ISAR News
Newsletter of the International Society for Antiviral Research

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30th ICAR (Atlanta, USA, 21-25 May, 2017) ISAR Elections and Feature Articles

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ISAR PRESIDENT'S MESSAGE

José Esté

It is with great pleasure that I salute all ISAR members and friends in this new issue of ISAR News. After a successful meeting in La Jolla, we are now very active in the organization of our 30th International Conference on Antiviral Research that will be held in Atlanta, Georgia, USA. The Program Committee led by Mark Prichard and Justin Julander provide below a short summary of the program. Further details on the confirmed speakers and detailed schedule will be provided through the ISAR-ICAR website (http://www.isar-icar.com) along with specific dates regarding registration and abstract submission.

A new conference organizer, Caliber Meetings & Events, is helping us in the preparation of the Atlanta meeting. I take the opportunity to welcome Mrs. Regina Mohr and her team to our organization and wish them success.

The society has been heavily active this summer in evaluating its operations and I am very happy to inform that ISAR is in excellent form to undertake our near and mid-term activities. Among other plans, the society will continue its efforts to encourage the participation of graduate students and postdocs by maintaining and hopefully increasing our support through merit awards and travel assistance, and by keeping registration rates to the lowest possible. I encourage young researchers to submit the best work for presentation and apply for a travel merit award. Excellence and scientific merit will be the prevailing criteria for selecting awardees.

Nominations for all ISAR awards are now open. I call upon all members of the society to nominate individuals for the Gertrude Elion Memorial Lecture

Award, the Antonín Holý Memorial Lecture Award and the William Prusoff Young Investigator Lecture Award. These are the highest distinctions the society has to honor the contribution of scientists to the fields of antiviral research and drug development. Eligibility criteria and how to submit nominations can be found in the Awards section of the ISAR ICAR website (http://www.isar-icar.com/?page=Awards).

The Chu Family Foundation Scholarship for Women Scientists is also now open for applications. Up to six awards will be given annually to advance the careers of women with potential for significant contribution in the field of antiviral research. Further details may be found at http://www.isar-icar.com/?page=wiscda or by requesting information through the society's email address info@isaricar.com.

Finally, I encourage all ISAR members and friends to participate in the multiple activities and committees the society has to offer. Please feel free to contact us with your thoughts, ideas and suggestions. Your participation is essential for the success of the society.

José Esté
President, ISAR

THE 30TH ICAR, ATLANTA, GA, USA

From the Program Committee (Mark Prichard and Justin Julander)

The International Society for Antiviral Research (ISAR) will host the 30th International Conference on Antiviral Research (30th ICAR) in Atlanta Georgia Sunday May 21st through Thursday May 25th 2017. The conference will be held at Hilton Atlanta, 255 Courtland Street NA, Atlanta, Georgia, 30303. This venue takes advantage of the energetic research community that includes the Centers for Disease Control and Prevention as well as Emory University.

Speakers at the meeting will present the latest scientific developments in antiviral research and will emphasize the interdisciplinary nature of this field. The conference is designed specifically to provide opportunities for all participants to establish and maintain close collaborative relationships among chemists, pharmacologists, biologists and regulatory agency representatives that are required for the discovery and development of effective antiviral therapies. It also serves to stimulate innovative thinking on the drug development process and provides specific events to welcome new scientists to our ranks to help them to establish successful careers. Attending this annual meeting is important for all ISAR members as it serves to strengthen existing contacts and provides an opportunity to add new contacts to their network by meeting new scientists working in the field.

This year the program will feature a Respiratory Virus Symposium, an Emerging Infections Symposium, an Antiviral Immunity Symposium, and the regularly scheduled Drug Development 101. Other regularly scheduled sessions include the Keynote Address and three lecture award talks with more details forthcoming in the next issue of ISAR news. Annual oral sessions on in vitro antiviral activity, medicinal chemistry, mechanism of action, animal models and clinical trials are also scheduled. Poster Sessions provide a great opportunity for students and investigators to present data. The meeting will also include networking opportunities for new members including a women in science event and a career development session.

We look forward to seeing you in Atlanta!

Important 2017 ICAR Dates

Abstract Open Date	November 7, 2016
Registration Open Date	November 7, 2016
Abstract Submission Deadline	February 17, 2017
Travel Merit Award and Travel Assistance Application Deadline	February 17
Travel Merit Award and Travel Assistance Notifications Sent	March 17
Abstract Acceptance Notifications Sent **If you note on your abstract that you intend to apply for a travel merit award, travel assistance or a visa, your acceptance notification will be sent on March 10th*	March 31
Advance Rate Registration Deadline	April 20
Registration Cancellation Deadline	April 20
Hotel Reservations Deadline	April 30
Conference Dates	May 21-25

2017 Chu Family Foundation Scholarships (Amy Patick)

The Chu Family Foundation Scholarship for Women Scientists Award Committee is now accepting applications for its 2017 Chu Family Foundation Scholarship for Women Scientists Program. The Chu Family Foundation Scholarship for Women Scientists will support the professional development of women with potential for significant contribution in the field of Antiviral Research by providing funds to attend a conference, visit another laboratory, take a course, or acquire specialized training.

Up to six awards will be given annually. Each award will consist of a $1500 stipend, a 2-year ISAR membership and a commemorative certificate. To be eligible to apply for this program, a woman scientist must currently be an undergraduate or graduate student or hold a doctoral degree and have no more than five years of cumulative postdoctoral experience. Candidates must currently be performing undergraduate, graduate or postdoctoral work in antiviral research and related areas. Graduate students and postdoctoral candidates must be a member of ISAR. A letter of support must be provided by a nominator, who should be the candidate's research Project Director, Department Chair, or Center Director. Other guidelines exist – please check the ISAR website (http://www.isar-icar.com) for more details. The nomination deadline is December 31st, 2016. If you have any questions please feel free to contact us at: info@isaricar.com.

