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Review

# Perspectives on antiviral drug development

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ABSTRACT

The 21st International Conference on Antiviral Research provided novel insights and approaches to drug discovery across a wide array of virologic fields. Topics ranged from the chemical synthesis of new compounds against the human immunodeficiency virus (HIV) to the long-term use of established drugs against influenza. A session on novel targets for HIV therapy focused on the importance of Apobec3G, LEDGF/p75 and other cellular factors as innovative ways to control infection. New targets for hepatitis B and C viruses were surveyed. There were also discussions as to how the development of new antiviral compounds might lead to novel mechanisms of drug resistance by HIV, herpesviruses and hepatitis viruses. These covered such issues as transmission dynamics, viral fitness, the acquisition of differential resistance patterns depending on viral subtype, and clinical outcomes. Drug efficacy, toxicity, patient adherence, treatment interruption and the importance of generic drugs in resource-poor settings were also extensively discussed. These topics will all play a pivotal role in drug development and the management of viral infections in the years to come.



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To hold a conference on antiviral research seems almost a paradox: those scientists who have the most important new data should be the least willing to divulge their hard-won secrets to their competitors! Despite this limitation, the 21st International Conference on Antiviral Research, held in Montreal on April 13–17, 2008, witnessed many outstanding presentations on the development of new therapies for a wide array of viruses, including the human immunodeficiency virus (HIV), respiratory and emerging viruses, hepatitis B and C viruses (HBV and HCV), poxviruses, non-HIV retroviruses, herpesviruses, papillomaviruses and others. From my vantage point as the keynote speaker for the opening session, I would like to share my thoughts on the current state of antiviral research and the challenges of the next decade.

## 1. HIV therapy

The 21st ICAR combined a number of sessions focusing on basic aspects of viral replication with others that dealt more directly with drug development. One of the best was on novel targets for HIV therapy, in which an outstanding array of speakers from different

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academic medical centers presented research on new ways to target the HIV life cycle. Warner Greene discussed Apobec3G and other molecules that appear to play an important role in innate defence mechanisms against viral infection Similarly, Zeger Debyser dealt with the important topic of LEDGF/p75 as a necessary co-factor for HIV integrase activity, and Eric Freed discussed HIV maturation and the involvement of cellular factors in this process. These and other talks are summarized in a separate paper in this journal by Greene et al. (in press). Each talk dealt with a unique pathway that links cellular and viral factors in ways that are essential for virus replication, and also represent obvious targets for drug development. Will it be possible to develop small molecular inhibitors that target these virus-host interactions in a way that will not be toxic to the patients who take them? The answer to this question will have a major impact on the future of HIV therapy.

## 2. Hepatitis C

In all likelihood, the virus other than HIV that has attracted the most attention in recent years is HCV. This topic must certainly be considered to be a lucrative area for drug research, since no specific antiviral therapy yet exists (Ronn and Sandstrom, 2008). Therefore, the opportunities for providing benefit for patients while generating profits seem immense, although, to be sure, the leadership will always be motivated by the prospect of developing a good drug, not just by potential sales. However, it must be recognized that, in contrast to HIV infection, hepatitis C is a curable disease (Lang, 2007). This is not a trivial consideration when one realizes that the use of ribavirin and pegylated interferon-alpha to control HCV replication can lead to presumed eradication of viral infection in 40–50% of patients infected with genotypes 1 and 4 and up to 75–90% of those infected with the more susceptible genotypes 2 and 3 (Deutsch and Hadziyannis, 2008). It must also be recognized that the mechanism of action of these drugs is still relatively poorly understood. In addition, their tolerability profile is less than ideal, and response rates for genotype 1 in particular are sub-optimal, creating incentives for developing new small-molecule inhibitors.

The outstanding session on hepatitis virus drug development at the 21st ICAR featured discussions on all of the HCV targets thus far identified, including the NS5B polymerase, NS3 helicase, and NS3/4 protease (Mathy et al., 2008; Wyles et al., 2008). Indeed, each of these targets now represents a major research endeavour for a number of pharmaceutical companies. Unfortunately, one aspect that HCV will almost certainly share with HIV is its capacity to develop drug resistance rapidly under conditions of selective pressure. As in the case of HIV, this is likely to result from a combination of incomplete adherence to treatment regimens and inadequate suppression of virus replication, either because the antiviral agents were unable to fully suppress viral growth or because of mutations that result in the emergence of drug-resistant species (Sulkowski, 2008). Most observers consider it highly improbable that treatment success will be achieved with a single drug, suggesting that double- or even triple-drug therapy will be needed. Also in parallel with HIV, the question of the genetic barrier for resistance (how many mutations within a target gene are needed for high-level biological resistance and how easy it will be for these mutations to accumulate) will be paramount.

