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Meeting report: 26th International Conference on Antiviral Research

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The 26th International Conference on Antiviral Research (ICAR) was held in San Francisco, California from May 11 to 15, 2013. This article summarizes the principal invited lectures at the meeting. The opening symposium on the legacy of the late Antonín Holý included presentations on his pioneering work with nucleotide analogs, which led to the development of several antiviral drugs including tenofovir. This drug has transformed the treatment of HIV infection and has recently become the first-line therapy for chronic hepatitis B. The Gertrude Elion Award lecturer described the anti-HIV activities of the CCR5 inhibitor cenicriviroc and the reverse transcriptase inhibitor fentavirin®, and also reviewed the evaluation of biodegradable nanoparticles with adjuvant activity. The William Prusoff Award winner reported on the creation of NAOMI, a computer model with 21 enzymes to predict the activity of nucleoside analogs against hepatitis C virus (HCV). Other invited lecturers discussed the development of countermeasures against severe dengue and the potential of RNA virus capping and repair enzymes as drug targets. Topics in the clinical symposium included the current status of the anti-HCV compounds sovaprevir, ACH-3102, miravirsen and ALS-2200; the evaluation of single-tablet regimens for HIV infection; and the investigation of cytomegalovirus resistance to CMX001. Two chemistry minisymposia examined strategies and tactics in drug design and the use of in drug discovery.

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1. Introduction

This article provides a summary of the invited lectures at the 26th International Conference on Antiviral Research, sponsored by the International Society for Antiviral Research (ISAR), which was held in San Francisco, California from May 11 to 15, 2013. The report begins with a synopsis of the symposium held in memory of the late Antonín (Tony) Holý, followed by brief summaries of lectures by the recipients of ISAR’s two major awards, the keynote address, the plenary lecture, the clinical symposium, and the two chemistry minisymposia. Because this paper simply provides overviews of oral presentations, it is not accompanied by references to the scientific literature. Any descriptions of favorable treatment outcomes should not be taken as recommendations for clinical use.

2. The legacy of Antonín (Tony) Holý: Nucleotides in the treatment and prevention of chronic viral infections

2.1. A personal note on the contribution and legacy of Tony Holý

Erik De Clercq, Rega Institute for Medical Research, Leuven, Belgium (Fig. 1A).

Erik described his first meeting with Tony Holý at a symposium on Synthesis of Nucleosides, Nucleotides and Polynucleotides, 3–5 May 1976 in Göttingen, Germany. He felt out of place, but privileged to be the only MD present among so many PhD chemists. Similarly, Erik found himself with many chemists at the NATO meetings in 1979 and 1983. The meeting, at Il Ciocco, Italy in May 1987, can be regarded as a model for ICAR meetings. (A photograph of the attendees at this meeting was included in the ISAR News 22-1). Tony Holý became a regular attendee at ICAR meetings.

Tony’s first clinical success was Duvira® gel which was licensed in Czechoslovakia for herpes labialis (see John Martin’s presentation below). The phosphonate compound, (S)-HPMPA, was too toxic for progression to clinical use but it was the first of a long series of compounds. Cidofovir (HPMPC) is used to treat herpesvirus infections, mainly cytomegalovirus (CMV), when resistance to first-line therapy occurs. Adefovir dipivoxil (ADV) was licensed to treat hepatitis B. But there is one drug which stands out as being exceptional. Tenofovir, as its oral prodrug, was approved for HIV therapy in 2001 and, in combination with emtricitabine (FTC) as Truvada, was approved in 2004. Atripla (combination of Truvada and efavirenz) was approved in 2006. Complera (in USA) [and Eviplera (in Europe)] was approved in 2011, and the “Quad pill” (Stribild (containing Truvada, elvitegravir and cobicistat) was approved in 2012 (in USA) and 2013 (in Europe). These single-tablet regimens, all of which contain tenofovir as a key component, have transformed HIV therapy and are giving patients many years of near-normal life.

When visiting Tony at Olomouc, Czechoslovakia, Erik noticed a UNESCO-classified monument dedicated to “The Holy Trinity”. That stimulated Erik’s thinking. He was one of a team, Tony Holý the chemist, Erik the MD and John Martin (also a chemist) from Gilead. It was the long and close collaboration among these three which enabled tenofovir to become a life-saving therapy. It seemed as if Erik and John were part of a different trinity, “a Holý trinity”. Erik showed several photographs of this “Holý trinity” in various exotic locations including the Rio Grande Gorge (New Mexico) in 1995 when the ICAR meeting was at Santa Fe (Fig. 2).

In 2003, John Martin presented Tony and Erik with a plaque of recognition by Gilead Sciences. In 2008, there was a campaign promoting Czech successes and Tony featured in a display at Prague airport (now called Vaclav Havel airport) – Tony was considered as the leading scientist of the Czech Republic. Truvada was approved for prophylactic use, to prevent the spread of HIV, on the very day that Tony died (16 July 2012).

2.2. A tribute to Antonín Holý

John Martin, Gilead Sciences, Foster City, CA, USA (Fig. 1B)

John may not have recognized himself as part of a “Holý trinity” but we were fortunate to have him as the next speaker. Like Tony and Erik, John has had a long and close association with ISAR.

Fig. 1. Legacy of Tony Holý: Erik De Clercq (left) and John Martin (right) giving their tributes.
Tony Holý was born in 1936. He synthesized his first nucleotide, (S)-DHPA in 1968, published in Science in 1978 and it was approved in Czechoslovakia as DuviC® gel. The first phosphonate, (S)-HPMPA was published in Nature in 1986. Although this compound was not progressed into a clinical drug, it led to cidofovir, approved in 1996 for the treatment of CMV retinitis in AIDS patients, and adefovir (PMEA) approved for therapy of hepatitis B. Ultimately, it was tenofovir that was to become a major success for treating HIV-infected patients. From its first introduction in 2001, its market share has increased to well over 40%. In 2002, the “Holy trinity” started thinking about a single-pill regimen. This led to Atripla being approved in 2006, Complera in 2011 and Strivid in 2012.

The “Holy trinity” has had another major success, enabling HIV-infected patients anywhere to be treated with tenofovir through the Expanded Access Program established by Gilead. Both Tony and Erik waived their royalties for sales in countries with poor access to health care. Tenofovir, in its various forms, is now available in over 130 countries and is distributed widely to the known HIV-infected patients. It is thought that this improved access to effective therapy has contributed to a marked reduction in HIV transmission, at least in part due to people being more willing to be tested for HIV, knowing that there is a good therapy available.