Apply for a travel merit award or for travel assistance to participate in the 30th ICAR

New this year, ISAR is pleased to announce the availability of travel merit awards. Travel assistance will be continued. The travel merit awards aim at stimulating the participation of students, postdocs and young researchers and provide them with the opportunity to be recognized for their scientific contribution to antiviral research. The sole criteria will be scientific merit and excellence of the work submitted for presentation during the 30th ICAR in Atlanta, GA. Stipends will vary depending on the region of origin of the presenting author: US/Canada $ 500.00, Europe: $ 800.00 and South America / Central America / Australia / Africa: $ 1000.00. Support may be increased depending on final sponsorship of the conference.

The best submitted abstracts will be selected based on the scores provided by four independent reviewers

Travel merit awards application deadline: 17th February (see ISAR website)

Requirements to be considered for a travel merit award:

- Submit an abstract and present the work at the meeting either as oral and/or poster presentation
- Submit a short CV including publication record
- Provide a nomination letter by the Head of the Department

Registration to the meeting will be mandatory to receive the grant.

The travel merit award will be available as cash at the meeting (receipt to be signed). Recipients of a travel merit award are required to attend and actively participate in the entire conference.

To apply for the travel merit award, please submit your abstract through the submission system. When you reach the final page of the submission form, you will be prompted to attach your CV and nomination.

Travel assistance

ISAR is also pleased to make available travel assistance aimed at stimulating the participation of young and senior researchers from countries for which it is difficult to finance their attendance to the meeting. The amount of support will partly cover the flight fee (economy class) from the country of residence of the presenting author.

Travel assistance application deadline: 17th February (see ISAR website).

Requirements to be considered for travel assistance:

- Submit an abstract and present the work at the meeting either as oral and/or poster presentation
- Submit a short CV including publication record
- Provide a nomination letter from the Head of the Department explaining how research was financed and the need for support

Registration to the meeting will be mandatory but the fee will be waved.

The travel assistance will be available as cash at the meeting (receipt to be signed). Recipients of travel assistance are required to attend and actively participate in the entire conference.

To apply for travel assistance, please submit your abstract through the submission system. When you reach the final page of the submission form, you will be prompted to attach your CV and nomination letter.

ISAR ELECTION CANDIDATES

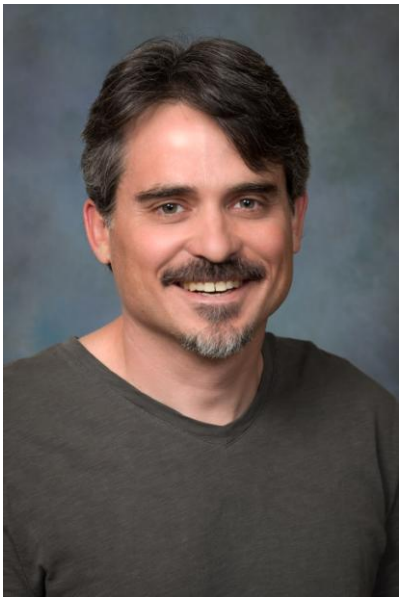
From the Nominations Committee (Bob Buckheit)

This year the Nominations Committee was charged with finding candidates to fill the office of treasurer and one board seat currently held by Brian Gowen and Jennifer Moffat, respectively. Their terms expire at the end of the 2017 ICAR. Brian and Jennifer have both agreed to run for a second term.

Following a recommendation from the Nominations Committee, the ISAR Board agreed unanimously that, in the interests of continuity, Brian Gowen should be the only candidate for the Office of treasurer. The ISAR membership will be voting to either accept or reject Brian serving a second 3-year term. There are two candidates for the single vacant Board seat, Maaike Everts and Jennifer Moffat. Both candidates have given of their time and talents to the Society and would make excellent Board members.

The election is being held electronically and will be open for one month. Please review the candidates' biographical sketches. Shortly before the election opens, we shall send an e-mail to all ISAR members explaining how to cast your vote. We strongly encourage all members to vote, and wish these excellent candidates the best of luck.

Treasurer



Dr. Brian Gowen received his Ph.D. degree in Biomedical Sciences from the University of South Carolina, School of Medicine in 2000, specializing in microbiology and immunology. Prior to that, he received a Bachelor's degree in microbiology from Colorado State University. Dr. Gowen trained as a postdoctoral fellow at the Rocky Mountain Laboratories campus of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, in Hamilton, Montana, from 2000-2004, where he studied host-bacterial pathogen interactions.

Brian joined the Department of Animal, Dairy, and Veterinary Sciences and the Institute for Antiviral Research at Utah State University (USU) in January of 2004. In 2012 he joined the faculty of the new USU School of Veterinary Medicine program and was appointed Adjunct Professor at Washington State University in the Department of Veterinary Microbiology and Pathology.

Brian specializes in preclinical development of antiviral therapies for the treatment of severe arenavirus and bunyavirus infections and modeling of viral hemorrhagic fever in rodents. He has 51 peer-reviewed publications, is the inventor on several patents, and serves on the editorial boards for the journals *Antiviral Research*, *Antiviral Chemistry and Chemotherapy*, and *Scientific Reports*. He has been an active member of ISAR since 2004 and continues to support the society as Treasurer (since 2014) and as a member of the Publications Committee (since 2009). He received the William Prusoff Young Investigator Award in 2011.

