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Review

Current antiviral therapies and promising drug candidates against respiratory syncytial virus infection

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ABSTRACT

Respiratory syncytial virus (RSV) is one of the most common viruses leading to lower respiratory tract infections (LRTIs) in children and elderly individuals worldwide. Although significant progress in the prevention and treatment of RSV infection was made in 2023, with two anti-RSV vaccines and one monoclonal antibody approved by the FDA, there is still a lack of postinfection therapeutic drugs in clinical practice, especially for the pediatric population. In recent years, with an increasing understanding of the pathogenic mechanisms of RSV, drugs and drug candidates, have shown great potential for clinical application. In this review, we categorize and discuss promising anti-RSV drug candidates that have been in preclinical or clinical development over the last five years.

INTRODUCTION

Respiratory syncytial virus (RSV) is a common virus that primarily infects children and elderly individuals and causes lower respiratory tract infections (LRTIs). Globally, RSV is responsible for approximately 33 million cases of acute lower respiratory tract infections each year, resulting in approximately 3.2 million hospitalizations and over 100,000 deaths among children under five years of age, particularly in developing countries (Scheltema et al., 2017; Shi et al., 2017). In elderly individuals and those with chronic health conditions, RSV can lead to severe respiratory illness and exacerbate existing conditions, contributing significantly to hospitalizations and mortality (Falsey et al., 2005). The high burden of disease highlights the critical need for effective preventive and therapeutic measures.

Clinical interventions for RSV can be classified into three categories: vaccines, monoclonal antibodies (mAbs), and small-molecule compounds. In 2023, two RSV vaccines (Abrysvo by Pfizer and Arexvy by GSK) were approved by the FDA respectively for individuals aged 60 years and older to prevent lower respiratory tract disease caused by RSV and for pregnant women to prevent RSV in babies from birth through 6 months of age (Fleming-Dutra et al., 2023; Melgar et al., 2023). For the pediatric population, monoclonal antibodies represent promising prophylactic treatments for RSV infection; notable examples include nirsevimab, which was approved by the FDA in July 2023 (Jones et al., 2023). Ribavirin is currently the only small molecule drug in clinical use for the treatment of severe RSV infection. However, its high cost, potential toxicity and limited efficacy have restricted its use (Fearns and Deval, 2016). Therefore, there is still an urgent need for new, efficient, and affordable drugs, especially in postinfection therapies, to combat RSV infection.

In this review, we categorize and discuss the anti-RSV drugs that have entered clinical development as well as some promising candidates that are expected to enter clinical development in the near future.

DRUGS THAT INHIBIT THE ENTRY PROCESS OF RSV

The RSV entry process consists of two main steps: attachment and fusion, which are mediated by the RSV glycoprotein (G) and fusion protein (F) (Fig. 1). Viral attachment is primarily mediated by the binding of the G protein to heparan sulfate proteoglycans (HSPGs) (Feldman et al., 1999) and C-X3-C motif chemokine receptor 1 (CX3CR1) (Tripp et al., 2001) on the cell surface. The F protein also contributes to attachment partially by interacting with intercellular adhesion molecule 1 (ICAM1) (Behera et al., 2001), epidermal growth factor receptor (EGFR) (Currier et al., 2016),

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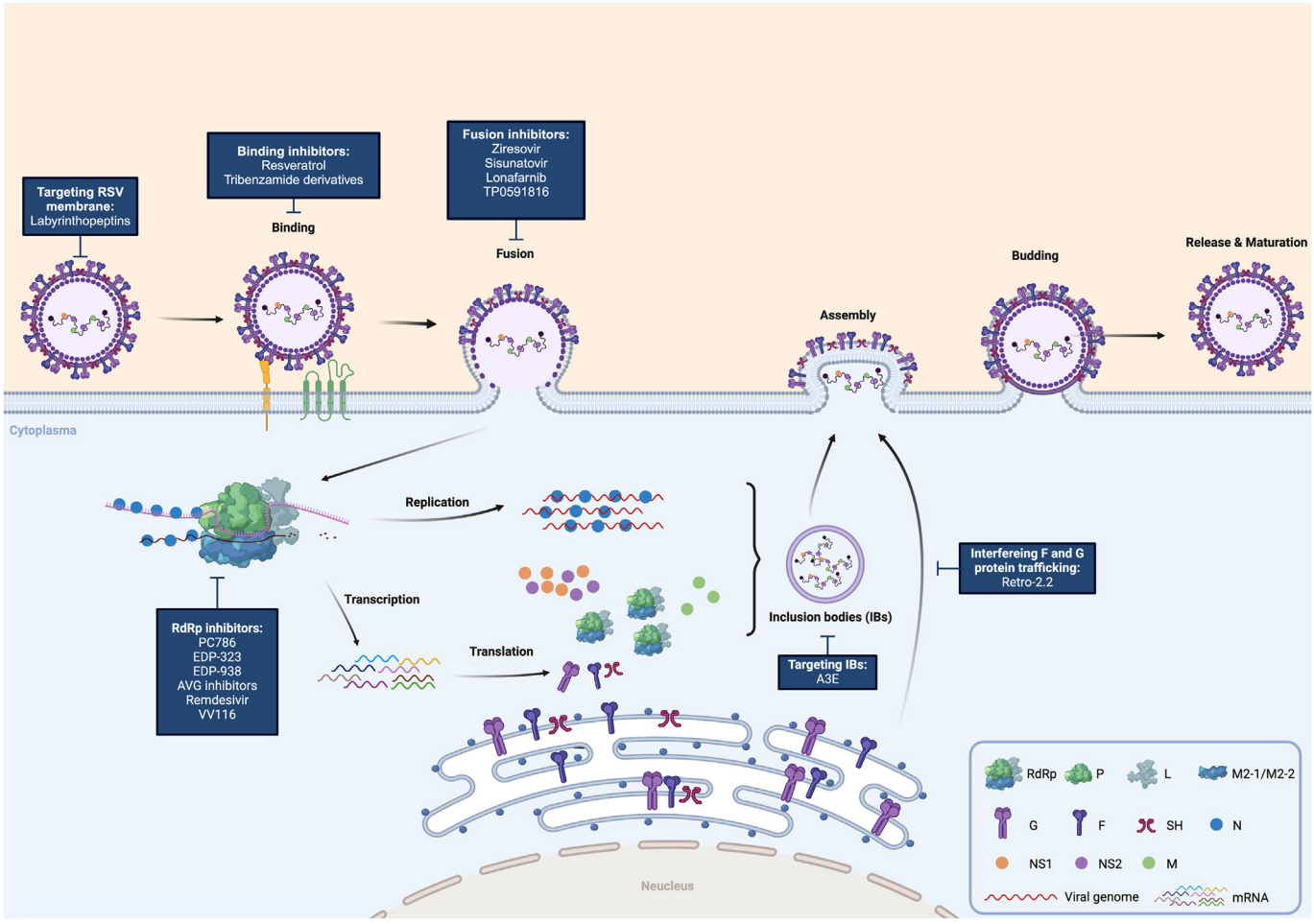


