ISAR News
Newsletter of the International Society for Antiviral Research
Editor Anthony Vere Hodge Guest editor Joana Rocha-Pereira

Report on the 29th ICAR La Jolla, CA, USA

IN THIS ISSUE

ISAR PRESIDENT'S MESSAGE

(José Esté)

It is with pleasure that I salute all ISAR members and friends as I take the role of President. I am truly honored and enthusiastic about working and serving the Society and its membership.

Our 29th conference in La Jolla was a great success in many ways. The quality of the science, oral and poster presentations maintained the standard we are accustomed year after year, participation increased and the meeting allowed for both formal and informal exchange of ideas and collaborations.

The success of the conference in La Jolla would not have been possible without the continual effort and unselfish interest of the officers, board of directors, committee chairs and all members of the various committees that organized and executed the multiple activities of the Society. Special thanks and appreciation go to Robert (Bob) Buckheit Jr. whose term as president of the Society ended with the meeting in La Jolla. Bob's leadership, dedication and commitment to ISAR have been instrumental for the conference's success. As he now takes the role of Past-President, I am confident Bob will continue guiding our steps into our next meeting in Atlanta and the challenging future that lies ahead. I would also like to thank the support and encouragement of our local hosts Dr. Douglas Richman and Dr. Karl Hostetler.

Our success would not be possible without the continuous support of our corporate and educational sponsors. Without their commitment many of our activities would not be the same. An increasing number of sponsors makes us confident on the interest and importance of our meeting. ICAR is a platform to communicate basic and translational research that feed back into their interests and to those of the scientific community they represent.

We are now beginning the organization of the 30th Conference on Antiviral Research to be held in Atlanta, Georgia. The conference will take place at the Hilton Atlanta, will begin on May 21, 2017, and will conclude on May 25, 2017. Mark Prichard and Justin Julander, as Co-chairs of the Program committee, will be leading the effort of preparing an outstanding scientific program. However, it is through the participation of our membership that science becomes the heart and matter of our meeting. ISAR is preparing to actively support

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

the participation of students, postdocs and early career investigators wishing to present their best science. Our scholarship program will provide support based on merit and the quality of the abstracts submitted for presentation. The goal will be to bring excellent science. At the same time, our Ambassador Program will serve to identify and support the participation of individuals who have been traditionally underrepresented in science or from lower income regions of the world.

Virus infections continue to represent multiple unmet medical needs. Emerging infections pose great scientific challenges and an increasing concern by the general population with high medical, social and economic impact: the global village makes all infections global. Antiviral research and antiviral drug development continue to represent a pillar in the battle against disease. ISAR-ICAR will remain in the frontline by disseminating knowledge and promoting the translation of fundamental research into technological and clinical applications.

Finally, I take the opportunity to invite and welcome all ISAR members and friends to actively participate in the organization of our meeting. A new e-mail address (info@isaricar.com) has been set for all to directly communicate their interests, queries, and ideas. Please feel free to contact us.

MEETING REPORT

29TH INTERNATIONAL CONFERENCE ON ANTIVIRAL RESEARCH
(R. Anthony Vere Hodge)

I. Introduction

The 29th International Conference on Antiviral Research (ICAR), sponsored by the International Society for Antiviral Research (ISAR), was held in La Jolla, CA, USA, from April 17-21, 2016. This account starts with Andrea Brancale's heart-felt tribute to his mentor and colleague, Chris McGuigan who died in March 2016. It continues with reports of lectures by the recipients of ISAR's three major awards, held in memory of Gertrude (Trudy) Elion, Antonín (Tony) Holý and William (Bill) Prusoff. The full ICAR meeting report, to be published later this year in Antiviral Research, will include summaries of the two keynote addresses and the main presentations within the three mini-symposia on "Structural Biology Symposium", "Diagnostic Technologies Symposium" and "DNA Virus Symposium".

I warmly thank the presenters for giving me a copy of their slides, for reviewing my draft and for sending me useful comments.

II. Chris McGuigan: A tribute to a remarkable innovator.
Andrea Brancale, Cardiff University, Cardiff, UK

Christopher (Chris) McGuigan, 1958-2016.
Much too young, Chris died from cancer on 11th March 2016.

Chris obtained 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), as Professor (1995-2016) and becoming the Pro Vice Chancellor (2012-3).

As Professor, Chris was an inspirational leader, training >40 Ph.D.s and >50 postdocs, some of whom presented their work at various ICARs. Chris published >220 papers and obtained >100 patents. ISAR selected Chris to be the first person to receive The William Prusoff Young Investigator Award in 2001. Just 3 years later, Chris was elected as the ISAR President-Elect, becoming President two years later (2006-2008). Collaboration with Erik De Clercq and Jan Balzarini led to the discovery of Cf1743 (FV-100) (Fig. 1) which has highly potent activity against varicella virus (VZV). FV-100 is currently in Phase III clinical trials in patients with shingles. Clearly, Chris was delighted to present Jan with the Elion Award in 2008.

Another compound, Cf2761 (INX-08189, often as INX-189) was synthesised and quickly shipped to Inhibitex on 11th Nov 2008. It 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 –

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

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 (Fig. 2) and tenofovir alafenamide, the "backbone" compounds in Gilead's single tablet regimens (STR) for treating patients infected with HCV and HIV, respectively.

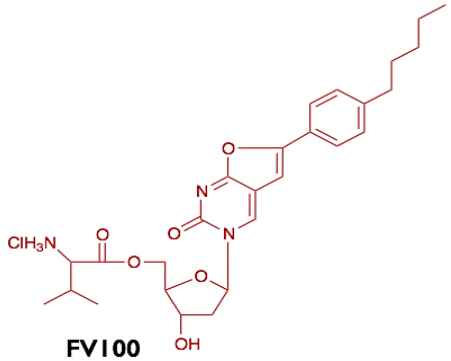

Figure 1. Structure of CF1743 (FV-100).

Moving the phosphoramidate (Protide) approach sideways from antivirals to anticancer, NUC-1031 (Acelarin®) (Fig. 3) has been licensed to Nucana. In a Phase I/II study in terminally ill patients with growing tumours, there was good disease control particularly with advanced gynaecological cancers. It is envisaged that Acelarin, used with chemotherapy, will reduce the development of resistance which often limits the use of standard chemotherapy.

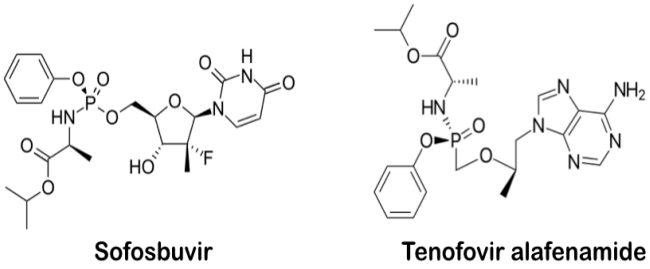

Figure 2. Structures of sofosbuvir and tenofovir alafenamide

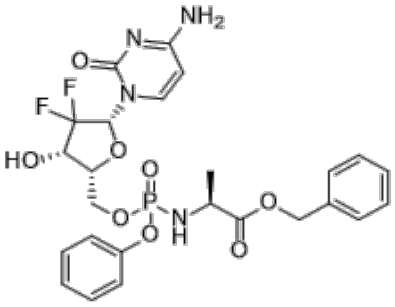

Figure 3. Structure of NUC-1031 (Acelarin®)

Andrea ended his tribute on a highly personal note. Chris had been a mentor, colleague and friend who died too soon. Our thoughts go to his family who have lost a husband and a father.

May I add my own comment? Andrea mentioned that Chris was the first recipient of the Prusoff award, in 2001. To my mind, his award lecture set a new standard. To this day, his mastery of slide creation, visually-exciting but with clear information, has rarely been equalled. In my report of the 28th ICAR, I mentioned that the Prusoff Award lecture, by Erica Ollman Saphire, sailed straight into my top ten ICAR lectures. My top ten certainly includes the Prusoff Award lecture by Chris. His presentation style is uniquely memorable, even after 15 years. My other lasting memory is Chris excitedly showing us photos of his new-born daughter.

Maybe, his most important legacies are the many young scientists whom he had helped, including Andrea Brancale who gave such a heart-felt tribute to his mentor, colleague and friend, Andrea has been an active member of ICAR for many years, being the ISAR web-master since about 2006.

