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MINI-REVIEW

Inhalation monoclonal antibody therapy: a new way to treat and manage respiratory infections

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Abstract

The route of administration of a therapeutic agent has a substantial impact on its success. Therapeutic antibodies are usually administered systemically, either directly by intravenous route, or indirectly by intramuscular or subcutaneous injection. However, treatment of diseases contained within a specific tissue necessitates a better alternate route of administration for targeting localised infections. Inhalation is a promising non-invasive strategy for antibody delivery to treat respiratory maladies because it provides higher concentrations of antibody in the respiratory airways overcoming the constraints of entry through systemic circulation and uncertainity in the amount reaching the target tissue. The nasal drug delivery route is one of the extensively researched modes of administration, and nasal sprays for molecular drugs are deemed successful and are presently commercially marketed. This review highlights the current state and future prospects of inhaled therapies, with an emphasis on the use of monoclonal antibodies for the treatment of respiratory infections, as well as an overview of their importance, practical challenges, and clinical trial outcomes.

Key points

- *Immunologic strategies for preventing mucosal transmission of respiratory pathogens.*
- *Mucosal-mediated immunoprophylaxis could play a major role in COVID-19 prevention.*
- *Applications of monoclonal antibodies in passive immunisation.*

Keywords Therapeutic antibodies · Respiratory viral infections · Prophylactic · Intranasal · SARS-CoV-2 · Inhaled delivery

Introduction

Therapeutic antibodies offer valuable tools in the medical field for treating a variety of disorders and have emerged as one of the dominant therapeutic modalities, with over 50 approved products and over 500 monoclonal antibody (mAb)-based therapies in clinical development (Parray et al. 2020b). mAbs are natural macromolecules that have a high affinity and specificity for binding to a wide range of antigenic targets by utilising unique pharmacokinetic (PK) and pharmacodynamic (PD) properties. Among the recently approved biologics, more than 90% were mAb-based drugs (Posner et al. 2019). This increasing success of mAbs can be attributed to their favourable safety, target specificity, and pharmacokinetics compared to traditional small-molecule drugs. There is no risk of the administered antibodies, in terms of getting metabolised in vivo into toxic metabolites, so, relative to small molecule drugs, the likelihood of therapeutic phase transition is very high. Antibody-based therapeutics have made significant improvements in autoimmune diseases, cancer bio-therapeutics, and patient survival rates with decreased side effects. However, limited success has been achieved in

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the case of viral targets. In recent years, immunotherapy has represented a potential intervention to mitigate virus spread and disease severity. A number of mAbs have been isolated from a variety of sources by utilising different strategies for therapeutics or preventive approaches against infectious viral diseases such as the human cytomegalovirus (Gerna et al. 2016), influenza (DiLillo et al. 2014; Tan et al. 2016; Biswas et al. 2020), human immunodeficiency virus (Kumar et al. 2012, 2018, 2019a; Khan et al. 2017), respiratory syncytial virus (Tang et al. 2019), SARS-CoV-2 (Pinto et al. 2020; Parray et al. 2020a; Schoof et al. 2020; Perween et al. 2021), Ebola (Flyak et al. 2018), Zika (Sapparapu et al. 2016), rabies (Kim et al. 2017), HBV (Hong et al. 2019), and dengue (Durham et al. 2019). Two of these mAbs are currently approved for the treatment of viral infections; palivizumab for the prevention of respiratory syncytial virus (RSV) infection in high-risk children (Olchanski et al. 2018); and ibalizumab has been introduced for the treatment of HIV-infected individuals who have acquired multidrug antiretroviral therapy (ART) resistance (Rizza et al. 2019). More recently, Inmazeb (atoltivimab, maftivimab, and odesivimab-ebgn), a mixture of three monoclonal antibodies, has been approved as the first FDA-approved treatment for adult and pediatric Zaire ebolavirus (Ebola virus) infection, opening a new avenue to explore more therapeutic mAbs for other viral infections (Markham 2021). Most of these therapeutic mAbs are typically administered intravenously (IV) or through a systemic passive immunisation strategy, although aerosol or subcutaneous delivery are preferred for some applications (Viola et al. 2018). One potential drawback of the systemic approach is the limited absorption of mAbs from the site of administration, via blood circulation, to the infected organs, that overall affects and limits therapeutic target access. Respiratory complications (caused by viral and non-viral agents, for example) primarily affects respiratory organs, limiting absorption of therapeutic mAbs assimilated via the systemic route (Guilleminault et al. 2014; Liang et al. 2020). However, researchers are exploring different alternative routes of therapeutic mAb administration to respiratory organs and one such potential approach might be using the mAbs through the inhaled route thereby overcoming such limitation (Fick et al. 2000). Passive administration of antibodies by an inhaled route can deliver protective levels of antibodies immediately and directly to the susceptible mucosal surface that is the primary route of infection entry. Inhalation may facilitate a more rapid onset of impact (within minutes to hours) on organs of the respiratory system compared to other routes of administration (days) because it is generally presumed that the concentration of a biomolecule at its site of action determines the potency (Borghardt et al. 2018). Recent advances in mAb-based prevention strategies have allowed the development of a new era of inhaled mAb-based public health intervention strategies (Desoubeaux et al. 2016; Desoubeaux et al. 2016; Kumar et al. 2019b, 2020, 2020). Because most respiratory viral infections begin at the mucosal surfaces in the upper respiratory tract, mucosal delivery of antibodies is not only effective for protection but also for reducing virus spread. Besides, the viruses at the mucous surface can be trapped by antibodies, thereby preventing mobility and restricting their diffusion to the environment, and the trapped viruses in the mucus can be shed from the body through normal mucous secretions.

The inhaled route of therapeutic biologicals may be more advantageous, especially in the case of respiratory disorders or distress. Respiratory diseases constitute a major public health issue worldwide: four of them are among the ten most common causes of death (pneumonia, tuberculosis, lung cancer, and chronic obstructive pulmonary disease (COPD) (Garantziotis and Schwartz 2010). They also represent a major socioeconomic burden through disability, health-care costs, and loss of productivity. Acute respiratory viral tract infections are responsible for a substantial share of human diseases worldwide. Medical and therapeutic interventions against viral respiratory tract diseases include vaccination, treatment with antiviral drugs, and symptom-based disease treatments (Weltzin and Monath 1999). By July 2021, the COVID-19 pandemic had reached more than 200 countries in which more than 180 million people got infected, and the infection was transmitted from one person to another through air droplets of an infected person via coughing, sneezing, or physical touch of infected surfaces. The disease is highly contagious with a mortality rate of around 2–3%. However, the data available suggests higher fatality rates in older age groups and medical workers dealing with the COVID-19 crisis (Petrosillo et al. 2020). Currently, many vaccine candidates are being produced, with many having completed late-stage clinical trials and being approved for vaccination in the battle against COVID-19. Improved hygiene and social distancing are the arsenals to contain this virus and reduce its spread. Given the magnitude of the crisis, immediate, novel alternative approaches are required to combat COVID-19 (Chen et al. 2020). However, passive antibody-based immunisation approaches represent feasible new tools. The prophylactic use of antibodies for intranasal administration or mucosal route can be potentially used as supportive therapy in the airways for the prevention of respiratory viral infections. In this review, we discuss the use of therapeutic antibodies as a potential measure to prevent respiratory illness. We have also highlighted the advantages, limitations, and potential applications of inhaled mAbs as compared to systemic therapy, with special reference to controlling disease spread, pathogenesis, and disease severity. Herein, we have addressed the important considerations, challenges, and future perspectives associated with the development of inhaled antibody-based approaches and prevention strategies. In particular, we have discussed the role of inhaled mAbs as a target therapy for viral targets.

