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Broad-Spectrum Antiviral Agents: A Crucial Pandemic Tool

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1. Introduction

Among the myriad infectious disease threats humans face from bacteria, prions, parasites, protozoa, fungi, ectoparasites, and viruses, it is viral infections that arguably constitute the biggest pandemic threat in the modern era. The replication rates and transmissibility of viruses are two major factors that underlie this threat. However, at least one additional factor plays an essential role: the lack of 'broad-spectrum' antiviral agents. Indeed, while bacteria can still cause substantial epidemics in parts of the world where access to clean water and/ or antimicrobials is limited, the pandemic threats posed by bacteria, such as from the plague-causing *Yersinia pestis*, has been substantially diminished in the antibiotic era [1]. For viruses that pose epidemic risks, on the other hand, current therapeutic options are more limited.

Viruses, by their obligate parasitical nature, must use host cell machinery for many functions. Thus, antiviral strategies must be directed at the virus specifically with care to avoid interfering with host cellular function. As such, the number of clear targets per virus may be limited. By contrast, bacterial protein synthesis, for example, occurs via ribosomes that belong to the bacteria and are disparate enough from human ribosomes in identity that specific antibiotics can be deployed to target only bacterial protein synthesis. This unique feature of viruses, which derives from their very nature, serves to delimit antiviral therapies in a manner not applicable to antibacterial therapies.

Additionally, other characteristics of viruses serve as obstacles to broad-spectrum antiviral agents. These include differences between RNA and DNA viruses, vastly different virally encoded proteins across viral families, single or double strand genomic structure, cytoplasmic or nuclear replications cycles, and degree of reliance on host proteins.

The existing armamentarium of antiviral drugs is rapidly expanding and now covers several viral families. However, very few existing antiviral agents have spectrums of activity that even slightly measure up to the spectrum of penicillin or sulfa, the first anti-bacterial agents discovered.

2. One virus, one anti-viral paradigm

The antiviral agents that are currently available for use are best thought of as highly-targeted against a specific virus or,

in some cases, members of a viral family. Current trends with antiviral drug development reflect large efforts to develop exquisitely targeted countermeasures against specific viruses, a trend exemplified by monoclonal antibodies and RNAi compounds.

For example, antivirals such as acyclovir, valacyclovir, and famciclovir all are utilized against various herpes family viruses such as herpes simplex virus 1 (HSV-1), HSV-2, and varicella-zoster virus (VZV) but the extent of their broad-spectrum nature does not even carry over to fellow herpes virus, cytomegalovirus (CMV). Acylovir, valacyclovir, and famciclovir are nucleoside analogs dependent on the virally encoded thymidine kinase enzyme for activity. There are separate specifically targeted antivirals such as ganciclovir, valganciclovir, foscarnet, or letermovir (this last is itself exquisitely targeted at just CMV) to be used in the treatment and prophylaxis of CMV. The tenuous nature of any rudimentary claim to broad-spectrum antiviral activity is also evident in acyclovir's 10-fold drop in activity against HZV compared to fellow viral family members HSV-1 and 2, despite targeting the same enzymatic function (thymidine kinase) [2,3].

Similarly, anti-HIV medications – of which there are now several classes – are primarily targeted at HIV-1 with antiretroviral drug classes such as non-nucleoside reverse transcriptase inhibitors (NNRTIs), certain protease inhibitors, and the gp41 fusion inhibitor enfuvirtide lacking efficacy even against HIV-2 [4]. It should be noted, however that nucleo(t)side reverse transcriptase inhibitors such as lamivudine, emtricitabine, and tenofovir do have activity outside of HIV as they are competitive substrate inhibitors for DNA synthesis and are also able to inhibit the reverse transcriptase enzyme encoded by the hepatitis B virus (HBV) [5], likely due to a shared evolutionary origin between HBV and retroviruses [6].

With the exception of nucleo(t)side reverse transcriptase inhibitors, anti-HIV medications, which are the most extensive group of antivirals available, are highly specific to HIV viral proteins such as the reverse transcriptase, protease, integrase, and gp41. Further, maraviroc, a host-side HIV antiviral, targets a cellular coreceptor exclusively used by only one group of HIV viruses (CCR5 tropic) [7].

