



ISAR News

Newsletter of the International Society for Antiviral Research

Editor Anthony Vere Hodge Guest editor, Joana Rocha-Pereira
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**La Jolla, CA, USA welcomes the 29th ICAR,
17-21 April 2016**

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ISAR PRESIDENT'S MESSAGE

I would like to offer a warm welcome to all of our members to the 29th International Conference on Antiviral Research which will be held in La Jolla, CA in April 2016. Our meeting this year will commence on the afternoon of Sunday April 17th with Drug Discovery 101 and conclude midday on Thursday April 21st. In between, Mark Prichard and the Program Committee have put together a top notch scientific program which includes two Keynote Addresses, two mini-symposia, our annual Prusoff, Elion and Holy award lectures, and a variety of podium presentations and posters based on submissions from our delegates. Mark has worked diligently this year to also incorporate a novel session on diagnostic technologies which will feature presentations from a variety of companies that provide us with the technologies necessary to more efficiently and quantitatively perform our research.

As always the meeting will prominently feature networking opportunities which is the hallmark of ICAR. From our sessions for Women in Science, our Young Investigator Reception, to all of the extended coffee and lunch breaks, the ICAR provide numerous opportunities to maintain long term friendships and meet new scientists. I look forward to personally welcoming you to La Jolla and ICAR in just a couple of short and very busy months.

28th ICAR Corporate and Educational Sponsors. PLATINUM: Gilead Sciences. GOLD: Chimerix, GlaxoSmithKline. SILVER: Alios BioPharma, Biota Pharmaceuticals, Elsevier B.V., JCR Pharmaceutical Co. Ltd., Southern Research Institute. BRONZE: ACS Infectious Diseases, Bristol-Myers Squibb, ImQuest BioSciences, Medivir AB, Novira Therapeutics, PTC Therapeutics, Toyama Chemical Co. Ltd, University of Minnesota Center for Drug Design, Institute for Antiviral Research Utah State University, and XpressBio.

Our meeting will commence this year with two Keynote addresses. Heinz Feldmann will present on his work with Ebola and present important information about the recent outbreak in West Africa. Richard Scheuermann from the J. Craig Venter Institute will then speak on viral genomics and the predictive ability of genomic analysis. This year's program also features two minisymposia which have been organized by Andrea Brancale, Bruno Canard, Erica Olmann Saphire, Rhonda Cardin and Graciela Andrei. The first symposium will cover topics in structural biology while the second will focus on DNA viruses. This year's educational DD101 session will highlight a cooperative program involving academic institutions, not-for-profit organizations and commercial partners in antiviral drug discovery to facilitate the development of antiviral products.

As per my last message I also encourage you to become involved in our Ambassador Program and introduce our Society and the Conference to someone new. The Society and meeting are warm and open places for new scientists to present their research as well as initiate or continue to build important networks of colleagues to advance the development of antiviral agents. Everyone that is a member certainly knows someone that would enjoy and contribute greatly to the meeting, so why not reach out and invite them to attend and relate to them your experiences with ICAR.

I am excited to announce the results of our recent election. This year we had an excellent slate of candidates and all will certainly play roles in the future of the Society and I'd like to thank Phil Furman and the Nominations Committee for drafting such a great group of nominees. I am also pleased to say that we had a record voter turnout this year and the final results confirmed how well respected all of the candidates were viewed within the Society. Johan Neyts was elected President Elect, Graciela Andrei was re-elected as Secretary and Mike Bray, Andea Brancale and Kathie Seley-Radtke were elected to seats on the Board of Directors. I look forward to working with all of the newly elected individuals as I step into the role of Past-President and wish all of the new electees the best of luck in leading the Society over the next two years.

The 29th ICAR in La Jolla will be a very special one for me as I end my term as President of the Society. I am now two-thirds of the way through my role as President-Elect, President and Past-President and in La Jolla I will hand over the reins of the Society to my highly capable successor José Esté of Barcelona. It's hard to believe how fast time flies

when you are doing something you love and I must admit that I have truly enjoyed being able to regularly work and interact with such a fine group of scientists from around the world to do good things (and avoid bad things) for our Society and the annual conference.

I expect our recently established efforts on behalf of Women in Science, Young Investigators, Career Forum and the Ambassador Program will continue to grow and flourish in the future. Much has been accomplished over the past couple of years and we still have much to do to assure that the Society remains as strong and interactive as it is and that we continue to find ways to bring young investigators into leadership positions within the Society. So I especially hope that you will join us in La Jolla so we can celebrate the end of my Presidency and the continued growth and evolution of the Society.

See you in La Jolla! Bob Buckheit

UPDATE ON THE 29TH ICAR **Program Committee (Mark Prichard)**

The International Society for Antiviral Research (ISAR) will host the 29th International Conference on Antiviral Research (29th ICAR) in La Jolla, California on Sunday April 17th through Thursday April 21st 2016. This venue lies within the vibrant research community in the San Diego area and will be held at the Hilton La Jolla Torrey Pines, 10950 North Torrey Pines Road, La Jolla, California 92037.

Speakers at the meeting will present the latest scientific developments in antiviral research and will emphasize the interdisciplinary nature of this field. The conference is designed specifically to provide opportunities for all participants to establish and maintain the close collaborative relationships among chemists, pharmacologists, and biologists that are required for the discovery and development of effective antiviral therapies. It also serves to stimulate innovative thinking on the drug development process and provides specific events to welcome new scientists to our ranks to help them to establish successful careers. Attending this annual meeting is important for all ISAR members as it serves to strengthen existing contacts and provides an opportunity to add new contacts to their network by meeting new scientists working in the field.

The formal commencement of the 29th ICAR will start on April 17th 2016 at 4:00 PM and will be marked by two Keynote Speakers: (Please see below for their photographs and biographies).

□ Heinz Feldmann, (NIH) will present his work on Ebola virus, starting with his research in Marburg, Germany, where the first filovirus outbreak occurred in 1967, through the recent West African Ebola epidemic. He will also provide a look ahead: what's needed, what should be the goals of Ebola research, where do we go from here?

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

This year the meeting will feature the following scientific sessions:

- The first short symposium will highlight recent developments on the use of structural biology in the discovery and development of antiviral drugs. The session is being organized by a trio of ISAR Prusoff Award winners: Andrea Brancale, Bruno Canard, and Erica Ollman Saphire and will include the following speakers:
 - Peter Cherepanov (Imperial College London)
 - Clodagh O'Shea (Salk Institute)
 - Eddy Arnold (Rutgers)
- The second symposium on DNA viruses is being organized by Rhonda Cardin and Graciela Andrei and will be held on the morning of Wednesday April 20th. This session will focus on recent advances in therapies and will include presentations by:
 - Thomas Lion (Children's Cancer Research Institute)
 - Margaret Stanley (University of Cambridge)
 - David Bernstein (University of Cincinnati)
 - Timothy Kowalik (University of Massachusetts)
 - Phil Pellett (Wayne State University)
- A Drug Discovery and Development 101 session entitled "Antiviral Drug Discovery and Development Center" will illustrate how the cooperation of academic institutions, not-for-

profit research organizations and commercial partners can drive the rapid development of therapies for emerging infections. This interactive session will highlight presentations by the following speakers:

- Maaïke Everts (University of Alabama at Birmingham)
- David Cowfer (Gilead Sciences)
- Bob Bostwick (Southern Research)
- Mark Denison (Vanderbilt University)
- Plenary presentations will also be provided by:
 - Pei-Yong Shi (University of Texas at Galveston)
 - Rob Jordan (Gilead Sciences)

The 29th ICAR will host a **Diagnostic Technologies Workshop** on the afternoon of Tuesday April 19th. This special workshop will present new technologies to help drive the development of effective new therapies for virus infections. Specifically, it will showcase rapid diagnostic technologies that can be used to identify viral infections in a timely manner to ensure that patients can benefit from effective antiviral therapies. More importantly, these technologies can maximize the power of clinical trials by identifying subjects that are infected with the virus of interest, yet remain free from other common viral infections that could mask a significant clinical response. This workshop will also highlight new technologies that can help drive the drug discovery process.

Each year ICAR features a Poster Awards competition and this tradition will continue in 2016. This year the Poster Award Committee, which is chaired by Kathie Seley-Radke, will review the candidates for awards. In past years, the competition has been intense and the Program Committee is fortunate to have dedicated members who are willing to serve on this important subcommittee. Cash prizes of up to \$1000 will be awarded in the categories of Graduate Student, Postdoctoral Fellow and Young Investigator. Awardees will also have the opportunity to present their work in the Oral Shotgun Presentation session. The prominence of the Poster Presentations at this meeting reflects the high quality of presentations and offers new and experienced investigators a high profile venue to present their work. The ICAR program and the posters presented will be placed on the Society's webpage such that members can review the material both before and after the meeting.

The Program Committee is committed to bringing you the most rewarding scientific experience at the

annual meeting. To this end, the Committee has worked diligently this year to make changes to the annual meeting in response to feedback we have solicited from our membership. We have endeavoured to keep the best features of the meeting while adding scientific sessions and events which we believe will heighten the experience for all attendees. As always, the Society will maintain its commitment to the newest ISAR members and to antiviral research by again sponsoring a Career Forum. At this function, the attendees can meet with established scientists and other professionals active in the pharmaceutical, biotech, academia, and the government sectors of antiviral research to discuss various career options. This highly interactive social event will provide participants with the opportunity to join one or more discussion groups to learn about potential career paths. There is no additional fee for the Career Forum, but since the available space is limited, attendees should indicate their interest when registering on-line for the ICAR meeting. Following the success of a special session on Women in Science (WIS) last year, it will be held again this year. It will include panel discussions to help provide advice for women scientists as their careers progress in this field. For more information, please see below the WIS article by Amy Patick.

This year all abstracts must be submitted online by January 15, 2016. This can be done through the ICAR website or by pasting this site into your browser:

<http://precis2.preciscentral.com/Link.aspx?ID=9173B653E25E110B>.

The Program committee welcomes the submission of late-breaker abstracts describing truly original and important results. However, the committee will be expecting a very high standard and only those abstracts fully meeting those standards will be accepted.

Biographies of the two keynote speakers

Heinz Feldmann was born in Lippstadt, Germany, in 1959. He received his B.Sc. in 1981 from the University of Giessen, Germany. Subsequently, he graduated from Medical School in 1987 (MD) and received his PhD in 1988 both from the University of Marburg, Germany. His postdoctoral research was conducted in the field of virology (filoviruses and hantaviruses) at the Institute of Virology, University of Marburg, Germany, and the Special Pathogens



HEINZ FELDMANN

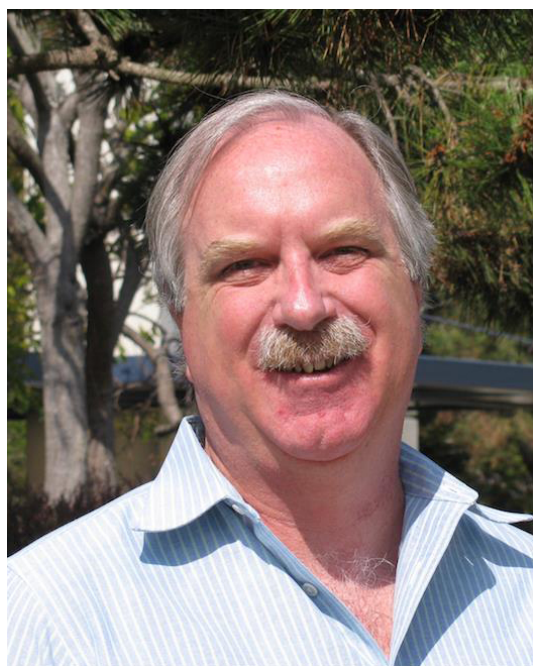
Branch at the Centers for Disease Control and Prevention in Atlanta, U.S.A., where he held a fellowship from the US 'National Research Council'.

Following his postdoctoral training he started as an assistant professor with the Institute of Virology at the University of Marburg, Germany. Subsequently, he was awarded associate professor at the same institution. During this time he was trained as an infectious disease specialist with focus on laboratory diagnostics. From 1999-2008, he held the position of Chief, Special Pathogens Program of the National Microbiology Laboratory, Public Health Agency of Canada.

Since 2008, he is the Chief, Laboratory of Virology at the Rocky Mountain Laboratories (RML), DIR NIAID, NIH, and the Chief Scientist of the RML BSL4 Laboratories. In addition, he is an Associate Professor with the Department of Medical Microbiology, University of Manitoba. Heinz Feldmann is the laboratory expert on high containment viruses (BSL4) and serves as a consultant on viral hemorrhagic fevers and related pathogens for the World Health Organization and, thus, has field experience and expertise in outbreak management.

His professional interest is in the pathogenesis and transmission of hemorrhagic fever viruses, such as filoviruses, arenaviruses and bunyaviruses, and other special viral pathogens (high containment, BSL3 and BSL4), and the development of countermeasures

against those pathogens. Given his area of expertise he also is a consultant and expert on bioterrorism-related issues. His scientific contribution includes over 320 scientific publications, 6 patents and over 200 invited lectures at conferences and seminars worldwide. He has been awarded with several honors including the 'Löffler-Frosch Award' from the German Society for Virology (DGV), the 'Dalrymple/Young Award' by the American Committee on Arthropod-Borne Viruses (ACAV), and Research Merit Awards from the Public Health Agency of Canada (PHAC) and the National Institute of Allergy and Infectious Diseases (NIAID).



RICHARD H. SCHEURMANN

Dr. Richard H. Scheuermann is the Director of Informatics at the J. Craig Venter Institute (JCVI) and a Professor of Pathology at U.C. San Diego. His current research is focused 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.

