ISAR News
Newsletter of the International Society for Antiviral Research

Editor: Aruna Sampath

IN THIS ISSUE

*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. As we move towards year's end, I take the opportunity to reflect on the tasks and accomplishments of 2017. The society could not be in a better shape. We have a consolidated number of members and our past conference was a success. I have received many notes of congratulations for the excellent program and the quality of presentations; organization with our new Congress Organizer went smooth and seamless from start to end; and we were able, after some years of financial effort, to return to a healthy situation. The society is now in an outstanding position to continue promoting excellence in science, distinguishing those who excel in antiviral research and stimulate the participation of students, postdocs and young investigators with commitment and passion for antiviral research and antiviral drug development.

This year was also of great significance to an institute that has been instrumental in the success of our society and in the development of novel antiviral agents. The Rega Institute for Medical Research in Leuven, Belgium, celebrated the opening of its new location, a brand new building with state of the art technology devoted to drug screening and biomedical research. I congratulate all the investigators at the new Rega and wish them success.

Many ISAR members, including myself, had the privilege and honor to accompany our president-elect, Johan Neyts, our Secretary Graciela Andrei and many other friends and colleagues at the Rega Institute during the two-day scientific symposium and celebration of the opening. On behalf of ISAR, I also congratulate John Martin, executive chairman of Gilead Sciences, for receiving an honorary doctoral degree from the KU Leuven. Such distinction implicitly recognizes one the most productive collaborations in antiviral drug development led by John Martin, Erik De Clercq and Antonín Holý.

We are now heavily involved in the planning of the 31st ICAR in Porto, Portugal, June 11-15, 2018. For the first time in many years the meeting will be held at a conference center, not a hotel venue. We hope this decision will allow participants to choose their accommodation without the society imposing it at the official hotel. Porto is a beautiful European city very attractive to tourists, and thus, it offers a wide range of hotels and accommodations to suit every need and price range. Porto can be reached from almost every major European city through a direct flight and from major U.S.A. airports. I encourage all participants to make their travel and accommodation arrangements at the earliest convenience and also benefit from our early bird registration fees.

The program for the 31st ICAR will maintain a balance between Keynote, invited speakers and selected presentations from submitted abstracts. Three focus symposia and a special session on technical issues will set the stage for an excellent line-up of speakers. Excellent science is the guiding standard. If you feel your work demonstrates excellence, I encourage you to submit your work. ISAR will continue its efforts in supporting the participation of young scientists. We look forward to seeing you in Porto.

I hope you enjoy this new issue of ISAR News. Your participation is essential. We want to hear your thoughts and opinions on what is important to you. Please feel free to contact us at info@isaricar.com.

José Esté
President, ISAR

THE 31ST ICAR, PORTO, PORTUGAL

From the Program Committee (Mark Prichard and Justin Julander)

The International Society for Antiviral Research (ISAR) will host the 31st ICAR in Porto, Portugal Monday June 11th through Friday June 15th, 2018. The conference will be held at the Alfândega Conference Centre, Rua Nova Da Alfândega, Edificio Da Alfândega, 4050-430 Porto, Portugal. This venue is scenically located along the banks of the Douro River and is conveniently located in the heart of Porto. 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.

Speakers at the meeting will present the latest scientific developments in antiviral research and will emphasize the interdisciplinary nature of this field. This year, the program will feature a Cytomegalovirus (CMV) Symposium, including speakers involved in the latest efforts to understand and control disease. Featured speakers include William Britt, Paul Griffiths, David Kimberlin and Randi Leavitt. An exciting development in the treatment of CMV that will be discussed at this year's ICAR is the development of letermovir, a terminase inhibitor that has successfully completed phase 3 clinical trials for CMV infection.

The conference will also feature an Emerging Infections Symposium, a Virus Evolution Symposium, and a Hepatitis Symposium. The 31st ICAR will also include a newly implemented Technical Session that will discuss innovations in technology and how they are being used in antiviral research. Other regularly scheduled sessions include the Keynote Address and four award lectures with more details forthcoming in the next issue of ISAR news. Annual oral sessions on in vitro antiviral activity, medicinal chemistry, clinical trials, respiratory, DNA and emerging viruses and hepatitis are also scheduled. Two poster sessions are also included, which provide a great opportunity for students and investigators to present their data and provides opportunities to further discuss research presented at the conference. The meeting will also include networking opportunities for new members including a Women in Science Roundtable, a Career Development session and a New Member reception.

We will also have a PechaKucha contest at the 31st ICAR in Porto! PechaKucha is a presentation format where you have 20 slides, each on the screen for only 20 seconds. Your slides advance automatically so you have to keep up with the slides, as you won't have control of the speed. Some tips on a good PechaKucha presentation – incorporate humor, a surprise or something that is unexpected. Bottom line, you want to entertain the team of judges as well as inform!

Why should you compete? There will be two cash prizes - $200 for first place and $100 for second place, but only graduate students and postdocs are eligible to compete.

How to sign up? When you submit your abstract, please indicate that you want to compete – only seven people, as well as an additional three alternates, will be selected. Selection will be based on abstract quality, novelty, and content of the work. Be sure to submit your abstract and sign up early. See you in Porto!

Chu Family Foundation Scholarships for Early-Career Women in Science (Katherine L. Seley-Radtke)

Purpose

The Chu Family Scholarships were initiated by The Chu Family Foundation (TFCC) and ISAR to support the professional development of early career level women with the potential for significant contribution in the field of antiviral research by providing funds to attend a specialized workshop, visit/work in another laboratory to obtain new skills, take a course, or acquire specialized training.

