ISAR News
Newsletter of the International Society for Antiviral Research

# Rome, Italy welcomes 28th ICAR

Editor, Anthony Vere Hodge Guest editors, Rhonda Cardin and Mike Bray


## *ISAR PRESIDENT'S WELCOME*

**Welcome to Rome!**

I'm excited to welcome everyone to The Eternal City for the 28th International Conference on Antiviral Research. As I celebrate the end of my first year as President of the Society I am looking forward to the opportunity to spend a week in Rome where I can not only enjoy an exciting week of great science and networking opportunities with friends and colleagues, new and old, but also to have the opportunity to visit such amazing historical spots such as the Coliseum, the Forum, the Vatican, and so many other sites which we have all learned about since we were kids in school. I would be remiss if I also didn't mention the fact that we have the opportunity to spend a week enjoying the finest Italian cuisine and fine wines.

This year's meeting continues a tradition of conferences that dates back to the second ICAR in Williamsburg, Virginia nearly three decades ago. Some of us still remember those early days of antiviral research, building on the accomplishments of scientists like Trudy Elion, Tony Holy, and Bill Prusoff to treat and eliminate diseases such as HIV and herpes simplex. All these years later, the use of highly active antiretroviral therapies for HIV and the treatment of hepatitis C stand as prime examples of what can be accomplished when scientists in the antiviral field work together towards a common end.

Our Society, a fine blend of academic and commercial science, as well as a mixture of chemistry, biology and pharmaceutical science, brings together scientists possessing a wealth of information that is necessary


for the treatment of viruses which continue to challenge public health. As we meet this year we know that HIV persistence continues to challenge our ability to end the AIDS pandemic, Ebola continues to infect large numbers of individuals in Africa and has made intercontinental jumps to infect people outside of Africa, the chikungunya epidemic continues to affect the Caribbean, and just recently measles jumped out of Disneyland to remind us of the critical importance of our work.

The ability of viruses to attack us and our ability to develop therapies and prevention products to eliminate the threats posed by viruses of all kinds – old, new and emerging – is the reason we gather in Rome to discuss how to continue the evolution of antiviral treatments. This year's meeting features keynote addresses, topical symposia, award presentations,

and invited plenary speakers as well as oral presentations and poster sessions from abstracts submitted by attendees.

Over the past years, local organizers have been essential to our meeting success and this year is no different. Our local organizer Romano Silvestri, (with significant assistance from our webmaster Andrea Brancale) has helped us to select the site for this year's meeting (Parco dei Principi Hotel) as well as identifying candidates for the prestigious Keynote Addresses. As always, we are grateful to our sponsors for supporting the meeting and also appreciate the support and patronage of the Italian Chemical Society this year.

I would also like to especially welcome new members of our worldwide scientific community to our Society and to the Conference. One of the hallmarks of the Society has always been to encourage young members to find networking and professional growth opportunities at the annual meeting. This year we will introduce our very first Women in Science scholarship winners, and our budget for travel awards to support young professionals throughout the world to attend the meeting continues to increase. We have also begun our outreach to under-represented scientific communities throughout the world through our ISAR Ambassador program in the hope that we can encourage and assist scientists from around the world to join the Society and attend the meeting.

During my tenure as President, I sincerely hope to increase our membership from regions such as Africa, Asia and South America, as well as increasing the numbers of attendees from Europe and North America. I also hope to develop new ways to keep our young members involved in the Society.

So, please join us in Rome – work, relax, network and enjoy your time with scientists who share your devotion to ending viral diseases and make friendships and collaborations that will last a lifetime. That is what ISAR and ICAR are all about. I look forward to meeting and conversing with everyone at the 28th ICAR in Rome.

**Robert W. Buckheit, Jr.**
***President, ISAR***

## *WELCOME TO ISAR NEWS*

Dear ISAR members,

Welcome to the spring, 2015 issue of ISAR News! You will find in this issue: a warm invitation to the 28th ICAR in Rome from our ISAR President, Bob Buckheit; important information about the meeting, including the exciting scientific program; a progress report of the Women in Science initiative, the ISAR election results and the financial statement for the 27th ICAR.

There are two feature articles which provide interesting information on current research on microbicides and favipiravir, contributed by Bob Buckheit and Brian Gowen, respectively. Anthony Vere Hodge has provided his personal view on the Ebola epidemic. This is followed by a profile and interview with ISAR member David Bernstein on his development of the rotavirus vaccine, then an article on recent advances in the roseolovirus field, both contributed by Rhonda Cardin. The final section provides a link to a list of future conferences that will be posted on the ISAR website.

As editor, I especially thank the efforts of Rhonda Cardin and Mike Bray for help in getting this issue out!

For the ISAR Publications Committee
Anthony Vere Hodge, Editor
Rhonda Cardin, Guest editor
Mike Bray, Guest editor

## *IN THIS ISSUE*



## *28TH INTERNATIONAL CONFERENCE ON ANTIVIRAL RESEARCH* (Mark Prichard)

**May 11–15, 2015 Parco dei Principi Hotel, Rome Italy**

This year the 28th ICAR will be hosted by the International Society for Antiviral Research (ISAR) on Monday, May 11th through Friday, May 15th. The meeting will be held in the Parco dei Principi Hotel, Rome, Italy. The main focus of the annual meeting is on new scientific developments in antiviral research, yet opportunities for networking with colleagues are equally important.

The conference was designed specifically to provide opportunities for all participants to establish and maintain the close collaborative relationships among chemists, pharmacologists, and biologists that are required for the discovery and development of effective antiviral therapies. It also serves to stimulate innovative thinking about the drug development process and provides specific events to welcome new scientists to our ranks to help them to establish successful careers. Thus, consistent with all of our past ICARs, there will be ample opportunity for everyone to strengthen existing contacts and add to their network contacts by meeting new scientists working in the field. The annual meeting provides a unique environment to socialize with your peers in an open and friendly atmosphere. This year the meeting will also have a free afternoon so you will have time to enjoy historic Rome.

The ICAR program and the text of all the abstracts will placed on the Society's webpage. This ''green'' initiative not only reduced costs associated with the meeting, but also extended the deadline for abstract submissions to about 2 months prior to the meeting, which was just enough time to complete peer review of the submissions, select oral and poster presentations, and publish the materials online. We believe this change was well received by the Membership and this year we plan to enhance the quantity of material provided online by providing a means to place poster presentations on the website. These initiatives will provide increased exposure for presented works and will make more data available to Members of the Society so they can further consider the presented data at their leisure when they return home from the meeting.

The conference will officially begin on Monday May 11, 2015 at 2:00 pm with **Drug Discovery and Development 101**. This interactive session will focus on microbicide product development. **Betsy Herold** will discuss pharmacokinetic and pharmacodynamic evaluations of products that prevent a broad spectrum of virus infections. Perception and acceptability issues will be summarized by **Kate Morrow**, and **Jacob Estes** will talk about the biology of primary HIV infection as evaluated in nonhuman primate

models. **Robert Buckheit** will then describe the development of an *in vitro* virus sterilization assay to define the required dosing of microbicide products.

Additional program highlights are:

## KEYNOTE ADDRESSES

- **Rafael De Francesco** from Istituto Nazionale Genetica Molecolare will outline the latest advances in the biology of HCV replication and antiviral targets
- **Armand Sprecher** from Doctors Without Borders will review the history and current status of the Ebola epidemic in Africa.
- **Michael Manns** from the University of Hannover, will deliver an address on the closing day of the conference to discuss new therapies in the clinic for HCV infection.

## WOMEN IN SCIENCE ROUNDTABLE

Featured speakers (see additional information below):

- **Gabriella Campadelli-Fiume**
- **María Paola Landini**
- **Jennifer Moffat**

## SYMPOSIUM ON RNA VIRUSES

Featured speakers:

- **Joana Rocha-Pereira** will discuss the development of norovirus countermeasures
- **Tony Fooks** will focus on the prevention of rabies with antiviral drugs
- **Jamie Whitehorn** will speak on the prophylaxis and treatment of dengue virus infections
- **Heiner Wedemeyer** will review hepatitis E virus infections
- **Thomas Baumert** will provide an overview of HCV and HBV entry inhibitors
- **John De Vincenzo** will discuss antivirals against respiratory syncytial virus

## SYMPOSIUM ON EMERGING VIRUSES

Featured speakers:

- **Mike Bray** will discuss progress in experimental therapies for Ebola virus infections
- **Anna Papa** will describe emerging viruses in the Balkans and Mediterranean region
- **Remi Charrel** will summarize the emergence of chikungunya virus
- **Bart Haagemans** will review the Middle East respiratory syndrome (MERS)

The honorees of the 2015 *Gertrude Elion Memorial Award*, the *William Prusoff Young Investigator Award,* and the *Antonín Holý Memorial Lecture Award* will give major presentations. This year we are also thankful for the patronage of the Italian Chemical Society.


Parco dei Principi Hotel

### Abstracts

ISAR is committed to conducting a meeting of the highest scientific standards for both oral and poster sessions. Thus, abstracts of original research in any area of antiviral drug discovery and development research are encouraged and will be evaluated for scientific merit by a panel of reviewers. Notification of acceptance and instructions for oral or poster presentations will be sent via e-mail by March 16, 2015. With the submission of an abstract, the author(s) agrees to disclose the structure of any compounds for which biological data are presented in a poster or oral presentation.

### Poster Awards Competition

ISAR will once again sponsor a poster awards competition for graduate students, postdoctoral fellows and young investigators. Further information on the awards is available on the ISAR website or from Mark Prichard, Program Committee chair (mprichard@peds.uab.edu). Any investigator who is awarded an oral presentation and would like to compete for a Poster Award should prepare and present a poster at the meeting and have slides available if they are selected for the Shotgun Poster Presentation.

### Shotgun Poster Presentation

This session will give graduate students, postdoctoral fellows, and other young investigators the opportunity to present their posters as short talks. Those who wish to be considered for this session should prepare 3–4 slides summarizing their poster, and the presenters will be chosen after review of the posters. Two presenters will be selected as co-chairs.

**Late-breaker Submissions**

Although the deadline for abstract submission was February 25th, a limited number of abstracts for oral and poster presentations may be submitted as late as March 29th. These late-breaker presentations will be reserved for a few submissions containing important recent data with cutting-edge implications and impact. Note: this mechanism should not be used as a means to submit tardy abstracts! Late-breaker abstracts will not be published in the ICAR Program.

