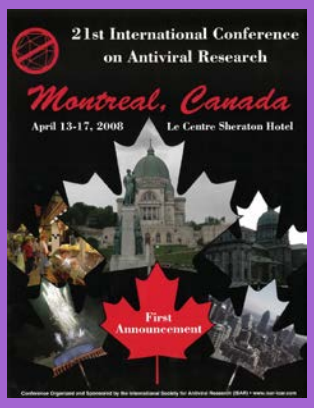
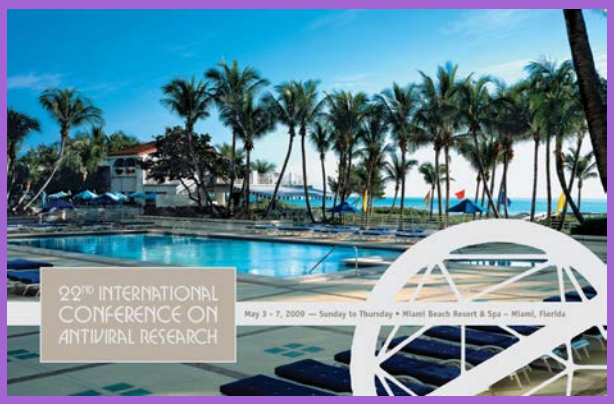
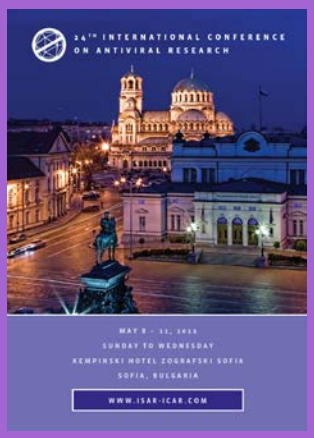
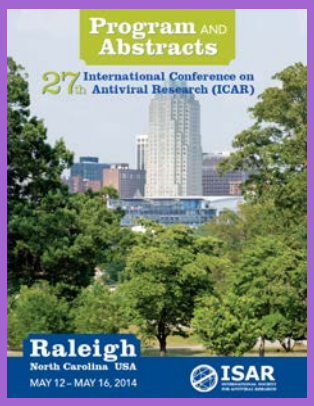
The International Society for Antiviral Research:

2008 – 2017 The Third Decade









The International Society for Antiviral Research:

The Third Decade

2008-2017

Foreword by Johan Neyts (ISAR President, 2018-2020)

Dear reader,

It is our pleasure to introduce this booklet which provides a most interesting review of the 3rd decade (2008-2018) of the International Society for Antiviral Research (ISAR).

The ISAR presidents during this period reflect on the functioning of ISAR in the years of their tenure as well as on the most important evolutions and discoveries in the field of antiviral research and drug development. We are very sad that former president Chris McGuigan passed away much too early. Chris made a major contribution to modernizing the society. We will always remember his enthusiasm.

It is notable that before the discovery of acyclovir in 1977 it was doubted that it would ever be possible to develop safe and effective antiviral drugs. However, potent antiretrovirals are now saving the lives of millions, turning HIV into a chronic infection and we have witnessed a medical revolution in the treatment and cure of hepatitis C. These truly remarkable achievements clearly demonstrate the potential of highly potent, selective and safe antivirals and allow us to look to the future with confidence and optimism.

There have also been in recent years exciting new developments in the treatment and prophylaxis of infections: with the influenza virus, resulting recently in the approval of an endonuclease inhibitor, the cytomegalovirus, resulting in the approval of a terminase inhibitor and the approval of post-exposure prophylactic treatment of HIV. Meanwhile major efforts are ongoing to develop potent drugs against RSV. Similarly, HBV infection is a manageable disease and important efforts are ongoing to identify a functional cure to hepatitis B.

Yet for many viruses, most of which are emerging or neglected, no drugs are available. Important challenges thus remain to be confronted. We are convinced that major advances will be made during the coming years. ISAR and ICAR will continue to be a forum for the dissemination of scientific findings and of debate on the development of new strategies to combat viral infections.

We thank Anthony Vere Hodge for serving as the editor of this interesting brochure and hope that you will enjoy reading it.

Kind regards,

José Esté Immediate Past President ISAR

Johan Neyts President ISAR

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1. Contributions from former Presidents

Introduction

The following request was sent by Bob Buckheit to all past Presidents:

Dear ISAR Past Presidents – the Society is currently working on final details of our Third Decade volume. As an addition to past volumes and to help consider the full history of the Society and the development of antiviral agents I would like to request a short paragraph from each of you with responses to the two following questions:

1. During your tenure as President what was the primary focus of antiviral research, i.e., what was the major threat to human health that was the subject of the most focus and development.
2. During your tenure as President what changes occurred within the Society that contributed to the future growth of the Society.

These are the replies which we have received. Perhaps it was too much to hope that every past President would contribute to this article but, if this publication inspires the "missing" Presidents, it would be a great addition to this historic review covering 30 years. It would be easy to add these new contributions to an electronic version of the "3rd Decade" booklet.

With Williamsburg being called the 2nd ICAR, which meeting was the first ICAR, Rotterdam or Il Ciocco? This question is still being asked, even during the preparation of this booklet. Both the First and Second Decade booklets list Rotterdam, The Netherlands, (April 30 – May 3, 1985) as the first ICAR, this being the first truly international meeting focused entirely on Antiviral Research.

George Galasso gave his view: As one of the principal originators of the ICAR, I must state emphatically that the first ICAR meeting should be Rotterdam. That is when I meet with Erick De Clercq and Fons Billiau and suggested that we initiate a Society with them as leaders. I could not, being a Government worker. They said the leadership should be from the US since most of the antiviral work at the time was in the US. That is when I approached Earl Kern and Rich Whitley to assume leadership with me as background support. That is why Richard became the first President and Earl ran the early meetings.

Erik De Clercq, in his 25th ICAR anniversary lecture at Sapporo (April 2012), explained the role of Il Ciocco, Italy (May 1987): As a clarification, Williamsburg of 1988 was the second International Conference on Antiviral Research (ICAR). There was no meeting called the 'First ICAR' but the Rotterdam meeting of 1985 has generally been referred to as the first ICAR. Erik considers Il Ciocco as the 'virtual first' because it can be regarded as a model for ICAR meetings and ideas about both ISAR and ICAR were developed at that meeting.

1st & 2nd Decade Presidents

Erik De Clercq (1990-1992)

I became President-Elect of ISAR in 1988, to proceed to President in 1990 at the occasion of the 3rd ICAR in Brussels. At that time, the major focus of antiviral research was still concentrated, as it had been from the 2nd ICAR meeting in Williamsburg, on herpesviruses. The impact of HIV, although discovered in 1983 as the cause of a disease (AIDS) first described in 1981, was at that time rapidly growing in importance, with AZT (zidovudine) being the only drug licensed for clinical use.

The ICAR meeting in Brussels marked the inauguration (inception) of all kinds of committees and activities associated with the Society, the most important aspect being the triangle relationship between the Society (ISAR), the conferences which it was going to organize (and still does) annually (ICAR), and, third, the Journal (Antiviral Research) that had been created in 1981, coincidentally the same year that AIDS had been identified.

Erik De Clercq

George Galasso (1992-1994)

Money for AIDS research was not released by President Reagan until 1988 after the death of Rock Hudson so it didn't make an impact on AIDS research and consequently on antiviral research until the early 90s. The major benefits were to AIDS, herpes and hepatitis.

The ISAR was still undergoing growing pains; we revised the By-Laws, and set up criteria for co-sponsorship of scientific meetings. The ISAR News was initiated with Bob Sidwell as the long running editor and John Drach was appointed the ISAR archivist.

We were undergoing financial difficulties, the Society was in debt for the first time. Measures were put in place to overcome the difficulties; dues were raised from $25 to $50 per year and stronger fund raising efforts were put into play and we were back in surplus.

George Galasso

Hugh J Field (1994-1996)

Recollections of a former President of ISAR

I was President during the period 1994-1996. This is about 10 years after HIV had first emerged as a major threat to human health. Up to this time most success with antivirals had been with herpesviruses. One of the features of antiviral research in the herpes field at this time was the friendly but strongly competitive rivalry between the researchers from the then Burroughs Wellcome and SmithKline Beecham companies promoting valaciclovir and famciclovir, respectively for the treatment and prevention of herpes simplex including genital herpes, ocular herpes, herpes encephalitis and varicella-zoster.

I recall that during the ICAR Santa Fe (1995) the big news broke that Burroughs Wellcome and the Wellcome Foundation were to be sold thereby producing a huge financial benefit for the Wellcome Trust research funds. However, Wellcome was acquired by Glaxo to become Glaxo Wellcome starting a process of amalgamation that would change the career paths for many of the existing Wellcome virus researchers.

On the HIV front there was much discussion of RT nucleoside and non-nucleoside inhibitors and the development of HIV antiviral resistance had already become a major focus of attention. Pandemic influenza was certainly recognized as a major threat during this era, but the importance of the active compounds Relenza® and oseltamivir were yet to emerge. There was relatively little interest yet in the hepatitis viruses as a potential antiviral target at this time.

Not long previously, there had been discussion as to whether or not the ICAR should be an annual meeting or just every other year! It was probably the rapid development of antiviral research in the HIV field that confirmed that an annual ICAR would prevail. Regarding development of ISAR, a lot of effort had been devoted to developing the present constitution and committee structure. I am not sure of the exact dates but early on, several of the current ISAR committees were still fairly informal without the production of annual written reports etc. These processes were established by then and another change, I think was now in train was the idea of fixed terms of office for the society officers and board of directors to ensure a regular turn-around. These changes had been recently codified

in a new version of the society bye-laws. [Editor's comment: The acceptance is mentioned by Joe within his contribution (in 2010)]

Hugh Field

3rd Decade Presidents

Christopher (Chris) McGuigan (2006-2008)

During Chris's tenure, the main focus of antiviral research was centered on HIV treatment and the exploration of novel targets. Indeed, the mini symposium in Montreal (2008) was dedicated to this theme. In addition, we could see the rapid increase in abstracts on the development on HCV inhibitors throughout the two years of his time as president. Once again, ISAR recognized this trend by organizing a dedicated mini-symposium at the 20th ICAR, in Palm Springs (2007).

As President, Chris opened the ISAR board meetings to the committee chairs. Also, it was Chris who initiated the conversion of ISAR from the paper age to the electronic age. Chris digitalized many of the Society's operations, as indicated by the quotes from the President's messages in the ISAR News.

2007: For the second time, an electronic election was conducted. E-mail ballots were sent to approximately 440 registered members of ISAR. More than 100 members responded casting more than 200 votes. This represents a greater than 25% turnout based on non-failing emails.

2008; As last year, we will run an electronic ballot from the President's office in Cardiff. It will be entirely e-mail based – so please check your e-mail address at the ISAR Website.

2008: Finally, this year we will be unveiling a new online membership list, which will replace the hard copy. Many societies have gone this route, and we believe it will offer members a number of advantages. The lists will be password protected and will represent a further benefit to membership. They will be much more easily searchable than the hard copy too! We are grateful to Brent Korba and his team for organizing this.

Another of Bob's ideas is being trialed in the Poster Sessions in 2008. A first for ICAR, we will have 'shotgun' posters, where a small number of posters from each session will be selected for short oral presentations. If you have a poster in Montreal – do come prepared with a few slides!

Lastly, my warm thanks to International Medical Press for their complimentary publishing of this year's *ISAR News* and to Courtesy Associates for their outstanding support for the meeting.

[Editor's note: Robert (Bob) Sidwell started the *ISAR News* in July 1991, continuing as Editor until 2008. Chris McGuigan was keen to convert the ISAR News to an electronic format. Hugh Field, then Editor-in-Chief of *Antiviral Chemistry & Chemotherapy* (AVCC) negotiated with International Medical Press to publish the *ISAR News* in AVCC, on a free access basis. This step not only reduced the cost to ISAR but also greatly increased its distribution.]

Andrea Brancale for Chris McGuigan

Amy K Patick (2008-2010)

During my tenure, the primary focus continued to be on antivirals directed towards human immunodeficiency virus (HIV). The creation and subsequent availability of HCV subgenomic replicons however, quickly led to an unparalleled amount of activity in the discovery and development of anti-HCV agents. Other efforts were directed towards pandemic response planning directed against avian influenza A (H5N1). The emergence of the 2009 H1N1 influenza pandemic in April 2009 not only led to a surge in antiviral discovery efforts

but also threatened the May 5th 22nd ICAR meeting in Miami, FL. On April 29th, WHO raised the influenza pandemic alert from 4 to 5. This led to a hurried teleconference among myself (President), Joe Colacino (President Elect) and Chris McGuigan (Past President). After reviewing the travel restrictions (none for U.S.), we decided to go ahead with the meeting and provide liberal refund policies for those whose countries did not allow travel. What better time could there have been for expert Virologists to come together to discuss antivirals!

During my tenure I continued to grow and promote the culture of open transparency, inclusion, honest communications and a willingness to let young (and old) investigators from a diverse backgrounds assume Society responsibility freely. Other changes that contributed to the future growth of the Society included incorporation of best practices from project management, including establishment of frequent telecommunications with developed agendas and follow-up with action items, establishment of a common set of templates and presentations (business meeting, Elion and Prusoff award, travel award, etc.) that could be handed down from President to President. Perhaps the biggest change was the purposeful recruitment and promotion of women in leadership and award positions within the Society. At the beginning of my tenure, no woman had yet to win the prestigious Trudy Elion award in 22 years and only 2 of 11 (18%) Boards of Directors were women. Today the number of woman in leadership positions has grown to 4 of 11 (36%) members of ISAR Board of Director and some awards (Prusoff) now boast women as recipients. But we still have a way to go to recognize more women across all major awards categories.

Amy Patick

Joe Colacinco (2010-2012)

My tenure as ISAR president began at the closing of the 23rd ICAR in San Francisco at which President Amy Patick passed the gavel to me. During this time, our economy was slowly rebounding from a severe recession which presented personal and professional financial challenges to our members. Nevertheless, ISAR remained financially healthy and ICARs were well attended. I was fortunate to follow Amy as president as she was a source of knowledge and guidance and left me with a scientifically and financially successful Society. As President, I worked with an excellent team of officers (Amy Patick Past President; Phil Furman, President-elect; Dale Barnard, Treasurer, and Susan Cox, Secretary), board members and committee chairs to maintain the Society's high standards of scientific excellence, enhance our relevance, continue its openness, and provide a welcoming atmosphere to new members. During my first year as president, the 24th ICAR was held in Sofia, Bulgaria where our local host was Dr. Angel Galabov. Bob Buckheit and his program committee worked diligently to put together a scientifically excellent program including a "Drug Discovery 101" session which we continued based on highly favorable feedback from ISAR members. Our initiative in career development and placement for junior investigators continued and our Career Happy Hours evolved into Career Breakfasts at which networking opportunities were made available. Tomas Cihlar and the Placement Committee enthusiastically organized and oversaw this event. Throughout my presidency, the highly effective and tireless fund-raising efforts of Roger Ptak were instrumental in keeping the Society solvent and able to meet its goals.

In 2010, we held an electronic election which was highly successful due to the efforts of Andrea Brancale who was chair of the ISAR website committee. The election also included voting on updates to the Society by-laws as discussed by the board and proposed by Jack Secrist, John Drach, and Phil Furman. These changes were regarding Board membership; candidacies for the offices of treasurer and secretary; term lengths for officers, board members, and committee chairs; appointments of committee chairs; filling office vacancies; roles and responsibilities of the President and Secretary; electronic communications and balloting; and non-budgeted expenses. The proposed changes were posted on our website for 30 days prior to the election and were accepted by the members.

During the second year of my presidency, The Silver Anniversary ICAR was held in Sapporo, Japan and was co-sponsored by the Japanese Association for Antiviral Therapy (JAAT). We received generous support for this conference from the Federation of Pharmaceutical Manufacturers' Association of Japan. Prof. Masanori Baba, who was the local host for this ICAR, was recognized for his efforts in securing this important funding. To commemorate the Society's 25th Anniversary, Society Founder and Former President Prof. Erik De Clercq delivered a lecture reviewing the previous 25 years of antiviral drug discovery and development. Through the efforts of Andrea Brancale, the ISAR website received a new look and new capabilities including an enhanced member directory, navigation to external links, facilitated membership renewal and conference registration, and electronic balloting. A significant change during this period was that rather than publishing the ICAR program and abstracts in *Antiviral Research*, they were made available on the ISAR-ICAR website to members with a user ID and password. This change enabled the conference organizers to extend the abstract submission deadline allowing greater flexibility for conference attendees and abstract reviewers.