Dr. Scheuermann has led three large public database development projects funded by the U.S. National Institutes of Health – 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/>).

On behalf of the Program Committee, I look forward to welcoming you to La Jolla and the 29th ICAR in April 2016.

INVITATION TO LA JOLLA (Karl Hostetler)

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 to the south with its world-class shopping to one-of-a-kind dining and beach culture to high culture. You'll find an amazing range of dining choices - from fine cuisine to quaint cafes, from internationally 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 the 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 here's the URL:

<https://weatherspark.com/averages/31573/4/San-Diego-California-United-States>

Looking forward to welcoming you on April 17th.

WOMEN IN SCIENCE (WIS) (Amy Patick)

The WIS committee is excited to announce the **4th Annual Women in Science Roundtable** which will be held Sunday, April 17, from 11:30 – 2:00 pm. This session is open to all ICAR attendees, both women and men and will address the challenges and opportunities encountered by women scientists while navigating the twists and turns of career progression in today's environment.

Come talk to scientists in industry, government and academic fields. This roundtable will utilize a lively "speed mentoring" approach in which moderators will move from table to table to facilitate small group conversations on a variety of topics including: Do Super-Women Exist: How to balance work and family through all life stages; Where do I

Go From Here: Maximize the benefits from the mentor/mentee relationship; Negotiation: Tips on how to secure a mutually advantageous outcome without selling yourself short; Is There a Glass Ceiling Left to Crack: How to manage work force equality; Awards and Recognition: Learn to self-promote effectively to achieve your professional goals and to gain recognition, etc. This roundtable is free for ICAR registrants; however, space is limited to the first 80 participants, so register now! To register, select the "Women in Science Roundtable" session under the 29th ICAR Events section when you register for the Conference. Lunch will be provided.

29TH ICAR: USEFUL INFORMATION

The 29th ICAR will run from 2 pm Sunday April 17th through 12 pm Thursday April 21st 2016.

Important Pre-ICAR dates

Abstract submission deadline January 31
Abstract acceptance notices sent February 26
Travel grant application deadline January 15
Travel grant notifications sent February 12
Late breaker abstracts can be submitted via the ISAR web site up to March 15, 2016.
Advance rate registration deadline March 18
Registration cancellation deadline March 18
Reservation at conference hotel at ICAR rate: deadline March 27

Registration fees

Category	\$ (USA)	Discount vs full rate
Advance rate to March 18	825	11%
Advance rate for ISAR members	675	27%
Advance rate for students	300	67%
Regular rate	925	-
Regular rate for ISAR members	775	16%
Regular rate for students	350	62%

Hotel Information

ISAR will host the 29th ICAR at the Hilton La Jolla
([Hilton La Jolla Torrey Pines](#))
10950 North Torrey Pines Road
La Jolla, CA 92037, US
TEL: +1-858-558-1500
Rate for ICAR attendees: \$199 Deadline: March 27th

Reservation link:

<https://resweb.passkey.com/go/ISAR16>



The ICAR rate includes guest room wireless internet. In addition the hotel will offer a complimentary shuttle to ICAR delegates from 6 – 10 pm Sunday – Wednesday to downtown La Jolla.

Check-in: 4:00 pm. **Check-out:** 11:00 am

Airport – Hotel ground transportation:

The hotel is approximately 20 minutes from the [San Diego International Airport](#). A taxi costs approximately \$45 one way and a [Super Shuttle](#) costs approximately \$16 one way.

Are you eligible for the U.S. Government Hotel Room Rate?

We have a small room block for those who require U.S. Government rate. To make a reservation, [click here](#).

ISAR ELECTIONS 2015 (Phil Furman)

Congratulations to Johan Neyts who was elected President-Elect, to Graciela Andrei who was re-elected as Secretary, and to Andrea Brancale, Mike Bray, and Kathie Seley-Radke who were elected to the Society's Board of Directors. An electronic (web-based) election was run from November 6th to December 6th for the offices of President-Elect and Secretary and three Board of Director seats. An outstanding slate of candidates was nominated for each of these positions. An e-mail was sent out to 391 registered members and 97 replied (25% of members actually voted), which was a slightly better response than previous years. Hopefully in the future more members will participate in these important elections.

ISAR President-Elect



Johan Neyts

Johan Neyts is full professor of Virology at the faculty of Medicine of the University of Leuven (KU Leuven) in Belgium where he teaches medical virology at the school of medicine and dentistry. The focus of his laboratory is the development of novel antiviral and vaccination strategies. He is author of ~360 peer reviewed papers, a number of book chapters and is inventor of several patents. So far 16 people have obtained their PhD degree under his guidance and 56 bachelor or master students have been trained in his laboratory. He has given >140 invited lectures, is an editor of the journal *Antiviral Research*, on the editorial board of other journals and *ad hoc* reviewer for >40 journals (including Nature, Nature Medicine, Science). He serves as an advisor to several companies and commissions and has been on the scientific advisory board of the Merieux Foundation.

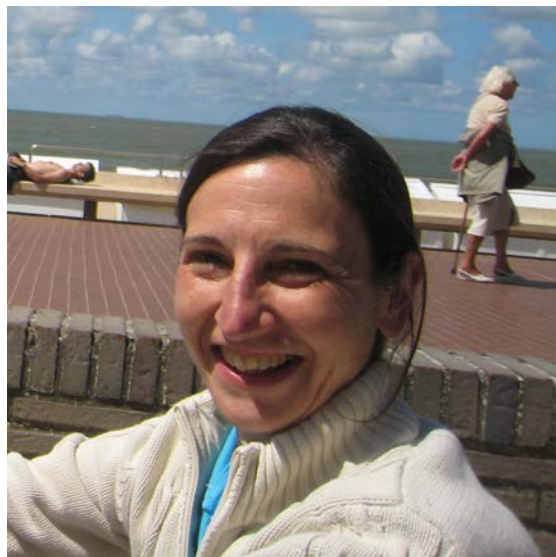
Johan was co-founder (developed the scientific concept) and Chief Scientific Officer (CSO) of the KU Leuven spin-off Okapi Sciences NV a biotech company that developed antivirals for veterinary use. Okapi Sciences was acquired in 2014 by Aratana Therapeutics (www.aratana.com) and the team and facilities in Leuven have since then been Aratana Therapeutics Europe. He is CSO of ViroVet (www.virovet.com), a new KU Leuven spin-off that is currently being incorporated. Research topics covered in his laboratory at the University in Leuven include the development of (i) novel antiviral

strategies against a number of RNA viruses including flaviviruses (dengue and others), picornaviruses (entero- and rhinoviruses), alphaviruses (Chikungunya and others), paramyxoviruses (RSV and others), rabies, noroviruses and the hepatitis E virus as well as (ii) a novel (thermostable) DNA vaccine technology that allows to simply launch live-attenuated RNA viruses from a easy to produce plasmid

Johan's laboratory has been actively involved in the development of antivirals against the hepatitis C virus, this includes amongst others the discovery of (i) of a class of non-nucleoside HCV polymerase inhibitors (together with Prof. G. Pürstinger, Univ. Innsbruck) that was licensed to Gilead and from which Tego buvir was developed and (ii) the anti-HCV activity of Alisporivir (together with Debiopharm in Lausanne) that was later developed by Novartis. Together with the Leuven Center for Drug Design & Discovery (CD3) his lab developed a class of potent and pan-serotype dengue virus inhibitors that is now being further developed in a joint effort with Janssen Pharmaceutica (Johnson & Johnson). Together with scientists at the Korean Research Institute for Chemical Technology his lab discovered the potent and pan-rhino/enterovirus activity of a novel class of compounds that is now being further developed in a joint effort with a large pharmaceutical company. Johan has attended 23 ICARs since 1990 and received in 2003 the William Prusoff Young Investigator Lecture Award from ISAR. He has been actively involved in the Society including as past-board member and chair of the membership committee.

Secretary

Graciela Andrei obtained her PhD in Biological Sciences at the Faculty of Sciences, University of Buenos Aires, Argentina, where she received a fellowship from the National Research Council (CONICET) (1984-1989). She then performed a post-doctoral training on antiviral chemotherapy with particular focus on herpesviruses, at the Rega Institute for Medical Research in Leuven, Belgium where she was recipient of a fellowship from the KU Leuven (1989-1996). She performed visiting research training at the Department of Biochemistry and Molecular Genetics, University of Alabama at Birmingham in 1997. She was then associate researcher at the Rega Institute (1997-2005) and since 2005 assistant professor at the Faculty of Medicine,



Graciela Andrei

Laboratory of Virology and Chemotherapy, Rega Institute, KU Leuven.

Her main scientific activities include: the unraveling of the mode of action of novel antivirals, the molecular mechanisms of drug-resistance in herpesviruses and poxviruses, the molecular anticancer mechanism of action of nucleotide analogues, and the development of organotypic epithelial raft cultures for the study of epithelio-tropic viruses. In 2009 she participated in the set-up of a translational research platform (i.e. RegaVir) for typing drug-resistance herpesvirus among immunocompromised patients that fail antiviral therapy. Since 1989, she is member of the American Society for Microbiology and of the International Society for Antiviral Research, and in 2012 she was elected secretary of the Antiviral Research Society. She is in the editorial board of the "Antiviral Research" and "PLOS One" journals.

Board of Directors

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

**Mike Bray**

producing the first DENV infectious clone. In 1995, he transferred to the Virology Division at the US Army Medical Research Institute of Infectious Diseases at Fort Detrick, where he worked for John Huggins, studying Ebola and other hemorrhagic fever viruses and poxviruses in laboratory animals and testing new antiviral drugs and vaccines. In 2002, he returned to NIH, where he is a medical officer in the Division of Clinical Research, NIAID. He attended his first ICAR (the 12th) in Jerusalem in 1999, where he gave a talk on mouse-adapted Ebola virus, and has attended almost every ICAR since. He served as the reviews editor of *Antiviral Research* from 2007-11, and became editor-in-chief in January, 2012.

Kathie Seley-Radtke is the Presidential Research Professor of Chemistry and Biochemistry at the University of Maryland, Baltimore County (UMBC). She earned her Ph.D. in Organic Chemistry from Auburn University and her research involves using a synthetic organic/medicinal chemistry approach to nucleoside and heterocyclic drug discovery and development. Current projects include the investigation of flexible nucleosides/nucleobases "fleximers" for use against SARS, MERS-CoV, Ebola, HCV and HIV, among other viruses, and cancer.

Kathie has given more than 100 invited talks worldwide in twenty-three countries, published over seventy peer-reviewed papers, and has organized a number of international conferences focused on medicinal chemistry and drug design. She is currently

the President of the International Society of Nucleosides, Nucleotides and Nucleic Acids (IS3NA),

**Kathie Seley-Radtke**

and has served as Chair of Poster Awards for the ISAR for a number of years. Notably, she initiated a new program for IS3NA, the Women's Career Development Scholarships, as well as to obtain funding for the Women in Science Scholarships for ISAR. Both initiatives were generously funded by the Chu Family Foundation. She is also a member of the American Chemical Society's Medicinal Chemistry Division Awards Committee, an Associate Editor for *Current Protocols in Chemical Biology*, as well as to have served as a standing member and reviewer for NIH, NCI, NSF and other funding agencies.

Andrea Brancale is a Reader in Medicinal Chemistry at the School Of Pharmacy and Pharmaceutical Sciences, Cardiff University, UK. He graduated in Medicinal Chemistry in 1996 at the University of Rome "La Sapienza". He then moved to Cardiff where he received his PhD in Medicinal Chemistry in 2001, under the supervision of Prof. Chris McGuigan. During this time he worked on a project focused on the synthesis of novel antiviral nucleoside analogues, which led to the discovery of a potent anti-VZV compound (Human Phase II successfully completed in Oct 2010). Following on from the PhD Dr. Brancale worked as a PostDoctoral Fellow (2001/2002) on a GSK- sponsored research project, led by Prof. Chris McGuigan, on the design of novel pro-nucleoside analogues as anti-HIV agents.

With the appointment as lecturer at the School of Pharmacy, Cardiff University, Dr. Brancale directed his research on the use of computer-aided techniques in the design and discovery of novel antiviral and

anticancer compounds. In the antiviral field, his main research projects are focused on *their silico* design



Andrea Brancale

of RNA- viruses inhibitors (including Dengue, WNV, HCV, Chikungunya virus and Coxsackie virus). He sits on the Editorial board of Antiviral Research and he is the Chemistry Editor for Antiviral Chemistry and Chemotherapy.

Andrea has been a member of ISAR since 2000 (elected ISAR Board member in 2013) and he has served the Society through the participation on the Website committee (2004-date; Chair 2006-date) and on the Publication Committee (2010-date). Since 2006 he is also the Webmaster of the ISAR website and during this time he has implemented several technical developments on the website, from the on-line registration and membership management to the enhancement of the social profile of the Society on Facebook, Twitter and LinkedIn.

CURRENT RESEARCH

New infection models for human norovirus promise to accelerate drug development

Christiane Wobus, University of Michigan Medical School, Ann Arbor, MI, USA

During a recent family vacation overseas, my family and I experienced what appeared to have been a classical case of human norovirus infections, although I was unable to collect samples to confirm my suspicion. After being exposed to aerosolized

vomit at a restaurant, the symptoms of vomiting and diarrhea started ~ 12 hours later and lasted roughly the same time. During the ordeal, my children kept asking if there was medicine they could take to stop the disease. However, all I could do was try to comfort them with the fact that the symptoms would stop soon and they would feel better the next day.

Later came the more complex question of why there was no medicine approved for human norovirus infections (or, for that matter, for a range of other diarrheal virus infections with similar symptoms). Of course there are many facets to fully address this question, ranging from viral factors, like genetic diversity and host specificity, to societal ones regarding how to allocate research dollars to different diseases, but there are also inherent difficulties in working with human noroviruses that have slowed scientific progress compared to other viral infections.