**Important Notice Regarding Publication of Abstracts**

The Program for the 28th ICAR, including titles of presentations and names of authors, will be put on the Society's web site on or shortly after April 1, 2015. All attendees are encouraged to submit their posters online and they will be made available on the website prior to the meeting.

**Online Abstract Submission**

All abstracts must be submitted online via SPLtrak following the instructions outlined below. Abstracts will not be accepted in any other manner. All abstracts are limited to 2500 characters and spaces including the title, authors/affiliations, and abstract body text. The character limit for abstracts that include a figure is 2000. The system will automatically impose these restrictions when you enter your abstract.

**Instructions for Abstract Submission**

- Create a new abstract submission account or sign in to your existing account.
- On the linked page, click on the ''Go to Abstract Submission'' link and follow subsequent instructions.
- Note that the title, authors, text, etc. are entered separately.
- After entering the abstract title, click on the ''Save'' button which takes you to the next task, ''Authors''. Fill in this section and click ''Save''.
- This will take you to the section to enter or upload the body of your abstract.
- On the ''Abstract Submission'' page you may edit or delete your abstract at any time until the abstract is officially submitted. Select ''Submit Complete Abstract'' under ''Status'' to submit the final version of your abstract.

Visit the ICAR website, www.isar-icar.com, for more information on this ICAR, including moderator biographies and registration. Don't forget to take advantage of the advance rate and save $100 when you register for the conference by April 17, 2015. If you are not yet an ISAR member, consider joining ISAR since the member's discount more than pays for your membership subscription! If you have any questions about the roundtable or registering for the conference, please contact the ISAR/ICAR Office at isar@courtesyassoc.com, or 202.973.8690.

## *ISAR WOMEN IN SCIENCE COMMITTEE*

**WIS Roundtable (Amy Patick)**

This session, the first event at ICAR, will be held on Monday, May 11, from 11:30–2:00 PM. It will be open to all ICAR attendees, both women and men, and will feature prominent women scientists who will talk about the challenges they faced and the lessons they learned while navigating the twists and turns of their personal career progression. Come network with other scientists in the industry, government and academic fields. The following speakers are confirmed:

- **Gabriella Campadelli-Fiume**, Microbiology and Virology, University of Bologna, Department of Experimental, Diagnostic and Specialty Medicine, Bologna, Italy
- **María Paola Landini**, Microbiology and Clinical Microbiology, University of Bologna, Department of Experimental, Diagnostic and Specialty Medicine, Bologna, Italy
- **Jennifer Moffat**, Microbiology and Immunology, State University of New York (SUNY) Upstate Medical University, Syracuse, NY

This roundtable is free for ICAR registrants; however, space is limited to the first 80 participants, so register now! To register, select the ''Women in Science Roundtable'' session under the 28th ICAR Events section when you register for the Conference. Lunch will be provided.

**WIS Career Development Award (Amy Patick)**

At ICAR 2015, the ISAR WIS Committee will announce the winners of the first Career Development Award. Up to five awards will be given annually to advance the careers 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. 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:

- be a current undergraduate or graduate student or hold a doctoral degree and have no more than five years of cumulative postdoctoral experience;
- be performing undergraduate, graduate or postdoctoral work in antiviral research and/or related areas.

More information about the award and additional guidelines can be found on the ISAR website, http://www.isar-icar.com. Further announcements will be made at the meeting concerning this exciting new scholarship program.

**WIS Mentorship Program (Rhonda Cardin)**

The ISAR WIS Committee launched an exciting new mentorship program at the 2014 ICAR in Raleigh, NC. Participants in the WIS Roundtable were asked if they wanted to be mentored or serve as mentors in the program. The mentees and mentors were matched to each other by the WIS Committee members after filling out a questionnaire on current interests, career goals, and what each member wanted to achieve by participating in the mentoring program.

The mentors and mentees had their first face-to-face meeting while still at the Raleigh meeting. For this first year of the mentoring program, we have 10 mentors and 15 mentees. There are two PhD students, 7 postdocs, 4 Research Associates or Fellows, and 1 government employee. The mentees are located at a variety of institutions from around the world, including Germany, Nigeria, United Kingdom, Bosnia and Herzegovina, South Korea, and the United States. The mentors are from the U.S. and Belgium and provide career advice and scientific expertise in academia and the pharmaceutical industry.

The program is off to a great start! The mentors and mentees have had subsequent contact either by email, phone, or even skyping, during the time since the last ICAR meeting and the response has been overwhelmingly positive from both mentees and mentors. This year, we hope to increase the numbers of mentors and mentees in the program even more! If you are interested in this program, be sure to attend the WIS Roundtable in Rome.

***ISAR ELECTION RESULTS* (Phil Furman)**

Congratulations to Rhonda Cardin and Roger Ptak, who were re-elected to the Society's Board of Directors. An electronic (web-based) election was run from November 20th to December 20th to fill two available Board of Director seats held by Rhonda and Roger, whose terms as Board members expire at the end of the 28th ICAR. An outstanding slate of candidates was nominated for the two Board Seats, including Roger and Rhonda, who agreed to run for a second term. An email was sent out to 604 registered members. However a disappointing total of 73 voters responded. This represents a 12% 'turnout', which is significantly lower than for the previous elections. Hopefully in the future more members will participate in these important elections. Please say hello to Rhonda and Roger at the meeting!

**Rhonda Cardin**

Rhonda is an associate professor at Cincinnati Children's Hospital Medical Center. She received her A.B. from Washington University in St. Louis in 1983, then began her PhD studies at Tulane University in New Orleans. After the lab moved to Louisiana State University in Baton Rouge, she received her PhD in microbiology in 1989. She received her postdoctoral training in Ed Mocarski's lab at Stanford University, on cytomegalovirus pathogenesis and latency.

**Rhonda Cardin**

In 1994, Rhonda joined the lab of Dr. Peter Doherty, 1996 Nobel Laureate in Medicine, at St. Jude Children's Research Hospital, to study gammaherpesvirus immunology. In 1998, she joined Park-Davis Pharmaceuticals as a senior scientist to oversee the in vivo herpesvirus antiviral program. After the Pfizer, Inc., merger with Parke-Davis and a short period at ChemoCentryx, Inc., a chemokine therapeutics company, she returned to academia in 2003. Her lab in Cincinnati studies CMV pathogenesis and latency.

Since 2003, Rhonda has been a co-PI for NIH contract evaluation of antivirals and vaccines in CMV and HSV animal models. In 2009, she was president of the Women's Faculty Association at CCHMC. She serves as a grant reviewer for the NIH and AHA, and is a reviewer for multiple journals, including *Antiviral Research*.

Rhonda joined ISAR in 2003 and has presented at ICAR each year, co-chaired herpesvirus plenary sessions, and currently serves on the finance, membership, publications, and Women in Science committees. For the past three years, she has served on the ISAR Executive Board.

**Roger Ptak**

Roger Ptak is an accomplished scientist with over 20 years of research and project management experience in antiviral drug discovery and development. He received his BS degree in biology from the University of Notre Dame in 1992. From 1993–99 his work supported the

**Roger Ptak**

discovery of novel herpesvirus and HIV-1 inhibitors at the University of Michigan.

In 1999 he joined the Southern Research Institute Department of Infectious Disease Research in Frederick, Maryland where he is currently Program Leader for the In Vitro Antiviral Drug Development Program. In this role he manages an extensive staff of scientists and research technicians responsible for execution of in vitro assays and assay development for the discovery and development of antiviral drugs and topical microbicides on multiple large government programs and a wide range of contract research projects for the biotechnology and pharmaceutical industry.

In addition to his work at Southern Research, Roger is affiliated with the Frederick County Hepatitis Clinic, where he serves as Board President and Treasurer. He has co-authored 68 peer-reviewed publications and review articles related to antiviral research, and he is an Ad hoc reviewer for multiple journals related to antiviral drug discovery and development.

As a member of ISAR since 1995, he has actively served the Society through participation on a number of committees including the Web Site and Conference Committees. Roger is currently a member of the Society's Board of Directors, and is the Chairman of the Finance Committee, for which he has helped raise over $1M to support ISAR/ICAR

## *FINANCIAL SUMMARY OF THE 27TH ICAR*

**Brian Gowen, ISAR Treasurer**

Having officially taken over the reins as the ISAR Treasurer at the conclusion of the Raleigh meeting, I am grateful for the support of Dale Barnard in facilitating the transition and thank him for his exceptional service throughout his 7 year tenure as the society's Treasurer. Remarkably, after the dust settled following the 27th ICAR, the net balance reflected a loss of a mere $480, which is negligible considering meeting expenses totaling $339,408.

No longer having financial support from the NIH through meeting grants, we are especially grateful for the ICAR sponsorship campaign efforts of Roger Ptak and the generosity of corporate and educational sponsors in support of the annual meeting. ISAR continues to be on solid financial ground with total assets exceeding $700,000. We greatly appreciate the continued support of the society through attendance at ICAR, membership and service. I look forward to seeing all of you in Rome.

27th ICAR, Raleigh, North Carolina, USA
May 12–16, 2014

| Revenues | |
|---|---|
| Registration | 147,795 |
| Award sponsorship | 17,500 |
| NIH grant | 0 |
| Corporate sponsorship | 147,767 |
| Other revenue | 25,866 |
| **Total Revenue** | **$338,928** |

| Expenses | |
|---|---|
| Advertising | 1,150 |
| Site selection trip | 554 |
| Food, beverage, events | 135,915 |
| Audiovisual | 30,102 |
| Hotel expenses | 9,716 |
| Exhibits/posters | 6,836 |
| Invited speakers | 13,807 |
| Courtesy Associates out of pocket | 8,825 |
| Courtesy Associates labor | 55,445 |
| Credit card Fees | 7,100 |
| Other (insurance, refunds, etc.) | 11,380 |
| Awards (Elion, Prusoff, Holy, poster, travel) | 58,578 |
| **Total Expenses** | **$339,408** |
| | |
| **Net Balance** | **–$480** |

## CURRENT RESEARCH

### HIV microbicides: learning from the past, planning for the future

**Bob Buckheit, Jr, ImQuest BioSciences**

Significant funding has been available over the past two decades from NIH, USAID, the Gates Foundation and other sources for the development of topical microbicides to prevent the sexual transmission of HIV. In the absence of an effective vaccine, and in concert with education, condom use, abstinence and circumcision, microbicides represent the best opportunity to stop the transmission and spread of the HIV in the female genital tract or the rectum.

