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REVIEW

New Developments and Challenges in Antibody-Based Therapies for the Respiratory Syncytial Virus

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Abstract: Since the discovery of the human respiratory syncytial virus (hRSV), multiple research efforts have been conducted to develop vaccines and treatments capable of reducing the risk of severe disease, hospitalization, long-term sequelae, and death from this pathogen in susceptible populations. In this sense, therapies specifically directed against hRSV are mainly based on monoclonal and polyclonal antibodies such as intravenous IgG (IVIG)-RSV and the monoclonal antibody palivizumab. However, these therapies are associated with significant limitations, including the need for the recruitment of a high number of convalescent volunteers who donate blood to procure IVIG-RSV and the costs associated with the need for repeated administrations of palivizumab. These limitations render this product not cost-effective for populations other than high-risk patients. These problems have underscored that it is still necessary to identify new safe and effective therapies for human use. However, these new therapies must benefit from a comparatively cheap production cost and the opportunity to be available to the high-risk population and anyone who requires treatment. Here, we review the different antibodies used to prevent the pathology caused by hRSV infection, highlighting therapies currently approved for human use and their clinical value. Also, the new, most promising candidates based on preclinical studies and clinical trial results are revised.

Keywords: prevention, treatment, antibodies, respiratory syncytial virus

Introduction

The human respiratory syncytial virus (hRSV) or human orthopneumovirus, based on its reclassification in 2016,[1,2] is a pathogen of primary global concern.[3–8] This infectious agent is responsible for seasonal outbreaks associated with significant morbidity and mortality.[3,5,7,9,10] High-risk populations for severe outcomes following hRSV infections consist of preterm children, especially those with biomedical complications such as bronchopulmonary dysplasia,[11] as well as the elderly.[3,7,10,12–15] In these high-risk populations, hRSV infection has a significantly higher likelihood of causing lower respiratory tract disease, leading to life-threatening pneumonia in many cases.[16,17] Nevertheless, it is important to note that healthy infants born at term are also at risk for severe hRSV pneumonia (albeit to a lesser degree than preterm infants), and due to the ubiquity of the virus, make up most cases.[4,12,13,18] Additionally, substantial evidence has emerged that infection with this virus, including infections acquired during infancy, is associated with long-lasting chronic sequelae, including neuropsychiatric alterations,[19–24] asthma, airway dysfunction, and susceptibility to allergies. These latter three consequences are associated with the highly inflammatory immune response that hRSV elicits. Therefore, it is a public health priority to prevent the severe health consequences brought by the immunopathology of hRSV infection, particularly in at-risk populations, either through active immunization, immunoprophylaxis, or early treatment.[21,22,25]

No vaccines against hRSV have been approved.[25–28] Furthermore, only a single prophylactic antibody product, palivizumab, is licensed in a limited selection of cases.[17,29,30] In this sense, in most cases of hRSV infection, the primary

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management strategies are prevention, symptomatic management, and supportive therapy.[31] To understand the lack of vaccines against hRSV, the immune response that the organism mounts against this virus during infancy offers critical insights. During early life, the immune response tends to be polarized toward a Th2 profile.[32,33] Thus, upon infection, hRSV promotes infants to develop an allergy-like Th2-biased immune response.[34,35] This response includes considerable lung and airway inflammation, and the establishment of ineffective immune memory leaves the individual susceptible to future reinfections.[8,18,36] A vaccine candidate once seen as promising, consisting of formalin-inactivated viral particles (FI-hRSV), was found to elicit this type of response in children[37,38] and led to vaccine-enhanced disease (VED) in case of re-exposure to the pathogen.[39] Natural hRSV infection after vaccination tragically resulted in severe illness in trial participants and two infant deaths.[40,41] Research since that event has emphasized the need to develop vaccine prototypes that could shift the adaptive response towards a Th1-biased immune response with efficacious antiviral capabilities that ideally would include the production of neutralizing antibodies and hRSV-specific T and B cells.[25,42–45] Preclinical research has suggested that this approach could be feasible in the immune system of newborns.[46,47]

