ISAR News
Newsletter of the International Society for Antiviral Research

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Welcome to the 31st ICAR

Porto, Portugal

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ISAR President's message (José Esté)

It is with great pleasure that I greet all ISAR members and friends in this new issue of ISAR News.

We begin the 31st ICAR in Porto, Portugal and I am happy to say that we are encouraged by the excellent quality of the program, the participation of scientists from all over the world and the opportunity to spend time in the beautiful city of Porto, with everything it has to offer to its visitors.

We are in debt to all speakers who accepted our invitation to participate, providing excellence and state-of-the-art in their respective fields. We thank all our corporate sponsors, big and small, because it is thanks to their contribution that we can bring the best antiviral research science to our meeting.

We are honored by the scientists receiving the ISAR Elion, Holý, WIS and Prusoff awards of excellence. We feel as our own their multiple contributions to science and public health. Thus, we pay tribute to them. We thank The Burroughs Wellcome Fund, Gilead Sciences, the Bristol-Myers Squibb endowment and the ISAR President's Fund

We are most grateful to all 31st ICAR corporate sponsors. At the time of printing, the confirmed sponsors are: PLATINUM: Gilead Sciences. GOLD: Janssen – Pharmaceutical Companies of Johnson & Johnson. SILVER: AbbVie, North Chicago, IL, USA; The Burroughs Wellcome Fund, Research Triangle Park, NC, USA; Chimerix, Durham, NC, USA; Emergent BioSolutions, Gaithersburg, MD, USA; JCR Pharmaceutical Co.; Ashiya, Japan; Southern Research Institute, Birmingham, AL, USA. BRONZE: ACS Infectious Diseases, Washington, DC, USA; AiCuris Anti-infective Cures, Wuppertal, Germany; Antiva Biosciences, South San Francisco, CA, USA; Center for Drug Design, University of Minnesota, Minneapolis, MN, USA; Elsevier, Amsterdam, The Netherlands; Institute for Antiviral Research, Utah State University, Logan, UT, USA; Oxeltis, Montpellier, France; Quanterix, Lexington, MA, USA; Riboscience, Sunnyvale, CA, USA; Sanofi, Paris, France; Toyama Chemical Co., Tokyo, Japan; Viroclinics Biosciences, Rotterdam, The Netherlands; ViroVet, Leuven, Belgium; XpressBio, Frederick, MD, USA. Additional support provided by: the EU H2020 ANTIVIRALS Consortium and the Porto and Northern Portugal Official Tourism Board, Porto Convention & Visitors Bureau.

for supporting these awards

We are happy to provide support to young investigators in the antiviral research field: fifty-seven individuals, selected through the merit of their presentations, are receiving financial assistance to come to the meeting. Additionally, three young women will receive The Chu Family Foundation Scholarships (TCFF) for Early Career Women, allowing them, not only to participate in ICAR, but to continue their training in fields such as advanced vaccinology, microbiology and molecular medicine. We will congratulate the winners during the meeting and thank, once again TCFF for the kind support of this initiative. I also wish to thank all ISAR members and ICAR participants. It is their involvement what gives meaning to what we do and the center of all ISAR-ICAR activities.

This is my last message as ISAR President and thus, I take the opportunity to reflect on the ISAR state of affairs. The Society is in excellent shape. Our financial exercise has been healthy, we retain a steady number of affiliates and a number of new initiatives have taken place. We have established the new ISAR award for Women in Science. I hope we will continue recognizing the scientific excellence of women until we no longer need to do so based on gender, but just on merit and equality. ISAR will actively search and identify a corporate sponsor to support this award.

We have started the ISAR scientific webinars, led by Raj Kalkeri of Southern Research. This activity has made us realize the need to revamp ISAR's communication strategies; a new Communications and Outreach committee will be formed to replace our Publications, Membership and Website committees. During the ICAR in Porto we will run our first Pechakucha contest as part of the New Attendees reception. This modality of oral presentation of scientific results should give a new twist to our way of welcoming new participants.

My thoughts are of great gratitude to many people who have provided unselfish commitment and dedication to the Society and to the organizing of the 30th ICAR in Atlanta and the coming 31st ICAR in Porto. I thank all ISAR Officers, members of the Board of Directors and committee chairs for providing advice and many times criticism to our choices or decisions. I need to highlight the work and dedication of Roger Ptak, our Financial Officer, Brian Gowen, our Treasurer, Graciela Andrei our Secretary, leading the ISAR merit-travel awards; Katherine Selley-Radkte, for leading the selection committee for the TCFF scholarships and our Program committee Co-chairs: Justin Julander and Mark Prichard. I need to thank the silent but dedicated work of peer-reviewers and award-committee members for taking their time to go through so much information to identify the best deserving science and merit. I am in great debt with Regina Mohr and Kelly Givan of Caliber Meetings and Events for their competence and helping in doing my job well.

Finally, I am confident in the future. ISAR cannot be in better hands than with the leadership of Johan Neyts as President, Kara Carter of Sanofi as the new President-Elect and Joana Rocha-Pereira and Pei-Yon Shi joining the board of directors. I congratulate them and wish then success.

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

José Esté, President, ISAR

WELCOME TO PORTO

(Joana Rocha-Pereira)

A warm welcome to Porto to all ISAR members!

What makes Porto a special place? Portuguese rock star, Rui Reininho, recently answered to CNN travel: "The baroque surprises, the escarpments of Romanesque granite, the almost obscene sincerity of the people, the impetuously golden river, the swooning camellias, the wild Atlantic filled with fish and seafood, the narrow streets awash with soap suds".

The 31st ICAR comes to Porto in mid-June, when the city is getting ready for its biggest annual festival S. João, which takes place on the night of June 23rd. Notice the decorations, the smell of roasted sardines and the "manjericos", a variety of basil in pots, which is being sold around the city. The fact that FC Porto has just become national soccer champion 2017/18 after four years without trophies gives the locals yet another reason to smile every day. Make sure you join the local celebrations and experience the Porto lifestyle, while enjoying the science and networking at ICAR.

Manjericos. Photo by Porto Conventions and Visitors Bureau and CM Porto.

Official opening of the Bolhão temporary market. Photo by Porto Conventions and Visitors Bureau and CM Porto.

For more info on Porto and places to visit please check the ISAR News, Vol. 27 No .3. Of notice is that the local food market of Bolhão is closed for restoration works. Still, you can visit (and shop at) the temporary market set up at the La Vie Shopping Center, Rua Fernandes Tomás 524. For more info/ agenda visit the TimeOut Porto

http://www.timeout.com/porto

or the city's websites

http://www.porto.pt/home

AN OVERVIEW OF THE 31st ICAR
(Justin Julander and Mark Prichard)

Welcome ICAR attendees! We are pleased that you can participate in this year's conference and look forward to the science that will be presented and the collaborations that will be formed. ICAR is a place where old friends can catch up and update one another on research as well as for new members to network with others in the field. We welcome you and hope you enjoy the meeting. As with past ICARs, the goal is to present the very best science in the field of antiviral research and to provide networking opportunities.

