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Review Article

Advances in antivirals for non-influenza respiratory virus infections

Frederick G. Hayden

Division of Infectious Diseases and International Health, Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA, USA.
Correspondence: Frederick G. Hayden, University of Virginia Health System, PO Box 801342, Charlottesville, VA 22908, USA. E-mail: fgh@virginia.edu

Progress in the development of antivirals for non-influenza respiratory viruses has been slow with the result that many unmet medical needs and few approved agents currently exist. This commentary selectively reviews examples of where specific agents have provided promising clinical benefits in selected target populations and also considers potential therapeutics for emerging threats like the SARS and Middle East respiratory syndrome coronaviruses. Recent studies have provided encouraging results in treating respiratory syncytial virus infections in lung transplant recipients, serious parainfluenza virus and adenovirus infections in immunocompromised hosts, and rhinovirus colds in outpatient asthmatics. While additional studies are needed to confirm the efficacy and safety of the specific agents tested, these observations offer the opportunity to expand therapeutic studies to other patient populations.

Keywords Antivirals, respiratory virus infection, transplantation, viral pneumonia, asthma, coronoviruses, respiratory syncytial virus, adenovirus, rhinovirus.

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Introduction

Considerable progress has been made in the development of influenza antivirals with two major classes of drugs, the adamantanes and neuraminidase inhibitors, being available for clinical use in most countries and a variety of agents in various stages of investigational development.[1,2] The wide-scale use of NAIs in some countries during response to the 2009 A(H1N1) pandemic provided much new observational data on the effectiveness of oseltamivir treatment in reducing the risk of severe influenza outcomes like pneumonia and hospitalization and of mortality in those hospitalized.[3–7] Such observations confirm the principle that selective inhibitors of influenza replication are associated with both symptom relief and complications reduction and suggest that timely antiviral therapy of other respiratory viral infections might provide similar benefits.

Unfortunately, we have only a few approved agents for other respiratory viruses and the use of these agents is typically limited to specific risk groups like infants and immunocompromised hosts. One challenge in developing both vaccines and therapeutics for non-influenza respiratory viruses is the diversity of these pathogens, representing six major virus families, primarily RNA but also DNA viruses, and numerous serotypes and genotypes. The pathogenesis of these infections ranges broadly depending on the virus, host, and clinical setting, and for many of these illnesses, it remains uncertain to what extent inhibition of viral replication would be associated with clinical benefits. Most of the treatment data regarding antivirals for non-influenza respiratory viruses have been derived from observational studies in immunocompromised hosts, and sometimes, infants, but recent randomized, controlled trials in specific target populations have helped to address the potential value of antiviral interventions. The following commentary, based on a presentations by the author at the 2nd meeting of the International Society of Influenza and Other Respiratory Viruses Antiviral Interest Group, Hanoi, November 2012, and at the XVth International Symposium on Respiratory Viral Infections, Rotterdam, March 2013, is a highly selective review of antiviral treatment interventions that show particular promise for specific respiratory viruses. It focuses primarily on clinical reports but also includes some observations from pre-clinical studies.

Coronaviruses

The recent cases and several clusters of severe illness due to a novel coronavirus (previously designated nCoV or HCoV-EMC and now Middle East respiratory syndrome coronavirus, MERS-CoV) in those residing in or traveling to several Middle Eastern countries[8–11] raise critical questions about

potential treatments and the lessons learned in therapeutic studies of severe acute respiratory syndrome (SARS) CoV-infected patients. In SARS patients, the role of antiviral therapy was supported by finding that viral load was positively correlated with the development of organ dysfunction and death.[12] SARS was characterized by protracted virus replication, peaking during the second week of illness, prominent host pro-inflammatory responses, and histologic evidence for diffuse alveolar damage. Few data regarding viral replication patterns and disease pathogenesis are currently available for MERS-CoV infections, although prolonged viral replication in the lower respiratory tract, extrapulmonary virus detection, lung injury, respiratory failure and often renal failure are notable features in reported cases.[8–11]

