ISAR News
Newsletter of the International Society for Antiviral Research

Report on the 27th ICAR 12–16 May 2014, Raleigh, NC, USA

President's message (Bob Buckheit)

It was great to see everyone in Raleigh last month. I thought our annual meeting was a terrific success and appreciate your contribution to the meeting. True to the ISAR brand, we were provided with fine scientific presentations, excellent Award Lectures, Keynotes and Symposia, an extraordinary EUVIRNA session, and a variety of networking opportunities. Once again, I think the meeting reinforced the special family-like feel that exists among ISAR members. I look forward to continuing this great tradition during the next two years as President of the Society as well as undertaking several new programs to enhance the benefits of your membership.

As always there are so many people to thank for all the effort that goes into the planning and execution of an ICAR meeting and I don't have room to even begin that effort. I believe Phil did an excellent job of recognizing everyone at our Banquet, including our Board members, Committee chairs, speakers, audiovisual team, and Courtesy Associates. However, as I begin my term as President I would like to thank and congratulate my predecessor Phil Furman on the completion of his tenure as President. Phil has contributed greatly to antiviral research and to the Society and I look forward to continuing to work closely with Phil over the next two years to take advantage of his experience and guidance. I am also looking forward to working with our President-Elect José Esté. José has contributed so much to the Society over the many years that I have been involved and it has always been a pleasure to work with him to further the goals of the Society. Mark Prichard organized an excellent program for the Raleigh meeting and, having spent many years as Program Chair myself, I fully understand the level of effort which goes into putting our programs and speakers together. The superb efforts of Roger Ptak to raise sponsorship money for the Society continue to keep our finances in fine order and enable us to hold our annual meeting. Graciela Andrei worked diligently to provide so many deserving young investigators travel grants to be sure they were able to attend and contribute to our meeting. ISAR has initiated a fantastic Women in Science Program and this year Amy Patick and her Committee expanded their efforts to an active mentoring program for young women in science. They will shortly announce the opening of their scholarship program. Andrea Brancale continues to improve the utility of our website and has recruited Ilane Hernandez Morales to lead and energize our social media presence on LinkedIn and Facebook. Anthony Vere Hodge and Mike Bray are working closely to improve the content of ISAR News in order to make the publication full of science and member news in addition to our customary reporting from Committees. Their efforts will also result in a much closer association of our Society with Elsevier and the journal *Antiviral Research*.

There are many more people to thank than I have room for here but I would be remiss if I did not specifically thank our outgoing Treasurer Dale Barnard for his many years of service to the Society and Hugh Field who after many years of service is stepping down from his role as Chair of the Publications Committee. One last thanks is also in order –to Justin Julander for the many years he spent as our official Society photographer and to Joy Feng who has so graciously and energetically assumed the role of photographer. There are many more people to thank individually than

I have room for here but I would be remiss if I did not emphasize that your efforts are very much appreciated.

As I think about what I would like to accomplish as President of our Society, many things come to mind. Like the many presidents before me, I obviously want to leave the Society in better shape than I found it. With that in mind, here are a couple of high priorities for me for the next two years:

President's Letter: During my tenure, I will communicate with you to keep everyone informed about projects that the Society is working on that I believe will be great additions to the many positive things we do for our membership. Please let me know what you think about these activities as well as other initiatives you have thought about that will improve the Society and make membership in the Society more valuable, especially if you would like to get involved in helping us with any of these initiatives.

Young Investigators: One of my primary goals over the next two years is to find ways to ensure that the next generation of ISAR leaders gets involved in the Society. ISAR must identify and train our future leaders to assure that the Society will be in good hands when the current leaders retire. As part of our efforts, I hope to find ways to enhance travel grants so that travel for Young Investigators is possible in these tough economic times and to establish an awards program for Young Investigators that can provide cash for travel to scientific meetings or for training that will help to enhance scientific careers. The Women in Science initiative is pioneering these types of award programs and I hope we can adapt them to further our educational mission and attract new sponsorships to the Society. This year's Young Investigator/New Member reception was very well attended and it was great for me to see all the bright and energetic faces in the crowd and to have the opportunity to meet most of the attendees. Now I want to be sure our young members can return and take on important roles within the Society. *If you were one of these individuals at the reception (or at the WIS luncheon) and would like to be part of an ongoing discussion group to examine ways to energize the young ISAR members, please reach out and let me know you want to get involved.*

Ambassador Program: Though most meeting attendees are from North America and Europe, every year we get a few from other corners of the globe. These attendees add greatly to the diversity of the Society and provide a different viewpoint on viruses and antivirals that are important for our understanding of the needs for future antiviral drug development. I would like to identify ways to increase attendance and membership from these places - like Africa, South America, and Asia. Basically we would like to have representatives of ISAR (Ambassadors) in all corners of the globe that can reach out within their local and regional geographic areas to promote ISAR and ICAR and hopefully attract a much more geographically and culturally diverse membership within ISAR. I will be attempting to connect with attendees from many areas (including North America and the various regions of Europe) to begin the process of establishing a subcommittee that will assist our current membership committee with generating interest in ISAR. *Like to help? Please let me know!*

ISAR News: In the past, ISAR has produced two issues of the ISAR News per year. Most of what has been included in the News has been reports from Committee chairs and the development of the ICAR program. Although these are important, the Society is going to make changes to the ISAR News to make the publication more relevant to our mission of education and a desire to make the News a valuable piece of your membership. The ISAR News will go to 4 issues beginning this year and in addition to the improved customary content we will begin to focus on activities among our members, new publications in the field, what our young members are doing, and interviews with Society members on a variety of topics. Our hope is that the ISAR News will become an important component of your membership in the Society and will have content that will make you look forward to receiving it and read it from cover to cover. I, and all members of the Publication Committee, welcome suggestions for how to enhance the content of ISAR News.