For new attendees, we hope our networking sessions will be of use and will help you forge friendships and collaborations with individuals that can help you expand your research. ICAR brings together chemists and virologists, as well as other important disciplines, who present their findings and discuss potential ways to advance their discoveries toward clinical development. This unique meeting fills an important niche in order to prevent or treat viral diseases. It is our goal to provide young scientists with opportunities to meet others within this field. Please attend our Women in Science roundtable on Monday June 11th and the New Member Reception and Career Development Panel on the afternoon of Wednesday June 13th. The New Member Reception will also include an exciting new event: the Pechakucha competition. Selected abstracts will be presented in a fast and fun format and the best presentation will receive an award. Don't miss the closing reception banquet as well where the poster awards will be presented.

The Program Committee wishes to congratulate the Women in Science (WIS) Speaker Award recipient, Dr. Angelle Desiree LeBeaud, who will give a talk entitled "Making the Invisible Visible: Arbovirus Transmission, Risk, Disease and Prevention in Kenya" on the morning of Tuesday, June 12th. We also congratulate the awardees for The Chu Family Foundation Scholarship for Women Scientists. They are María Laura Morell from Buenos Aires, Argentina, Alba Torrents de la Peña from Amsterdam, Netherlands and Crystall Swarbrick from Singapore. These deserving individuals have demonstrated their potential for significant contributions in the field of antiviral research and we commend them on this award. Their bios can be found in the 31st ICAR Program.

We wish to congratulate the major award recipients selected by the Awards Committee chaired by Rich Whitley. Dr. Paul Griffiths has been awarded the Gertrude Elion Memorial award and will present his work with HCMV in a talk titled "Quantitative Studies of HCMV in a Human Challenge Model" at 8:15 AM on Thursday.

We will also be pleased to hear from Dr. Chris Meier, who is receiving the Antonín Holý Memorial Award. His talk "From Nucleoside Monophosphate Prodrugs to Nucleoside Tri-phosphate Prodrugs -- The Challenge, a Possible Solution and Further Improvements" will be presented on Wednesday at 8:30 AM.

The William Prusoff Young Investigator Award is being given to Dr. Ester Ballana, who will present her work with HIV in her talk "Regulation of Nucleotide Metabolism: From Virus Restriction to Therapeutic Implications in HIV infection and Beyond" on Tuesday at 8:30 AM.

Don't miss the symposia throughout the conference. Topics covered include Virus Evolution, Emerging Infections, Respiratory Viruses, Viral Hepatitis, Cytomegalovirus, and HIV. Invited speakers with a diverse range of expertise will present their research as a part of these symposia, which should surely benefit those in attendance. Our oral and poster sessions will provide further opportunities for learning and for facilitating collaborations. We anticipate a great conference and thank you for your attendance.

WOMEN IN SCIENCE (Rhonda Cardin)
WIS Roundtable (Kara Carter)

The WIS Committee warmly welcomes all ICAR participants, particularly those who have

registered for the 6th Annual Women in Science Roundtable. We hope that you will enjoy this session, which is the first event on the first day of ICAR, being held on Monday, from 12:00 – 1:45 PM. This event is free, but it's limited to 80 participants. At the time of writing, a few places remain, please visit the ISAR web site, select "Women in Science Roundtable" in the Events section to register.

We ask all those who have registered to sign in between noon and 12:30 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.

Please join us to network with fellow scientists in industry, government, and academia who conduct all aspects of antiviral research. This roundtable will provide an opportunity to participate in a panel discussion with our 2018 WIS Speaker Award recipient, Angelle Desiree LaBeaud, Stanford University School of Medicine; Joana Rocha-Pereira, Rega Institute KU Leuven; and Heather Greenstone, NIAID, NIH, as well as other antiviral research scientists. Drinks and light sandwiches will be provided.

POSTER AWARDS (Jennifer Moffat and Brian Gentry)

The much anticipated poster competition will be held again this year in Porto! The three categories eligible for the cash prizes, which range from $250 to $1000, are 1. student (graduate or undergraduate), 2. postdoctoral and 3. junior investigator. Note that you must have registered your desire to be judged when you submitted your abstract, as well as your category.

When you check in at registration, you will be given a tag for your poster, so that the judges can identify you. It is important that you be at your poster during the designated judging times. If you are not there when the judges come by, you will not be considered further. The judges will also be looking for several poster presenters who exhibit great communication skills – a few outstanding presenters will be selected for the 5 minutes shotgun talks on the last day of the meeting. So…sharpen your presentation skills and practice those elevator talks – remember you will have only 3 minutes to impress the judges when then stop at your poster. See you in Porto!

ISAR WEBINARS (Raj Kalkeri)

The ISAR webinar series began in the fall of 2016 and is going strong. There have been 11 talks to date, and the webinar committee has the following confirmations for June and July:

- June 21st, 11 AM EST
  Charles Wells, MD, Head of Infectious Disease Clinical Development at Sanofi
  "Integrating clinical research into epidemic response by studying the Ebola experience"
- July 19th, 11 AM EST
  Thomas Monath, MD, FASTMH, Chief Scientific Officer, Crozet BioPharma
  "Yellow fever: Recent resurgence and challenges for prevention and control"

ISAR webinars are primarily aimed at society members, but they are available to any researcher who logs in through the GoToWebinar link. However, the archived files on the society website are accessible only to members.

The ISAR webinars committee is still seeking speakers for the rest of the year. If you have a lecture that you have prepared for a meeting or for teaching, and you would like to share it with ISAR members, or if you wish to suggest a speaker to deliver a webinar, please contact the webinar committee:

- Raj Kalkeri rkalkeri@southernresearch.org
- Aruna Sampath sampatha1@ebsi.com
- Mike Bray mikebrayavr@gmail.com
- Kara Carter kara.carter@sanofi.com

You can support the ISAR webinar series by logging in to enjoy each lecture as well as by publicizing the webinars. Please forward the email announcements to colleagues and to online groups of which you are a member. We are looking forward to seeing you through the second season of the exciting webinar series.

ELECTION RESULTS (Bob Buckheit)

Kara Carter, President-Elect

Kara is Head of Antiviral Drug Discovery at Sanofi. She started her virology journey as an undergraduate at Stanford University in the laboratories of Dr. Ann Arvin and Dr. Charles

Prober, working in collaboration with Chiron to develop a diagnostic to differentiate between HSV-1 and HSV-2 infection. Her graduate work was in the laboratory of Dr. Bernard Roizman at the University of Chicago, studying molecular virology of HSV and receiving her PhD in 1996. As an NSF funded post-doc in the laboratory of Dr. Elliott Kieff at Harvard University she studied EBV transformation of human B cells, applying the emerging technology of transcriptional profiling in collaboration with Lou Staudt's lab to characterize lymphoblastoid cell lines and established EBV containing cell lines.

Moving into industry at both PRAECIS Pharmaceuticals and Genzyme Corporation, Kara led a number of virology, immunology and oncology programs focusing mostly on small molecule drug discovery. While at Genzyme, she also played a role in the antiviral in-licensing efforts at Genzyme to support the transplant business unit and contributed to the acquisition of AnorMED. After Sanofi acquired Genzyme, Kara spent two years supporting in-licensing activities in Infectious Disease, Immunology, Multiple Sclerosis, and Rare Disease while working with the Infectious Disease unit to develop a strategy to start internal virology drug discovery.