A wide range of agents were reported to have anti-SARS-CoV activity in pre-clinical studies,[12–16] and a considerable number of therapeutic interventions directed at inhibiting CoV replication or modifying the host responses to infection were attempted in SARS patients. Although corticosteroids were widely used for treating those with progressive SARS-related pneumonia in efforts to reduce excessive pro-inflammatory responses and presumed immune-mediated tissue damage, their benefits were not conclusively demonstrated, and various reports documented increases in the plasma viral loads, opportunistic infections, and both immediate and delayed (e.g., osteonecrosis) side effects.[12,17–19] In addition, systematic reviews of the observational reports concluded that the common use of multiple agents in combination, varying dose regimens, paucity of studies with systematic data collection, complications from immunosuppressive therapy, and the lack of randomized, controlled trials meant that existing data were inconclusive with regard to putative antivirals and thus inadequate to determine appropriate management of SARS infections.[12,18,19]

The use of available agents like ribavirin and HIV protease inhibitors was not associated with proven benefit in SARS patients, although retrospective studies reported that severe outcomes (ARDS or death) occurred less often in those receiving a combination of lopinavir/ritonavir and ribavirin with corticosteroids compared with historic controls receiving only ribavirin with corticosteroids.[20,21] Early combination treatment was also associated with fewer nosocomial infections, less use of pulse corticosteroids for progressive disease, and lower nasopharyngeal viral loads over time, perhaps related to corticosteroid-sparing effects.[21] Of note, in mice, high ribavirin dosing at 75 mg/kg starting 4 hour prior to SARS virus exposure and then given twice daily for 3 days was found to increase virus lung titers and prolong the duration of virus detectability,[22] and it is unclear whether ribavirin might have had similar effects in treated humans. One small pediatric study found no correlation between ribavirin administration and plasma SARS RNA levels.[23] In SARS patients, ribavirin was associated also with significant toxicities, including hemolytic anemia and metabolic disturbances like hypocalcaemia and hypomagnesaemia.[24] One recent *in vitro* study found that very high ribavirin concentrations were inhibitory for MERS-CoV in Vero and LLC-MK2 cells but that when combined with recombinant human interferon-alfa2b, lower concentrations were inhibitory.[25] Consequently, ribavirin's possible role in treating CoV infections remains uncertain.

SARS-CoV impairs the induction of interferons and their associated antiviral effects but is inhibited by exogenous interferon in cell culture studies.[15] Injection of pegylated interferon-alfa2b was highly protective given 3 days before and reduced lung viral levels and histopathology when initiated 1 day post-infection in a cynomolgus macaque model of SARS-CoV,[26] and both a hybrid interferon and an interferon inducer, mismatched double-stranded poly(I:C), reduced lung viral titers in a murine model.[14] Intranasal application of interferons or the interferon inducer poly(I:C) was protective and reduced virus replication in an aged mouse model of SARS.[27] Interferons also have immunomodulatory effects, and in an aged macaque model of SARS, treatment with type I interferon reduced pathology and diminished pro-inflammatory gene expression, including interleukin- 8 (IL-8) levels, without affecting virus replication in the lungs.[28] One observational Canadian study in SARS patients with progressive illness found that synthetic interferon alfacon-1 in conjunction with corticosteroids appeared to reduce time to resolution of pulmonary infiltrates, improve oxygen saturation, reduce the duration of supplemental oxygen use, and sped resolution of serum LDH elevations compared with corticosteroids alone.[29] Interferon alfacon-1 was generally well tolerated, although associated with transient reductions in neutrophil counts and elevations in transaminase levels. Of note, the MERS-CoV has been shown to be readily inhibited by type I and III interferons in human bronchial epithelium *ex vivo*.[30,31] Such observations are sufficiently encouraging to support controlled studies of systemic interferon in affected patients. In addition, one approved agent for selected parasitic infections, oral nitazoxanide, may have interferon-inducing properties, is inhibitory for various respiratory viruses including influenza and a canine CoV *in vitro*,[32] and has shown promising dose-related activity in a phase 2, placebo-controlled, randomized trial in treating uncomplicated influenza[33] Consequently, nitazoxanide would be an interesting agent to test alone and in combination with other antivirals for CoV infections.

The protective efficacy of SARS-CoV-neutralizing antibodies, including humanized and human monoclonals directed to the spike protein, has been demonstrated in various animal models.[15,34,35] These studies found potent antiviral effects without evidence for the immune enhancement. Passive immunotherapy with convalescent plasma from SARS patients was used in treating SARS patients in

Hong Kong and Taiwan in open-label fashion with apparent clinical benefits and rapid decreases in plasma viral load (from up to >10e5 copies/ml to undetectable levels 24 hour after infusion).[36,37] Among 80 patients given convalescent plasma in Hong Kong, a higher day 22 hospital discharge rate was observed among patients who were received plasma before day 14 of illness compared with later (58·3% versus 15·6%; $P < 0{\cdot}001$) and among those who were viral RT-PCR positive but SARS-CoV seronegative compared with those seropositive at the time of plasma infusion.[36] Efforts to develop neutralizing human monoclonals for MERS-CoV are in progress, as is screening for other inhibitors.