On the other hand, one should not exaggerate comparisons between HIV and HCV infection, in part because HIV causes profound immune dysregulation, while HCV does not. This may help explain why immunomodulating agents such as IFN and possibly ribavirin can clear HCV infection, but not HIV. Unlike HIV, HCV does not integrate into the host cell genome, thus alleviating problems of viral dormancy and eventual deployment from latently infected cells. This notwithstanding, the development of HCV drug resistance is all but inevitable, as has been documented with the use of NS3/4A protease inhibitors in replicon and clinical studies (Tong et al., 2008). This may mean that the first company to market a new HCV drug might quickly find that their product is prone to drug resistance, thereby giving an advantage to a competitor who develops another drug against the same target.

Might these considerations impede the rapid development of products offering quick hope for patients infected by HCV? Probably this will not happen, as the hope of improving on drug profiles and combinations of drugs to be used in therapy will promote competition, This should be balanced against the fact that being the first company to bring a drug to market often translates into a leadership position in drug sales that may be difficult to challenge. Another important consideration is that improved HCV diagnostics may reduce the incidence of new infections, thereby diminishing future market size.

## 3. Do unexpected results play a role in drug discovery?

Another important issue in regard to drug discovery research, and of course other areas as well, is the role of unanticipated observations. There are many examples of compounds that have been developed for a disease other than that for which they eventually became widely used. The development of antiviral nucleosides owes much to the chemists who have toiled over many years (Jurovcik and Holy, 1976). In some cases, drug development may have been fairly straightforward, but, in others, some drugs have turned out to have secondary, potentially beneficial properties that were not anticipated when initial research was carried out.

An excellent example is the anti-HIV drug 3TC, which is highly prone to the development of resistance because of the M184V mutation in reverse transcriptase that develops rapidly in tissue culture and during monotherapy in the clinic (Diallo et al., 2002). Once it was discovered that this mutation conferred very high levels of 3TC resistance, there was a chance that the companies involved with the product might have abandoned its development. However, the decision to proceed with the investments needed for the clinical use of 3TC was facilitated by the demonstrations that the M184V mutation suppressed viral replication by reducing replicative fitness, and that 3TC could be used synergistically with zidovudine to suppress HIV replication (Campbell et al., 2005; Diallo et al., 2003).

The issue of drug development is multifaceted, involving complex decisions by scientists, companies, investors and granting agencies as to whether a novel scientific approach should be supported. The case of HIV is illustrative, in the sense that during the early days of the epidemic, few individuals understood how important and how lucrative a drug development target might be. It took many years of research before it was understood that treatment with antiretroviral drugs was likely to be life-long. This realization only came once it was clear that the DNA form of the HIV genome integrated into host cells, and that it was virtually impossible to conceive of the eradication of the virus due to this issue as well as that of viral latency (Asante-Appiah and Skalka, 1999). We next had to grapple with the issue of drug resistance and the understanding that successive generations of antiretroviral drugs would be required for multiple reasons, including both resistance and toxicity. There was also an absolute need to improve on the first generation drugs, which were relatively toxic, and therefore promoted non-adherence (and, by corollary, resistance), in favor of better-tolerated drugs that would promote adherence and diminish the likelihood of resistance development. The advent of the triple co-formulation known as Atripla is an excellent example of suc-

cess that has worked to improve adherence to complex regimens (Killingley and Pozniak, 2007).

At the same time, the HIV field witnessed a number of clinical trials that attempted to simplify treatment through the use of drugs over diminished periods of time. For example, trials were performed on structured treatment interruptions, which assessed whether an individual could take anti-HIV drugs for several months, achieving complete suppression of viral replication before resuming therapy at a later time. Unfortunately, all such clinical trials have now been shown to put patients at risk of resumption of active HIV disease as well as the development of drug resistance (El-Sadr et al., 2006). Furthermore, subjects who were placed in the treatment-interruption arms also seem to have become more prone to developing numerous toxicities, as well as AIDS-related cancers.

## 4. Viral drug resistance

It is worth remembering that concern as to the rapid development of drug resistance were long expressed with regard to compounds that are now in widespread use to treat viral diseases other than HIV. An excellent example is the use of acyclovir (ACV) and ganciclovir (GCV) for a number of herpesvirus infections and for cytomegalovirus (CMV) infection complicating solid-organ transplantation (Hodson et al., 2005). It was feared that resistance might be quick to develop against these drugs through mutations in the viral thymidine kinase and/or DNA polymerase enzymes. Indeed, while such mutations can occur, resistance has not developed to the levels that were feared 10 or 15 years ago, so that the public health issues surrounding resistance to anti-herpesvirus agents are not in the forefront of concern (Biswas and Field, 2008).

