Pharmacologic Advances in the Treatment and Prevention of Respiratory Syncytial Virus

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Currently, only 2 drugs have been approved for the treatment of respiratory syncytial virus (RSV). Palivizumab is a monoclonal antibody for the prevention of RSV in high-risk children. Ribavirin is approved for treatment of severe RSV disease; however, its effectiveness in improving outcomes is questionable. During the past 40 years, many obstacles have delayed the development of safe and effective vaccines and treatment regimens. This article reviews these obstacles and presents the novel development strategies used to overcome many of them. Also discussed are promising new antiviral treatment candidates and their associated mechanism of action, the significant advances made in vaccine development, and exciting, new studies directed at improving outcomes through pharmacologic manipulation of the host response to RSV disease.

Respiratory syncytial virus (RSV) is the leading cause of pediatric viral respiratory tract infections. The World Health Organization estimates an annual mortality rate of \(\sim 160,000\) deaths worldwide [1]; more inclusive all-cause mortality rates related to RSV approach 600,000 deaths [2]. RSV is also the second leading cause of viral death in elderly individuals [3]. By 18 months of age, 87% of children have developed RSV-specific antibodies [4]; by 3 years of age, virtually all children have been infected. In the United States alone, RSV infection results in \(>120,000\) childhood hospitalizations and up to 500 deaths [5]. Compared with influenza, RSV accounts for \(>9\) times more deaths in children younger than 1 year [6–11].

Only 2 US Food and Drug Administration (FDA)–approved drugs are currently available for RSV disease. Palivizumab is indicated for RSV prevention in high-risk infants, including those with chronic lung disease, those with congenital heart disease, and those born prematurely [12]. This indication is based on hospitalization rates that are \(\sim 5\) times greater in high-risk versus non–high-risk infants. However, among all infants hospitalized with severe RSV disease, \(\sim 70\%\) are term infants with no underlying risk factors compared with 10%–20% of high-risk infants [13]. Thus, previously healthy infants constitute most RSV hospital admissions [14, 15] but are not considered candidates for palivizumab therapy. Ribavirin has been used for the treatment of severe infections despite limited evidence of benefit [16, 17], potential for toxic effects in healthcare workers [18], and high cost [19]. The American Academy of Pediatrics does not generally recommend ribavirin treatment for RSV infections [20]. There is an urgent need for safe and effective drugs to treat and prevent RSV disease.

This review begins with a description of the RSV structure and mechanism of cellular invasion. It then summarizes the pharmacology and innovative strategies used to develop RSV treatment and prevention drugs. Concluding remarks emphasize promising anti-RSV drug candidates and their current development status.

VIRAL DRUG TARGETS

RSV is a negative-sense, single-stranded, enveloped RNA paramyxovirus. The RSV genome encodes a total of 11 proteins [21–23], many of which are under investigation as possible drug targets (Figure 1 and Table 1). There are 2 major antigenic subgroups, A and B, which are defined by different envelope proteins and cocirculate each year. Infectivity of the virus is determined by the surface glycoproteins, F and G, which also serve as targets for neutralizing antibodies [26]. The F glycoprotein exists only on the surface membrane and is highly
Antisense technology, introduced in 1996, MedImmune’s RSV immune globulin intravenous (RSV-IGIV), consisting of a high concentration of polyclonal, anti-RSV IgG antibodies purified from the plasma of healthy individuals [54], became the first FDA-approved product, RI-001 (ADMA Biologicals) (M. Sorrentino, personal communication), is now being evaluated in phase 2 clinical trials in immunosuppressed, RSV-infected patients at risk for lower respiratory tract illness [39]. Although human plasma products harbor certain risks, stringent purification requirements have been implemented for all human plasma–derived products to significantly minimize the risk of infection transmission [56]. Moreover, polyclonal antibodies contain a mixed population of antibodies targeting multiple viral epitopes, thus overcoming the mutagenic potential intrinsic among viruses. These studies are ongoing, and the results have not yet been published.