Board member

Dr. Maaike Everts is an Associate Professor at the University of Alabama at Birmingham (UAB) in the School of Medicine, Department of Pediatrics, Division of Infectious Diseases. Since 2009, she has

held the position of Associate Director for the Alabama Drug Discovery Alliance (ADDA), which is a collaboration between UAB and Southern Research – a not-for-profit research institute also located in Birmingham, AL. The goal of the ADDA is to find new small molecule drugs for unmet medical needs, in a variety of therapeutic areas. She also provides campus-wide assistance to physician-investigators throughout the IND application process, and provides Quality Assurance for the UAB Vector Production Facility, which manufactures novel biological drugs for Phase I clinical trials.

She is the administrative director for the Antiviral Drug Discovery and Development Center (AD3C; PI Rich Whitley), a multi-institutional consortium funded by a U19 grant from the National Institute of Allergy and Infectious Diseases (NIAID). In this role and with the other responsibilities on campus, she is familiar with all aspects of antiviral research, and facilitates interdisciplinary communication between all participating institutions and content experts.

Maaike received a M.Sc. in Pharmaceutical Sciences from the University of Groningen and a Ph.D. in Pharmacokinetics and Drug Delivery from the Groningen University Institute for Drug Exploration (GUIDE), the Netherlands. Her thesis was entitled 'Selective delivery of dexamethasone to inflamed endothelium via E-selectin', under mentorship of Drs. G. Molema, D.K.F. Meijer and L.F.M.H. de Leij. Subsequently, she completed postdoctoral training under the supervision of Dr. David T. Curiel in the Division of Human Gene Therapy, UAB, in order to pursue her research interest in targeted gene delivery for the treatment of cancer, using adenoviral vectors.

She joined the faculty of the Department of Pathology at UAB in August 2005 as an Instructor, and continued her research on targeted therapies using gene therapy and nanotechnology approaches, continued to climb the academic ladder and transitioned to her current position in (small molecule) drug discovery.

Dr. Jennifer Moffat trained at Stanford University School of Medicine where she received her doctorate in Microbiology and Immunology and did a postdoctoral fellowship in Pediatric Infectious Diseases. She is an internationally recognized expert on varicella-zoster virus, and her research has focused on developing mouse models to study the pathogenesis and treatment of this virus.

The current emphasis of her research group is evaluating antiviral compounds for VZV in a unique humanized SCID mouse model, which is supported by

an NIH contract. She has received multiple NIH and New York State awards for her projects on the molecular basis of VZV disease, as well as contracts with pharmaceutical companies.

In 2005, Jennifer received the SUNY Chancellor's Award for Scholarship and Research. She has served on several NIH review panels and is on the editorial board of Journal of Clinical Virology and Antiviral Research. Dr. Moffat is a board member of the International Society for Antiviral Research and has contributed to the annual conference by chairing sessions, judging posters, and mentoring in the Career Development and Women in Science events. Dr. Moffat has authored about 30 peer-reviewed articles, invited reviews, and book chapters. She was co-editor of a recent issue of Current Topics in Microbiology that covered advances in VZV research.

CURRENT RESEARCH

Monoclonal Antibody Antivirals: ZMapp™ and Beyond (Larry Zeitlin and Kevin J. Whaley, Mapp Biopharmaceutical, Inc.)

Monoclonal antibodies (mAbs) are an appealing platform for anti-viral drugs due to their high potency and specificity, as well as to their excellent clinical safety and efficacy record. With over 40 mAbs approved by the United States Food and Drug Administration and European Medicines Agency, many of the manufacturing, formulation, and regulatory challenges of mAb drug development are well understood. The utility of antibodies has been well recognized for over a century since Kitasato and

von Behring first used passive immunization to treat diphtheria. More recently, studies in non-human primates have even shown the effectiveness of mAbs late in infection with highly virulent and lethal viruses such as Nipah, Hendra, and Ebola (1-3).

ZMapp is a cocktail of three mAbs against Ebola virus (Figure 1) that first came to public prominence in August 2014, during the 2014-2016 Ebola virus outbreak, when it was used under expanded access provisions in the first Ebola Virus Disease (EVD) patients repatriated to the United States. In collaboration with the U.S. government, IND-enabling studies and clinical manufacturing were performed, and an IND was filed in the beginning of February 2015, allowing for the initiation of the PREVAIL II clinical trial.

The trial, conducted in Liberia, Sierra Leone, Guinea and the United States and sponsored by the National Institute of Allergy and Infectious Diseases, was initiated to evaluate the efficacy of ZMapp in treating EVD and concluded on January 29, 2016. The study closed short of its enrolment goals due to the waning of the Ebola epidemic. The trial compared an optimized standard of care to a regimen of optimized standard of care plus ZMapp. Trial participants were randomly assigned to one of the two study arms, with 36 participants eventually assigned to each arm. Mortality in the ZMapp-treated participants was 40 percent lower (8 of 36; 22 percent mortality) than the mortality in participants receiving standard of care alone (13 of 35; 37 percent mortality). However, with the smaller-than-intended sample size, this difference did not reach the pre-defined threshold for declaring statistical significance.

ZMapp-treated participants displayed an increased rate of viral clearance from the bloodstream, more rapid resolution of symptoms and earlier discharge from care than participants in the standard of care group. While the trial did not ultimately enrol enough patients to produce definitive results, the drug was well-tolerated and showed promise. As a result, Mapp submitted an Expanded Access Protocol (EAP) to the U.S. Food and Drug Administration to make ZMapp available to patients during the product's ongoing development. An EAP is a U.S. regulatory mechanism for making an unlicensed drug available for the treatment of a serious or life-threatening disease for which no approved therapeutic is available.