Christiane Wobus

I have been studying noroviruses since co-discovering the first murine norovirus (MNV-1) and developing the first norovirus cell culture system as a postdoctoral fellow at Washington University in St. Louis (1, 2). These breakthroughs were followed by the establishment of multiple reverse genetics systems over the years (3). Together, these technological advances have made the murine norovirus system a widely used model that permits mechanistic studies of norovirus biology *in vitro* and *in vivo*. For a discussion on the murine norovirus system and its many contributions to the field, the reader is referred to a recent review (4).

The versatility of the system has also lent itself to anti-norovirus drug development efforts, which was

recently reviewed (5). While studies of murine noroviruses will help us identify general principles of enteric viruses or noroviruses as well as cross-genus and broad spectrum antivirals, there are species specific differences between human and murine noroviruses that cannot be addressed studying murine noroviruses or other human norovirus surrogates. Thus, ultimately the field needs to establish broadly available, robust infection systems to study human noroviruses directly.

The first human norovirus, Norwalk virus, was discovered in 1972 after analysis of fecal samples collected during an outbreak of non-bacterial gastroenteritis at an elementary school in Norwalk, Ohio, USA in 1968 (6). Two decades later, its viral genome was cloned and sequenced (7), shepherding in the molecular area of norovirus research. Since then, molecular epidemiology has highlighted the extensive diversity of human norovirus strains and continuing genetic drift of strains and recombination between strains (8). Furthermore, the availability of full-length clones of human noroviruses has allowed the study of recombinant proteins and development of human norovirus reverse genetics systems. However, due to the narrow species specificity of noroviruses, the development of animal models has been challenging and remains in its infancy.

To date, only a limited number of HuNoV strains have been shown to infect non-native animal hosts, specifically mice deficient in the recombination activating gene (Rag) and the common gamma chain (γ c) (9), gnotobiotic pigs (10), gnotobiotic calves (11), macaques (12), and chimpanzees (13). However, no single animal model recapitulates all aspects of HuNoV infection. For example, symptomatic infections exhibiting clinical signs (i.e., diarrhea) are only observed in gnotobiotic pigs and calves but not the other species. On the other hand, human norovirus infection in mice offers the genetic tractability of this small animal host, for example to identify host factors of infection, and their wide availability to the scientific community promises to accelerate discoveries. Thus, each model has certain strengths to allow the study of specific aspects of human norovirus biology.

Importantly, a combination of small and large animal models are needed during drug development to provide critical data during investigational new drug (IND)-enabling studies. Hence, the availability of multiple models for drug development is exciting. Yet, much remains to be investigated. To date, only a handful of studies have tested antiviral strategies, mostly vaccine strategies, in human norovirus animal

models. Therefore, future efforts are needed to demonstrate the utility of the existing animal models for testing of a broad range of antiviral strategies, including prophylactic and therapeutic regimens and small molecule inhibitors. Equally important are studies to expand the use of these animal models to the wide range of human norovirus strains, beyond the few GII.4 strains and Norwalk virus (GI.1) tested to date. In addition, human norovirus infection models also need to be developed that recapitulate the fecal-oral transmission cycle and enable virus passages by the natural infection route.

For drug development, the availability of a cell culture system to cultivate viruses is at least as important as animal models as it enables, for example, the development of live attenuated vaccine strains and provides a platform for screening and optimizing of antiviral compounds. However, the norovirus field has struggled since the discovery of the first norovirus to develop a reproducible culture model (14). It was not until last year that the first successful cultivation of a human norovirus strain was reported (15). The study determined that a GII.4 human norovirus was able to grow in a human B cell line (BJAB cells) but it required the presence of a co-factor for optimal infection; namely bacteria expressing histo-blood group antigen-like glycans on their surface or synthetic histo-blood group antigens. This discovery is an important and critical first step towards a broadly applicable, high yield human norovirus culture system that is widely used in the field. With regards to antiviral therapies, some of the studies to look forward to in the near future will be the testing of antiviral efficacies of compounds and neutralizing activities of antibodies.

The human norovirus mouse model and B cell culture system are clearly in their early days and many variables in each system still need to be worked out. However, their potential for addressing both basic science questions and use in translational research is large. Thus, both models have given the norovirus community critical additional tools that will ultimately reduce human norovirus infections as the cause of ~one fifth of all acute gastroenteritis cases worldwide (16).

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ANTIVIRALS ON THE HORIZON

MERS-coronavirus: a moving target?

Adriaan de Wilde, Clara Posthuma and Eric Snijder. Molecular Virology Laboratory, Department of Medical Microbiology, Leiden University Medical Center, Leiden, The Netherlands

Emerging coronaviruses - In the spring of 2012, less than a decade after the impact of the SARS epidemic, a second zoonotic coronavirus causing lethal respiratory infections in humans emerged, this time not in South East Asia but in the Middle East. Since then, over 1,600 laboratory-confirmed infections with this Middle East Respiratory Syndrome coronavirus (MERS-CoV) have been registered, with an associated mortality rate of 35-40%.

MERS-related casualties are now steadily approaching the number officially listed for the 2003 SARS epidemic (774 deaths). In contrast to that latter outbreak, however, which was contained within 6 months, MERS-CoV now has been circulating in the Middle East for about 4 years, while regularly being exported from the region by infected travelers. In mid-2015, its potential socioeconomic impact was highlighted in South Korea, where an air travel-related outbreak resulted in 186 confirmed MERS cases, 36 deaths, and the isolation of about 17,000

(possibly) exposed individuals. In this light, the annual massive pilgrimages to Saudi Arabia remain a

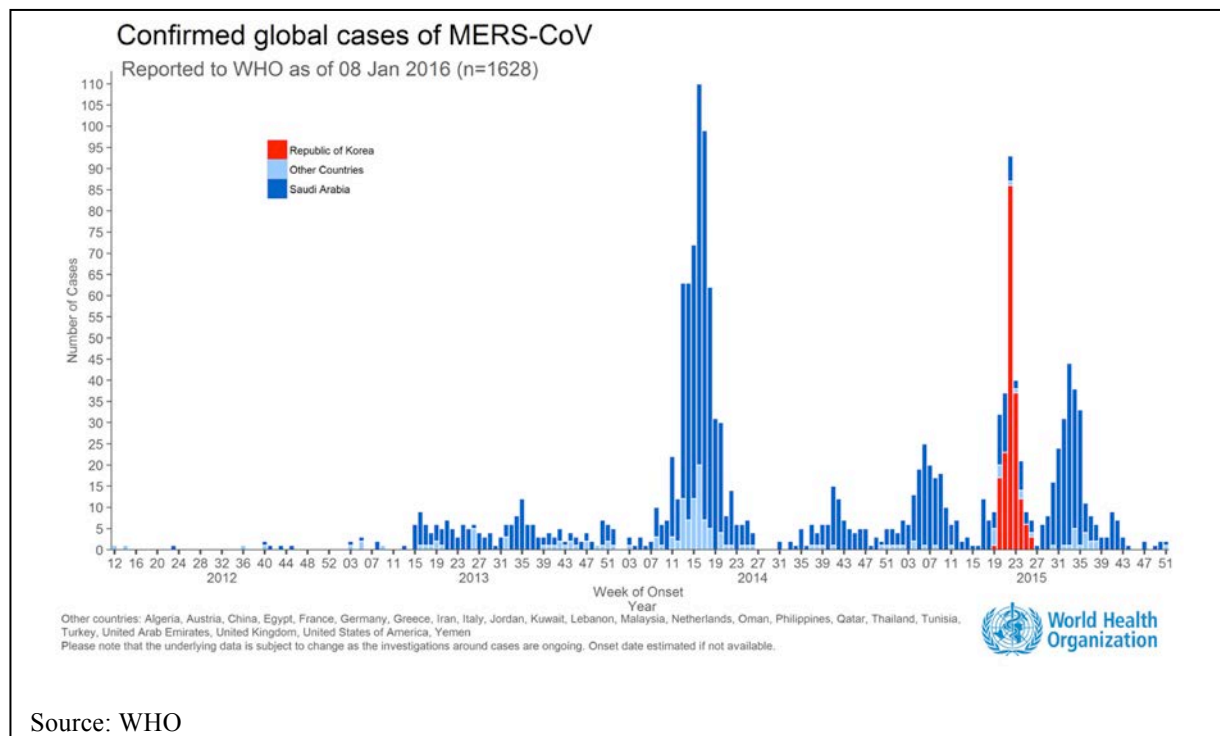


Eric Snijder, Clara Posthuma, Adriaan de Wilde

particular public health concern. Dromedary camels presently remain the only confirmed animal reservoir of the virus. During the 2015 Hajj period, again, public awareness and restrictions on the consumption of raw dromedary meat and milk may have contributed to preventing further spread of the virus. However, given the high seroprevalence of MERS-CoV antibodies in dromedaries and the probably frequent exposure of humans to infected animals, the reported poor transmissibility from dromedaries to humans probably remains the major restriction factor.

Also, interhuman transmission was initially deemed to be very inefficient (R_0 estimates well below 1), but – as highlighted by the events in Korea – this may be quite different during hospital-related outbreaks, with R_0 values possibly approaching those inferred for SARS-CoV (*i.e.* in the range from 2 to 3). Thus far, secondary infections among family members and health care workers have caused the majority of MERS cases, with high mortality among patients with underlying diseases. Nevertheless, a significant proportion of infections are in patients with no known history of contact with dromedaries or MERS patients, underlining the importance of the hunt for (potential) additional animal reservoirs, including bat and rodent species.

In general, the MERS outbreak has made it painfully clear that, despite 10 years of SARS-CoV research, we are essentially empty-handed when it comes to countering these potentially lethal coronaviruses. There is no approved vaccine or antiviral medication available that can prevent, cure or even delay coronavirus infection in humans, even though the course of infection with both SARS-CoV and MERS-CoV is relatively slow. The incubation period for MERS-CoV infection is 2-14 days (average 5-6 days), with patients generally being most infectious during their second week of illness. Thus, in contrast to many RNA virus infections that develop much more rapidly, there seems to be a



genuine window of opportunity for antiviral treatment.

Coronavirus drug targets - Coronaviruses stand out for their exceptionally large +RNA genomes (26-34 kilobases) and the complexity of their genome organization and expression. Their >20-kilobase replicase gene is followed by a set of structural and accessory protein genes, most of which are expressed from their own subgenomic mRNA. The MERS-CoV pp1a and pp1ab replicase polyproteins are proteolytically cleaved into 16 nonstructural proteins (nsps) by protease domains residing in nsp3 (PLpro for papain-like protease) and nsp5 (Mpro for main protease). Together with the viral RNA polymerase and helicase domains (12), residing in nsp12 and nsp13, respectively, these constitute common RNA virus targets for directly-acting antivirals (DAAs). During the post-SARS era, the two protease domains have been explored most extensively, also because crystal structures were obtained that enabled structure-based drug design (SBDD), a step that still needs to be made for the coronavirus RNA polymerase and helicase enzymes (6).

In addition to these common +RNA virus enzymes, the coronavirus replicase incorporates a variety of more unusual or unique domains, which may each constitute interesting and novel drug targets. These include two cap-modifying methyl transferases (in nsp14 and nsp16), a nucleotidylating activity (the N-terminal domain of nsp12), and – most remarkably in a virus with an RNA genome – an endoribonuclease (nsp15 NendoU) and an exoribonuclease (nsp14 ExoN). Whereas substrate and role of NendoU remain to be identified, ExoN has received considerable attention over the past decade, as it was demonstrated to direct a proofreading mechanism that thus far is unique in the RNA virus world. ExoN acquisition likely was a key event in coronaviral genome expansion, eventually leading to their current genome size. There is increasing evidence that ExoN interacts with the RNA polymerase and nascent strand to excise erroneously incorporated nucleotides. This presents an additional challenge for the development of nucleoside inhibitors, since their efficacy will likely be determined by both their propensity to be incorporated by the nsp12 RNA polymerase and their ability to resist excision by the proofreading nsp14 ExoN.

MERS-CoV animal models - The evaluation of MERS intervention strategies requires animal models for infection and disease, preferably in small animals although dromedary camels are also being explored for this purpose now (6). A recent study by Müller *et*

al. suggests that MERS-CoV infections in humans may often remain asymptomatic, with only a fraction – mainly patients with underlying disease or healthcare workers exposed to high virus doses – developing clinical disease (10). Such a course of infection is also observed in most of the available animal models, in which virus replication is accompanied by mild clinical signs. Rabbits, rhesus macaques, and marmosets have been explored as animal models, each having their specific pro's and con's (13). Identification of dipeptidyl peptidase-4 (DPP4) as a MERS-CoV receptor, followed by the dissection at the molecular level of the interaction between the viral spike protein and DPP4 homologs from a variety of species, has been instrumental in understanding the MERS-CoV host range.

DPP4 sequence variation explained, for example, why mice, hamsters, and ferrets are insensitive to MERS-CoV infection. Subsequently, these insights supported the selection of alternative small-animal models and the development of transgenic mice expressing human DPP4. The latter models are still being improved and it is currently being evaluated to which extent they reproduce the course of infection in human MERS patients. For the moment, these mice definitely offer a useful starting point for the evaluation of candidate vaccines and therapeutics, however, the number of animal studies that assess the *in vivo* efficacy of virus inhibitors is still limited.

