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## 5.20 Antiviral Drugs for Acute Infections

**KL Powell and E Thomas**, ReViral Ltd, Stevenage Bioscience Catalyst, Stevenage, United Kingdom

**GS Cockerill**, Durham University, Stockton on Tees, United Kingdom; and ReViral, Stevenage Bioscience Catalyst, Stevenage, United Kingdom

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### 5.20.1 Introduction

The purpose of this article is to review the unique challenges that are offered by the development of treatments for acute as opposed to chronic viral diseases. To an extent, the outstanding success of treatments for chronic virus infections including human immunodeficiency virus (HIV) and hepatitis C virus (HCV) detailed in previous articles has served to encourage investment in research and development aimed at the treatment of acute viral infections.

Each acute viral infection offers a unique set of epidemiological and technical characteristics that contribute to the overall possibility of the discovery of useful therapeutic agents. It would be impossible in the space available to examine all acute virus infections so we have chosen to compare and contrast the apparently similar respiratory virus infections caused by orthomyxoviruses (influenza (flu)), rhinoviruses, adenoviruses, and paramyxoviruses including respiratory syncytial virus (RSV). We will consider the challenges of drug discovery in each virus family and how these are being overcome.

We will review in detail the discovery efforts aimed at RSV as a general example of an acute viral infection. This virus illuminates the challenges and promise of working in the field. RSV is also the acute virus infection of most current interest to the industry post the emergence of multiple potent therapeutic combinations to treat HCV.

Finally, we will review the interesting challenges of emerging viral infections. Global warming, the subsequent migrations of viral vectors, and the popularity of global travel are all combining to spread little known viruses around the world and to threaten its human populations.

### 5.20.2 Respiratory Virus Targets of Research Into Acute Viral Infections

The graph later (Fig. 1) shows an overlay of the epidemics of four common respiratory virus families in the United Kingdom over a 10-year period. The RSV epidemic (black line) is a consistent feature every winter. Other paramyxoviruses assume less importance. The rhinoviruses (of which there are more than 150 serotypes) are present through much of the year, while influenza virus epidemics are much less predictable. From this timeline, it is clear that the feared global pandemic of influenza is very much overdue. Adenoviruses become important when groups of seronegative individuals congregate (e.g., army recruits or college students) or when the virus attacks the immunocompromised.

The differences seen in the epidemiology of these four virus families show that one cannot generalize on the “respiratory virus” theme and that each virus needs to be considered from multiple aspects before embarking on a drug discovery project.

The key issues to consider when initiating a discovery project are the following:

- *Prevalence*: the significance of the disease burden caused by the virus
- *Diagnosis*: specimen accessibility and speed and accuracy of testing
- *Alternative therapeutic approaches*: vaccines, immunotherapy, etc.
- *Therapeutic window*: ability to intervene in a timely fashion to significantly improve the outcome for patients
- *Competition*: relative progress of other discovery projects and the opportunity/threat they offer

A common issue for all therapeutic areas in the drug industry has for many years been the choice of target protein(s) suitable for each disease. In the virology field, this has become much less complex. For each virus, multiple targets are available and are well understood. Often, the limiting step in starting an antiviral discovery project is making the commercial case that the return on investment will be sufficient to justify the work. This issue is particularly the case for acute viral infections. The history of such projects is often that they fail to get off the ground because the commercial case is based on attempting to treat the “otherwise healthy” population. This approach is often superficially attractive simply because the numbers of such patients are so large. The real medical need *and* the commercial opportunity lie in finding the patient groups where an acute infection can be catastrophic. These patients may be the very young, the elderly or the immunocompromised.

Table 1 lists the four virus families we have chosen to illustrate the issues in discovery of agents to combat acute virus infections. We will discuss each in turn, followed by the issues around emerging virus infections.

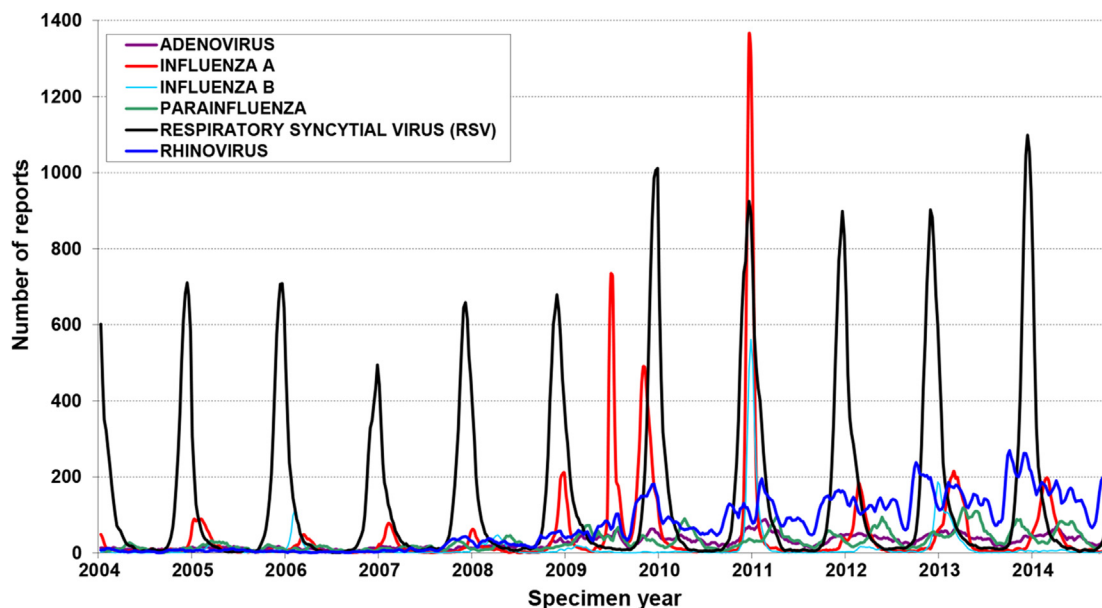


Fig. 1 Six major respiratory viruses reported from PHE and NHS laboratories (LabBase) in England and Wales between weeks 01/2004 and 44/2014 (3-week moving average).

**Table 1** Respiratory viruses as targets of drug discovery

<i>Virus family</i>	<i>Vaccine status</i>	<i>Prevalence</i>	<i>Approved drugs</i>	<i>Active discovery research</i>
Rhinovirus	None (multiple serotypes)	Very widely distributed; common infection	None	Limited
Orthomyxovirus (influenza)	Multiple	Epidemic and potential for pandemics	Multiple targeting different viral functions	Limited
Adenovirus	Limited (largely for army personnel)	Limited	None	Limited
Paramyxovirus	Passive immunotherapy with Synagis for RSV; multiple vaccines in research phases	Seasonal epidemics with a reliable periodicity	Ribavirin	Active

### 5.20.3 Rhinoviruses

#### 5.20.3.1 Reasons to Develop Antiviral Drugs for Rhinovirus Infections

Rhinoviruses are known as the cause of the common cold—one of the mildest infections known to medicine. Most adults see two to five infections a year, and although they may cause irritation and some morbidity, they generally are well tolerated. Attempts to treat the common cold with agents like interferons or capsid binders have generally been targeted at the “otherwise healthy” populations. This approach has led to failure, with limited benefits not compensating for the side effects observed. It has also led to a widespread reluctance from the industry to invest in antiviral discovery programs for “the common cold.”

Severe outcomes of rhinovirus infections are now widely appreciated in asthmatics, chronic obstructive pulmonary disease (COPD) patients, and those with cystic fibrosis. The problems of developing vaccines or passive immunotherapies for patients who are infected by a virus that may be one of > 150 serotypes mandate efforts to develop pan-rhinovirus inhibitors.

Rhinoviruses are a member of the picornavirus family of small single-stranded RNA viruses, and lessons learned through discovery efforts for this group provide useful starting points for research into newly discovered or appreciated small RNA viruses causing significant disease burdens. These include the coronaviruses (SARS-CoV and MERS-CoV) and enteroviruses, which share similar target proteins. A broad-spectrum inhibitor of these viruses would be attractive for use in the life-threatening diseases they can cause.