Despite much discouragement in its early years, the field has recently made great strides in understanding how a microbicide must act to prevent HIV transmission. Tenofovir, TDF, dapivirine and maraviroc have all progressed to pivotal human clinical trials as vaginal gels and/or intravaginal rings.

Over the past two decades, I've been engaged in research on HIV, and my company, ImQuest BioSciences, is actively involved in microbicide development. To inform ISAR members about progress in the microbicide field, I've invited three experts to share their thoughts on lessons learned over the past two decades and how those lessons can be applied in the future. Let me begin with a basic overview on microbicides to provide some orientation.

#### What is a topical microbicide?

Topical microbicides are chemical or physical agents that function locally to prevent the transmission of HIV to its target cells in the vagina or rectum. Development of an effective microbicides is challenging, due to the complex environment in which the product must act.

Despite significant investments in research, the biology of HIV infection in the vagina or rectum is still not completely understood. The complexity includes

1. uncertainties as to the form of the infectious virus (cell-free or cell-associated);
2. the structure of the target tissue and the location and numbers of target cells;
3. the role of natural defense mechanisms such as cervical mucus, lactobacilli, and antiviral factors comprising the innate immune system;
4. inflammation from microtrauma and coinfections that promotes infection; and
5. the presence of biological matrices such as semen, cervico-vaginal and rectal fluids.

A successful microbicide will thus need to be stable and long-lasting to prevent virus transmission in this highly complex microenvironment.

To date, candidate topical microbicides have included acid buffers, natural defense molecules, surfactants, detergents, and replication inhibitors targeting different steps of HIV replication, including cell entry and reverse transcription. Unfortunately, products such as nonoxynol-9, C31G, cellulose sulphate, BufferGel, PRO2000, and carrageenan all failed to demonstrate efficacy in clinical trials. Most recently, however, the field has been energized by the successful Phase 3 trial of tenofovir gel.

The positive result demonstrates that potent antiretroviral products can prevent virus transmission, and also indicates that additional research and development are required to further improve efficacy. Tenofovir gel was highly effective when taken every day but the trials showed that daily dosing was poorly accepted. Dosing at longer intervals (eg, once monthly) is seen as a preferred requirement. Additionally, as for HIV therapy, combinatorial highly active antiretroviral prevention strategies have begun to evolve and be clinically evaluated. Major funds are being invested in developing new formulation strategies for the long-term delivery of microbicide products. Requirements for IND-directed development have been published in FDA guidance documents.

Fountain in Piazza Navona

#### Gaps in microbicide development

As research and development continue, resources are being expended to better understand the differences between microbicides and therapies. The lines have become increasingly blurred as antiretroviral agents have been successfully used for pre-exposure prophylaxis (PrEP). Efforts have been initiated to develop a combination of vaginally and/or rectally delivered microbicides with PrEP agents and vaccines.

While it is clear that wide variety of opportunities to prevent transmission may be eventually utilized in synergistic fashion, it is equally clear that behavioral studies to understand product acceptance are critical to success. Because men and women in different parts of the world may have different preferences, there is a critical need to develop products in a variety of formats, including gels, rings, films, suppositories and implantable devices. It has also become increasingly evident that a

successful product must be designed and evaluated as a synergy of the active ingredient and the delivery vehicle. Strategies are now evolving to deliver active ingredients to target tissues, fluids, and pathogens, and to dissociate product application from coitus.

One of the more difficult parameters to be determined by microbicide developers is how dosing levels correlate with pharmacokinetics and pharmacodynamics (PK/PD). The overall consensus from both failed and successful trials is that ''more is better'', and that one should dose as high as possible to assure that effective concentrations of the active pharmaceutical ingredient (API) are present where and when needed to prevent virus transmission.

*Ex vivo* and *in vivo* evaluations in mice and monkeys have provided information on the permeability and tissue uptake of the API, to better understand the PK/PD properties of the compound and how they relate to dosing. However, the tissue concentrations achieved with high dosing levels of a microbicide are significantly higher than the inhibitory concentrations achieved using cell-based *in vitro* assays. Levels of API differ substantially when evaluations are performed on the epithelial versus stromal layers of the vagina, suggesting the importance of a better understanding of dosing, distribution, and PK/PD.

In light of the types of cells used in the ***in vitro*** evaluations, the lack of robustness of the assays in terms of their quantitative endpoints and timing of endpoint analysis, and the importance of understanding dosing and the prioritization of compounds for clinical use, it is critically important to understand the dosing requirements of an API as early as possible in the development process.

## Lessons learned

After two decades of research and development, where does the microbicide field stand, and where will it be headed in the future? I posed these questions to three experts:

- Joseph Romano, former chief of product development at the International Partnership for Microbicides;
- Ian McGowan, principal investigator at the U. of Pittsburgh-based Microbicide Trials Network;
- Betsy Herold, director of the Translational Prevention Research Center at Albert Einstein College of Medicine

### What important lessons have been learned over the past two decades of microbicide development and testing?

***Joe Romano:***

The biggest lesson learned is the importance of the end user in product design and evaluation. Assumptions that were made on user preferences led to the development of products which were not used in large, expensive clinical trials. It has been clearly shown that the techniques for assessing product acceptability by the end-user and estimating actual product use were inadequate. The consequences have significant ramifications, particularly in terms of funding for large Phase 3 studies. What is the enthusiasm level for going forward? What data will funders require to be assured that adherence will not be a problem?

Even if a product is successful in a Phase 3 trial with intense adherence counseling, what are its prospects for uptake and use post-approval? The adherence issue is also a major driver in terms of alternative product development, specifically long-acting injectable products which involve a dosage form familiar to the target populations, such as injectable contraceptives, and to mitigate the compliance risks.

In terms of preclinical development, the field has yet to devise a means of defining dose. Nonhuman primate, explant and biopsy models exist, but have not yet been proven as effective and relevant means of defining dose. In the end, the field continues to look for maximum-tolerated or maximum-formulatable doses as opposed to lower, yet still effective dose options. This adds cost, increases safety risks, and puts a higher burden on the dosage form in terms of drug delivery level, all of which make product development more challenging.

The biggest clinical issue is how to conduct large, expensive Phase 3 trials with products that are user-controlled, and achieve the necessary level of adherence to demonstrate safety and efficacy. The world cannot fund more Phase 3 trials of products that people do not actually use. A major ethical consideration will be the emerging changes in standards of care for HIV prevention. Now that Truvada has been approved, and tenofovir gel and the dapivirine intra-vaginal ring (IVR) may also be approved, it will be very challenging to run placebo-controlled trials of new microbicide products in the future.

***Ian McGowan:***

Perhaps the most important lesson we have learned over the last two decades is that self-reported behavior of product use is very unlikely to provide an accurate account of adherence. This has profound implications for the ability of clinical trials to characterize the safety, acceptability, and efficacy of candidate microbicides.

This observation has catalyzed the need to develop objective methods to characterize product use, sexual behavior and HIV exposure. The development of the *ex vivo/in vitro* explant model has also provided the opportunity to generate preliminary data on product efficacy in Phase 1, as well as the construction of PK/PD models to assist with dose optimization.

***Betsy Herold:***

Over the past twenty years of product development, a major lesson learned has been understanding the need for more predictive preclinical and Phase 1 studies. We have also discovered the significant limitations of current animal models and their ability to predict efficacy, toxicity and pharmacokinetics and pharmacodynamics. We have learned a lot from ***ex vivo*** challenge and wash studies, with regard to the development of rational combinations of microbicide products.

We have also found out that more intensive PK/PD studies, better measures of adherence and better behavioral research are required earlier in development. PK/PD and behavioral studies should all be conducted with sexually active populations, including adolescents, especially since we now know that the sex act itself and the presence of semen affect PK/PD, and thus would inform dosing. These studies should precede Phase 3 trials.

**How should these lessons be applied to future microbicide development?**

***Joe Romano:***

The most important issue facing future microbicide development is the broader context of HIV prevention and treatment within which it will need to occur. With treatment expansion (and its high impact on prevention), male circumcision, continuing massive investment in vaccines, expansion to injectable prevention options and serious discussion of a cure for HIV infection, it is not clear what the value of microbicides will be going forward. This is particularly true if either or both tenofovir gel and dapivirine ring are successful.

We will therefore need to carefully consider the added value of another microbicide in this context, and the enthusiasm levels for investment by funding agencies. From the perspective of cost-effectiveness and their impact on the epidemic, the case for microbicides will need to be clearly made in a world with other options that are further along and of high interest.

***Ian McGowan:***

All stages of microbicide development should now include objective measures of the microbicide product. These can potentially be used to improve adherence at an individual level (in open-label studies) or at a site-specific level (in double-blind studies). The *ex vivo/in vitro* explant model should be incorporated into all Phase 1 studies of vaginal and rectal microbicides as a means of defining dosages to be taken into later-stage development. This will be facilitated by the use of dose-ranging Phase I study designs.

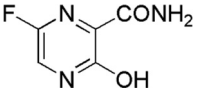
***Betsy Herold:***

We currently have too many similar drugs and formulations being advanced simultaneously. The budgets of big pharmaceutical companies permit this level of development, but it cannot be successfully performed with HIV prevention funding, which primarily originates from nonprofit organizations. We should prioritize our development programs based on the specific population being targeted. Finally, we need to implement greater sharing across development groups. Competition can drive better science, but with limited funding, groups should work together to develop the best products.

Pantheon and Fontana del Pantheon

**T-705 (favipiravir): a new broad-spectrum antiviral with applications from influenza to Ebola**
**Brian Gowen, Utah State University**

The Ebola epidemic has focused the world's attention on novel antiviral therapies, especially a cocktail of monoclonal antibodies with a catchy name, ZMapp. However, another new drug, favipiravir, which has gotten less publicity, may hold greater promise for the treatment of Ebola and other severe infections (Figure 1). For the past 10 years I've tested favipiravir against a range of RNA viruses in various rodent models, so I'd like to provide some information on the drug for the benefit of ISAR members who are less familiar with it. For a more detailed perspective on the compound and its development, I refer readers to a recent review in *Antiviral Research* (Furuta et al., 2013).




*Structure of favipiravir (Avigan®), initially designated T-705.*

In 2004, I transitioned from a postdoctoral fellowship to the Institute for Antiviral Research at Utah State University, where I began my study of highly pathogenic RNA viruses, including a number belonging to the *Arenaviridae* and *Bunyaviridae* families.