MERS-CoV inhibitors - Within a few months after MERS-CoV isolation, and supported by the availability of various susceptible cell lines, cell culture-based antiviral screening assays were developed to facilitate the testing of specific inhibitors and compound libraries in BSL-3 facilities (3,8). Several compounds were reported to either target viral functions directly or (presumably) act by modulating host factors relevant for MERS-CoV replication. Some of the first studies focused on more general inhibitors of virus replication, like mycophenolic acid, cyclosporin A, ribavirin, and various types of interferons, which all inhibit MERS-CoV replication to a certain degree. Unfortunately, approved drugs that target the active site of the DPP4 receptor do not block infection.

In the DAA category, most of the work was focused on inhibitors of the two viral proteases, polymerase, helicase, as well as spike protein-directed fusion inhibitors (1,6,7,14). The MERS-CoV PLpro and Mpro crystal structures revealed considerable differences with the corresponding SARS-CoV enzymes, explaining why they are not inhibited by SARS-CoV protease inhibitors (6). By

now, SBDD has produced various MERS-CoV-specific protease inhibitors that are active *in vitro* and must be explored *in vivo*. Although several nucleoside analogues have been tested as potential coronavirus polymerase inhibitors (11), this field definitely merits further exploration in particular now that an *in vitro* coronavirus polymerase assay has become available. Ribavirin, however, is only active at concentrations that reduce cellular GTP levels and most likely does not affect the coronaviral polymerase directly. Recent biochemical studies have revealed that several key replicative enzymes, e.g. polymerase, exoribonuclease and one of the methyl transferases, are activated by smaller nsp cofactors like nsp7, nsp8, and nsp10. These interactions are essential for virus viability and constitute interesting potential targets for small-molecule inhibitors.

Structural information on the MERS-CoV spike protein's receptor-binding domain, alone and in complex with DPP4, rationalized the development of antibodies that block virus attachment and entry. These may turn out to be potent prophylactics and/or therapeutics, for example to protect front-line medical personnel and other risk groups. Due to the considerable divergence among known coronaviruses, a general DAA drawback is their lack of cross-reactivity, which will - presumably - limit their use in combating future emerging coronaviruses. A second DAA-associated issue, the evolution of viral escape mutants, may be circumvented or delayed by administering combinations of DAAs and/or host-directed antivirals (HDAs).

In the HDA category, cyclosporin A, which targets members of the host's cyclophilin protein family, was reported to block infection of cultured cells by multiple coronaviruses, including MERS-CoV. Furthermore, a systems biology approach revealed that inhibition of the phosphatidylinositol 3-kinase signaling pathway reduces MERS-CoV infection, in line with increasing support for a role in pathogenesis of altered lipid metabolism and composition. This may be linked to the formation of the membranous replication structures that are thought to support viral RNA synthesis. Targeting the formation of these organelles, e.g. with the drug K22 (9), may constitute an innovative antiviral approach with *pan*-coronavirus potential.

To explore the possibility of repurposing previously approved drugs, which offer a potential shortcut towards rapid application in the treatment of MERS patients, several laboratories, including our own, have screened compound libraries (3,4,7). About a dozen MERS-CoV inhibitors that are active

in the low-micromolar range were identified and are currently awaiting evaluation of their *in vivo* efficacy. Three of the compounds identified in our lab, the coronavirus entry inhibitors chlorpromazine and chloroquine as well as the well-known HIV-1 protease inhibitor lopinavir, previously had been identified as SARS-CoV inhibitors in cell culture. Although the latter two compounds proved to be not very effective in SARS-CoV animal models, the EC₅₀ values for inhibition of MERS-CoV replication that we observed in cell culture are in the same range as the C_{max} values in human plasma, which makes it worthwhile to test these compounds in animal models.

In a recent study by Chan *et al.*, (2) treatment of marmosets with lopinavir/ritonavir and interferon- β 1b improved the outcome of MERS-CoV infection, suggesting these repurposed drugs may constitute a treatment option. On the other hand, they reported that treatment with mycophenolate mofetil worsened the clinical signs, once again illustrating that translation of *in vitro* data to animal experiments, and - ultimately - to clinical settings, needs to be executed with great care. Currently, only a few MERS patients have been treated with antiviral drugs, mainly combination therapies of interferon, ribavirin, and/or lopinavir. In most cases, treatment was ineffective or the outcome appeared inconclusive, due to the small number of patients and initiation of treatment late in their illness.

Future prospects - The 2003 SARS-CoV epidemic and the continuing MERS-CoV outbreak illustrate the toll that lethal coronavirus infections can take on society. Multiple close and distant relatives of SARS-CoV and MERS-CoV continue to circulate in animal reservoirs. Their zoonotic transfer continues to be a realistic scenario for which we are still poorly prepared, although in the case of MERS-CoV a recent study offers hope that it may be possible to drastically reduce the frequency of zoonotic transfer by systematic vaccination of reservoir species living in close proximity of the human population (6). A rational and balanced approach should incorporate:

- the characterization of known and novel drug targets by further dissection of coronavirus molecular biology and pathogenesis,
- a detailed assessment of the efficacy of currently available prophylactic and therapeutic options, and
- a systematic hunt for potential *pan*-coronavirus inhibitors, most likely by identifying common host factors involved in coronavirus replication.

Along these lines, and in spite of the uncertainties commonly associated with emerging RNA virus

infections (like geography, population, and air traffic that can dramatically accelerate virus spread from affected regions), it may be possible to define solid starting points for a rapid anti-coronaviral response.

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ICAR THROUGH THE YEARS

As an introduction to the interview featured in this issue, Erik De Clercq was asked to recall the beginning of the ISAR and his memories of the past ICAR meetings.

ISAR and ICAR remembrances by Erik De Clercq

In the 1970s my interest shifted from interferon to polynucleotides as inducers of interferon, and further to the antiviral potential of nucleoside analogues, and by 1979, I reported on my first nucleoside analogue, BVDU, which exhibited a selective activity against HSV-1. This resulted from the collaboration that I started with R.T. (Dick) Walker in 1976 (the same year that I also started collaborating with Antonín (Tony) Holý). The collaboration with Dick Walker fostered the idea of organizing a NATO ASI (Advanced Study Institute), which finally took place in Sogesta, close to Urbino (Italy). It was co-organized by R.T. Walker, E. De Clercq and Fritz Eckstein and was the first meeting ever focused on the chemistry and biological properties (antiviral and antitumor activity) of nucleoside analogues.

NATO ASIs have the unique characteristic that they last for 2 weeks, so as to maximize the interactions between the participants, which are in principle, drawn from NATO member states. At the beginning of such ASIs, participants generally complain that they have to be away from home for 2 weeks, but at the closure of the meeting, they feel sad they have to return back home. I remember John Moffatt, a pioneer in the chemistry of nucleoside analogues and participant at the Sogesta meeting, giving an extra class of 3 hours on chemistry of nucleoside analogues on an afternoon which was reserved for recreation or sports. Our first NATO meeting was so successful that it stimulated the organizers, R.T. Walker and myself, to organize a second one, in Les Arcs (France) in June 1983.



Meeting in Les Arcs (France), June 1983

Prominent participants at this NATO ASI included, among others, Tony Holý, Bill Prusoff, Morris Robins, Rich Whitley, John Montgomery, Shiro Shigeta, Masanori Baba, and only one native from France, Gilles Gosselin. Also present in Les Arcs were Purnell W. Choppin, who later on would become the President of the Howard Hughes Medical Institute, and Harald zur Hausen, Nobel laureate in 2008. Again, the success of the Les Arcs meeting would stimulate the organizers to try a third time, in May 1987, in Il Ciocco, close to Barga in the Tuscany region of Italy (where Dr. Paul Janssen was expected but finally did not come). Bob Gallo (and Flossie Wong-Staal) joined us there for one day. The meeting in Il Ciocco would be our third and last NATO meeting. From then the International Conferences on Antiviral Research (ICARs) took over.

According to George Galasso, whom I had met several times in the past (i.e. in Szeged, June 1980), we must have discussed the possibility of starting conferences on antiviral research (ICAR) and a society on antiviral research (ISAR) for the first time in Rotterdam at a TNO (Netherlands Organization of Applied Scientific Research) meeting, 30 April-3 May 1985), but the discussions that really heralded the ICAR conferences and ISAR society were those held at a special meeting which we had within the NATO ASI in Il Ciocco (May 1987).

While both the “Rotterdam” and “Il Ciocco” meeting could be considered as the first ICAR meeting, the meeting in Williamsburg in 1988 was definitely the second. Meanwhile, the ISAR had started with R.J. Whitley as the First President. In the elections, he got most votes out of 4 candidates (R.J. Whitley, E. De Clercq, Priscilla Schaffer and Bo Öberg). I ended second, so that I became Vice-President (or President-Elect), and would become the

next President two years later. That was in 1990, which coincided with the third ICAR in Brussels that I chaired.

According to the “doctrine” of Galasso, the ICAR meeting should be held annually, two years in a row in the US (East side or West side, alternating), interrupted by one year somewhere else (Europe, Asia, Africa or Australia) so as to reflect the membership quota; 2/3 American (US) for 1/3 the rest of the world. This rule was implemented from 1990, and as ever since remained enforced till today. Thus, the fourth ICAR was in New Orleans and the fifth ICAR in 1992 was in Vancouver (which was, for convenience, considered the West Coast of the US, after New Orleans was considered as located at the East Coast).

Then followed in 1993, the 6th ICAR in Venice (Italy), the 7th in 1994 (Charleston) (which was presided by George Galasso), the 8th in 1995 (Santa Fe, New Mexico), the 9th in 1996 (Urabandai, Japan) (which was presided by Shiro Shigeta, who later on became President of Fukushima Medical College), the 10th in 1997 (Atlanta, Georgia) (presided by Raymond Schinazi), the 11th in 1998 (San Diego) (where both R.J. Whitley and I were awarded the highest award of ISAR, that of excellence in antiviral research), the 12th in 1999 (Jerusalem) (where R.J. Whitley spoke about the death of Trudy Elion, our only member Nobel laureate, who had passed away at the age of 82 a few weeks before the meeting),



Erik De Clercq and Trudy Elion

the 13th in 2000 (Baltimore), the 14th in 2001 (Seattle), the 15th in 2002 (Prague) (with Antonín Holý as chairman), the 16th in 2003 (Savannah, Georgia), the 17th in 2004 (Tucson, Arizona), the 18th in 2005 (Barcelona, Spain) (with José Esté as

chairman), the 19th in 2006 (Puerto Rico), the 20th in 2007 (Palm Springs, California), the 21st in 2008 (Montreal, which, unlike Vancouver, was not considered US but outside America, probably because they speak French there). Following Canada, we returned to the US with Miami in 2009 for the 22nd meeting and, in 2010 (San Francisco) for the 23rd meeting. The 24th meeting was in Sofia, Bulgaria, in 2011, and to break with the “Galasso doctrine”, we had the next (25th) meeting (in 2012) again outside the US, in Sapporo (Hokkaido, Japan) (with Masanori Baba as the local chairman). In 2013, we returned to San Francisco for the 26th meeting (in memory of Antonín Holý who passed away in July 2012). In 2014, the 27th ISAR took place in Raleigh (North Carolina), and in 2015, the 28th meeting was in Rome, Italy. In 2016, the 29th meeting will take place in San Diego, and if the periodicity is respected, in 2017, the 30th meeting should be somewhere at the East side of the US, perhaps up north, where the Spring is cool and refreshing. Among the pioneers who contributed to the success of ICAR and ISAR, Elion and Holý have already been mentioned. Every year they are commemorated at the ICAR meetings by annual prizes in their name, and so is the name of Bill Prusoff, who, with the first description of idoxuridine (IDU) in 1959, laid the basis for the antiviral chemotherapy era.

ISAR MEMBER PROFILE ***ERIK DE CLERCQ***

Interviewed by Joana Rocha-Pereira

An inescapable figure in the world of antivirals, his life story intertwines with the history of antiviral research itself. In the year that marks his 75th birthday, meet Erik De Clercq, Belgian virologist and Emeritus Professor of the University of Leuven, in his own words.

JRP – Professor, I would like to start by asking you about your career choices: What spiked your interest for Chemistry in the first place? Why study Medicine?

EDC - When I was 4 or 5 years old, my father took me to the lab where he worked as a chemist (in a fertilizers plant). I remember the first smell of sulfuric acid; that was my first contact with the world of Chemistry, which I found fascinating. I started to study Medicine precisely because of my love for Chemistry. There was a lot of Chemistry in the first year of Medicine

JRP – But if you always loved Chemistry so much, how did you end up studying Medicine and not something more purely Chemistry or Engineering for example?

EDC- At the age of 18 when I entered the University and I had to make a choice, I hesitated between Physics, Chemistry and Mathematics. The reason was that a friend of mine came by and he had failed his first year of Medicine. He said “it is terrible because it’s only Chemistry” he had to learn. So, he showed me his books and I thought “oh, that is great. You can do Medicine through Chemistry”. For me this was like heaven! And my mother was dreaming of having her only son becoming a medical doctor.



**Erik De Clercq,
Rega Institute for Medical Research
(P. De Somer Office), Leuven, Belgium**

JRP – So this was not a case of family tradition, a family of medical doctors?

EDC- No, no. Nobody in my family had ever been at the university before. My father was a technician-chemist and my mother was a dressmaker, working with several girls who wanted to learn how to make dresses. So, I grew up surrounded by many girls, even though I was an only child. But the reason why I did Medicine was actually because of the heavy load of Chemistry in the first year. And then, in the 2nd and 3rd year I even wrote the course of Biochemistry. The Professor of Biochemistry did not

have a course (a syllabus), so I wrote it from my notes and these were then distributed to the 250 fellow students of my year. I just wrote the course since I liked it so much, and then the “praeses” (the chairman of the students) asked me whether he could photocopy and distribute my notes to my fellow students. I did not object, in fact I was quite honored by this. The “praeses” himself could afford even to buy a car with the money he made on my notes (the students had to pay a small amount). He did not share the profit with me and I was not interested; I could not drive, why would I need a car, anyway?