John ended his tribute by showing photographs of Tony at his 70th and 75th birthdays, the latter in Prague in 2011.

2.3. Tenofovir in the treatment of HIV infection

Robert Schooley, University of California, San Diego, CA, USA

In 1999, at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC, 26–30 September, San Francisco, CA, USA), the first results were reported of a 1-year study of a three-drug combination containing tenofovir (TDF) in the treatment of HIV-infected, treatment-naïve patients. TDF was comparable to d4T-containing combination for efficacy but it had fewer side effects. Compared to AZT, TDF was both more efficacious and had a better safety profile. Over 144 weeks, d4T therapy gave marked side effects, especially mitochondrial toxicity which was not a feature of treatment with TDF. As noted above, the next step was to combine TDF with emtricitabine (FTC), known as Truvada®, (licensed 2004). In a ground-breaking move, Gilead and BMS cooperated to simplify HIV therapy by combining three drugs into a single pill (Truvada with efavirenz) to form a single, once-a-day pill, Atripla® (licensed 2006).

By 2012, tenofovir was being used worldwide to treat 3.5 million HIV-infected patients, about 44% of all HIV patients receiving antiretroviral therapy. Many of them are part of the expanded access in developing countries. As an example of the impact of these initiatives, life expectancy has increased by about ten years in regions of rural Sub-Saharan Africa. Some patients have been taking tenofovir for 12 years.

2.4. Tenofovir in the prevention of HIV infection

Robert Grant, University of California, San Francisco, CA, USA

There is a clear need for the prevention of HIV transmission. Even recently, there have been about 2.5 million new HIV-infected people per year, worldwide, of whom about 40% are young adults. In the USA, the rate of new infections has remained at ~50,000/year since 1991. In part, there continue to be so many new infections because half of new transmissions happen during the acute phase of HIV infection, before patients know their HIV-infection status. Also, many patients are not on suppressive therapy; in one of the best places for therapy, San Francisco, only a minority (44%) of HIV-infected people are on therapy, whereas the average for the USA is even less (28%).

Prevention can be attempted by starting therapy either prior to exposure (PrEP) or post exposure (within 72 h but before clinical signs) (PEP). Truvada (FTC/TDF) is being evaluated as it is once-daily dosing, has a good degree of “forgiveness” for missed doses and drug resistance may occur, but only rarely and at a high cost to the viral replication capacity. A clinical trial, with prophylactic dosing (PrEP) revealed many problems, mainly due to poor adherence. In men who have sex with men (MSM), there was better efficacy than in women, but the adherence rates in women were low (from 35% to only 20%). One factor may have been the very long consent forms, which included 7 pages of potential side effects. With so many missed doses, intention-to-treat analyses become rather meaningless, so the analyses focused on outcomes relative to the amount of drug taken. Most (93%) of new infections were in subjects with no detectable drug. In contrast, it seems that there were no seroconversions in subjects taking the drug daily. Comparing subjects taking 2, 4 or 7 tablets per week, the risk of transmission increased with fewer doses per week but even two doses per week gave a slight reduction in transmission risk.

Some other factors emerged from this trial. Over the trial period, there was a trend toward safer sex (increasing condom use). Oral Truvada (FTC/TDF) appeared to be well tolerated with clinical side effects reported in <10% of subjects, generally seen in the first week and resolved while still on therapy. There were no detected cases of drug resistance to TDF but there was resistance to FTC in two cases who were already infected at baseline. An important conclusion from this work is that prophylactic therapy may help to destigmatize therapy. PrEP is now being progressed in open-label studies.

2.5. Nucleotide analogs in chronic hepatitis B – from hope to reality

Henry Chan, Chinese University of Hong Kong

Hepatitis B is naturally a slowly progressive disease which can lead to death in 30–50 years. So drug efficacy has been judged by reduction in viral load and the time taken for drug resistance to appear. Ever since the introduction of lamivudine, hepatitis B therapy has been improving. Adefovir dipivoxil (ADV) gave better control of viral load than previous therapies but at 5 years, only 60% of patients had undetectable HBV levels and resistance was present in ~10% of patients. ADV was not really active enough.

Nearly all treatment-naïve patients achieve viral suppression with tenofovir (TDF) therapy and there is still no resistance at 2 years. At 5 years, 344/348 patients had a liver biopsy which...
showed that 73% of patients had improved fibrosis scores (≥2 units) and that most other patients had no worsening. This was the most substantial efficacy seen for reducing liver fibrosis.

TDF is now internationally accepted as the first-line therapy for hepatitis B and recent guidelines include the option of monotherapy with TDF. However, ADV-resistant HBV remains a problem as these patients do not respond well to TDF.

2.6. Nucleotides in the treatment and prophylaxis of herpes and other DNA virus infections

Richard Whitley, University of Alabama at Birmingham, AL, USA

For three decades, acyclovir (ACV) has been the mainstay for the treatment of herpes simplex virus (HSV) types 1 and 2 infections in the newborn. Currently, following treatment of the acute disease, thrice-daily ACV therapy is often continued for 6 months. Future options being considered are to use valacyclovir (VACV) for 1 year, to combine ACV therapy with CMX001, a prodrug of cidofovir, and to investigate the use of PCR to give information on virus levels just before birth.

For cytomegalovirus (CMV) infections, ganciclovir (GCV) has been the drug of choice although dose reductions are often needed due to safety concerns. When investigating the pharmacokinetics of valganciclovir (VGCV) in the newborn, the area-under-the-curve (AUC) for drug plasma concentrations were much reduced at day 35 compared to day 6. In the newborn, renal function increases rapidly with age. Therefore the drug dose was adjusted to give similar AUC values at 6 and 35 days. A Phase II trial is fully accrued comparing VGCV for either 6 weeks or 6 months – data are expected June 2013.

Further in the future, combination therapy with CMX001 may be investigated. This drug is currently in Phase II trials for prevention of CMV disease in transplant patients. CMX001 is showing promise in clinical trials in patients with adenovirus and/or cytomegalovirus infections, but this progress was not included in this presentation.

