



ISAR News

Newsletter of the International Society for Antiviral Research

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

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ISAR PRESIDENT'S MESSAGE

Dear ISAR members,

On behalf of our officers and board members, I'm pleased to welcome everyone to La Jolla and the 29th International Conference on Antiviral Research. I wish you a highly successful meeting, and I hope that when it's over, you'll walk away impressed with the quality of the scientific presentations and with some new additions to your research network.

As we gather in La Jolla, we're deeply saddened by the loss of Chris McGuigan, a friend and colleague for many years. Chris was a pillar of the antiviral research community, a long-time member and past president of ISAR. For me and many others, he was also a mentor, colleague and good friend. His many accomplishments will be honored at the 29th ICAR, and we will feel his presence in spirit. His work will live on with the advances he pioneered and the many students and scientists he mentored, many of whom are active members of the Society. On behalf of ISAR, we send our condolences to the McGuigan family and to his many friends and colleagues on this tragic loss.

As Chris would wish, we will again have a cutting-edge program in La Jolla, offering great science and the all-important time to network and reconnect with friends from around the world. Mark Prichard and his program team have worked hard to attract top speakers, and they've also revamped the abstract submission process and developed a new workshop on Diagnostic Technologies.

29th ICAR Corporate and Educational Sponsors. PLATINUM: Gilead Sciences. GOLD: Alios BioPharma, GlaxoSmithKline. SILVER: AbbVie, Chimerix, JCR Pharmaceutical Co. Ltd., Southern Research Institute. BRONZE: ACS Infectious Diseases, Antiva Biosciences, Center for Drug Design – University of Minnesota, Elsevier B.V., ImQuest BioSciences, Institute for Antiviral Research – Utah State University, Kineta, Medivir AB, Riboscience LLC, Toyama Chemical Co. Ltd, and XpressBio.

The meeting will begin with a tribute to Chris and his contributions to science and to our society, followed by two keynote addresses. The first, by Richard H. Scheuermann of the J. Craig Venter Institute, will explore how the availability of whole-genome sequence data, combined with standard representations of phenotypic characteristics from large numbers of viral isolates, is allowing extensive genotype-phenotype association studies that go well beyond traditional phylogenetic lineage tracing. He will illustrate these concepts by focusing on two areas: the use of statistical genomic analysis to predict influenza virus evolution in the face of adaptive immunity and the identification of novel genetic determinants of disease severity in enterovirus D68.

The second keynote address, by Heinz Feldmann of the NIAID Rocky Mountain Laboratory, will take a very different direction, focusing on the past, present and future of Ebola virus. Heinz did his initial training and research in Marburg, Germany, which was the site of the first filovirus outbreak. He will review the history of Marburg and Ebola viruses from their discovery through the recent West African epidemic. He will then provide a look ahead: what research is needed, where do we go from here? Lessons learned in West Africa are clearly critical to understanding how to prevent such a widespread epidemic in the future and to limit its global spread through air travel.

We can also look forward to award lectures from two distinguished senior scientists and a promising younger investigator. Doug Richman from UC San Diego will receive the Gertrude Elion Award; Robert Vince of the University of Minnesota will receive the Antonin Holý Award; and Jerome Deval of Alios Biopharma will receive the Prusoff Young Investigator Award. Their presentations, reviewing some of their past accomplishments and focusing on priorities for future research, will be high points of the meeting.

The 29th ICAR will also feature three symposia, the first of which will cover a variety of topics in structural biology, which has become so important for progress in antiviral research. Speakers from the San Diego/La Jolla area will include Clodagh O'Shea from the Salk Institute and 2015 Prusoff Award winner Erica Ollman Saphire from the Scripps Research Institute.

The second symposium will examine important aspects of Zika virus, which has been spreading rapidly in Central and South America and causing alarm because of its association with fetal anomalies and Guillain-Barré syndrome. Pei-Yong Shi will lead off with an overview of Zika and its relationship to other flaviviruses, and Justin Julander and Johan Neyts will follow with discussions of animal models, antivirals and vaccine development.

The third symposium will focus on DNA viruses. Effective antiviral therapies have been developed for

some DNA viruses, but unexpected genetic variation, including the discovery of quasispecies within a host, has highlighted the need for new antivirals and combination therapies. Among the speakers and topics will be Thomas Lion on monitoring adenovirus infections, Paul Lambert on new approaches to papillomavirus diseases and David Bernstein on the current status of vaccines against *Herpes simplex* virus.

In addition to these excellent symposia, a diagnostic technologies workshop on Tuesday afternoon will showcase new, rapid methods to identify viral infections and ensure that patients benefit from effective antiviral therapy. Importantly, such new technologies can potentially maximize the power of clinical trials, by identifying patient populations that are infected with the virus of interest, but are free from other common infections that could mask a clinical response. The workshop will also highlight new techniques that can help drive the drug discovery process.

This will be my final message as ISAR President. Two years have flown by, and as I now turn over the Presidency to José Esté and the role of President-Elect to Johan Neyts, I'm confident that ISAR is in good hands and our future is bright. During my term as President, I've focused on increasing our membership through the new Ambassador Program, and have explored ways to involve young investigators in the Society and ICAR. In future, I hope to continue to address these goals, which are essential for our continuing success.

I wish everyone a highly successful and enjoyable 29th ICAR, and look forward to meeting everyone during the conference.

Bob Buckheit
President, ISAR

IN MEMORY OF CHRIS McGUIGAN

Christopher (Chris) McGuigan, a highly successful antiviral drug developer and long-time member of ISAR, passed away on March 11, 2016. He was the first recipient of the William Prusoff Young Investigator Award in 2001, and was elected President-Elect of ISAR in 2003, becoming President in 2006. At the time of his death, he was Pro-Vice Chancellor of Research and Innovation at the University of Cardiff and Chair of the Welsh Life Sciences Hub.

Chris received his Bachelor of Science in 1979 and his Ph.D. in Anti-cancer Drug Design in 1982, both from the University of Birmingham, UK. After a postdoctoral stay with Morris Robins, he was a lecturer at University College London from 1985-90 and at the University of Southampton from 1990-94. He then joined the Welsh School of Pharmacy in Cardiff, where



Chris McGuigan ISAR President 2006-2008

he was appointed Professor in 1995 and spent the rest of his career.

Chris was an exceptionally bright medicinal chemist, with a very broad background and insights into widely different fields of human health research. He was best known for inventing a wide variety of phosphoramidate ProTides, which optimize intracellular drug delivery and circumvent metabolic bottlenecks in the activation of nucleoside-based antivirals and anticancer drugs. At least four compounds based on this technology have entered clinical trials, including Acelarin, now in Phase III evaluation for ovarian cancer and NUC3373, which is in Phase I trials for breast and colon cancer. This work inspired the research leading to the prodrugs tenofovir alafenamide and sofosbuvir, the “backbone” drugs in the single-tablet regimens which have transformed therapies for HIV and HCV infection.

Chris was also the co-inventor of a highly potent and selective anti-VZV drug and of its phosphoramidate prodrug, which originated from a long and close collaboration with our group at the Rega Institute of the KU Leuven. The prodrug is currently in Phase III clinical trials. He also developed INX-189 for the treatment of hepatitis C, which reached Phase II trials, but was not pursued due to unexpected side-effects when trialed in conjunction with another drug. He also co-invented new glucosamine phosphates with potential use in osteoarthritis.

His many honors include the European Commission's prestigious René Descartes Prize for European Scientific Collaboration, given in 2001 as a joint award with five other collaborative European teams; the 2004 GlaxoSmithKline International Achievement Award; the 2006 Royal Society of Chemistry award in medicinal chemistry; and the 2012 Cardiff University Business Innovation Award. In 2013, he was invited by the Welsh Minister for Economy, Science and Transport to establish and chair the Life Sciences Hub Wales, a major business growth facility and a focal point for life science business in the UK.

In addition to his own achievements, Chris was an outstanding manager of a team of scientists from all over the world. He was quite demanding and extremely “punctual,” but a master at motivating his team members. At his annual Laboratory Away Day, when Ph.D. candidates and postdocs presented their results and future plans, he always invited a foreign expert to judge the results, and it was amazing to see how the students and collaborators were inspired by his drive and enthusiasm. He also possessed the art of teaching in a very entertaining manner, and could explain scientific results and their potential implications to an audience of scientists and non-scientists like no one else. Over his career, he trained more than 100 researchers, including more than 45 Ph.D. students.

Chris was an exceptionally warm, charming and generous person, with profound social and entertaining abilities. He was often the center of attention at meetings, and always had fun stories to tell. Collaborations with Chris often led to close friendships. It was an enormous privilege for our group in Leuven to collaborate with him for many years.

Chris died much too young. He still had many ideas to work out, and so many responsibilities that directly impacted the advancement of science and human health. We owe him our deep gratitude and respect for his achievements and the unforgettable interactions we had on so many occasions. We will miss him.

-- Jan Balzarini, Maria-José Camarasa, Anna Karlsson and Carlo-Federico Perno, and on behalf of their research teams.

WELCOME TO THE 29th ICAR

We are delighted to welcome our colleagues to the 29th ICAR in La Jolla. It's a pleasure and an honor to share our hometown with lead investigators contributing to exciting and dynamic progress in our field. From the remarkable list of past accomplishments in HIV and HCV, to new scientific developments with herpes-viruses, respiratory viruses and emerging global threats such as dengue, chikungunya, Zika and Ebola viruses, antiviral research has come a long way since the first

ICAR, and promises to make critically important contributions over the next few years.

We are confident that the venue will match the excellent program and list of participants for this meeting. The La Jolla Mesa co-locates many major institutions, including the University of California San Diego, the Scripps Research Institute, the Salk Institute, the Sanford Burnham Prebys Medical Discovery Institute, the La Jolla Institute, and the J. Craig Venter Institute, as well as a large number of pharma and biotech companies, which participate in this exciting progress. The meeting venue, located centrally on the Mesa, is in a beautiful setting.