Other inhibitors of the spike (S) protein and its receptor interactions have been described. For example, in a rhesus macaque SARS model, siRNA inhibitors targeting the SARS-CoV genome at S protein- and nsp12-coding regions reduced SARS-CoV-induced fever, numbers of infected cells, and histologic findings of diffuse alveolar damage, compared with control or a non-specific siRNA, when given intranasally as prophylaxis or post-infection.[38] Pre-clinical reports suggest that inhibitors of angiotensin-converting enzyme-2 (ACE-2), one of the attachment sites for the SARS S protein, and other S protein inhibitors like mannose-binding lectin (MBL) might provide therapeutic benefit in SARS. However, the MERS-CoV does not use ACE2 but rather dipeptidyl peptidase 4 (DPP4 or CD26) to initiate infection[39] and has a much broader spectrum of cell infectivity, including human, swine, and bats cells than SARS-CoV.[40] Consequently, ACE2 inhibitors would be unlikely to exert specific inhibition of hCoV-EMC. Identification of the receptor used by MERS-CoV may provide selective inhibitors of this interaction, but available agents that inhibit the enzymatic function of DPP4 apparently do not.[39]

One study of SARS patients found that they had SNPs affecting MBL expression and reduced levels of serum MBL compared to controls without SARS,[41] although serum MBL levels did not correlate with disease severity. Serum MBL concentrations vary widely due to mutations of the promoter and coding regions of the human MBL gene. Recombinant and plasma-derived human MBL bind to the S protein through one or more N-linked glycosylation sites and inhibit SARS-CoV replication in susceptible cell lines at concentrations below those observed in the serum of healthy individuals.[42] The cell entry inhibitory effect appears to be mediated in part by blocking viral binding to C-type lectins but apparently not to the ACE2 receptor.[42] No *in vivo* therapeutic studies have been reported in SARS, but high doses of recombinant human MBL showed activity in a lethal Ebola virus model in mice.[43] Because MBL binds to carbohydrates on the surface of a wide range of respiratory viruses, including influenza, paramyxoviruses, and coronavirus, and other important pathogens, MBL is a potential therapeutic intervention of general interest.

Respiratory syncytial virus

Respiratory syncytial virus is a well-recognized cause of morbidity and, in those at the extremes of age or with severe immunocompromising conditions, mortality. It is the leading cause of bronchiolitis in infants and young children, and one analysis estimated that in 2005, RSV infections were associated with approximately 34 million episodes of acute lower respiratory illness (ALRI), or about 22% of ALRI, in children below the age of 5 years.[44] These illnesses led to hospitalization in about 10% of cases and to between 66 000 and 200 000 deaths globally, with 99% of these deaths in low- and middle-income countries.[44] In contrast, in developed countries like the United States, RSV is associated with many more deaths in adults aged 65 years and older than in children.[45]

The available antiviral options for RSV are quite limited. Much work has been carried out on developing antibody preparations, and the anti-F protein monoclonal palivizumab is currently approved for use for prophylaxis in high-risk children.[46] While effective in reducing RSV-related hospitalization by about 50%, its very high cost limits availability to well-resourced countries. Aerosolized ribavirin is approved for treating hospitalized children with serious RSV illness, but it is used very infrequently in this population due to its difficult delivery method, modest antiviral and clinical effects, cost, and concerns about healthcare worker exposure to a potential teratogen. The American Academy of Pediatrics recommends against its routine use.[47]