Systemic versus inhalation route

Therapeutic antibodies are administrated via systemic (via the intravenous route, intramuscular, or subcutaneous injection) and non-systemic (localised) routes. The most common route for the administration of mAb-based therapeutics is a systemic route and is well adapted for the targeting of disseminated ailments (Jones and Martino 2016). However, several studies have shown that systemic administration is not the sole optimal mode of delivery for all antibody-based therapeutics (Koleba and Ensom 2006; Hansel et al. 2010). The non-systemic routes involve localised use of therapeutic antibodies where antibodies are injected, either at or near the area of disease or injury, allowing direct diffusion of the antibody to the region of the target site where a therapeutic effect is expected (Jones and Martino 2016). Ranibizumab, used for the treatment of wet age-related macular degeneration, a disease of the eye, is the first monoclonal antibody approved for targeted localised therapy by the Federal Drug Administration (FDA) and is recommended to be administered by intravitreal injection once a month (Moreno et al. 2017). The other non-systemic routes that have potentially been explored in recent years are the fistula tract, localised subcutaneous, intratumoural, peritumoural, and intranasal delivery (Fig. 1). Detailed information about these non-systemic routes (except the inhaled route) has been discussed in different review articles (Schweizer et al. 2014; Jones and Martino 2016; Bodier-Montagutelli et al. 2017).

The inhalation route for administering therapeutic reagents is often used to treat lung conditions such as asthma or chronic obstructive pulmonary disease, by prescribing medications in the form of inhalants. Inhalation provides a variety

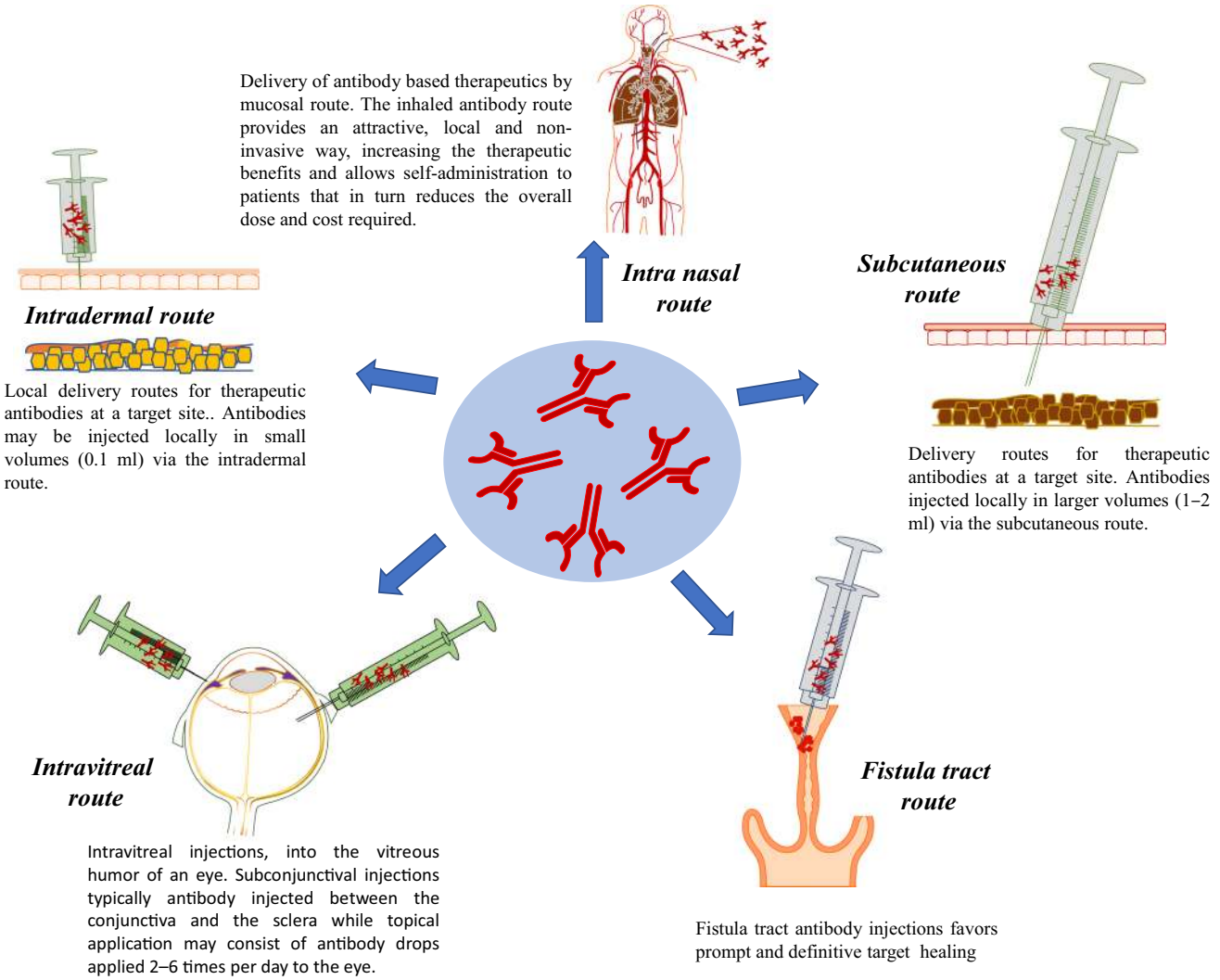

Fig. 1 Simplified schematic representation of non-systemic treatment routes. Overview of the local non-systemic delivery routes such as nasal, intradermal, subcutaneous, subconjunctival, intravitreal, and fistula tract antibody routes

of benefits in the treatment of these respiratory diseases compared to other routes of administration, by reducing pulmonary symptoms like prevention of airway inflammation and constriction. In respiratory illnesses, the respiratory track is the main affected area where the disease spreads to other parts of the respiratory system. Targeted delivery of mAbs to the lungs through the systemic route results in very low mAb concentrations in the lungs, thus exposing the rest of the body to possible therapeutic side effects, including toxicity and cytokine release syndrome (Respaud et al. 2015; Burgess et al. 2018). For example, bevacizumab (Avastin) is a monoclonal antibody that blocks the growth of tumour blood vessels by targeting a protein called VEGF. It is used for the treatment of various cancers, and its delivery through systemic routes results in side effects such as high blood pressure, bleeding, blood clots, slow wound healing, and kidney damage (Li and Kroetz 2018). As a result, the inhaled route is a more appealing, local, and non-invasive alternative to the systemic route for such deliveries, permitting usage for the treatemnet of different types of cancers, while avoiding potential side effects (Abbas et al. 2019; Somasundaram et al. 2020). Furthermore, inhalant therapy allows patients to self-administer or be treated at a nursing home, thereby reducing the overall dose and cost requirements (Fahy et al. 1999; Cruz-Teran et al. 2021). Evaluation of the effectiveness of aerosol delivery of anti-tumour mAbs in lung cancer mouse models revealed that mAbs administered through the airway-inhaled route met their target antigen in the tumour at concentrations twice those achieved after intravenous delivery and are pharmacologically effective in limiting tumour development (Hervé et al. 2014). Furthermore, the pharmacokinetics of various mAbs administered through the airways in mice and non-human primates (NHPs) revealed small lung-to-bloodstream passage and antibody accumulation in the lungs (Bodier-Montagutelli et al. 2017). Similarly, preclinical studies of inhaled anti-IL-13 Fab′ fragments have shown promising results in animal models of asthma in terms of reducing airway inflammation and hyperresponsiveness (Hacha et al. 2012).