**Monoclonal anti-RSV antibodies.** Monoclonal anti-RSV antibodies target a single viral epitope. Palivizumab, the only FDA-approved mAb for RSV, targets the highly conserved RSV F glycoprotein, inhibiting viral entry into host cells [57]. It has demonstrated no clinical benefit for the treatment of RSV disease and thus is indicated only for RSV prevention. Motavizumab (MEDI-524; MedImmune) is a second-generation humanized IgG1 monoclonal antibody, developed from palivizumab [58], with ~70-fold higher affinity for the RSV F glycoprotein and 20-fold greater neutralizing capacity [59]. In a rat model, motavizumab had 50–100 times greater anti-RSV activity in the lower respiratory tract compared with palivizumab [60] and reduced RSV viral load in the upper airways, where palivizumab has minimal effect [59]. In a large phase 3 noninferiority study comparing motavizumab to palivizumab for RSV prevention in high-risk children, motavizumab demonstrated 26% fewer RSV hospitalizations (P<.01) and a 50% reduction in the incidence of RSV-specific outpatient lower respiratory tract infections (P = .005) [61]. Moreover, motavizumab significantly reduced viral load by day 1 after treatment in children hospitalized with RSV, suggesting it may be beneficial for RSV treatment and prevention [62]. Motavizumab is currently pending FDA approval.

Most RSV mAb candidates target the more conserved F glycoprotein; however, recent evidence suggests that mAbs targeting the G glycoprotein may impart dual anti-RSV activity. The RSV G glycoprotein has been shown to induce lung inflammation by binding to the chemokine receptor CX3CR1 and initiating a cascade of inflammatory mediators [63, 64]. Although still in early preclinical studies, an mAb targeting the CX3C motif on the RSV G glycoprotein (mAb 131–2G) was shown to reduce both lung inflammation and RSV titers in BALB/c mice [42].
<table>
<thead>
<tr>
<th>Protein</th>
<th>Function</th>
<th>Drug candidates</th>
<th>Mechanism</th>
<th>Development status</th>
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</thead>
<tbody>
<tr>
<td><strong>Envelope glycoproteins</strong></td>
<td></td>
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</tr>
<tr>
<td>F</td>
<td>Mediates fusion and entry of the virion into the host cell and promotes fusion of infected host cells to facilitate cell-to-cell transmission (syncytial formation) [26]</td>
<td>Motavizumab, MEDI-524 [32]</td>
<td>mAb</td>
<td>Fusion inhibitor</td>
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<tr>
<td></td>
<td></td>
<td>TMC-353121 [33–35]</td>
<td>Fusion inhibitor</td>
<td>Preclinical, ongoing</td>
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<td></td>
<td></td>
<td>BMS-433771 [36]</td>
<td>Fusion inhibitor</td>
<td>Phase 1/2, discontinued</td>
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<td></td>
<td>RFI461 [37]</td>
<td>Fusion inhibitor</td>
<td>Phase 1/2, discontinued</td>
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<td></td>
<td></td>
<td>VP-14637 [38]</td>
<td>Fusion inhibitor</td>
<td>Phase 1, discontinued</td>
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<td></td>
<td></td>
<td>BTA9881 [39]</td>
<td>Fusion inhibitor</td>
<td>Phase 1, ongoing</td>
</tr>
<tr>
<td>G</td>
<td>Mediates viral attachment [26]</td>
<td>MBX-300 [40, 41]</td>
<td>Attachment inhibitor</td>
<td>mAb</td>
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<td></td>
<td></td>
<td>mAb 131–2G [42, 43]</td>
<td>Attachment inhibitor</td>
<td>mAb</td>
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<td>SH</td>
<td>Structural component; believed to inhibit TNF-α signaling [27]</td>
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<td><strong>Nucleocapsid proteins [24]</strong></td>
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<tr>
<td>N</td>
<td>Major nucleocapsid protein [28]</td>
<td>ALN-RSV01 [44]</td>
<td>sRNA</td>
<td>sRNA</td>
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<td></td>
<td></td>
<td>RSV-604 [45]</td>
<td>N-protein inhibitor</td>
<td>N-protein inhibitor</td>
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<td>P</td>
<td>Phosphoprotein</td>
<td></td>
<td></td>
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<tr>
<td>L</td>
<td>Large polymerase subunit</td>
<td>YM-53403 [46]</td>
<td>Benzazepine derivative</td>
<td>Peptide-conjugated PMO</td>
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<tr>
<td></td>
<td></td>
<td>AUG-2 [47]</td>
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<tr>
<td><strong>Nucleocapsid-associated proteins [25]</strong></td>
<td></td>
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<tr>
<td>M2–1</td>
<td>Transcription elongation factor</td>
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<tr>
<td>M2–2</td>
<td>Regulator of transcription</td>
<td></td>
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<tr>
<td><strong>Matrix protein: M1</strong></td>
<td>Mediates virus assembly [29, 30]</td>
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<td><strong>Nonstructural proteins</strong></td>
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<td>NS1</td>
<td>Antagonize</td>
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<tr>
<td>NS2</td>
<td>interferon-induced antiviral responses</td>
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**NOTE.** mAb, monoclonal antibody; BLA, biologic license agreement; TNF-α, tumor necrosis factor-α; sRNA, small interfering ribonucleic acid; PMO, phosphorodiamidate morpholino oligomers.
duced in the 1980s, involves the targeting of messenger RNA (mRNA) and viral RNA by oligonucleotides. First-generation oligodeoxyribonucleotides were composed of synthetic DNA molecules 15–20 nucleotides in length that were complementary to small segments of target mRNA. To improve stability against cellular nucleases, phosphodiester bonds were later substituted with phosphorothioate; however, this occurred at the expense of lower sequence specificity and higher toxicity [65].