2.7. Future potential and therapeutic opportunities for nucleoside phosphonates

Tomas Cihlar, Gilead Sciences, Foster City, CA, USA

Over a period of 3 decades, including 2013, there have been 7 approved therapies arising from Tony Holý’s initial work on phosphonates. These include agents for the treatment of infections with HIV, hepatitis B and herpesviruses. The discussion of future opportunities included new drug development against HIV, HBV, and other DNA viruses. For HIV infection, a new prodrug for tenofovir (TFV), tenofovir alafenamide (GS-7340, TAF) is currently in Phase III development. In comparison with TDF, TAF delivers higher levels of TFV diphosphate into PBMCs at much lower doses. TAF is being tested as a part of new single tablet regimen containing TAF, FTC, elvitegravir and a pharmacoenhancer cobicistat. In Phase II, the efficacy of the combination was similar to that of the recently approved Stribild<sup>®</sup>, with a trend toward less impact on bone and renal parameters. CMX-157, a phospholipid-based prodrug of TFV is currently in Phase 1. In healthy subjects, CMX-157 showed promising levels of parent TFV and its active metabolite in PBMCs.

TAF is also being tested for the treatment of chronic HBV infection. A Phase Ib 4-week dose escalation study with up to 120 mg TAF has been recently completed with data analysis in progress. LB-83080 is a dipivoxil prodrug of a novel guanine nucleoside phosphonate that demonstrated potent anti-HBV efficacy in a phase II 48-week study at doses of 90–150 mg. Examples of other novel antiviral clinical applications of nucleoside phosphonates for the control of herpesvirus infections include CMX001, a potent phospholipid prodrug of cidofovir, tested for the prophylaxis and treatment various DNA virus infections (mainly CMV and adenovirus). Unlike the parent drug cidofovir, CMX001 is administered orally and exhibits substantially improved safety profile than the parent compound. CMX001 (100 mg twice weekly) is being tested in Phase III trials in immunocompromised patients. The recently described anti-herpesvirus activity of tenofovir was also discussed. Although tenofovir has much less activity against HSV than HIV, clinical data suggested that the use of topical gel gives sufficiently high drug levels to reduce HSV-2 transmission. Tenofovir topical gel is being tested for the prophylaxis of HSV-2 transmission. A large Phase III study (FACTS-001) is currently in progress in Africa.

While targeting RNA viruses by nucleoside phosphonates remains a major challenge, several examples of potential additional applications of nucleoside phosphonates, beyond antiviral therapy, were mentioned. Some new phosphonates have good activity in cell culture against Plasmodium, the malaria pathogen. In addition, GS-9219, a produrg of PMEG, is in advanced stages of development for applications in veterinary oncology.

At the end of his presentation, Tomas announced the establishment of a new ISAR award in medicinal chemistry as a memorial to Tony Holý. The first award will be presented at the 2014 ICAR in Raleigh, North Carolina, USA. The awardee will receive a commemorative plaque, a monetary award and will have opportunity to present a lecture at ICAR on research work. The nominee must be a senior scientist of international stature in medicinal chemistry and who has made innovative contributions impacting antiviral drug discovery and/or development.

3. Gertrude Elion Memorial Award Lecture: My antiviral research in Fukushima, Leuven and Kagoshima

Masanori Baba, Kagoshima University, Kagoshima, Japan (Fig. 3)

Masanori Baba opened his lecture with thanks to his “great professors,” Shiro Shigeta and Erik De Clercq. He graduated from Fukushima Medical College in 1980 and entered the Graduate School of Medical Sciences. His initial studies at Fukushima, from 1980 to 1986, were with varicella zoster virus (VZV). Soon, he was collaborating with Erik, discovering the potent activity of BVDU and BVara U against VZV, and this led to his time as a postdoc at Leuven from 1986 to 1989. His close colleagues were Rudi Pauwels, Jan Balzarini and Dominique Schols. The group was investigating the HIV activity of a new class of compounds, phosphonyl purine derivatives. His first paper included Tony Holý as a co-author. They discovered the anti-HIV activity of PMEA (adefovir) which was followed later by PMPA (tenofovir). This group developed a rapid and efficient assay to test compounds. The paper “Rapid and automated tetrazolium-based colorimetric assay for the detection of...
anti-HIV compounds,” published in the Journal of Virological Methods in 1988, has been cited 1248 times.

Testing compounds led to the surprising discovery of the 6-substituted uracil derivative HEPT which had good activity against HIV-1 but was totally inactive against HIV-2. The compound was shown to be an inhibitor of HIV-1 reverse transcriptase (RT) through an allosteric mode of action. A number of HEPT derivatives were synthesized by Mitsubishi Chemical Corp. (Japan) and the optimized compound (MKC-442, emivirine) was developed by Tri- angle Pharmaceuticals (USA) but further development was halted in 2002 after comparing emivirine with abacavir in a Phase III trial.

Masanori returned to Fukushima in 1989 and moved to Kogoshima University in 1994. Three projects have produced interesting results: the discovery and development of CCR5 inhibitors with activity against HIV-1; the identification of festinavir™ (4’-ethynyl-d4T) as a novel nucleoside HIV-1 RT inhibitor; the discovery and development of biodegradable nanoparticles (NPs) with efficient antigen-carrying capacity giving potent adjuvant activity.

In collaboration with Takeda Pharmaceutical Co., two CCR5 inhibitors, TBR-652 or cenicriviroc (Fig. 4) and TBR-220 (TAK-220) were discovered and are now in Phase I/II and Phase I clinical trials respectively. In cell culture, a CCR5 HIV-1 mutant resistant to cenicriviroc was obtained but only after cultivation of PBMCs for 67 weeks. This mutant virus was not cross-resistant to TBR-220. After cultivation with TBR-220 for 200 weeks, no resistant HIV was obtained.

At the 2012 ICAR, Hiroaki Mitsuya included a summary of progress with festinavir (4’-ethyl-d4T, 4Ed4T) as a novel nucleoside HIV-1 RT inhibitor; the discovery and development of biodegradable nanoparticles (NPs) with efficient antigen-carrying capacity giving potent adjuvant activity.

Andrea Brancale, Cardiff University, Cardiff, Wales, UK (Fig. 6)

Andrea began his lecture with a reference to a 1959 paper entitled “Synthesis and biological properties of iododeoxyuridine, an analog of thymidine” by William D. Prusoff. The discovery of bicyclic nucleic acids (BCNAs) was certainly a good example of irrational drug design. A key step was dependent on the UK Royal mail and the Belgian postal service. A nucleoside analog, with no activity against HSV, apparently had activity against VZV (EC50 1 μM). Repeat testing showed that the compound itself was inactive but that the postal services had inefficiently converted the nucleoside into a bicyclic compound (about 1% conversion) which actually led to FV100 which has been progressed to Phase II trials.

