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Meeting Report

Meeting report: 27th International conference on antiviral research

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ABSTRACT

The 27th International Conference on Antiviral Research (ICAR) was held in Raleigh, North Carolina, USA from May 12 to 16, 2014. This article summarizes the principal invited lectures. John Drach (Elion Award) described the early days of antiviral drugs and their novel modes of action. Piet Herdewijn (Holý Award) used evolutionary pressure to select DNA polymerases that accept nucleoside analogs. Replacing thymine by 5-chlorouracil led to the generation of a new form of *Escherichia coli*. Adrian Ray (Prusoff Award) demonstrated how prodrugs can markedly improve both the efficacy and safety of potential drugs. The keynote addresses, by David Margolis and Myron Cohen, tackled two emerging areas of HIV research, to find an HIV "cure" and to prevent HIV transmission, respectively. These topics were discussed further in other presentations – a cure seems to be a distant prospect but there are exciting developments for reducing HIV transmission. TDF-containing vaginal rings and GSK-744, as a long-lasting injection, offer great hope. There were three mini-symposia. Although therapy with TDF/FTC gives excellent control of HBV replication, there are only a few patients who achieve a functional cure. Myrcludex, an entry inhibitor, is active against both HBV and HDV. The recent progress with HBV replication in cell cultures has transformed the search for new antiviral compounds. The HBV capsid protein has been recognized as key player in HBV DNA synthesis. Unexpectedly, compounds which enhance capsid formation, markedly reduce HBV DNA synthesis. The development of BCX4430, which is active against Marburg and Ebola viruses, is of great current interest.

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1. Introduction

This article provides an overview of the invited lectures at the 27th International Conference on Antiviral Research, sponsored by the International Society for Antiviral Research (ISAR), which was held in Raleigh, North Carolina, USA from May 12 to 16, 2014. It begins with reports of lectures by the recipients of ISAR's three major awards, held in memory of Gertrude Elion, Antonín Holý and William Prusoff. These are followed by brief summaries of the keynote addresses and the three mini-symposia on "Hepatitis B virus", "Research Triangle Park" and "Challenges in HIV infection, treatment and prevention". Because this review article simply provides short accounts of oral presentations, it is not generally accompanied by references to the scientific literature. Any descriptions of favorable treatment outcomes should not be taken as recommendations for clinical use.

2. Gertrude Elion memorial award aecture: collaborative antiviral studies for the discovery of drugs to treat cytomegalovirus infections

John C. Drach, Ph.D., University of Michigan, Ann Arbor, Michigan, USA (Fig. 1).

Gertrude B. (Trudy) Elion was born in New York City and was pleased to work for the 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 her pioneering work in purine biosynthesis which paved the way for the discovery of drugs to treat organ rejection, cancer and viral diseases.

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

The focus of John's presentation was on the research conducted in his own and his collaborators' laboratories that ultimately led to the invention of three compounds which were discovered to have antiviral activity against human cytomegalovirus (HCMV) 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 Karen Biron, Charles Shipman, Leroy Townsend, and Jiri Zemlicka. To date, there are only five FDA-approved drugs for treatment of HCMV infections: cidofovir, fomivirsen, foscarnet, ganciclovir and valganciclovir.

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 1950s and '60s. This led to the synthesis of a trichloro analog in Townsend's laboratory at the University of Utah and later the discovery of its activity against HCMV in John's laboratory. Much work, in both their laboratories at the University of Michigan, established that it and its 2-bromo analog (BDCRB) have excellent activity against HCMV with very low cytotoxicity. Surprisingly, it was found to be inactive against other herpes viruses and it did not need conversion to a triphosphate to be active against HCMV. Collaborative studies with Karen Biron at Burroughs Wellcome established that, unlike many other anti-virals that inhibit viral DNA synthesis such as ganciclovir (GCV), these compounds acted by a novel mechanism, inhibition of viral DNA processing. It was the viral resistance studies which revealed the viral targets, pUL89 and pUL56. These two proteins, with pUL104, form a

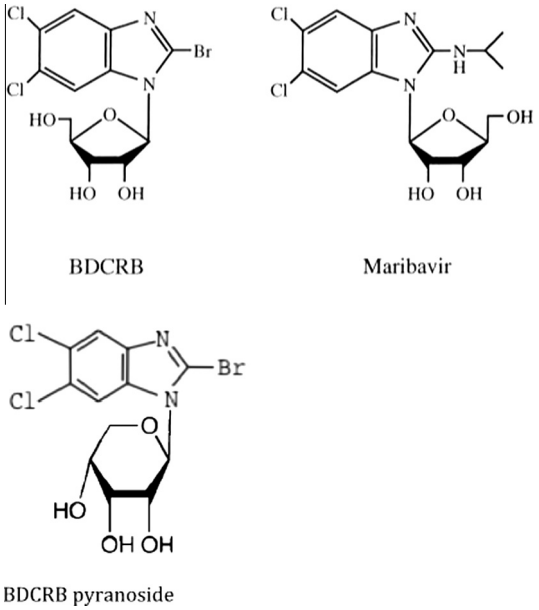

Fig. 2. Structures of BDCRB, BDCRB pyranoside and maribavir.

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