More recently, a variety of other mechanisms of oligonucleotide-induced antiviral activity have emerged. Those showing the most promise include 2–5A antisense compounds, phosphorodiadimate morpholino oligomers, and small interfering RNAs (siRNAs). Of these, only siRNAs have advanced to clinical trials and are discussed herein. For a thorough review of antisense approaches targeting RSV, see Cramer [66].

RNA interference is a posttranscriptional mechanism of gene silencing that occurs in plants, animals, and humans [67, 68]. It is important for the regulation of gene expression and participates in host defense against viral infections. The discovery that synthetic, double-stranded siRNAs could be used to inhibit protein synthesis by targeting mRNA transcripts in mammalian cells led to the emergence of a new field of drug discovery [69] spanning a variety of human diseases, including cancer, metabolic diseases, and viral infections [70]. For RSV, siRNAs targeting the P protein [71], NS1 protein [72], and N protein genes [28] have been evaluated. Of these, an siRNA targeting the N protein (ALN-RSV01; Alnylam Pharmaceuticals) is currently being studied in humans. In a phase 2 clinical trial, ALN-RSV01 or placebo was administered intranasally to 85 healthy adult volunteers 2 days before and 3 days after viral inoculation. Subjects receiving ALN-RSV01 experienced a 38.1% reduction in RSV infection (P<.01) and a 95% increase in the number of subjects who remained free of infection compared with placebo-treated subjects. In a second, recently completed phase 2 study, safety and tolerability of ALN-RSV01 among adult lung transplantation patients naturally infected with RSV were demonstrated. Although not powered to study efficacy, results showed improvement in lung function at the 90-day end point [73]. Larger clinical trials in infants are needed to evaluate safety and efficacy; however, ALN-RSV01 offers a promising targeted approach to treating infant RSV disease.