Shortly after my arrival, I had the good fortune to get involved in a collaborative effort to evaluate the broad-spectrum potential of a novel and promising anti-influenza virus agent. The developmental name of the compound was T-705, and Don Smee, Bob Sidwell and Dale Barnard were leading efforts to evaluate the compound against multiple strains of influenza virus, including H5N1.

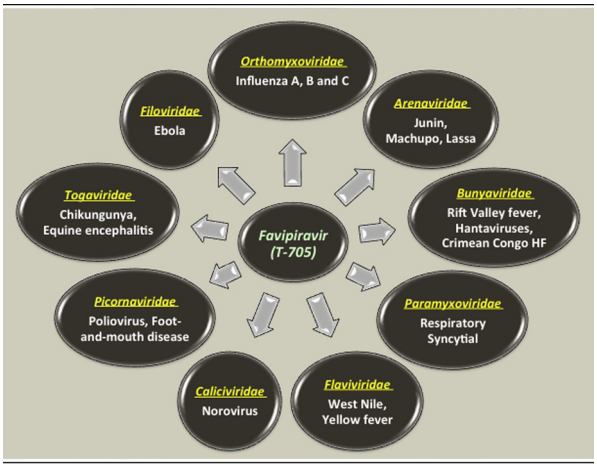
Little did I know that this small-molecule pyrazine derivative would turn out to be one of the most exciting developments in the field of antiviral research, with potential for broad applications across multiple virus families. In 2002, Yousuke Furuta and coworkers from the Toyama Chemical Co. (Toyama, Japan) had published an initial report of the potent anti-influenza activity of a novel pyrazine derivative, T-705 (Furuta et al., 2002). Several years later, basic mechanistic studies demonstrated the direct inhibitory activity of the compound against the influenza viral RNA-dependent RNA polymerase (RdRP) (Furuta et al., 2005). The antiviral activity could be reversed by the addition of purines and purine nucleosides.

Importantly, the effect was not due to inhibition of inosine monophosphate dehydrogenase (IMPDH) and consequent reduction in GTP pools, which are associated with the cellular toxicity of nucleoside analogs such as ribavirin. Once inside the cell, favipiravir is metabolized by host cellular enzymes to the active favipiravir ribofuranosyl triphosphate (T-705-RTP), the species with influenza RdRP-inhibitory activity.

Additional insights into the mechanism of action have been reported over the past few years. Baranovich and coworkers documented increased influenza virus mutation frequency in MDCK cells, leading to virus extinction through lethal mutagenesis (Baranovich et al., 2013). In work first presented at the 26th ICAR in San Francisco, Jin and colleagues found that T-705-RTP could be used as a substrate by the influenza virus polymerase in the elongation mode, and that the resulting ambiguous base-pairing due to misincorporation is consistent with the finding of lethal mutagenesis (Jin et al., 2013).

More recently, Arias et al. found that mouse norovirus RNA isolated from favipiravir-treated mice showed reduced infectivity and increased mutation frequency (Arias et al., 2014). On the other hand, in work out of Furuta's lab, analysis of influenza polymerase primer extension products showed that T-705-RTP is incorporated into nascent RNA and prevents further incorporation events (Sangawa et al., 2013). Efforts to select for drug resistance have met with little success, and only 4-9.5-fold resistance has been reported with chikungunya virus (Delang et al., 2014), suggesting that T-705 has a high genetic barrier against resistance.

Though there is still much to be learned about its mechanism of action, favipiravir has progressed through clinical development. It was approved in Japan as an anti-influenza medication in March of 2014 and is presently in Phase 3 clinical trials in the USA for the same indication. In addition to its potent anti-influenza activity, my colleagues and I at USU and researchers at other institutions have found favipiravir to be broadly active against multiple RNA viruses from the *Arenaviridae*, *Bunyaviridae*, *Caliciviridae*, *Filoviridae*, *Flaviviridae*, *Orthomyxoviridae*, *Paramyxoviridae*, *Picornaviridae* and *Togavirdae* families (Figure 2) (Furuta et al., 2013).




*The expanding spectrum of antiviral activity of favipiravir.*

A number of recent pre-clinical efficacy studies in rodent models of viral hemorrhagic fever (HF) support the continued development of favipiravir as a potential treatment for Argentine HF, Rift Valley fever, Crimean-Congo HF and Ebola HF (Furuta et al., 2013; Scharton et al., 2014; Caroline et al., 2014; Oestereich et al., 2014a; Smither et al., 2014; and Oestereich, 2014b). The efficacy of favipiravir against Ebola virus has also been evaluated in nonhuman primates, but the results have yet to be published.

Favipiravir is one of two investigational new drugs being considered during the current Ebola epidemic that has ravaged several countries in western Africa. This past December, in an effort led by the French Medical Research Institute INSERM in partnership with Médecins Sans Frontières (MSF), clinical evaluation of favipiravir was initiated in Guéckédou, Guinea.

Preliminary study findings released by MSF are encouraging and indicate that mortality was reduced by 50% in favipiravir-treated patients that presented with moderate to low viral burden without severe visceral disease. In cases where the visceral disease was more advanced and high levels of viral RNA were detected by PCR, no benefit resulted from therapeutic intervention (more details are provided in the article by A. Vere Hodge). The interim results underscore the importance of early diagnosis and treatment and sup-

ports the continuation of the clinical evaluation of favipiravir during the current and future Ebola outbreaks. The expected approval of favipiravir in the USA as an influenza drug and further evidence demonstrating efficacy as an Ebola medicine will likely pave the way to additional indications against other severe RNA viral infections.

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## A personal view: An update on the Ebola epidemic

**Anthony Vere Hodge, Reigate, UK**

### *Introduction*

During the preparation of my summary on the Ebola epidemic (ISAR News no. 24.2) in October 2014, the Ebola outbreak was a major topic in the news. In the UK, the TV news reports showed Ebola care centers in West Africa overwhelmed by the numbers of ill people coming to the centers, many only to be turned away. The international community was becoming aware that more help was needed urgently, not just in providing and staffing new care centers but also to evaluate potential vaccines and drugs.

In my summary, my aim was to provide ISAR members with an account of the difficulties in delivering these potential therapies and the progress which may be expected in the next 3 months (to this issue of ISAR News). I concluded with my opinion that only the GSK vaccine and favipiravir were being produced with an urgency and on a sufficiently large scale to have a marked effect on this outbreak. Necessarily, as actual data and information are scarce, I was expressing my own personal opinions and I shall be doing the same in this update.

### *Current situation*

During the past 3 or 4 months, huge progress has been made. Containment has brought down the number of new cases per week. A clinical trial with favipiravir was started in December 2014. The first supplies of the GSK Ebola vaccine arrived in Africa late January 2015 and a trial started early February.

During the last few months of 2014, the three most affected countries, Guinea, Sierra Leone and Liberia, had two aims: (1) to isolate 70% of patients with Ebola infection and (2) to ensure that 70% of people, who had died from Ebola infection, would have a dignified and safe burial. By the end of 2014, the weekly numbers of new cases were falling markedly (WHO situation reports). Whereas the weekly total of new cases was about 700 in November 2014, for the week ending 25th January 2015, the total was just 99 cases, the first time it had been under 100 since 29th June 2014.

In the next two weeks, the totals were 124 and 144 respectively. This could be a warning of failure but it may also be, at least partly, due to better tracing and monitoring of contacts. In each of these three weeks, the news from Liberia has been particularly encouraging, with less than 10 new cases/week. WHO reports that the Ebola epidemic has moved into a new phase. The focus has shifted from slowing virus transmission to ending the epidemic by finding and monitoring all contacts.

### *GSK Vaccine*

Prior to the current Ebola epidemic, the original plan was to develop a bivalent chimpanzee adenovirus 3 (ChAd3)-vectored vaccine, including the Zaire and Sudan strains of Ebola virus, primarily for biodefense.

The results of the first Phase I/II trial of this bivalent vaccine was reported on 26th November 2014. Two doses were evaluated, each in 10 volunteers. There was a dose-dependent response with the higher dose giving the better immune response. Unfortunately, the higher dose was also associated with minor adverse events in 7 of the 10 subjects. Although there were such few subjects in this trial, the result was somewhat disappointing. However, this is not the vaccine which is being progressed with the urgency needed to potentially impact the current Ebola epidemic.

In collaboration with the World Health Organization (WHO), it was agreed to progress a monovalent ChAd3 vaccine encoding the surface glycoprotein of the Zaire strain of Ebola virus, the strain of the current outbreak. Ease of manufacture was a key factor in this decision. In August 2014, it was agreed that the ChAd3 vaccine be evaluated in Phase I/II trials at three clinical sites (Oxford, United Kingdom, Lausanne, Switzerland and Bamako, Mali). The aim was to immunize and evaluate 240 participants, by late November, 2014. In anticipation of success, GSK started the manufacture of vaccine so that worthwhile quantities could be available to immunise at least all health care workers early in 2015. The results of the first Phase I/II trial of this monovalent ChAd3 vaccine, carried out at Oxford University, UK, was reported on 28th January 2015 (Rampling et al., 2015).

This monovalent ChAd3 vaccine was administered to 60 healthy adults at one of three doses ($1 \times 10^{10}$, $2.5 \times 10^{10}$, and $5 \times 10^{10}$ viral particles). Over the next 4 weeks, safety, antibody levels and T-cell responses were assessed. One volunteer withdrew for personal reasons – this individual suffered no side effects. The other 59 volunteers completed the trial. There were a few minor adverse events but this vaccine was considered to be well tolerated. In both groups, the antibody levels increased from day 14 to day 28, being marginally higher in the high-dose group. In this high-dose group, the range was 58 to 4051 (geometric mean titer of 469). For comparison, the bivalent ChAd3 vaccine ($2 \times 10^{10}$ viral particles) in macaques induced slightly higher antibody titers (range 967 to 6600) which gave effective protection. The T-cell responses were higher at day 14 than at day 28 in all three groups. The levels were more consistent and slightly higher in the high dose group than the other two groups.

The good safety data from this trial enabled the start of trials in Lausanne and Bamako, in early October 2014. As of mid-December 2014, about 250 volunteers had received the ChAd3 vaccine with no reports of serious vaccine-related adverse events. These encouraging data have led to sending the first batch of vaccine (300 doses) to Liberia in January 2015 (GSK statement, 28th January). Vaccine supply needs for Sierra Leone and Guinea are being evaluated. It is intended to start giving the vaccine to health care workers. I understand that a trial was started 2nd February 2015 (Daily Mail, 6th February 2015, 'Encouraging' Ebola drug results in Guinea).