Fig. 1. The life cycle of RSV and the indication of drugs targets different steps of RSV life cycle. Adapted from Fig. 1 in reference (Hu et al., 2020). Created in https://BioRender.com. Agreement number: IY27JWMIPF.

and nucleolin (Tayyari et al., 2011). Following successful attachment, fusion is mediated by the F protein, which undergoes a conformational change from its prefusion to postfusion form, allowing viral RNA entry into the host cell cytoplasm (Walsh and Hruska, 1983; Mclellan et al., 2013). In addition to fusing their envelope directly with the plasma membrane, RSV has been reported to enter host cells via macropinocytosis. The RSV G protein can activate ATPase Na^+/K^+ transporting subunit alpha 1 (ATP1A1) signaling, which subsequently triggers the transactivation of EGFR. The EGFR activation leads to downstream signaling events that cause actin rearrangement and membrane ruffling. These dynamic membrane extensions engulf extracellular fluid and RSV particles, forming large vesicles known as macropinosomes. RSV presumably remains in its enveloped form within the macropinosomes, where fusion occurs, facilitating entry into the host cell.

The clinical interventions used to prevent viral entry fall into three categories: monoclonal antibodies, small-molecule compounds and vaccines. In this section, we review several promising monoclonal antibodies (Table 1) and small-molecule compounds that interfere with RSV entry (Table 2).

Monoclonal antibodies

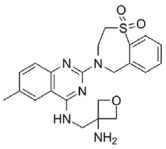
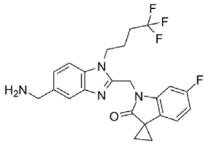
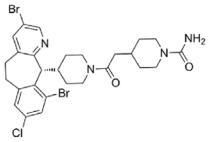
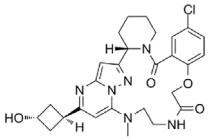
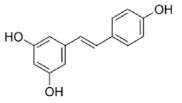
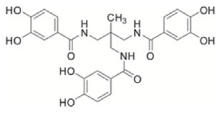
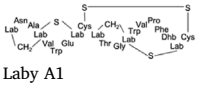
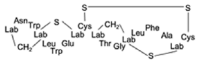
Nirsevimab (MEDI8897)

Nirsevimab, a highly potent monoclonal antibody, was developed by MedImmune LLC as a potential RSV vaccine surrogate. The antibody was optimized from the parent antibody D25, which was identified from a panel of anti-RSV IgG1 mAbs selected from the memory B cells of human donors. Nirsevimab works by targeting a highly conserved epitope on the prefusion form of the RSV F protein (Wilkins et al., 2023). Crystallographic analysis revealed that nirsevimab binds to the prefusion conformation of the RSV F protein from both subtypes A and B. This binding involves extensive interactions with the F1 and F2 subunits, blocking the conformational change necessary for viral entry into host cells.

Table 1
Current anti-RSV monoclonal antibodies under clinical development.

mAbs	Target	Clinical Development	References
Nirsevimab (MEDI8897)	Site Ø	Approved in 2023	Hammitt et al. (2022); Drysdale et al. (2023); Jones et al. (2023); Wilkins et al. (2023)
Clesrovimab (MK-1654)	Site IV	Phase III	Tang et al. (2019); Maas et al. (2021)
RSM01	Site Ø	Phase I	Levi et al. (2023)
Palivizumab	Site II	Approved in 1998	Johnson et al. (1997)
TNM001	Unknown	Phase IIb/III	NA

Table 2
Small-molecule compounds inhibit RSV entry.

Compounds	Chemical structure	Target	Mode of action	Clinical development	References
Ziresovir (RO-0529, AK0529)		F protein	Targeting the RSV F protein by binding to its heptad repeat C (HRC) region	NDA in China	Zheng et al. (2019)
Sisunatovir (RV521)		F protein	Targeting a central region created by the trimeric structure of the F protein	Phase 2a	Devincenzo et al. (2020); Cockerill et al. (2021)
Lonafarnib		F protein	Binding within the central cavity of the prefusion F protein trimer	NA	Sake et al. (2024)
TP0591816		F protein	Inhibiting the function of F protein	NA	Yoshida et al. (2020)
Resveratrol		HSPGs	Competing to bindthe HSPGs with RSV	NA	Filardo et al. (2020); Xiong et al. (2024)
Tribenzamide derivatives compound 2f		RSV virion	Inhibiting the binding of virions to cells	NA	Issmail et al. (2023)
Labyrinthopeptins	 Laby A1  Laby A2	RSV membrane	Interacting with phosphatidylethanolamine in the viral membrane, disrupting the integrity of virus particles	NA	Ferir et al. (2013); Blockus et al. (2020)

*Lab, Dhb and Dha are the abbreviations of the unusual amino acids labionin, didehydrobutyrine and didehydroalanine.