JRP – Was the Krebs cycle the latest thing?

EDC- The Krebs cycle may have already been a topic of the course. I remember vaguely that the urea cycle was there but the Professor himself gave a course that was concentrated on physic-chemistry and specially the physics of proteins. So, we had to learn a lot of pH and pK values, etc. For most of the students, it was very boring but I enjoyed it thoroughly. The Professor also talked about the activity of water which is something that I never understood, and not of interest for medical students.

JRP- How do you recall the university was like back then? A different environment than today? How was the access to information, books...? There were not as many students, a more familiar environment?

EDC- Oh yes, it was totally different. A Professor at that time was a God. You could not even touch or talk to them. It was impossible to simply knock on his door and walk in. It was even advised never to approach a Professor. The access to information, you had to find things yourself, we had some books in French or German, not even in English. French was at that time the routine language, even when I started to work here at the [Rega] Institute, the language I heard around me was French. Now it is, of course, English. There were good contacts among the students but the Professors we saw close by only at the time of the examinations. These were all oral examinations, I remember that for Biochemistry we did not even have the time to prepare, we just appeared before the Professor and he started shooting the questions. Sometimes the planning of these exams was such that for Anatomy and Biochemistry, two major courses, these were in the same morning, without any stop or pause in between.

JRP- So, when you meet someone young these days and he/she asks you “I have to decide what I want to study”, what advice do you give them?

EDC- That is very difficult. For me, it was very difficult. When I left high school, I did not really know. It was obvious I should go to University as I

was the Primus (Primus perpetuus, the best student) of my year. The only alternative I had was to become a priest but I did not feel like I had the vocation to do so. Except for that, I could start Engineering, Chemistry, History, Geography, anything. It was difficult to decide. My family left me quite free, my father would, of course, not object that I studied Chemistry and my mother was openly saying she was dreaming of having her son become a medical doctor and in particular a “house doctor”, so she could then open the door to all the patients coming in to consult the doctor.

JRP – She had the business sense?

EDC- She was very ambitious. She was also very religious, so she would not have minded if I had become a priest. I was also very interested in Art, especially the Italian Renaissance painters. My favorites were Michelangelo and Raphael, so it's perhaps not surprising that my only son was named Rafaël. He has not become a painter but a philosopher.

JRP- At the University at some point you discovered Microbiology. How did that happen?

EDC- Well, it was normal that the best students of the year could work in a laboratory. Since in my 3rd year I got the highest grade, I looked for advice on where to work. The Professor of Biochemistry did not accept any medical students. Then, I had contact with the Professor of Physiology who said the best laboratory to work in Biochemistry was the laboratory of Prof. Christian de Duve.

JRP- de Duve who gave his name to the de Duve Institute? The Nobel Prize?

EDC- Yes! I asked what he was doing: this was cell fractionation and this did not appeal to me, so I declined. I met de Duve himself later in life, when he had already won the Nobel Prize, and maybe I told him I made a terrible mistake by not coming to his lab! Then I wanted to work in Chimie Hormonologique (this was the Chemistry of hormones); what fascinated me were the steroid hormones, cortisone for instance (but also estrogens and so on). Then I had, of course, to find a laboratory where they worked on such subject. So, I ended up in a lab which was headed by a Prof. Raymond Devis. This was a bad choice in the sense that instead of doing fundamental research on the chemistry of hormones, I was assigned to do diagnostic tests to determine the concentrations of hormones. Instead of steroids, which were my favorites, I had to work on catecholamines: adrenaline, noradrenaline... In addition, this was all in French. At that time, the

University of Leuven was totally bilingual (French/Dutch)...

JRP – Yes, I heard that the University of Leuven was first totally bilingual but then there was someone who decided to separate it in French-speaking and Dutch-speaking?

EDC- Well that was a political decision that followed later on. This happened in the 1960s. The people in the laboratory were French-speaking but for my experiments I did not need much conversation. What did I do in those days? Thin-layer chromatography and spectrophotometry. This was not the kind of work I really enjoyed. Anyway, my lab work was combined with my studies of Medicine. At this time, I had already moved on to the clinical years, so I had already contact with patients. I enjoyed the contact with the patients much more than the contact with the spectrophotometer! So I knew I was on the wrong track.

In the exams of the 4th year of my medical studies I met for the first time with the Professor of Microbiology, who was Prof. Piet De Somer. He later became the first rector of the Flemish University of Leuven. At the examination he asked whether I would like to come to work with him; he had heard I was working on catecholamines, so he said “That doesn’t sound very exciting, why don’t you come to work with me?”. “What do you expect me to do?” I asked him. “Well, you can work on viruses” he answered, and so started my career on viruses, or more specifically, interferon (IFN).

JRP- At the time polio was the big topic? Please tell a bit more about Prof. De Somer.

EDC- Prof. De Somer was a self-made man, also a medical doctor. He followed his father’s footsteps; his father was a general practitioner but De Somer had seen his father working like a slave, so he said “I’m never going to see patients!”. He then became interested in antibiotics; he was fascinated by the discovery of penicillin (this at the end of the World War II). The problem at the time was that penicillin was not available in sufficient amounts, so he set up a company to produce large amounts of penicillin, called RIT (Recherches Industrielles Thérapeutiques). It was a small company which was set up in Genval, which is not far from Leuven, but in the Walloon region, the French-speaking part of Belgium. This explains why all conversations were in French.

JRP- This was then the genesis of the Rega Institute? I find it fascinating that today the Rega is an Institute where close collaborations with industry are key, where the translational aspect of research is really strong, and the “valorisation” [exploiting

project learning and outcomes to optimise their value and impact] aspects are central. In other universities these are sometimes aspects people write about in grant applications but don’t really understand them or put them to practice. And this really was at the origin of the Institute...

EDC- Indeed. Penicillin was the first enterprise of De Somer. Valorisation was here before the Rega, the teaching and the research, it was already there. That was De Somer’s pioneering task and he followed the goal of solving societal problems. Then in the 1950s, polio became the big thing (this was all before my student time), De Somer was very interested in polio as it was a very important problem. De Somer pioneered on the development of polio vaccines, based on the Salk (inactivated) vaccine. Then Sabin came along and developed the live attenuated vaccine; there was a strong dispute between Salk and Sabin on the value of each vaccine. I’ve never met Jonas Salk but I met Albert Sabin personally, he even became a friend of De Somer.

I remember a time when I was the youngest collaborator of De Somer. RIT was the company that was created to produce penicillin, then also produced the polio vaccine for the whole of Europe. So, De Somer did not invent the polio vaccine but he made it available for Europe. By 1962 the problem of polio was “resolved”, when De Somer invited me to join his team. I first said no. When I told one of my fellow students who was at the time the praeses of the School of Medicine, he told me “You are stupid, De Somer is going to be the most important man in Leuven and you just cannot refuse him”. So I felt a bit guilty but I had a second chance, the 5th year exam in the Medical School, which was then on viruses. I prepared well for that exam. So, luckily he asked me again, and I gladly accepted the invitation, which of course would determine my life.

From then on, I had to work on viruses and interferon (IFN). In 1957 Isaacs had discovered IFN, which was considered to be the weapon to fight all virus infections (like penicillin for bacteria). De Somer had a very high belief in IFN, so I had to work on IFN and, of course, on the activity of IFN against viruses. Now you must realize that at that time (1960s) IFN was regarded as mysterious substance, an esoteric principle induced by viruses, also used to terminate the replication of viruses but no one knew the structure. This was before sequencing techniques were available. Then, my first contribution, was to find out that IFN could be induced by synthetic polymers (that was in 1968)

JRP – And these polymers were double-stranded RNA?

EDC- I wished! The person who did this was Maurice Hilleman and his group. He is one of my big heroes. He discovered that you could induce IFN with double-stranded RNA (dsRNA). I remember, this was in 1967, when he had 5 consecutive papers in PNAS. He worked for Merck which had a member (Max Tishler) in the National Academy of Sciences. So, the first one was on the dsRNA from a mycophage, the second was on poly I:C (totally synthetic), the third on dsRNA from reovirus, the 4th on dsRNA from MS2 coliphase, and the 5th was on *in vitro* studies with dsRNAs. So, when these papers came out, they had an enormous impact; what I had discovered was a synthetic molecule such as polyacrylic acid. At the same time, Tom Merigan at Stanford had discovered that you could induce IFN with another polymer, pyran copolymer. De Somer published 2 papers in the *Journal of Virology* on the induction of IFN by polyacrylic acid, with his name first. That was how things were at the time. He invited me to discuss and correct the paper but he did not write a word. I was, however, very honored to be second author of the paper.

JRP – But then, when you arrived here at the Rega Institute how was it at the time, in the late 1960s? It was in this building already? How was the atmosphere? Were there many people working with viruses?

EDC- Yes, it was already this building. This office where we are now was the bureau of De Somer. Bacteria and antibiotics were gone, polio was resolved, and the focus was on IFN, on its mode of action. Also some groups were concentrated on immunology, in particular transplant immunology – that was Prof. Michel Vandeputte (who is now 85). The atmosphere was good, very competitive, everyone wanted to do his best. De Somer was a very enthusiastic person, driven more by the business type of approach. Certainly he was not a chemist, and he was not interested in chemistry. He only wanted to know if what I was doing would be worth exploiting in commercial terms. That means business.

JRP – So, you then went to Stanford for two years?

EDC- Yes, that was to consolidate my interest in doing research because after finishing my medical studies I hesitated between Internal Medicine and research. Many times I discussed this with De Somer. There was also the Professor of Internal Medicine (J. Vandenbroucke) who was very much interested in guiding my further career. For me, it was not obvious whether I would select pure research or Internal

Medicine. At a certain moment, they came together and agreed I would work 50/50 for each of them. I quickly realized that would be 100% for both. I had to start somewhere so I started with De Somer, one month ahead of Internal Medicine. That was sufficient to orient my career. Sometimes I think about it and I still regret it because I enjoyed seeing patients (unlike De Somer). The severely ill or cancer patients had a great impact on me. I felt very involved with these cancer patients, I still recall some very clearly, e.g. a patient with acute leukemia.

JRP- But would you not feel that choosing the path you've chosen has saved many more lives than if you had gone on to pursue internal medicine?

EDC- In the long run, yes. But this is a decision you have to take when you're 25 and you think "what is going to give me more satisfaction?" To have seen a few patients for which I tried very hard to alleviate their pain or to have infected 50 mice and not to alleviate their pain but give them pain? Who is going to tell you that they are pleased with your endeavors?



**Erik de Clercq with Tom Merigan
Stanford University, 1969**

The mice are not going to tell you this. This is a kind of balance you have to make at the age of 25, what do you want to do with your life? De Somer realized this and saw me hesitating. His plan was then to send me immediately overseas to consolidate my

desire to do research – Stanford was a good place for this. The second reason was the good climate and the academic environment would be perfect, and the work I could do was a continuation of what I was doing with De Somer. In addition to that, I also got married at the time and my wife did not mind a 2-year honeymoon in California.

I must say my days in California were wonderful in all aspects. My boss there, by the name of Tom Merigan, was a very enthusiastic man. He is now 80 years old. Whenever I came with results, he immediately wanted to publish them. I was the one who had to calm him down and say “Let’s confirm it first”. So, I was planning to go there for one year with an Eli Lilly fellowship. One can say that was my first ever company connection. But I enjoyed my time at Stanford so much that I prolonged my stay there for another year (with a Damon Runyon fellowship) and even started to think about staying there. My wife also wanted to stay there longer. Then De Somer came to visit us and said “This was not the arrangement, you have to come back. We expect you back”. And so, I came back.

JRP – Could you then start your own group?

EDC – Yes, but I must admit there was not much to start with. You see, in the meantime the university had split, so what was already in the making for many years had finally happened. De Somer had become the rector of the Flemish University of Leuven and the Rega was, still a part of that as the research institute of the company, RIT. The company itself was working towards production of IFN. After the separation of the university in the Flemish/ French part there was a second big change, an invasion of people coming from a company called SKF (Smith, Kline and French). The same company went on to become GlaxoSmithKline. I remember that a 20-person delegation from SKF came in 1968. (So I only saw the beginning of a process that led to the acquisition of RIT by SKF, and then I left for Stanford). We at the Rega didn’t realize the importance of this at the time. The decision that SKF took was that they would take over the plant but not the research unit [Rega Institute]. For De Somer this decision was unacceptable and he broke all contacts with the industrial part (SKF and RIT) and did not want even to further collaborate with them. This decision was taken in 1970.

JRP – So you needed a funding source? The problems of today were also the problems of 1970!?

EDC – Sure! I had to look for and apply for grants but De Somer used his influence to ensure we got

funded. He then became very famous and the first layman rector of the Catholic University of Leuven.

JRP – At this point you had perhaps your first students? Who left a memory, for either good or bad reasons?

EDC- The first one came in 1972 – a Texan cowboy by the name of Bill Stewart III. He was a good scientist but his major talents were artistic (drawing) and the fact that he could get away with women. Then Irwin Braude, he was the opposite, very kind and timid. He came to continue the work of Stewart on the purification of IFN. My part in IFN took a turn in 1978/79 and in 1980, and resulted in two leading papers in *Nature* about the cloning of IFN. As I told you, in the beginning we did not know how IFN looked like. Weissman was the first to clone alpha IFN and we (by “we” I mean the group of Walter Fiers in Gent with Jean Content at the Pasteur Institute in Brussels and myself) described beta IFN in 1980. For me, this was a kind of swan song for IFN. I did this work here in Leuven by myself with my technician but in Fiers’ lab there was a student involved, his name was Rik Derynck who later on would go to Genentech and further onto San Francisco (UCSF). It was at the end of the 1970s that I fundamentally changed my area of research from IFN to nucleosides and nucleotides.