Awards

Up to three awards will be given annually to advance the careers of early career level women with

potential for significant contributions in the field of basic, applied, and clinical aspects of antiviral research and antiviral drug development. Each award will consist of a $3000 stipend, a 2-year ISAR membership and a commemorative plaque. The stipend must be used within a year of its award and the winners must present their research at the next International Conference for Antiviral Research (ICAR) As a result, the award should be used for both the proposed external training and attending the ICAR. However, if the total cost exceeds the $3000 limit, applicants are still eligible to apply for the ICAR travel award funds. The funds are not meant, however, to just attend ICAR.

Eligibility

To be eligible to apply for the TFCC award, the early career level woman scientist must currently be either a (i) graduate student or (ii) hold a doctoral degree and have no more than four years of cumulative postdoctoral experience. The applicant must currently be doing graduate or postdoctoral research in the general field of antiviral research – this includes virology, chemistry, molecular biology or another virally-related focus.

The criteria for selection include, but are not limited to, the level of interest in antiviral research, the ability to do independent scientific work, the potential for a high level of scientific endeavor in antiviral research, as well as the extent of scientific accomplishments and scientific leadership/mentoring skills. Graduate students and postdoctoral candidates must be members of ISAR. A letter of support must be provided by a nominator, who may be the candidate's research project director, Department Chair, or Center Director. Information on how to become an ISAR member can be found at http://www.isar-icar.com/?page=Membership

2018 TFCC Application Process

All grant applications must be submitted electronically by December 31st, 2017. Once submitted, nomination materials become the property of the Selection Committee and will not be returned. Winners will be selected by the TFCC Selection Committee by January 31st, 2018 and will be informed of their status by email. The winners must present their research at the next ICAR meeting. (Note: winners are still eligible for ICAR travel awards to attend ICAR).

Each candidate must submit:

- A statement describing her academic accomplishments and future career goals. The candidate should include an explanation of how the planned use of the award (workshop, training, specialized course, external lab visit, etc.) will help her career. The length may not exceed 2 pages, single-spaced.
- A CV of any length.
- A letter of support from the candidate's research project director, department chair or center director. Recommenders should describe how the planned use of the award (meeting, course, lab visit, etc.) will benefit the candidate's scientific and career development.
- Any candidate who wishes to use the award money to visit another scientist's laboratory must also submit a letter from the head of the laboratory indicating that the proposed visit is permissible.
- Any candidate who wishes to use the award money to attend a specialized course or workshop or course must provide a detailed description of the conference/course including the date, location, and other pertinent details, including a link to online information.

Additional Information:

Candidates may apply more than one time but women who have previously won the award are not eligible for a second award. In addition, any candidate that has won a TFCC Scholarship from the International Society of Nucleosides, Nucleotides and Nucleic Acids (IS3NA) is also ineligible to apply. In general, the career development activity should not be one for which the applicant's advisor is already funded. After completion of the training or course, etc., the recipient must provide a brief report of the work that was supported by the award to ISAR. This report will then be sent to The Chu Family Foundation.

All nominations will be submitted online. The nominations link will be available starting 19th October 2017. For questions please contact the TCFF Chair, Katherine Seley-Radtke, with the words The Chu Family Foundation Scholarship in the subject title.

The nomination deadline is December 31st, 2017.

Travel grant awards and travel assistance (Graciela Andrei)

Travel grant awards

ISAR is pleased to announce the availability of travel grant awards and travel grant assistance for the 31st ICAR. The travel grants 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. Stipends will vary, depending on the region of origin of the presenting author: Europe, $400 and North America, Asia, and Australia, $800. 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. The travel grant awards application deadline is 9th March, 2018.

Requirements to be considered for a travel grant award:

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

Registration for the meeting is mandatory to receive a grant.

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

To apply for the travel grant, 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 both young and senior researchers from countries where it is difficult to finance their attendance at the meeting. The amount of support ($1,000) will partly cover the flight fee (economy class) from the country of residence of the presenting author. Support may be increased depending on final sponsorship of the conference. Thr travel assistance award application deadline is 9th March, 2018.

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 waived. The travel assistance will be available as cash at the meeting (receipt to be signed). Recipients of a travel grant award are expected to attend and actively participate to the entire conference.

To apply for travel grant 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.

ANTIVIRALS ON THE HORIZON

RSV Therapeutics on the Horizon (Jerome Deval and Julian A. Symons)

Alios BioPharma, Inc., a Janssen Pharmaceutical Company, South San Francisco, CA, USA.

Respiratory syncytial virus (RSV) causes one of the most common upper respiratory tract infections that take place during the winter season. In the majority of otherwise healthy adults, RSV infection usually lasts a week or two and results in mild cold-like symptoms. However, RSV infection can also lead to severe lower respiratory dysfunction such as pneumonia and bronchiolitis in vulnerable populations such as infants, elderly and immunocompromised persons.

RSV is the most frequent cause of hospitalization of infants and young children in industrialized countries. Approximately two-thirds of infants are infected by RSV in their first year of life, resulting in an estimated 132,000-172,000 hospitalizations in the US, and 2.1 million out-patients visits annually among children under 5 years old. Severe RSV infections are also frequent among elderly patients, a population that often remains undiagnosed. RSV infection in the elderly results in approximately 177,000 hospital admissions and approximately 10,000–14,000 deaths per annum in the US. Costs associated with hospitalization are estimated to exceed $1 billion annually.