In a phase IIIb randomized open-label study (HARMONIE, Clinicaltrials.gov Identifier: NCT05437510) (Drysdale et al., 2023), nirsevimab significantly reduced the incidence of RSV-related hospitalizations in infants by 83% and the incidence of severe RSV-related LRTIs by 75.1%. In another phase III randomized, double-blind, placebo-controlled study (MELODY, ClinicalTrials.gov Identifier: NCT03979313) (Hammitt et al., 2022), nirsevimab significantly reduced the incidence of medically attended RSV LRTIs by 74.5%, hospitalizations due to severe RSV-related LRTIs by 75.1%, and overall all-cause LRTI hospitalization rates by 58.04% compared with those of the placebo group.

Owing to the outstanding performance of nirsevimab in phase III clinical trials, the FDA granted approval to Beyfortus (nirsevimab-alip) in July 2023 for the preventing of lower respiratory tract disease caused by RSV in neonates and infants who are either born during or entering their first RSV season. Additionally, this approval extends to children up to 24 months old who are still at risk for severe RSV disease during their second RSV season (Jones et al., 2023).

Clesrovimab (MK-1654)

Merck isolated the antibody RB1 from human memory B cells of adults with potent neutralization effects against a wide range of RSV A and B clinical isolates. RB1 targets a highly conserved epitope in antigenic site IV of the RSV F protein. MK-1654 was optimized from RB1 by introducing YTE mutations in the Fc region (Tang et al., 2019).

In a phase IIa double-blind, randomized, placebo-controlled study (ClinicalTrials.gov Identifier: NCT04086472) (Maas et al., 2021), 80 participants aged from 18 to 55 years were given either a placebo or one of four doses of MK-1654 (100 mg, 200 mg, 300 mg, 900 mg) via intravenous infusion 29 days prior to inoculation with 4 log10 PFU RSV A Memphis 37b. The viral load, area under the curve (VL-AUC), and incidence of symptomatic RSV infection decreased with increasing doses of MK-1654 up to 200 mg, but no further decrease was observed at higher doses. There were no serious adverse events or dose-dependent patterns of adverse events in the MK-1654-treated subjects.

Currently, a phase IIb/III trial (ClinicalTrials.gov Identifier: NCT04767373) was completed on 9 July 2024, though its results have not yet been published. Additionally, a Phase III trial (ClinicalTrials.gov Identifier: NCT04938830) is ongoing, with an expected completion date of 27 October 2025. Both trials aim to evaluate the efficacy and safety of clesrovimab in pediatric populations (up to 1 year old).

RSM01

RSM01 is a fully human IgG1 monoclonal antibody developed by the Bill & Melinda Gates Medical Research Institute (Levi Micha and White Joleen, 2022). It targets the antigenic site Ø of the prefusion F protein. A phase I clinical trial (ClinicalTrials.gov Identifier: NCT05118386) (Levi et al., 2023) for RSM01 showed that it was well tolerated in healthy adults, with no serious adverse events. The pharmacokinetics revealed a

median time to a maximum concentration of 6–7 days postintramuscular (IM) injection, dose-proportional increases in the maximum concentration and AUC, and a terminal half-life of approximately 79 days. This study also used population pharmacokinetics modeling to predict that a 50 mg IM dose would achieve effective concentrations in infants, supporting its potential for once-per-season dosing to prevent RSV.

Other mAbs against RSV

Palivizumab is the first FDA-approved humanized monoclonal antibody that targets a conserved epitope in antigenic site II of the F protein (Johnson et al., 1997). However, its use in clinical settings is limited because of the need for repeated injections, high cost, and uncertain efficacy. Another RSV-F protein mAb, TNM001, developed by Trinomab, is under clinical development and has reached phase IIb/III trials (ClinicalTrials.gov Identifier: NCT06083623). However, no data are available on this mAb.

Fusion inhibitors

Ziresovir (RO-0529, AK0529)

Ziresovir is a potent, selective and orally bioavailable RSV F protein inhibitor. It was modified and optimized from a lead compound from the benzoazepine quinoline (BAQ) series discovered from a high-throughput screen hit (Zheng et al., 2019). Ziresovir targets the RSV F protein by binding to the heptad repeat C (HRC) region. Resistance selection generates strains that carry mutations D486 N, D489A, D489V and D489Y in the F protein's HRC region. Ziresovir showed high potency, with an EC_{50} of 0.02–0.04 μM in the CPE assay, against both laboratory strains of RSV (Long, A2 and B18537) and clinical RSV strains. *In vivo* studies, female BALB/c mice were orally administered 12.5 mg/kg or 50 mg/kg RSV twice a day for 4 consecutive days after RSV inoculation. The viral titers in the lungs of the mice that received 12.5 mg or 50 mg/kg were reduced by more than 1 log10 and 1.9 log10 units, respectively.

In the latest phase III trial (AirFLO Study, Clinical: NCT04231968), ziresovir met the primary endpoint of reducing signs and symptoms scores and the key secondary endpoint of reducing the viral load. Compared with the placebo, the drug showed rapid onset of clinical effects, with a 30% additional reduction in signs and symptoms scores and a 77% additional reduction in the viral load. The safety profile of ziresovir is excellent, supporting its potential for regulatory approval and use in clinical settings. In December 2022, China's National Medical Products Administration (NMPA) accepted and granted a Priority Review to the New Drug Application (NDA) for the clinical use of ziresovir in treating RSV infection.