#### 5.20.3.2 Classes of Rhinovirus Agents

##### 5.20.3.2.1 Capsid binders

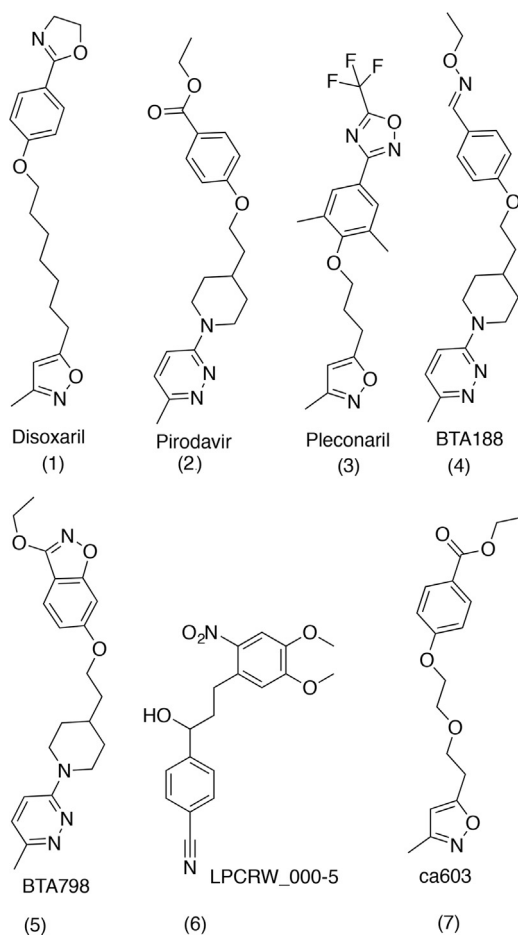
Early discovery efforts in several companies identified different types of hydrophobic small molecules that inhibited rhinovirus replication. These compounds were shown to bind to the virus particle and to interfere with the early stages of viral replication. Classic experiments by Rossmann’s group determined the three-dimensional structure of example inhibitors bound to virus particles and showed that they were bound to a canyon in the external structure of the viral capsid protein VP1.<sup>1</sup>

A number of structural studies subsequently have confirmed this binding mode with more recently developed compounds on poliovirus<sup>2</sup> and enterovirus 71,<sup>3,4</sup> as well as rhinovirus. In rhinovirus itself, a consistent binding mode can be observed for inhibitors, with a range of interactions with key residues postulated, most notably H-bonding and  $\pi$  interactions with residue Y152. The mutations Y152P and V191L were observed in naturally derived serotypes, and alongside the A150V mutation that is observed across multiple serotypes, all these changes overcome the antiviral effect of inhibitors by reducing the binding affinity of the drug modification at or proximal to the binding site.

In the case of the recently described LPCRW\_0005, the distance of the A150 residue from the binding position of the compound (> 8 Å) suggests a different effect. The hypothesis proposed is that this mutation stabilizes a collapsed conformation of a portion of the protein that impedes inhibitor access.<sup>5</sup>

As rational as these structural arguments appear, the major feature of drug development in this structural type has been the modification of features that have an effect on both binding affinity and the pharmacokinetic profile. The structures of these inhibitors are long, with multiple freely rotating bonds (Fig. 2). In addition, metabolically labile groups, for example, ester and oximes, are common (CA603 (7), pirodavir (2), and BTA188 (4); Fig. 2). Pleconaril was the first molecule in which these issues were addressed (through the incorporation of the trifluoromethyl-substituted oxadiazole system) and demonstrated satisfactory oral pharmacokinetics.<sup>6</sup> The latest inhibitor BTA798 (5) (vapendavir)<sup>7</sup> utilizes a benzisoxazole replacement for the labile functionality. This isostere appears to provide an orally bioavailable compound, although the bioavailability of 94% in rats is reported at a rather large dose of 50 mg kg<sup>-1</sup> and retains the potential for the saturation of any metabolic processes that may occur at lower doses closer to the therapeutic range.

The most recently described inhibitor type (6) (LPCRW\_0005)<sup>5</sup> certainly demonstrates a different perspective on site binding mode for capsid inhibitors. Due to the compound’s decreased size over other inhibitors, it occupies a fraction of the conventional binding pocket. As such, it provides an interesting new template for further medicinal optimization.<sup>8</sup>



**Fig. 2** Capsid inhibitor structures.

The Janssen group developed a series of capsid binders that showed potent activity against selected strains of rhinovirus. As the series developed, an appreciation emerged of variation in the sensitivity of various rhinovirus serotypes and the need for compounds with a wider spectrum of activity.<sup>9</sup> This work culminated in pirodavisir (2) (R77,975), which entered clinical trials in challenge studies.<sup>10</sup> As with most capsid binders, the physicochemical properties of the compound made formulation difficult, and an intranasal spray was developed. The compound was tested both in the prophylaxis and treatment modes. There was a clear antiviral effect when the compound was used six times a day in the prophylactic mode, but the treatment data and the effect on the symptoms of the “cold” were disappointing.

Pleconaril originated from research at Winthrop that was later acquired by Sanofi, and pleconaril was licensed to ViroPharma. Using clinical trial data obtained with an oral formulation of the drug ViroPharma attempted to obtain a new drug application (NDA). The trials<sup>11</sup> showed a clear effect on the outcome of a common cold with a benefit of about a day in the resolution of clinical symptoms. Unfortunately, the side effects, although moderate (largely GI-related), were considered too severe by the FDA for the limited benefit. The drug also induced the metabolism of contraceptives, and two women on the trial became pregnant. This outcome very clearly demonstrates the uphill task of developing a medicine for what is considered to be a “trivial” infection.

Detailed analysis of the clinical trial and laboratory data on pleconaril highlights some other interesting challenges for this type of rhinovirus inhibitor. There was very wide variation in the sensitivity of the various serotypes of rhinovirus to the drug, with some insensitive to inhibition. Resistant virus variants were readily isolated during therapy although their relative “fitness” was not assessed (in a recent paper extending the interest in capsid binders to other picornaviruses, Kelly et al.<sup>12</sup> clearly demonstrate the fitness cost of VP1 resistance mutations to the virus.)

In 2007, Schering-Plough in-licensed pleconaril from ViroPharma and began developing an intranasal formulation for the prevention of rhinovirus-induced exacerbation of asthma. A recent update of the results on the <https://clinicaltrials.gov> website (NCT00394914) show that although patients were entered on the trial when they came into contact with a family member with a proven rhinovirus infection, only 8 out of about 600 recruits were found to be infected.

Vapendavisir (5) (from Aviragen Therapeutics, previously known as Biota Pharmaceuticals), described earlier, is currently in a phase II trial in asthmatics. Vapendavisir displays a broader spectrum of activity against virus isolates than pleconaril. The phase

II study seeks to monitor moderate-to-severe asthmatics during the rhinovirus season and to start dosing with drug or placebo when they are proven to be infected, and its outcome, including measurements of asthma exacerbation, is anticipated in late 2016 (<http://www.aviragentherapeutics.com>).

Various groups are exploring the possibility of challenge studies in asthmatics to provide more controlled and hence more clear-cut results. The Rega group is continuing to explore the possibility of more advanced capsid binders.<sup>3</sup> Further work in this area is also exploring the possibility of extending the activity to other members of the picornavirus family.<sup>12,13</sup> Mello et al.<sup>14</sup> showed that some rhinovirus isolates in group C (which do not replicate in traditional monolayer cell culture) may not be inhibited by capsid binders. This information will need to be taken into account in the design of new agents.

