infected cells. Our results demonstrate that incubation of MBX-2168 alone and with dCF in cytomegalovirus-infected cells resulted in 53.1 and 39.4 pmol triphosphate/106 cells, respectively (25.8% reduction). Incubation of MBX-2168 alone and with dCF in uninfected HFF cells resulted in 17.4 and 7.7 pmol triphosphate/106 cells, respectively (55.7% reduction). We therefore conclude that dCF antagonizes the anti-viral effect of MBX-2168 by inhibiting the production of triphosphate, the active compound

22. Ursolic Acid Acts as an Antiviral Agent in Rotavirus Infection *In Vitro* by Interfering with Viroplasm Formation

María Julieta Tohmé, B.S.[1], María Cecilia Gimenez, B.S.[1], María Isabel Colombo, Ph.D.[1], Laura Ruth Delgui, Ph.D.[1]
[1]*Instituto de Histología y Embriología de Mendoza (IHEM)- CONICET*

Rotavirus (RV) is one of the most important pathogens causing severe gastroenteritis, which remains to be a leading cause of morbidity and mortality in infants and children worldwide.Since no specific treatment is currently available, this work was intended to explore the ursolic acid (UA), a natural triterpenoid with extensively studied biological properties, as a possible anti-RV agent *in vitro*.

A dose-dependent anti-RV activity was observed when UA was incorporated at all stages of RV replication cycle, which was not due to a direct effect of UA over viral particles viability. The inhibitory effect of UA was demonstrated by a significant decrease in the levels of the main RV proteins (VP6 and VP7) and in the viral progeny titer in the infected cells. With the purpose of dissecting the replication step targeted by the UA, we separately analysed the early and late stages of infection. We observed a significant decrease in i) the level of VP6 and NSP2 proteins; ii) the number and size of viroplasms; and iii) the viral progeny titer when UA was included in the early stages of the replication cycle. We analyzed the mechanism of action and observed that UA induces the degradation of lipids causing a significant reduction in the number and size of lipid droplets in UA-treated cells, directly affecting viroplasm formation and the RV replication cycle.

Altogether, our results describe a robust anti-RV effect mainly interfering with the viroplasm formation, pointing to UA as an attractive alternative therapy.

23. Preliminary *In Vitro* Antiretroviral Activity of a *Nigella sativa* Seed Formulation (A-zam) against HIV-1

Olufunmilayo Oyero, Ph.D.[1], Adekunle Onifade, Ph.D.[1], Masanori Baba, M.D.[2]
[1]*University of Ibadan, Ibadan, Nigeria;* [2]*Kagoshima University, Kagoshima, Japan*

Unavailability of the active antiretroviral therapy (ART) to the teeming population living with human immunodeficiency virus type 1 (HIV-1) infection in the Western and Central Africa means that they have to seek an alternative treatment option. Therefore, traditional herbal medicine seems to be a common option. This study was aimed at validating the efficacy of such a remedy, A-zam, against HIV-1 *in vitro*. A-zam was examined for its anti-HIV-1 activity and cytotoxicity in acutely and chronically infected cells. The anti-HIV-1 activity was determined by the inhibition of cytopathic effect in acutely infected MT-4 cells using the MTT method, while it was determined by the inhibition of p24 antigen production in chronically infected OM-10.1 cells using ELISA. The cytotoxicity of A-zam was also determined by the MTT method in the chronically infected cells. A-zam did not show anti-HIV-1 activity in acutely infected cells. The cells displayed definitive cytopathic effect and only 23.9% – 24.9% survived at 250-6250 fold dilutions of the drug. Interestingly, Alpha-zam selectively inhibited the p24 antigen production in OM-10.1 cell after stimulation with TNF-α The highest inhibition (84.6%) was achieved at the 100-fold dilution, suggesting that A-zam may have a potential anti-HIV-1 activity in chronically infected cells. The results of the present study appear connected with results in previous human study, where decrease of plasma viral load, increase of $CD4^+$ T-cell count and improved quality of life were observed in patients. These results suggest that A-zam may be a good candidate for alleviating immunosuppressive conditions like HIV-1/AIDS.

24. Targeting at Glu224 and Trp229 in the Non-nucleoside Binding Pocket of HIV-1 Reverse Transcriptase

Ge Meng, Ph.D.[1], Erik De Clercq, Ph.D.[2], Fener Chen, Ph.D.[1]
[1]*Fudan University, Shanghai, China;* [2]*Leuven University, Leuven, Belgium*

The nonnucleoside inhibitor binding pocket (NNIBP) of HIV-1 RT is a well-known binding pocket for drug design against HIV-1. Many data including the crystal structures of both the unliganded HIV-1 RT and the RT-inhibitor complexes were reported. A movie was produced out of the selected 30 crystal structures via comparing the NNIBP among 30 items of recently published open form HIV-1 RT crystal structure. All the selected HIV-1 RT crystal structures were aligned before each individual crystal picture was snapshot for making the movie. The first frame of the movie started with the closed form of HIV-1 RT apo-enzyme. The frame sequence in the movie was arranged according to the molecular weights of the ligands binding with the HIV-1 RT NNIBP. The movie indicated that the amino acid (AA) residue Glu224 is quite flexible comparing with other constant AAs, such as Trp229. Glu224 is quite close to the solvent exposing area of the NNIBP, while Trp229 is quite crucial to constitute the so-called important "primer grip". Designing further NNRTIs should consider both the constant skeleton and the varying flexible features in order to search for new potential HIV-1 RT inhibitors. The fragment similar to propyl amino group might be introduced into new NNRTIs to aim at Glu224 via forming a possible hydrogen bond. The heterocyclic aromatic ring system (such as indole, indazole, etc.) suitable for Trp229 should be kept in the skeleton of NNRTIs. These hints might provide some guidance for further designing new type of HIV-1 RT inhibitors.

25. Transcriptomic and Proteomic Profiles of Human Cells Following Exposure to a Host-targeted Antiviral

Lisa Evans DeWald, Ph.D.[1], Chloe Starr, B.S.[1], Andrea Harris, Ph.D.[1], Michael Lacy, Ph.D.[1], Anthony Treston, Ph.D.[1], Kelly Warfield, Ph.D.[1]
[1]*Emergent BioSolutions Inc, Gaithersburg, Maryland*

The development of host-targeted antivirals (HTAVs) is an attractive and innovative approach for broad-spectrum antiviral drug development. As viruses are obligate intracellular pathogens, they are critically dependent upon host factors for infection, replication, and spread. N-linked glycosylation is a necessary component for the replication of many viruses as it is required for the proper folding, trafficking, and/or receptor binding of some viral proteins. Certain iminosugars are known to interfere with the N-linked glycosylation pathway by targeting and inhibiting α-glucosidases I and II in the endoplasmic reticulum (ER). Perturbing ER α-glucosidase function can prevent these enzymes from removing terminal glucose residues on N-linked glycans, interrupting the interaction with chaperone proteins and preventing proper folding of some viral glycoproteins. Iminosugars such as UV-4B have demonstrated broad-spectrum antiviral activity *in vitro* and *in vivo* against multiple viruses and are considered as promising HTAV α-glucosidase inhibitors. We generated α-glucosidase I and II knockout cell lines using Huh-7 cells and CRISPR/Cas9 technology and evaluated and compared the transcriptomic and proteomic profiles to cells treated with UV-4B. The number of differentially expressed proteins was greater in α-glucosidases I or II knockout cells (38 or 82 proteins, respectively) than cells treated with 200 μM UV-4B for 8 or 48 hours (12 or 5 proteins, respectively) when compared to the proteomic profile of parental Huh-7 control cells (≥ 2-fold change, $p < 0.05$). These data will provide further insight into the antiviral mechanism and possible off target effects of this class of HTAVs.

26. A Population Study of HBV Genome Diversity: Implications for Rational Drug Design

Guangdi Li, Ph.D.[1], Samad Amini-Bavil-Olyaee, Ph.D.[2], Marijn Thijssen, M.S.[3], Philippe Lemey, Ph.D.[3], Marc Van Ranst, Ph.D.[3], Mahmoud Reza Pourkarim, Ph.D.[3]
[1]*Department of Public Health, Central South University, Changsha, Hunan, China, Changsha, Hunan, China;* [2]*Cellular Sciences Department, Amgen Inc., One Amgen Center Drive, CA 91320, USA, Thousand Oaks, California, United States of America;* [3]*KU Leuven, Department of Microbiology and Immunology, 3000 Leuven, Belgium, Leuven, Leuven, Belgium*

The high level of HBV genome diversity determines genotype classification and induces drug resistance to current anti-HBV therapies. Nevertheless, a comprehensive analysis of HBV genome-wide diversity in large-scale patient population remains lacking. We retrieved 4593 full-genome sequences from our cohort and NCBI database. We used Los Alamos hypermut tool to determine hypermutated sequences. HBV genotypes were determined using NCBI subtyping tools. We retrieved drug binding positions of 6 FDA-approved HBV inhibitors and protein structures from literature and PDB databases. HBV nucleotide and amino acid compositions were comparable across 8 major genotypes. The genome-wide genetic diversity within HBV genotypes was the lowest (mean: 2.8%), while dramatic jumps were observed between genotypes (11.8%). At the protein level, similar diversity patterns of HBV polymerase (3.3%), PreS1 (2.7%), PreS2 (5.16%), S (2.1%), PreC (2.91%), Core (3.05%) and X (4.72%) were consistent across 8 genotypes. A complete conservation across subtypes was detected at 218 (8.6%) of 2550 protein positions, and the highest level of conservation was observed at the polymerase C terminus. In the full-length HBV genome, 3 of 11 known drug binding sites were fully conserved, whereas all FDA-approved inhibitors were confronted with natural occurring polymorphisms in their binding sites, some of them were genotype-specific polymorphisms. Moreover, 12 of 26 (46.2%) vaccine-targeted positions were fully conserved and several positions had high proportions of polymorphisms. This large-scale analysis of full-length HBV genome provided a detailed mapping of natural diversity across major genotypes, and highlighted the conserved regions for rational drug design.

27. Antiviral Activity Assessment of Polyoxometalates with a Focus on Zika Virus

Rachele Francese, M.S.[1], Andrea Civra, Ph.D.[1], Massimo Rittà, M.D., Ph.D.[1], Manuela Donalisio, Ph.D.[1], Monica Argenziano, Ph.D.[2], Roberta Cavalli, Ph.D.[2], Ali Mougharbel, M.S.[3], Ulrich Kortz, Ph.D.[3], David Lembo, Ph.D.[1]

[1]Dept. of Clinical and Biological Sciences; Lab. of Molecular Virology and Antiviral Research; University of Turin, Turin; [2]Dept. of Drug Science and Technology; University of Turin; [3]Department of Life Sciences and Chemistry, Jacobs University, Bremen, Germany

Polyoxometalates (POMs) are discrete polynuclear metal oxides with a large structural and compositional variety, and a multitude of associated physicochemical properties. In the search for new antiviral compounds, three solution-stable POMs (TeW_6, $TiW_{11}Co$ and Ti_2PW_{10}) were screened *in vitro* against eleven viruses, chosen as representative of different viral characteristics. Subsequently, in order to perform a preliminary study of the mechanism of action, we focused on zika virus (ZIKV), a virus still lacking of specific antivirals and vaccines and representing an emerging issue to the global health system.

The POMs' antiviral activity was determined by virus inhibition assays and virus inactivation assays. $TiW_{11}Co$ and Ti_2PW_{10} turned active against ZIKV, rhinovirus, respiratory syncytial virus, vesicular stomatitis virus, adenovirus, papillomavirus 16, herpes simplex virus 1 and 2, cytomegalovirus and vaccinia virus, but not against rotavirus. By contrast, TeW_6 showed antiviral activity only against ZIKV and herpes simplex viruses. None of them displayed virucidal activity. All the three POMs inhibit ZIKV infection with EC_{50}s in the low micromolar range and Ti_2PW_{10} exhibited the greatest selectivity index. We demonstrated that Ti_2PW_{10} targets the entry process of ZIKV infection and it is able to reduce ZIKV progeny production. In conclusion, we identified three POMs, never tested before as antivirals, with a broad spectrum antiviral activity and, for the first time, a POM endowed with a strong antiviral activity against ZIKV and able to inhibit the entry process of ZIKV infection. This polyanion could represent a starting point to develop an effective therapeutic to treat ZIKV infection.

28. Discovery of Phenylalanine Derivatives as Potent HIV-1 Capsid Inhibitors from Click Chemistry-based Compound Library

Gaochan Wu, M.S.[1]

[1]School of Pharmaceutical Sciences, Shandong University

The HIV-1 capsid (CA) protein plays essential roles in both early and late stages of HIV-1 replication and is considered an important, clinically unexploited therapeutic target. Taking the reported HIV CA inhibitor PF-74 as lead compound, we designed and expeditiously synthesized a series of 1,2,3-containing phenylalanine derivatives *via* CuAAC reaction. Among them, 13m exhibited the best anti-HIV-1 activity (EC_{50} = 4.33 μM, SI > 13.33), being similar to the lead PF-74 (EC_{50} = 5.95 μM, SI > 11.85). Further SPR results demonstrated that this series of phenylalanine derivatives targeted to CA protein. Through molecular dynamics simulation, we can conclude that 13m has two different binding modes to HIV-1 CA monomer, which increases the possibility of inhibiting CA protein. The subsequent experiment to determine the action stage suggested that 13m inhibited the replication of HIV-1 in both the early and late stages. We envisioned that the the conformationally dynamic CTD-NTD interface still have ample space for further modification to form potential interaction with nearby hotpot residues. Ongoing study in our lab will be reported in due course.

29. Viral RNA-dependent RNA Polymerase Inhibitor 7-Deaza-2´-C-methyladenosine Prevents Death in a Mouse Model of West Nile Virus Infection

Ludek Eyer, Ph.D.[1], Martina Fojtikova, M.S.[1], Radim Nencka, Ph.D.[2], Ivo Rudolf, Ph.D.[3], Zdenek Hubalek, Ph.D.[3], Daniel Ruzek, Ph.D.[1]

[1]Department of Virology, Veterinary Research Institute, Brno, Czechia; [2]Institute of Organic Chemistry and Biochemistry, The Czech Academy of Sciences, Prague, Czechia; [3]Institute of Vertebrate Biology, The Czech Academy of Sciences, Brno, Czechia

West Nile virus (WNV) is a medically important emerging arbovirus causing serious neuroinfections in humans. No approved antiviral therapy is currently available against WNV infection. In this study, we have evaluated the antiviral activity and cytotoxicity of 2´-C-methyl-, 2´-O-methyl-, 3´-O-methyl-, 3´-deoxy-, and 4´-azido-modified nucleosides *in vitro*. Our results demonstrate that 2´-C-methyl- or 4´-azido-modified nucleosides are highly effective inhibitors of WNV replication, showing nanomolar or low micromolar anti-WNV activity and negligible cytotoxicity in cell culture. 7-Deaza-2´-C-methyladenosine, a representative of C2´-methylated nucleosides, significantly protected WNV-infected mice from disease progression and mortality. Treatment at 25 mg/kg (twice daily) starting at the time of infection (day 0) resulted in 100% survival of the mice. This compound was highly effective, even if the treatment was initiated 3 days post-infection, at the time of a peak of viremia, which resulted in a 90% survival rate. However, the antiviral effect of 7-deaza-2´-C-methyladenosine was absent or negligible when the treatment was started 8 days post-infection (i.e., at the time of extensive brain infection). The 4´-azido moiety appears to be another important determinant for highly efficient inhibition of WNV replication *in vitro*. However, the strong anti-WNV effect of 4´-azidocytidine and 4´-azido-aracytidine was cell type-dependent and observed predominantly in PS cells and was much less pronounced in Vero cells. Our results indicate that 2´-C-methylated or 4´-azidated nucleosides merit further investigation as potential therapeutic agents for treating WNV infections, as well as infections caused by other medically important flaviviruses.

30. Identification of RUVBL1 and RUVBL2 as Novel Cellular Interactors of Ebola Virus Nucleoprotein

M. Jane Morwitzer, B.S.[1], Sina Bavari, Ph.D.[2], St Patrick Reid, Ph.D.[1]

[1]Department of Pathology & Microbiology, University of Nebraska Medical Center, Omaha, Nebraska, United States of America; [2]United States Army Medical Research Institute of Infectious Diseases, Frederick, MD, Maryland, United States of America

Ebola virus (EBOV) is a highly virulent filovirus that has become a global public health threat in recent years. There remains no licensed therapeutics available to prevent or treat infection, thus development of effective therapeutic strategies that target EBOV is urgently needed. Productive viral infection relies on successful recruitment of host factors. To date, several investigations have identified specific host-pathogen interactions for various EBOV proteins, however, relatively little is known about the nucleoprotein (NP). In the present study, we aimed to identify novel EBOV targets by elucidating NP-host protein-protein interactions (PPIs). Mass spectrometry (MS)-based proteomics was used to identify candidate NP cellular interactors. Candidate interactors RUVBL1 and RUVBL2 belonging to the AAA+ (ATPases Associated with various cellular Activities) family were confirmed to interact with NP in co-immunoprecipitation (Co-IP) and immunofluorescence assays (IFA). RUVBL1/2 are key members of the R2TP complex, a specialized HSP90 co-chaperone associated with the assembly and maturation of multi-subunit complexes. NP was also found to associate with additional members of the R2TP complex by super-resolution microscopy, strongly suggesting EBOV NP recruits this complex for function during infection. HSP90 inhibitors are already known to inhibit EBOV, thus impairment of NP may be the mechanism of action. Small molecule inhibitors targeting the ATPase domain of RUVB1/2 or the phosphopeptide domain of PIH1D1 could be developed to inhibit the complex and in turn NP function. Future studies will address the precise role of the R2TP complex during EBOV infection.

31. HBc Nuclear Interactome Reveals Multiple Roles of RNA-binding Proteins in Viral Replication and Provides Insights for the Development of Novel Host-Targeting Agents

Hélène Chabrolles, Ph.D.[1], Héloise Auclair, Ph.D.[1], Thomas Lahlali, Ph.D.[1], Serena Vegna, Ph.D.[1], Yohann Couté, Ph.D.[2], Lucid Belmudes, Ph.D.[2], Christophe Combet, Ph.D.[1], Fabien Zoulim, M.D., Ph.D.[1], David Grierson, Ph.D.[3], Benoit Chabot, Ph.D.[4], Julie Lucifora, Ph.D.[1], **David Durantel, Ph.D.**[1], Anna Salvetti, Ph.D.[1]

[1]CRCL – INSERM U1052, Lyon, France; [2]INSERM U1038 – CEA Grenoble, Grenoble, France; [3]University of British Columbia, Vancouver, Canada; [4]Sherbrooke University, Sherbrooke, Canada;

Converging evidences suggest that the Hepatitis B virus core protein (HBc), beside its well-known structural role to form nucleocapsids in the cytoplasm, could have important regulatory functions in the nucleus of infected hepatocytes, including the control of viral and/or cellular gene expression. To elucidate these functions, we performed a proteomic analysis of the cellular factors interacting with nuclear HBc in human hepatocytes. This interactome revealed a majority of highly interconnected RNA-binding proteins (RBPs), which participate in several steps of mRNA metabolism, including transcription, splicing and nuclear egress. We focused on two major HBc-interacting factors, SRSF10 and RBMX that were previously involved in cell differentiation and DNA repair. Functional analyses performed by a siRNA approach indicated that RBMX and SRSF10 were able to differentially regulate the levels all viral RNAs most likely by acting at different steps of the viral life-cycle. Similarly, a small compound, affecting the phosphorylation of selected RBPs and repurposed from HIV research, significantly impaired HBV replication by strongly reducing viral RNA accumulation in a pangenomic manner. Very interestingly this compound enabled in combination with IFNa a long-lasting control of HBV replication *in vitro*. Altogether, these results strongly suggest that HBc interacts with some selected RBPs to control the fate of viral and/or cellular RNAs and provide new critical information for the development of novel host-targeting antiviral agents (HTA).

32. Antibody Coated Liposomes for Transmucosal Vaccination

Saurabh Bhargava, M.D., MPH[1], Vishal Bhargava, Ph.D.[2]

[1]United Institute of Pharmacy, Allahabad, India; [2]GTB Hospital, Kanpur, India

The critical role of vaccine delivery system in "rational vaccine design" has been widely recognized. Thus research work was envisaged involving development of antibody coated liposome for transmucosal immunization against hepatitis-B which may offer increased uptake of nanoliposome through transmucosal surface of nasal route and sustaining release of HBsAg to evoke relatively high IgA titre in mucosal surface.

Liposomes were prepared by a lipid cast film method & then IgG antibody was cross linked on the surface. Coated liposomes were characterized *in-vitro* for their shape, size, percent antigen entrapment and stability. Fluorescence microscopy was performed to confirm the deposition pattern in respiratory tract. The *in-vivo* part of the study comprised of estimation of IgG response in serum and sIgA in various body secretions using specific ELISA.

Observation of fluorescence images of nasal mucosa, lungs and spleen, revealed that these antibody coated liposome, were significantly taken up by mice respiratory mucosal surface, which made them promising carriers for mucosal vaccination.

Considerable immune responses were produced by the developed system that may be due to the induction of MALT as well as contribution of the peripheral airways. The higher immunity induced by ACL HBsAg may be attributed to its cationic nature, antibody coating and subsequent mucoadhesive property. Thus mucosal immunization with lipid vesicle through nasal administration may be effective in prophylaxis of diseases transmitted through mucosal routes as well as systemic infections. The strategy can be made more appropriate by determination of paracellular transport, nasal mucociliary clearance, mucosal toxicity assessment etc.

33. Evaluation of the Concentration-Dependent Emergence of Antiviral Resistance in Venezuelan Equine Encephalitis Virus to ML336 using Next Generation Sequencing

Jasper Lee, B.S.[1], Jennifer Golden, Ph.D.[2], Colleen Jonsson, Ph.D.[1]
[1]University of Tennessee Health Science Center, Memphis, Tennessee, United States of America; [2]University of Wisconsin-Madison, Madison, Wisconsin, United States of America

Venezuelan equine encephalitis virus (VEEV) is a New World Alphavirus that causes neurological disease and death in humans and equines following transmission from infected mosquitoes. Despite the high infectivity of VEEV and its potential use as a bioterrorism agent, there are no FDA-approved antivirals to treat a VEEV infection. We have reported the discovery of a small molecule, ML336, with antiviral activity at a nanomolar concentration against VEEV. Antiviral resistance of earlier stage hit (905) mapped to mutations in the nsP2 and nsP4 genes. To further explore the resistance profiles of ML336 and newer derivatives, we have developed a method to evaluate resistance to small molecules in VEEV using next-generation sequencing technology. To examine concentration dependent-resistance, we passaged VEEV strain TC-83 through cell culture at doubled concentrations of ML336, starting at the EC_{50} concentration. We have optimized a tiling approach to amplify the whole viral genomes using a set of 25 primer pairs for library preparation and sequencing on the Illumina MiSeq platform. Sequencing reads were mapped to a reference genome and analyzed for variants. Using this method, we discovered several mutations in the nsP3 and nsP4 genes that emerged as well as some that reverted to wildtype in the population at increased concentration. Thus, we show that mutations causing resistance to small molecules can be detected and evaluated on a population-based level. From here, understanding the dynamics of resistance of new derivatives will help determine optimal drug candidates and optimal dosing regimens for minimizing the emergence of resistant viruses.

34. HTS and Bioassay-guided Fractionation Identified Hopanetriol Analogs from *Aschersonia* Extract with Anti-flavivirus Activity

Julia Ma, B.S.[1], Fang Guo, M.D., Ph.D.[1], Xuexiang Zhang, M.S.[2], Lin Zhang, M.S.[1], Zhao Gao, Ph.D.[1], Michael Goetz, Ph.D.[3], Anne Dombrowski, Ph.D.[1], Timothy Block, Ph.D.[1], Ju-Tao Guo, M.D.[1], Sung Ryeol Park, Ph.D.[1], Matthew Todd, Ph.D.[1], Jason Clement, Ph.D.[1], Jinhong Chang, M.D., Ph.D.[1]
[1]Baruch S. Blumberg Institute; [2]Fang Guo <guofang1972@gmail.com>; [3]Baruch S. Blumberg.org

A pilot screen of a diverse set of 2,000 natural product extracts (800 partitioned plant extracts, 640 prokaryotic extract and 560 fungal extracts) was performed using a dengue virus infection of HEK293 cell line-based IFN-β promoter reporter assay (Guo, F., et al. 2014, Antiviral Research). Six crude extracts were identified with selective antiviral activity by using MTT and virus yield reduction assays. Using bioassay-guided fractionation, from one of the hits, a fermentation extract from a fungus of genus *Aschersonia*, three structurally related hopane triterpenoids 1-3 were purified and identified as antiviral components. The compounds were identified based on HRMS and NMR methods. These hopanetriol analogs are active against members of flaviviruses (dengue, yellow fever and zika virus), but inactive against remotely related viruses such as arenavirus (tacaribe virus) and picornavirus (encephalomyocarditis virus). Furthermore, using time-of-addition study and dengue virus sub-genomic replicon assay, it was suggested that the hopanetriols are most likely targeting the intracellular replication step of the flaviviruses. Although various hopanetriol analogs have been isolated from fungus previously, this study represents the first report of their antiviral activities. The detailed mechanism-of-action and methods of scale up production are currently under investigation.

35. Studies Towards Pan-Flaviviral Protease Inhibitors

Crystall Swarbrick, Ph.D.[1], Gerasimos Rassias, Ph.D.[2], Vasiliki Zogali, M.S.[2], Kitti Chan, M.S.[1], Subhash Vasudevan, Ph.D.[1]

[1]Program in Emerging Infectious Diseases, Duke-NUS Medical School, Singapore; [2]Department of Chemistry, University of Patras, Greece

The Flaviviridae family includes high profile viruses dengue and zika for which there are currently no antiviral treatments available. The flaviviral RNA genome is directly translated into a single polyprotein which is cleaved by viral and host proteases. Our research here focuses on a rational structure-chemistry approach to develop non-peptidic small molecules that can specifically inhibit these proteases. Starting with an inhibitor identified in a West Nile Virus *in silico*drug discovery campaign we undertook a scaffold hopping exercise to discover new lead compounds. Following a structure-activity-relationship study of the new series, compound 17 was found to inhibit DENV2 and ZIKV protease at IC50 values of 1.16 and 0.52 μM respectively which are amongst the lowest reported values in the literature so far. In a second iteration of this work we decided to test the inhibitory activity of "prodrugs" of the active compounds to examine their toxicity and potencies *in cellulo*. This led to the discovery of a "pro-drug" derivative of compound 17 that was efficacious and potent *in cellulo*achieving low micromolar EC_{50} against DENV2, thus promising a well-tolerated series of compounds targeting the flaviviral protease. The *in cellulo*mechanism-of-action of the lead compound was investigated using a time-of-addition assay which suggested that the compound interfered with the early stages of replication and specifically inhibited intramolecular cleavages in NS3 that have recently been shown to have a trans-dominant inhibitory effect on DENV replication. The implications of our data will be discussed.

36. Development of a Complete Set of Antibodies for Yellow Fever Virus and Their Application in Antiviral Drug and Vaccine Development

Zhao Gao, Ph.D.[1], Lin Zhang, M.S.[1], Julia Ma, B.S.[1], Alexander Ball, Ph.D.[2], Ju-Tao Guo, M.D.[1], Jinhong Chang, M.D., Ph.D.[1]

[1]Baruch S. Blumberg Institute; [2]GeneTex, Inc.

Despite the availability of a highly effective yellow fever virus (YFV) vaccine, outbreaks of yellow fever occur frequently. A recent YFV reemergence in Africa and South America has resulted in a vaccine shortage, highlighting the persistent medical need for the development of antiviral agents and additional vaccine resources to manage and prevent future outbreaks. Basic research on YFV has lagged with the assumption that vaccination would prevent and eliminate the disease. Accordingly, relatively few commercially available antibodies (mainly against the envelope protein) are available. We developed a nearly complete set of rabbit polyclonal antibodies against the three YFV structural proteins (i.e., capsid, prM and envelope) and five of the non-structural proteins (i.e., NS1, NS2B, NS3, NS4B and NS5) using synthetic or recombinant peptides. The sensitivity and specificity of these antibodies were determined using YFV-infected cells and cell lysates for western blot and immunofluorescence assays. We performed co-localization studies of YFV proteins with double-stranded RNA and host factors in YFV-infected cells, which provided a powerful approach to examine YFV replication as well as the mechanism-of-action of BDAA, a YFV NS4B inhibitor in preclinical development. Furthermore, two quantitative assays, an in-cell western assay and a high-content image-based fluorescence assay, were developed using the NS4B antibody. The ability of these two antibody-based assays to quantify the effect of antiviral compound on YFV was confirmed through comparison with a classical nucleic acid-based assay (qRT-PCR) and a labor-intensive virus yield assay. We are currently optimizing these NS4B antibody-based assays for adaptation into high-throughput screening systems.

37. Hepatotoxicity and Nephrotoxicity in *Plasmodium berghei*-Infected Mice Treated with Lopinavir/Ritonavir plus Amodiaquine or Artesunate – A Consequence of Drug/Drug Interactions

Tolulope Oke, M.S.[1], Oyindamola Abiodun, Ph.D.[1]
[1]*Department of Pharmacology and Therapeutics, College of Medicine, University of Ibadan, Ibadan, Nigeria., Ibadan, Oyo, Nigeria*

HIV-infected people on antiretroviral drugs in malaria endemic countries will inevitably take antimalarial drugs when infected with malaria. Our previous studies have shown that the interactions between the two drugs enhanced antimalarial activity, but information on the safety is limited. Thus, this study evaluated the effect of lopinavir/ritonavir (80/20mg/kg, LR) an antiretroviral drug on the safety of amodiaquine (10mg/kg, AQ), or artesunate (4mg/kg AS) in mice infected with chloroquine resistant *P. berghei* in a 4-day suppressive test. Drugs were given once daily for three days. Treatment with LR and AQ or AS enhanced the antimalarial activity of AQ and AS. However, treatment with these combinations resulted in pronounced hepatotoxicity and nephrotoxicity as revealed by elevated level of serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, creatinine and bilirubin in experimental mice. Histological evaluation of the hepatic tissues of mice treated with antimalarial alone showed mild liver injury. In contrast, severe portal, central venous congestion, periportal cellular infiltration and diffuse vacuolation of hepatocytes were reported in hepatic tissues of animals treated with the antimalarial drugs plus LR. In addition, there was a moderate to severe renal cortical congestion, diffuse tubular and glomerular degeneration, necrosis and haemorrhagic foci in the parenchyma of the kidney in mice treated with antimalarial drugs plus LR. It appears that co-administration of lopinavir/ritonavir with amodiaquine or artesunate is associated with pronounced toxicity. This study provides important information in the management of HIV infected patient on antiretroviral drugs that need to be treated with antimalarial drugs.

38. A Cell-based Luminescence Assay for High-throughput Screening of Potential Mayaro Virus Antivirals

Aline Tolardo, M.S.[1], Jyothi Parvathareddy, B.S.[2], Jo Davisson, Ph.D.[3], Aaron Lindstrom, Ph.D.[3], Gene Ananiev, Ph.D.[4], Colleen Jonsson, Ph.D.[2], Luiz Tadeu Figueiredo, M.D., Ph.D.[1]
[1]*Ribeirão Preto Medical School, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil;* [2]*Department of Microbiology, Immunology, and Biochemistry, University of Tennessee Health Science Center, Memphis, Memphis, Tennessee, United States of America;* [3]*Purdue University, West Lafayette, Indiana, United States of America;* [4]*Small Molecule Screening & Synthesis Facility (SMSF),University of Wisconsin (Madison), Madison, Wisconsin, United States of America*

Alphavirus are important arboviruses that cause public health issues in Brazil, generating epidemics with great economic and social impact and major economic losses. As there is no specific antiviral treatment for these viruses, therapeutic drugs are used to combat the symptoms and signs manifested by the disease in mild and moderate cases. We have developed a cell-based luminescence assay for screening of potential Mayaro virus that measures the cytopathic effect (CPE) induced by the virus (BeAr505411) infection in Vero cells (ATCC CCL81) using the luminescent-based CellTiter Glo system. The assay is validated in 384-well plates in a 72h format with Z values > 0.7, signal-to-background > 30 and signal-to-noise > 10. Two compounds library were tested (631 and 22 compounds respectively) at 10 uM concentration, six compounds inhibited viral-induced CPE by >50%, with EC50/CC50 values comparable to those determined by other cell-based assays, thereby validating this assay accuracy and ability to simultaneously evaluate compound cellular availability and/or toxicity.

39. Airway Proteases as Antiviral Drug Target for Influenza Virus and Possibly Other Respiratory Viruses

Manon Laporte, M.S.[1], Mohammed Benkheil, Ph.D.[1], Annelies Stevaert, Ph.D.[1], Lieve Naesens, Ph.D.[1]
[1]Rega Institute for Medical Research, KU Leuven, Leuven, Belgium

Several respiratory viruses, including influenza, corona- and parainfluenza virus, rely on host cell proteases for activation of the viral protein involved in membrane fusion. Airway protease inhibitors could represent a unique class of host cell-targeting drugs with broad antiviral activity.