Development of inhalation-based antibody treatment for humans is underway for various respiratory diseases, and early clinical studies have confirmed that it is an effective and safe approach to prevent respiratory tract diseases (Leyva-Grado et al. 2015; Van Heeke et al. 2017). Administration of anti-influenza virus broadly neutralising antibodies (bnAbs) through intranasal and aerosol routes showed higher prophylactic protection as compared to systemic routes and controlled the advanced stage infection with a much reduced dose of the administrated bnAb (Hart et al. 2001; Ibañez et al. 2011). (Fig. 2a). In comparison to parenteral treatment, inhalation of Abs gave better protection and greater therapeutic response in pneumonia models using influenza virus (Leyva-Grado et al. 2015).

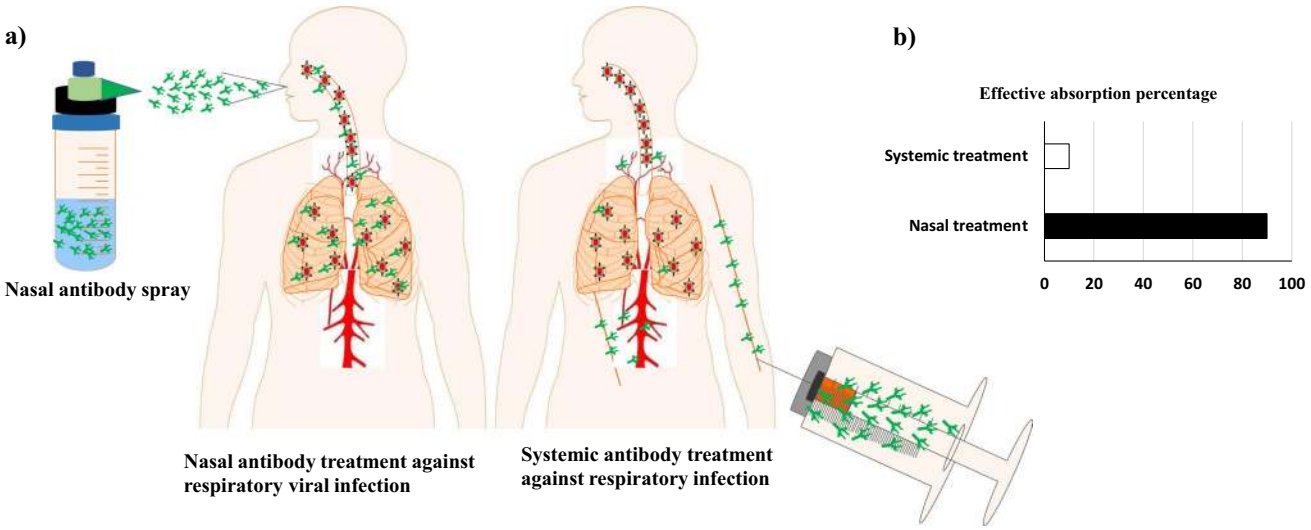

Fig. 2 Schematic representation of the antibody-based prevention strategies for respiratory infections. **a** The delivery of antibody-based therapeutics by mucosal route. The inhaled antibody route provides an attractive, local, and non-invasive way. It increases the therapeutic benefits and allows self-administration to patients that in turn reduces the overall dose and cost required. The mAbs in lungs by systemic route results in very low concentrations of the mAbs in the lungs, and exposing the rest of the body to potential adverse effects such as, toxicity, thickening of serum, and cytokine release syndrome. Delivering mAbs by inhaled route will not only neutralise virulence of respiratory virus outbreak as well as will provide protection and a unique preventive strategy. **b** The dose of mAbs needed at mucosal surfaces is substantially low to treat an established proliferating infection as compared to systematic or intravenous route (Bodier-Montagutelli et al. 2017; Zhang et al. 2020). The delivery of mAbs in lungs by systemic route results in very low absorption concentrations of the mAbs in the lungs (~10%) as compared to mucosal route (~90%)

Inhaled delivery of therapeutics against viral infections might evolve as a game changer. The intranasal presence of mAbs will have a better success rate in preventing the virus from getting a foothold to establish infection, thereby conferring protection and a unique prevention strategy during an emergency respiratory virus outbreak pandemic (Leyva-Grado et al. 2015; Abbas et al. 2019). The delivery of antibodies by the inhalant route will facilitate early stage contact with the pathogen in the respiratory tract, wherein the airborne infections originate and spreads. Thus, even a low concentration of the antibodies at the site of infection could potentially be effective in virus neutralisation (Fig. 2b) and overcome poor distribution of the antibodies, observed when using a systemic route, due to low expression of neonatal Fc receptor (FcRn) in epithelial cells of the upper airways and alveolar macrophages in all species (Sakagami et al. 2006; Bequignon et al. 2019; Eichhoff et al. 2019). Figure 3 depicts a schematic description of antibody-mediated protection.

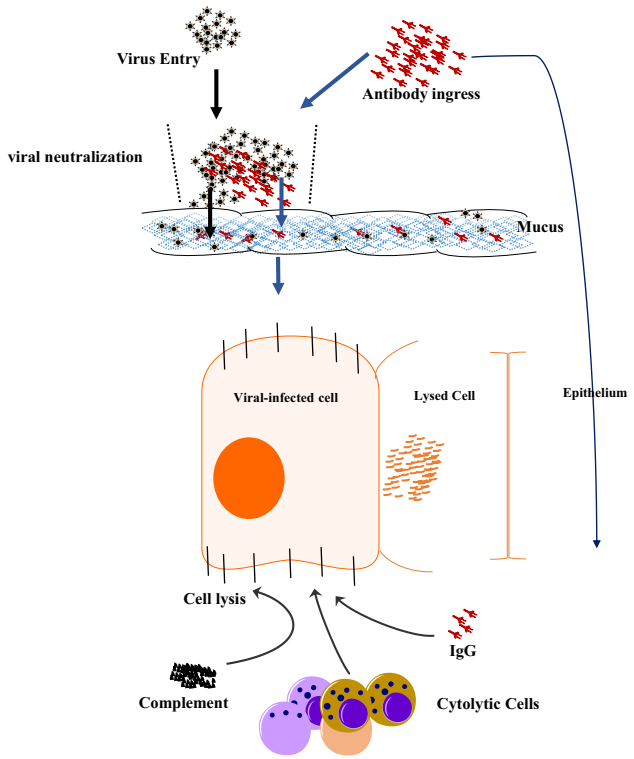

Fig. 3 Diagrammatic representation of the antibody-mediated protection from respiratory tract viral infection. Neutralising antibodies delivered to mucosal surfaces protects via two different mechanisms: (i) direct neutralisation of the free virus particles, which prevents virus from reaching host target cells and prevents virus from establishing infection and, secondly, via (ii) immune exclusion, antibodies can bind to virus-infected cells that are eliminated via antibody-dependent cellular cytotoxicity and cytolytic T cell activity