My years as president of ISAR were concurrent with exciting advances in antiviral drug discovery and development. In 2011, two HCV protease inhibitors were approved by the FDA for the treatment of chronic HCV infection, a disease which reached epidemic proportions during this time resulting in significant mortality and morbidity. Other direct antiviral agents for HCV were in late stage development at this time and offered great promise for reducing or eliminating the need for interferon and ribavirin and providing a clinical cure for this lethal disease. As of this writing, that promise has largely been fulfilled by the work of Society members.

At the close of the Sapporo meeting I had the great honor of passing the gavel to Phil Furman. I can only hope that I left the Society in as good a shape for Phil as Amy left it for me!

Joe Colacinco

Phillip (Phil) Furman (2012-2014)

During my tenure as President we saw the approval of sofosbuvir, which led the way to a cure for HCV infections. HIV and HBV continued to receive a great deal of focus. Eradication of HIV was a topic of great interest and research. HBV research focused on targeting ccc DNA as well as other potential targets involved in the HBV replication cycle. New therapeutic approaches including drugs other than nucleoside analogs and immunotherapeutic approaches were being explored. The Ebola outbreak, which killed over 11,000 people, began in Guinea December of 2013 and declared an international health emergency by WHO in 2014. Subsequently Ebola as well as other emerging viruses have received much more attention.

During my tenure as President several changes/additions occurred within the Society. To honor Antonín (Toni) Holý and his legacy, the Antonín Holý Memorial lecture award was established and funded by Gilead Sciences, Inc. The second addition was the establishment of the Women in Science Program by Amy Patick. The program was such a success that it became a permanent part of ICAR. Eventually Amy and her committee introduced a mentoring program and a scholarship program to the Women in Science Program. So as to maintain a historical record of ISAR and ICAR the Archives Committee was established. The officers and board re-evaluated and changed the ISAR membership fee structure.

Phil Furman

Robert (Bob) Buckeit (2016-2016)

During my term as President (2014-2016) the world of antiviral drug discovery and development continued to celebrate successes in the approval of new and improved drugs to treat HIV infection as well as apparent cures for HCV. During my years as President a shift in focus from these viruses to a focus on HBV and emerging threats

such as Zika, Dengue and Ebola occurred. In 2015 and 2016 a major outbreak of Zika infections occurred in Brazil and a large outbreak of Ebola occurred in the Democratic Republic of Congo with an unusually large number of cases and fatalities. Thus, my term was marked by a shift to finding a cure for HIV, treatments and cure for HBV and a real focus on emerging viral threats.

The main goals of my years as President of the Society was to continue efforts to bring more chemistry back to the Society's annual meeting and membership with the first Antonin Holy Memorial Award given in 2014. Additionally I engaged members of the Society from around the world to focus on the growth of ISAR membership in areas where we had minimal presence by establishing the ISAR Ambassador's Program. This program was designed to provide ISAR information to the individuals in various geographic locations in the world and to empower them to recruit new members to ISAR from their locales. Lastly, my term included a major focus on energizing young members of the Society through networking activities and social functions as well as bringing these young scientists into prominent roles within the Society's committees in order to provide for a transition of leadership from current management to the next generation of scientists needed to keep the Society thriving. I thought it was important to provide a venue where young investigators could meet established ISAR members and Officers in a social environment to get to know one another. During my term we also began efforts to establish an ISAR webinar to provide increased visibility to the Society as well as add value to the membership. The Women in Science Program that had been established during my President Elect years became active with the establishment of the Chu Family Foundation Scholarship Awards first presented in 2015. Finally, in order to add greater value to a membership in ISAR, during my tenure as President the ISAR News was greatly improved by doubling the number of issues that were prepared each year and by greatly increasing the scientific content of each issue through submission of scientific reviews and the use of guest editors.

Bob Buckeit

José Esté (2016-2018)

During this last decade we have witnessed how research and development of antiviral drugs have clearly impacted on the well-being of humans and society in general. Highly active antiretroviral therapy (ART) has been recognized as an effective strategy to thwart and contain the spread of HIV infection. Undetectable viremia following effective ART, restores health and quality of life of HIV individuals, limits HIV transmission and prevents the spread of infection in unprecedented ways.

Now, antiretroviral treatment has been simplified to single pill regimens with fixed-dose combinations (FDC) or by reducing the composition to minimal drug components once undetectable viremia has been achieved. FDC allow for increased adherence to treatment and reduced drug-related unwanted effects. Current efforts are also focused on the development of long-acting antiretrovirals that could be used for both HIV treatment and prevention. The recent LATTE-2 clinical trial (Margolis et al. *Lancet* 2017) evaluating long-acting injectable formulations of cabotegravir and rilpivirine, taken once every four or eight weeks, showed maintained viral suppression in most participants. This study demonstrated efficacy comparable to daily three-drug oral therapy and paves the way to even simpler and effective ART regimens.

Fundamental and clinical anti-HIV research has shifted towards the identification of ways to intervene and cure HIV infection. Despite enormous advances in our understanding of the pathogenesis of disease, the immunology of HIV infection and of host-pathogen interactions, sufficient knowledge to design effective, curative strategies is still not there yet. HIV latency, as the means to purge the virus reservoir, is the target of current efforts but we are also beginning to identify immune-based strategies as potential curative options.

Direct acting antivirals targeting hepatitis C virus (HCV) infection have become standard care and are recognized as a true scientific “miracle”. Hepatitis C is a curable disease and we begin to envision the difficult but

possible eradication of HCV through the use of effective health measures and antiviral treatment. Containment and eradication of HCV appear now to be more in the hands of politicians, stakeholders and public health officials.

The 2013-2016 Ebola virus epidemic in West Africa was the most widespread outbreak of Ebola virus disease in history (WHO Ebola Response Team, *N Engl J Med*, 2014). This outbreak reminds us once more of the urgent unmet medical need for an effective vaccine and antiviral treatment against Ebola virus. Recently, a vaccine appeared to provide protection against the virus two years after injection (Huttner et al. *Lancet* 2018). A number of small molecule antivirals, including GS-5734, brincidofovir (BCV, CMX001) and favipiravir are being evaluated for their clinical safety and efficacy.

Finally, biological sciences are being revolutionized by big data, new genome sequencing and imaging technology. The antiviral field is no exception to this revolution. New generation sequencing is changing the way we recognize and diagnose the emergence of drug-resistance and prevent treatment failure. Genomics and proteomics are helping the identification of host factors as new targets for drug development and cryo-electron microscopy and tomography offer unprecedented, high-resolution images of virus particles. The future looks promising.

With a surmounting number of scientific meetings and conferences, increasing budget difficulties for many academic and biotech laboratories and a complex economic environment, ISAR recognized the need to optimize it resources. The Society must maintain its financial health, make strong efforts for ICAR to be economically feasible and at the same time encourage participation from all stakeholders. A new Conference Organizer was hired to run the 30th and future conferences with the hope of optimizing our costs and improve efficiency. The ISAR finance committee took on the challenge of seeking advice and making decisions on how to invest and optimize its reserve funds. Past presidents, the current leadership, a number of volunteers provided input, and a number of investment decisions were taken. Careful observation of economic markets and wise decision-making should allow the Society to count with financial health and security for the future. Additionally, strong efforts were made to keep expenditures at bay and make the conference a financially viable experience without compromising the scientific program and the participation of students, postdocs and young investigators.

The Society has already recognized the need to promote and encourage the participation of women in science and the Women in Science Roundtable has been running for some years with excellent appreciation from ICAR participants. In 2017, we created the ISAR Women in Science Award to recognize woman scientists who have made outstanding contributions to the field of antiviral research. This award will now be one of the four ISAR awards of excellence given annually at ICAR. We hope this award will endure until there is no further need to highlight the dedication of women in science based on gender but on equality, scientific merit and excellence alone.

The way people communicate and exchange information has changed dramatically and so ISAR-ICAR needs also to revamp its communication strategy. During my tenure as President we recognized the need to modernize our communication structure to increase ICAR attendance and ISAR membership. A decision has been taken to create a new Communication and Outreach committee (COC) that will oversee the way we contact and communicate with the membership, stakeholders, ICAR participants and the public in general. The former Publications, Website and Membership committees will now merge into the COC. At the same time, professionals in the communication business should provide advice and guidance. Additionally, the Society will now actively promote the organizing of the ISAR webinars with a specific subcommittee and budget. We hope our decisions will contribute to the growth of ISAR and to the dissemination of science.

José Esté

2. ISAR Awards for Outstanding Contributions

Introduction

Over its three decades, the International Society for Antiviral Research has established a variety of awards to recognize outstanding contributions. Most of these have been discussed in the previous decade summaries and are available on the Society's website, so they will be covered here in a more abbreviated form. It was recognized early that outstanding contributions to the area should be recognized, not only at the senior investigator level, but also for younger scientists. The Society had the wonderful good fortune to have luminaries in the area as loyal and enthusiastic supporters and participants in the meetings, and it was a popular decision in each case to set up awards that honor these people and establish criteria that reflect the character and contributions of these scientists. The initial two such awards were the Gertrude B. Elion Memorial Lecture Award and the William H. Prusoff Young Investigator Award. More recently, the Antonín Holý Memorial Award has been added to this prestigious list. And finally, the first Women in Science Award was given in 2017, and it is intended to be an annual award that will be included in the next decade booklet.

Gertrude B. Elion Memorial Lecture Award

From the beginnings of the Society, Gertrude (Trudy) Elion was an important participant in the meetings, and was very active both at the sessions and in conversations with scientists of all ages, expertises, and affiliations. Her presence and support were important early as the Society and its International Conference on Antiviral Research became established, and she continued to participate through the rest of her life. Trudy Elion, jointly with George H. Hitchings and Sir James Black, was awarded the 1988 Nobel Prize in Physiology or Medicine for work on drug discovery. Her work over the years involved a large number of drugs, and as her career unfolded, it became somewhat more focused on antiviral drugs, including acyclovir and AZT, to name two. Even after her retirement in 1983 she continued to be involved in drug discovery research at Burroughs Wellcome as a Scientist Emeritus and Consultant. At the meetings she was interested in all the research that was being presented and discussed, and anyone at the meeting could start up a conversation with her about the field or their own work. Trudy passed away in early 1999 at age 81, and later that year efforts by many scientists connected with the Society resulted in the establishment of the award at the Jerusalem ICAR meeting. The first Elion Award was presented at the 2000 ICAR meeting, which was held in Baltimore, Maryland. The award has been supported by Glaxo Wellcome (now GlaxoSmithKline) up until 2017. The Award criteria are multifaceted. The award is given to an outstanding senior scientist of international stature, either in antiviral research or in a scientific field that is connected to it. Awardees have not only scientific preeminence, but also embody some or many of the characteristics of Trudy Elion, which include: a genuine love of science, a character that engenders both respect and admiration, a reputation for scientific integrity, and approachability for scientists of all ages.

The Elion award winners for the third decade are shown in Table 2.1.

A look at the winners makes it clear that the Society embraces contributions from all relevant scientific disciplines, and any type of organization. The winners range from chemists to clinicians, and the affiliations are organizations from academia, industry, and research institutes. The same diversity of award winners can be seen in the first two decades, as well. Chemists such as Karl Hofstetler and Michael Sofia have made major contributions in the construction of potential drugs, and of course in the drug discovery cycle where structural modifications are made in response to the biological activities and toxicities of molecules. Biologists, biochemists, virologists, and pharmacologists, which include Jan Balzarini, Karen Biron, Bo Oberg, Earl Kern, John Drach, and Philip Furman, have been instrumental in developing the scope and limitations of the activity of potential new drugs, and in interfacing with both chemists and clinicians. Finally, clinicians such as Douglas Richman have been critical in the establishment of favorable dose regimens in humans to maximize antiviral effects and minimize toxicities of drugs on their way to approval and afterwards, as well.

The Elion Award gives the Society the opportunity to acknowledge and celebrate the legion of accomplishments by the scientists on the above list. All of them embody of the spirit and character of Trudy Elion in a variety of ways.

Table 2.1. Gertrude B. Elion Memorial Awardees (period 2008-2017)

Year	Awardee (Affiliation)	Title of Elion Award Lecture
2008	Jan Balzarini (Rega Institute for Medical Research)	Carbohydrate-binding agents: a novel tool for the inhibition of enveloped viruses.
2009	Karen Biron Pathfinder Pharmaceuticals (Glaxo Wellcome, RTP)	Following acyclovir: the quest for a more potent CMV drug.
2010	Bo Öberg (Medivir, Astra, Karolinska Institute)	Uncommon combinations.
2011	Earl Kern (University of Alabama at Birmingham)	Why develop a drug for smallpox, a disease that has been eradicated?
2012	Karl Hofstetler (University of California at San Diego)	Using phospholipid mimicry to increase efficacy and safety of acyclic nucleoside phosphonate antivirals.
2013	Masanori Baba (Kagoshima University)	My antiviral research in Fukushima, Leuven and Kagoshima.
2014	John Drach (University of Michigan)	Collaborative antiviral studies for the discovery of drugs to treat cytomegalovirus infections.
2015	Philip Furman (Pharmasset, Triangle, Burroughs Wellcome)	Sofosbuvir: a search for a cure.
2016	Douglas Richman (University of California at San Diego)	Antiretroviral drugs: history and future
2017	Michael J. Sofia (Arbutus, Pharmasset)	Viral hepatitis – the search for a cure.

William Prusoff Young Investigator Award

William (Bill) Prusoff, trained as a pharmacologist, was involved in antiviral research and drug discovery from the early days of antiviral drug development, and was responsible for one of the earliest approved drugs, idoxuridine for the treatment of topical herpesvirus infections. Along with his collaborator at Yale University, Tai-shun Lin, he was also responsible for one of the first anti-HIV drugs, stavudine. Stavudine was initially synthesized

as a potential anti-cancer drug by Jerome Horwitz at the Michigan Cancer Foundation (now the Karmanos Institute). Horwitz similarly synthesized zidovudine (AZT), another of the initial anti-HIV treatments discovered and advanced to FDA approval by Burroughs Wellcome.

Bill Prusoff became well known for his efforts in the antiviral area, and was a speaker at conferences around the world. He was a strong supporter of the International Society for Antiviral Research from its inception and an enthusiastic regular attendee of the International Conference on Antiviral Research. He was known to everyone and appreciated by all who knew him. One of his obvious attributes was the spirit of a young scientist, which he kept throughout his life. At one of the meetings he quipped that his spirit was in its 30's but his body in the hundreds! He not only mentored many young scientists, but was highly supportive of young scientists around the world. In recognition of his efforts, Bristol-Myers Squibb endowed the Young Investigator Award, which has been presented at each ICAR meeting beginning in 2001. Bill had a positive attitude, a light heart, and a commitment to the development of new drugs that would help mankind. His success in that regard speaks for itself. Bill passed away in 2011at age 90, and was able to enjoy a decade of interacting with the winners of the Prusoff Award.

The award is given to an outstanding young scientist, not older than 45 years of age, who has demonstrated dedication, excellence and achievement in any field related to antiviral research, from basic science through clinical evaluations, and who has the potential for continuing contributions to the field and to society in general. The award is designed to recognize outstanding young scientists who have not yet reached their peak scientific maturity, but are well on the way.

The Prusoff award winners for the third decade are shown in Table 2.2.

A look at the scientific accomplishments of this group of awardees makes it clear that they were outstanding young scientist pursuing an impressive diversity of directions related to antiviral research and drug discovery. Again, the international character of the award is obvious, and winners through the years have continued on to make impressive scientific accomplishments.

Antonín Holý Memorial Award

Antonín (Tony) Holý was an innovative and outstanding chemist from the Czech Republic. He became well known for his work in the area of nucleosides, and he did pioneering research on a variety of different nucleoside classes. He is best known for his preparation of the acyclic nucleoside phosphonates that have become anti-HIV and anti-HBV drugs through his collaboration with Erik De Clercq of the Rega Institute and through the efforts of the outstanding scientists at Gilead Sciences led by John Martin. Tony and Erik worked together for many years, and became revered personalities in antiviral circles around the world. That Tony was able to achieve this recognition coming from the Czech Republic through many years when the country was behind the Iron Curtain makes it all the more remarkable. Tony's scientific impact goes far beyond the phosphonates, however, and he has made innovative contributions in many other directions. Tony passed away at age 75 in 2012.

In recognition of his many achievements, Gilead Sciences established the Antonín Holý Memorial Award, which was first presented in 2014. The award is presented to a scientist working the field of medicinal chemistry, a senior scientist of international stature who has made innovative contributions that have had an impact on antiviral drug discovery and/or development. The awardee is to have had a career-long impact on medicinal chemistry and antiviral research as evidenced by publications, patents, presentations, and other similar criteria.

The Holý award winners during the third decade are shown in Table 2.3.

All of the winners are internationally known and outstanding chemists involved in research relating to medicinal chemistry. They have contributed to a number of the drugs that are now approved as antiviral agents, and represent in outstanding fashion the impact that medicinal chemistry can have on human disease treatment.