In the case of human influenza A and B viruses, the surface protein hemagglutinin (HA) requires proteolytic activation by a trypsin-like protease. During the past years, several type II transmembrane serine proteases (TTSPs) and kallikreins (KLKs) were associated with cleavage activation of the HA0 precursor protein (reviewed in Laporte and Naesens, Curr Op Virol 2017).

In this study, we compared all members of the TTSP (18 TTSPs) and KLK (16 KLKs) families for their HA0 cleavage activities towards the circulating human influenza (sub)types [A/H1N1 (from 2009 and 1918); A/H3N2; B/Yamagata; and B/Victoria], plus the potentially pandemic avian A/H7N9 virus. First, we analyzed the cleavage pattern and fusion activation of HA0 after overexpression of the 18 TTSP and 16 KLKs in HEK293T or HeLa cells. Secondly, we used siRNA knockdown to determine which proteases are essential for influenza virus replication in human airway epithelial Calu-3 cells. Third, expression of these proteases in human lung tissue and several human airway epithelial cell lines was determined by RT-qPCR.

Our comprehensive analysis is the first study in which all TTSP and KLK family members are directly compared for their activating role in human influenza A and B viruses. This will enable to rationally design airway protease inhibitors for influenza and potentially other respiratory viruses.

40. Micropatterned Viral Membrane Clusters for Antiviral Drug Evaluation

Soohyun Park, B.S.[1], Joshua Jackman, Ph.D.[2], Xiaobin Xu, Ph.D.[3], Paul Weiss, Ph.D.[4], Nam-Joon Cho, Ph.D.[1]
[1]School of Materials Science and Engineering, Nanyang Technological University, Singapore, Singapore, Singapore; [2]School of Chemical Engineering, SungKyunKwan University (SKKU), Suwon, Korea (Republic of); [3]School of Materials Science and Engineering, Tongji University; [4]California NanoSystems Institute, University of California, Los Angeles

The function of biological nanoparticles, such as membrane-enveloped viral particles, is often enhanced when the particles form higher-order supramolecular assemblies. While there is intense interest in developing biomimetic platforms that recapitulate these collective properties, existing platforms are limited to mimicking individual virus particles. Here, we present a micropatterning strategy to print linker molecules selectively onto bioinert surfaces, thereby enabling controlled tethering of biomimetic viral particle clusters across defined geometric patterns. By controlling the linker concentration, it is possible to tune the densities of tethered particles within clusters while enhancing the signal intensity of encapsulated fluorescent markers. Time-resolved tracking of pore formation and membrane lysis revealed that an antiviral peptide can disturb clusters of the membrane-enclosed particles akin to the targeting of individual viral particles.

41. Benzoannulenes Derivatives as Antiviral Agents with the Focus on Alphaviruses and Flaviviruses

Syed Ahmed, Ph.D.[1], Nicole Haese, Ph.D.[2], Vibha Pathak, M.S.[1], Jaden Cowan, B.S.[1], Nicholas May, Ph.D.[3], Corinne Augelli-Szafran, Ph.D.[1], Mark Suto, Ph.D.[1], Victor DeFilippis, Ph.D.[2], Thomas Morrison, Ph.D.[3], Mark Heise, Ph.D.[4], Daniel Streblow, Ph.D.[2], Ashish Pathak, Ph.D.[1]

[1]Southern Research, Birmingham, Alabama, United States of America; [2]Vaccine and Gene Therapy Institute, Oregon Health & Science University, Beaverton, Oregon, United States of America; [3]University of Colorado School of Medicine, Aurora, Colorado, United States of America; [4]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America

Arthropod-borne viruses have developed a complex life cycle that alternates between insect and vertebrate hosts. These arthropod-borne viruses mainly belong to the virus families called Togaviridae, Flaviviridae, and Bunyaviridae. Alphavirus is a genus within the Togaviridae family, which includes Chikungunya Virus (CHIKV) and Venezuelan Equine Encephalitis Virus (VEEV). Flavivirus is a genus of viruses within the Flaviviridae family, which includes the West Nile Virus (WNV) and Dengue Virus (DENV). Currently, there are no approved treatments for any of these viruses indicating a substantial need for the development of antiviral agents capable of targeting these viruses. In our continuous medicinal chemistry efforts, we have identified a novel seven-membered benzoannulene amide, SRI-34963 that shows antiviral activity in the low micromolar range (EC_{90} = 0.4 μM) against CHIKV using Telomerized Human Fibroblast (THF) cells and shows a viral titer reduction (VTR) of 3.9 log units at 10 μM with no observed cytotoxicity (CC_{50} > 40 μM). However, *in vitro* ADME properties of this compound were not optimal, thus requiring further medicinal chemistry efforts. Subsequently, we have identified a novel compound, SRI-39689, that exhibits a three-fold improvement *in vitro* microsomal stability while retaining antiviral potency. This compound was also found to possess submicromolar antiviral activity against WNV, DENV and VEEV. This structure-activity relationship study and biological results, including the *in vivo* data of SRI-39689 in a murine model against CHIKV, will be discussed.

42. Discovery of Broad-spectrum Influenza Antivirals with a High *In Vitro* Genetic Barrier to Drug Resistance by Targeting the Influenza Polymerase PA-PB1 Subunit Interactions

Jiantao Zhang, Ph.D.[1], Yanmei Hu, M.S.[1], **Jun Wang, Ph.D.**[1]

[1]University of Arizona

Influenza virus is a persistent human respiratory pathogen that leads to seasonal influenza epidemics and occasional influenza pandemics. The clinical efficacy of current influenza antivirals is compromised by emerging drug-resistant mutants. To develop next-generation of antiviral drugs with a high genetic barrier to drug resistance, we chose the viral polymerase PA-PB1 protein-protein interactions as the drug target. As the viral polymerase is highly conserved among both drug-sensitive and -resistant influenza A and B viruses, we expect PA-PB1 inhibitors will have broad-spectrum antiviral activity and a high genetic barrier to drug resistance. To test this hypothesis, we established two strategies to identify PA-PB1 inhibitors: one is *in silico* docking, and another is high-throughput screening. Specifically, using the X-ray crystal structure of PA, we performed *in silico* docking to search for compounds that can bind to the PB1-binding site in PA.In parallel, we developed split-luciferase based high-throughput screening assays for detecting PA-PB1 protein-protein interactions. Both strategies yielded PA-PB1 inhibitors with confirmed mechanism of action by disrupting PA-PB1 interactions. More importantly, they have shown broad-spectrum antiviral activity against a panel of human clinical isolates of influenza A and B viruses. Serial passage experiments failed to select drug-resistant mutants. Overall, targeting PA-PB1 interactions appear to be a valid approach to develop the next-generation of novel influenza antivirals.

43. Quinolinone Compounds Potently Inhibit Venezuelan Equine Encephalitis Virus Replication

Nicole Haese, Ph.D.[1], Nicholas May, B.S.[2], Sharon Taft-Benz, Ph.D.[3], Shuklendu Karyakrate, Ph.D.[4], Omar Moukha-Chafiq, Ph.D.[4], Lynn Rasmussen, M.S.[4], Robert Bostwick, Ph.D.[4], Corinne Augelli-Szafran, Ph.D.[4], Mark Suto, Ph.D.[4], Nathaniel Moorman, Ph.D.[3], Victor DeFilippis, Ph.D.[1], Mark Heise, Ph.D.[3], Ashish Pathak, Ph.D.[4], Daniel Streblow, Ph.D.[1], Thomas Morrison, Ph.D.[2]

[1]Vaccine and Gene Therapy Institute, Oregon Health & Science University; [2]University of Colorado School of Medicine; [3]University of North Carolina School of Medicine; [4]Southern Research

Venezuelan equine encephalitis virus (VEEV), is a re-emerging alphavirus that can cause encephalitis resulting in severe human morbidity and mortality. Despite its high morbidity rate there are no virus-specific treatments available. To close this gap, we completed a high-throughput screen with large drug libraries to identify compounds that block alphavirus replication. We identified a quinolinone compound capable of inhibiting VEEV replication at micromolar concentrations. We performed studies to understand the antiviral breadth and mechanism of action for this compound family. The most potent analog SRI-34329, (IC_{90}= 0.12 mM), was active against vaccine and virulent strains of VEEV, with reduced activity against other alphaviruses. Time of addition studies revealed that SRI-34329 needs to be administered within 12hrs of virus inoculation to potently inhibit VEEV replication. Consistent with these results, RNA profiling experiments showed a decrease in viral RNA synthesis by SRI-34329 treatment, indicating an early block in viral replication. Sequencing of resistant mutants generated against SRI-34329 identified mutations in the nonstructural protein 2 (nsP2). Reverse genetic reintroduction of a single amino acid change in nsP2 into wildtype VEEV conferred the resistance phenotype against SR-34329. This novel group of anti-VEEV compounds offers a new potential treatment option for VEEV infections.

44. Development of Well-characterized Animal Models of Zaire Ebolavirus Infection for Licensure by Animal Rule

Malen Link, Ph.D.[1], Chia-Wei Tsai, Ph.D.[1]

[1]U.S. Department of Health and Human Services, Office of Assistant Secretary for Preparedness and Response, BARDA, Washington, District of Columbia, United States of America

The mission of the Biomedical Advanced Research and Development Authority (BARDA) is to develop and make available medical countermeasures for public health emergencies that arise from naturally emerging or intentional biological chemical radiological and nuclear threats, as well as influenza and emerging infectious diseases. Zaire ebolavirus (ZEBOV) infections cause viral hemorrhagic fever (VHF) with case fatality rates of up to 90% in humans, with death often occurring within 7 to 10 days post-infection. In 2006, the Secretary of Homeland Security determined that the Ebola virus presents a material threat against the United States population sufficient to affect national security. As such, BARDA is currently funding multiple efforts to develop novel vaccines and therapeutics for Ebola virus. However, the sporadic nature of ZEBOV outbreaks, the high mortality associated with infection, and the inability to ethically perform challenge studies in humans means the evaluation of any ZEBOV countermeasures in the absence of another large outbreak will necessitate the use of the U.S. Food and Drug Administration's (FDA) "Animal Rule". Licensure by the Animal Rule will require a well characterized animal model of infection which is able to predict the response to the countermeasure in humans. To date, non-human primate models of ZEBOV infection have not been rigorously defined through natural history studies. This talk will describe BARDA's needs and plans for animal model development for ZEBOV infections, as well as Sudan ebolavirus and Marburg virus, to support licensure of novel countermeasures by the FDA Animal Rule.

45. A Dengue Fluorescent Reporter Virus Combined with an Automated Robotic System for High Content Image-Based Antivirals Screening

Li-Hsin Li, M.S.[1], Suzanne Kaptein, Ph.D.[1], Johan Neyts, Ph.D.[1], Pieter Leyssen, Ph.D.[1], Kai Dallmeier, Ph.D.[1]
[1]*Rega Institute for Medical Research, KU Leuven, Leuven, Belgium*

Dengue virus (DENV) is an important mosquito-borne flavivirus threatening almost half of the world's population. Prophylaxis and potent anti-DENV drugs are urgently needed. Here, we developed a high content imaging-based (HCI) assay with DENV type 2 expressing the fluorescent protein mCherry (DENV2-mCherry) to improve the efficiency and robustness of the drug discovery process. For the construction of the reporter virus, the mCherry gene followed by the ribosome-skipping 2A sequence of the *Thosea asigna* virus (T2A) was placed upstream of the full DENV2 open reading frame. The biological characteristics including mCherry expression, virus replication kinetics, and plaque phenotype was examined and validated in BHK, Vero and C6/36 cells. A robust image-based antiviral assay combined with an automated robotic system was then developed, with Z' factor of 0.7 (n=3). For assay validation, the antiviral effect of a panel of reference compounds with different molecular mechanisms of anti-DENV activity was assessed: the (i) glycosylation inhibitor Celgosivir, the (ii) NS4b targeting compounds NITD618 and a novel class of highly potent dengue inhibitors that we recently published *(Bardiot et al., 2018)*, and (iii) two nucleoside viral polymerase inhibitors (2'CMC and 7'DMA). The inhibition profiles obtained, as quantified by means of HCI were compared to the reduction of viral RNA yield, as quantified by RT-qPCR. Both methods resulted in very comparable inhibition profiles. In conclusion, we developed a powerful and robust assay. A fully automated data generation and processing pipeline makes the new reporter virus assay amenable to high-throughput screening of large libraries of small molecules.

46. Studying Host Lipid Rafts in Early Phases of Influenza A Virus (IAV) Life Cycle for Identification of Hemagglutinin Interacting Host Raft Proteins

Dileep Verma, Ph.D.[1], Dinesh Gupta, Ph.D.[1], Sunil Lal, Ph.D.[2]
[1]*International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi, Delhi, New Delhi, India;*
[3]*School of Science, Monash University, Malaysia, Malaysia*

Binding of Influenza A Virus (IAV) to host cell followed by entry inside are rather complex events. IAV host binding requires multiple simultaneous interactions between viral hemagglutinin (HA) and its host receptor sialic acid (SIA). However, exact mechanism to form multiple HA-SIA interactions is poorly understood. Similarly, IAV enters the host cell via multiple endocytic routes making this process even more complicated[1]. Also, a cellular endocytic pathway regulated by lipid rafts termed 'raft-dependent endocytosis', has so far been poorly investigated for IAV host entry. In this study, we observed co-localization of IAV with host lipid raft (GM1) and its disruption significantly reduced IAV host binding. Interestingly, cyclodextrin mediated inhibition of raft-dependent endocytosis also showed significantly reduced IAV host internalization. In summary, our data collectively demonstrates that host lipid rafts are selected by IAV as host attachment factor for multivalent binding and IAV utilises these micro-domains to exploit raft-dependent endocytosis for host internalization, a virus entry route previously unknown for IAV. Since IAV hemagglutinin (HA) is known to regulate two crucial events in IAV life cycle, receptor binding followed by endocytosis and membrane fusion; we further attempted to identify possible raft protein/s interacting with IAV HA. During our preliminary investigation, we have identified few raft proteins as potential interactors of IAV HA. Currently, we are further validating their interactions and functional roles in IAV life cycle. Through this study, we aim to enhance the way we understand IAV host binding, entry via endocytosis and membrane fusion inside the host.

47. ProTide Activation Pathway: Trapping the Reactive Cyclic Phosphorus Intermediates

Eliska Prochazkova, Ph.D.[1], Rafael Navrátil, M.S.[2], Zlatko Janeba, Ph.D.[1], Jana Roithova, Ph.D.[3], **Ondřej Baszczyňski, Ph.D.**[4]

[1]Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Flemingovo nám. 2, Prague 6, 166 10,, Prague, Czechia; [2]Department of Organic Chemistry, Faculty of Science, Charles University, Hlavova 2030/8, Prague 2, 128 43,, Prague, Czechia; [3]Institute for Molecules and Materials, Radboud University Nijmegen, Heyendaalseweg 135, 6525 AJ Nijmegen, Nijmegen, Netherlands; [4]Department of Organic Chemistry, Faculty of Science, Charles University, Hlavova 2030/8, Prague 2, 128 43, Prague, Czechia

Prodrug concept is based on a modification of an original drug molecule by attaching a chemical group to mask the active drug, which helps the original drug to overcome various biological barriers. The masking groups are designed to be activated in the target cells either enzymatically or chemically.

ProTide strategy, consisting of a modified phosphate/phosphonate group with aminoacid ester and phenol, allows an efficient delivery and direct release of the nucleoside monophosphate (or its phoshonate analogue) into the target cells, bypassing the most problematic first phosphorylation step. ProTide approach is an important milestone in chemistry of nucleotide analogues, leading to a discovery of novel state-of-art antivirals such as tenofovir alafenamide (HIV), sofosbuvir (HCV) and GS-5734 (Ebola).

We designed two photoactive ProTide analogues to experimentally prove existence of the cyclic *species* within ProTide activation pathway. ^{31}P NMR spectroscopy coupled with *in situ* irradiation and mass spectroscopy (MS) were used to monitor the ProTides activation, which was triggered by either UV light or MS ionization in real time. Using ^{13}C NMR spectra and the signal splitting caused by spin-spin interaction between carbon and phosphorus nuclei ($J_{C\text{-}P}$), the structures of particular intermediates were determined. As the studied highly reactive intermediates could not be observed *via* NMR spectroscopy, we applied MS analysis coupled with UV/IR spectroscopy to characterize the proposed cyclic species. Our data represent the first confirmation of the long-time predicted mechanism of ProTide prodrugs activation.

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48. Simvastatin Suppresses Ebola Virus-mediated Inflammation in Human Monocyte-derived Macrophages

Punya Shrivastava-Ranjan, Ph.D.[1], Anita McElroy, M.D., Ph.D.[2], Jessica Harmon, M.S.[1], Stuart Nichol, Ph.D.[1], Christina Spiropoulou, Ph.D.[1]

[1]VSPB, DHCPP, NCEZID, CDC, Atlanta, GA-30329, Atlanta, Georgia, United States of America; [2]University of Pittsburgh, Pennsylvania and Centre for Disease Control and Prevention, Atlanta, Pittburgh, Pennsylvania, United States of America

Ebola virus (EBOV) infection frequently triggers a strong proinflammatory response, which has been associated with severe Ebola virus disease (EVD). Besides lowering cholesterol, statins exert anti-inflammatory and immunomodulatory effects, which may be used to reduce systemic inflammation. In this study, we evaluated whether statins influence the production of proinflammatory cytokines induced by EBOV infection in human monocyte-derived macrophages. Simvastatin significantly reduced levels of major proinflammatory cytokines reported to be elevated in EBOV-infected patients and associated with EVD severity. These findings suggest that statins have the potential to curb the inflammatory response associated with EBOV infection.

50. Characterizing the Therapeutic Potential of Nipah Virus Defective Interfering Particles

Stephen Welch, Ph.D.[1], Natasha Tilston, Ph.D.[2], Shannon Whitmer, Ph.D.[1], Jessica Spengler, D.V.M., Ph.D.[1], Markus Kainulainen, Ph.D.[1], Michael Lo, Ph.D.[1], Linda Rennick, Ph.D.[2], Stuart Nichol, Ph.D.[1], W Paul Duprex, Ph.D.[2], Christina Spiropoulou, Ph.D.[1]

[1]Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America; [2]Center for Vaccine Research, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States of America

The error-prone nature of RNA-dependent RNA-polymerases drives the diversity we observe in RNA viral populations. Arising within this diversity is a sub-set of defective viral genomes (DVGs) that retain replication competency, termed defective interfering (DI) genomes. These defects are caused by aberrant RdRp re-initiation onto the same RNA template (deletion DI species) or onto the newly synthesized nascent RNA strand (copyback DI species). DI genomes have previously been shown to alter the dynamics of a viral population by their ability to interfere with standard virus replication and/or by stimulating the innate immune response. Here, we present work carried out using Nipah virus (NiV), a highly-pathogenic BSL-4 paramyxovirus, investigating whether the interference capability of DI genomes can be utilized as a therapeutic. High-MOI passaging of both NiV clinical isolates and recombinant NiV in Vero-E6 cells generated an extensive DVG population, from which DIs were further identified using both PCR and NGS techniques. Assays were established to generate and purify both naturally occurring, and *in-silico* designed, DI genomes as fully encapsidated, infectious, virus-like particles (DIPs). We demonstrate that several of these NiV DIP candidates, representing both copyback and deletion DI species, were able to reduce NiV titers by up to 4 logs *in vitro*. Investigating the RNA sequence requirements for an effective DI, and dissecting the molecular mechanisms that contribute to DI generation and inhibition of viral replication, could potentially allow us to use them as vaccine adjuvants or broad-spectrum antivirals.

51. The Aryl Hydrocarbon Receptor Inhibition Blocks Dengue and Zika Flaviviruses Infection

María Florencia Torti, B.S.[1], Federico Giovannoni, Ph.D.[1], Elsa Damonte, Ph.D.[1], Francisco Quintana, Ph.D.[2], Cybele Garcia, Ph.D.[1]

[1]Lab. of Antiviral Strategies, Biochem. Dept.,FSc., University of Buenos Aires- IQUIBICEN- CONICET, Buenos Aires, , Buenos Aires, Argentina; [4]Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard MedicalSchool, USA, Boston, Massachusetts, United States of America

The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that has been classically associated with the clearance of xenobiotics. Recently, numerous studies have indicated that AHR is capable of modulating the immune system. Regarding to viral infections, it was shown that the stimulation of AHR not only reduces the survival of mice infected with influenza A virus, but also enhances the hepatitis C virus assembly and production *in vitro*. Dengue virus (DENV) belongs to the *Flaviviridae* family and has four serotypes (DENV-1,2,3,4) that are capable of causing illness in humans after the bite of infected mosquitoes of the genus *Aedes*. Nowadays, specific treatments do not exist, thus it is crucial the development of new antiviral strategies. Previous results from our group indicates that the blockade of AHR, inhibits the Zika Virus (ZIKV) replication *in vitro*. In the present study we evaluated the impact of the pharmacological modulation of AHR on the DENV infection *in vitro*. Agonists and antagonists of AHR were used to treat A549 cell cultures before the infection with DENV1-4. From the supernatants of the cultures, we determined the viral yields. We also performed, real-time RT-PCR and indirect immunofluorescence to quantify the viral genome and protein, respectively. The treatment with 20μM of the AHR antagonist CH223191 decreased the viral yield 95±4% and the protein expression in a 84,5±0,5%. The data obtained suggests the AHR signaling pathway is involved in the DENV and ZIKV replication *in vitro*, whereby it is a potential therapeutic target against flaviviruses.

52. Identification and Characterization of Inhibitors of Hepatitis E Virus Replication

Ila Nimgaonkar, B.S.[1], Qiang Ding, Ph.D.[1], Mohammad Shahrad, B.S.[1], Nicholas Archer, B.S.[1], Hahn Kim, Ph.D.[1], Alexander Ploss, Ph.D.[1]
[1]Princeton University, Princeton, New Jersey, United States of America

Hepatitis E virus (HEV) is a (+)-sense, single-stranded RNA virus of the *Hepeviridae* family. HEV causes 20 million infections annually and is responsible for 60,000 deaths worldwide. HEV can cause up to 30% mortality in pregnant women and severe liver disease immunocompromised individuals, and therefore is a greatly underestimated public health concern. Although a vaccine for HEV exists, it is only licensed in China, and there is currently no effective, non-teratogenic treatment. Emergence of resistance mutations against ribavirin, the only currently available direct-acting antiviral, exacerbates the situation.

HEV encodes three open reading frames (ORFs). ORF1 is the largest viral gene product, encoding the replicative machinery of the virus including an RNA-dependent RNA polymerase and arguably offers the most promising therapeutic targets. Thus, we screened a library of ~60,000 small molecules for inhibitory activity against proteins encoded by ORF1. Compound C was selected as a promising therapeutic candidate based on its potency and cytotoxicity profiles. Follow-up studies confirmed that Compound C shows dose-dependent inhibition against HEV replication, without compromising general protein translation. Structure-activity relationship studies point to specific functional groups within Compound C mediating its biological activity, and parallel approaches to elucidate Compound C's mechanism of action are in progress. We are concurrently in the process of assessing the efficacy of compound C in primary hepatocyte culture and humanized mice.

These studies may provide important mechanistic insights into this globally prevalent pathogen, and lead to the development of a desperately needed therapy to treat hepatitis E in humans and animals.

53. Nucleotide Prodrug Remdesivir (GS-5734) Protects African Green Monkeys from Lethal Nipah Virus Bangladesh Challenge

Michael Lo, Ph.D.[1], Friederike Feldmann, Ph.D.[2], Joy Gary, D.V.M.[1], Robert Jordan, Ph.D.[3], Roy Bannister, Ph.D.[3], Jacqueline Cronin, Ph.D.[4], Nishi Patel, M.S.[1], John Klena, Ph.D.[1], Stuart Nichol, Ph.D.[1], Tomas Cihlar, Ph.D.[3], Sherif Zaki, M.D., Ph.D.[1], Heinz Feldmann, M.D., Ph.D.[4], Christina Spiropoulou, Ph.D.[1], Emmie De wit, Ph.D.[4]
[1]Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America; [2]Rocky Mountain Veterinary Branch, National Institutes of Health, Hamilton, Montana, United States of America; [3]Gilead Sciences, Foster City, California, United States of America; [4]Laboratory of Virology, National Institutes of Health, Hamilton, Montana, United States of America

The World Health Organization has listed Nipah virus (NiV), a virus that causes severe and often lethal respiratory and neurological disease in humans, as an emerging pathogen likely to cause major epidemics or even pandemics. The recent NiV outbreak in Kerala, India with 23 cases and 21 deaths again stressed the urgent need to develop prophylactic and therapeutic countermeasures against NiV. To date, very few antivirals have shown efficacy in animal models of NiV disease. Remdesivir (formerly GS-5734) is a nucleotide analog prodrug with broad-spectrum antiviral activity against filo-, corona-, and paramyxoviruses, including both Malaysian and Bangladesh (NiV-B) genotypes of NiV *in vitro*. Here, we tested the efficacy of remdesivir against NiV-B using the African green monkey model of NiV disease. Animals were inoculated with a lethal dose of NiV-B and a once-daily intravenous remdesivir treatment was initiated one day later and continued for 12 days. Mild respiratory signs were observed in 2 of 4 treated animals, whereas all control animals developed signs of severe respiratory disease. In contrast to control animals which all succumbed to the infection on day 7 or 8 after challenge, all remdesivir-treated animals survived the lethal challenge, indicating that the compound is a promising antiviral treatment for NiV infection.

54. Heme Oxygenase-1 Inhibits Influenza A Virus via the Induction of Interferon Response

Peng Zhang, Ph.D.[1], Linlin Ma, Ph.D.[1], Huiqiang Wang, Ph.D.[1], Haiyan Yan, Ph.D.[1], Sheng Tang, Ph.D.[1], Danqing Song, Ph.D.[1], Jiandong Jiang, Ph.D.[1], Yuhuan Li, Ph.D.[1]
[1]Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College

Heme oxygenase-1 (HO-1) is a cellular enzyme that can be induced by virus infections and suppresses the replication of many medically important viruses, such as HIV, HCV, HBV, EV71, IAV, RSV, DENV, ZIKV and EBOV. In our continuing efforts toward understanding the antiviral mechanism of HO-1 against influenza A virus, we found that HO-1 induced the interferon response might be responsible for its anti-IAV activity. We found that HO-1 directly interacted with IRF3 to promote its phosphorylation/nuclear translocation and subsequent activation of type I IFN expression. Previous study found that the expression of MAPK phosphatase 5 (MKP5) was significantly increased in response to IAV infection and MKP5 downregulates the expression of type I IFN through interacting with IRF3 to induce its dephosphorylation. We found that HO-1 could decrease MKP5 expression induced by IAV and relieve IRF3 from interaction with MKP5. However, there was no interaction between HO-1 and MKP5. In conclusion, our studies clearly demonstrate that HO-1 both directly interacted with IRF3 and liberated IRF3 from MKP5 inhibition to promote its phosphorylation and IRF3-type I IFN responses.

55. Inhibition of Human Norovirus Replication by a Novel Class of Indolylarylsulfones *In Vitro* and in Zebrafish Larvae

Jana Van Dycke, M.S.[1], Valentina Naccarato, M.S.[2], Giuseppe La Regina, Ph.D.[2], Eloise Mastrangelo, Ph.D.[3], Delia Tarantino, Ph.D.[3], Johan Neyts, Ph.D.[1], Romano Silvestri, Ph.D.[2], **Joana Rocha-Pereira, Ph.D.**[1]
[1]Rega Institute, KU Leuven, Leuven; [2]Sapienza University of Rome, Rome, Italy; [3]Università degli Studi di Milano, Milan, Italy

Human noroviruses are the leading cause of viral gastroenteritis outbreaks worldwide. Potent and safe antiviral therapy is urgently needed to reduce the burden of norovirus disease in vulnerable populations and as prophylaxis, i.e. to reduce transmission during an outbreak.

After screening ~1000 compounds from the Drug Design and Synthesis Center at Sapienza University against the GV mouse norovirus (MNV) in infected RAW 264.7 cells, the molecule 3-(3,5-dimethylphenyl)sulfonyl-5-chloroindole N-(pheylmethanol-4-yl)carboxamide (RS5105) had anti-norovirus activity (EC_{50} 0.53±0.07 mM). After structural modifications, RS5111 was the most potent derivative with EC_{50} values of 0.16 ± 0.06 mM against MNV and 1.2 ± 0.6 mM against the human norovirus (HuNoV) GI replicon. Time-of-drug-addition studies revealed that RS5111 acted at the onset of viral replication, like the nucleosides 2'-C-methylcytidine and favipiravir. Although RS5111 did not directly inhibit the activity of the MNV RNA-dependent RNA polymerase (RdRp), it rendered the catalytic site less efficient, thus could act as an allosteric inhibitor of the RdRp. After six months of selective pressure, two RS5111-resistant variants were independently selected and both harbor one mutation in VPg (which acts as a primer at the 5'-end of the viral genome) and three mutations in the RdRp. Susceptibility of the reverse engineered mutants to RS5111-treatment is being evaluated in CD300lf-expressing Huh-7-Lunet cells. Finally, RS5111 efficiently reduced HuNoV GII viral RNA levels by 0.5-1 $\log_{10}$ in HuNoV-infected zebrafish larvae water. Overall, we here present a class of novel norovirus inhibitors, active in vitro and in vivo against the most relevant HuNoV genogroups, with a high barrier to resistance.

56. Creation of a Potent Long Acting Emtricitabine

Dhruvkumar Soni, M.S.[1], Aditya Bade, Ph.D.[2], Nagsen Gautam, Ph.D.[3], Jonathan Herskovitz, B.S.[4], Ibrahim Ibrahim, M.D.[4], Nathan Smith, B.S.[4], Yazen Alnouti, Ph.D.[5], JoEllyn McMillan, Ph.D.[5], Howard Gendelman, M.D.[6], Benson Edagwa, Ph.D.[7]

[1]Graduate research assistant, University of Nebraska Medical Center, Omaha, Nebraska, United States of America; [2]Instructor, Omaha, Nebraska, United States of America; [3]Research Assistant Professor, Omaha, Nebraska, United States of America; [4]Graduate research assistant, Omaha, Nebraska, United States of America; [5]Associate Professor, Omaha, Nebraska, United States of America; [6]Chairman, Department of Pharmacology and Experimental Neuroscience., Omaha, Nebraska, United States of America; [7]Assistant Professor, Omaha, Nebraska, United States of America

Transformation of existing antiretroviral drugs into potent, long acting and human immunodeficiency virus (HIV) reservoir targeted antiretroviral therapies (ART) was realized by novel chemical and polymer designs. A ProTide of emtricitabine (FTC) named M2FTC was synthesized and encapsulated into poloxamer 407-coated nanocrystals (NM2FTC) by high-pressure homogenization. Nuclear magnetic resonance and mass spectrometry confirmed the chemical structure of M2FTC. Cell uptake, retention, and antiretroviral efficacy of the NM2FTC were investigated. The spherical NM2FTC particles were stable and exhibited drug loading of 80%, negative surface charge, average particle size of 300 nm and a narrow polydispersity index. Cellular uptake and retention of NM2FTC were more than 30-fold greater compared to FTC treatments. A single treatment of macrophages with NM2FTC produced sustained intracellular FTC-triphosphate (FTC-TP) levels for one month. EC_{50} tests and protection against viral infection demonstrated increased drug potency in macrophages and CD4+ T cells and sustained prevention (for one month) against viral infection. A single intramuscular injection of NM2FTC (45 mg/kg FTC equivalents) to rats showed prodrug levels of >50 ng/mL in blood at day 28 compared to undetectable FTC levels within seven days M2FTC was detected in liver, spleen and lymph nodes of these rats for up to 28 days. FTC-TP was detectable for up to one month in lymph nodes and spleen cells after NM2FTC treatment. An FTC ProTide formulation was produced and exhibited sustained, stable and potent long-acting properties. NM2FTC can be developed for human use for both prevention and treatment regimens.

57. Discovery of a Novel Series of Compounds that Target the Chikungunya Virus (CHIKV) nsP4 RNA-Dependent RNA Polymerase

Jodie Hamrick, B.S.[1], Guo-Hua Chu, Ph.D.[1], Charlotte Bowsher, B.S.[1], Rose Langsjoen, Ph.D.[2], Scott Weaver, Ph.D.[3], Dan Pevear, Ph.D.[1], **Glen Coburn, Ph.D**.[1]

[1]VenatoRx Pharmaceuticals, Inc., Malvern, Pennsylvania, United States of America; [2]Human Pathophysiology and Translational Medicine, University of Texas Medical Branch, Galveston, Texas, United States of America; [3]Health Institute for Human Infections and Immunity, University of Texas Medical Branch, Galveston, Texas, United States of America

Chikungunya virus (CHIKV) is a mosquito-borne arbovirus that causes self-limiting febrile illness in humans. A significant fraction of patients, however, experience long term sequelae including intense arthralgia and musculoskeletal pain that can persist for several years. To identify inhibitors of CHIKV, we have optimized and validated a cell-based assay for high throughput screening (HTS) and conducted a hit finding campaign against a diversified library of drug-like small-molecule compounds. Our HTS led to the identification of a series of compounds that are potent, selective and non-cytotoxic inhibitors of CHIKV replication. Time of drug addition studies indicate that the inhibitor series blocks CHIKV replication at a step that is consistent with RNA replication. We demonstrate that a single amino acid variant, L436M, located within a highly conserved polymerase box motif in nsP4 is sufficient to confer resistance to multiple compounds from the series. Localization of the determinants of resistance to the active site of nsP4 suggests that this series of inhibitors targets the CHIKV RNA-dependent RNA polymerase. The reduced plaque size observed following introduction of L436M into CHIKV suggests that this mutation may induce a significant fitness penalty. The *in vitro* properties of the lead compounds strongly support further investigation as a potential therapy for CHIKV infection.

