



ISAR News

Newsletter of the International Society for Antiviral Research

**29th ICAR, 17-21 April 2016
at La Jolla, CA, USA**

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ISAR PRESIDENT'S MESSAGE

As I enter the last six months of my presidency, I'm amazed how fast time has moved. Soon we'll convene in La Jolla for the 29th ICAR, and I'll hand over the reins to José Esté as our next President. We'll also know the results of the election for President-Elect, for which we have two excellent candidates in Rhonda Cardin and Johan Neyts. After many years of participation and service to ISAR, it's great to know that we continue to attract such high quality people, who will lead our Society forward.

The program for the 29th ICAR is coming together nicely under the leadership of Mark Prichard, and we're just entering the abstract submission phase, using our new electronic submission system. I hope that everyone will find the site easy to use, and I look forward to your feedback. The best part of the new submission website is that we can modify many of its features, to provide a much better experience for both abstract submitters and reviewers.

As this issue of ISAR News goes to press, I hope that everyone will have taken a moment to vote for our new officers and board members. For many years, voting has unfortunately remained fairly constant at around 20% of our membership. This year Phil Furman and the Nominations Committee have solicited an excellent slate of candidates, who have all been heavily involved with ISAR and represent the future of our Society. I hope that we'll double the turn-out this year, especially since voting is now easy, using the system set up by our webmaster Andrea Branchale.

The past year has also seen some new

developments in ISAR that I hope will produce lasting benefits. First, Raj Kalkeri has formed an initial team of ISAR Ambassadors around the world, who are now hard at work soliciting new sponsors and members. The Ambassador Program utilizes the ISAR website, Facebook and other social media to spread the word about the society and our annual meeting. If you would like to get more involved in ISAR, I strongly recommend that you join our Ambassador Program and help bring more people to the meeting in California. We all know scientists from our local geographic areas and countries who would benefit from attending ICAR, and it will greatly benefit from their new ideas and vision.

In another important development, the Women in Science Committee is now soliciting applications for the second WIS scholarship program - now proudly known as the Chu Family Foundation Women in Science Scholarships. Thanks to generous funding from the Chu family, up to five scholarships will be awarded for 2016. Applications are due by December 31st, so please encourage women students and postdocs to submit their applications.

Unfortunately, one of my goals as President that has not yet materialized is my desire to use the WIS program as a model for developing ways to ensure that all young scientists are able to attend ICAR and contribute to the Society. During my last six months in office, I would like to develop a committee of young researchers that would meet at ICAR and have regular conference calls between meetings, to discuss how the Society could promote more participation from graduate students, postdocs and other young investigators.

Over the years, we've had special sessions at ICAR featuring talks by our young members, such as the Shotgun Poster presentations and a fantastic EUVIRNA session at Raleigh. We've also held Young Investigator receptions during the meeting (always one of my favorites!). I hope that many young scientists from around the world will want to get involved in the Society through membership on this new committee, and will work with me to promote participation in ICAR. If you're interested, please email me, so that we can get started!

I hope everyone will enjoy this information-packed issue of ISAR News, and appreciates the efforts of our Publications Committee to expand it to four issues per year. It takes plenty of work to pull these issues together in a timely fashion, and I know that the guest editors spend a lot of time sending out reminders for submission of articles. I also hope that our newsletter will begin to feature more news items

submitted directly by our membership. Please let us know what's going on with you and your research, such as new grants, publications, and products.

To summarize: *Submit abstracts, apply for Chu Family scholarships and volunteer for the Ambassador or Young Investigator programs!* I look forward to seeing everyone in La Jolla in April.

Bob Buckheit, ISAR President

UPDATE ON THE 29TH ICAR

The 29th International Conference on Antiviral Research will be held at the Hilton La Jolla Torrey Pines Hotel in La Jolla, California from Sunday, April 17th through Thursday, April 21st, 2016. This venue will take advantage of the vibrant research community in the San Diego area. While the meeting will focus on the latest scientific developments in antiviral research, it will also emphasize the interdisciplinary nature of the field and will foster collaborations by providing dedicated time for networking with colleagues.

ICAR is designed to provide opportunities for virologists, chemists, pharmacologists and clinicians to establish and maintain the close collaborative relationships that are needed for the discovery and development of effective antiviral therapies. It also serves to stimulate innovative thinking on the drug development process, and provides specific events to welcome new scientists to our ranks to help them to establish successful careers. The breadth of viruses discussed and topics covered provide a rich environment to learn how scientists in different fields approach problems common to the development of all antiviral therapies.

The conference will begin with a session on *Drug Discovery and Development 101* at 2 PM on Sunday, April 17th. Rich Whitley, a past President of ISAR, will introduce the new "Antiviral Drug Discovery and Development Center" funded by NIAID/NIH. This consortium illustrates how the cooperation of US academic institutions with a not-for-profit research organization and a commercial partner can lead to the rapid development of therapies for emerging infections. This interactive session will feature presentations by Maaïke Everts, Mark Denison, Bob Bostwick and Rob Jordan.

The 29th ICAR will begin at 4 PM on April 17th, with presentations by two keynote speakers:

- ◆ Heinz Feldmann, M.D., Ph.D. (NIAID/NIH) will speak on "Ebola virus: past, present, future", reviewing research from the original discovery of the filoviruses in Marburg, Germany through the present

West African epidemic. He will also provide a look ahead: what research is needed, where do we go from here?

♦ Richard H. Scheuermann, Ph.D. (J. Craig Venter Institute) will speak on: “Decoding Viral Genomics in the Next Generation Era”. The availability of whole-genome sequence data, combined with standard representations of virus phenotypic characteristics from large numbers of viral isolates is allowing for extensive genotype-phenotype association studies that go well beyond traditional phylogenetic lineage tracing. His lecture will demonstrate the use of statistical genomics analysis to predict influenza virus evolution in the face of adaptive immunity and to identify novel genetic determinants of disease severity in enterovirus D68.

The first of two symposia will take place on the morning of Monday, April 18th and will highlight recent developments in the use of structural biology to discover and develop antiviral drugs. The session is being organized by a trio of Prusoff Young Investigator Award winners: Andrea Brancale, Bruno Canard, and Erica Ollman Saphire.

The second symposium, focusing on DNA viruses, is being organized by Rhonda Cardin and Graciela Andrei and will be held on the morning of Wednesday, April 20th. It will feature recent advances in therapies and will include presentations by Thomas Lion on adenovirus infections, Margaret A. Stanley on papillomavirus, David Bernstein on herpesvirus vaccines, and Timothy Kowalik on the evolution of human cytomegalovirus.

Each year ICAR features a Poster Awards competition, and the tradition will continue in 2016. The committee, chaired by Kathie Seley-Radke will review the candidates for awards. In past years, the competition has been intense and the Program Committee is fortunate to have dedicated members who are willing to serve on this important subcommittee. Cash prizes of up to \$1000 will be awarded in the categories of Graduate Student, Postdoctoral Fellow and Young Investigator. Awardees will also have the opportunity to present their work in the Shotgun Presentation session.

The prominence of the poster presentations at ICAR reflects their excellent quality and offers both new and experienced investigators a high-profile venue to present their work. The ICAR program, the posters presented and many of the posters will be placed on the ISAR website, so that members can review the material before and after the meeting.

The Program Committee and the Society are committed to bringing you the most rewarding

scientific experience. In response to feedback from our membership, the Committee has worked diligently this year to make changes to the meeting format, keeping the best features of ICAR, while adding scientific sessions and events which we believe will heighten the experience for all attendees.

Following the success of the session on Women in Science at the Rome ICAR, it will be held again in 2016, and will include panel discussions to provide advice to women scientists as their careers progress. The Society will also maintain its commitment to the newest ISAR members by once again sponsoring an interactive Career Forum, in which attendees meet with established scientists and other professionals in the pharmaceutical, biotech, academic and government sectors to discuss various career options. There is no additional fee for the Career Forum, but space is limited, so attendees should indicate their interest when registering for the meeting.

On behalf of the Program Committee, I look forward to welcoming you to the San Diego area and the 29th ICAR in April 2016. *Mark Prichard*

Important dates for the 29th ICAR:

Abstract submission deadline January 15

Abstract acceptance notices sent *February 26

Travel grant application deadline January 15

Travel grant notifications sent February 12

Advance rate registration deadline March 18

Registration cancellation deadline March 18

*If you mention in your abstract application that you need a travel grant or a visa, the acceptance note will be sent on February 5th.

WOMEN IN SCIENCE

2016 Chu Family Foundation scholarships: Application deadline is December 31st

Thanks to a generous donation from the Chu family, as many as five young women with the potential to make significant contributions to the field of antiviral research will receive \$1500 scholarships in 2016. The funds may be used to attend a conference, visit a laboratory, take a course or acquire specialized training. In general, the career development activity should not be one for which the applicant's advisor is already funded. The awards will also include a 2-year membership in ISAR and a commemorative certificate.

To be eligible, an applicant must be working in an area of antiviral research and either be an

undergraduate or graduate student, or have no more than five years of cumulative postdoctoral experience. Graduate students and postdocs must be a member of ISAR at the time of application.