III. Gertrude Elion Memorial Award Lecture

Antiretroviral drugs: History and future.

Douglas (Doug) Richman, University of California San Diego, CA, USA

Bob Buckheit presents the Elion award to Doug Richman.

Doug first paid tribute to Trudy Elion for her pioneering work with nucleosides. In his Elion Award lecture, Doug briefly described the difficulties of the early days of the HIV epidemic but ends on the bright prospects for both treatment and prevention.

AIDS was first described in 1981 and HIV (human immune-deficiency virus) was discovered in 1983. In 1985, AZT (3'-azido-3'deoxythymidine) was the first drug to show antiretroviral activity, the first clinical data being reported in the Lancet (March 1986). In July 1987, the efficacy of AZT in the treatment of patients with AIDS or AIDS-related complex was reported in the New England Journal of Medicine (NEJM). For that time, this was a large-scale, long-term trial, 282 subjects for 24 weeks. At 24 weeks, there was just 1 death in the AZT group vs 19 in the placebo group. This one study was sufficient for FDA approval.

Even in this first 24-week trial, there was a clear warning sign. In the group of less seriously ill patients (those with AIDS-related complex), the CD_4 cell counts in the AZT group remained significantly ($p<0.003$) higher than placebo group through to week 20. At week 24, there were too few patients to give a clear result. In the AIDS group treated with AZT, the mean CD_4 cell counts remained higher than in placebo group through to week 20. However, after an initial rise above baseline at week 4, there was a steady decline.

Sequential isolates (designated A036B, A036C and A036D) were taken at 2, 11 and 20 months from an individual patient being treated with AZT. There was about a 3 $\log_{10}$ reduction in AZT susceptibility (Science 1989). Doug commented that his grant application, to further investigate HIV resistance, was turned down because the reviewers asserted that essential enzymes for virus replication could not tolerate mutations. Doug recalled a comment by Arthur Schopenhauer (1788-1860) who noted that truth passes through three stages: first, it is ridiculed, second, it is violently opposed, and third, it is accepted as self-evident.

During the next decade, it became clear that HIV resistance was a problem for each class of antiretroviral monotherapy, that sequential monotherapy led to multi-class resistance and that resistant HIV was being transmitted. Combination therapy with indinavir (IDV), AZT and lamivudine (3TC), vs IDV alone or AZT/3TC, gave the best efficacy (reduction of HIV RNA) throughout the two-year study (Merck 035, NEJM 1997). This study showed the way forward, with several combinations able to reduce plasma HIV RNA levels to below the limit of detection, which was 400 copies/mL at the time. Most years, from the mid-1990s to the present, there has been a new drug or a new drug combination receiving FDA approval. Some notable advances were the approval of truvada (TDF, a prodrug of tenofovir) in 2001, the introduction of atripla, the first single tablet regimen (STR) in 2006, and the approval of tenofovir alafenamide (TAF) in 2015.

In a combined analysis of two Phase III studies comparing Stribild (containing TDF) with the same combination but with TAF), the primary efficacy outcomes slightly favoured the TAF arm over the TDF arm. At 48 weeks, 92 and 90% patients had undetectable HIV RNA (<50 copies/mL), respectively and at 96 weeks, 87 and 85%, respectively. One of the most important points is that, with these current regimens by 96 weeks, the virological failures with resistance were only 1.2 % and 0.9%, respectively. All these resistant strains were genotypically susceptible to dolutegravir. Although the efficacy parameters for the TAF and TDF were similar, the TAF arm had an improved safety profile.

With the approval of improved therapies, and better understanding how to use these therapies, the proportion of patients, with newly detected drug resistance, has been decreasing with the year of antiretroviral therapy (ART) initiation. There has been a marked improvement comparing therapy initiation prior to 1999 and after 2007. It is easier to avoid drug resistance than to limit it following sub-optimal therapy. Unfortunately, transmitted drug resistance is still a problem, especially from patients who have had ART for more than 5 years.

From about 2005, there has been steady increase in the estimated proportion of HIV-infected patients receiving ART, from under 10% in 2005 to about 40% in 2014. The increase is largely due to patients in Africa receiving ART. In 2014, about 16 million patients world-wide were having ART, of these, about 12 million were in Africa. On the positive side, it has been estimated that over 8 million deaths have been averted. On the negative side, widely anticipated factors, contributing to HIV drug resistance in low and middle income countries (LMICs), have been confirmed: suboptimal regimens, limited resources to monitor viral load, drug distribution failures and perinatal ART rather than treating pregnant women. What does the future hold?

In the short term, the availability of TAF and dolutegravir (DTG) should provide marked improvements in ART in LMICs. Looking further ahead, there is the prospect of ART with prolonged intervals (several months) between doses.

Figure 4. Structure of cabotegravir (GSK-744), an HIV integrase inhibitor.

Cabotegravir (GSK-1265744, CAB) (Fig. 4) an integrase inhibitor, was investigated in a Phase I trial (n = 10 subjects/cohort), comparing monthly and quarterly repeat dosing. The 4 cohorts each had a loading dose (LD) of 800 mg intramuscular (im), then followed by a maintenance dose (MD) of CAB either 200 mg sub-cutaneous (sc) q 4 w 3 times, 200 mg im q 4 w 3 times, 400 mg im q 4 w 3 times or 800 mg im at 12 w, respectively. The target plasma concentration of CAB was 0.6 µg/mL. With the 12 w dosing interval, the CAB trough level was about 1 µg/mL. The 200 mg sc and im dosing were similar, both less that the 400 mg im dosing (trough levels about 2 and 3 µg/mL, respectively).

CAB and rilpivirine (RPV), an HIV NNRTI, are both under development as long-acting injectable nanosuspensions. In a Phase IIb trial, CAB + RPV (im) were compared to 3-drug oral ART (CAB + ABC/3TC). The patients were randomised after a 20 week induction period during which they were treated with daily oral CAB 30 mg + ABC/3TC, only those patients achieving HIV-1 RNA <50 c/mL were eligible to start the maintenance period (MP). Enrolled patients were randomized 2:2:1 to CAB + RPV every 8 weeks (Q 8 W), every 4 weeks (Q 4 W), or remained on oral CAB + ABC/3TC (n = 115, 115 and 56, respectively). The primary endpoints were safety and virological failure (HIV RNA >50 c/mL) at 32 weeks into the MP (intention-to-treat maintenance exposed (ITT ME)). There was excellent virological success, 109 (95%), 108 (94%) and 51 (91%) patients, respectively, maintaining undetectable HIV RNA levels. The non-responders (HIV RNA >50 c/mL) were 3 (3%), 1 (~ 1%) and 1 (2%), respectively. There were only 2 patients who discontinued due to lack of efficacy, one each in the Q 8 w and oral groups. There seemed to be a good safety profile, with injection site reactions being common but acceptable.

MK-8591 (4'-ethynyl-2-fluoro-2'-deoxyadenosine, EFdA) (Fig. 5) is being developed by Merck, licensed from Yamasa. EFdA is a highly potent HIV RT inhibitor (PBMC, EC_{50} = 0.2 nM). It is a non-obligate chain terminator but it prevents translocation of the RT. Following a single oral dose (50 mg/kg) to monkeys, the peak plasma concentration of EFdA is just over 10 µM, reducing to about 10 nM at nearly 180 h (7 days). In rhesus PBMCs, EFdA is taken up and converted to the diphosphate (DP) and triphosphate (TP) rapidly, >100 µM at the first time point. At 7 days, the DP and TP are above 10 µM. This suggests the potential for once a week oral dosing.

In a Phase Ib study, a single 10 mg oral dose in HIV-infected patients resulted in a 1.6 $\log_{10}$ decrease in viral load at day 7. The intracellular half-life ($t_{1/2}$) of EFdA-TP was 103 h. There was no evidence of resistance out to day 10 (1.8 $\log_{10}$ decrease in viral load). Parenteral formulations have given effective drug levels for 180 days. This suggests that twice yearly dosing will be possible.