58. 1,5-Dicaffeoylquinic Acid Blocks EBOV Replication Counteracting the IFN-beta Production Inhibition by the VP35 Ebola Virus Protein

Angela Corona, Ph.D.[1], Elisa Fanunza, M.S.[1], Cristiano Salata, Ph.D.[2], St. Patrick Reid, Ph.D.[3], Simona Distinto, Ph.D.[1], Cinzia Sanna, Ph.D.[1], Jane Morwitzer, M.S.[3], Aldo Frau, Ph.D.[1], Daniela Rigano, Ph.D.[4], Gian Luca Daino, Ph.D.[1], Giuseppina Chianese, Ph.D.[4], Carmen Formisano, Ph.D.[4], Orazio Taglialatela Scalfati, Ph.D.[4], Alì Mirazimi, Ph.D.[5], Enzo Tramontano, Ph.D.[6]

[1]Department of Life and Environmental Sciences University of Cagliari, Cagliari, CA, Italy; [2]Department of Molecular Medicine, University of Padova, Italy. Public Health Agency of Sweden, Sweden, Padova, PA, Italy; [3]Department of Pathology and Microbiology, 985900 Nebraska Medical Center1, Omaha, Nebraska, United States of America; [4]Department of Pharmacy, University of Naples Federico II,, Naples, NA, Italy; [5]Public Health Agency of Sweden; Karolinska University Hospital; National Veterinary Institute., Uppsala, Sweden; [6]Department of Life and Environmental Sciences University of Cagliari; IRGB, CNR., Cagliari, CA, Italy

Ebola virus (EBOV) is one of the deadliest infective agents whose high lethality is linked to the ability to efficiently bypass the host's innate antiviral response. EBOV multifunctional protein VP35 plays a major role in viral replication both as polymerase cofactor and masking agent. VP35, in fact, hides the non-self 5'-ppp dsRNA from the cellular receptor RIG-I, preventing its activation and inhibiting the IFN-b production. Blocking VP35-dsRNA interaction and IFN-b suppression is a validated strategy to overcome EBOV infection. We have previously established a robust fluorescence-based biochemical assay to measure VP35-dsRNA interaction and a miniaturized gene reporter cell-based assay to measure the VP35 inhibition of the IFN-b production. Hence, we screened a library of natural extracts and found that 1,5-dicaffeoylquinic acid (DCA) inhibits dsRNA-VP35 binding with an IC50 value of 8.5 μM, it reverts the EBOV VP35 inhibition of interferon production, while it does not induce IFN production by itself. Furthermore, DCA was then tested in an EBOV minigenome replication, showing no inhibition of the VP35 polymerase cofactor activity. While, when DCA was tested on the replication of an EBOV isolate derived from the 2014 West Africa outbreak in IFN-susceptible A459 cells, it was able to inhibit viral replication with an EC_{50} value of 9.1 μM, showing no significant cytotoxicity. Overall, our data indicate that DCA is a powerful inhibitor of EBOV replication targeting VP35 and subverting the viral inhibitory effect on IFN production.

59. Erythrosin B Protects Mice from Lethal Challenge of Zika Virus

Yuekun Lang, Ph.D.[1], Zhong Li, Ph.D.[1]

[1]Wadsworth Center, NYSDOH, Albany, New York, United States of America

Many flaviviruses, such as Zika virus (ZIKV), Dengue virus (DENV1-4) and yellow fever virus (YFV), are significant human pathogens. Infection with ZIKV, an emerging mosquito-borne flavivirus, is associated with increased risk of microcephaly in newborns and Guillain-Barré syndrome and other complications in adults. Currently, specific therapy does not exist for any flavivirus infections. In this study, we found that erythrosin B, an FDA-approved food additive, is a potent inhibitor for flaviviruses, including ZIKV and DENV2. Erythrosin B was found to inhibit the DENV2 and ZIKV NS2B-NS3 proteases with IC50 in low micromolar range, via a non-competitive mechanism. Erythrosin B can significantly reduce titers of representative flaviviruses, DENV2, ZIKV, YFV, JEV, and WNV, with micromolar potency and with excellent cytotoxicity profile. Erythrosin B can also inhibit ZIKV replication in ZIKV-relevant human placental and neural progenitor cells. Mice treated with Erythrosin B were significantly protected from lethal challenge of Zika virus. As a pregnancy category B food additive, erythrosin B may represent a promising and easily developed therapy for management of infections by ZIKV and other flaviviruses.

60. Developing Pan-Bunyavirus Antivirals by Targeting the Conserved Viral Endonuclease Domain

Sebastiaan ter Horst, M.S.[1], Marcella Bassetto, Ph.D.[2], Andrea Brancale, Ph.D.[2], Johan Neyts, Ph.D.[1], Joana Rocha-Pereira, Ph.D.[1]

[1]Rega Institute for Medical Research, KU Leuven, Leuven, Belgium; [2]Cardiff School of Pharmacy and Pharmaceutical Sciences, Cardiff, United Kingdom of Great Britain and Northern Ireland

The order of Bunyavirales contains many human pathogens, three of which are in the top-10 'priority list of infectious diseases' of the WHO, i.e. Rift Valley fever virus (RVFV), Crimean Congo hemorrhagic fever virus (CCHFV) and Lassa virus. With possible disease outcomes such as encephalitis, hemorrhagic fever and mortality, bunyaviral infections are often devastating. The great diversity of bunyaviruses makes drug development under the one-drug-for-one virus paradigm particularly challenging. Therefore, we focus on discovering viral targets that are highly conserved among bunyaviruses, enabling the identification of anti-bunyavirus compounds with a broad spectrum of activity. To assess the *in vitro* effect of small-molecule inhibitors, high-content imaging-based antiviral assays have been setup using fluorescently labeled orthobunyavirus (Bunyamwera virus) and phleboviruses (RVFV and Severe fever with thrombocytopenia syndrome virus). Through comparative genomic analysis, we identified the L-protein endonuclease domain as the most conserved among bunyaviruses. A selection of reported influenza endonuclease inhibitors was tested, and two diketoacids (L742001 hydrochloride and L311227) were found to inhibit orthobunyavirus replication [EC50 11±2μM and 7±3μM, respectively]. Initial mechanistic studies are ongoing to confirm whether their inhibitory effect is attributable to the same mechanism as for influenza viruses. Moreover, their antiviral effect will be assessed against other pathogenic orthobunyaviruses including La Crosse (LACV) and Oropouche virus. A structure-based virtual screening of commercial compounds on the endonuclease crystal structures of LACV and Hantaan virus, and on homology model structures for RVFV and CCHFV endonucleases, identified 292 small-molecules. These are currently being assessed for their effect on viral replication.

62. Anti-Adenoviral Activity of Exopolysaccharides Produced by Lactic Acid Bacteria

Liubov Biliavska, Ph.D.[1], Yulia Pankivska, Ph.D.[1], Olga Povnitsa, Ph.D.[1], Svitlana Zagorodnya, Ph.D.[1]

[1]Zabolotny Institute of Microbiology and Virology, NAS of Ukraine, Kyiv, Ukraine

The lactic acid bacteria and their metabolites are considered potential candidates in antiviral therapy to prevent treat viral infections in human with remarkable efficacy and might have significant contribution in medicine and pharmaceutical industries in the future. Cytotoxicity of 10 exopolysaccharides (EPSs) of lactic acid bacteria of the genus *Lactobacillus* (1), *Leuconostoc* (8) and *Pediococcus* (1) was determined by MTT assay. The influence of the EPSs on the infectivity of human adenovirus type 5 (HAdV-5) and on the cell cycle under a condition of adenovirus infection was studied using plaques reduction assay and flow cytometric analysis, respectively. All EPSs exhibited little cytotoxic effect, their CC50 values were >2.7 mg/ml. The EPSs showed virucidal activity and reduced the HAdV-5 infectivity to 85%. All detected EPSs added to cells at the end of the virus adsorption period decreased adenovirus production. However, only EPS 26a (produced by *Lactobacillus sp.*) reduces the titer of virus obtained *de novo* and inhibited HAdV-5 plaques formation by 100%. The use of EPSs did not led to the normalization of the life cycle of HAdV-5 infected cells to the level of non-infected cells, as the number of cells in the S phase was decreasing by 5-22% and was no cells transition up to G1 phase, which indicates on the blocking of the mitoses in infected cells. The EPS 26a produced by *Lactobacillus sp.* possessed distinct anti-HAdV-5 activity, that is based on the obstruction of HAdV-5 reproduction, inducing the formation of non-infectious virus progeny.

63. *In Silico* Evaluation of the Affinity of Antivirals Against HCV NS5 Protein in Dengue Virus

Laura Mahecha, B.S.[1], Gian Pietro Miscione, Ph.D.[2], Miguel Parra, Ph.D.[1], Manuel Ruiz Muneval[2], Karina Salvatierra, Ph.D.[3]

[1]*Science faculty, Biological sciences department, Universidad de los Andes, Bogotá, Colombia., Bogotá, Colombia;* [2]*Computational Bio-Chemistry group (COBO). Universidad de los Andes, Bogotá, Colombia., Bogotá, Colombia;* [3]*Grupo de Investigación en Genética Aplicada (GIGA)-IBS-CONICET, UNaM, Posadas, Misiones, Argentina., Misiones, Argentina*

The viruses of *flaviviridae* family cause several diseases like hepatitis C (HCV) and others like dengue fever (DENV) and zika (ZIKV). According to the world health organization (WHO), HCV causes more than 71 million of infections worldwide, of which approximately 400.000 develop cirrhosis, hepatocarcinoma and eventually death. However, there are treatments for the disease using drugs designed against the ARN polymerase of the virus (NS5 protein). On the other hand, the incidence of dengue has grown dramatically around the world in recent decades. One recent estimate indicates cause 390 million infections per year, of which 96 million manifest clinically (with any severity of disease). There is no current cure or specific treatment for dengue/ severe dengue. For this reason, and knowing that structure of *faviviridae* family NS5 protein reveals a conserved domain conformation, we probed computationally the drugs designed against HCV on DENV. We use molecular dynamics and molecular docking to anchor the antivirals of HCV (Dasabuvir (ABT-333), ABT-072, Filibuvir, GS-9669, Lomibuvir, Nesbuvir, and Setrobuvir) on DENV. In this way, antivirals tested in this study are promising to move on to *in vitro* studies and could be use in the future as treatment for dengue fever.

64. Bicyclic Carboxamides as Hepatitis B Virus (HBV) Core Protein Assembly Modulators

Yanming Du, Ph.D.[1], Nicky Hwang, B.S.[1], Matthew Campagna, B.S.[1], Shuo Wu, Ph.D.[1], Ju-Tao Guo, M.D.[1]

[1]*Baruch S. Blumberg Institute, Doylestown, Pennsylvania, United States of America*

Hepatitis B Virus (HBV) capsid core protein assembly has been an attractive target recently for developing antivirals with a new mechanism of action. In addition to the heteroaryldihydropyrimidines (HAPs) and sulfonyl carboxamides, which are in clinical tests, other chemical structures have also been explored. Here we describe the hit-to-lead optimization of a benzamide discovered from our high-throughput screening. A new bicyclic carboxamide lead featuring an electron deficient core structure was discovered. Evaluations of its ADMET (absorption, distribution, metabolism, excretion and toxicity) and pharmacokinetic (PK) profiles demonstrate improved metabolic stability and good bioavailability.

65. HIV-1 Non-B Subtype Infected Patients Progress Faster than Subtype B Patients; Determined by Higher Genetic Stability of Non-B Following Korean Red Ginseng Treatment

Jung-Eun Kim, M.S.[1]

[1]*University of Ulsan College of Medicine, SEOUL, Korea (Republic of)*

Many reports on subtype B have shown that long-term nonprogressors harbor defective *nef* genes more frequently than progressors. However, there is no such data on non-B. To determine whether there is a subtype difference in the disease progression in HIV-1 infected patients, we alanyzed the annual decrease of CD4 + T cells (AD) between subtypes B and non-B nationwide. In addition, we compared the response to Korean red ginseng (KRG) and the proportion of gross deletion in *nef* gene by KRG treatment. We amplified *nef* and *pol* genes encoding integrase by nested-PCR and determined 4,838 *nef* in 281 and 752 *pol* sequences in 23 patients, respectively. KRG treatment significantly slowed AD and increased the proportion of gΔnef in both subtypes. AD was faster in non-B than in subtype B infected patients irrespective of KRG treatment. Focused on the patients treated with KRG, AD was also significantly faster in non-B than in subtype B. In addition, the proportion of gΔ*nef* was significantly higher in subtype B than in non-B and the difference was significant from 7 months of KRG treatment. The same results were observed when the KRG dose was adjusted. In the same way, the proportion of genetic defects in *pol* gene encoding integrase was also significantly higher in subtype B than in non-B ($P<0.01$). Non-B progresses faster than subtype B infection. Non-B HIV-1 was significantly resistant to the induction of genetic defects by KRG than subtype B.

66. Novel Piperazine Derivatives as Capsid Assembly Modulators for the Hepatitis B Virus

Huixin Luo, Ph.D.[1], Shuo Wu, Ph.D.[1], Qiong Zhao, Ph.D.[1], Junjun Chen, Ph.D.[1], Haiqun Ban, Ph.D.[1], Ju-Tao Guo, Ph.D.[1], Yanming Du, Ph.D.[1]
[1]*Baruch S. Blumberg Institute*

Chronic hepatitis B viral infection has a low cure rate under the current treatment; one of the approaches under study to improve this is targeting the assembly of the viral capsid to block further replication and propagation. Here we present piperazine-derived inhibitors of capsid formation. The optimization of an early hit benzamide compound from a high-throughput screening led to the discovery of this novel chemical series. We will also discuss the development of the lead compounds through structure-activity evaluations and modeling aided design.

67. Cidofovir and (S)-HPMPA Tyrosinamide Prodrugs with an Alkenyl Modification in the Long-chain N-alkyl Modifier are Potent Inhibitors of HSV-1, CMV and BKPyV

Jinglei Lyu, M.S.[1], Jiajun Fan, B.S.[1], Boris Kashemirov, Ph.D.[1], Caroll Hartline, Ph.D.[2], Emma Harden, Ph.D.[2], Mark Prichard, Ph.D.[2], Charles McKenna, Ph.D.[1]
[1]*University of Southern California, Los Angeles, California, United States of America;* [2]*University of Alabama, Birmingham, Alabama, United States of America*

Cidofovir ((*S*)-HPMPC) and its adenine analog (*S*)-HPMPA are acyclic nucleoside phosphonates (ANPs) with broad spectrum activity against DNA viruses. Cidofovir has low oral bioavailability and cell permeability due to its phosphonic acid group, which ionizes at physiological pH.

We have introduced a tyrosiniamide ANP ester prodrug strategy in which the ANP phosphonate equipped with a lipophilic alkyl group attached to the amido N. The modular design provides facilely variable substructures for optimizing antiviral potency and tuning other pharmacological properties. The C-16 alkyl tyrosinamide prodrugs of cidofovir and (*S*)-HPMPA (USC-505 and USC-087, respectively) show significantly enhanced potency vs a range of DNA viruses.

The lipophilic long chain alkyl modifier in the promoiety is presumed to interact with the hydrophobic interior of cellular membranes. Here we examine the effect of introducing unsaturation (a *cis*or *trans* double bond) into the alkyl substructure to modulate this interaction. A series of *N*-alkenyl cidofovir and (*S*)-HPMPAprodrugswas synthesized and found to be at least 5x more potent vs HSV-1*in vitro* (EC_{50}0.1-0.04 μM) than USC-087 or USC-505 and exceptionally potent (EC_{50}0.001-0.0005 μM)vsHCMV. All four *N*-alkenyl prodrugs had EC_{50}values of 0.03-0.08 μM vs BKPyV.

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68. Nipah Virus Attachment Glycoprotein (NiV-G) Counteracts the Antiviral Effector Protein Tetherin

Bom Nae Rin Lee, M.S.[1], Haewon Byun, M.S.[1], Hector Aguilar-Carreno, Ph.D.[1]
[1]*Cornell University, Ithaca, New York, United States of America*

Nipah virus (NiV), a family of paramyxovirus, has its reservoir in fruit bats (Pteropus), can cause fatal disease with approximately 75% mortality rate in human. Understanding how NiV counteracts the antiviral effectors of the host immune system can help to define novel targets for future antiviral therapy. Here, we report that NiV can specifically counteract the antiviral effector protein tetherin via its attachment glycoprotein (NiV-G). It has been previously reported that tetherin, an interferon-inducible protein restricts the release of NiV and may critically contribute to the host's control of NiV. The present study, however, has demonstrated that NiV-G induces a drastic decrease of both fruit bat and human tetherin. We found that the receptor-binding domain of NiV-G is responsible for this tetherin counteraction. Interestingly, unlike HIV-1 accessory protein Nef and Vpu, which is known to inhibit tetherin, NiV-G's antagonism of tetherin was independent of dynamin-mediated endocytosis. The mechanism underlining the NiV-G interaction with tetherin remains to be determined. Understanding this novel NiV immune evasion in fruit bat and human will provide more insights into the pathogenicity of this deadly BSL4 pathogen.

69. Development and Characterization of Oral Combination Vaccine against Hepatitis B & Influenza

Prakash Gosain, M.D., MPH[1], Saurabh Jain, Ph.D.[1], Mani Bhargava, M.D., MPH[2]
[1]*Himalayan University, India;* [2]*ICFAI University, India*

Vaccination has not only become vital but a lot of revolutionary changes are being observable in the field of vaccine delivery. Vaccine antigens administered by the oral route are often degraded during gastrointestinal transit. Bile salt stabilized vesicles i.e. bilosomes are found to be effective in preventing antigen degradation and enhance mucosal penetration. The aim of the present work was to prepare a combination vaccine system against hepatitis-B (HBsAg) and influenza(r-H1N1Ags).

Bilosomes containing HBsAg and r-H1N1Ags were prepared by a lipid cast film method. Antigen loaded bilosomes were characterized *in-vitro* for their shape, size, percent antigen entrapment and stability. Fluorescence microscopy was c arried out to confirm the uptake of bilosomes. The *in-vivo* study comprised of estimation of IgG response in serum and sIgA in various body secretions using specific ELISA.

Bilosomes formed were multilamellar and were stable in gastric and intestinal fluids. Fluorescence microscopy suggested that bilosomes were taken up by gut-associated lymphoid tissues. In-vivo data demonstrates that bilosomes produced both systemic as well as mucosal antibody responses upon oral administration at higher dose levels as compared to intramuscular immunization but fail to produce any synergistic effect.

Thus, HBsAg potentiates the production anti-r-H1N1 antibody. Also measurable sIgA in mucosal secretions were observed. Thus, bilosomes are a promising carrier for oral combination vaccines. This approach could be adapted for human use because mucosal surfaces are initial sites of infection and it therefore seems logical to attempt to develop vaccination strategies that evoke appropriate localized responses to counteract early events of pathogenesis.

70. Function, Activation and Control of Innate Immune Networks to HSV Infection

Grace Zhou, Ph.D.[1]
[1]*Shenzhen International Institute for Biomedical Research, Shenzhen, China*

Analyses of 20 cell lines from which individual genes associated with innate immunity had been knocked out revealed the following: (i) Knockout of some genes is associated with increases in the expression of overlapping networks of genes and significant loss of ability to support the replication of HSV-1. (ii) Knockout of other genes is associated with decreases in the expression of overlapping networks of genes and overall no effect on viral replication. (iii) The phenotype of cells from which a gene was deleted reflects the sum total of the effects of genes up or down regulated as a consequence of the deletion. (iv) Key functions associated with innate immunity are normally repressed and must be activated in response to infection. (v) Studies on a limited subset of cellular genes suggest that HSV-1 relies on the functions of constitutively expressed and inducible cellular genes to suppress innate immunity genes inimical to virus replication. The recruited genes identified to date include LGP2, HDAC4 and GADD45g. The accrued evidence suggests that the cellular genes recruited by HSV-1 act independently on the same or at least overlapping set of innate immunity genes. The targets of recruited genes identified to date include IFI16, MDA5 IFIT1 and RIG-1.

71. Novel NNRTIs with Bicyclic Cores – Attempts to Improve Solubility and Resistance Profile

Ladislav Prener, B.S.[1], Ondřej Baszczyňski, Ph.D.[2], Martin Dračínský, Ph.D.[3], Jan Weber, Ph.D.[3], Michala Zgarbová, M.S.[3], Eric Hu, Ph.D.[4], Eric Landson, Ph.D.[4], Petr Jansa, Ph.D.[4], Zlatko Janeba, Ph.D.[3]
[1]*Institute of Organic Chemistry and Biochemistry, CAS and University of Chemistry and Technology, Prague, Prague, Czechia;* [2]*Institute of Organic Chemistry and Biochemistry, CAS and Dept. of Organic Chemistry, Charles University, Prague, Czechia;* [3]*Institute of Organic Chemistry and Biochemistry, CAS, Prague, Czechia;* [4]*Gilead Sciences Inc., Foster City, California, United States of America*

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are essential agents in the current combination therapy regimens used in the treatment of HIV-1 infections. Poor solubility, which results in low bioavailability and causes difficulties during drug formulation, is one of the main limitations of the NNRTIs currently used in the clinic. Furthermore, emergence of the resistant viral strains is another critical issue faced in the treatment of AIDS nowadays. Thus, development of novel drugs with increased genetic barrier to resistance is of a high interest.

Herein, our discovery of new series of NNRTIs bearing modified purine, tetrahydropteridine and pyrimidodiazepine moieties is disclosed. The compounds display low nanomolar activities against the wild type virus as well as some of the clinically relevant mutants and improved solubility compared to the FDA approved NNRTIs.

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72. Development of Bipolymer based Novel Nanoparticles in Microsphere System as Vaccine Adjuvant

Nikhil Kapoor, M.D., MPH[1], Varun Bhargava, M.D., MPH[2], Saurabh Bhargava, M.D., MPH[3]
[1]Manav Bharti University; [2]GTB Hospital, India; [3]United Institute of Pharmacy, India

Novel strategies are required for the achievement of safe and effective immunization beyond conventional strategies. Frequent booster dosing can be avoided by development of mucosal/adjuvant vaccine delivery system, which can produce bothhumoral and cell-mediated responses. The work envisaged usescombined hydrophilic(gelatin nanoparticles,GN) with a hydrophobic polymeric system(PLGA microspheres) which creates a biodegradable system for HBsAgdelivery.

GN& PLGA microspheres were prepared by double emulsification method and composite system by phase separation method.Composites were optimized and characterized *in-vitro* for their shape, size by Scanning &Transmission Electron Microscopy,%antigen entrapment and stability. Fluorescence microscopy was carried out to confirm the uptake. *In-vivo* study comprised of estimation of IgG response in serum and sIgA in various body secretions using specific ELISA. The *in-vitro* studies exhibited an initial burst release from gelatin nanoparticles, degradation of antigen from PLGA microspheres & a continuous release from composite system. This supports the hypothesis to formulate single shot vaccine with such system (to mimic booster dosing). The fluorescence studies showed the selective uptake of composites by NALT.

Humoral response generated by single dose of composites was comparative to marketed formulation receiving booster dose. Further, composite system generated effective sIgA antibody which was not elicited by marketed formulation. Thus, it could be concluded from present study that bipolymer based composite system are capable to provide sufficient protein stability and can be a promising candidate for development of single shot vaccine, not only against Hepatitisbut against all those diseases that invade host by mucosal surfaces.

73. Biological Evaluation of Novel Small-molecule Antiviral Agents versus Tick Borne Encephalitis Virus

Paola Zanetta, M.S.[1], Friederike Hucke, D.V.M.[1], Friese Daniela, B.S.[1], Marcella Bassetto, Ph.D.[2], Andrea Brancale, Ph.D.[2], Joachim Bugert, M.D., Ph.D.[1]
[1]Bundeswehr Institute of Microbiology, Virology, Munich, Germany; [2]School of Pharmacy, MedChem, Cardiff, United Kingdom of Great Britain and Northern Ireland

Tick Borne Encephalitis Virus (TBEV) is a flavivirus causing a flu-like illness and meningoencephalitis in the human host. TBEV is transmitted by Ixodes ticks and endemic in temperate climate zones suitable for the vector, mainly in Europe and Asia, but not in the Americas. Several inactivated TBEV vaccines are on the market, but so far, there are no TBEV specific therapeutics. A number of de novo synthesized compounds previously found active versus flaviviruses and non-toxic in human HUH7 hepatoma cells, were tested versus TBEV in human cell lines where TBEV causes cytopathogenic effects. Several compounds with IC50 in the uM range and minimal toxicity were identified and compared to compounds with known antiflaviviral activity already on the market/ candidates for drug repurposing (e.g. Ribavirin™ and Sofosbuvir™). The most effective compound in our assays is ten times more effective than Ribavirin™, and twice as effective than Sofosbuvir™ in Huh7 cells, with an SI of 52. Data on performance in cells of CNS origin of our original hit and of a newly prepared analogue, is currently being generated. These results will be reported in this presentation. This work provides the foundation for further investigation of promising novel structures as antiviral agents against TBE virus.

74. Ultra-diluted Extract of *Atropa belladonna* Restrict Japanese Encephalitis Virus Infection through Modulation of Type-I Interferon in Chorioallantoic Membrane of Chick

Mousumi Chakravarty, M.S.[1], Urmita Chakraborty, Ph.D.[2], Arghyadeep Bhattacharjee, M.S.[1], Satadal Das, M.D.[2]

[1]Regional Research Institute For Homoeopathy, Kolkata, West Bengal, India, India; [2] Regional Research Institute For Homoeopathy, Kolkata, West Bengal, India.

Abstract: Japanese encephalitis (JE) is one of the leading prevalent encephalitis throughout the world. The role of ultra-diluted extract of Atropa belladonna (ABUD) has been evaluated in some studies. Type I interferons are important controlling factor in the JE virus infection. Thus the present study is aimed to evaluate the role of ABUD in modulation of IFN-α and IFN-β and their association in controlling the viral load. Twelve-day-old fertilised eggs of Black Australorp were pretreated with belladonna followed by infection with JE virus keeping matched control sets. After incubation for 48 hours the eggs were harvested and brain tissue were observed and collected for viral load determination, and gene expression studies for IFN-α and IFN-β by RT-PCR. Among the control group with infection, brains were liquefied due to haemorrhagic liquefactive necrosis. However, the medicine pre-treated group was apparently normal and there were no visible changes in the brain. There were significantly high viral load in the infected group as compared to ABUD pre-treated group. Significant upregulation of IFN-α and IFN-β were observed in the medicine treated group which correlated with the lowest viral load. Ultra-diluted extract of A. belladonna may prevent the JE virus replication through the induction of Type 1 interferons.

75. Prediction of Biological Activity of Fluorinated Derivatives of Triazoles

Krystyna Naumenko, Ph.D.[1], Svitlana Zagorodnya, Ph.D.[1], Ganna Gudz, Ph.D.[2], Yurii Shermolovich, M.D., Ph.D.[2]

[1]Zabolotny Institute of Microbiology and Virology NAS of Ukraine, Kyiv, Ukraine; [2]Institute of Organic Chemistry NAS of Ukraine, Kyiv, Ukraine

Modern trends in the development of antiviral drugs are aimed at finding new compounds that containing new radicals in the structure that can enhance their properties. Today, methods of computational biology are actively involved in the search for new antiviral compounds, which allow us to analyze a large range of compounds and to select promising ones for testing their properties. The purpose of the work was to predict the biological activity of fluorinated derivatives based on the triazoles (G6-G25, G29) for the presence of antiviral and antitumor activity. All studied compounds were synthesized in the Institute of Organic Chemistry NAS of Ukraine. The research was carried out using the program PASS (Prediction of Activity Spectra for Substances). By predicting PASS, compounds G17-G19 that contain in the structure arabinopyranosyl and ribofuranosyl fragments, may have antiviral activity, in particular against herpesviruses, Pa/Pi ranged from 0.216/0.083 to 0.339/0.043. According to the obtained results, compounds G6-G9, G14-G20, G22, G25, and G25 (contain 2*H*-1,2,3-triazole) do not have antiviral activity. However, for these compounds, anti-tumor activity was predicted, Pa/Pi ranged from 0.218/0.214 to 0.572/0.051. It was also found that compounds G16 and G21 may be caspase 3 stimulants (Pa/Pi=0.310/0.032), and compounds G14-G16, G18-G21 are capable of inhibiting DNA polymerase and nucleic acid synthesis (Pa/Pi=0.356/0.021). It should be noted that compounds G10-G13 may be chemosensitizer, (Pa/Pi=0.501/0.020), while not having antiviral, anti-tumor activities. The analyzed data allow us to select promising compounds for further study of the antiherpetic activity of fluorinated derivatives of triazoles.

76. Development and Characterization of an Aerodynamic System for Pulmonary Delivery of Influenza Vaccine

Saurabh Bhargava, M.D., MPH[1], **Priyanka Gosain, M.D., MPH**[2], Varun Bhargava, M.S.[2]

[1]United Institute of Pharmacy, India; [2]GTB Hospital, India

The name *influenza* is Italian and means "influence", Commonly referred to as the flu, is an infectious disease caused by RNA viruses of the family Orthomyxoviridae , that affects birds and mammals. The aim is also to develop and characterize aerodynamic systems with r-H1N1Ags for safely deposition in alveoli to enhance the bioavailability and control release of influenza antigen after pulmonary administration in animal model. This Induces not only systemic humoral (IgG) responses, but also cell-mediated (IL-4, IFN-γ) and mucosal immune responses (IgA, IgG), non-invasive, propellant & needle free delivery of vaccine.

The chitosan microparticles were prepared by ionic gelation method of chitosan with tripolyphosphate(TPP). The formulations were optimized on the basis of particle size, tap density & entrapment efficiency. The external morphology of the optimized formulation was studied by TEM & SEM. The zeta potential was determined along with stability studies at accelerated tempreatures. The in-vivo studies involved determination of antibody titres in serum and mucosal secretions and uptake studies by fluorescence microscopy.

The results show that as the preparation was reduces to lyophilized form which increased the stability as compared to conventional liquid formulations. The microparticles of uniform size distribution were obtained owing to the repulsion between the positively charged particles. The fluorescence images show the uptake of microparticles by various organs and the ELISA results shows comparable IgG responses along with IgA.

77. Tackling Chikungunya via Repurposing

Ashok Kumar Patel, Ph.D.[1], **Praveen Kumar Tripathi**[1]
[1]*KSBS, Indian Institute of Technology Delhi, Delhi, India*

Chikungunya, a mosquito borne febrile illness is caused by chikungunya virus of *togaviridae* family belonging to the alphaviruses. The clinical manifestations ranges from substantial morbidity i.e. high grade fever, maculopapular rashes, stomach upset, headache etc. to fatal conditions of encephalopathy. The 11.8kb positive sense viral RNA genome codes for five structural and four non-structural proteins (nsPs). Among these, the non-structural protein-2 (nsP2), is a multifunctional protein of 88kDa harbouring helicase, NTPase and protease activity.The nsP2 protease initiates the cleavage of polyprotein into individual functional proteins and hence an attractive drug target.

In this study, we aimed to target Chikungunya nsP2 protease employing the concept of repurposing. Virtual screening and docking using approved molecules performed utilizing the *RASPD* and *ParDOCK*. The interactions were validated via MD simulations (AMBER14 suite). The nsP2 protein was expressed in bacteria and was purified using Ni-NTA affinity, ion-exchange and Gel filtration chromatography. The *E. coli* expressed protein was characterized for intact and peptide mass in mass spectrometry. Bimolecular interaction studies were performed using surface plasmon resonance and thermo Fluor® assay. Inhibition of protease activity were established using fluorescence based assay. Physical changes in the protein after binding of the ligands were studies using small angle x-ray scattering experiments.The viral inhibitory potential of the molecules were established utilizing the plaque reduction assay.

78. Computer-aided Design, Synthesis and Evaluation of Novel Non-nucleoside Inhibitors of the Viral Polymerase as Antiviral Agents Against Norovirus

Gilda Giancotti, Ph.D.[1], Salvatore Ferla, Ph.D.[1], Ilaria Rigo, M.S.[1], Valentina Naccarato, M.S.[2], Romano Silvestri, Ph.D.[2], Johan Neyts, Ph.D.[3], Andrea Brancale, Ph.D.[1], Joana Rocha-Pereira, Ph.D.[3], **Marcella Bassetto, Ph.D.**[1]
[1]*Cardiff University;* [2]*Sapienza University of Rome;* [3]*Rega Institute for Medical Research*

Norovirus represents the first cause of food-borne illness worldwide, leading to extensive outbreaks of gastroenteritis, a life-threatening condition in the developing countries. 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, leading to an ample need for the development of antiviral treatments. Four non-nucleoside small molecules, selected through an *in silico* screening of chemical compound libraries on the structure of the human norovirus (HuNoV) polymerase, were found to inhibit the HuNoV GII.4 polymerase in biochemical assays. However, the inhibitory effect of these molecules on murine norovirus (MNV) plaque formation in a plaque reduction assay was limited , mainly due to solubility issues. Starting from these findings, the chemical scaffolds of these hits were rationally modified and assessed with a series of *in silico* simulations, in order to maintain a good predicted binding to the viral polymerase, while improving solubility and stability properties. This approach led to the development of different series of novel small molecules, which all inhibit the target enzyme with varying potencies in the low micromolar range. The rationale behind the new structural modifications will be discussed in this presentation, along with the synthetic pathways optimised to prepare these novel compounds and their biological evaluation in both enzymatic and cell-based assays.

