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Editorial overview: Anti-infectives

Phillip Furman and Michael J Sofia

Current Opinion in Pharmacology 2016, 30:iv–vi

For a complete overview see the [Issue](#)

Available online 25th August 2016

<http://dx.doi.org/10.1016/j.coph.2016.08.002>

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Phillip Furman



194 Parkside Drive, St. Augustine, FL 32095,
USA
e-mail: p.furman@aol.com

Dr Phillip Furman received his Ph. D. in microbiology from Tulane University and did his postdoctoral training at Duke University. He joined Burroughs Wellcome in 1975 and served as the Director of the Division of Virology at Burroughs Wellcome from 1989 until Burroughs Wellcome was acquired by Glaxo Smith-Kline in 1995. He is a co-inventor of Retrovir[®] (AZT), the first antiviral approved for the treatment of HIV infection. He also was involved in the development of numerous antiviral agents, including Zovirax[®] (acyclovir), Valtrex[®] (valacyclovir), Retrovir[®] (AZT), Emtriva[®] (FTC), and Sofosbuvir (PSI-7977, Sovaldi[®]) for HCV. Dr Furman's research has led to the understanding of the mechanism of action of a number of FDA approved antiviral agents including Zovirax[®] (acyclovir), Retrovir[®] (AZT), Emtriva[™] (FTC), and Sofosbuvir. Dr Furman was a co-founder of and Chief Scientific Officer at Triangle Pharmaceuticals. He served as the Vice President of Biological Sciences for Pharmasset, Inc. until Pharmasset's acquisition by Gilead. He has served on several NIH study sections. He is a member of the editorial board for Antiviral Research and has been a reviewer for various journals. He has over 100 publications. Dr Furman is a member of the International Society for Antiviral Research where he has served as chairman of the Society's finance committee, a member of the Board of Directors, and President-elect, President and Past President of the Society. In 2015 he received the Gertrude Elion award for his contributions to the field of antiviral research from the International Society for Antiviral research.

With the discovery and development of acyclovir, the last 40 years have seen a rapid growth in the discovery and development of antiviral drugs for various viral diseases including: herpes viruses, HIV, influenza virus, hepatitis B and more recently hepatitis C virus infections. Advances in our understanding of the molecular biology and biochemistry of virus replication, the ability to clone and express virus and cellular proteins and determine the molecular sites of action have now made it possible to develop and screen new antiviral drugs in a more purposeful manner. In addition, a developing understanding of how viruses interact with the host immune system has fostered new ways to combat viral infections. New technologies have also provided new insights into how drugs interact with target biomolecules to help accelerate the search for new cures. This issue will highlight the current state of antiviral drug discovery and prospects for the future.

An estimated 130–200 million people worldwide are infected with hepatitis C. Over many years chronic hepatitis C virus (HCV) infection typically leads to chronic liver disease, cirrhosis and eventually to hepatocellular carcinoma. Before 2011, the standard of care for treating HCV consisted of 48 weeks of a combination of pegylated interferon alpha and ribavirin. Because of the debilitating adverse effects associated with this treatment, the focus over the last 20 years has been to develop interferon-free therapies. A major advance in HCV antiviral therapy was the ability to cure HCV infections with sofosbuvir, a viral polymerase inhibitor, in combination with other direct acting antiviral drugs that target other virus-encoded proteins. Two viral proteins that were proven to be ideal drug targets were the NS3-4A protease and NS5A regulator of HCV RNA replication. [McCauley and Rudd](#) provide an overview of the development of multiple generations of NS3-4A HCV protease inhibitors. [Gao et al.](#) discuss the development of NS5A inhibitors and their mechanism of action.

While antiviral drugs are available to treat hepatitis B (HBV) infections, an HBV cure remains an elusive goal. Current treatments for chronic HBV infection include nucleos(t)ide analogues that effectively suppress viral replication but not cure the infection. Consequently life-long therapy is frequently required to prevent disease progression. However, long-term therapy generally results in drug resistance and poor patient compliance. Alternatively, treatment with IFN- α can lead to a small percentage of patients achieving a functional cure it is associated with numerous side effects, and is contraindicated in many patient populations. New drugs with different modes of action that prevent resistance and when used in combination improve viral clearance and eventually deliver an HBV cure are clearly needed. New targets for HBV drug discovery might include those

Michael J Sofia



Arbutus Biopharma, Inc., 3805 Old Easton Rd, Doylestown, PA 18902-1901, USA
e-mail: msofia@arbutusbio.com

Michael J Sofia, PhD is currently Chief Scientific Officer at Arbutus Biopharma, Inc. Previously he was CSO and Co-founder of OnCore Biopharma which merged with Tekmira in March 2015 to form Arbutus Biopharma. He also currently holds a professorship at the Baruch S. Blumberg Institute for Hepatitis Research and an Adjunct Professorship at the Drexel University School of Medicine. Before founding OnCore Biopharma, Mike Sofia was Sr Vice President of Chemistry at Pharmasset, Inc. until Pharmasset's acquisition by Gilead in January 2012. He has also held senior research leadership positions at Bristol-Myers Squibb and Transcell Technologies and held research positions at Eli Lilly and Company and E.R. Squibb. Mike Sofia did his postdoctoral training at Columbia University and received his PhD in organic chemistry from the University of Illinois, Urbana-Champaign. He earned his BA degree in chemistry from Cornell University. Mike has introduced numerous drugs into clinical development for the treatment of diseases in the areas of infectious disease and inflammatory diseases. He has authored over 100 publications, 10 book chapters and numerous abstracts and is an inventor on more than 51 US patents. He is the principle inventor of sofosbuvir (Sovaldi, Harvoni) currently marketed as a treatment for the cure of HCV infection. Mike is the recipient of the 2014 Pennsylvania Bio Scientific Achievement Award, the 2015 Heroes of Chemistry Award of the American Chemical Society, Foreign Policy Magazine's 2014 Global Thinkers Award, the Economist Magazine's 2015 Innovation Award in Biosciences and the 2016 IUPAC-Richter Prize for his contributions to the discovery of a cure for HCV.