While Mapp continues the work necessary for ZMapp to be licensed, it is available via the EAP (funded by Biomedical Advanced Research and Development Authority; BARDA) to Ebola patients wishing to have access to this experimental treatment in participating countries.

The 2014-2016 Ebola virus outbreak highlighted the absence of available vaccines or therapies for filoviruses. Fortunately, by the resolution of the outbreak, one vaccine (VSV-EBOV) and one therapeutic (ZMapp) were shown to have promising results in controlled clinical trials that may be supportive of eventual licensure. However, these products specifically target Ebola virus (formerly known as Ebola Zaire), and have no activity against the related Bundibugyo and Sudan ebolaviruses, nor the more distantly related Marburg viruses, Marburg and Ravn, which all together have caused fourteen sporadic and unpredictable deadly outbreaks responsible for over 900 infections and over 500 deaths since 2000 (4). Further, because of their high specificity for Ebola virus, these products are unlikely to have activity against any new filovirus variants that emerge, such as the recently identified Cuevaviruses.

To address this unmet need, Mapp and its collaborators have identified fully human mAbs that potently neutralize all the species of ebolavirus inclusive of Ebola, Bundibugyo and Sudan ebolaviruses as well as a separate human marburgvirus mAb that has been shown to protect non-human primates from both Marburg and Ravn viruses. ZMapp has provided excellent proof-of-concept for this approach, and development of these second-generation filovirus mAb therapeutics is ongoing.

The past decade has been a golden age for mAbs for oncology and autoimmune indications. Mapp's hope is that antiviral mAbs will soon enter a golden age of their own.

Acknowledgements:
The work described here has been funded in part with funds from the DHHS Office of the Assistant Secretary for Preparedness and Response; BARDA, under contract numbers HHSO100201400009C and HHSO100201600021C and by the Defense Threat Reduction Agency under contract HDTRA1-13-C-0018.

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ANTIVIRALS ON THE HORIZON

Development of an antiviral for Lassa fever

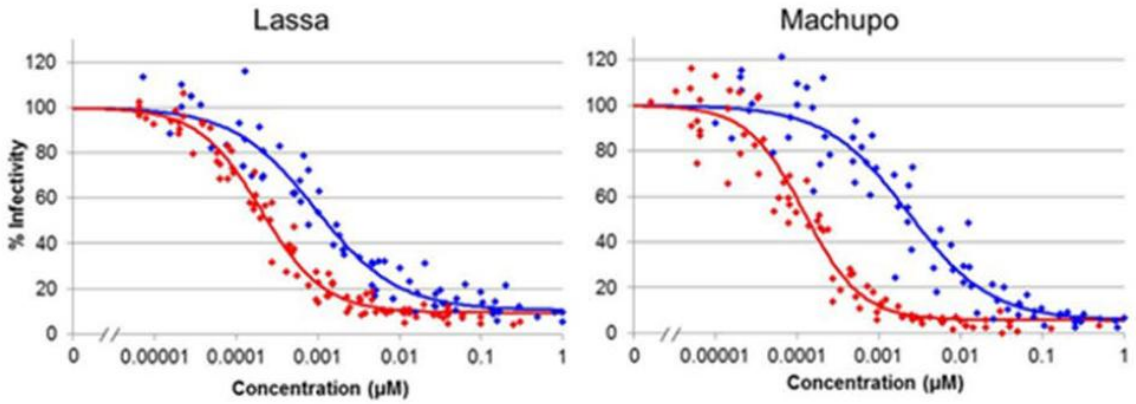
Sean Amberg, Kineta Inc.

Viral hemorrhagic fever is a serious illness characterized by extensive vascular damage and bleeding diathesis, fever, and multiple organ involvement. The public health risk associated with viral hemorrhagic fever has long been appreciated, but the recent West African Ebola outbreak has further raised awareness. Several different viruses cause hemorrhagic fever. These viruses are distributed throughout four families, the *Arenaviridae*, *Bunyaviridae*, *Filoviridae*, and *Flaviviridae*.

Hemorrhagic fever viruses are designated as Category A by the Centers for Disease Control and Prevention (CDC), defined as those pathogens with the highest potential impact on public health and safety, potential for large-scale dissemination, capability for civil disruption, and greatest unmet need for public health preparedness. One of the most prominent hemorrhagic fevers is Lassa fever, a disease caused by an arenavirus. The World Health Organization (WHO) recently convened a panel of public health experts and scientists to prioritize the emerging pathogens most likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist. Lassa fever was identified as one of the eight disease priorities needing urgent R&D attention by the WHO (5).

Kineta is developing LHF-535, a small molecule antiviral, for the treatment and prevention of Lassa fever and other hemorrhagic fevers such as Argentine (Junín), Bolivian (Machupo), and Venezuelan (Guanarito) hemorrhagic fevers. LHF-535 has demonstrated good bioavailability and pharmacokinetics in pre-clinical models, supporting once-daily oral administration. It has shown protective efficacy in a lethal mouse model using a related arenavirus (Tacaribe). A clear development path was established after a successful pre-IND interaction with FDA in 2015. Kineta recently received a Wellcome Trust Translation Fund award to support continued advancement of LHF-535 through IND-enabling toxicology and manufacturing and phase I safety studies in humans.

LHF-535 is an optimized analog of the benzimidazole derivative ST-193, an inhibitor of virus entry (3). LHF-535 is more potent than ST-193. This scaffold was identified using lentiviral pseudotypes (replication incompetent recombinants) incorporating the Lassa viral envelope glycoprotein to assess the viral entry function. The envelope glycoprotein mediates attachment of the virus and subsequent entry into the host cell. As an essential component of the viral life cycle, viral entry can be an attractive target for the development of antiviral pharmaceuticals.



