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Beyond interferon

Interferon (IFN)-α has reigned supreme for decades as biotech's blockbuster antiviral. That looks set to change with a raft of antibody and nucleic acid therapies progressing through the pipeline.

Fifty years after its identification by Jean Lindenmann and Alick Isaacs, 27 years since it was first produced in recombinant form in the lab of Charles Weissmann and 25 years following approval of Hoffmann-La Roche's Roferon A, IFN's stranglehold on the antiviral market for biologics might finally be about to loosen. A new generation of biotech firms is focusing on antibody treatments and nucleic acid therapies that target cellular proteins as well as viral components. But progress has been slow and fitful. And the combination of rapidly adaptive and elusive viral pathogens with a profusion of new therapeutic strategies and novel targets could spell trouble in the clinic.

As illustrated by this focus (funded by principal sponsor Pfizer and supporting sponsor Gilead Sciences), the vast majority of the 50 or so antiviral treatments now approved are small molecules targeting a limited number of viral enzymes. The hegemony of the small molecule should be no surprise: viruses are intracellular parasites and the limitations of antibodies and most other biologics in penetrating cell membranes is well known. In addition, the heterogeneity of many viral pathogens (hepatitis C virus (HCV) has six different major genotypes varying in sequence by as much as 30%) and their propensity to mutate (HIV can evolve in days) has made it difficult to identify cross-reactive antibodies that are able to neutralize a variety of primary isolates. This is one reason why many biotech firms are developing either polyclonal antibody approaches or cocktails of two or more monoclonal antibodies (mAbs) targeting different viral epitopes.

Several technological breakthroughs are, however, helping matters. With over 2,000 unique viral genomes already lodged in GenBank, advances in sequencing technology are transforming our ability to characterize emerging viral pathogens or resequence existing ones to look for drug resistance or a change in receptor tropism. It is a mark of progress that the genome sequence of SARS (severe acquired respiratory syndrome) coronavirus was obtained in a mere six days following isolation of the viral nucleic acid.

At the same time, the ability to assemble megabase sequences and synthesize viral genomes progresses apace. Work in 2002 to reconstitute a poliovirus from synthetic fragments and the more recent creation of a hybrid influenza virus containing all eight genes from the 1918 pandemic strain have provided key insights into virulence factors and host-virus interactions (p. 1383).

Large-scale, high-throughput 'omic approaches that study the influence of viral infection on host cell gene expression, protein composition, metabolites, etc. are also yielding new targets and revealing insights into the process and timing of the viral life cycle and its pathogenesis. Such studies are being aided by breakthroughs in virus culture, as illustrated by the demonstration two years ago of functional HCV genomic replicons that produce robust levels of infectious virus in cell culture.

All of these advances are contributing to an increased understanding of viral infection and eradication. But until recently, progress has been slow. Although the ability of both viral RNA and DNA to activate IFN production was reported by Isaacs back in 1963, it took four decades to identify the role of toll-like receptors (TLRs) in sensing viral infection; RIG-I and MDA5 were only recently identified in the cytoplasm as sensors of viral RNA; and DAI, the first reported cytosolic sensor for viral DNA, was just reported in October (*Nature* **448**, 501–505, 2007).

We now also know some of the key actors in mediating antiviral activity of the type I IFN response. These include protein kinase PKR and 2′,5′-oligoadenylate synthetase/RNase L system, the adenosine deaminase ADAR1, the Mx GTPases and now also cellular microRNAs (*Nature* **449**, 919–922, 2007). New members of the expanding IFN protein family (e.g., recently identified type III IFN-λ; interleukin 29) are also being turned into therapies. All this suggests that we have sampled only the tip of the therapeutic iceberg in terms of the host.

Targeting host proteins means a lack of selective pressure on the virus to evolve resistance, unlike traditional therapies binding viral proteins. In addition, many of the direst outcomes of viral disease are due to aberrant host immune responses (e.g., the cytokine storm elicited by 1918 influenza or Ebola virus); if it were possible to reduce the severity of such responses, patient outcomes might be improved. By addressing host proteins co-opted by different types of viral pathogen, broad-spectrum agents might also be created, maximizing commercial potential for companies and facilitating treatment selection by physicians.

But no one should underestimate the difficulty of moving these antivirals through the clinic. First, the complexity of human biology means that the task of identifying the key points for medical intervention could be more difficult than for simple viral targets. And drugs that target essential or integral cellular proteins may also induce harsher side effects (although this has not been insurmountable for other indications and current antiviral treatments are not exactly nontoxic).

Perhaps the most serious concern is the paucity of animal models that replicate the pathogenesis of human disease, which makes antiviral R&D an entirely different prospect from that of antibacterials, where preclinical studies are so often good predictors of clinical efficacy. The best large animal model for HIV, for example, is simian immunodeficiency virus infection of macaques (chimpanzees injected with HIV fail to develop a human-like disease). To recognize the limitations of such models, look no further than the recent high-profile failure of Merck's HIV trivalent V520 vaccine—which monkey studies had predicted would be protective.

Supplanting the dominance of IFN and existing small molecules approved for the antiviral market will not be easy. But it is encouraging that at last so many different approaches are progressing to the clinic, with investment from both big pharma and biotech. And for deadly pathogens that have evolved over the millennia to elude human immune defenses, the more therapeutic avenues available to break cycles of infection, the better.