Each applicant must submit:

- A CV and a statement, not exceeding two pages, describing her academic achievements and goals, including an explanation of how the award will help her career.
- A letter of support from her research project director, department chair or center director.
- If the funds will be used to visit another scientist's laboratory, the candidate must submit a letter from the head of the lab.
- If the funds will be used to attend a meeting or take a course, the candidate must provide a description of the activity, including a link to online information.

Successful candidates will have demonstrated their ability to do independent scientific work, their potential for a high level of scientific endeavor and their leadership skills.

For more information, and to apply online for a scholarship, go to

<http://www.isar-icar.com/?page=wiscda>

Applications must be submitted by December 31st. Winners will be selected by the CFF Award Committee by March 1st, 2016, and the awards will be presented at the 29th ICAR in La Jolla.

SOCIAL NETWORKING

ISAR and social networking: an interview with Ilane Hernández Morales

Ilane (pronounced “Elaine”) studied veterinary medicine in her home country of Mexico. In her first research project, she joined a group developing a DNA

vaccine against *Salmonella* infections in chickens, and her thesis won the Award for Excellence in Veterinary Public Health from PAHO in 2009. However, when the novel swine-origin H1N1 virus emerged in Mexico that year, she switched her focus to influenza diagnostics and epidemiology. Working jointly for the Ministry of Agriculture and the FAO, Ilane and her colleagues validated new diagnostic tests and screened specimens from hundreds of pig farms. She notes, “I quickly realized that I preferred virology to bacteriology.”

In 2010, Ilane moved to The Netherlands to enter a masters program at Wageningen University in

cellular and molecular biotechnology, focusing on development of next-generation viral vaccines. When it came time for further training, her supervisor drew her attention to the European Training Network



Ilane Hernández Morales

on (+)RNA Virus Replication and Antiviral Drug Development (EUVIRNA). She applied for a Ph.D. position in the consortium, and in 2012 became a EUVIRNA fellow, conducting research on dengue virus in a project that reflects a strong interaction between academic science and the pharmaceutical industry.

Her day-to-day work is at Janssen Infection Diseases and Vaccines, part of J&J Belgium, under the supervision of Dr. Marnix Van Loock, in collaboration with Prof. Johan Neyts at the Rega Institute. She is studying the response of primary human mononuclear cells to dengue virus infection, aiming to establish a more relevant *in vitro* model for antiviral drug testing and to identify potential new antiviral targets, using genome-wide transcriptomic analysis.

What are your main research interests?

My primary interest is the study of virus-host interactions. I would like to contribute to the field of antiviral drug development by identifying new targets for prevention or treatment.

I'm also strongly committed to bringing new knowledge and research collaborations back to Mexico and to learn linking basic research to the “real world.” I hope to make a positive impact as an individual – and specifically as a woman scientist – in under-represented groups, developing societies and in science itself.

How did you become ISAR's "focal point" for social networking?

I attended the 2014 ICAR in Raleigh, where the emphasis given to connecting with young scientists impressed me. Networking was a priority, not only among experienced researchers, but more importantly with young ones. I was very motivated by all the members who invested so much time, effort and "heart" in sessions such as Women in Science and career discussion and networking.

At that time, I already knew Andrea Branchale, who was my mentor in EUVIRNA. I told him the great joy I felt meeting and learning from all the people attending ICAR, and asked how I could become part of such a great team. He suggested that I join the ISAR Communications Committee and help manage the ISAR Facebook page and Twitter media. I could only say "Yes!" It was the right moment of inspiration, not just because of the friendly environment, but also to match my long-standing wish to work in science communications.

What is your personal experience with social networking and science?

I started following virology news by listening to Vincent Racaniello's podcast, "This Week in Virology," while on the bus going from Antwerp to the J&J lab. It's been extremely valuable – like reading three scientific papers in one hour!

Also, in the EUVIRNA training program, I attended a workshop on science dissemination and society outreach through social media. I got some "tips and tricks" from professors and experienced teams on blogging, Facebook and Twitter. Together with EUVIRNA fellows, we prepared a blog about viruses and antiviral research, which was reviewed by Professor Racaniello. He gave us serious feedback that helped me to get some experience in this kind of communication.

What do you do personally as ISAR's social media coordinator?

One of my main activities is to follow science news sources such as *Science*, *Nature* and CDC for items of interest to our members, which I then post on ISAR's Facebook page or send out on Twitter. For each item, I include a link to the source and a short comment or paragraph explaining the information.

I also contact scientists to ask permission to use figures from their publications. This has been very rewarding, because they typically are willing to share, and they also get to know ISAR. It's incredible how much networking a simple image can bring. For

example, a picture that I posted from the "new attendees" reception at the Rome ICAR reached almost 500 people in less than a week -more than the total attendees!

How can ISAR members make use of our social media sites?

First, go to Facebook, Twitter or LinkedIn and sign up for an account, then look for ISAR in the network and LIKE the page (Facebook) or FOLLOW (on Twitter). Once you've signed up, then every time ISAR posts something new, you'll receive a paragraph called a "post" from Facebook or a 140-character "tweets" from Twitter, and if you're interested, you can follow the link to the complete story. The ISAR LinkedIn page is mostly managed by Andrea Branchale, for sharing information about ISAR activities.

Once you have a Facebook account, you can post information on the ISAR page by using the "Post" space. You may respond to posts using the "comment" space. Once you've signed up for Twitter, you'll see the "tweets" automatically in your notification page. You may respond to a new tweet in two ways: "re-tweet," to share it with your followers; and "reply," to post your comments.

Members can make use of these sites in many ways, such as:

- Use ISAR social media to enhance communication with ISAR members and promote Society activities;
- Network with ISAR members and with others doing antiviral research;
- Find reminders for important ISAR deadlines, such as nominations for the WIS award and ICAR abstract submission;
- Promote the Ambassador Program.
- Find photos from past ICARs, including the poster sessions and the banquet;
- Share a link to a recent publication;
- Exchange information from other webpages and sites, such as news from research groups, job openings, etc.

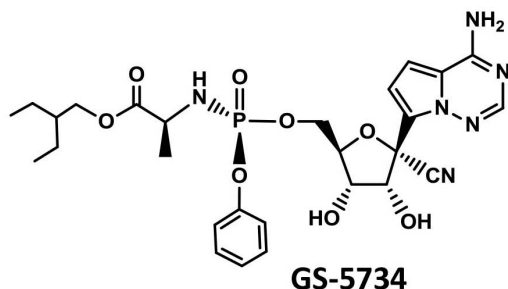
I encourage you to give it a try – there's a big benefit that you can only see once you've tried! The best thing is that social media is flexible and offers different resources for all personalities. Other agencies and communities, such as CDC, WHO, NASA, etc., have had great success using social media. If you would like more information, or have a news item that we could publicize through the ISAR social network, email me at

ilane.hernandezm@gmail.com

CURRENT RESEARCH

New Gilead compound used to treat Ebola patient in London

Those of us who follow news of the Ebola epidemic are aware of the case of the Scottish nurse who was accidentally infected in late 2014 while working as a volunteer in Sierra Leone, was treated at the Royal Free Hospital in London and discharged this past January, but was readmitted to the same hospital in early October, when her Ebola virus infection relapsed in the form of acute meningitis (see link below). This recurrent infection is an example of the increasingly recognized ability of Ebola virus to persist in anatomical sites that are relatively inaccessible to the immune system, such as the chambers of the eye, the central nervous system and the seminal vesicles. Fortunately, it's the only known example to date of a recrudescence involving the central nervous system.

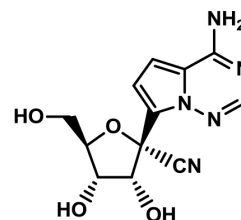


Another unusual feature of this case is the antiviral medication used to treat the nurse, a new Gilead compound, GS-5734 (above) (Gilead Sciences Press Release, Oct 21, 2015). According to ISAR member Robert Jordan, who heads the Gilead team developing antivirals against respiratory viruses, the parent compound was originally discovered as part of the hepatitis C program, targeting the HCV polymerase, but the strong clinical efficacy of sofosbuvir, especially in combination with ledipasvir, resulted in the molecule being evaluated for other indications, including respiratory viruses such as respiratory syncytial virus (RSV).

The story of how GS-5734 moved from *in vitro* testing against respiratory viruses in California to an Ebola patient in a high-security unit in London provides a good example of how a promising drug can be fast-tracked in an emergency. It began in 2013, when Robert decided to expand the testing of Gilead nucleosides and nucleotides from RSV to two other members of the paramyxovirus family, the

highly virulent Nipah and Hendra viruses, by establishing a collaboration with Michael Lo in the Viral Special Pathogens Branch at the CDC in Atlanta.

By May 2014, when the Ebola epidemic in West Africa began to spread, the CDC researchers began testing the Gilead compounds against filoviruses and identified a modified 1'-cyano-substituted adenine C-nucleoside ribose analogue GS-441524 as a novel inhibitor of the West African Ebola strain and other Ebola species (below).