LHF-535 exhibits enhanced in vitro antiviral activity against Old (Lassa) and New World (Machupo) arenavirus targets. Human 293T cells were infected with lentiviral pseudotypes incorporating either Lassa (strain Josiah) or Machupo (strain Carvallo) envelope glycoproteins in the presence of various amounts of either ST-193 (blue) or LHF-535 (red). Each curve was fit to data from ten representative experiments, with each dot representing a single concentration from one experiment (average of three or four replicates).

ST-193 was found to inhibit a broad array of hemorrhagic arenaviruses (3), although not the type species, lymphocytic choriomeningitis virus. ST-193 inhibits pH-dependent cell-cell fusion mediated by either the Lassa or the Junín envelope protein, and also inhibits GP1 subunit shedding (6), an indicator of fusion activation. In a lethal guinea pig model of Lassa pathogenesis, ST-193 provided a significant survival benefit and markedly reduced viremia (2).

The arenavirus envelope is a class I viral fusion protein, and it is processed into three subunits: a stable signal peptide (SSP) that remains associated with the mature complex, the N-terminal GP1, and the C-terminal GP2 that spans the viral lipid envelope. A proposed mechanism of action is that inhibitors stabilize a prefusion interaction between SSP and GP2, thus preventing the conformational rearrangements normally activated by acidic pH (4). Indeed, compound sensitivity maps to a region of about 30 amino acids within the GP2 subunit (3); this region includes the C-terminal ectodomain and the predicted transmembrane domain, overlapping the region thought to interact with SSP (4), and is one of the more conserved arenavirus domains.

Interestingly, several distinct chemical scaffolds have been identified that appear to share a common mechanism with LHF-535 (4). Competition for a common binding site has been observed and viral resistance patterns are overlapping. Most of these scaffolds exhibit much more potent activity against either Lassa, an Old World arenavirus, or against the New World hemorrhagic arenaviruses (e.g., Junín). LHF-535 is distinct in that it potently inhibits both groups (3).

Whether the mechanism of action of LHF-535 has applicability beyond arenaviruses is unclear. If the mechanism is specific to the unusual tripartite nature of the arenavirus envelope, then it seems unlikely that similar inhibitors could be identified for other virus families. However, a team from Bristol-Myers Squibb identified an HCV entry inhibitor to which resistance mapped to an analogous region (transmembrane domain) of the E2 envelope protein (1). Thus, the conformational rearrangements undergone by viral envelope proteins to facilitate entry may provide drugable targets to varying degrees across virus families.

Acknowledgements:

Development of LHF-535 is funded by NIAID 5R01AI093387 and by the Wellcome Trust Translation Fund award WT-200439/Z/16/Z. This content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health, the Wellcome Trust, or Kineta.

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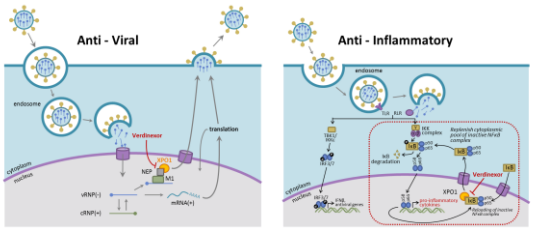
Verdinexor, a selective inhibitor of nuclear export, as a broad spectrum antiviral

Sharon Tamir, Karyopharm Therapeutics Inc.

Pandemic and highly pathogenic influenza strains are a significant threat to global public health, fueling the need for new anti-influenza therapeutics. Approved treatments for influenza, such as adamantanes and neuraminidase (NA) inhibitors, target viral components, however resistance to these agents has limited the usability of these drugs to treat emerging influenza threats.

The development of therapeutics targeting host cell proteins essential for viral replication may slow the selection for viral resistance and offer the potential for broad-spectrum activity. A critical step in the replicative life cycle of influenza virus is nuclear export of influenza viral ribonucleoprotein (vRNP), a process mediated by endogenous host cell nuclear export protein Exportin 1 (XPO1). Therefore, inhibition of this host cell pathway should disrupt the replication, packaging and release of virions and reduce the selection for drug resistance (see figure) (1).

Karyopharm Therapeutics is a clinical stage pharmaceutical company focused on the development of Selective Inhibitor of Nuclear Export (SINE™) compounds.The company was founded in 2008 by Sharon Shacham PhD and is headquartered in Newton, Massachusetts with a subsidiary in Munich, Germany. Karyopharm is developing the SINE compound



Inhibition of Influenza virus replication and proinflammmatory cytokine production by XPO1 inhibitors

verdinexor (KPT-335) for the treatment of severe influenza in adult patients requiring hospitalization.

Preclinical safety, toxicology and pharmacology studies have been conducted including models of influenza infection, replication, pathology and mortality. Safety, tolerability and pharmacology of multiple ascending doses of verdinexor have been evaluated in healthy volunteers. Studies with verdinexor have demonstrated:

• Marked nuclear accumulation of vRNP and inhibition of influenza replication in vitro with potent broad-spectrum activity against a variety of influenza A (H1N1, H2N2, H3N2, H5N1, and H7N9) and B strains (1).

• Synergy with the neuraminidase inhibitor oseltamivir (10).

• No evidence of selection for drug resistance (13).

• Efficacy in mouse and ferret models following oral dosing initiated before or after infection, with reductions in pathology, pro-inflammatory cytokines, enhanced survival outcomes and superiority to oseltamivir (1, 4, 5, 6, 10).

• Efficacy in mouse models with delayed treatment initiation for up to 4 days post-infection (10, 13).