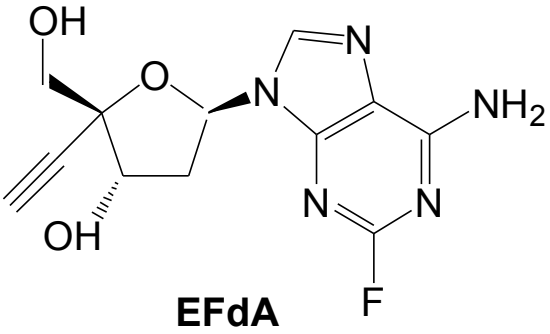

Figure 5. Structure of EFdA (MK-8591), an HIV RT inhibitor.

Both CAB and EFdA look set to transform HIV therapy. It is likely that an induction period, using oral dosing will be necessary due to safety concerns in the event of a hypersensitivity reaction. Thereafter, 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 PMICs may be largely avoided. The prospect of interrupting HIV transmission holds out hope that the HIV epidemic may be steadily controlled.

IV. The Antonín Holý Memorial Award Lecture

Acyclonucleosides to Ziagen.

Robert (Bob) Vince, Center for Drug Design, University of Minnesota, USA

Bob Buckheit presents the Holý award to Bob Vince.

Bob started by acknowledging that the work of Antonín (Tony) Holý had influenced his own work. When he joined the laboratory led by Howard Schaeffer, the team were focussed on nucleic acid chemistry. Bob was inspired by a molecular biology course on nucleic acids in his first year of graduate school. It was taught by Professor Roger Mantsavinos who had just arrived from Erwin Chargaff's lab at Columbia University. When Howard moved to Burroughs Wellcome to become head of the medicinal chemistry division, Bob moved to the University of Minnesota. Bob thanked Bill Shannon, who has attended many ICARs including this one, for their long-term collaboration.

Bob proposed the design and synthesis of acyclonucleosides as potential antitumor and antiviral agents based on the lectures presented by Dr Mantsavinos. The first of this series, acycloadenosine, was published in 1971 (J. Med. Chem. **1971**, *14*, 367). Although Howard Schaeffer had later synthesized and drafted this paper, he sent a letter to Bob suggesting that Bob should be an author as it had been his idea to synthesize these acyclonucleosides. This compound was shown to be a substrate for adenosine deaminase – so it was a biologically active molecule. It remained unknown if it could be recognised by a kinase to form the corresponding monophosphate (acycloadenosine-MP). With Howard's move to Burroughs Wellcome and Bob's move to Minnesota, this idea was shelved until acycloguanosine was later found active as an antiherpes agent at Burroughs Wellcome. Subsequently in 1978 (Nature, **1978**, *272*, 583), the antiherpesvirus activity of acycloguanosine was published. Over 3 decades later, acyclovir (ACV) and its oral prodrug, valacyclovir (VACV), are still in use today. It is interesting to note that tenofovir, synthesised by Tony Holý, is also an acyclonucleotide –it is included, as its prodrug, in some of the most used single tablet regimens (STR) for the therapy of HIV infected patients.

Ara-adenosine (araA) was a known antiherpesvirus compound. It was activated by kinases to give the mono-, di- and tri-phosphate which inhibited the viral polymerase. However, araA was also a substrate for adenosine deaminase to give ara-inosine which was inactive. Bob wondered if the corresponding carbocyclic araA would be stable. This compound, known as cyclaradine, was adenosine deaminase resistant and had low systemic toxicity. Just before Bob was due to present his synthesis of cyclaradine at a meeting, he was told that Bill Shannon of Southern Research Institute had found that the compound had good activity against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) and that he had suggested that Bob should consider withdrawing his presentation. Being unaware of the patent implications, Bob delivered his presentation as planned. An important lesson had been learnt the hard way!

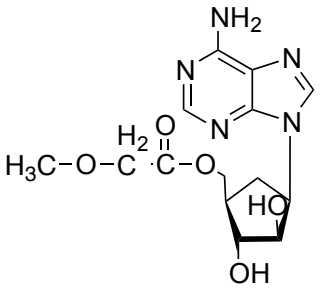

Figure 6. Cyclaradine methoxyacetate.

The 5'-methoxyacetate prodrug, cyclaradine-MA (Fig. 6), was active in a topical model of genital infections in guinea pigs with HSV-2. Cyclaradine-MA (as 1% and 5 % topical formulation) was compared to ACV (1% and 5%). Both compounds had good activity

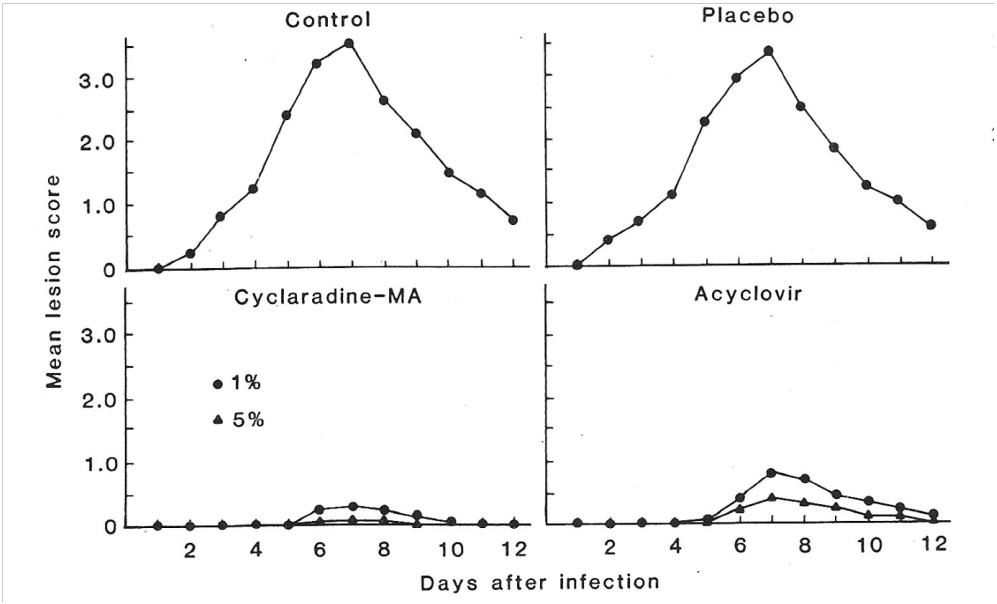

Figure 7. Cyclaradine and acyclovir: in vivo anti-HSV-2 activity in guinea pig infection.

in this model, with cyclaradine apparently having slightly greater activity (Fig. 7).

Unexpectedly, there was a marked difference during the follow-up period. After ACV treatment, there were HSV-2 recurrences, whereas there were no recurrences following cyclaradine-MA treatment. Bob and Bill Shannon were co-authors of the publication (Science, **221**, 1405 (1983)). Although cyclaradine seemed to be an interesting compound, it was not developed as there could be no compound patent protection.

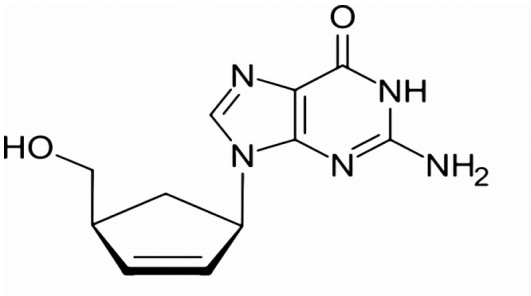

Figure 8. Structure of (-)carbovir.

The next major advance came with the synthesis of a guanosine analog which became known as carbovir (Fig. 8). As in cyclaradine, the oxygen was replaced with a carbon but a double bond was used to give a ring with a similar shape to the ribofuranose. Mei Hua synthesised the first carbovir compound. To improve oral bioavailability, various alkyl analogs of carbovir were synthesised (Fig. 9). All these compounds were very active as HIV RT inhibitors, each analog being converted intracellularly to carbovir-MP which was then further phosphorylated to the active carbovir-TP. On 5th December 1988, a patent was filed with Bob and Mei as the inventors.

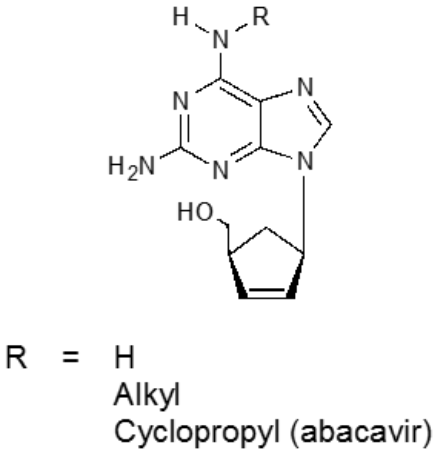

Figure 9. Structures of some 6- substituted carbovirs covered by the Vince patent.