As explained by Robert Jordan and Tomas Cihlar at Gilead, the 1'-cyano group provides potency and selectivity for viral polymerases, while the C-linked pyrrolo[2,1-f][1,2,4]-triazin-4-amine base is stable to deglycosylation. This seminal discovery triggered a focused collaborative program that started in August 2014 and involved CDC, the US Army Medical Research Institute of Infectious Diseases (USAMRIID) and Gilead, with the aim of identifying a suitable prodrug of GS-441524. The efforts yielded GS-5734, which has potent *in vitro* activity against multiple filoviruses, with EC₅₀ values in the 0.1-0.2 μ M range. (Warren et al, Abstract LB-2, IDWeek 2015; USAMRIID Press Release, Oct 9, 2015).

The promising *in vitro* data led to further collaboration between Gilead and USAMRIID to evaluate GS-5734 in a macaque model of lethal Ebola virus disease. A team headed by Travis Warren tested multiple different treatment doses and regimens, and obtained complete protection when they gave a daily iv dose of 10 mg/kg, beginning on day 3 postinfection. As some of the animals were already viremic when treatment began, the result was very impressive: USAMRIID Science Director Sina Bavari stated in a press release "This is the first example of a small molecule which can be easily prepared and made on a large scale, that shows substantive postexposure protection against Ebola virus in nonhuman primates."

As a consequence of the successful *in vivo* testing, Gilead filed an IND this past July for the use of GS-5734 to treat Ebola virus disease, and Phase I testing in healthy human volunteers began in August. When

the Scottish nurse was hospitalized in early October, sufficient data had been obtained to support compassionate use of the drug.

As described by Robert and Tomas, GS-5734 employs a phosphoramidate prodrug strategy that is similar to sofosbuvir and the recently approved tenofovir alafenamide. The prodrug structure enables the molecule to permeate the cell membrane and rapidly enter the cytoplasm. The ester bond is then cleaved by a cellular hydrolase, followed by chemically catalyzed release of phenol to yield the negatively charged Ala-nucleotide conjugate, which is cleaved by an amidase to release the monophosphate nucleotide. Cellular kinases then quickly produce the triphosphate molecule, which is incorporated into viral RNA, terminating its synthesis. The prodrug strategy thus avoids the slow first phosphorylation kinetics of nucleoside analogues and greatly enhances intracellular concentration of the active triphosphate metabolite.

Additional *in vitro* testing at USAMRIID and at the University of North Carolina, Chapel Hill has found that GS-5734 is also active against the MERS coronavirus. It will be interesting to see if GS-5734 will have as great an impact on the treatment of Ebola, MERS and other severe RNA viral infections as sofosbuvir has had on the therapy of chronic hepatitis C.

(Thanks to Travis Warren, Robert Jordan, Tomas Cihlar and Michael Lo for information and editing of this article.)

http://www.nytimes.com/2015/10/22/world/europe/new-clues-into-ebola-as-ill-nurse-improves.html?_r=0

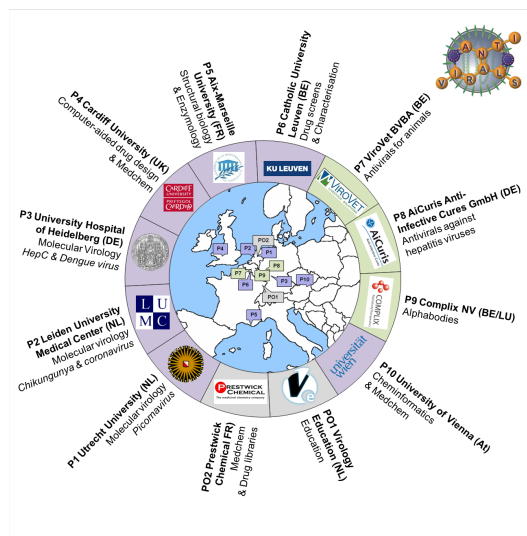
ANTIVIRALS: a new European Training Network for antiviral research

Following the success of EUVIRNA (www.euvirna.eu), whose participants received many prizes at ICAR 2014, a new training network has been funded by the European Union: ANTIVIRALS. Its mission is to prepare 15 talented young researchers for leading roles in antiviral drug discovery in European industry or academia, by providing them with a multi-disciplinary, intersectoral training program that may lead to a Ph.D. degree.



The ANTIVIRALS partnership includes seven outstanding European academic partners and four industrial partners (see map and logo above). All are leaders in their field of expertise, ensuring state-of-the-art training, and their skills are highly complementary. Three of the academic partners (Utrecht University, Leiden University Medical Center, University Hospital of Heidelberg) specialise in various aspects of molecular virology, while the other four (Cardiff University, Université d'Aix Marseille, University of Leuven, University of Vienna) focus on the identification and development of novel antiviral compounds and strategies.

The four industrial partners include a pharmaceutical R&D company specialising in antiviral drug discovery and development (AiCuris), another large company specialised in medicinal chemistry (Prestwick Chemical), a small company that pioneers an exciting novel class of biopharmaceuticals (Complix), and a small business that develops antiviral drugs for animals (ViroVet). A company specialising in training (Virology Education) will contribute its expertise to the programme.



Labs and companies in the ANTIVIRALS network

To make a serious impact, the next generation of scientists must do more than good research. The ANTIVIRALS network will therefore organise training both on relevant research topics, such as virus replication, structural biology and medicinal chemistry, and on a wide range of transferable skills, including teamwork, science communication, dissemination and societal outreach, ethics, biosafety,

innovation and entrepreneurship and intellectual property rights.

The selected group of young researchers consists of fourteen women and one man from 12 different countries. They were chosen from hundreds of applicants from all over the world, and they excel in enthusiasm, laboratory skills and their potential to become researchers with a broad view and the desire to make a societal impact. They will each work on their own projects, which aim to gain insight into antiviral drug development for a selected group of viruses.

In three years, you'll have the opportunity to meet these young interdisciplinary, intersectoral researchers at their final conference, hopefully at ISAR 2018!

For more information, go to www.antivirals-etn.eu or contact the project manager antivirals-etn@uu.nl.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement 642434.



RegaVir: Rapid evaluation of drug-resistant herpesviruses

For more than 40 years, scientists at the Rega Institute have made important contributions to the development and clinical application of antivirals against herpesviruses. That tradition continues with the creation of RegaVir, the Research Group for Antiviral Resistance. Graciela Andrei and Robert Snoeck, the program directors, would like to make sure that ISAR members are aware of what this reference center has to offer.

RegaVir provides clinicians with rapid genotyping and and/or phenotyping of clinical isolates of human cytomegalovirus, herpes simplex virus 1 and 2, varicella-zoster virus and human herpesvirus 6. The staff also provide assistance with the interpretation of results and treatment options.

Since 2009, RegaVir has performed about 1,000 herpesvirus drug-resistance tests, and is now

recognized as the Belgian reference center for drug-resistant DNA viruses. Thanks to funding from the Belgian National Cancer Plan, an interactive network of hospitals in Belgium and abroad has been established and is continuously growing. RegaVir carries out herpesvirus drug-resistant tests, assists clinicians in the choice of the adapted therapy and promotes scientific interactions in this network.

The rationale for the establishment of RegaVir lies in the increasing importance of antiviral therapy for herpesviruses, which cause significant morbidity and mortality among cancer and leukemia patients, recipients of stem cell and solid organ transplants, neonates, patients with genetic immune deficiencies and HIV+ individuals. These viruses often reactivate and cause persistent infections that require prolonged treatment, increasing the risks for selection of drug resistant mutants. It is remarkable that the antiviral-resistance of HSV has remained at a low level (<1%) for three decades in immunocompetent individuals, but they are also susceptible to herpesvirus infections in "immune-privileged" sites, such as the eye and the central nervous system; the latter is life-threatening, and requires rapid therapeutic decisions.

Except for acyclovir, its oral prodrug valacyclovir and famciclovir, current FDA-approved drugs for herpesviruses are associated with some toxicity. Ganciclovir, its oral prodrug valganciclovir, foscarnet and cidofovir may produce hematologic abnormalities (primarily neutropenia, anaemia, and thrombocytopenia). Ganciclovir has also caused long term-reproductive toxicity, and cidofovir and foscarnet are nephrotoxic. Alternative antiviral regimens are therefore preferred, to avoid cumulative toxicity and the selection of multidrug-resistant viruses.

Physicians typically recognize drug-resistant herpesviruses based on signs of infection in patients. RegaVir aims to support clinical decision-making by providing prompt characterization of the virus. Correct use of the few available drugs is necessary to avoid selection of multiple-resistant viruses. Simultaneous adjustment of antiviral and immunosuppressive therapy enhances the success of treatment, and also decreases health care costs. For more information, please go to www.regavir.org or contact us at

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Hamburg BSL-4 lab is an active player in antiviral drug testing

In March, 2014, *Antiviral Research* published two reports of the efficacy of the novel antiviral favipiravir (T-705) against Ebola virus infection in IFN receptor-knockout mice. One study, by Steve Lever's group at the DSTL at Porton Down in the UK showed that aerosol-infected mice were protected by treatment beginning an hour after virus challenge [1]. The other, from Stephan Günther's team at the Bernhard Nocht Institute of Tropical Medicine in Hamburg, found that intranasally-infected mice were protected against death when treatment was started as late as 6 days postinfection, when the mice were viremic and showed biochemical evidence of liver injury [2].