Notwithstanding the troubled history of hRSV vaccine development, intense research efforts in the past decades have led to several vaccine candidates in various stages of preclinical and clinical research, including subunit vaccines,[48,49] viral vector vaccines,[50–52] DNA-based vaccines,[53,54] and recombinant *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG)-based vaccines,[55–58] among others.[48,49,56–64] As with other areas of drug development, current efforts have tapped into the now extensive structural knowledge of hRSV to identify novel pharmacological targets. However, despite these efforts, none of these vaccine candidates have been approved for clinical use yet. This fact highlights the importance of exploring and developing other prophylactic and therapeutic strategies against this pathogen as the search for a safe and effective vaccine continues.

Protection against the disease caused by hRSV has already been evaluated through therapeutic venues different from vaccination.[25,65,66] The only licensed pharmaceutical products against hRSV consist of a monoclonal antibody against the Fusion protein of the virus (F-hRSV), palivizumab (Synagis, MEDI-493),[29,67] and ribavirin,[68,69] a broad-spectrum antiviral which does not act through a mechanism of action explicitly targeting hRSV structural components. Both products have only limited effectiveness in preventing severe disease by hRSV. Additionally, polyclonal immunoglobulin products, such as intravenous immune globulin (IVIG), have been approved for use against hRSV. Still, the advent of palivizumab caused the FDA to suspend polyclonal immunoglobulin use in favor of the more modern and effective monoclonal antibody.[70]

The present review explores the use of antibody products against hRSV, discussing their history of development and the types of products in clinical use and highlighting key advantages and weaknesses. Next, we discuss the clinical value of antibody products in clinical use against hRSV, focusing on anti-infective effectiveness and other critical clinical outcomes such as hospitalization and death. Finally, we provide a brief overview of novel antibody products undergoing preclinical or clinical development.

History of Antibody Use Against hRSV

HRSV was first isolated during the 50s from a colony of chimpanzees and named chimpanzee coryza agent (CCA).[71] This virus is classified as a single-stranded, negative-sensed RNA virus with a genome consisting of 10 genes, coding for 11 proteins (9 structural and 2 non-structural).[36,72] Elucidation of hRSV structure, gathered through decades of research, has provided numerous potential pharmacological targets as structural and nonstructural proteins. Among the structural proteins, the ones that have elicited the most interest as possible pharmacological targets are the fusion glycoprotein (F-hRSV), the attachment glycoprotein (G-hRSV), the nucleoprotein (N-hRSV), and the membrane protein (M-hRSV).[18]

After failing to demonstrate the safety of the FI-hRSV vaccine in the immunized pediatric population, new therapies were explored to control the severe prognosis induced by hRSV infection in the risk population.[18,36,39–41] However, to date, only two specific therapeutic drugs have been approved against hRSV, both immunoglobulin-based prophylactic agents.[25] These are polyclonal immunoglobulin isolated from convalescent sera (so-called intravenous immunoglobulin; IVIG)[73,74] and the humanized monoclonal antibody palivizumab.[17,29,30,67,74] Of the two, only palivizumab remains in clinical use, owing to IVIG's unreliability of production, batch-to-batch variability, cost, and lack of superiority.[75–78]

Types of Antibodies Against hRSV in Current Clinical Use

As previously mentioned, there are two immunoglobulin-based products approved for clinical use against RSV: polyclonal antibodies formally referred to as respiratory syncytial virus intravenous immune globulin (RSV-IVIG, RespiGam®)[73,74] and the humanized monoclonal anti-F antibody palivizumab.[17,29,30,67,79] However, no antibodies targeting other proteins of hRSV, either structural or non-structural, have been approved for clinical use (Table 1).