However, ribavirin has been used frequently in hematopoietic stem cell transplant (HSCT) recipients, because of their high mortality risk when RSV lower respiratory tract illness (LRTI) develops.[48] A systematic review of observational studies across multiple of centers found that compared with no ribavirin use, ribavirin treatment, regardless of route or whether combined with an immunomodulatory regimen (intravenous immunoglobulin [IVIg], RSV immunoglobulin, or palivizumab), was associated with reduced frequencies of progression to LRTI.[49] Less frequent progression to LRTI and significantly fewer deaths in those with LRTI were observed among patients treated with combinations of aerosolized ribavirin and an immunomodulatory agent than in those treated with ribavirin alone. However, a recent retrospective analysis of one center's experience concluded that the addition of palivizumab to aerosolized ribavirn did not improve outcomes in RSV-infected HSCT recipients.[49a] A recent randomized controlled trial comparing two aerosolized ribavirin regimens found that intermittent delivery (2 g over 2 hours every 8 hours) appeared to be more effective in preventing lower respiratory progression than a standard continuous one (6 g over 18 hoursr) and was easier to administer.[50] While data on oral ribavirin are very limited, one study suggested favorable outcomes in HSCT recipients with upper respiratory RSV infection when used in combina-

tion with IVIg and palivizumab.[51] However, a recent retrospective analysis of hematologic malignancy and HSCT patients with RSV or other paramyxovirus infections concluded that oral ribavirin was not clinically effective in preventing mortality.[52] In lung transplant recipients with RSV or human metapneumovirus infections, observational studies suggest that ribavirin given intravenously or orally may be beneficial with regard to improving clinical outcomes and recovery of lung function,[53,54] but the uncontrolled nature of these findings precludes firm conclusions. Further controlled studies of oral ribavirin, which is less expensive and easier to administer than aerosolized ribavirin, are warranted in these important patient groups.

A number of RSV investigational agents have received some degree of recent clinical testing, although development of several apparently has been stopped at this time. For example, a potent anti-F antibody, motavizumab, was shown to have antiviral effects in hospitalized children[55] but was not superior to palivizumab in seasonal RSV prophylaxis in at-risk children and had increased cutaneous adverse events relative to palivizumab.[56] A placebo-controlled RCT of a single motavizumab injection did not find reductions in upper respiratory tract viral titers or illness measures in infants aged < 12 months and hospitalized with RSV illness [Ramilo et al.,r presented at the 8th Annual Respiratory Syncytial Virus Symposium, September 27–30, 2012, Santa Fe, NM]. More potent monoclonals to F protein are in development. Among those in active clinical development, there is a polyclonal high-titer RSV immunoglobulin (RI-001; Adma Biologics Inc., Hackensack, NJ, USA) being tested in immunocompromised patients to prevent progression from upper to lower respiratory tract illness, a topically applied F protein inhibitor (MDT-637; MicroDose Therapeutx, Monmouth Junction, NJ, USA) and an orally administered F protein inhibitor (GS-5806; Gilead Sciences, Inc., Foster City, CA, USA). The results of double-blinded, placebo-controlled studies with GS-506 to test efficacy in experimental RSV infection in adult volunteers (NCT01756482) and safety in young children hospitalized for RSV illness (NCT01797419) are expected to be available shortly. Because the envelope glycoprotein F plays an important role in RSV fusion with and entry into the host cell, it serves as an attractive target for developing RSV entry inhibitors, although resistance emergence has been a notable limitation in earlier studies.[57]

The agent that has progressed furthest in testing is a double-stranded oligonucleotide directed against the viral N gene (ALN-RSV01; Alnylam Pharmaceuticals, Cambridge, MA, USA). This siRNA, complementary to the mRNA that encodes the N protein, showed robust antiviral effects both *in vitro* and in a murine model, with over a 1000-fold reduction in lung virus titers,[58] and was active when given intranasally to volunteers experimentally infected with RSV.[59,60] In a placebo-controlled RCT of 24 lung transplant recipients with RSV infection, aerosolized ALN-RSV01 (0·6 mg/kg) given daily for 3 days was generally well tolerated and significantly reduced the risk of new or progressive bronchiolitis obliterans syndrome (BOS) at Day 90 compared with placebo (6·3% versus 50%).[61] There were no differences in upper respiratory tract viral loads, but those in the lower could not be tested. Consequently, a larger phase 2b RCT was conducted at 33 sites in six countries at the same dose but extended to 5 days administration, again added to standard of care.[62] The primary endpoint of BOS at Day 180 among the 77 lung transplant patients in the intent-to-treat-infected population tended to be lower with inhaled ALN-RSV01 (30·3% versus 13·6%; $P = 0·058$) and was significantly lower among the 73 patients in the per-protocol analysis (28·1% versus 9·8%). Deaths occurred in 2 placebo and 1 siRNA recipient that were unrelated to treatment. These encouraging results warrant further studies of this novel siRNA therapeutic in other risk populations and support the study of siRNA inhibitors for other respiratory viral infections.[59]