During this cross-training tenure in Business Development, she participated in five major in-licensing deals. In 2014, Kara founded the Antiviral Drug Discovery group at Sanofi focusing on HBV and HIV cure initiatives, emerging infections and viral respiratory diseases and managing a global team in the US, France and China. As part of this work, major collaborations have been established with INSERM, Institute Pasteur Shanghai, Fudan University, Vanderbilt University, Oregon Health Sciences University and NIAID.

Since the start of this group, Sanofi virology has moved two programs into preclinical development with first in man studies planned for late 2018 and will shortly be initiating two POC studies, one each in HIV and HBV. Kara serves on the SAB for the Antiviral Drug Discovery and Development Center. A member of ISAR for 15 years, Kara has served on several committees including Finance, New Member, Publication and Women in Science. She has been a mentor through the ISAR Women in Science program and co-leads the ISAR Webinar Series.

Joana Rocha-Pereira, new member of the Board of Directors

Joana Rocha-Pereira is a Research Associate in the laboratory of Prof. Johan Neyts, at the Rega Institute for Medical Research, in Leuven (Belgium). Joana started her research career studying the replication of noroviruses in 2008,

Joana Rocha-Pereira, board member

after graduating in Pharmaceutical Sciences at the University of Porto, Portugal. She obtained a PhD degree in 2013 for her work on the identification of small molecule inhibitors of the replication of noroviruses. Since then, she joined the Neyts lab, where she has optimized norovirus mouse models of infection. As a part of her Marie Curie fellowship, she has been leading the biology efforts on a norovirus drug discovery campaign together with the Center for Drug Design and Discovery (CD3).

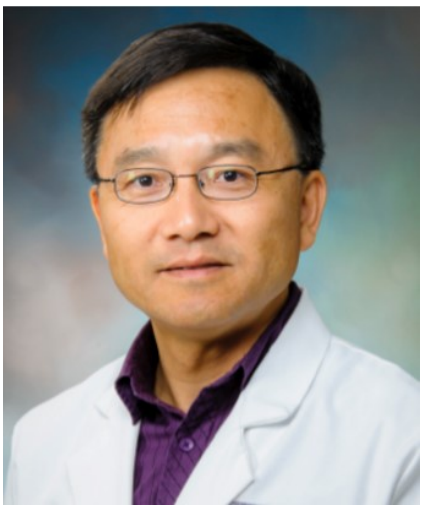
Her research interests extend to other enteric viruses and to bunyaviruses, on which she worked as a team member in two EU-funded consortia. She is the author of 15 papers in peer-reviewed journals (11 of which as first author) and has given a number of lectures on the topic of norovirus at international meetings. Joana is an Associate Editor of Antiviral Chemistry and Chemotherapy and a member of the Editorial Board of Frontiers in Pharmacology. Joana first attended the 25th ICAR in Sapporo, Japan (2012) and since then has become an enthusiastic and active member of ISAR. She is currently a member of the Publications, Membership, Poster Award, and The Chu Family Foundation Scholarship for Early Career Women in Science Committees.

Pei-Yong Shi, new member of the Board of Directors

Pei-Yong is the I.H. Kempner Professor of Human Genetics of the University of Texas Medical Branch. He received his B.Sc. from the Nanhing Normal University, China in 1989 and his Ph.D. from Georgia State University, USA, in 1995. He then completed his postdoctoral training in 1998 in Yale University, School of Medicine.

Pei-Yong has been working on flavivirus replication, antiviral drug discovery, and vaccine

research for 27 years. His unique experience in public health laboratory (Wadsworth Center, New York State Department of Health; 8 years), pharmaceutical companies (Novartis and Bristol-



Pei-Yong Shi, board member

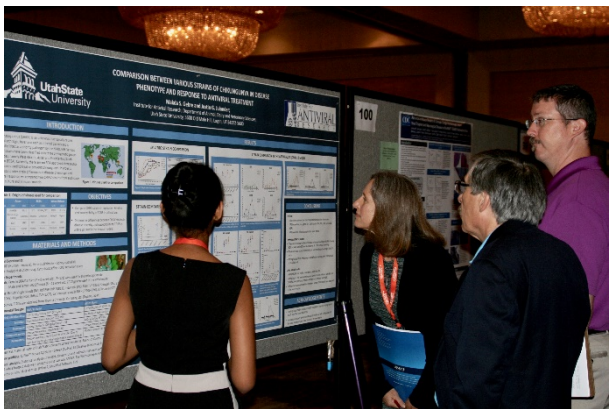
Myers Squibb; total 10 years), and academia (University of Texas Medical Branch, Yale, and other universities; total 9 years) allows his work to focus on the interface between basic and translational research.

His basic research illuminates the mechanism of viral replication that could be utilized for the development of novel diagnosis, antivirals, and vaccines. In return, his translational research provides unique tools and systems to discover the molecular mechanism of viral replication. Pei-Yong has published over 230 peer-reviewed papers in the leading journals in virology and general sciences, including Nature, Science, Cell, PNAS, Host Cell & Microbe, and PLOS Pathogens. His work has generated bodies of knowledge that have significantly advanced our understanding of flavivirus replication, diagnostics, antiviral discovery, and vaccine development.

Besides his academic excellence, Pei-Yong has an also strong track record of senior leadership role at leading pharmaceutical company (e.g., Executive Director at Novartis Institute for Tropical Diseases) where he set up antiviral strategies and executed drug discovery and development. He aspires to integrate his expertise in academia, industry, and government to advance basic and translational research. His recent work on Zika virus has established the first reverse genetic system for the virus, developed a live-attenuated vaccine currently advancing to clinical trial, developed rapid diagnostic assays currently under FDA approval, and identified genetic changes that may contribute to the recent explosion of Zika epidemics.

MEMORIES FROM PAST ICARs
1, 5 and 10 years ago (Brian Gentry)

ICAR always provides an open and friendly environment to interact with our colleagues, as Enzo Tramontano, Masanori Baba and José Esté did last year in Atlanta.



Jennifer Moffat as chair of the Poster Award Committee was very engaged while judging posters last year in Atlanta.

Julie Dyall, Priscilla Yang, Rhonda Cardin, Karen Buckheit and Inger Damon, participants of the panel discussion during the WIS roundtable last year in Atlanta.

Andrea Brancale and Chris Meier had another enjoyable chat in San Francisco during the banquet of the 26th ICAR meeting in 2013.

Five years ago, Erik De Clercq and Tomas Cihlar had also a very enjoyable time in San Francisco, 2013.

The poster awardees in 2008 at the 21st ICAR held in Montreal, Quebec, Canada together with Mark Prichard and past ISAR President Chris McGuigan

Ten years ago in Montreal, past ISAR President Chris McGuigan, giving an enthusiastic and inspiring talk. His optimism, good humor, and love for science will remain among us.

YOUNG RESEARCHERS ON THE HORIZON

This section of ISAR News aims to highlight the career of PhD students, postdocs and young investigator awardees at past ICAR meetings.

