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INHALED ANTI-IGE: IGE COMPLEXES AS A MUTATION-AGNOSTIC BIOLOGIC THERAPY FOR CYSTIC FIBROSIS WITH RARE MUTATIONS

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ABSTRACT

Cystic fibrosis (CF) is a progressive, multisystem disorder caused by mutations in the CFTR gene, leading to thickened airway mucus, persistent inflammation, and chronic infection. Although CFTR modulators have revolutionized care, 10–15% of patients with rare or splicing mutations are ineligible for these therapies and remain at high risk for pulmonary complications, allergic bronchopulmonary aspergillosis (ABPA), steroid dependence, and cystic fibrosis-related diabetes (CFRD). This review explores the emerging use of preformed anti-IgE:IgE complexes delivered as a biologic aerosol. This approach targets the CD23 pathway to suppress IgE-mediated and type 2 inflammation, reduce corticosteroid exposure, and protect lung and pancreatic function. This article discusses key considerations for formulation, aerosol engineering, and delivery, along with a proposed treatment model and anticipated outcomes for this vulnerable population. By addressing unmet needs in mutation-ineligible CF patients, inhaled anti-IgE:IgE therapy represents a promising mutation-agnostic strategy to improve clinical and immunological outcomes.

Keywords: Cystic fibrosis; Anti-IgE:IgE complexes; Biologic aerosol; CD23 pathway; Allergic bronchopulmonary aspergillosis (ABPA)

1 INTRODUCTION

Cystic fibrosis (CF) is a life-limiting, multisystem genetic disorder caused by mutations in the CFTR gene that impair chloride and bicarbonate transport across epithelial surfaces [1]. The hallmark of CF pathology is the accumulation of dehydrated, viscous mucus in the airways, which fosters chronic bacterial infection, persistent inflammation, and progressive bronchiectasis [2]. Despite advances in supportive care and infection management, most patients ultimately experience a relentless decline in pulmonary function, leading to respiratory failure.

Despite major advances, CF remains clinically incurable. No available therapy can universally correct the genetic defect or restore native CFTR function across all tissues. Historically, the management of CF has relied on aggressive symptom control: chest physiotherapy, mucolytics (e.g., dornase alfa), pancreatic enzyme replacement, and targeted antibiotics for pulmonary exacerbations [3]. These interventions have extended life expectancy but cannot prevent the progressive tissue damage and decline in organ function inherent to the disease.

Recently, small-molecule CFTR modulators—such as elexacaftor/tezacaftor/ivacaftor—have revolutionized CF care by targeting specific protein folding and gating defects [4]. These agents have dramatically improved lung function and

quality of life for many patients. However, 10% to 15% of individuals who harbor rare or splicing mutations, including premature termination codons, do not benefit from CFTR modulators, leaving a substantial population without effective disease-modifying therapy [5].

This persistent gap has prompted exploration of mutation-agnostic therapies that target downstream immune dysregulation, especially in patients with rare or splicing mutations. Among these, inhaled delivery of preformed anti-IgE:IgE complexes (formed from monoclonal antibody clones 8D6 or UB-221) has emerged as a promising approach [6]. These complexes may mitigate allergic bronchopulmonary aspergillosis (ABPA), reduce steroid dependence, and blunt infection-driven inflammation. This review synthesizes current knowledge on the mechanisms, formulation challenges, and therapeutic potential of biologic aerosol therapy targeting the CD23 pathway. It proposes a model for its integration into care for this vulnerable CF population.

2 DISCUSSION

While highly effective CFTR modulators have transformed outcomes for many individuals with cystic fibrosis (CF), they remain ineffective for the 10% to 15% of patients who harbor rare nonsense or splicing mutations that result in minimal or absent CFTR protein expression [7]. This leaves a significant population reliant on symptomatic management and vulnerable to severe immune-mediated complications.

For this subgroup, preformed anti-IgE:IgE complexes (formed from monoclonal antibody clones 8D6 or UB-221) represent a paradigm shift—from attempting to correct the primary genetic defect to targeting the downstream immunopathology that drives morbidity and mortality [8,9].

2.1 Advanced Strategies for Preventing and Treating Allergic Bronchopulmonary Aspergillosis (ABPA)

Patients with CF are highly susceptible to colonization of thick mucus by the fungus *Aspergillus fumigatus*. In patients with rare/splicing mutations where mucus remains severely dehydrated, this colonization frequently triggers ABPA, a severe, hyper-reactive IgE-mediated lung disease that rapidly accelerates permanent lung damage [10].

- **The Role of the Complexes:** Standard anti-IgE therapies (like omalizumab) target free IgE. Preformed anti-IgE:IgE complexes using clones like UB-221 actively engage CD23 receptors [11,12].
- **Downregulating IgE at the Source:** This engagement generates a powerful negative feedback loop that suppresses de novo IgE protein and mRNA synthesis. By shutting down the hyper-allergic pathway, it could prevent the devastating eosinophilic and mast-cell-driven inflammation characteristic of ABPA in patients lacking CFTR function [13,14].