Sisunatovir (RV521)

RV521 was identified through a lead optimization process that began with hit compounds from a physical property-directed profiling exercise conducted at Reviral (Cockerill et al., 2021). RV521 targets a central region created by the trimeric structure of the F protein. Key interactions include π-bonding with phenylalanine residues (Phe140 and Phe488) from two different monomers and a hydrogen bond with the backbone carbonyl of threonine 397 from the third monomer. Additionally, the aminomethylene group of RV521 closely interacts with Asp489, indicating the necessity of a basic group in the structure of the inhibitor. *In vitro*, RV521 had a mean IC_{50} of 1.2 nM against a range of RSV A and B laboratory strains and clinical isolates. *In vivo* studies using a BALB/c mouse model of RSV infection demonstrated significant reductions in lung viral titers with RV521 treatment. Doses of 50 mg/kg resulted in a 98% reduction in viral titers, confirming the drug's potent antiviral activity in a preclinical setting.

In a randomized, double-blind, placebo-controlled phase IIa trial (ClinicalTrials.gov Identifier: NCT03258502) (Devincenzo et al., 2020), 66 healthy adult participants were inoculated with RSV-A Memphis-37b and randomly assigned to receive either 200 mg or 350 mg of RV521 or a placebo twice daily for 5 days. The results for the viral load demonstrated 63.05% and 55.25% reductions for the 350 mg and 200 mg doses, respectively. In addition, compared with the placebo, RV521 significantly reduced the total symptom score and nasal mucus weight. The treatment was well tolerated, and no treatment-related serious adverse events were reported. Pharmacokinetic assessments revealed that RV521 plasma concentrations reached the target trough levels necessary for efficacy.

However, a multicenter, 3-part, phase II study in infants hospitalized due to RSV LRTIs (REVIRAL 1, ClinicalTrials.gov Identifier: NCT04225897) was terminated owing to strategic considerations. Another phase II study (ClinicalTrials.gov Identifier: NCT04267822) for the treatment of adult subjects who had undergone hematopoietic cell transplantation with RSV-related URTIs has been terminated for unknown reasons.

Lonafarnib

Lonafarnib was identified as a potential RSV inhibitor through a drug repurposing screen using the ReFRAME library of 12,000 molecules (Sake et al., 2024). It has emerged as one of the top candidates, significantly reducing RSV infection without notable cytotoxicity. Lonafarnib was tested against recent clinical RSV subtype A and B strains and has demonstrated broad-spectrum antiviral activity. The IC_{50} values ranged from 10 to 118 nM. In a mouse model of RSV infection, the oral administration of lonafarnib at 60 mg/kg demonstrated significant antiviral efficacy (a 50–80% reduction in RSV RNA levels). Lonafarnib-treated mice experienced less weight loss. Histological analysis revealed fewer cellular infiltrates in the lung tissue of the dosed animals.

Lonafarnib effectively suppressed RSV-induced syncytium formation in infected cells. Long-term exposure to lonafarnib resulted in the accumulation of specific resistance mutations (T335I and T400A) in the RSV F protein. These mutants conferred resistance to lonafarnib and two other known F protein inhibitors (presatovir and BMS-433771). Cocrystallization of the RSV F protein with lonafarnib revealed that lonafarnib binds within the central cavity of the prefusion F protein trimer. This binding site overlaps with the hydrophobic pocket used by other fusion inhibitors, with key interactions involving the aromatic side chains of F137, F140, and F488 located in the fusion peptide and the heptad repeats adjacent to the viral transmembrane region, respectively.

TP0591816

The antiviral activity of TP0591816 was initially evaluated using the XTT assay in HEp-2 cells infected with RSV strains, including wild-type and mutant strains resistant to known fusion inhibitors (Yoshida et al., 2020). The results revealed potent antiviral activity against RSV A2 (EC_{50} = 0.255 nM) and RSV 18537 (EC_{50} = 0.0824). In a mouse model of RSV infection, TP0591816 was administered subcutaneously 1 h before RSV inoculation at doses of 1 mg/kg, 10 mg/kg, and 100 mg/kg. The treatment resulted in a dose-dependent reduction in lung virus titers, with decreases of 0.72 log10, 0.92 log10, and 2.04 log10, respectively, compared with those of the vehicle control. Additionally, TP0591816 treatment led to a decrease in lung weight, indicating reduced inflammation and lung pathology.

The anti-RSV effect of TP0591816 is primarily due to its ability to inhibit the F protein. Syncytium formation assays revealed that TP0591816 effectively blocked the cell-cell fusion mediated by the RSV F protein. When RSV was serially passaged with increasing inhibitor concentrations, a TP0591816-resistant virus strain was obtained that carried the L141F mutation in the F protein. Collectively, these experiments indicate that TP0591816 specifically targets the RSV F protein.

Other promising entry inhibitors of RSV

Resveratrol

Resveratrol, a natural compound known for its antioxidant, anti-inflammatory, and antimicrobial properties, is a therapeutic agent against respiratory viral infections, including influenza virus, RSV, and coronaviruses (Filardo et al., 2020). In a recent study, resveratrol was shown to target early stages of the RSV life cycle, particularly viral attachment to host cells. Competitive binding assays revealed that the antiviral activity of resveratrol was compromised in the presence of soluble heparin or after the enzymatic removal of HSPGs from host cells, indicating that resveratrol interacts with HSPGs (Xiong et al., 2024).

Tribenzamide derivatives

The antiviral potential of compound 2f was identified through screening different caffeoylquinic acid (CQA) derivatives for their ability to inhibit RSV infection in HEp-2 cells (Issmail et al., 2023). Compound 2f emerged as a promising candidate due to its potent inhibitory activity against both RSV-A and RSV-B strains, with IC_{50} values of 35 nM, 44 nM and 5.4 μM against RSV-A2, RSV-Long and RSV-B strains, respectively, with no detectable cytotoxic effects at concentrations up to 100 μM during a 48 h treatment period. Compound 2f also showed potent antiviral efficacy *in vivo* when it was administered either prophylactically or simultaneously with RSV infection. In a pre-exposure prophylaxis regimen, mice treated with 15 mg/kg of compound 2f or the vehicle control presented a significant reduction in the viral burden in lung tissues of 0.5 log10 and a reduction of 0.87 log10 in the amount of viral RNA in the BALF compared with those in the control group. When compound 2f was mixed with active RSV and inoculated intranasally, a significant reduction of 2.6 log10 in the lung viral load was observed compared with that in the sham-treated group. Therefore, it can be inferred that the antiviral activity of 2f is directed against the virion itself rather than the host cell. Further studies indicated that when 2f was washed out before infection, its antiviral activity was completely lost, suggesting that it needs to be present during the initial interaction between the virus and the host cell to be effective.