We look forward to interacting with all of you, and hope you have an enjoyable and fulfilling experience at the 29th ICAR in La Jolla.

Karl Hostetler Doug Richman
Local Organizers

A BRIEF GUIDE TO LA JOLLA



The 29th ICAR site is located on the Torrey Pines Mesa, home to the University of California, San Diego, the Scripps Research Institute, the Salk Institute, the Sanford Burnham Prebys Medical Discovery Institute and the J. Craig Venter Institute. The JCVI is a recent addition to our area in a beautiful new building overlooking the Pacific. We are fortunate to have Richard Scheuermann, Director of Informatics at the JCVI, as one of our leadoff speakers. The area is also home to many of the 40+ publically traded biotech companies and innumerable startups.

The conference hotel is the Hilton La Jolla / Torrey Pines located in one of the most exceptional settings in Southern California. Atop the bluffs of La Jolla and overlooking the legendary Torrey Pines Golf Course, site of the 2008 US Open and San Diego's annual PGA Tour event. With nearly 60,000 square feet of event and meeting space, the hotel provides a setting to inspire, reward and entertain attendees. Unique in San Diego, each of the 394 guestrooms has a private balcony or patio with ocean, gardens or golf course views.

Amenities include access to exclusive guaranteed daily tee times at the highly coveted Torrey Pines Golf Course, guest privileges at the Spa at Torrey Pines and award-winning dining at Torreyana Grille. You will experience a feeling of seclusion yet remain close to everything that San Diego has to offer. Explore the stylish boutiques, museums and exceptional cuisine of La Jolla, followed by a relaxing visit to the spa or just unwind beside the pool. Enjoy the excitement of the San Diego Zoo, Sea World or the Wild Animal Park, as well as, exploring the miles of unspoiled beaches and nature trails of the Torrey Pines Reserve.

La Jolla is a few miles south, with its world-class shopping to one-of-a-kind dining, from beach culture to high culture. You'll find an amazing range of dining choices, from fine cuisine to quaint cafes, renowned restaurants to neighborhood favorites. For every occasion, for every budget, breakfast, lunch and dinner, there's a perfect menu right around the corner. The choice of celebrities and bargain-hunters alike, shoppers will find the priceless and the popular, the world's most luxurious brands and everyday values.

The Museum of Contemporary Art San Diego (MCASD) is the region's foremost forum devoted to the exploration and presentation of the art of our time, presenting works across all media created since 1950. Located in the coastal community of La Jolla and downtown San Diego, MCASD showcases an internationally recognized collection and a dynamic schedule of exhibitions.

Del Mar: A few miles north is the more relaxed surfing beach village of Del Mar, less crowded with miles of an excellent family-friendly beach and many restaurants. Karl Hostetler's favorites are Rusty's Surf Shop and Jake's restaurant on the beach.

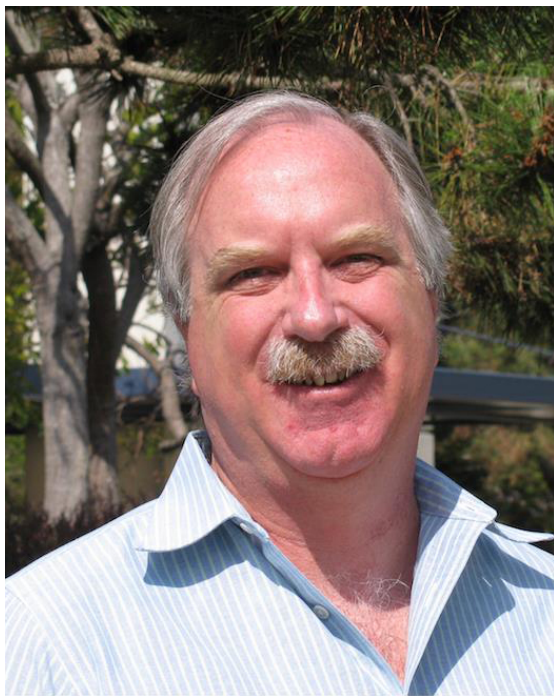
The weather is generally mild at this time in April with a low chance of moderate or heavy rain (6%). If you want to check into the weather more seriously, go to <https://weatherspark.com/averages/31573/4/San-Diego-California-United-States>

Looking forward to seeing you on April 17th.

Karl Hostetler



KEYNOTE SPEAKERS



Richard H. Scheuermann is Director of Informatics at the J. Craig Venter Institute and Professor of Pathology at UC San Diego. His research focuses on the development of novel computational methods and knowledge representation standards for the analysis of genomic sequence, gene expression, flow cytometry and biological network data in the areas of immunology and infectious disease research.

Richard has led three large NIH-funded public database projects: the Influenza Research Database (www.fludb.org), the Virus Pathogen Bioinformatics Resource Center (www.viprbrc.org) and the Immunology Database and Analysis Portal (<https://immport.niaid.nih.gov/>).



Heinz Feldmann is Chief of the Laboratory of Virology at the NIAID/NIH Rocky Mountain Laboratories. He is a globally recognized expert on highly pathogenic viruses requiring BSL-4 containment, and serves as a consultant on viral hemorrhagic fevers and outbreak management for the World Health Organization.

Heinz graduated with a B.Sc. degree in 1981 from the University of Giessen, Germany, then received a combined MD/Ph.D. degree in 1988 from the University of Marburg. His postdoctoral research in Marburg and with the Special Pathogens Branch at the US CDC focused on filoviruses and hantaviruses. He joined the Canadian National Microbiology Laboratory in Winnipeg in 1999 as chief of special pathogens, then moved to the NIAID Rocky Mountain Laboratories in 2008.

He has received a number of honors, including the Löffler-Frosch Award from the German Society for Virology, the Dalrymple/Young Award from the American Committee on Arthropod-Borne Viruses, and Research Merit Awards from the Public Health Agency of Canada and NIAID/NIH.

PROGRAM OF THE 29TH ICAR**Sunday, April 17th****2:00-4:00 Accelerating Antiviral Drug Development through Cooperation of Government, Academia and Industry**

- Introduction and overview of the Antiviral Drug Discovery and Development Center
Maaïke Everts, Ph.D., U of Alabama at Birmingham, AL, USA
- Compound management & High-throughput screening; Partners in discovery research
David Cowfer, Ph.D., Gilead Sciences, Foster City, CA USA
- High-throughput screening assays to identify antiviral agents for influenza A
Robert Bostwick, Ph.D., Southern Research, Birmingham, AL, USA
- Hit-to-lead chemistry in antiviral drug discovery
Ashish Pathak, Ph.D. Southern Research, Birmingham, AL, USA
- A small molecule inhibitor of dengue virus replication incorporates into the viral particle and blocks infectivity.
Alec Hirsch, Ph.D., Oregon Health and Science University, Portland, OR, USA
- The nucleoside prodrug GS-5734 broadly inhibits coronavirus infection and selects for resistance mutations in the nsp12 RNA-dependent RNA polymerase
Mark Denison, M.D., Vanderbilt U, Nashville, TN, USA
- Animal models of chikungunya virus infection and disease
Dan Streblow, Ph.D., Oregon Health and Science University, Portland, OR, USA

4:30-6:15 Keynote Addresses

Memorial address for Chris McGuigan, Ph.D.
Andrea Brancale, Ph.D.
Cardiff University, Cardiff, Wales

Decoding viral genomics in the Next-Generation Era
Richard Scheuermann, Ph.D.
J. Craig Venter Institute, La Jolla, CA, USA

Ebola virus: Past, present, future
Heinz Feldmann, M.D., Ph.D.
NIAID/NIH, Hamilton, MT, USA

6:15-8:15 Opening Reception

Grand Ballroom Pre-Function Area

Antiviral Research

Monday, April 18th**8:30-12:00 Structural Biology Symposium**

- Structural basis for retroviral DNA integration
Peter Cherepanov, Ph.D., Rutgers University, Piscataway, New Jersey, USA
- Combining structure, DNA, chemistry and camels to develop novel antiviral therapies
Clodagh O'Shea, Ph.D., Salk Institute, La Jolla, CA, USA
- Successful structure-based design of anti-AIDS drugs targeting HIV-1 reverse transcriptase: Overcoming resistance through strategic flexibility
Eddy Arnold, Ph.D. Rutgers University, Piscataway, NJ, USA
- RNA viral nucleases : from genome stability to innate immunity evasion.
Francois Ferron, Ph.D., Centre National de la Recherche Scientifique - Aix-Marseille Université, Marseilles, France
- Antibodies against Ebolavirus: A global collaboration
Erica Ollman Saphire, Ph.D., The Scripps Research Institute, San Diego, CA, USA

1:30-2:10 Gertrude Elion Award Lecture

Antiretroviral drugs: History and future
Douglas Richman, M.D.
Director, Center for AIDS Research, UC San Diego

2:10-4:30 Oral Session 1. *In Vitro* Evaluation and Drug Resistance

Author and reviewer awards from *Antiviral Research*

Update on clinical development of brincidofovir
Michelle Berrey, M.D., Chimerix, Durham, NC, USA

Development of GS-5734: A novel adenine nucleotide prodrug for treatment of Ebola virus infection
Rob Jordan, Ph.D., Gilead Sciences, Foster City, CA, USA

4:30-6:30 Poster Session 1**Tuesday, April 19th****8:30-9:00 Antonín Holý Award Lecture**

Acyclonucleosides to Ziagen
Robert Vince, Ph.D.
Director, Center for Drug Design, U. of Minnesota

9:00-10:45 Oral Session 2. Medicinal Chemistry

10:45-12:00 Oral Session 3. *In Vitro* Antiviral Activity**1:30-1:45 ISAR Business Meeting****1:45-2:30 Symposium on Zika Virus**

- Zika: What can we learn from other flaviviruses?
Pei-Yong Shi, Ph.D., University of Texas Medical Branch, Galveston, TX, USA
- Modeling Zika virus: cell culture and animal models for use in antiviral studies
Justin Julander, Ph.D., Utah State U, Logan, UT
- Antiviral and vaccine strategies against Zika virus
Johan Neyts, Ph.D., U of Leuven, Leuven, Belgium

2:45-4:45 Diagnostic Technologies Symposium

- Introducing the Roche cobas® 6800/8800 Virology Assays
Pedro L. Rodriguez, Ph.D., Roche Diagnostics Corporation, Indianapolis, IN, USA
- Advancing multiplex molecular diagnostics
Scott O'Brien, GenMark Diagnostics, Carlsbad, CA, USA
- FocusDx: Flexible solutions for molecular testing
Michelle Tabb, Ph.D., Focus Diagnostics, Cypress, CA, USA
- Luminex applications in research and clinical settings
Aaron Benfield, Ph.D., Luminex Corporation, Austin, TX, USA
- FilmArray – Point-of-impact rapid diagnostic improves patient care
Lou Banks, BioFire Diagnostics, Salt Lake City, UT, USA
- High-content imaging and analysis, “The Cellomics Way”
David Sweeney Ph.D., Thermo Fisher Scientific, Waltham, MA, USA

Wednesday, April 20th**8:30-9:00 William Prusoff Young Investigator Award Lecture**

New frontiers in antiviral drug development: Inhibiting the polymerase of (-)strand RNA viruses

Jerome Deval, Ph.D.