Thanks for taking the time to read this, my first installment of a President's Letter to the membership. I look forward to working with all of you to make the Society an important part of your scientific family!

Scientific report: Highlights of 27th ICAR, 12–16 May 2014, Raleigh, NC, USA (Anthony Vere Hodge)

I. Introduction

This review provides an overview of the conference highlights. As this is a research conference, any references to clinical results should not be taken as a recommendation for clinical use. I wish to thank all those authors who have kindly provided me with copies of their presentations and for giving me valuable comments.

This summary has abridged reports on the lectures by the recipients of the Society's three major awards and the keynote presentations. Please see the Scientific Report (published in the same issue of *Antiviral Research*) for the full reports and an account of the three mini-symposia (*Hepatitis B virus, Research Triangle Park* and *Challenges in HIV Infection, Treatment and Prevention*).

II. Gertrude Elion Memorial Award Lecture: Collaborative Antiviral Studies for the Discovery of Drugs to Treat Cytomegalovirus Infections

John C. Drach, University of Michigan, Ann Arbor, Michigan, USA

Gertrude B. (Trudy) Elion was born in New York City and was pleased to work for Burroughs Wellcome Co. when based in New York but was concerned when it transferred to Research Triangle Park, North Carolina, not many miles from this year's meeting site. However, within just a few months she declared that she was "at home" in North Carolina. She was awarded the Nobel Prize in Physiology or Medicine in 1988 for career accomplishments in the discovery of drugs to treat organ rejection, cancer, and viral diseases.

The focus of John's presentation was on the research stages conducted in his and his collaborators' laboratories that ultimately led to the invention of three compounds which were discovered to have antiviral activity and which later entered clinical trials: BDCRB pyranoside (GW275175X) (Phase I), maribavir (Phases I, II and III) and cyclopropavir (Phase I). His major collaborators included Drs. Karen Biron, Charles Shipman, Leroy Townsend, and Jiri Zemlicka.

Being inspired by the presence of a naturally-occurring 5,6-dimethylbenzimidazole nucleotide in Vitamin B12, research on benzimidazole nucleosides was initiated by medicinal chemists in the 1950's and '60's. This led to the synthesis of a trichloro analog and its 2-bromo analog (BDCRB) in Townsend's laboratory at the University of Utah and later the discovery of their activity against human cytomegalovirus (HCMV) in John's laboratory. Surprisingly it was not active against other herpesviruses and did not need conversion to a triphosphate to be active. Collaborative studies with Karen Biron at Burroughs Wellcome established that these compounds acted by a novel mechanism, inhibition of the terminase which cuts newly synthesised HCMV DNA into unit lengths for packaging into virions. Although BDCRB had many desirable properties *in vitro*, it had poor pharmacokinetics in mice and monkeys due to hydrolysis of its glycosidic bond. Further work led to BDCRB pyranoside and maribavir. Both compounds had excellent activity against human CMV, low toxicity, and excellent pharmacokinetics. Quite unexpectedly, they had different mechanisms of action.

Figure 1. Phil Furman presenting the Elion Award to John Drach

BDCRB pyranoside like BDCRB, inhibited HCMV terminase. In contrast, maribavir inhibits DNA synthesis, albeit indirectly via inhibition of the viral kinase (pUL97) which phosphorylates another viral protein, pUL44. Phosphorylated pUL44 is necessary for viral DNA synthesis; thus inhibition of pUL97 by maribavir inhibits viral DNA synthesis.

Cyclopropavir(CPV) was synthesized in the laboratory of Dr. Jiri Zemlicka, Karmanos Cancer Institute, Detroit, Michigan. It is a non-nucleoside guanosine analog which is also very active against human CMV. Like GCV, it is phosphorylated by the kinase encoded by UL97. It is more potent *in vitro* and *in vivo* than ganciclovir but has a somewhat different pattern of resistance. Cyclopropavir is currently in phase I clinical trials for the treatment of HCMV infections.

III. The Antonín (Tony) Holý Memorial Award Lecture: From modified nucleoside to a chemically modified genome.

Piet Herdewijn, Rega Institute for Medical Research, KU Leuven, Belgium

The 2013 ICAR started with a symposium, on the legacy of the late Antonín Holý, at which the establishment of a new ISAR award in medicinal chemistry was announced. The awardee is to be a senior scientist of international stature in medicinal chemistry and who has made innovative contributions impacting antiviral drug discovery and/or development. Piet is the first to receive this award.

In the late 1970s, the potent activities of BVDU and BVaraU against HSV-1 and VZV were discovered; this activated Piet to start antiviral research with the synthesis of carbocyclic BVDU. Through to the early 1990s, he synthesized several other nucleosides with bicyclic bases having good activity against HSV-1 and VZV. During the 1990s, emphasis switched to investigating the effect of modifying the sugar ring, in particular the synthesis of six-membered rings containing an oxygen or a double bond.