• Safety and tolerability in healthy subjects at projected therapeutic doses and exposures with a pharmacodynamic (PD) biomarker of target engagement.

The annual ICAR meetings have been a great opportunity for Karyopharm to collaborate, share knowledge and advance our anti-viral program.

Data demonstrating broad-spectrum efficacy of verdinexor was acquired through NIAID and the anti-viral screening program.

Although the clinical development focuses on verdinexor as a treatment for influenza, preclinical data also show efficacy of verdinexor across a broad spectrum of ssRNA and dsDNA viruses. In an in vitro screen against a panel of ~50 viruses, verdinexor and other SINE compounds were found to inhibit the replication of ~20 viruses with strong activity against HCV, HIV, RSV, VEEV, human herpesviruses, Tacaribe virus and a host of oncoviruses (HPV-11, EBV, HCMV) (6). This broad antiviral activity offers a novel, single-agent strategy for the treatment of viral coinfections and defence against cancer (2,9).

Verdinexor was potent and highly effective in mouse and ferret models of influenza infection. Importantly, delaying treatment in the mouse model for up to 4 days post infection was as effective as starting treatment one day post infection (13). Furthermore, verdinexor completely suppressed expression of pro-inflammatory cytokines that were unregulated due to influenza infection (5). Proinflammatory cytokine release is in large part responsible for the "flu-like" syndrome and therefore, verdinexor treatment is postulated to relieve symptoms in addition to suppressing the underlying viral infection.

During the last three years, we had the pleasure to present in ICAR meetings. Oral presentation in ICAR 2013 (3) poster presentation in ICAR 2014 (5), oral presentation and poster presentations in ICAR 2015 (7, 8, 6).

About a week after the 2015 ICAR meeting, we initiated our first clinical trial with verdinexor. Karyopharm conducted a randomized, double-blind, placebo-controlled, dose-escalating Phase 1 clinical trial of verdinexor in healthy human volunteers. This study was designed to evaluate the safety and tolerability of verdinexor in healthy adult subjects. Verdinexor was found to be generally safe and well tolerated. Mild-to-moderate adverse events of similar number and grade as placebo were reported, but no serious adverse events. ICAR 2016 was a great opportunity for us to present 3 oral presentations and one poster presenation (9, 10, 11, 12). The RSV project, presented by Patty Jorquera –UGA and Patty was awarded with 2nd place in the ICAR poster awards (Post-Doctoral Category).

We are fortunate to have amazing collaborators and great support at the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health. Karyopharm plans to continue the clinical development of verdinexor as a treatment for certain viral indications with an initial focus on influenza. We are seeking a global licensing partner with expertise in antiviral therapies to develop and commercialize verdinexor.

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UV-4B: A host-targeted therapeutic to treat dengue viral infection

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Dengue virus (DENV), a member of the Flavivirus genus, is the causative agent of dengue fever. There are four distinct DENV serotypes. While infection with one serotype confers life-long immunity against the homologous serotype, it does not confer protection against other serotypes. Instead, antibodies to one serotype from a previous dengue infection increases the risk of more serious forms of the illness, dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). The global burden for DENV infection is very significant; with an estimated 100 million symptomatic infections per year. There is no drug currently available for treatment of DENV infection and a vaccine is approved only in a limited number of countries and is not applicable for people at highest risk (young children and the elderly).

Emergent Biosolutions Inc. is developing an antiviral UV-4B, for the treatment of DENV infection. UV-4B shows in vitro antiviral activity against all four DENV serotypes, including clinical isolates, when tested in a yield reduction assay. In vivo, UV-4B has shown efficacy in an antibody dependent enhancement (ADE) model of DENV infection.

In this model, the minimal effective dose for UV-4B was determined to be 10 mg/kg via oral gavage with significant protection observed when administered as late as 24-48 hours after infection (1, 2).

The proposed mechanism of action of UV-4B is through the inhibition of the enzymatic activities of endoplasmic reticulum α-glucosidases. Several enveloped viruses including dengue virus are dependent on these cellular enzymes for proper

processing of their proteins. Since the proposed mechanism of action for UV-4B is via a host glycosylation pathway that affects infectivity and virus particle assembly, it is anticipated that selection for viral resistance against UV-4B is less likely to occur than against directly acting antiviral agents.

In an *in vitro* study that evaluated the potential for DENV-2 to become resistant to UV-4B, 38 cycles of treatment with UV-4B did not demonstrate any clear pattern for causing drug induced resistance when compared to the vehicle control (unpublished). Furthermore, in a study which involved passaging of DENV-2 in a STAT1x2 knockout mouse model, treatment with UV-4B resulted in a reduction in serum virus titer compared to vehicle treatment alone that was sustained through 5 passages of virus demonstrating efficacy of UV-4B through multiple rounds of virus replication in vivo (3).

The pharmacokinetic characteristics of UV-4B have been studied in mice, rats, ferrets and dogs. In vitro assessments of protein binding, blood-to-plasma distribution, metabolic stability, as well as inhibition potential of human cytochrome P450 enzymes have been completed. In vitro and in vivo safety pharmacology studies have been conducted. The toxicological profile of UV-4B has been evaluated in acute oral toxicity studies in mice, rats, and dogs; in non-GLP repeat-dose toxicity studies in mice, rats, and dogs up to 7 days; in GLP repeat-dose toxicity studies in mice and dogs up to 14 days; and in GLP genotoxicity studies.