Scientific Director, Alios Biopharma, South San Francisco, CA

9:00-12:00 DNA Viruses Symposium

- Adenovirus monitoring and treatment in immunocompromised patients
Thomas Lion, M.D., Ph.D. Children's Cancer Research Institute (CCRI), Vienna, Austria

- Using preclinical models for papillomavirus-induced disease to define novel therapeutic and preventative strategies.

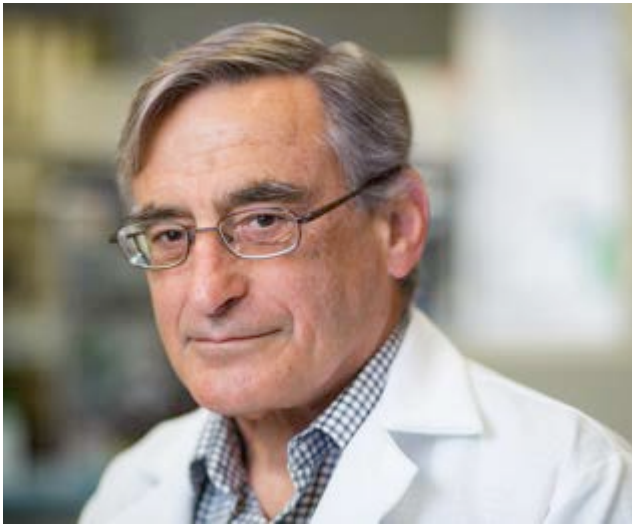
Paul F. Lambert, Ph.D., U of Wisconsin, Madison, WI, USA

- Leveraging population genetics to reveal clinically relevant aspects of CMV evolution,
Timothy Kowalik, Ph.D., U of Massachusetts Medical School, Worcester, MA, USA
- Roseoloviruses: ships or icebergs in the “Sea of Pathogens”?
Phil Pellett, Ph.D., Wayne State U, Detroit, MI, USA
- Update on *Herpes simplex* virus vaccines; are we getting closer?
David Bernstein, M.D., U of Cincinnati, Cincinnati, OH, USA

1:30-4:30 Oral Session 4. Mechanism of Action Studies**4:30-6:30 Poster Session 2****Thursday, April 21st****8:30-10 Clinical Session**

- Role of adenovirus species and type in virologic response to brincidofovir
Randall Lanier, Ph.D., Chimerix, Durham, North Carolina, USA
- Clinical pharmacokinetics of MBX-400, a potent antiviral in development for CMV and HHV6
Jennifer Brooks, M.S. Microbiotix, Inc., Worcester, Massachusetts, USA
- Oral favipiravir for severe Ebola virus infection
Rui-Yuan Cao, Ph.D., *Wu Zhong, Ph.D.*, Beijing Institute of Pharmacology and Toxicology, Beijing, China

10:30-12:00 Oral Session 5. Animal Models of Infection

ISAR AWARD WINNERS
Winner of the Gertrude Elion Memorial Lecture Award: Douglas D. Richman, M.D.

Doug Richman is Distinguished Professor of Pathology and Medicine at the University of California, San Diego, and Director of the Center for AIDS Research. His laboratory investigates many aspects of the natural history and molecular pathogenesis of HIV infection, and has been at the forefront of the evaluation of antiretroviral therapies and the study of HIV latency.

Doug received his M.D. degree and performed a medical residency at Stanford University, then spent two years as a research associate in the NIAID/NIH Laboratory of Infectious Diseases. After a fellowship at Beth Israel Hospital and Children's Hospital Medical Center of Harvard, he joined the UCSD faculty in 1976.

With the emergence of HIV in the early 1980s, his laboratory performed pioneering studies of the pathogenesis of AIDS and assessment of the first antiretrovirals [1,2]. His group was the first to identify HIV drug resistance [3,4], and later documented the impact of resistance on treatment failure, the presence of mixtures of different viral phenotypes and genotypes in the same patient and the pre-existence of drug-resistant mutants in untreated patients. These studies helped to establish the importance of drug resistance assays in the day-to-day management of HIV infection.

Doug's team at UCSD also joined with others in identifying latently infected CD4 cells as the obstacle to eradication of HIV infection through antiretroviral therapy [5,6]. Major areas of investigation have included the development of assays to measure the viral reservoir in various body compartments, characterization of various subsets of CD4 lymphocytes as targets of intervention strategies and efforts to reliably measure the impact of such interventions. His

research has also focused on virological and host determinants of HIV transmission and their implications for the development of an effective vaccine.

What are the greatest challenges for HIV research?

Now that we've developed antivirals to suppress the virus and its consequent transmission, the major issues for antiretroviral therapy are resources and delivery of treatment to all HIV-infected individuals. There are two critical challenges for HIV research: to develop a vaccine for people not yet infected, and for those already infected, we need to find a cure. This is a new opportunity for drug discovery.

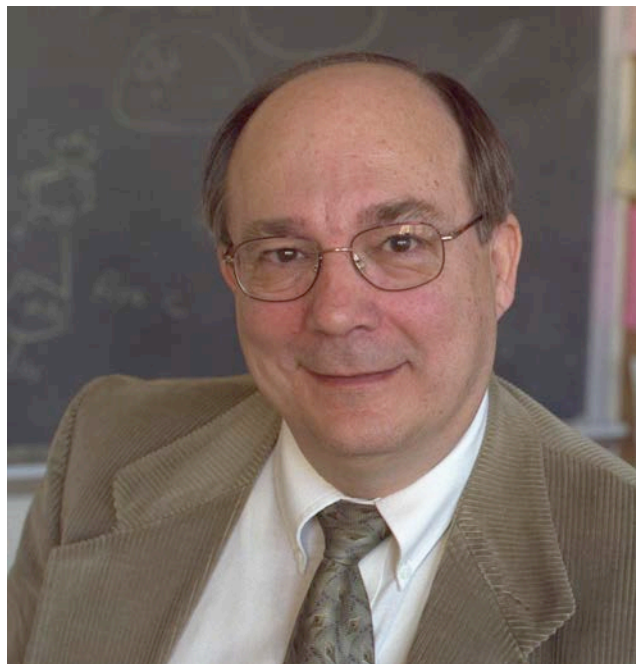
What part of your career has been the most exciting?

There have been two "most exciting" periods. The first was being involved in the clinical development of the first antiretroviral drug (AZT) and identifying the development of drug-resistant mutants, which has turned into a major aspect of both drug development and clinical management. The second was documenting that the latent reservoir was the obstacle to a cure. This has grown into a major objective of current research.

How has ISAR contributed to your career?

I of course enjoy meeting old friends (some of them are actually getting old) and meeting new ones who are doing interesting things. What is remarkable is that when I first went to an ICAR, our only drugs were amantadine and vidarabine. Now we have more than 50 antivirals and have treated millions infected with HIV and HBV and will cure millions with HCV.

1. Fischl MA, Richman DD, et al. The efficacy of 3'-azido- 3'-deoxythymidine in the treatment of patients with AIDS and AIDS-related complex: double-blind, placebo-controlled trial. *New Engl J Med* 317: 185-191, 1987.
2. Richman DD, et al. The toxicity of 3'-azido-3'-deoxythymidine in the treatment of AIDS and AIDS-related complex: a double-blind, placebo-controlled trial. *New Engl J Med* 317: 192-197, 1987.
3. Richman DD, Andrews J. Results of continued monitoring of participants in the placebo-controlled trial of zidovudine for serious human immunodeficiency virus infection. *Am J Med.* 1988; 85:208-13.
4. Larder BA1, Darby G, Richman DD. HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. *Science.* 1989; 243:1731-4.
5. Wong JK et al. Recovery of replication-competent HIV despite prolonged suppression of plasma viremia. *Science.* 1997; 278:1291-5.
6. Finzi D, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. *Science.* 1997; 278:1295-300.



Winner of the Antonín Holý Memorial Lecture Award: Robert Vince, Ph.D.

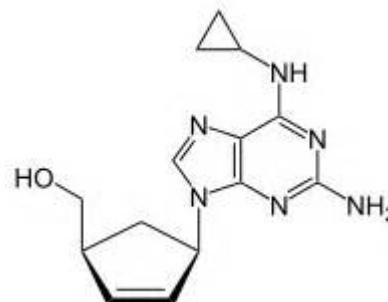
Robert (Bob) Vince is Director of the Center for Drug Design and Professor of Medicinal Chemistry at the University of Minnesota. He is best known for his research on carbocyclic nucleoside analogues, which led to the development of the highly effective HIV reverse transcriptase inhibitor abacavir.