Parainfluenza virus

Parainfluenza virus (PIV) illness can be very severe in immunocompromised hosts, particularly HSCT recipients. The results with ribavirin have been quite mixed. Aerosolized ribavirin has not resulted in reductions in viral shedding or survival benefit in HSCT with PIV pneumonia, while oral or intravenous ribavirin has provided apparent benefit in individual HSCT recipients and hematologic malignancy patients with PIV illness.[48] A recent retrospective analysis concluded that oral ribavirin did not reduce mortality in hematologic malignancy patients with paramyxovirus infections compared with supportive care alone,[52] whereas oral ribavirin seems to have been associated with benefit in lung transplant patients with paramyxovirus infections.[54] A new investigational agent for severe PIV infection is DAS181, a fusion construct that includes a sialidase from *Actinomycosis viscosus* that cleaves both a2,6- and a2,3-linked sialic acid receptors on host cells.[63] Consequently, its antiviral spectrum includes influenza viruses and it is active when topically applied in animal influenza models, including avian H5N1 and H1N1pdm09 viruses,[63–65] and has shown antiviral effects in a phase 2 RCT in uncomplicated human influenza.[66] Of note, the H-N protein of PIV also binds to sialic acid receptors, and DAS181 is inhibitory for PIV in cell culture, in human airway epithelium, and given intranasally in a cotton rat model.[67] DAS181 has been administered on a compassionate use basis for treating HSCT and lung transplant patients with severe PIV illness with apparent clinical benefit and antiviral effects in some cases.[68–70] This host-directed agent is available on compassionate use from its sponsor (formerly Nexbio, now Ansun Biopharma, Inc., San Diego,

CA, USA), and an open-label study is being undertaken at the NIH for this particular problem.

Adenovirus

Adenovirus infections are often very severe in immunocompromised hosts but occasionally in those in the community as well.[71,72] There are currently no approved antivirals for adenovirus treatment, but a number of agents have some degree of *in vitro* inhibitory activity.[73] Ribavirin has variable *in vitro* activity at high concentrations[74] and proven largely ineffective in treatment of serious infections. Intravenous cidofovir, a nucleoside phosphonate analog, has become the standard treatment for most immunocompromised patients with adenovirus disease, but its use is associated with nephrotoxicity in up to 50% and neutropenia in 20% of patients.[75,76] Donor leukocyte infusion and use of *in vitro*-expanded adenovirus-specific T cells have been used in some patients.[76]

The most promising anti-adenovirus antiviral in clinical development is the orally administered, lipid ester derivative of cidofovir, designated CMX001or brincidofovir (Chimerix, Durham, NC, USA). *In vitro* CMX001 provides higher intracellular levels compared with the parent molecule and is over 50-fold more active than cidofovir for adenoviruses.[77] It was shown to be inhibitory for lethal adenovirus infection in a Syrian hamster model.[78] In addition to the advantage of being orally bioavailable, CMX001 also has lower risk of nephrotoxicity compared with cidofovir during clinical use. One case series of 13 immunocompromised patients, the majority of whom were HSCT recipients, described its use in severe adenovirus disease.[79] All had adenoviremia, and six had disseminated disease involving other organs. Following onset of the adenoviral disease at a median of 75 days post-transplant, they were initially treated with cidofovir, but then switched to CMX001 because of either persistent viral replication or nephrotoxicity. Prolonged courses of CMX001 were associated with good virologic responses, including at least 100-fold reductions in plasma adenoviral DNA levels in nine patients. Some delay in mortality was also observed among those with virologic responses. Two current CMX001 studies will provide further insights regarding its clinical utility for adenoviral infections in high-risk populations. One is a controlled trial of pre-emptive therapy in HSCT patients with adenoviremia that has finished enrollment and is under analysis (NCT01241344), and the other is an open-label study of treating a variety of serious DNA viral diseases, including those due to adenoviruses, in immunocompromised hosts (NCT01143181). An initial press release (14 August 2013) indciated that CMX001 100 mg BIW decreased levels of adenoviremia and showed potential benefits in reducing both progression to adenovirus disease and all-cause mortality, compared to subjects who received placebo or CMX001 given once weekly. Phase 1 safety and pharmacology studies have been completed in healthy volunteers.[80] CMX001 is a promising agent that also warrants testing in non-immunocompromised hosts with severe adenovirus illness.