Choice and constraints of drug delivery device

The inhalation route is mostly investigated for small molecular drugs and is underutilised for protein biotherapeutics due to a lack of supportive clinical data demonstrating its efficacy and the constraints associated with the inhaled protein production (Mayor et al. 2021). A successful inhaled administration of a biotherapeutic requires a harmonious relationship between the formulation, the inhaler device, and the patient. The device must be linked to deposit a pharmacologically active and safe mAb in the lung region of interest, efficiently and consistently. There are a variety of inhalation devices that are delivered directly to the airways. The three most commonly used inhalation devices are nebulisers, dry powder inhalers (DPIs), and metered-dose inhalers (MDIs) (Moroni-Zentgraf et al. 2018).

Nebulisers (jet, ultrasonic, and mesh) use a liquid solution of the medicine to produce aerosol droplets and are used to deliver them to the lungs and airways. Because the production process for nebulised formulations does not include additional drying procedures, they are less expensive to make and test. However, the suitability of nebulisers for the protein molecule is less favourable because prolonged storage of proteins in liquid solutions can result in protein instability and conformational changes via degradation pathways (i.e. deamination and hydrolysis), temperature, pH changes, and aggregation (via aqueous carrier agitation) (Kane et al. 2013; Respaud et al. 2014). A study conducted by Respaud et al. (2014) shows that the use of surfactants in antibody formulations considerably minimise aggregation formation during aerosolisation in mesh nebulisation. Human immunoglobulin preparations were successfully deposited into the conducting airways as well as the alveoli of treated lungs when nebulised with an eFlow® nebuliser in both rat and NHP studies (Vonarburg et al. 2019).

DPIs are propellant-free, portable, and simple-to-use inhalation devices that deliver medication in the form of a dry powder to the lungs. DPIs deliver drugs as a solid aerosol, whereas powder formulations have inherent stability and shelf life advantages. They do not necessitate cold chain storage or the reconstitution of powders into nebulisation solutions. Spray drying is a new technique for processing antibody dry particles. Pure antibody solutions, on the other hand, have been demonstrated to significantly agglomerate during this process (Faghihi et al. 2017). Such destabilisation is rationally linked to shearing stress in the nozzle, heat stress during drying, and surface adsorption of contaminants. Excipients such as trehalose and Tween 20 are used to protect proteins from

disintegration during the spray-drying process (Cleland and Jones 1996). Trehalose has a high glass transition temperature, low hygroscopicity, and great water replacement efficacy, making it one of the most promising inhibitors of antibody aggregation. The surfactants like Tween 20 have also been demonstrated to compete with protein molecules at the air–liquid interface, preventing protein unfolding and aggregation (Mumenthaler et al. 1994; Jayasundera et al. 2011). The recent phase 1 double-blind, randomised research of inhaled interleukin-13 monoclonal antibody supports the development of inhaled antibodies as a viable future therapy option for parenteral mAbs. Single and repeat doses of dry powder anti-IL-13 fragment antibody provided through inhalation were shown to be well tolerated over up to 10 days (Burgess et al. 2018). Inhaled dry-powder COVID-19 antibodies are being developed by biotechnology companies to treat COVID-19 infections for inhalation into the lungs and are in early-stage clinical trials.

The MDI is a device that delivers a particular amount of medication to the lungs in the form of a short burst of a reliable, consistent dose of aerosolised drug, which is often self-administered by the patient by inhalation. Propellers are used in pMDIs to create aerosols for inhalation (Ibrahim et al. 2015). There is currently no approved pMDI product for inhaled biologics therapy. Proteins and peptides are generally hydrophilic, making them insoluble in non-polar propellants (Liao et al. 2005). The inability of biologics to dissolve in propellants limits the dose range that can be supplied per actuation (Fathe et al. 2016; Liang et al. 2020).

Inhalation antibody prophylaxis for protection against respiratory infections

Respiratory viruses that infect humans enter the body through the respiratory route, as aerosols formed by coughing or sneezing from other infected hosts. Large aerosol particles are typically trapped in the nasal turbinates and sinuses, where they can cause upper respiratory tract (URT) infections. Smaller particles in the lower respiratory tract can enter and cause infections in the alveolar areas with a higher mortality rate in respiratory diseases. Most of the viruses infecting URT cause an acute infection and infect humans seasonally (e.g. RSV, rhinovirus, parainfluenza, influenza A, adenovirus, human metapneumovirus, human bocavirus, and coronavirus). The most common syndromes caused by URT viruses are bronchiolitis and pneumonia (Manjarrez-Zavala et al. 2013). The epithelial cells of the mucosal surfaces are the first port of entry in most respiratory viral infections. The virus will not be able to establish an infection if the virus attachment is blocked at the point of entry. Antiviral agents, such as antibodies, have proven to be effective in preventing virus attachment and establishing infection. For example, the recent development of llama antibody-based strategies gives broad coverage of all the seasonal strains of the influenza virus, providing better hope for the development of future antibody-based strategies against influenza. Due to being smaller in size and shape as a part of their nature, llama antibodies can bind to cryptic epitopes that are not accessible through conventional antibodies (Harmsen and De Haard 2007). To date, no conventional mAb has been isolated that has the breadth and potency to neutralise all strains of influenza, A and B viruses. However, the isolated llama antibodies were effective against the multitude of influenza A and B viruses infecting humans (Cohen 2018). The nasal spray, containing a recombinant adeno-associated virus (AAV) vector engineered to express a protein derived from llama antibodies, showed protection in mice studies conducted against all known strains of flu viruses infecting humans and preventing them from further multiplying (Eichhoff et al. 2019).

Palivizumab is a humanised anti-RSV mAb used to reduce the risk of hospitalisation by 55% when given intramuscularly (IM). In a recent study related to RSV, it has been demonstrated that topical application of this mAb was approximately 100 times more effective than systemic delivery. In preclinical animal studies, inhaled antibody delivery in RSV (Gomi et al. 2018) and influenza has been shown to be effective (Ye et al. 2010). Similarly, a study conducted by Schepens et al. showed that VHHb nanobodies delivered intranasally, block viral infection as effectively as those administrated before infection (Van Heeke et al. 2017). The use of bnAbs as an alternative therapy for influenza virus-infected patients via the intranasal or aerosol route significantly decreases the amount of mAb required for protection by 1 log compared with the administration via the intraperitoneal or intravenous route with a higher survival rate (Soto et al. 2020). Scientists have developed a rhesus monkey model of RSV infection and the studies based on the same have shown that the virus inoculum was directed to the upper airways only, whereas subsequent viral shedding was observed from both upper and lower respiratory tract secretions (Grandin et al. 2016). Grandin et al. (2015) created a Cynomolgus macaque model of mild infection using human RSV (hRSV), a common respiratory virus that causes infection in premature infants and children and is associated with high mortality when combined with other chronic diseases. This study showed that virological, clinical, and immunological parameters were also influenced by age and co-infection or morbidity (Grandin et al. 2015). Earlier animal studies have demonstrated that serum antibodies having high neutralising activity against the respiratory syncytial virus (RSV) can provide important prophylactic and therapeutic benefits when delivered either systemically (Prince et al. 1985; Hemming et al. 1985) or by topical instillation