Leen Delang, postdoctoral scientist, Rega Institute of Medical Research, Leuven, Belgium

With three generations of pharmacists in my family, I was born to become a pharmacist as well. Nevertheless, as a teenager, I was firmly convinced of the opposite. When I turned eighteen and still in doubt about my professional future, I decided to use the help of a 'study choice' test. Only one profession stood out as the perfect match: the pharmacist. At that moment, I had to admit that the acorn does not fall far from the tree!

During my pharmacy studies, my master thesis research at the division of Immunology of the Rega Institute at KU Leuven was my first 'close encounter' with research. Before that, pursuing a career in research had never come into my mind as a possibility. Attracted by the, perhaps naive idea to make a difference for thousands of patients by

discovering antiviral drugs, I decided to enroll in a PhD in the lab of Prof. Johan Neyts at the Rega Institute in Leuven. During my PhD work, which focused on developing strategies to prevent the emergence of antiviral drug resistant hepatitis C viruses, I took my first steps in the antiviral research field. The HCV field was moving very rapidly at that time and it was very exciting to be contributing to this with our lab. In September 2011, I defended my doctoral thesis, after which I decided to start as a post-doc in the same research group.

With sofosbuvir on its way to market approval for the treatment of HCV infections in that period, I wanted to focus my efforts on another virus. I choose to investigate antiviral strategies for viruses which are more neglected and, in some regards, less interesting for pharmaceutical companies (i.e. minor market potential), as I believe that this is an important task for academic research teams. I started to work on the chikungunya virus, an alphavirus transmitted by mosquitoes.

Pieter Leyssen had introduced this virus in our lab in the aftermath of the large chikungunya virus outbreak on the Reunion Island in 2006, but nobody of the research group was studying this virus in depth at that time. I rapidly became fascinated by this virus which was so powerful in killing our cells! This was in sheer contrast to the HCV for which I mostly used replicon cell models during my PhD research. During my postdoc years we majorly expanded our toolbox for alphaviruses, we established a mouse model for chikungunya virus and we started several collaborations with other virology groups and with medicinal chemists.

One of the most rewarding aspects of being a postdoc to me is supervising students. I really enjoy transferring my enthusiasm about viruses and antivirals, and even about mosquitoes, to young people. Experiencing how they grow as a scientist during their PhD or master thesis and assisting in this process is very nice. When my first PhD student defended her PhD thesis last year, I was so proud! Currently I am supervising 5 PhD students in our team; three of them will defend in the second half of 2018.

To learn more about another aspect of arboviral infections, i.e. the vector, I spent 6 months in the laboratory of Anna-Bella Failloux at the Pasteur Institute in Paris to learn how to rear mosquitoes and to infect these mosquitoes with arboviruses. She is recognized worldwide as an expert in the transmission of arboviruses by mosquitoes. This research stay was both a career and a life changing experience.

It was amazing to live in Paris and to work in such a renowned institute with so much history as the Pasteur Institute. Every morning I walked by the office of Françoise Barré-Sinoussi, a female researcher who won the Nobel Prize for her work on HIV, which was in a certain way inspiring. Furthermore, it was a humble and meaningful experience to be the dummy of the lab again. Learning in a short time period how to handle mosquitoes and infect these in BSL3 conditions was truly a challenge!

The practical organization of my stay in Paris was challenging as well, especially for my husband who had to take care of our two little boys while I was abroad. Luckily, I could count on many people in my environment who did a lot of effort to help my family while I was in Paris. Without their help, this would not have been possible.

The focus of my current research is partly based on the expertise I gathered in Paris. I am the project leader of the alphavirus research in our research group. This includes that I follow up on the screening of compounds to identify molecules with antiviral activity against chikungunya virus and other alphaviruses. Hit molecules are optimized in collaboration with several medicinal chemists. For the characterization of the mechanism of action of the most interesting molecules and the evaluation of the efficacy in the chikungunya virus mouse model, I can count on my small but brave chikungunya team consisting of one PhD student (Sofie Jacobs) and one post-doc (Rana Abdelnabi).

In addition, I am establishing a mosquito rearing facility and a mosquito infection platform for BSL3 viruses in the Rega Institute. This ‘mosquito toolbox’ will allow coupling our renowned expertise in antiviral drug discovery and the study of antiviral drug-resistance to the mosquito expertise, which will be unique in the world. Gaining expertise in working with mosquitoes is of key importance as well as an urgent call, as arboviruses are expanding their territories to more temperate regions including the South of Europe. The recent outbreak (September 2017) of chikungunya in two different regions in Italy and the dengue outbreak on the island of Madeira (October 2012) are good examples that we will most likely experience more arbovirus outbreaks in Europe in the future. For the coming years I hope to put our mosquito facility on the map and collaborate with researchers from all over the world on arboviruses and their vectors.

Once the mosquito work is up and running in the Rega Institute, then this will be my most significant research accomplishment until now. Furthermore, I was very proud to be invited for a keynote lecture at the International Meeting on Arboviruses and their Vectors in Glasgow in September 2017. This meeting brought together around 200 experts in the arbovirus research field. This invitation thus recognized my contributions and expertise in the field of arboviruses. I am also proud of the several opportunities that I had to

communicate about science to a non-professional audience. I believe that it is very important that scientists communicate about their research to the general public. In February 2016, I got the opportunity to give an interview on the Belgian national radio about the Zika virus. I was also an invited speaker by two Belgian societies (Actueel Denken en Leven and Markant) for which I gave a lecture about emerging viruses and epidemics. I also very much value the scientific prizes that I was lucky to receive, including the poster prizes at ICAR meetings.

The largest disappointment of my research career was not getting an extension of my post-doctoral fellowship from the Flemish government. One of the key reasons for not getting this extension was my limited international mobility. After finishing my PhD, I started a family and gave birth to two lovely boys. Going abroad while being pregnant or with a little baby was not a realistic option.

When my youngest son was 1.5 years old, I started my research stay as a visiting postdoc in the Pasteur Institute for 6 months. To make this feasible in combination with my family, I took the first early morning Thalys train from Brussels to Paris on Monday and I returned on Friday afternoon to spend the weekend with my family. Although this research stay was very exciting and without doubt very useful to me and my research career, it was also a difficult period for my family. I therefore very much regretted that this 'short' 6 months research stay was not valued more by the funding body.

This also underlines the struggle that researchers experience sometimes to combine professional life with personal life. However, losing one battle does not mean that you will lose the war! Thanks to the indispensable help of my promotor, who could find a budget to keep me in the lab, I am still able to do in my professional life what I like most.

The first ICAR meeting that I attended was the 21st ICAR meeting in Montréal in 2008. This meeting was also my first international scientific meeting and the first time overseas. I really enjoyed the nice interactions between chemists and virologists! Much to my surprise, I also won the poster prize in the PhD student category. Since then, I have attended ICAR meetings almost yearly. I always look forward to attend, among others because of the friendly atmosphere and the efforts that are being done to make new people feel welcome and to support the participation of young scientists.