He obtained a bachelor's degree in pharmacy at SUNY Buffalo in 1962, then stayed on to join the research group of Howard Schaeffer, receiving his Ph.D in medicinal chemistry for studies of the synthesis and biochemical activity of acyclic nucleoside analogues [1]. Their investigation of acycloadenosine was an early step on the road to the discovery of acyclovir.

Schaeffer then moved to Burroughs Wellcome and began working with Gertrude Elion, while Bob joined the medicinal chemistry faculty at the University of Minnesota. His major focus was the characterization of carbocyclic nucleoside analogues, which appeared to have promising anticancer and antiviral activity [2]. By the early 1980s, he had demonstrated that carbocyclic arabinofuranosyladenine (cyclaradine) was active against herpesvirus infection in guinea pigs [3]. However, the emergence of HIV revealed the true importance of these compounds, as some carbocyclic dideoxynucleoside analogues were found to inhibit reverse transcriptase.

The initial series of compounds, dubbed "carbovir" were 6-substituted derivatives of the parent compound, 2',3'-dideoxy-2',3'-didehydroguanosine. The molecule with a cyclopropyl group on the 6-amino nitrogen of the

adenine ring, which became known as abacavir (below) was selected for commercial development [4].



Abacavir proved to be rapidly absorbed from the GI tract, and had good CNS penetration. Although Glaxo licensed the carbovir in 1988, abacavir did not reach the market until 1998, when it was released as *®*Ziagen.

The commercial production of abacavir and related molecules was markedly facilitated by Bob's development of the bicyclic molecule γ -lactam 2-azabicyclo [2.2.1]hept-5-en-3-one. This compound, now known in the world of medicinal chemistry as "Vince lactam," is a convenient starting point for the synthesis of a variety of carbocyclic nucleosides [5], and also provides a scaffold for other therapeutic molecules, such as glycosidase inhibitors.

The royalties from abacavir enabled the University of Minnesota to establish the Center for Drug Design, which Bob has directed since 2002. Among his many honors, he was inducted into the Medicinal Chemistry Hall of Fame by the American Chemical Society in 2007 and was awarded an honorary Doctorate of Science degree by his alma mater, SUNY–Buffalo, in 2010. The International Society for Nucleosides, Nucleotides and Nucleic Acids selected him for the 2010 Imbach Townsend Award.

What are the most important challenges for the development of new antiviral drugs?

The most important challenges are identifying new targets for drug design. Back in the early 70s, the general thinking was that nucleoside analogs were not good candidates for antiviral agents because they would have to act like anticancer agents and would be too toxic to be useful. We know today that that is not true.

What period of your career has been the most exciting?

The most exciting part of my career has been director of the Center for Drug Design. The availability of royalty funds from the development of Ziagen has allowed me to initiate new research projects in areas unrelated to those previously funded by my research grants. Thus, in addition to our antiviral and anticancer projects we've established programs in areas such as detection of early Alzheimer's disease, protection of DNA damage and stimulation of DNA repair agents, interferon stimulation, anti-aging, wound healing, etc.

What aspect of research have you found most satisfying?

Just spending time in the lab each day with my research group and discussing the results and details of ongoing projects.

1. Schaeffer HJ, Gurwara S, Vince R, Bittner S. Novel substrate of adenosine deaminase. *J Med Chem.* 1971;14:367-9.
2. Vince R, Daluge S. Carbocyclic arabinosyladenine, an adenosine deaminase-resistant antiviral agent. *J Med Chem.* 1977; 20:612-3.
3. Vince R, Daluge S, Lee H, Shannon WM, Arnett G, Schafer TW, Nagabhushan TL, Reichert P, Tsai H. Carbocyclic arabinofuranosyladenine (cyclaradine): efficacy against genital herpes in guinea pigs. *Science.* 1983; 221:1405-6.
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Winner of the William Prusoff Young Investigator Award : Jerome Deval, Ph.D.

Jerome Deval is a Scientific Director and head of the Biochemistry group at Alios BioPharma, where his team focuses on the discovery and development of novel antivirals against a number of clinically important RNA viruses, including respiratory syncytial virus (RSV), hepatitis C and influenza.

One of their lead candidates, the novel nucleoside analogue ALS-8176 [1,2], entered Phase I trials in early 2013, and is now being evaluated in RSV-infected adults and hospitalized infants. The HCV polymerase inhibitor ALS-2200/VX-135 reached Phase II clinical trials, while their newest anti-HCV nucleotide analog, AL-335, is currently being tested in Phase II combination therapy. Jerome is also a member of the team that discovered a novel class of influenza polymerase inhibitors; one of them, AL-794, is being tested for safety and efficacy in an influenza challenge study.

Jerome obtained his Ph.D. in Applied Microbiology from the National Center for Scientific Research (CNRS), University of Provence, Marseille, France, in 2004, under the mentorship of Bruno Canard. He then spent two years as a postdoctoral fellow at McGill University with Matthias Gotte, where he continued to study the HIV reverse transcriptase and developed biochemical assays for the HCV polymerase. He joined Roche Pharmaceuticals as a research virologist in 2006, then moved to Alios BioPharma in South San Francisco in 2009.

One of Jerome's main responsibilities at Alios is to develop *in vitro* methods to identify novel nucleoside analogues aimed against a large spectrum of RNA viruses [3-5]. Alios became an affiliate of Janssen, the pharmaceutical division of Johnson & Johnson, in 2014, and he became Scientific Director in January, 2015.

What are some of the most important challenges for antiviral researchers?

I believe transitioning the focus from chronic to acute viral infections represents an important change, and a tough challenge, in the way we need to think about drug discovery and drug development. There are now a number of ongoing clinical studies, with first-in-class drug candidates, that will soon inform us on the potential to effectively treat acute viral infections in hospital and outpatient settings.

During your career, what aspect of research have you found most satisfying?

I consider myself a bench scientist, so I really enjoy finding the time to be in the lab to conduct experiments. For example, I still get excited by a SDS PAGE when a novel protein construct is being expressed and purified for the first time. I also love the experience of testing newly synthesized molecules in the first biological assay. Being in a work environment that brings together biologists and chemists, where scientific discoveries translate to new drug candidates with the potential to save lives, is incredibly satisfying. This is also why I really enjoy working on viruses against which no effective therapies are yet available.

What new laboratory methods hold the most promise for antiviral drug development?

A lot of the projects in which I am currently involved are limited by the ability to produce large amounts of functional protein target(s). Recent progress in rapid screening and optimization of protein production conditions using modern molecular biology and biochemistry methods has really opened new avenues for drug discovery. This is particularly true for large protein complexes such as influenza and RSV polymerases. Combined with recent breakthroughs in crystallography, these advances in protein biochemistry will further enable structure-based drug design as a method of choice for antiviral research.

How has ISAR contributed to your career?

My first ICAR was in 2002 in Prague. Over the years, I have developed friendships with many other ISAR members, some of whom have become collaborators or colleagues. The conference always gives me the opportunity to keep up with academic and industry research that is directly relevant to my work.

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3. Deval J, et al. Inhibition of viral RNA polymerases by nucleoside and nucleotide analogs: therapeutic applications against positive-strand RNA viruses beyond hepatitis C virus. *Curr Opin Virol.* 2014 Dec;9:1-7.
4. Jin Z, et al. Biochemical Evaluation of the Inhibition Properties of Favipiravir and 2'-C-Methyl-Cytidine Triphosphates against Human and Mouse Norovirus RNA Polymerases. *Antimicrob Agents Chemother.* 2015; 59:7504-16.
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WOMEN IN SCIENCE



The Women In Science (WIS) committee is looking forward to ICAR in La Jolla! Pictured above are its happy members at the 28th ICAR in Rome; from left to right are Graciela Andrei, Kara Carter, Amy Patick, Heather Greenstone, Kathie Seley-Radtke, Jennifer Moffat, Rhonda Cardin and Karen Buckheit.

WIS Roundtable (Amy Patick and Karen Buckheit)

The 4th Annual Women in Science Roundtable, the first event on the first day of ICAR, will be held on Sunday, April 17, from 11:30-2:00 PM. It is open to both women and men, and will feature discussions on the challenges and opportunities encountered by women scientists while navigating the twists and turns of career progression in today's environment.



Kara Carter leads a discussion with roundtable attendees at her table at the 29th ICAR in Rome.

Please join us to network with fellow scientists in industry, government, and academia, who conduct all aspects of antiviral research. This roundtable will use a lively 'speed mentoring' approach, in which moderators will move from table to table to facilitate small group conversations on the following topics:

- Do Super-Women Exist? How to balance work and family through all stages of life. (Moderators: Kathie Seley-Radtke and Zlatko Zenaba)
- Where do I Go From Here? Maximize the benefits of the mentor-mentee relationship (Moderators: Jennifer Moffat and Bart Tarbet)
- Negotiation: Tips on how to secure a mutually advantageous outcome without selling yourself short (Moderators: Rhonda Cardin and Robert Buckheit)
- Is There a Glass Ceiling Left to Crack? How to manage workforce equality (Moderators: Karen Buckheit and Heather Greenstone)
- Awards and Recognition: Learn effective self-promotion to gain recognition and achieve professional goals (Moderators: Graciela Andrei and Enzo Tramontano)
- Communication and Management Styles: Understanding gender differences (Moderators: Kara Carter and Bobby Buckheit)

The event is free, but it's limited to 80 participants, so register now! Select "Women in Science Roundtable" in the Events section when you register for ICAR. Lunch will be provided.

2016 Chu Family Foundation Scholarships (Amy Patick)

Thanks to a generous donation from the Chu family, seven young women with the potential to make significant contributions to the field of antiviral research will receive Chu Family Foundation (CFF) Scholarships in 2016. This year, there were 19 applicants from all over the world: Northern Ireland, Finland, Greece, Italy, Argentina, Hong Kong, Spain, Australia, and the United States. All were highly competitive. Five were chosen to receive \$1500 scholarships, and two received \$750 honorable-mention awards.