79. Systematic Design and Synthesis of Novel Small Molecule Inhibitors of Chikungunya Virus

Verena Battisti, M.S.[1]
[1]*University of Vienna, Vienna, Austria*

The Chikungunya virus is the causative agent of the Chikungunya fever, an illness characterized not only by a rapid onset of high fever but also by severe myalgia and leads in some cases also to death. Even years after the infection, some patients suffer under recurrent myalgia, which causes an impaired quality of life. Since its re-emerging in 2005, the disease had massive outbreaks infecting millions of people in more than 40 countries not only in Asia and Africa, but also in America and Europe (France and Italy). Currently, there are no specific antiviral drugs or vaccines available to prevent or treat the infection, although the predicted outbreak of a new epidemic in a Mediterranean city like Rome is highly probable. Therefore, the design and development of novel effective antiviral drug compounds are immensely needed.

In 2014, Kirchebner discussed a series of novel small molecules Chikungunya inhibitors. From the starting point CIM016321, a hit discovered by HTS by the Centrum voor Innovatie en Stimulatie van Medicijnonwikkeling (CISTIM) and KU Leuven, she produced a total of 59 analogues in a hit to lead optimization program.

Based on the most effective compounds, a series of new promising molecules was now designed, synthesized and tested against not only the chikungunya virus but also Enterovirus 71, Zika virus and Norovirus. Hereby, the concept of bioisosterism and the Topliss tree of decision where used for a systematic variation of substitution pattern. In addition, the 4-step-synthesis established earlier was optimized, resulting in a higher overall yield.

80. An Imidazopyridine (BSBI252-C4) that Affects HBV Subviral Particle Antigenicity, and Interferes with its Assembly

Liren Sun, M.S.[1], Fanny Zhang, Ph.D.[2], John Kulp, Ph.D.[3], Timothy Block, Ph.D.[4], TianLun Zhou, M.D., Ph.D.[5]
[1]*liren.sun@bblumberg.org, doylestown, Pennsylvania, United States of America;* [2]*Fanny.zhang@bblumberg.org, Pennsylvania, United States of America;* [3]*John.Kulp@bblumberg.org, Pennsylvania, United States of America;* [4]*Timothy.Block@bblumberg.org, Doylestown, Pennsylvania, United States of America;* [5]*Tianlun.zhou@bblumberg.org, Doylestown, Pennsylvania, United States of America*

Drugs that inhibit hepatitis B virus (HBV) viral replication have little effect upon circulating levels of subviral particles (SVPs) which are comprised mostly of DNA and capsid free S polypeptides. Moreover, since integrated genomes of HBV, common in chromic carriers, still produce SVPs, long after HBV viremia has been managed, chronically infected patients still have high levels of S antigenemia. This could be responsible for maintaining chronicity and preventing HBV antibody development. Here we describe a small molecule, identified from a screen of 19,000 compounds, that appears to alter the conformation of the HBV S polypeptide. That is, in tissue culture systems, although total levels of intracellular and secreted HBsAg were not affected, non-cytotoxic levels of imidazopyridine C4 caused the secreted S to be undetected by conformation specific mAb. Virion secretion, as well as HBV virion infectivity were also greatly reduced. The affect was selective, in that key cellular polypeptides such as alpha 1 antitrypsin, apolipoprotein A1 and albumin, were not affected by the compound. Hepatitis delta virus (HDV) infectivity, in culture, which also depends upon a functional HBV S polypeptide, was also significantly reduced by incubation with C4. These data are consistent with the hypothesis that imidazopyridine C4 may selectively alter the conformation and function of HBV S polypeptide. The specific mechanism of action, and potential as an HBV and HDV therapeutic are under investigation, and will be discussed.

81. Biological Evaluation of Antiviral Agents versus Encephalitis Viruses Using Live Cell Microscopy: Optimization of Parameters for a Model of the Blood Brain Barrier

Lisa Hurler, M.S.[1], Paola Zanetta, M.S.[2], Rohan Narayan, M.S.[3], Daniela Friese, B.S.[1], Joachim Bugert, M.D., Ph.D.[1]

[1]Bundeswehr Institute of Microbiology (IMB), Munich, Germany; [2]ERASMUS program – Università degli Studi Milano Bicocca, Milan, Italy; [3]Cardiff School of Pharmacy and Pharmaceutical Sciences, Cardiff, United Kingdom of Great Britain and Northern Ireland

The goal of this project was to lay foundations for a complex infection model of the blood-brain-barrier to evaluate antivirals versus viruses causing encephalitis. Initially measles and vaccinia viruses were selected, as GFP reporter viruses were available and experiments could be done under S2 conditions. Measles virus (*Paramyxoviridae*) is a highly infectious human pathogen that can lead to high fever, pneumonitis, conjunctivitis, and the typical measles rash. Use of the efficient live-attenuated vaccine has recently lapsed in developed countries leading to small and medium scale outbreaks. While vaccination is safe, wildtype measles infection can lead to potentially fatal medium and late term complications (e.g. MIBE/SIBE and SSPE). Vaccinia virus (*Orthopoxviridae*) was used for the eradication of variola virus in 1980. Vaccination can lead to severe complications including postvaccinial encephalitis. Effective small molecule antivirals would be useful to treat manifest cases and complicated infections/vaccinations.

The project established live-cell microscopy of single and multiple cell infections (glial and endothelial cells) using reporter viruses in the ibidiBOX live cell culture system. The infection kinetics of GFP-expressing Measles virus IC323, and Vaccinia virus v300 were analysed in overnight live cell experiments. Initial experiments with the insert model allowed us to optimize the tightness of endothelial cell barriers. These results were used to inform the parameters for setting up an endothelial cell barrier/readout in the ibiPore Flow system. The findings of this project are a first step towards a model of the blood-brain-barrier that allows observations in realtime under a confocal laser scanning microscope.

82. *In Vitro* Evaluation of the Role of Alcoholic Preparation of *Eupatorium perfoliatum* plant and *Crotalus horridus* Venom against Dengue Virus Infection

Moonmoon Sinha, M.S.[1], Urmita Chakraborty, Ph.D.[1], Arghyadeep Bhattyacharjee, M.S.[1], Mousumi Chakravarty, M.S.[1], Debabrata Sarkar, M.D.[1], Satadal Das, M.D.[1]

[1]DACRRI, Kolkata, under Ministry of AYUSH, Govt. Of India, Kolkata, India

The mosquito borne positive, single stranded, dengue virus, has became a life threat to mankind, throughout the world due to unavailability of specific therapeutic regimen for its treatment. Although various research works toward development of antiviral agent against dengue virus infection is being carried out in various fields of science, in traditional medicine it has been noted that *Eupatorium perfoliatum* plant and *Crotalus horridus* venom, in alcoholic preparations were commonly used clinically in the prevention and treatment of dengue virus pathogenesis. Although, the exact mechanism of its action is still unknown. Thus, to validate these findings we were interested to study the direct biological effect of *E. perfoliatum* and *Crotalus horridus* extracts which were in nanodiluted and potentised form, on cell line infected with dengue virus. One control study was also done with potentised alcohol. Hence, on the basis of initial cytopathic effect and cytokine gene expression studies using RT PCR, it was observed that these medicines have specific role in both preventive as well as curative aspect. Therefore, further research works are needed to reveal its antiviral potential against dengue virus infection.

83. Design and Evaluation of Amidine and Non-Amidine Encephalitic Alphavirus Inhibitors With Prophylactic and Therapeutic Efficacy In Infectious Murine Models

Jennifer Golden, Ph.D.[1], Donghoon Chung, Ph.D.[2], Colleen Jonsson, Ph.D.
[1]University of Wisconsin-Madison, Madison, Wisconsin, United States of America; [2]University of Louisville, Louisville, Kentucky, United States of America; [3]University of Tennessee Health Science Center, Memphis, Tennessee, United States of America

New World alphaviruses cause significant disease in humans and equines in the Americas. While a trivalent vaccine is available for horses, the vaccine is not 100% effective and there remain no FDA approved treatments for human infection. Due to the absence of effective therapeutic countermeasures, the potential for outbreaks driven by climate change, and potential use of these viruses as biological threats, we have focused on the development of small molecule inhibitors of Venezuelan- Western- and Eastern Equine Encephalitis Viruses (V/W/EEEV, respectively). Our first disclosure involved ML336, a potent, nontoxic amidine resulting from a unique chemical rearrangement that inhibited an VEEV-induced cytopathic effect, dramatically reduced *in vitro* viral titer, and afforded *in vivo* protection in mice. Through the development of new synthetic methods and optimization, structural insights were revealed that have been leveraged to afford two distinct scaffolds with improved physiochemical properties that have translated to 100% survival in lethal mouse model of VEEV (Trinidad Donkey strain). *In vitro* assessment of these compounds also show promise against WEEV and EEEV. Furthermore, advanced compounds have demonstrated prophylactic and therapeutic efficacy in VEEV infected mice and shown promising protection in preliminary experiments with EEEV infected mice. Using *in vitro* viral RNA polymerase assays, these compounds have been found to directly act against the viral replicase complex, resulting in the inhibition of viral RNA synthesis. As a result, next generation amidines and novel non-amidine inhibitors are currently being optimized in parallel for *in vivo* efficacy and preclinical evaluation.

84. Down Regulation of IL1 Beta Gene by Quercetin ; An Important Cytokine Marker Responsible for Determining Complications in Dengue Fever

Moonmoon Sinha, M.S.[1], Urmita Chakraborty, Ph.D.[1], Arghyadeep Bhattyacharjee, M.S.[1], Mousumi Chakravarty, M.S.[1], Debabrata Sarkar, M.D.[1], Satadal Das, M.D.[1]
[1]DACRRI, Kolkata under Ministry of AYUSH, Govt.of India, Kolkata, India

Among various cytokines, IL-1 Beta is the main cytokine which is responsible for different complication and death in dengue fever. There are reports that the plant polyphenolic flavonoid Quercetin have antiviral role in dengue fever, but there is no study to find out whether it can also act during complications of dengue fever. Thus, in this paper I targeted to see whether Quercetin can cause downregulation of IL1Beta gene to prove its probable efficacy in complications of dengue fever. The dengue virus type-2 was inoculated in HepG2 cell line along with pre and post treated Quercetin experimental sets as well as the control cells. The IL1beta gene was monitored in Real time PCR studies with specific primers and other molecular study materials. It was found that Quercetin can downregulate IL-1 beta gene significantly, diminishing the viral load in the infected cells. This important finding may be extrapolated clinically in the treatment of complicated dengue fever.

85. Fetal Protection against Zika Virus Using a Vesicular Stomatitis Virus Vectored Vaccine

Justin Julander, Ph.D.[1], Bose Sayantan, Ph.D.[2], Ashley Dagley, M.S.[1], Sean Whelan, Ph.D.[2]
[1]Institute for Antiviral Research, Utah State University, Logan, Utah, United States of America; [2]Department of Microbiology, Harvard Medical School, Boston, Massachusetts, United States of America

Zika virus (ZIKV) infection during pregnancy can result in congenital defects the most severe being microcephaly. Using a recombinant vesicular stomatitis virus expressing the pre-membrane and envelope proteins (prME) of ZIKV in place of the native attachment and fusion glycoprotein (G) we examined whether maternal vaccination protects developing fetuses from congenital defects. An initial toxicity study demonstrated the safety of the VSV-ZIKV vector in AG129 mice lacking type I and II interferon receptors. Females were vaccinated using a prime/boost schedule. Vaccinated females were treated hormonally and bred to non-vaccinated males. The vaccinated female mice had detectable neutralizing antibody titers present prior to challenge with a Malaysian strain of ZIKV on day 7 of pregnancy. Following necropsy at day 18 of pregnancy (11 days post-virus infection), levels of ZIKV RNA in maternal brain samples were similar to uninfected females and significantly ($P<0.001$) lower than mice vaccinated with wild-type VSV. A similar reduction in ZIKV RNA was observed in placental and fetal samples, demonstrating protection of fetuses in vaccinated females. Fetal head lengths were also significantly ($P<0.05$) larger than WT vector controls, which was similar to sham-infected controls. These studies demonstrate the tolerability and efficacy of a VSV-ZIKV vaccine in a mouse model of congenital Zika disease. [Supported in part by contract HHSN272201700041I/HHSN27200004, Task A11, NIAID, NIH]

86. Towards the Development of Novel Anti-HBV Agents: Design, Synthesis and Biological Evaluation of *N*-hydroxyimides as RNaseH Inhibitors

Vasiliki Pardali, M.S.[1], Erofili Giannakopoulou, M.S.[1], Tiffany Edwards, M.S.[2], John Tavis, Ph.D.[2], Grigoris Zoidis, Ph.D.[1]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Athens, Athens, Greece; [2]Saint Louis University School of Medicine, Saint Louis, Missouri, United States of America

Hepatitis B Virus (HBV) is a DNA virus of the *Hepadnaviridae* family. Long-term HBV infections constitute a major cause of end-stage liver disease and chronic carriers are at risk of developing cirrhosis, liver failure and hepatocellular carcinoma. Current antiviral therapy (immunomodulators, nucleos(t)ide analogues) rarely eradicates the virus resulting in de novo HBV reactivation during chemotherapy. Moreover, HBV's high mutation rate can lead to drug resistance. In order to cure HBV infection, it is crucial to develop new therapies that target different stages in the viral life cycle that are capable of achieving more than viral suppression.

HBV RNaseH is a metalloenzyme that belongs to the nucleotidyl transferase superfamily and its active site contains four carboxylates that bind to two Mg^{2+} ions required for the RNA cleavage. However, the potential of RNaseH as a drug target for HBV treatment, was never seriously explored until recently. The importance of the RNaseH prompted the development of novel scaffolds, bearing a metal-chelating motif, as potent inhibitors.

Utilizing findings in the literature and our previous publications, we have rationally designed and synthesized a series of metal-chelating agents (*N*-hydroxyimides) to optimize our lead compound. The novel analogues were tested for their anti-HBV activity, and they were considerably potent with IC50 values in the mid nM range. Our studies indicate that this class of compounds is a valuable platform for antiviral development.

87. Metal Chelating Agents with Improved Inhibitory Activity against Hepatitis C Virus

Erofili Giannakopoulou, M.S.[1], Vasiliki Pardali, M.S.[1], Efseveia Frakolaki, M.S.[2], Vassilios Myrianthopoulos, Ph.D.[1], Emmanuel Mikros, Ph.D.[1], Ralf Bartenschlager, Ph.D.[3], Niki Vassilaki, Ph.D.[2], Grigoris Zoidis, Ph.D.[1]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Athens, Athens, Greece; [2]Molecular Virology Laboratory, Hellenic Pasteur Institute, Athens, Greece; [3]Department of Infectious Diseases, Molecular Virology, University of Heidelberg, Heidelberg, Germany

Hepatitis C Virus (HCV) infections pose a major public health threat globally, with infected individuals being at risk of developing chronic liver disease, cirrhosis and hepatocellular carcinoma. Despite the great advances in treatment options, patients may still not have access to effective treatments due to high cost. Moreover, current chemotherapy is associated with numerous side effects and viral resistance, and without a vaccine at the horizon, the global burden of HCV infections remains high.

Based on literature reports on metal-chelating antivirals we have previously designed and synthesized novel indole-diketopiperazine heterocycles with activity against Hepatitis C virus. Trying to investigate the role of the metal binding group, structural modifications were undertaken to obtain a novel class of metal chelators. Here we report the design and synthesis of a series of compounds described as bicyclic-substituted hydantoin analogues, which were evaluated for their ability to inhibit HCV replication exhibiting really low EC_{50} values, which was a marked improvement over that of the parent compounds.

Several substituents were incorporated to the lead compounds, which, along with the performed docking-scoring calculations, were used to better characterize the Structure-Activity Relationships of the synthesized derivatives. All the compounds were fully characterized and evaluated for their effect on HCV RNA replication and cell viability. Biological results suggest that the novel class of the metal-chelators, presented herein, offers a highly promising starting point for the design of potent anti-HCV agents.

88. Pressurized DNA State Inside Herpes Capsids – A Novel Antiviral Drug Target

Alex Evilevitch, Ph.D.[1]
[1]*University of Illinois at Urbana-Champaign, Department of Pathobiology, Urbana, Illinois*

Drug resistance in viruses represents one of the major challenges of healthcare. We discovered a novel mechanism of action (MOA) and specific compounds to treat all nine human- and animal herpesviruses. This MOA targets the pressurized genome state in a viral capsid, "turns off" capsid pressure and blocks viral genome ejection into a cell nucleus, preventing viral replication and eliminating the risk of drug resistance. This pivotal finding presents a platform for discovery of broad-spectrum treatments for herpesviruses and other emerging and existing viral infections with genome pressure dependent replication.

89. Identification of Sterol Regulatory Element Binding Protein-dependent Lipidomic Reprogramming as a Broad-spectrum Antiviral Target

Jasper Chan, M.D.[1], Shuofeng Yuan, Ph.D.[1], Hin Chu, Ph.D.[1], Zi-Wei Ye, Ph.D.[1], Lei Wen, M.S.[1], Bingpeng Yan, Ph.D.[1], Kelvin To, M.D.[1], Richard Kao, Ph.D.[1], Kwok-Yung Yuen, M.D.[1]
[1]*State Key Laboratory of Emerging Infectious Diseases, Department of Microbiology, The University of Hong Kong, Hong Kong, Hong Kong*

Viruses are obligate intracellular microbes that exploit the host metabolic machineries to meet their biosynthetic demands, making these host pathways potential therapeutic targets. Integrative transcriptomic and lipidomic analysis with simultaneous mapping of dysregulated gene expression and dysregulated lipids showed that the glycerophospholipid metabolism was the most affected pathway in cells infected with Middle East respiratory syndrome coronavirus (MERS-CoV). Screening of a bioactive lipid mediators library showed that AM580, a retinoid derivative and RAR-αagonist, is highly potent in interrupting the life cycle of a broad spectrum of viruses, including MERS-CoV, SARS-CoV, influenza viruses, Zika virus, enteroviruses, and adenovirus. Treatment with AM580 significantly improved the survival rate, body weight, and viral load of human dipeptidyl-peptidase 4-transgenic mice infected with MERS-CoV. Using click chemistry, the overexpressed sterol regulatory element binding protein (SREBP) was shown to interact with AM580, which accounts for its broad-spectrum antiviral activity. Our study showed that AM580 exhibits broad-spectrum antiviral activity against various emerging and respiratory viruses via disruption of the host lipid metabolism. Further studies should be conducted to elicit the full spectrum of viruses that can be inhibited by the broad-spectrum AM580 and the downstream lipid biosynthesis pathways involved in AM580-treated cells.

90. High-throughput Screening of 200K Small Molecules Identified Antiviral Compounds against Middle East Respiratory Syndrome Coronavirus

Jihye Lee, M.S.[1], Chul Min Park, Ph.D.[2], Jong Hwan Song, Ph.D.[2], Hyoung Rae Kim, Ph.D.[2], Seungtaek Kim, Ph.D.[3]
[1]*Respiratory Virus Laboratory, Emerging Virus Group, Discovery Biology Department, Institut Pasteur Korea, Seongnam, Gyeonggi, Korea (Republic of);* [2]*Center for Convergent Research of Emerging Virus Infection, Korea Research Institute of Chemical Technology, Daejeon, Korea (Republic of);* [3]*Zoonotic Virus Laboratory, Emerging Virus Group, Discovery Biology Department, Institut Pasteur Korea, Seongnam, Gyeonggi, Korea (Republic of)*

Since its first emergence in Saudi Arabia in 2012, Middle East respiratory syndrome coronavirus (MERS-CoV) has continually spread to neighboring countries of the Arabian Peninsula. Due to the human-to-human transmission, disease severity and high fatality, the MERS-CoV presents a significant threat to public health worldwide. However, there are limited treatment options against MERS-CoV infection. In an effort to identify potential drug candidates, we screened a library of 200,000 small molecules in Vero cells using a high-throughput image-based assay. In the primary screening, 964 compounds that inhibited >90% MERS-CoV infection with >90% cell viability were identified. By sorting out chemically and biologically unfavorable molecules, we selected 274 compounds as primary hits and subsequently evaluated their antiviral efficacy by dose-response curve (DRC) analysis. Classification of the active hits based on their selective index ($SI=CC_{50}/IC_{50}$) indicated enrichment of three chemical scaffolds. For further study, we selected several compounds with the highest antiviral effect from each scaffold. Time-of-addition assay suggests that these compounds mainly act on the early stages of the viral life cycle. In addition, these compounds inhibited severe acute respiratory syndrome coronavirus (SARS-CoV) infection. Although their inhibitory effect remains to be tested in the animal model, our results may offer therapeutic options for the treatment of coronavirus infection.

91. Evaluation of Sex as a Variable for Influenza Virus Infection and Treatment with Oseltamivir in Mice

Brett Hurst, Ph.D.[1], Bart Tarbet, Ph.D.[1]
[1]*Institute for Antiviral Research, Utah State University, Logan, Utah, United States of America*

According to the National Institutes of Health (NIH) Notice Number NOT-OD-15-102, NIH research should focus on improving the health outcomes of men and women and thus sex should be considered as a biological variable for the development and testing of preventive and therapeutic interventions. Since our research has primarily been completed in female mice, here we evaluated the suitability of male BALB/c mice for testing therapeutic compounds against influenza virus infection. We found that the amount of virus required for infection as well as the effective concentration of oseltamivir varied depending upon influenza virus strain. Male BALB/c mice infected with influenza A/California/04/2009 (H1N1pdm) required three-fold more virus to induce similar mortality compared to female mice and a dose of 30 mg/kg/day of oseltamivir only protected 80% of mice from mortality, while female mice were 100% protected by just 10 mg/kg/day of oseltamivir. Male BALB/c mice infected with influenza A/Victoria/3/75 (H3N2) were more susceptible to virus infection and were protected by a dose of 10 mg/kg/day of oseltamivir while female mice required a dose of 30 mg/kg/day of oseltamivir to provide significant protection from mortality. Male mice infected with highly pathogenic influenza A/Vietnam/1203/2004 (H5N1) were more susceptible to virus infection and oseltamivir provided protection at a dose of 30 mg/kg/day while female mice were only protected by a dose of 100 mg/kg/day. These data support the idea that therapeutic compounds should be evaluated in animals of both sexes. *[Supported by Contract HHSN272201700041I from the Respiratory Diseases Branch, DMID, NIAID, NIH]*

92. Lipid Based Nanoparticulate System for Effective Vaccine Delivery

Marut Agarwal, M.D., MPH[1], Prateek Gupta, M.D., MPH[2], Saurabh Bhargava, M.D., MPH[3]
[1]*Dr. H S Gour University, India;* [2]*KRV Hospital, India;* [3]*United Institute of Pharmacy, India*

The search for innovative ways of vaccination has intensified recently with declining vaccine coverage and growing public concern about new virulent disease outbreaks. The work envisaged here explores potential of Solid Lipid Nanoparticles(SLN) in efficient protein delivery through surface modifications using subcutaneous route(SC).

The SLN were prepared by Solvent Injection Method & optimized. The characterization included Transmission & Scanning Electron Microscopy, X-Ray Diffraction Analysis, *In-vitro* release, Kinetics of uptake by flow cytometer, Evaluation of cell apoptosis, T-cell proliferative assay, TH1/TH2 cytokine profile and Internalization studies by spectral bioimaging. *In-vivo* study comprised fluorescence studies and estimation of IgG in serum, sIgA in various body secretions using specific ELISA.

The particulate system is better carrier system for immunization because of less diffusivity and restricted movement.SLNs themselves act as signal for the phagocytic cells.Surface modified SLNs can entrap greater amount of antigen, provide its sustained release and rapidly internalized by the antigen presenting cells. *In-vitro* T-cell proliferation and induction of TH1 type of immune response clearly marks, potential of this novel carrier system. Fluorescence studies showed better uptake of surface modified SLNs. Higher and more sustained antibody titer obtained with surface modified SLNs suggests their better immunological potential. Thus, SC immunization could be an efficient alternative approach for vaccination against hepatitis.

The formulations developed in this study can be further explored for the incorporation and delivery of other proteins and peptides should subsequently be subjected to pilot plant scale-up & clinical trial to establish their potential for subcutaneous immunization against hepatitis-B.

94. To Identify Plant Based Potential Antiviral/s against Chikungunya Virus

Ashok Patel, Ph.D.[1]
[1]*Kusuma School of Biological Sciences, IIT Delhi, India, New Delhi, India*

Chikungunya, a mosquito-borne viral disease is now a global public health problem. To curtail the virus in outbreak situation, a ready to use drug for chikungunya is necessary. Using the literature mentioned plant extracts, we used three assays to screen and identify indigenous plants with CHIKV inhibitory activity. Our preliminary results showed that the aqueous extract of five plant extracts exhibited antichikv activity by inhibiting viral attachment, four plant extracts exhibited replication inhibition through inhibition of helicase activity, two plants showed inhibition of protease activity. Two plant extracts showed both viral attachment inhibition and replication inhibition. These findings taken in the context of the human safety of these plant extracts, based on their use in traditional ayurvedic practice, warrant further work to standardize these plant extracts as a source for a carefully standardized herbal drug development for chikungunya infection.

96. Influenza Antivirals: Recent Developments

Frederick Hayden, M.D.[1]
[1]*University of Virginia School of Medicine, Charlottesville, Virginia, United States of America*

Randomized, controlled trials (RCTs) have not found intravenous peramivir or zanamivir superior to oral oseltamivir in hospitalized influenza patients, although zanamivir's spectrum includes many oseltamivir-resistant variants. RCTs testing antibody-based therapeutics have yielded mixed results. Three oral inhibitors (favipiravir, pimodivir, baloxavir marboxil) targeting components of the influenza polymerase complex (PB1, PB2, and PA endonuclease, respectively) are inhibitory for viruses resistant to currently available antivirals and show synergy when combined with NAIs in pre-clinical models. Favipiravir, approved in Japan in 2014 with very restricted indications because of its potential teratogenicity, has demonstrated virologic but variable clinical efficacy in uncomplicated influenza. Pimodivir has shown dose-related antiviral efficacy in uncomplicated influenza A illness, although variants with PB2 substitutions conferring reduced susceptibility emerge commonly during monotherapy. Pivotal RCTs of pimodivir added to standard of care (primarily NAIs) in high-risk outpatients and in hospitalized patients are in progress. Single-dose baloxavir, approved in Japan and the USA in 2018, significantly shortens illness in otherwise healthy and higher-risk outpatients with uncomplicated influenza compared to placebo. Its efficacy is similar to a 5-day course of oseltamivir, but baloxavir appears more effective in influenza B. Its antiviral efficacy is superior to th at of oseltamivir, but emergence of variants with PA substitutions at position I38 conferring reduced susceptibility occur commonly. Further RCTs testing baloxavir treatment in children and, combined with NAIs, in hospitalized patients are in progress. Antiviral combinations offer the best strategy to enhance potency and reduce resistance emergence in treating higher-risk influenza patients and those hospitalized with serious illness.

97. Structural Analysis Kobuviral RNA Polymerase Reveals a Novel Fold of the N-terminus among Picornaviruses

Anna Dubankova, M.S.[1], **Evzen Boura, Ph.D.**[1]
[1]*Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Prague*

RNA ependent RNA polymerase (3D^{pol}) is a key enzyme for the life cycle of all picornaviruses. The 3D^{pol} enzymes catalyze formation of phosphodiester bond between RNA nucleotides. The polymerase is active only after proper proteolytical processing. The newly created first residue is a conserved glycine in all the 3Dpol enzymes that were analyzed so far. This glycine is buried in a conserved pocket which is essential for enzymatic activity. However, this glycine is not conserved in the genus kobuvirus. Instead kobuviruses (i. e. Aichi virus) have a serine residue. Intrigued by this anomaly we sought to solve the crystal structure of kobuviral 3D^{pol} enzyme.

We determined the crystal structure of Aichi 3D^{pol} at 2.3 Å resolution. The structure uncovered the typical right hand fold. But the structure also revealed a unique fold of the 3D^{pol} N-terminus. The very first serine residue is also inserted into a charged pocket via a water bridge suggesting that throughout the evolution of picornaviruses the mechanism of 3D^{pol} activation after precursor cleavage remains conserved.

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98. Heme Oxygenase-1 Inhibits Influenza A Virus via the Induction of Interferon Response

Peng Zhang, Ph.D.[1], Linlin Ma, Ph.D.[2], Huiqiang Wang, Ph.D.[1], Haiyan Yan, Ph.D.[1], Sheng Tang, Ph.D.[1], Danqing Song, Ph.D.[1], Jiandong Jiang, Ph.D.[1], Yuhuan Li, Ph.D.[1]

[1]*Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing;* [2]*Shanghai University of Medicine and Health Sciences*

Heme oxygenase-1 (HO-1) is a cellular enzyme that can be induced by virus infections and suppresses the replication of many medically important viruses, such as HIV, HCV, HBV, EV71, IAV, RSV, DENV, ZIKV and EBOV. In our continuing efforts toward understanding the antiviral mechanism of HO-1 against influenza A virus, we found that HO-1 induced the interferon response might be responsible for its anti-IAV activity. We found that HO-1 directly interacted with IRF3 to promote its phosphorylation/nuclear translocation and subsequent activation of type I IFN expression. Previous study found that the expression of MAPK phosphatase 5 (MKP5) was significantly increased in response to IAV infection and MKP5 could downregulate the expression of type I IFN through interacting with IRF3 to induce its dephosphorylation. We found that HO-1 could decrease MKP5 expression induced by IAV and relieve IRF3 from interaction with MKP5. However, there was no interaction between HO-1 and MKP5. In conclusion, our studies clearly demonstrate that HO-1 both directly interacted with IRF3 and liberated IRF3 from MKP5 inhibition to promote its phosphorylation and IRF3-type I IFN responses.

99. The Performance of ARCHITECT i2000SR in the Determination of HBsAg Qualitative II, Anti-HBc II and Anti-HBs Assays Utilized for Routine Laboratory Hepatitis B Testing

Nafija Serdarevic, Ph.D.[1]

[1]*Clinical Center University of Sarajevo, Department of Clinical biochemistry and Immuology, Sarajevo, Bosnia and Herzegovina*

The routine diagnosis of Hepatitis B Virus (HBV) infection is often assessed by using a panel consisting of HBsAg, Anti-HBc and Anti-HBs assays. The aim of the current study was to evaluate the key performance characteristics of these three assays that were developed for the ARCHITECT i2000sr (ABBOTT) I system. The HBsAg Qualitative II, Anti-HBc II, and Anti-HBs assays were tested side by side with the corresponding ARCHITECT assays. Clinical specificity was assessed using unselected blood donor and routine diagnostic specimens, clinical sensitivity was determined using pedigreed positive specimens. The clinical sensitivity of the HBsAg Qualitative II assay was found to be 100,00 % using 496 known positive samples including different genotypes and mutants. The Anti-HBc II assay also showed 100,00 % sensitivity, detecting all specimens from patients with acute, chronic and past/resolved HBV infection with anti-HBc antibodies. The specificity for blood donor specimens of the assays under evaluation was 99.96% (5108/5110) for HBsAg Qualitative II and 99.86% (5162/5169) for Anti-HBc II. The quantitative Anti-HBs assay, standardized to the WHO International Reference Preparation, 2008 (code 07/164), had an LoB of 0.53 mIU/mL, LoD of 0.77 mIU/mL, and an LoQ of 2.00 mIU/mL. It showed performance within acceptance criteria for linearity, imprecision, and bias across the entire measuring range from 2.00 mIU/mL up to 1000.00mIU/mL. The key performance characteristics of three assays used for routine Hepatitis B testing, HBsAg Qualitative II, Anti-HBc II, and Anti-HBs are equivalent to the corresponding determination of hepatitis B in blood.

100. Phenotypic Characterization of CMV Terminase Complex Genotypic Variants Observed in Subjects with Virologic Failure in a Phase 3 Study (P001) of Letermovir

Juile Strizki, Ph.D.[1], Hong Wan, Ph.D.[1], Valerie Teal, Ph.D.[1], Carolee Welebob, Ph.D.[1], Cyrus Badshah, M.D.[1] Sunwen Chou, Ph.D.[2], Cameron Douglas, Ph.D.[1]

[1]Merck and Co., Inc., Kenilworth, New Jersey, United States of America; [2]Oregon Health and Sciences University and VA Medical Center, Portland, Oregon, United States of America

Resistance to the CMV terminase inhibitor letermovir maps primarily to a "hot spot" (aa 229-369) in the pUL56 subunit. In a Phase 3 trial, CMV UL56 and UL89 genotypic variants were observed at the time of virologic failure among subjects who experienced CMV breakthrough. Phenotypic analysis was used to determine the impact on letermovir susceptibility of uncharacterized CMV variants detected in letermovir-treated subjects. Uncharacterized UL56 and UL89 variants observed in CMV from letermovir-treated but not placebo subjects were phenotyped by introducing substitutions into a wild-type CMV bacterial artificial chromosome containing a SEAP reporter. The resulting mutants were evaluated for susceptibility to letermovir in infected ARPEp cells using a SEAP yield reduction assay. Among the newly-identified UL56 variants evaluated, only the pUL56 E237G and R369T substitutions conferred reduced susceptibility to letermovir, with EC_{50} changes of 13- and 52-fold, respectively. Other UL56 variants encoding the M3V, S255L, E485G +/- del(445-447), Y575C, F626S, L726V, T775S, del(789-791), V814A and R816W substitutions and the pUL89 I531T substitution had no effect on letermovir activity (EC_{50} fold change; 0.5 to 1.1). Replication of the pUL56 F626S and pUL89 I531T mutant viruses was measurably impaired relative to wild-type virus. Phenotypic assessment of previously uncharacterized substitutions in pUL56 and pUL89 showed only pUL56 E237G and R369T substitutions were associated with reduced susceptibility to letermovir. Additional real world clinical data are needed to better understand the impact of terminase complex variants on clinical response to letermovir.