**Fusion inhibitors.** Fusion is a critical step in the life-cycle of RSV. Inhibition of this step leads to reduction in viral load and syncytia formation [33, 74]. On viral coalescence with target cell membranes, the F glycoprotein undergoes a conformational change exposing hydrophobic pockets or epitopes (Figure 2) [75]. Binding of these exposed targets by RSV fusion inhibitors prevents viral entry in the host cell [76]. Several small-molecule fusion inhibitors have been screened, each targeting a slightly different epitope within the F glycoprotein (Table 2). Despite this, only 2 remain under investigation (Table 1). BTA9881 is currently in phase 1 clinical trials, and preclinical studies in rats suggest that TMC-353121 is a highly potent (up to 90% inhibition of virus replication) anti-RSV drug candidate. A comprehensive review of RSV fusion inhibitors was recently published by Bonfanti and Roymans [33].

**Other small-molecule compounds.** Other small-molecule compounds have been engineered to inhibit RSV by binding RSV-specific epitopes, including G, L, and N proteins (Figure 1 and Table 1). MBX-300 (Microbiotix) targets the RSV G glycoprotein, resulting in inhibition of viral attachment to host cells [40]. As previously discussed, binding of the G glycoprotein also alters RSV-induced inflammatory responses [63]. In preclinical studies, MBX-300 was found to be safe in both rats and monkeys and demonstrated specific and potent anti-RSV activity [37, 40, 41].

Most anti-RSV compounds being actively pursued disrupt viral entry into the cell either through the F or G glycoprotein. YM-53403 (Yamanouchi Pharmaceutical) is a novel compound targeting the RSV L protein, which together with the P and N proteins make up viral RNA polymerase (Figure 1) [82]. Sudo et al [46] demonstrated potent anti-RSV activity against both subgroups A and B, presumably by interfering with RNA synthesis. The half maximal effective concentration of YM-53403...
against all RSV strains studied were 76- to 105-fold more potent than ribavirin. Preclinical studies are ongoing for YM-53403.

RSV604 is an oral benzodiazepine that targets the RSV N protein (Arrow Therapeutics). Like YM-53403, its putative mechanism of anti-RSV activity is inhibition of viral RNA polymerase. It displays submicromolar activity against many clinical isolates of A and B RSV antigenic subgroups. In contrast to most fusion inhibitors, RSV604 was shown to be active when administered after infection. Moreover, it significantly reduced viral spread in vitro when given up to 24 h after infection [45]. RSV604 is in ongoing phase 2 clinical trials.