Table 2.2. William H. Prusoff Young Investigator Awardees (period 2008-2017)

Year	Awardee (Affiliation)	Title of Prusoff Award Lecture
2008	Bruno Canard (Aix-Marseille University)	The structure and mechanism of RNA virus replication enzymes: endless challenges for drug design.
2009	Mark Prichard (University of Alabama at Birmingham)	Viral kinases as targets for antiviral therapy.
2010	José Esté (Hospital Germans Trias i Pujol)	Coreceptors and cellular factors as targets for antiviral drugs.
2011	Brian Gowen (Utah State University)	Development of countermeasures against pathogenic arenaviruses.
2012	William Delaney (Gilead Sciences)	HBV and HCV: parallels, contrasts and future directions for therapy.
2013	Andrea Brancale (Cardiff University)	From irrational to rational antiviral drug design.
2014	Adrian Ray (Gilead Sciences)	Use of nucleotide prodrugs to enhance selectivity of anti–HIV and –HCV agents.
2015	Erica Ollmann Saphire (Scripps Research Institute)	Remodel, repurpose, rearrange; how viruses leverage the few proteins they encode.
2016	Jerome Deval (Alios BioPharma)	New frontiers in antiviral drug development: inhibiting the polymerase of (–) strand RNA viruses
2017	Maaike Everts (University of Alabama at Birmingham)	Collaborating in drug discovery: challenges and solutions.

Table 2.3. Antonín Holý Memorial Awardees

Year	Awardee (Affiliation)	Title of Holý Award Lecture
2014	Piet Herdewijn (Rega Institute for Medical Research)	From modified nucleoside to a chemically modified genome.
2015	Dennis Liotta (Emory University)	Novel therapeutics for treating viral diseases, cancers and inflammatory disorders.
2016	Robert Vince (University of Minnesota)	Acyclonucleosides to Ziagen.
2017	C. K. (David) Chu (University of Georgia)	Nucleosides: a rich source of antiviral agents.

ISAR Women in Science Award

The inaugural ISAR WIS Award was presented to Priscilla L. Yang (Harvard Medical School, Boston, MA, USA) by Rhonda Cardin, chair of the WIS committee, at the 30th ICAR, Atlanta, GA, USA, 2017. Priscilla's lecture title: Small molecule inhibitors of viral entry inspired by the humoral immune response to viral infection.

The WIS Award has become an annual event.

Special Award of Thanks

Joe Colacino (then ISAR President) presented the award to Roger Ptak during the ISAR Board Meeting held on May 8th, 2011 in Sofia, Bulgaria, 2011. This was a special award of thanks for his fund-raising. This may seem to have been a simple occasion but ISAR owed him a very big vote of thanks for all that he had done, and continues to do. Put simply, ICAR could not have continued without his input. The Plaque states:

Roger Ptak
Chair of the ISAR Finance Committee

For Your Professionalism and Motivation.
Thank You for Working Behind the Scenes
to Ensure ICAR's Success

ISAR Service to the Society Award

Occasionally the Society has chosen to honor a member for service to the Society well above and beyond what is expected. Over its first two decades of existence, ISAR has given only two such awards, to George Galasso and Earl Kern. During the third decade, one such award was made, to Erik De Clercq of the Rega Institute for Medical Research in Leuven, Belgium, in recognition of his continued dedication, support and service to the Society and its members. This rare award was presented by then president Joe Colacino to Dr. Erik De Clercq at the 25th anniversary meeting in Sapporo, Japan in April 2012. Erik treated the audience to a series of entertaining and interesting reminiscences spanning his career and all with a link to Japan.

John A. (Jack) Secrist III

3. The Continued Growth and Importance of Antiviral Drug Discovery

Drugs that can cure millions of people worldwide who have hepatitis C virus infections? Therapies that have virtually eliminated AIDS and turned HIV infection into a chronic, but highly suppressed disease, enabling many more people to live normal lives? All in a single tablet that needs to be taken only once a day? Antivirals that act by mechanisms previously unknown? Yes! This and more have occurred during the third decade of the International Society for Antiviral Research (ISAR). We have witnessed a continuation of basic and applied studies that resulted in an ongoing stream of drugs to treat viral diseases. ISAR members and other scientists, clinicians, and administrators from academia, government, industry, and research institutes combined their talents and hard work to bring forth many new antiviral drugs, nearly 30 of which were approved for human use by the United States Food and Drug Administration (FDA), see Table 3.1. There were additional approvals by regulatory agencies in Europe and Japan, some of which were later included in combinations approved by the FDA and are included in Table 3.1.

Work that occurred during the first two decades of ISAR and preceding years initially concentrated on drugs to treat herpesvirus infections and acute infections such as influenza, respiratory syncytial virus, and hepatitis B. While these efforts were ongoing human immunodeficiency virus (HIV) was recognized as the cause of the then developing acquired immunodeficiency disease syndrome (AIDS) pandemic. This led to expanded and shifting efforts to develop drugs to treat HIV infections. At the same time hepatitis B and C infections were not ignored and some progress was made. These developments are summarized and discussed in the booklet *The International Society for Antiviral Research: The Second Decade*.

As the third decade of ISAR began and resistance to earlier HIV drugs emerged, expanded efforts were made against this virus. Likewise as the enormity of the problem of chronic hepatitis C virus (HCV) infection was recognized, this virus received expanded attention. (The World Health Organization estimates that 2-3% of the world's population is infected with HCV.) The successful expanded work and the development of drugs to treat HCV infections was possible in no small part due to the development of *in vitro* models of the virus. Other viruses were not ignored and drugs with new mechanisms of action such as letermovir to treat cytomegalovirus infections were found. Great progress also has been made in understanding and improving the pharmacokinetics of many drugs, especially those to treat HIV, HBV, and HCV infections. Although many early drugs were effective, they required patients to take multiple tablets or capsules two, three, or more times per day. Almost predictably, this resulted in poor patient acceptance of therapies and resulted in the emergence of drug-resistant viruses and disease relapses. The development and use of prodrugs and combinations with them has resulted in therapies that are much more acceptable to patients, often requiring only the administration of a single table or capsule once a day!

The drugs given approval by the United States Food & Drug Administration (FDA) during ISAR's third decade are shown in Table 3.1. For an explanation for the few additional drugs, please see footnote.

Human immunodeficiency virus

Great progress has been made in the treatment of HIV infections and the prevention of AIDS. As shown in Table 3.1, 13 new drugs were approved by the FDA between 2007 and 2018 to treat HIV infection. All but five of these are combinations of drugs that act by different, synergistic mechanisms. Of the five single active-ingredient drugs, four were approved by 2011. One of these (raltegravir) acts by a mechanism not previously available, inhibition of HIV integrase, which is the enzyme responsible for integrating HIV proviral DNA into host DNA. The mechanisms of the other three were similar to those found in previous drugs. Namely maraviroc acts by antagonism of the binding of human chemokine receptor CCR5 present on CD4+T-cells to HIV-1 gp120 protein thereby preventing HIV binding and infection. The other two drugs are second-generation non-nucleoside reverse transcriptase inhibitors (NNRTI's). They prevent the replication of the HIV genome by binding to reverse

transcriptase at a position separate from the active site of the enzyme. They have the advantage that they are active against HIV that has become resistant to first generation NNRTI's such as nevirapine. Three of these four drugs typically are administered twice a day but better pharmacokinetics permitted rilpivirine to be administered only once a day. Although approved as single active ingredient drugs, predictably all of these most often are used in combination with other HIV drugs. The fifth single-ingredient drug approved recently in 2018, ibalizumab (Trogarzo®®), is the first HIV therapy approved in 10 years that has a new mechanism of action; it can be effective in difficult-to-treat patients with limited options. It is a monoclonal antibody that binds to host cell-surface glycoprotein CD4 found on immune cells to protect them from HIV adherence and absorption.

The majority of FDA approved drugs to treat HIV infection in this time period are fixed-dose combinations of two to four drugs. Typically they include some combination of a nucleoside reverse transcriptase inhibitor (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) and an integrase inhibitor. The major reasons for these combinations are to utilize different mechanisms of action to greatly reduce the incidence of HIV resistant to any one drug and to obtain synergistic antiviral effects. Combination is especially important with NNRTI's because resistance to their antiviral effect develops more readily than to other inhibitors. The use of two NRTI's that inhibit the catalytic site, or a NRTI with a NNRTI, to inhibit reverse transcriptase at two different loci, have proven to be effective combinations. Some combination drugs include a compound devoid of antiviral activity, cobicistat. It is a pharmacokinetic enhancer and is included because it inhibits the activity of a cytochrome P450 isoenzyme found in human liver. This enzyme is responsible for the metabolism and inactivation of several antiviral drugs, therefore its inhibition increases the duration and extent of the activity of anti-HIV drugs used in the combination. Table 3.1 provides details on the combination drugs.

An important advance in drug design utilized in both single-ingredient and combination drugs was the introduction of prodrugs. These analogs of active compounds either circumvent a step needed in the metabolic activation of a drug from an inactive form or significantly enhance the oral absorption of the drug, or both. Examples include TDF (tenofovir disoproxil fumarate) and TAF (tenofovir alafenamide) which are contained within the drug combinations, Complera®, Stribild®®, Genvoya®, and Biktarvy®.

Special problems exist in the design and production of all the combination drugs. These involve not only the therapeutic challenges of finding the best combination of ingredients and dosages for each component, but also the pharmaceutical challenge of how to combine different compounds into a single capsule or tablet. Problems such as different rates of dissolution and solubility in different parts of the gastro-intestinal tract must be addressed. Equally important is how to prevent chemical reactions among the ingredients in the dose form itself so that the combination drug can go from manufacturer to pharmacy to patient without degradation. These challenges have been overcome for all of the combination drugs approved by the FDA and listed in the Table 3.1.

Hepatitis B virus

Progress also has been made in the development of drugs to treat hepatitis B virus (HBV) infections (Table 3.1). The earlier discovery that hepatitis B virus utilized a reverse transcriptase as part of the process to replicate its DNA genome and produce infectious virus strongly suggested that reverse transcriptase inhibitors identified as drugs to treat HIV might inhibit HBV as well. This proved to be correct and a NRTI approved in 1995 for the treatment of HIV, lamivudine, was approved in 1998 for HBV treatment. Since that time two other NRTI's have been approved, telbivudine and tenofovir. These are more effective than the earlier HBV drugs and less likely to select drug-resistant virus strains. Telbivudine is unique among the NRTI's because its sugar moiety is the "unnatural" L-ribose, not D-ribose found in naturally-occurring nucleosides and in the other NRTI's. Two prodrugs of tenofovir have been approved for HBV treatment, Viread® (TDF) and Vemlidy® (TAF). Both need to be taken only once a day but Vemlidy® proved as active but with a superior safety profile to the older prodrug, Viread®. Even though great progress has been made in highly suppressing HBV in virtually all patients, only a relatively few patients achieve a functional cure.

Hepatitis C Virus

Of all the antivirals discussed herein, the greatest progress has been made in the development of drugs to treat hepatitis C virus (HCV) infections. In the time frame of the third decade of ISAR, we have gone from the use of interferon, usually with ribavirin, which produced incomplete results with adverse effects, to much safer drugs that now result in cures. This has come about as the result of the development of a number of new single-ingredient and combination drugs. Key to the development of these drugs was the establishment of *in vitro* models of HCV replication, understanding how the virus replicates, and the identification of key non-structural proteins essential for that replication. Three such proteins have been utilized successfully as targets for the new drugs. Their functions were initially unknown other than they were not part of the virus structure and consequently were simply referred to as non-structural proteins. Subsequent research identified their roles in viral replication which are as follows: (*i*) non-structural protein 3-4A (NS3-4A) is the primary viral protease needed to cleave a viral poly protein into active proteins needed for viral function and to inhibit the production of host interferon, (*ii*) NS5A is essential for HCV RNA replication, but its precise role(s) in the process are poorly understood, and (*iii*) NS5B is the RNA-dependent RNA polymerase needed to replicate the viral RNA genome.

The first partially successful new HCV drugs had a single active ingredient. Boceprevir, telaprevir, and simeprevir are older inhibitors of the viral protease. A more recent single-ingredient drug, daclatasvir, inhibits the NS5A protein. All these drugs were initially used in combination with interferon, usually with ribavirin and sometimes with the older drugs. Sofosbuvir is a nucleoside inhibitor of the RNA polymerase (NRPI) and is still the only NRPI with FDA approval. It has a high genetic barrier to viral resistance so that it is used without interferon. Although sofosbuvir was initially used alone, it was closely followed by combination with a NS5A inhibitor (ledipasvir) to give the highly effective drug Harvoni® (Table 3.1).

A problem with developing drugs to treat HCV is that this virus has six major strains (genotypes) and some drugs are active against one genotype but not others. The first protease inhibitors boceprevir, telaprevir, and simeprevir are active only against genotype 1, which is the most common strain in the United States. Types 1-3 are worldwide with 4 and 5 primarily in Africa and 6 in Asia. Because of relatively high HCV infection rates in China and other sites in Asia, drugs active against only type 1 were inadequate for the worldwide pandemic. This led to the successful development of drugs active against all genotypes (see Epclusa® and Vosevi®, below). Of the other single-ingredient drugs the polymerase inhibitor sofosbuvir is more broadly active, it is effective against types 1 - 4 whereas daclatasvir is active against type 3. These two often are used together but not in a single dose form. Combination dose-form drugs have been the most successful against all strains including genotype 1. For example Viekira Pak® and Harvoni® combine four and two separate drugs, respectively, that act by different mechanisms (Table 3.1) to give high efficacy against genotype 1. Viekira Pak® is unusual in that it contains ritonavir, a drug initially developed to treat HIV. But its role in this combination is as an inhibitor of a liver cytochrome P450 enzyme and thereby to prevent the rapid metabolism of the ingredients active against HCV.

Technivie®, another combination with ritonavir, and Zepatier® provide coverage against genotype 4 but it was not until recently that drug combinations were achieved and approved to treat all genotypes, including type 6. Epclusa, a combination of sofosbuvir and a NS5A inhibitor (Table 3.1) was approved in 2016 and gave cure rates ~95% for all genotypes. Addition of a protease inhibitor gave the combination named Vosevi®; this combination inhibits all three of the HCV target enzymes mentioned above. In contrast, Mavyret® combines inhibitors of only the protease and the NS5A protein. Both have the benefit of the components being combined into a single table that is taken only once per day. Vosevi® probably approaches the ideal HCV drug that can cure virtually all HCV patients. It comes as a single tablet taken once per day for no more than 12 weeks to cure a chronic viral infection in nearly all patients.

Influenza viruses

There has been but one new drug approved in the United States to treat influenza during ISAR's third decade. Rapivab® (peramivir injection) has a mechanism similar to the influenza drugs Tamiflu® (oseltamivir) and Relenza® (zanamivir) approved in 1999, namely inhibition of the viral neuraminidase. It has the advantage of being administered as a single dose but it must be given as an intravenous solution.

There are exciting new developments and a new mechanism of action with influenza drugs, but none have yet been approved for use in the United States. Xofluza® (baloxavir marboxil) was very recently approved in Japan and is under review by the FDA. It acts via a new mechanism by inhibiting a process called viral "cap-snatching". The endonuclease portion of the viral RNA polymerase removes the 5´-terminus from cellular messenger RNA's (mRNA's) to utilize them in the biosynthesis of viral mRNA's. Inhibition of this process prevents viral replication at a point prior to where the neuraminidase inhibitors act. Initial studies indicate that only a single dose of the drug may be needed to treat influenza. Other drugs such as favipiravir and pimodivir also target influenza RNA polymerase but are in earlier stages of development or FDA review.

Human papilloma viruses

In 2006 the FDA approved the first topical botanical as an antiviral drug to treat genital warts. Veregen is a partially purified fraction of a water extract of green tea leaves. It is a mixture of catechins and other green tea components. Catechins are bioflavonoids, polyphenols and antioxidants with evidence of anti-tumor activity and immune stimulation – it does not appear to have specific anti-viral activity. Veregen is specifically indicated for the topical treatment of external genital and perianal warts in immunocompetent adults. It is supplied as an ointment for topical administration.

Herpesviruses

In contrast to the many drugs that were developed and approved in the first two decades of the ISAR to treat various herpesvirus infections, only two were approved in the third decade of our society. One of these approvals was for a new dose form of the first safe and effect herpes antiviral drug, acyclovir. In 2013 the new dose form named Sitavig® was approved for recurrent herpes labialis, cold sores caused by herpes simplex virus type 1. It is unique because of its dose form. It contains acyclovir in a buccal tablet containing a proprietary muco-adhesive. One buccal tablet is applied as a single dose to the upper gum region and held in place with slight pressure for 30 seconds to ensure adhesion and dissolution. The tablet should be applied within one hour after the onset of symptoms and before the appearance of any signs of lesions.