These carbovirs were licensed to GlaxoSmithKline (GSK). Cyclopropylcarbovir was synthesised as GSK claimed that the cycloalkyl chains were not covered by the patent. However, as for all the other alkyl analogs of carbovir, cyclopropyl carbovir was converted to carbovir-MP and to the active form, carbovir-TP. Following a lawsuit, GSK had to pay University of Minnesota $600 million and royalties. Although the cyclopropyl group was not essential, GSK had done so much work with this compound that it was this carbovir analog that was developed to become abacavir. The royalties have enabled the university to start and fund the Center for Drug Design, with Bob as director.

V. The William Prusoff Young Investigator Award Lecture

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

Jerome Deval, Alios BioPharma, San Francicsco, CA, USA

Bob Buckheit presenting the Prusoff award to Jerome Deval.

Jerome started by thanking Bob for his introduction: Jerome had obtained his Ph.D. in applied microbiology from the National Center for Scientific Research (Le Centre National de la Recherche Scientifique, CNRS), University of Provence, Marseille, France in 2004. Jerome's mentor was Bruno Canard who had been the Prusoff awardee in 2008.

Jerome started by noting that there are very few small-molecule drugs approved for negative strand (-) RNA viruses, none of these being virus replication inhibitors. In 2010, there was just a single (-) RNA virus replication inhibitor in clinical trials, T-705 which is now known as favipiravir. It has been approved in Japan for treating serious influenza infections and is in Phase III trials in the USA. In 2016, favipiravir and VX-787 were in Phase III and Phase II trials, respectively, for influenza infections, and five other compounds in Phase I trials. [BCX 4430 and GS-5734 are for Ebola infections and were included in ICAR lectures in 2014 and 2015 respectively.] Only one compound (ALS-8176, is being tested for respiratory syncytial virus (RSV) infections, this being the subject of this presentation. All these compounds are viral polymerase inhibitors but only four, favipiravir, ALS-8176, BCX3340 and GS-5734, are nucleoside analogs.

There are no effective therapeutics for RSV infections which may be serious, even fatal, in children. Clearly there is an important unmet clinical need. Although the main RSV targets for potential drags have been fusion protein or any part of the polymerase complex, Jerome and his colleagues decided to screen only nucleoside analogs. Past experiences with herpes viruses, (HSV-1 and -2, VZV), HIV, HBV and HCV have shown that nucleoside analogs have provided the drugs with good broad spectrum activity against many strains of the virus and have shown a high genetic barrier, limiting the problems due to virus resistance. Therefore, a small screening campaign was initiated in 2010. A selection of 100 structurally diverse nucleoside analogs were tested for activity against RSV vs lack of inhibition of cellular replication. This screen resulted in just one hit, 2'difluoro-4'azido-cytidine which was known to inhibit HCV but also known to have safety issues.

Structure activity relationship (SAR) studies proved to be difficult. The aim was to discover a compound which had good selective activity for RSV, with the measures of selectivity being a lack of activity against HCV and cellular replication. There were many dead-ends but one compound, ALS-8112, emerged as a good candidate. It had good activity against RSV (EC_{50} = 0.1 to 1 μM against all tested A and B clinical isolates) and lacked cytotoxicity (CC_{50} >100 μM). ALS-8112 lacked activity against HCV and rhinovirus, both (+) RNA viruses and against influenza virus, a segmented (-) RNA virus. However, it had activity not only against RSV but also against two other non-segmented (-) RNA viruses, parainfluenza virus type 3 (EC_{50} = 1.3 μM) and vesicular stomatitis virus (EC_{50} = 3.4 μM).

As expected for a nucleoside antiviral, ALS-8112 is activated to the ALS-8112-TP which inhibits the RSV RNA-dependent RNA polymerase (RdRp). ALS-8112 is efficiently phosphorylated to ALS-8112-MP by deoxycytidine kinase (dCK). In human primary lung cells, high levels of ALS-8112-TP (~800 pmol/10^6 cells) were formed. The half-life of ALS-8112-TP was about 29 h. ALS-8112-TP inhibited RSV polymerase (IC_{50} = 0.020 μM) and parainfluenza virus type 1 (IC_{50} = 2.3 μM) but not the polymerases of influenza virus or HCV. In collaboration with Rachel Fearns at Boston University, it was confirmed that ALS-8112-TP was incorporated efficiently into an RNA chain by RSV polymerase using a poly G template, about 13-fold less than for the natural cytidine-TP. When 4 residues had been added, there was chain termination. This is the first example of RNA chain termination in RSV.

Upon prolonged incubation of RSV with ALS-8112, four resistance mutations (designated QUAD), were selected. Three of the four mutations (A789V, L795I,

I796V) are within the conserved motif B of the polymerase domain of the L protein, the other being M628L. In collaboration with Marty Moore, Emory University, it was confirmed that these QUAD mutations, when introduced into the L gene, gave resistance to ALS-8112.

Although ALS-8112 seemed to be a promising candidate compound, it lacked sufficient oral bioavailability. As for various other antiviral drugs, possible prodrugs were made. The di-isobutyl ester (ALS-8176, Fig. 10) was selected. In a primate efficacy model, oral ALS-8176 reduced RSV in lung samples by >4 $\log_{10}$ (to below the limit of detection) and by ~ 3 $\log_{10}$ in nasal samples.

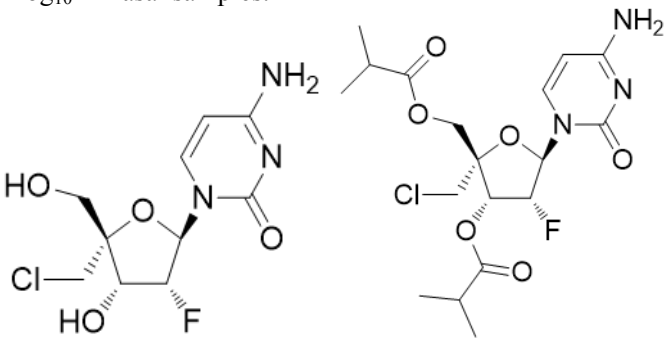

Figure 10. ALS-8112 and oral prodrug, ALS-8176 (4'-chloromethyl-2'-deoxy-3',5'-di-O-isobutyryl-2'-fluorocytidine).

In a Phase 1 study (n = 76), oral ALS-8176 dosing regimens were increased up to 2 loading doses (LD) of 750 mg followed by up to 26 maintenance doses (MD) of 500 mg twice daily for 14 days. No safety signals were identified. In a human RSV-challenge study, ALS-8176 was assessed in healthy volunteers. Of 62 participants inoculated with RSV (ITT population), 35 (56%) met the definition for RSV infection and were included in the ITT-infected population. There were three dosing regimens of ALS-8176, each twice daily for 5 days: 350 mg each dose, 750 mg LD and 150 mg MD for 9 doses, 750 mg LD and 500 mg MD for 9 doses. About 12 hours after the first detection of RSV or on the morning of day 6, whichever occurred first, subjects were randomised and received the first dose of ALS-8176 or placebo. The primary efficacy end point was the area under the curve (AUC) for viral load in nasal washes, as determined by a RT-PCR assay for RSV RNA. There appeared to be an advantage when a loading dose was used, the reductions in AUC for viral loads being 73.4%, 85.3% and 88.0% vs. placebo, respectively (Fig. 11).

A secondary end point was the clearance rate of RSV RNA (the slope of the viral load change). It was most rapid in the two regimens with a loading dose, there being reductions even at the first post-dosing sample at 12 h. In contrast, the viral load in the placebo group peaked about 3.5 days after randomisation. Importantly, this peak in RSV viral load was associated with a peak of symptoms. In the three treated groups, the mean symptom score and the mucus weights remained at about baseline throughout the observation period.

This proof-of-concept study suggested that ALS-8176 was not only efficacious but that it appeared to be more active than a RSV-fusion inhibitor tested in a previous study of similar design. ALS-8176 is currently being evaluated in young children. It is hoped that the results may be available by the end of the year (2016).