An investigational new drug application has been open since February 2014. The first clinical study to determine the safety, tolerability and pharmacokinetics of UV-4B administered orally in healthy subjects was completed recently (NCT02061358). The study comprised of 64 subjects in 8 cohorts (8 subjects per cohort , 2 placebo:6 UV-4B treated) in which UV-4B was administered from 3-1000 mg. All 64 subjects were safely dosed with no severe adverse events. The pharmacokinetics data showed low inter-individual variability and linearity over a broad dose range. A second Phase 1 clinical study has been initiated to determine the safety and pharmacokinetics of UV-4B administered orally as multiple ascending doses to healthy volunteers (NCT02696291). UV-4B is also being developed for influenza as an additional indication (4).

Acknowledgements

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COMMENTARY

Responding to an emerging infectious disease outbreak: Development of new antiviral drugs

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We are immersed in a world of new and evolving viruses that threaten the world's public health status, broaden epidemiology awareness and alter international medical countermeasure priority lists to wane spread of disease. The media has not recessed from reporting on influenza, MERS, Ebola, or Zika, as examples. Many nations and international organizations have aligned their responses in order to prevent pandemic events from worsening.

In the United States, the Public Health Emergency Medical Countermeasures Enterprise, PHEMCE, established by the U.S. Department of Health and Human Services (HHS) is responsible for coordinating US Federal efforts to enhance preparedness and response for emerging infectious disease (EID). Under the Pandemic and All-Hazards Preparedness Act (PAHPA) in 2006, the Assistant Secretary for Preparedness and Response (ASPR) was established and the Biomedical Advanced Research and Development Authority (BARDA) which sits within the ASPR, was given the authority to advance the development and procurement of medical countermeasures (MCM) to address these threats.

Initially, BARDA's prime mission was focused on addressing Chemical, Biological, Radiological and Nuclear (CBRN) medical countermeasures requirements and pandemic influenza needs by focusing on advancing drugs through the late stage of development to licensure and thereafter stockpiling for the Strategic National Stockpile. Since 2014, however, BARDA has been engaged more frequently in developing EID medical countermeasures. Recent outbreaks of Ebola, MERS and now Zika have tested and validated BARDA's ability to rapidly respond, divert resources and lead the Nation's response in facilitating the advanced development and manufacturing of vaccines, therapeutics, and diagnostics to address the current need.

BARDA's experience with Ebola can provide a case study for antiviral therapeutic MCM development considerations with responding to an EID.

1) *Rapidity in discovery and monoclonal antibodies*: The traditional timeline for drug development (10-15 years) does not map to the timeline necessary to provide a rapid response and make available MCMs during a pandemic. There is a need for reduced timelines in discovery, lead identification, pre-clinical testing and manufacturing.

During the Ebola outbreak, BARDA contracted with Regeneron who leveraged their platform technologies which allowed for rapid identification and preclinical validation of fully human monoclonal antibodies to develop a novel GMP antibody therapy cocktail in just nine months compared to the traditional multi-year development cycle. This capability highlights a critical component of response during public health emergencies - platform technologies that could allow quick turnaround times.

2) *Small molecule discovery*: Due to the long lead times with small molecule discovery, medicinal chemistry needed for optimization and complicated synthesis pathways, this drug class is not positioned to be a candidate in a rapid response mode. However, if the drug is already in development for given indication it could be accelerated or re-purposed from a prior indication.

During the Ebola outbreak, BioCryst did have a candidate nucleoside analog in development at NIH/NIAID for Ebola and Marburg indications that was able to be redirected to focus entirely on Ebola during the West Africa Outbreak. BARDA worked closely with NIH by assisting with GMP manufacturing and other non-clinical studies to rapidly advance the development of this potential candidate. Therefore, small molecule drugs in an outbreak are only advantageous if there has been prior development.

3) *Accelerate clinical development*: A good antiviral candidate that has demonstrated efficacy *in vitro* or in animal models is limited unless there is a human safety profile and even better, human efficacy data to support the use of the drug. Many rare infectious diseases do not naturally occur in humans with frequencies high enoughy to test drugs in clinical trials with proper statistical power. Therefore many of these MCMs have no option but to pursue a regulatory path under the Animal Rule (3) with expanded safety testing in humans.

The Ebola outbreak allowed for a unique opportunity to assess efficacy and safety of leading candidates in the field4. ZMapp™, was rapidly accelerated through clinical testing in a Phase I/II trial that was intended to be used to support licensure. ZMapp™ went through extensive manufacturing campaigns utilizing a proprietary tobacco plant based expression system as a unique platform for scaling production to move rapidly into the clinic. Collection of safety and efficacy data in human populations through clinical studies is a rare opportunity during EID epidemics and can provide valuable data to support drug use.

4) *Drug development services*: Our experience has taught us that not every pharmaceutical company has the internal capability to simultaneously coordinate clinical studies, animal studies and manufacturing when in a response mode. BARDA has established core services that can be leveraged by pharmaceutical companies as needed, providing access to BSL4 suites for animal efficacy studies, which in the case of Ebola during the height of the outbreak, were in high demand, utilize manufacturing centers to rapidly generate GMP product (noted is the expression of Ebola mAbs in CHO cells that was achieved with BARDA's Centers for Innovation in Advanced Development and Manufacturing [CIADMs]) and provide clinical and logistical expertise to rapidly move drugs into endemic regions for distribution in clinical trials during the outbreak. The core services, which BARDA and other US Government agencies can provide, may make available critical resources (e.g. to rapidly advance drug development) inaccessible within the traditional pharmaceutical company.

Responding to an EID outbreak requires commitment and partnership with drug sponsors to accelerate drug development on unprecedented timelines. For known infectious diseases, as was the case with Ebola, BARDA was able to leverage drugs

already in development which allowed for a more effective response. However for new viruses or previously low profile viruses, like Zika virus, having access to platform technologies may be advantageous to leverage for rapid discovery of MCMs. Core Services or economic incentives may be needed to encourage industry and pharmaceutical companies to work with the USG in developing therapeutics in a response to the rapidly changing landscape of new emerging viral threats.