In an attempt to rationalize the discovery of nucleoside analogs, which were good inhibitors of hepatitis C virus (HCV), Andrea started by modeling the HCV polymerase. However, “Pol is just one player”; nucleosides have a long path from drug to active triphosphate. Clearly, it would be useful to have a global model, including all the enzymes typically involved in nucleoside activation (or inactivation). So NAOMI was born.

Most of the enzymes involved are well characterized, several crystal structures are known and there are plenty of data on both substrates and inhibitors. The aim is to predict the activation/metabolism pathway, it should be fully automated, give a clear output and be as fast and accurate as possible. Currently, NAOMI has 21 enzymes. The accuracy of each model enzyme is improved by training with a known set of compounds and making adjust-

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**Fig. 4.** Structure of TBR-652 (TAK-652, cenicriviroc).

**Fig. 5.** Structure of festinavir (4’-ethyl-d4T, 4Ed4T).

**Fig. 6.** William Prusoff Young Investigator Award winner: Andrea Brancale.
ments to fit the experimental data. An example of a possible output was shown: ribavirin to its triphosphate showing all the enzymes which play a role. Progress so far: NAOMI is fast, with good accuracy, and it is fully automated, but questions remain. Are there more enzymes to include and is a compound a substrate or an inhibitor?

Another potential HCV target is the helicase. It has a nucleoside-TP binding site, a long channel for holding the dsRNA and possible allosteric sites. It is difficult to predict the structure of a small molecule which would bind strongly into the long channel but “Ligbuilder” produced such a compound (Fig. 7). The large number of chiral centers makes it an impractical molecule to synthesize, but chemists can recognize patterns enabling simpler compounds to be designed. In this case, the first compound made was active (EC\(_{50}\) 0.26 μM).

The next step forward was to link the computer to a joystick pointing device which allows the operator to control the position of the molecule in 3D. As the molecule approaches the enzyme, the computer calculates the forces between the molecule and the enzyme and quickly feeds that back to the joystick.

In another example of computer-aided design, the NSp2 protein is thought to be a good target for the inhibition of the chikungunya virus (CHIKV, an arbovirus) replication. No crystal structure was then known but a model was built using the NSp2 of Venezuelan equine encephalitis virus (VEEV). The model was used to screen the ZINC database containing more than 5 million compounds. The best 9 compounds were evaluated biologically and one had activity with some selectivity (EC\(_{50}\) 5 μM, CC\(_{50}\) 72 μM). At this stage, the crystal structure of the CHIKV NSp2 became available and their model proved to be accurate. SAR studies led to a better compound (EC\(_{50}\) 3 μM, CC\(_{50}\) 100 μM). The conclusion is that human input remains a key part of computer-aided design.

5. Keynote address: Know thine enemy: Using virology and immunology to develop a multifaceted approach to dengue antivirals

Eva Harris, University of California, Berkeley, CA, USA (Fig. 8)

Dengue virus has four serotypes (DENV-1, 2, 3 and 4), each of which includes several genotypes which can be sub-divided into clades. It is estimated that about 100 million people become ill each year but, fortunately, only rarely (about 500 thousand cases) does the infection develop into a rapidly progressing disease, often fatal. Many people, possibly 400 million, become infected but have no symptoms. This is important because a previous infection gives protection to a later infection with the same strain but enhances disease progression with a different strain. Understanding the reason for this is vital to develop safe dengue vaccines.

DENV has two mechanisms for entry into cells: via receptor attachment and via antibody. The latter mechanism explains how a previous infection can enhance disease progression – instead of antibody binding to the virion and leading it to its inactivation, the bound antibody gives the virus an additional route into Fc receptor-bearing target cells.

A mouse model, using minimally adapted DENV (any of the 4 serotypes) causes a self-limiting disease in mice. Transfer of antibody alone can mediate a lethal disease (known as antibody-dependent enhancement, ADE), in which the viral load is increased about 10- to 20-fold. A fusion loop antibody is cross-reactive against all serotypes. When a single mutation is specifically introduced, the mutated monoclonal antibody loses a glycosylation site, disabling its ability to bind to the cellular receptor. In the mouse model, this disabled antibody (non-FcR-binding MAb) inhibits ADE. This approach may not be able to prevent the common, relatively mild disease due to DENV but it would be a great advance to be able to prevent the progression to serious, often fatal, disease associated with ADE.

6. Plenary address: RNA synthesis, capping and repair in (+)RNA viruses, novel targets for drug design

Bruno Canard, Harvard Medical School, Boston, MA, USA

In this plenary presentation, Bruno reviewed the crucial role played by the non-coding regions at each end of the genomic RNA in the replication of RNA viruses. To prevent cellular 5’–3’ nucleases from degrading the viral genomic RNA and to allow the viral RNA to bind to host ribosomes, the virus has to acquire a cap. Essentially this can be done in one of three ways: to create a cap using viral enzymes, to steal a cap from a host RNA molecule or to use the host capping process in the nucleus. Each of these strategies has been adopted by different viruses.

The initial step, to synthesize viral RNA, is called “priming” and involves a polymerase repeatedly adding a few nucleotides, then leaving the template and starting again many times – referred to as “distributive” synthesis. Once primed, the “processive” polymerase creates the long viral RNA.

The flavivirus genome ends in a highly conserved non-coding region ending in: 5’-m\(_7\)G-A-G-hairpin-region. This part is so highly conserved, that, when the input virus is mutated (for example, from A-G to G-G), the output virus will have reverted to A-G. Similarly, dengue viruses have the conserved A-G, and the polymerase seems to be able to create this A-G without a template. Flaviviruses have capping enzymes, for example a protein (NSp5) having a
methyltransferase domain which is able to catalyze two types of methylation, 7-Me on guanine and 2’-OMe on adenine.

Coronaviruses have by far the longest genomes (about 30,000 bases) of the (+)RNA viruses; other viruses have genomes up to 15,000 bases. Like flaviviruses, coronaviruses have viral enzymes involved in making a cap. For example, the NSp16 protein has 2’- O-methyltransferase activity. Surprisingly, the corresponding NSp16 protein in the SARS coronavirus seems to have the correct sequence to be a capping enzyme, but it has no activity in vitro. However, NSp16 forms a complex with NSp10 to give enzymatic activity. Also, the complex (NSp10/NSp14) acts as an efficient exonuclease for correcting a cap mismatch. The coronavirus polymerase (NSp12) forms a complex (with NSp7, NSp8 and NSp14) which has proofreading ability. Presumably, coronaviruses have evolved this capability which enabled them to have a much larger genome than other (+)RNA viruses.