Jerome then switched focus, to influenza virus. Favipiravir has been approved in Japan for serious influenza infections and is still in Phase III trials in the USA. It is known that favipiravir-TP can be incorporated by influenza RNA polymerase, either base-pairing with cytidine (17-fold less than guanine) or uridine (30-fold less than adenine). Jerome and his colleagues were interested to discover what other polymerases could be inhibited by favipiravir-TP. They confirmed that norovirus RNA polymerase was inhibited but also that favipiravir-TP was a substrate for human mitochondrial RNA polymerase. This finding suggests that there is an opportunity to discover an analog of favipiravir which has better specificity for influenza RNA polymerase. Jerome's conclusion was that they are still far from having such a nucleoside analog. However, there are some non-nucleoside inhibitors of influenza polymerase in early clinical trials, for example, AL-794, S- 033188 and VX-787. Although a suitable nucleoside analog may be hard to find, it may potentially lead to the most effective drug.

VI. My personal conclusions.

Each year, ISAR presents three major awards, this year to Doug Richman (Elion award), Bob Vince (Holý award) and Jerome Deval (Prusoff award). Doug and Bob have each made important contributions to the HIV field. The path towards discovery of HIV therapies, which combine good safety with the ability to prevent the emergence of HIV resistance, is an amazing success story. Even now, starting a new chapter, cabotegravir and EFdA both have the potential not only to be used for therapy but also to prevent transmission. Atripla showed the way how two companies can work together to create a new, simple and effective single-tablet regimen. Likewise, if EFdA and cabotegravir were to be combined into one long-acting injection (e.g. once every three months), it would have the potential to limit HIV transmission even in the poorer countries of the world. These two compounds have complementary

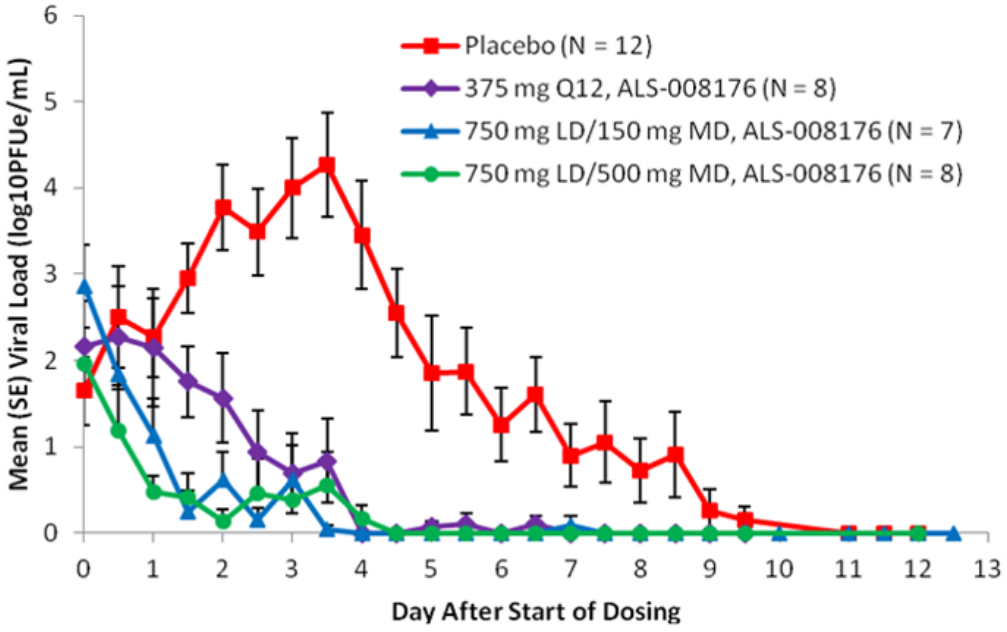

Figure 11. ALS-8176 human RSV-challenge study in healthy volunteers. (DeVincenzo et al, NEJM, 2015).

activities, first to reduce HIV DNA production, then to inhibit its incorporation into host DNA.

We know that preventing transmission is an achievable aim. When trial subjects took Truvada (FTC/TDF) once daily prior to exposure (PrEP), transmission was essentially prevented, there being no seroconversions in subjects taking the drug daily. However, this trial also proved that once daily dosing was not an acceptable regimen for most of the trial participants. If women can have an injection of EFdA/cabotegravir with their monthly contraceptive injection, HIV transmission may become a practical reality.

Whereas there are several excellent HIV therapies, Jerome Deval pointed out that there are very few small molecule drugs approved for negative strand (-) RNA viruses, none of these being virus replication inhibitors. In particular, RSV infections in young children can be serious, even fatal but there are no effective therapies. Jerome and his colleagues set out to discover a nucleoside analog to selectively inhibit RSV polymerase. They chose this aim because nucleoside analogs have the potential to be active against a broad range of virus strains and have a high genetic barrier to resistance. Indeed, nucleoside analogs have become the backbone of the therapies for herpesviruses, HBV, HCV and HIV infections.

Jerome described the work leading to the discovery of ALS 8112 and its oral prodrug, ALS-8176. The proof-of-concept trial in human subjects infected with RSV showed that ALS-8176 was highly effective and well tolerated. Currently, there is an ongoing clinical trial in infants (1 to 12 months old) hospitalized with an RSV infection (ClinicalTrials.gov, Identifier: NCT02202356). The primary outcome measures cover safety issues, the secondary aims covers the effects on the RSV infection, including viral RNA concentrations in nasal aspirates, emergence of resistance and changes in RSV polymerase. Also, pharmacokinetic parameters will be measured. The estimated date for completion is September 2016.

Although the efficacy of ALS-8176 in the adult trial was excellent, it is hard to predict how effective ALS-8176 will be in infants who have little or no natural immunity to RSV. However, one hopes that ALS 8176 has the potential to become a game-changer for patients with RSV infections.

The three awardees gave excellent lectures which set the standard for the rest of the meeting. Together with the La Jolla sunshine, this was a memorable ICAR – I warmly thank the ISAR organisers for delivering another outstanding meeting.

POSTER AWARD RECIPIENTS
(Katherine Seley-Radtke)

Kathie Seley-Radtke and Bob Buckheit with the poster awardees

This year's poster competition involved a total of 42 entries over the three categories. As always, the competition was stiff and made for difficult decisions for the poster judges. In the end, the following winners were selected:

Category 1: Graduate Student (1st place: $1000; 2nd place: $500 each)
- 1st: Michael Norris, #102: Targeting Intracellular Ion Homeostasis for the Control of Respiratory Syncytial Virus
- 2nd (Tie): Cecilia Cima, #029: Microwave-Assisted Synthesis of Nucleotide Phosphoramidates
- 2nd (Tie): Simon Weising, #071: Synthesis of Nucleoside Triphosphate Prodrugs (NTP) of Abacavir and Carbovir

Category 2: Post-doctoral (1st place: $1000; 2nd place: $500 each)
- 1st: Paula Ordonez Suarez, #025: Effect of SAMHD1 on the Anti-HIV-1 Activity of Nucleoside Analogues in Monocytoid Cells
- 2nd (Tie): Joana Rocha-Pereira, #081: Interferon Lambda (IFN-λ) Prevents Infection with the Murine Norovirus by Blocking Mouse-to-Mouse Transmission
- 2nd (Tie): Jessica Spengler, #151: Humanized Mouse Models of Filovirus Disease: Screening Model for Vaccines and Therapeutics?
- 2nd (Tie): Patricia Jorquera, #072: KPT-335, a Selective Inhibitor of Nuclear Export (SINE) Compound, Reduces Respiratory Syncytial Virus (RSV) Replication *In Vitro*

Category 3: Young Investigator (1st place: $1000; 2nd place: $500)
- 1st: Radim Nencka, #159: Rational Design of Selective Phosphatidylinositol 4-Kinase IIIbeta Inhibitors as Highly Potent, Broad-Spectrum Antiviral Agents
- 2nd: Michael Lo, #042: Broad-spectrum Antiviral Activity of GS-5734, a Novel Adenine Nucelotide Analog Prodrug Across the Families Filoviridae and Paramyxoviridae
-

In addition, the poster committee selected several posters for shotgun talks, which were presented in the last session of the conference. All but one of the winners selected presented their work. Unfortunately Jessica Spengler, poster #151, had already left the conference so was unable to participate.