BARDA's work does not conclude at the end of an outbreak or public health scare. Although the above 4 concepts highlight how BARDA worked closely with pharmaceutical companies in a response mode to accelerate development of MCMs and to make them available during the outbreak, the utility of these drugs is still limited in use to clinical trials because they will not have achieved regulatory approval. BARDA is committed to the continued development of successful candidates to move them forward to licensure to increase our preparedness posture should an outbreak repeat itself or elevate to a pandemic.

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ISAR MEMBER PROFILE

M. Javad Aman

Javad is the President and Chief Scientific Officer of Integrated BioTherapeutics Inc., a Gaithersburg, Maryland, USA based biotechnology company.

Tell us about your career path

I am a molecular biologist with a deep interest in virology. I did my Ph.D. work at the University of Mainz, Germany on the mechanisms of action of type 1 interferons in hematopoietic cells. During this time, I developed a strong interest in cell signaling processes initiated by cytokines. During my post-doctoral fellowship at the University of Virginia I worked on signal transduction of IL2, IL4 and IL-13 and discovered the human IL-13 receptor. My interest in signaling led me to work on membrane microdomains that are often used by various cellular response mediators and also viruses such as HIV.

In 2000, I joined the US Army Medical Research Institute of Infectious Diseases (USAMRIID) where I had a chance to use my knowledge of membrane microdomain to initiate a project on filoviruses. During this time, we worked out a method to generate Ebola virus-like particles (VLPs) and went on to demonstrate its utility as a vaccine for filoviruses. This work led to several high impact publications in J Exp Med, PNAS, and JID. In 2007 I ventured out of USAMRIID to start the biotechnology company Integrated BioTherapeutics (IBT).

How did you start Integrated Biotherapeutics?

I started IBT in 2007 with a focus on emerging infectious diseases and biodefense and with the initial objective of transitioning some of the discoveries we had made at USAMRIID to actual products. Unlike most biotech companies I started IBT entirely based on government grants and contracts and with no private equity. Over the past 9 years we have been able to secure over $45M in government funding, and have also supplemented this capital with antiviral and anti-bacterial services that we offer to the pharmaceutical industry. The combination of product development and discovery services is a unique feature of our business model. In the meantime, the company has grown to 34 people, and now operates a state of the art laboratory and a vivarium for small animals.

A primary focus of IBT is the development of broadly protective therapeutic antibodies against several viral targets including filoviruses, arenaviruses, and alphaviruses. Over the past few years we have developed strategies to drive broadly neutralizing antibody response in macaques using engineered filovirus glycoproteins and VLPs. In collaboration with Steven Foung's lab at Stanford and Yuxing Li's lab at University of Maryland, we succeeded to generate the first in class broadly neutralizing antibodies that are protective against multiple filoviruses. This is a critical milestone in the fight against filoviruses.

During the 2014 Ebola virus disease (EVD) outbreak, we were lucky that at least some products against the Zaire strain were nearing the finish line. But other filovirus species like Sudan, Bundibugyo, and Marburg viruses have also caused sizable outbreaks. It is impossible to predict what species will hit the next time, so we should be prepared. Our broadly neutralizing antibodies offer a potential solution for this problem.

What aspect of your research have you found most satisfying?

Although I am operating a business, the most exciting part of my day to day work is looking at data and discussing it with our scientists. Being in the position to do research and yet see a direct link to real applications and the mesmerizing thought that what you make in your lab today may, some day, save a person's life is a satisfaction no amount of money can buy. We are so grateful to funding agencies as the grant funding allows us to do our research without the pressure from investors whose timelines often don't take the unpredictable nature of scientific research into account.

What are your thoughts on antibody-based therapeutics?

I know that ISAR is heavily focused on small molecule antivirals, and this is understandable. But we should remember that the immune system evolved in the first place to fight invading pathogens. Yet, in the 21st century of over 40 FDA approved monoclonal antibodies only two are for infectious diseases. I think this is primarily driven by the focus of the pharmaceutical industry on the lucrative market of cancer and inflammation, rather than an inherent difficulty of making effective antibody-based therapeutics for infectious diseases. Recent advancements in antibody manufacturing is driving down the cost of goods.

Structural biology and advances in protein engineering are helping us design much smarter antibodies with higher specificity and affinity, as well as broader reactivity. Novel technologies are evolving to generate bispecific and tri-specific antibodies that could fundamentally change what can be achieved with antibody as a drug.

We have seen better antibodies emerging for RSV, influenza, HIV, alphaviruses such as chikungunya, Zika, and filoviruses. This increased activity within this space driven by the urgency of the recent large outbreaks (Ebola, Zika, influenza), will hopefully result in major breakthroughs and growing number of FDA-approved antibody-based therapeutics for infectious diseases.

How has ISAR contributed in your career?

As a scientist whose research is focused on antiviral antibodies and the ISAR focus being on small molecule I am not a typical ISAR member. However, our company works extensively with pharmaceutical industry for testing antivirals, mostly small molecules in vitro and animal models. For our team the annual ISAR meeting is a unique opportunity to get updated on the newest developments in the field and new methodologies that could directly be applied in our service business. Maybe the best part of attending ISAR meetings is the opportunity to network with the best scientists in the field and access to important resources through these contacts.

However, I would like to see ISAR pay more attention to antibodies and try to attract scientists working on antiviral antibody therapeutics to attend ISAR. Having scientists from both sides of the aisle with

their unique perspectives will only enrich future ISAR meetings.

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