Labyrinthopeptins

Labyrinthopeptins were screened in a cell-based assay from a small library of natural products with proven biological activity (Blockus et al., 2020). Laby A1 and A2, class III lanthipeptides isolated from *Actinomadura namibiensis* DSM6313, demonstrated potent antiviral activity, with IC_{50} values of 0.39 μM for Laby A1 and 4.97 μM for Laby A2. The CC_{50} for Laby A1 was 79 μM, and for Laby A2, it was not determined due to its limited solubility above 100 μM. These compounds showed potent efficacy against multiple RSV strains. To establish a mouse model of rHRSV-A-Luc infection, the mice were intranasally dosed with 30 μL of 2 mg/mL Laby A1/A2 or the solvent control every 24 h for 8 days. Treated mice presented a significant reduction in the luminescence signal intensity in the noses of treated mice, indicating lower viral loads. However, no significant reduction in viral load was observed in the lungs, likely due to poor delivery of the compounds to the lower respiratory tract. Time-of-addition experiments revealed that Laby A1/A2 inhibited RSV infection only when RSV was present during virus inoculation, indicating its role as an entry inhibitor. Preincubation of RSV particles with Laby A1/A2 significantly reduced virus infectivity. Further studies indicated that Laby A1/A2 interact with phosphatidylethanolamine in the viral membrane, disrupting the integrity of virus particles. Importantly, these compounds remained effective against RSV strains with mutations conferring resistance to other entry inhibitors, such as palivizumab and BMS-433771, suggesting a unique mode of action that is not compromised by known resistance mutations.

DRUGS THAT TARGET RSV AFTER ENTRY

Upon entering the host cell cytoplasm, RSV undergoes key steps involving transcription and replication (Fig. 1). The polymerase complex (N, P, and L proteins) transcribes the negative-sense RNA genome into mRNA, which is translated into viral proteins. The *M2* gene encodes M2-1, which enhances transcription, and M2-2, which regulates the switch to replication (Gilman et al., 2019). The polymerase then produces a full-length positive-sense genome (antigenome) as an intermediate, which templates new negative-sense genomes. These genomes are encapsulated by the N protein into a helical ribonucleocapsid (RNP), which is essential for subsequent RNA synthesis and new viral particle production, which later assemble and bud from the host cell, continuing the infection cycle (Hu et al., 2020). In this section, we review promising post-entry drug candidates for RSV, with a focus on polymerase inhibitors (Table 3).

Replication inhibitor

PC786

PC786, a potent nonnucleoside inhibitor of the RSV L protein (Coates et al., 2017), exhibited strong antiviral activity against both RSV-A and RSV-B, with IC_{50} values ranging from 0.09 to 0.71 nM for RSV-A and from 1.3 to 50.6 nM for RSV-B. *In vivo*, once-daily administration of 2 mg/mL RSV resulted in undetectable viral loads in RSV-infected BALB/c mice, and in a cotton rat model, intranasal treatment at concentrations greater than 3.3 mg/mL reduced the lung viral load to below the detection limits. Interestingly, it has shown high potency for late therapeutic intervention in a human airway epithelium model (Brookes et al., 2018). Administration of PC786 (700 nM) beginning on day 3 postinoculation reduced the viral load to below detectable limits by day 6. The IC_{50} for viral load reduction from day 3 to day 10 was 154 nM. PC786 primarily inhibits the replication and transcription activities of the RSV polymerase. It potently inhibited RSV RNA-dependent RNA polymerase (RdRp) activity, with an IC_{50} of 2.1 nM and an IC_{90} of 21.8 nM. A resistant strain with a Y1631H mutation in the L protein identified through RSV passaging under increasing drug concentrations presented a 660-fold reduction in sensitivity, confirming that the RSV L protein is the target of PC786.

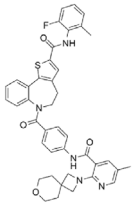
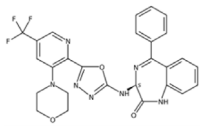
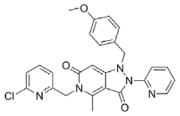
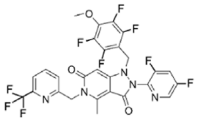
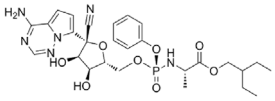
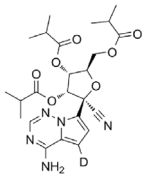
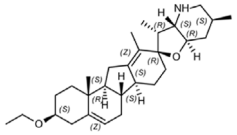
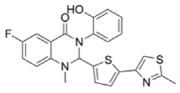
In a randomized, double-blind, placebo-controlled phase 1b/2a trial on healthy male and nonpregnant female subjects aged 18–55 years (ClinicalTrials.gov Identifier: NCT03382431) (Devincenzo et al., 2022), compared with the placebo, nebulized PC786 was found to be safe and effective at reducing the RSV viral load by 32%–34%, score of symptom and weight of mucus.