No vaccines are approved for the prevention of RSV infection. Palivizumab, a monoclonal antibody directed against the RSV fusion (F) protein, is approved only for prophylaxis to prevent serious lower respiratory tract disease caused by RSV in high risk infants, but therapeutic efficacy has not been established. Ribavirin is the only approved treatment of serious RSV infections in hospitalized children, but its use via aerosol delivery is minimal due the inconvenient route of administration, lack of evidence for efficacy, and safety concerns. Therefore, novel therapeutics are needed for use both in the outpatient setting, to reduce the severity of infection and prevent hospital admissions, and in the hospital setting, to ameliorate the severity of symptoms and duration of time spent in the hospital.

In the last five years, a limited number of small molecule candidates for RSV treatment have entered human clinical trial evaluation. Conventionally, these molecules are classified into two categories: fusion and non-fusion (or replication) inhibitors. Since the early 2000s, several compounds have been identified that inhibit virus-cell membrane fusion and cell-cell syncytium formation by binding to the RSV F protein. GS-5806 (presatovir; Gilead) is the most advanced RSV fusion inhibitor in clinical development, and is under investigation in Phase IIb studies in hospitalized adults and patients undergoing either hematopoietic cell and lung transplants. Other RSV fusion inhibitors currently in early-stage clinical trial evaluation are the small molecule inhibitors; RV521 (ReViral), JNJ-678 (Janssen), and AK-0529 (Ark Biosciences) and the inhaled nanobody, ALX-0171 (Ablynx).

Non-fusion (or replication) inhibitors represent the second main class of anti-RSV agents. These molecules act at the intracellular level to disrupt viral replication by interfering with the polymerase complex that mediates viral genome replication and transcription. Although the first RSV replication inhibitors were reported over a decade ago (i.e. AZ-27, RSV-604, BI-compound D), suboptimal potency and ADME properties hindered their progression either into clinical development or into later stage efficacy studies. To date, the only RSV replication inhibitor to reach human safety and efficacy evaluation is ALS-8176 (lumicitabine), a nucleoside analog prodrug discovered and developed by Alios BioPharma (for recent review on RSV replication inhibitors: [1]).

The discovery of ALS-8112, the parent molecule of the prodrug ALS-8176, was the result of a screening campaign using a focused library of structurally diverse nucleoside and nucleotide analogs tested against RSV in an *in vitro* infectious assay [2]. The main scaffold identified from this screen was 2´difluoro-4´azido-cytidine. Further modifications at the 2´- and 4´- positions to improve anti-RSV potency and selectivity, led to the identification of ALS-8112 (2´fluoro-4´chloromethyl-cytidine). *In vitro*, ALS-8112 inhibits a broad panel of RSV A and B subtypes, as well as related pneumo-, paramyxo- and rhabdoviruses [3]. In particular, we recently reported that ALS-8112 inhibits RSV and human metapneumovirus with similar *in vitro* potency [4].

The molecular target of ALS-8112 was determined by two independent methods. The viral RNA polymerization function of the RSV L protein was identified as the target of ALS-8112 inhibition, first, by selecting and characterizing drug resistance-associated mutations located in the L gene. When introduced into a wild-type RSV genome, four amino acid mutations (M628L, A789V, L795I, and I796V) were phenotypically associated with resistance to ALS-8112 [3]. Enzymatic assays using purified recombinant RSV polymerase were critical to validate the mode of action of ALS-8112. In these assays, the 5´-triphosphate form of ALS-8112 (ALS-8112-TP) caused immediate chain termination of RNA synthesis and inhibition of the viral polymerization activity.

This inhibitory effect was specific to RSV polymerase, since ALS-8112-TP did not inhibit polymerases from host or viruses unrelated to RSV such as hepatitis C virus (HCV). Because of the low oral bioavailability of ALS-8112, a series of 2´, 3´-diester prodrugs were evaluated for improved pharmacokinetic properties. One prodrug, ALS-8176, formed high levels of monophosphate and triphosphate in the lungs when administered orally to nonhuman primates. Because of its high oral bioavailability, ALS-8176 was evaluated for *in vivo* efficacy in African Green monkeys infected with RSV. At the end of treatment, RSV RNA was undetectable (< 50 copies/mL) in bronchoalveolar lavage samples from all four ALS-8176-treated animals whereas mean RSV RNA titers in the placebo-treated animals were 8.6×10^5 copies/mL [3]. Subsequently, a randomized, double-blind, clinical trial evaluated ALS-8176 given for 5 days to healthy adults inoculated with RSV [5].

The reduction in viral load area under the curve (AUC) in nasal washes associated with ALS-8176 treatment varied from 73% to 88% depending on the dose regimen compared to placebo-treated subjects. RSV RNA was undetectable 1.3 to 2.3 days after the start of ALS-8176 treatment compared with 7.2 days for placebo. Assessment of symptom scores and quantity of mucus produced also showed a clear effect on RSV-induced disease. This is an important result that represents the first proof-of-concept validation that an RSV replication inhibitor can be efficacious in humans. ALS-8176 is currently in clinical development for the treatment of RSV infection in hospitalized infants and adults (ClinicalTrials.gov identifier: NCT02202356, NCT02935673).

ALS-8176 is the only RSV replication inhibitor currently in later stage, phase 2b, clinical trials, however, other molecules that target the RSV replication are progressing into human clinical studies. PC786 (pulmocide) is an RSV polymerase

inhibitor designed for delivery via inhalation that recently entered phase 1 clinical studies. In addition, there are several companies reporting pre-clinical programs on RSV replication inhibitors including EDP-938 (developed by Enanta) that is planned to reach phase I clinical trials later in 2017. Other companies such as Ark BioSciences and Aviragen Therapeutics have also publically reported pre-clinical activities on RSV replication inhibitors.