RSV-IVIG was the first antibody-based product approved against hRSV. However, its effectiveness and cost-effectiveness were questioned shortly after its approval.[76] Furthermore, as a polyclonal product obtained from convalescent patients, RSV-IVIG is associated with high batch-to-batch variability, thus making its effectiveness, pharmacokinetic profile, and adverse effects unpredictable. Therefore, IVIG was discontinued after the approval of palivizumab, which showed clear superiority and greater consistency.[75] RSV-IVIG is thus no longer used in standard clinical practice.

In contrast, palivizumab is an anti-F-hRSV humanized monoclonal antibody that acts as a neutralizing agent against hRSV.[29,80] It is indicated for immunoprophylaxis in high-risk preterm infants.[17,30,67,79,81,82] However, its high cost, the requirement for frequent administrations (as many as one per month during five months before the epidemic season), moderate effectiveness, and use limited to prophylaxis (having shown a lack of effectiveness in post-infection therapy) highlight the need for a superior agent in clinical practice.[30,79,83]

In general, the field of monoclonal antibodies for both prophylactic and therapeutic purposes offers promising potential.[84] These agents provide exquisite target specificity and high affinity, thus potentially achieving potent therapeutic effects with comparatively limited adverse effects. Consequently, in addition to palivizumab, several antibody products against hRSV are under either preclinical or clinical development.[70,84–90] Two antibodies are undergoing clinical research:[80,85] motavizumab (MEDI-524), which failed in Phase III clinical trial to promote cutaneous reaction in volunteers,[85,88,89,91–93] and nirsevimab (MEDI8897),[86,94] which recently attained regulatory approval in the United Kingdom (UK) and in the European Union (EU).[95] They are both anti-F immunoglobulins that act as neutralizing antibodies.[86,88]

Palivizumab, motavizumab, and nirsevimab all target F-hRSV.[29,85,94,96] Despite this protein gathering most research interest as a target for antibody development,[97] the generation of antibodies against G-hRSV,[96,98–100] M-hRSV,[101] and N-hRSV[90,102] has been explored as well.

Clinical Value, Efficacy, and Outcomes of Current Antibody Products

The use of monoclonal antibodies for therapeutic and prophylactic purposes has seen an explosive increase in use during the past decades owing to their usually favorable safety and effectiveness, making for some of the most successful therapies in cancer, autoimmunity, and infectious diseases.[103,104] Unfortunately, in the specific field of hRSV infections, this progress has not been as spectacular as in other areas. The two immunoglobulin products employed against hRSV thus far enjoy only limited effectiveness, and their unfavorable cost-effectiveness ratio makes their target population considerably narrow.[65,73,74,78,105] An exception consists of the population of preterm infants and infants with lung complications, among whom palivizumab has been described to possess favorable cost-effectiveness.[77] Conversely, even as this population could benefit from this antibody, due to the ubiquity of hRSV, most severe cases of hRSV occur in infants without biomedical complications, a population which is excluded from prophylaxis.[4,12] These observations highlight the possibility for expanding the therapeutic arsenal against hRSV to a broader group of patients. As previously mentioned, only palivizumab sees current regular use due to the discontinuation of IVIG,[25,30] although, because of its recent approval, nirsevimab is also expected to soon reach common use.[95]

Palivizumab is reserved for preterm infants with biomedical complications, most notably bronchopulmonary dysplasia.[30,79,82] Efficacy is moderate: nearly 55% in preventing hospitalization.[17,67,79,106–108] Because of its short half-life and lack of any active immunization effect, the therapeutic benefit of palivizumab is short-lived. Thus, it requires frequent administrations (as much as five injections over the autumn and winter). This makes it a costly therapeutic strategy for the management of hRSV. Because it acts as a neutralizing antibody, palivizumab is best used as prophylaxis to prevent the infection of many host cells. Thus, avoiding subsequent respiratory pathology and having little value as a treatment once disease, especially severe, immune-mediated disease, has been established. Additionally, escape from neutralization has been reported because of the high tendency of F-hRSV to suffer mutations,[109] highlighting the need to

Table 1 The Landscape of Approved, Clinical, and Preclinical Investigational Immunoglobulins Against hRSV