The scholarship funds may be used to attend a conference, visit a laboratory, take a course or acquire specialized training. The awards 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 be an undergraduate or grad student, or have no more than five years of cumulative postdoctoral experience. The CFF and WIS Committees will present the awards at ICAR.

WIS Mentoring Program (Rhonda Cardin and Jennifer Moffat)

The Mentoring Program was launched at the 2014 ICAR in Raleigh, NC, when Roundtable participants were asked if they would like to be mentored or serve as mentors. Mentees and mentors were matched after

filling out a questionnaire on their current interests, career goals, and what each of them wanted to achieve.

After its start in Raleigh, the program grew significantly at the 28th ICAR in Rome, when women registrants were asked to fill out the questionnaire before the meeting. The WIS Committee then matched prospective mentors and mentees so that they could have their first face-to-face meeting in Rome. It was a huge success, as many new female ISAR members participated in the program. There was definitely a buzz in the air as mentors and mentees met for the first time!

After two years, 14 mentors have been matched with 25 mentees. The mentors are from the USA, Belgium, and Brazil, while the mentees are located around the world, including Germany, Nigeria, Bulgaria, United Kingdom, Bosnia and Herzegovina, The Netherlands, Canada, Luxembourg, France, South Korea, India, and the USA.

Following their first face-to-face meeting, mentors and mentees have contact either by email, phone, or skype. Mentors provide career advice and scientific expertise in academia and the pharmaceutical industry. The response has been overwhelmingly positive. Significantly, the program has brought together women scientists from all aspects of antiviral research and at different stages of career development, and many new relationships have been forged.

This year, we hope to increase the numbers of mentors and mentees even more! If you've attended previous Roundtables, please consider joining the mentoring program, and if you've been a mentee, maybe it's time for you to become a mentor! We especially need mentors from Europe, in the same time zone as some of the mentees. If you're interested in joining this program, be sure to attend the WIS Roundtable, where there will be a designated meeting place for mentors and mentees. Look for the "WIS Mentoring Program" sign! More information will be provided for additional meeting times at the meeting.

Changing of the Guard! (Rhonda Cardin)

First, let's have a huge round of applause for Amy Patick, Chair of the WIS Committee and former ISAR President, for her ideas and limitless energy to create the exciting WIS Program that has brought so many opportunities to ISAR women scientists. Her creativity and passion have left a positive impact on ISAR, as seen by the success of the WIS Roundtable, WIS and CFF Scholarships, and Mentoring program. Amy will soon pass the torch, but not before she has one last hurrah in La Jolla! She will remain an active member of the WIS committee, especially the CFF Scholarship program.

After the conclusion of the 29th ICAR, Rhonda Cardin will become WIS Chair. Rhonda has played an important role in leading the Mentoring Program, which will now be led by Jennifer Moffat. Karen Buckheit will take charge of the WIS Roundtable, and she'll be

looking for new ideas from ISAR members to make the event even more helpful to women scientists. Finally, many thanks to all the members of the WIS Committee for their hard work and dedication as we move forward.



The 9th ICAR in Fukushima, Japan. *Front row, left to right:* Masaro Kaji, Rich Whitley, George Galasso, Hugh Field, Earl Kern, local host Shiro Shigeta, Mrs. Shigeta, Erik De Clercq, John Martin. *Second row:* Yoshio Koyanagi, Dennis Lambert, Lorne Tyrrell, unidentified, Paul Lietman, John Huggins, Marleen and Koen Andries, Doug and Eva Richman. *Third row:* Naoki Yamamoto, unidentified, Yoichi Minamishima, Kaneo Yamada, Akira Matsuda, unidentified, Katsuhiko Ono, Kunitada Shimotono, Masanori Baba, unidentified, Charles and Carole Flexner. *Fourth row:* Ray Schinazi, Masahiko Ito, Tomoyuki Yokota, Kazuo Takahashi.

ICAR THROUGH THE YEARS

20 years ago: 1996 ICAR in Fukushima, Japan

The 9th ICAR was held at the Urabandai Nekoma Hotel on 19-24 May, 1996. The meeting was jointly sponsored by the Japanese Association for Antiviral Chemotherapy, with Shiro Shigeta of Fukushima Medical College as the lead local organizer. A number of members of the JAAC are shown in the photo above.

In 1996, Hugh Field was ISAR President, George Galasso was Past-President and Earl Kern was President-Elect. Koen Andries was secretary, Jack Secrist was treasurer and Rich Whitley chaired the program committee.



Mike Ussery and Joe Colacino study posters at the 9th ICAR. Joe confesses "I still have that awful tie."

The ISAR award lectures had not yet been instituted. Plenary presentations included David Ho speaking on HIV; Karen Lindsay on therapeutic trials for hepatitis C; Akira Matsuda on SAH hydrolase inhibitors; and John Huggins on therapy of emerging virus infections.

10 years ago: 2006 ICAR in San Juan, Puerto Rico

The 19th ICAR was held at the Caribe Hilton Hotel. Jack Secrist was ISAR President, John Drach was Past President and Chris McGuigan was President Elect. Amy Patick was secretary, John Morrey was treasurer and John Drach chaired the program committee.

The Elion Award was presented to Bob Sidwell, who gave a lecture on “Influenza: Search for a cure.” Tomás Cihlar received the Prusoff Young Investigator Award, and spoke on “Understanding the biological attributes of nucleoside phosphonates: from the first (cidofovir) to the newest (GS-9131).”



Left to right: Erik De Clercq, George Galasso, Hugh Field, Earl Kern, Jack Secrist, Chris McGuigan and Amy Patick.



Jim Noah, Bob Buckheit and Tracy Hartman judge posters.



ISAR President Jack Secrist presents Tomás Cihlar with the William Prusoff Young Investigator Award.



Bob Buckheit recalls that in 2006 “ISAR was going through some financial issues... Things were cut back to the bare bones, and we ran out of food at the reception.” This photo appears to show members discussing possible sources of nutrition, and who should climb the trees in search of coconuts.

ISAR member profile: José Esté

ISAR President-elect José Esté is head of the HIV Pathogenesis Laboratory at the AIDS Research Institute IrsiCaixa, Hospital Germans Trias i Pujol in Badalona (Barcelona), Spain. He did his undergraduate studies at Western University, Ontario, Canada; obtained a masters degree in biochemistry from the Venezuelan Institute for Scientific Research; and performed Ph.D. research in medical science at the Katholieke Universiteit in Leuven, Belgium.



The HIV Pathogenesis Laboratory at IrsiCaixa. Left to right: María Pujantell, Judith Grau, Ester Ballana, Roger Badia, José Esté, Eva Riveira-Muñoz and Guillem Angulo.

How did you get started in antiviral research?

My interest in antiviral drug testing began when I was a student in Venezuela, working in the AIDS lab of the National Institute of Hygiene in Caracas. After finishing our routine work, a colleague and I would spend our afternoons evaluating the antiviral activity of a large collection of compounds, extracts and natural products. I soon found myself applying to study at KU Leuven and to work at the Rega Institute for Medical Research, under the guidance of Erik De Clercq.

At the Rega, I began studying the mechanism of HIV entry, which was then a focus of intensive research, with great expectations for its potential as a drug target. The chemokines CCL3, CCL4 and CCL5 had just been identified as inhibitors of HIV-1 replication, and the chemokine receptors CCR5 and CXCR4 (then termed “fusin”) were known to be coreceptors for HIV entry into CD4+ cells. This helped to explain HIV tropism, which previously had been thought of as either “macrophage-tropic” or “T-cell-tropic”. CCR5 became the target of drugs now in use (1, 2), and it’s also the

center of current gene-editing strategies attempting to cure HIV infection.

The bicyclams, a class of entry inhibitors with an elusive mode of action, also became part of my research. Bicyclams were finally identified as specific antagonists of CXCR4 (3, 4). The prototype became a marketed drug for mobilizing stem cells (5, 6), and also an excellent tool to study virus-coreceptor interactions and entry. Since that time, my research interests have focused on how cellular cofactors affect virus replication and how they might be used to intervene in infection and disease.

Working for Erik in Leuven also resulted in my first contact with ISAR. I attended ICAR for the first time as a graduate student in the mid-90s, and I’ve participated continually over the years, but I never expected to be so deeply involved in the management of the Society!

HIV research in Barcelona

On completing my Ph.D. studies, I joined the Retrovirology Laboratory of the Hospital Germans Trias i Pujol in Badalona (Barcelona), which was later to become the AIDS Research Institute IrsiCaixa. I was excited to be leading my own research group at a relatively early stage of my career, in a place where fundamental and clinical research combine to provide solutions for patients. I am also a faculty member of the immunology program of the Universitat Autònoma de Barcelona.

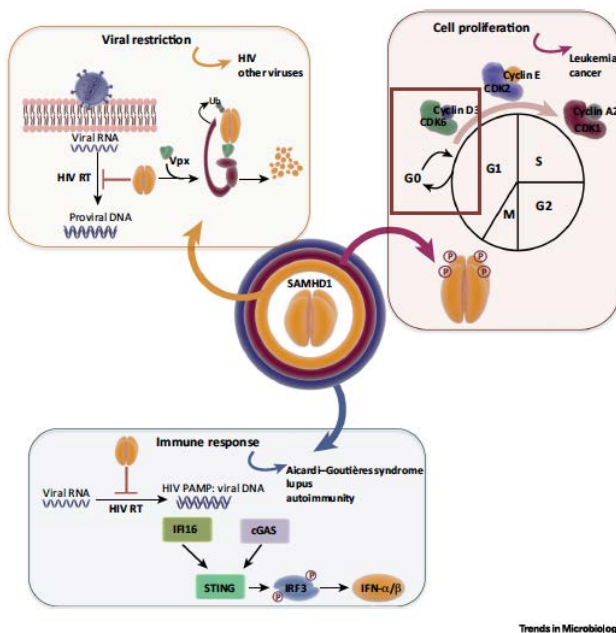
Our clinical unit follows some 2000 patients, many of whom participate in clinical trials and collaborate in our research. During my time at the IrsiCaixa, I’ve witnessed how HIV infection has been converted from a deadly disease with poor treatment options to a manageable chronic condition, and I’m happy that I’m still seeing patients I first met 19 years ago! We now have the knowledge and the tools to halt AIDS, but political will, full access to medicines and education are needed to control the spread of infection in less fortunate countries that have been hit hard by the pandemic.