However, it should be recognized that the issues of herpes simplex virus (HSV) and CMV drug resistance are distinct, as are the mechanisms of actions of ACV and GCV, which target them. There are also important differences in the HSV and CMV target genes in regard to pathogenesis and transmission. It is fortunate that HSV strains that are resistant to ACV seem to be relatively incapable of being reactivated from latency, and hence are not capable of efficient sexual transmission. This notwithstanding, HSV drug resistance can be life-threatening in immunocompromised patients. Similarly, CMV resistance to GCV in transplant recipients is a major cause of morbidity and mortality. This underlines that the CMV field is in need of new, well-tolerated drugs that will overcome problems of resistance in regard to existing agents. However, many pharmaceutical companies have clearly decided to avoid this area, probably because of the perception that overall market share is too small to warrant major investments. Perhaps governments and granting agencies should do more to support research in this area, as they have done for certain types of vaccine development and defense against bioterrorism.

Although the transmission of ACV-resistant hespesviruses does not seem to be a major concern, this in sharp contrast to the situation regarding HIV, for which the transmission of drug-resistant strains has become a major public health problem, which in all likelihood will pose severe challenges in developing countries in regard to the sustained ability of effective treatment regimens (Bennett et al., 2008; Vardavas and Blower, 2007). The problem may be further exacerbated by the likelihood that some HIV subtypes will develop certain mutations at differential rates, compared to what has been observed with viruses of subtype B origin. A good example is the greater propensity of subtype C viruses than subtype B to select for the K65R mutation in reverse transcriptase (Brenner et al., 2006), which seems to occur after exposure to a wide array of nucleoside analogs. This has important implications not only for the treatment of HIV disease, but also in regard to potential prophylactic approaches that depend on using antiretrovirals as microbicides or for pre-exposure prophylaxis (Wilson et al., 2008).

## 5. Viral fitness and other evolving concepts

The issue of viral fitness is important not only in understanding pathogenesis, but for assessing our ability to use certain drugs over longer periods than might first have been expected. An excellent example is the use of 3TC in cases in which the M184V mutation has appeared (Campbell et al., 2005). Numerous clinical trials have shown that the continued use of the drug might provide virologic benefit, because the mutation simultaneously confers diminished viral fitness alongside high level resistance to 3TC (Eron et al., 2004). This has created the rationale for the continuing use of 3TC, despite drug resistance, for the purpose of maintaining the M184V mutation. Such an option became popular after clinical trials that showed the 3TC-mediated fitness benefit could have clinical relevance (Gallant, 2006). However, this opinion was mostly prevalent at a time when few other treatments were available to subjects who had failed their anti-retroviral regimens.

Today, the situation in regard to HIV therapeutics has changed considerably, and individuals who have failed on earlier drugs have a wide array of therapeutic options from which they might benefit. In the case of the protease inhibitors, the options now include the use of such drugs as darunavir and tipranavir, which often have excellent activity against viruses containing a wide array of mutations associated with resistance to earlier protease inhibitors such as lopinavir, saquinavir or amprenavir (Huang et al., 2008; Marcelin et al., 2008; Pellegrin et al., 2008). The advent of the fusion inhibitor enfuvirtide (T-20) also represents an important option for patients who have failed previously available classes of drugs (Lalezari et al., 2003). Most recently, of course, the advent of CCR5 inhibitors, e.g. maraviroc, and of integrase inhibitors, e.g. raltegravir, has meant that patients who display resistance against drugs used in previous therapy now have access to new agents that effectively reduce viral load (Cooper et al., 2008; MacArthur and Novak, 2008). It is thus no longer necessary to rely on a compound's secondary potential to achieve therapeutic benefit, since logic dictates that we should always use drugs that directly suppress viral load.

## 6. What happens when new drugs imperil older ones?

Drug development issues can also be discussed in the context of what is widely perceived as an excellent antiviral drug, in spite of some difficulties associated with its use. Notably, enfuvirtide (T-20) is an excellent compound that had been extensively relied upon for the treatment of drug-resistant HIV infections, until its sales were affected by the development of new products such as raltegravir, maraviroc, tipranavir and darunavir that were much better tolerated (Cooper et al., 2008; Harris et al., 2008; McCoy, 2007). Two major reasons for the fall of T-20 into disfavour include the fact that it is the most expensive antiretroviral drug, making it unpopular among payers, and that it must be injected subcutaneously twice daily, making it more inconvenient and uncomfortable for patients than oral drugs. Although these considerations are not trivial, it should be remembered that many groups have attempted to develop orally available fusion inhibitors during the past decade, but there are still no examples of practical success. This illustrates some of the hazards of drug development when many other products are available for treatment. However, it can still be predicted that the use of T-20 will resume if other antiviral products are not soon developed, because resistance will inevitably emerge to the newer drugs listed above.