JRP – This was around the time that you met Antonín Holý?

EDC – Yes, exactly in 1976, a crucial year. I was invited to a very small meeting of 25-30 people at the Max Planck Institut für Biophysikalische Chemie, in Göttingen. The meeting was organized by a chemist for chemists. I think it was the very first meeting that I attended with chemists – which made them very curious about this MD participating. I was considered a very strange if not endangered species, I’m sure. Most of the people there became my good friends and collaborators; some were pioneers in nucleoside chemistry like Helmut Vorbrüggen, who gave his name to the Vorbrüggen reaction, John Moffatt (Syntex), John Montgomery (Southern Research Institute), Wolfgang Pfeleiderer (Konstanz), David Shugar (Warsaw), whose 100th birthday we celebrated just a few months before he passed away, and a chemist from Prague, Antonín Holý. He was rather shy and it was love at first sight. He was a real chemist (I’m just a pseudo-chemist). I had given a talk on the potential use of nucleoside analogues as antivirals. Holý listened very well and we agreed to test his nucleoside analogues for antiviral activity.

JRP – At the time, you were working with herpes viruses?

EDC- Yes, especially herpes simplex. At the same meeting, there was another participant whom I also met for the first time, Dick Walker from Birmingham, UK. Both he and Holý would become my very dynamic co-workers – Holý even more so than Walker. In the beginning, the work was very slow because Holý was a very careful man, and suspicious too. Let's say that he did not fully trust me. He sent me 3 compounds, when he could have sent 20 or 30 or more. The success rate was almost unbelievable, one of the compounds was active – this means 33%!

JRP – The highest success rate I ever heard of!

EDC- What is even more astonishing is that this discovery made it into *Science*! One compound, DHPA, in retrospect my first compound that was ever marketed (in Czechoslovakia) was the subject of a *Science* paper. You must see that in the context of that year because it was also in 1978 that acyclovir was mentioned for the first time. So, our compound was since then in competition with acyclovir. That was a very big competitor! DHPA then became approved/ marketed in Czechoslovakia as an ointment for *herpes labialis*. I've even never believed that it worked! Several times I discussed that with Holý who was a good chemist but of course not a physician. I said "Tony, I'm not sure that this (DHPA) works" then he said to me "Yes, but the herpes blisters disappear". "Of course – I said – they always disappear!"

JRP –The communication between the chemists and the biologists is not always easy, right?

EDC- No. In my interactions with Holý I had to be the physician; once you are a physician, you stay a physician your whole life. So, I had to convince the chemist that he had to prepare better compounds. The marketing of DHPA was, after a while, discontinued, but it was the first.

JRP- So, we arrive now in the 1980s, around the time HIV came along

EDC- Yes. In 1980 I had my first PhD student, his name was Johan Descamps. He was a PhD student with me for 5 years but he never finished because he already got a position with what later on became GSK (GlaxoSmithKline). The first student who actually got his PhD with me was Jan Balzarini, in 1984. He started to work in the lab in 1979. Later on, of course, I had many students who are also now professors: Johan Neyts, Dominique Schols, Lieve Naesens, Robert Snoeck and Graciela Andrei.

In 1985, a student, who was a pharmacist, walked into my office. His name was Rudi Pauwels. He now has a company called Biocartis, working on diagnostics. When he walked into my office he said

"I want to work with you". We discussed briefly what the subject would be. I proposed him a subject on the mode of action of IFN, in fact on the so-called 2-5A oligonucleotide that was formed during IFN action. But after a few months, Rudi came to me and since HIV was getting more and more impact, he said "I want to work on HIV". I was of course very surprised because in the whole lab, my technicians were very scared of HIV. You must realize that nowadays, no one is scared of HIV anymore. I read in the newspaper yesterday of a person who said "I'm gay and I'm not scared of HIV. I do not use condoms." But in 1985 the situation was totally different

JRP- Was this newspaper article about a study with Truvada among people who refuse to use condoms?

EDC- Yes. The name Truvada was not mentioned in that study but... coincidentally in 2012, on the exact same day (16th July) that the FDA approved Truvada for the prevention of HIV, – my co-inventor Holý - died. The 16th of July. They call it PrEP for pre-exposure prophylaxis – for prevention of HIV infections. Although the aim of the study was to prevent HIV transmission, in fact it became more a measure of adherence to daily-dosing therapy.



Rudi Pauwels and Erik De Clercq

JRP – So it was 1985 and everybody was very intimidated by HIV

EDC- That's right. In 1985 HIV was considered to be a death sentence. So when Rudi came and he volunteered to work on HIV, I was also scared. But Rudi was a risk taker and wanted to do it, it was more of a problem for me than for him! Then I found a very good companion with Prof. Jan Desmyter. He was a colleague, not really a pupil of De Somer, but he settled down here in the Rega Institute and he wanted to help. He was the head of the Laboratory of Clinical Virology. The issue was that no one in the parent building of the Rega accepted that we should

work with HIV. This was considered to be too dangerous. So the fact that I got a volunteer to work with HIV caused a problem. Prof. Desmyter said “if you do not find a place to work, I offer you some space” and so he reserved a room, a biosafety level 2 lab (not even level 3) where with all precautions (gloves, masks, etc) Rudi accepted to work in these conditions. Where did he get the cells? And the virus? He got the cells from Luc Montagnier (Pasteur Institute, Paris) and the virus from Robert Gallo (National Cancer Institute, Bethesda). Later on, we would find out that the virus from Gallo was also the virus from Montagnier! At that time (1985), we did not know. It was a big task at that time to get the virus to grow in cell culture. We had expected that it would be very slow and difficult but within 2-3 months Rudi managed to have the system developed. Much faster than we ever had thought.

JRP- Were you already using this co-culture method at the time?

EDC- We used many different methods and we published on that at the end of the 1980s two papers in the *Journal of Virological Methods*. The second paper was on the colorimetric method. That is one of our most cited papers – more than 1000 citations for that paper alone.

So, Rudi had quickly managed to set up the assay and we could start testing – that was the purpose, to find a cure for HIV. His work really contributed very much to that. At that time I got in contact with Paul Janssen. Dr. Paul Janssen is certainly one of the most famous Belgians of all times. There was once here a selection of the most famous Belgians. The winner was Father Damien who worked with patients with leprosy in Molokai, one of the Hawaiian Islands. Paul Janssen ended second. But regarding drug development, he was by far number 1. He has been nominated for a Nobel Prize several times but he never got it. I remember that in 1986, I wrote down the date – 5th of November – because it should go down in history, I spent the full day with him. That means 8 hours including lunch and dinner. The conclusion of that meeting was that we should join forces to find the cure for AIDS.

According to Paul Janssen – we called him Dr. Paul – our collaboration should be very pragmatic. He reasoned that “if I bring that virus here, everybody will leave” [1986]. “So you (and Rudi Pauwels) have the system working and you are at a Catholic university so if something happens, then you could dedicate the work to God” he said. He would send the chemicals, the whole battery of compounds he had, around 80.000 at that time. Rudi Pauwels would do

the testing. Obviously, we did not have the chance to screen all 80.000 compounds so we had to make a selection, of about 600 compounds. The purpose was to identify leads that we could be further improved upon later on.

This brings us to 1987, even at that time we had to do a lot of paperwork to be able to start, which took about a year’s time. That led to the identification in 1989 of the TIBO compounds. The name TIBO stood for tetrahydroimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one and -thione, its discovery was totally unexpected because it was structurally related to the benzodiazepine tranquilizers. Serendipity is the key word here. That resulted in some excitement. Here, the paper was published in the February 1st 1991 issue of *Nature*. That made of course a lot of fuss here in Belgium, I mean, the collaboration between a pharmaceutical company and the Rega Institute. We had discovered the potential cure for AIDS. A cure was of course at that time not really the goal but at least an effective treatment.

This was the first compound of a new series which later on was named non-nucleoside reverse transcriptase inhibitors (NNRTIs). To be completely honest, the TIBOs were not the first NNRTIs because we had, again by serendipity, discovered another class before. Back in 1987, at a time I had my first talk with Paul Janssen, we were contacted by my good friend Dick Walker (Birmingham, UK). He had a visiting scientist from Japan by the name of Hiromichi Tanaka, from Showa University (Tokyo). Dick said Hiromichi had brought some compounds with him but he was afraid to send them to me. I don’t know why but he had Dick Walker send those compounds to me. I looked at the structure and it was obvious that these compounds had been synthesized as potential anti-herpes agents. So, Dick Walker just asked me to test them for herpes [he did not know I had already the system for HIV] “and if they are not active just throw them out” he said.

At the time, I had a Japanese fellow joining us by the name of Masanori Baba. He was a postdoc from the laboratory of Shiro Shigeta, my co-worker for herpes simplex and varicella-zoster. Masanori had done medical studies and Shigeta wanted him to get more exposure to antivirals, especially for herpes, so he sent him to us. He arrived here in 1986, and had already MD and PhD degrees. Masanori was supposed to be here for 1 or 2 years but stayed for 3 and even got the prospect of getting a permanent appointment to stay as Professor at our university. But this would never materialize, he would have had to give up all potential promotions at home, so he had

to go back after 3 years (it was his last chance) to get a position at his home university, Fukushima Medical University. Later on, he became a professor in Kagoshima University, he would even become vice president of that university. I consider him, Rudi Pauwels and Dominique Schols [who had been working in the lab of Immunology with Prof. Vandeputte] the dream team. The three together were very complementary, and all were devoted to find a solution for HIV.

Hence, I gave the compounds from Tanaka to Masanori to test on HIV. I told him “these are Japanese compounds, you are Japanese, perhaps you know how to make them to work”. To my surprise (at the end of 1987, before the work with Paul Janssen had started) he came to me and said “Believe it or not, one of these compounds, TS-II-25, is active against HIV” and especially against HIV-1. At the time, we had only the system for HIV-1 but years later we confirmed these had no activity against HIV-2. I said to Masanori, “I do not believe this. There is no logic! This is an acyclic nucleoside (like acyclovir). There is absolutely no reason that this compound should be active against HIV. Maybe that’s because the preparation was contaminated with AZT”. AZT was known and licensed in 1987. I was really worried that the compounds that we obtained from so many different sources were contaminated by another product.

Before proceeding (and starting to dream) I felt the need to confirm our initial findings and to ask the chemist to produce a new batch of drug, so the new batch was tested and showed the same activity. Only we didn’t know initially how the compound acted. Later on (when the TIBOs were discovered), I felt the urge to inform Paul Janssen about another compound (that was not his compound) that showed a similar profile against HIV – the Japanese had called these the HEPT compounds – but Paul Janssen was this kind of personality: if a compound did not come from his lab, then it could not be important. I even drew for him a kind of structure where I had put the TIBO on top of the HEPT compounds and said “you see, Paul, there are some similarities in the structures” and then he looked at me and said “you have a lot of imagination!”. But the feeling was there, and 5 years later (in 1995) Eddy Arnold and his colleagues put the structures on top of each other and confirmed what I had predicted; the HEPT and the TIBO compounds really overlapped structurally very nicely. Anyway, the HEPT compounds were then further studied by Masanori Baba when back in Japan and the compound class was licensed to MKC (Mitsubishi

Kasei Corporation) but they did not know what to do with it. At a certain stage, I had many discussions with them and they decided not to further develop it. They sublicensed it to Triangle Pharmaceuticals, which was later on incorporated into Gilead. In the meantime, the HEPT derivative (MKC 442, emivirine) was studied up to phase III but then further development was stopped.

JRP - What happened then to the TIBO compounds?

EDC – This was linked to the departure of Rudi Pauwels from the Rega, which was a big shock for me. He started here in 1985, by 1991 he had his thesis work finished, which was in pharmaceutical sciences. I remember very well his thesis defense. There were Piet Herdewijn, our most famous medicinal chemist, the head of the pharmaceutical department Prof. De Ranter, Paul Janssen, Luc Montagnier, Desmyter and myself. The work of Rudi was of such caliber that he should get the greatest distinction with congratulations of the jury members. In the jury were 7 people: 3 pharmacists and 4 MDs (Paul Janssen was also an MD). All 4 MDs voted for congratulations, only the pharmacists thought this had never happened and therefore they did not vote for it. In the end he got his degree with congratulations. He deserved it because the work was of such pioneering impact that no one would ever be able to do better.

The sad part is that the academic authorities in Leuven refused him a professorship – even if Paul Janssen was willing to sponsor it. There were two reasons for this: first that he was a pharmacist and not an MD, second that he had not gotten particularly high marks in his academic career. He did not get the academic position and decided to quit. I was really really shocked by this. Rudi was, in retrospect, a uniquely brilliant student. Since the will to create things was part of his nature, he started a company called Tibotec, with the support of Paul Janssen. You understand now why it was called Tibotec (derived from TIBO). For me it was very hard, I felt like I had lost a son and for many years I was very angry with him, we had no contact for 5 years. Now everything has been regularized, and I still consider him a genius.

He has written in his biographical notes “I have had two (scientific) fathers: Paul Janssen and Erik De Clercq”, he has been honest in this way and he is a special character. He is an entrepreneur. After Tibotec, he started Virco. At one time Rudi had difficulties with Tibotec and Virco, but this was eventually resolved. He had additional training in Lausanne in nanotechnology and then he created Biocartis for the diagnosis of several diseases (i.e.

infectious, malignant,...). He once said to me that every ten years he wanted to do something new but I've told him "if you do this once or twice in your life that is more than enough".