### 5.20.3.2.2 Protease inhibitors

Picornaviruses encode a protease encoded by the 3C gene. The 3C protease is essential for replication and is responsible for cleavage of the viral polyprotein into the active enzymes and structural components. Viral encoded proteases have been extensively explored as targets for chronic viral infections. These efforts inspired pioneering work on the equivalent rhinovirus enzyme by the Agouron group (later acquired by Pfizer). This team used a structure-based approach to optimize 3C protease inhibitors, culminating in ruprintivir (8) (formerly AG-7088), a potent agent active against all the rhinovirus isolates tested and some other picornaviruses.<sup>15</sup> The compound is a peptidomimetic whose design is based upon the picornaviral cleavage-site recognition characteristics. In these proteases, most cleavages occur between glutamine and glycine residues. In addition, the rhinovirus 3C protease catalytic triad of cysteine, histidine, and glutamic acid with a geometry similar to those observed in trypsin-like serine proteases suggested the incorporation of a covalent modifier warhead, specifically the  $\alpha,\beta$ -unsaturated ester present in AG-7088. Incorporation of a cyclic butyramide at P1 provided the optimal structure shown in Fig. 3. A detailed description of the optimization of the structural elements P2, P3, and P4 has been published.<sup>16</sup>

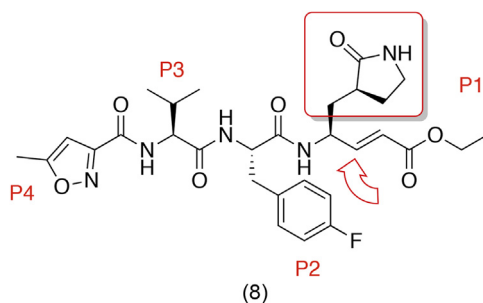
The poor aqueous solubility of ruprintivir rendered formulation challenging, but adopting a nasal spray formulation enabled a clinical challenge study to explore the effectiveness of the drug against experimentally acquired infection.<sup>17</sup> While significant effects on some viral parameters were seen (especially with five times a day prophylactic dosing), there was little effect on the development of rhinovirus colds. As high concentrations of drug were reached in the nasal epithelium, this raises questions concerning the bioavailability of such drugs in the upper respiratory tract (URT) on one hand and the relevance of the experimental challenge model on the other.

### 5.20.3.2.3 Polymerase inhibitors

All picornaviruses encode an RNA polymerase (3D gene product) that in principle appears an ideal target for broad-spectrum inhibitors, as all share a somewhat invariant RNA sequence (reviewed in Ref. 18). An enormous amount of academic work has explored the structure of RNA polymerases from many picornaviruses and in many states (for review, see Ref. 19). A variety of picornavirus polymerase inhibitors have been discovered through screening programs or testing of nucleoside libraries, encompassing both purine and pyrimidine nucleosides<sup>14,20</sup> as well as potential nonnucleoside inhibitors.<sup>18</sup> The clinical impact of inhibitors of polymerases for chronic viral infections suggests that optimized versions of these leads might have high utility.

### 5.20.3.3 Opportunities for Combination Therapies

Given the extreme plasticity of the picornavirus genome due to its error-prone RNA polymerase, combination therapy will undoubtedly be important in the development of effective broad-spectrum treatments. These may include not only improved small-molecule inhibitors of the types discussed earlier but also biological agents like interferons and soluble viral receptors.



**Fig. 3** Ruprintivir (8), showing the position of cysteine attack (red arrow) and key butyramide modification (red box) in P1. P2–4 indicate other optimization pockets.

## 5.20.4 Influenza Viruses

### 5.20.4.1 Reasons to Develop Antiviral Drugs for Influenza Virus Infections

There has been considerable success in the development of both vaccines and antiviral drugs to treat influenza infections, but the unmet medical need is still high. This is largely due to the plasticity of the viral genome that both mandates the manufacture of new vaccines for each virus “season” and allows for the rapid development of resistant virus. The impetus to develop new approaches to influenza comes largely from the potential emergence of a new “pandemic” virus to which the population has little resistance.

As with other respiratory viruses, influenza is already a significant problem in the elderly, the immunocompromised, and the asthmatic population. According to the WHO, influenza occurs globally with an annual attack rate estimated at 5–10% in adults and 20–30% in children. Worldwide, annual epidemics are estimated to result in about 3–5 million cases of severe illness and about 250,000–500,000 deaths.

### 5.20.4.2 Classes of Influenza Agents

#### 5.20.4.2.1 Ion channel blockers

From early discovery efforts using phenotypic cellular screens for antiinfluenza activity, amantadine was discovered to have potent inhibitory effects. At the time of this discovery, little was known about virus genes and the proteins they encode. In the clinic, the drug was shown to have modest efficacy. Analogs of amantadine were synthesized and found to have a slightly improved profile. The most widely studied was rimantidine, which was extensively used in the former Soviet Union (reviewed by Zlydnikov et al.<sup>21</sup>).

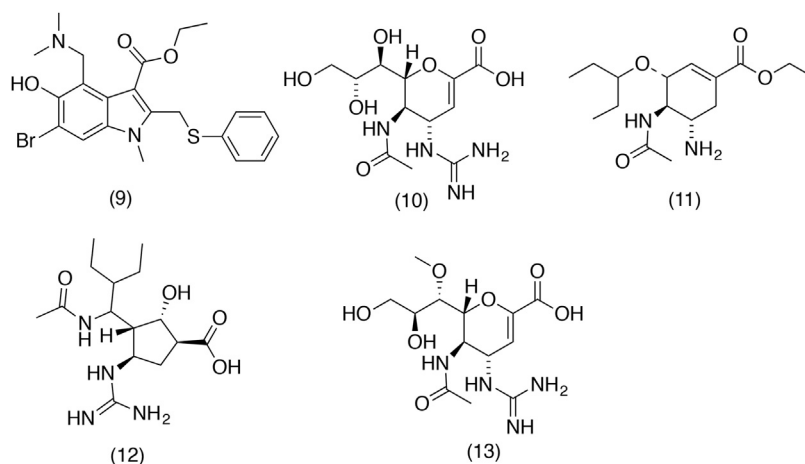
Resistant mutants were easily isolated and mapped to the viral M2 protein. We now know that this protein is an ion channel encoded within the viral genome. With the discovery of the more active neuraminidase (NA) inhibitors and the development of widespread resistance to both amantadine and rimantadine in the clinic, the interest in this target has reduced. Molecular studies of resistant mutants have identified the mechanism of resistance within the structure of the M2 protein, and the area is deserving of more attention as the interest in combination therapies for this virus family grows. Recently, work has been reported on novel scaffolds working on the same target<sup>22</sup> and on novel adamantane analogs.<sup>23</sup>

#### 5.20.4.2.2 Fusion inhibitors

The fusion activity of the influenza hemagglutinin has been shown to be essential for the release of the viral particle from endosomes, allowing replication to begin. Arbidol (Fig. 4 (9)) is a small indole derivative that was discovered and developed in Russia and is approved and used there and in China,<sup>24</sup> which acts (at least in part) through this mechanism. The clinical trial data reported from the Russian and Chinese studies are not dissimilar to those obtained with the NA inhibitors, but only one clinical study is reported on <https://clinicaltrials.gov> (NCT01651663). Unfortunately, the compound is clearly suboptimal with relatively poor activity and off-target effects. There have been some attempts to improve on Arbidol’s selectivity and activity using its indole scaffold, but as yet, no candidate compounds have emerged.<sup>25,26</sup> The target remains to be exploited but probably through a new lead discovery exercise.

#### 5.20.4.2.3 Neuraminidase inhibitors

By far, the most widely used antivirals for influenza are the NA inhibitors. The NA enzyme is encoded by the viral genome and is present in the external surface of the virus particle. NA has roles in both entry and exit of the virus from the host cell and in the passage of virus through mucus-rich surfaces. Inhibitors of the enzyme are natural substrate analogs based around the structure



**Fig. 4** Arbidol (9), zanamivir (10), oseltamivir (11), peramivir (12), and laninamivir octanoate (13).

of the viral receptor, sialic acid. The approved NA inhibitors zanamivir (Fig. 4 (10)) (Relenza) and oseltamivir (Fig. 4 (11)) (Tami-flu) are potent inhibitors of the enzyme<sup>27,28</sup> and of virus replication in tissue culture. Zanamivir has poor physicochemical characteristics and was formulated for intranasal dosing, while oseltamivir is an oral prodrug that has seen more widespread use. Both drugs showed clear effects in well-controlled experimental challenge models of influenza infection in volunteers.<sup>29,30</sup> It has been far more difficult to prove that the compounds have a significant effect on naturally acquired influenza infections. Indeed, the controversy is still active; while the drugs clearly have an effect on viral load, their effects on URT symptoms do not seem to relate to virus infection as they are seen in patients without proven infection.<sup>31</sup>

At the time of the discovery and development of these drugs, attention was focused on the treatment of seasonal influenza, but anxiety about potential pandemics of newly emerging influenza strains led to extensive stockpiling by government agencies of both agents. This stockpiling activity has had a significant effect on the return on investment on the development of the drugs and illustrates well how the commercial environment can vary for different viruses causing URT infections.