101. Elevation of D-dimer is Linked to Disease Severity and Predicts Fatal Outcomes in H1N1 Infection

Nafija Serdarevic, Ph.D.[1]

[1]Clinical center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

To assess whether an increased D-dimer level was related to worse renal, heart, and respiratory outcomes in critically ill patients with H1N1 infection and whether D-dimer could serve as a biomarker of severity. D-dimer levels in Plasma were serially measured on 130 H1N1 patients (45 lethal and 85 non-lethal cases). 79 H1N1 patients and 71 healthy volunteers were selected as controls.

Results: Plasma D-dimer level in H1N1 patients was significantly higher than those in normal controls (P <0.001).The plasma D-dimer level in the death group was significantly higher than that in the survival group (P <0.001). Plasma D-dimer levels were positively correlated with hypersensitive C-reactive protein (HsCRP) and procalcitonin (PCT), liver indicators(ALT and AST)and cardiac indicators (CK, CKMB, LDH)., as well as severity indicators PSI and APACHE II scores (r = 0.501 and 0.320, P <0.001). The area under the ROC curve for prediction of patient death at a plasma D-dimer level of 2943 ug/L FEU was 0.822, with a sensitivity of 83.9% and a specificity of 74.2%, better than HsCRP and PCT. The survival rate of the group of patients with D-dimer> 3943 ug/L FEU was significantly lower than that of patients with D-dimer≤2000 ug / L FEU (P = 0.024). Plasma D-dimer levels have a certain correlation with the severity and prognosis of H1N1. The higher the plasma D-dimer level, the lower the survival rate of patients. Monitoring D-dimer levels can help physicians to determine the severity and prognosis of H1N1.

102. Design, Synthesis and Biological Evaluation of Peptidomimetic Aldehydes as Anti-EV71 and Anti-MNV Inhibitors

Wenhao Dai, M.S.[1], Joana Rocha-Pereira, Ph.D.[2], Johan Neyts, Ph.D.[3]
[1]*Chinese Academy of Sciences Shanghai Institute of Materia Medica,China Pharmaceutical University;*
[2]*KU Leuven · Rega Institute for Medical Research;* [3]*KU Leuven · Department of Microbiology and Immunology*

The 3C protease($3C^{pro}$) and 3C-like protease($3CL^{pro}$) have long been considered as attractive antiviral targets. They play crucial roles in the replication of several viruses such as enteroviruses and noroviruses. Enterovirus 71 (EV71) is threatening the public health around the world, which is not only the primary pathogen of hand, foot and mouth disease (HFMD), but also associated with some central neurological syndromes. Noroviruses are the primary cause of sporadic and epidemic acute gastroenteritis, and more than 20 million cases of acute gastroenteritis break out in the US every year. However, to date there are no marketed drugs to prevent those associated diseases.

By investigating the SAR of Rupintrivir (AG7088), a new series of peptidomimetic aldehydes were designed, synthesized and evaluated on enterovirus 71(EV71) and murine norovirus (MNV)'s cell-based replication. Most of the compounds exhibited good antivirus activity. Two compounds DC401924 and DC401986 displayed anti-EV71 activities (EC_{50} = 0.10 ± 0.01 μM and 0.06 ± 0.01 μM), compounds DC401986 and DC401608 showed potential anti-MNV activities (EC_{50} =0.31 ± 0.06 μM and 0.29 ± 0.29 μM). In summary, this study provided important insight for developing a broad-spectrum antiviral drug.

103. Vitamin D Serum Concentration at Patients with Hepatitis B

Nafija Serdarevic, M.D., Ph.D.[1]
[1]*Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina*

In addition to its well-known effect on calcium metabolism, vitamin D has various roles such as regulation of inflammatory processes, immune response, cell proliferation, and differentiation. Hepatitis viruses can cause inflammatory liver disease and vitamin D deficiency was reported in patients with hepatitis C virus (HCV) infection. Vitamin D deficiency is a common finding in chronic liver disease patients but there is not much data on serum vitamin D levels of hepatitis B virus (HBV) infected patients. The study included 57 patients with HBV infection and 19 age-matched healthy controls. Serum 25-OH vitamin D levels were measured by Cobas 601E (Roche) Chemiluminescence assay. Determination of antiHBs and anti-HCV was done using VITROS 5600 (Orto Clinical Diagnostic). Data are presented as mean ± standard deviation. Spearman's rho and Mann-Whitney U tests were used as appropriate. A test result of $p<0.05$ was considered statistically significant. Mean serum vitamin D levels were lower in HBV infected patients by 3.79 ng/mL (27%) compared to the controls ($p<0.037$). There was no correlation between vitamin D levels and antiHBs or antiHCV in the patient population, however, the control group showed an inverse correlation between these markers ($r2=0.228$, $p<0.039$). Vitamin deficiencies are common in various viral hepatitis types and we showed that the serum vitamin D levels of HBV patients were lower than controls. Vitamin D is suggested to decrease viral replication so maintaining normal vitamin D levels might be beneficial in viral hepatitis. Furthermore, we suggest vitamin D supplementation in deficient individuals.

104. From Oxetane to Thietane: Extending the Antiviral Spectrum of 2′-Deoxy-2′-spirocyclic Uridine Derivatives by Substituting Oxygen for Sulfur

Tim Jonckers, Ph.D.[1], Abdellah Tahri, Ph.D.[1], Jean-François Bonfanti, Ph.D.[2], Pierre Raboisson, Ph.D.[1], Bart Stoops, M.S.[1], Marnix Van Loock, Ph.D.[1], Olivia Goethals, Ph.D.[1], Peggy Geluykens, B.S.[3], Edwin Gong, Ph.D.[1], Guenter Kraus, Ph.D.[1]
[1]*Janssen Pharmaceutica N.V., Beerse, Antwerpen, Belgium;* [2]*Janssen-Cilag, Val de Reuil Cedex, Rouen, France;*
[3]*Charles River, Beerse, Antwerpen, Belgium*

In continuation of our efforts to identify novel nucleoside inhibitors for the treatment of viral pathogens, we initiated a discovery research program to find novel nucleos(t)ide inhibitors for emerging pathogens like Dengue and Chikungunya. Based on the previously discovered 2′-deoxy-2′-spiro-oxetane uridine analogues, which display activity against HCV, we envisaged its sulfur analog as an interesting congener from both a synthetic as biological point of view. Here we report on our observation that 2′-deoxy-2′-spiro-thietane uridine derivatives display an enlarged antiviral spectrum as they not only inhibit the HCV virus, which belongs to the flavivirus family, but they also demonstrate activity against Dengue virus and alphaviruses like Chikungunya virus.

105. RIG-I Agonist as a Therapeutic Agent against Filovirus Infections

Xiangguo Qiu, M.D.[1], Logan Banadyga, Ph.D.[1], Wenguang Cao, Ph.D.[1], Shihua He, Ph.D.[1], Marie-Line Goulet, M.S.[2], Rongtuan Lin, Ph.D.[2]

[1]Special Pathogens Program, National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, Manitoba, Canada; [2]Lady Davis Institute-Jewish General Hospital, McGill University, Montreal, Quebec, Canada

Ebola virus (EBOV) and Marburg virus (MARV), both members of the *Filoviridae* family, are causative agents of severe viral hemorrhagic fever. Most recently, EBOV incited an epidemic in West Africa from 2013 to 2016 with over 30,000 infected people and 11,000 deaths. However no clinically-approved therapeutic or vaccine exists yet. We have developed an immunotherapeutic, known as 5'pppRNA, that is capable of broad-spectrum inhibition of a variety of DNA and RNA viruses, including both EBOV and MARV. Because 5'pppRNA mimics viral double-stranded RNA with a 5' terminal triphosphate (5'ppp), it serves as a potent activator of the innate immune system via the RIG-I signalling cascade and is capable of inducing a broad and diverse antiviral response. Indeed, preliminary evidence revealed that 5'pppRNA completely blocked EBOV infection at concentrations as low as 1 ng/ml, suggesting that this molecule may represent a powerful new therapeutic. Subsequent efficacy testing in mice infected with either mouse-adapted EBOV or MARV demonstrated that early treatment with 15 ug/kg 5'pppRNA on days 1 and 2 post-infection (dpi) resulted in complete survival, reducing virus levels in the blood and normalizing biochemical markers typically associated with filovirus disease. Moreover, a single, higher dose of 25 ug/kg 5'pppRNA given on 1 dpi resulted in 100% survival of EBOV-infected animals and over 80% of MARV-infected animals. 5'pppRNA represents a promising new therapeutic capable of potently inhibiting filovirus infection. Future work will focus on optimizing the treatment regimen and drug delivery, prior to eventual efficacy testing in non-human primates.

106. Phenotypic Impact of Single Tenofovir Resistance Mutations on HIV-1 Subtype C Virus

Onyisi Christiana Didamson, B.S.[1], Michelle Gordon, Ph.D.[1]

[1]Department of Virology, University of KwaZulu Natal, Durban, KwaZulu Natal, South Africa

Tenofovir (TDF) is a recommended first-line antiretroviral regimen for the treatment of HIV infection. Yet, can be compromised by the emergence of drug resistance mutations. *In vitro* study is required to demonstrate the influence of mutations on tenofovir susceptibility. Here we studied the replication capacity and the phenotypic effects of four single mutations (A62V, K65R, S68D, and Y115F) that are frequently found with tenofovir resistance.

The HIV-1 RT mutations were introduced by site-directed mutagenesis and confirmed by sequencing. Recombinant mutants were generated by co-transfection of a CEM-GXR25 derived T-cell line with an NL43-deleted-reverse transcriptase backbone and the mutants derived RT amplicons. The replication capacity of each mutant virus were conducted by infecting CEM-GXR25 cells and the percentage positive green fluorescent protein of infected cells for a period of seven days were measured using flow cytometry. The impact of the mutant viruses on susceptibility to TDF was assessed in a luciferase based assay. The 50% effective concentration (EC50) was calculated using Graph Pad Prism. Drug susceptibility was expressed as the fold change in EC50 of mutant virus compared with the wild type virus

The study showed no statistical significance difference between the replication capacity of the wild-types and the mutant viral strains in the absence of tenofovir selection pressure. While in the presence of tenofovir selection pressure K65R, K65R_S68N and Y115F replicate more than the wild-types strains. This study demonstrated that tenofovir resistance mutations can impact on TDF drug susceptibility.

This work will contribute to the management of HIV-1 infected patients.

107. Mercaptobenzamide Thioesters as HIV Inactivators: SAR Evaluation, Computational Modeling and Thermodynamic Studies

Marco Robello, Ph.D.[1], Herman Nikolayevskiy, Ph.D.[1], Michael Scerba, Ph.D.[1], Evan Pasternak, B.S.[1], Mrinmoy Saha, Ph.D.[1], Tracy Hartman, M.S.[2], Caitlin Buchholz, M.S.[2], Robert Buckheit, Jr., Ph.D.[2], Stewart Durell, Ph.D.[3], Daniel Appella, Ph.D.[1]

[1]Synthetic Bioactive Molecules Section, LBC, NIDDK, NIH, Bethesda, Maryland, United States of America; [2]ImQuest Biosciences, Frederick, Maryland, United States of America; [3]Laboratory of Cell Biology, NCI, NIH, Bethesda, Maryland, United States of America

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. Mercaptobenzamide thioesters 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 a series of mercaptobenzamide prodrug analogs (Fig. 1) to investigate their structure-activity relationship (SAR) profiles. To probe the relationship between antiviral activity and toxicity, we generated an improved computational model for the binding of mercaptobenzamide thioesters (SAMTs) to the HIV-1 NCp7 C-terminal zinc finger, revealing the presence of a second low-energy binding orientation. Finally, using NMR-derived thiol–thioester exchange equilibrium constants, we propose that thermodynamics plays a role in determining the antiviral activity observed in the SAR profile.

108. SAR Studies of 4-Acyl-1,6-dialkylpiperazin-2-ones Based Arenavirus Cell Entry Inhibitors

Michael Plewe, Ph.D.[1], Landon Whitby, Ph.D.[2], Eric Brown, B.S.[3], Shibani Naik, Ph.D.[3], Nadia Sokolova, Ph.D.[3], Vidyasagar Gantla, Ph.D.[3], Joanne York, B.S.[4], Jack Nunberg, Ph.D.[4], Dale Boger, Ph.D.[5], Greg Henkel, Ph.D.[3], Ken McCormack, Ph.D.[3]

[1]Cullgen, San Diego, California, United States of America; [2]Vividion, San Diego, California, United States of America; [3]Arisan Therapeutics, San Diego, California, United States of America; [4]Montana Biotechnology Center, Missoula, Montana, United States of America; [5]Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, San Diego, California, United States of America

The hemorrhagic fever arenaviruses represent serious threats to public health, particularly in regions of Africa and South America where the viruses are endemic. These viruses are classified as Category A pathogens by the Centers for Disease Control (CDC) due to their high mortality rates and the currently limited therapeutic options for treatment. In previous reports, 4-acyl-1,6-dialkylpiperazin-2-ones were shown to inhibit cell entry of both Old World (Lassa) and New World (Machupo and Junin) hemorrhagic fever arenaviruses. Herein we describe the synthesis and structure-activity-relationship (SAR) of this chemical series consisting of over 350 diverse compounds. Initial scanning libraries varying either N1 or N4 substituents were tested for their ability to inhibit cell-cell fusion mediated by the Lassa virus envelope glycoprotein. After the identification of potent N1 and N4 substituents additional analogs varying R6, with iterative N1, N4 and R6 substituent combinations thereof, were synthesized and broad-spectrum arenavirus inhibitory activity was characterized using VSV pseudotyped virus assays expressing the glycoproteins from Lassa, Machupo and Junin. A comparison of activities in pseudotyped vs. replicative Tacaribe virus (a BLS2 arenavirus closely related to Machupo and Junin) assays subsequently confirmed that activities against pseudotyped viruses translate to the inhibition of replicative viruses. Additional characterizations of *in vitro* human liver microsome metabolic stability and solubility led to the identification of nanomolar, broad-spectrum and potentially metabolically stable analogs suitable for evaluation in *in vitro* and *in vivo* animal studies. *This work was supported in part by the National Institutes of Health (R43AI112097, R44AI112097, CA078045 and AI074818).*

109. The Ribavirin Analogue Methyl 1-benzyl-1H-1,2,3-triazole-4-carboxylate Inhibits Influenza Replication and Possesses Immunomodulatory Properties *In Vitro* and *In Vivo*

Carolina Sacramento, Ph.D.[1], Natalia Fintelman-Rodrigues, Ph.D.[1], Andressa Marttorelli, Ph.D.[1], Caroline de Freitas, M.S.[1], André Ferreira, Ph.D.[1], Cristiana Garcia, Ph.D.[1], Alexandre Machado, Ph.D.[1], Andrea Surrage, Ph.D.[1], Milene Miranda, Ph.D.[1], Maria de Lourdes Ferreira, Ph.D.[1], Luiz Pinheiro, Ph.D.[1], Nubia Boechat, Ph.D.[1], Fernando Bozza, Ph.D.[1], Thiago Souza, Ph.D.[1]
[1]*FIOCRUZ*

Influenza virus represents one of the main causes of acute respiratory infections, and causes a major public health burden. Neuraminidase inhibitors, such as oseltamivir, are the sole class of anti-influenza drugs in clinical use. Nevertheless, oseltamivir-resistant strains have been described, motivating the search for novel compounds with different targets. Ribavirin is a guanosine analogue with a broad spectrum antiviral action, including anti-influenza. Ribavirin targets viral DNA/RNA polymerases and regulates cytokine production, despite its high cytotoxicity. We aimed to study the anti-influenza activity of the ribavirin analogue, compound 5b. Compound 5b was less cytotoxic and more potent than ribavirin by inhibiting influenza replication on MDCKs, presenting a selective index of 3,000-fold higher comparing to ribavirin, indicating its higher safety *in vitro*. Our compound inhibits influenza RNA polymerase activity in a dose-dependent manner and disrupts the balance between the viral genome transcription and replication. Otherwise than ribavirin, compound 5b does not affect cellular enzyme inosine monophosphate dehydrogenase activity. Compound 5b at a dose 200 mg/kg administered orally to Swiss mice showed no toxicity *in vivo*. Our drug demonstrated immunomodulatory properties by reducing the production of influenza-dependent and influenza-independent pro-inflammatory cytokines *in vitro* and *in vivo*. Besides, the treatment of influenza-infected C57BL/6 mice with compound 5b reduced viral RNA levels in the lungs of the animals, modulated cell-mediated inflammation in bronchoalveolar lavage (BAL) and lungs, and prevented influenza-induced enhancement of pro-inflammatory cytokines in the BAL. Altogether our data suggest that compound 5b is a potent inhibitor of influenza polymerase with desirable immunomodulatory properties.

110. Filociclovir is a Potent *In Vitro* and *In Vivo* Inhibitor of Human Adenoviruses

Islam Hussein, Ph.D.[1], Karoly Toth, D.V.M.[2], Jennifer Brooks, M.S.[1], Ann Tollefson, Ph.D.[2], Baoling Ying, M.D.[2], Jacqueline Spencer, B.S.[2], John Morrey, Ph.D.[3], Mark Prichard, Ph.D.[4], William Wold, Ph.D.[2], Terry Bowlin, Ph.D.[1]
[1]*Microbiotix, Worcester, Massachusetts, United States of America;* [2]*Saint Louis University School of Medicine, St. Louis, Missouri, United States of America;* [3]*Utah State University, Logan, Utah, United States of America;* [4]*University of Alabama at Birmingham, Birmingham, Alabama, United States of America*

Human adenovirus (HAdV) infection is common in the general population and can cause severe acute respiratory disease among children and epidemics in military recruits. Clinical manifestations also include pneumonia, keratoconjunctivitis, hemorrhagic cystitis, gastroenteritis, meningoencephalitis, and hepatitis. Infections in immunocompromised individuals are similar in scope, but more severe, particularly in bone marrow transplant recipients. The options for controlling HAdV infections are very limited. Live oral vaccines reduce the risk of respiratory illness and are in routine use by the US military, but currently are not available to civilians and only provide protection against types 4 and 7. No antiviral drug has been approved for treating adenoviruses. Therefore, there is an unmet medical need for a safer alternative. Filociclovir(FCV) is a methylenecyclopropane nucleoside analog, which has successfully completed Phase I human clinical safety studies and is now being developed for the treatment of human cytomegalovirus-related disease in immunocompromised patients. We show here that FCV is a potent inhibitor of human adenoviruses 5, 6, 7 and 8 with EC_{50}values ranging between 1 – 3.6 μM and CC50of 95 – >150 μM in human foreskin fibroblast cells. We also show that the oral administration of FCV daily for 14 days at doses of 10 and 30 mg/kg to immunosuppressed Syrian hamsters infected intravenously with HAdVC6 inhibited virus replication, mitigated liver damage and prevented morbidity and mortality. These findings suggest that FCV could potentially be developed as a pan-adenoviral inhibitor.

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111. Evaluating the Effectiveness of Three Broad Spectrum Antivirals Against Chikungunya Virus in Clinically Relevant Human Cell Lines

Evelyn Franco, B.S.[1], Xun Tao, B.S.[1], Kaley Hanrahan, M.S.[1], Jieqiang Zhou, B.S.[1], Ashley Brown, Ph.D.[1]
[1]*University of Florida, Orlando, Florida, United States of America*

Chikungunya virus (CHIKV) is an arthritogenic alphavirus with high morbidity rates for which no medical countermeasures exist. The antiviral potential of three approved broad-spectrum antivirals was evaluated against CHIKV in clinically relevant human cell lines. Increasing concentrations of ribavirin (RBV), interferon-α (IFN-α), and favipiravir (FAV) were evaluated against CHIKV-infected cells derived from connective tissue (HT-1080), neurons (SK-N-MC), and skin (HFF-1) over three days. Supernatants were sampled daily and viral burden was quantified by plaque assay on Vero cells. RBV anti-CHIKV activity was observed at high concentrations (≥ 100 µg/ml) that were cytotoxic in all cell lines. Moreover, these concentrations are supra-therapeutic in man, indicating the lack of clinical potential for RBV as a CHIKV treatment strategy. IFN-α suppressed CHIKV replication in all three cell lines, yielding EC_{50} values of 21.66 IU/mL in HT-1080 cells, 6.128 IU/mL in SK-N-MC cells, and 8.279 IU/mL in HFF-1 cells. Importantly, these concentrations are achievable in man. FAV substantially inhibited CHIKV production in HT-1080 cells (EC_{50}=41.92µM) and delayed replication in SK-N-MC cells (EC_{50}=99.45µM) at physiologically-relevant concentrations; but, was ineffective against CHIKV-infected HFF-1 cells. Intracellular FAV and FAV-RTP (the active metabolite of FAV) levels increased with higher external FAV exposures in HT-1080 and SK-N-MC cells, but was not detected in HFF-1. These findings indicate that FAV does not penetrate into HFF-1 cells, explaining that lack of anti-CHIKV effect. Our findings show that FAV and IFN-α were effective in multiple CHIKV-infected cell lines at clinically-relevant concentrations. Further investigation into the clinical potential of these agents are warranted.

112. Identification of a Novel, Potent, Broad-Spectrum and Drug-Like Heterocyclic Chemical Series of Arenavirus Entry Inhibitors

Greg Henkel, Ph.D.[1], Michael Plewe, Ph.D.[1], Shibani Naik, Ph.D.[1], Eric Brown, B.S.[1], Nadia Sokolova, Ph.D.[1], Vidyasagar Gantla, Ph.D.[1], Alexandra Fetsko, M.S.[1], Younjun Shin, Ph.D.[1], Lihong Zhang, M.D.[2], Birte Kalveram, Ph.D.[2], Alex Freiberg, Ph.D.[2], **Ken McCormack, Ph.D.**[1]
[1]*Arisan Therapeutics, San Diego, California, United States of America;* [2]*University of Texas Medical Branch, Galveston, Texas, United States of America*

Both Old and New World Arenavirus clades contain species that can be pathogenic to humans and induce arenavirus hemorrhagic fever (AVHF). NIAID has classified six arenaviruses as Category A priority pathogens due to their mortality/morbidity rate, potential for human-human contact and risk as a potential biological warfare agent. In Africa, each year, Lassa virus alone has been estimated to cause up to 300,000 infections and 5,000 deaths, and hospitalized survivors often suffer permanent sequelae. Therapeutic and prophylactic treatments for Lassa fever are currently limited to ribavirin, which may have serious side effects but exhibits some therapeutic efficacy when administered intravenously in the early stages of infection, whereas passive immunotherapies and a vaccine have been shown to be effective against Junin virus. Here we report a novel [5,6]-fused heterocyclic chemical series, identified through pharmacophore analyses of two distinct and previously reported chemical series of arenavirus glycoprotein/cell entry inhibitors, which exhibits potent broad-spectrum arenavirus inhibition. Top compounds within this chemical series exhibit low to subnanomolar broad-spectrum (Lassa, Machupo, Junin, Guanarito and Tacaribe) arenavirus activity against both pseudotyped and replicative viruses. Lead candidates have been identified with ADMET and oral bioavailability properties suitable for validation in animal efficacy models, with once or twice-a-day oral dosing. *This work was supported by the National Institutes of Health (R44AI112097) and NIAID preclinical services.*

113. Exploring PA-PB1 Protein–Protein Interaction as a Target for Next-Generation Anti-influenza Therapeutics

Yanmei Hu, M.S.[1], Jiantao Zhang, Ph.D.[1], Chunlong Ma, Ph.D.[1], Jun Wang, Ph.D.[1]
[1]*University of Arizona, Arizona, United States of America*

Influenza viruses are respiratory pathogens that are responsible for seasonal influenza and sporadic influenza pandemic. The therapeutic efficacy of current influenza vaccines and small molecule antiviral drugs is limited due to the emergence of multidrug-resistant influenza viruses. In response to the urgent need for the next generation of influenza antivirals, we utilized a fast-track drug discovery platform by exploring multi-component reaction products for antiviral drug candidates. Specifically, molecular docking was applied to screen a small molecule library derived from the Ugi-azide four-component reaction methodology for inhibitors that target the influenza polymerase PAC-PB1N interactions. One hit compound 5 was confirmed to inhibit PAC-PB1N interactions in an ELISA assay and had potent antiviral activity in an antiviral plaque assay. Subsequent structure-activity relationship studies led to the discovery of compound 12a, which had broad-spectrum antiviral activity and a higher *in vitro* genetic barrier to drug resistance than oseltamivir. Overall, the discovery of compound 12a as a broad-spectrum influenza antiviral with a high *in vitro* genetic barrier to drug resistance is significant, as it offers a second line of defense to combat the next influenza epidemics and pandemics if vaccines and oseltamivir fail to confine the disease outbreak.

114. On the Sensitivity of Viral Membranes to Lipid Peroxidation

Consuelo Correa Sierra, M.D., Ph.D.[1], Luis Schang, D.V.M., Ph.D.[1]
[1]*Baker Institute for Animal Health/ Cornell University, Ithaca, New York, United States of America*

There are clinical antivirals against only 10 of the many medically relevant enveloped viruses. Virion structures, such as capsids and envelopes, have been proposed as antiviral targets. Virions are metabolically inert; they cannot modify or repair their envelopes. A group of small molecules have been proposed to inhibit entry of enveloped virus by inducing lipid peroxidation. To test whether virions are more sensitive to lipid peroxidation than cells, we analyzed the effects of two classic lipid peroxidators, lipophilic AMVN and hydrophilic AAPH, on Vero and HFF viability and HSV-1 plaquing efficiency. Cells or virions were incubated with lipid peroxidators at 37°C for 2h. Dose response, CC50, and EC_{50} were evaluated by four parameters fitting curve and student's t test. HSV-1 virions were not much more sensitive to lipid peroxidators than cells [SI, AMVN: HFF, 4.5 (p 0.004); Vero, 4.9 (p 0.002); AAPH: HFF, 7.4 (p 0.0004); Vero, 3.3 (p 0.014)]. The model also predicts antioxidants to drastically protect virions, in contrast to cells which block and repair lipoperoxidated lipids. Lipophylic VitE, in BSA carrier, protected against lipophylic AMVN, [protection index-PI – EC_{50} antioxidant/EC_{50}, HFF, 2.6 (p 0.316); Vero, 4.7 (p 0.001)] and hydrophilic VitC protected against hydrophylic AAPH [(PI, HFF, 4.6 ($p<0.0001$); Vero, 4.9 (p 0.081)]. VitE partially protected against AAPH (HFF, p 0.014) and VitC against AMVN (Vero, p 0.003).

In conclusion, HSV-1 virions are not particularly sensitive to two classic lipid peroxidators and generic lipid peroxidators have not much specificity for virions over cells.

115. Development and Assessment of an Antibody that Binds to Parechovirus A3

Eric Rhoden, B.S.[1], Kimbell Hetzler, Ph.D.[2], Deborah Moore, B.S.[1], Heather Jost, M.S.[1], Naomi Dybdahl-Sissoko, M.S.[1], William Weldon, Ph.D.[1]
[1]CDC; [2]IHRC, contracting company for the CDC.

Parechoviruses, of genus *Parechovirus* within the *Picornaviridae* family, are associated with a wide variety of clinical manifestations. Parechovirus A3 (PeV-A3) is known to cause sepsis-like illness, meningitis, and encephalitis in infants and young children. There are no specific therapies currently available to treat PeV-A3-infected children. This emphasizes the importance of PeV-A3 as an emerging agent of serious diseases in young children.

Our laboratory generated a mouse monoclonal antibody (clone AB6-BA9-AH7) directed against PeV-A3. In a cell-based virus neutralization assay, the antibody reduced viral infectivity of PeV-A3 but did not neutralize PeV types A1, A2, A4, A5 and A6. A direct ELISA was developed to assess the binding of the antibody to clinical strains of PeV-A3. Interestingly, in addition to PeV-A3, the antibody could also bind to PeV-A1, A2, A4 and A6 but not PeV-A5 in the direct ELISA, suggesting differences in epitope structure between PeV-A3 and the other parechoviruses. No binding was demonstrated to representative strains of neurotropic enteroviruses: poliovirus, enterovirus-A71, enterovirus D-68, coxsackievirus B5 and echovirus 11. The antibody, when tested in combination with the PeV-A3-specific inhibitor posaconazole (POS), resulted in a synergistic antiviral effect.

Our studies demonstrate that antibody AB6-BA9-AH7 may be a valuable diagnostic tool or aid in further studies that lead to the development of therapies for diseases caused by PeV-A3 infection.

116. Characterization of a Cytomegalovirus (CMV) Cidofovir Resistant Mutant Virus by Quantitative Replication Ratio (Ro) Analysis

Edward Murray, B.S.[1], Keith Kinek, M.S.[1], Jay Grobler, Ph.D.[1], Jian Liu, Ph.D.[2], Dabbu Jaijyan, Ph.D.[2], Hua Zhu, Ph.D.[2], Philip McKenna, Ph.D.[1]
[1]Department of Infectious Diseases and Vaccines, MRL, Merck & Co., Inc., Kenilworth, New Jersey, United States of America; [2]Department of Microbiology, Biochemistry and Molecular Genetics, Rutgers – New Jersey Medical School, Newark, New Jersey, United States of America

Human CMV is a widespread Herpesvirus that results in a lifelong infection that is well controlled by the immune system in healthy individuals. CMV disease occurs in those with undeveloped immune systems such as infants and those who are immunosuppressed like transplant patients. In the transplant population, viral infection or reactivation can be life threatening. Nucleotide analogs Ganciclovir and Cidofovir that target CMV DNA polymerase were approved over 20 years ago and are still commonly used to treat CMV infection. Drug resistant CMV is becoming more common and problematic. Characterization of drug resistant mutant viruses is typically done using methods such as PCR or reporter enzymes that indirectly measure viral replication and not necessarily the spread of infectious virus. Using a CMV GFP virus, we identified a Cidofovir resistant double mutant virus capable of growth in high concentration of drug over time. Here we use this mutant virus as a tool to apply a quantitative method that determines the replication ratio (Ro) of wild type and mutant virus. A high content imaging system that can detect and count CMV infected cells over time allowed us to determine and compare the rate of viral replication and spread (Ro). Using this approach, we were able to define viral fitness for wild type and mutant viruses in terms of replication rate (Ro) and demonstrate how the replication kinetics of the two viruses change in the presence of antiviral compounds.

117. Immunotherapy using Triple-antigen Virus-like Vesicles Demonstrates Efficacy in a Mouse Model of Hepatitis B Virus Persistence

Timur Yarovinsky, M.D., Ph.D.[1], Stephen Mason, Ph.D.[1], Manisha Menon, Ph.D.[1], Marie Krady, Ph.D.[1], Bhaskara Madina, Ph.D.[1], Xianyong Ma, Ph.D.[1], Safiehkhatoon Moshkani, Ph.D.[2], Carolina Chiale, M.S.[2], Anasuya Chattopadhyay Pal, Ph.D.[3], Raj Kalkeri, Ph.D.[4], Kevin Walters, Ph.D.[4], Bijan Almassian, Ph.D.[1], John Rose, Ph.D.[3], Michael Robek, Ph.D.[2], Valerian Nakaar, Ph.D.[1]

[1]CaroGen Corporation, Farmington, Connecticut, United States of America; [2]Department of Immunology and Microbial Disease, Albany Medical College, Albany, New York, United States of America; [3]Department of Pathology, Yale University School of Medicine, New Haven, Connecticut, United States of America; [4]Infectious Disease Research, Drug Development Division, Southern Research, Frederick, Maryland, United States of America

Chronic hepatitis B virus (HBV) infections put more than 250 million people worldwide at risk of liver cirrhosis or hepatocellular carcinoma. Although current therapies are effective at suppressing the virus, they frequently do not lead to cure and leave an unmet need. A promising approach for a functional cure, defined as clearance of HBV surface antigen (HBsAg) with or without anti-HBV surface antibody seroconversion, involves T cell-directed immunotherapy. This strategy can overcome the immune tolerance to HBV antigens caused by persistent HBV replication and eliminate HBV-infected cells. A previous study used virus-like vesicles (VLVs), an artificial virus comprised of the RNA-dependent RNA polymerase from Semliki Forest virus and the envelope glycoprotein from vesicular stomatitis virus, to express HBV middle S antigen and demonstrated induction of HBV-specific T cell responses. Here, we used VLVs expressing three HBV proteins (polymerase, core, and middle surface) from a single VLV vector, to induce HBV-specific T cell responses against all three antigens in naïve mice. Furthermore, using a mouse model of persistent HBV replication after transduction with adeno-associated virus encoding HBV, we show that priming with the triple-antigen VLVs followed by a boost with plasmid DNA expressing HBV antigens resulted in a sustained decrease of serum HBsAg, reduction of HBV RNA in the liver, and induction of HBV-specific CD8+ T cells. These results demonstrate the effectiveness of VLVs expressing multiple HBV antigens and highlight the promise of VLVs as a component of comprehensive immunotherapy to treat chronic hepatitis B.