TIBO itself was not what you could consider a practical lead. It was a very potent compound and should have been developed but the synthesis took at least 10 steps; it was an expensive synthesis. I think Paul Janssen once told me there was even an explosive step involved! They wanted then to develop newer compounds which led to the development of a new series called DATA (diaryltriazines), and finally it was a DAPY (diarylpyrimidine) compound that was developed at Janssen – first it was etravirine, and then rilpivirine, with the commercial name Edurant. Paul Janssen considered that as his "number 1 compound" or "champion". It was in fact the final compound. What gives me the greatest satisfaction is that rilpivirine has come together with tenofovir in the same pill, which makes the circle come round. The combination of rilpivirine with tenofovir disoproxil fumarate and emtricitabine was licensed under the name of Complera in the US and Eviplera in the EU.

That was a long way from where I started, but you must understand that not everything is what you can call a success story. In the meantime, the HEPT compounds completely disappeared. One thing is for sure, you can only have successes if a compound survives many bad inconveniences. The TIBOs were the beginning and the end of my collaboration with Janssen, and Johan Neyts has now continued this collaboration with them on dengue.

JRP – AZT was the first drug licensed to treat HIV, at a time when HIV was considered a lethal disease. When did this start to change?

EDC – Yes, 90% of the people that had the infection died within a few years. That did not change much with AZT. It would never have been approved if it was offered to the FDA today. It is incredible that it has not disappeared given that it is such a toxic drug for the bone marrow. Of course, in 1987 we did not have anything else... AZT certainly had its merits, it kept the patients alive. Now, patients don't accept side effects anymore... The situation changed around 1995 after the protease inhibitors were shown to be very good alternatives. The term HAART (highly active antiretroviral therapy) was launched – that was really combination therapy. It was clear that AZT alone would not do the job, it had to be combined with (or replaced by) other compounds.

JRP- So, tell me about the discovery of tenofovir...

EDC – I started collaborating with Dr. Holý in 1976, as I mentioned before. An important milestone, which I mention because I experienced it myself, was in 1995. This was the year that lamivudine was introduced, a drug from GSK. The Belgian TV (VTM) asked me to give my comments on lamivudine. Prof. Desmyter, my long-time colleague and collaborator, should have given his comments but he was not a good speaker. He recommended me instead. I agreed but I wanted to make sure they knew I was not involved with the discovery of this drug. It was not my compound! But I agreed to give my objective view on this. They came over here (Rega Institute) with the cameras etc. I was at this time used to media exposure. We had just received the visit of Queen Fabiola here at the institute. I had also been invited to meet Princess Diana in London. The TV came to talk about the compound from GSK but then I said "I have my own compound coming into the news! I have to wait until it's published in *Science*" (the 17th of November 1995).

This was tenofovir. It was not called tenofovir at that time, it was still PMPA. I knew that they had obtained fantastic results at the primate center in Seattle (Tsai et al). Gilead was of course involved.



Queen Fabiola visiting the Rega Institute

They had a paper in which they had compared PMPA with AZT against SIV (the simian immunodeficiency virus). That is as close as you can get to HIV. The results were truly fantastic, once-daily injection of tenofovir from 1 day before to 1 day after infection, could completely block the infection. I mean completely, the results were like day and night, 100% infection in the control group, the treated ones had 0% infection. They had sent me this paper but release of the data had to wait until the 17th of November. This was the very first *in vivo* data on tenofovir, we had patented it in 1992 and published in 1993. I told VTM "you can come and interview me the 17th of November". But this was on

a Friday and on Fridays I was teaching in Kortrijk (at the KULAK). I thought they would then like to come on Monday, but “No, no, no, we come to interview you in the classroom where you are teaching and film your lesson as well”. They came with the cameras and a lot of people, at 2 pm. The students were excited to be on TV. The journalist asked me to give my ordinary lecture. I explained the structure (as you can imagine) of PMPA, then the journalist asked “if I understood, it looks as if you have discovered the morning-after pill”. You can imagine, live on TV, they ask you something like that! What answer did I give? I evaded the question by saying “Yes, but it’s not a pill yet!”. They still had to give it as an injection. The wonderful thing is, this is now the compound that is in the pill of Truvada, 20 years later. What I predicted on TV came true! The Rector of the KULAK was very proud that this all happened at his university.

Tenofovir was very rapidly developed at Gilead, which bring us to the importance of Gilead. Without them we could not had gone so far. You need (and this is a conclusion I want to make at this stage) three persons if you want to be successful in the development of antiviral drugs – the first and most important is the chemist, and I emphasize this again. Antonín Holý was a real chemist, I just had an attraction to formulas. The second is the microbiologist, and the third, unexpectedly maybe, is the company – in this case it was Gilead, represented by his CEO, John C. Martin. John Martin is a real chemist as well, he got his PhD in chemistry in Chicago, if I recall correctly. He worked as a chemist his whole life, before he continued his career in management. He started at Syntex, which is now part of Roche. He was co-inventor of ganciclovir, which is still used in the treatment of CMV infections. Then he moved to Bristol Myers, where he became the head of the chemistry department.

It was at Bristol Myers that we first saw each other, we met around 1986. This was around the same time I met Paul Janssen. But since they were working at competing companies, there was no collaboration between them. Those were the early days of HIV drugs, we discussed the possibility to collaborate. I had these two leads – the Holý lead, the phosphonates - and the Janssen lead – TIBO compounds. I remember that one evening John Martin asked me “If you had to choose, which one would you develop?”. It was a very difficult question, “I would take both of them” I said. What you could expect of the TIBOs was that they were nontoxic but they may quickly lead to resistance. Whereas if you take a phosphonate

like tenofovir then that compound may easily lead to toxicity but it will not lead to resistance.

In 1986, I had also a 20-minute audience with Giulio Vita, then CEO of Bristol Myers (BM) at Park Avenue, New York (while Paul Janssen gave me 8 hours). We agreed on the development of phosphonate compounds at end of the 1980s, but this changed in 1990-91, when Bristol Myers merged with Squibb and became BMS. That made a terrible change in hierarchy. John Martin had seen it coming and left before his position was taken over by Squibb. He followed the invitation to join a company that had just started in 1987 in the San Francisco Bay area. The founder was a certain Michael Riordan, who later would leave the company. It was started in 1987, with the goal of creating antisense oligonucleotides. This was before they realized that antisense would not make any sense! John Martin had worked with the phosphonates at BM. The first thing we then did was to bring the technology that we had developed with Holý from Bristol Myers to Gilead. That was a very big change which I can consider a milestone in my career. The 2nd of July 1991, four people came together at a neutral place – which was Paris. Not in a fancy place but in a Best Western hotel. We were in fact sitting on the street (the streets in Paris are normally very pleasant): Michael Riordan,



**John Martin, Erik De Clercq and Antonín Holý
8th ICAR in Santa Fe, New Mexico, 1995**

John Martin, Holý and me. That is where we decided to bring the whole package agreement to Gilead, since BMS did not want to continue the development. So in principle, we could have contacted any big companies. We could, for instance, have contacted Janssen, but Holý and I were not salesmen... We did not have the knowledge or

experience to contact such companies. We did not want to ring the bell at all these companies. Gilead was a small company in Foster City close to San Francisco; it was a risky undertaking to have faith in this company, but I reckoned it was equally risky for them to engage in the phosphonates. There are so many small companies that want to make it.

Here we had one important asset – that was John Martin. Because we knew him and we knew of his dedication to this kind of compounds. If he had not been there, we would never have taken it to this company. Somehow, we were finding ourselves in the same boat. They had to survive, they were looking for a new drive, so the phosphonates were an excellent choice. And for us, it was a question of survival as well, so it was a win-win situation, profitable for both sides. Today, if we found such compounds, the same thing would not happen again, since the company has grown exponentially since we first met in 1990. Holý and I had our positions as Directors/ Professors, so we would not have been in the unemployment lines but the compounds would not have been developed.

JRP- You would need to find a new Gilead for that.

EDC- Yes, a new Gilead, but this happens just once in your life!

JRP- In the middle of all of this, the antiviral field was also growing? There was ISAR and ICAR

EDC- In the introduction to this interview, I have described my whereabouts with ISAR and ICAR.

JRP- Tenofovir then came out of your hands, and went into clinical trials...

EDC- An important step forward was to make the prodrug, because phosphonates in general are not taken up orally. This is the case with adefovir and with tenofovir. We helped to develop the prodrug, and that is the work of Lieve Naesens, the prodrug of tenofovir is tenofovir disoproxil fumarate, abbreviated to TDF. It was licensed in 2001 under the name Viread. It is still available now, but the patent dates back from 1997. So this means that Viread's is going to expire in 2017. By then, it will be replaced by a new prodrug of tenofovir, which is called tenofovir alafenamide (TAF), which in comparison with the old prodrug, has the advantage of being dosed 30 times lower – 10 mg instead of 300 mg. That has two advantages. Regarding nephrotoxicity, patients who already have kidney malfunction can still take this new derivative. The second problem is bone demineralization, which has not been detected so far in patients who have taken the compound for 10 years – there were no bone fractures. But there is demineralization. But with lowering the dose 30-fold,

then of course you lower the risk. TAF will be further developed in several combinations, the first of which (combination with elvitegravir, emtricitabine and cobicistat) has already been approved in November 2015 in the USA and the EU. After tenofovir went out of our hands, we made new derivatives, all of them have been considered by Gilead: they still keep the patent rights, but are not going to develop them until it's needed. Now with tenofovir alafenamide, Gilead is safe until 2024. What will happen after that, nobody knows. Tenofovir alafenamide is still my business because part of the agreement with Gilead was that we would have the same rights in prodrugs as on tenofovir.

JRP- Later on you received some important awards including the European Inventor Lifetime Achievement Award in 2008

EDC – I'm particularly proud of that award, because I did not even know it existed. I had not applied for it; that was a total surprise. I did not earn any money for that! The justification of the Award Committee was that those people who are given this kind of award already have a lot of money!

JRP – And then you received the “Dr. Paul Janssen Award for Biomedical Research”?

EDC – That was by far the most rewarding. Not in terms of money, but because of the name of Janssen: I had to split it with my co-laureate Tony Fauci. The jury decided to give it to both of us. And since Tony is an employee of the NIH, he cannot receive money according to their rules.

JRP – What do these awards mean to you? In terms of legacy, for example. Do you think about what you will leave behind? Do these bring you any satisfaction, or something else does?

EDC – It does mean very much. Maybe I feel a little bit awkward in this sense. In my life I've tried to get some important awards and I've failed. I've gotten some awards for which I did not apply. My conclusion is that whatever you ask for, you do not get and *vice versa*!

JRP - But then the question would be: what would you like people to remember you for?

EDC – I would like to be remembered, yes. One thing I dreamed of when I was still very young was inventing a drug against cancer. In the 1970s, I was very much interested in the reverse transcriptase (RT), discovered, by Temin and Baltimore. I was working on IFN and started to work on the RT as well. So I had two loves: IFN and RT. There was a certain Spiegelman who had published some 20 papers, like every month, on the role of the RT in cancer – they were in almost every issue of PNAS. The scientific

community was convinced that the RT had an important role in all types of cancer. RT activity was measured by the incorporation of dTTP into DNA, normally there were measured in counts per minute, but he made counts per 10 min. I found a compound named suramin, which was used in the treatment of sleeping sickness. I just took it from the shelf, it was called Moranyl. It was extremely active against the RT. When I put this finding next to Sol Spiegelman's papers I thought "Maybe I have discovered an anticancer drug!". For a while I was dreaming of the anticancer drug. I did not tell anybody! This was at the time (1975) when I was my own boss, and I could do whatever I liked. So I was injecting leukemic cells into mice, then treating them with suramin to see if that could save them from the cancer. But it did not! I was very, very disappointed. I did not tell anybody, until in 1978, when I got Bob Gallo to visit us.

I must say I had a good relationship with Bob Gallo. I told him about suramin, a very good RT inhibitor for murine retroviruses but it did not have activity against leukemia. "That is a great finding, you should publish it" he said. He was the editor of *Cancer Letters*, so he accepted the paper without modifications. I forgot about suramin until in 1983 I received a phone call at home from Sam Broder of the National Cancer Institute, congratulating me for the discovery of suramin. "Yes, and so what?" I said. "You can read the next part of it in *Science*". It was the first compound ever found active against HIV, with a very nice acknowledgement of my *Cancer Letters* paper. Gallo was co-author on that paper, and it's obvious where Sam Broder got the news. This was the story with the RT and suramin. Suramin was in fact tested at NIH in patients. The *Science* paper reported the activity in cell culture, but then they published in *The Lancet* about the activity in patients. It was not that bad...

In retrospect, the advantage of suramin is that you can give it only once a week by the intravenous route, because it has such a long half-life. The problem is that it's a very toxic compound. It was because of the discovery of suramin that I was invited to the first brainstorming meeting ever at NIH on how to treat HIV (June 1985). I was invited because suramin was a candidate, but then at the meeting they announced that they had a new compound, known by the code number BW A509U, that they got from Burroughs Wellcome which was very nicely active against HIV. The cell culture data was very fascinating, better than for suramin. Then, everybody in the room was of course dying to know the structure. Sam Broder, who presented the data, said he did not know the structure

himself. He had just gotten some hundreds of compounds from Burroughs Wellcome. "There is one man in the room here who knows" he pointed to Dave Barry from Burroughs Wellcome. He said "Yes, I know the structure, but I'm not going to tell you. The only thing I can tell is that it is a nucleoside and it is not acyclovir". A few months later, October 1985, the anti-HIV activity of AZT was published. It made a splash all over the world. A clear example of how a compound is discovered without the biologist knowing the structure.

JRP – To finish, you have certainly contributed to the prestige of the Rega Institute. In 2016, the Rega will move to a new building. What is yet to come? What would you wish for the future of the Rega Institute?