***Favipiravir***

Because favipiravir is somewhat less active against Ebola than influenza, a higher dosage is being used for the Ebola trial than for influenza trials. As it will be important to limit virus replication as quickly as possible, a loading dose would be used: the first day (day 0), at h0: 2400 mg; h8: 2400 mg; h16: 1200 mg. day 1 to day 9: 1200 mg twice daily (www.clinicaltrials.gov Efficacy of Favipiravir Against Ebola [JIKI] ClinicalTrials.gov Identifier: NCT02329054). For comparison, the dosing schedule in the Phase III influenza trials is 1800 mg twice a day on day 1, then 800 mg twice a day on day 2–5. In the Ebola trial, there would be three groups, all similar from the patients' point of view but separate for trial analysis. Patients would be assigned to Group A1 (adult with $\leqslant$72 h, since symptom onset), Group A2 (adult but symptom duration >72 h.) or Group C (children, dosage adjusted for weight). There would be no placebo control group. The primary endpoint would be mortality at day 14. Secondary endpoints would include plasma virus loads and appearance of virus resistance. There would be three centers: MSF Ebola treatment center, Guéckédou, Guinea, French Red Cross Ebola care center, Macenta, Guinea and ALIMA Ebola care center, N'zérékoré, Guinea. It was intended to recruit 225 patients. An independent panel would monitor the trial for safety and efficacy.

Trevi Fountain

By the end of December 2014, recruiting had begun at Guéckédou and ALIMA. Early in February 2015, the monitoring panel examined the results of 69 patients (older than 14). They discovered a statistically significant increase in survival rates in those with low to moderate levels of virus in their blood compared to those of patients previously treated at Guéckédou and ALIMA centers. The panel recommended that these encouraging results be made public.

The preliminary data from the JIKI trial was presented on 25th February at the Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, WA, USA (Daouda Sissoko 2015). From 17th December 2014 to 20th January 2015, 80 patients received favipiravir, 69 adults/adolescents and 11 children. I am not aware of any available data on the outcome in the children. The median duration of illness prior to treatment was 5 days. The virus levels were assessed by Ebola virus RT-PCR (based on cycle threshold [CT]). Mortality in the trial was compared to that in the three month period preceding the trial in the same centers. There were two main conclusions:

(1) In patients presenting with high virus load and who already had serious visceral involvement, favipiravir treatment did not improve their outcome. There were 29 patients (42%) with baseline CT (BCT) $<20$; of these, 23 (79%) had baseline creatinine levels $\geqslant 110$ ÂμM/L. Most of these patients had severe kidney failure and died.

(2) Patients with moderate or low virus load (BCT $\geqslant$ 20) appeared to have reduced mortality (15% vs. 30%, $p = 0.05$). Although this p value is normally accepted as significant, one should be cautious as the comparator group is historical controls. Favipiravir was well tolerated. Viral RNA levels and pharmacokinetic data were obtained. Although details of these data will be available at a later date, a graph was presented showing the CT values at baseline (D0) and at D2 and D4. Most of the survivors had markedly decreasing virus loads from D0 to D2 and D4, with many of the D4 CT values being $\geqslant 35$. In contrast, there appeared to be little change in virus loads in those who did not survive. To my mind, the graph adds persuasive evidence that favipiravir treatment is beneficial to patients presenting early.

In the historical control group, abnormal baseline creatinine values and high virus load seemed to be a good predictor of mortality which was 100% for patients with BCT $<20$ but only 7% with BCT $\geqslant 20$.

I agree with the comment ''Should the trial show a significant reduction in mortality, it could encourage people to come sooner to treatment centers, hence creating a virtuous cycle: the earlier patients come, the more chance they have to survive, the less they expose others to the virus. Favipiravir could be a key factor in stopping Ebola transmission.'' (Daily Mail, 6th February, 2015 'Encouraging' Ebola drug results in Guinea) That is particularly true as the efficacy of favipiravir decreases as the start of treatment is delayed.

How may the efficacy of favipiravir be improved? When considering what the dosing schedule should be for the Ebola trial (Mentré et al., 2015), the plasma half-life of favipiravir was taken into account. However, as Brian Gowen discussed above, the active form of favipiravir is the triphosphate (favipiravir-RTP). It is the half-life of favipiravir-RTP, in the absence of circulating favipiravir, that is an important parameter when estimating the dosing frequency. Also, if favipiravir-RTP half-life is much longer that the dosing interval, that would give a biochemical rationale for using a loading dose. In Madin-Darby canine kidney (MDCK) cells, the half-life of favipiravir-RTP was about 5 to 6 hrs (Smee et al., 2009).

This paper also mentions unpublished information that in A549 Human cell line the half-life of favipiravir-RTP is about 2 hours. I am not aware of any data in primary human cells. If the half-life in patients is only 2 hours (much shorter than the 8-hourly dosing interval on the first day of treatment for Ebola), that would not provide a biochemical rationale for a loading dose. Instead, a loading dose may have been chosen to reduce viral replication quickly. If there are no safely issues, should the high dose be continued as long as the patient is free from severe symptoms?

Also, I note that, in the trial protocol, one of the non inclusion-criteria are patients with an inability to take the drug orally (e.g. due to encephalopathy or severe vomiting). In my previous summary, I reported on Brian Gowen's research work in animal models and the conclusions that favipiravir absorption was impaired in animals with severe symptoms. ''In reality, patients suffering from Ebola hemorrhagic fever would not likely be able to keep down oral medications, and therefore intravenous, intramuscular or subcutaneous delivery formulations would be the most relevant to treating such patients.'' Rather than terminating therapy when a patient becomes seriously ill, I would suggest that the dose should be high (say 2400 mg three times daily) but switch delivery from oral to intravenous. That would seem to be a practical, pragmatic option in the short term but it would be interesting to know how changes in favipiravir absorption translate into changing the formation and stability of favipiravir-RTP. While there are still, unfortunately, patients seriously ill with Ebola infection, it seems important to use this opportunity to investigate how favipiravir use can be modified to help this group of patients.

***Improving outlook?***

Although this Ebola epidemic is far from over, it is ebbing and hopefully will continue to do so. If so, the window of opportunity for testing therapies, vaccines and drugs, is closing. A clinical trial with brincidofovir was started but terminated due to lack of available patients. Personally (see my previous summary), I think

it is unethical to have a standard-of-care placebo group and so it does not surprise me that the doctors at the care centers resisted calls for placebo-controlled trials. This debate has caused delays which is likely to mean that possible new therapies will not now be tested. It would have been better to have some data rather than none – sometimes ''better not to shoot for the moon''.

To date (February 2015), the human cost has been great, with a case fatality rate around 54% to 62% with little change over time. One hopes that favipiravir will continue to decrease the mortality rate. Especially, I admire the health care workers who put their lives at risk; so far, 816 of them have had confirmed Ebola infections and 488 have died. Perhaps the GSK vaccine will help prevent any more health workers dying. Our next ISAR News is due at the time of ICAR in Rome (May 11–15, 2015) – let us hope for continued good news.

Daouda Sissoko, et al., 2015. Favipiravir in patients with Ebola virus disease: early results of the JIKI trial in Guinea. *Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, WA, USA.* Abstract Number: 103-ALB

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## *ISAR MEMBER PROFILE*

**David I. Bernstein**

### Cincinnati Children's Hospital Medical Center

David Bernstein has been at the forefront of human vaccine development and evaluation for over thirty years. Little did he know as a young boy growing up near Yankee Stadium in New York City that one day, his research would save the lives of children worldwide from rotavirus infection, a virus which caused approximately 500,000 infant deaths each year.

David began his career in infectious diseases at SUNY-Buffalo where he received a MA degree in microbiology and his MD degree in 1977. His pediatric training was undertaken at the University of Southern California and the New England Medical Center in Boston, Massachusetts. He then moved back to California where he completed an Infectious Diseases fellowship at UCLA. It was there that he became interested in herpesviruses and vaccines. At UCLA, he investigated the immune response to herpes simplex virus (HSV) and developed a western blot which allowed for the first time the ability to differentiate between HSV-1 and HSV-2 antibodies.

In 1980, he moved to Cincinnati and joined the faculty at Cincinnati Children's Hospital and the JN Gamble Institute of Medical Research, where he continued his evaluations of the immunobiology of genital herpes infections. He also began studies on a second virus, rotavirus, and along with his colleague, Richard Ward, he began investigating the protective immune responses to rotavirus. This work led to the development of a live attenuated human rotavirus vaccine which became the GlaxoSmithkline rotavirus vaccine, Rotarix, currently available in over 135 countries.

David has actively participated in ICAR for over 17 years, with numerous presentations of his antiviral and vaccine studies. He was elected to the Board of Directors for ISAR and has served on the Editorial Boards for *Antiviral Research* and *Antimicrobial Agents and Chemotherapy*. He has published over 250 articles and book chapters on infectious diseases, vaccines and antivirals, and has served on over 20 national committees for vaccine development and design. In Cincinnati, David served as the Director of the Division of Infectious Diseases and the Albert Sabin Professor of Pediatrics at Cincinnati Children's Hospital from 2000–2010. Since 2002, he has served as the Director of the Gamble Program for Clinical Studies.

Since 2001 and currently, David directs one of seven NIH funded Vaccine and Treatment Evaluation Units (VTEU) in the United States which evaluates efficacy of vaccines in human trials. He has conducted or participated in vaccine studies for rotavirus, influenza, HPV, CMV, HSV, and Norovirus. He has also led the NIH funded Cincinnati contract to study anti-herpesvirus therapeutics since 2000 and has evaluated both antivirals and vaccines in HSV and CMV animal models.

Over the years, David has actively mentored young physician-scientists and junior faculty who are interested in clinical trials and infection studies. In recognition of his major contributions to the field of infectious diseases and vaccine development, David was recently the recipient of the prestigious Stanley Plotkin Lectureship in Vaccinology Award from the Pediatric Infectious Diseases Society.