Approval Status	Product	Product Type	Pharmacological Target	Effectiveness	Half-Life	Comments	References
Withdrawn	IVIG	Polyclonal antibody mixture	Various viral proteins	Low	Variable	Withdrawn due to palivizumab's proven superiority	[73,78,147]
Approved for clinical use	Palivizumab (Synagys, (MEDI-493)	Humanized monoclonal antibody IgG class	F-hRSV	50–55% in the prevention of hospitalization when used in high-risk populations	20–30 days	Only agent in current clinical use specific against hRSV Aerosolized presentations have been evaluated in preclinical research	[14,17,25,27,30,66,78,79,84,105,107,116,148,149]
In clinical research	Motavizumab (MEDI-524)	Humanized monoclonal antibody IgG class	F-hRSV	More than two-fold increase in effectiveness over palivizumab in the prevention of hospitalizations[79]	20–30 days	Trials delayed due to significant incidence of adverse effects	[75,85,88,89,92,93,106]
	Nirsevimab (MEDI8897)	Human monoclonal antibody IgG class	F-hRSV	Significantly increased effectiveness over palivizumab (70% in the prevention of lower tract respiratory infection and hospitalization)	62.5–72.9 days	Attained approval in the UK and in the EU.	[86,94,95,129]
	Suptavumab (REGN2222)	Human monoclonal antibody IgG class	F-hRSV	5 to 10-fold increase in effectiveness over palivizumab	36 days	Discontinued after failing phase III clinical trials	[130,131]
	ALX-0171	Trimeric nanobody	F-hRSV	Better in vitro and in vivo neutralizing capacity compared to palivizumab	Not reported	Currently in clinical trials	[134–136]
	HNK20	IgA class	F-hRSV	Showed efficacy in animal models (mice and rhesus monkeys), which could not be recapitulated in clinical trials.	Not reported	Designed for intranasal administration	[132,133]

In preclinical research	Anti-N-hRSV antibodies	Murine monoclonal antibody	N-hRSV	Not evaluated. Demonstrated to have a nanomolar affinity for N-hRSV	Not reported	Shown to possess specificity and high target affinity. Proposed as a novel diagnostic tool.	[90]
	131–2 G	Murine monoclonal antibody	G-hRSV	Not evaluated in humans. Reduction of viral titers in mice	Not reported	In early preclinical research	[100]
	3D3	Human monoclonal antibody	G-hRSV	Not evaluated in humans Reduces immune cell lung infiltration and viral load in Balb/c mice	Not reported	In early preclinical research	[146,150]
	2B11	Human monoclonal antibody	G-hRSV	Not evaluated in humans Reduces immune cell lung infiltration and viral load in Balb/c mice	Not reported	In early preclinical research	[146]

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target more conserved structures, such as N-hRSV,[43] or G-hRSV, both of which have been described as possessing conserved domains.[99,110,111]

It is worth noting that the effectiveness of immunoglobulin products against hRSV, including palivizumab, has been questioned despite its status as an FDA-licensed product. A systematic review of the Cochrane database evaluated the use of IVIG, palivizumab, and motavizumab in clinical settings in high-income countries and found that neither therapy was different from the placebo for any of the clinical outcomes that were analyzed.[78] Furthermore, immunoglobulins did not significantly reduce mortality or length of hospitalization in children.[78] Additionally, studies have found that palivizumab provided no significant benefit in pulmonary outcomes, including forced expiratory volume and clearance index, in adolescent subjects born extremely prematurely.[112,113] The reasons for this lack of long-term benefit remain unclear, but it could be hypothesized that, given that palivizumab acts, as indicated previously, merely as a neutralizing antibody, its usefulness might stem exclusively from early prophylaxis, having only limited therapeutic value once infection and immunopathology have been established in the respiratory tract.[17,30,67,79,107,108] These results highlight that supportive therapy is the most valuable intervention for severe hRSV infections.[28] Therefore, there remains an unmet need to prevent severe disease, underscoring the significant potential for developing prophylactic and therapeutic agents that may substantially improve clinical outcomes.