EDP-323

EDP-323 is an orally administered small molecule that inhibits the RSV L protein by binding to the capping domain of the L protein (Rhodin et al., 2022). The antiviral activity of EDP-323 was tested against several RSV-A and RSV-B strains, including clinical isolates. EDP-323 demonstrated potent antiviral activity, with EC_{50} values ranging from 0.11 to 0.44 nM across different RSV strains and cell lines. The EC_{90} values were fairly low, highlighting the high potency of the compound (e.g., an EC_{90} of 0.52 nM in HEp-2 cells against the RSV-A Long strain). EDP-323 was administered both prophylactically and therapeutically to RSV-infected mice to evaluate the *in vivo* efficacy of EDP-323 (Levene et al., 2022). Compared with vehicle, EDP-323 (400 mg/kg) significantly reduced live virus titers and viral RNA levels. In addition, the treated mice presented lower levels of inflammatory cytokines and less lung tissue damage.

So far, a phase I (ClinicalTrials.gov Identifier: NCT05587478) (Mills et al., 2023), randomized, double-blind, placebo-controlled study has been completed. The safety, tolerability, and pharmacokinetics of

Table 3
Small-molecule compounds targeting the postentry steps of RSV.

Compounds	Chemical structure	Target	Mode of action	Clinical development	References
PC786		L protein	Inhibiting the RSV polymerase function	Phase 1b/2a	Coates et al. (2017); Brookes et al. (2018); Devincenzo et al. (2022)
EDP-323	NA	L protein	Inhibiting the RSV L protein by binding to the capping domain of the L protein	Phase 2a	Levene et al. (2022); Rhodin et al. (2022)
EDP-938		N protein	Inhibits RSV primary transcription and/or processes prior to onset of primary transcription	Phase 2b	Rhodin et al. (2021); Ahmad et al. (2022)
AVG inhibitor	 AVG-233  AVG-388	L protein	Locking the polymerase in an initiation conformation, preventing the necessary structural reorganization for RNA elongation	NA	Cox et al. (2018); Sourimant et al. (2022)
Remdesivir		RdRp	Incorporating into the viral RNA chain and causing premature termination of RNA synthesis	NA	Mackman et al. (2021)
VV116		RdRp	Similar mode of action of remdesivir	NA	Zhang et al. (2022)
A3E		M2-1	Hardening IBs and preventing the formation of functional sub-compartments within the IBs	NA	Bailly et al. (2016); Risso-Ballester et al. (2021)
Retro-2.2		Syn5 and Sec16A	Disrupting the trafficking of hRSV F and G glycoproteins to the plasma membrane	NA	Le Rouzic et al. (2023)

EDP-323 were assessed in healthy adult subjects (aged from 18 to 60 years). The results indicated that EDP-323 was well tolerated at doses up to 800 mg once daily for 7 days. Pharmacokinetic analysis revealed that EDP-323 was rapidly absorbed and supported once-daily dosing. Enanta Pharmaceuticals is currently recruiting for a randomized, phase IIa (ClinicalTrials.gov Identifier: NCT06170242), double-blind, placebo-controlled study to evaluate the safety, pharmacokinetics and antiviral activity of multiple doses of orally administered EDP-323 against respiratory syncytial virus infection on adult population (aged from 18 to 60 years).

AVG compounds

AVG-233 was a lead compound from a high-throughput screening of a 57,000-compound library designed to find inhibitors of the RSV RdRp complex (Cox et al., 2018). *In vitro* experiments demonstrated that AVG-233 exhibited nanomolar activity against both laboratory-adapted and clinical RSV strains, with a promising selectivity index [SI = 50% cytotoxic concentration (CC_{50})/half-maximal effective concentration (EC_{50})] > 1660. Despite its predicted oral bioavailability in mice, the *in vivo* efficacy of AVG-233 was initially disappointing. However, further optimization led to the identification of AVG-388, which demonstrated potent antiviral efficacy in the RSV mouse model when administered orally (Sourimant et al., 2022). The optimized compound AVG-388 resulted in a reduction of 1.9 log10 $TCID_{50}$/mL in the lung viral load at a dose of 150 mg/kg twice daily without any adverse effects.

AVG compounds likely interfere with the polymerase initiation process. The docking pose of AVG-233 at the interface of the L protein's capping, connecting, and methyltransferase (MTase) domains suggests that it locks the polymerase in an initiation conformation, preventing the necessary structural reorganization for RNA elongation (Sourimant et al., 2022).

Remdesivir and its derivatives VV116

Remdesivir is a nucleotide analog prodrug with broad-spectrum antiviral activity against a range of viruses, including filoviruses,

coronaviruses, paramyxoviruses, Ebola virus, and Nipah virus (Warren et al., 2016; Lo et al., 2017, 2019). Upon entering cells, it undergoes metabolic activation to form the active triphosphate metabolite (1-NTP). This metabolite mimics adenosine triphosphate (ATP) and competes with natural substrates for incorporation into the viral RNA chain by RdRp. Once incorporated, it causes premature termination of RNA synthesis, effectively inhibiting viral replication (Mackman et al., 2021). Prodrug exploration led to the discovery of remdesivir as a potent RSV replication inhibitor (Mackman et al., 2021). Remdesivir demonstrated an EC_{50} of 0.015 μM against RSV in HEp-2 cells. In an African green monkey model of RSV infection, prophylactic IV administration of remdesivir at 10 mg/kg resulted in a greater than 2 log10 reduction in the peak lung viral load, indicating significant antiviral efficacy.

In addition to remdesivir, its derivative VV116 also potently inhibits RSV. VV116 is an oral derivative of remdesivir (RDV) that was developed to overcome the extensive hepatic first-pass effect of RDV, limiting its intravenous administration. The anti-SARS-CoV-2 efficacy of VV116 was initially investigated (Xie et al., 2021). These promising results led to further studies on its potential against RSV (Zhang et al., 2022). VV116 had an EC_{50} of 1.20 ± 0.32 μM against RSV in A549 cells. *In vivo*, the low dose of VV116 (25 mg/kg) had antiviral effects comparable to those of 100 mg/kg ribavirin, reducing the number of viral RNA copies and infectious titers by ~1.5 log10 and ~2.0 log10, respectively. The medium dose (50 mg/kg) of VV116 resulted in greater activity, decreasing virus titers below the detection limit. Histopathological analysis of lung tissues from treated mice revealed that VV116 significantly reduced lung inflammation and injury compared with those in the vehicle-treated group.