I also very much appreciate the attention that is given to female scientists. For early career female scientists, it is very motivating and inspiring to listen and talk to female role models at the Women in Science roundtables! Also, the Chu Family foundation scholarships for early career women in science and the Women in Science speaker award are very good initiatives. Furthermore, ICAR meetings bring together a unique mix of diverse disciplines related to antiviral research and cover many different viruses. This is way the meetings are so interesting. One of my favorite ICAR meetings was the 25th ICAR in Sapporo, Japan, where I really enjoyed the Japanese culture and food. Also, the 28th ICAR in Rome is high on my list of favorite meetings. I am convinced that the upcoming meeting in the beautiful city of Porto will be a great meeting again!

Marcella Bassetto, School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, United Kingdom

As a young researcher in medicinal chemistry, I have focussed my work on the search for new small-molecule antiviral agents since my very first steps in the field of drug discovery. I completed my Masters degree in pharmaceutical chemistry in Italy, at the University of Padova, in 2010, and with my graduation research project. I started working on the application of computer-aided techniques for the identification of novel inhibitors of the Chikungunya virus replication. I then moved to Cardiff, UK for my PhD studies, with which I focussed on the in silico selection and synthesis of novel antiviral compounds against hepatitis C virus.

After completing my PhD and a first year of post-doctoral work for Cardiff University, which regarded the development of novel fluorinated candidate drugs against prostate cancer, I moved to Rome to join IRBM Science Park, a pharmaceutical company previously part of the Merck group, as research chemist. Here I had the occasion to acquire many new skills, mainly for the critical evaluation of competitive and successful strategic approaches for the development of pharmaceutically active compounds, and for the

identification of still underexploited and unmet medical needs.

Even if I really appreciated working in the private sector, I quickly realised that the ideal environment for me to pursue my own research ideas was the academia. I went back to academic research as research associate for Cardiff University in 2015, and here I could continue expanding my main research interest, antivirals, working on different projects for the identification of novel chemical agents that interfere with the replication of chikungunya and Zika viruses, norovirus and human respiratory syncytial virus.

My present research is mainly focused on the application of several in silico techniques, such as docking-based screenings of commercial libraries of compounds, or ligand-based three-dimensional shape database search methods, to the study of a given biological target or of a hit molecule to be optimised. I use these methods to identify in silico new potential hits with a certain biological activity, and these hits are subsequently purchased if commercially available, or synthesised if not available, and then tested in a range of biological assays by different collaborators all over Europe and beyond. Once one or more hits are identified, their structures are then chemically modified to improve their interactions with the target and to explore their biological potential, and different series of analogues are synthesised according to optimised organic chemistry routes.

Over the course of my doctoral and post-doctoral research experience, I have had the occasion to apply these general methods to several different projects, not only for the search of new antivirals, but also to identify novel bioactive molecules with anticancer activities. For example, and novel small-molecule agents that interfere at different levels of the visual cycle, as potential treatment strategies against a range of vision dysfunctions.

Being now in my first independent position as research fellow in medicinal chemistry, my main research focus at present is the identification of both nucleoside and non-nucleoside potential antivirals against chikungunya and Zika viruses. As I had the opportunity to experience different work settings and environments, and I had the occasion to work on various medicinal chemistry projects both in academia and in the private sector, I have spent a lot of time and consideration on deciding where to direct my future career. I have identified, without any doubt, the antiviral research field as the most challenging and exciting for me to work on.

Having being involved on different antiviral projects since the very beginning of my research activities, attending ICAR has always been an important and unmissable appointment in my schedule. Since the first ICAR I attended in Sofia in 2011, I have been to the conference almost every year, and my attendance has not only hugely impacted my research work, but it has also contributed to my professional and personal development, and it has made me a much better scientist than I was before every single time I went.

Going to the annual meetings of the Society has given me the opportunity to encounter all the main experts in the field, to witness in first person the most recent research efforts and advances for the development of new antivirals. It has given me new ideas to better develop my own work, and it has been fundamental to start building my own network of collaborations. This is the occasion for me to remind myself who are the professional examples I would like to follow, which are my aspirations and what kind of outstanding research I would like to carry out in first person. These meetings represent a huge boost to my motivation as a scientist, and when I go back to the laboratory I feel refreshed in my enthusiasm to carry out my research, and completely inspired.

Attending the conference has also given me a significant lift in my self-confidence and self-motivation, as my research work has been recognised as noteworthy twice: in 2011, in Sofia, I won the first prize in the category “graduate students” with my poster presentation on novel antiviral agents against chikungunya virus, and then I won the first prize also for the category “post-docs” in 2017 in Atlanta, when my poster on novel inhibitors of Zika virus replication was first selected for a shot-gun presentation, and then it was chosen for the prize. Being given these recognitions has made me feel even more enthusiastic about my work on antivirals, it has made me realise that what I do is appreciated by experts in the field, and it gave me a significant push to want to do much more and better research.

Overall, such experiences are of immense value for the career development of young researchers like me, as they give them the opportunity to see what the most brilliant scientists worldwide do, and to meet so many inspirational people, that it becomes impossible not to want to be part of this exciting research world. Behind the scenes of the ICAR meetings, the ISAR has the remarkable ability to bring and keep together all these exceptional men and women who dedicate their energies and passion to antiviral research. I believe the Society plays a crucial and essential role not only for the fruitful collaborations that originate when all these brilliant people get together, but also, and most importantly, it has a major function for the formation of the next generations of scientists in antiviral research.

On a personal note, the boost in motivation that I receive when I attend an ICAR meeting is

extremely important and useful not only for my research work, but also for my interactions with colleagues, collaborators and other people who share my research interests, most importantly with students.

Both in my academic and industrial work, I have always invested a lot of energies to train, mentor and motivate younger researchers, trying to manage their research activities while transferring them my passion for science and drug discovery. During the course of the years, I have developed the ability to positively engage with the students, providing my day-to-day supervision, guidance and advice, adjusting my interaction with them based on their individual needs and abilities, and in different cases. I have used my motivation to help undergraduate students in understanding how they could best develop their future careers. I enjoy transferring my knowledge to students and younger scientists and I am always more than happy and enthusiastic to have them involved in my research projects: being most of these projects related to antiviral research, I noticed that it is quite straightforward for them to get immediately very enthusiastic about the scientific aims of finding new antivirals.

I am convinced that this is a research field that still offers endless opportunities and challenges for the future generations, as it is so easy to get people to be passionate about it. Also for this aspect, I believe the Society does a wonderful job in helping PhD students and younger scientists to attend the ICAR meetings. With the travel grants it awards every year, it makes possible to attend the conference for young scientists who could not be attending otherwise, and this way it gives them the opportunity to live an inspirational experience that for sure will have a significant impact on their future careers.

This activity of promoting the participation of students and post-docs is very important to attract the interest of the next generation of scientists in the antiviral field, and with the travel merit awards the Society gives them an important occasion also to improve their skills, as they can present their work to such an outstanding audience, who can provide invaluable feedback and suggestions for the further development of their projects and careers. Overall, I am extremely enthusiastic to work on antiviral research and this is what I would like to continue doing in the future: being involved with the Society, in particular at the ICAR meetings, has certainly contributed to make me feel this way.