Novel Investigational Agents

Novel antibody products should meet several desirable criteria to develop reliable pharmacotherapies.[84,104,114] First, an affinity for their intended target should be very high to avoid off-target effects at their designated doses. Also, pharmacokinetic properties need to be optimized, including a comparatively long half-life and efficient distribution to target tissues to ensure that few administrations afford the intended therapeutic effect. On that note, several modification strategies, such as glycosylation or strategic amino acid modifications, have enhanced pharmacokinetics in other antibody products.[114,115] Another interesting pharmacokinetic change involves designing alternative administration routes different from injectable, such as inhalable or intranasal, which could provide enhanced local protection at the site of infection and improve patient compliance.[76] On that note, proof of concept research has demonstrated that the administration of aerosolized palivizumab resulted in the successful pulmonary deposition of the antibody in an animal model, an approach which could be beneficial as a prophylaxis to prevent severe disease by controlling local viral spread in respiratory tissue after an early infection, suggesting that inhalable presentations of this antibody could be approved for clinical use in the future.[116]

Additionally, the use of humanized or fully human is preferred to murine or chimeric antibodies due to their lower risk of eliciting anti-immunoglobulin antibodies.[104] Another critical consideration is the immunoglobulin class: while IgG and IgM antibodies can elicit complement-dependent cytotoxicity, IgA products may be better suited for local administration at viral entry points. Lastly, the pharmacological target must be designed carefully. Immunoglobulins targeting surface proteins of the virus, such as F-hRSV, G-hRSV, or M-hRSV, would be expected to act as neutralizing antibodies and thus be best suited for either prophylaxis or early therapy upon known exposure (Figure 1).

On the other hand, directing antibodies against either proteins found inside the viral membrane (such as N-hRSV, P-hRSV, or L-hRSV) or nonstructural proteins would potentially allow these antibodies to attach to infected cells (Figure 1). However, to date, few antibody candidates are in preclinical testing and do not include the F protein of the virus but are antibodies against the N and G proteins (Table 1). N-hRSV, unlike F-hRSV and G-hRSV, is not a surface protein but rather can be presented through the histocompatibility complex type I (MHC-I) or directly via membrane expression[117] in infected cells, whereas F-hRSV and G-hRSV are available at the viral surface. Anti-N antibodies could thus serve as therapeutic agents for early infection control through effector functions of the immune system, such as complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and phagocytosis.[118–126] Also, these antibodies could potentially facilitate the generation of adequate immunological memory by recruiting antigen-presenting cells to the site of infection.[42,55]

Nirsevimab is a human immunoglobulin of the IgG1 class that works as a neutralizing antibody through binding to the prefusion conformation of F-hRSV. As a result, viral neutralization is significantly heightened as compared to immunoglobulins that bind the post-fusion conformation.[127,128] Nirsevimab features targeted mutations to the Fc region