(by drops) into the airway (Prince et al. 1987; Hemming et al. 1988). Similarly, Weltzin et al. (1996) also showed that intranasal treatment with HNK20, a mouse IgA mAb (against RSV F glycoprotein) reduces upper and lower respiratory tract infection in rhesus monkeys. Because of their particular structure and glycosylation pattern, IgA antibodies may bind to mucins in the airway epithelium, extending their half-lives in the mucosa (Li et al. 2020). In mice and non-human primates, prophylaxis of immunocytokines (e.g. IL-7 Fc) has demonstrated improved efficacy against airborne lethal viruses for several weeks via transcytosis in the lung tissues, leading to recruitment of T cells from circulation and their subsequent residency as tissue-resident memory-like T (TRM-like) cells (Kang et al. 2015). In contrast, limiting the response of pleiotropic molecules (e.g. IL-7 Fc), which are envisioned as adjuvant molecules, to the site of action may lessen systemic side-effects and allow for increased efficacy with a lower dose (Leyva-Grado et al. 2015; Sécher et al. 2019).

Another potential area, where researchers are exploring the fate of the development of chicken immunoglobulin (IgY)-based nasal spray as an effective prevention strategy against respiratory viral infections, is under development (Abbas et al. 2019). IgY is similar to human IgG and is present in both sera and the egg yolk of chickens. IgY antibodies do not react with the human Fc receptor and rheumatoid factor present on the cell surface, hence eliminating the risk of complement activation (Kovacs-Nolan and Mine 2012; Somasundaram et al. 2020). The IgY antibodies have three to five times more affinity for their target antigens, while IgG helps in faster reactivity of these antibodies to invading pathogens (Stuart et al. 1988; Lemamy et al. 1999; Rahman et al. 2013). IgY antibodies are well tolerated by the human system as eggs are a part of routine diet in humans (Abbas et al. 2019; Pérez de la Lastra et al. 2020). These differences provide great advantages for the successful application of IgY to humans as an alternative. Additionally, IgY antibodies are functional at a pH ranging from 4 to 9 and are stable up to 65 °C. The high content of sialic acid in IgYs increases the half-life of these Abs (Abbas et al. 2019). The prophylactic use of IgY Abs for intranasal administration could be potentially used in the airways for the prevention of viral infections. IgY Abs have shown greater binding affinity and neutralising activity against various bacterial and viral infections in humans and animals (Somasundaram et al. 2020). In vivo studies have shown that intranasal treatment of mice with virus-specific IgY before or after influenza B virus infection has a protective effect by minimising viral replication in the lungs (Wen et al. 2012). In a related study, when intranasal IgY is administered 1 h before infection, 100% of mice are protected against lethal challenge by H5N1. The use of IgY Abs over IgGs in nasal spray provides several advantages, such as cost-effectiveness, convenience, and high doses of administration due to the lack of FcRn interactions (Li et al. 2015). The safety of intranasal IgY delivery has been successfully proved as a better treatment option for acute and chronic pharyngitis in humans (Xie et al. 2004). Studies have shown that the IgY antibody derived from chicken yolks is effective in neutralising severe acute respiratory syndrome (SARS) (Fu et al. 2006) and cystic fibrosis (Nilsson et al. 2008). Some of the leading pharmaceutical companies are exploring the fate of the IgY-based nasal spray for SARS-CoV-2 prevention.

Filoviruses, including Ebola, has the potential to be transmitted via virus-laden droplets deposited on the mucus membranes. Recent studies conducted using ZMapp, a cocktail of Ebola-neutralising mAbs in mice, have suggested that topical delivery of ZMapp to the mouse airways facilitates the rapid elimination of Ebola pseudovirus (Yang et al. 2018). These results suggest that in mucosal delivery, the antibody requirement would be many times less as compared to systemically delivered preparations, making it more cost-effective. One of the major challenges that impedes the progress of many antiviral mAbs is the potentially higher cost associated with the production of recombinant antibodies, as compared to small molecule antivirals. Intranasal or mucosal delivery of mAbs can overcome this challenge, though more studies are needed to support the hypothesis.

Inhaled delivery in special context to SARS-CoV-2, as a future prospective

There are 66 vaccine candidates for COVID-19 in clinical trials as of February 2021 (Mullard 2020). Many COVID19 vaccines have demonstrated the effectiveness of up to 95% in phase III trials. The recent emergence of SARS-CoV-2 variants has raised concern about the effectiveness of the current vaccines against the mutant strains. In January 2021, variants began to be reported from the USA, France, Italy, Denmark, and others (Fontanet et al. 2021).

One potential alternative strategy for combating respiratory viral infections is to prevent viral entry before it spreads throughout the body. During early infection, the viral load on the mucus membrane surface is likely to be low. Treatment with a low dose of mAb during early mucous infections could substantially neutralise the virus from further spread (Leyva-Grado et al. 2015). Consequently, the delivery of therapeutic antibodies could be useful as a preventative measure in an emergency. The antibodies required to trap the virions on the mucus surface do not need to be neutralised. Aggregation or agglutination by antibodies may allow more efficient entrapment of virus in mucous and subsequent clearance, which greatly expands the potential of antibody-based methods for protection (Forthal 2014). Secondly, antibodies directed against host cell receptors can

be used to target pathogens to block their receptor-mediated attachment to mucosal cells. Owing to their low molecular size, antibodies diffuse largely unimpeded into human mucus, where the Fc region of the antibody induces low affinity adhesive interactions with mucus mesh that prompts multivalent antibody interactions to capture the pathogen, stopping it from entering the underlying tissue (Saltzman et al. 1994; Olmsted et al. 2001). The two potential drawbacks that potentiate the requirement for inhaled antibody administration for respiratory infections are, first and foremost, a minuscule amount of mAbs reaching the lungs and large bronchoalveolar-lavage (BAL) space. Second, most of the medications that treat respiratory diseases work in the organs of the respiratory system rather than in the periphery (Labiris and Dolovich 2003). The development of nasal spray treatments for SARS-CoV-2 is underway, and early clinical studies have confirmed that this approach is safe and can be used to prevent respiratory spread of SARS-CoV-2 (Westover et al. 2020; Zhang et al. 2020). Inhaled antibodies have the potential to be employed as a treatment, particularly for individuals who are not hospitalised and have a lower pathogen load. However, in some cases, antibodies might be provided as a prophylactic strategy. Pharmaceutical companies are making several efforts to develop antibody-based prophylactic sprays to create a durable antibody barrier in the nasal cavity to catch, bind, and neutralise the SARS-CoV-2 virus before it can reach and enter the cells that cause infection. The preclinical COVID-19-inhaled mAb study demonstrates the therapeutic efficacy of these inhaled antibody reagents in animal models, with an average effective adult human dose of between 1 and 3 mg (Piepenbrink et al. 2021). Prabakaran et al. (2009) have reported that passive transfer of neutralising serum antibodies through the intranasal route in a challenge experiment, prevented virus replication in the lower respiratory tract of naïve mice. Elevation of interleukin-6 (IL-6) is one of the chronic clinical symptoms in COVID-19-infected patients. Researchers are exploring using Foralumab to treat COVID-19 patients with lung damage and elevated IL-6 levels. Foralumab is a fully human anti-cluster definition 3 monoclonal antibody (anti-CD3 mAb) that binds to the CD3 epsilon unit of the IL-6 receptor. Binding of this mAb to the IL-6 receptor reduces its excessive level in the blood (Schoof et al. 2020). Elevated IL-6 levels drive chronic inflammation and is associated with severe lung damage (Mojtabavi et al. 2020). To evaluate the safety and tolerability, a phase 1 clinical trial has recently started in healthy volunteers using a nasally administered dose regimen with a nasal spray device. The inhaled administration of Foralumab induces disease-modifying Treg cells in the cervical lymph node to cross the blood–brain barrier and provide an anti-inflammatory signal via an IL-10-dependent pathway to downregulate the activated glial cells in the brain and help in maintaining homeostasis (Ogura et al. 2017; Ilan et al. 2018). Some of the studies conducted on inhaled delivery of mAbs are detailed in Table 1.