Unlike Sitavig® that is only a new dose form of an old drug, the approval of Prevymis® (letermovir) in 2017 marked the availability of a new drug to treat cytomegalovirus (CMV) infections for the first time since the approval of fomivirsen in 1998. Importantly it heralded the introduction of a drug that acts by a new and unique mechanism. Letermovir acts by inhibition of the CMV "terminase", the three-protein complex responsible for the cleavage of concatemeric viral DNA into genome-length segments and its packaging into virions. Although it has a similar mode of action to experimental benzimidazole nucleosides, it is not a nucleoside but a highly substituted quinazoline analog. It is indicated for prophylaxis of CMV infection and disease in patients that receive a CMV-seropositive allogeneic hematopoietic stem cell transplant. It is available as a tablet for once per day oral administration and as a solution for intravenous injection.

Table 3.1. Antiviral Drugs Approved by the United States Food & Drug Administration during Third Decade of International Society for Antiviral Research*

Drug to Treat Brand Name	Generic Name, Components	Mechanism of Action Target	Company	Year Approved
HIV				
Selzentry	maraviroc	HIV entry blocker, CCR5-gp120	Pfizer	2007
Isentress	raltegravir	HIV integrase (strand transfer) inhibitor	Merck	2007
Intelence	etravirine	HIV NNRTI	Tibotec	2008
Edurant	rilpivirine	HIV NNRTI	Tibotec	2011
Complera®	emtricitabine, rilpivirine, tenofovir disoproxil fumarate	HIV NRTI HIV NNRTI HIV NRTI	Gilead	2011
Stribild®	elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate	HIV integrase (strand transfer) inhibitor Liver CYP3A inhibitor NRTI NRTI	Gilead	2012
Triumeq	abacavir, dolutegravir, lamivudine	NRTI HIV integrase (strand transfer) inhibitor NRTI	ViiV HealthCare	2014
Prezcobix	darunavir cobicistat	HIV protease inhibitor Liver CYP3A inhibitor	Janssen	2015
Genvoya®	elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide	HIV integrase (strand transfer) inhibitor Liver CYP3A inhibitor NRTI NRTI	Gilead	2015

Drug to Treat Brand Name	Generic Name, Components	Mechanism of Action Target	Company	Year Approved
HIV (continued)				
Evotaz	atazanavir, cobicistat	HIV protease inhibitor Liver CYP3A inhibitor	Bristol-Myers Squibb (BMS)	2015
Juluca	dolutegravir, rilpivirine	HIV integrase (strand transfer) inhibitor NNRTI	ViiV HealthCare	2017
Biktarvy®	bictegravir, emtricitabine, tenofovir alafenamide	HIV integrase (strand transfer) inhibitor NRTI NRTI	Gilead	2018
Trogarzo®	ibalizumab-uiyk	monoclonal antibody to cell CD4	TaiMed Biologics	2018
Hepatitis B				
Tyzeka	telbivudine	HBV NRTI	Idenix	2006
Viread®	tenofovir disoproxil fumarate	HBV NRTI	Gilead	2008
Vemlidy	tenofovir alafenamide	HBV NRTI	Gilead	2016
Hepatitis C				
Victrelis	boceprevir	HCV NS3/4A (protease) inhibitor	Merck	2011
Incivek	telaprevir	HCV NS3/4A (protease) inhibitor	Vertex	2011
Sovaldi	sofosbuvir	HCV N NS5B polymerase inhibitor	Gilead	2013
Olysio	simeprevir	HCV NS3/4A protease inhibitor	Janssen	2013

Drug to Treat Brand Name	Generic Name, Components	Mechanism of Action Target	Company	Year Approved
HCV (continued)				
Viekira Pak®	ombitasvir, paritaprevir, ritonavir dasabuvir	HCV NS5A protein inhibitor HCV NS3/4A (protease) inhibitor Liver CYP3A inhibitor HCV NN NS5B polymerase inhibitor	AbbVie	2014
Harvoni®	ledipasvir, sofosbuvir	HCV NS5A protein inhibitor HCV N NS5B polymerase inhibitor	Gilead	2014
Technivie®	ombitasvir, paritaprevir, ritonavir	HCV NS5A protein inhibitor HCV NS3/4A protease inhibitor Liver CYP3A inhibitor	AbbVie	2015
Daklinza	daclatasvir	HCV NS5A protein inhibitor	BMS	2015
Zepatier®	elbasvir, grazoprevir	HCV NS5A protein inhibitor HCV NS3/4A protease inhibitor	Merck	2016
Epclusa	sofosbuvir, velpatasvir,	HCV N NS5B polymerase inhibitor HCV NS5A protein inhibitor	Gilead	2016
Vosevi®	sofosbuvir, velpatasvir, voxilaprevir	HCV N NS5B polymerase inhibitor HCV NS5A protein inhibitor HCV NS3/4A protease inhibitor	Gilead	2017
Mavyret®	glecaprevir, pibrentasvir	HCV NS3/4A protease inhibitor HCV NS5A protein inhibitor	AbbVie	2017

Drug to Treat Brand Name	Generic Name, Components	Mechanism of Action Target	Company	Year Approved
Influenza				
Rapivab®	peramivir injection	Influenza neuraminidase inhibitor	Biocryst	2014
HPV				
Veregen	kunecatechins	Topical botanical, Immunologic	Medigen	2006
Herpes Simplex				
Sitavig®	acyclovir buccal tablets	HSV DNA polymerase inhibitor	BioAlliance	2013
Cytomegalovirus				
Prevymis®	letermovir	CMV DNA terminase inhibitor	Merck	2017

*List extends beyond third decade to include drugs approved in 2006 & 2007 that were not in *The Second Decade* booklet and approvals through March 2018.

Abbreviations and terms used follow.

CYP3A: Human liver cytochrome P450/3A, enzyme that metabolizes several antiviral drugs.
HBV: Hepatitis B virus
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus
HPV: Human papilloma virus, cause of genital warts
NNRTI: Non-nucleoside reverse transcriptase inhibitor
NRTI: Nucleoside reverse transcriptase inhibitor
NN NS5B: Non-nucleoside NS5B RNA polymerase inhibitor
N NS5B: Nucleoside NS5B RNA polymerase inhibitor
NS3/4A: HCV non-structural protein 3, a serine protease
NS5A: HCV non-structural protein 5A transcriptional activator, a protein essential for RNA replication, precise role(s) poorly understood.
NS5B: HCV non-structural protein 5B, a RNA-dependent RNA polymerase

Emerging Viruses

The search for and development of drugs to treat emerging infections caused by viruses such as Ebola, Zika, noroviruses, West Nile encephalitis virus, severe acute respiratory syndrome (SARS) virus, monkey pox virus, etc. have not been ignored and some successes achieved. There also has been activity to develop drugs to counter possible bioterrorism threats using smallpox virus or drug-resistant mutants of other viruses. Because drugs specific for infections caused by these viruses have not been approved by the FDA and due to the conciseness of this overview, the reader must look elsewhere for details, such as the ICAR reports (www.isar-icar.com).

John C. Drach

4. The early days of Antiviral Research

The 30th ICAR, in 2017, marked the 40th anniversary of the publication (Elion et al., 1977) describing the first truly selective antiviral agent. Acyclovir was the first antiviral drug which combined good activity with such an excellent safety profile that it still stands as the benchmark for all other antiviral drugs, even 40 years later. Acyclovir, and its prodrug valacyclovir, are still widely used worldwide. It was time for the antiviral field to have its own dedicated journal, Antiviral Research (AVR, 1981), and its own international meeting (Rotterdam, 1985) at which an international society was proposed. The International Society of Antiviral Research (ISAR) was born shortly thereafter (1987), organizing its first conference at Williamsburg in 1988 (called the 2nd ICAR, since the Rotterdam meeting, although not called as such, was considered to be the "the first" ICAR). Ever since, AVR and ISAR have remained closely inter-linked, each supporting the other.

As ICAR enters its fourth decade, increasing numbers of attendees were born well after the 1980s. Now, it is well known that antiviral drugs, albeit still only a small number, have transformed millions of lives. Before acyclovir, the possibility of safe, effective antiviral drugs was doubted. This introduction illustrates the vision that held a small band of researches together, encouraging each other to push against an apparent glass ceiling.

The year 1981 marked the appearance of the first issue of the new journal, Antiviral Research (AVR), but, ironically, it also marked the birth of the term AIDS (Acquired Immune Deficiency Syndrome). This disease would subsequently, in 1983, be identified as a viral disease caused by the human immunodeficiency virus (HIV, name chosen in 1987), which would later launch worldwide attempts to curb the infection by antiviral (i.e. anti-HIV) agents. For AVR, the advent of HIV and the anti-HIV agents meant an enormous boost.

Vaccination has since the inception of AVR been hailed as the primary measure to combat viral infections in animals and humans, but while the worldwide eradication of smallpox has been rightfully attributed, to a great extent, to a global vaccination campaign, for other viral infections, including poliomyelitis, the final extinction has still not been achieved. Yet, for polio, two effective vaccines have been available for many years: the inactivated, injectable "Salk" vaccine and the oral, live "Sabin" vaccine. Other virus infections, such as yellow fever and measles, still occur despite the presence of effective vaccination measures, and for other widely spread virus infections no vaccines have (so far) been developed (Dengue)* or are even envisaged (HIV).

For hepatitis B virus (HBV) and human papilloma virus (HPV), which were already considered as possible candidates for vaccination in our inaugural Editorial in 1981, effective vaccines have in the meantime arisen. For hepatitis C virus (HCV), vaccination may, given the success of the direct-acting antivirals (DAAs), no longer be needed, and for influenza A and B, a virtual "status quo" has been reached over the past few decades in that the recommended (preventive) approach is based upon annual vaccination with a mix of inactivated influenza A and B virus strains which have to be adjusted yearly according to those strains that are circulating.

In 1981 we anticipated that 'the novel forms of bioengineering' would have a strong impact on the design and manufacture of viral vaccines. We did not have to wait long to see fulfillment of this prediction: the carrier serum-derived vaccine made available in the early 1980s was soon replaced by a formulation containing pure viral proteins produced by recombinant technology. Today vaccine research and development without deployment of molecular biology has become unthinkable. Viral strain identification and characterization by genome sequencing (influenza strains), rapid isolation of emerging viruses (SARS and MERS), monitoring of molecular consistency of classical attenuated vaccines (Sabin's polio vaccine) are examples of the profound transformation that vaccine technology has undergone.

*Footnote: For Dengue, a vaccine (Dengvaxia®) has been approved in some countries.

We also foresaw an exponential increase in our knowledge of the immune defense mechanisms and we expressed the hope that this would open avenues towards 'new forms of antiviral therapy or prophylaxis'. Today our insight in the network of humoral factors, cellular receptors and ligands of the immune system has indeed become infinitely more rich and detailed. But, unfortunately, we have also learned that viruses (e.g. herpes viruses, HIV) have more ways to use this network's intricacy for their own profit than we have means to use them to combat infection.

While interferon, that just had been cloned in 1980, was considered to be a viable approach for the treatment of varying viral infections, its practical use was finally confined to its application (in its pegylated form), combined with ribavirin, in the treatment of chronic hepatitis C. This combination would remain the standard of care (SOC) till 2011, then continued but with the new DAAs added. With the advent of sofosbuvir in December 2013, the combination of peginterferon with ribavirin would become obsolete.

The positive message is that interferon has been of some help for some time, and that we now have both Type I interferons in pegylated formulations, generally assumed to have a more favorable tissue distributions than the 'naked' forms. Moreover, we know that interferon-alpha has definite potential for the treatment of virus infections, in particular those with a protracted course. Therefore, we feel happy to have these preparations on the shelf, ready for use against unexpected emergence of new viruses or in special cases where treatment with antivirals would appear to need some adjuvant.

The use of serotherapy, i.e. the injection of immunoglobulins, considered to be rather unsuccessful in 1981, has remained so over the past few decades, one exception being the monoclonal antibodies tailored for the treatment of respiratory syncytial virus (RSV) infections.

Back in 1981 there were very few antiviral drugs around. These were idoxuridine (IDU) and trifluridine (trifluorothymidine, TFT), launched in 1962 and 1964, respectively, for the topical treatment of herpetic eye infections (i.e. herpetic keratitis). In 1964 amantadine had been discovered as an anti-influenza A agent, but it would never receive wide acceptance for the treatment of influenza, also because it quickly led to the emergence of resistance. Ribavirin was discovered in 1972, and for all the following years it was searching for its niche, which it finally found, in combination with peginterferon, in the treatment of hepatitis C.

In 1976, Whitley and his colleagues reported the use of the first antiviral (vidarabine) ever to be administered systemically in the treatment of varicella-zoster virus (VZV) infections, i.e. herpes zoster. Already announced in our Editorial of 1981 were bromovinyldeoxyuridine and acycloguanosine (in the Editorial misspelled as "acylcloguanosine"). Acycloguanosine would be worldwide known as acyclovir for the (systemic and topical) treatment of herpes simplex virus (HSV) infections, and (oral) for herpes zoster (shingles). Oral bromovinyldeoxyuridine (BVDU) would become licensed in many countries for the treatment of herpes zoster.

What in 1981 at the time of our Editorial could not be anticipated was the advent of HIV, and the explosion of anti-HIV agents it would lead to. Roughly, half of the current armamentarium for the treatment of viral infections exists of drugs effective against HIV (De Clercq & Li, 2016).

Back in 1981 we speculated about the likelihood that specific antiviral substances may originate from "the discovery and extensive characterization of various virus-encoded enzymes". Little did we knew at that time of the discovery of HCV (in 1989), which would reveal the existence of a number of virus-encoded proteins that would serve as the target(s) for a whole new generation of antiviral agents, of the DAAs (Li & De Clercq, 2017), which would revolutionize the treatment of hepatitis C and ensure a cure for this dreadful viral disease.

Acknowledgments

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E. De Clercq

A. Billiau

5. Keeping to the founding aim of ISAR, to present high quality science, across a broad spectrum of antiviral research, at ICAR.

Introduction

During the first few years following the foundation of ISAR, ICAR was *the* international meeting which was solely focused on antiviral research. By the end of the first decade, and even more so at the end of the second decade, ISAR felt the effects of competition from other meetings, some focused on a particular virus, some broad ranging. This report aims to illustrate how many ISAR members, particularly the Program Committee, have worked tirelessly to bring us ICARs filled with a wide spectrum of research in several dimensions, from basic virology to clinical trials, from chemistry to biology, from technology to legal, etc. Undoubtedly, this strategy has helped ISAR remain at the forefront of antiviral research.

Generally, the lectures, given by the recipients of the major awards, have set a high standard (see section 2). The keynote and plenary lectures (see Table 5.1) have sometimes been chosen to present complementary information on a particular virus but more generally have been selected to cover different viruses. The mini-symposia (Table 5.2) may be repeated from one year to another (e.g. clinical, emerging viruses) but often focus on new areas each ICAR. Looking through the tables, one can see the variety of speakers (academia, industry) and their topics. Rather than attempt to give a summary of each lecture, I have selected topics, mainly for their continuing interest through the years. Generally, I have not included examples focusing on early research or on antivirals which have been replaced by newer compounds. These selected topics were reported previously either in the ISAR News or the ICAR meeting reports (www.isar-icar.com).

The Poster sessions have been a feature of ICARs throughout the three decades. Over the years, there has been an enormous spectrum of topics presented by scientists of all ages and backgrounds. To further illustrate the range of topics presented at ICAR, Table 5.3 includes the First Prize winners together with the topics presented.

Highlights from Keynote and Plenary lectures (Table 5.1)

21st ICAR, 2008, Montreal

I remember feeling privileged to hear Takaji Wakita describing the first successful replication of HCV in cell culture in 2005. It is remarkable that HCV, which produces more virus (10^{12} virions/day) in patients than any other virus, has presented such a challenge to replicate in cell culture.

22nd ICAR, 2009, Miami Beach

Christopher Lipinski is well known for his ‘rule of five’ (see below), which actually has only four rules! These were devised having considered 7,483 named drugs. If a candidate compound has any one of these undesirable attributes, consider carefully if it should be progressed. If it has more than one of these properties, it is unwise to progress. The fifth rule might be that there are always exceptions, for example, if the compound is a substrate for a natural transporter.