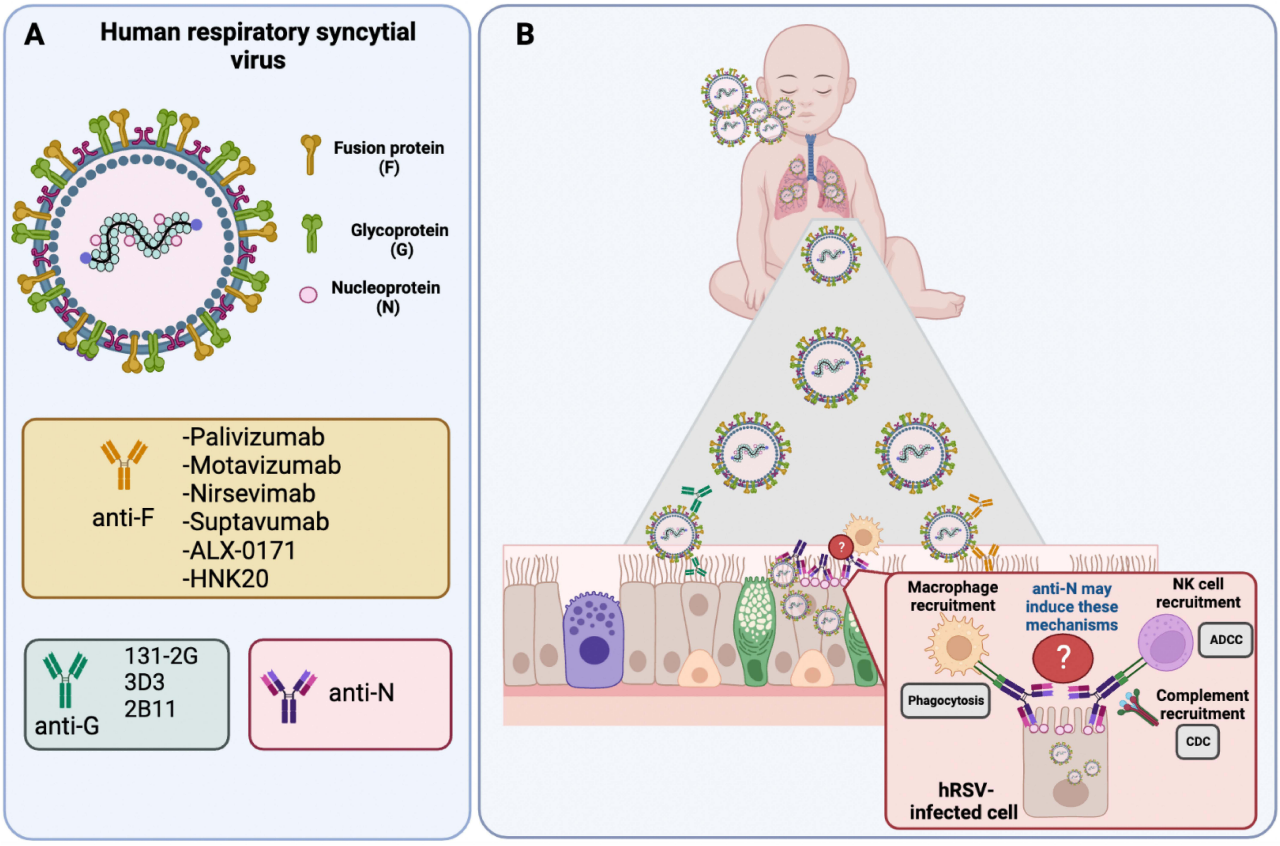

Figure 1 hRSV proteins as targets during the design of monoclonal antibodies against hRSV and their role during pathogenesis. (**A**) Schematic representation of hRSV and its proteins used as targets for developing monoclonal antibodies. (**B**) Role of anti-F (yellow), anti-G (green), and anti-N (Pink/purple) antibodies and their role during hRSV-induced pathogenesis in the lung epithelium.

Notes: Figure 1 is adapted from the templates "Baby", "Generic virus", "Antibody IgG", "Lungs", "Natural Killer cell", "Macrophage", "Ciliated epithelial cell", and "Enterocyte", created with BioRender.com (2022).

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity.

of palivizumab, namely a three amino acid substitution (YTE), which has resulted in a significantly enhanced half-life compared to palivizumab when administered through the intramuscular route.[94,95] Additionally, clinical studies showed a decrease of 70% in developing lower tract respiratory infections (LTRIs) associated with hospitalizations.[94] This fact makes it attractive from economic and patient compliance perspectives, as fewer immunizations per person per season should be required, saving costs and helping achieve better patient compliance.[86,94,129] After being granted Fast Track designation in the United States (US) in 2015, nirsevimab cleared its first Phase 1/2 clinical trial in 2016, entered Phase 3 trials in 2019, and attained its first two approvals in the EU and the UK in 2022.[95]

Motavizumab is an investigational anti-F-hRSV humanized monoclonal neutralizing antibody that has spent several years in the clinical development phase. This antibody was created through modifications in palivizumab's complementarity-determining region, which drastically increased potency compared to palivizumab.[85,88,89] However, the lack of clear superiority of motavizumab versus palivizumab in clinical trials,[93,106] together with a high incidence of adverse effects,[93] has meant that this antibody has not been able to clear clinical research and obtain approval from the US FDA.