Another significant factor in the use of NA inhibitors has been concern with the development of significant levels of resistance to the drugs. This was enhanced by the emergence of an H1N1 influenza during the 2007–08 influenza season that carried a mutation for oseltamivir resistance and that spread rapidly.<sup>32</sup> Together with the mutation for oseltamivir resistance, this virus carried compensatory mutations that allowed it to replicate normally. The virus spread around the world even in the absence of selective pressure with the drug, but subsequent seasons have not seen a rise in oseltamivir resistance rates above the background level of about 3% of all isolates. The level of resistance to other NA inhibitors is even lower (<1%), but it is not clear if this is due to a real difference in the ease of mutant generation or to the much lower use of the other drugs.<sup>33</sup>

Efforts have continued to develop improved NA inhibitors with enhanced activity, physicochemical properties, and ability to inhibit virus isolates resistant to other NA inhibitors. Peramivir (Fig. 4 (12)), developed by BioCryst, is a more costly NA inhibitor that can be given by infusion and is recommended in cases where oral or IV administration is difficult.<sup>34</sup> Laninamivir octanoate (Fig. 4 (13)) is a long-acting NA inhibitor developed by Biota in collaboration with Daiichi Sankyo. This drug is approved for use in Japan but remains in phase II trials in the rest of the world. The compound is given by the inhaled route as a single administration, and drug levels are maintained over a 5-day period.<sup>35</sup>

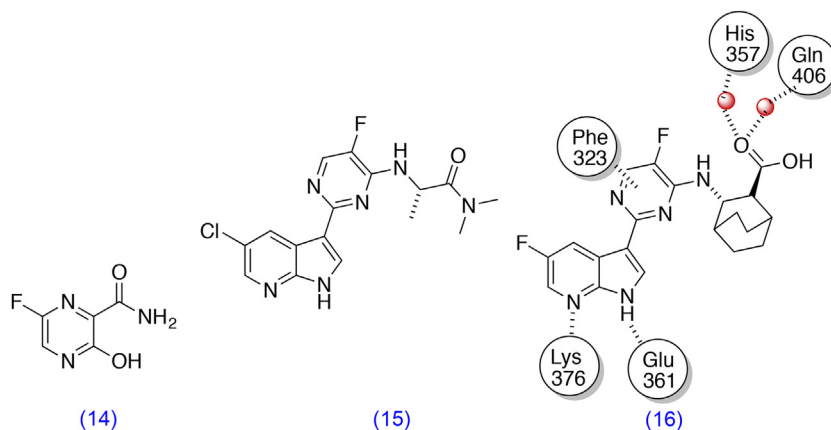
#### 5.20.4.2.4 Polymerase inhibitors

As with all other viruses, the RNA polymerase of influenza makes an attractive target for new drugs. Polymerase inhibitors for the influenza virus have been identified either by screening programs, through nucleoside chemistry or more recently through target-driven approaches to the subunits of the enzyme.

Favipiravir (T-705) (Fig. 5 (14)) is the polymerase inhibitor in most advanced development for influenza infections. This compound was discovered at Toyama Chemical in Japan through lead optimization of a screening program hit. The compound is activated by cellular enzymes to a triphosphate form, which then inhibits the viral polymerase.<sup>36</sup> Its activity against influenza is in the range of 0.2–10  $\mu\text{M}$  in *in vitro* assays. Favipiravir has shown activity in two Japanese phase III trials and is licensed in Japan for stockpiling against pandemic influenza. Currently, the drug is in phase III trials in the United States to treat influenza in adults, using a much higher dose (Japanese dose is a 1.6 g loading dose followed by 400 mg twice a day, while the US dose is a loading dose of 3.6 g plus 400 mg four times a day). Favipiravir has weak activity against a wide variety of RNA viruses, including Ebola virus. Clinical trial data are awaited on the efficacy of the drug against the latter.

A wide variety of pyrimidine and purine nucleosides have been claimed to have activity against influenza viruses. Unfortunately, to date, none of these have been found to be sufficiently selective for the virus over host cell enzymes to develop further.

A nonnucleoside polymerase inhibitor VX-787 was developed by Vertex and licensed to Johnson & Johnson in 2014 and renamed JNJ-872. This compound was discovered as an inhibitor of the “cap-snatching” activity of the PB2 subunit of the viral



**Fig. 5** Favipiravir (14). A representative hit (15) from the phenotypic screening program undertaken at Vertex and its optimization, showing the key interactions of VX-787 (16) with residues within the cap-binding domain.



RNA polymerase and indeed occupies the 7-methyl GTP cap-binding site.<sup>37</sup> In preclinical studies, the compound showed excellent activity against influenza in animal models of the disease. Unfortunately, the compound has no activity against influenza B strains. Interesting activity over a longer window of activity than that seen with NA inhibitors stimulated investment by BARDA in the phase III program on this compound for treatment of patients hospitalized with influenza infection.

As with many influenza programs, VX-787 was discovered utilizing a phenotypic cellular assay.<sup>38</sup> The initial screen was limited to 1000 compounds but identified several with measurable antiviral activity. The identification of a kinase inhibitor template as a hit was perhaps not only a reflection of the focused source of compounds but also an example of the successful reuse of drug-like compound types provided by kinase-based screening sets. Specifically, a series of pyrimidine azaindoles emerged from the screen with significant activity and are represented by compound 15 (Fig. 5). The project was supported by crystallography, with several structures generated of compounds bound to the GTP cap-binding domain revealing key hydrogen-bonding interactions between the azaindoles and lysine and glutamic acid side chains in the binding site. Further interactions were delineated in the clinical compound for the carboxylic acid, introduced as part of the optimization process and resulting in VX-787 (Fig. 5 (16)).

The endonuclease activity of the PA subunit of the polymerase was targeted by the Merck group in the 1990s.<sup>39</sup> Although this project did not lead to clinical candidates, the leads became an excellent starting point for the very successful program that led to HIV integrase inhibitors (the enzyme shares a similar active site). Two companies have PA inhibitors in clinical trials: S-0033188, from Shionogi, is in phase 1 in Japan, and Alios (J&J) has AL794 in a challenge study in the United States (<https://clinicaltrials.gov>, NCT02588521).

#### 5.20.4.3 Combination Therapy for Influenza

Clear clinical needs and interesting opportunities exist for further antiinfluenza research. For a truly effective approach to pandemic management, a combination regimen using different inhibitor classes would be appropriate, and in this context, the concept of combining polymerase PA and PB2 inhibitors to provide a broad-spectrum therapeutic is appealing.

### 5.20.5 Adenoviruses

#### 5.20.5.1 Reasons to Develop Antiviral Drugs for Adenovirus Infections

Adenoviruses are the cause of a variety of important human and animal infections, and yet, there has been little progress in the development of antiviral drugs to treat these diseases. Given the size of the adenovirus genome, the number of attractive targets encoded therein, and the stability of a double-stranded DNA viral genome, antiviral drugs could clearly be developed were sufficient commercial incentive to exist. The three major opportunities are infectious viral conjunctivitis, lung infections in the immunocompromised (especially in transplant patients), and epidemics of adenovirus pneumonia in young adults (especially military recruits or students brought into close proximity due to enlistment or starting college).