Shotgun Talks
- #034, Andre Civra: Oxysterols Potently Inhibit Human Rotavirus Infection by Hampering the Virus-cell Penetration Process
- #051, Valeria Cagno: Gold Sulfonated Nanoparticles Displays a Virucidal Activity Against HSPGs Dependent Viruses
- #072, Patricia Jorquera: KPT-335, a Selective Inhibitor of Nuclear Export (SINE) Compound, Reduces Respiratory Syncytial Virus (RSV) Replication *In Vitro*
- #102, Michael Norris: Targeting Intracellular Ion Homeostasis for the Control of Respiratory Syncytial Virus
- #151, Jessica Spengler: Humanized Mouse Models of Filovirus Disease: Screening Model for Vaccines and Therapeutics?
- #159, Radim Nencka: Rational Design of Selective Phosphatidylinositol 4-Kinase III beta Inhibitors as Highly Potent, Broad-Spectrum Antiviral Agents

The team of hard working poster judges this year included Kathie Seley-Radtke (Chair), Graciela Andrei, Andrea Brancale, Bobby Buckheit, Jinhong Chang, Brian Gentry, Robert Geraghty, Zlatko Janeba, Justine Julander, Raj Kalkeri, Suzanne Kaptein, Chris Meier, Jennifer Moffat, Guy Pilkington, Roger Ptak, Luis Schang, Enzo Tramontano, ZQ Wang, and even our new President, José Esté. Thanks goes out to the judges for giving up their time to help with this important aspect of ICAR, and we look forward to seeing more outstanding posters (and giving away more money!!) in Atlanta next year!

ISAR BUSINESS MEETING REPORT
(Brian Gowen and Graciela Andrei)

ISAR held its annual business meeting during the 29th ICAR on Tuesday, April 19. Brian Gowen (Treasurer) presented a brief summary of the society's finances.

Net assets at the end of the 2015 fiscal year totaled approximately $675,000 from several bank and investment accounts, and a CD which matures in October of 2016 (Table 1).

ASSETS STATEMENT
International Society for Antiviral Research
30 September 2015

Assets	
Bank Accounts	$ 351,872.72
CD's	$ 106,747.65
Investments	$ 215,950.87
TOTAL	$ 674,571.24
Liabilites	
Accounts Payable	$0
TOTAL	$0

Table 1. Fiscal year 2015 net assets

This is down from approximately $721,000 at the end of the 2014 fiscal year and is largely due to the net $45,378 deficit from the 2015 meeting in Rome, Italy (see ISAR News Vol. 25.3). Also presented was the year-end financial statement reflecting our revenue sources and expenses for 2015 (Table 2)

International Society for Antiviral Research
Financial Statement 2015
12/31/15

2015 Income		
Membership Dues	$	8,105.00
Sponsorship Support	$	143,034.20
Chu Family Foundation	$	10,000.00
Member Support	$	1,500.00
Registrations for ICAR	$	157,648.99
Gain/Loss Investments	$	(3,368.53)
Total	$	316,919.66
2015 Expenditures		
Administrative	$	28,234.96
WIS Expenses	$	7,742.88
ICAR 2016	$	6,549.87
ICAR 2015	$	305,354.12
Total	$	347,881.83
Net Income	$	(30,962.17)

Table 2. Year-end financial statement for 2015

Graciela Andrei (Secretary) provided a report on the 2016 ISAR Membership and on attendance at the 29th ICAR in San Diego as of April 4, 2016 (Fig. 12). Thirty-three countries are represented in the Society, with a total of 399 members up to March 29, 2016 *versus* 401 members for 2015. A total of 258 delegates from 20 different countries attended the 29th ICAR..

This year, the Society received 60 applications for a travel grant award and because of the restricted amount of available budget, some of the grant applications could not be funded. Based on the scientific comparison of the submitted abstracts, a ranking was established following the scores provided by 4 independent reviewers. The Society awarded a total of 44 Travel Grants (23 for PhD students, 8 for post-doctoral fellows and 13 for senior investigators) to help these members defray the costs of attending the conference. Depending on the distance to be travelled, awardees received a grant in the range of $250 to $1600. The total amount awarded was $41,525. A world-wide distribution [Africa (2), North America (12), South America (3), Asia (12) and Europe (15)] of the Travel Grants was reported. As shown in Table 3, considerable travel funds have been made available by the Society during the past few years to increase the attendance of young investigators at the meeting.

Importantly, next year the Society will make available travel grant awards (selected based on merit of the abstract submitted) and travel assistance (aimed at stimulating the participation of researchers from countries that are unable to finance their attendance to the meeting). Applicants are encouraged to apply and to read the instructions for travel grant award and for travel assistance applications on the website.

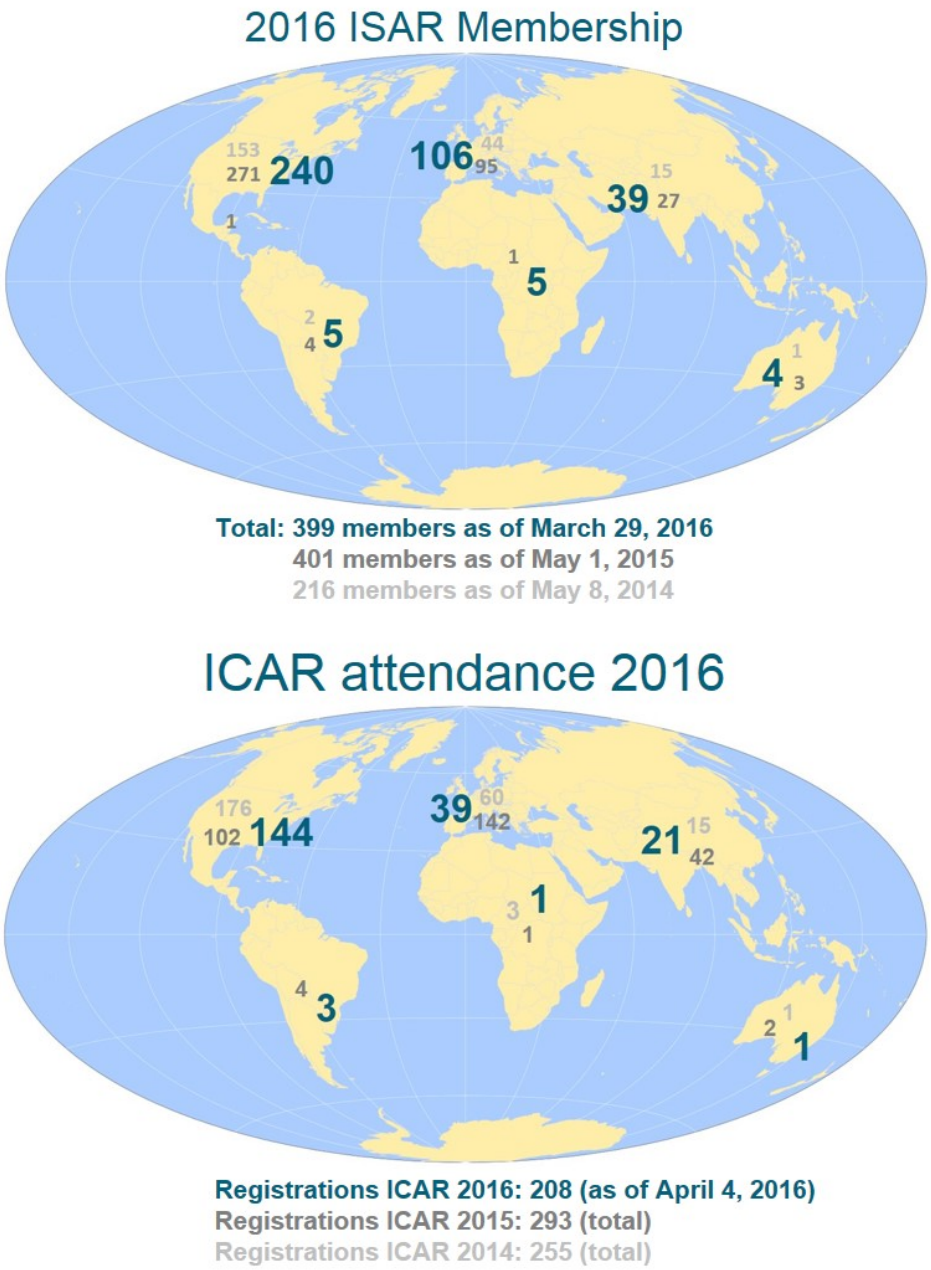

Figure 12. 2016 ISAR membership and ICAR attendance

	2012 (Sapporo)	2013 (San Francisco)	2014 (Raleigh)	2015 (Rome)	2016 (San Diego)
Number of awards	16	44	30	52	44
Total amount awarded	$32,940	$44,815	$34,910	$34,045	$41,525

Table 3. Evolution of ICAR Travel Awards

WOMEN IN SCIENCE
(Rhonda Cardin)

Rhonda Cardin, Kathie Seley-Radtke and Kara Carter

WIS Roundtable (Amy Patick and Karen Buckheit)

The **4th Annual Women in Science Roundtable,** the first event on the first day of ICAR, was held on Sunday, April 17, from 11:30-2:00 PM.