Probably because it demonstrated the efficacy of favipiravir late in the course of infection, the paper from the Hamburg BSL-4 lab attracted wide interest, and it has been downloaded some 15,000 times, more than any other article in the history of AVR. The two simultaneous reports on the anti-Ebola activity of favipiravir may have helped to jump-start efforts to deliver the drug to patients in the West African epidemic: an open-label Phase II trial began 6 months later at two treatment centers in Guinea, as a collaboration between INSERM and Médecins Sans Frontières (see NCT02329054 on www.clinicaltrials.gov).

The first report of antiviral drug testing by the Hamburg lab appeared in 2004, when Stephan and his colleagues described the utility of RT-PCR in drug screening [3]. However, antiviral testing has accelerated in the past two years, as postdoc Lisa Oestereich (below) has taken the lead in evaluating antivirals against several highly pathogenic viruses. She was first author on the study of favipiravir treatment of Ebola-infected mice, and in a follow-up paper, she and colleagues in Hamburg and in France performed mathematical modeling of the effect of favipiravir therapy on the kinetics of Ebola virus replication, using data from the earlier paper [4].

For her doctoral thesis at the BNI, Lisa developed a new mouse model of Lassa fever, and in a recently published paper, she and coworkers describe the use of that model to demonstrate favipiravir's activity against Lassa virus, alone or in combination with ribavirin [5]. Lisa and her colleagues have also examined the efficacy of favipiravir, ribavirin and arbidol in mice infected with Crimean-Congo hemorrhagic fever virus [6].



Lisa Oestereich in the BSL-4 lab in Hamburg

Antiviral drug testing is but a small part of the activities of the Department of Virology at the BNI in Hamburg (<http://www.bnitm.de>). Under the leadership of Stephan Günther (shown below, with colleagues), the Hamburg lab is a WHO Collaborating Centre for Arbovirus and Haemorrhagic Fever Reference and Research. Stephan's team also took the lead in establishing the European Mobile Laboratory in West Africa, which has played a major role in the response to the Ebola epidemic.



Danny Asogun of the Irrua Specialist Teaching Hospital, Nigeria and Stephan Günther and Beate Becker-Ziaja of the BNI, Hamburg.

Stephan's research in Hamburg dates from 1993, when he began a postdoctoral fellowship at the Heinrich Pette Institute, studying hepatitis B virus. The direction of his career underwent a major change in 1998, when he accepted a position as a research group leader at the BNI and shifted his focus to tropical medicine and viral hemorrhagic fevers. In 2000, he published his first paper on Lassa fever, a report of a case imported into Germany [7]. He has since become a world authority on the disease, as

author or co-author of more than 50 articles. In 2005, Stephan became head of the Department of Virology at the BNI, director of the BSL-4 lab and of the WHO Collaborating Centre.

In addition to antiviral drug testing, Stephan's group performs routine diagnostic services for more than 50 different tropical and emerging viruses, testing samples from about 3000 patients each year, including cases imported into Europe. They also routinely carry out isolation and biobanking of Lassa, Ebola and other BSL-4 viruses, providing them to academia and companies within the European Virus Archive (<http://www.european-virus-archive.com/>).

Since 2007, the Laboratory of Virology has had a very successful collaboration with the Irrua Specialist Teaching Hospital in Nigeria, focusing on the development of rapid diagnostics and research on the pathogenesis and immunology of Lassa fever. Other collaborative research projects are under way in Guinea and Ghana.

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6. Oestereich, L., et al., *Evaluation of antiviral efficacy of ribavirin, arbidol, and T-705 (favipiravir) in a mouse model for Crimean-Congo hemorrhagic fever*. PLoS Negl Trop Dis, 2014. 8(5): p. e2804.
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FILOVIR and INFLUENZAVIR: online resources for antiviral researchers

Any ISAR member interested in influenza and Ebola virus infections should know about two

websites that provide access to a wealth of scientific resources on those diseases. At www.filovir.com and www.influenzavir.com you'll find links to recent news items, scientific publications, official reports, notices of upcoming conferences and other useful information. Both sites interface with the worlds of social networking and micro-blogging via Twitter, which through manually curated annotation and filtering delivers timely, updated scientific news. In particular, FILOVIR has provided daily coverage of the Ebola epidemic in West Africa, with tweets of news alerts almost in real time.



Luca Zinzula at the Max Planck Institute, Munich

The websites are the brainchild of Luca Zinzula (above), who created them in 2008-9, while he was a Ph.D. candidate in the lab of Enzo Tramontano in Cagliari, Sardinia. The concept of FILOVIR was born when Luca found that, despite the existence of numerous virus-related databases on the internet, the information they presented was highly disparate, and it was limited to specific sub-fields and disciplinary areas. Especially for Ebola and Marburg viruses, there was no middle ground between the extreme level of detail of repositories intended for specialists and the superficial (and frequently incorrect) information on non-scientific websites.

Luca's concept was to bring together information from a wide range of authoritative third-party resources in real time in a single web environment, in which every tool would be readily accessible and navigable. His goal was to create a virtual space where a researcher could find abstracts of the latest publications, pin-point the location of the latest outbreak, retrieve a genome sequence or a protein structure, or hear about upcoming conferences, with everything "just a click away". FILOVIR went live in January 2009, and one year later,

INFLUENZAVIR went online as a twin site focused on influenza viruses.

Once he had created the two websites, Luca realized that he would need help to maintain them, and he was fortunate to obtain the support of two colleagues, Massimiliano Orsini, a bioinformatician expert in genomic databases, and Cristian Romagnani, a biologist who has moved to the field of network systems and big data analysis. Luca presented the websites in a poster at the 28th ICAR in Rome. In recognition of his efforts for the benefit of the virology community, he was recognized by *Antiviral Research* as the first recipient of an annual award for “most promising antiviral researcher.”

Luca is a native of Sardinia. Before beginning his scientific studies, he spent several years working as a professional scuba diver, and was frequently involved in rescue and conservation activities for endangered marine species, with a special focus on monitoring infectious disease casualties. After hanging up his fins, he did undergraduate work in biochemistry and virology at the University of Cagliari, then continued there for his doctoral research with Enzo Tramontano. He received his Ph.D. from the University of Rome Tor Vergata in 2012 for studies characterizing the dsRNA-binding activity of the Zaire ebolavirus VP35 protein.

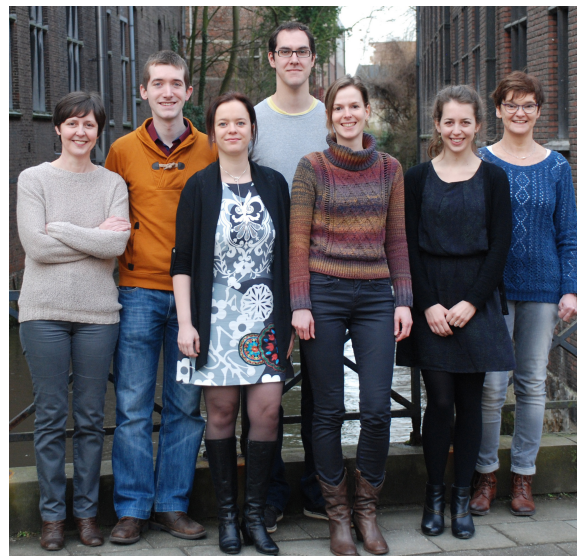
Since the beginning of 2014, Luca has been a postdoctoral fellow in the lab of Wolfgang Baumeister at the Max-Planck Institute of Biochemistry in Martinsried, Munich, learning cryo-electron micro-scopy and using the technique to further investigate the role of the VP35 protein in filovirus replication and innate immune antagonism. In addition to his current work with cryo-EM, Luca's wide-ranging scientific interests include the expression, purification and characterization of recombinant viral proteins, *in vitro* assays of protein-RNA binding and immune evasion by highly pathogenic RNA viruses. In 2013, he and Enzo published of a remarkably thorough review article in AVR on the latter topic:

Zinzula L, Tramontano E. 2013 Strategies of highly pathogenic RNA viruses to block dsRNA detection by RIG-I-like receptors: hide, mask, hit. *Antiviral Res.* 100:615-35.

ISAR MEMBER PROFILES

ISAR member: Lieve Naesens

Lieve is an associate professor in the Laboratory of Virology and Chemotherapy at the Rega Institute, Katholieke Universiteit Leuven, Belgium. She is clearly very happy at the University of Leuven, as she began her undergraduate studies there in 1982, and has spent her entire career in the Rega Institute.



Left to right: Lieve Naesens, Pieter Vrijens, Annelies Stevaert, Wim van Dam, Evelien Vanderlinden, Manon Laporte and Ria Van Berwaer.

How did you first get started in antiviral research?

My passion for virology began during my masters studies, when I did my thesis on the recombinant hepatitis B vaccine. I then by chance was invited for an interview with Erik De Clercq, and was charmed by his positive and enthusiastic attitude towards young researchers. I immediately decided to do my PhD work in his lab.

At that time, the acyclic nucleoside phosphonates (ANPs) had just been discovered, and I was very lucky to be able to work on their preclinical development. My doctoral project focused on the pharmacokinetics and efficacy of antiretroviral ANPs in animal models, and my direct mentor was Jan Balzarini. I also had close interactions with the team of Antonín Holý in Prague. In collaboration with Gilead, I was the first to demonstrate the *in vivo* efficacy of the oral prodrug of tenofovir (4), soon before it became a leading HIV blocker. At the end of my Ph.D. period, I got the chance to compile my insights into this successful drug class in a highly

cited review article in *Antiviral Chemistry & Chemotherapy* (3).