7. Clinical symposium

7.1. Clinical development of sovaprevir and ACH-3102: Two second-generation direct-acting anti-HCV agents

Hetal Kocinsky, Achillion Pharmaceuticals Inc, New Haven, CT, USA

Sovaprevir (ACH-1625) is an HCV protease inhibitor (PI). Pharmacokinetic studies (PK) showed that the drug targets the liver. No boosting with ritonavir is needed. In a dose-escalation Phase I study, doses from 50 to 2000 mg were well tolerated, both as single or multiple doses. Once-daily dosing for 5 days gave a reduction in HCV RNA load (3.8–4.2 log10 for all doses). In a Phase Ia trial, sovaprevir (200, 400 or 800 mg once daily) was administered with ribavirin (RBV) and compared to placebo. At 28 days, all doses were active (viral load reduced by 2–4 log10 by day 4) but there was little dose response. At 12 weeks, the sustained viral response (SVR) was between 77% and 85% but without a real dose response. Sovaprevir appeared to retain activity against strains resistant to previous PIs. There were some elevated ALT levels at the 400 and 800 mg doses but these were reversible while still on drug. Development is continuing with the 200 and 400 mg doses.

ACH-3102 is an inhibitor of NS5A. This viral protein has no known enzymatic activity but domain 1 binds to viral RNA and domain 2 guides viral assembly. A Phase I PK study evaluated doses from 25 mg to 1000 mg. ACH-3102 has a long plasma half-life (T1/2) of about 250 h or 10 days. It is active against all genotypes and strains resistant to earlier NS5A inhibitors. It appears to have a high genetic barrier to resistance. Single doses from 25 to 300 mg gave about a 4 log10 reduction in viral load, but there was no real dose response. In a Phase Ia trial (n = 8), ACH-3102 was administered with RBV. As this drug has such a long T1/2, a loading dose (225 mg) was given on day 1 and 75 mg given once daily thereafter. The end-points were sustained viral response for 4 and 12 weeks (SVR4 and SVR12). Two patients had multiple resistant mutations to earlier drugs, but still responded. SVR4 and SVR12 were 5/8 (63%) and 6/8 (75%), respectively. A few patients had loss of detectable virus by week 2. There were no viral breakthroughs, but one patient relapsed after therapy and was then put on dual therapy.

The combination of sovaprevir and ACH-3102 has also been investigated. There was no change in their PK when combined, either in fed or fasted subjects. There were three segments in a Phase Ia study: segment 1, sovaprevir (400 mg) was combined with ACH-3102 (150 mg loading dose, 50 mg maintenance dose) and RBV (vs placebo control). Segment 2 was the same, except that 200 mg sovaprevir was used. In segment 3, those on placebo previously were offered active therapy. So far, 160 patients have received ACH-3102. This trial (ACH120-007) is ongoing.

7.2. Preclinical and clinical studies of miravirsen, a novel anti-HCV therapeutic targeting the host factor miR-122

Amy Patick, Patrick Pharmaceutical Consulting on behalf of Santarion Pharma, San Diego, CA, USA

Within the 5’UTR of HCV, there are two six-nucleotide regions, known as seed sites 1 and 2 (S1 and S2). These sites are highly conserved through all genotypes of HCV and bind to a host micro-RNA (miR-122) which is present in liver cells. This interaction prevents the degradation of the viral RNA and thereby enables HCV to replicate. Miravirsen is a 15-base oligonucleotide containing 8 blocked bases (5’-30’CCmGmTcmAmCmTmC’mC-C’-3’). It binds to miR-122 and so prevents its binding to viral RNA.

In cell culture, miravirsen is active against all genotypes 1–6 of HCV. It retains activity, as expected, against resistant strains to all the direct acting anti-HCV drugs. In a test to investigate resistance, using telaprevir as a positive control, there were many resistant colonies present at 25 days with telaprevir. With miravirsen (80 µM), there were 148 colonies present at 15 days, but none sequenced so far has had mutations.

In a chimpanzee study, miravirsen (1 or 5 mg once weekly for 12 weeks) gave a 2–3 log10 reduction in viral load with the 5 mg dose. Early Phase I and Phase IIa studies have been completed. PK studies confirmed dose-dependent plasma and liver levels. The only "safety issue" was the expected prolonged cholesterol reduction via its known effect on fatty acid metabolism. In a proof-of-concept study (SPC6649-203), treatment-naive patients with genotype 1 chronic HCV infection were treated with miravirsen (3, 5 or 7 mg) given once weekly for 4 weeks (5 doses) and the patients were followed to week 18. There was a clear dose response and, after dosing, the reduction in viral load continued until week 8. With the 7 mg dose, the mean reduction in viral load was 3 log10 and 4/9 patients became HCV RNA undetectable. Treatment was well tolerated. The miR-122 binding region of HCV RNA from every patient was sequenced at baseline, at 5 weeks and at 4 weeks if the virus levels had risen above the nadir. No significant changes were detected in the miR-122 binding region (i.e. excluding those at baseline). Further trials, in combination with other antiviral compounds, are planned.

7.3. ALS-2200/VX-135, and the role of nucleoside analogs in the treatment of chronic hepatitis C

John Fry, Ailiox BioPharma Inc, South San Francisco, CA, USA

ALS-369 is a uridine nucleotide analog showing good anti-HCV activity with good selectivity; ALS-2200 is the oral produrg and VX-135 is a single diastereoisomer of ALS-2200. Inside cells, the active form is the triphosphate analog, which acts as a chain terminator; the triphosphate acts as a chain terminator; the T1/2 is about 40 h, long enough to allow once daily dosing. It took passing in cell culture for 5 months to obtain a resistant mutant, S282T, giving a shift in EC50 of about 100 h. No significant changes were detected in the miR-122 binding region (i.e. excluding those at baseline). Further trials, in combination with other antiviral compounds, are planned.
In a similar Phase II trial, ALS-2200 (200 mg) was given with RBV. The reduction in viral load was 4.2 log₁₀, 5/8 patients reached LLOQ and two of these reached LOD. In similar trials, patients with genotypes 2, 3 or 4 appear to respond similarly to those with genotype 1. Future plans include testing with the Bristol-Myers Squibb's NSSA inhibitor, daclatasvir, initially in patients with genotype 1 and then extending to patients with other genotypes in the second half of 2013, pending data from the initial study.