- Solubility; log P >5
- Molecular weight >500
- Sum of oxygen and nitrogen atoms >10
- Number of hydrogen donors >5

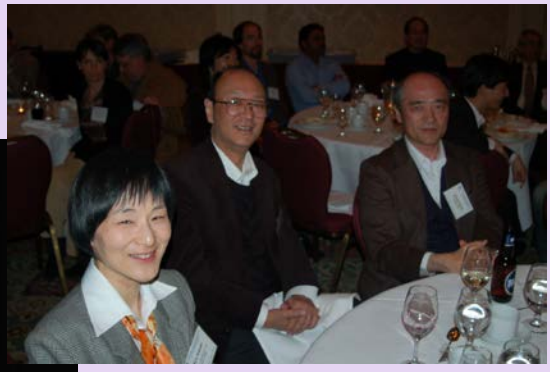
Table 5.1. Keynote and Plenary lectures

Year	Speaker (Affiliation)	Keynote/Plenary address Title
2008	Mark Wainberg (McGill University, Montreal, Canada)	Keynote The next decade of antiviral chemotherapy
2008	Takaji Wakita (National Institute of Infectious Disease, Tokyo, Japan)	Plenary HCV culture system and antiviral development.
2008	Daniel Streblow (Oregon Health and Science University, Beaverton, OR, USA)	Plenary Role of angiogenesis and wound repair factors in the acceleration of allograft rejection by cytomegalovirus.
2009	Christopher Lipinski (Melior Discovery, Waterford, CT, USA)	Keynote Beautiful biology but bad chemistry
2009	Ronald Swanstrom (University of North Carolina, Chapel Hill, NC, USA)	Plenary A strong dominant negative mutation in the HIV-1 Gag protein defines a new drug target
2010	John Martin (Gilead Sciences Inc, Foster City, CA, USA)	Keynote Recent progress in the simplification of HIV therapy and future prospects
2010	Samuel Broder (Celera Corporation Inc, Rockville, MD, USA)	Plenary Celebrating AZT! Antiretroviral drugs from bench to bedside to the world
2011	Albert (ADME) Osterhaus (Erasmus Medical Center, Rotterdam, the Netherlands)	Keynote Emerging virus infections and intervention strategies
2011	Raina Fichorova (Brigham & Woman's Hospital, Boston, MA, USA)	Plenary Vaginal microbicides
2011	Ralf Bartenschlager (University of Heidelberg, Heidelberg, Germany)	Plenary New insights into the hepatitis C virus (HCV) replication cycle and impact on known and novel drug targets
2011	Esteban Domingo (Universidad Autónoma de Madrid, Madrid, Spain)	Plenary Molecular mechanisms of viral resistance to nucleotide analogues and implications for lethal mutagenesis strategies
2012	Hiroaki Mitsuya (National Cancer Institute, Frederick, MD, USA)	Keynote Structure-guided development of AIDS therapeutics: successes, challenges and opportunities

2013	Eva Harris (University of California, Berkeley, CA, USA)	Keynote Know thine enemy: Using virology and immunology to develop a multifaceted approach to dengue antivirals
2013	Bruno Canard (Harvard Medical School, Boston, MA, USA)	Plenary RNA synthesis, capping and repair in (+)RNA viruses, novel targets for drug design
2014	David Margolis (University of North Carolina, NC, USA)	Keynote Eradication therapies for HIV: building the critical path
2014	(Myron Cohen, University of North Carolina, NC, USA)	Keynote HIV prevention 2014–2021: managing aspiration and expectation
2015	Raffaele De Francesco, (Istituto Nazionale di Genetica Molecolare ‘‘Romeo ed Enrica Invernizzi” (INGM), Milano, Italy)	Keynote From the elucidation of the HCV life-cycle to the development of highly effective antivirals.
2015	Michael Manns, (Hanover Medical School, Hanover, Germany)	Keynote Advances in HCV therapies.
2015	Armand Sprecher, (Médicins Sans Frontières, Operational Center of Brussels, Belgium)	Keynote The MSF response to the West African Ebola outbreak.
2016	Richard H. Scheuermann, J. (Craig Venter Institute (JCVI), Rockville, MD, USA)	Keynote Decoding viral genomics in the next-generation era
2016	Heinz Feldmann, (National Institute of Allergy and Infectious Diseases, Hamilton, MT, USA)	Keynote Ebola virus: past, present, future
2017	Ann Palmenberg (University of Wisconsin at Madison, USA)	Keynote The elusive rhinovirus C: Historical context and biological enigma.
2017	Mark A. Pallansch (Centers for disease control and prevention, Atlanta, GA, USA)	Keynote Antivirals at the interface with public health: a case study of polio.
2017	Eric Hunter (Emory vaccine center, Atlanta, GA, USA)	Keynote Impact of transmitted HIV phenotype on host-virus interactions and disease progression - implications for treatment and cure.
2017	Pei-Yong Shi (University of Texas Medical Branch, Galveston, USA)	Keynote Zika virus antiviral and vaccine development.

21st ICAR – Montreal 2008





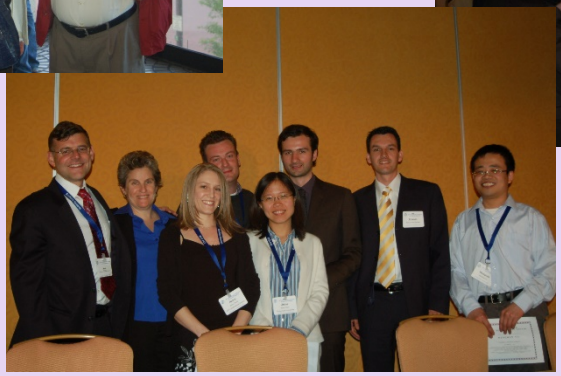
22nd ICAR – Miami Beach 2009





23rd ICAR – San Francisco 2010






24th ICAR – Sophia 2011






25th ICAR – Saporro 2012






26th ICAR – San Francisco 2013

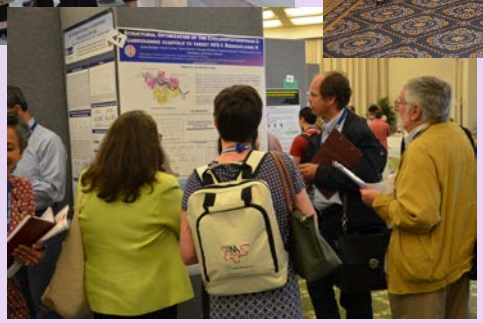




27th ICAR – Raleigh 2014


28th ICAR – Rome 2015



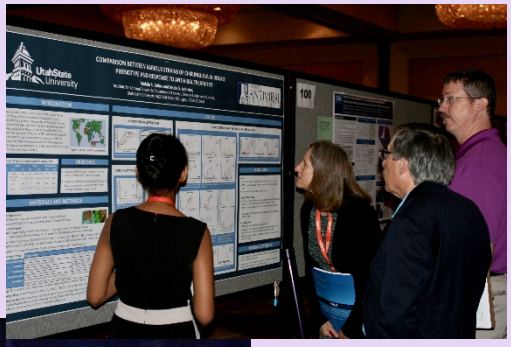




29th ICAR – La Jolla 2016






30th ICAR – Atlanta 2017


23rd ICAR, 2010, San Francisco

John Martin (a previous ISAR President and an Elion awardee) vividly illustrated the gain in patient life-style when fixed-dose combination pills were introduced, from many pills taken throughout the day to a single pill once daily. Truvada (emtricitabine [FTC]/tenofovir disoproxil fumarate [TDF]) and Epzicom (lamivudine [3TC] and abacavir [ABC]) in 2004, and, particularly, AtriplaR (efavirenz [EFV]/FTC/ TDF) in 2006, had a great impact. At that time in the USA, >85% of patients were taking Truvada or AtriplaR.

24th ICAR, 2011, Sofia

The keynote and plenary lectures all reported on research at early stages, Albert (ADME) Osterhaus discussed ongoing work with HIV, human metapneumonia virus (although widespread, discovered only in 2001), monkeypox, measles, West Nile virus and Chikungunya virus, (detected in Italy in 2007). Raina Fichorova described the failures and limited progress of vaginal microbicides in preventing the spread of HIV. Ralf Bartenschlager gave a good summary of the HCV targets for antiviral compounds. As HCV has 6 or 7 genotypes, more than 100 subtypes and each existing as quasispecies, it presents a daunting challenge to any antiviral drug therapy. Yet with no means of viral latency or integration, therapy leading to a sustained virological response (SVR) has the potential for a complete cure. Esteban Domingo considered lethal mutagenesis strategies for those viruses which exist as quasispecies. If the copying fidelity was to become too low, then no viable progeny would be formed.

25th ICAR, 2012, Sapporo

Hiroaki Mitsuya reported on new RT inhibitors being developed, for example, festinavir (Ed4T, 4′ethynyl-d4T) and EFdA (4′ethynyl-2-fluoro-2′deoxy-adenine). Festinavir was first developed at Yale University, USA, licensed to Oncolys BioPharma, a Japanese company, which progressed festinavir to Phase I trials and is now being developed by Bristol–Myers Squibb. It is a once daily RT inhibitor which is active against viruses resistant to both tenofovir and abacavir.

26th ICAR, 2013, San Francisco

Eva Harris described how dengue virus (DENV) has two mechanisms for entry into cells: via receptor attachment and via antibody. The latter mechanism explains how a previous infection can enhance disease progression – instead of antibody binding to the virion and leading it to its inactivation, the bound antibody gives the virus an additional route into Fc receptor-bearing target cells. She illustrated how this knowledge could be used in vaccine design.

27th ICAR, 2014, Raleigh

This is an example when two speakers (David Margolis and Myron Cohen) were asked to give complementary talks on HIV infections. David concluded that elimination of HIV from an individual was still a distant prospect. In contrast, Myron had encouraging news about the prospects for preventing HIV transmission. Most progress was being made with dapivirine rings containing TDF. These had been designed to stay in the vagina for a month. Phase III trials were ongoing. A long-acting HIV integrase inhibitor, GSK 1265744 (generally known as GSK 744), was administered i.m. in a Phase I trial which confirmed that the drug may be administered at 3-month intervals. In the absence of a proven HIV vaccine, pre-exposure prophylaxis (PrEP) with drugs has become the most promising strategy to reduce HIV infection rates among high-risk populations.

Also, in a trial which enrolled 1,763 HIV sero-discordant couples (couples that have one partner who is HIV-infected and the other who is HIV-uninfected), successful anti-HIV therapy was very effective in preventing HIV transmission.

28th ICAR, 2015, Rome

Raffaele De Francesco and Michael Manns were asked to give complementary reports on the great advances recently achieved in drug therapies for HCV infections. There are now various IFN-free options for potential HCV therapies. Although there are different combinations with efficacy against genotypes 1 and 4, only sofosbuvir (SOF)-containing regimens are active against all genotypes (1–6), the best being SOF with daclatasvir. In clinical use, this combination (once daily for 12–24 weeks) shows activity against genotypes 1–4, but initial data indicate that this combination will be effective against genotypes 5 and 6. In Phase III trials, the combination of SOF with Gilead's new NS5A inhibitor (GS-5816) is being tested at once-daily dosing for 8–12 weeks against all genotypes. Other IFN-free combination are currently being tested in Phase II clinical trials aimed at developing what today is considered an aspirational regimen, once daily, single pill, 8 weeks, 100% SVR12 for all genotypes.

Armand Sprecher gave a memorable lecture, to my knowledge unique for ICAR. In 2014, MSF's role in the current Ebola outbreak started on the 13th March with an alert from the Ministry of Health, Guinea asking for help with an outbreak in which an infection in 15 people had led to 9 deaths. On 18th March, a MSF team arrived in Guéckédou. Just 3 days later, the infection was identified as Ebola. On 23rd March, just 10 days after the initial alert, MSF opened their Ebola treatment unit (ETU) in Guéckédou. On 25th March, the Liberian Ministry of Health notified MSF of four Ebola deaths. The next day, MSF set up an ETU in Macenta which is in Guinea but close to the border with Liberia. The next day (27th March), four Ebola cases were identified in Conakry, Guinea. On 1st April, MSF opened their ETU in Conakry. By this time, MSF had sent 60 staff out into the field. About three weeks later (26th April), MSF opened their ETU in Liberia. To my mind, the speed of this response is truly impressive.

Of 5176 confirmed cases of Ebola infected patients being cared for in MSF centers, there were 2449 survivors. Although the epidemic has had a huge human cost, there is a great joy every time a survivor leaves to go home. Armand Sprecher's conclusion ''Let's not do this again".

29th ICAR, 2016, La Jolla

Richard Scheuermann illustrated how the much improved viral genome sequencing has open up a new area of research – old questions can now be answered. Prior to 2004, only 60 complete influenza A genome sequences were known. As of 6th April 2016, a total of 31,460 complete influenza genome sequences were known, of these, 28,308 were for influenza A, nearly 20,000 of these being sequenced by JCVI. Using these large databases, it has been possible to follow how adaptive immunity drives influenza A virus evolution during a pandemic and the identification of virulence determinants (causing paralysis) of enterovirus D68 during the outbreak in the USA (mid-August 2014 to mid-January 2015).

Heinz Feldmann described the ongoing efforts to improve the outcome of any future Ebola outbreak: strengthening public health, improving community awareness, negotiating cross-border co-operation and continuing international support. Although the rVSV-EBOV vaccine was deemed to be safe to use, there were unwelcome side effects – however, it was highly effective in preventing Ebola disease, apparently providing protection within 10 days in a ring vaccination trial (index case contacts and their contacts vaccinated). Two virus polymerase inhibitors may have useful efficacy. Favipiravir was tested in Guinea towards the end of this outbreak.

There seemed to be a benefit to those patients who had low or moderate base line viral loads. GS-5734 was much more active than favipiravir against Ebola in a nonhuman primate model, but no clinical data were available. However, GS-5734 is a very promising drug for any future Ebola outbreak. We need to have adequate stockpiles of drugs and vaccine. This has been by far the worst Ebola outbreak but we now have some tools to limit any future Ebola outbreak.

30th ICAR, 2017, Atlanta

Ann Palmenberg explained how rhinovirus-C (RV-C) had remained "hidden" for 5 decades. It is widespread and associated with children who have severe asthma. Preliminary information suggested an emergence of RV-C, from RV-A, about 3-5,000 years ago. The receptor for RV-C is cadherin-3 (CDHR3). There are two variants, Tyr_{529} which is the ancestral protein and Cys_{529} which appears to be unique to our human race. However, the Cys_{529} variant first appeared in modern humans a long time ago, being detected in some ancient modern-human remains which were discovered in Africa. The dates showed that Cys_{529} was already present within the human population before the "out of Africa" event, around 50,000 years ago, but this could not have been under evolutionary pressure from RV-C. The first study of genome-wide ancient DNA (~8500-3000 years before present) was from Anatolian Neolithic farmers, who became Europe's first farmers. Within that Anatolian population, 25% had the Cys_{529} variant, 75% had the Tyr_{529} form. In samples from central Europe dating about 1000 years before present, the proportions had reversed (85% and 15%, respectively). In modern times, the majority of humans have both genes for the Cys_{529} protein, ranging from 53% in Africa to 87% in Asia, with the Americas (75%) and Europe (68%) having intermediate values. Could it be that RV-C, having evolved, was putting pressure on human evolution?

Pei-Yong Shi considered that lifetime immunity after a single dose is a feature that is critical for a successful Zika vaccine. He discovered that deleting a 10-nucleotide section from the three prime untranslated region (3'UTR), (10-del ZIKV) gave a highly attenuated virus, perhaps suitable as a vaccine. He gave the results obtained in many tests for safety and efficacy. In pregnant mice, the vaccine prevented *in utero* transmission of Zika virus. In male mice, the vaccine prevented prolonged infection in testis and protected against testis damage. These studies have addressed two major concerns arising from clinical studies. This Zika vaccine may be one of only a few game-changing therapies described early during its evaluation at ICAR – I understand that, since the 2017 ICAR, this vaccine has been selected for progression.

Highlights and comments on Mini-symposia (Table 5.2)

21st ICAR, 2008, Montreal

Some mini-symposia, such as that on HIV targets, discussed early research options which did not lead to useful therapies. Likewise, some antiviral compounds, such as apricitabine (NRTI) seemed to be highly effective against HIV with a high genetic barrier to viral resistance and a good safety profile, but disappeared after several years of development. In contrast, tenofovir (TFV) was reported to be more effective against HBV than adefovir and it became the drug of choice for treating chronic HBV infections.

Although not part of the Clinical symposium, the activity of ST-246 against poxviruses was reported. Plasma levels of ST-246, at 500 mg, suggested that once-a-day dosing should be possible. Comparing the monkey and human PKs, good activity against poxviruses in humans should be readily achievable. ST-246 was well tolerated. We were to hear more of ST-246 in later ICARs.