Radim Nencka – Head of the Junior Research Team, Institute of Organic Chemistry and Biochemistry (IOCB), Prague, Czech Republic

My scientific career started at Charles University, Faculty of Pharmacy in Hradec Kralove (Czech Republic).Thanks to the Erasmus/Socrates program, I was able to spend almost half a year at the University of Crete (Greece), where I performed my masters thesis under supervision of Prof. Stratakis working in the field of physical organic chemistry. It was a very exciting time for me and it was the moment, when I decided to follow a scientific career, because I realized it gives you a unique freedom of thinking and creativity.

Then, by happy coincidence, I obtained a PhD position in Prof. Antonín Holý's group at the IOCB Prague (Czech Republic) and I spent several years under the supervision of Dr. Hrebabecky working on few different topics including carbocyclic nucleoside derivatives and thymidine phosphorylase inhibitors. Just before finishing my PhD, I met Prof. Serge Van Calenbergh at a conference and asked him if he would accept me for a postdoc position. Since I had won a prize for the best oral communication of young scientists at the very same conference, it was probably quite an easy decision for him. So I spent over a year at the University of Gent (Belgium) in his group and just when I was about to return from Belgium, I was asked by Dr. Havlas, former director of the IOCB Prague, if I would take care of a part of the former Prof. Holý group since he was just about to retire. I humbly accepted and became a group leader at IOCB Prague.

I must say that both my stays abroad were quite productive from scientific point of view. My first stay in Greece was definitely an eye-opening experience. Everything was new and I had to learn a lot, starting from new chemistry and ending with

communication in foreign environment. The postdoctoral experience in Belgium was, on the other hand, more about independent research. I had the opportunity to select a research topic and try to turn my own ideas into reality.

I believe that both these stays abroad gave me a great chance to focus on my work as well as many new scientific impulses. It was also very useful for further networking.

Personally, I can see numerous unmet medical needs in antiviral arena. Recent progress in the cure of hepatitis C give us a lot of hope for future therapies of further diseases such as hepatitis B. In addition, the emerging viruses such as dengue will definitely stay in the spotlight for some time. We can expect many interesting results in this scientific fields in the upcoming years. From a longer perspective, however, we will have to face issues that are more challenging. Although it may sound a little bit science fiction, I believe that we can achieve a cure of HIV and if yes, we should not stop and go for cure of at least some of herpesviruses. Indeed, we will have to find some novel targets and maybe completely new approaches towards treating diseases caused by these viruses, but I must say that I am optimistic and I believe that we will prevail.

The major focus of our group is modern medicinal chemistry and chemical biology. Our priority is to discover and develop novel therapeutic agents against selected diseases and prepare chemical tools, which will facilitate understanding of pathological processes and provide clues for their effective treatment. Our major scientific area is antiviral agents, but we also participate in projects focused on neuro-degenerative diseases and metabolic syndromes.

Our antiviral program is focused on novel therapies against viruses of the *Flaviviridae* family and our major target is the NS5 protein that contains viral methyltransferase and RNA-dependent RNA polymerase. Currently, we are trying to rationally design novel inhibitors of these two enzymes based on both nucleoside derivatives as well as non-nucleoside scaffolds. In addition, we are preparing chemical tools that would allow us to understand how these viruses invade our cells and hijack various host factors.

I believe that we have done nice work on inhibitors of phosphatidylinositol 4-kinases as potential broad-spectrum antiviral agents. We were able to identify compounds that exert low nanomolar activity against PI4KIIIb, while being inactive against other lipid and protein kinases. Since PI4KIIIb is an important host factor implicated in replication of numerous (+)RNA viruses, these compounds possess profound effect against viruses such as human rhinovirus, Coxsackievirus B3 and hepatitis C virus. In addition, identification of the first nucleoside inhibitors of Zika virus and evaluation of their triphosphates in Zika virus RNA dependent RNA polymerase assay is also significant.

I must stress that the collaboration with my excellent colleagues Daniel Ruzek and Evzen Boura was essential for success of these endeavours. I must stress that the collaboration with my excellent colleagues Daniel Ruzek and Evzen Boura was essential for success of these endeavors.

Probably every one of us has experienced a disappointment during a submission of some manuscript, but that is simply the life that we have chosen. I do not have any particular recipe how to deal with it. I try to work on the topics that I believe are important and can lead to better human life.

Since I am just passing through the evaluation period to be promoted to senior group leader at the IOCB, I hope that I will have more time and resources for highly ambitious projects with higher degree of risk. I would like to focus on several difficult molecular targets, in particular, inhibition of protein-protein interactions. There are also several ideas that I have had for some time in my head and I hope I will be able to realize or at least test their feasibility. Generally, I am quite excited about the upcoming challenges and I believe that some of these ideas will result in completely new scientific programs in my group.

I have a very good experience with young people in my group, so far. Even though supervising and teaching students all the necessary skills from scratch is time consuming, I find it highly rewarding since one can instill the right lab behavior in them and encourage their creativity. It is always great if the students get enough attention from older, more experienced members of the group. Therefore, I am happy that I have several highly experienced scientists in my group willing to help me with mentoring the master and PhD students. This I see as one of big advantages of working in my group. We have a saying: “It’s OK to ask twice, we are here to help.” And this indeed applies to teaching all techniques. On the other hand, I encourage students to come up with their original solutions and ideas.

It is important to choose the right topic and a lab that has solid experience with it. As I mentioned before, I believe a group should have several more experienced people, postdocs or even scientists, who can help the students to learn the right techniques and serve as good examples. The rest depends on the attitude of the student. I believe that enthusiasm is the most important factor for successful accomplishment of PhD studies and your work should become your love and obsession.

Sometimes it is hard to deal with an unsuccessful experiment but think it over and try again!

I like to say that my group is my second family. To be honest, most of my friends are also my colleagues and therefore my professional life is highly interconnected with my personal life. I must say that my wife has been very tolerant of this over the years and she has always supported me and my professional career.

ISAR is the only professional society that I am a member of, which probably speaks for itself. I have been attending the ICAR meetings since I was a PhD student. It has always potentiated the research in my group and we have always been finding important connections and new collaborations at this conference. After all these years, ICAR is the event I like the most because a number of participants have become my friends.

NEWS AND COMMENTS

(Graciela Andrei)

This section aims to highlight recent articles with interesting findings in the field of vaccines and antivirals that will have a considerable impact.

Vaccine waning and mumps re-emergence in the United States, Lewnard JA, Grad YH. Sci Transl Med. 2018;10.

Outbreaks of mumps during the last decades have prevented the elimination of mumps virus transmission in the United States. In the prevaccine era, more than 90% of children born in United States suffered from mumps infections by 20 years of age. Following the introduction of a live attenuated vaccine (i.e. Jeryl Lynn vaccine) in 1967, the incidence of mumps declined substantially, in particular after the 1977 recommendation for routine use of the mumps vaccine among infants as part of the measles-mumps-rubella (MMR) vaccine.

In the late 1980's, outbreaks among vaccinated middle school- and high school-aged children lead to the recommendation of administration of a second MMR dose at 4 to 6 years of age, which was followed by sustained reductions in mumps incidence. However, reappearance of mumps cases began in 2006 as documented by a series of outbreaks on American university campuses [1]. The age of infection of these outbreaks was 18 to 29 years, which was older compared to the prevaccine average of 5 to 9 years. Similar outbreaks recently occurred also in Canada, Western Europe, and Asian countries with routine MMR vaccination [2-4].