VACCINES

Numerous obstacles have prevented the development of an effective RSV vaccine. The population most vulnerable to severe RSV disease, children aged < 6 months [83, 84], may respond inadequately to vaccination because of immunologic immaturity or immune suppression caused by maternal antibodies [5, 85, 86]. In the 1960s, a formalin inactivated RSV vaccine was studied in human infants for the first time. Not only did it fail to protect against subsequent wild-type RSV disease, children aged 6 months [83, 84], may respond inadequately to vaccination because of immunologic immaturity or immune suppression caused by maternal antibodies [5, 85, 86]. In the 1960s, a formalin inactivated RSV vaccine was studied in human infants for the first time. Not only did it fail to protect against subsequent wild-type RSV disease, children aged 6 months [83, 84], may respond inadequately to vaccination because of immunologic immaturity or immune suppression caused by maternal antibodies [5, 85, 86]. In the 1960s, a formalin inactivated RSV vaccine was studied in human infants for the first time. Not only did it fail to protect against subsequent wild-type RSV disease, children aged 6 months [83, 84], may respond inadequately to vaccination because of immunologic immaturity or immune suppression caused by maternal antibodies [5, 85, 86]. In the 1960s, a formalin inactivated RSV vaccine was studied in human infants for the first time. Not only did it fail to protect against subsequent wild-type RSV disease, children aged 6 months [83, 84], may respond inadequately to vaccination because of immunologic immaturity or immune suppression caused by maternal antibodies [5, 85, 86]. In the 1960s, a formalin inactivated RSV vaccine was studied in human infants for the first time. Not only did it fail to protect against subsequent wild-type RSV disease, children aged 6 months [83, 84], may respond inadequately to vaccination because of immunologic immaturity or immune suppression caused by maternal antibodies [5, 85, 86]. In the 1960s, a formalin inactivated RSV vaccine was studied in human infants for the first time. Not only did it fail to protect against subsequent wild-type RSV disease, children aged 6 months [83, 84], may respond inadequately to vaccination because of immunologic immaturity or immune suppression caused by maternal antibodies [5, 85, 86]. In the 1960s, a formalin inactivated RSV vaccine was studied in human infants for the first time. Not only did it fail to protect against subsequent wild-type RSV disease, children aged 6 months [83, 84], may respond inadequately to vaccination because of immunologic immaturity or immune suppression caused by maternal antibodies [5, 85, 86]. In the 1960s, a formalin inactivated RSV vaccine was studied in human infants for the first time. Not only did it fail to protect against subsequent wild-type RSV disease, children aged 6 months [83, 84], may respond inadequately to vaccination because of immunologic immaturity or immune suppression caused by maternal antibodies [5, 85, 86]. In the 1960s, a formalin inactivated RSV vaccine was studied in human infants for the first time. Not only did it fail to protect against subsequent wild-type RSV disease, children aged 6 months [83, 84], may respond inadequately to vaccination because of immunologic immaturity or immune suppression caused by maternal antibodies [5, 85, 86]. In the 1960s, a formalin inactivated RSV vaccine was studied in human infants for the first time. Not only did it fail to protect against subsequent wild-type RSV disease, children aged 6 months [83, 84], may respond inadequately to vaccination because of immunologic immaturity or immune suppression caused by maternal antibodies [5, 85, 86]. In the 1960s, a formalin inactivated RSV vaccine was studied in human infants for the first time. Not only did it fail to protect against subsequent wild-type RSV disease, children aged 6 months [83, 84], may respond inadequately to vaccination because of immunologic immaturity or immune suppression caused by maternal antibodies [5, 85, 86]. In the 1960s, a formalin inactivated RSV vaccine was studied in human infants for the first time. Not only did it fail to protect against subsequent wild-type RSV disease, children aged 6 months [83, 84], may respond inadequately to vaccination because of immunologic immaturity or immune suppression caused by maternal antibodies [5, 85, 86].

Live vaccines. RSV vaccine development is currently focused on live, attenuated strains for intranasal administration. This strategy accomplishes several goals: it induces local mucosal and systemic immunity; the intranasal route partially escapes the suppressive effects of maternal serum antibodies [93]; compared with inactivated vaccines, live intranasal vaccines are more immunogenic and provide broader protection [94]; and live, attenuated vaccines are not associated with enhanced disease [95]. It is unlikely that a single vaccination will impart complete protection against RSV disease as evidenced by natural reinfection occurring throughout life [5, 96, 97]. Thus, the goal for a successful vaccine should be to prevent serious RSV-associated lower respiratory tract infections in those at risk.

The balance between attenuation and immunogenicity is critical in vaccine development. Live vaccine candidates have been developed using serial passages at decreasing temperatures (cold passage) and chemical mutagenesis to produce temperature-sensitive mutants. These cpts viruses will replicate at the low temperatures of the upper respiratory tract but not at the high temperatures of the lower respiratory tract [95]. Initial vaccine candidates developed using these attenuation methods were found to be either too reactive or overattenuated, and mutations were often unstable [98, 99]. The latest strategy to safely and effectively attenuate RSV is through reverse genetics [95], which involves producing infectious virus in cell culture completely from cloned complementary DNAs [100, 101]. This method introduces targeted mutations to achieve more precise levels of attenuation while maintaining sufficient immunogenicity. Recombinant RSV A2 cp248/404/1030/ΔSH (MEDI-559; MedImmune and National Institute of Allergy and Infectious Diseases) is a recombinant temperature-sensitive RSV with a deletion of the SH gene [102, 103]. The SH protein has been shown to decrease Th1 responses, thereby inhibiting the host antiviral response. A virus lacking the SH protein would thus impart greater immunogenicity [104]. It is the first vaccine candidate to be sufficiently attenuated for young infants (1–2 months of age). A phase 1/2a study is currently recruiting