119. Demonstration of Safety and Immunity of a Live-attenuated RSV Vaccine Candidate in a Newly Developed, Non-human Primate (NHP) Model for hRSV Vaccine Evaluation

Raj Kalkeri, Ph.D.[1], Steffen Mueller, Ph.D.[2], Robert Coleman, Ph.D.[2], Zhaohui Cai, Ph.D.[1], Shuling Lin, B.S.[1], Kim Hagelin, B.S.[1], Brian Green, M.S.[1], Krista Salley, B.S.[1], Fusataka Koide, M.S.[1]

[1]Southern Research, Maryland, United States of America; [2]Codagenix, Farmingdale, New York, United States of America

Human respiratory syncytial virus (hRSV) causes lower respiratory tract infections (bronchiolitis and pneumonia) in premature babies and immuno-compromised adults. Due to the limited treatment options, RSV remains an unmet medical need. The establishment of a well characterized non-human primate (NHP) model for RSV infection is critical for the development of effective prophylactic and therapeutic interventions.

To develop an NHP model suitable for vaccine testing, African Green Monkeys (AGMs) (N=4) were inoculated intranasally and intratracheally with 1e6 PFU of wild type hRSV (strain A2) followed by evaluation for hRSV shedding in oropharyngeal (OP) and transporo tracheal lavages (TOTL) by sensitive RT-qPCR upto 28 days post-infection. Immunogenicity was tested by hRSV Focus Reduction Neutralization Test (FRNT), and IFNγ ELISPOT Assay. A live attenuated RSV vaccine (MinL4.0, Codagenix) was tested in this model (N=4) by inoculation on day 0 and 28, followed by immunogenicity (FRNT and ELISPOT) and attenuation (virus shedding in OP and TOTL samples by RT-qPCR) assessment up to day 49. MinL4.0 is 100% identical at the amino acid level to the wild type hRSV, but is slowed for translation in human cells. Presenting every wild type epitope leads to improved immunogenicity. Wild type hRSV infection in AGMs as evidenced by viral load, B and T-cell responses was demonstrated. Detailed virological and immunological endpoints will be presented.

AGM model for hRSV would be useful for preclinical evaluation of vaccines and antivirals and could play a crucial role in the development of specific countermeasures against RSV.

121. Metabolically Improved Stem Cell Derived Hepatocyte-like Cells Support HBV Life Cycle and are a Promising Tool to Study HBV, Anti-HBV Antiviral Drugs and Drug Resistance

Tine Tricot, M.S.[1], Hendrik Jan Thibaut, Ph.D.[2], Kayvan Abbasi, M.S.[2], Ruben Boon, Ph.D.[3], Manoj Kumar, Ph.D.[1], Johan Neyts, Ph.D.[2], Catherine Verfaillie, M.D., Ph.D.[1]
[1]Stem Cell Institute, KULeuven; [2]Laboratory of Virology, Rega Institute, KULeuven; [3]Stem Cell Institute, KULeuven The Massachusetts General Hospital Cancer Center, Harvard Medical School

Worldwide, 260 million people are chronically infected with the hepatitis B virus (HBV). Although nucleoside viral polymerase inhibitors are highly efficient to treat the disease, life-long treatment is necessary as the covalently closed circular DNA (cccDNA) is retained in the hepatocyte nucleus. Hence, there is an urgent need for therapeutics that allow to cure patients. Primary human hepatocytes (PHH) are currently the standard for HBV studies. However, because of donor organ shortage and the labour-intensive work, alternatives for HBV studies are needed. Therefore, the use of human pluripotent stem cell (hPSC) derived hepatocyte-like cells (HLCs) in HBV infection models is being explored. The Verfaillie-lab succeeded to (i) generate a hPSC line that overexpresses three liver-specific transcription factors (HC3x) and (ii) optimise medium conditions for HC3x-HLCs, which generate a more mature hepatocyte progeny, with drug metabolizing capabilities similar to PHH. We demonstrate that HC3x-HLCs can efficiently be infected with HBV. This was demonstrated by the expression of HBV core (HBc) and surface antigens (HBs). A clear release of HBs and e-antigens was detected via ELISA, increasing over time, indicating functional cccDNA formation. Moreover, high titers of infectious virus were detected in the culture supernatant when back-titrated on HepG2-NTCP cells. Additionally, we validated the system for use in antiviral drug studies using various known HBV inhibitors. As HC3x-HLCs can be kept for long-term culture, we are now assessing if cell-to-cell spread is occurring, and exploring if the selection of resistant variants to drugs such as lamivudine can be detected following long-term culture.

125. Safety, Tolerability, and Pharmacokinetics of the Iminosugar UV-4B Administered Orally as a Single Dose in Healthy Subjects

Kevin Spurgers, Ph.D.[1], Anthony Treston, Ph.D.[1], Marla Woodfolk, M.D.[2], Lisa Beth Ferstenberg, M.D.[2], Urban Ramstedt, Ph.D.[2], Kelly Warfield, Ph.D.[1], Matthew Duchars, Ph.D.[2], Mona Sharma, B.S.[1], Chandra Nimbal, Ph.D.[1], Grace Lin, M.S.[1], Mansoora Khaliq, Ph.D.[1], Brain Kaufman, B.S.[2], Preeya Lowe, M.S.[1], Aruna Sampath, Ph.D.[1], Elna van der Ryst, Ph.D.[3], Michael Callahan, M.D.[1]
[1]Emergent Biosolutions, Gaithersburg, Maryland; [2]Unither Virology; [3]TRN

UV-4B is an iminosugar oral drug candidate for the treatment of dengue virus infection. UV-4B has *in vitro* activity against diverse viruses including dengue, influenza A, and filoviruses. UV-4B also demonstrates *in vivo* efficacy against both dengue and influenza A. The antiviral mechanism of action of UV-4B is thought to be through inhibition of endoplasmic reticulum-resident alpha glucosidase 1 and alpha glucosidase 2 enzymes. This inhibition is hypothesized to prevent proper folding of virus glycoproteins, thereby impacting virus lifecycle and fitness of nascent virions. The iminosugar chemical class has a history of safe and effective use in humans. Here we report a first-in-human Phase 1a study to evaluate the safety, tolerability, and pharmacokinetic parameters of UV-4B in healthy subjects. Sixty-four subjects received single oral doses (aqueous solution) of UV-4B (UV-4 hydrochloride salt) equivalent to 3, 10, 30, 90, 180, 360, 720, or 1000 mg of UV-4, or placebo. Single doses of UV-4B were safe and well tolerated. No serious adverse events, nor dose-dependent frequency in adverse events were observed. Clinical laboratory results, vital signs, and physical examination data did not reveal any safety signals. Dose-limiting toxicity was not observed. UV-4 was rapidly absorbed and distributed after dosing. Time to reach maximum plasma concentration (0.5-1 hour) appeared to be independent of dose. Exposure increased approximately in proportion with dose with good linearity. UV-4 was quantifiable in pooled urine over the entire collection interval for all doses. These data suggest that therapeutically relevant doses of UV-4B can be safely administered to humans.

126. Measles: A Role for Virus Persistence?

Diane Griffin, Ph.D.[1]
[1]*Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America*

Measles continues to be an important cause of death in children despite the availability of a safe and efficacious vaccine. Target cells for measles virus (MeV) replication are epithelial cells, endothelial cells, B cells, T cells and macrophages. Studies of children with measles and experimental infection of rhesus macaques have shown that infectious virus can be recovered from PBMCs, respiratory secretions and urine only before and during the rash (a manifestation of the cellular immune response to MeV). After clearance of infectious virus, MeV RNA persists for weeks in these peripheral sites and for months in lymphoid tissue with occasional periods of reactivation. Levels of MeV and MeV RNA correlate with cyclical changes in circulating MeV-specific T cells, progressive maturation of the antibody response and development of bone marrow-resident long-lived plasma cells. Persistence of MeV RNA likely contributes to development of life-long immunity, measles-associated immune suppression and late complications such as subacute sclerosing panencephalitis.

127. Remdesivir (RDV, GS-5734), a Broad Spectrum Antiviral Agent

Richard Mackman, Ph.D.[1]
[1]*Gilead Sciences, Foster City, California, United States of America*

Remdesivir (RDV, GS-5734) has recently emerged as a rare example of a broad spectrum antiviral agent with the potential to treat multiple RNA viruses including filoviruses, pneumoviruses, flaviviruses, paramyxoviruses and coronaviruses. Effective treatments for emerging viruses with high outbreak potential are severely limited, a realization that reached global prominence during the 2013-16 Ebola virus (EBOV) outbreak that claimed >11,000 lives. At the start of this crisis, we screened a fit-for-purpose library of nucleos(t)ide analogs targeting RNA-dependent RNA polymerases (RdRp), and identified a novel 1'-CN modified *C*-nucleoside and its phosphoramidate prodrugs as potent anti-EBOV agents. Structure activity relationships combined with computational modeling identified RDV with the 1'-CN modification and the 2-ethylbutyl alaninyl monophosphoramidate *Sp* prodrug as optimal. *In vitro*, RDV has anti-EBOV EC_{50} = 84-200nM in relevant cell types, and EC_{50}= 30 to 250nM, toward many RNA viruses including MERS-Coronavirus, SARS-Coronavirus, dengue, Zika, Marburg, Nipah, and measles. The active triphosphate metabolite, RDV-TP, is a potent and selective delayed chain terminator of viral RNA replication. Challenges associated with the robust scale-up of RDV were overcome to support *in vivo* efficacy studies, clinical development, and stockpiling. In EBOV-infected monkeys, once daily IV administration initiated on day 4 post infection demonstrated 100% survival. Efficacy observed in animal models of Marburg, Nipah and MERS-Coronavirus infections support the broader potential for RDV treatment. RDV has been provided for compassionate use in the latest DRC Ebola outbreak and is the only small molecule antiviral being investigated in an ongoing Ebola randomized controlled trial.

128. 101 Years of Influenza: Lessons from the 1918 Pandemic

Jeffery Taubenberger, M.D., Ph.D.[1]
[1]*NIAID, NIH, Bethesda, Maryland, United States of America*

2018-2019 marks the centennial of the "Spanish" influenza pandemic, which caused at least 50 million deaths worldwide. The unprecedented nature of the pandemic's sudden appearance and high fatality serves as a stark reminder of the threat influenza has posed for over a millennium. Sequencing and reconstruction of the 1918 virus is now allowing scientists to answer many questions about the virus's origin and pathogenicity, although many other questions remain. The 1918 influenza A virus (IAV) was a novel "founder virus" that initiated the current era of IAV circulation by evolving into progeny pandemic viruses via genetic reassortment: all influenza A pandemics and seasonal epidemics since that time, and indeed almost all cases of human influenza A worldwide (excepting human zoonotic infections, e.g., from poultry-adapted IAVs such as H5N1 and H7N9), have been caused by descendants of the 1918 virus. These include not only the antigenically "drifted" descendants of the 1918 H1N1 virus itself, but also the genetically reassorted pandemic viruses that appeared in 1957 (H2N2), 1968 (H3N2), and 2009 (H1N1pdm). Despite our modern arsenal of antibiotics, vaccines, antiviral drugs, and intensive care treatment, we are still doing a poor job of preventing influenza deaths. The most important lesson from the devastation of the 1918 pandemic may be the need to produce better antivirals, effective vaccines against multiple bacterial pneumopathogens, and effective, broadly protective, 'universal' influenza vaccines to prevent, or at least mitigate the impact of, future pandemics, and to prevent deaths from seasonal influenza in the periods in between pandemics.

130. A Hemagglutinin Stalk-based Universal Influenza Virus Vaccine

Florian Krammer, Ph.D.[1]
[1]*Icahn School of Medicine at Mount Sinai, New York, New York, United States of America*

Influenza virus infections are a significant cause of morbidity and mortality worldwide. Current vaccines show acceptable efficacy against antigenically matched viruses by inducing strain specific antibodies against the membrane-distal globular head domain of the viral hemagglutinin, but fail to protect against drifted and pandemic strains. The membrane-proximal stalk domain of the viral hemagglutinin exhibits a high degree of conservation across influenza virus subtypes, and monoclonal antibodies directed against this region typically show broad neutralizing activity. However, these antibodies are rare and usually not induced/boosted by regular seasonal vaccines. Here, we developed a universal influenza virus vaccination strategy based on the conserved stalk domain of group 1 and group 2 hemagglutinins. By sequential vaccination of mice and ferrets with chimeric hemagglutinin constructs that share the same stalk domain but have divergent head domains we were able to specifically boost broadly neutralizing antibody titers against conserved epitopes in the hemagglutinin stalk. Animals vaccinated with these constructs were protected from morbidity and mortality induced by infection with a panel of heterologous and heterosubtypic influenza A viruses, including avian influenza virus subtypes of concern like H5N1 and H7N9. The induced antibody response was long-lived and also interfered with virus transmission between animals. The present data suggest that this vaccine strategy has the potential to provide broad influenza virus protection in humans and clinical trials are currently ongoing. A universal influenza virus vaccine would represent a major advance towards the control of influenza worldwide and would significantly enhance our pandemic preparedness.

131. Research for Preparedness for Arboviruses and Hemorrhagic Fever Viruses in Subsaharan Africa

Amadou Sall, Ph.D.[1]
[1]*Pasteur Institute, Dakar, Senegal*

132. WHO's Global Program on MERS: Improving Global Preparedness and Response to High Threat Emerging Respiratory Pathogens with Significant Public Health and Economic Consequences

Maria Van Kerkhove, Ph.D.[1]
[1]*MERS-CoV Technical Lead, World Health Organization, Geneva, Switzerland*

Since its identification in Saudi Arabia in 2012, Middle East Respiratory (MERS) has become a global public health threat. Typical of an emerging zoonosis, MERS-CoV has an animal reservoir, i.e. dromedary camels in which the virus causes little to no disease. Many details about the extent of circulation and the mechanisms of transmission within dromedaries, or factors related to zoonotic transmission and differences in circulating MERS-CoV strains, remain unknown. The virus has jumped from camels to humans principally in countries on the Arabian Peninsula, causing significant morbidity and mortality in humans. However, the geographic range of spillover risk extends across large parts of Africa, the Middle East and into South Asia. Human-to-human transmission in health care facilities can be amplified, causing large outbreaks, as has been seen in the Middle East and in the Republic of Korea, with significant public health and economic impacts. As of March 2019, more than 2,279 cases from 27 countries have been reported to WHO.

More than six years after the first human cases of MERS were identified, the world remains under threat from this pathogen. The critical needs for research have been identified by the public health community and used to inform the WHO R&D MERS-CoV Roadmap and a broader Public Health Research Agenda. More focused efforts in our activities and investments to address scientific and public health research questions, accelerate promising medical interventions and are more strategic on where activities are conducted globally will go further to address remaining public health unknowns.

134. Can We Predict Arbovirus Epidemics?

Scott Weaver, Ph.D.[1]

[1]*Emerging Viruses and Arboviruses and Department of Microbiology and Immunology, University of Texas Medical Branch, Galveston, Texas, United States of America*

The recent emergence in the New World of West Nile, chikungunya and Zika viruses and their rapid spread to near pandemic proportions took arbovirologists and public health officials by surprise, and prompted discussions about shifting from a reactive to a proactive role in anticipating and controlling such events, and ultimately predicting and preparing for future emergences. These outbreaks underscore the increasing threat of zoonotic arboviruses, both due to increasing risks for intentional or nefarious introductions to new geographic regions, as well as the ability of some to initiate human-amplified, urban transmission cycles involving *Aedes aegypti*and sometimes other peridomestic *Aedes*(*Stegomyia*) spp. mosquitoes, leading to even higher burdens of disease. Examination of the factors involved in these past introductions reveal several common patterns, but also underscore the stochastic elements that will make predictions highly challenging. Examples drawn from retrospective studies of chikungunya and Zika virus emergence will be discussed to underscore the difficulties in both detecting and predicting initial stages of emergence, as well as spread, relying on both common features and stochastic determinants.

135. Human Intravenous Immunoglobulin Provides Protection Against Enterovirus 71 Infection in a Mouse Model

Christopher Peterson, M.S.[1], Brett Hurst, Ph.D.[1], **E. Bart Tarbet, Ph.D.**[1]

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

Enterovirus 71 (EV-71) is a picornavirus that can cause disease in young children, including encephalitis, meningitis, pulmonary edema, and acute flaccid paralysis. In a mouse model for EV-71 infection that includes rear-limb paralysis, onset of disease occurs between day 9 and 14 post-infection (p.i.), and mortality is often preceded by appreciable weight-loss. Human Intravenous immunoglobulin (hIVIG) is a therapeutic pool of antibodies from plasma donors approved to treat a variety of conditions, including immunodeficiencies, chronic lymphocytic leukemia, and pediatric HIV infections. It has also been used off-label to treat EV-71 infections. Here we determined the effectiveness of hIVIG in treating EV-71 infections in four-week-old AG129 mice. We observed that a single administration of hIVIG at 4h p.i. could provide over 50% protection, and hIVIG administration could be delayed until 48h p.i. and still provide protection, although administration at 72h p.i. was not protective. However, some variability was observed between hIVIG treatments, suggesting that the timing for IVIG administration may be crucial. In addition, we observed that Carimune® NF and Gammunex®-C both contained EV-71 neutralizing antibodies and that Carimune® NF reduced several pro-inflammatory cytokines (MCP-1, RANTES, MIP-1α, IFN-α) in the brain and/or spinal cord by 2.5- to 13-fold. Although protection from Carimune® NF showed some variability depending on time of administration, the average protection was 50% when administered no later than 4h p.i. Thus, these results support the use of hIVIG in the treatment of EV-71 infections in humans. *[Supported by Contract HHSN272201000039I from the Virology Branch, DMID, NIAID, NIH]*

136. A Novel Human Skin Tissue Model to Study HCMV and Evaluate Antiviral Drugs *In Vivo*

Megan Lloyd, Ph.D.[1], Rebecca Harris, B.S.[1], Michael Tighe, B.S.[2], Prashant Upadhyaya, M.D.[1], Eain Murphy, Ph.D.[3], Jennifer Moffat, Ph.D.[1]

[1]SUNY Upstate Medical University, Syracuse, New York, United States of America; [2]Trudeau Institute, Saranac Lake, New York; [3]Forge Life Science, Doylestown, Pennsylvania, United States of America

HCMV causes congenital birth defects and complications in transplant patients, with few antiviral treatment options. HCMV infections manifest in multiple forms, including skin lesions and rashes. Previously, it was unknown whether adult human skin would support HCMV and could be used to evaluate antivirals. We used a TB40/E HCMV-fLuc-eGFP strain expressing luciferase and eGFP to evaluate virus growth in HFF cells, skin-organ culture (SOC), and a skin xenograft mouse model (SCID-hu). Bioluminescence and fluorescence were correlated and detected one day post-infection, while infectious particles were released around day 5. Bioluminescence produced by HCMV-infected HFFs also corresponded to viral DNA load (qPCR). Human skin was obtained from reduction mammoplasties and prepared for culture on NetWells or implantation into mice. In SOC, HCMV was detected for 14 days using *in vivo* imaging (IVIS), and HCMV foci were observed by fluorescence microscopy. Cidofovir, letermovir, and foscarnet prevented HCMV infection in SOC. In skin explants, HCMV infects fibroblasts, endothelial cells, hematopoietic cells and likely Langerhans cells. A new SCID-hu model for HCMV was developed using adult human skin xenografts placed subcutaneously in SCID/beige mice. HCMV was inoculated directly into the xenografts, and infection measured by IVIS over 14 days. Cidofovir treatment significantly reduced viral growth on day 14. Early results suggest HCMV may move through the mouse's circulation, as HCMV was detected in a contralateral skin xenograft. Development of this model is ongoing. Establishing an efficient model for HCMV will be useful to study the virus and evaluate antiviral compounds.

137. Exploring Small Molecule Synthetic Inhibitors of HSV-1 Infectivity

Jody Cameron, B.S.[1], Furkat Mukhtarov, M.S.[1], Nargess Hosseini, Ph.D.[2], Devon Schatz, B.S.[2], Consuelo Correa-Sierra, M.D.[1], Frederick West, Ph.D.[2], **Luis Schang, D.V.M., Ph.D.1**

[1]Cornell University, Ithaca, New York, United States of America; [2]University of Alberta, Edmonton, AB, Canada

Whereas high affinity virion binding is commonly mediated by specific protein receptors, most human pathogenic viruses attach first to cellular glycans. This primary attachment constitutes an attractive target for broad spectrum antivirals. We had identified EGCG as a broad-spectrum inhibitor of viral attachment (EC50, 0.08-10 μM). We proposed that the pyrogallol and gallate moieties were critical for inhibition, whereas the hydroxylated benzopyran was not. ECG also inhibited HSV-1 infectivity (EC50, 0.18 μM), whereas EC, containing no pyrogallol, was inactive. We then synthesized gallate-esters of flexible or rigid, planar or non-planar linkers with no benzopyran moiety. Di-gallates attached to flexible 2-6-carbon alkyl linkers inhibited HSV-1 infectivity modestly (EC50, 6-10 μM). A rigid non-planar cyclohexane linker increased potency (EC50, 0.1-0.6 μM), although 1-4-cis-di gallate was inactive. Di-gallate esters of a rigid planar catechol or related cores yielded EC50 between 0.65-30 μM, depending on the gallates position. Tri-, tetra-, or penta-gallates of planar or non-planar rigid or flexible linkers were the most potent, with EC50 as low as 0.07μM. Replacement of the ester with amide groups resulted in loss of activity. We thus tested replacements of the ester group in lauryl or octyl-gallates, which also inhibited HSV-1 infectivity (EC50 0.1-2 μM). Substitution of the ester with a keto group decreased potency by ~2-fold, whereas its removal decreased potency as much as 18-fold. Methylation of the gallate hydroxyls resulted in loss of activity. In conclusion, selected poligallates inhibit HSV-1 infectivity at nanomolar concentrations and the labile ester links can be replaced by ketones.

138. Disrupting Transcriptional Feedback Yields an Escape-Resistant Antiviral

Sonali Chaturvedi[1], Leor Weinberger, Ph.D.[1]
[1]*Gladstone Institutes, San Francisco, California, United States of America*

From bacteria to cancers, it has long been recognized that drug-resistant mutants emerge quickly, causing significant morbidity and mortality. Antiviral resistance in herpesviruses is of particular concern with herpes simplex virus type 1 (HSV-1)—a leading cause of blindness—and human herpesvirus 5, cytomegalovirus (CMV)—a leading cause of birth defects and transplant failure—exhibiting substantial resistance to standard-of-care antivirals in the clinic. Combination therapies, which limit resistance by necessitating multiple viral mutations, can be effective but increase the risk of off-target effects and associated toxicity and are absent for most viral diseases. Here, we present proof-of-concept for a novel approach that disrupts viral auto-regulatory circuits with a single molecule and limits resistance by requiring multiple viral mutations. We develop DNA-based circuit-disruptor oligonucleotide therapies (C-DOTs) that exploit this mechanism by interfering with transcriptional negative feedback in human herpesviruses (CMV and HSV-1) thereby increasing viral transcription factors to cytotoxic levels. C-DOTs reduce viral replication >100-fold, prevent emergence of resistant mutants in continuous culture, are effective in high-viremic conditions where existing antivirals are ineffective, and show efficacy in mice. Strikingly, no C-DOT-resistant mutants evolved in >60 days of culture, in contrast to approved herpesvirus antivirals where resistance rapidly evolved. Overall, the results demonstrate that oligonucleotide therapies targeting feedback circuits are escape resistant and could have broad therapeutic applicability to viruses, microbes, and neoplastic cells.

139. Inhibition of DNA Viruses by Ribosylindole Nucleosides

Scott James, M.D.[1], Caroll Hartline, M.S.[1], Emma Harden, B.S.[1], Leroy Townsend, Ph.D.[2], John Drach, Ph.D.[2], Brian Gentry, Ph.D.[3], Mark Prichard, Ph.D.[1]
[1]*University of Alabama at Birmingham, Birmingham, Alabama, United States of America;* [2]*University of Michigan, Ann Arbor, Michigan, United States of America;* [3]*Drake University, Des Moines, Iowa, United States of America*

Inhibition of the terminase complex of human cytomegalovirus (CMV) by letermovir has proven to be an effective strategy for the prophylaxis of these infections in immunocompromised hosts. Other potent inhibitors of this target include benzimidazole and indole nucleosides that are i) highly potent *in vitro* and *in vivo*, ii) structurally unrelated to letermovir, and iii) active against the most common letermovir-resistant isolates of the virus.

The antiviral activity of a set of representative compounds was evaluated against 7 distinct human herpesviruses (HSV-1, HSV-2, VZV, CMV, EBV, HHV-6B, HHV-8), as well as BK polyomavirus, papillomavirus, and adenovirus with *in vitro* antiviral assays. Two compounds of interest, 2,5,6-trichloro-1-(β-d-ribofuranosyl)indole-3-carboxamide oxime (1855) and methyl 2,5,6-trichloro-1-(β -d-ribofuranosyl)indole-3-formimidate (1857) were among those evaluated with CMV yield reduction assays.

We report a very limited spectrum of antiviral activity that is limited only to CMV and none of the other DNA viruses tested. Both 1855 and 1857 are presumed to inhibit the CMV terminase and nanomolar concentrations of these compounds were shown to result in 10-fold reductions of infectious virus.

These studies confirmed the outstanding efficacy of the compounds against CMV and support their further development for the inhibition of these infections including the mapping of mutations that confer resistance to this class of molecules.

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140. Neuraminidase-Targeted Immunotherapy of Influenza: Repurposing Zanamivir as a Targeting Ligand for Delivery of an Attached Immunogenic Hapten to Virus/Virus-Infected Cells

Xin Liu, B.S.[1], Boning Zhang, B.S.[1], Philip Low, Ph.D.[1]
[1]*Department of Chemistry and Institute for Drug Discovery, Purdue University, West Lafayette, Indiana, United States of America*

Neuraminidase inhibitors constitute a first-line treatment for influenza virus infections. However, neuraminidase inhibitors suffer from several limitations, including poor pharmacokinetics, limited therapeutic window and drug resistance problems. Thus, there is an urgent need for new anti-influenza drugs with novel mechanisms of action.

In this study, a bifunctional small molecule was designed and synthesized by conjugating the neuraminidase inhibitor, zanamivir, with a dinitrophenyl (DNP) group. This zanamivir-DNP conjugate forms a bispecific molecular "bridge" between influenza virus/virus-infected cells and endogenous circulating anti-DNP antibodies, which are abundantly present in all human serum. This "marking" step then initiates an immune response leading to the clearance of the antibody-coated virus/virus-infected cells via mechanisms such as antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

We demonstrate that our zanamivir-DNP conjugate not only preserves zanamivir's high binding affinity binding to all isoforms of neuraminidase, but also recruits anti-DNP antibodies to the surface of virus-infected MDCK cells. Moreover, zanamivir-DNP conjugate is shown to induce killing of neuraminidase-expressing cells through CDC and ADCP effects. Finally, we demonstrate that zanamivir-DNP conjugate is superior to zanamivir alone in protecting DNP-immunized mice infected with a lethal dose of influenza virus (100 LD50, A/Puerto Rico/8/1934) in three aspects: (1) zanamivir-DNP conjugate is more potent than zanamivir when administrated intranasally; (2) low dose of zanamivir-DNP conjugate can cure infected mice following intraperitoneal injection; (3) zanamivir-DNP conjugate preserves its efficacy in protecting infected mice when treatment is delayed until 72h post-infection.

141. Validating Enterovirus D68 -2Apro as an Antiviral Drug Target and the Discovery of Telaprevir as a Potent D68-2Apro Inhibitor

Rami Musharrafieh, B.S.[1], Chunlong Ma, Ph.D.[1], **Jun Wang, Ph.D.**[1]
[1]*University of Arizona*

Enterovirus D68 (EV-D68) is a viral pathogen that leads to severe respiratory illness and has been linked with the development of acute flaccid myelitis (AFM) in children. No vaccines or antivirals are currently available for EV-D68 infection, and treatment options for hospitalized patients are limited to supportive care. Here, we present the expression of the EV-D68 2A protease ($2A^{pro}$) and characterization of its enzymatic activity. Furthermore, we discovered telaprevir, an FDA-approved drug used for the treatment of Hepatitis C virus infections, as a potent antiviral against EV-D68 by targeting the $2A^{pro}$ enzyme. Using FRET-based substrate cleavage assay, we showed that the purified EV-D68 $2A^{pro}$ has proteolytic activity selective against a peptide sequence corresponding to the viral VP1-2A polyprotein junction. Telaprevir inhibits EV-D68 $2A^{pro}$ through a nearly irreversible, biphasic binding mechanism. In cell culture, telaprevir showed submicromolar to low micromolar potency against several recently circulating neurotropic strains of EV-D68 in different human cell lines. To further confirm the antiviral drug target, serial viral passage experiments were performed to select for resistance against telaprevir. An N84T mutation near the active site of $2A^{pro}$ was identified in resistant viruses, and this mutation reduced the potency of telaprevir in both the enzymatic and cellular antiviral assays. Collectively, we report for the first time the *in vitro* enzymatic activity of EV-D68 $2A^{pro}$ and the identification of telaprevir as a potent EV-D68 $2A^{pro}$ inhibitor. These findings implicate EV-D68 $2A^{pro}$ as an antiviral drug target and highlight the repurposing potential of telaprevir to treat EV-D68 infection.

142. Human Retroviruses (HTLV-1 and HIV): Current Therapy and Prevention

Robert Gallo, M.D.[1]
[1]*Director, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, Maryland, United States of America*

HTLVs (found in 1979-1982) and HIVs (1983-1984) are the two types of pathogenic retroviruses. After years of much resistance, these discoveries were made possible by new capacity to grow T cells based on Il-2 and new sensitive detection method based on reverse transcriptase assays. Though far less variable than HIVs, very slight differences (particularly in the 3" region of their genomes) among the HTLVs determine different subtypes of HTLV-1 which new evidence indicates determines variation in pathogenicity: HTLV-1 (A and B) resulting in adult –cell leukemia (ATL) and paralytic CNS disease, HTLV-1 (C) in immune disorders, and HTLV-2 almost non-pathogenic. Three is no vaccine nor any anti-viral therapy for HTLV-1. In fact, there is no evidence to indicate such drugs would be useful (to be discussed).

HTLV-1 remains an extremely underfunded and inadequately developed field. Nonetheless, technology and concepts from HTLV-1 research fueled the idea that AIDS would be caused by another retrovirus. The much higher replication of HIV made it a possible target of anti-viral drugs. The historical use of AZT demonstrated for the first time that specific anti-virals could control a systemic virus infection correlating with objective data for the decline in virus levels. This culminated in the use of combined drugs that vastly improved the lives of the infected. Today there are three major goals: a) Vaccine – little serious progress; b) so-called "cure" – significantly not achieved; c) prevention by anti-viral drugs: – this works and is being tried regionally for attempts at eradication.

143. Effects of Broadly Neutralizing Antibody Combinations in HIV-1 Infection

Marina Caskey, M.D.[1]
[1]*Rockefeller University, New York, New York, United States of America*

Combination antiretroviral therapy (ART) is highly successful in suppressing viral replication and preventing disease progression, however it cannot eradicate HIV-1 infection, and it does not accelerate the elimination of infected cells. HIV-1 persists in a latent state as integrated proviruses in resting memory CD4+ T cells that are not accessible to ART. Efforts to identify strategies to eradicate or induce treatment-free long-term HIV-1 remission are critical. Broadly neutralizing antibodies (bNAbs) differ from ART in that they can recruit immune effector functions through their Fc domains to accelerate clearance of viruses and infected cells. In addition, immune complexes are potent immunogens that can foster development of host immune responses. Several bNAbs are undergoing clinical evaluation. 3BNC117 and 10-1074 are bNAbs that bind to the CD4 binding site (CD4bs) and to the base of the V3 loop in HIV-1 envelope gp-120. Both antibodies show exceptional breadth and potency *in vitro*, and protect against or suppress infection in animal models. The combination of 3BNC117 and 10-1074 have additive effects and provide broader coverage of viral strains. We will discuss results from both preclinical and clinical studies of 3BNC117 and 10-1074 and their potential role in strategies aiming to achieve long-term viral remission.

144. Long Acting Antiretrovirals

Howard Gendelman, M.D.[1]
[1]*University of Nebraska Medical Center, Omaha, Nebraska, United States of America*

The presentation will review how antiretroviral therapy (ART) has transformed human immunodeficiency virus infections from certain death to a manageable chronic disease. It will also discuss all current therapeutic limitations. Notably, ART requires strict adherence to drug regimens which does not eliminate drug toxicities and viral resistance. While success can be defined by reducing viral transmission and positively affecting treatment outcomes by long term inductions of latent of highly restricted viral infection. We posit that all can be improved through long-acting ART formulations. While early in development, results are encouraging. Moreover, opportunities in abound for further improving treatment outcomes and even in complete viral eradication. These include the improved targeting of viral reservoirs, the development of novel therapeutic delivery systems, the adjustment(s) of drug dosing volumes, eliminating injection site reactions and in achieving prolonged timed intervals for drug administrations. While these can be accomplished through implantable devices further improvements can be made through long-acting parenteral-administered ART prodrugs. Perhaps most notables are the recent successes in sequential ART and viral excision strategies. These are employed to eliminate integrated proviral DNA. All will be discussed towards an eye towards the final goal of HIV-1 eradication.