At the start of my postdoctoral period, I left the field of antiretrovirals, but not the ANPs. Having worked with adefovir and tenofovir, it was easy to move to anti-DNA virus ANPs like cidofovir. Collaborating with my colleagues Graciela Andrei, Robert Snoeck and Johan Neyts, my new research focused on two DNA viruses: adenovirus and HHV-6. Both are important pathogens, especially for recipients of organ or stem cell transplants, but unfortunately they are very much neglected in antiviral drug development.

I also became involved in the HHV-6 Foundation, which aims to keep this neglected virus on the research agenda. For many years, I have been a member of their scientific board. During this “DNA virus period”, I was assisted by my first two graduate students; our focus was on the virus-host interactions for HHV-6 and adenovirus, and how this can be combated with novel inhibitors (1,5,8). It was also during this period that I was appointed for academic teaching (I teach virology and immunology).

In a recent issue of ISAR News, Rhonda Cardin discussed HHV-6 as a potential antiviral target. Is it a focus for your lab?

As I just mentioned, I’m on the scientific board of the HHV-6 Foundation, where my main role is to give advice on antiviral therapy. At the moment, however, I’m not performing any drug development for HHV-6, since the need for new therapies is not clear. In the clinic, patients are treated with the classical anti-herpetic agents, such as ganciclovir and foscarnet. Brincidofovir also appears to be a promising new drug for HHV-6 infections.

What are the current priorities of your research group?

After working for several years on DNA viruses, I decided to shift my focus to influenza, because it was becoming evident that the current antivirals, which are neuraminidase inhibitors, are not sufficient, and new drugs are clearly needed. From a virological viewpoint, this was a new virus, but from a technical/experimental standpoint, I could rely on expertise I had acquired with other viruses.

My group now has two main topics for influenza antivirals: inhibitors of the polymerase complex and inhibitors of viral entry. The first encompasses inhibitors of PA, PB1 or PB2, or a cellular factor associated with the viral polymerase. Regarding the influenza PA endonuclease, I am the driving force

behind a network of academic researchers with expertise in medicinal chemistry, structural biology, enzymology and virology (6,7). Our cell culture and biochemical data are of high and direct relevance for the development of PA inhibitors, a drug class that several pharmaceutical companies are working on. Inhibitors of viral polymerases are a good fit for our lab, because this concept has been a continuous line of research in my career.

The second topic includes inhibitors of the hemagglutinin, such as fusion inhibitors (9), or compounds that interfere with a cellular factor involved in virus entry, such as compounds that inhibit endocytosis or the proteolytic activation of HA (10). The influenza virus hemagglutinin is an amazing research topic. Even though this protein has been studied extensively, there are still knowledge gaps regarding its link to receptor signaling and the biochemical details of its proteolytic cleavage or species adaptation. Hence, we use hemagglutinin inhibitors as tools to resolve these basic scientific questions. As for drug development, the hemagglutinin is not an easy target, given its subtype-dependent and variable structure. Because influenza viruses evolve very rapidly and easily develop drug resistance, I believe that inhibitors of a cellular factor will have high clinical relevance. Some of these strategies are explained in our recent review article on influenza virus entry inhibitors (10).

My influenza team now has seven coworkers. As the PI, I’m responsible for project design, mentoring graduate students, grant applications, writing papers, etc... I also have a network of medicinal chemists, mainly at European universities, with whom I collaborate to design and synthesize inhibitors.

You’ve also received funding to work on drugs against malaria and tuberculosis. How do you happen to be doing that?

This is a very interesting translational aspect of my research. As an expert on ANPs, I hypothesized that these compounds may act like product inhibitors of hypoxanthine-guanine phosphoribosyltransferase, which is a crucial enzyme in *Plasmodium* parasites and mycobacteria. The validity of the concept was proven in collaboration with the teams of Luke Guddat in Brisbane, Australia and the late Antonín Holý in Prague. Since our first joint publication in 2009 (2), this has become a totally new concept in antiparasitic drug design. The project has been very successful, with many high-impact papers and citations.

My current role in this network is the pharmacological aspect, relating to prodrug design, cell permeability and cytotoxicity. I strongly believe that pharmacologists should look at potentially new applications of inhibitor concepts. For instance, nucleoside analogues have been very successful as anticancer and antiviral drugs, and they can be equally relevant in the fields of antiparasitic or antibacterial therapy.

You might be described as a medicinal chemist with a strong interest in virology, but a willingness to take on other problems. Is that accurate?

I consider myself a pharmacologist-virologist. I don't do medicinal chemistry, but to reveal the interaction of a molecule with its viral target, I need to understand the SAR of inhibitors, so some basic knowledge of chemistry is required.

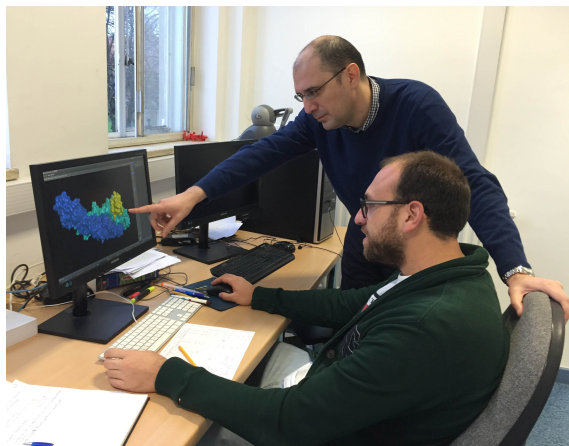
My goals are to find innovative drugs that inhibit viruses and elucidate their mechanism of action. The aim is not only to discover new inhibitors, which may have only short-term clinical relevance, but to use the inhibitors to understand viruses. It's a nice balance between applied and basic research.

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ISAR Member: Andrea Brancale

Reader in Medicinal Chemistry, School of Pharmacy and Pharmaceutical Sciences, Cardiff.



ISAR members know Andrea (standing, above, with Cardiff colleague Salvatore Ferla) as the winner of the 2013 Prusoff Young Investigator Award, but not all of us are familiar with the direction of his career, which has increasingly explored the use of computer-

based methods to design new antivirals and anticancer drugs.

Andrea's involvement with antiviral research began in 1994-6, when he did an undergraduate project in Romano Silvestri's lab at the Università "La Sapienza" in Rome, investigating novel non-nucleoside RT inhibitors. After receiving his degree, he did his doctoral work in Chris McGuigan's lab at the Welsh School of Pharmacy, focusing on the design, synthesis and evaluation of novel antiviral nucleosides. He became a research associate in 2001, and has continued as a staff member.

How did you choose to do graduate studies in Cardiff?

After finishing my undergraduate degree and military service, I wanted to do doctoral research in medicinal chemistry, possibly abroad. I applied to several places in the UK and the US, and Chris McGuigan replied right away. It was very exciting to join Chris's lab and continue to work in the antiviral field. In particular, I was very happy to have the opportunity to work on nucleoside analogues. Difficult chemistry sometimes, but very satisfying when it works as planned!

What were your goals when you began your research career? What aspects have you found most satisfying?

I always wanted to have a career as an active, independent researcher, and I consider myself very lucky to have achieved it. The best part of my job is the possibility of interacting with a wide variety of collaborators in different fields. It's never boring, and I'm always learning something new.

Cardiff University, and my school in particular, is a dynamic and stimulating place, always committed to excellence. In particular, it's an ideal place to foster collaborations and develop new ideas: in the time I've been there, seven patents have been filed based on projects I've contributed to, and ten students have received their Ph.D. under my supervision. My current group of three postdocs and five graduate students is involved in a variety of collaborative projects, and we receive funding from both the public and the private sector.

Virologists tend to think about drug development in terms of viruses and virus families. As a medicinal chemist, how do you visualize antiviral drug discovery?

To a certain extent, chemists like to work in

specific fields, especially if they have solid collaborations with biologists, but they're also happy to move in a different direction if they have an indication that their beloved compounds could be interesting in another therapeutic context.

From the point of view of computational chemistry, fidelity to a specific research area is even more tenuous, as the methods are "neutral," and can be applied to almost any drug design project [1]. For example, I've collaborated on projects spanning all the way from designing antivirals against chikungunya virus [2] to modeling simulations on small peptides for treatment of gastrointestinal diseases.

What new approaches are you using in your research?

I'm applying several different structure-based methodologies, including molecular docking, homology modeling and molecular dynamics. Of course, we also make use of traditional organic synthetic methods and classical medicinal chemistry approaches to design and synthesize novel potential drugs.

More recently, I've made a strategic decision to expand my research into the developing area of molecular modeling software. In particular, I've become interested in how researchers relate with the computer and how an interactive interface between the human and the computer would improve the quality of *in silico* drug design. This has led our group to develop a haptic-driven molecular modeling simulator, which we presented at ICAR in Miami.

