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Combating emerging viral threats

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Synopsis

Most approved antiviral therapeutics selectively inhibit proteins encoded by a single virus, thereby providing a “one drug-one bug” solution. As a result of this narrow spectrum of coverage and the high cost of drug development, therapies are currently approved for fewer than ten viruses out of the hundreds known to cause human disease. This perspective summarizes progress and challenges in the development of broad-spectrum antiviral therapies. These strategies include targeting enzymatic functions shared by multiple viruses and host cell machinery by newly discovered compounds or by repurposing approved drugs. These approaches offer new practical means for developing therapeutics against existing and emerging viral threats.

Although hundreds of viruses are known to cause human disease, antiviral therapies are approved for fewer than ten. Most approved antiviral drugs target viral enzymes, most commonly proteases and polymerases. Such direct acting antivirals (DAAs) have shown considerable success in the treatment of HIV and hepatitis C virus (HCV) infections. However, this approach does not scale easily and is limited particularly with respect to emerging and Re-emerging viruses against which no vaccines or antiviral therapies are approved. A major limitation of the commonly developed DAAs is their narrow spectrum of coverage, ranging from a single viral genotype to several related viruses at the most. Given an average cost of over two billion dollars and an 8- to 12-year timeline to develop a new drug (1), targeting viruses individually makes drug development expensive and slow. Moreover, given the unpredictable nature of virus emergence, this approach cannot provide adequate global health protection and national security preparedness. Finally, resistance to conventional DAAs typically emerges rapidly. This issue can be partly circumvented through combination drug treatment, but drug-drug interactions and cumulative toxicity often complicate this strategy.

Emerging and re-emerging pathogens for which no specific, licensed treatments exist include the flavivirus dengue, estimated to infect 400 million people annually, the coronaviruses SARS-CoV and MERS-CoV, associated with outbreaks in 2002 and 2012, respectively, and the filovirus Ebola, responsible for the current large-scale epidemic in

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Broad-spectrum antiviral drugs are under development to treat emerging viral diseases such as Ebola and dengue for which no specific, licensed treatments exist

Africa. There is an urgent need for novel drugs against these and many other viral diseases. This need is unlikely to be met solely by the prevailing drug-development approach.

Broad-spectrum drugs can play a role in addressing this need (see the figure). They drastically reduce the time and cost associated with the early stages of drug development per approved indication and diminish the clinical risks in the more advanced phases. Off-label use of approved broad-spectrum antivirals against new viral indications can provide further economic incentives as well as facilitate readiness for future outbreaks of emerging pathogens. A broad-spectrum therapeutic could also be administered before a viral threat has been accurately diagnosed, increasing likelihood of viral control.

The concept of broad-spectrum antivirals was first introduced in the 1970s. One of the earliest broad-spectrum antiviral agents, ribavirin, inhibits viral DNA or RNA synthesis. In the U.S., ribavirin is approved for the treatment of HCV and respiratory syncytial virus. Although ribavirin was reported to benefit the resolution of many emerging viral infections preclinically (2), it yielded marginal to no benefit in the clinic. Ribavirin is today administered together with interferon, a soluble immune factor that is active against most vertebrate-infecting viruses and that was approved for HCV treatment in 1991 (3). However, interferon treatment has only shown partial success rates, requires intramuscular injections, has serious side effects, and is expensive.

More promising, next-generation nucleotide and nucleoside analogues have been recently developed. For example, the synthetic adenosine analog BCX4430 inhibits replication of more than 20 RNA viruses in nine families, including coronaviruses and flaviviruses, both in vitro and in animal models (4). It protects nonhuman primates from filovirus disease and has a favorable preliminary preclinical safety profile. T-705 (Favipiravir), another nucleoside analogue, also has in vitro and in vivo efficacy against several RNA viral families (5). Human trials for the treatment of both influenza and Ebola with T-705 are ongoing. CMX001 (Brincidofovir), a lipid conjugate of the nucleotide analogue cidofovir, shows in vitro activity against multiple DNA viruses including herpesviruses and papillomavirus (6). It has a favorable pharmacokinetic profile and has advanced to phase III trials. However, because of the extensive sequence and structural diversity of virally encoded proteins, design of broad-spectrum DAAs is seldom feasible. Thus far, only one class of molecules, nucleoside inhibitors, has shown promise in the clinic.