Challenges and advancements associated with antibody-based prevention and therapeutic approaches for inhaled delivery

Respiratory infections can be fatal. Therapeutic antibodies have the potential to confer protection against emerging viral infections, before a vaccine is developed. The appropriate route of administration of the antibodies is crucial for a favourable outcome. The major challenge that arises with mucosal delivery of mAbs comes from their frequent dosing and the short half-life of nasal antibodies. The concentration of active mAb in the lungs relies on the interplay of multiple pulmonary kinetic mechanisms, including the physicochemical properties of the mAb, its composition, and the device for inhalation as well (Ibrahim et al. 2015). Additionally, patient features, such as inhalation abilities, may also impair pulmonary effectiveness. The mucosal airway environment with continuous secretion and elimination of mucus coating likely necessitates at least once-a-day delivery to ensure adequate concentrations of mucosal Abs. Secondary infections (such as bacterial infections) and other pathological disorders (such as chronic sinusitis, COPD and cystic fibrosis (CF)) can potentially reduce the therapeutic efficacy of antibodies by thickening the mucus. The mucus in CF has a higher density of disulphide cross-links, which tightens the mucus mesh space even more, lowering the overall efficiency of the treatment (Yuan et al. 2015; Sécher et al. 2019). Higher concentrations of therapeutic biomolecules delivered in large quantities can have a detrimental influence on drug absorption owing to local adverse effects and, in certain circumstances, can damage the nasal mucosa. As a result, it is critical to recognise that the nasal cavity has limited capacity and that the dosage for nasal administration must be relatively modest (Ross et al. 2004). These limitations has been tried to overcome by improving mucosal delivery methods. Recent advancements in treatment with a mAb via the aerosol route have significantly decreased the amount of antibody required for protection as compared with its administration via the systemic route (Maillet et al. 2011; Leyva-Grado et al. 2015). The other alternative method that has shown tremendous success is the use of engineered antibodies as a DNA delivery method. The engineered antibody gene can be directly delivered to nasal cells using a viral vector-based system, leading to the expression of antibodies and avoiding the continuous need for antibody dosing (Patel et al. 2020). This gene-based antibody delivery method is beneficial and safe for administration in the

Table 1 List of monoclonal antibodies in various stages of preclinical development against respiratory viral infections

Name	Delivery route	Origin	Mechanism	Target	Disease/Pathogen	Stage	References
Foralumab (Tiziana Life Sciences)	Nasal or oral	Anti-CD3 human monoclonal antibody	Anti-inflammatory effect	Interleukin-6 (IL-6) receptor	COVID-19	Phase 2	Karnam et al. (2020) and https://www.globenewswire.com/news-release/2021/02/02/2167825
Palivizumab	Intranasal	Humanised monoclonal antibody (IgG)	Neutralisation via blocking viral fusion	Antigenic site of the F protein of RSV	RSV	Preclinical animal studies	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01906032/full
Genetically engineered IgG Fc domain with enhanced binding affinity to mucin	Nasal spray formulation	Eureka's E-ALPHA® phage library	Neutralisation	SARS-CoV-2 S1 spike protein	COVID-19	Preclinical animal studies (hACE2-transgenic mice model)	Zhang et al. (2020)
Diomat biopolymer loaded with Active Motif's 414–1 human IgG monoclonal antibodies	Nasal spray	Recombinant human IgG antibodies	Neutralisation	Receptor-binding domain	COVID-19	In vitro stage	Wan et al. (2020)
ALX-0171	Nasal spray	Trimeric nanobody	Neutralisation	Antigenic site II of RSV F protein	RSV	Phase, I/IIa trial	Larios Mora et al. (2018)
Monovalent and bivalent VHH nanobodies (Ablynx)	Intranasal	llamas nanobodies	Neutralisation	Antigenic site B in H5 hemagglutinin	Influenza A virus	Preclinical animal studies	Ibañez et al. (2011)
Bispecific nanobody	Intranasal	Alpaca spike immunised immune library	Neutralisation	Receptor-binding domain	COVID-19	Preclinical animal studies (hACE2-transgenic mice model)	Wu et al. (2021)
Single-domain antibodies (nanobodies)	Intranasal (stable in aerosolised delivery)	Yeast surface-displayed library of synthetic nanobody	Locks spike into inaccessible down-state	Spike	COVID-19	In vitro stage (animal studies not done)	Schoof et al. (2020)

high-risk population, which includes immunocompromised hosts, pregnant women, etc. (Hollevoet and Declerck 2017).

The AAV and AdV are the most widely used vectors for gene delivery vehicles, but a substantial fraction of the human population has active antibodies to AAV2 (32%) and AdV (55%) (Chirmule et al. 1999), which can improve the adhesive trapping of these viral vectors in mucus mesh and inactivate their ability to transduce target cells. Additionally, nAbs to AAV1, AAV2, AAV5, AAV6, AAV7, and AAV8 are also present in the airways of healthy individuals (Halbert et al. 2006; Calcedo et al. 2009). Repeated dosing of these gene delivery vectors may lead to increased levels of nAbs to AAV and AdV, thus hampering the overall effect (Kim et al. 2016). ALX-0171 (Ablynx) is a trimeric nanobody, composed of three identical antibody domains linked end to end by flexible peptides that bind epitopes in the antigenic site II of the RSV F protein (Detalle et al. 2016; Larios Mora et al. 2018). The trivalent nanobody has shown better breadth and potency than the already marketed antibody palivizumab for RSV A and B strains. The ALX-0171 was given by nebulisation through a face-mask thus depositing in the upper and lower airways, showed faster and highly potent antiviral therapeutic effects even at lower dosages in the respiratory tract (Larios Mora et al. 2018). A phase, I/IIa trial on hospitalised RSV-infected children (aged 1–24 months) revealed a reduction in viral load in nasal swabs after daily treatment with ALX-0171 via inhalation device for three consecutive days (Cunningham et al. 2021). Despite encouraging results in numerous animal models, research has been halted due to a lack of effectiveness data during a phase 2 study in children (in Japan) (Sécher et al. 2019). An intranasal treatment is critical, especially when treating an acute disease in a clinical setting, where the administered dose is a limiting factor and makes it more cost-effective.

