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Editorial overview: Antivirals and resistance: Advances and challenges ahead

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Synthesized by William Prusoff in the late 1950s, idoxuridine (5′-iodo-2′-deoxyuridine) became the first approved antiviral agent in 1962. This nucleoside analogue has been used topically to treat eye and skin infections caused by herpes simplex virus. There was slow progress in the discovery and development of new antiviral drugs for a number of years until the emergence of human immunodeficiency virus (HIV) infections as a major threat to human health worldwide. Research in the HIV field has led to approval of more than 30 antiretroviral drugs in the last three decades. As a consequence of these advances HIV infection and AIDS have become a chronic rather than a fatal disease in many parts of the world.

The remarkable progress in molecular, cellular and structural biology that we have witnessed in the last decades has allowed a deeper understanding of viral replication cycles and provided new opportunities for therapeutic intervention. Drug discovery programs targeting hepatitis C virus (HCV) replication and propagation have been particularly successful. Boceprevir and telaprevir (two serine protease inhibitors) became in 2011 the first directly acting agents approved for treatment of HCV infection. More recently (in December 2013), the HCV RNA polymerase inhibitor, sofosbuvir, received approval after showing that it could cure HCV infection in at least 90% of the treated patients, if properly combined with ribavirin or other more recently approved directly acting agents.

Despite having a few dozen drugs available for treating some important viral diseases, the approved compounds available for treatment target only infections caused by a limited number of pathogens (e.g. HIV, HCV, hepatitis B virus, herpes simplex virus, varicella-zoster virus, human cytomegalovirus or influenza virus). There are important viral infections that lack effective treatments. For example, dengue virus infects millions of people in more than 100 countries, and causes a severe disease that claims around 25,000 lives every year. Effective antiviral drugs are also missing for other viruses that cause alarm and havoc because of their high mortality (e.g. Ebola virus or Crimean-Congo hemorrhagic fever virus). In addition, the periodic emergence of new (more pathogenic) strains of known viruses, or previously unknown viruses presents continuing concerns for public health and reminders of the need for effective treatments.

Even in the case of successful antiviral therapy, the sword of Damocles still threatens in the form of the potential emergence of resistance. A lesson learned from research carried out over the last decades is that resistance is less likely to appear in those patients treated with regimens showing the highest potency and the greatest effects on viral suppression. In this Special

Issue, we present a collection of articles that provide updates on recent developments in antiviral drug resistance, targeting viruses of major clinical relevance or public health interest such as HCV, hepatitis B virus, HIV, herpes simplex virus, influenza virus and coronaviruses.

The Special Issue contains five reviews on anti-HCV therapies that cover the most important inhibitors and viral targets. About 15% of the approximately 300 million people infected with HCV worldwide will end up suffering serious complications of hepatitis C. For many years, the only approved therapies were combinations of interferon and ribavirin. However, only about 60% of treated patients showed substantial responses to treatment due to host and viral factors that limit their efficacy. Discontinuation of interferon treatment is not uncommon due to severe side effects including fatigue, headache, fever, myalgias, and depression. Failure with interferon has been observed in many patients, but interferon-resistance mutational patterns are rather complex and difficult to predict. In their review, Perales *et al.* [1] discuss amino acid replacements found in different HCV proteins upon passage of the virus in the presence or absence of interferon α. Interferon resistance in HCV is far more complex than resistance to directly acting antiviral agents such as boceprevir or telaprevir. Determinants of interferon resistance locate at specific residues of the HCV core protein, as well as the interferon sensitivity determining region (ISDR) and the interferon and ribavirin resistance determining region (IRRDR), both located within the viral NS5A protein. However, there are coincidences and discrepancies in the literature related to specific mutations and amino acid substitutions conferring resistance, and it is clear that environmental conditions have a major impact on the mutational patterns observed.

Although a major antiviral agent in the treatment of HCV infection, ribavirin has been used to treat many other viral infections (most notably, viral hemorrhagic fevers) with multiple proposed effects on virus replication and propagation. Ribavirin is a synthetic guanosine analogue with a broad spectrum of antiviral activities, including inhibition of viral RNA-dependent RNA polymerases, interference with RNA capping activity, or a mutagenic effect due to misincorporation of ribavirin during viral RNA replication. In their review, Beaucourt and Vignuzzi [2] describe ribavirin resistant and susceptible variants in different RNA viruses (e.g. poliovirus, foot-and-mouth disease virus, Chikungunya virus and HCV). Some of these variants result in viruses having polymerases with higher or lower fidelity. These variants could be helpful to improve the efficacy of current mutagenic compounds and identify new drugs with previously unknown antiviral mutagenic activity.

Approved HCV protease inhibitors such as boceprevir, telaprevir and simeprevir or related drugs in advanced clinical trials (e.g. asunaprevir or faldaprevir) and their resistance profiles are reviewed in the article by Kieffer and George [3]. Treatment with HCV protease inhibitors improves previous standards of care with genotype 1, but this is less evident for genotypes 2 to 6. Baseline prevalence of HCV resistance variants is a major threat to the success of therapy. Future goals in the development of better HCV protease inhibitors include reducing the number and impact of adverse events, as well as shortening the duration of treatment.