The perspective of having more than one replication inhibitor available for RSV treatment provides the opportunity to explore combination therapies. We have recently published *in vitro* antiviral synergy resulting from the combination of ALS-8112 with AZ-27 [6]. We therefore predict that synergistic effect between drugs and lack of broad cross-resistance induced by mutations in RSV polymerase will become strong arguments in favor of potential combination treatments, following the successful model of HIV and HCV therapeutics. In conclusion, recent efforts to discover and develop novel fusion and non-fusion RSV inhibitors are maturing with an emerging pre-clinical and clinical pipeline of exciting RSV therapeutic drug candidates.

The next step in clinical development will be to assess the potential of these molecules to address the medical burden associated with RSV infection in infants and adults, both in outpatient and hospital settings.

References:

1. Fearns R, Deval J. (2016) New antiviral approaches for respiratory syncytial virus and other mononegaviruses: Inhibiting the RNA polymerase. Antiviral Res.134:63-76.
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3. Deval J, Hong J, Wang G, Taylor J, Smith LK, et al. (2015) Molecular basis for the selective inhibition of respiratory syncytial virus RNA polymerase by 2'-Fluoro-4'-Chloromethyl-Cytidine Triphosphate. PLoS Pathog 11: e1004995.
4. Meng J, Deval J, Jekle A, Symons J. Development of ALS-8112/ALS-8176 as an effective replication inhibitor of human metapneumovirus. 30th ICAR - International Society for Antiviral Research, Atlanta, May 2017. Oral presentation.
5. DeVincenzo JP, McClure MW, Symons JA, Fathi H, Westland C, et al. (2015) Activity of Oral ALS-008176 in a Respiratory Syncytial Virus Challenge Study. N Engl J Med 373: 2048-2058.
6. Deval J, Fung A, Stevens SK, Jordan PC, Gromova T, et al. (2016) Biochemical Effect of Resistance Mutations against Synergistic Inhibitors of RSV RNA Polymerase. PLoS One 11: e0154097.

COMMENTARIES

Responding to emerging epidemics: Funding development of Rapid Response Vaccine Platforms (Ajoy C. Chakrabarti)

Platform & Portfolio Lead Polio, Bill & Melinda Gates Foundation, Seattle WA
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The Bill & Melinda Gates Foundation (BMGF) hosts a yearly event, the Product Development Challenge (PD Challenge) Forum, where key participants from industry, product development partnerships (PDPs), academia, Non-Government Organizations (NGOs) and BMGF Grantees gather to discuss current & future challenges related to product development for drugs and vaccines with global health applications.

A highlight of the 2016 PD Challenge Forum was that the assembled participants were asked to select the most important area for the BMGF to focus on for 2017. Development and validation of rapid response technology platforms for production of vaccines to respond to emerging epidemics were identified as the top priority by a majority of the participants. That led to many follow-on discussions about how to advance this epidemic rapid response concept both within the BMGF and externally.

The goal of developing rapid response platforms to interrupt epidemics dovetailed nicely with the recent launch of the Coalition of Epidemic Preparedness (CEPI -http://cepi.net/), which views such platforms as essential to meeting their goals regarding epidemic preparedness. BMGF personnel are now working closely with CEPI to develop the review and assessment process for platform technologies. The goal for CEPI will be to identify and fund the best of these new platform technologies by mid-2018. A formal announcement for a “Call for Proposals” (CfP) on development of platform technologies will be sent out in early September 2017.

The CfP will be aimed at developers who believe that their platform technology and manufacturing

operations can eventually meet the following attributes:

- Target a 16-week timeframe from identification of antigen to product release for clinical trials
- Target a 6-week timeframe from administration of first dose to achievement of clinical benefit (i.e. immune response likely to result in clinical benefit)
- Produce 100,000 vaccine doses within 8 weeks to impact an emerging outbreak (i.e. from Go-decision to scale-up to production, fill, finish, and release)

Given these parameters, certain technologies are expected to be particularly well suited. For example, both DNA- and RNA-based vaccine platforms should be amenable to meeting the tight timelines for release of clinical trial material. However, other vaccine technologies are more advanced in terms of established large-scale commercial production, process optimization and completion of regulatory reviews. An ideal scenario would involve receiving submissions related to multiple platform technologies at various stages of development. However, the current breadth of platform technologies was not well understood.

As a prelude to launching the CfP, it was felt that learning more about what platform technologies are currently available would be useful. Hence, a "Request for Information" (RFI) was sent out by CEPI in March 2017 to gather data on the current status of rapid response platforms, both for vaccines and therapeutic agents (typically monoclonal antibodies). A review of the summary findings from that RFI is informative in terms of understanding the general landscape of technologies that are currently under development. The geographic dispersion of respondents to the RFI is shown in Figure 1.

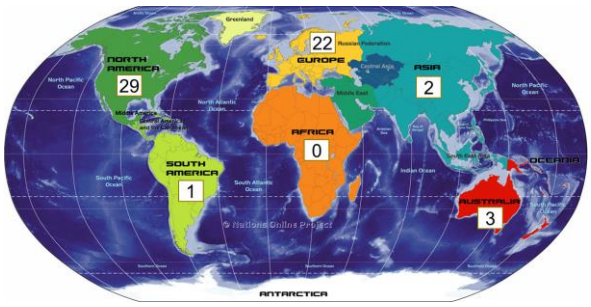

Figure 1: Breakdown of submissions by region.