Table 5.2. Mini-symposia

Year	Title of mini-symposium
2008	Novel targets for HIV therapy
2008	Clinical symposium: clinical update on antiviral drugs
2009	Development of novel therapies for hepatitis C virus (HCV)
2009	Clinical symposium: clinical update on antiviral drugs
2009	Perspectives and challenges in the development of topical microbicides
2010	Antiviral drug resistance
2010	Clinical symposium: clinical update on antiviral drugs
2010	Prodrug chemistry and antiviral drug development
2011	Emerging diseases and antiviral therapy
2011	Medicinal chemistry and drug discovery
2011	Clinical symposium
2012	Clinical symposium
2012	Therapy of infections endemic to Japan and Asia
2012	Clinical development of antiviral agents
2012	Building a better clinical candidate: issues, strategies and tools
2013	The legacy of Antonín (Tony) Holý: Nucleotides in the treatment and prevention of chronic viral infections
2013	Clinical symposium
2013	Chemistry: Strategies and tactics in drug design
2013	Chemistry: Prodrugs as tools in drug discovery and development
2014	Hepatitis B virus
2014	Research Triangle Park
2014	Challenges in HIV infection, treatment and prevention
2015	RNA viruses
2015	Antiviral chemistry
2015	Emerging viruses
2016	Structural biology
2016	Zika virus
2016	Diagnostic technologies
2016	DNA viruses
2017	Antiviral immunity
2017	Emerging infections

22nd ICAR, 2009, Miami Beach

Of the various targets discussed during this mini-symposium on HCV, the HCV NS5A protein became the most important drug target. This was ICAR's introduction to NS5A as a drug target. Previous work had implicated domain I having a key role in viral RNA replication. Another major drug target, not discussed here but well known, is the viral polymerase.

In the Clinical session, there was an update on the efficacy of tenofovir against HBV infections. There were reports on various other less important drugs, for example a Phase I trial in healthy patients with CMX001 (hexadecyloxypropyl prodrug of cidofovir).

23rd ICAR, 2010, San Francisco

In the mini-symposium on viral resistance, there were reports on HIV, HCV and on improvements to the detection of resistance. Over the past decade, the proportion of HIV patients receiving three classes of drugs (nucleoside reverse transcriptase inhibitor [NRTI], non-nucleoside reverse transcriptase inhibitor [NNRTI] and protease inhibitor [PI]) has increased. Having combination therapy, particularly when available as a single-pill therapy, had greatly reduced the problems of HIV resistance in the clinic.

In clinical trials with HCV patients, resistance to PIs and NNRTIs occurs very quickly, within 3–7 days. Whereas PIs and NNRTIs have varying activities against different HCV genotypes, NRTIs are active against all HCV genotypes. A clinical trial, tested the combination of an NRTI (R7128, 1,000 mg twice daily) with a PI (R7227, 900 mg twice daily). Over a 14 day dosing period, the viral load fell by 4–5 $\log_{10}$ IU/ml. Virus resistance studies suggested that there was no resistance to R7128.

The clinical symposium included updates on two HIV therapies apricitabine and a quad tablet, containing elvitegravir (EVG, 150 mg), emtricitabine (FTC, 200 mg), TDF (300 mg) and cobicistat (150 mg). CMX001 was being evaluated for prophylaxis or treatment of CMV, tenofovir in three year safety and efficacy study in chronic HBV and famciclovir (either as a single dose or twice in one day) in recurrent HSV infections. There was one novel therapy, a DNA vaccine derived from two plasmids corresponding to gB and pp65 proteins of CMV. The vaccine reduced various measures of CMV infection in transplant patients: the time to initial viral detection was prolonged, the duration of viremia was decreased, peak viral load was decreased and the viral load AUC was reduced by 40%.

24th ICAR, 2011, Sofia

The emerging diseases mini-symposium included talks on Japanese encephalitis, Congo hemorrhagic fever (CCHF), the potential of RNA capping as a target for antivirals against (+)RNA viruses and the use of filovirus-virus like particles (VLPs) which offer a safe alternative to working with viruses such as Marburg and Ebola.

The drug discovery mini-symposium included the compound which was to become the game-changer for HCV therapy. Michael Sofia (Pharmasset, USA) started his presentation with the comment that, to his knowledge, there was no link between his surname and the site of this ICAR (Sofia, Bulgaria). He described the results from the Phase IIb clinical trials for HCV therapy using the guanosine analogue, PSI-352938, and the uridine nucleotide analogue, PSI-7977, either alone or combined, treating for 14 days. All groups gave a good reduction in HCV load (approximately 5 $\log_{10}$) but the viral load dropped slightly more rapidly with the combination therapy, the best seen so far in HCV clinical trials. As the combination of PSI-7977 and PSI-352938 is able to clear HCV in cell culture systems and shows promising preliminary human clinical results, it is hoped that further trials will show that it will result in SVRs in patients without using IFN (see below).

The clinical symposium included talks on three compounds which were to become approved drugs.

CMX001 is a prodrug for cidofovir (see above) and has a plasma half-life of 6.5 days. It is being developed for therapy of the DNA viruses, adenovirus and HCMV, and as a biodefence against poxviruses. It is also active against papillomaviruses, which do not encode a viral DNA polymerase, but viral resistance maps to the viral protein, large T antigen (LTAg), which is required for viral DNA replication.

The currently approved prodrug of tenofovir (TFV) is tenofovir disoproxil fumarate (TDF), which is widely used in HIV therapy, mainly as part of the single-tablet regimen AtriplaR. TDF improves the oral bioavailability of TFV in plasma, but targeted delivery of TFV into cells could further enhance treatment efficacy, yet may reduce the risk of renal and bone effects by lowering the plasma concentrations of TFV. A series of amidate prodrugs of TFV was synthesized and GS-7340 was selected (later, known as TAF). Short-term monotherapy with GS-7340 (either 50 mg or 150 mg) was more effective than TDF (300 mg) in treatment-naive HIV-infected patients. Reduced systemic exposure is likely to reduce the risk of TDF-associated toxicities. As TDF is part of combination regimens used extensively as the backbone for HIV therapy, GS-7340 is well positioned to potentially replace TDF as the standard prodrug of TFV (see below).

AIC246 (formerly ST-246, see above) was initially discovered to be active against poxvirus. At this ICAR, the activity (EC_{50} approximately 5 nM) was reported to be highly specific for HCMV, whilst not active against murine CMV. The dose–response curve is unusually steep, the EC_{90} being approximately 7 nM. The mechanism of action is via inhibiting the HCMV terminase complex, consisting of UL56, UL89 and UL104, which cleaves HCMV progeny DNA into unit genome lengths as the viral DNA is packaged into virions. As there is no comparable human cell complex, there is potential for high selectivity. As current HCMV therapies all target the viral polymerase, no cross-resistance would be expected. Of 10 Phase I trials planned, 9 have been completed.

25th ICAR, 2012, Sapporo

The clinical symposium included an update on AIC246, then known as letermovir. However, this session was notable for the presentation by Michael Sofia *(Gilead Sciences Inc., Princeton, NJ, USA)* on GS-7977, formerly known as PSI-7997, a nucleotide prodrug for the treatment of HCV. The ELECTRON Phase IIb trial proved to be a game-changer for HCV therapy. There were initially four groups, with a GS-7977 monotherapy group added later: GS-7997 +RBV for 12 weeks; GS-7977 +RBV+PEG-IFN to week 4, then GS-7997 +RBV to week 12; GS-7977 +RBV+PEG-IFN to week 8, then GS-7997 +RBV to week 12; GS-7977 +RBV+PEG-IFN to week 12; GS-7977 monotherapy for 12 weeks. The first four groups all gave 100% SVR, the monotherapy gave 60% SVR. There were no virological breakthroughs. There were no safety issues. How many clinical trials give 100% cure rates?

In another Phase IIb trial, GS-7977/RBV therapy (12 weeks) compared treatment-naïve patients to those previously non-responders to PEGIFN/RBV. Both groups had similar reductions in HCV RNA load, 100% of patients reaching the limit of detection (LOD) by 4 weeks and remaining below LOD to week 12. At four weeks after therapy, the proportions of patients achieving SVR were 10/10 and 1/9, respectively. Future studies in patients, who were previously non-responders, will evaluate longer treatment times and combinations with other antivirals.

The three mini-symposia (therapy of infections endemic to Japan and Asia, clinical development of antiviral agents and building a better clinical candidate: issues, strategies and tools) gave good summaries of the early research in these areas.

26th ICAR, 2013, San Francisco

This ICAR opened with a full session on “The legacy of Antonín (Tony) Holý: Nucleotides in the treatment and prevention of chronic viral infections”, led by Erik De Clercq (Rega Institute, Belgium) and John Martin (Gilead

Sciences, USA), both past presidents of ISAR. Erik described their 3-way collaboration, Tony the chemist, Erik a medic and John with his industrial experience. Their collaboration was surely nurtured by their regular attendance at ICAR – Erik showed a photograph of the three of them "at work" above the Rio Grande Gorge, New Mexico in 1995, when ICAR was in Santa Fe. It was tenofovir, in its various prodrug forms, that was to become a major success for treating HIV-infected patients. These collaborators also initiated work on a single-pill, once daily, regimen. This led to AtriplaR being approved in 2006 – a therapy which transformed patients' lives. The collaboration has had another major success, enabling HIV-infected patients anywhere to be treated with tenofovir through the Expanded Access Program established by Gilead. Both Tony and Erik waived their royalties for sales in countries with poor access to health care. Tenofovir (as TDF or TAF) has also become the treatment of choice for HBV-infected patients. For further information, see Erik's tribute below.

The clinical symposium included topics which appeared important at the time but have now been overtaken by newer therapies; drug candidates (HCV), a dual CCR5/CCR2 antagonist and a single-tablet (HIV). In contrast, CMV resistance profile of CMX001 remains of interest; the prior use of ganciclovir (GCV), which is most likely to lead to resistance mutations in the UL97 gene of CMV, will not compromise subsequent therapy with CMX001. In contrast, previous therapy with cidofovir (CDV), when dosage may be limited by toxicity, should be avoided. Instead, CMX001 should be used for patients failing on GCV therapy.

Both mini-symposia, "Chemistry: Strategies and tactics in drug design" and "Chemistry: Prodrugs as tools in drug discovery and development" signal a shift towards including more chemistry at ICAR, inspired by Phil Furman who became president after the previous ICAR. Although most topics were at an early research stage, Mike Sofia gave an update of sofosbuvir. A new clinical trial, testing a combination of sofosbuvir and daclatasvir (BMS790052, NS5A inhibitor), gave 100% SVR. Sofosbuvir has been combined with ledipasvir (GS5885, NS5A inhibitor) as a single pill and is now starting Phase III trials. Sofosbuvir was likely to be the first anti-HCV nucleotide analog to reach the marketplace.

27th ICAR, 2014, Raleigh

The hepatitis B virus mini-symposium included good updates on a range of topics but one stands out having current interest. Over the previous few years, there had been much progress towards understanding the critical role of the HBV core protein – it is much more than just a protective coat for the genome because it plays a major role in the HBV life cycle. The core protein, being 183 amino acids long, is known as Cp183. The first 149 amino acids are involved in core assembly whereas the last 34 residues, rich in serines and arginines, bind to RNA. Phosphorylation of the serines, particularly S155, S162 and S172, is required for specific packaging of full length HBV RNA complexed to the polymerase (reverse transcriptase – pregenomic RNA; RT-pgRNA). This RT-pgRNA complex initiates encapsidation.

There was a special session on local activity in Research Triangle Park. One report was on the novel nucleoside analog BCX4430 which exhibits broad-spectrum antiviral activity and confers post-exposure protection against Ebola and Marburg viruses. Even in the current Ebola epidemic in West Africa, care workers were becoming infected and dying. Drugs, which are being investigated for treating these diseases, are progressed under the FDA ''Animal Rule''. In cell culture assays, BCX4430 is active against Ebola and Marburg viruses, (EC_{50} ca 1 μM).

Although a report on Truvada [a combination pill containing TDF and emtricitabine (FTC)] was included in this session, please see the following session.

Challenges in HIV. A cure for HIV infections seemed to be a distant prospect. In contrast, preventing transmission of HIV is a proven possibility. Truvada was taken once daily to prevent HIV transmission, known as pre-exposure prophylaxis (PrEP). Although the adherence rates were unexpectedly poor, that minority of patients, who took essentially all their pills, were well protected. Whereas daily dosing seems to be acceptable for patients living with HIV, another option for PrEP is desirable.

Since 2005, rhesus macaque models have been used in a long series of investigations. GSK-1265744 (generally known as GSK-744) is an HIV integrase inhibitor. It can be formulated with nano-particles to provide an injectable drug depot. In the macaque model, GSK-744, injected once monthly, gave full protection against repeated rectal and vaginal exposures. Because metabolism of GSK-744 is much slower in humans than macaques, it was expected to remain effective in humans for up to three months. A Phase I study confirmed that drug levels remained above the predicted effective level with a 20-week dosing interval. A Phase II trial is planned. Another approach is to use vaginal rings, which have been in clinical use as contraceptive devices for years. In the macaque model, TDF-containing rings, replaced every 4 weeks, gave full protection. A Phase III trial has just been initiated.

Another option, elvitegravir (EVG) and TAF, are being evaluated in a biodegradable polymer.

28th ICAR, 2015, Rome

The session on RNA viruses included a wide range of viruses: norovirus, rabies, dengue, hepatitis E, Hepatitis C and respiratory syncytial virus (RSV).

Antiviral chemistry mini-symposium updated work by Chris Meier (University of Hamburg, Germany). At previous ICARs, he had reported on his cycloSal approach to deliver the nucleoside monophosphate (NMP) into a cell. Although there are many compounds which have poor antiviral activity due to inefficient phosphorylation to the monophosphate (MP), the limiting step may be at the phosphorylation to the di- or tri-phosphate (DP, TP). The focus of this presentation was the development of a strategy to synthesize prodrugs of nucleoside triphosphates (NTPs). Chris was able to demonstrate that such masked NTPs can enter cells and regenerate the TP inside cells, although further optimization would be desirable. This work opened the door to a new area of research, investigating nucleotide triphosphates which are inactive in cell culture assays but which are highly active as inhibitors of viral polymerases.

Emerging viruses session included chikungunya, viruses in the Balkans, Crimean-Congo hemorrhagic fever virus (CCHFV), tick-borne encephalitis virus (TBEV), West Nile virus (WNV) and Middle East respiratory syndrome (MERS).

29th ICAR, 2016, La Jolla

The structural biology symposium included three topics, on HIV, coronaviruses and Ebola, all describing early-stage research.

The symposium on diagnostic kits was a new venture for ICAR, a good innovation. It was introduced by Mark Prichard. For many years, there seemed to be little progress - as there were no antiviral compounds to treat specific viruses, there was no market for diagnostic assays - no assays, no way to develop a specific antiviral. Recently, technological developments in assays have broken this negative cycle. Having used one of the platforms in his diagnostic laboratory for 16 months, Mark commented that he had no idea that there were so many cases of adenovirus infections in the pediatric population in the hospital. He recruited 6 firms to describe their assay platforms

All the presenters gave an account of their diagnostic assays, not just the machinery but also the science and techniques used within the diagnostic platform. Most manufacturers have devised instruments which are small in size, moderately to easily portable, easy to set up and simple to operate. Sample preparation varies between simple and none required. Most steps are automated and the results, often in just over 1 h, are presented in an easily-understood format. Several firms offered panels which included both viral and non-viral agents, selected because these cause a particular set of clinical symptoms. The aim is to make it easy for the physician to choose the correct test first time and avoid having several tests in sequence. Many of the assays and panels are approved by the USA

FDA (Food and Drug Administration). With such rapid progress being made, it seems that physicians are close to having bedside answers within an hour.

The DNA viruses symposium started with a review of human adenovirus (HAdV), its 7 species and many serotypes. Adenovirus infections become a major clinical problem in transplant patients. There are no highly effective antivirals, but brincidofovir (BCV, CMX001), appears to have a better safety profile than its parent compound, cidofovir, although data in immunocompromised patients are limited.

Papilloma viruses encode HPV16 oncogenes (E6 and E7) which have been studied in HPV16-transgenic mice. It is also possible to study the effect of host factors, in particular, the potential of estrogen to act as a co-factor. Without an inserted estrogen pellet, no cancer was detected. It was discovered that estrogen contributed to the progression of cervical cancer. Furthermore, if the estrogen pellet is removed, the cancer regresses. Although the role of estrogen in human cervical cancer remains to be demonstrated, the known risk factors (HPV + oral contraceptives, HPV + many pregnancies, HPV + hormone replacement therapy (HRT)) all point towards estrogen being a factor.