Coming from a medicinal chemistry background, this was a completely new research field for me, but I quickly became fascinated by it. Recently, I attended a very interesting Faraday Discussions meeting on "Molecular Simulations and Visualization." Anyone who is interested in understanding where new software and methods are heading should look at the conference papers:

<http://pubs.rsc.org/en/journals/journalissues/fd#!issueid=fd014169&type=current&issnprint=1359-6640>

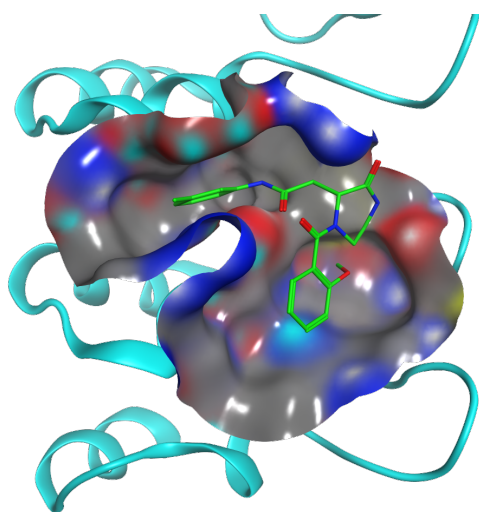
How does research on antiviral drugs overlap with the development of other therapies?

The development of antivirals shares some common ground with the anticancer field, and nucleoside analogues are very important drugs in both fields. In fact, this is not the only common aspect. We are increasingly seeing how some drugs designed to hit target host cell pathways are finding new applications in the antiviral field. Some of the

clearest examples are cyclin-dependent kinase inhibitors, such as roscovitine, that were developed as anti-cancer agents, but have also shown antiviral activity.

Efforts to develop new drugs often lead to disappointment, but are sometimes unexpectedly successful. What has been your own experience?

Disappointment is the most common emotion a researcher faces in his career, so we have to learn to forget failures quickly and use them to move forward with more impetus. I've had several small and some big disappointments in the last few years, but I tend to remember only the successes!



Potential interaction of a virtual screening hit compound with the BCL-3 protein, leading to reduced motility of malignant cells, blocking metastasis.

At the moment, our most exciting project focuses on the development of an anti-metastatic agent, based on the recently discovered role of the BCL3 protein in cancer cell motility, especially for mammary cancer (above). It began with a virtual screening simulation just four years ago, but has since become the foundation stone of a spin-off company, Tiziana Life Sciences (<http://www.tizianalifesciences.com>) which is now listed in the AIM section of the London Stock Exchange.

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ANTIVIRALS ON THE HORIZON

New drugs for flaviviral diseases



Pei-Yong Shi, Department of Biochemistry and Molecular Biology, UTMB Galveston

Pei-Yong has devoted much of his career to the study of flavivirus replication and the development of antiviral countermeasures. He received his undergraduate degree in Nanjing, China in 1989, then did graduate work in molecular virology in Margo Brinton's lab at Georgia State, receiving his Ph.D. in 1995. After a postdoctoral fellowship at Yale, he joined Bristol-Myers Squibb as a Principal Scientist to develop HIV and HCV therapeutics from 1998 to 2000. He then moved to the Wadsworth Center of the New York State Department of Health, where he directed the flavivirus replication and antiviral program. In 2008, he joined the Novartis Institute for Tropical Disease in Singapore as head of the Dengue Unit, and in 2010 became executive director for disease biology.

Pei-Yong's career has recently taken a big step upwards with his selection as the I. H. Kempner Professor of Human Genetics in the Department of Biochemistry and Molecular Biology at the University of Texas Medical Branch in Galveston. He also has appointments in the UTMB Center of Structural Biology and Molecular Biophysics and the Department of Pharmacology and Toxicology. Together with Sheemei Lok and Subhash Vasudevan,

he is guest editor of a current virtual symposium on flavivirus drug discovery in *Antiviral Research*.

The major focus of your career has been drug discovery for flaviviruses. What are the principal diseases for which antivirals are needed?

Although vaccines are the best countermeasures against flaviviruses, approved vaccines are currently available only for yellow fever, Japanese encephalitis and some tick-borne encephalitis viruses. Antiviral drugs are needed for agents lacking approved vaccines, and dengue virus (DENV) is the top priority within this category. Even for those diseases for which vaccines are available, such as yellow fever, the low vaccination rates in many endemic regions mean that effective therapies are still needed.

Do lessons learned from the development of drugs against hepatitis C apply to DENV and other flaviviruses?

Yes, many lessons can be learned from HCV drug discovery. For example, the pan-genotype coverage and high resistance barrier of sofosbuvir show a clear advantage of the nucleotide analog approach. It would be ideal if a single compound could be identified that inhibits a broad spectrum of flaviviruses. Compared to hepatitis C, a chronic disease that is treated for at least 12 weeks, the duration of therapy for dengue or other flaviviral diseases is expected to be no more than a week, so that the toxicity barrier will be much lower.

What approaches are most promising for flavivirus drug development?

Over the past decade, both academia and industry have made effort to develop inhibitors of flaviviruses (especially DENV). Various approaches have been taken; each approach has proven to have its own challenges (Lim et al., 2013).

Nucleoside/nucleotide analogs exhibit the attractive features of broad-spectrum coverage and a high resistance barrier. These advantages have already been demonstrated by an adenosine analog (NITD-008) in both DENV cell culture and mouse model (Yin et al., 2009). However, a number of scientific hurdles still need to be addressed. For example, for an anti-DENV drug, in what cells and tissues does the virus replicate during the acute phase of infection in humans? How could we engineer compounds to be selectively loaded onto these sites? For those who are interested in the nucleoside/nucleotide approach, please refer to our recent review on this topic (Chen et al, 2015).

Protease inhibitors appear to be less promising. In contrast to the HCV protease, for which peptidomimetic drugs have been successful, the two positively-charged amino acid residues located immediately upstream of the flavivirus protease cleavage site make this approach challenging. More effort is needed to develop a DENV protease inhibitor.

Compounds targeting the DENV envelope and capsid proteins have also been reported, but the physical/chemical properties of these inhibitors prohibit further development. Other types of compounds, such as NS4B inhibitors (Xie et al., 2015), remain to be explored. Drugs that target host factors required for viral replication, such as alpha glucosidase inhibitors, or that play a critical role in disease development, such as mast cell stabilizers, are worth investigating.

In addition to small-molecule drugs, therapeutic antibodies are being explored for DENV and other flaviviruses, and antibodies active across serotypes have recently been reported in cell culture and in mouse models. Potent serotype-specific antibodies have also been reported, but this approach will require at least four antibodies, each inhibiting one DENV serotype. Some of them are expected to enter clinical trials soon.

What is the relationship between the development of a dengue vaccine and the need for antivirals?

Vaccines and antivirals complement each other for disease control and intervention. Recent results for front-runner dengue vaccines have shown great promise, despite certain limitations (e.g., weak efficacy against DENV serotype 2 for the CYD-TDV vaccine). The ongoing vaccine trials will continue to unravel many questions about dengue diseases and immune response in humans; such information will facilitate antiviral development, especially when antiviral candidates reach clinical trials. I'm really excited to witness and participate in the effort to translate our knowledge about dengue disease to benefit patients.

How would an antiviral drug against DENV be used in endemic areas?

Safety and efficacy are the two most important parameters for any therapeutics. For travelers to a dengue-endemic area, prophylactic dosing may be sufficient to prevent disease during a short visit. For people living in endemic areas, it is likely that multiple treatment courses (either prophylactic or

therapeutic) will be needed, making drug safety even more important.

Dengue is clearly the primary target for drug development, but would other flavivirus diseases benefit from an effective therapeutic?

Just as success in developing HCV drugs should benefit dengue antiviral development, success in therapeutic development against DENV is expected to facilitate discovery for other flaviviruses. Due to similarities among flavivirus proteins, it would be ideal if an inhibitor of DENV would cross-inhibit other viruses, even if at a lower efficacy. Such inhibitors would then be good starting points for chemical modifications to improve their efficacy against other flaviviruses. This strategy remains to be experimentally investigated.

What is the role of rapid diagnostic testing in flavivirus drug development?

Rapid point-of-care diagnostics will be essential, especially for recruitment of dengue patients with early, acute infection for clinical trials. Like other acute viral infections, the treatment window for dengue patients is short. The feasibility of such short treatment window can only be experimentally addressed using a safe and efficacious compound in a clinical setting. Once efficacy and safety have been established, one could conceive of treating febrile patients in areas with ongoing dengue outbreaks without a confirmed diagnosis.

What other new initiatives are you planning in Galveston?

An opportunity that I find especially exciting is to help build partnerships between UTMB and leading research institutes in China, especially the Wuhan Institute of Virology of the Academy of Sciences, which is opening China's first BSL-4 laboratory. We hope to establish working relationships for the exchange of scientists and collaborative research projects.

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Lim SP, Wang QY, Noble CG, Chen YL, Dong H, Zou B, Yokokawa F, Nilar S, Smith P, Beer D, Lescar J, Shi PY. Ten years of dengue drug discovery: progress and prospects. *Antiviral Res.* 2013;100:500-12.

Xie X, Zou J, Wang QY, Shi PY. Targeting dengue virus NS4B protein for drug discovery. *Antiviral Res.* 2015 Jun;118:39-45.