Most of the applications came from North America and Europe. It is hoped that submissions from other areas will increase as awareness of the new funding opportunities associated with CEPI rises. The distribution of responses based on the type of organization that was submitting the response is shown in Figure 2.

The majority of responses coming from biotechnology companies was anticipated as the RFI was seeking novel approaches to manufacturing large amounts of vaccine under tight timelines. Given that many of the submissions consisted of multiple entities (primarily via consortia or partnerships), this sort of analysis may be potentially misleading, as often two types of organizations are submitting together. In those situations, the type of organization was classified by the member submitting the response.

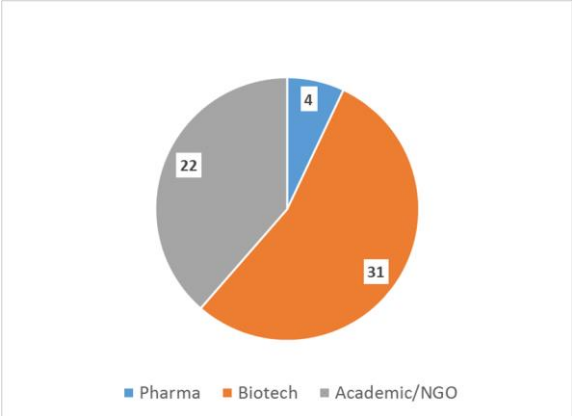

Figure 2: Distribution of responses by type of organization.

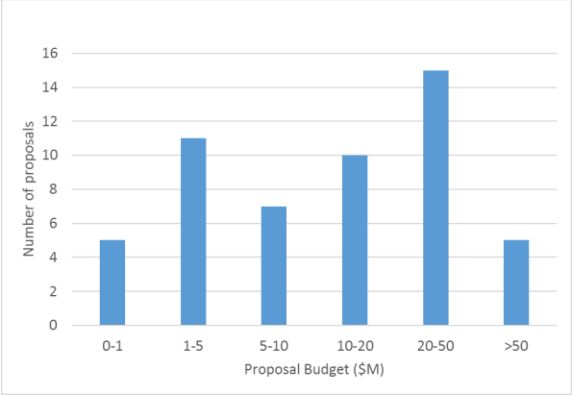

Figure 3. Distribution of RFI responses by budget requested (US$, millions).

Finally, the proposed budgets for work submitted in response to the RFI are shown in Figure 3. The budgets and associated scopes of work represented a broad array of planned activities, ranging from limited lab studies to proposals to develop pilot-plant capabilities and fund clinical studies. As such, the value of a detailed analysis of the proposed budgets is

inherently limited. However, it is useful to understand from a funding envelope perspective that the majority of proposals were for > $10 million. Thus, any effort to fund multiple (3-4, for example) proposals based on different platform technologies should be expected to cost at least $50 million. Assuming that clinical data was being requested, the overall budget for supporting multiple platforms in future grants could rise to be $100 million or more.

The impact of the RFI data generated on the design of the upcoming CfP has been significant. The coming months will reveal the scope of rapid response technologies that are available and what additional work is needed to allow for the platforms to be validated. It is hoped that publications, such as this one, will continue to raise awareness of CEPI and the importance of rapid response vaccine platforms in preparing for future epidemics.

Resources to support product development for antiviral agents and vaccines at NIAID (Sara E. Woodson[1], Heather L. Greenstone[2], and Mindy I. Davis[3])

[1]Product Development Project Manager, HHS/NIH/NIAID/DMID Virology Branch
[2]Program Officer for Animal Model Antiviral Evaluations, HHS/NIH/NIAID/DMID Virology Branch
[3]Program Officer for Antiviral Discovery, HHS/NIH/NIAID/DMID Virology Branch

Iododeoxyuridine was first described in the literature in 1959, and it later became the first antiviral drug licensed to treat ocular herpes simplex virus (HSV) infection [1, 2]. This publication marked the dawn of antiviral drug discovery. However, for many in the medical field, antiviral drugs were thought to be an impossible therapeutic goal due, in part, to the theory that antiviral therapeutic dosages would be too toxic for use. Only a handful of compounds were identified in the 1960s, despite much interest in the field. Since early drug discovery was expensive and few laboratories could conduct the testing, there was an obvious need to help advance the field.

In 1971, the Collaborative Research Program was established at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH) as an extension of an existing interferon research and resources program. Over the years, that program has evolved into a comprehensive suite of contract services, collectively known today as the Preclinical Services Program of the Division of Microbiology and Infectious Diseases (DMID) (hereafter referred to as the PCS Program).

The PCS Program provides four types of research services: *In Vitro* Assessment, Preclinical Models of Infectious Diseases, Therapeutic Development Services, and Vaccine Development Services [3]. The PCS Program helps to fulfill NIAID's mission to "conduct and support basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases" [4]. These resources, which are provided through a pool of pre-qualified contractors, are intended to lower the risk of, and assist with, drug discovery, testing, and preclinical development of promising products. A broad overview, information about selection criteria, and other information is provided below for a few of the service areas that are most relevant to the ISAR newsletter readership.