Figure 2. Piet Herdewijn giving the Antonín (Tony) Holý Memorial Award Lecture

Back in 1984, Erik De Clercq showed Piet a paper on AIDS, one of the authors being Phil Furman. This publication stimulated the search for anti-HIV compounds. Many compounds were discovered with potent activities and Piet worked out the first structure-activity studies of anti-HIV dideoxy nucleosides. Then Piet's work took a different pathway. It is possible to link several nucleotides together to form aptamers. For example, the above antiviral nucleosides, which have a 6-membered ring in place of the natural furanose, could be incorporated into hexitol nucleic acid (HNA) aptamers. X-ray studies revealed that the structures of HNA-HNA duplexes were simila to that of an RNA-RNA duplex with the same base sequence. HNA-containing aptamers were shown to be potent and specific inhibitors of HIV replication. It took four years to engineer a polymerase which would utilise HNAs to assemble a strand complementary to a DNA template. This success stimulated the concept that it may be possible to generate new forms of biologically active DNA.

In order to pursue this idea, a culture system with twin growth chambers was devised. The aim was to replace thymine with 5-chlorouracil using *Escherichia coli* (*E. coli*). Initially, the nutrient contained 10% 5-chlorouracil and 90% thymine. With each cycle, seeding one chamber from the previous one, the proportion of 5-chlorouracil was increased. After 180 days, in which there had been about 4000 generations of *E. coli*, thymine had been replaced totally by 5-chlorouracil. An interesting outcome was that the alternative base led to a change not only in the genotype but also in the phenotype; the "new" *E. coli* particles were much longer than the original.

This is the first example of a DNA polymerase being adapted through evolutionary pressure to accept a nucleotide analog, resulting in the generation of a new living organism.

IV. The William Prusoff Young Investigator Award Lecture: Use of nucleotide prodrugs to enhance selectivity of anti–HIV and –HCV agents

Adrian S. Ray, Gilead Sciences Inc., Foster City, CA, USA

Adrian started his lecture with photos of William (Bill) Prusoff and reminisced of his days with Bill, Raymond Schinazi and Yung-Chi (Tommy) Cheng.

Adrian presented examples to illustrate two models of how a prodrug-strategy can transform a potential drug into a much improved clinical candidate. In the first, the prodrug alters the distribution of the pharmacologically active nucleotide analog to tissues where viral infection is taking place (on-target) and away from tissues resulting in adverse events (off-target). In the second, the prodrug improves the activity of potentially-selective drug candidate via by-passing an inefficient activation (phosphorylation) step. Sofosbuvir (Sovaldi®), a prodrug of 2'-F-2'-*C*-MeUMP, was approved in the USA on 6th December 2013 for treatment of patients infected with hepatitis C virus (HCV). This is a fine example of a prodrug enhancing the activity of the parent compound.

Figure 3. Phil Furman giving the William Prusoff Young Investigator Award to Adrian Ray

As an example of how prodrugs can improve targeted delivery, the history of the GS-6620 program was presented. Although the C-adenine analogue (2'CMe-4-aza-7,9-dideazaA, C-Nuc1) was 30-fold less active than the corresponding N-nucleoside, MK608, in a HCV replicon assay, their triphosphates were equally effective against HCV NS5B polymerase and, in primary human hepatocytes, C-Nuc1 was phosphorylated to the triphosphate more efficiently than the N-Nuc (MK608). This illustrates the importance of using primary human tissues.

C-Nuc1 seemed to have a benign *in vitro* toxicity profile, including not inhibiting the mitochondrial DNA polymerase gamma, but it had very significant toxicity in animals. In a collaboration between Gilead and Craig Cameron at Pennsylvania State University, the researchers sought to identify the toxicity target(s) for ribonucleotide analogues, including C-Nuc1 and drugs that had been stopped in Phase II trials. All the latter were efficiently incorporated into RNA by the mitochondrial RNA polymerase (>70% of the corresponding natural nucleotide). The triphosphate of C-Nuc1 was also an efficient substrate (22% the rate of ATP). In contrast, ribavirin was poorly incorporated (about 5%) and sofosbuvir was below the limit of detection (= 0.02%). More extensive *in vitro* and cell culture evaluation of the compounds could have saved the expense of taking them into clinical trials.

The Gilead team sought analogs that were not incorporated by this RNA polymerase. Adding a CN group to the 1' position to C-Nuc1 did not change the activity as an HCV NS5B polymerase inhibitor (IC_{50} 0.3 μM) but it did reduce incorporation in the mitochondrial RNA assay (<0.02%). However, a prodrug was required to bypass an inefficient activation step. A nucleotide prodrug, GS-464335 (a mixture of diastereoisomers at phosphorous) was well absorbed in dogs (>80%) with about 80% of the absorbed drug being taken up by the liver. Inside cells, GS-464335 was converted to the corresponding monophosphate which was efficiently converted to the triphosphate. A pure stereoisomer was selected and named GS-6620. In a Phase II trial (900 mg, bid 5 days), the mean reduction in HCV load was about $\log_{10}$ 1.5. Two subjects achieved HCV RNA < 25 IU/ml. However, the pharmacokinetics and antiviral responses were highly variable. Whereas the activity results were disappointing, clinical proof of concept was observed in terms of safety. GS-6620 did have a markedly improved safety profile relative to C-Nuc1. The story of GS-6620 illustrates both how nucleotide prodrugs enable further progression of candidates and also the complexity of predicting the behaviour of nucleotide prodrugs across species. One wonders what cell culture test or animal model may have predicted such variability.