Nebulisation is a medication conveyance framework used to deliver medication in the form of a mist inhaled into the lungs and is one of the preferred methods used for uniform and quick delivery of mAbs to the lungs while minimising protein degradation and aggregation (Respaud et al. 2015; Hertel et al. 2015). The other, more favoured way to increase the concentration of mAbs in the inhaled fraction is to couple the mAb with nanoparticles. The use of nanoparticles as delivery systems allows for a reduction in antibody dosing, increases area of coverage, reduces immunogenicity, and controlled release (Sousa et al. 2017). However, the half-life of inhaled Abs in humans is approximately 16–24 h (~ 1 day) (Koussoroplis et al. 2014; Matthews et al. 2020). The encapsulation of antibodies in nanoparticles allows for the slow release of these antibodies, resulting in an increase in their overall bioavailability. The post-nebulisation stability profile of mAbs in the respiratory tract is a practical challenge. Gai et al. (2020) have shown that a nanobody developed against the nCOV-19 showed high stability post-nebulisation. To increase antibody retention in respiratory mucosa, Zhang et al. (2020) engineered a human antibody that recognises SARS-CoV-2 S1 spike protein with a higher affinity for mucin and was found to be effective in both nasal and lung areas 7 days after viral exposure in a mouse model (Matthews et al. 2020). Other concerns include the possibility of immunogenicity of antibodies used in the nasal spray due to the anticipated long-term frequent use as prophylaxis. However, the use of engineered antibodies with an increased in vivo half-life will significantly reduce the dosing and the risk of immunogenicity (Harding et al. 2010; Borrok et al. 2017).

The other potential challenge with inhaled delivery of mAbs is the optimal biodistribution of therapeutic antibodies. Antibody allocation fundamentally depends upon the rate of extravasation in the tissues. Generally, extravasation of mAbs in living systems occurs via three different processes, i.e. passive diffusion, convective diffusion, and transcytosis (Ryman and Meibohm 2017). The functioning of these processes depends on the size and physicochemical properties of the biomolecules. Due to the large size of IgG molecules, most of the antibodies from the blood to tissues are distributed through convective transport. Antibodies are large macromolecules that exhibit restricted distribution to the lungs once injected through an intravenous route. After pulmonary delivery, an inhaled antibody enters systemic circulation very slowly via the airways. In the respiratory organs, the inhaled concentration of mAb is predicted to be higher than that of the blood compartment. Consequently, the concentration profile within the blood compartment might not mirror the actual kinetics of inhaled mAb within the lungs (Guillon et al. 2019). The movement of inhalation and the speed at which aerosol particles are released from the system and pass through the airways also have a strong effect on the patterns of pulmonary deposition. In general, in terms of overall lung deposition and distal airway penetration, a design technique for the inhalation system that pairs slow-moving aerosol with smaller drug particles has so far been seen as the most efficient process (Thompson 1998; Zierenberg 1999; Borghardt et al. 2018).

The lungs are naturally absorptive to several therapeutic peptides and proteins as compared to any other portal of entry into the body. The large absorption surface of the lung is covered with a thin layer of fluid that makes it attractive for the dispersion of inhaled aerosol therapeutics in high concentrations. There are several pharmacokinetic (PK) processes unique to the pulmonary system and the inhalation pathway due to the complexity of the lung, making pulmonary PK typically distinct and much more complicated than that delivered by other pathways (Weber and Hochhaus 2013). The production of inhaled medications and the production of inhalation products should therefore be based on a clear understanding of the entirety of all processes of

pulmonary PK (Borghardt et al. 2018). Moreover, the presence of antiproteases in the lung surface fluids prevents proteolytic degradation of therapeutic proteins and, in turn, increases their bioavailability. The reduced mucociliary movements in the lungs further promote absorption as compared to the nasal passages and gastrointestinal tract, where the lateral movement of the bulk fluid reduces the residence time of molecules at the absorptive surface (Patton 1996; Patton et al. 2004). It is critical that therapeutic proteins have a longer residence period within the nasal canal in order to maintain the appropriate concentration and delivered volume following nasal delivery so that the therapeutic dosage can be absorbed (Arora et al. 2002). Different formulation methods including keeping the pH of the nasal formulation within the range of pH 4.5 to 6.5, are frequently used to produce therapeutic protein deposition inside the nasal mucosa (Pavis et al. 2002). To increase the residence time in the nasal cavity, different dosage forms, such as gelatin, ointments, liposomes, microspheres, and emulsions, have been used.

The other major challenge associated with inhaled therapeutics is the lack of suitable animal models for preclinical studies because of the disparities between human and animal model anatomy, physiology, and respiratory patterns, making it difficult to draw a clear correlation between them. The surface area of the olfactory mucosa differs among species. Rats and mice have long been employed as test animals. In rats, the olfactory region accounts for more than half of the nasal cavity's total surface area, but in humans, the olfactory region accounts for about 3% to 5% of the total nasal cavity surface area. When comparing data from animal trials to human data, it is critical to take into account anatomical and histological distinctions Dahl and Mygind, 1998; Lochhead and Thorne 2012; Gizurarson 2012). Macaques are the most appropriate model due to their close similarity to human infants displaying similar ventilation parameters, nose breathers like infants and body weight in the range of a full-term newborn human (Guillon et al. 2019). In recent experiments, researchers has utilised lambs as animal models to studying the pathogenesis, immunological response, and pharmaceutical testing and quantifying the total dosage emitted by the nebuliser per administration by weighing the nebuliser before and after administration and calculating the nebulised volume (Ackermann 2014; Larios Mora et al. 2018). The preterm and neonatal lamb lung has developmental, anatomical, cellular, physiologic, and immunologic characteristics similar to human babies. Furthermore, the lamb lung is vulnerable to respiratory viruses such as RSV strains that infect babies and induce comparable bronchiolar abnormalities (Sitthicharoenchai et al. 2020). A schematic representation of the respiratory system of human, mice, and lamb is shown in Fig. 4.