involved in steps of the HBV life cycle, such as viral entry, formation and clearance of cccDNA, and capsid assembly. [Cole](#) discusses examples of small molecules that inhibit HBV replication by disrupting the encapsidation of HBV pregenomic RNA and recent advances in the understanding of nucleocapsid formation. HBV can impact the natural history and pathogenesis because the virus can evade, subvert, activate and regulate components of the host immune response. In their review [Chang and Liu](#) discuss aspects of the host innate and adaptive immune responses relevant to HBV infection and highlight several immune modulatory approaches to treating chronic HBV infection that are in clinical development. cccDNA, which is critical in maintaining HBV in hepatocytes, is an important target for preventing viral reactivation and disease recurrence following cessation of antiviral therapy, and therefore, is an important target for curing HBV infection. Recent advances and future directions in efforts to eliminate and/or regulate cccDNA are discussed by [Revill and Locarnini](#).

Major successes in the ability to treat important viral diseases have been achieved. However, in the last few years an increasing rise of new infectious diseases or of other diseases considered to be under control has been observed. We have become more aware of emerging or reemerging viruses such as dengue virus, Ebola virus, influenza virus and more recently Chikungunya virus, Middle East Respiratory Syndrome (MERS), and Zika virus, for example, as these viruses have become more wide spread and now present a major health threat. Emerging viral diseases pose ongoing health threats, particularly in an era of globalization. Factors such changes to local ecosystems that perturb the balance between pathogen and principal host species, environmental changes, trade, migration, and increasing concentrations of human populations are considered to be responsible for the emergence or reemergence of diseases caused by these and other viruses. Another factor that likely has played a role in the emergence or reemergence of viral diseases is the ability of these viruses to quickly adapt to and exploit these varying conditions. Most emerging viral diseases in each of these categories are RNA viruses. Viruses with RNA as their genetic material have higher mutation rates due to the high error rate of their polymerase and the lack of proofreading ability. As the incidence of disease caused by emerging or reemerging viruses continues to grow, the challenge will be to find new antiviral agents or repurpose old drugs that can effectively treat these new diseases.

The review by [Kaptein and Neyts](#) focuses on several drugs that underwent clinical evaluation as potential therapies for dengue virus infection and the lessons learned that might prove helpful in the design of future trials. The current outbreak in West Africa, the largest and most complex Ebola outbreak since its discovery with more cases and deaths in this outbreak than all others combined. Survival can be improved with supportive care with oral or intravenous fluids and treatment of specific symptoms. As yet no therapeutic treatment is available. However, a number of potential treatments, including antiviral therapies, are currently being evaluated. [Cardile et al.](#) highlight those therapeutics that underwent clinical trials during the West Africa outbreak and discuss promising candidates currently in development.

Influenza viruses are significant human respiratory pathogens that cause both widespread seasonal infections and episodic pandemics. The worst pandemic on record occurred in 1918, killing approximately 50 million people worldwide. Recent infections caused by H5N1, highly pathogenic avian influenza viruses, have raised concern about the emergence of another

pandemic. The two main classes of antiviral drugs used to treat influenza virus infections are neuraminidase inhibitors, such as zanamivir and oseltamivir, which inhibit both type A and type B or inhibitors of the viral M2 protein, such as amantadine and rimantadine that inhibit only type A influenza virus. If taken soon after infection these drugs are able to reduce the severity of symptoms and can be taken prophylactically to decrease the risk of infection. However, virus strains do emerge that show drug resistance to both classes of drug. Consequently new safe and effective drugs with a high barrier to resistance are needed to treat influenza virus infections either alone or in combination. In their review [Naesens *et al.*](#) provide an overview of some approaches to targeting the viral hemagglutinin, polymerase complex or nucleoprotein, for which antiviral leads are in the (pre)clinical stage.

The development and implementation of new technologies continue to play a role in enabling the discovery of novel antiviral drugs. One such technology that has emerged and become a powerful tool in the drug discovery process is Structural biology. Structural biology has

been instrumental in directing not only lead optimization and target identification but also for lead discovery. In the review by [Brancale *et al.*](#) the evolution of the use of X-ray crystallography in the determination of the structure of viral proteins and the role of crystal structures in the discovery and optimization of antiviral compounds is discussed.

With the discovery of new drugs to effectively treat HIV and cure HCV, the field of antivirals is making progress in the effort to control or eradicate these viruses from the human condition. Yet many more viruses plague human health and there is a need of innovative drugs to treat them. It is only through continued research in understanding the fundamental biology of viruses and how they impact the host and the multidisciplinary drug discovery endeavor that we can continue to make progress toward developing drugs that will treat these diseases and perhaps in the future eradicate them.

Conflict of interest statement

Nothing declared.