Conjunctivitis is an ocular inflammation that can be caused by a virus, a bacterium, or an allergen. Adenovirus infections account for up to 90% of all viral conjunctivitis. Rapid diagnostic tests at point of care are now available and would aid rapid treatment. There are signs of interest in this area from specialist ophthalmic companies. It is difficult to get accurate estimates of the numbers of patients, as in most countries infection is not notifiable.

Adenovirus infection in the immunocompromised patient is a major threat. Infection is especially common in young recipients of stem cell transplants. Given the otherwise excellent prognosis for these patients, their significant numbers, and the complete lack of treatment options, this indication may represent an “orphan drug” designation with an attractive price to support development.

Military support has enabled the development of a vaccine against adenovirus types 4 and 7 that is used extensively by the US army. The complex nature of the adenovirus family mitigates against the development of a pan-family vaccine.

#### 5.20.5.2 Classes of Adenovirus Agents

##### 5.20.5.2.1 Polymerase inhibitors

Cidofovir is a nucleotide analog that was discovered in Prague by Holy's group<sup>40</sup> and developed by Gilead as a treatment for cytomegalovirus (CMV) retinitis in AIDS patients (a major problem before the development of effective combination regimens). It was the first nucleotide analog to be approved for human use. The compound was active against a range of DNA viruses, including adenovirus, but its use was limited by its nephrotoxicity and lack of oral availability.

Chimerix used a proprietary lipid conjugate technology to produce an orally available prodrug of cidofovir, brincidofovir (CMX001), with the primary aim of reducing the impact of CMV in the immunocompromised. Brincidofovir is orally available and avoids some of the issues with cidofovir therapy. During its development, the compound became the target of a social media campaign for its compassionate use in a young patient with adenovirus infection, as no other therapy was available. Data from an ongoing open label phase III trial in 20 stem cell transplant patients with adenovirus infection that completed enrollment in Aug. 2015 are awaited (<https://clinicaltrials.gov>, NCT02087306). Unfortunately, this trial appears not to have shown a therapeutic benefit, although viral load was reduced (<http://www.chimerix.com>, May 9, 2016).

### 5.20.5.2.2 Other targets

Nicox is developing NCX 4240 for viral conjunctivitis. NCX 4240 is Carrageenose (iota-carrageenan), a sulfated galactose polymer derived from red seaweed with antiviral properties. Carrageenose inhibits viruses from binding to and entering human cells, reducing viral replication and associated symptoms. Carrageenose is already available without prescription for the treatment of respiratory viral infections. Antiviral activity has been demonstrated in preclinical studies, including three of the most important adenoviruses causing conjunctivitis. Nicox plans to conduct clinical investigation of NCX 4240 as a medical device (<http://www.nicox.com>, 2016).

## 5.20.6 Paramyxoviruses

### 5.20.6.1 Reasons to Develop Antiviral Drugs for Paramyxovirus Infections

The paramyxoviruses are quite distinct from the orthomyxoviruses (Influenza viruses) and have a completely different genomic structure and epidemiology, despite both groups causing infections of the respiratory tract. RSV is clinically the most important member of the Paramyxoviridae family and was first isolated in 1956. There are two major serotypes of RSV, A & B, which alternate with each other and which cause similar disease. RSV is highly infectious and is transmitted through respiratory secretions via close contact with infected individuals, through droplets or through contaminated surfaces. In healthy adults, RSV is one of the causes of “winter colds,” but in infants, the virus causes 1–2 weeks of respiratory tract disease. Infants can continue to excrete virus for several weeks. By age 2, virtually all children have been infected by the virus. Infection by RSV induces only partial protection, and subsequent infection can occur even in the same winter season. RSV is a significant pathogen of the very young, the immunocompromised, and the elderly:

- *RSV in new born infants:* In the United States, between 100,000 and 126,000 infants under 1 year have been hospitalized in each of the last 5 years. There are about 2.1 million outpatient consultations for the under 5 s with RSV each and every year. Each of these infants is a prime candidate for a safe and effective oral therapy. The mortality rate in the very young at risk infants is between 2% and 3% in most developed countries including the United States. Care of babies with RSV infection imposes a major burden on the hospital sector and limits capacity to undertake routine surgery.
- *RSV in the immunocompromised or other medically compromised patients:* RSV is a major issue in those who are immunocompromised through natural causes, by cancer or chemotherapy, or deliberately for transplantation. Although numerically less significant, the considerable investment in such patients mandates their treatment.
- *RSV in the elderly:* There is increasing awareness of the burden caused by RSV in the elderly. In years without a major influenza epidemic (i.e., most years; see Fig. 1), RSV is a more significant cause of morbidity and mortality in the over 60s. There are more than 2 million consultations with physicians in the United States each year due to RSV infection. The virus is also a significant problem in adults with COPD, where it is a major cause of exacerbations. In care homes, RSV causes annual epidemics during the winter season.

#### 5.20.6.1.1 Intervention opportunities

As for influenza infections, otherwise healthy adults will develop a severe cold but will normally recover unaided. Consequently, therapies are being developed to treat firstly infants and those children where the disease is more severe both in terms of duration and the severity of the possible outcomes. Studies have shown that such children see up to three physicians prior to hospital admission, presenting multiple prescribing opportunities.<sup>41</sup> Secondly, in the “compromised” adult patients, the treating physician would generally be well aware of the need to survey his or her patients for RSV infection and to use effective remedies quickly and efficiently. Finally, in the adult population, treatment during a local epidemic would be of use to prevent the spread of this life-threatening infection. The concept that there is insufficient time for therapeutic intervention during respiratory virus infections, derived from the influenza field, is now regarded as outmoded.<sup>42</sup> Due to the longer duration of RSV disease in both infants and adults, it is now widely accepted by the experts in the field that a small-molecule drug could be effective either for treatment or for prophylaxis.<sup>43</sup>

### 5.20.6.2 Antiviral Agents for RSV

Two agents are approved for the treatment of RSV infections. The first, ribavirin, is a nucleoside analog that was discovered to have anti-RSV activity in a screening program. Its clinical use is restricted due to limited antiviral potency, inherent toxicity, and teratogenic potential. The other approved agent is the prophylactic monoclonal antibody Synagis (paluvizimab), marketed by AstraZeneca. This antibody, which interacts with the F glycoprotein of the virus (see in the succeeding text), has been shown to provide protection in infants and has gained widespread use to protect premature babies. The cost of therapy (about \$5000 per infant for the winter season) limits wider uptake.<sup>43–45</sup> There is thus an obvious clinical need for new small-molecule inhibitors of the virus.

#### 5.20.6.2.1 Fusion protein inhibitors

RSV encodes two surface glycoproteins, the F and G proteins. G is dispensable in tissue culture, but its deletion attenuates virus infectivity. The F protein is essential for the entry of the virus into the host cell. Expression of the protein at the cell membrane causes

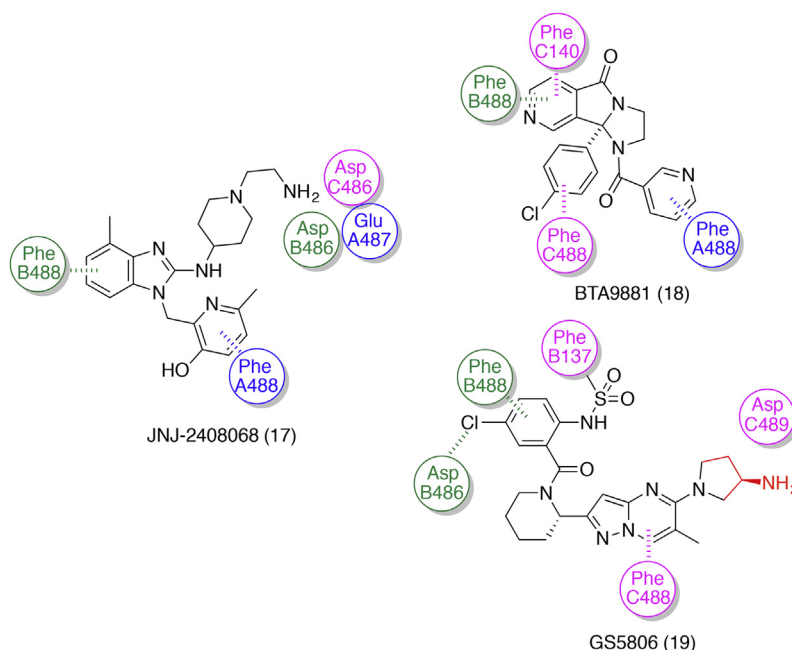
cell-to-cell fusion, leading to the giant syncytia characteristic of RSV infection. Since the early discovery that inhibitors of the fusion of RSV virus particles and host cells could be readily identified by high-throughput screening, a great deal of work has been done to refine the potency and selectivity of a variety of structural types of inhibitor. Early work in the field has been surveyed in previous reviews.<sup>46,47</sup> More contemporary research has led to a high-resolution, three-dimensional understanding of the fusion process and its inhibition.