7.4. Cenicriviroc, a novel, once-daily, potent dual CCR5 and CCR2 antagonist under investigation for treatment of HIV infection

Eric Lefebvre, Tobira Therapeutics, South San Francisco, CA, USA

The discovery and structure of cenicriviroc (CVC) are included in the Eliion Award lecture (see above). It is a CCR5 and CCR2 receptor antagonist at nM concentrations. CCR5 is present mainly on monocytes and is the receptor for HIV in about 80% of treatment-naive patients. CCR2 is involved in monocyte-related immune activation. With a plasma T½ of 30 to 40 h, once daily dosing with CVC is possible.

In a Phase Ib trial, CVC (100 and 200 mg) is being compared with EFV with all treatment arms having open label Truvada, the randomisation being 2:2:1, respectively. The treatment-naive patients had to have CCR5-tropic HIV. The primary objective is to compare the efficacies and safety of CVC and EFV at 24 weeks. The trial will continue to week 48. The results at week 24 were reported in this presentation. The proportions of patients achieving virus control (HIV RNA <50 copies/ml) were 76%, 73% and 71%, respectively. To test for a shift in viral tropism it was necessary to have HIV RNA levels at least 100 copies/ml. There were 4 and 2 cases in the 100 and 200 mg CVC groups respectively. Of these, one patient had a tropism shift. CVC was well tolerated. The proportions having any grade of adverse events were 9%, 9% and 32% respectively, discontinuations were 0%, 1% and 5%. Lipids (cholesterol) levels were down for both CVC groups, but up in the EFV group. sCD14 was used as a marker for activation of monocytes; the levels were down in the CVC groups and raised in the EFV group.

PK studies investigated drug-drug interactions. The study design was to administer CVC daily from days 1 to 10, then add the other drug(s) from day 11 to 20 and take samples for PK analysis on days 10 and 20. With boosted PIs or with ritonavir, the area-under-the-curve (AUC) for CVC was increased 3.6-fold. Similar studies investigated the interaction between CVC and EFV. CVC had no effect on EFV levels, but EFV reduced the AUC of CVC by 50%. Dosage adjustments would be necessary but this is not a problem if CVC is included in a combination pill. Looking to the future, the Phase II 48 week data are expected in July 2013. Phase III trials are being planned.

7.5. The STaR study: Single tablet regimen rilpivirine/emtricitabine/tenofovir DF is non-inferior to efavirenz/emtricitabine/tenofovir DF in ART-naïve adults

Damian McColl, Gilead Sciences, Foster City, CA, USA

The introduction of single-tablet, once daily regimens have greatly improved HIV-infected patients' lives. The STaR study is the first to compare two such regimens, each patient taking just one tablet daily. The two regimens were rilpivirine/ emtricitabine/tenofovir DF (RPV/FTC/TDF) and efavirenz/emtricitabine/tenofovir DF (EFV/FTC/TDF). As RPV is taken with food and EFV taken while fasting, this was an open-label study. The primary endpoint was the proportion of subjects with HIV-1 RNA <50 copies/ml at week 48 with 12% non-inferiority margin. Randomization was stratified by HIV-1 RNA level (<100,000 copies/mL or >100,000 copies/mL) at screening, but some analyses were done with RNA levels ≤100,000, >100,000 up to 500,000 and >500,000. The data presented were for week 48, but the trial is continuing to week 96. (For full details of the trial design and primary results, see abstract 204.) The focus of this report was to give a few key outcomes and those results which are not included in the abstract; the groups will be designated as single-tablet with rilpivirine (stRPV) and stEFV.

The proportions of patients reaching the primary endpoint (HIV RNA <50 copies/ml) were 86% and 82% for stRPV and stEFV respectively. This met the non-inferiority criteria. Virological failures were 8% and 6% respectively, drug discontinuations were 2% and 8% respectively (some due to intolerance to EFV), patients for whom there was no data at week 48 were 6% and 13% respectively. With both treatments, the proportions of patients achieving HIV control decreased with increasing initial viral load: HIV RNA (copies/ml) ≤100,000, 89% and 82%; >100,000–500,000, 83% and 82% and >500,000, 72% and 80%, respectively. Similarly, the virological failures increased: 5 and 3, 10 and 9, 25 and 16, respectively. Clearly, those patients, who maintained HIV control, did not have viable resistant virus.

Virological resistance could be investigated only in those patients with HIV RNA at least 400 copies/ml: 20 (5%) and 7 (2%), respectively. Virelral resistance was detected in 17 (4%) and 3 (1%), respectively, mainly in those patients with the highest initial viral load. The numbers of patients with nervous system events were 117 (30%) and 198 (51%), respectively. Overall, stRPV was non-inferior to stEFV for efficacy; stRPV had improved tolerability compared to stEFV, but that came at the cost of a few more cases of viral resistance.

7.6. CMV resistance profile of CMX001

Randall Laniere, Chimerix Inc., Durham, NC, USA

This presentation focused on viral resistance studies both in cell culture and in samples from clinical trials. However, Randall started by giving advance notice of an adenosivirus pre-emptive therapy trial (CMX001-202) in pediatric and adult hematopoietic stem cell transplant (HSCT) patients. The data are expected to be available about September, 2013.

In cell culture studies with CMV (strain AD169), a resistant strain was detected only after 10 months. The novel mutant (D542E), in the gene (UL54) encoding the CMV polymerase, was about 10-fold resistant to CMX001 but remained sensitive to ganciclovir (GCV) and foscarnet (FOS). This mutant virus appeared to have reduced fitness in cell culture.

In a Phase II trial (CMX001-201), the patients enrolled were primarily treatment-naïve subjects. CMX001 was used at 40, 100 and 200 mg, each twice weekly and 100 and 200 mg once weekly. Although good activity was obtained with the two higher doses given twice weekly, taking into account side effects, 100 mg twice weekly is the optimum dose. The 40 mg dose was comparable to placebo. Therefore this was a “good” trial for investigating the selection of resistant virus due to under-dosing. None of the samples (n = 171) contained the D542E mutation or any other known resistance mutations for CMX001. A polymorphism (R1052C) was detected in 3 patients, but this strain retained sensitivity to CMX001, cidofovir (CDV), GCV and FOS.