The WIS Roundtable in La Jolla used a lively 'speed mentoring' approach, in which moderators moved from table to table to facilitate small group conversations on the following topics:

- **Do super-women exist?** How to balance work and family through all stages of life. (Moderators: Kathie Seley-Radtke and Zlatko Janeba)
- **Where do I go from here?** Maximize the benefits of the mentor-mentee relationship (Moderators: Jennifer Moffat and Bart Tarbet)
- **Negotiation:** Tips on how to secure a mutually advantageous outcome without selling yourself short (Moderators: Rhonda Cardin and Robert Buckheit)
- **Is there a glass ceiling left to crack?** How to manage workforce equality (Moderators: Karen Buckheit and Heather Greenstone)
- **Awards and recognition:** Learn effective self-promotion to gain recognition and achieve professional goals (Moderators: Graciela Andrei and Enzo Tramontano)
- **Communication and management styles**: Understanding gender differences (Moderators: Kara Carter and Bobby Buckheit)

Once again, it was a very successful Roundtable event, with the participants engaging in discussion on these important topics. We were especially happy to welcome our male ISAR members at the Roundtable!

Jennifer Moffat moderates the group conversation.

2016 Chu Family Foundation Scholarships (Amy Patick)

Thanks to a generous donation from the Chu family, seven young women with the potential to make significant contributions to the field of antiviral research received Chu Family Foundation (CFF) Scholarships in 2016. This year, there were 19 applicants from all over the world: Northern Ireland, Finland, Greece, Italy, Argentina, Hong Kong, Spain, Australia, and the United States. All were highly competitive. Five were chosen to receive $1500 scholarships, and two received $750 honorable-mention awards. Each award includes a 2-year ISAR membership and a commemorative certificate.

The awardees of $1500 are:

- Lindsay Broadbent (Postdoc; Queens University Belfast, Belfast UK) for attendance at 10th International Resp Sync Virus Symposium
- Nam Nam Cheung (Grad student; The University of Hong Kong, Hong Kong, China) for attendance at 4th Antiviral Congress
- Nicole Haese (Postdoc; Oregon Health & Science University; Oregon, USA) for attendance at 29th ICAR
- Jessica Spengler (Postdoc; Centers for Disease Control and Prevention; GA, USA) for attendance at 29th ICAR
- Shuo Wu (Postdoc; The Baruch S. Blumberg Institute; PA, USA) for attendance at 29th ICAR

The awardees of $750 (honorable mention) are:

- Erofoli Giannalkopoulou (Grad student; Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Athens, Greece; Athens, Greece) for attendance at 29th ICAR
- Valeria Cagno (Grad student, University of Torino; Montcalieri, Italy) for attendance at 29th ICAR

The scholarship funds may be used to attend a conference, visit a laboratory, take a course or acquire specialized training. The awards also include a 2-year membership in ISAR and a commemorative certificate. To be eligible, an applicant must be working in an area of antiviral research and be an undergraduate or grad student, or have no more than five years of cumulative postdoctoral experience. The CFF and WIS Committees presented the awards at ICAR.

WIS Mentoring Program (Rhonda Cardin and Jennifer Moffat)

The Mentoring Program was launched at the 2014 ICAR in Raleigh, NC, when Roundtable participants were asked if they would like to be mentored or serve as mentors. Mentees and mentors were matched after filling out a questionnaire on their current interests, career goals, and what each of them wanted to achieve.

After its start in Raleigh, the program has grown significantly and has been a huge success. Following their first face-to-face meeting at ICAR, mentors and mentees have contact either by email, phone, or skype. Mentors provide career advice and scientific expertise in academia and the pharmaceutical industry. The response has been overwhelmingly positive.

After matching mentors and mentees at the La Jolla ICAR, the WIS Mentoring program continues in 2016 with 7 mentors and 8 mentees. They work in all realms of antiviral research at universities, institutes, and companies, and they focus on chemistry, pharmacology, virology, and other aspects of drug development. They span the career spectrum from graduate students to Directors and Presidents. The women in the program are also geographically diverse, coming from Argentina, Belgium, Canada, Germany, Nigeria, and the United States. Within the U.S., mentors and mentees come from Alabama, California, Oregon, Louisiana, Maryland, Michigan, New York, Pennsylvania, and Utah. It is remarkable that ISAR brings women together for professional support across these domains and distances.

Moving forward! (Rhonda Cardin)

After the conclusion of the 29th ICAR, Amy Patick stepped down as WIS Chair, handing over this position to Rhonda Cardin. Jennifer Moffat assumed the leadership of the WIS Mentoring Program from Rhonda. For the next WIS Roundtable, Karen Buckheit will be in charge of the Roundtable, and she'll be looking for new ideas from ISAR members to make the event even more helpful to women scientists. Amy Patick will continue to lead the Chu Family Foundation Scholarships Program. Finally, many thanks to all the members of the WIS Committee for their hard work and dedication as we move forward!

ISAR: THE THIRD DECADE

(Anthony Vere Hodge)

At the 28th ICAR in Rome, Bob Buckheit (ISAR President) asked the Publication Committee to take on the task of organising the publication of a booklet "The Third Decade" to follow on from the two previous booklets. That early notice gave us some thinking time. What trends and themes should be included? Although no practical steps were taken, the topic was identified as being one of the most important to discuss at the Publication Committee meeting at the 29th ICAR in La Jolla.

Prior to the end of ICAR, Bob Buckheit and Phil Furman kindly (bravely?) offered to take on the organisation of "ISAR: The Third Decade". Listed below are some preliminary thoughts but we warmly welcome other comments and suggestions. Please send your ideas to Bob Buckheit and Phil Furman (info@isaricar.com)

- *What have been the major themes over the third decade?*
- *The smooth, evolutionary transition from the old guard to the new.*
- *From paper to digital.*
- *How has ICAR changed?*

Continuing the trend, already evident during the second decade, from companies using ICAR as a meeting to make new announcements to ICAR becoming a training meeting, informing researchers about areas outside their own. Such cross-fertilization has helped to stimulate long-term collaborations.

Other trends: Fund-raising efforts (thanks to Roger Ptak and the Finance committee) have steadily improved the financial position of ISAR. More positive efforts to reach out to potential new ICAR attendees. Co-sponsorship of meetings (e.g. Japan).

- *How has the role of women in ISAR developed?*
- *What are the future challenges for the fourth decade?*

ANTIVIRALS ON THE HORIZON

New antiviral therapies from Gilead Sciences (Robert Jordan)

Gilead Sciences has announced several developments in recently approved and investigational antiviral therapies designed to transform and simplify care for people with life-threatening viral illnesses around the world. These developments include a novel tenofovir prodrug for treatment of HIV and HBV, a pan-genotype single tablet regimen for HCV and a novel nucleoside prodrug for treatment of Ebola. The highlights from these recent announcements are described below.

Tenofovir alafenamide (TAF) is a novel prodrug of tenofovir. TAF was designed to improve upon the renal and bone safety profile of tenofovir disoproxil fumarate (TDF) containing regimens. The development of TAF was initiated to address observations that older patients with HIV or HBV may be at increased risk for development of age- and treatment-related comorbidities, including low bone mineral density and renal impairment. This is due to the combination of viral infection, antiviral treatments and the natural aging process. TAF-based regimens allow for more efficient delivery of tenofovir to target cells and tissues at substantially lower doses than TDF-based regimens. While TAF and TDF generate the same active metabolite, tenofovir diphosphate (TFV-DP), TAF achieves higher intracellular levels of TFV-DP in relevant cell types, resulting in similar efficacy at lower doses compared to TDF.