For an excellent detailed overview of F protein structure and function, see Battles et al.,<sup>48</sup> who described a structural analysis of inhibitor interaction with the prehairpin structure of the RSV fusion protein. In that work, a number of inhibitor structures were docked into a trimeric model of the fusion complex based upon the crystal structure of JNJ-250685 bound to a prefusion construct. Although not all-encompassing, a rational description of the binding of these drug-like and structurally diverse inhibitors is evident from these studies. Fig. 6 provides an annotated version of the binding modes of JNJ-2408068 (17), Biota-9881 (substituting in this analysis for the structurally related BTA-C585 (18) and GS-5806 (19)). Most evident is the hydrophobic  $\pi/\pi$  nature of the binding of the Biota compound (18), with JNJ-258606 and presumably GS-5806 taking advantage in addition of further energetically beneficial polar interactions by virtue of the amines they incorporate.

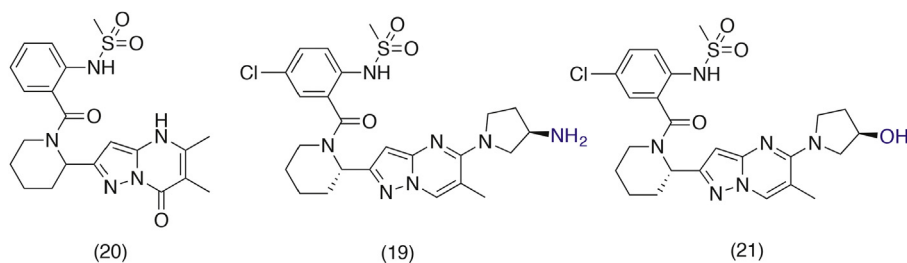
All of these inhibitors exhibit potency against laboratory strains of RSV and are orally bioavailable. The discovery and progress toward clinical evaluation of presatovir (GS-5806) have been described recently.<sup>49</sup> A moderately active screening hit (20, Fig. 7) with a poor oral pharmacokinetic profile was transformed in an efficient manner into the clinical compound. Of note is the role of the pendant amine in presatovir, perhaps incorporated to target potential salt-bridge binding interactions as described earlier. A further recent disclosure<sup>50</sup> draws a comparison between the improved lung distribution properties of presatovir and its alcohol analog (21, Fig. 7). This advantage of the basic amine-containing compound is rationalized as product of the interaction at lung epithelial cells with phospholipids, phosphatidyl choline, or fatty acids in the pulmonary surfactant.

To date, less information is available regarding the Biota compound BTA-C585. In 2014, Draffan et al.<sup>51</sup> disclosed a generic structure for a compound that is potent in the human epithelial airway model ( $EC_{50}$  8.4 nM), but with some variability in clinical isolate data (most  $EC_{50}$ s appear around 100 nM), and exhibits oral bioavailability (59% is quoted in rat and 107% in dog at a dose of 20 mg  $kg^{-1}$ ). Efficacy in the cotton rat model is described, with a 99% reduction in viral titer observed at 100 mg  $kg^{-1}$ . A 2011 patent supporting this generic structure describes example 22 (Fig. 8) as one of the more potent examples (2.2 nM in an RSV A2 cytopathic effect assay).<sup>52</sup>

The failure of a single fusion inhibitor to reach the market may reflect an attrition rate typical of pharmaceutical development in general but leaves open the question of clinical validation. In that context, the first successful clinical study with a fusion inhibitor was recently reported by Gilead with GS-5806.<sup>53</sup> This compound given rapidly reduced viral load and symptoms of RSV disease in volunteers with confirmed RSV infection. The compound is leading a group of fusion programs from J&J, Biota Holdings, Teva, ARK Therapeutics, and ReViral. Table 2 gives an overview of the stage of development of these efforts, all of which are or will be in clinical studies in 2016.

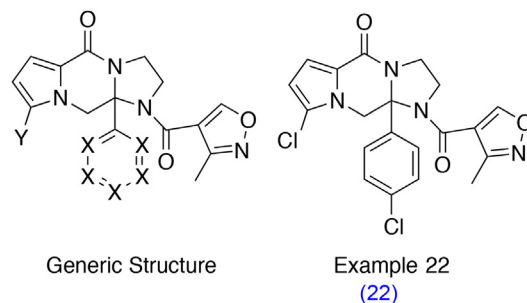


**Fig. 6** An annotated schematic of the proposed binding modes of JNJ-2408068 (17), BTA-9881 (18), and GS-5806 (19).<sup>48</sup> Key binding interactions are shown for each inhibitor with colors indicating an individual component of the trimeric fusion protein complex.



Compound	EC <sub>50</sub> (RSVA2)	PPB (Human, %)	EC <sub>50</sub> Fold shift in plasma	F (% , rat)
20	65	93.5	13	2
19	1.5	94.4	13	67
21	1.5	94.5	10	42

**Fig. 7** Selected pharmacokinetic and potency data for hit compound (20), presatovir (19), and the hydroxyl analog (21).



**Fig. 8** Generic structure and potent example from Biota.

**Table 2** Fusion inhibitors under pharmaceutical development

Compound	Company	Status
GS-5806 Presatovir	Gilead	Completed a challenge study and now in phase II study in stem cell transplant patients
JNJ-2408068	Johnson & Johnson	Extensively studied preclinical candidate with suboptimal PK characteristics. Superseded by TMC-353121 and a new fusion inhibitor JNJ-53718678 for which little data are in the public domain. A phase I study in hospitalized infants is underway
VP-14637/MDT-637	Teva—MicroDose Therapeutx (MDT)	Difficult to formulate compound discovered by ViroPharma and licensed to MDT. Reformulated and partnered with Gilead but returned. MDT acquired by Teva. A challenge study was undertaken but no data yet released
BTA-C585	Biota	Completed phase I in 2015. Challenge study underway in Apr. 2016 at relatively high doses. Clinical hold reported on Aviragen (Biota) website ( <a href="http://www.aviragen.com">http://www.aviragen.com</a> , May 2016) due to a cardiovascular issue
AK0529	Ark Biosciences Inc.	Out-licensed by Roche, no challenge study was undertaken but a phase Ib study in hospitalized infants underway in Australia
RV521	ReViral	Entering phase I in 2016

There is an active debate about the ultimate clinical utility of fusion inhibitors given the relatively rapid emergence of resistance mutants during in vitro studies. This was first observed in the pioneering work of the BMS group.<sup>54</sup> Subsequently, Yan et al.<sup>55</sup> showed that mutants obtained to a novel fusion inhibitor structure mapped to the same region of the protein as other fusion inhibitor mutants. This group claimed that one of their mutants was equally pathogenic to the wild-type virus in a murine model of RSV.