145. The Advancement of HIV NRTTIs for Extended-duration Dosing

Izzat Raheem, Ph.D.[1]
[1]*Merck, West Point, Pennsylvania, United States of America*

Despite the prevalence of highly efficacious and diverse therapeutic options for the treatment of HIV, real-world effectiveness remains suboptimal. This is driven in part by poor patient adherence, often resulting in treatment failure or discontinuation. Extended duration dosing (ExDD) options with >Q6-mo dosing intervals have the potential to be transformative in the HIV space, not only addressing issues of adherence, but also providing patients with a valuable improvement in treatment convenience. Given the extremely low daily input rates and doses required to enable ExDD formulations, recent discovery efforts in our laboratories have focused on compounds in the nucleoside reverse transcriptase translocation inhibitor (NRTTI) class, MK-8591 (EFdA) in particular. Herein, we describe our on-going efforts to advance ExDD bioerodible and non-erodible implantable formulations of our NRTTIs. We present a overview of the NRTTI mechanism, our discovery efforts to identify structurally novel back-ups to MK-8591, as well as a summary of clinical progress of MK-8591 to date. Framed in the context of MK-8591 implants for HIV prevention, we will present implant design and optimization strategies including modulation of compound physicochemical properties, polymer/formulation selection, and implant drug loading. Key data from on-going *in vitro* and *in vivo* preclinical and clinical studies will also be presented.

147. Antiviral Treatment for Patients with Yellow Fever – a New Frontier

Michael Jacobs, M.D., Ph.D.[1]
[1]*Royal Free London NHS Foundation Trust, London, United Kingdom of Great Britain and Northern Ireland*

Yellow fever virus is transmitted by mosquitoes and causes acute viral haemorrhagic disease. It is endemic in tropical regions of Africa and Central and South America, where epidemics regularly occur. Approximately 1 in 7 patients with yellow fever develop a severe clinical syndrome, with a very high case-fatality rate despite supportive care.

There are currently no specific antiviral agents for treatment of yellow fever. Here, I will review potential antiviral candidates and describe the first in world clinical treatment of yellow fever virus infections with the experimental nucleoside analogue galidesivir (BCX4430; BioCryst, Durham, US). I will discuss the future of antiviral treatments for this devastating illness.

148. Small Molecules for Big Problems in Large Animals

Nesya Goris, Ph.D.[1]
[1]*ViroVet, Leuven, Belgium*

Every second 46 pigs, 11 cattle, 36 small ruminants and nearly 2000 chickens are being consumed globally, totaling 65 billion animals annually. The unprecedented expansion of the global middle class (3.5 billion people in 2018 predicted to increase to 5.2 billion in 2028) will be a major driving force behind an even larger upsurge in animal protein consumption. As a result, animal production systems are massively intensifying. And when things go wrong, they go wrong on an equally large scale as exemplified by dramatic news images of outbreaks of African and classical swine fever, foot-and-mouth disease, highly pathogenic avian influenza and the like.

Animal health and animal welfare is, however, not only affected by the above disruptive diseases. Every year, the cattle industry in the US and the EU suffers more than 1.5 billion dollars in production losses due to endemic bovine viral diarrhea (pestiviral infection) despite the availability of more than 80 commercial vaccines. Similarly, porcine reproductive and respiratory disease (arteriviral infection) inflicts 2 billion dollars in losses to the American and European pig industry even though killed and live vaccines are readily available and vastly applied.

The livestock industry is progressive in nature and eagerly willing to adopt new disease control strategies, especially in light of a government-driven reduction in antibiotic use. Small-molecule antiviral drugs are rapidly gaining attention as alternative and adjacent disease prevention and treatment options. This talk will explore the pros and cons of small molecules for viral diseases of livestock.

149. Inhibition of Arenavirus Infection by a Novel Fusion Inhibitor

Brian Gowen, Ph.D.[1], Jonna Westover, Ph.D.[1], Kie-Hoon Jung, Ph.D.[1], Vidyasagar Gantla, Ph.D.[2], Eric Brown, B.S.[2], Shibani Naik, Ph.D.[2], Brittney Downs, B.S.[1], Ashley Dagley, M.S.[1], Greg Henkel, Ph.D.[2], Ken McCormack, Ph.D.[2]
[1]Utah State University; [2]Arisan Therapeutics

In the Americas, five New World arenaviruses (NWA) are known to cause life-threatening viral hemorrhagic fever. Without FDA-licensed vaccines or antivirals, these viruses are considered high priority pathogens by the NIAID and CDC. The envelope glycoprotein (GPC) mediates arenavirus entry through a process of pH-dependent fusion of the viral and host endosomal membranes. Consequently, the GPC is recognized as a viable target for small-molecule fusion inhibitors. Here, we report on the antiviral activity and preclinical development of a novel fusion inhibitor, ARN75039, against Tacaribe virus (TCRV), a close relative to the pathogenic NWA. In TCRV pseudotyped and native virus assays, the compound was active in the nanomolar range with virus yield reduction selectivity index (SI_{90}) exceeding 1000. Pharmacokinetic analysis of orally administered ARN75039 revealed an extended half-life in mice supporting once-daily dosing, and the compound was well tolerated at the highest tested dose of 100 mg/kg. In a proof-of-concept prophylactic efficacy study, doses of 10 and 35 mg/kg of ARN75039 dramatically improved survival outcome and potently inhibited TCRV replication in serum and various tissues. Additionally, in contrast to surviving mice that received ribavirin or placebo, animals treated with ARN75039 were cured of TCRV. In a follow-up study, impressive therapeutic efficacy was demonstrated under conditions where treatment was withheld until after the onset of clinical disease. Taken together, the present data strongly support continued development of ARN75039 as a candidate treatment for severe NWA infections. *Supported by the NIH (HHSN272201700041I, HHSN272201100019I and R44AI112097).*

150. Broad-spectrum Antiviral Remdesivir Provides Superior *In Vivo* Therapeutic Efficacy against MERS-CoV Compared to a Combination of Lopinavir/Ritonavir Plus Interferon Beta

TImothy Sheahan, Ph.D.[1], Amy Sims, Ph.D.[1], Sarah Leist, Ph.D.[1], Alexandra Schäfer, Ph.D.[1], John Won, B.S.[1], Ariane Brown, B.S.[1], Alison Hogg, Ph.D.[2], Darius Babusis, Ph.D.[2], Michael Clarke, Ph.D.[2], Jamie Spahn, Ph.D.[2], Laura Bauer, Ph.D.[2], Scott Sellers, Ph.D.[2], Danielle Porter, Ph.D.[2], Joy Feng, Ph.D.[2], Tomas Cihlar, Ph.D.[2], Robert Jordan, Ph.D.[2], Mark Denison, Ph.D.[3], Ralph Baric, Ph.D.[1]
[1]University of North Carolina at Chapel Hlll, Chapel Hill, North Carolina, United States of America; [2]Gilead Sciences Inc., Foster City, California, United States of America; [3]Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America

Coronaviruses (CoVs) have a natural predilection for expansion into new host species giving rise to novel human diseases recently exemplified by the emergence of severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV), the causative agent of a severe respiratory syndrome associated with > 2200 cases and > 800 deaths in 27 countries since 2012. Zoonotic CoVs similar to epidemic strains are circulating in reservoir species increasing the likelihood of novel CoV emergence in the future. Currently, there are no approved therapeutics for any human CoV. Remdesivir (RDV, GS-5734) is a monophosphoramidate prodrug of an adenosine analog that targets the viral RNA-dependent RNA polymerase (RdRp) and has been shown to inhibit replication of multiple virus families. We demonstrate potent *in vitro* antiviral activity of RDV against a diverse panel of CoV including, SARS- and MERS-CoV, endemic human CoVs OC43 and 229E, as well as *deltacoronaviruses* that have the most divergent RdRp of known CoVs. Combinations of lopinavir, ritonavir and interferon beta (LPV/RTV+IFNb) are currently under clinical evaluation for the treatment of MERS-CoV infection. We show that RDV and IFNb have superior antiviral activity to LPV *in vitro* and that LPV concentrations required to inhibit MERS-CoV exceed the clinical drug concentrations attainable in humans. Therapeutic RDV significantly reduced MERS-CoV lung viral loads, and improved respiratory function and disease outcomes in mice while LPV/RTV+IFNb only improved respiratory function. Thus, we provide the first *in vivo* evidence of the potential for RDV to treat MERS-CoV infections.

151. A Genome-Wide CRISPR Screen Identifies N-Acetylglucosamine-1-Phosphate Transferase as a Potential Antiviral Target for Ebola Virus

Mike Flint, Ph.D.[1], Payel Chatterjee, B.S.[1], David Lin, Ph.D.[2], Laura McMullan, Ph.D.[1], Punya Shrivastava-Ranjan, Ph.D.[1], Eric Bergeron, Ph.D.[1], Michael Lo, Ph.D.[1], Stephen Welch, Ph.D.[1], Stuart Nichol, Ph.D.[1], Andrew Tai, M.D., Ph.D.[2], Christina Spiropoulou, Ph.D.[1]

[1]Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America; [2]University of Michigan Medical School, Ann Arbor, Michigan, United States of America

There are no approved therapies for Ebola virus infection. To find potential therapeutic targets, we performed a screen for genes essential for Ebola virus (EBOV) infection. We identified *GNPTAB*, which encodes the α and β subunits of N-acetylglucosamine-1-phosphate transferase, an enzyme involved in the trafficking of lysosomal hydrolases. We found that EBOV infection of a *GNPTAB*- knockout cell line was impaired, and that this effect was reversed by reconstituting GNPTAB expression. EBOV infection of fibroblasts from mucolipidosis II (MLII) patients, a genetic disorder associated with mutations in *GNPTAB*, was also reduced, whereas cells from their healthy parents were permissive. Fibroblasts from patients with mucolipidosis III (MLIII), a less severe form of disease, were also less susceptible to EBOV infection than cells from healthy individuals. Impaired EBOV infection correlated with loss of the expression of cathepsin B (CatB), known to be essential for EBOV entry. GNPTAB activity is dependent upon its proteolytic cleavage by the SKI-1/S1P protease. Inhibiting this protease with the small molecule PF-429242 blocked EBOV entry and infection. These data indicate that disruption of GNPTAB function may represent a strategy for a host-targeted therapy for EBOV.

152. Efficacy of a ML336 Derivative against Venezuelan and Eastern Equine Encephalitis Viruses

Colleen Jonsson, Ph.D.[1], Xufeng Cao, Ph.D.[2], Jasper Lee, Ph.D.[1], Jon Gabbard, Ph.D.[3], Yong-Kyu Chu, Ph.D.[3], Elizabeth Fitzpatrick, Ph.D.[1], Justin Julander, Ph.D.[4], Dong-Hoon Chung, Ph.D.[3], Jennifer Stabenow, M.S.[1], Jennifer Golden, Ph.D.[5]

[1]University of Tennessee Health Science Center, Memphis, Tennessee, United States of America; [2]University of Wisconsin, Madison, Wisconsin, United States of America; [3]University of Louisville, Louisville, Kentucky, United States of America; [4]Utah State University, Logan, Utah, United States of America; [5]University of Madison, Madison, Wisconsin, United States of America

Currently, there are no licensed human vaccines or antivirals for treatment of or prevention from encephalitic alphaviruses infections. Because epidemics are sporadic and unpredictable, and endemic disease is common but rarely diagnosed, it is difficult to identify all populations requiring vaccination; thus, an effective post-exposure treatment method is needed to interrupt ongoing outbreaks. To address this public health need, we have continued development of ML336 to deliver a molecule with prophylactic and therapeutic potential that could be relevant for use in natural epidemics or deliberate release scenario for Venezuelan equine encephalitis virus (VEEV). We report findings from *in vitro* assessments of four analogs of ML336, and *in vivo* screening of three of these new derivatives, BDGR-4, BDGR-69 and BDGR-70. The optimal dosing for maximal protection was observed at 12.5 mg/kg/day, twice daily for 8 days. BDGR-4 was tested further for prophylactic and therapeutic efficacy in mice challenged with VEEV Trinidad Donkey (TrD). Mice challenged with VEEV TrD showed 100% and 90% protection from lethal disease when treated at 24 and 48 hours post-infection, respectively. We also measured 90% protection for BDGR-4 in mice challenged with Eastern equine encephalitis virus. In additional assessments of BDGR-4 in mice alone, we observed no appreciable toxicity as evaluated by clinical chemistry indicators or interferon induction up to a dose of 25 mg/kg/day over 4 days. Lastly, the resistance of VEEV to BDGR-4 was evaluated by next-generation sequencing which revealed specific mutations in nsP4, the viral polymerase.

153. Sofosbuvir, a Clinically Approved Antiviral Drug, Inhibits Zika Virus Replication

Giselle Barbosa-Lima, Ph.D.[1], Carolina Sacramento, Ph.D.[1], André Ferreira, Ph.D.[1], Patricia Reis, Ph.D.[1], Camila Zaverucha-do-Valle, Ph.D.[1], Mayara Mattos, B.S.[1], Yasmine Vieira, Ph.D.[1], Caroline Freitas, M.S.[1], Milene Miranda, Ph.D.[1], Pablo Trindade, Ph.D.[2], Stevens Rehen, Ph.D.[2], Hugo Faria Neto, Ph.D.[1], Fernando Bozza, Ph.D.[1], Almicar Tanuri, Ph.D.[3], Karin Brüning, Ph.D.[4], Patricia Bozza, Ph.D.[1], Thiago Souza, Ph.D.[1]

[1]FIOCRUZ, Rio de Janeiro, Brazil; [2]IDOR; [3]UFRJ; [4]BMK Consortium: Blanver Farmoquímica Ltda; Microbiológica Química e Farmacêutica Ltda

Zika virus (ZIKV) causes significant public health concerns because of its association with congenital malformations, neurological disorders in adults and death. Considering the necessity to mitigate ZIKV-associated diseases, antiviral interventions are an urgent necessity. Sofosbuvir is clinically approved for use against hepatitis C virus and targets the protein that is most conserved among the members of the *Flaviviridae* family, the viral RNA polymerase. Indeed, we found that sofosbuvir inhibits ZIKV RNA polymerase, targeting conserved amino acid residues. Sofosbuvir inhibited ZIKV replication in different cellular systems, such as brain organoids, hepatoma, neuroblastoma and neural stem cells. In addition to the direct inhibition of the viral RNA polymerase, we observed that sofosbuvir also induced an increase in A-to-G mutations in the viral genome. We also investigated the *in vivo* activity of sofosbuvir against ZIKV. Neonatal *Swiss* mice were infected with ZIKV and treated with sofosbuvir at 20 mg/kg/day, a concentration compatible with pre-clinical development of this drug. We demonstrated that sofosbuvir reduced acute levels of ZIKV from 60 to 90% in different anatomical compartments, such as the blood plasma, spleen, kidney, and brain. Early treatment with sofosbuvir doubled the percentage and time of survival of ZIKV-infected animals. Sofosbuvir also prevented the acute neuromotor impairment triggered by ZIKV. In the long-term behavioral analysis of ZIKV-associated sequelae, sofosbuvir prevented loss of hippocampal- and amygdala-dependent memory. Our results indicate that sofosbuvir inhibits ZIKV replication both *in vitro* and *in vivo*, which is consistent with the prospective necessity of antiviral drugs to treat ZIKV-infected individuals.

154. Single-dose Efficacy of Viral Replicon Particle Vaccines for Prevention of Lassa and Crimean-Congo Hemorrhagic Fever

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

[1]Viral Special Pathogens Branch, Centers for Disease Control & Prevention, Atlanta, Georgia, United States of America

Lassa fever, caused by Lassa virus (LASV), is a rodent-borne arenaviral zoonosis with a high burden of disease in endemic regions of West Africa. Crimean-Congo hemorrhagic fever virus (CCHFV) is a tick-borne agent that causes severe disease exclusively in humans. We generated LASV and CCHFV viral replicon particle (VRP)-based platforms, consisting of virus genome lacking the glycoprotein gene. VRPs replicate in the first cells encountered but do not spread due to lack of de novo synthesis of viral glycoprotein. In the Strain 13 guinea pig model, single-dose subcutaneous vaccination (1×10^7 FFU) elicited 100% protection against all clinical signs after LASV challenge. The capacity of VRPs to replicate in the first cells encountered contributes to vaccine efficacy, since degradation of VRP viral genome by gamma irradiation reduced protection against lethality to 60% and did not prevent clinical disease. Interestingly, post-exposure vaccination (1 day) protected all animals from fatal outcome, though clinical signs were still observed. Similar to the success of the LASV VRP, high dose (4.4×10^5 TCID50) single-dose subcutaneous vaccination of $IFNAR^{-/-}$ mice with CCHFV-based VRP prevented disease following lethal CCHFV challenge. Even a low dose (4.6×10^3 TCID50) protected the majority of animals (67%) against clinical signs of disease. These data provide support for the VRP platform as a safe, scalable, and efficacious vaccine candidate for hemorrhagic fever viruses.

155. A Novel Class of Small Molecule Inhibitors Targeting the Chikungunya Virus Capping Machinery with a High Barrier to Resistance

Rana Abdelnabi, Ph.D.[1], Kristina Kovacikova, M.S.[2], Julia Kirchebner, Ph.D.[3], Pieter Leyssen, Ph.D.[1], Arnaud Marchand, M.S.[4], Patrick Chaltin, Ph.D.[4], Gerhard Pürstinger, Ph.D.[3], Thierry Langer, Ph.D.[5], Gilles Quérat, Ph.D.[6], Bruno Coutard, Ph.D.[6], Martijn van Hemert, Ph.D.[2], Johan Neyts, Ph.D.[1], **Leen Delang, Ph.D.[1]**

[1]KU Leuven, Rega Institute for Medical Research, Leuven, Belgium., Leuven, Belgium; [2]Molecular Virology Laboratory, Department of Medical Microbiology, Leiden University Medical Center, Leiden, Netherlands; [3]Department of Pharmaceutical Chemistry, University of Innsbruck, Innsbruck, Austria, Innsbruck, Austria; [4]Centre for Drug Design and Discovery , KU Leuven, Leuven, Belgium; [5]University of Vienna, Department of Pharmaceutical Chemistry, Vienna, Austria, Vienna, Austria; [6]Aix Marseille Université, CNRS, AFMB UMR7257, Marseille, France, Marseille, France

Despite the worldwide re-emergence of the chikungunya virus (CHIKV) and the high morbidity associated with CHIKV infections, there is no approved vaccine or antiviral treatment available. Here, we report on the identification of a novel class of CHIKV inhibitors, tentatively named the CHVB series. Several analogues within the series inhibited the replication of CHIKV isolates in cell culture with EC_{50} values in the low µM range. In virus yield assays, the most potent analogues reduced the viral load with 4-5 log_{10} without adverse effects on the cells. CHVB-resistant variants were selected and found to carry (i) two mutations in the gene encoding non-structural protein 1 (nsP1) (responsible for viral RNA capping), (ii) one mutation in nsP2 and (iii) one mutation in nsP3. Reverse-engineering suggested that nsP1 is the target of CHVB, since both nsP1 mutations were needed to achieve 10-fold resistance. Introducing the nsP2 and nsP3 mutations in addition to the nsP1 mutations further increased resistance to the level of $CHVB^{res}$ virus obtained after passaging. Interestingly, the $CHVB^{res}$ virus proved cross-resistant to the MADTP series, a class of CHIKV capping inhibitors that we described earlier, suggesting a similar mode of action. Indeed, in enzymatic assays, CHVB proved a potent inhibitor of the methyltransferase and guanylyltransferase activities of Venezuelan equine encephalitis virus nsP1. In summary, we identified a class of CHIKV inhibitors that target the viral capping machinery. The potent anti-CHIKV activity in addition to the high barrier to resistance make this chemical scaffold a potential candidate for CHIKV drug development.

156. Development of a Nucleoside Analog for Norovirus

Randall Lanier, Ph.D.[1], Maggie Anderson, B.S.[1], Mark Mullin, B.S.[1], Marion Morrison, M.D.[1], John Dunn, Ph.D.[1], Karoly Toth, D.V.M.[2], Jacqueline Spencer, B.S.[2], Baoling Ying, M.D.[2], Dean Selleseth, B.S.[1], Myra Hosmillo, Ph.D.[3], Komal Nayak, M.S.[3], Andrew Bae, B.S.[1], Sarah Gurley, M.S.[1], Tim Tippin, Ph.D.[1], Heidi Colton, M.S.[1], Matthias Zilbauer, M.D., Ph.D.[3], Ian Goodfellow, Ph.D.[3], Brent Korba, Ph.D.[4], Phiroze Sethna, Ph.D.[1], Dennis Walling, M.D.[1], Odin Naderer, Ph.D.[1]

[1]Chimerix; [2]St Louis University; [3]University of Cambridge; [4]Georgetown University

Human noroviruses (NV) cause epidemic acute gastroenteritis and may be associated with severe disease, especially in immunocompromised patients. There are currently no vaccines or antivirals indicated for NV. CMX521 is a ribonucleoside analog with pan-genotypic norovirus activity *in vitro* (EC_{50}s 0.12-4.1 µM) that inhibits activity of the NV polymerase (IC50s 1-2 µM). *In vivo*, oral delivery of 150 mg/kg CMX521 twice daily in an acute mouse norovirus (MNV) model significantly reduced fecal MNV shedding in immunocompetent mice and extended survival in a lethal model (immunocompromised mice). CMX521 is not mutagenic or clastogenic, and multiple studies have demonstrated a low potential for cytotoxicity, or mitochondrial toxicity. CMX521 was tested for safety and pharmacokinetics in a Phase 1 double-blind, single-dose escalation clinical study (CMX521-101), in which healthy subjects (38 adults divided into 5 cohorts) were randomized to receive single oral doses of CMX521 (200 mg to 2400 mg) or placebo. Single oral doses of CMX521 up to 2400 mg were generally well-tolerated and no clinically significant laboratory or electrocardiogram findings were noted. The concentration of the active antiviral (CMX521-triphosphate[TP]) was evaluated in duodenal biopsies (n=7/subject) taken 4h after a single dose of 2400 mg of CMX521 in three subjects. CMX521-TP was detected in all samples but was below the target internally established from in vitro studies. The low concentration of CMX521-TP in duodenal biopsies, combined with the high doses needed for efficacy in animal models, suggests that enhanced delivery of CMX521 to target cells is needed to optimize activity.

157. Rottlerin, a Small Bioactive Compound, Inhibits La Crosse Virus (LACV)-induced Neuronal Damage by Limiting Virus Release from the Golgi

Durbadal Ohja[1], Vidon Nair, Ph.D.[2], Karin Peterson, Ph.D.[3]
[1]*NIAID, Hamilton, Montana, United States of America;* [2]*Staff Scientist, Hamilton, Montana, United States of America;* [3]*Senior Investigator, Hamilton, Montana, United States of America*

La Crosse Virus (LACV) is a member of the California serogroup of mosquito-borne Orthobunyavirus and induces a rare, but life-threatening neurological disease in children. Currently, neither a vaccine nor FDA approved antiviral therapies are available to prevent or treat LACV encephalitis. To study potential compounds that could affect LACV-induced neuronal damage, we conducted a screen of more than 3,500 FDA approved and bio-active classical compounds through the National Center for Advancement of Transnational Science (NCATS) to identify compounds that inhibited LACV-induced death of the human neuronal cell line, SHSY5Y. The initial screen revealed 38 potential compounds, which were subsequently narrowed to four potential compounds for further *in vitro* and *in vivo* testing. Of these four compounds, only Rottlerin inhibited LACV-induced apoptosis in multiple neuronal cell lines (N2a, C17.2, SHSY5Y and hNSC) and primary murine neurons. Rottlerin had potent antiviral activity against LACV (EC_{50}, 0.16-0.38 µg/ml) with selectivity index of 5 to 37.8. Rottlerin treatment reduced virus release by these cell lines by up to 3 logs, suggesting suppression of virus infection or replication. Time of addition studies demonstrated that Rottlerin could inhibit virus replication when added up to 12 hours post infection. Confocal and Electron microscopy analysis indicated that Rottlerin treatment inhibited virus release from the Golgi, by a PKC-δ independent mechanism. *In vivo* Rottlerin was inhibit LACV-induced disease in mice by 48% and 66% following i.p. and i.c. route of treatment, respectively. Collectively, these studies indicate that Rottlerin is an effective inhibitor of LACV replication and neuronal apoptosis.

158. An Industry Perspective on Developing Dengue Antiviral Small Molecules

Marnix Van Loock, Ph.D.[1]
[1]*Janssen Pharmaceutica NV (J&J), Global Public Health Research & Development, Beerse, Belgium*

Dengue is the most important mosquito-borne viral disease in the world, representing a major unmet medical need. The importance of this growing public health concern was recently illustrated by WHO, listing dengue as one of the top 10 threats to global health in 2019. The disease imposes a heavy burden to the affected individuals, to the health care systems, and to the economies of endemic countries. Vector control is the most widespread tool to curb dengue epidemics, which so far has been proven to be insufficient. Therefore, additional means such as vaccines, diagnostics and antivirals are required to aid in a coordinated and integrated approach. The discovery and development of small molecule dengue virus inhibitors as a tool to prevent and/or treat dengue disease faces major hurdles in combining pan-serotypic efficacy, safety, and optimal drug-like properties. At Johnson & Johnson Global Public Health, our mission is to make relevant innovations that save lives, cure patients and prevent disease for underserved populations. We are committed to global health challenges by harnessing resources and expertise from across our company that combine research and development, access to care and advocacy to advance health around the world; as illustrated by our fight against dengue.

159. Rational (and Sometimes Irrational!) Strategies in Nucleoside Drug Design

Kathie Seley-Radtke, Ph.D.[1]
[1]*University of Maryland, Baltimore County (UMBC), Baltimore, Maryland, United States of America*

Nucleoside and nucleotide analogues have held an important role in the field of medicinal chemistry for several decades. The naturally occurring nucleosides represent a unique starting point for drug design due to their involvement in numerous critical biological processes as well as the fact that they serve as essential building blocks for both DNA and RNA synthesis. Because nucleoside/tide analogues mimic the structure of the natural nucleosides such that they are recognized by cellular or viral enzymes, modifications to their structure typically lead to disruption and/or termination of replication or other biological processes. Moreover, modifications to their structure can be designed and manipulated to improve their potency or bioavailability, lessen toxicity and side effects, or overcome issues with delivery. As a result, even small changes to their structure can have profound effects. Currently there are more than 30 nucleoside/tide analogues on the market approved for use in treating viruses, cancers, and other conditions, with many others in clinical and preclinical trials. It is hoped that the examples discussed will provide some insight to virologists and others outside the field of medicinal chemistry as to the rationale behind their development, why certain drugs were successfully developed, why many candidate compounds encountered barriers and never proceeded to the market, as well as to highlight new directions and recent developments for current nucleoside/tide antivirals.

160. In Search of Novel Antivirals using Structure-based Drug Design Approaches

Andrea Brancale, Ph.D.[1]
[1]*Cardiff University, United Kingdom of Great Britain and Northern Ireland*

Drug discovery is a long and expensive enterprise. Computer-based techniques can help in speeding up the initial stages of the drug discovery process allowing identification of novel potential biologically active compounds *in silico* before committing to their synthesis in the lab. This offers an advantage also on costs, as the synthesis of novel compounds is often the slow and expensive step at the beginning of a drug discovery project. Millions of candidates can often be screened for the cost of one multi-step synthesis. In addition to these applications, computer-aided techniques are becoming increasingly useful in understanding more complex biological processes. For example, by examining how proteins interact with each other within a specific biological pathway, it is possible to identify specific mechanisms, which could be the target for novel therapeutics. For these reasons, computer-aided drug design has now become an integral part of the modern drug discovery activities.

In this presentation some examples of the molecular modelling techniques, in particular structure-based methodologies, that have successfully been applied in antiviral drug design will be discussed, highlighting the strengths and limitations of these computer-aided drug design approaches.

161. Antivirals against Chikungunya Virus from a Medchem Perspective: Challenges and Lessons Learned

María-Jesús Pérez-Pérez, Ph.D.[1]
[1]*Instituto de Química Médica (IQM, CSIC), Madrid, Spain*

Chikungunya virus (CHIKV), an alphavirus transmitted by the bites of infected *Aedes* mosquitoes, is now considered as a global pathogen. In the last decade, significant efforts have been made to identify compounds that effectively inhibit CHIKV replication, but so far there is no drug approved against CHIKV infection and no novel compound has entered clinical trials. Up to now, the strategies followed to identify compounds active against CHIKV have been mostly centered in drug repositioning/repurposing and in large phenotypic screenings. On the other hand, target-based assays and structure-based drug design, strategies that have been successfully employed to identify and optimize hit compounds for antiviral chemotherapy, have been much less explored for CHIKV. This presentation will highlight some representative examples for each of these approaches from a medchem perspective. In addition, our own research on triazolopyrimidines against CHIKV will be used to illustrate how collaborative efforts combining the expertise of medicinal chemists, virologists and biochemists results in the identification of new targets for CHIKV inhibition.

162. Drug Discovery using DNA-Encoded Chemical Libraries

Anthony Keefe, Ph.D.[1]
[1]*X-Chem Pharmaceuticals, Waltham, Massachusetts, United States of America*

X-Chem Pharmaceuticals operates a proprietary DNA-encoded chemistry platform that numbers over 220 billion unique compounds and has been successfully applied to a wide range of target classes and therapy areas. This platform permits affinity-based screening of the entire encoded library simultaneously and thereby enables the facile discovery of truly novel chemical equity to initiate drug discovery programs. The X-Chem platform has yielded over fifty licensed therapeutic programs and has also been used to initiate multiple internal drug discovery programs within X-Chem. Example discovery programs will be presented with a view to introducing this technology and the opportunities that it presents.

163. Novel ProTide Prodrugs of Tenofovir and Their Antiviral Properties

Filip Kalčic, M.S.[1], Ondřej Baszczyňski, Ph.D.[2], Jan Weber, Ph.D.[3], Michala Zgarbová, M.S.[3], Jan Hodek, Ph.D.[3], Zlatko Janeba, Ph.D.[3]

[1]Institute of Organic Chemistry and Biochemistry CAS; Charles University, Department of Organic Chemistry; [2]Charles University, Faculty of Science, Department of Organic Chemistry; [3]Institute of Organic Chemistry and Biochemistry CAS

In the field of antiviral nucleoside analogues, the prodrug moieties are crucial for the efficient delivery of an active compound into the cell cytoplasm. The prodrug moiety is enzymatically cleaved inside the cell and the parent compound is released and further metabolized (phosphorylated). The current endpoint of prodrug development is represented by the so-called ProTide technology which nowadays dominates the field of medicinal chemistry with its excellent pharmacokinetic properties.[1]

Herein, we disclose synthesis and antiviral evaluation of a new series of ProTides derived from tenofovir. We optimized the synthesis of target compounds and compared their anti-HIV-1 and anti-HBV potency with clinically used tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF).

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164. Cell-type Dependence of Metabolic Products and Antiviral Potency for T-705 and T-1105

Johanna Huchting, Ph.D.[1], Evelien Vanderlinden, Ph.D.[2], Chris Meier, Ph.D.[3], Lieve Naesens, Ph.D.[2]

[1]University of Hamburg, Chemistry Department; KU Leuven, Rega Institute for Medical Research; [2]KU Leuven, Rega Institute for Medical Research; [3]University of Hamburg, Chemistry Department

Besides its anti-influenza virus effect, T-705 (favipiravir) showed potency against numerous RNA viruses in cell-based experiments and beyond. Intracellular phosphoribosylation, yielding T-705-ribonucleoside monophosphate (RMP), and subsequent phosphorylation steps give the active metabolite, T-705-ribonucleoside triphosphate (RTP), which interferes with viral RNA synthesis. For T-705 activation and thus antiviral potency, the first metabolic step has been suggested a bottleneck.

We performed a parallel study including three different viruses that revealed higher antiviral potency of the non-fluorinated analogue T-1105 compared to T-705 in MDCK cells. In contrast, when comparing activity against the same viruses in A549 or Vero cells, we found that T-1105 was less active than T-705. In line with the antiviral data, metabolism experiments revealed that in MDCK cells, T-1105-RTP levels were significantly higher than T-705-RTP, while this ranking was reversed in A549, Vero and HEK293T cells. Interestingly, under all studied conditions we found higher T-1105-RMP than T-705-RMP levels. Taken together, our data suggest that antiviral potency of T-1105 in non-MDCK cells was highly limited by inefficient conversion of T-1105-RMP *en route* to T-1105-RTP and that this effect was less pronounced for T-705. On the other hand, conversion of T-1105-RMP to the NAD-analogous T-1105-RAD metabolite, recently discovered by us, appeared similarly efficient among all cell types, implicating that this metabolite did not contribute to virus inhibition, nor did it seem to cause toxicity in our model.