Other promising drug functions in the post-entry phase

Retro-2.2

Retro-2.2 is an optimized derivative of Retro-2 that was identified as an inhibitor of the toxin ricin. Retro-2 and its optimized derivative, Retro-2.1, have demonstrated antiviral activities against various viruses, including polyomaviruses, papillomaviruses, Ebola and Marburg viruses, and SARS-CoV-2 (Nelson et al., 2013; Sivan et al., 2016; Shtanko et al., 2018; Holwerda et al., 2020). The development of Retro-2.2 was aimed to increase the efficacy of Retro-2.1, resulting in a molecule that is twice as effective as Retro-2.1 against Shiga toxins. Retro-2.2 effectively inhibits hRSV replication in HEp-2 cells, with an IC_{50} of approximately 1.6 μM (Le Rouzic et al., 2023). The compound does not affect early virus entry stages. Treatment with Retro-2.2 at 2 μM induced a log10 decrease in the viral titer and reduced plaque size, indicating an impairment in progeny virion release and syncytia formation.

Retro-2.2 impacts the cellular retrograde transport pathway by downregulating Syntaxin-5 (Syn5), a SNARE protein involved in cellular retrograde transport that potentially affects Sec16A, which is involved in the endoplasmic reticulum secretion pathway. This mechanism potentially disrupts the trafficking of hRSV F and G glycoproteins to the plasma membrane. By inhibiting the proper localization of these proteins, Retro-2.2 prevents the formation of functional viral particles and syncytia, effectively reducing viral replication and spread.

Cyclopamine (CPM) analogs with modified A-ring structures

CPM, a known Smoothened receptor (Smo) antagonist, was identified as a potent inhibitor of RSV replication (Bailly et al., 2016). To avoid unwanted hedgehog (HH) pathway signaling antagonism, CPM analogs with modified A-ring structures (A3E, A3M, A3P) were designed to reduce this activity while enhancing the RSV inhibitory effect (Risso-Ballester et al., 2021). Among these modified drugs, A3E results in nearly complete loss of HH activity ($IC_{50} > 20$ μM in SHH reporter assays) and has potent *in vitro* efficacy ($IC_{50} = 1.0 \pm 0.34$ μM) against RSV *in vitro*. In a mouse model of RSV infection, the intraperitoneal injection of 5 mg/kg, 15 mg/kg or 30 mg/kg A3E resulted in a significant, dose-dependent reduction in RSV replication (50%–75%) in the lungs. In addition, compared with control mice, treated mice presented reduced lung inflammation and improved histopathological scores.

The mode of action of the drug involves targeting the biomolecular condensates formed by RSV, known as inclusion bodies (IBs). These IBs, which are essential for viral replication, are liquid-like structures formed through liquid-liquid phase separation (LLPS) (Hu et al., 2020). CPM and its analog A3E disorganize and harden these IBs, disrupting their function. The compounds act directly on the liquid properties of the IBs, preventing the formation of functional subcompartments within the IBs, such as IB-associated granules. This hardening effect is likely mediated by targeting the RSV transcription factor M2-1, since a specific mutation (R151K) in M2-1 confers resistance to these compounds.

EDP-938

EDP-938 was identified through a series of chemical optimizations based on 1,4-benzodiazepine inhibitors of RSV (Rhodin et al., 2021). EDP-938 was effective against multiple RSV-A and RSV-B strains, with EC_{50} values ranging from 28 to 72 nM for CPE inhibition and from 54 to 110 nM for viral load reduction in various cell lines, including HEp-2, A549, Vero, and BHK cells. In RSV-infected african green monkeys, the oral administration of EDP-938 at 100 mg/kg twice daily resulted in a significant reduction in the viral load. EDP-938 led to a 4 log10 reduction to below the detection limit (100 copies/mL) in both bronchoalveolar lavage at 5 dpi and nasopharyngeal swabs at 7 dpi, whereas the viral titer peaked in the vehicle control group at 5 dpi. With respect to the mode of action of EDP-938, it mainly targets the RSV N protein. Mutations in the N protein, particularly at residues M109 and I129, are associated with resistance. RSV N is a multifunctional protein that plays a crucial role in viral RNA synthesis, encapsidation, and interactions with both viral and host proteins (Hu et al., 2020). However, the precise mechanisms by which EDP-938 interferes with the functions of the N protein remain to be further elucidated.

A phase IIa, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov Identifier: NCT03691623) (Ahmad et al., 2022) evaluated the efficacy and safety of EDP-938 on adult population (aged from 18 to 55 years). In Part 1, a total of 115 participants received 600 mg once daily, 300 mg twice daily after a 500 mg loading dose, or placebo. In Part 2, 63 participants received 300 mg once daily after a 600 mg loading dose, 200 mg twice daily after a 400 mg loading dose, or placebo. Both groups presented significant reductions in the RSV viral load (72.5%–80.2%) and total symptom score (62.0%–79.3%) with EDP-938 compared with the placebo group. In another phase IIa trial (ClinicalTrials.gov Identifier: NCT04196101), participants aged from 18 to 75 years receiving 800 mg once daily for 5 days and experienced a significant reduction in the RSV load and symptoms. The mean viral load AUC was 37.00 days × log10 copies/mL for the EDP-938 group compared with 46.96 for the placebo group. Symptom severity was also lower, with a greater percentage of participants achieving undetectable viral loads by day 5 (16.7% for EDP-938 vs. 6.3% for placebo). Currently, two others phase II trails are recruiting. While one phase II trial (ClinicalTrials.gov Identifier: NCT04816721) aims to evaluate safety, tolerability, pharmacokinetics, clinical outcome and antiviral activity on hospitalized and non-hospitalized children aged from 28 days to 36 months, the other phase IIb trial (ClinicalTrials.gov Identifier: NCT05568706) aims to evaluate the its efficacy and safety in non-hospitalized adults with acute respiratory syncytial virus infection who are at high risk for complications.