Hepatitis C protease (NS3/4A) inhibitors, such as simeprevir, are quintessential targeted agents as many have activity only

against specific genotypes (e.g. 1 and 4 for simeprevir) of HCV let alone other viruses. Many HCV polymerase (NS5B) inhibitors and NS5A inhibitors are similarly constrained in spectrum of activity to specific HCV viral proteins encoded by specific genotypes – for example ledipasivir is only active against genotype 1 – though a pan-genotypic combination regimen has been developed [8]. However, there is always the specter of new HCV genotypes evolving which may have less susceptibility to these agents [9].

Influenza antivirals (available in the US) are also highly targeted with adamantane (amantadine and rimantadine) class antivirals effective only against influenza A. Neuraminidase inhibitors such as oseltamivir, zanamivir, and peramivir are effective against both influenza A and B as is the endonuclease inhibitor baloxavir [10,11]. However, given all of these target proteins that are specific to influenza viruses, they are not broad-spectrum in nature.

The antisense CMV antiviral fomivirsen, the monoclonal antibody targeting the RSV fusion protein (palivizumab), and the host-directed monoclonal antibody targeting the HIV receptor CD4 (ibalizumab) were all designed with intended specificity. The smallpox antiviral tecovirimat inhibits a highly conserved envelope protein, p37, in orthopox viruses and is a vital tool for the large orthopoxvirus family, which includes emerging and re-emerging viruses [12–15].

In sum, most antivirals are designed with the aim of blocking the function of one specific crucial viral protein which is likely to be unique to a specific virus or viral family. When drugs such as nucleo(t)side reverse transcriptase inhibitors cross viral families it is due to a homologous protein that happens to exist in another viral family.

3. Antivirals with broad spectrum properties

While most antiviral therapies are targeted at narrow viral ranges, a few antiviral compounds have characteristics that qualify them as broad-spectrum in nature.

For example, the influenza RNA dependent RNA polymerase inhibitor, favipiravir (available in Japan), exhibits broad spectrum RNA virus activity with efficacy against the polymerase of Ebola and Lassa fever [16–18]. These activities of favipiravir highlight the potential for targeting a protein universal to RNA viruses.

Cidofovir, a nucleotide analog, has a spectrum of activity that can be considered somewhat broad, with activity against DNA viruses including herpes, polyoma, adeno, and pox viral families. Its less toxic derivative, which remains in development, brincidofovir has been shown to have in vitro activity outside DNA viruses and has been used in the treatment of the RNA-genome filovirus, Ebola, but no human efficacy was noted and it is unclear if in vitro findings were the result of cell toxicity vs. a true antiviral effect [19–21] .

Ribavirin, a nucleoside analog that inhibits viral polymerase enzymes, also might be characterized by broad spectrum activity against RNA viruses such as RSV, hepatitis C, influenza A and B, parainfluenza viruses, hepatitis E, metapneumovirus, Crimean-Congo Hemorrhagic Fever (CCHF) and New and Old-World Hemorrhagic Arenaviruses (e.g. Lassa Fever, Junin). It was also used unsuccessfully during the outbreak of the RNA coronavirus SARS. DNA viruses such as adenoviruses are also inhibited by ribavirin [22]. The antiviral mechanism may not be the same in all viral families and could also include immune modulation. There are also serious toxicity concerns with ribavirin which may be an indication of a cost incurred by broad-spectrum antiviral agents.

Important to note is that nucleo(t)side analogs such as cidofovir and ribavirin, along with HIV nucleto(t)side analogs, because of their mechanism of action being focused on nucleic acid synthesis may have a larger breadth of activity and possibly greater toxicity against the host. However, highly targeted specificity is seen with the hepatitis B antiviral telbivudine despite being part of this class.

An antiviral in development, the nucleoside analog remdesivir, has been shown to have effect against both filoviruses and coronaviruses [23].

Host immunomodulatory compounds such as interferon and imiquimod can be conceptually thought of as broad spectrum. However, they do not target a virus directly as they augment intrinsic antiviral activities possessed by the immune system of the host.