Thus, our results add an important perspective to the development of broadly active antivirals and once more suggest overcoming metabolic bottlenecks as an important strategy.

165. Development of Novel hDHODH Inhibitors as Potent Broad Spectrum Antiviral Agents

Nora Constanze Fohrmann, M.S.[1], Katharina Pfaff, M.S.[1], Matthias Winkler, M.S.[1], Johannes Kirchmair, Ph.D.[2], Gilles Querat, Ph.D.[3], Chris Meier, Ph.D.[1]

[1]University of Hamburg, Department of Chemistry, Hamburg, Germany; [2]University of Hamburg, Center for Bioinformatics, Hamburg, Germany; [3]Aix-Marseille University, Faculty of Medicine, Marseille, France

As a consequence of climate change and a growing tourism, viral infections increasingly appear in geographical areas where they have not been observed before. To be prepared to combat such emerging viruses and to prevent potential health crises of epidemic proportions, potent broad-ranged treatment strategies have been intensively researched during the last years. Some of these emerging infections are caused by bunya viruses, against which neither preventative measures nor efficient therapeutic strategies currently exist.

With the intention of finding an active agent for treatment of bunya virus infections, we carried out a high throughput substance screening in infected cells. Thereby we identified a class of anthranilic acid based inhibitors which furthermore show a broad range of activity against various RNA virus species (e. g. Ebola, Zika, Lassa) with IC50 values in the single-digit nanomolar range. Using a biochemical *in vitro* approach on the one hand and an *in silico* approach on the other hand, we identified dihydroorotate dehydrogenase (DHODH) to be the target enzyme of our inhibitors. DHODH is a cellular enzyme which is involved in the *de novo* biosynthesis of pyrimidine nucleotides and thus is mandatory for viral replication. However, ADME studies revealed that our first generation inhibitors exhibit low stability in hepatic microsomes and thus will probably be metabolized during first liver passage. By performing hydrolysis studies in liver extract, we were able to find the main site of metabolism and replaced it, supported by molecular modelling using x-ray crystal structures of our best first generation inhibitors.

166. Optimizing Diarylbenzopyrimidines as HIV-1 Non-nucleoside Reverse Transcriptase Inhibitors for Superior Antiviral and Improved Drug Resistance Profile

Sheng Han, M.S.[1], Erik De Clercq, Ph.D.[2], Christophe Pannecouque, Ph.D.[2], **Ge Meng, Ph.D.**[1], Fener Chen, Ph.D.[1]

[1]Fudan University, Shanghai, Shanghai, China; [2]Leuven University, Leuven, Belgium

A novel series of diarylbenzopyrimidine analogues (DABPs) was developed from modification of our previously reported DABP hybrid (1) by employing a strategy of structure-based optimization and substitution decoration. The target compound shared a structure motif of 4-cyanovinyl-2,6-disubstitued phenyl to form the potential non-nucleoside inhibitors against HIV-1 reverse transcriptase (NNRTIs). Several core-structure modifications were established showing the improved antiviral and resistance profiles by reducing the binding free energy of the conformation of inhibitors upon interacting with HIV-1 RT. The biological screening showed that a highly potent compound 2 with 2-methyl-6-nitro substituted group on the phenyl ring (EC_{50} = 1.5 nM against WT, 1.6 nM against K103N, 1.9 nM against E138K, 3.5 nM against Y181C, 8 nM against L100I). Molecular docking and SAR analysis provided further insights into the interaction of between these DABPs with the active binding pocket of HIV-1 RT, which could provide the deeper understanding of the key structural aspects of their interactions.

Figure 1. Designing rationale of novel diarylbenzopyrimidine analogues based on our previous studies

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167. Structure-Based Design of Nucleoside Triphosphate Mimics and Their Broader Implications for Discovery of Viral DNA and RNA Polymerase Inhibitors

Sergio Martinez, Ph.D.[1], Weijie Gu, B.S.[1], Brent De Wijngaert, B.S.[1], Shrinivas Dumbre, Ph.D.[2], Hans Vanbuel, B.S.[1], Piet Herdewyn, Ph.D.[2], Steven De Jonghe, Ph.D.[1], Kalyan Das, Ph.D.[1]

[1]Division of Virology and Chemotherapy, Rega Institute for Medical Research, KU Leuven, Leuven, Vlaams-Brabant, Belgium; [2]Rega Institute for Medical Research, Department of Medicinal Chemistry, KU Leuven, Leuven, Vlaams-Brabant, Belgium

Active-site metal chelating groups play an important role in antiviral drug design. Discovery of scaffolds that will effectively substitute for the metal chelation of triphosphate moiety of NTP/dNTP would lead to a foundation for developing new classes of viral RNA and DNA polymerase inhibitors. Till now all nucleos(t)ide analog drugs targeting viral RNA/DNA polymerases are chain terminators. They must be converted to NTP/dNTP mimics by multiple phosphorylation steps by cellular kinases, a significant hurdle.

We are taking a structure-based approach to designing chemical motifs as substitutes for the triphosphate moiety of NTP/dNTPs. Fifteen amino-acid phosphoramidate nucleotides have been synthesized as the primary screening set. These compounds contain tenofovir (TFV) or dAMP as a nucleotide monophosphate backbone and expanded by the addition of amino acids such as Asp, Glu, His, Arg, Phe or Gly. Crystal structures of the individual compounds bound to a polymerization-competent complex of HIV-1 reverse transcriptase (RT) have been determined. The compounds are bound at the polymerase active site by base pairing with the first template base overhang. The acyclic substitution for the ribose ring in TFV permits higher adaptability of the compounds. This flexibility helps to position different amino acid side-groups to interact with different parts of the dNTP pocket while the compounds chelate with a catalytic metal ion. These structures provide the design features for improving metal chelation affinity and interactions with the conserved residues in the binding pocket. Additionally, we attempt to reduce the overall negative charge of the compounds to improve their cellular permeability.

168. Potent Peptidomimetic Inhibitors of NS2B-NS3 Protease from Dengue and Zika Viruses

Dahai Luo, Ph.D.[1], Jun Ping Quek, B.S.[1], Torsten Steinmetzer Steinmetzer, Ph.D.[2]

[1]Lee Kong Chian School of Medicine, Nanyang Technological University, EMB 03-07, 59 Nanyang Drive, Singapore 636921, Singapore, Singapore; [2]Institute of Pharmaceutical Chemistry, Philipps University, Marbacher Weg 6, 35032 Marburg, Germany.

Flavivirus NS2B-NS3 protease plays an essential role in viral replication by processing the viral polyprotein into individual proteins. The viral protease is therefore considered as an ideal antiviral drug target for dengue and zika infections. To facilitate the development of protease inhibitors, we report three high-resolution co-crystal structures of NS2B-NS3 protease from Zika viruses (bZiPro) with peptidomimetic inhibitors. Compounds 1 and 2 possess small P1′ groups that are cleaved by bZiPro, which could be detected by mass spectrometry. On the other hand, the more potent compound 3 contains a bulky P1′ benzylamide structure that is resistant to cleavage by bZiPro, demonstrating that presence of an uncleavable C-terminal cap contributes to a slightly improved inhibitory potency. The N-terminal phenylacetyl residue occupies a position above the P1 side chain and therefore stabilizes a horseshoe-like backbone conformation of the bound inhibitors. The P4 moieties show unique intra- and intermolecular interactions. Our work reports the detailed binding mode interactions of substrate-analogue inhibitors within the S4-S1′ pockets and explains the preference of bZiPro for basic P1-P3 residues. These new structures of protease-inhibitor complexes will guide the design of more effective NS2B-NS3 protease inhibitors with improved potency and bioavailability.

EMBO Young Investigator Lecture

169. The Challenge of Developing Antivirals to Treat Eradicated Disease

David Evans, Ph.D.[1]
[1]*Li Ka Shing Institute of Virology, University of Alberta, Canada*

Although smallpox was declared eradicated in 1979, the threat posed by its re-emergence from any of several possible sources remains a public health concern. This existential threat has driven ongoing research into how to detect smallpox, safely vaccinate against the disease, and devise drug treatments. Currently, only one drug (tecovirimat) has received FDA approval as a treatment for smallpox, but it's widely recognized that single-drug therapy can be compromised by drug resistance and thus the search continues to find a second antiviral. I will describe the work that we've done to show how nucleoside phosphonate drugs, in particular, the prodrug cidofovir (CDV or HPMPC), inhibit Orthopoxvirus DNA synthesis. These collaborations have provided insights into the properties of drug-resistant viruses and the complex ways in which CDV blocks the replication and recombination reactions catalyzed by poxvirus DNA polymerases. More particularly, these observations can help explain the high-barrier to resistance against these compounds and offer support for their ongoing development as a second smallpox therapy.

170. Novel Utilization of Smallpox Medical Countermeasures – Challenges to Vaccination Against Endemic Orthopoxvirus Disease (Monkeypox)

Victoria Olson, Ph.D.[1]
[1]*CDC, Atlanta, Georgia, United States of America*

In 1980, the World Health Organization announced the eradication of the first disease, smallpox, after a concerted global vaccination effort. Despite this tremendous public health achievement, smallpox remains a feared disease, having killed more than 300 million individuals during the 20th century before eradication. Concerns have escalated in recent years as technology has advanced to allow the reconstruction of viruses from published genomic sequences. Bioterrorism preparedness has focused on stockpiling medical countermeasures against high-consequence pathogens that will provide protection and treatment of disease. Considerable progress has been achieved in the development of vaccines as well as anti-viral therapies against smallpox. However, since smallpox no longer exists in nature, understanding of the use of medical countermeasures must be inferred from studies against other endemic *Orthopoxvirus*diseases. *Monkeypox virus* is the *Orthopoxvirus* that causes the most severe human disease today. Monkeypox is endemic in several regions of Africa, causing substantial (~10%) case fatality rates. This presentation will focus on the successful implementation of vaccination for 1,000 healthcare workers in the Democratic Republic of Congo with a potentially safer, attenuated smallpox vaccine (IMVAMUNE®). The challenges presented conducting this trial within resource-poor regions will be discussed as well as creative solutions and opportunities for future medical countermeasures evaluations. Saving lives should smallpox ever re-emerge depends upon understanding how medical countermeasures can be appropriately and effectively used against smallpox.

171. Polio Eradication: Need for Antivirals and Progress to Date

Marc Collett, Ph.D.[1]
[1]*ViroDefense, Inc., Rockville, Maryland, United States of America*

Poliovirus is close to being eradicated globally. Close, but no cigar. Several revelations have conspired to challenge this, the largest and most expensive public health initiative ever. The Sabin oral vaccine (OPV), while eliciting both systemic and mucosal protective immune responses, in rare cases, can give rise to circulating vaccine derived polioviruses (cVDPV) with full virulence and outbreak potential. The planned cessation of OPV use should address this. This leaves only the inactivated Salk polio vaccine (IPV), while good at protecting against neurologic disease, does not prevent virus replication and community spread. Finally, OPV recipients who are unknowingly immunodeficient, in rare cases, can become chronically infected with vaccine virus and excrete immunodeficiency-associated, vaccine derived poliovirus (iVDPV) for months, even years. These individuals are personally at increased risk for serious disease, and from a public health perspective, represent a threat to polio eradication. Anti-poliovirus drugs may mitigate these risks. Toward this end, ViroDefense is advancing clinically two direct acting anti-poliovirus compounds. This effort is being orchestrated by the Poliovirus Antiviral Initiative (PAI), a consortium managed by the Task Force for Global Health and comprised of the WHO, CDC, Rotary International, FDA (CBER), NIAID, the Bill & Melinda Gates Foundation, and ViroDefense. An update will be provided.

172. Update and Challenges in Research and Development of Dengue and Zika Antivirals

Subhash Vasudevan, Ph.D.[1]
[1]*Duke NUS Medical School, Singapore, Singapore*

Directly Acting Antivirals (DAAs) against dengue viruses (DENV 1-4 serotypes) and zika virus strains (ZIKV) are urgently needed and several screening campaigns of large chemical libraries and focused screens on FDA approved drugs have been reported that will be briefly reviewed. These two important human-disease causing members of the flavivirus genus carry a single-stranded positive sense RNA genome of ~11,000 nucleotides that encodes a polyprotein precursor of ~3,400 amino acid residues which is cleaved into three structural proteins (capsid:C, pre-membrane/membrane;prM and envelope:E) and seven non-structural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5). The virion structure by cryo-EM analysis is fundamentally similar for DENV and ZIKV, and novel antibodies that can target the surface epitope formed by the E protein to neutralize the virus both *in vitro* and in mouse infection models are under early phase development (eg Tarakaraman et al., 2018 for ZIKV). Small molecule inhibitors that target the structurally conserved viral protease (NS3 with its NS2B cofactor) and polymerase (NS5) will be discussed from the view point of opportunities and challenges in development of novel DAAs (Low et al., 2018) including a brief mention of the leading candidate drug under development for DENV infection that targets the NS4B protein.

173. Investigational Therapies for Chronic Hepatitis B: *Does Anything Really Work?*

Tim Block, Ph.D.[1]
[1]*Baruch S. Blumberg Institute, Doylestown, Pennsylvania, United States of America*

As indicated at www.hepb.org, there are more than 30 experimental therapies in the pipeline for the management of chronic hepatitis B. Several are now in Phase III. Expectations are high. This presentation will review the portfolio of new HBV drugs in development and express opinions as to the promise the different candidates hold. There will also be a more detailed discussion of a few of the newer approaches, particularly two strategies that are very unusual and being developed at the Blumberg Institute.

174. Therapeutic Strategies to Combat Cytomegalovirus Infection

Rhonda Cardin, Ph.D.[1]
[1]*Louisiana State University School of Veterinary Medicine, Baton Rouge, Louisiana, United States of America*

Human Cytomegalovirus (HCMV), a beta-herpesvirus, is a ubiquitous pathogen that infects 50-90% of the world's population. For successful infection, HCMV relies on multiple strategies to subvert the host response. In humans, HCV infection usually results in a symptomatic infection but is life-threatening to immunocompromised individuals such as transplant recipients, HIV patients, and newborns. During diminished immunity, widespread infection ensues following primary infection or reactivation from latent infection, leading to tissue damage, graft rejection or following congenital infection, hearing loss and neurological deficits. HCMV is also associated with cardiovascular disease, diabetes, autoimmune diseases, and several cancers such as glioblastoma, colon cancer, and breast cancer, most likely due to its broad tropism for multiple tissues and cell populations during both primary and latent infection. The role that HCMV plays in these diseases is not well understood but it is possible that even in immune-competent individuals, HCMV contributes to increased morbidity and mortality. Thus, to effectively prevent or treat HCMV infection, continued efforts to better understand HCMV biology and discovery of novel antiviral strategies will be essential to fully combat HCMV infection. Recent advances in new mechanisms of action, safety, and highly efficacious antivirals has the potential to alter the HCMV disease and treatment landscape, although continued efforts will be needed to counter emergence of drug-resistant viruses. New therapeutic strategies will be discussed in the context of HCMV disease modeling and therapeutic evaluations in small animal models to shed light on improved antiviral strategies for HCMV infections.

175. A Small Molecule Human STING Agonist that Induces Antiviral Cytokine Response and Stimulates the T Lymphocyte Activation

Xiaohui Zhang, M.D., Ph.D.[1], Bowei Liu, M.D.[1], Liudi Tang, B.S.[2], Julia Ma, B.S.[1], Qing Su, Ph.D.[1], Nicky Hwang, B.S.[1], Mohit Sehgal, Ph.D.[1], Junjun Cheng, Ph.D.[1], Xuexiang Zhang, M.S.[1], Yinfei Tan, Ph.D.[3], Yan Zhou, Ph.D.[3], Zhongping Duan, M.D.[4], Victor DeFilippis, Ph.D.[5], Usha Viswanathan, Ph.D.[1], John Kulp, Ph.D.[1], Yanming Du, Ph.D.[1], Ju-Tao Guo, M.D.[1], **Jinhong Chang, M.D., Ph.D.[1]**
[1]Baruch S. Blumberg Institute; [2]Drexel University College of Medicine; [3]Fox Chase Cancer Center; [4]Youan Hospital; [5]Oregon Health and Science University

STING is an ER protein that serves as a molecular hub for activation of innate immunity by multiple cellular DNA sensors. With its potential of bridging the innate and adaptive immunity, STING is considered as a therapeutic target for breaking host immune tolerance to viruses and tumor antigens. We previously reported a cell based HTS platform, which allows for identification of STING pathway agonists (Liu AVR 2017). We report herein a carboxamide compound termed BNBC that induces proinflammatory cytokine response in a manner dependent on the expression of functional human STING, but not mouse STING. In addition, BNBC induced type I and III IFN dominant cytokine responses in primary human fibroblast cells, PBMCs from healthy donors, as well as PBMC-derived M1 macrophages and dendritic cells. Furthermore, BNBC promoted the maturation of dendritic cells, which suggests a potential role of BNBC on the activation of CD4+ and CD8+ T cells. To examine the effect of pharmacological activation of STING pathway in virus replication, we demonstrated that BNBC induced an antiviral state against Yellow fever, Dengue and Zika viruses in primary human skin fibroblasts. Furthermore, direct treatment of hepatitis B virus infected HepG2-NTCP cells with BNBC resulted in suppression of cccDNA transcription and reduction in viral replication. Taken together, BNBC is a human STING agonist that not only induces innate antiviral immunity against a broad spectrum of viruses, but also stimulate the activation of adaptive immune response, which is important for treatment of chronic viral infections, such as hepatitis B.

176. Antiviral Properties and Liver Specific Delivery of a TLR1/2 Ligand in HBV and/or HDV Infected Models

Julie Lucifora, Ph.D.[1], Brieux Chardès, M.S.[1], Myriam Lamrayah, M.S.[2], Manon Desmares, M.S.[1], Rayan Farhat, Ph.D.[1], Laura Dimier, B.S.[1], Capucine Phelip, M.S.[2], Floriane Fusil, Ph.D.[3], François Loïc Cosset, Ph.D.[3], Fabien Zoulim, M.D., Ph.D.[1], Anna Salvetti, Ph.D.[1], Bernard Verrier, Ph.D.[2], **David Durantel, Ph.D.[1]**
[1]CRCL – INSERM U1052, Lyon, France; [2]IBCP, Lyon, France; [3]CIRI – INSERM U111, Lyon, France

HBV/HDV co-infection is the most aggressive viral hepatitis and current treatments are suboptimal. Recent studies and clinical trials highlighted the therapeutic potential of immunestimulators to restore immune responses to HBV. Our goal was to explore the anti-HBV/HDV effect of free or nanoparticular TLR1/2 agonists *in vitro* and *in vivo* in monotherapy.

HBV/HDV-infected human hepatocytes, HepaRG cells, as well as AAV-HBV transduced mice were treated with TLR1/2 agonist. HBV and HDV replications were followed by ELISA, qPCR, qRT-PCR, Southern, western and northern blot analyses.

Pam3CSK4 (TLR1/2-ligand) was amongst the best TLR agonists tested that reduced both HBV and HDV replication markers. Importantly, its antiviral effect was fast and long-lasting after treatment cessation *in vitro*. It was associated with an activation of the canonical NF-kB pathway as demonstrated by analyses of mRNA and cytokines production, as well as knock-down experiments. Mechanistically, a stepwise implementation of different antiviral processes was observed, including a decline of both viral episomes. To prevent systemic immune activation and improve its dual efficacy (i.e. in hepatocytes and liver immune cells), Pam3CSK4 was encapsulated in biodegradable nanoparticles (NP) that mostly accumulate in the liver. Interestingly, Pam3CSK4-NP led to a stronger antiviral activity as compared to free Pam3CK4 in HBV-infected cells *in vitro* and *in vivo*.

Our data highlight the potential of innate immunity stimulators, such as TLR1/2 agonists, as direct antiviral effectors in hepatocytes and overall modulators of immune responses. This work further supports the clinical evaluation of TLR agonists as immune adjuvants in more complex immune-therapeutic strategies.

177. SMCHD1 and PML Mediate IFN-α Suppression of Hepadnaviral cccDNA Transcription

Junjun Chen, Ph.D.[1], Jinhong Chang, Ph.D.[1], **Ju-Tao Guo, M.D.**[1]
[1]*Baruch S. Blumberg Institute*

Covalently closed circular (ccc) DNA of hepadnaviruses exists as an episomal minichromosome in the nucleus of infected hepatocyte and serves as the transcriptional template for viral mRNAs. Due to its critical role in viral replication and extraordinary stability, elimination and/or transcriptional silence of cccDNA is essential for the "functional" cure of HBV infection. We reported previously that IFNα treatment induced a prolonged suppression of DHBV cccDNA transcription, which is associated with the reduction of histone modifications specifying active transcription, but not the increase of histone modifications related to the silence of gene expression, such as $H3K9^{me3}$ and $H3K27^{me3}$. In order to identify the cellular genes that mediate IFN suppression of cccDNA transcription, we screened IFN-stimulated genes by RNA interference technology and found that down-regulating the expression of structural maintenance of chromosomes flexible hinge domain containing 1 (SMCHD1) or promyelocytic leukemia (PML) increased basal levels of cccDNA transcription activity and partially attenuated IFNα suppression of cccDNA transcription. On the contrary, over-expression of SMCHD1 or PML significantly inhibited cccDNA transcription. SMCHD1 is a non-canonical SMC family protein and has been implicated in various epigenetic processes with unknown mechanisms. PML is a nuclear domain 10 component and involves in suppression of many DNA viruses and HBx function. Further mechanistic analyses demonstrated that both SMCHD1 and PML are recruited to cccDNA minichromosomes and phenocopy the epigenetic modifications of cccDNA–associated histones induced by IFN-α. We thus conclude that SMCHD1 and PML mediate IFN-α suppression of hepadnaviral cccDNA transcription.

178. Advances in HBV Ribonuclease H Drug Development

Tiffany Edwards, M.S.[1], Qilan Li, Ph.D.[1], Nathan Ponzar, B.S.[1], Austin O'Dea, M.S.[1], Cassandra Kukla, B.S.[1], Mufuza Akter, Ph.D.[1], Grigoris Zoidis, Ph.D.[2], Marvin Meyers, Ph.D.[1], Ryan Murelli, Ph.D.[3], John Tavis, Ph.D.[1]
[1]*Saint Louis University, St. Louis, Missouri, United States of America;* [2]*University of Athens, Athens, Greece;*
[3]*City University of New York, New York, New York, United States of America*

The Hepatitis B virus (HBV) ribonuclease H (RNaseH) is an attractive drug target because it is the only viral enzyme not currently targeted by anti-HBV therapies. The RNaseH degrades the viral RNA after it has been copied into DNA during reverse transcription. Ablating RNaseH activity prevents synthesis of the viral plus-polarity DNA strand, blocking production of progeny DNA genomes. We are pursuing drug discovery against the RNaseH.

Screening ~1000 compounds predicted to bind the two Mg^{++} ions in the RNaseH active site identified >130 RNaseH inhibitors, primarily in four chemotypes, the α-Hydroxytropolones (αHT), N-Hydroxyisoquinolinediones (HID), N-Hydroxypyridinediones (HPD), and Napthyridinones (HNO). The best compounds have low nanomolar EC_{50}s and therapeutic indexes >350 in cell culture. Solubility limits in simulated body fluids and stability in hepatocytes are being assessed. Structure-activity relationships are apparent for all four chemotypes. RNaseH inhibitors are synergistic with lamivudine. RNaseH inhibitors from different chemotypes are synergistic with each other indicating they may adopt different binding poses in the active site and/or inhibit the RNaseH when it is in different conformations. HPD and αHT screening hits can inhibit HBV replication in FRG chimeric mice with humanized livers. Low throughput screening of 954 compounds targeting metalloenzymes carrying a single divalent cation failed to reveal additional hits, indicating that targeting both cations simultaneously is likely necessary for RNaseH inhibition.

Evaluation of HBV RNaseH inhibitors has validated the RNaseH as an attractive antiviral target, identified four chemical scaffolds worthy of medicinal chemistry optimization, and recently opened windows into HBV's interaction with cells.

179. Discovery and Mechanistic Studies of Novel Suppressors of Tat-mediated HIV Expression

Jenn Yi, B.S.[1], **Cole Schonhofer, M.S.**[1], Brandon Razooky, Ph.D.[2], Jeanne Chiaravalli, B.S.[3], Brittiny Dhital, B.S.[3], Marianne Harris, B.S.[4], Fraser Glickman, Ph.D.[3], Zabrina Brumme, Ph.D.[5], Charles Rice, Ph.D.[2], ian Tietjen, Ph.D.[1]
[1]Simon Fraser University, Burnaby, BC, Canada; [2]Laboratory of Virology and Infectious Disease, The Rockefeller University, New York, New York, United States of America; [3]High-Throughput and Spectroscopy Resource Center (HTSRC), The Rockefeller University, New York, New York, United States of America; [4]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada; [5]Simon Fraser University; British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

Latent reservoirs harbouring dormant, replication-competent proviruses are the main obstacle to HIV eradication. A "Block-and-Lock" approach, which uses Pro-Latency Agents (PLAs) to inhibit viral reactivation even after proviral stimuli, could theoretically lead to drug-free remission. However, few PLAs are reported to induce "Block-and-Lock", indicating a likely need to discover additional PLAs. The HIV Tat protein is required for latency reversal and is a promising PLA target. The Jurkat-derived "JurTat" cell line, which contains an inducible Tat-Dendra protein that drives mCherry expression from an HIV LTR, was used to screen 97,152 compounds from the Rockefeller University HTSRC chemical library by high-throughput microscopy. Compounds that selectively inhibited mCherry expression, and thus Tat function, were confirmed by flow cytometry. Compounds of interest were then assessed for PLA properties in J-Lat cells containing HIV-GFP provirus and primary cells from HIV-infected donors. We identified 96 compounds which inhibited >50% of Tat-driven mCherry but not Dendra expression, of which 5 were selected for further study. The most potent compound, C11, inhibited latency reversal in J-Lat cells without cytotoxicity at an EC50 of approximately 3 μM. 10 μM C11 and other compound hits further suppressed up to 36% of PMA-induced virus production from PBMCs isolated from HIV-positive donors. Mechanistic studies suggest that C11 inhibits CDK9, a component of the host p-TEFb complex required for Tat-mediated transcription. We report novel inhibitors of Tat-mediated HIV expression. These compounds can be used to probe mechanisms of HIV transcription and inform ongoing "Block-and-Lock"-based strategies.

180. Exploring Virus-host Cell Interactions to Battle Against Highly Pathogenic RNA Viruses

Marjo Puumalainen, Ph.D.[1]
[1]Karolinska institutet, Oncology-Pathology Department, Science for Life Laboratory, Stockholm, Sweden

Recent incidents of RNA viruses such as Ebola virus (EBOV) and Crimean-Congo Hemorrhagic Fever virus (CCHFV) causing lethal hemorrhagic fever and Zika virus causing microcephaly in newly born babies have put pressure on finding new strategies to target emerging RNA viruses, as to date no effective approved cure exists. RNA viruses generally have very high mutation rates contributing to the development of antiviral resistance to compounds that are directed against specific viral proteins. Therefore it is of interest to target cellular endogenous proteins required for virus replication processes and thereby potentially bypass the antiviral resistance problem.

This multidisciplinary project focuses on exploring virus-host interactions of emerging RNA viruses and to validate these as novel targets for antiviral therapy. Here, we show a development of phenotypic antiviral screening assay for identifying new small molecular inhibitors against pathogenic RNA viruses. Using our antiviral screening funnel, we have identified and characterized a new small molecular inhibitor that eradicates Zika virus infection rescuing virus-induced cell death in neuronal cells. Additionally, an analogue of the compound was tested in a BSL-4 laboratory at the Public Health Agency of Sweden showing a decrease in EBOV and CCHFV virus levels, indicating a broad spectrum antiviral activity. The target protein of the compound was assessed by cutting-edge thermal protein profiling method revealing interesting novel host targets import for viral replication.

Altogether with the novelties of this project, we expect to open a new area of research for RNA viruses and importantly explore new ways to treat virus-infected patients.

181. Development of Medical Countermeasures against Nipah Virus: A Field Perspective

Emily Gurley, Ph.D.[1]
[1]*Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America*

Nipah virus could pose a global health threat because of its high case fatality (40-75%), capacity for person-to-person transmission, and lack of any effective medical countermeasures. More effective therapies to treat Nipah virus would be valuable public health tools because they could reduce mortality, improve healthcare seeking, and therefore, enhance surveillance efforts. A number of practical aspects of Nipah virus surveillance should be when developing and planning for trials of these therapeutics. First, without investments in improved diagnostics for Nipah, human studies of therapeutics are practically impossible. There are no commercially available diagnostics, and no rapid tests. By the time patients are diagnosed, they are typically either dead or already recovering from infection. Second, patients ill with Nipah virus infection typically present for care when they develop more severe symptoms, such as convulsions or altered mental status, suggesting that the brain is already infected. Most animal experiments treat animals prior to clinical onset, or early in the course of illness. Trials in humans should align the clinical stage between humans eligible for treatment and animals for whom the treatment worked. Third, there should be additional discussion about appropriate end-points for animal and human studies of therapeutics. Nipah infection is highly fatal, but among survivors in Bangladesh, a significant proportion of survivors suffer from permanent and debilitating neurological and cognitive deficits. In a setting where families may divert expenses for necessities to treat patients with chronic illness, improved survival should be considered alongside quality of life outcomes.

182. Viral Compartmentalization and Rapid Evolution of Drug-resistant Herpes Simplex Virus (HSV-1) Infection in a Hematopoietic Stem Cell Transplantation (HSCT) Patient

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

HSV-1 is a prevalent human pathogen that can cause severe disease in immunocompromised patients. These patients often require prolonged antiviral therapy increasing the risk of drug-resistance. Investigating the evolution of HSV infections is crucial for understanding pathogenesis and emergence of drug-resistance. HSV-1 compartmentalization, viral evolution, emergence of drug-resistance and heterogeneity of viral populations were investigated in an HSCT recipient in order to improve the management of herpesvirus infection. Five HSV-1 isolates were recovered from an HSCT patient who had recurrent orofacial infections treated consecutively with acyclovir, foscavir and cidofovir. Drug-resistance was determined genotypically [conventional Sanger sequencing of the viral thymidine kinase (TK) and DNA polymerase (DP) genes) and phenotypically (drug-susceptibility profile]. Next generation sequencing (NGS) to determine heterogeneity of the viral isolates and plaque purification to isolate viral clones were performed retrospectively. There was a rapid evolution of drug-resistant viruses with six viral variants (TK mutant, DP mutant, or double mutant) appearing within 3 months. Most isolates showed population heterogeneity of HSV-1 variants. Remarkably, two isolates recovered the same day from distinct body sites showed difference in viral variants and heterogeneity. While only one viral clone, i.e. TK(R222H)+DP(L778M), could be obtained from one of these isolates, four distinct viral clones were obtained from the other isolate, i.e. TK(A189V)+DP(L778M), TK(wt)+DP(L778M), TK(A189V)+DP(L802F) and TK(wt)+DP(L802F). This compartmentalization was also visible by NGS. Typing of drug-resistance at multiple time points and at multiple body sites can be useful to adjust antiviral therapy and avoid emergence of multi-drug resistance.

183. *In Vitro* and Clinical Resistance Profile of RV521, a Small Molecule Respiratory Syncytial Virus Fusion Inhibitor in Clinical Development

Elaine Thomas, Ph.D.[1], Daniel Brookes, Ph.D.[1], Claire Scott, Ph.D.[1], John DeVincenzo, M.D.[2], Young-In Kim-Hoehamer, Ph.D.[2], Neil Mathews, Ph.D.[1], Alex Bedernjak, Ph.D.[1], Stuart Cockerill, Ph.D.[1], Rachel Harland, Ph.D.[1], Ken Powell, Ph.D.[1], Eddy Littler, Ph.D.[1]

[1]ReViral Ltd, United Kingdom of Great Britain and Northern Ireland; [2]U Tennessee Center for Health Sciences, Children's Foundation Research Institute at LeBonheur Children's Hospital

RSV s a major cause of lower respiratory tract infections, manifesting as bronchiolitis or pneumonia in infants, children, and elderly or immunocompromised adults. No effective antiviral treatment currently exists. RV521 is a potent, orally available small molecule RSV fusion inhibitor in development for the treatment of RSV infection in infants and adults. Therapeutic administration of RV521 safely and effectively reduced viral load and disease severity in a Phase 2a human RSV challenge model.

In order to understand the resistance potential of RV521 *in vitro* we performed repeated passage of RSV in the presence of increasing concentrations of RV521. Resultant RSV resistant to RV521 harboured mutations in RSV F protein and demonstrated reduced *in vitro* fitness and growth, with a severe inability to compete with wildtype RSV in competitive fitness assays.

To monitor clinical resistance potential mutation detection analysis was performed on samples from RV521 and placebo subjects from the human RSV challenge study. Sequence analysis of RSV F-gene identified only 3 amino acid variants, one of which was a site of natural variation previously reported in Memphis-37 infected subjects. The observed RSV F protein variants were not associated with rebound in viral load, nor with prolongation of viral shedding or clinical RSV symptoms.

In conclusion, RSV harbouring RV521 resistance mutations in F protein demonstrate slower growth and are unable to complete with wildtype virus i*n vitro*. In addition, a low frequency of emergent mutations to RV521 were detected in subjects experimentally challenged with RSV.

AUTHOR INDEX

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