Table 2. Respiratory Syncytial Virus Fusion Inhibitors

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>F1 interaction</th>
<th>Structure</th>
<th>Route of administration</th>
<th>Subgroup</th>
<th>Model</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMC-353121</td>
<td>Johnson &amp; Johnson/</td>
<td>Hydrophobic cavity on HR1 surface of 6HB</td>
<td>Benzimidazole derivatives</td>
<td>Inhaled or oral</td>
<td>A/B</td>
<td>Cotton rat</td>
<td>[33-35]</td>
</tr>
<tr>
<td>VP-14637</td>
<td>ViroPharma/RSVCO</td>
<td>Hydrophobic cavity on HR1 surface of 6HB; similar mechanism to TMC-353121</td>
<td>Triphenolic compound</td>
<td>Inhaled</td>
<td>A/B</td>
<td>Cotton rat/humans</td>
<td>[33, 36, 38, 77]</td>
</tr>
<tr>
<td>BMS-433771</td>
<td>Bristol-Myers Squib</td>
<td>Hydrophobic cavity on surface of HR1 trimeric coiled-coil</td>
<td>Benzimidazole derivatives</td>
<td>Oral</td>
<td>A/B</td>
<td>Cotton rat/nice</td>
<td>[38, 78]</td>
</tr>
<tr>
<td>RFI-641</td>
<td>Wyeth Research</td>
<td>Interacts with F protein in its native state</td>
<td>Disulfonated stilbene</td>
<td>Inhaled</td>
<td>A/B</td>
<td>Mice, African green monkey/humans</td>
<td>[79]</td>
</tr>
<tr>
<td>BTA9881</td>
<td>Biota Holdings/AstraZeneca</td>
<td>Inhibition of F protein assumed based on inhibition of syncytium formation</td>
<td>Imidazoisoindolone derivative</td>
<td>Oral</td>
<td>A/B</td>
<td>Rodent/humans</td>
<td>[80, 81]</td>
</tr>
</tbody>
</table>

NOTE. F1, fusion 1 protein; HR, heptad repeat; 6HB, 6-helix bundle.
healthy children between the ages of 1 and 24 months to evaluate immunogenicity, viral shedding, safety, and tolerability [39]. Other vaccine candidates under development using these attenuation strategies include recombinant RSV A2 cpts248/404/ΔNS2 and recombinant RSV A2 cpts530/1009ΔNS2, which include a deletion in the NS genes. The NS protein decreases type I interferon signaling, thus inhibiting host response [105]. Similar to SH deletions, virus lacking the NS proteins will be more immunogenic. Despite often having up to 5 mutations to protect against reversion to wild-type RSV, there is still concern regarding genetic stability with these vaccine candidates. To address this concern, highly attenuating gene deletion vaccines were developed, including ΔNS1, ΔM2–2, and ΔM2–2NS2 [106, 107]. These vaccine candidates maintained a high level of immunogenicity when evaluated in chimpanzees and induced protection after wild-type RSV challenge; further evaluation in humans is needed [106–108].