EDC - I would say very honestly that more important than any building, or any brick of that building, are the people (or brains, if you wish)... I'm not impressed by nice new buildings or their equipment; I've always worked in the smallest places with the simplest equipment. People and serendipity are key to making new discoveries (of new compounds). You should never neglect unexpected findings! The best example in my experience is perhaps the discovery of the bicyclams (AMD3100, now known as plerixafor or Mozobil). As a lesson for the future, I would say "Keep your eyes open to unexpected findings – they may lead to big discoveries". All big discoveries in the past have been made by unexpected observations. Take as an example the greatest discovery of the past century, penicillin.

NEWS ITEMS

Ebola update: So near, yet so far by Anthony Vere Hodge

In the ISAR News, issues from 24.2 (2014), I have tried to give the ISAR Membership an account of the ongoing Ebola outbreak. This update, as in the previous accounts, includes my personal views.

The World Health Organization (WHO) is continuing to issue their weekly Ebola Situation Reports; this update covers the period from the WHO report dated 29th July 2015 to 25th November 2015. From mid-May to mid-July, the number of new cases/week remained about 20 to 30. From the end of July onwards, there were about 5 or less cases/week. On 7th November, WHO declared that Ebola virus transmission had been stopped in Sierra Leone. In

Guinea, the most recent Ebola patient, a baby born in an Ebola center, tested negative for the second time. All known contacts to the previous cases have completed their 21-day follow-up period – a hopeful step towards ending transmission. Was there a significant factor which caused the sudden change from 20 to 30 cases/week to about 5 cases/week, then reducing to zero?

The rVSV-ZEBOV vaccine (Merck) is being evaluated in a Phase III trial (ça suffit!) using a “ring vaccination” design, as used years ago to eradicate smallpox (WHO report dated 31st July 2015). All the contacts and the contacts of those contacts would be offered the vaccine. To provide a test of efficacy, half the rings around an index case would be offered immediate vaccination, the other rings would be offered vaccination 21 days later. Alongside this trial, all front-line workers were offered vaccination to confirm safety and immunogenicity. An interim analysis of the ring-vaccination data, published in *The Lancet*, indicated that the vaccine appeared to be highly effective – a few vaccinated people developed Ebola disease within 9 days or less, most probably due to becoming infected before vaccination. So far, not a single person has had Ebola disease 10 days or more after vaccination.

Following this result, the Data and Safety Monitoring Board (DSMB) recommended that the trial be continued but that all contacts be offered vaccination immediately. This change was approved by the National Regulatory Authority and the National Ethics Committee of the Republic of Guinea and has been implemented since 27th July 2015. On 1st September, the eligibility criteria for the trial were amended to allow the vaccination of children aged 6 years and above.

It may be just a coincidence that the change in vaccination policy matched the sudden decrease in the number of new cases/week (week ending 19th July, 25 cases, 26th July, 7 cases, then <5 cases in each of the next 4 weeks). I have not seen any further analysis of the Phase III trial but further results may be expected at the turn of the year.

Following the welcome news that Liberia was declared free of Ebola transmission on 3rd September, Sierra Leone on 7th November and the most recent case in Guinea testing Ebola negative on 16th November, more attention can switch to the survivors. With a large cohort of nearly 17,000 people, this is the first time that it is possible to gain extensive data of the persistence of Ebola virus and of the long-term clinical symptoms in survivors (WHO News, Report on the Persistence of Ebola Virus, dated 14th October

2015 and Deen et al. 2015). Persistence of Ebola virus RNA for many months has been confirmed in some survivors. Ebola RNA has been detected in various “immune privileged” sites, including the inside of the eye, semen, amniotic fluid, the placenta, breast milk and the central nervous system. In a clinical study, 93 participating men submitted “baseline” semen samples; of these, 9/9 men, who were within 3 months of the start of their illness, were positive (100%), 26/40 men, tested between four and six months, were positive (65%), 11/43 men, tested between seven to nine months, were positive (26%) and one participant was positive at 9.5 months (272 days or about 9 months, after discharge from the Ebola treatment center). This is far longer than previously known for the persistence of infectious Ebola virus. In a virus-isolation study examining semen specimens obtained from eight survivors of EVD or Marburg virus disease in previous epidemics, the longest period, that infectious virus was found in semen after the onset of symptoms, was 82 days. In the ongoing study, virus-isolation assays are under way.

This study will continue gathering data and giving the men practical help. As part of the monitoring programme in survivors of both sexes, WHO recommends that semen samples be tested at 3 months after the onset of Ebola disease and at monthly intervals until virus negative. Fortunately, the risk of sexual transmission of Ebola virus appears to be very low, but cases have been reported. In an editorial, (*N Engl J Med* published 16th November 2015), Armand Sprecher refers to a case of a woman in Liberia who became ill with Ebola disease after the country had been free of Ebola for 30 days. Her only known risk factor was sexual contact with a male survivor. Fewer than 20 suspected sexually transmitted infections have been reported. The various medical agencies are keen to give survivors and their families the support they need to treat their remaining medical needs, such as joint pain, eye problems and sexual hygiene.

Pauline Cafferkey, a UK nurse, became infected with Ebola virus in December 2014 while volunteering with Save the Children in Sierra Leone. She was repatriated back to the UK and taken to the specialist unit in the Royal Free Hospital, London early January 2015. Her condition was reported to be critical. She was treated with blood plasma from another British nurse, William Pooley, who had recovered from an Ebola infection. Pauline’s condition improved and, a few days later, was released from hospital, apparently fully recovered.

Pauline was taken back to the Royal Free Hospital in October 2015 when residual Ebola virus caused her to develop meningitis. Again, she was reported to be critically ill. Gilead Sciences Inc (Press conference 21st October 2015) confirmed that they had a request the previous week for compassionate access to GS-5734, a novel nucleotide analog, and that the drug had been shipped later the same day. Norbert Bischofberger (Gilead) commented “*It is very encouraging to hear that the patient in question is doing better and is no longer in a critical condition.*” Pauline was treated with GS-5734 for 14 days. At that time, following the demonstration of good efficacy against Ebola in monkeys, Gilead had recently initiated a Phase I trial in healthy volunteers.

Could Pauline’s recovery been due to the efficacy of GS-5734? Travis Warren (US Army Medical Research Institute of Infectious Diseases, USAMRIID) reported at IDWeek 2015 that rhesus monkeys were completely protected from an Ebola infection when GS-5734 treatment was started 3 days post-infection. Their conclusion was that GS-5734 was the first small-molecule antiviral agent which gave robust therapeutic efficacy in the monkey model of Ebola virus disease. Pauline’s experience certainly adds information about the drug’s safety and leaves open the possibility that GS-5734 is an effective therapy for Ebola survivors with late-onset symptoms.

For the structure of GS-5734 and an account of its early development, please see the previous issue (25.2) of the ISAR News (www.ISAR-ICAR.com). Gilead are continuing with Phase I studies and completing the evaluation of GS-5734 in the monkey-Ebola model. Meanwhile, Gilead is planning to evaluate GS-5734 in West Africa (L M Jarvis, 2015). Ebola survivors are being tested for residual virus and those having virus will be treated for a short time, up to two weeks, and the virus levels will be measured again. The experience with the testing of semen samples (see above) confirms that suitable subjects are available but that the window of opportunity is short.

Although the current Ebola outbreak is well past its peak, it is important to gain as much information now of the safety and potential efficacy of GS-5734 in patients infected with Ebola virus. Initial testing in cell-culture assays has indicated that GS-5734 is active against different strains of Ebola virus, against other filoviruses such as Sudan and Marburg viruses and against hemorrhagic viruses, including Lassa virus and Middle East Respiratory Syndrome (MERS) virus. There will surely be a need for a good

therapy to treat these virus infections. Also, the current Ebola outbreak is not yet over.

Unfortunately, this Ebola outbreak continues, as reported in the WHO Ebola situation report dated 25th November: *A cluster of three confirmed cases of Ebola virus disease (EVD) were reported from Liberia in the week to 22 November. The first-reported case was a 15-year-old boy who tested positive for EVD after admission to a health facility in the Greater Monrovia area on 19 November. He was then transferred to an Ebola treatment centre along with the 5 other members of his family. Two other members of the family – the boy’s 8-year old brother and his 40-year-old father – subsequently tested positive whilst in isolation. In addition to the family, 149 contacts have been identified so far, including 10 health workers who had close contact with the 15-yearold prior to isolation. Investigations to establish the origin of infection are at an early stage. Liberia was previously declared free of Ebola transmission on 3 September 2015.*

I am concerned that there is no mention that the health workers had been previously given the Ebola vaccine so that these contacts may be regarded as low risk contacts. As it is so difficult to predict where a person with Ebola disease, either newly infected or with re-emergence of persistent virus, may present themselves, perhaps all health workers should be offered the Ebola vaccine. If this Ebola outbreak is to be terminated, the use of all the available tools needs to be maximised; the vaccine to limit the spread of Ebola virus, favipiravir, which seems to be of benefit to patients with low baseline virus levels, and GS-5734 which may become available via the clinical trial. My hope is that these tools, together with the well-established monitoring and isolation systems, will finally enable those, who are working so hard on the front line, to close down this longest Ebola outbreak.

Extract from WHO Situation report dated 16th December 2015:

Investigations into the origin of infection of the cluster of 3 confirmed cases of EVD reported from Liberia in the week to 22 November have established that the cluster arose as a result of a rare re-emergence of persistent virus from a survivor.

The WHO Situation report dated 6th January 2016 confirmed that there were no recent cases of Ebola infection. In Liberia during the week ending 3rd January, of 301 survivors’ semen tested, 31 were positive for Ebola virus RNA. The corresponding data from Guinea and Sierra Leone is being compiled.

The end of this Ebola outbreak seems so far away but now maybe within reach. Let us hope that Heinz Feldmann (NIH), in his Keynote presentation at the forthcoming ICAR, will have good news to report.

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Lisa M Jarvis, What we've learned from the race for an Ebola Cure. 2015. Chemical & Engineering News, 93: Issue 45, 20-22, published 16th November 2015.

ICAR 2015 FINANCIAL SUMMARY *by Brian Gowen*

Having paid all of the expenses associated with the 28th ICAR, the final numbers reflect that the cost of the meeting exceeded the revenue and sponsorship support by \$45,378. Despite the deficit, ISAR remains in good financial standing with assets totaling over \$660,000. The leadership of the society is actively exploring NIH and other funding opportunities that would help support the meeting so that we can avoid or limit such deficits in the future.

ISAR is grateful for the hard work of Roger Ptak in his ICAR sponsorship campaign efforts and the generosity of corporate and educational sponsors in the face of difficult economic times. Many thanks to the ISAR membership and meeting attendees for their support of, and participation at, the annual ICAR. I look forward to a great meeting in La Jolla in 2016.

28th ICAR, Rome, Italy, May 11-15, 2015

Revenue

Registration	\$152,773
Award Sponsorship	\$17,500
NIH Grant	\$0
Corporate Sponsorship	\$123,034
Other Revenue	<u>\$2,500</u>
Total Revenue	\$295,808

Expenses

Advertising	\$3,325
Food, Beverage, Events	\$80,124
Audio Visual	\$30,634
Venue/Hotel Services	\$72,138
Invited Speakers	\$22,282

Courtesy Associates – Out of Pocket	\$3,495
Courtesy Associates – Labor	\$62,801
Credit Card Fees	\$7,217
Registration Supplies	\$2,003
Awards (Elion, Prusoff, Holy, Poster, Travel)	<u>\$57,166</u>
Total Expenses	\$341,185

Net Balance – **\$45,378**

CALENDAR OF FUTURE MEETINGS

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

JOB OPPORTUNITIES

1. A postdoctoral position in Immunology and Proteomics Team is available in the Poxvirus and Rabies Branch.

The branch is part of Division of High-Consequence Pathogens and Pathology (DHCPP) within the National Center for Emerging Zoonotic Infectious Diseases (NCEZID) at Centers for Disease Control and Prevention (CDC) and located at Atlanta, GA. The current position involves, but not limited to immunological studies during vaccine responses and pathogenesis in animal model (prairie dog). Recent graduate students (less than four years of Ph.D.) with experience in virology, immunology or systems biology are encouraged to apply. The position will be funded through ORISE fellowship and offers excellent benefits. If you are interested and need additional information, please email Dr. S. Sathesh Panayampalli at spanayampalli@cdc.gov.

2. A postdoctoral position is available in the laboratory of Dr. Hana Golding, Chief of the Lab of Retrovirus Research, CBER, FDA at the White Oak Campus, Silver Spring, Maryland. The ongoing research performed involves study of Respiratory Syncytia Virus (RSV) and influenza viruses, with emphasis on avian influenza strains with pandemic potential like the H5N1 and H7N9. We are presently addressing humoral immune responses following RSV or influenza infections and vaccination. Emphasis is on understanding the role of adjuvants and different vaccine modalities in eliciting broadly cross reactive protective antibodies. The advanced techniques developed in the lab include whole

genome gene-fragment phage display libraries (GFPDL), high throughput Surface plasmon resonance (SPR), recombinant vaccines and protein expression in bacterial and mammalian systems. Eligible candidates should have a recent MD or Ph.D., or equivalent (within 2 years of the degree). Experience with molecular biology, protein

expression and purification is required. Candidates with research experience in Phage Display libraries are preferred. Background in infectious diseases and immunology is highly desired. To apply, contact Dr. Golding at Hana.Golding@fda.hhs.gov

ISAR News is an official publication of the International Society for Antiviral Research. It is published four times a year as a free article in *Antiviral Research*

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

and is posted on the ISAR website (<http://www.isar-icar.com>).

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