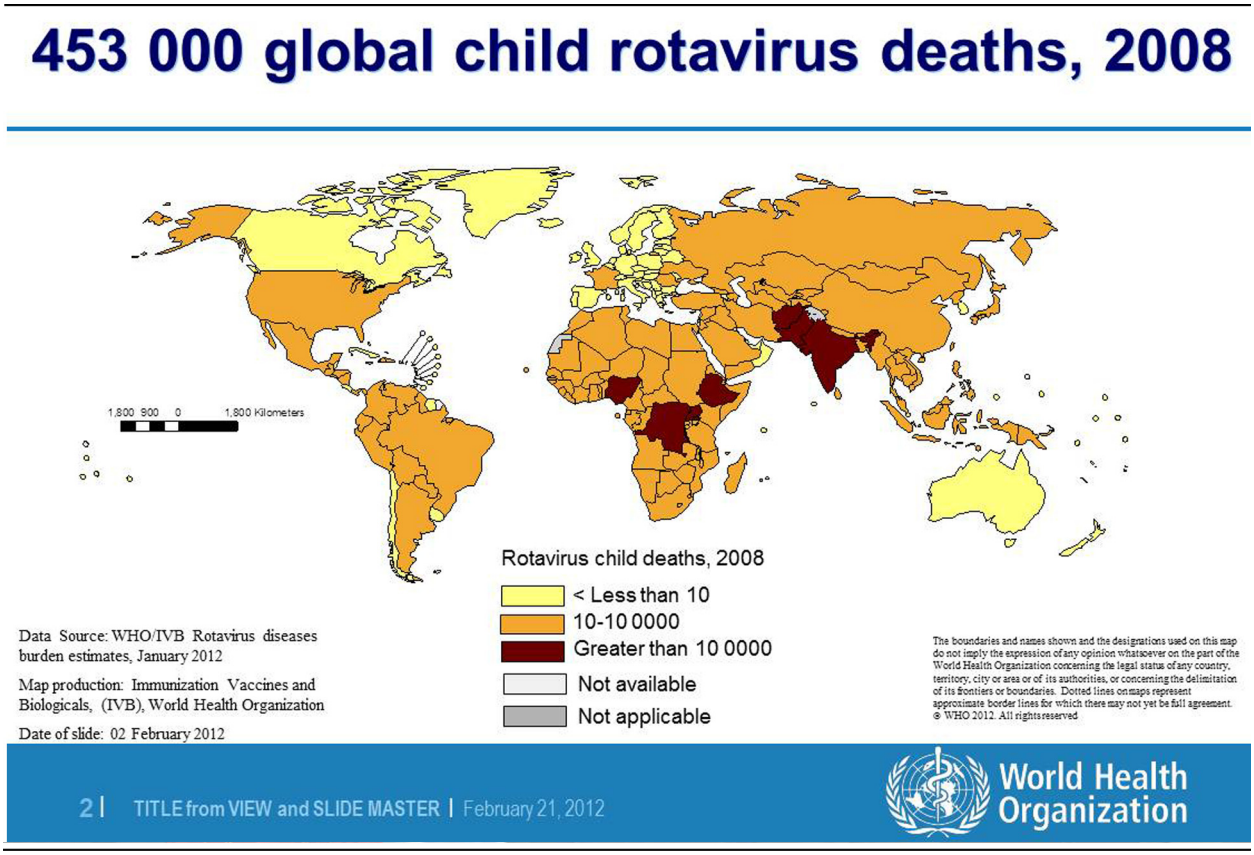
Here, in an interview with Rhonda Cardin, David reviews his early studies of rotaviruses and the history of vaccine development, and discusses what still needs to be accomplished to save even more infants from severe rotavirus infections.

***How did you become interested in rotavirus?***

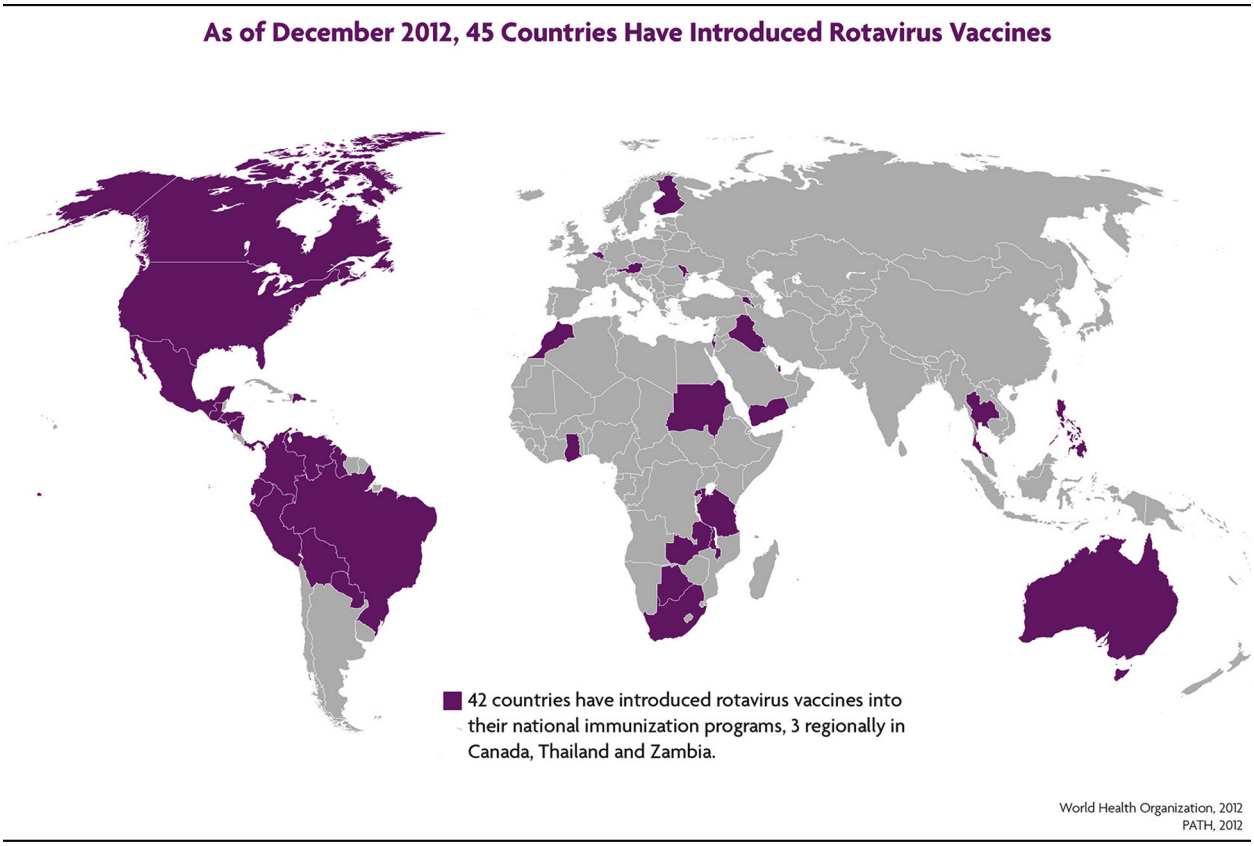
There are few biological agents that have a greater impact on childhood morbidity and mortality than rotaviruses. Infection with rotavirus often results in more severe illness than other pathogens. As such, before the use of vaccines, rotavirus accounted for a higher percentage of gastroenteritis episodes requiring medical intervention. Nearly every child in the world experiences at least one rotavirus infection by three years of age. During peak rotavirus seasons, approximately 70% of all gastrointestinal hospitalizations in the United States were due to rotavirus-associated gastroenteritis, with rotavirus illness resulting in 60,000 hospitalizations and 20–70 deaths annually (Glass et al., 1996).

Globally, rotavirus disease has an even more dramatic impact on infant health (see Figure 1). Although rates of rotavirus illness among children are similar throughout the world, the resulting mortality differs substantially. Prior to a vaccine, it was estimated worldwide that rotavirus illness was responsible for approximately 500,000 deaths annually, representing 5% of all deaths in children younger than 5 years old (Tate et al., 2008). Greater than 90% of these deaths occurred in Africa and Asia, and still remains at this high level. Over 100,000 deaths occur annually in India and sub-Saharan Africa and 35,000 deaths occur in China.

In the early 1980's, knowledge about rotavirus infection was limited, therefore, we developed better methods to culture the virus and began studies to evaluate the immune response to rotavirus. This put us in an ideal position to perform early studies of rotavirus, including human challenge studies, studies of natural history of rotavirus infections, and vaccine evaluations.




Global deaths of children from rotavirus disease, 2008.




Countries which now include rotavirus vaccines in their national immunization programs.

***Can you briefly describe the history of rotavirus vaccine?***

The history of human rotavirus vaccines began within a few years after the discovery of human rotaviruses in 1973. Although killed vaccines had been developed because natural rotavirus infections can induce excellent protection, vaccine efforts have been directed mostly at the development of orally delivered live attenuated rotavirus vaccines. The success of oral polio vaccines and the advantages of inducing mucosal protection also favored live attenuated vaccines. Early efforts concentrated on the use of animal rotavirus strains, labeled the Jennerian approach, because it relies on the natural attenuation of animal viruses in humans for safety and largely heterotypic immune responses for protection.

The initial vaccines were developed from rhesus monkey and bovine rotavirus strains because it was believed they would be naturally attenuated for humans. After multiple trials with animal strains, some of them conducted by our group in Cincinnati, it was determined that consistent protection required these strains to be modified to contain human rotavirus genes. Therefore, the next vaccines developed were reassortant vaccines between animal and human strains. These vaccines contained the genes encoding the human rotavirus VP7 or the VP7 and VP4 proteins, the two rotavirus proteins that elicit neutralizing antibody, with the remainder of the genes from an animal strain (Kapikian et al., 2001).

The first reassortant vaccine was based on rhesus rotavirus (RRV). Early trials led by me (Bernstein et al., 1995) used three reassortant viruses containing the VP7 gene of human G1, G2 and G4 rotavirus strains together with RRV(a G3 virus) were successful and became the tetravalent rhesus rotavirus vaccine marketed as Rotashield™. This vaccine was shown to be protective and safe and was approved for use in 1998. However, less than one year after its introduction into the US childhood immunization program, the CDC found evidence that Rotashield™ produced a small excess of intussusception cases in vaccinees. Intussusception is a form of intestinal blockage caused when a segment of the bowel prolapses into a more distal segment of the intestine. Rotashield™ was therefore removed from the marketplace and its use was never extended outside the United States. The pathogenic mechanism underlying the association of the Rotashield™ vaccine with intussusception is not understood.