Human rhinovirus

Human rhinovirus (HRV) infections are the most frequent infections that humans experience and are implicated in causing a wide range of respiratory tract syndromes. In addition to being the most frequent cause of colds, HRV infections are the leading cause of exacerbations of asthma and chronic obstructive pulmonary disease. Past studies of the capsid-binding anti-HRV agent pleconaril showed that early treatment exerted antiviral effects and reduced the duration of uncomplicated HRV colds by about 1 day.[81] Symptomatic improvement in pleconaril-treated subjects was related to the drug susceptibility of the infecting HRV, and strains with >10-fold reduced susceptibility emerged in about 11% of recipients.[82] However, it was not approved for clinical use largely because of potential drug interaction concerns. Recently, another capsid-binding anti-HRV agent designated BTA798 (or vapendavir) (Biota Holdings Ltd, Notting Hill, Vic., Australia) showed dose-related antiviral effects in experimentally infected volunteers[83] and beneficial effects in a phase 2 placebo-controlled RCT in asthmatics with cold symptoms (NCT01175226).[84] Among the 300 persons enrolled, 93 had a documented HRV infection. Oral vapendavir (400 mg twice daily for 6 days) was associated with significantly lower upper respiratory symptom scores early in the illness and continuing up to 2 weeks compared with placebo. Vapendavir recipients also had significant improvements in secondary outcomes including higher peak expiratory flow rates on day 5, reduced overall use of asthma relief medications, and less frequent HRV RNA detection on day 3 (74% versus 91%). This modest degree of antiviral effect raises the possibility that more potent inhibition might be able to provide even greater clinical benefits.

Intranasal recombinant interferon-alpha2b was shown to be effective in preventing HRV colds when used for post-exposure prophylaxis[85,86] but ineffective for treatment of established colds[85] and also associated with local side effects. Recently, 14 days treatment with an inhaled interferon-beta designated SNG001 (Synairgen plc, Southampton, England) was associated with therapeutic efficacy in a phase 2, placebo-controlled RCT of adult asthmatics receiving inhaled corticosteroids who had a history of deterioration with colds (NCT01126177).[87] Among 147 enrolled, 134 met the criteria for a cold; HRVs represented 68% of the respiratory viruses detected. Although the trial did not meet its primary endpoint (changes in the shortened Asthma Control Questionnaire) in the overall population, among the subset of

"difficult to treat" asthma patients representing about one-half of those enrolled, inhaled SNG001 was associated with significant improvements in asthma symptoms, 65% fewer moderate exacerbations, improved morning peak expiratory flow rates, and reduced use of relief bronchodilators. While the findings in the oral vapendavir and inhaled interferon-beta studies need to be confirmed in larger trials, the results suggest that early antiviral treatment of colds in asthmatics can moderate asthma exacerbations.

Conclusions

In summary, currently, there are many unmet medical needs and few approved agents for the non-influenza respiratory virus infections. Recent studies have provided encouraging results in serious respiratory viral infections in hospitalized immunocompromised hosts and in outpatient asthmatics with colds. While additional trials are needed to confirm the efficacy and safety of the agents discussed above, these or other selective antivirals offer the opportunity to expand therapeutic studies to other patient populations. One of the challenges in developing more effective therapeutics is the diversity of respiratory viruses and the differences in disease pathogenesis across viruses and patient groups. In addition to DAS181 for PIV, several agents in clinical development for influenza (e.g., favipiravir, nitazoxanide) have *in vitro* activity against several other respiratory viruses.[32,88] In addition, analogous to work in influenza,[89] one forward-looking strategy is understanding how respiratory viruses interact with host cellular pathways during replication and identifying potential viral–host protein interactions to target. For example, one large mRNA gene expression database search identified 67 common pathways among seven different respiratory viruses; of the top five pathways, 53 had differentially expressed genes affected by at least five of the seven viruses.[90] Such studies might lead to identifying existing drugs that could be repurposed to target these pathways and eventually to broader spectrum antiviral agents.

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Conflicts of interest

Since 2008 FGH has served as an unpaid consultant to multiple companies involved in developing antivirals for respiratory viral infections including several investigational agents discussed in this article (Synairgen; Nexbio, now Ansun).

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