1. *In Vitro* Assessment for Antimicrobial Activity

This service provides resources to stimulate research and discovery of new antiviral therapies. Specific and broad-spectrum screens are available and the current panel contains 47 different viruses. The available viruses in the in vitro antiviral panel are dynamic, and viruses are added or removed based on current NIAID programmatic priorities. For example, Zika virus was added in 2016 to allow rapid screening of potential drug candidates against this re-emerging pathogen. Hepatitis C virus (HCV) was removed from the panel in 2017 since numerous drugs have been developed and licensed for the treatment of HCV infections. The panel includes primarily human viruses with a few animal viruses that correspond with in vivo models such as the mouse and guinea pig cytomegaloviruses. The in vitro antiviral assays are replication-based and include assessment of the efficacy and cytotoxicity of the test article so that a selectivity index can be calculated.

To access these services, product submitters (hereafter referred to as "submitters") must discuss the request with the relevant program officer and fill out an in vitro service request form (SRF). The information in this form allows NIAID to evaluate the request. Readiness for *in vitro* testing is evaluated based on the following: rationale for antiviral activity, mechanism of action, availability of high quality drug, product development plan, scientific priority, and availability of resources. A variety of molecules can be tested, such as purified small molecules of known composition, peptides with known sequence, or antibodies. Serum or extracts are generally not

accepted. NIAID requests that submitters disclose the composition of the molecule.

Examples of how the *in vitro* assessment services have been used by the extramural community include validating binding or enzymatic assay hits in an in vitro infectious assay, such as for Ebola virus which can only be tested under high-containment (BSL-4) conditions; determining if a molecule developed for one virus has broad spectrum activity with other members of the family or other virus families; and assessing initial activity of a new molecule in the broad screen to evaluate whether it shows any activity in the other available virus families.

2. Preclinical Models of Infectious Diseases.

This service provides resources for assessing antiviral products and vaccines *in vivo*, developing novel models, or refining existing models of viral diseases; 40 different animal models of viral diseases are available. Most studies are conducted in mice or hamsters; testing in non-human primates is available for a limited number of viruses including filoviruses and Zika virus. Investigators who wish to access these services must submit an *in vivo* SRF.

Selection and prioritization for *in vivo* testing is based on factors such as the quality of *in vitro* and/or prior in vivo data, manufacturability of the product, the likelihood that the product will be developed, and availability of resources. Acceptance for testing in non-human primates generally requires proof of prior activity in a small animal model. After acceptance for testing, a product-specific protocol is developed with input from the submitter, the relevant contractor, and NIAID staff; NIAID has the final authority on the protocol. Upon completion of a study, a report is generated by the contractor, reviewed by NIAID, and then provided to the submitter. The data can be used by the submitter as desired, for example, in a publication, as part of a grant proposal, to further the knowledge base of the product, or to inform decisions about the product's development potential.

3. Therapeutic and Vaccine Development Services

These services include a group of contractors that can fulfill needs for optimization, testing, and more advanced stages of preclinical development in areas such as structure-activity relationships, synthesis/re-synthesis of compounds, pharmacokinetic analysis, feasibility and product development plans, formulation studies, toxicology, assay development, and cGMP manufacturing, among others. Preliminary data to support the product's developmental stage are required. Each request must be discussed with appropriate DMID staff from the respective scientific program and service type. Selection criteria for these services align with product category, and include program priorities and availability of resources. If the request is approved, the submitter will be invited to submit a formal proposal; senior leadership in DMID review all requests.

All of the preclinical services offered by NIAID are open to investigators at academic institutions, not-for-profit organizations, small and large biotech companies, and governments worldwide. There is no need to have a previously established relationship with NIAID to utilize the services. DMID ensures that a submitter's intellectual property rights are protected.The services help advance discovery and preclinical development of products by providing testing to address specific resource-limited gaps. These preclinical services are not intended to be the sole source of development assistance.

After the cost of product shipment, services are offered at no cost to the submitter; however, resources for the services are limited and cannot be guaranteed to be available upon request. The submitter is obligated to sign a non-clinical evaluation agreement, provide preliminary data about the product, provide the product or the starting materials to the contractor, acknowledge the contribution of NIAID's support in publications/presentations, and report achievements about the product to NIAID. Data generated by the contractors are returned to the submitter and can be used to support future product development activities such as: go/no-go product development decisions, grant submissions, US Food and Drug Administration (FDA) Investigational New Drug (IND) filings, and lifting of FDA clinical holds.

Developing therapeutics and vaccines for viral diseases continues to be a challenge, with limited resources often making it difficult to bring promising products through the developmental pathway, and ultimately to those in need. NIAID has been supporting the discovery, testing, and preclinical development of products to better cure, treat, or prevent viral disease since 1971. While this article has focused on antivirals and vaccine services for viral diseases, it should be noted that services are also available through the PCS Program for the development of products for fungal, bacterial, and parasitic diseases. NIAID welcomes and invites you to visit the resources webpage https://www.niaid.nih.gov/research/microbiology-and-infectious-diseases-resources,

for more information about the services, eligibility, and program contact information.

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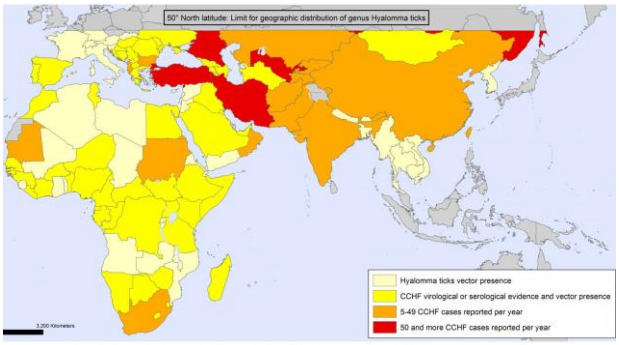
MEETINGS

2nd International Conference on Crimean-Congo Hemorrhagic Fever (Mike Bray)

Crimean-Congo hemorrhagic fever (CCHF) is the most widely distributed tick-borne viral disease of humans. The causative agent, an orthonairovirus in the family *Nairoviridae* (previously classified as a bunyavirus), has been recovered from ticks over a huge geographic region, extending from Spain across southern Eurasia to China and down the length of Africa. Sporadic cases and clusters of human infection have been observed throughout the endemic area, but are most common in Balkan countries and the Middle East (reviewed by (Bente *et al*., 2013)).