Adrian switched to HIV. There has been a shift in the focus of antiretroviral therapy (ART), from solely control of HIV replication to now include tolerability in older, possibly obese, patients. The first approved prodrug of tenofovir (TFV) was TFV disoproxil fumarate (TDF). More recently, TFV alafenamide (TAF) has been progressed into clinical development. A key difference in the properties of the two prodrugs is their stability in plasma, with half-lives of 0.4 and 90 minutes, respectively. The EC_{50} values for TFV, TDF and TAF are 1.2, 0.015 and 0.003 μM respectively. Whereas the gain in cell culture EC_{50} value may be modest, importantly, this is not the only gain. The increased stability of TAF allows it to load on-target cells and tissues (e.g., lymph nodes) for a longer period of time resulting in increased lymphoid cell and tissue levels at greatly reduced circulating TFV, leading to less exposure to off-target tissues (e.g., kidney). Clearly the lower dose of TAF (25 mg) relative to TDF (300 mg) will give TAF a marked advantage when considering combination pill therapy.

Adrian went on to describe how a prodrug approach transformed a new nucleotide project. Their starting point was GS-2128 (D4APi) which had good activity against both wild-type (wt) and resistant HIV strains but was an active inhibitor of mitochondrial polymerase gamma. On comparing the known structures of HIV RT and mitochondrial polymerase gamma, differences in the 2' binding pocket were noted. This led to GS-9148 in which 2'-F was added to GS-2128.

Compared to TFV, GS-9148 was about 3-fold less active against wt HIV but maintained better activity against resistant strains. Most importantly, it was inactive (>300 μM) against mitochondrial polymerase gamma. More than 50 prodrugs were synthesised and evaluated in metabolism studies and in dogs. This led to GS-9131. Whereas tenofovir is efficiently utilised by renal uptake transporters, GS-9148 was poorly taken into the kidney. No adverse renal findings were observed with the prodrug (GS-9131) in 28-day studies in rats, dogs and monkeys at the highest doses tested (300 mg, 20 mg and 30 mg/kg daily, respectively).

In summary, this work has given examples of the prodrug approach being used successfully both to increase selectivity (by loading on-target tissues vs off-target tissues) and to increase activity (via bypassing metabolic constraints).

V. Keynote addresses:

A. Eradication Therapies for HIV: Building the Critical Path.

David Margolis, University of North Carolina, NC, USA

In HIV-infected patients, there is a long-lasting reservoir of HIV in the form of integrated viral DNA in resting CD4+ memory cells of the host immune system. It has been estimated that their half-life ($t_{1/2}$) is about 73 years. Therefore, even if it were possible to eliminate 100% of viral replication,

Figure 4. Keynote speakers David Margolis (left) and Myron Cohen (3rd from left) with Phil Furman (ISAR president, 2nd from left) and Bob Buckheit (ISAR President-Elect, right)

a reservoir of HIV would remain. There may be reservoirs in other long-lived cells. To date, there is only one known HIV patient who has been cured of his infection, the "Berlin Patient".

To reduce the reservoir of HIV, it was suggested that activation of integrated HIV in resting CD4+ T cells would lead to HIV RNA synthesis and possibly result in cell death either due to viral cytopathic effects or resulting from HIV-specific immune responses. A small clinical trial was set up to test this hypothesis. Vorinostat (VOR), a clinically approved drug for treating certain cancers, has been shown to bind to the active site of histone deacetylases. After a single dose, there was an increase in HIV RNA (1.5 to 5-fold, mean 2.6-fold). Of these subjects, 5 elected to continue with multiple doses. Whereas a single VOR dose did increase the expression of HIV RNA, neither single nor multiple doses removed the HIV reservoir.

B. HIV Prevention 2014-2021: Managing Aspiration and Expectation.

Myron Cohen, University of North Carolina, NC, USA

Myron noted that there are 2.5 million new HIV infections each year. In this context, anal sex may be an important factor because just one or a few virions of HIV can be infective. Although anal sex has been associated with homosexual couples, it is not uncommon amongst heterosexual couples (about 1 in 30).

Although behavioural education should be encouraged, it can never be the whole answer. Various approaches to the prevention of HIV transmission are being evaluated but most progress is being made using drugs. Dapivirine rings, containing TDF, are designed to stay in the vagina for a month. Phase III trials are ongoing. A long-acting HIV integrase inhibitor, GSK 1265744 (generally known as GSK 744), is administered i.m. once every 3 months. Phase I trial has been completed and Phase II trial is being planned.

By analogy with tuberculosis therapy, could HIV transmission rates decrease with effective ART? In 2005, the HIV Prevention Trials Network (HPTN) initiated a study (HPTN 052) which enrolled 1,763 HIV-sero-discordant couples. The infected partner had to be well enough not to require immediate ART. The couples were randomised to have either immediate or delayed ART. Both groups received the same supportive care.

Myron reported the 10th annual review of this study. In the delayed ART group, there had been a total of 28 cases of HIV transmission with the HIV strain linked to the partner and 11 cases of unlinked transmission. In the one case of HIV transmission in the

immediate ART group, further investigation suggested that the infection event was on day 1. Clearly, early ART is highly beneficial. CDC guidelines now recommend that all HIV infected patients should have ART.

VI. Conclusion

The three major award lectures exemplified the strength of ICAR, covering very different areas of research. John Drach (Elion Award) described his journey through the early days of antiviral research which led to the identification of novel modes of antiviral action. Piet Herdewijn (Holý Award) used evolutionary pressure to create DNA polymerases to accept novel nucleosides. The replacement of thymine by 5-chlorouracil led to the generation of a new form of *E. coli*. I suggest that this work has important implications in conventional antiviral research. With HIV and HCV protease inhibitors, the genetic barrier is limited by the ability of the viral protease and its substrate (the viral polyprotein cleavage sites) to co-mutate so that the virus can become resistant to the antiviral drug. So far, polymerase inhibitors have not suffered the same fate but this work shows that a poor choice of nucleotide analogue could result in a resistant virus with a new type of RNA. Adrian Ray (Prusoff Award) demonstrated how the prodrug concept can markedly improve both the efficacy and safety of potential drugs. Their progress with HIV and HCV therapies has been remarkable.