Another anti-F-hRSV antibody that underwent clinical trials is Suptavumab (REGN2222). While it has emerged that it grants significantly more protection than palivizumab against the disease caused by hRSV,[130] phase III clinical trials were not successful and Suptavumab was discontinued in 2017.[131]

Other neutralizing monoclonal antibodies against hRSV preclinical or early clinical phases of development include the anti-F IgA HNK20,[132,133] the trimeric anti-F-hRSV antibody ALX-0171,[134–137] and the anti-G-hRSV murine monoclonal antibody 131-2-G.[100]

A novel therapeutic approach toward hRSV infection immunoprophylaxis consists of antibodies directed against the nucleoprotein (N-hRSV).[84] Anti-N-hRSV antibodies have been generated and are under preclinical investigation. Their proposed role includes diagnostic through detecting N-hRSV in infected samples[90] and prophylactic and therapeutic uses against hRSV infection. As discussed previously, these agents are directed against a protein that is not present on the surface of hRSV but has been demonstrated to be expressed on the surface of infected cells. Thus, a potential use for these antibodies would be in the early control of an established infection by facilitating the selective killing of infected cells through effector functions of the immune system (Figure 1).[118,123,138] Additionally, it is hypothesized that, given N-hRSV is more conserved than F-hRSV, anti-N antibodies could be more resistant to the escape variants that evade neutralization by palivizumab and nirsevimab.[109,137,139–141] It is noteworthy that the development of pharmaceutical products targeting N-hRSV is still at early stages, but several preclinical products have been reported. Apart from the aforementioned anti-N antibodies used in potential diagnostic purposes,[90] studies have reported the use of this protein in immunization platforms employing nanoparticles,[49,60] as well as a recombinant BCG vaccine expressing N-hRSV.[55–58]

As mentioned in this article, the search for new therapeutic targets other than the F protein of the virus is under evaluation. Along these lines, the development of an antibody against the G protein of the virus called 131–2G, which blocks the binding of the G protein to CX3CR1, which is a receptor reportedly employed by hRSV for viral attachment and possibly for subsequent entry into lung epithelial cells (Figure 1),[142–145] has shown promising protection results in mice.[99,100] This antibody has since been superseded by the human monoclonal antibodies 2B11 and 3D3, both of which have shown promising data in preclinical studies, showing reductions of viral load and cellular infiltrate in lung tissue and bronchoalveolar lavage.[146]

Concluding Remarks

The pharmaceutical arsenal against hRSV has proven to be slow growing, and the only currently approved pharmaceutical product specific for this virus has an unsatisfactory clinical profile. Antibodies or antivirals against hRSV face the complex challenge of requiring high affinity for its intended target, either rapid neutralization or quick eliciting of effector immune functions, depending on the mechanism of action, resistance toward immune evasion by viral variants, and a prolonged half-life. Promisingly, recent developments in drug discovery and development allow for newfound optimism. Recent studies in structural biology have provided a detailed picture of the viral structure of hRSV, providing numerous potential targets for pharmacological modulation. Apart from agents in current clinical research, various others are in preclinical phases. Through mechanisms of action that involve effector functions of the immune system, it could be expected that agents directed against novel targets could provide new therapeutic strategies in the fight against hRSV. On the other hand, vaccine development against hRSV continues. The main challenge in this field involves eliciting a long-term immune response polarized toward the Th1 phenotype, to avoid the incidence of vaccine enhanced disease. Improvements in our understanding of the immune response to hRSV will likely facilitate the emergence of new promising vaccine candidates able to curb the morbidity and mortality caused by this pathogen.

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