What are the current priorities for HIV research?

HIV infection is treatable and manageable, but there is still no cure, and an effective vaccine is nowhere in sight. Despite outstanding advances in deciphering the immunology and pathogenesis of HIV infection, the knowledge and tools to design effective preventive and therapeutic vaccines are still not available, including the unambiguous identification of adequate surrogate markers of protection. Evaluating the efficacy of HIV vaccines therefore requires long and costly clinical trials, just to have a glimpse of their potential use. However,

there is now cautious optimism regarding the early clinical development of a number of vaccine candidates and broadly neutralizing antibodies, and the field has come to realize that without a vaccine there won't be an end to HIV.

My lab's current line of research attempts to understand host-pathogen interactions, how HIV cofactors affect virus replication and the cellular mechanisms that affect virus persistence. HIV integrates into the cellular genome, and cells may become latently infected for life. If antiretroviral treatment is interrupted for any reason, viremia rebounds within days and treatment needs to be resumed. How HIV is reactivated is a subject of intensive research world-wide, as it is perceived as a strategy to purge latently infected cells. Even though this strategy may eventually prove to be wrong, it will certainly represent the basis of future and effective treatments aiming at eradicating HIV from the body.



Trends in Microbiology

The cellular protein SAMHD1 functions as a triphosphohydrolase, reducing intracellular titers of dNTP required for DNA synthesis, cell proliferation or HIV-1 reverse transcription. Mutations in *SAMHD1* are associated with aberrant DNA synthesis and auto-immune disease. From (7), with permission.

My group has recently identified the biochemical pathway leading to the activation and deactivation of SAMHD1, a host factor that restricts HIV-1 infection in non-proliferating cells such monocytes, macrophages and dendritic cells (7). Intracellular restriction of HIV replication appears to be tightly dependent on and

controlled by the cell cycle. A precisely orchestrated system allows cells to proliferate, and any deviation leads either to aberrant cell proliferation and cancer or to DNA damage, apoptosis or cell death.

Cell proliferation is also tightly linked to how cells detect incoming pathogens and trigger an innate antiviral response. Thus, this same system in which cellular checkpoints control DNA replication and transcription may provide the basis to understand innate immunity to HIV infection, how and when provirus is awakened and transcribed and importantly, how cell proliferation is affecting the persistence of HIV through, for example, homeostatic cell proliferation of infected cells.

We are beginning to explore how drugs targeting the cell cycle and cell proliferation (8, 9) may be used to intervene in HIV replication and latency and to block the expansion of infected cells. The recent identification of proviral DNA integration into genes associated to cancer and cell-cycle regulation (10), and the observation that such regulation appears to serve as an important mechanism of viral persistence, may indicate that therapies that target HIV-infected proliferating cells may be implemented to cure HIV infection (11).

The importance of ISAR

ISAR has meant a lot to my scientific career. Many times the conference has served as a perfect platform for me to convey and discuss my group's research and effectively seek the collaboration of others. I've learnt a great deal about drug development and the close collaborations between academia and industry that are required to bring a new drug closer to the patient.

In a time when many complementary scientific meetings occur simultaneously, and technology has brought us closer together, ICAR still represents an excellent platform with a characteristic multi-disciplinary component, that stands out from other meetings focused on virology, drug development or medical science. It provides the perfect stage for students and young researchers to come into contact with scientists and stake-holders in identifying, characterizing and developing new antiviral agents, all the way from the drawing board to the bench to the clinic. ISAR is making great efforts to support and encourage the participation of young researchers, and I invite them to become involved in the Society, as I once did.

In 2010, I received the William Prusoff Young Investigator Award. I've been a member of the ISAR Board of Directors for a number of years, and was elected President-Elect in 2015, with my term as

President beginning at the end of the meeting in La Jolla. As I now prepare to take over the leading role, I can only feel indebted to ISAR.

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ISAR member profile: Kathie Seley-Radtke

Recently reelected to the ISAR Executive Board for a second term, Kathie has been a Society member since the early 1990's and has served as Chair of Poster awards for the past four years. She is currently a Professor of Chemistry & Biochemistry at the University of Maryland, Baltimore County (UMBC), the UMBC Presidential Research Professor, and also the President of the International Society of Nucleosides, Nucleotides & Nucleic Acids (IS3NA).



The Seley-Radtke Research Group at UMBC. Left to right, front row: Saifidin Safarov, Kathie, Aarti Shah; middle row: Alex Kuznetsov, Natalie Steenrod, Mary Yates, Therese Ku; back row: Mithun Raje, Brian O'Conner, Alex Vega, Matt Shirley and Brian Cawrse.

How did you get started in antiviral research?

It seems like I've always loved science. Growing up in Erie, PA, I was in a combined high school-college program, and it was genetics I found most attractive. For my first research project, I bought two black-and-white-spotted mice at a pet shop and bred them until they produced a pure black strain. It took a year and a half, and at one point I had more than 200 mice in my bedroom, which drove my parents (and our cat) crazy!

Eventually my interests shifted from mice to chemistry, when I had two wonderful organic chemistry professors at St. Petersburg College in Clearwater, Florida. A few years later I found myself gravitating towards medicinal chemistry, because I wanted to do

something applied, and the chance to spend my life looking for ways to cure diseases was very exciting.

Stew Schneller was the chair of the chemistry department at the University of South Florida, and I joined his lab as a graduate student in 1990. My initial project focused on synthesizing cyclobutyl nucleosides related to lobucavir, with the goal of inhibiting hepatitis B virus. Two years into my Ph.D., Stew moved to Auburn University to become Dean, and so I moved to Auburn to finish up my research. By then I was working on a series of carbocyclic 5'-nor nucleosides, specifically unnatural L-like nucleosides. After receiving my Ph.D. from Auburn, I stayed on with Stew as a postdoc for another two years, and continued to focus on the design and synthesis of carbocyclic nucleoside analogues as antivirals.

Carbocyclic nucleosides and other molecules

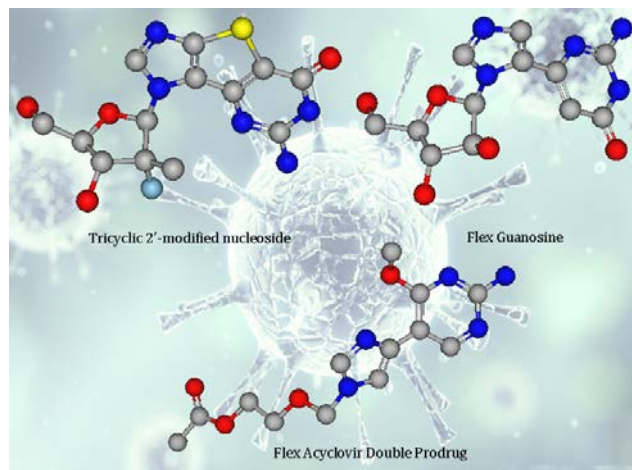
At the time we were especially interested in the inhibition of S-adenosylhomocysteine hydrolase, as a way of shutting down viral and parasitic replication pathways. Our compounds were screened against many viruses, so we often changed targets based on the results of drug screening. This work brought me into contact with many long-term collaborators at the Rega Institute, including Erik de Clercq, Jan Balzarini, Johan Neyts, Graciela Andrei, Robert Snoeck and Lieve Naesens, and also with researchers at other institutions, including Brent Korba, Earl Kern and Dale Barnard, all of whom have remained good friends.

After I left Stew's group to begin my independent career at Georgia Tech, I continued to work on carbocyclics, but also decided to expand the scope of my projects and the potential viral target landscape. My primary focus turned to the design and synthesis of ribose and 2'-deoxyribose nucleoside analogues. One of my first NIH-funded projects was centered on a series of nucleosides with "expanded purine" and "extended pyrimidine" nucleobases¹, related to Nelson Leonard's expanded lin-benzoadenosine analogues.² While doing basic chemistry, our main priority remained in development of novel antivirals, and it was from the expanded purine project that the "fleximers" that my lab is known for ultimately evolved. Since then we've seen success for these structurally unique nucleosides against a number of viruses, and even some parasites.

The development of novel "fleximers"

Since joining UMBC, my primary focus has been the synthesis and characterization of various classes of flexible nucleosides.^{3, 4} As shown in Figure 1, these molecules have a "split purine" heterocyclic base that permits them to turn and rotate, while remaining

connected by a single carbon-carbon bond. They therefore retain the key features needed for hydrogen-bonding and base-pairing, but are also able to reposition within an enzyme binding site, when faced with steric or electronic clashes.⁵⁻⁷ Because viral drug resistance often develops through point mutations in enzyme binding-sites, the fleximers possess advantages over conventional, rigid nucleoside analogues.



Some of our structurally diverse nucleosides. Upper left: 2'-modified thiophene-expanded purine analogue that showed activity against HCV; Upper right: Flex-G, first guanosine analogue reported to inhibit S-adenosylhomocysteine hydrolase – an adenosine metabolizing enzyme; Bottom: double prodrug of Flex-Acyclovir – first nucleoside analogue reported to exhibit potent activity against coronaviruses, specifically MERS-CoV.

My team at UMBC has pursued several different types of fleximers with various modified sugars, including a series of 2'-modified analogues related to sofosbuvir and gemcitabine,^{8, 9} as well as carbocyclic fleximers^{10, 11} and 2'-deoxy analogues.¹² Some of these molecules inhibit a variety of viruses and parasites, but our primary focus is now on the recently developed doubly-flexible analogues because of their potent activity against coronaviruses.