Other investigators developed vaccines based on WC3, a bovine rotavirus strain. Initially, a monovalent vaccine containing the VP7 gene of a human G1 rotavirus and the remainder of the genes from WC3 was

developed after we obtained inconsistent results with WC3. This vaccine was reported to be effective but because of the idea that serotype-specific protection was necessary, a quadrivalent vaccine was developed containing three viruses with gene substitutions of the VP7 gene with human G1, G2 or G3, and one virus containing a VP4 gene substitution with a human P[8] gene. We and others tested this quadivalent vaccine and found it to be safe and effective. Finally, by adding a reassortant virus containing a human G4 VP7 to the above 4 viruses, a pentavalent vaccine, RotaTeq™, was developed by Merck Research Company.

A large trial of over 60,000 infants found that the vaccine was highly effective, reducing all G1–G4 rotavirus gastroenteritis by 74.0 percent, severe rotavirus gastroenteritis by 98.0 percent, and hospitalizations and emergency room visits by 94.5% (Vesikari et al., 2006). Importantly, there was no association with intussusception. RotaTeq™ was licensed in 2006 by the FDA for use in infants.

Since the pivotal trial was published, multiple trials of RotaTeq™ have been conducted around the world (reviewed in Chandran and Santosham, 2008). It is now one of the two major rotavirus vaccines being administered to infants in the world today (see Figure 2). However, as appears to be true of all rotavirus vaccines, it appears to be less effective in less developed areas of the world. In the poorest settings, such as Africa and Asia, efficacy has only been 40–50%. In general, this correlates with the lower immune response in these settings.

Attenuation of human rotavirus strains was another avenue of vaccine development pursued by us and others. The use of human strains for vaccine candidates is based partly on data from our group showing that natural infection can provide protection against subsequent infection or disease. The human strains considered as vaccine candidates are either naturally attenuated, as thought to be the case with neonatal strains, or attenuated by culture adaptation and multiple passage, the strategy used by us. These vaccines are each composed of one strain and therefore, rely on homotypic and heterotypic mechanisms of protection.

Rotarix™, the other US approved vaccine, is based on the attenuated human strain, 89-12, which we isolated from an infant with rotavirus gastroenteritis in Cincinnati, Ohio (reviewed in Ward and Bernstein, 2009). It is a G1P[8] strain, representing the most common strain worldwide. We were able to attenuate the 89-12 isolate by multiple passages in tissue culture. Results of our multi-center efficacy trial showed that two doses of this vaccine provided 89% protection against any rotavirus disease and 100% protection from severe disease. The 89-12 strain was further purified by limiting dilution and passage in tissue culture by GlaxoSmithKline. The final product was called RIX4414 and is now marketed as Rotarix™ (GlaxoSmithKline), a two dose oral vaccine. Initial testing showed that the vaccine was safe and immunogenic, and that it did not interfere with other concomitantly administered childhood vaccines.

Similar to RotaTeq™, the pivotal vaccine trial with RIX4414 involved over 63,000 infants in Latin America and Finland (Ruiz-Ralacios et al., 2006). The vaccine was safe, and importantly, was not associated with intussusception. Efficacy data from a subset of 20,000 infants from this trial showed 85% protection against severe rotavirus diarrhea and hospitalization. Protection against more severe gastroenteritis was 100%. It was also demonstrated that protection was high (86%) not only against severe rotavirus diarrhea caused by G1P[8] strains but also against G3P[8], G4P[8] and G9P[8] strains which all shared the VP4 P[8] genotype. Efficacy against the few G2P[4] infections (a strain that is not matched for either VP4 or VP7) was 41%. However, in an integrated analysis, efficacy against G2[P4] was 71.4% against severe disease and 81.0% against disease of any severity. More recently, a study in Mexico showed efficacy of over 90% against a fully heterotypic G9P[4] rotavirus strain.

In a trial conducted in six European countries, protection by Rotarix was 87% against any rotavirus gastroenteritis, 96% against severe disease and 100% against hospitalization due to rotavirus. In this study, efficacy against G3, G4 and G9 strains was similar to that against G1 strains and was over 95%. Efficacy against the unrelated G2 strains was 85%, again suggesting that heterotypic or non-neutralizing antibody responses are also involved in protection.

As discussed above, efficacy in less developed countries is decreased. In a study of African infants, efficacy against severe disease was 61.2% and was even lower in Malawi infants, 49.4% compared to 76.9% in South Africa. Despite this lower efficacy, it is important to understand that because of the higher mortality rates, more lives will be saved in countries like Malawi compared to those with lower mortality, despite the lower efficacy with either vaccine. The post-licensure effectiveness of Rotarix™ has been verified in several studies (reviewed in Jiang et al., 2010). Perhaps, most importantly, vaccination has been associated with reduced mortality from diarrheal associated disease in Mexico and Brazil.

In addition to live oral rotavirus vaccines, a number of non-live vaccine candidates have been developed and evaluated in animal models (reviewed in Glass et al., 2014). Non-live vaccine candidates were developed in an attempt to formulate a vaccine that would be more effective or safer than live oral vaccines. The non-live candidates studied include DNA vaccines, inactivated purified triple and double layered virus particles, recombinant virus like particles (VLPs) containing VP2 and VP6, with or without VP4 and VP7, inactivated virus, and recombinant expressed proteins including VP6 and portions of VP8 protein. To date, none of these candidates have been tested in humans.

***What has been the impact of the vaccines?***

An impressive impact of rotavirus vaccines was quickly observed (reviewed in Rha et al., 2014). Post-licensure evaluations have shown substantial decreases in rotavirus diseases wherever evaluated. In the US, the CDC reported that by 2010, annual hospital admissions due to rotavirus illness were decreased by 80% in children less than 4 years of age. The effects of herd immunity were also remarkable. Rotavirus hospitalizations decreased by 70% among children between 5–14 years of age who were too old to have received the rotavirus vaccines when they were initially introduced. Similar reductions have been observed in adults. It is now estimated that within the next few years, rotavirus vaccines could prevent 240,000 deaths each year. As an example, mortality in Mexico due to diarrhea fell from an annual median of 18.1 deaths per 100,000 children at baseline to 11.8 per 100,000 children in 2008 (a 35% reduction).

***What challenges remain?***

As discussed above, although rotavirus vaccines are extremely effective in all developed countries, they are less protective in lesser developed countries for reasons that are not well understood. Possible contributing factors include higher levels of transplacental and breast milk antibody that could inhibit vaccine virus replication, malnutrition, micronutrient deficiencies, interfering gut flora, and differences in epidemiology. Nevertheless, it is important that we develop more effective vaccine strategies, based either on altering the composition of live virus vaccines, adjusting the vaccination schedule, or implementing non-live vaccine strategies. Perhaps the largest impediment to increasing the effect of rotavirus vaccines is increasing their distribution to the areas of greatest need.

Our experience with rotavirus spans over more than 3 decades. We are proud of our accomplishments and the role we have played in developing several rotavirus vaccines that are now decreasing hospitalizations and deaths due to this ubiquitous virus.

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## *ANTIVIRALS ON THE HORIZON*

### Roseoloviruses: is it time for new antivirals?

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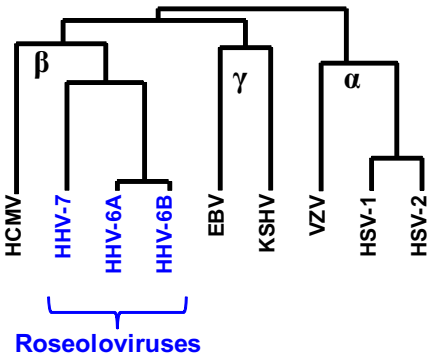
Many ISAR members are probably familiar with human cytomegalovirus but most likely know less about the other beta-herpesviruses, human herpesvirus-6 and human herpesvirus-7. A recent NIH workshop brought together clinical and scientific experts to highlight advances in our knowledge of roseolovirus pathogenesis and association with human disease, with the ultimate goal of identifying barriers and research priorities going forward. Long associated with febrile childhood illnesses, the association of roseoloviruses with severe disease complications has gained ground as more is learned about their unique biology.

In this article, I provide a brief overview and update on the roseoloviruses, leading to the question of whether they will be a future target for antiviral therapy. Readers who wish to learn more should refer to a set of articles in the December 2014 issue of *Current Opinions in Virology* based on presentations at the workshop (see list below).

First, what are the roseoloviruses? This group of viruses is comprised of human herpesvirus 6 and 7 (HHV-6 and HHV-7), representing the newest members of the beta-herpesvirus subfamily of *Herpesviridae*, and closely related to human cytomegalovirus (HCMV), which is the most characterized beta-herpesvirus. The roseoloviruses are ubiquitous, with HHV-6 infection in 97% of children by the age of 3 years old.

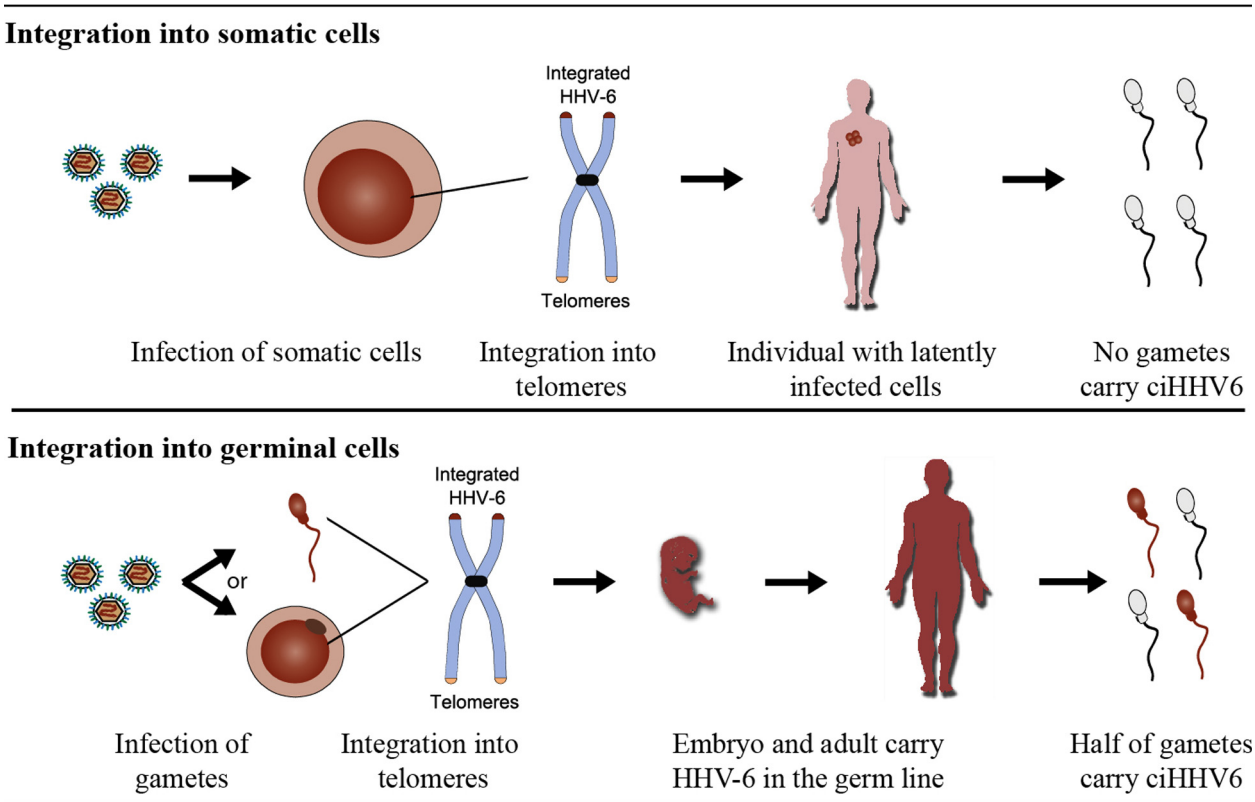
For many years, roseola infantum (*exanthema subitum*) and febrile seizures seemed to be the only diseases that were clearly associated with HHV-6 and HHV-7. It also became apparent that infection with these viruses could impact morbidity and mortality in transplant recipients as well as in AIDS patients.

