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Editorial overview: Antiviral strategies: Antiviral drug development for single-stranded RNA viruses

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Margo A. Brinton is a Regents Professor in the Department of Biology at Georgia State University. Her research is focused on flavivirus and arterivirus host cell interactions and replication mechanisms. Specific research areas for flaviviruses include functional analysis of the alleles of a mouse gene that confers resistance/susceptibility to flavivirus-induced disease, characterization of interactions between viral genome RNA structures and pro-viral host proteins and analysis of cellular innate immune and stress responses induced or counteracted by flavivirus infections. Her research on the arterivirus, simian hemorrhagic fever virus, is focused on delineating mechanisms regulating subgenomic mRNA abundance and on analyzing viral protein functions. Her lab has tested multiple candidate antiviral drugs against flaviviruses and arteriviruses.

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Richard K. Plemper is Distinguished University Professor in the Institute for Biomedical Sciences at Georgia State University. His research focuses on the biology of respiratory RNA viruses with particular emphasis on the entry and replication machineries of pediatric pathogens of the paramyxovirus and pneumovirus families. His laboratory has made numerous contributions to developing

The reviews in this year's Antiviral Strategies section focus on the discovery of efficacious antiviral drugs for emerging and reemerging single-stranded positive and negative strand RNA viruses of public health importance. Articles on pathogens in two families of positive strand RNA viruses, the flaviviruses and coronaviruses, and in three families of negative strand RNA families, the orthomyxoviruses, filoviruses, and rhabdoviruses, were included. Vaccines for many of these viruses are not available, or vaccine efficacy is moderate. Members of each family constitute a major clinical need for effective therapeutics, but drug development efforts against these pathogens are at very different stages and the desirable drug profiles are distinct.

Prior to the global outbreak of severe respiratory syndrome coronavirus (SARS-CoV) in 2002, the known isolates of human coronaviruses caused mild upper respiratory disease. The recent emergence of the Middle East respiratory syndrome coronavirus (MERS-CoV) suggests that additional zoonotic coronaviruses will continue to periodically emerge into the human population in the future. Nucleotide and nucleoside analogue inhibitors have been developed for use against many RNA viruses. However, the unique RNA-dependent RNA proofreading activity of the CoV 3′ to 5′ exoribonuclease is responsible for increased resistance of these viruses to nucleotide and nucleoside analogue inhibitors. Pruijssers and Denizen [1] describe the recent development of nucleotide and nucleoside analogue inhibitors with the ability to inhibit multiple CoVs.

Multiple efficacious drugs targeting the activities of various hepatitis C virus (HCV) nonstructural proteins have been successfully developed and when they are used in combination to treat persistent HCV infections effect greater than a 95% chance of achieving a cure. Luna *et al.* [2] present an insider's overview of the failures and successes over a period of ~40 years that led to the successful development of viable cell culture models for HCV and the discovery of efficacious anti-HCV drugs. This success story in the field of antiviral development provides insights that may be applicable to the discovery of antivirals for additional human disease viruses in the future.

Although HCV and viruses, such as Zika virus, West Nile virus, and dengue virus, are all members of the family Flaviviridae, they belong to different taxonomic genera, *Hepacivirus* and *Flavivirus*, respectively, and differ in many of their characteristics. These include the use of different host

novel drug screening technology, isolating druggable targets, and identifying, developing, and characterizing novel antiviral candidates. Inhibitors directed against influenza virus, respiratory syncytial virus, and measles virus that were discovered by his laboratory are at different stages of experimental and formal development.

proteins for virion attachment and entry, different protease structures that affect drug targeting and the lack of an NS5A protein for the members of the genus Flavivirus. Efficacious antiviral drugs targeting nonstructural proteins of members of the genus Flavivirus have so far not been developed. Zou and Shi [3] review the strategies being used to discover antiviral drugs for Zika virus. Different arthropod-borne flaviviruses cause different diseases and the target population must be considered when developing antiviral drugs. The need for antiviral drugs to treat Zika virus infections in pregnant women to prevent congenital defects in the developing fetus significantly limits the types of drugs that can be used.

Two articles focus on treatment of influenza infections. Within the selected group of negative strand viruses, the influenza viruses are responsible for the highest incidence rate by far. In interpandemic years, they cause acute respiratory infections with the highest disease burden in the elderly. Major efforts have been directed at the development of influenza therapeutics and last year the first new inhibitor class in nearly two decades was approved for human use, although the standard-of-care drugs are still the neuraminidase inhibitors. The article by O'Hanlon and Shaw [4] discusses the development and possible clinical impact of the novel influenza virus PA endonuclease inhibitor baloxavir marboxil with particular emphasis on clinical trial data and the prospect of emerging viral resistance to inhibition. The discussion summarizes how approval of baloxavir marboxil has redefined priorities within the influenza drug development field towards proactively addressing the resistance problem at the discovery stage and exploring combination therapy options.

Having thus recently expanded our therapeutic arsenal against influenza, the review by Morgan and Klein [5] utilizes influenza as an example for summarizing the emerging appreciation of the impact of biological sex and sociocultural gender norms, roles, and relations on exposure to infection, progression of disease, and access to, and acceptance of, treatment. Spanning an arc from animal models of influenza to clinical data, the authors discuss the current insights into the correlation between biological sex and immune responses to influenza virus infection and the efficacy of vaccines and antiviral drugs. Biological factors are then juxtaposed with an evaluation of the effect of sociocultural factors on administration of influenza intervention and patient compliance.

Compared to influenza, a very different clinical threat is presented by Ebola virus infection. The majority of the past Ebola virus outbreaks have been limited both geographically and in size, but case fatality rates were devastatingly high. Drug development efforts against filovirus infections received a major boost by the unusually large 2013–2016 outbreak in West Africa that resulted in over 11 000 casualties and the spread of disease to both Europe and North America. After an overview of the filovirus replication cycle, Edwards and Basler [6] provide a succinct overview of the current stage of experimental filovirus inhibitors and drug candidates undergoing clinical testing. Both direct-acting and host-targeted antiviral candidates are discussed, reflecting the need for the development of broad-spectrum pan-filovirus inhibitors.

Rabies is a neglected disease in terms of drug discovery, since both pre-exposure and post-exposure prophylaxis treatments are available. However, two factors identified in the article by DuPont *et al.* [7], demonstrate why complacency is not in order. Firstly, cost, logistical, and availability restrictions limit access of the most at-risk populations to the immunoglobulin

component of rabies prophylaxis, building a case for the value of its replacement with a suitable small-molecule drug. Secondly, the current vaccine does not cross-protect against newly emerging zoonotic lyssaviruses of phylogroup II. Following a summary of past anti-rabies virus drug development efforts, the authors outline essential features of a viable drug candidate that provide guidance for early stage drug discovery efforts.

Most of the viruses examined in this special issue exist as quasispecies populations. The rapid development of viral resistance has emerged in several cases as a major threat to long-term therapeutic success. With an expanding number of therapeutics approved for human use and promising drug candidates under preclinical and clinical development, however, novel opportunities for drug combination treatments can be anticipated that should be considered and validated early in development. In parallel, the increasing appreciation of the impact of both biological and sociocultural factors on treatment efficacy should be translated to the development of efficacy models and clinical trial designs to maximize the prospect that optimal treatment options for in-need patient populations will be developed.

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