The resurgence of mumps among young adults is troubling since as many as 10% of mumps infections acquired after puberty may be associated with severe complications such as orchitis, meningitis, and deafness, in contrast to a milder disease in children typically developing fever and parotid gland swelling. In addition, most mumps cases in recent outbreaks were reported among young adults who received the two recommended vaccine doses, raising concerns about suboptimal performance of the Jeryl Lynn vaccine currently in use. Although two doses of mumps vaccine were unable to fully protect against mumps during these outbreaks, available data indicate that double vaccination has a protective effect against the severity of the disease in young adults [5]. Thus, patients who have received two vaccine doses had less severe symptoms compared to patients who were partially vaccinated or not immunized.

The recent mumps outbreaks in vaccinated communities could be due to the waning of vaccine-derived immunity or to the emergence of mumps virus strains escaping vaccine-driven immunological pressure. Distinguishing between these possibilities is critical to determine whether the re-emergence of mumps can be prevented by modifying vaccine dosing schedules or whether a new vaccine needs to be developed.

To this end, Lewnard and Grad set up a study, reported in Sci Transl Med in March 2018 [6], to distinguish waning of vaccine-derived protection from long-term changes in vaccine effectiveness against circulating mumps strains. Data from six epidemiological studies of mumps vaccine effectiveness performed over past decades in the United States and Europe were pooled. The authors tested whether the strength of vaccine-derived immune protection declines with time following administration of the vaccine (which would suggest vaccine waning) or whether the degree of protection has changed over recent decades (which would be accompanied by shifts in the circulating population of mumps virus lineages).

Vaccine-derived immune protection against mumps was estimated to wane on average 27 years (95% confidence interval, 16 to 51 years) after vaccination. After accounting for this waning, no evidence that the emergence of heterologous virus genotypes contributed to changes in vaccine effectiveness over time was found. A mathematical model of mumps transmission confirmed the central role of waning immunity to the vaccine in the re-emergence of mumps cases. In contrast, changes in the circulating genotypes of mumps virus over this same period could not be associated with reductions in vaccine effectiveness. Furthermore, their modeling suggests that mumps virus strains escaping vaccine protection would be expected to cause disproportionate incidence among younger children, which has not been observed in most of the recent outbreaks.

Based on these findings, the authors propose the routine use of a third vaccine dose at 18 years

of age, or booster dosing throughout adulthood, as a strategy to maintain immune protection in the population. Clinical trials designed to assess the benefit of extending vaccine dosing schedules or new vaccines to address the problem of waning vaccine-induced protection are needed.

In January 2018, the Advisory Committee on Immunization Practices (ACIP) recommended use of a third dose of mumps virus–containing vaccine in persons at increased risk for mumps during an outbreak to improve protection against mumps disease and related complications [7].

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Oral Antibiotic Treatment of Mice Exacerbates the Disease Severity of Multiple Flavivirus Infections. Thackray et al. Cell Rep. 2018;22:3440-53 e6.

Flaviviruses, e.g. West Nile (WNV), dengue (DENV), and Zika (ZIKV) viruses, account for approximately 400 million infections annually, with billions of human beings at risk and lack of specific approved antiviral therapy. Though most of WNV and DENV infections in humans are subclinical, severe illness occurs in only a subset of individuals. Some factors, such as patient age, underlying immune or chronic disease status, and polymorphisms in immune genes (e.g., CCR5, OAS1, and TNF) have been associated with increased susceptibility to WNV and DENV infections [1, 2]. Host immune factors that control WNV replication and dissemination (including type I interferon responses, serum anti-WNV IgM titers, FoxP3+ CD4+ T regulatory cells, and CD8+ T cell responses) have also been studied extensively. In DENV, disease severity is linked to well-recognized host immune mechanisms, including Fc-g receptor-mediated antibody-dependent enhancement of infection of myeloid cells and plasma levels of secreted NS1 protein.

Yet, these factors do not account for most adverse outcomes and how environmental factors contribute to flavivirus disease severity is poorly understood. The study carried out by Thackray and collaborators [3], published in March 2018 in Cell Reports, aimed at unravelling the impact of antibiotics on disease severity in mice infected with flaviviruses. This interesting work showed that treatment of mice with oral antibiotics resulted in increased susceptibility to severe WNV, DENV, and ZIKV infections. An antibiotic cocktail comprised of vancomycin, neomycin, ampicillin, and metronidizole, referred to as VNAM, administered orally, resulted in lethality, impaired host immunity, and increased WNV burden. VNAM treatment brought about fewer WNV-specific CD8+ T cells and Tregs in the draining popliteal lymph node and spleen. Adoptive transfer of both primed CD4+ and CD8+ T cells reversed the effect of VNAM treatment on WNV susceptibility. Though treatment of mice with ampicillin or vancomycin alone was sufficient to alter WNV outcome, the addition of metronidizole was required to generate the fully vulnerable phenotype. Antibiotic treatments that resulted in enhanced WNV susceptibility generated changes in the gut bacterial community and in the abundance of specific bacterial taxa. Only 3 days of treatment with ampicillin was sufficient to alter host immunity and WNV outcome. Importantly, the effects of oral antibiotic treatment occurred after termination of treatment, indicating that continuous exposure to antibiotics was not necessary to increase susceptibility to flavivirus infection.

These remarkable findings allowed the identification of oral antibiotic treatment as a potential risk factor for disease severity during subsequent flavivirus infection, suggesting that depletion and/or perturbation of the microbiota may adversely affect host antiviral immunity.

Oral antibiotic treatment that perturbs the gut microbiota of mice was also shown to inhibit poliovirus and reovirus replication, mouse mammary tumor virus transmission, and murine norovirus infection and persistence while oral antibiotic treatment delayed lymphocytic choriomeningitis virus clearance and increased

influenza virus pathogenesis in mice [4-6]. Altogether, these studies suggest that differential interactions between specific viruses, microbial community members, and/or the host may modulate the outcome of infection.

Based on data obtained in mice in the investigations performed by Thackray's group, it seems imperative to examine in humans whether exposure to oral antibiotics, as well as to other agents that alter the microbiota, is linked to severe disease during infection with flaviviruses or other pathogens requiring a rapid induction of T cell regulatory responses for protection.

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STING agonists enable antiviral cross-talk between human cells and confer protection against genital herpes in mice. Skouboe et al. PLoS Pathog. 2018;14:e1006976.

Mammalian cells express pattern recognition receptors (PRR), making them able to detect microbes. PRRs are activated following binding to conserved molecular structures, i.e. pathogen-associated molecular patterns (PAMPs), to induce expression of antiviral and pro-inflammatory proteins. As most PAMPs are expressed only by microbes and not by host cells, the innate immune system responds specifically to microbes. In addition to pathogen-specific PAMPs, DNA is a potent stimulator of antimicrobial responses [1]. To discriminate between non-self DNA derived from microbes from the own host genetic material, DNA sensors are present in compartments expected to be free of host DNA, i.e. in the cytosol, as well as in endosomal membrane structures. As DNA is a highly immunostimulatory molecule and the immune responses induced by DNA have antiviral activity, viruses with DNA genomes have evolved mechanisms to evade sensing and signaling through the pathways stimulated by DNA [2].