CMV is one of the largest and most complex of human viruses. In this report, samples (48) from 18 patients were obtained from various sites (including urine, plasma, saliva) and deep sequenced. From 4.1×10^{10} CMV bases sequenced, 859,441 single nucleotide polymorphisms (SNPs) were detected, of these, 153,975 were polymorphic sites. This diversity is markedly more than for other herpes viruses, (Epstein-Barr virus (EBV), HHV-6A or HHV-6B) and also the RNA virus, West Nile Virus (WNV). The prevalence of pre-existing drug resistance alleles were around 1% for a panel of drugs, including those currently approved and three in development. In the viral DNA polymerase gene (UL 54), there were resistance alleles for GCV, foscarnet (FOS) and CDV. It is similar for the genes encoding the viral kinase (pUL97) which phosphorylates (activates) GCV and is inhibited by maribavir (MBV), for the viral terminase (pUL56) which is inhibited by letermovir (AIC246), and for the target epitope (pUL 75) for the monoclonal antibody, MSL-109.

30th ICAR, 2017, Atlanta

Emerging infections mini-symposium included reports on GS-5734 and Lassa fever,

During the recent Ebola outbreak, in collaborated with researchers at Gilead Sciences, the novel antiviral compound GS-5734 was shown to have activity against Ebola virus. GS-5734 was also tested against lethal Nipah virus infection in nonhuman primates

Another group reported that GS-5734 was active against circulating human CoV in various assays (*in vitro* and *in vivo*). Therefore, it has the potential to be effective against MERS-CoV in the Middle East and, hopefully, emerging CoV of the future.

Lassa virus, which causes Lassa fever, is endemic in a region across West Africa. A VSV (vesicular stomatitis virus)-based Lassa vaccine, similar to that for Ebola, was effective in challenge models against clade 4 and 5 viruses but a lack of models for clades 1, 2, and 3 has slowed further laboratory investigations. Nevertheless, the VSV-Lassa vaccine is considered a frontline candidate. Although ribavirin is considered to be the standard therapy for Lassa fever, treatment of guinea pigs and non-human primates with favipiravir demonstrates superior protection from lethal disease. Furthermore, in the guinea pig model, favipiravir reverses signs of advanced disease even when treatment is initiated at 9 days post-infection, typically within 36-48 hours. As favipiravir is already licensed for treating influenza infections in some countries, these results support further trials in treating Lassa fever in humans.

Posters: Spectrum of topics illustrated by award winners (Table 5.3)

Over the years, there has been an enormous spectrum of topics presented by scientists of all ages and backgrounds. In particular, ISAR has encouraged younger researchers (students, Ph.D. and young investigators) by offering prizes for the best posters and their presentation. Each year, a hard-working team of senior ISAR members have had the difficult task of judging the posters, many of which have been of similar high standard. It has been so difficult to judge the relative merits of posters prepared by scientists from different disciplines. In some years, this problem was resolved by having joint winners. To further illustrate the range of topics presented at ICAR, particularly from the younger generation, Table 5.3 includes the First Prize winners together with the topics presented. The poster titles are not included as many were very long.

Table 5.3. Poster awardees and their topics

Date Category	Author	Poster topic
2008 Student Ph.D. Investigator	 Leen Delang Ester Ballana Zhengqiang Wang	 Mevastatin potentiates the HCV activity of inhibitors. AlphaV integrin-mediated adhesion of macrophages vs HIV From RT inhibitor to RT/IN dual inhibitor
2009 Student Ph.D. Investigator	 Tilmann Schulz Sophie Duraffour Dirk Daelemans	 Bioreversible protection of nucleosidediphosphates Selection of HPMPDAP-resistant Camelpox A Llama antibody inhibits HIV Rev multimerization *in vitro*
2010 Student Ph.D. Investigator	 Edwin Rios Morales Dimitri Topalis Dirk Roymans	 Diastereoselective synthesis of pronucleotides Is the Large T Antigen a target for SV40? Small-molecule inhibition of RSV fusion
2011 Student Ph.D. Investigator	 Marcella Bassetto Tania Matamoros Karine Alvarez	 Computer-aided design of anti-CHIKV compounds Excision of AZT & d4T altered by deletions in HIV-1 RT Phosphoramidate dinucleosides as inhibitors of HCV
2012 Student Ph.D. Investigator	 Marcus Schroeder Edwuin Hander Rios Morales Bart Tarbet	 Deoxyhypusine synthase inhibitors vs HIV-1 Synthesis and activity of cycloSal-pronucleotides Efficacy of Fluzone and Flumist in mice
2013 Student Ph.D. Investigator	 Annelies Stevaert Hendrik Jan Thibaut Yanming Du	 Influenza mutants to show binding of compound Enterovirus capsid Antivirals vs hemorrhagic fever viruses
2014 Student Ph.D. Investigator	 Pietro Scaturro Fang Gao, Benjamin Morin Uma Singh Sharon Tamir	 Dengue virus capsid inhibitor Sting agonist induces immune response against HBV Inhibitors for (-)RNA virus polymerase Synthesis of FMCA & FMCAP as anti-HBV agents Anti-influenza activity of KPT-335

Date Category	Author	Poster topic
2015 Student Ph.D. Investigator	 Namn Cheung, Ilane Hernandez-Morales, Obiaara Ihenacho, Michael Norris, Hannah Peters, Matthias Winkler Roger Badia Dimitrios Topalis	 RNA respiratory viruses, Antiviral for dengue virus, HIV NNRTI, Respiratory syncytial virus, Anti-coronavirus activity, Synthesis of ribavirin-phosphoramidites ST7612A1 as an HIV-1 latency reactivation agent Resistance to nucleotides in HPV-positive cells
2016 Student Ph.D. Investigator	 Michael Norris Paula Ordonez Suarez Radim Nencka	 Respiratory syncytial virus Anti-HIV activity of nucleotide analogues Broad-spectrum antiviral agents
2017 Student Ph.D. Investigator	 Tiffany Edwards, Edurne Garcia-Vidal Therese Ku Sietske Speerstra Matthias Winkler Marcella Bassetto, Evelien Vanderlinden with Johanna Hutchting Leen Delang	 Inhibition of HBV Acitretin as a novel strategy to clear HIV reservoir Flexible purine analogue inhibitors of NCp7 Broad-spectrum antiviral molecules Nucleoside triphosphate-prodrugs against HCV Thienopyrimidines as antivirals against Zika Virus Anti-influenza activity of T-705 and T-1105 Can drug-resistant chikungunya virus be transmitted by mosquitoes?

What has ICAR meant to me?

My first contact with ICAR was indirect – I was a joint author of a poster presented by a colleague at the 2nd ICAR in Williamsburg (April 1988). In June that year, I presented a poster at Antivirals 88 in Helsinki, Finland, this being my first antiviral conference. I was made to feel so welcomed into the antiviral world by an elderly gentleman, Bill Prusoff. Of all the attendees, it was Bill whom I remember most clearly, creating a deep impression. I had the good fortune to meet Bill many times over the years. As always, he was a charming companion.

The 3rd ICAR was in Brussels, Belgium in 1990, where I met Erik De Clercq who was to become a life-long friend. Over the years, I have been fortunate to have joined the "25 ICARs club". During those early years, Wellcome, with acyclovir, and Beechams, with famciclovir, were rivals. But Trudy Elion set the "ICAR culture" that good science was the top priority. We Beecham scientists had read every word of the Elion papers and were much impressed by the group who had shown how acyclovir could have good efficacy but retain an excellent safety profile by being activated by a herpes viral thymidine kinase enzyme. Trudy's interest and kindness led to my long-term friendships with scientists from Wellcome and Roche. To this day, ICAR retains that friendly culture.

At the 19th ICAR in San Juan (2006), I was asked by Hugh Field (a past President) to join the Publication committee and Jack Secrist (then President) accepted Hugh's suggestion that I take over the job of writing the meeting reports – I had a hard act to follow, Kirk Field having done so for several years. I am grateful to Hugh and Jack for starting me on this path, and for the five following ISAR Presidents for their support. Most of the main presenters have kindly sent me copies of their slides and I have incorporated their comments into my reports.

Although this has taken a lot of my time, I feel that I have gained a much greater understanding of those presentations, greatly broadening my antiviral base. Also, I have become aware of various trends.

For me, the clinical symposium was one of ICAR's highlights. Our early research work should lead, albeit indirectly, to new therapies which help our brothers and sisters around the world. As times changed, less firms were willing to send staff to ICAR to present the results of their clinical trials. The last clinical symposium (2013) was disappointing (see above). Since that time, there have been some of the most exciting clinical trials ever. In December 2013, the FDA approval of sofosbuvir signaled the end of IFN-containing therapies for HCV. Various combinations of drugs, usually containing sofosbuvir, have had cure rates either close to 100% or even 100% for some cohorts. Surely ICAR has both a responsibility to report these land-mark results and to celebrate these great achievements. Likewise, the prospects, for prevention of HIV transmission, look bright, Truvada^{R} has proved that the prevention of HIV transmission is possible but that once-a-day dosing was not acceptable; the use of long-acting drugs (once a month to a few times/year) has the potential to vastly reduce the number of newly-infected HIV patients. I hope that the ISAR Program committee will reinstate the clinical symposium and restore the quality by choosing speakers to invite.

There have been many excellent presentations at ICAR but there are a few that excited me so much that I remember them still – my "Top Ten". The inaugural Prusoff Award lecture (2001) was by Chris McGuigan who set a new standard of clarity, exciting delivery and great science. At his first ICAR as President (2007), he gave a similarly stimulating lecture (see tribute by Andrea Brancale). My next entry is a combination of presentations on sofosbuvir, starting with Mike Sofia reporting the ELECTRON clinical trial with the first, to my knowledge, having 100% cure rates, Phillip Furman continuing the story with his Elion Award lecture (2015) and Mike Sofia in his Elion Award Lecture (2017). Piet Herdewijn, in the inaugural Holý Award lecture, reported how he used evolutionary pressure to create a new organism incorporating a nucleoside analog, I think the first to do so. Erica Ollmann Saphire (Prusoff Award lecture, 2015) showed how viruses remodel, repurpose and rearrange their few encoded proteins to perform many tasks; her skillful use of colors transformed her slides from pretty pictures to accurate scientific clarity. Douglas Richman (Elion Award lecture, 2016) described the long-acting drugs, cabotegravir (CAB, GSK-744) and MK-8591 (4'-ethynyl-2-fluoro-2'-deoxyadenosine, EFdA). As EFdA inhibits the viral polymerase and CAB is an integrase inhibitor, these two drugs have complementary activities. An injection 2 or 4 times a year could give effective ART for patients with HIV infection or prevent transmission to uninfected subjects. The problems now associated with poor delivery of ART, and hence the potential for HIV resistance, in PBMCs may be largely avoided. The prospect of interrupting HIV transmission holds out hope that the HIV epidemic may be gradually controlled. Another entry is the Prusoff Award lecture (2016) by Jerome Deval. He reported on the efficacy of ALS-8176, the oral prodrug of the nucleoside analog, ALS-8112, in a human RSV-challenge study. The reduction in viral load and symptoms was especially notable when a loading dose was used. The viral load area under the curve (AUC) were reduced by >85% and the symptoms essentially remained at base line. A clinical trial in young children is ongoing. Hopefully, ALS-8176 will be a game-changer for the therapy of RSV infections.

So far, my "Top Ten" has 7 entries. I hope that future ICARs will complete my ten.

Anthony Vere Hodge

6. Outlook for the 4th Decade – a personal view

Key success factors for the first three decades.

From its beginning, ISAR has maintained the following key aspects:

1. Broad spectrum in many dimensions (viruses, research, discipline, employment).
2. At ICAR, to present science of the highest quality.
3. To provide a warm welcome to all ICAR participants and to provide opportunities for networking, especially giving encouragement to new attendees.
4. To fulfil the aim of educating antiviral researchers worldwide by publishing ISAR News and ICAR meeting reports.
5. Financial stability.

Even during the first decade, ISAR became aware of competition within the antiviral community. During the second and third decades, there was increasing competition from other antiviral conferences, including some excellent meetings organized by other learned societies, but ISAR and ICAR have thrived and entered the fourth decade successfully. Certainly, all the above core ISAR attributes have been, and will be, vital for continuing success. But are these sufficient for the 4th decade?

Especially during the third decade, there have been various trends which need to be considered and managed. Communication technology has been transformed, leading to younger researchers using new outlets. Another factor is that our Society relies on a loyal group of individuals willing to give their time. Presidents, Board members, Committee Chairs and all the committee members have volunteered their time and contributed to the success of each ICAR.

Communication: adopting new technology.

During the past decade, communications have been by e-mail to ISAR members, via the web site, by publication of the ISAR News and the ICAR meeting reports (on the web site and on free access in Antiviral Chemistry and Chemotherapy [AVCC], then in Antiviral Research [AVR]). Both the ISAR News and the meeting reports have the potential to reach many more people than are members of ISAR.

For all the past decade, there has been a Facebook page within the web site and, a little later, a LinkedIn page was established but these have been little used. Recently, with the strong support of the ISAR management, it is planned to make Social Media and webinars an important part of our communication strategy. This will surely help ISAR to reach the next generation.

Although ISAR should use these new opportunities, the established communications may well reach different cohorts of antiviral researchers. The readership, of ISAR News and ICAR meeting reports, has been greatly increased by publication in established journals, initially Antiviral Chemistry and Chemotherapy (AVCC) and latterly in Antiviral Research (AVR). Only one meeting report (27th ICAR at Raleigh, 2014) was published in AVR under a commons license (free access) and this was associated with a much higher number of viewings/downloads than any of the other reports: Following 5000 views/downloads by the end of 2017, there were another 220 during 2018, about 2/3rds of ICAR's attendance. As expected, most viewers were from North America followed by Europe but 275 viewers came from China.

The Ambassador program, initiated by Bob Buckheit, has the potential to reach out to new members in countries currently poorly represented. I welcome the current leadership's support of this program as personal contact may be one of the most effective ways to recruit new members.

Financial stability.

We owe a huge debt to all our sponsors who have provided so much support each year. This funding has enabled the Society to organize its activities and provide assistance to young investigators, postdocs and graduate students. We gratefully thank all our corporate sponsors for their support during the third decade of ISAR. The Society has recognized the vital need to optimize it resources. The health of the Society and the success of our conferences will strongly depend on how well we manage our assets and resources.

For the past decade, Roger Ptak, more than any other, has sought funding from potential sponsors. He has done this work so quietly and efficiently that it is hard to remember a time when ISAR was facing financial difficulties. We all owe Roger a great vote of thanks.

Long-term friendships.

Birgit Zonsics, one of the students in the ANTIVIRALS European Training Network (ISAR News, 28.S1, 2018), noted:

Many young researchers find the term networking a little intimidating. But the ANTIVIRALS network is very different. It started as collaboration between long-standing research collaborators and friends in the field of antiviral research.

Hugh J Field (section 1, above) noted:

One of the features of antiviral research in the herpes field at this time was the friendly but strongly competitive rivalry between the researchers from the then Burroughs Wellcome and SmithKline Beecham companies promoting valaciclovir and famciclovir, respectively, for the treatment and prevention of herpes simplex including genital herpes, ocular herpes, herpes encephalitis and varicella-zoster.

Such friendships were initiated by Trudy Elion (Burroughs Wellcome and Nobel Prize recipient) who set the ISAR standard that, while respecting our company's loyalties, good science bound us together in friendships.

Maaike Everts, (William Prusoff Young Investigator Awardee, 30th ICAR, Atlanta) noted that a key success factor for the collaboration was "The 'glue' which holds the whole project together, Rich Whitley."

Throughout the 3 decades, many long-term friendships have been initiated and renewed at ICARs. I agree with Birgit, Hugh, Trudy and Maaike, that long-term friendships will remain vital to the continued success of ISAR/ICAR.

Key success factors for the 4th decade

Success through the next decade will depend on optimizing communications, financial stability and long-term friendships, these being key factors which should to be added to ISAR's core attributes of the first three decades. Of these, friendships may prove to be the most critical parameter, being the "glue" which will hold ISAR together and ensure the success of future ICARs. For myself, I have been fortunate to attend ICAR over 25 times. There are many reasons for my attendance but the most important has been to meet long-term friends.

Anthony Vere Hodge

7. In Memoriam

William (Bill) H Prusoff, the "Father of Antivirals"

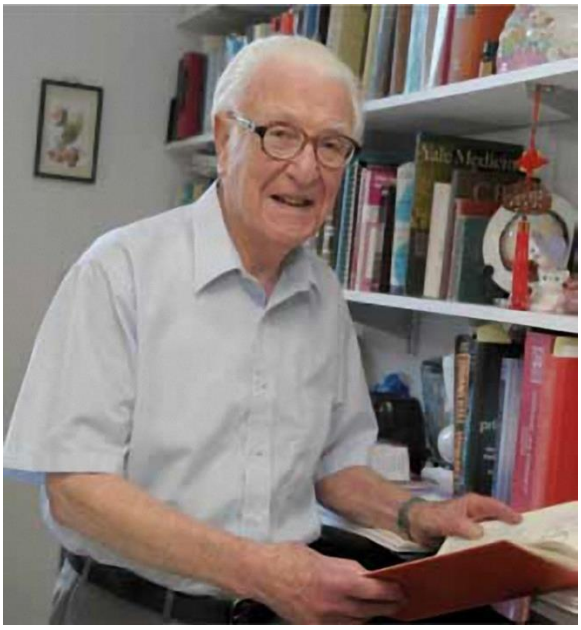


Fig. 7.1 William (Bill) Prusoff
(Courtesy of Raymond Schinazi.)