Nucleoside inhibitors of the HCV RNA-dependent RNA polymerase are well represented by the recently approved drug sofosbuvir (a fluoromethyluridine derivative). The approval of this drug has allowed the introduction of interferon-free treatments against HCV genotypes 2 and 3, and successful therapies against other resilient HCV genotypes. In his review, Götte [4] describes mutational patterns associated with resistance to sofosbuvir and other nucleoside inhibitors in clinical development. A key amino acid substitution involved in resistance to many of these drugs is S282T. However, it is only transiently observed in clinical cases. Alternative resistance pathways probably involving polymorphic sites could be relevant for the acquisition of resistance to these drugs. Structural studies should be helpful to elucidate their mechanistic role in resistance.

Another potential target of antiviral intervention in HCV is the NS5A protein. The review by Lim and Gallay [5] focuses on drugs in advanced clinical trials acting on this protein whose role in HCV replication and propagation has not been completely elucidated. NS5A has three domains, and drugs such as daclatasvir or ledipasvir select for mutations in domain I, while resistance to alisporivir maps in domain II. Daclatasvir and ledipasvir are directly acting antiviral agents with a low genetic barrier that block RNA replication and virion assembly. Alisporivir binds cyclophilin A and disrupts its interaction with NS5A. In contrast to directly acting antiviral agents, alisporivir has a higher barrier of resistance. However, its efficiency has to be further validated in clinical studies.

About 5% of the world's population is chronically infected with hepatitis B virus (HBV). Although currently available therapies include interferon variants, the approval of lamivudine in 1998 as the first nucleoside analogue effective on HBV infection was a significant advance. HBV and HIV reverse transcriptases share important biochemical and structural properties and drugs designed to inhibit the HIV-1 reverse transcriptase were found to be successful inhibitors of the HBV polymerase. Menéndez-Arias *et al.* [6] provide an overview of the mechanisms of action of approved nucleos(t)ide inhibitors of HBV polymerase, the development of resistance to those drugs and some insight into the development of novel compounds

targeting HBV genome replication. Significant advances in these lines of research have allowed the use of drugs with a very slow rate of development of drug resistance (e.g. entecavir and tenofovir). As in the case of the HIV infection, future challenges in the treatment of HBV infection include the eradication of the virus.

The development of antiretroviral drug resistance has been extensively studied in recent years and the topic of many qualified reviews. In this Special Issue, we have included an update on resistance to the integrase inhibitors and the clinical significance of this resistance. Dolutegravir, the most recently approved antiretroviral drug, is a strand transfer inhibitor of the HIV integrase showing some significant differences from the previously approved drugs within this class (raltegravir and elvitegravir). In their review, Grobler and Hazuda [7] provide information from clinical trials revealing the significant overlap in the overall resistance profile of all approved integrase inhibitors. These observations are context-dependent and the genetic background has an important influence on the expression of resistance.

Influenza is one of the major infectious threats to public health worldwide. The huge death toll of the 1918 influenza pandemic and the rapid global spread of the virus are major factors contributing to this perception. Effective antiviral drugs will be required whenever the situation becomes alarming. However, there are not many effective drugs and the quick development of resistance is major drawback of available therapies. In his review, Hurt [8] notes how resistance to M2 ion channel inhibitors (e.g. amantadine and rimantadine) was quickly selected after their extensive usage, and provides a detailed review on the emergence and quick propagation of oseltamivir-resistant influenza A (H1N1) viruses. This is attributed to the relatively low impact on viral fitness of the resistance-associated substitution H275Y, in the influenza virus neuraminidase. A few studies also suggest that development of resistance to related drugs such as zanamivir or laninamivir is likely to occur at a slower pace, but in the absence of large clinical trials this is still an unsolved question. As pointed out for oseltamivir, the development of resistance could be also dependent on the specific serotype.

Before the discovery of HIV and the subsequent search for antiretroviral drugs, herpesviruses represented the major focus of antiviral drug discovery and development. James and Prichard [9] review mechanisms of action and drug resistance mainly associated with treatment with inhibitors of the viral polymerase. In addition to currently approved nucleoside analogues (acyclovir, penciclovir, cidofovir, etc.), pyrophosphate analogues (e.g. foscarnet), and related drugs in development (e.g. brincidofovir, valomaciclovir, etc.), the authors discuss other potential targets such as the helicase-primase complex, including investigational drugs such as pritelivir and amenamevir. As in the case of HIV and HCV, having drugs targeting different viral functions could facilitate the introduction of potent combination therapies.

The 2002-2003 epidemic caused by the severe acute respiratory syndrome (SARS) coronavirus resulted in nearly one thousand deaths, and caused serious concern and alarm around the world. More recently, evidence of infections caused by a related Middle East respiratory syndrome (MERS) coronavirus has renewed interest in this family of viruses as targets of antiviral intervention. Adedeji and Sarafianos [10] review current advances in the development of drugs active against coronaviruses. Promising drugs in preclinical development include inhibitors of the viral papain-like proteinase, the viral helicase and entry inhibitors. These drugs are expected to replace or complement medications given during the initial outbreak of SARS that included ribavirin with or without corticosteroids, or even combinations of interferon and ribavirin, whose effectiveness has not been fully tested in clinical trials.

Collectively, these reviews underline the significant progress in the field but also uncover problems and potential venues for further investigation. It should be noted that some of the treatments approved in recent years are extremely expensive and not affordable for people in countries with lower incomes. Although political and economic measures should alleviate this problem in part, there is still a need for affordable and effective therapies that could replace the current ones. On the other hand, an unsatisfactory coverage or suboptimal treatment of infected populations constitutes a perfect scenario for the development of resistance that could jeopardize the efficiency of current therapies even in the developed world.

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