The keynote addresses tackled two emerging areas of HIV research. David Margolis summarised the work aiming to eradicate HIV from infected subjects and Myron Cohen described the current progress with approaches to prevent HIV transmission. HIV ''cure'' still seems to be a distant prospect but prior to exposure prophylaxis (PrEP) has been shown to be an achievable aim. Although daily dosing is a barrier to success, future prospects look bright.

Further information on other presentations at this ICAR, can be found in the full Scientific Report published in *Antiviral Research*.

Elsevier has introduced a new ''usage dashboard'' showing the number of times an article has been viewed. I am pleased to see that, to 31st May 2014, my Scientific Report on the 26th ICAR has been viewed 1195 times.

I would like to add my thanks to the ISAR Officers and Conference Committee for organizing another interesting and successful ICAR.

Poster Award Recipients at the 2014 ICAR (Katherine Seley-Radtke)

This year's ICAR saw more than 50 posters submitted for judging by the poster awards committee. This year's hard-working judges included the chair of the poster awards committee Kathie Seley-Radtke, along with committee members Graciela Andrei, Andrea Brancale, José Esté, Anthony Ham, Brian Gentry, Gilles Gosselin, Chris Meier, Jennifer Moffat, Johan Neyts, Luis Schang and Zhengqiang Wang.

In the Young Investigator category, the first place prize ($750) went to Sharon Tamir for poster 57 - ''Anti-influenza and anti-inflammatory activity of KPT-335, a selective inhibitor of nuclear export (SINE) in mice and ferrets''. Second place ($500) went to Tietjen for poster 77 - ''Discovery of novel acylguanidine-based small molecules that block influenza A M2 ion channel activity and drug-resistant virus''.

In the Postdoc category, there was a three-way tie ($500 each) between:

- Fang Gao for poster 119 – ''Sting agonist induces a potent innate antiviral immune response against hepatitis B virus'';
- Benjamin Morin for poster 136 – ''A versatile in vitro assay identified inhibitors and stimulators of non-segmented negative-sense RNA virus polymerase function''; and
- Uma Singh for poster 72 – ''A convergent synthesis of anti-HBV agent, FMCA and its prodrug FMCAP''.

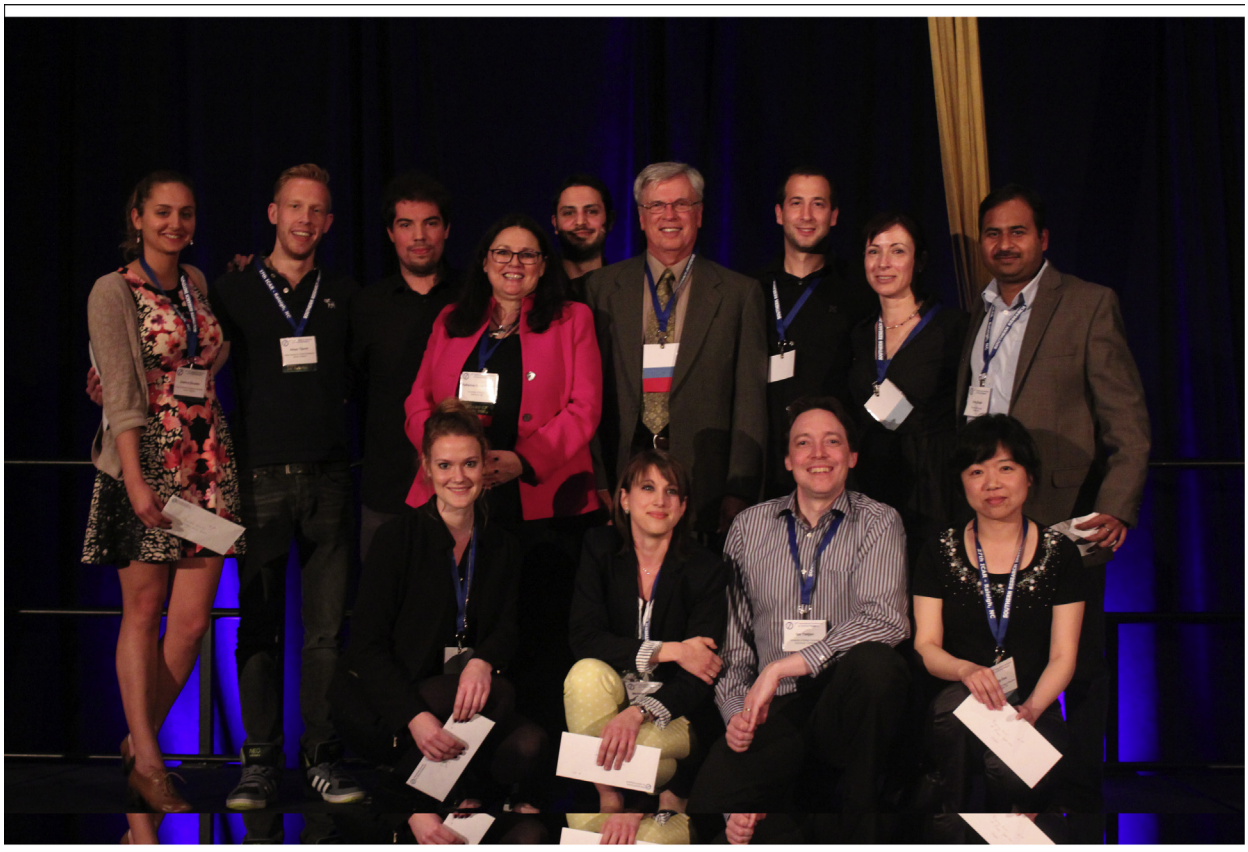
In the Graduate Student category, the first place prize ($750) went to Pietro Scaturro for poster 201 – ''Characterization of the mode-of-action of a potent dengue virus capsid inhibitor''. For the first time in ICAR history, there was a five-way tie for second place ($500 each)!! The winners were:

- Thiago Dinis de Oliveira for poster 39 – ''Investigating the highly potent D-carba-DT in primer extension assays'';
- Aloys Tijsma for poster 78 – ''An enterovirus 71 mouse model with central nervous system involvement'';
- Michela Cancellieri for poster 82 – ''Rational design, synthesis and structure activity relationships of a series of anti-CHIKV compounds'';
- Ina Karen Stoeck for poster 185 – ''Identification of host factors involved in lipid droplet homeostasis and the replication of hepatitis C and dengue virus by RNA9 screening''; and
- Joanna Zmurko for poster 198 – ''Host-pathogen interaction as a potential target for development of antivirals; role of SUMOylation in DENV life cycle''.

In addition to the poster awards, six posters were selected for the 5-minute shotgun talks which closed out the conference:

- Matthew Howe for poster 51 – ''A novel allosteric small molecule inhibitor of inducible Hsp70 reduces dengue virus infection'';
- Ian Tietjen for poster 77 – ''Discovery of novel acylguanidine-based small molecules that block influenza A M2 ion channel activity and drug-resistant virus'';

Figure 5. 27th ICAR Poster Award winners with Katherine Seley-Radtke and Phil Furman



- Farah Alayli for poster 100 – "The dengue virus NS1 protein modulates innate immune signaling early during infection";
- Chandrav De for poster 115 – "Dioxolane L-nucleoside analogue, L-BHDU, inhibits VZV replication by depleting the cellular dTTP pool";
- Fang Gao for poster 119 – Sting agonist induces a potent innate antiviral immune response against hepatitis B virus"; and
- Ekaterina Taneva for poster 158 – "Pharmacokinetics and pharmacodynamics of tenofovir disoproxil fumarate in the female genital tract".

All of the talks were excellent – concise and to the point and most importantly, kept on time!

Congratulations to all of the poster winners (Figure 5) and we look forward to an equally exciting competition next year!

International Society for Antiviral Research (ISAR): Women in Science (Amy Patick)

At the 2013 ICAR, ISAR launched its first Women in Science (WIS) Roundtable, which was a great success with 41 participants. This forum allowed Society members and ICAR attendees, both women and men, to come together to discuss the challenges and opportunities encountered by female scientists while navigating the twists and turns of career progression in today's environment. The roundtable utilized a lively "speed dating" approach in which participants moved from table to table to discuss a variety of topics. Based on this success, the ISAR Officers and Board formalized the Society's interest in developing Women in Science initiatives by forming the new WIS Committee chaired by Amy K. Patick and including prominent ISAR women scientists: Graciela Andrei, Rhonda Cardin, Kara Carter, Heather Greenstone, Ann Kwong, Jennifer Moffat, Anneke Raney, Katherine Seley-Radtke and Karen Watson-Buckheit. At the recent 27th ICAR in May 2014, WIS hosted the 2nd Annual Women in Science Roundtable following a format similar to that held in 2013 with 43 participants (Figures 6–9). In addition, the WIS committee has established a Career Development Scholarship Fund, and ISAR has provided initial seed funding in the amount of $10,000 to establish the fund. ISAR Career Development Awards will support the professional development of women with potential for significant contribution in the field of antiviral research by providing funds to attend a conference, visit another laboratory, take a course, or acquire specialized training. Each award will consist of a $1500 stipend, a 2-year ISAR membership and a

Figure 6. The 2nd annual Women in Science Roundtable attracted many participants

Figure 7. WIS Committee members (from L to R): Rhonda Cardin, Graciela Andrei, Katherine Seley-Radtke, Lauren Deaton, and Amy Patick

Figure 8. WIS Committee members (from L to R): Karen Watson-Buckheit, Kara Carter, and Heather Greenstone

Figure 9. WIS Committee Member Jennifer Moffat at the 2nd annual WIS Roundtable

commemorative certificate. The WIS Committee also recently developed a pilot Mentorship program for ISAR women scientists and started a LinkedIn page for ISAR WIS members. The ISAR WIS Committee eagerly looks forward to continue its mission to support women scientists through initiatives such as the scholarship awards and ICAR roundtables and to expand its membership.

Business meeting (Graciela Andrei)

The Society held its business meeting during the 27th ICAR in Raleigh. The President, Treasurer, Secretary, and the Committee Chairs presented their reports.

Phil Furman, President of the Society, announced the results of the elections held last year and congratulated the President-elect, José Esté (AIDS Research Institute-IrsiCaixa and AIDS Unit, Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, Spain); Treasurer, Brian Gowen (Department of Animal, Dairy and Veterinary Sciences, Utah State University, Logan, UT, USA); and the new Board Member, Jennifer Moffat (Department of Microbiology and Immunology, SUNY Upstate Medical University, Syracuse, NY, USA). These candidates were strongly supported and duly elected. An electronic (web-based) election was run and an e-mail was sent to 390 registered members. A total of 97 voters responded, representing a 25% 'turnout' which is 5% higher than for the previous election.