Extensive use has been made of the differentiated human airway epithelium model of RSV replication to measure the “fitness” of resistant mutants<sup>48</sup> where mutants that had become less sensitive to fusion inhibitors paid a cost in replication efficiency. Clinical

data further showed that although resistant mutants do occur when humans are treated with fusion inhibitors, Gilead's GS-5806 was very effective in reducing both virus load and the signs and symptoms of disease.<sup>53</sup>

### 5.20.6.2.2 RSV RNA replication

To replicate its RNA, RSV requires four viral proteins—the M2-1 protein (only required for transcription), the nucleocapsid (N), phosphoprotein (P), and large (L) proteins. This complex provides a variety of potential targets for viral inhibition. In vitro replicon systems are now available, which measure the role of N, P, and L in RNA duplication. The role of the three proteins is gradually becoming clearer, and we are starting to see the fruit of research in emerging development programs aimed at these targets. A recent publication, for example, examines a druggable pocket at the N–P interface using high-resolution 3D structures.<sup>56</sup> This group identified compounds based on docking studies using this structure, which confirm that the site is a viable target.

Several compounds targeting different aspects of RSV replication are in various stages of preclinical and clinical development (see Table 3).

The Alios research program<sup>58</sup> was directed toward the identification of nucleosides that could inhibit RSV polymerase by chain termination. A large number (>100) of structurally diverse nucleosides were designed and screened in a cell-based RSV assay. The nucleoside analogs were also converted to their 5'-triphosphates and screened for inhibition of RSV RNA-dependent RNA polymerase activity. One compound, 4'-azido-2'-deoxy-2',2'-difluorocytidine (23, Fig. 9), exhibited potent inhibition of the cytopathic effect of long-strain RSV, with an EC<sub>50</sub> of 1 μM. Furthermore, the corresponding triphosphate was identified as a potent RSV polymerase inhibitor with an IC<sub>50</sub> of 0.3 μM.

An intensive, primarily safety-guided optimization process furnished a selective inhibitor of RSV. The isobutyryl prodrug of this inhibitor, termed ALS008176 (24, Fig. 9), showed acceptable oral bioavailability in hamsters, rats, and monkeys and has progressed into clinical trials.

PC786, most likely the subject of a recent patent filing by Pulmocide Ltd.,<sup>59</sup> appears to be a derivative of a series of RSV inhibitors exemplified by YM-53403 (25), originally described by Yamanouchi<sup>60</sup> and further elaborated by Gilead<sup>61</sup> and AstraZeneca.<sup>62</sup> They are high-molecular-weight, low-solubility compounds that in their AstraZeneca and Gilead guises can be characterized as weak bases. The structural modifications in this evolution are shown in Fig. 10.

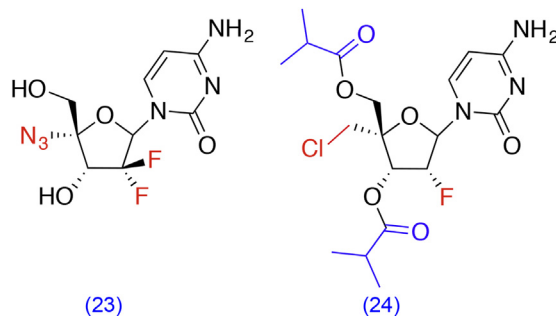
PC786 is intended for inhaled dosing, presumably through increasing molecular weight and clogP, and in this context, the addition of a fluoro toluidine fragment into the molecule is noteworthy; an earlier representative of this chemotype, however, was retained poorly in lung tissue.<sup>59</sup>

### 5.20.6.3 Combination Therapy for RSV Infection

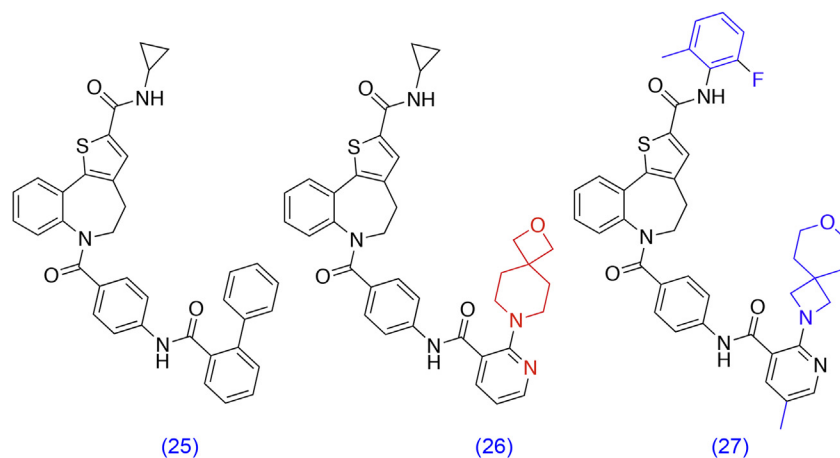
Although treatment of RSV infections will likely be short term, longer-term regimens will be optimal for the elderly where prophylaxis may be required. Combination therapies targeting multiple different viral targets would optimize antiviral effect and reduce the risk of significant resistance emerging.

**Table 3** Other small-molecule inhibitors of RSV replication in development

Compound	Company	Status
ALS-008176	Alios (now part of J&J)	Nucleoside analog that inhibits RNA polymerase activity. Potent activity in viral challenge studies. Currently in early phase II trials in infants
PC786	Pulmocide	A nonnucleoside RNA polymerase inhibitor with physical characteristics suitable for inhaled administration. Currently in formal preclinical studies
Ribavirin	M,S&D and multiple generics	Licensed medicine whose limited activity against RSV is still a matter of controversy. Major mechanism against RSV is probably hypermutation via the RNA replication complex <sup>57</sup>
RSV604	Novartis	RSV 604 interacts with the N protein and proved to be effective in early clinical studies



**Fig. 9** The initial hit nucleoside (23) discovered by Alios and its optimized prodrug ALS-008176 (24). The isobutyryl prodrug functionality is shown in blue. Key optimization modifications are highlighted in red.



**Fig. 10** The optimization of the original Yamanouchi series (25) to the Pulmocid compound (27) via AZ (26).

### 5.20.7 Emerging Virus Infections

As the impact of climate change on the spread of insect vectors grows, viruses are emerging, which are well-documented human pathogens but whose geographic range has been limited. The large increase in global travel for business and leisure has also created the opportunity for any virus to be transported around the world in hours and days.<sup>63</sup>

When any new virus emerges, a clamor arises for a new vaccine or drug to control the infection and hurried clinical trials using agents with limited preclinical validation result. Rarely do such repurposing efforts prove useful; genomic and functional diversity across viral pathogens mandates specific drug optimization efforts, despite the precedent from broad-spectrum antibacterial agents. An alternative approach is to identify antiviral agents working through host targets, but this field remains in its infancy. Here, we present a brief overview of recent viral epidemics to illustrate these points and end with an alternative scenario for pandemic preparedness.

#### 5.20.7.1 Coronaviruses

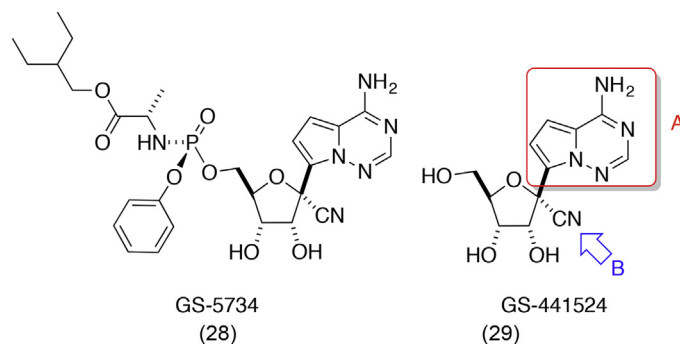
SARS-CoV appeared in 2003. It appears to have spread from small mammals in China to humans and then to have passed from human to human via close contact with respiratory secretions either directly or through fomites.<sup>64</sup> The virus is a member of the corona virus family some members of which were known to cause mild symptoms like those of the common cold. The SARS epidemic spread rapidly by air travel of infected patients and caused about 8000 infections, with a mortality rate of about 10% (<http://www.WHO.int>). The epidemic was controlled by strict public health measures—isolating patients and providing high-quality support. The virus has caused no new case since 2004.