A different broad-spectrum antiviral strategy is to target the host. Host proteins or pathways required by multiple viruses are attractive targets for broad-spectrum antivirals with an often added benefit of higher genetic barrier to resistance. The most clinically advanced representatives of this class are the cyclophilin A inhibitors DEB025 (Alisporivir) and SCY-635 (7). These compounds act in a multifaceted way that includes impairing protein folding and augmenting innate immune responses. They inhibit a diverse group of RNA and DNA viruses, including HCV, dengue virus, HIV, influenza, and SARSCoV, both in vitro and in animal models and have shown promise as anti-HCV drugs in phase II/III trials. ER α -glucosidase is another host protein that serves as a broad-spectrum antiviral target. Glycoproteins of many enveloped viruses depend on host glucosidases to achieve proper folding. Iminosugars, such as celgosivir, are competitive substrates for α -glucosidases with

activity against multiple unrelated viruses both in tissue culture and in rodents (8). Little to no efficacy has been found thus far with celgosivir in clinical studies, but further investigation of glucosidase inhibitors is warranted.

Repurposing approved drugs that target host functions required by several viruses is a cost- and time-effective route to broad-spectrum antivirals. One area of investigation targets host factors involved in regulating intracellular viral trafficking. For example, the host kinases cyclin G associated kinase (GAK) and AP2-associated protein kinase 1 (AAK1) regulate viral trafficking during entry, assembly, and release of unrelated viruses (9). The approved anticancer drugs erlotinib and sunitinib potently inhibit GAK and AAK1, respectively, and show in vitro activity against HCV (9), several flaviviruses, Ebola virus, and HIV. The combination of erlotinib and sunitinib protects mice from lethal dengue and Ebola virus challenges and is being advanced into clinical trials for dengue and Ebola. The kinase inhibitors dasatinib, imatinib, and nilotinib are additional approved anticancer drugs with broad antiviral activity (10, 11). Another drug that may be repurposed is nitazoxanide, FDA-approved for the treatment of parasitic diarrhea. It inhibits replication of respiratory viruses, HIV, HCV, flaviviruses, and other viruses and has reduced the duration of flu symptoms in clinical studies (12). Nitazoxanide blocks maturation of the influenza hemagglutinin, but the target remains unknown. Further approved drugs whose therapeutic potential against emerging viruses is being evaluated include chloroquine, an antimalarial agent (13), and atorvastatin, which alters host lipid metabolism (14).

Focusing on host functions is a useful expansion of potential antiviral drug targets, but this approach faces its own challenges. Cellular proteins function in a complex network of interactions, and a complete understanding of the drug's mechanism of action is often elusive. Moreover, an achieved in-vitro phenotype often does not translate into an in-vivo outcome. Toxicity is another major concern. Nevertheless, it may be feasible to identify a therapeutic window where the drug level is sufficient to inhibit viral replication with minimal cellular toxicity. Furthermore, shifting from an indication requiring long-term therapy (e.g. months to years for cancer) to a shorter duration sufficient to treat most acute viral infections can help limit toxicity. Emergence of resistance typical of DAA monotherapy can also complicate treatment with host-targeted approaches, as in the case of the CCR5 antagonist maraviroc (15). Nevertheless, the time to resistance with other host-targeted approaches appears longer and the level of resistance lower than with DAAs, as exemplified by treatment with cyclophilin inhibitors (7).

Taken together, meeting the clinical needs presented by emerging viruses will best be achieved by a combinatorial approach that includes discovery of novel broadly acting DAAs and host-targeted therapies as well as repurposing of already approved drugs.

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Antiviral drugs that selectively inhibit unique viral proteins provide a “one drug, one bug” solution, while broad-spectrum drugs can restrict multiple viruses by inhibiting either common viral enzymatic functions or host factors commonly required by several viruses. The lower panels depict specific stages of the viral life cycle (blue rectangles) often targeted by each class of drugs. Specific examples of broad-spectrum compounds are denoted in orange with the corresponding targeted proteins or pathways in grey. CypA (Cyclophilin A).