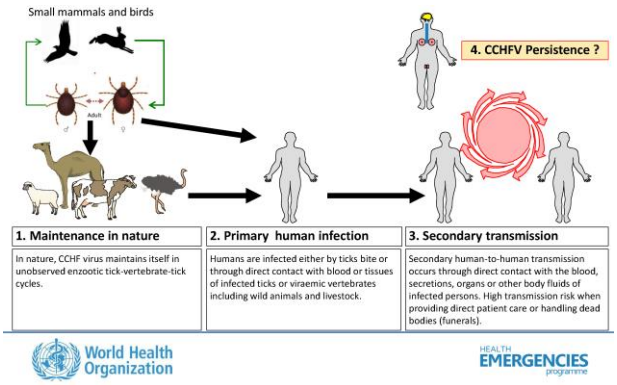
In recognition of increasing scientific interest in CCHF, an international conference devoted to the disease was held in Thessaloniki, Greece in 2015 (Papa et al., 2015). Its success led to the organization of a second meeting, also held in Thessaloniki, from September 10-12, 2017, which was attended by more than 100 researchers from 25 countries. Presentations at the conference covered a wide range of questions in the areas of epidemiology, virus replication, maintenance and transmission in tick vectors, immunology and vaccine development, diagnostic methods and antiviral therapy. Summaries will appear in a forthcoming meeting report, to be published in *Antiviral Research.*

As its name suggests, CCHF was first recognized as a distinct disease in an outbreak in the Crimea in 1944, associated with the exposure of Soviet soldiers and farm workers to large numbers of tick bites. A virus isolated in the Belgian Congo in 1956 was shown 11 years later to be identical to the Crimean agent, leading to the combined name of "Crimean-Congo," and over subsequent decades closely related viruses were isolated from ticks, wild and domestic animals and human cases over a huge geographic area. Spain recorded its first indigenous case last year, and studies have shown the virus to be widespread in ticks in that country.



Distribution of the principal tick vector of CCHF (pale yellow), of countries where serologic testing shows evidence of endemicity (yellow), and countries reporting from 5-49 (orange) and more than 50 cases (red) per year. Courtesy of Pierre Formenty, WHO.

CCHF is most common in Turkey, where the first patient was diagnosed in 2002. Strikingly increased numbers of cases were detected in subsequent years, with a total exceeding 5000 by 2009, and more than 1000 per year from 2010-13, with a case fatality rate of just under 5%. The increase may have resulted in part from the re-occupation of abandoned farmland in eastern Turkey, leading to high tick exposures, but it is also likely that many mild cases that occurred before 2002 were not specifically diagnosed. Interestingly, the past two years have seen a significant decline in reported cases of CCHF in Turkey; whether this is a result of public health educational efforts to reduce tick exposure, or has been caused by other factors, is not known.



Maintenance of CCHFV in nature and modes of transmission to and between humans. Courtesy of Pierre Formenty, WHO

As shown in the figure above, CCHFV circulates silently through persistent infection and vertical transmission in ticks, principally of the genus *Hyalomma*, with periodic amplification when ticks take blood meals from various small or large animals (Gargili *et al*., 2017). Neither wild nor domestic mammals show any signs of illness, so that humans are the only animals to develop a visible disease when infected with CCHFV, and are thus the only "sentinel" species indicating the presence of the virus in a region.

Human infections result most commonly from tick bites, though exposure may also occur through direct contact with the blood or tissues of viremic animals. Secondary human-to-human transmission has been observed, typically when a patient with unrecognized disease is treated by health care workers who fail to take precautions against blood-borne agents, though CCHF appears to be somewhat less contagious than the similar, but more severe Ebola virus disease. As indicated in the above figure, it is possible that CCHF resembles Ebola in the persistence of virus in "sanctuary" sites in convalescent patients, but studies are needed to confirm the hypothesis.

Mild cases of CCHF are characterized by fever and lethargy, but severe infections take on the features of viral hemorrhagic fever, with progressive hypotension leading to shock and variable degrees of hemorrhage. The development of bleeding in subcutaneous tissues, leading to the formation of extensive bruises, is characteristic of the disease. Early case reports indicated that the fatality rate from CCHF was typically in the range of 30-50%, but as surveillance efforts have expanded and detection methods have improved, overall case fatality rates have declined, and large series, such as those from Turkey, have had fatality rates of less than 5%. The presence of high seropositivity rates in domestic animals and humans in areas where few or no human cases have been reported suggests that most human infections are mild. As in the case of Ebola virus disease, severe infections leading to hospitalization may only receive a specific diagnosis when nosocomial transmission is observed.

As suggested by the lack of observed illness in wild and domestic animals infected with CCHFV, common laboratory animals do not develop detectable disease when infected with the virus. However, success has been achieved in recent years in modeling major features of the human illness in interferon-deficient mice, and recent work reported at the Thessaloniki meeting described a severe illness resembling the human disease in cynomolgus macaques.