Recent advances in molecular tools and technologies have shown that HHV-6 is actually comprised of two related (90% sequence identity) but distinct viruses, HHV-6A and HHV-6B, based on epidemiology, detection in human tissues, and association with human diseases. Consequently, both HHV-6 viruses and HHV-7 were recently classified as members of a subgroup within the beta-herpesvirus family, as shown in the figure, and termed "roseoloviruses" due to their association with roseola infantum.




Dendrogram of the herpesviruses. (Modified from *Current Opinion in Virology, 2014, 9:170–177;* provided by Laurie Krug and Phil Pellett.)

Since its discovery in 1986, HHV-6 has been associated with a number of diseases besides roseola. Although HHV-6 is ubiquitous, a clear association has been shown with neurological conditions including febrile seizures, encephalitis and cognitive dysfunction such as amnesia or delirium following transplantation. HHV-6 has also been linked to epilepsy and multiple sclerosis (with HHV-6 detection in MS lesions) but further studies are needed. HHV-6 also contributes to other transplant complications such as immunosuppression, delayed engraftment, acute graft versus host disease (GVHD), hepatitis, and pneumonitis, just to name a few. Recently, an association of HHV-6 with heart failure and myocarditis and neurological deficits in infants with congenital HHV-6 infection has been reported. Other conditions that have been linked with HHV-6 infection include chronic fatigue syndrome, HIV/AIDS progression, and cancer (Hodgkin's lymphoma, gliomas, and cervical cancer) but additional studies are needed to confirm these associations.




Integration of HHV-6 into chromosomes. (Provided by Ben Kaufer and Louis Flamand; *Current Opinion in Virology,* 2014, 9:111–118.)

The roseoloviruses share similarities with HCMV but also have unique features. Compared to HCMV, HHV-6 (both A and B strains) and HHV-7 have smaller genomes (159–170 kb for HHV-6 and HHV-7 vs. 235 kb for HCMV). HHV-6 and HHV-7 were first isolated from peripheral blood mononuclear cells (PBMCs) and shown to infect T cells. Similar to HCMV, the HHV-6 viruses infect astrocytes and glial cells, perhaps accounting for their association with neurological complications, as well as monocytes, dendritic cells, and epithelial cells.

The cell surface receptors for viral entry have been identified: HHV-6A binds to CD46, HHV-6B binds to CD134, and HHV-7 binds to CD4. In contrast, HCMV utilizes EGFR and Integrins as receptors, again highlighting differences in cell tropism. The HHV-6 viruses encode approximately 100 genes, however, their proposed functions are based on their similarity to HCMV genes or other herpesvirus homologs and remain to be confirmed. Interestingly, and unlike HCMV, HHV-6 and HHV-7 encode an origin binding protein (OBP), found in alpha-herpesviruses such as herpes simplex virus (HSV), which binds the origin of lytic replication (oriLyt) to initiate viral DNA replication.

Similar to other herpesviruses, HHV-6 and HHV-7 establish lifelong persistent or latent infection and can reactivate to produce infectious virus, often in settings of immunodeficiency. HCMV establishes latency in myeloid lineage cells such as $CD34^+$ hematopoietic cells and monocytes. HHV-6 also appears to establish latent infection in $CD34^+$ hematopoietic cells but further studies are needed to determine if other cell types serve as latent reservoirs.

Reactivation from latency of both HCMV and the HHV-6A and -6B viruses contribute to complications in the immunocompromised patient. During hematopoietic stem cell transplantation and solid organ transplantation, both HCMV and the roseoloviruses can reactivate and produce infectious virus. HHV-6B can be detected in 30–50% of transplant recipients following reactivation. Indeed, presence of HHV-6 in transplantation can lead to reactivation of HCMV and increased allograft rejection. Similarly, when the donor is HCMV-positive, there is increased risk for HHV-6 viremia. Co-infection of HHV-6 with HIV also increases the progression to AIDS. This is also seen during co-infection of rhesus macaques with HHV-6 and SIV, the simian homolog of HIV.

By far, the most intriguing and unique feature of the human roseoloviruses is the integration of the entire ~100 kb viral genome into telomeres on human chromosomes. HHV-6 integration, the most characterized, is referred to as chromosomally-integrated HHV-6 (ciHHV-6). Integration of viral genomes has not been detected with other human herpesviruses. Two important features of HHV-6A, HHV-6B, and HHV-7 play a role in viral integration: first, telomere sequences are found at the ends of the viral genomes that are homologous to human telomere sequences, and second, an integrase gene (U94) is encoded by the viruses and is related to the parvovirus ***Rep*** gene. U94 binds both ssDNA and dsDNA and presumably mediates both integration and excision of HHV-6A and HHV-6B.

Approximately 1% of the human population harbors integrated HHV-6A and 6B in their germline, and thus ciHHV-6 is inherited by children from parents. In individuals with ciHHV-6, viral DNA can be detected at very high levels in the blood due to the presence of integrated viral DNA in every cell. Significantly, 86% of the approximately 1% of congenitally HHV-6 infected infants harbor the ciHHV-6 form of infection. The other 14% of congenitally HHV-6 infected infants are thought to become infected by *in utero* transmission of HHV-6, similar to HCMV transmission. Further studies are needed to understand the role of integration in roseolovirus biology.

Currently, there are no antiviral drugs specifically licensed to treat roseolovirus infections. Treatment of HHV-6B, the most common roseolovirus, relies on anti-HCMV drugs such as cidofovir (CDV) or ganciclovir (GCV), which are less effective against HHV-6 compared to HCMV. Other drugs with varying degrees of activity against HHV-6 may become available; however, drugs specifically developed against HHV-6 are not expected. The most promising drug to treat HHV-6 and HCMV infections is brincidofovir (CMX001), which shows potent activity against both viruses and also has broad spectrum activity against other human DNA viruses. However, drug resistant HHV-6 viruses have been isolated.

One unique drug target for HHV-6 could be the U94 integrase gene; however, its role in HHV-6 biology has not been fully characterized. To date, there has been a lag in the development of roseolovirus animal models but recent advances should aid in the evaluation of antiviral compounds. The recent identification of primate homologs of HHV-6 and HHV-7 in pig-tail macaques is expected to provide new insights into pathogenesis. It will be extremely interesting if integrated viral genomes are found with these new animal viruses, thus shedding new insights into this aspect of roseolovirus biology. As more is learned about the role or association of roseoloviruses with human diseases and effective drugs become available, investigational clinical studies will also need to be conducted.

A case in point, a recent study in Berlin may significantly turn the tide on investigating HHV-6 infection and disease associations. In heart failure patients with persistent symptoms, HHV-6 was found in 16% of heart biopsies, with detection of HHV-6 virions, viral proteins, and viral transcripts, thus indicating actively replicating HHV-6 in myocardial tissue. Interestingly, 1.1% of these patients

harbored ciHHV-6, with ciHHV-6A as the predominant integrated virus.

Antiviral therapy with valganciclovir (ValGCV), commonly used for HHV-6 transplant complications, showed that HHV-6B-infected patients responded better than HHV-6A patients. Moreover, six ciHHV-6 heart failure patients with severe persistent symptoms treated for six months significantly improved, with decreased or no detectable symptoms of both heart failure and HHV-6 viral replication. This study also confirms that infectious virus can be produced from the integrated HHV-6 genome. Further studies such as this will be important for establishing the role of the roseoloviruses in various disease associations.

In summary, recent advances in the roseolovirus field have rapidly established these beta-herpesviruses as significant human pathogens. As the impact of the roseoloviruses on human health becomes clearer, it may become critical for the antiviral community to see the need for specific therapeutic interventions against HHV-6A, HHV-6B, and HHV-7. To learn more, readers are encouraged to visit the HHV-6 Foundation website (http://www.hhv-6foundation.org).

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## *CALENDAR OF FUTURE CONFERENCES*

Simon Tucker has prepared a calendar of future conferences on antiviral therapy, medicinal chemistry and other topics of interest. ISAR members can access the calendar by logging in to the society website (http://www.isar-icar.com).

## *A NEW EUROPEAN NETWORK*

A new European Network on Antiviral Research is now looking for 15 talented early-stage researchers who have the potential to become leaders in antiviral drug discovery. Check the ISAR Career page for more information (http://www.isar-icar.com/?page=Careers).

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*ISAR News* is an official publication of the International Society for Antiviral Research. It is published four times a year as a free article in *Antiviral Research* (http://www.journals.elsevier.com/antiviral-research) and is posted on the ISAR website (http://www. isaricar.com).

*ISAR News* is prepared by the ISAR Publications Committee: Anthony Vere Hodge (chair), Masanori Baba, Andrea Brancale, Mike Bray, Rhonda Cardin, José Esté, Joy Feng, Brian Gowen, Justin Julander, Aruna Sampath, Luis Schang, Ashoke Sharon, Bart Tarbet and Simon Tucker.