CONCLUSIONS AND PERSPECTIVE

RSV remains the most common viral pathogen responsible for LTRIs in both children and the elderly. Despite significant research efforts, there are still limited interventions available against RSV infection. Fortunately, the advancements in understanding the structure of RSV proteins and the pathogenic mechanisms of RSV have paved the way for the development of new RSV inhibitors.

To date, under developing anti-RSV therapeutics have predominantly focused on inhibiting the establishment of infection (pre-entry phase) and viral replication (post-entry). Selected targets largely concentrate on structural proteins which are directly responsible for the viral life cycle. For drug development aimed at blocking RSV entry, the F protein has been a major target due to its well-characterized structure and its primary role as a neutralization determinant. For post-entry phases, the RdRp complex which is essential for RSV transcription and replication, has been the main target. However, the non-structural proteins (NS), NS1 and NS2 are often overlooked in drug development. They do not play direct roles in RSV structure or replication but are critical in suppressing host antiviral responses, which helps establish the infection and facilitate the replication. By antagonizing interferon pathways, dampening adaptive immunity and apoptotic mechanisms, NS1/2 contribute substantially to RSV's capacity to evade immune detection. Exploring the potential of such immune modulatory viral proteins may open new avenues for therapeutic strategies targeting RSV infection.

It is worth noting that most current antiviral drugs are designed to target viral proteins; however, the high mutation rate of viral genomes remains a significant challenge, leading to the frequent emergence of drug-resistant strains. As an RNA virus, RSV is particularly prone to mutations due to its high error rate in genome replication and the lack of proofreading mechanisms in its polymerase. Consequently, antiviral drugs targeting RSV proteins also face the issue of resistance development. Over the long run of human evolution, an ongoing "arms race" between humans and viruses has imprinted "genetic markers" in the human genome that can impact the viral life cycle. The proteins encoded by these "genetic markers" play critical roles in either inhibiting or facilitating viral infection and replication. Unlike viral genes, human genes have a much lower mutation rate, making essential host proteins involved in viral replication promising targets for antiviral drug development with a reduced risk of resistance. Designing drug targeting these host proteins could offer a potential pathway for long-term, resistance-mitigated antiviral therapies.

Furthermore, most current efforts in anti-RSV therapeutic development primarily aim at directly inhibiting viral entry or replication. However, viral load is not the sole determinant of RSV disease severity. Some clinical studies have reported conflicting results regarding the correlation between RSV viral load and disease severity, indicating that other factors are undoubtedly involved (El Saleeby et al., 2011; Hasegawa et al., 2015; Garcia-Maurino et al., 2019; Mcginley et al., 2022). Among these, immune-induced pathology is recognized as a critical contributor to RSV pathogenesis. In patients with severe RSV infections, overwhelming lung or systemic inflammation is frequently observed, characterized by intense infiltration of inflammatory cells, elevated levels of pro-inflammatory cytokines, and other indicators (Russell et al., 2017). Managing such excessive immune activation poses significant challenges in clinical practice. Extensive laboratory research has shed light on how RSV triggers inappropriate inflammation and which immune cells or cytokines are involved in promoting these processes. Despite these advancements, few of these promising findings have been successfully translated from the laboratory to clinical application. The complexity of immune responses makes it difficult to regulate them with single-target approaches. Moreover, when considering potential therapeutic targets, it is crucial to account for the diverse physiological roles of immune factors to minimize unintended side effects. Nevertheless, advancing research and facilitating the clinical translation of these findings hold immense potential for improving outcomes in severe RSV cases. Such efforts could provide significant value in developing more effective treatments and improving the prognosis of patients with severe RSV infections. Lastly, age is another critical factor that should be carefully considered in the development of anti-RSV therapies. RSV primarily affects two vulnerable populations: infants and the elderly, owing to their distinct immunological characteristics, an immature immune system in infants and immunosenescence in the elderly, respectively. Moreover, unlike elderly patients, RSV infection in infants often induces a Th2-skewed immune response, contributing to unique immune pathogenesis and distinct clinical manifestations in this age group (Openshaw et al., 2017). These differences underscore the need for age-specific approaches when developing RSV therapies. Treatments that are effective in the elderly or young adults may not necessarily work in infants. It is noteworthy that the FDA recently placed a hold on all RSV vaccine trials involving infants under two years of age or RSV-naive children aged 2–5 years, following reports of increased severe illness in pediatric populations during the mRNA-1345 (mRESVIA) trial. However, as of May 2024, this vaccine has been approved by the FDA for market use in adults aged 60 years and older, targeting the prevention of both RSV and hMPV. This highlights the importance of considering age-related differences when designing and testing RSV therapies. Drug efficacy and safety must be evaluated separately for different age groups, as a one-size-fits-all approach may not be appropriate for combating RSV infection in both infants and the elderly.

Overall, in this review, we have categorized the progress made on therapeutic drugs that inhibit RSV infection and their modes of action. These studies have identified promising drug candidates targeting different stages of the RSV life cycle, including entry inhibitors that prevent the virus from attaching and penetrating host cells, fusion inhibitors that block the fusion of the viral membrane with the host cell membrane, polymerase inhibitors and so on. Each of these therapeutic approaches offers unique mechanisms to counteract RSV infection. Notably, some of these promising drug candidates have entered clinical development, bringing hope that they will soon become accessible in clinical practice. Overall, while RSV remains a major cause of LTRI in children and the elderly, the continuous research and development efforts are essential for discovering and bringing new effective treatments to clinical use.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to declare.

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