Of greatest interest to antiviral researchers is the status of specific therapy for the disease. A number of case reports from the 1980s and '90s claimed a beneficial effect of treatment with oral or intravenous ribavirin, but the reports were based on a handful of patients and lacked a control group. Larger studies that have appeared since 2000 have given a mixed picture, with some appearing to show a benefit of therapy, especially when treatment is begun early after disease onset, while other patient series have failed to show an effect (reviewed in (Keshtkar-Jahromi, 2011)). Carefully controlled clinical trials are therefore needed to determine the efficacy, if any, of ribavirin and to assess the benefit of novel therapeutic agents, such as favipiravir.

This and other questions were the focus of a World Health Organization (WHO) report earlier this year, which provided an authoritative review of the epidemiology and pathogenesis of CCHF in humans and identified important targets for research (Al-Abri et al., 2017). The following future directions for research and public health efforts were listed in the report:

1. Standardization of case definitions for the early detection of CCHF patients;
2. Development of assays for CCHF RNA quantification that are rapid, precise and easy to implement at the point of care in resource-limited settings;
3. Design and execution of a randomized controlled trial to properly validate or refute the efficacy of ribavirin, favipiravir and monoclonal antibodies;

4. Development of an algorithm as an aid to help clinicians rapidly establish the presumptive clinical diagnosis;
5. Sero-epidemiological studies for human and animal infection in the region, including in non-endemic countries;
6. Development of a set of risk communication messages for high-risk groups;
7. Identification of best surveillance practices for animal health for the early detection of potential spillover into humans;
8. Design and implementation of studies to develop CCHF or anti-tick vaccines for animals;
9. Ranking of areas by risk estimation and the spatial–temporal forecasting of CCHFV circulation and future outbreaks.

These goals were presented and discussed by Pierre Formenty from WHO in the concluding session of the meeting.

A proposal to form an International Society on CCHF was put forward on the second day of the meeting in Thessaloniki, and was approved by acclamation. Anna Papa, Ali Mirazimi and Roger Hewson were elected president, vice-president and secretary, respectively. An advisory council, consisting of researchers from 10 countries where CCHF is endemic, plus representatives from the USA and Germany, has since been created. For more information on the 2017 meeting and the new International Society, go to http://www.med.auth.gr/cc-conference-2017

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Opening of the new Rega Institute building at KU Leuven (Mike Bray)

The opening of the new Rega Institute building at the University of Leuven (KU Leuven), Belgium was celebrated in a two-day event on September 13-14. The new facility forms part of the medical school complex on the Gasthuisberg medical campus and replaces the much smaller building on the Minderbroederstraat which had housed the Institute since 1954.

The opening ceremony on September 13th was chaired by ISAR president-elect Johan Neyts. It began with a video presentation of the history of the Institute, whose name honors Hendrik Joseph Rega, a professor of anatomy who played a major role in leading the university through the turbulent period of the early 18th century.

The first Rega Institute, founded in 1882, was a two-story building that contained laboratories for research and teaching of medicinal chemistry and bacteriology. The scope of work expanded with the generation of antisera and other products before and after World War I, and was greatly increased in the late 1940s and 1950s, under the leadership of Pieter De Somer, when his company's success in the large-scale production of penicillin provided sufficient capital to support construction of a new Rega Institute of Medical Research. By the 1960s, De Somer had removed all links between his company and the Institute, but the concept of a partnership between science and industry to accelerate medical progress has continued to be a successful strategy, most evident in the collaboration with Gilead Sciences in the development of tenofovir.

Following a series of presentations by leading figures at KU Leuven and the Belgian government and videotaped remarks by Peter Piot, the former executive director of UNAIDS, the highlight of the afternoon was the presentation of an honorary degree to John Martin, the executive chairman of Gilead Sciences. In his speech accepting the degree, John

underlined the importance of collaboration in scientific research, as exemplified by his long-term partnership with Antonín Holý and Erik De Clercq, which led from the early evaluation of nucleotide analogue prodrugs to the remarkable success of tenofovir, which has prevented millions of deaths from AIDS, and is a component of therapy for some 90% of HIV-infected people who receive antiviral therapy.

Erik De Clercq congratulates John Martin on receiving the degree of *Doctor Honoris Causa.*

The scientific symposium on September 14th featured a series of keynote lectures on the range of scientific problems studied by Rega Institute investigators. Those of greatest interest to virologists were a presentation by Ab Osterhaus from the University of Veterinary Medicine, Hannover, Germany on "Emerging virus infections and intervention strategies"; by Phil Murphy from the US NIAID in Bethesda, Maryland on "Bridging virology, immunology and clinical medicine with chemokine receptors"; and by Robert Gallo from the Institute of Human Virology, University of Maryland, on "Discoveries of human retroviruses."

An important feature of the new Rega Institute laboratory is the P3 facility, shown above, which will make possible the study of all agents of human disease except for those, such as Ebola virus, which require maximum P4 containment. The centerpiece of the lab is a state-of-the-art fully automated drug testing unit, which will be used for high-throughput screening of compound libraries for activity against a wide range of viral pathogens.

At the reception following the award ceremony: Johan Neyts and Masanori Baba; Graciela Andrei and Tomas Cihlar.

A view inside the new P3 containment lab, showing unit for drug screening (photo courtesy of Pieter Leyssens).

Photos, videos and information about the opening celebration and the Rega Institute are available at http://rega.kuleuven.be/about/onr
Images used in this article were obtained from the website.

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