Coronaviruses are small RNA viruses that encode a replicase and a protease most similar to the rhinoviruses (see in the preceding text) and other targets. Attempts have been made to utilize the knowledge gained from the latter to accelerate drug development,<sup>65</sup> but more than a decade later, no strong candidate molecule has emerged. The coronavirus replicase complex has been studied extensively since 2003 and is quite different from other small RNA viruses.

The failure to go from promising ideas to candidate drugs probably resulted from a lack of commercial market for a SARS drug, but then, in 2012 another Coronavirus, MERS-CoV, emerged. This virus is thought to have transferred to humans from bats (bats are a natural reservoir for many coronaviruses) with camels as a major intermediate host. MERS-CoV does not spread readily from human to human. Nevertheless, the virus has caused small epidemics, mainly in Saudi Arabia. In total, there have been about 1644 cases and 590 related deaths. Cases have been exported to several countries including South Korea, where more than 100 cases resulted though infection in a healthcare setting. Good infection control measures are very effective. The arrival of a second coronavirus with significant healthcare impact has reawakened interest in both vaccine and drug research.

#### 5.20.7.2 Ebola

Ebola is caused by a filovirus and was first recognized in 1976 in Sudan and the Congo. The most recent outbreak began in 2014 and is the largest to date (> 28,657 cases and 11,325 deaths). The infection has about a 50% mortality rate and has been transported via air travel. The natural hosts of Ebola virus are thought to be fruit bats. Infection of humans occurs through contact with dead animal tissue or body fluids; human-to-human transmission occurs by similar routes. Ebola virus belongs to the Filoviridae family of the Mononegavirales, in the same order as the Paramyxoviridae family. Given clinical precedent with these related viruses, the viral RNA polymerase is a logical target for drug discovery. Several groups have screened nucleoside libraries to identify leads. Of existing nucleoside antivirals, favipiravir (see section “[Influenza Viruses](#)”), brincidofovir (see section “[Adenovirus](#)”), and BCX4430



**Fig. 11** The phosphoramidate prodrug GS-5734 (28) and its parent nucleoside GS-441524 (29).

(BioCryst)<sup>66</sup> have all shown some activity in animal models. Unfortunately, none were used early enough in the epidemic to obtain indications of clinical efficacy. Further work is underway to look for selective Ebola virus nucleoside inhibitors.

GS-441524 was identified as a novel inhibitor of the West African Ebola strain and other Ebola species. The 1'-cyano group (29, Fig. 11) provided potency and selectivity for viral polymerases, while the C-linked pyrrolo[2,1-f][1,2,4]-triazin-4-amine base fragment (28, Fig. 10) is stable to deglycosylation. A program to identify a suitable prodrug of GS-441524 provided GS-5734, a monophosphoramidate, which has potent in vitro activity against multiple filoviruses, with EC<sub>50</sub> values in the 0.1–0.2 μM range (Ref. 67; <http://www.usamriid.army.mil>, Oct. 9, 2015). In a rhesus monkey model of Ebola infection, the compound was effective in a therapeutic mode.<sup>68</sup> GS-5734 has activity against not only filoviruses but also arenaviruses and coronaviruses. The compound's clinical potential mandated its use in a Scottish nurse who had contracted the Ebola infection while working with patients in Sierra Leone. She was treated at the Royal Free Hospital in London and discharged Jan. 2015 but was readmitted to the same hospital in Oct. 2015, when her Ebola virus infection relapsed in the form of acute meningitis.

As a consequence of the successful in vivo testing, Gilead filed an IND July for the use of GS-5734 to treat Ebola virus disease, and phase I testing in healthy human volunteers began in August. When the Scottish nurse was hospitalized in early October, sufficient data had been obtained to support compassionate use of the drug.

### 5.20.7.3 Nipah and Hendra Viruses

These viruses belong to the Paramyxoviridae family in the order Mononegavirales, and as such are quite closely related to RSV. Both viruses' natural hosts are fruit bats. Hendra virus was first described in 1994 as the causative agent of an equine epidemic in Hendra, a town in Queensland, Australia. The fatality rate is high—74% in horses and 60% in humans, infected by contact with diseased horses. More than 50 outbreaks of Hendra have occurred since the virus emerged. A vaccine is available for horses, but there are little data on efficacy. Nipah virus emerged in 1998 on pig farms in Malaysia with 257 human infections and 105 deaths. The virus may have the ability for transfer between humans as it causes respiratory infections. Again, the virus's natural host is thought to be a fruit bat. Fruit bats excrete the virus in urine, which probably contaminates pig feed. Since 1998, eight further outbreaks have occurred in Bangladesh and the neighboring areas of India.

The emergence of both viruses probably relates to the loss and change of habitat due to human encroachment. Both viruses would appear to have the potential for widespread dissemination, and further discovery work is justified. Ribavirin has been used in experimental animal models and patients with equivocal results.<sup>69</sup> The discovery efforts described earlier for the related RSV provide a rationale for exploration of fusion inhibitors and nucleosides.

### 5.20.7.4 Zika Virus

Although Zika virus was discovered in the 1940s during surveys of arthropod-borne viruses in Uganda, it received very little attention until the recent outbreak in South America. The virus moved across the Pacific from about 2007 and arrived in South America in 2014 and Brazil in 2015. It is thought that between 0.4 and 1.3 million cases were infected in 2015 in Brazil. The virus appears to be spreading much more rapidly in the Americas than was seen in Africa, giving little opportunity for the development of countermeasures.

Zika is a member of the Flavivirus genera of the Flaviviridae family, other members of which include yellow fever virus (YFV), West Nile virus, and dengue virus. As such, there are good reasons to think that effective vaccines and antiviral medications will be developed for the infection. In the most recent outbreak, manifestations of Guillain–Barre syndrome and fetal abnormalities have been associated with Zika infection, and it is unclear whether these result from the larger patient population or whether the virus evolved CNS tropism during its spread. The rapid spread of Zika is probably due to increased human travel and the northerly spread of the viral vectors *Aedes aegypti* and *Aedes albopictus*.<sup>70–72</sup>

The very successful antiviral discovery programs for the related flavivirus hepatitis C provide a solid platform for the discovery of anti-Zika compounds.

### 5.20.7.5 Yellow Fever

A recent resurgence of YFV in Angola has already spread to China, Kenya, and the Congo and has reawakened awareness of the infection. YFV is a flavivirus (the name derives from yellow fever) that causes between 81,000 and 170,000 cases per year and about 60,000 deaths, despite the availability of an effective and affordable vaccine. A current shortage of vaccine stocks has precipitated a lively debate about increasing the number of people protected by diluting the vaccine (an untested measure). This outbreak illustrates the dangers of complacency in infectious disease; an antiviral treatment for YFV would be very useful in such a rapid-response context.

### 5.20.7.6 Alternative Approach to Emerging Infections

The previous section illustrates the growing threat from viruses emerging or reemerging from reservoirs in the changing environment. Each new emergence stimulates fresh research efforts, but these frequently lack the sustained commitment and investment to provide clinically effective agents and the episodic threat abates. Greater coordination between international agencies might provide for discovery programs at relatively nominal cost to produce credible lead molecules for the identifiable viruses that threaten us. Such a small investment could save thousands of lives in future emerging viral epidemics.

### 5.20.8 Conclusions

The aim of this article was to survey the progress in the discovery of new antiviral drugs to treat acute viral infections. The antiviral therapeutic area is one of the great success stories of the pharmaceutical industry. In the case of HIV infections, we have seen the introduction of more than 20 new drugs used in ever more sophisticated combinations and formulations to extend the life span of infected individuals to near normal, with a good quality of life. In hepatitis C, we have seen effective cures for patients, reducing treatment times from a year to a few weeks. This success can now be applied to acute viral infections. Using four examples of respiratory tract infection, we have sought to illustrate the different challenges that need to be overcome to bring a new medicine to patients. Although the scientific challenge is far from trivial, the greater problem is to make the investment case support the discovery effort.

*See also:* 5.18. Direct-Acting Antiviral Agents for the Treatment of Hepatitis C Virus Infection.

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