The regulatory approval of three TAF-based fixed-dosed combinations for treatment of HIV are supported by clinical data that shows similar levels of antiviral efficacy at a dose less than one-tenth compared to that of TDF. In addition, there was notable improvement in surrogate laboratory markers of renal and bone safety as compared to TDF in clinical trials in combination with other antiretroviral agents. The long-term clinical significance of these changes has not been established. Because TAF enters cells more efficiently than TDF, it can be given at a lower dose resulting in >90% percent less tenofovir in the bloodstream. This improved safety profile has provided expanded options for appropriate patients receiving long term therapy based on tenofovir.

Recent studies presented at 14th European Workshop on HIV & Hepatitis in Rome, Italy explored the potential for TDF and TAF to cause mitochondrial toxicity *in vitro*. These data would help address concerns by physicians that high levels of TFV-DP within cells could be cytotoxic. This concern was based upon the observation that some HIV-infected patients treated with nucleoside reverse transcriptase inhibitors (NRTIs), particularly dideoxynucleosides, have experienced a range of clinical symptoms due to mitochondrial toxicity. These older NRTIs deplete mitochondrial DNA (mtDNA) by inhibiting mitochondrial DNA polymerase γ. The results of the current studies show that neither TAF nor TDF inhibited mtDNA synthesis in human T-cell lines at supra-pharmacological drug exposures *in vitro*. These data are consistent with an established lack of inhibition of mitochondrial DNA polymerase γ by the active metabolite TFV-DP, and indicate that despite delivering higher intracellular levels of TFV-DP than TDF, TAF still has low potential for inhibiting mtDNA synthesis in T-cells of HIV-infected and TAF-treated patients.

The FDA approved the first TAF based HIV therapy, a four drug single tablet regimen consisting of elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg and tenofovir alafenamide 10 mg as a complete regimen for the treatment of HIV-1 infection in patients 12 years of age or older who are treatment naïve or who are replacing their current HIV-1 medicines and whose healthcare provider determines they meet certain requirements. This approval was followed by the approval of another single tablet regimen consisting of emtricitabine 200 mg/rilpivirine 25 mg and tenofovir alafenamide 25 mg, which is indicated as a complete regimen for the treatment of HIV-1 infection in patients 12 years of age and older in treatment naïve patients with a viral load less than or equal to 100,000 copies per milliliter or to replace a current regimen in patients whose healthcare provider determines they meet certain requirements.

Subsequently, the FDA separately approved FTC/TAF, a fixed dose combination of emtricitabine 200 mg/tenofovir alafenamide 25 mg, indicated in combination with other antiretroviral agents for the treatment of HIV-1 in patients 12 years of age and older. (FTC/TAF is not indicated for use as pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.). Please see the full Prescribing Information, including Boxed Warnings, for each of Gilead's TAF-based products, available at Gilead.com.

TAF is also being evaluated for use in chronic HBV patients and is awaiting regulatory approval. Recent data from two Phase 3 clinical trials evaluating investigational use of once-daily tenofovir alafenamide (TAF) 25 mg in treatment-naïve and treatment-experienced adults with HBeAg-negative and HBeAg-positive chronic HBV infection demonstrated that TAF was non-inferior to TDF based on the percentage of patients with HBV DNA levels below 29 IU/mL at 48

weeks of therapy. Importantly, TAF also demonstrated less impact on renal and bone laboratory safety parameters compared to TDF, similar to observations made in HIV-infected patients. The most commonly reported adverse events in both studies included headache, upper respiratory tract infection, nasopharyngitis and cough, and occurred at similar rates in patients receiving either TAF or TDF.

One of the challenges faced by physicians treating HCV is providing effective regimens to treat all HCV genotypes. Recently, Gilead Sciences announced data on an all oral pan-genotypic regimen for the treatment of chronic HCV infection that has completed phase 3 trials and has been submitted for regulatory approval in the US and EU. The once-daily tablet containing the nucleotide analog polymerase inhibitor sofosbuvir (SOF) 400 mg and the pan-genotypic NS5A inhibitor, velpatasvir (VEL) 100 mg can be used with or without ribavirin (RBV) for the treatment of HCV GT 1-6 in treatment-naive or –experienced adults with chronic infection, whether non-cirrhotic or cirrhotic.

The data (Table 4) supporting this regimen come from four Phase 3 clinical studies evaluating this regimen for the treatment of genotype 1-6 chronic HCV infection. After 12 weeks of treatment, these data show high cure rates of sustained virologic response 12 weeks after completion of therapy (SVR12) in multiple patient populations infected with HCV of different genotypes, either alone or with RBV for advanced cases of cirrhosis. Achieving SVR12 is considered a virologic cure. The most common adverse events in the four studies were headache, fatigue and nausea, and were comparable in incidence to the placebo group included in ASTRAL-1.

The global response to the recent Ebola epidemic in West Africa was hampered by the lack of effective therapeutics to treat Ebola virus disease (EVD). Gilead has developed a novel investigational adenosine nucleoside prodrug, GS-5734, to treat EVD. GS-5734 inhibits Ebola virus (Kikwit and Makona variants), Sudan virus, and Marburg virus in cell-based assays (EC_{50} = 0.06 to 0.24 μM). GS-5734 is highly selective for viral polymerases and inhibits a surrogate viral RNA polymerase from respiratory syncytial virus (IC_{50} = 1 μM) but not human mitochondrial RNA or DNA polymerases (IC_{50} > 200 μM).

Following IV administration in nonhuman primates, GS-5734 is rapidly converted to active nucleotide triphosphate (NTP) in PBMCs, and distributes to testes, epididymis, eyes, brain and other tissues relevant to infection. Intravenous administration of 10 mg/kg GS-5734 on Day 3 post infection protected 100% of rhesus monkeys against Ebola virus challenge. In addition, systemic viral load and EVD disease signs were significantly reduced. GS-5734 represents the first known small-molecule antiviral agent that demonstrates robust therapeutic efficacy in a nonhuman primate model of EVD against multiple variants of Ebola virus. The compound is currently in phase II clinical development.

Table 4. Single-tablet regimen containing the nucleotide analog polymerase inhibitor sofosbuvir (SOF) and the NS5A inhibitor, velpatasvir (VEL): results of Phase III trials.

Study	Population	N	Treatment	Duration	SVR12 Rates
ASTRAL-1 *116 patients received placebo (SVR12=0%)*	Genotypes 1,2,4,5,6 19 percent (121/624) with cirrhosis	624	SOF/VEL	12 weeks	Overall: 99% (618/624) GT1: 98% (323/328) GT2: 100% (104/104) GT4: 100% (116/116) GT5: 97% (34/35) GT6: 100% (41/41)
ASTRAL-2	Genotype 2 14 percent (38/266) with cirrhosis	134	SOF/VEL	12 weeks	99% (133/134)
		132	SOF+RBV	12 weeks	94% (124/132)
ASTRAL-3	Genotype 3 30 percent (163/552) with cirrhosis	277	SOF/VEL	12 weeks	95% (264/277)
		275	SOF+RBV	24 weeks	80% (221/275)
ASTRAL-4	Genotypes 1-6 All with Child-Pugh class B (decompensated) cirrhosis	90	SOF/VEL	12 weeks	83% (75/90)
		87	SOF/VEL+RBV	12 weeks	94% (82/87)
		90	SOF/VEL	24 weeks	86% (77/90)

UPCOMING MEETINGS OF INTEREST

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

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

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

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

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

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

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

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

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

The 19th EUROPIC will take place in les Diablerets, Switzerland, on 4-8 September, 2016. Topics will range from hepatitis A and polio to foot-and-mouth disease, with sessions focusing on the virus life cycle, viral genetics, eradication strategies, antiviral therapy and other topics. Eckard Wimmer will give the opening keynote lecture, and Johan Neyts will chair the session on antivirals. For more information, contact Johan or go to http://www.europic2016.org/

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

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

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

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

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

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

The summer school is organized and led by Enzo Tramontano and Elias Maccioni of the Department of Life and Biological Sciences at the University of Cagliari; Parolin at the University of Padova; and Stuart Le Grice of the Center for Cancer Research at

the NCI in Frederick, MD, USA. For information on the 2016 summer school and to review the programs of the 2012 and 2014 meetings, go to http://people.unica.it/iaaass/

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