Joe Colacino, Past President of the Society and Conference Committee Chair, invited Romano Silvestri to present Rome, Italy, as the location for the 2015 conference, May 11-May 15. The 28th ICAR meeting will take place at the Parco dei Principi Hotel with Romano Silvestri as local organizer. The locations for the 29th and 30th ISAR meetings are being discussed. Members are requested to send their

preferences for the top three host cities for the 2016 and 2017 ICAR meetings to Courtesy Associates (ISAR@courtesyassoc.com).

Dale Barnard, Treasurer, presented a summary of the accounts for 26th ICAR held in San Francisco, CA 2013 (Table 1). Although the 26th ICAR Meeting in San Francisco was expected to provide a favourable balance, it resulted in a deficit of $81,315. This negative balance could be attributed to the low number of walk-in registrations, the failure to obtain NIH funding and the higher than expected costs of food and beverages.

The Society's financial report for 2014 is provided in Table 2, showing a positive balance ($53,409).

Table 1. Summary accounts for 26th ICAR, San Francisco, CA 2013

26th ICAR
San Francisco, CA
2013

REVENUE	Estimate	Final
Registration	$193,850	$170,030
Award Sponsorship	$10,000	$10,000
NIH Contribution	$0	$0
Corporate Sponsorship	$175,000	$122,600
Other Revenue	$5,000	$7,500
Total	$383,850	$310,130
EXPENSE		
Advertising	$1,300	$3,027
Site Selection Trip	$3,000	$0
Food and Beverage	$159,700	$182,592
Audio Visual	$32,100	$47,846
Hotel Expenses	$5,000	-$6,164
Exhibits/Posters	$9,000	$7,027
Invited Speakers	$22,000	$17,318
Conference Bags	$2,500	$2,228
Shipping	$3,000	$1,015
Onsite Staffing	$500	$606
Courtesy Associates - Out 0f Pocket	$7,300	$6,927
Courtesy Associates - Labor	$69,000	$65,739
Credit Card Fees	$12,000	$6,951
Other	$2,000	$3,689
Cancelled Registrations	$0	$5,060
Awards	$35,500	$47,584
Board Travel	$2,200	$0
Total	$366,100	$391,445
Estimated Balance	$17,750	
Final Balance		-$81,315

Table 2. Financial statement of ISAR for 2014

International Society for Antiviral Research
Financial Statement for 2014
5/2/2014

2014 Income		
Membership Dues		$6,425
Corporate Support		$122,175
Registrations for ICAR		$108,390
Interest		$64
	Total	$237,054
2014 Expenditures		
Administrative		$2,597
ICAR		$180,805
Membership Services		$243
	Total	$183,645
Balance		$53,409

Table 3. Net assets statement of ISAR for 2014

NET ASSETS STATEMENT
International Society For
Antiviral Research
5/2/2014

Assets	
Bank Accounts	$505,962
CD's	$103,549
Investments	$213,071
TOTAL	$822,582
Liabilities	
Accounts Payable	$0
TOTAL	$0
NET ASSETS	**$822,582**

Dale Barnard thanked Roger Ptak (Chair of the Financing/Corporate Sponsorship Committee) for securing corporate sponsorship for the 26th ICAR meeting. The Society's balance sheet shows net assets of $822,582 (Table 3).

A report on the 2014 ISAR Membership was provided by Graciela Andrei, Secretary of the Society. Eighteen countries are represented in the Society, with a total of 216 members as April 2014. A total of 272 attendees from 22 different countries registered for the 27th ICAR. A total of 112 ISAR members and 160 non-ISAR members were present in Raleigh. Considering that non-ISAR members registered at the meeting automatically become members for one year, the total membership of the Society at the end of the meeting is expected to be 376.

This year, the Society awarded a total of 29 Travel Grants (10 for PhD students, 10 for post-doctoral fellows and 9 for investigators) to help defray the costs of attending the conference. The total amount awarded was $34,910 or €25,330. A world-wide distribution [Africa (3), North America (7), Asia (5) and Europe (14)] of the Travel Grants was reported. Travel funds are intended to contribute towards travel expenses but not meeting registration or hotel expenditures. Members were encouraged to consult the ISAR website for instructions on applying for travel grants (contact person: Graciela Andrei at graciela.andrei@rega.kuleuven.be) and to apply early to avoid missing out.

Tomas Cihlar, Chair of the Career Development Committee, provided a report from this Committee which organizes the ICAR Career Forum each year. Representatives of different sectors, including academia, government, small Biotech, mid-size Pharma, large Pharma and CROs, were present at the Career Forum. The Society would like to acknowledge and thank this year's career discussion moderators: Jennifer Moffat and Johan Neyts (Academia), Gerardo

Garcia-Lerma and Christopher Tseng (Government), M. Javad Aman and Klaus Klumpp (Biotech), Joy Feng and Raj Kalkeri (Mid-size Pharma), Steve Ludmerer and Jun Tang (Large Pharma) and Jim Noah and Eric Stavale (CRO) for their participation at the 27th ICAR Career Forum. This forum provides an opportunity for discussions on career lines and choices, and helps students to establish contact with senior members and learn from their experiences. Placement advertisements continue to be offered at the ISAR website, under Career opportunities. International advertisements of available positions are open to everyone and do not require ISAR membership. Advertisements will be posted for 3 months and are free of charge. Tomas Cihlar (tomas.cihlar@gilead.com) and Andrea Brancale (brancalea@cf.ac.uk) are the contact persons for posting placement advertisements.