Last year we published the first report of a nucleoside analogue (Flex-Acyclovir) that inhibits the MERS coronavirus¹³, and we'll soon be reporting our most recent results with additional analogues, which have exhibited even better selectivity and potency. In the meantime, our colleagues in Leuven and Leiden have been screening several prodrugs of the double fleximers, and the corresponding triphosphate of Flex-Acyclovir is about to enter testing as well. We're also

synthesizing a second series of doubly-flexible analogues based on tenofovir.

In a related project, we've been collaborating with Sina Bavari and Veronica Soloveva at USAMRIID and with Sam Lee, Doug Mayers and others at CoCrystal to develop antivirals against Ebola virus. We hope to report results for that project in the coming months as well.

A third project centers around disrupting the protein-protein interactions of the HIV nucleocapsid protein, NCp7 with Flex-base analogues. In terms of other heterocyclic base inhibitors, we also work closely with two groups in Russia. My collaboration with Mikhail Novikov of Volgograd Medical University have uncovered a number of potent non-nucleoside inhibitors of various viruses,¹⁴ including HIV. A second project with my good friend Anastasia Khandzhinskaya and our former joint graduate student Lena Matugina at the Engelhardt Institute of Molecular Biology in Moscow focuses on some non-nucleoside/carbocyclic nucleoside hybrid molecules to fight tuberculosis.

You've also received funding to work on anticancer drugs - how did that come about?

This dates back to my first project at Georgia Tech, involving expanded purines and extended pyrimidines. About eight years ago one of my grad students, Kartik Temburnikar, was assigned to tackle the extended pyrimidine part of the project. These were a series of C-nucleosides with thieno- and pyrrolo-pyrimidine bases. Interestingly, we had made the thiophene-expanded purine base back in 2000¹, and it exhibited some anti-cancer activity, but it got buried in the excitement over the fleximer project, and was somewhat forgotten. When Kartik came across that paper four years ago, he decided to send both the nucleobases and the nucleosides for screening, and thank goodness he did!

To make a long story short - Jan Balzarini did some tox studies, and this gave us our first clue that the compounds might have some value against cancers. Screening by NCI revealed low-nanomolar activity against a number of important cancers. A UMB collaborator observed tumor shrinkage of 50% in 7-14 days in a mouse melanoma xenograft model, with no toxicity (unlike temozolomide, the standard of care, which is fairly toxic). As a result, we then screened against other cancers, and recently obtained funding to test these compounds in animals, targeting leukemia and non-small-cell lung, pancreatic and triple-negative breast cancer. We're encouraged that these compounds may provide a cheaper alternative to some very expensive drugs.

You've also collaborated extensively with scientists in Russia -- how did that begin?

In 2001, I was recruited by the Department of Defense to collaborate on smallpox research with Russian scientists, as part of the Cooperative Threat Reduction Program, and I started going to Russia several times a year. In 2006, I was selected as a Jefferson Science Fellow at the National Academy of Sciences, and spent a year at the State Department in Washington, working with former weapons scientists as well as other Russian virologists and chemists on some projects emerging and re-emerging infectious diseases. These efforts were focused on the U.S. nonproliferation efforts to prevent the use of biological pathogens for biowarfare and bioterrorism. Once again I spent a lot of time in Russia, and also in Indonesia.

Following my time at the State Department, I went back to Russia for several months each year to help with various scientific issues at the U.S. embassy in Moscow, including the ever-changing political landscape for scientists in Russia. I succeeded in establishing several research collaborations which continue today. One of the most rewarding aspects of science is the opportunity to cross both scientific disciplines and international borders.

The importance of ISAR in my career

As a medicinal chemist, I've been extremely fortunate to work closely with excellent collaborators, many of whom I met through ISAR! In addition to those mentioned above, for the coronavirus project our group has collaborated with Johan Neyts and Dirk Jochmans in Leuven and most recently with Eric Snijder, Adriaan de Wilde and Clara Posthuma at Leiden Medical University in the Netherlands. When Johan and Dirk first discovered our compounds' anti-coronavirus activity, they introduced me to Eric and his group (see their article in last ISAR News discussing their work on coronaviruses, including MERS-CoV and our results with Flex-Acylovir and related analogues).

Needless to say, we're very excited about these findings with our doubly flexible nucleosides (one example is shown in the bottom of the figure), as there is still no cure for SARS or MERS.¹³ And, given the outbreak last year in South Korea, the finding that a nucleoside can successfully evade the rather vigilant coronavirus proofreading mechanisms is groundbreaking. We recently filed a joint patent on this novel approach and are looking forward to pursuing this very exciting lead. But to bring this full circle, ISAR has definitely played a key role in my success and I look forward to ICAR each year - it is an excellent opportunity to see old friends, catch up on

groundbreaking results and of course, meet face to face with our collaborators.

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ANTIVIRALS ON THE HORIZON

In search of protease inhibitors of the SARS and MERS coronaviruses

Rolf Hilgenfeld, University of Lübeck, Lübeck, Germany

It has been 13 years since the outbreak of severe acute respiratory syndrome (SARS) shocked the world. Before that time, coronaviruses were regarded as relatively harmless for humans, and I was one of the few scientists who bothered to investigate them, in spite of difficulties getting the work funded. My colleagues and I succeeded in determining the first crystal structure of any coronavirus protein, namely the main protease. This article describes the situation concerning the structure-based design of coronavirus protease inhibitors at the time of the SARS outbreak, and what has been achieved since that time.



Rolf with Tsinghua colleague Zihe Rao in July, 2003, the weekend after Beijing was declared free of SARS and lab workers were allowed to leave the campus.

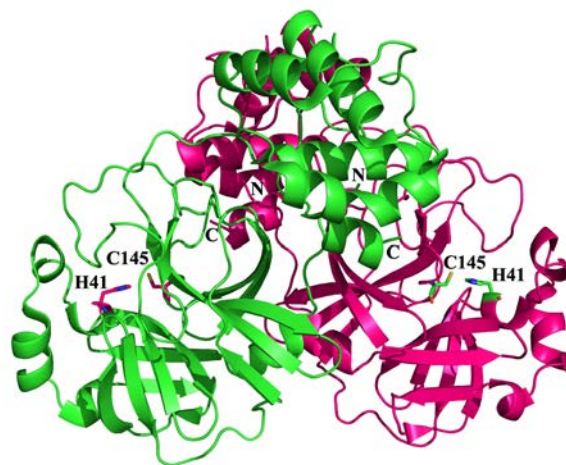
My group, then at the University of Jena in the former East Germany, started working on coronavirus main proteases (M^{pro} , also called 3C-like proteases) at about the turn of the millenium. I chose to start this project because of a general interest in cysteine proteases, and not necessarily with antiviral drug design

in mind. By 2002, we had determined the first crystal structure of a coronavirus protein, the M^{pro} of transmissible gastroenteritis virus (TGEV), a porcine coronavirus [1]. The structure revealed a novel helical domain, in addition to the classical chymotrypsin-fold, and the necessity of dimer formation for catalytic activity, which motivated us to synthesize a simple chloromethyl-ketone inhibitor.

In 2003, during the SARS epidemic, we published the second coronavirus structure, the M^{pro} of human coronavirus 229E, as well as a homology model for the corresponding SARS-CoV enzyme [2]. On the basis of our structure of the TGEV M^{pro} in complex with our chloromethyl-ketone inhibitor and some docking experiments, we proposed that rupintrivir (AG7088), which was under development at that time by Pfizer as an inhibitor of the rhinovirus 3C protease, would "nearly fit" the substrate-binding site of the SARS-CoV M^{pro}, and could therefore be a starting point for the design of anti-SARS drugs [2]. This prediction was verified a little later: while rupintrivir is inactive against the SARS CoV, derivatives of this Michael acceptor compound that lack the p-fluorobenzyl group in the P2 position are potent inhibitors [3].

Subsequent to the on-line publication of our 2003 paper in *Science* [2], I was invited by the Chinese government to come to Beijing for an emergency meeting during the peak of the SARS epidemic, when there were more than 3000 cases in the city. At this event, I met Zihé Rao, who invited me to stay with him at Tsinghua University and work on the crystal structure of the SARS-CoV M^{pro}, which we published a few months later [4]. These three M^{pro} structures laid the cornerstones for the design of antiviral drugs against coronaviruses, and were used by many researchers for that purpose [5].

During the years following the SARS outbreak, many structures of other coronavirus proteins were determined, mainly by the groups of Zihé Rao in Beijing; Peter Kuhn, Ray Stevens and Kurt Wüthrich in San Diego; Bruno Canard in Marseille; and my own group in Lübeck. We focused on nonstructural proteins (Nsp) encoded by open reading frame 1a, in particular the X domain [6], the SARS-unique domain [7,8], Nsp7-8 [9], and Nsp9 [10]. Unfortunately, the goal of anti-coronavirus drug design got a bit lost in the rush for new structures! One reason was that funding for research on the SARS CoV declined rapidly in many countries after the 2006. This was partly the fault of the virology community itself, as many colleagues believed that the SARS epidemic was a one-time event that would never be repeated.



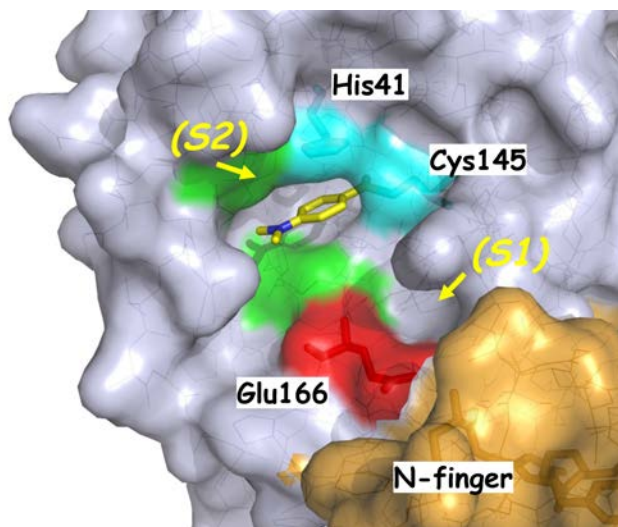
Structure of the SARS CoV main (3C-like) protease [4].