**Vector vaccines.** An alternative method for overcoming genetic instability, while maintaining immunogenicity, is through the delivery of RSV proteins using viruses with substantially greater growth and stability [95]. The vector vaccine candidate recombinant bovine/human parainfluenza virus type 3 (PIV3)/RSV F2 (MEDI-534) delivers RSV F using a bovine/human chimeric parainfluenza type 3 genome. Recombinant bovine/human PIV3/RSV F2 protected monkeys against challenge with wild-type RSV and generated high titers of RSV- and human PIV3-neutralizing antibodies [109]. Safety was demonstrated in a phase 1 study of RSV-seropositive adults; further studies are needed to determine safety and immunogenicity in children [110]. Other viruses engineered to express RSV F and/or G glycoproteins include Newcastle disease and Sendai viruses, both of which demonstrated immune protection in rodent models [111, 112].

**Subunit vaccines.** Purified RSV F, G, and M proteins have been evaluated for their potential to induce neutralizing and protective antibodies. The following subunit vaccines have advanced to clinical trials: (1) 3 RSV F subunit vaccines (purified F protein 1–3) [114, 115]; (2) a combined subunit vaccine containing F, G, and M proteins (Sanofi Pasteur) [116]; and (3) BBG2Na, a G peptide conjugated to streptococcal protein G [117]. Only modest rises in antibody titers have been observed in seropositive populations. Safety and efficacy in RSV-naive infants and young children have not been determined. Drawbacks to this vaccine approach include poor immunogenicity, immunosuppressive effects of maternally acquired antibodies, and potential for vaccine-enhanced disease.

**DRUGS TARGETING THE HOST RESPONSE TO RSV DISEASE**

Despite >50 years of RSV research, the immunopathologic features and incomplete immunity associated with infant RSV disease remain problematic in the development of effective vaccines and treatments. Novel approaches for altering the host response to RSV, rather than directly targeting the virus, are in the early stages of investigation. Some of these include MBX-300, fosfomycin, and the active metabolite of leflunomide (A77–1726). MBX-300, as previously discussed, targets the RSV G glycoprotein directly but also competes with the potent chemokine, fractalkine, for binding to CX3CR1 in host cells, resulting in reduction of the RSV-induced inflammatory response [63].

Fosfomycin is a structurally unique antibiotic shown to possess in vitro and in vivo immunomodulatory activity [118–120]. Initial studies performed in airway epithelial cells demonstrated that fosfomycin suppressed the RSV-induced transcription of RANTES [121], a chemokine shown to play an important role in RSV lung inflammation [122].

Davis et al [123] demonstrated that RSV is associated with reduced alveolar fluid clearance, a process that is crucial for efficient gas exchange in the lungs. They revealed that intranasal administration of A77–1726 to RSV-infected BALB/c mice prevents the RSV-induced decrease of alveolar fluid clearance and the onset of arterial hypoxemia [124].

**CONCLUSIONS**

Palivizumab remains perhaps the greatest advancement in RSV pharmacotherapy. Motavizumab, its more potent successor, demonstrates activity in both the upper and lower airways. Despite its pending FDA approval for RSV prevention in high-risk children, evidence suggests it may also play a role in RSV treatment [64]. Of the many RSV treatment candidates evaluated, 3 have advanced to clinical trials and remain ongoing (Table 1). The siRNA ALN-RSV01 has received a great deal of attention for its innovative mechanism of action and promising clinical data; however, safety and efficacy in infants remain to be determined.

Vaccine development has made considerable progress during the past 50 years. Recombinant RSV A2 cpts248/404/1030/ΔSH (MEDI-559) remains the first and only vaccine candidate to be tested in the target infant population since the 1960s formalin inactivated RSV trials. Its immunogenicity among infants is currently being evaluated in ongoing clinical trials. The vectored vaccine candidate, recombinant bovine/human PIV3/RSV F2, takes advantage of the substantially greater growth and stability of the human PIVs compared with RSV. Clinical studies will be needed to determine safety and immunogenicity in infants.

Lastly, it is likely that immunomodulating agents will have a significant impact on RSV disease. Although still in early, preclinical stages, immunomodulatory agents will likely play an important role in combination with direct antiviral agents.
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