Robert Buckheit on behalf of Mark Prichard, Chair of the Programme Committee, discussed the features of the 27th ICAR program and acknowledged the members of the Program Committee: Randall Lanier and Ronald Swanstrom, Chapel Hill, North Carolina, USA; Timothy Block, Doylestown, Pennsylvania, USA; Chris Meier, Hamburg, Germany; Tomas Cihlar, Foster City, California, USA; Donald Smee, Logan, Utah, USA; Johan Neyts, Leuven, Belgium; David Bernstein, Cincinnati, Ohio, USA; Andrea Brancale, Cardiff, Wales, UK.

Amy Patick, Chair of the Women in Science Committee, discussed the WIS roundtable. The topics of discussion included this year were:

- negotiations;
- is there a glass ceiling left to crack?
- communication and management style;
- do ''superwomen'' exist?
- awards and recognitions.

Amy acknowledged the members of the WIS Committee and also introduced the WIS Career Development Scholarships as well as the ISAR-WIS LinkedIn Group.

There being no further business, Phil Furman closed the meeting.

European Training Network, EUVIRNA, at 27th ICAR (Frank van Kuppeveld)

EUVIRNA is a network funded by the EU-FP7 Marie Curie programme and has the aim to train a selected group of 20 young scientists in a multidisciplinary and intersectoral setting to become the future leaders of the field in (+)RNA virus replication and antiviral drug development. Prof. Frank van Kuppeveld (University of Utrecht, The Netherlands) is the coordinator of the EUVIRNA consortium that consists of six leading European academic groups and three companies from the Netherlands, Germany, Belgium, France and Wales. The consortium has set the goal to integrate the different approach of the two sectors and train the fellows to know the best of both worlds. This is done by an extensive course programme that addresses both scientific knowledge and methods important for understanding virus replication and antiviral drug development (i.e. molecular virology, structural biology, microscopy, bioinformatics, high-throughput screening, structure-based drug design, medicinal chemistry, and clinical virology) and complementary skills, such as Intellectual Property Rights, presentation skills, innovation, entrepreneurship, and dissemination of science. Furthermore, a secondment programme made sure that the fellows experienced different research environments and facilitated tight collaborations between the partner institutions of EUVIRNA.

In total, 17 PhD students and 1 postdoc visited the ICAR. This conference provided them a unique opportunity to present and discuss their results with world-leading scientists and experts from companies in the field of antiviral drug development. All students presented their results during the poster session. In addition, they all provided shotgun presentations at the EUVIRNA session that was organized as part of the ICAR meeting. The research subjects ranged from basic virology studies (i.e. the study of cellular factors involved in virus replication or biochemical and structural characterization of viral proteins) to identification or design and subsequent characterization of novel small molecule inhibitors of different (+)RNA viruses. The excellent collaborations between the fellows was demonstrated by the multiple authorship of the posters and joint publications. The scientific and presentations skills were remarkable and were rewarded with an excellent assessment by the jury of the ICAR poster awards: five out of six poster prizes in the young researchers category were awarded to EUVIRNA fellows!

(Supported as an Initial Training network by the Marie Curie programme of the EU Framework 7 Programme under Grant Agreement number 264286)

Invitation to 28th ICAR in Rome (Romano Silvestri and Joe Colacino)

The 28th ICAR will be held at the Parco dei Principi Hotel in Rome, Italy from Monday, May 11th to Friday, May 15th, 2015. The hotel (Figure 10) is in an ideal location in one of the most refined areas of Rome, overlooking the Villa Borghese gardens (Figure 11). It is only a few minutes away from Via Veneto, the Spanish Steps, the Trevi Fountain and the world famous Via Condotti. The hotel, which has been recently renovated, can accommodate up to 900 people in elegant and comfortable rooms. The venue includes a large fitness center and areas designated for water treatment, relaxation and beauty.

Figure 10. Entrance to the Parco dei Principi Hotel which overlooks the Villa Borghese gardens

Figure 11. Villa Borghese and gardens

In addition to the high-quality scientific program, all attendees of the 28th ICAR will have ample opportunity to tour Rome and its environs independently or as part of organized tours and trips. Rome is the city with the highest concentration of historical and architectural riches in the world. Over 16% of the world's and 70% of Italy's cultural treasures are located in Rome. The historical center of Rome, located within the Aurelian Walls, contains nearly three thousand years of antiquity and is a priceless testimony to the cultural, artistic and historical legacy of Europe. Rome, the heart of Roman Catholic Christianity, also hosts the city state of the Vatican. And of course, participants will also enjoy the best in Italian food and wine.

All Roads Lead to Rome[1] for the 28th ICAR! You can throw Three Coins in the Fountain[2] On An Evening in Rome[3]. We promise you will not want to say "Arriverderci, Roma."[4] We look forward to seeing you in Rome!

Visit the ISAR web site.....

Visit the ISAR Web site at http://www.isar-icar.com to discover more about the 28th ICAR, such as hotel accommodations, abstract submittals, and preliminary programs. Further information on the conference will be posted on the ICAR website by September 2014. If you have any questions, please contact the ISAR/ICAR Office at 202-973-8690 or by email at ISAR@courtesyassoc.com.

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[1]The Stranglers, 1983
[2]Jule Styne and Sammy Cahn, 1954
[3]Sandro Taccani and Umberto Bertini, 1962
[4]Renato Rascel, Pietro Garinei and Sandro Giovannini, 1955