Yin Z, Chen YL, Schul W, Wang QY, Gu F, Duraiswamy J, Kondreddi RR, Niyomrattanakit P, Lakshminarayana SB, Goh A, Xu HY, Liu W, Liu B, Lim JY, Ng CY, Qing M, Lim CC, Yip A, Wang G, Chan WL, Tan HP, Lin K, Zhang B, Zou G, Bernard KA, Garrett C, Beltz K, Dong M, Weaver M, He H, Pichota A, Dartois V, Keller TH, Shi PY. An adenosine nucleoside inhibitor of dengue virus. *Proc Natl Acad Sci U S A.* 2009

NEWS FROM ISAR MEMBERS

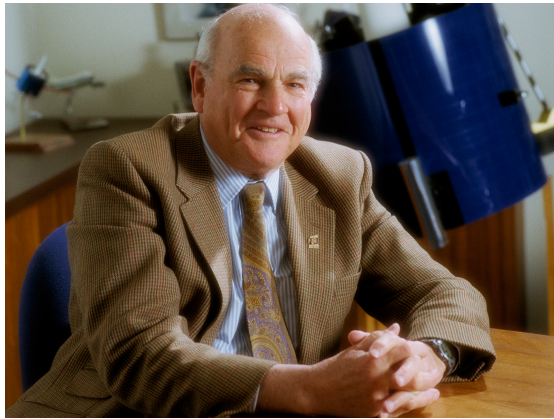


Blumberg Institute marks 50th anniversary of discovery of the Australia antigen

This year marks the 50th anniversary of the discovery of the Australia antigen, subsequently identified as the hepatitis B virus surface antigen, by Baruch Blumberg and his colleagues at the National Institutes of Health and the Fox Chase Cancer Center. By providing a specific serum marker of hepatitis B, the discovery led to rapid progress in multiple areas, including the development of diagnostic tests, improved safety of blood transfusion and production of the first hepatitis B vaccine. The ability to detect asymptomatic infections also revealed the huge numbers of people around the world with chronic hepatitis B and its relationship to terminal cirrhosis and hepatocellular carcinoma.

This 50th anniversary is a particularly special event for the Hepatitis B Foundation and its director, ISAR member Tim Block. Tim and his wife Joan established the Foundation in 1991 as a public health, advocacy and outreach organization committed to helping people with hepatitis B. In 2000, they created the Institute for Hepatitis and Virus Research, as an independent, non-profit organization dedicated to finding therapies "to improve the quality of lives of those affected by hepatitis B and liver cancer." Dr. Blumberg (below) maintained an office at the Institute until his death in 2012. After his passing, the Institute was renamed in his honor.

The Blumberg Institute is located within the Pennsylvania Biotechnology Center, a life sciences "incubator" in Doylestown, PA, which is home to



Barry Blumberg, discoverer of the hepatitis B surface antigen and recipient of the 1976 Nobel Prize in Medicine.

more than 320 scientists, staff and entrepreneurs, working in 35 start-up companies and nonprofit organizations. Among the companies are Forge Sciences, created by Tom Shenk and Lillian Chiang to explore a broad range of antivirals; Arbutus, founded by Mike Sofia and colleagues to focus on hepatitis B and liver cancer; Novira, started by Lalo Flores and George Hartman to develop new HBV antivirals; and PMV Pharma, created by Arnie Levine and Tom Shenk to pursue p35 agonists.

For a number of years, Drexel University College of Medicine maintained a translational research division at the Biotech Center, which included on-site faculty members Tim Block, Ju-Tao Guo, Ying Su and Jinhong Chang. In March 2015, they and their lab groups joined the Blumberg Institute, making it one of the largest centers for HBV research in the United States.

In addition to hepatitis B, the Blumberg Institute also has strong programs in antivirals against RNA viruses. Its filovirus antiviral program has produced novel imino sugars shown to have efficacy in animal models. In 2013, the Merck Company donated its collection of natural products, including the Schering Plough legacy, to the Institute, which now has one of the most diverse and “druggable” libraries of natural products in the world. Institute scientists screen them for antiviral and anticancer leads, and make the collection available to other researchers and institutions.

Other Blumberg Institute activities of potential interest to ISAR members include:

- “Out and Up”: established professionals from universities and the pharmaceutical and biotech

industry may be offered faculty appointments, funding or space to develop their ideas;

- Recent college graduates may perform 1- or 2-year research fellowships, working with mentors on assigned projects;
- Graduate students in masters or Ph.D. programs may obtain adjunct appointments at the University of Pennsylvania, Drexel University and other nearby institutions.

To mark the 50th anniversary of the discovery of the Australia antigen, the Blumberg Institute is sponsoring a collection of invited articles in *Antiviral Research*. The symposium papers review a range of novel therapies for hepatitis B that are now on the horizon. They can be accessed at

<http://www.journals.elsevier.com/antiviral-research/symposia/symposium-hepatitis-b/>

Two new projects at the Institute for Antiviral Research

ISAR member Bart Tarbet reports two new projects at Utah State University. The first is a response to recent outbreaks of enterovirus D68 in the midwestern USA and of EV-71 in China and other areas: the IAR has received a contract from extramural NIAID/NIH to develop mouse models of enterovirus infections and use them to evaluate therapeutics. Bart will direct the study. Funding for the first two years will support model development, and if that’s successful, additional funds will cover drug testing.

The other project is something new for the IAR. In October, 2014, Bart met Dr. Emmanuel Assana, a professor of veterinary medicine in Cameroon in Central Africa, at the annual meeting of the International Society for Vaccines. After a discussion of possible research collaborations, they decided to apply for a grant to establish a laboratory in Ngaoundéré, Cameroon for the surveillance and detection of emerging and re-emerging zoonoses. The government’s Minister of Livestock, Fisheries and Animal Industries has supported the proposal, recommending that the lab be included in the National Program for the Prevention and Fight against Emerging and Re-emerging Zoonoses, part of the USAID program on Global Health Security and Emerging Pandemic Threats.

Although the award is not yet official, recent word from USAID is that the proposal has been submitted to its implementing partners in One Health Central and Eastern Africa. If the grant is approved, Bart will

help set up the lab and provide training in biosafety and biosecurity, and personnel from Cameroon will train in virology and diagnostics in the IAR and the Utah Veterinary Diagnostic Laboratory. Bart would enjoy hearing from ISAR members who have suggestions for a larger scope of activities for this project, such as the study of infectious disease transmission at the wildlife-livestock interface and environmental drivers of emerging infectious diseases.

ISAR ELECTIONS

This year the Nominations Committee was charged with finding two candidates for the position of President-Elect, two for the post of Secretary, and six candidates for three positions on the Board of Directors. They have all given of their time and talents to the Society and would make excellent Board members.

The election was held through the ISAR website beginning on November 7th, and has just concluded. We hope that all members voted, and were able to make the difficult choice among this slate of excellent candidates!

For President-Elect: two candidates



Rhonda Cardin is an Associate Professor in the Division of Infectious Diseases at Cincinnati Children's Hospital Medical Center. She received her A.B. from Washington University in St. Louis and her Ph.D. in Microbiology from Louisiana State University in 1989. She then joined Dr. Ed

Mocarski's laboratory at Stanford University for postdoctoral studies on murine cytomegalovirus pathogenesis and latency. In 1994, she joined the laboratory of Dr. Peter Doherty at St. Jude Children's Research Hospital to work on murine gammaherpesvirus pathogenesis and immunology.

In 1998, Rhonda joined Parke-Davis Pharmaceuticals as a senior scientist, where she supervised the evaluation of anti-herpesvirus compounds in animal models and was also part of the HIV entry inhibitor program. After the Pfizer merger, she joined ChemoCentryx, Inc. to work on chemokine therapeutics for diseases and vaccine strategies. In 2003, she joined the faculty of Cincinnati Children's Hospital Medical Center. Her research focuses on murine cytomegalovirus pathogenesis and latency as a model for human cytomegalovirus and is currently NIH-funded. Since 2003, she has served as co-PI on a NIH contract for evaluating novel antivirals and vaccine strategies in CMV and HSV animal models.

She joined ISAR in 2003 and has actively attended and presented at ICAR and has served as a poster judge and herpesvirus co-chair. She is currently a member of the Finance, Membership, and Publications Committees and has served on the ISAR Executive Board for the past four years. She is also a member of the Women in Science Committee and has led efforts to develop the Women in Science mentoring program.



Johan Neyts is full professor of virology at the faculty of Medicine of the University of Leuven (KU Leuven) in Belgium, where he teaches medical virology at the school of medicine and dentistry. The focus of his laboratory is the development of novel

antiviral and vaccination strategies. He is author of ~360 peer reviewed papers and holds several patents. Sixteen people have obtained their Ph.D. degree under his guidance and 56 bachelor or master students have been trained in his laboratory. He is an editor of *Antiviral Research* and is on the editorial board of several other journals.

Johan was co-founder and CSO of the KU Leuven spin-off Okapi Sciences NV a biotech company that developed antivirals for veterinary use. He is CSO of ViroVet (www.virovet.com), a new KU Leuven spin-off that is currently being incorporated. Research topics covered in his laboratory at the University in Leuven include the development of novel antiviral strategies against a number of RNA viruses, including flaviviruses (hepatitis C, dengue and others), picornaviruses (entero- and rhinoviruses), alphaviruses (chikungunya and others), paramyxoviruses (RSV and others), rabies, noroviruses and the hepatitis E virus, as well as a novel thermostable DNA vaccine technology.