Bill (Fig. 7.1) was born in Brooklyn, New York on 25th June 1920 and died on 3rd April 2011, aged 90. Bill and his wife, Brigitta, had two children and three grandchildren. During his school days, the family moved to Miami, Florida. Bill obtained a degree in chemistry from the University of Miami and a doctorate from Columbia University. He used to delight in telling his story that he had applied to Yale Medical School but was rejected with his application fee returned as his application was so poor. Yet he was to become a faculty member of Yale for 57 years and was awarded two of Yale's highest honors, the Peter Parker Medal and the Lifetime Achievement Award. At Yale in 1959, Bill synthesized idoxuridine which was to become the first FDA approved antiviral drug, used to treat herpes keratitis. Hence he became known as the 'father of antiviral chemotherapy'. Later, he developed d4T (stavudine) for HIV/AIDS and he was largely responsible for ensuring that it was made available to those in need, such as in Africa. Bill established the W. H. Prusoff Foundation at Yale which has supported numerous programs.

As one of the original ISAR members, Bill has been closely associated with the Society from its earliest days. Bill was the first recipient of the Society's Award of Excellence in 1988. He was a regular attendee of ICAR, his last active role being at Savannah, Georgia in 2003 when he presented ISAR's William Prusoff Young Investigator Award to Johan Neyts. The following year, he declared 'I would like to be at the meeting because my spirit is in its 20s, but my body is in the thousands'. Maybe, but, in 2005, we were delighted to see Bill again at ICAR in Barcelona.

Adapted from ISAR News 21.1 (2011) Antiviral Chemistry & Chemotherapy **22.**2 87-94

Earl Kern

Antonín Holý: Organic Chemist Whose Inventions Reshaped the Antiviral Drug World

Fig. 7.2. Antonín Holý (1936–2012)

After a long, incapacitating illness due to the complications of Parkinson's disease, Antonín Holý (Fig. 7.2) passed away on July 16, 2012, at his home in Prague. He was born on September 1, 1936 in Prague (at the time, Czechoslovakia) where he would also graduate in 1959 as an organic chemist, and spend his whole life at the Institute of Organic Chemistry and Biochemistry (IOCB), from 1994 to 2002, as its Director. Dr. Antonín Holý was honored several times with prestigious awards in his home country, the Czech Republic, and obtained honorary degrees from the Universities of Olomouc (Czech Republic), České Budéjovice (Czech Republic), Ghent (Belgium), and Manchester (United Kingdom). The pioneering work of Dr. Antonín Holý was concentrated on the acyclic nucleoside phosphonates, which conquered a key position in the treatment of AIDS, hepatitis B, herpes, and poxvirus infections. The basic discovery of this class of compounds was published 26 years ago in *Nature* (1986;323:464–467) and would be the subject of another *Nature* paper in 2006 (2006;439:745–748).

Antonín Holý laid the basis for a number of antiviral drugs (Vistide^{R}, Hepsera^{R}, Viread®^{TM}, Truvada^{R}, Atripla^{R}, Complera®^{TM} and Stribild®^{TM} mainly for the treatment of AIDS and hepatitis B.

Truvada was the first anti-HIV drug ever to be approved for the prophylaxis of HIV infections, by the US FDA on July 16, 2012, exactly the same day that Antonín Holý died.

Through his discoveries, Antonín Holý contributed to saving the lives of millions of people worldwide by protecting them from such widespread diseases as AIDS and hepatitis B. With his discovery of the acyclic nucleoside phosphonates (Nat Rev Drug Discov 2005;4:928–940), Holý added a new dimension to the therapy of AIDS, which, now that Truvada has been approved for the prophylaxis of HIV, may be heralded as a step forward in the eventual eradication of the disease.

Antonín Holý was a reserved, humble scientist, soft spoken even before, due to his illness, his voice completely faded away. He was a gifted, highly productive chemist, who had only one passion in life—change the world with medically useful drugs, whether antiviral or antitumoral. His molecules have changed the world of the antivirals.

In the Czech Republic, Antonín Holý has entered the hall of fame, only preceded by other Czech heroes such as Gregor Mendel (the founder of genetics), Jaroslav Heyrovský (the discoverer of polarography), and Otto Wichterle (the pioneer of the soft lens). The Czech Republic should be proud of counting Antonín Holý as one of theirs, and so should be all of us who have known Dr. Antonín Holý as a Chemist, a Scientist and a Friend. With Dr. Antonín Holý, not only the Czech Republic, but the whole world has lost a true captain of research, a great inventor and innovator, and a real statesman of Science.

Adapted from Medicinal Research Reviews, 33, No. 1, 1–2, 2013

Dr. Erik De Clercq (A life-long collaborator and friend of Antonín Holý)

Chris McGuigan: A tribute to a remarkable innovator.

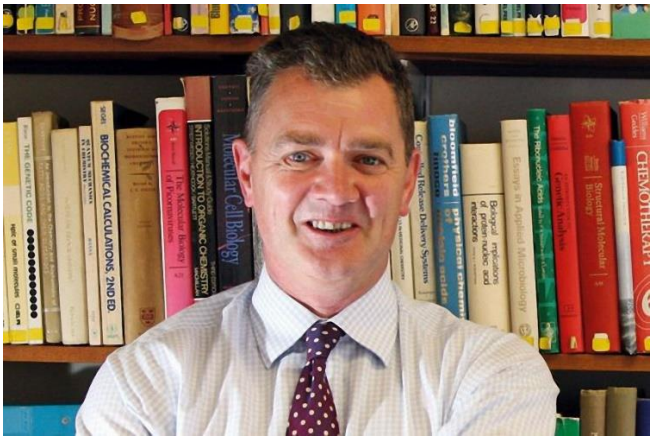


Fig. 7.3. Christopher (Chris) McGuigan, 1958-2016.

In 2001, ISAR awarded for the first time the William Prusoff Young Investigator Award and the lecture was given by Chris McGuigan (Fig. 7.3), a superb nucleoside chemist from Cardiff University. Chris was already an accomplished scientist by then: he started his career obtaining his B.Sc., Chemistry, Hons (Class 1), at the University of Birmingham (1979) and his Ph.D. on Anticancer Drug Design (1982). He moved to University of Edmonton, Alberta, Canada (1982-84) as a post-doctoral fellow, then to University of Exeter as Demonstrator (1984-85), to University College London as Lecturer (1985-90) to University of Southampton as Lecturer (1990-94). His career at the Welsh School of Pharmacy began as a Reader (1994-95), and then Professor (1995-2016). In this role, Chris was an inspirational leader, training >40 Ph.D.s and >50 postdocs, published >220 papers and obtained >100 patents.

The Prusoff award presentation reflected Chris's brilliancy and the importance of his research, coupled with a flawless ability to present his work in an exciting, yet scientifically rigorous, manner. The main highlights of that presentation were two important scientific ideas that were destined to make a huge impact. The first one was the discovery, in collaboration with Erik De Clercq and Jan Balzarini, of a novel family of nucleoside analogues with highly potent activity against varicella zoster virus (VZV). That project lead to the identification of Cf1743 (FV-100) (Fig. 7.4) which is currently in Phase III clinical trials in patients with shingles. The second, and possibly the most important, scientific innovation that Chris presented, was the design and development of the ProTide approach, an incredibly efficient phosphoramidate prodrug technology to deliver nucleoside monophosphates into cells. Jan Balzarini (Fig 7.5) was also an important collaborator in this discovery and indeed, in 2001, together with four other collaborative European Teams, they received the European Commission's René Descartes Prize for European Scientific Collaboration.

Chris developed the ProTide throughout his career and he applied it to a variety of projects. For example, compound, Cf2761 (INX-08189, often as INX-189), a ProTide developed in collaboration with Inhibitex, was shown to have excellent activity against Hepatitis C virus (HCV) (EC_{50} 10 nM). The clinical milestones were quickly achieved, first into man - May 2010 and first efficacy in patients - March 2011. Unfortunately, the trials were stopped due to toxicity concerns. However, it did prove that the phosphoramidate prodrug approach was successful and it was adopted by others. Perhaps the most evident legacy of Chris' work is represented by sofosbuvir and tenofovir alafenamide (Fig. 7.6), the "backbone" compounds in Gilead's single tablet regimens (STR) for treating patients infected with HCV and HIV, respectively. In addition, the ProTide approach was also applied successfully by Chris, in collaboration with NUCANA, in the anticancer field: NUC-1031 (Acelarin®) (Fig. 7.7) is currently in phase III for the treatment of pancreatic cancer.

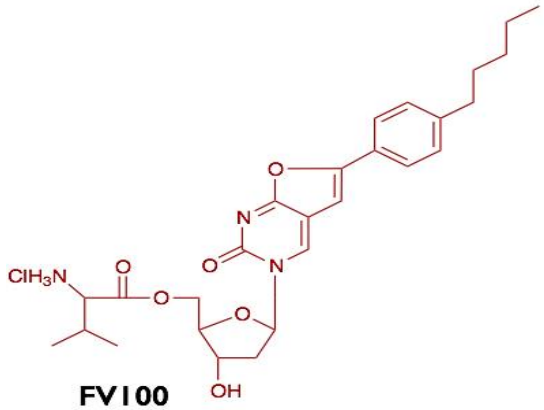


Fig. 7.4. Structure of FV100, the prodrug (alanine ester) of Cf1743.

Fig. 7.5. Chris McGuigan, as ISAR President, presents Jan Balzarini with the Elion award in 2008.

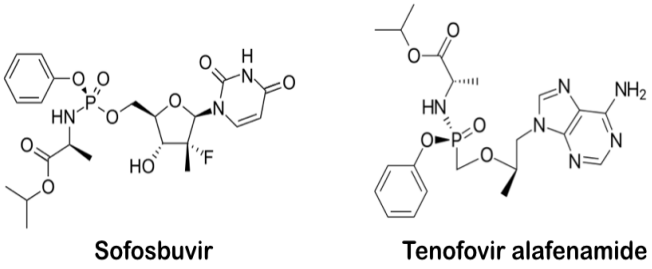


Fig. 7.6. Structures of sofosbuvir and tenofovir alafenamide

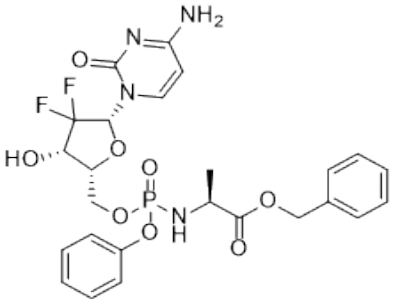


Fig. 7.7. Structure of NUC-1031 (Acelarin®)

Chris was an active member of ISAR, becoming president from 2006 to 2008. Even in this role, his incredibly positive personality emerged: motivated, enthusiastic and driven, always very critical in the positive and constructive sense of the word, always very collaborative. Chris was also an extraordinary mentor and friend. He died far too soon. We still miss him dearly, but his scientific and personal legacy will stay with us for a very long time.

Andrea Brancale

8. ICAR & ISAR details

Conferences of the Society (1st Decade)

	Date	Location	Organizer (Local Host)
1	April 30 – May 3, 1985	Rotterdam, The Netherlands	George Galasso. Erik De Clercq, NATO (Huub Schellekens)
2	April 10 – 14, 1988	Williamsburg, VA	Earl Kern, George Galasso, Richard Whitley, Bill Shannon, SRI
3	April 22 – 27, 1990	Brussels, Belgium	Erik De Clercq
4	April 21 – 26, 1991	New Orleans, LA	Ken Soike
5	March 8 – 13,1992	Vancouver, Canada	Steve Sacks
6	April 25 – 30. 1993	Venice, Italy	Earl Kern, Richard Whitley, (Giorgio Palu, Fernando Dianzani), Sistema Congressi
7	Feb 27 – March 4, 1994	Charleston, SC	Earl Kern, Richard Whitley, (David Gangemi), Conference Table
8	April 23 – 28, 1995	Sante Fe, NM	Earl Kern, Richard Whitley, (Gregory Mertz), Conference Table
9	May 19 – 24, 1996	Urabandai, Japan	Earl Kern, Richard Whitley, (Shiro Shigeta, Kazuo Takahashi), Tokyu Tourist Corp.
10	April 6 – 11, 1997	Atlanta, GA	Earl Kern, Richard Whitley, (Raymond Schinazi), Imidex, USA

Conferences of the Society (2nd Decade)

	Date	Location	Organizer (Local Host)
11	April 5 – 10, 1998	San Diego, CA	Earl Kern, Richard Whitley, (Karl Hostetler, Doug Richman), Conference Table
12	March 21 – 26, 1999	Jerusalem, Israel	Earl Kern, Richard Whitley, (Ehud Katz), Kenes Ltd.
13	April 16 – 21, 2000	Baltimore, MD	Earl Kern, Richard Whitley, (George Galasso), Courtesy Associates
14	April 8 – 12, 2001	Seattle, WA	Earl Kern, Richard Whitley, (Larry Corey), Courtesy Associates
15	March 17 – 21,2002	Prague, Czech Republic	Earl Kern, Richard Whitley, (Antonín Holý), Courtesy Associates
16	April 27 – May 1, 2003	Savannah, GA	Earl Kern, Courtesy Associates
17	May 2 – 6, 2004	Tucson, AZ	Earl Kern, (Leroy Townsend), Courtesy Associates
18	April 10 – 14, 2005	Barcelona, Spain	John Drach (José Esté), Courtesy Associates
19	May 7 = 11, 2006	San Juan, Puerto Rico	John Drach, Jack Secrist, Courtesy Associates
20	April 29 – May 3, 2007	Palm Springs, CA	Jack Secrist, John Drach, Amy Patick, Courtesy Associates

Conferences of the Society (3rd Decade)

	Date	Location	Organizer (Local Host)
21	April 13 – 17, 2008	Montreal, Canada	Bob Buckheit, Courtesy Associates
22	May 3 – 7, 2009	Miami Beach, FL	Bob Buckheit, Courtesy Associates
23	April 25 – 28, 2010	San Francisco, CA	Bob Buckheit, Courtesy Associates
24	April 8 – 11, 2011	Sofia, Bulgaria	Bob Buckheit, (Angel Galabov), Courtesy Associates
25	April 16 – 19, 2012	Sapporo, Japan	Bob Buckheit, (Hiroaki Mitsuya, Masanori Baba) Courtesy Associates
26	May 11 –15, 2013	San Francisco, CA	Mark Prichard, Courtesy Associates
27	May 12 – 16, 2014	Raleigh, NC	Mark Prichard, Courtesy Associates
28	May 11 – 15, 2015	Rome, Italy	Mark Prichard, (Romano Silvestri), Courtesy Associates
29	April 17 - 21,2016	La Jolla, CA	Mark Prichard, (Karl Hostetler, Douglas Richman), Courtesy Associates
30	May 21 – 25, 2017	Atlanta, GA	Mark Prichard, Justin Julander, Courtesy Associates

Presidents of the Society

Richard J. Whitley	1988-1990
Erik De Clercq	1990-1992
George J Galasso	1992-1994
Hugh J Field	1994-1996
Earl R. Kern	1996-1998
John C. Martin	1998-2000
Karen K. Biron	2000-2002
John C. Drach	2002-2004
John A. Secrist III	2004-2006
Christopher McGuigan	2006-2008
Amy K Patick	2008-2010
Joseph M. Colacino	2010-2012
Phillip Furman	2012-2014
Robert W. Buckheit, Jr.	2014-2016
José Esté	2016-2018

President-Elect

Johan Neyts	2016-2018

Other Officers of the Society

Secretary

Earl R. Kern	1988-1994
Koen Andries	1994-2000
Brent Korba	2000-2003
Amy K. Patick	2003-2006
Joe Colacino	2006-2008
Susan Cox	2008-2012
Graciela Andrei	2012-2019

Treasurer

William M. Shannon	1988-1994
John A. Secrist III	1994-2003
John Morrey	2003-2007
Dale Barnard	2007-2014
Brian Gowen	2014-Present

For the ISAR Awards of Excellence (see Table in the 2nd Decade booklet), please see Section 2 above for the Awards in the 3rd Decade.

On behalf of the Society, thanks are extended to all the members who assisted in the production of this booklet. Your contributions are much appreciated.

Anthony Vere Hodge
(Editor for 3rd Decade booklet)

The International Society for Antiviral Research: The Third Decade