Toll-like receptor (TLR) 9, the first DNA sensor described, is expressed in the endosomal membrane and monitors the endosomal content for unmethylated, CpG-rich DNA. Because, in contrast to microbial DNA, cellular DNA is mostly methylated and has a low CpG content, TLR9 detects foreign DNA based both on location and chemical composition of the DNA. Only a limited number of cell types, mostly plasmacytoid dendritic cells, expresses TLR9. Therefore, this receptor is not the central sensor of viruses in the cells most often infected by viruses. RIG-I-like receptors recognize RNA species in the cytosol and to distinguish between host and pathogen RNA, RIG-I senses 5′-triphosphate containing RNA, a structure often formed in viral RNA [3].

During recent years, interest in cytosolic PRRs sensing DNA has considerably increased. Several receptors, including the protein absent in melanoma (AIM2), gamma-interferon-inducible protein (IFI16) and cyclic GMP–AMP synthase (cGAS), have been proposed to be crucial for cytosolic DNA recognition. cGAS is activated upon DNA binding to produce the cyclic dinucleotide (CDN) 2'3'-cGAMP, which in turn binds and activates the adaptor protein, stimulator of interferon genes (STING), triggering type I IFN expression. In contrast to TLRs, STING is expressed broadly, including in epithelial cells.

Herpes simplex virus 2 (HSV-2), the leading cause of genital ulcers, is also known to increase the risks of HIV-transmission [4]. So far, attempts at delivering an effective anti-HSV-2 vaccine have not succeeded. During the last years, there has been a growing interest in immunomodulatory therapy as a means to treat infections. Although the TLR7 agonist imiquimod has been shown to have anti-HSV-2 activity in individual patients, no significant effects were observed in clinical trials, and the compound also exhibited significant side effects including local inflammation [5].

Although the use of STING ligands has been investigated for anti-tumor activity in a variety of mouse models, anti-inflammatory effects in an experimental autoimmune encephalitis mouse model [6, 7], and for potential as adjuvants in vaccines [8], the efficacy of STING agonists as antiviral therapeutics has remained largely under-explored. Skouboe and colleagues now reported in PLoS Pathog that natural and non-natural STING agonists strongly induced type I IFNs in human cells and in mice in vivo, without stimulating

significant inflammatory gene expression [9]. Further, systemic treatment with 2'3'-cGAMP resulted in reduce genital HSV-2 replication and improvement of the clinical outcome of infection. Importantly, local application of CDNs at the genital epithelial surface induced local IFN activity, with only limited systemic responses. This treatment conferred complete protection against disease in both immunocompetent and immunocompromised mice. When comparing CDNs and TLR agonists, only CDNs acted directly on epithelial cells, leading to a more rapid and IFN-focused immune response in the vaginal epithelium. The findings of Skouboe's research pointed to specific activation of the STING pathway in the vagina evoking induction of the IFN system but limited inflammatory responses that allowed control of HSV2 infections in vivo. These data highlight the potential for immunotherapy in treatment of virus infections and suggest that STING-directed therapy may have a potential that should be further explored.

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Fragment-derived inhibitors of human N-myristoyltransferase block capsid assembly and replication of the common cold virus. Mousnier A et al. Nat Chem. 2018, May 14.

Rhinovirus (RV) is responsible for most of the cases of common cold, and is frequently linked to exacerbation and morbidity in important respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis [1, 2].

Rhinovirus is a member of the *Picornaviridae* family, which includes other important human and animal pathogens, such as poliovirus (PV), foot-and-mouth disease virus (FMDV), coxsackie virus, hepatitis A virus and enterovirus 71 (EV-A71). To date, no specific treatment for RV infection is available despite the importance of RV as a pathogen in respiratory disease [3]. The enormous RV serotype diversity (over 100 serotypes are known) prevent the generation of broad-spectrum vaccines. Further, rapid emergence of resistance is observed for inhibitors that target the virus capsid, due to RV rapid replication and high mutation rate.

The RV genome consists of one single-stranded (+) sense RNA molecule that is translated by host ribosomes into a single polyprotein. This polyprotein is processed by viral proteases to produce the capsid precursor protein and a number of non-structural proteins necessary for the completion of the viral life cycle. The capsid precursor is processed further into three capsid proteins, VP0, VP3 and VP1, triggering a cascade of protein self-assembly that ultimately leads to the formation of infectious virions.

This cascade starts with the formation of a VP0/VP1/VP3 complex. VP0 is encoded at the N terminus of the viral polyprotein, and in various picornaviruses it is N-myristoylated by the host cell N-myristoyltransferase (NMT). NMT transfers myristate from myristoyl coenzyme A (Myr-CoA) to the N terminus of a range of proteins during protein translation and is widely conserved across all the eukaryotic species. Higher organisms, such as humans, express two NMT proteins (NMT1 and NMT2) in most tissues.

PV mutagenesis studies suggested that VP0 N-myristoylation plays an essential role in capsid assembly and infectivity [4, 5], indicating that host NMT may be an attractive antiviral drug target being marginally susceptible to serotype variation and emergence of resistance as NMT is an unalterable factor in viral replication. Mousnier and collaborators [6] described in this article the discovery of IMP-1088 [1-(5-(3, 4-difluoro-2-(2-(1,3,5-trimethyl-1H-pyrazol-4-yl)ethoxy)phenyl)-1-methyl-1H-indazol-3-yl)-N,N-

dimethylmethanamine], a picomolar dual inhibitor of the human N-myristoyltransferases NMT1 and NMT2.

IMP-188 was discovered through a fragment reconstruction approach that started from two very weak HsNMT inhibitors identified in high-throughput screens against heterologous *Plasmodium falciparum* targets. By analyzing the crystallographic binding modes determined in the parasite NMTs, the authors constructed fragment-like compounds with remarkable cooperative inhibitory effects and complementary binding modes. The identification of cooperative binding between weak-binding fragments led to rapid inhibitor optimization through fragment reconstruction, structure-guided fragment linking and conformational control over linker geometry.

A specific impact of IMP-1088 on de novo N-myristoylation of NMT substrate proteins with no impact on protein synthesis was demonstrated by using a powerful chemical-targeting approach in cells infected with RV, confirming that it is a selective target of IMP-1088.

The authors demonstrated that inhibition of the co-translational myristoylation of a specific virus-encoded protein (VP0) by IMP-1088 potently blocks a key step in viral capsid assembly, delivering a low nanomolar antiviral activity against multiple RV strains, poliovirus and foot and-mouth disease virus, and protection of cells against virus-induced killing. This study highlights the potential of host myristoylation as a drug target in picornaviral infections. The authors suggest that human NMT merits further investigation as a drug target in myristoylation-dependent picornavirus infections, with potential applications in the treatment of RV-induced exacerbations of asthma, COPD, cystic fibrosis and other picornaviral diseases.

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