Johan has attended 23 ICARs since 1990. In 2003, he received the William Prusoff Young Investigator Award. He has also served as a board member and chair of the membership committee.

For secretary: two candidates



Graciela Andrei obtained her Ph.D. in Biological Sciences at the Faculty of Sciences, University of Buenos Aires, Argentina in 1989. She then performed postdoctoral training on antiviral chemotherapy, with a particular focus on herpesviruses, at the Rega Institute for Medical Research in Leuven, Belgium from 1989-1996. She was a visiting researcher at the University of Alabama at Birmingham in 1997, then joined the Rega Institute, KU Leuven as an associate

researcher, where since 2005 she has been assistant professor in the Faculty of Medicine, Laboratory of Virology and Chemotherapy.

Graciela's main scientific activities include the unraveling of the mode of action of novel antivirals, the molecular mechanisms of drug resistance in herpesviruses and poxviruses, the molecular anticancer mechanism of action of nucleotide analogues and the development of organotypic epithelial raft cultures for the study of epitheliotropic viruses. In 2009, she participated in the set-up of the RegaVir, a translational research platform for typing drug-resistant herpesviruses in immuno-compromised patients who fail antiviral therapy.

She has been a member of ISAR since 1989, and in 2012, she was elected secretary. She is a member of the editorial board of *Antiviral Research* and *PLOS One*.



Kara Carter has 28 years of experience in virology research and the discovery and development of antiviral agents. Following undergraduate research at Stanford University, in collaboration with Chiron to develop an HSV-2-specific diagnostic, she received her Ph.D. in virology at University of Chicago in the laboratory of Dr. Bernard Roizman, identifying novel genes of HSV-1 and elucidating the mechanisms of their protein products. She performed postdoctoral studies at Harvard University and Brigham and Women's Hospital in the laboratory of Dr. Elliott Kieff, focusing on EBV-induced transcriptional changes of infected B cells and their effect on transformation. She then moved to PRAECIS Pharmaceuticals, where she led drug discovery

programs in RSV, influenza, HSV and HCV, focusing on cellular targets.

In 2004, Kara moved to the Genzyme Corporation, where she led drug discovery programs in virology, immunology and oncology, as well as supporting the Transplant Business Unit in the evaluation and acquisition of antiviral products to complement their portfolio. She is currently Head of Antiviral Research at Sanofi. She is an ISAR member and has served as a member of the Women in Science committee.

For Board of Directors: 6 candidates for 3 positions



Andrea Brancale is a Reader in Medicinal Chemistry at the School of Pharmacy and Pharmaceutical Sciences at Cardiff University. He graduated in Medicinal Chemistry in 1996 at the University of Rome "La Sapienza," then moved to Cardiff, where he received his Ph.D. in Medicinal Chemistry in 2001 under the supervision of Prof. Chris McGuigan. He then worked as a postdoctoral fellow on a GSK- sponsored research project on the design of novel pro-nucleoside analogues as anti-HIV agents.

Since his appointment as lecturer, Andrea's research has focused on the use of computer-aided techniques in the design and discovery of novel antiviral and anticancer compounds. In the antiviral field, his research has focused on the *in silico* design of RNA virus inhibitors, including dengue, WNV, HCV, chikungunya virus and Cocksackie virus. He is the Chemistry Editor for *Antiviral Chemistry and Chemotherapy*.

He has been a member of ISAR since 2000 and was elected a board member in 2013. He has also been a member and chair of the Website committee since 2006 and the Publications Committee since 2010. He has been the ISAR Webmaster since 2006, and has implemented several technical developments, including online registration and membership management and enhancement of ISAR's social profile on Facebook, Twitter and LinkedIn.



Randall Lanier is Vice President for Biology at Chimerix, Inc. Before joining Chimerix in 2007, he contributed to the HIV and cancer programs at Burroughs Wellcome, GlaxoWellcome and GlaxoSmithkline, where he supervised a clinical virology/immunology laboratory, led teams for drug discovery and was involved in preclinical and clinical development, product differentiation, post-marketing support and licensing opportunity evaluation.

Randall has over 20 years of experience in the discovery and development of antivirals, and has focused much of his career on understanding the activity, mechanism, and resistance profiles of nucleoside analogs used for prevention and treatment of viral disease caused by HIV, CMV, adenovirus, and poxviruses. He received his undergraduate degree in biology from New College and Ph.D. in Cellular and Molecular Biology from the University of Texas Health Science Center in San Antonio.



Kathy Seley-Radtke is the Presidential Research Professor of Chemistry and Biochemistry at the University of Maryland, Baltimore County. She earned her Ph.D. in Organic Chemistry from Auburn University. Her research involves a synthetic organic/medicinal chemistry approach to nucleoside and heterocyclic drug discovery and development. Current projects include the investigation of flexible nucleosides/nucleobases "fleximers" for use against SARS, MERS-CoV, Ebola, HCV, HIV and other viruses. She has published over 70 peer-reviewed papers, and is the President of the International Society of Nucleosides, Nucleotides and Nucleic Acids (IS3NA).

Kathy has chaired the ICAR poster awards for a number of years. Notably, she initiated a new program for IS3NA, the Women's Career Development Scholarships, as well as to obtain funding for the Women in Science scholarships for ISAR, both of which have been generously funded by the Chu Family Foundation. She is a member of the ACS Medicinal Chemistry Division Awards Committee and is an associate editor for *Current Protocols in Chemical Biology*.

Mike Bray has had a more than 40-year career in medicine and research. After serving two years as an Army medic in Viet Nam, he completed undergraduate studies at the University of Oregon, then attended Dartmouth Medical School. Following training in internal medicine and pathology, he worked as a forensic pathologist in Washington, D.C. In 1986, he began research on dengue virus in Ching-Juh Lai's lab in the NIH Laboratory of Infectious Diseases, where he and co-workers succeeded in producing the first DENV infectious clone.

In 1995, he transferred to the Virology Division in USAMRIID at Fort Detrick, where he worked for



John Huggins, studying Ebola and other hemorrhagic fever viruses and poxviruses in laboratory animals and testing new antiviral drugs and vaccines. In 2002, he returned to NIH, where he is a medical officer in the Division of Clinical Research, NIAID.

Mike attended his first ICAR (the 12th) in Jerusalem in 1999, where he gave a talk on mouse-adapted Ebola virus, and has attended almost every ICAR since. He served as the reviews editor of *Antiviral Research* from 2007-11, and became editor-in-chief in January, 2012.



Karen Watson Buckheit has been involved with ISAR for over 15 years and is a regular ICAR attendee. She graduated from Hood College in

Frederick, MD with a B.A. in Biology in 1996 and obtained her M.S. in 2006 evaluating the selection and characterization of resistant viruses to the pyrimidinedione anti-HIV compounds under development by ImQuest BioSciences. For the past 15 years she has led ImQuest's research and development activities directed at the development of topical microbicides to prevent the sexual transmission of HIV. For the past decade she acted as Director of the Topical Microbicide Program and Prevention Sciences, which involved management of various microbicide development programs for a variety of federal and commercial entities.

Karen's interests have also expanded into other areas of women's health, and she is involved in the continuing development of ImQuest's programs to identify prevention and treatment agents for HIV, HSV-1, HSV-2, HPV and various bacterial and fungal organisms. She has been first author or co-author of more than 30 papers on topical microbicide development. She has assisted with the development of ISAR programs for Drug Discovery and Development 101 and serves on the Women in Science committee.



William E. Delaney IV earned his Ph.D. from Pennsylvania State University in 1998, working on *in*

vitro models of hepatitis B virus (HBV) replication. He then completed a postdoctoral fellowship with Dr. Stephen Locarnini in Melbourne, Australia where he studied drug-resistant HBV strains. In 2000, he joined Gilead Sciences, where has participated in the discovery and development of multiple compounds for the treatment of chronic viral hepatitis.

Bill initially worked as a clinical virologist in support of the approved HBV nucleotide prodrugs adefovir dipivoxil and tenofovir disoproxil fumarate, which included characterization of the first clinical adefovir resistance mutations. Following their approval, he focused on HCV, which included leading discovery efforts on NS3 protease inhibitors and overseeing biological support for other programs, including the NS5A inhibitor program that led to Ledipasvir. He is currently senior director of biology and heads Gilead's Viral Hepatitis Discovery Biology group. He has been an ISAR member since 1999, received the William Prusoff Young Investigator Award from the Society in 2012 and was elected to the ISAR Board of Directors in 2013.

ICAR 2015 SCIENTIFIC REPORT

The official report on the 2015 ICAR in Rome, Italy, written by Anthony Vere Hodge and reviewed and approved by the ISAR Publications Committee, is available for free download from PubMed or the ScienceDirect website.

Vere Hodge RA, 2015. Meeting report: 28th International Conference on Antiviral Research in Rome, Italy. *Antiviral Res.* 123:172-87.

CALENDAR OF FUTURE MEETINGS

Simon Tucker is updating the calendar of future conferences on antiviral therapy, medicinal chemistry and other topics of interest that he posted on the ISAR website last year. ISAR members can access the calendar by logging in and downloading the pdf.

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.isar-icar.com>).

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