Antibody-dependent enhancement (ADE) of viral entry is a major concern in many viruses that aggravate the symptoms in secondary infections (Kumar et al. 2020). ADE has also been observed for coronaviruses (Wan et al. 2020). Several studies have shown that the serum antibodies induced by the SARS-CoV spike enhance viral entry into Fc receptor-expressing cells (Kam et al. 2007; Jaume et al. 2011; Wang et al. 2014). A study showed that cats immunised with a recombinant vaccinia virus expressing the spike (S) protein antigen of the coronavirus causing feline infectious peritonitis leads to more severity in future infections as compared to the control group that was challenged with the coronavirus (Corapi et al. 1992). The postulated mechanism behind this was found to be the induction of infection-enhancing antibodies causing ADE (Corapi et al. 1992; Hohdatsu et al. 1998). A study conducted on nAbs

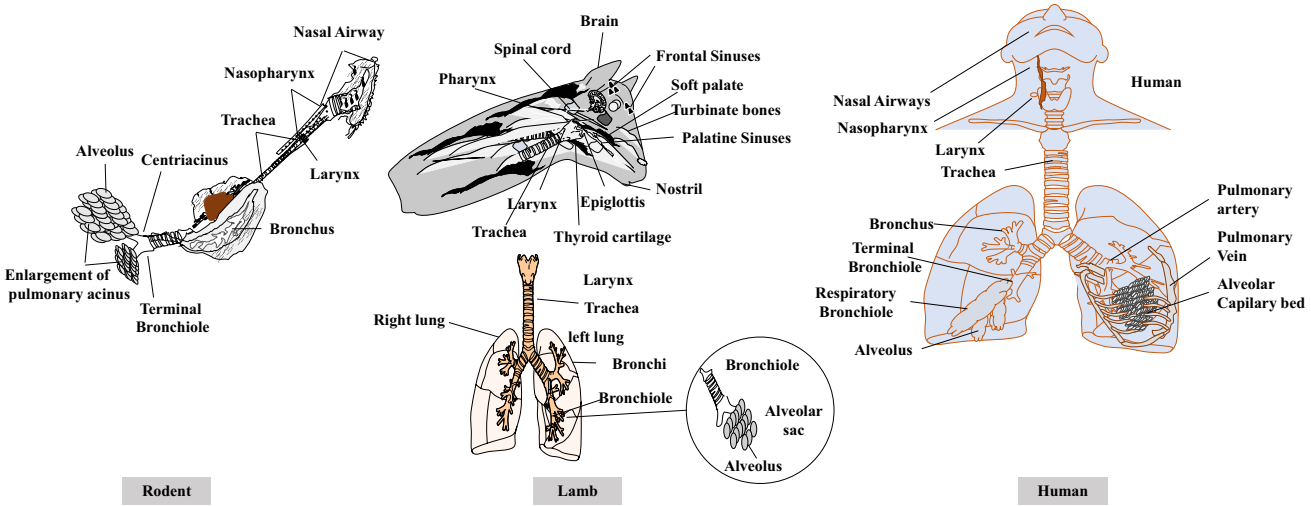

Fig. 4 Schematic view of the respiratory system of mice, lamb, and humans with their parts

targeting receptor-binding domain (RBD) of MERS-CoV, also supports this and clearly shows the binding of neutralising Ab triggers the spike to undergo conformational changes that mediate viral entry into Fc receptor-expressing cells, enhancing infection via ADE (Wan et al. 2020).

Moreover, the current practical challenge that must be explored is the suitability of the isotype of antibody that should be used for intranasal administration, whether it should be IgA or IgG. In the natural mucosal respiratory system, IgA antibodies are more abundant and provide better protection against respiratory infections, but practically, the production and purification of IgA antibodies is a big challenge (Weltzin et al. 1996). Unlike IgG antibodies, which are easily purified using protein A and G resins due to their affinity for the Fc region, IgA antibodies are not easily purified, and there is currently no suitable method for IgA purification. However, the effectiveness of antibodies in preventing respiratory infection seems to rely mostly on their abundance and localisation, with only a minor influence on the isotype. Mucosal antibodies, IgA or IgG, are closer to the site of infection than serum antibodies, and this may, therefore, better reflect the protective capacity against respiratory infections (Jacobino et al. 2018).

Additionally, the efficacy of inhaled antibody treatment depends on several factors, like the antibody format used (scFv, sdAbs, Fab, IgG, IgM, IgA, or IgY), a characteristic that may limit transport through biological membranes (nasal mucosa) (Samson et al. 2012; Parray et al. 2020a). Secondly, the optimal concentration and dosing of the antibody to be used should be assessed, as absorption of the antibody varies from patient to patient (Dupuis-Girod et al. 2014, 2016).

The other practical challenges with the formulation of antibodies as an inhaled delivery system are the requirement of immunoglobulins with favourable biophysical and biochemical properties that can withstand the high forces associated with formulation, delivery, and inhalation. In addition, the choice of the formulation solvent is a critical factor. The molecular, pharmacological, and functional integrity of the antibodies must be maintained during the formulation and delivery process to achieve effective and safe treatment (Respaud et al. 2015). The stability and functionality of the antibodies in various aerosolisation formulations, like polyols, surfactants, sugars, and small amino acids, has been found to have minimal impact on molecular integrity and pharmacological activity. However, the concentration of these stabilisers should be kept to the minimum possible limit to reduce side effects (Montharu et al. 2010; Respaud et al. 2015). Recent studies conducted using llama antibodies with a delivery formulation showed that naturally occurring single domain antibodies are highly soluble, stable, and showing biophysical characteristics well suited for respiratory delivery (Van Heeke et al. 2017).

Epidemiological studies revealed that pathogenicity of severe COVID-19 cases is higher in older age groups as compared to children and their plausible correlation with pre-existing anti-coronaviruses antibodies might have some role in COVID-19 pathogenesis. Moreover, these studies have shown by the presence of pre-existing antibodies that the community would have acquired from viruses which are closely related and have already been endemic in the community. A seroepidemiology and seroprevalence study conducted on human coronavirus HKU1 (HCoV-HKU1) infection in Hong Kong supports the hypothesis that the community contains pre-existing immunity to related coronaviruses (Chan et al. 2009). However, the pre-existing antibodies to other seasonal coronaviruses have been shown to have no effect on COVID-19 severity. Meanwhile, ADE concern cannot be completely neglected for coronavirus infections, especially with the possibility of the co-infection/re-infection with other related viruses or the emergence of new quasispecies harbouring mutations (Ricke 2021).

Perspectives

Antibody-based therapies have many advantages over vaccine-induced immunity as they provide accelerated protection, are effective in high-risk populations, and can be made available faster than vaccinations in emergencies and outbreaks. A rapid and strategic development of highly targeted preventive and therapeutic antibody-based strategies has the potential to alter the course of an epidemic. Recent outbreaks of viral pathogens (SARS-COV-2) have provided us with an impetus towards developing alternatives to vaccines.

Passive transfer of antibodies through the intranasal or mucosal route for the prevention and treatment of SARS-CoV-2 and as a prophylactic is a promising alternative approach for a large population, particularly for developing countries. It provides a promising strategy to prevent SARS-CoV-2 infection and control disease severity, to be used as a stand-alone antiviral prophylaxis tool, complementary to future vaccination programs. This approach is suitable to block infection in people who are at high risk of transmitting or causing disease spread in the community, including front-line health-care staff, marginalised populations, the elderly, the immunocompromised, and those with existing comorbidities. In addition, mAbs can be rapidly developed and tested unlike vaccines and may offer a quick solution to overcome community transmission as well as disease progression. In the future, safety issues regarding the human use of mucosal mAbs are likely to be addressed by clinical trials and will open a new way forward towards health management of airborne respiratory infections.

In summary, inhaled therapeutics are most effective when they are designed and administered in their intended location

in the airways, in tandem with a well-designed inhalation unit that will confer optimal therapeutic concentrations in the respiratory system. The development of cross-reactive and cross-protective antibodies in inhaled formulations effective against diverse coronaviruses (MERS, SARS, CoV-2) would extend their use and aid as a pandemic preparedness tool and minimise the economic burden.

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Declarations

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Conflict of interest The authors declare no conflict of interest.

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