Trial CMX001-350 enrolled therapy-experienced patients (n = 210) with life-threatening or serious diseases or conditions caused by one or more dsDNA viruses. Many patients (107) had CMV infections. Of these, 21 had known GCV-resistant mutations in the UL97 gene encoding the kinase which activates GCV. Such mutants retained sensitivity to CMX001 and there was no discernible effect on the response to CMX001 therapy. However, 14 patients had known resistance mutations to CDV and they had reduced responses to CMX001 therapy; the reduction in viral
load was 0.43 (mean)/0.25 (median) log_{10}, and none achieved CMV levels <200 copies/ml. In contrast, those patients, without resistant mutations, had a 0.81 (mean)/1.0 (median) log_{10} decrease in viral load and many patients (26/49) had CMV levels <200 copies/ml.

In summary, the prior use of GCV, which is most likely to lead to resistance mutations in the UL97 gene of CMV, will not compromise subsequent therapy with CMX001. In contrast, previous therapy with CDV, when dosage may be limited by toxicity, should be avoided. Instead, CMX001 should be used for patients failing on GCV therapy.

8. Chemistry minisymposium: Strategies and tactics in drug design

An introduction to the molecular forces involved in drug-target binding set the scene for this mini-symposium. Three different strategies for drug discovery were exemplified.

In his presentation “Molecular recognition in drug design”, Daniel (Dan) Cheney of Bristol-Myers Squibb, Wallingford, CT, USA described how the strength of hydrogen bonds (H-bonds) could be represented by the energy gained (all values in this presentation were in kcal/mol in the gas phase; as energy is gained, the values are negative). There are two general considerations: the ligand competes with water for the receptor and H-bonds need order. This latter requirement may mean that the formation of H-bond(s) can be at the cost of reduced entropy for a protein with a high degree of flexibility (i.e. high entropy). For H-bonds, the range is from ~8 for strong bonds to about ~2 or ~1 for weaker bonds. Much stronger (about double) bonds are formed if an NH_{4}^{+} group is attached to an aromatic ring. Halogen bonding is usually in the range ~2 to ~1 but can be ~3 when attached to an electron-deficient ring. Several other types of interaction are in the range ~2 to ~1: π-π, polar, van der Waals.

A rapidly emerging field of research is the kinetics of binding. The activity of a drug may be influenced not only by the strength of binding (e.g. its K_{i} value), but by the length of time the drug is attached. In a protein pocket open to water, the residence time may be short, while in a more protected protein pocket that is better shielded from water, the residence time may be longer. An example of inhibitors of fatty acid synthesis was given to illustrate this concept.

How a fragment-based drug discovery process led to an HCV NS3/4A inhibitor was described by Susanne Saalau-Bethell of Astex Pharmaceuticals, Dublin, CA, can fit well into a target site, but the binding will be weak (e.g. IC_{50} = 500 μM). Therefore, sensitive detection systems, such as NMR, are required. X-ray crystallography is often used to confirm a candidate. As an example, 176 fragments were tested in groups of 4 for binding in the tunnel which is formed when the C-terminus of the HCV helicase binds to the protease. Although EC_{50} values were about 500 μM, 16 fragments were identified as hits. X-ray crystallography is an essential aid for SAR studies, Also, AstexViewer, a computer program giving chemists a view of the ligand/protein binding, was lighted various factors that should be considered. A slide from the 1950s stated “GI tract designed to solvate”. Not water solubility, but cyclohexane solubility may be a guide to oral absorption. A “grease-ball” molecule, administered in a capsule, may have good oral bioavailability.

It is commonly thought that an increase in lipophilicity will decrease water solubility. In a study of many drugs, comparing water solubility with lipophilicity, the correlation coefficient (R) was 0.54, implying that other factor(s) must play a role. Sometimes, adding a highly polar group can help. For example, adding a phosphate to amprenavir (fosamprenavir) gave improved water solubility. Because the phosphate group is removed enzymatically at the surface of the intestine, the more lipophilic parent compound is easily absorbed. Other examples illustrated that phosphates, which are too stable, may give water solubility, but may not increase absorption. Highly crystalline, high melting-point solids have too much lattice energy for water to solvate the crystal. For example, adding an ethyl group greatly increased water solubility by reducing the lattice energy.

When considering a prodrug, it is important to ensure that the released moiety is not harmful. Formaldehyde has often been seen to be of potential concern. The speaker referred to one of his earlier publications entitled “Your prodrug releases formaldehyde: Should you be concerned? No!” (Dhareshwar and Stella, 2003).

Many drugs have bioavailabilities in the range 30–50%. A well known example within the antiviral field illustrates how this can be improved. Valacyclovir, a prodrug of acyclovir, works so well because it not only improves the physical properties, but also utilizes a cellular carrier system.

Cidofovir (CDV) is concentrated in the kidneys by organic anion transporters and this leads to nephrotoxicity. In the Eliion Award lecture at ICAR 2012, Karl Hostetler described how he tried to mimic lysolecithin in order to utilize lipid transport pathways and thereby avoid the nephrotoxicity associated with CDV. Randall LaNier of Chimerix Inc., Durham, NC, USA gave some of the improved properties of hexadecyloxypropyl-CDV (CMX001) and some recent clinical results. PK studies confirmed that there is essentially no CDV in plasma from a CMX001 dose. This explains the lack of nephrotoxicity. It is thought that the mono-lipophilic chain, rather than a bi-chain, allows better passage through the cell wall by the molecule flipping over within the lipid bilayer. CDV is released only within the cell. By using the prodrug, intracellular levels of CDV- DP are about 350-fold greater than those from CDV.

In a current expanded access protocol (study 350, n ~210), about 1/3 of the patients are children and 2/3 are adults. Most have either adenovirus (ADV) or CMV infections, but some have dual infection. With ADV, most patients have responded well with a >1 log_{10} reduction in viral load and may reach undetectable levels. In a phase II trial in CMV patients, CMX001 at 100 mg twice weekly is the optimum dose. Treatment starts when CMV DNA levels ex-

In a Phase IIa trial in treatment-naïve patients, triple therapy gave a high SVR (88%). Phase III trials are the next goal.