4. Repurposing antivirals

Because many antivirals were initially developed as single agent targeted compounds, the possibility exists that repurposing of existing antiviral agents against other targets might be possible.

Ganciclovir (and valganciclovir its oral ester form that converts to ganciclovir after oral administration), primarily used against CMV, also exhibits the ability to inhibit two other DNA viruses in vitro: adenovirus and hepatitis B virus [24,25].

Tenofovir, in addition to its activity against HIV and HBV, has activity against the DNA polymerase of HSV. Foscarnet, a pyrophosphate analog that blocks the pyrophosphate binding sites of viral polymerase is primarily considered an antiviral exclusively used for resistant herpesvirus infections but has also demonstrated activity versus the reverse transcriptase (an RNA dependent DNA polymerase) of HIV-1 and HIV-2. Anti-HIV activity is also possessed by the HBV reverse transcriptase inhibitors adefovir and entecavir. Adefovir also possesses activity against the DNA-possessing poxviruses and herpesviruses [26–30].

The HIV protease inhibitor lopinavir (given in combination with ritonavir) has been repurposed for use in the treatment of coronaviruses SARS and MERS which possess proteases, though clinical efficacy has not been shown to date [31].

Other antiviral agents such as idoxuridine and trifluridine, both topical ophthalmic nucleoside analog antivirals, exhibit activity against HSV and other DNA viruses such as vaccinia and adenovirus [32].

Interestingly, an anti-parasitic and anti-bacterial medication, nitazoxanide, has been shown to have antiviral activity, through a distinct mechanism, against hepatitis B, hepatitis C, norovirus, rotavirus, dengue, HIV, yellow fever, Japanese encephalitis, and influenza [33].

5. The need for a broad-spectrum antiviral strategy

The paucity of true broad-spectrum antiviral agents leaves a major chasm in preparedness for viral infectious disease

emergencies. The current antiviral discovery process and strategy is driven by an overarching aim of finding treatments for *specific individual* viruses of concern and not against viral families, let alone larger groupings of viruses akin to gram-positive or gram-negative spectrum antibacterial agents. This fact, coupled with the inherent and unique challenges with viral class pathogens, will make broad spectrum antiviral agent development difficult. However, as many antiviral agents might be amenable to repurposing and some (favipiravir, ribavirin, cidofovir, and brincidofovir) have already shown broad-spectrum properties, the task is not impossible.

To this end, a program to test current commercially available 'off the shelf' antivirals against off-target viruses should be pursued. This process does occur currently and was part of the response to the 2013–2014 west Africa Ebola outbreak [34] but is largely performed post-viral emergence and not pre-emptively or part of initial antiviral development. Antivirals in development against specific targets should also be systematically assessed for broad-spectrum antiviral activity. Lastly, identifying targets common to distinct viral families that are genetically similar would also be of great use in antiviral drug development. The broad-spectrum strategy should be pursued as a complement to (not in lieu of) the pursuit of targeted therapies such as monoclonal antibodies which also hold great promise for treating specific viral infection as evidenced by the successful deployment of monoclonal antibody products against Ebola, Hendra, Nipah, and hopeful future successes against HIV and influenza [35,36].

It should be emphasized, however, that there may be a need to balance broad-spectrum activity against toxicity against the host, as mentioned with nucleos(t)ide analogs. The toxicity and lack of broad-spectrum antiviral agents are both a function of the fact that viruses employ host cell machinery for a great amount of their activity. Given that context, it is important to encourage the development of monoclonal antibodies and immune-modulation as well as viral family specific antivirals.

When an emerging infectious disease or pandemic strikes, if it is of bacterial or fungal origin it could be almost assured that clinicians, microbiologists, and pharmacologists could craft an effective regimen from amongst existing antimicrobials. This exact phenomenon occurred with the emergence of *Candida auris*, carbapenem-resistant Enterobacteriaceae (CRE), and multi-drug resistant *Neisseria gonorrhea*. By contrast, nearly every novel viral epidemic of regional or global importance has been characterized by the common refrain that supportive care is the mainstay of therapy with drug trials coming, for the most part, post-outbreak. Antimicrobial R&D strategies and funding should take that into account and place high priority on the development of broad-spectrum antivirals.

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