After 2006, we continued to design and synthesize some peptide aldehydes [11] and a few non-peptidic benzotriazoles [12] as inhibitors of the SARS-CoV M^{pro}, but then even my own group started to change its focus, targeting the enterovirus 3C protease. We created the peptidomimetic Michael acceptor compound SG85 [13], which had superb activity in cell culture against enterovirus (EV) 68 (the causative agent of the "summer flu" that hit the midwest USA in 2014), EV71 (the virus causing hand, foot and mouth disease), and human rhinoviruses [13-16].

We did not re-activate our antiviral design efforts against the coronaviral M^{pro} until the MERS-CoV surfaced in late 2012. Recognizing that a few thousand cases of severe CoV disease would never make the development of an antiviral drug commercially viable, and that serious enterovirus infections are far more common, we now aimed at designing inhibitors that would be (nearly) equipotent against enteroviruses, betacoronaviruses such as SARS-CoV and MERS-CoV, and alphacoronaviruses such as HCoV NL63. However, the goal was difficult to reach, with the most challenging target being the alphacoronavirus M^{pro}, which has a far smaller and less flexible S2 pocket than the corresponding proteases of the enteroviruses and the betacoronaviruses.

In the course of this study, we synthesized dozens of compounds and determined quite a number of crystal structures, until we finally found some alpha-ketoamides that fulfilled our design goal. Remarkably, the most potent of these molecules has an EC₅₀ of 5 nM against MERS-CoV in Huh7 liver cells. In addition to the CoV main protease, we also became interested in the other polypeptide-processing enzyme of coronaviruses, the papain-like protease, and determined

the crystal structure of the PL^{pro} of MERS-CoV [17] and its complex with human ubiquitin [18].



Structure of the covalent reaction product between the SARS-CoV M^{pro} and compound XP59, 1-(4-dimethylaminobenzoyloxy)benzotriazole [12].

We continue to draw tremendous intellectual satisfaction from the combination of structural analysis and chemical synthesis. Even though the future of the MERS outbreak cannot be determined, we will not interrupt our work because of declining funding or the common beliefs of the majority of virologists.

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A tribute to the late Kris Krawczynski

Dr. Krzysztof (Kris) Krawczynski and his wife, Dr. Elzbieta Krawczynska, died on January 28th in a tragic car accident near Atlanta. Kris retired from the CDC in May, 2015, after 31 years with the Division of Viral Hepatitis, where he was chief of the Experimental Pathology Laboratory. Among the major accomplishments of his career were the identification of hepatitis C virus antigen and hepatitis E virus antigen in the liver of infected patients and in animal models and the study of immunity to hepatitis B virus in nonhuman primates. His productive collaborations with the NIH and FDA and with prominent research centers in Europe, Asia, and Australia contributed to major public health gains.

Kris was an active member of the American Association for the Study of the Liver Diseases (AASLD) and hardly missed any of the annual meetings. He enjoyed the camaraderie with other attendees, which resulted in many lasting friendships. In recognition of his excellence in research, he was elected a Fellow of the AASLD in 2014.

I had the honor of knowing Kris since 1996, when he invited me to the United States as a postdoctoral fellow. When I first met him, I found a warm and welcoming person with a great sense of humor and a tremendous passion for scientific research. My relationship with Kris flourished over the next two decades, as I was first his postdoc, then a team member, and finally a colleague and friend. His energy and curiosity were inexhaustible. In addition to his dedication to research, he enjoyed world travel, and he

would enthusiastically share his experiences and sightseeing recommendations.

In our last conversation, just a few hours before his death, Kris was the same affectionate and caring person I met 20 years ago, still enthusiastic about hepatitis research and recent advances in the field. I'm grateful for our long association, especially for his guidance during the early years of my career and for our long relationship as friends and colleagues. I also cherished my friendship with his lovely and hospitable wife, Elzbieta. I miss them both very much.

Saleem Kamili, Ph.D.
Acting Branch Chief
Laboratory Branch, Division of Viral Hepatitis
CDC, Atlanta, GA

UPCOMING MEETINGS OF INTEREST

XXII IRT in Paris, 18-22 July

Kathie Seley-Radtke would like ISAR members to know that the XXII International Round Table on Nucleosides, Nucleotides and Nucleic Acids will be held on 18-22 July at the Institut Pasteur in Paris. The meeting is being organized by researchers from the Institut Pasteur, the Université d'Orléans and the Université Paris-Descartes, in collaboration with the International Society of Nucleosides, Nucleotides and Nucleic Acids (IS3NA, <http://www.is3na.org>).

The IRT, held every other year, brings together chemists, molecular biologists, biochemists, biologists and medicinal chemists interested in understanding all aspects of the field. Topics at the Paris meeting will include:

- Approved drugs: from bench to bedside
- Anti-cancer, anti-infective and other biologically active nucleos(t)ides
- Innovation-driven nucleos(t)ide chemistry
- Nucleotide signaling molecules
- Synthesis and structure of nucleic acids
- Oligonucleotides for therapeutic applications and biotechnology
- Biochemistry of nucleosides and nucleic acids

The XXII IRT aims to put at the forefront the latest developments in innovation-driven nucleoside, nucleotide and oligonucleotide chemistry, both in academia and industry, for dealing with the new challenges of our century.

The deadline for abstract submission is April 25th. For more information, go to the meeting website <http://www.paris-irt2016.org>

or contact Kathie Seley-Radtke, President of IS3NA.

Tofo Advanced Study Week on Arboviruses in Tofo, Mozambique 28 August – 1 September

An Advanced Study Week on Arboviruses will take place at Praia do Tofo, Inhambane, Mozambique, from Aug 28-Sept 01, 2016. The conference is being organized by ISAR members Rolf Hilgenfeld of the University of Lübeck, Germany, and Subhash Vasudevan of Duke/National University of Singapore, in collaboration with Dr. Eduardo Samo Gudo, the scientific director of the National Institute of Health of Mozambique.

The study week will focus principally on dengue, Zika, and chikungunya viruses, but other arboviruses such as West Nile or Japanese Encephalitis will be included. The following scientific sessions are planned:

- Dengue, West Nile, Zika and chikungunya outbreaks, past and present
- Molecular biology of flavi- and alphaviruses
- Differential diagnostics
- Vaccine development
- Antiviral drugs
- Vector control
- Public health issues and outbreak response

To encourage discussion and scientific interactions, the meeting will be limited to 55 participants, allocated on a first-come, first-serve basis.

The event will take place at Tofo Del Mar, a newly renovated hotel situated directly on the beautiful Indian Ocean beach. Tofo is 22 km from Inhambane airport, which has flights from Maputo, Mozambique, and Johannesburg, South Africa. Additional information is at <http://www.emerging-viruses.org>

The meeting will build on the success of the Advanced Study Week on Ebola and Other Filoviruses, held in Tofo in 2015 (see www.ebola-conference.org).

19th EUROPIC, September 4-8, Les Diablerets, Switzerland

EUROPIC is a series of every-other-year international conferences on picornaviruses, sponsored by the European Study Group on the Molecular Biology of Picornaviruses. The first meeting was held in 1979 in Enkhuizen, The Netherlands.

The 19th EUROPIC will take place in les Diablerets, Switzerland, on 4-8 September, 2016. Topics will range from hepatitis A and polio to foot-and-mouth disease, with sessions focusing on the virus life cycle, viral genetics, eradication strategies, antiviral therapy and

other topics. Eckard Wimmer will give the opening keynote lecture, and Johan Neyts will chair the session on antivirals. For more information, contact Johan or go to europic2016.org

4th Antivirals Congress, Barcelona, Spain, 18-21 September

Mike Bray, editor-in-chief of *Antiviral Research*, would like ISAR members to know that AVR is sponsoring the 4th AVC in the coastal town of Sitges, near Barcelona, Spain on 18-21 September. This every-other-year conference was held in Amsterdam in 2010 and 2014 and in Boston in 2012.

The 4th AVC will feature an extensive line-up of expert plenary speakers in antiviral drug and vaccine development, including Ralf Bartenschlager, Christian Drosten, Marie-Paule Kieny, Lieve Naesens, Jose Este, Johan Neyts, Jens Bukh, Kathie Seley-Radtke, Stephan Gunther, Thijn Brummelkamp, Sheemei Lok and Subhash Vasudevan. For more information, go to <http://www.antivirals.elsevier.com/>

Third Summer School on Innovative Approaches for Novel Antiviral Agents in Cagliari, Sardinia, 28 September – 3 October

Enzo Tramontano would like inform ISAR members about a meeting on “Innovative approaches for the identification of novel antiviral agents” that will be held in Cagliari from September 28-October 3. The summer school is designed to provide graduate students and postdoctoral fellows with the opportunity to interact with internationally recognized experts in the antiviral field and to critically review the scientific literature, share ideas and discuss new paradigms for future investigations.

Each day of the 3-day conference will consist of a morning series of plenary lectures, an afternoon of small thematic discussion groups and evening presentations of the young scientists’ research. The meeting will bring together 40-50 grad students and postdocs and 15-20 top investigators in virology, biochemistry, crystallography, molecular modeling and medicinal chemistry. Senior scientists at the 2012 and 2014 summer school included ISAR members Giorgio Palù, Jan Balzarini, Ben Berkhout and Stephan Ludwig.

The summer school is organized and led by Enzo Tramontano and Elias Maccioni of the Department of Life and Biological Sciences at the University of Cagliari; Parolin at the University of Padova; and Stuart Le Grice of the Center for Cancer Research at the NCI in Frederick, MD, USA. For information on the 2016 summer school and to review the programs of the 2012 and 2014 meetings, go to <http://people.unica.it/iaaass/>

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(<http://www.journals.elsevier.com/antiviral-research>)

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