Nigel Liverton of Merck described how a conventional SAR study, starting with the known compound BILN-2061, led to vaniprevir, a NS3/4A protease inhibitor. In a Phase II dose-ranging study in patients with HCV genotype 1, vaniprevir (100, 200, 400 and 800) gave impressive SVRs at 24 weeks (86%, 92%, 91%, and 87%, respectively).
ceed 1000 copies/ml. Patients who have prior mutant strains resistant to CDV do not respond as well as treatment-naive patients. However, even in the “failure” cases, the viral load often remained below 1000 copies/ml, in contrast to placebo-treated patients whose viral load increased well over 1000 copies/ml.

An HIV attachment inhibitor, with very low water solubility, was partially absorbed, but the oral AUC remained virtually unchanged with dose. Encouraged by the Sundeep and Valentino paper, John Kadow of Bristol-Myers Squibb, Wallingford, CT, USA reported on using a phosphorus prodrug. PK properties were much improved, AUC both much higher and with a dose response. Bioavailability was unchanged by food. However, the T1/2 was so short that the duration of plasma concentrations above the EC90 values was less than 12 h. A radio-controlled capsule was used to investigate the effects of drug release in different parts of the intestinal tract. This led the team to use a slow-release formulation of the produg. This is an example in which both produrg and formulation approaches were used together.

Amidate produrgs of TFV are being evaluated as potential replacements for the licensed TDF. Richard Mackman of Gilead Sciences, Foster City, CA, USA reported on two such produrgs, GS7340 (TAF) and GS9131. (For information about TAF, see the report by Tomas Cihlar above). New data were shown for GS9131. In a Phase I trial, the PK of doses 10 and 30 mg without food and 30 mg with food were investigated. In PBMCs, the levels of the active moiety (TFV-DP) were 3- and 10-fold higher respectively than from the 300 mg dose of TDF. In terms of the reduction of HIV RNA, a 30 mg dose of GS9131 was comparable to a 300 mg dose of TDF.

Mike Sofia of OnCore Biopharma, Doylestown, PA, USA gave a useful overview of nucleosides and nucleotides produgs being investigated for the treatment of hepatitis C. All have the advantage that the active moiety is a nucleotide-triphosphate analog targeting the HCV polymerase (NS5B) which is highly conserved across all genotypes. The produrg approach has been used extensively, not just to aid oral absorption, but it has also been useful to take advantage of a transporter system and to give liver targeting. The nucleoside analogs have all needed high drug levels. The greatest progress has been made with nucleotide analogs. Sofosbuvir (GS7977, PSI-7977) (400 mg once daily for 14 days) gave a 5 log10 reduction in HCV RNA levels. When combined with RBV, the SVR was 78%. Even better, the combination of sofosbuvir and daclatasvir (BMS790052, NS5A inhibitor) gave 100% SVR. Sofosbuvir has been combined with ledipasvir (GS5885, NS5A inhibitor) as a single pill and is now starting Phase III trials. Sofosbuvir is likely to be the first anti-HCV nucleotide analog to reach the marketplace.

10. Conclusion

This ICAR demonstrated the rapid pace of progress in many areas of antiviral research. Perhaps more than in recent years, reports on clinical results and on chemistry-related topics were well represented. It is impossible to record all of them here, but it is hoped that this report is indicative of the range of topics covered.

A highlight of this conference was undoubtedly the symposium on “The legacy of Tony Holy”. The first two speakers, Erik De Clercq and John Martin, were his closest collaborators. As a result of the work of these three researchers, HIV-infected people throughout the world are living near-normal lives. Robert Schooley, Robert Grant, Henry Chan, Richard Whitley and Tomas Cihlar focussed on the different areas inspired by Tony’s work.

This year, the two major award lectures covered very different areas of research – a good illustration of ICAR’s strength in bringing differing disciplines together. The keynote address, the plenary lecture, the clinical symposium and the mini-symposia gave a good overview of progress in the area of antiviral research. Those presentations reporting clinical results are a vital part of ICAR meetings because beautiful research science needs to lead to useful drugs. The clinical symposium proved that antiviral chemotherapy is continuing to make important new progress although the areas of progress seem to vary from year to year. This year, there were fewer reports on HBV than last year. In contrast, the encouraging progress with HCV therapies was maintained. There is the prospect that the first nucleotide analog will be licensed by the time of our next ICAR meeting. The combination of a nucleotide analog and a NS5A inhibitor looks set to transform HCV therapy across all genotypes. As for HIV, single-pill, once-daily regimens are following on quickly. The established HCV protease inhibitors may become little used. As always, there are drug casualties – the HCV polymerase inhibitor IDX184 was progressing well last year, but development was stopped due to cardiotoxicity concerns relating to another drug with a similar structure.

A new approach, using a microRNA, miravirsen, has shown encouraging positive results in a Phase II trial and an update was given at this ICAR. For over a decade, the mainstays of HSV and VZV therapies have been acyclovir, its prodrug valaciclovir and famciclovir. Last year, there were encouraging reports on a herpes-virus helicase/primase inhibitor, AIC-316, but there were no updates this year. Since ICAR, the clinicaltrials.gov site has been updated with the statement “clinical hold due to non-clinical studies.” Valganciclovir has long been the key therapy for CMV infections but now CMX001 is continuing to show promise in Phase II trials. The therapy of HIV-infected patients has already been transformed by the introduction of single-pill, once-daily regimens and now the choice of such regimens has expanded with Quad®, becoming a licensed drug. Other single-pill regimens are progressing.

Over several years at ICAR, but notably not in 2012, there were presentations updating the progress of apricatinib (ATC) through clinical trials. ATC showed exceptional barrier to HIV resistance. Both at ICAR 2012 and at this meeting, there were reports on another interesting nucleoside analog, festinavir (4’ethynyl-d4T), which has good activity against many resistant HIV mutants. The other interesting nucleoside analog, voricanavir, has good activity but no data was shown at this ICAR. For over a decade, the mainstays of HSV and VZV therapies have been acyclovir, its produg valaciclovir and famciclovir. Last year, there were encouraging reports on a herpes-virus helicase/primase inhibitor, AIC-316, but there were no updates this year. Since ICAR, the clinicaltrials.gov site has been updated with the statement “clinical hold due to non-clinical studies.” Valganciclovir has long been the key therapy for CMV infections but now CMX001 is continuing to show promise in Phase II trials. The therapy of HIV-infected patients has already been transformed by the introduction of single-pill, once-daily regimens and now the choice of such regimens has expanded with Quad®, becoming a licensed drug. Other single-pill regimens are progressing.

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