It is important to point out that pressure from community groups has helped to drive the development of new HIV drugs virtually since the beginning of the epidemic. This has probably not occurred to the same extent in the case of viral diseases such as HCV or even influenza. Today, pressure in regard to new drug development also doubtless emanates from political sources, but it does not apply in the same way to viral illness caused by HCV, HSV, CMV, and others.

## 7. Fear of an influenza pandemic

Because fear of a new pandemic is widely expressed, influenza drug development remains a high priority. Most recently this discussion has revolved around H5N1 strains of influenza. The worldwide use of anti-influenza drugs such as Tamiflu and Relenza has increased significantly in recent years, not so much for treatment as for prophylaxis by individuals who consider themselves to be at risk or by communities or individuals who fear that an outbreak of H5N1 might soon occur (Ong and Hayden, 2007). Hence, governments have been persuaded to stockpile these drugs in large quantities, creating a boom in sales for their manufacturers, even though an H5N1 epidemic has not occurred and hopefully will never occur.

The fear of epidemic influenza, rather than the reality, thus represents another motivating factor in regard to drug development, as society must concern itself with future epidemics, rather than waiting for disaster to occur. This approach to preparedness is not unique to infectious diseases. As examples, responsible societies enact measures designed to protect against earthquakes, tsunamis, and other types of natural disasters. Are there other viruses or infectious agents against which preparedness should figure prominently in public policy?

## 8. The future and generic drugs

An area of increasing importance in HIV therapeutics is the development of generic forms of antiviral drugs and their role in treating patients in developing countries. Despite some level of debate on this topic in regard to patent protection issues, there is now widespread consensus that agreements must be reached to permit anti-retrovirals to be produced at the lowest possible cost to treat the largest possible number of infected people. This has been accomplished through protracted, often difficult compromise and negotiation between governments, pharmaceutical companies, funding agencies and other stakeholders (Nunn et al., 2007).

A related issue is the potential ability of generic drug manufacturers to produce anti-HIV drugs at lower cost than in developed countries. Indeed, a number of anti-retrovirals, including zidovudine (ZDV) and dideoxyinosine (ddI), are now available as generics in almost all western countries. Most importantly, this list will expand over the next several years to include such products as 3TC and saquinavir. The question in this case is whether or not current third-party payers (governments, insurance companies, etc.) will insist that generic drugs be used in place of brand-name pharmaceuticals, once a sufficiently large number of generics, that might be potentially co-formulated, become available. For example, a triple regimen consisting of generic ZDV, 3TC, and ritonavir-boosted saquinavir would probably not be considered unreasonable by many clinicians and scientists. In all likelihood, such a combination would suppress viral load in relatively durable fashion, in spite of the fact that marginally less toxic regimens might also be available. The real issue is whether the use of a far more expensive drug combination would be warranted, compared to a generic regimen that would cost far less.

Will pressure begin to emerge over the next 5 years for such a change, which would result in considerable financial savings? Only time will tell. However, it is important that this subject be anticipated in advance of a full debate, because it could impact the future development of HIV drugs. It also has relevance to drug development in areas other than HIV, such as tuberculosis and malaria, because these are also disease entities for which there are strong geopolitical pressures. Certainly, it is difficult to conceive of a situation in which patented drugs are not only being developed by generic companies for use in developing countries, but in which brand-name pharmaceutical companies are fully involved in this process. We should hope that the HIV precedent will lead to more rapid availability of drugs on a global scale for other diseases. Clearly, world leaders must find ways to make this happen, without removing financial incentives from those companies that can make progress against diseases that take a disproportionate toll in developing countries.

## 9. The unsung heroes: the chemists

I would like to conclude my comments by pointing out the critical role of organic and medicinal chemists in drug development, which is never sufficiently highlighted at conferences. These scientists are truly the unsung heroes of our field, because they are the ones who conceive the difficult and complex synthesis of compounds that are eventually turned into drugs. Yet it is usually the clinicians who lead the clinical trials that result in approval by the Food and Drug Administration who receive recognition for the final development of these products. This reflects the fact that press coverage of successful drug development commonly intensifies as the results of Phase III studies are reported at meetings or in the scientific literature.

Which of these two groups, the chemists or the clinicians, has contributed true ingenuity to product development? What can we do to better recognize the chemists, without whose contributions the field of antiviral drug development would not exist, let alone flourish? Some companies do provide rewards to their chemists for patent inventions, but a better system of incentives should be encouraged, including financial rewards for work, beginning with initial synthesis and moving forward to later scale-up of production, stability of formulations, and other steps in the complex, multi-factorial drug development process. This is not to take anything away from hard-working, intelligent clinical investigators, but rather to suggest that a better balance is needed in regard to recognizing scientific accomplishment.

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