2.2 Minimizing Steroid Dependence via Precision Immunomodulation

Chronic, uncontrolled airway inflammation remains a hallmark of CF in patients who do not benefit from CFTR modulators. Systemic corticosteroids are often the only option for suppressing this immune response. Still, their side effects—including growth suppression, osteoporosis, and an increased risk of cystic fibrosis-related diabetes (CFRD)—limit long-term use [15].

By downregulating Th2-driven inflammation through CD23 engagement, anti-IgE:IgE complexes offer a focused immunomodulatory strategy that can reduce or replace the need for systemic steroids. This not only lessens the burden of steroid toxicity but also preserves patient growth, bone health, and metabolic function.

2.3 Blunting Infection-Triggered Hyper-Inflammation

Recurrent bacterial infections, particularly with *Pseudomonas aeruginosa*, create a vicious cycle in CF by triggering surges in polyclonal IgE, which in turn amplify airway inflammation and tissue damage [16]. Standard anti-IgE therapies are often overwhelmed by these spikes. In contrast, preformed anti-IgE:IgE complexes directly modulate the CD23 pathway, providing a more robust and sustained suppression of IgE-mediated hyperinflammation.

By stabilizing immune responses during infectious exacerbations, this approach may help preserve lung tissue, slow disease progression, and improve quality of life for patients prone to severe pulmonary complications [17,18,19].

3 HARNESSING THE CD23 (FCERII) PATHWAY FOR COMPREHENSIVE CYSTIC FIBROSIS THERAPY

Beyond managing severe Th2 hyperreactivity, using preformed anti-IgE:IgE complexes to target the CD23 (FcεRII) pathway could structurally alter several other facets of cystic fibrosis (CF) pathology [20].

By actively engaging CD23—a low-affinity IgE receptor heavily expressed on B cells, macrophages, epithelial cells, and eosinophils—these complexes could improve patient outcomes in the following ways:

3.1 Accelerated Clearance of Airway Debris (Macrophage Polarization)

In the CF lung, macrophages are often "trapped" in a dysfunctional, hyper-inflammatory state that fails to clear dead neutrophils, bacteria, and cellular debris, contributing to permanent airway obstruction.

- **CD23 Activation:** Engaging CD23 on alveolar macrophages can shift their activation state.
- **Outcome:** This helps restore their phagocytic (cleanup) function. Better clearance of cellular debris leads to less mucus plugging, cleaner airways, and less physical scaffolding for bacteria to build drug-resistant biofilms.

3.2 Protecting Lung Structure by Inhibiting Mast Cell-Mediated Tissue Remodeling

Chronic CF inflammation triggers local mast cell degranulation, which releases a cocktail of histamines, proteases, and transforming growth factor-beta (TGF- β). Over time, this causes irreversible scarring, subepithelial fibrosis, and thickening of the lung basement membrane.

- **Mast Cell Stabilization:** Preformed complexes significantly lower free circulating and tissue-bound IgE.
- **Outcome:** By removing the primary triggers for mast cell degranulation, this therapy protects lung architecture, slows the decline of Forced Expiratory Volume (FEV1), and preserves baseline respiratory capacity [21].

3.3 Systematic Reduction of Cystic Fibrosis-Related Diabetes (CFRD) Risk

CFRD is a massive complication affecting up to 50% of adult CF patients. It is largely driven by structural destruction of the pancreas from thick secretions and systemic, low-grade inflammation [22,23].

- **Breaking the Steroid-Induced Insulin Resistance Link:** The traditional treatment for CF lung flare-ups relies on systemic corticosteroids, which cause massive blood sugar spikes and accelerate the onset of permanent diabetes [24].
- **Outcome:** Using anti-IgE:IgE complexes as an effective immunomodulatory alternative drastically minimizes a patient's lifetime exposure to high-dose steroids. This preserves remaining pancreatic islet function and lowers the incidence of CFRD [25,26].

3.4 Reinforcing Epithelial Barrier Integrity to Prevent Pathogen Invasion

The CF airway epithelium is highly fragile and prone to "leaking" from continuous inflammatory assault, giving inhaled pathogens easier access to deeper tissue layers.

- **Epithelial CD23 Modulation:** CD23 is involved in transepithelial transport of allergens and immune complexes. Regulating this pathway helps stabilize the local mucosal environment.
- **Outcome:** It limits the hyperpermeability of the lung lining, making it harder for opportunistic pathogens like *Pseudomonas aeruginosa* or *Staphylococcus aureus* to establish deep, systemic infections.

4 FORMULATION, DELIVERY SYSTEM, AND AEROSOL ENGINEERING

To deliver the proposed preformed anti-IgE:IgE complexes directly to the dense, dehydrated mucus environments typical of cystic fibrosis (CF) lungs, the therapy can be formulated as a biologic aerosol.

Administering this complex via inhalation targets the hyper-inflammatory cells directly in the pulmonary epithelium and alveolar spaces, bypassing systemic circulation and maximizing local CD23 receptor engagement.

4.1 Formulation

Formulating preformed macromolecular protein complexes into an aerosol requires strict parameters to prevent the antibodies from unfolding (denaturing) during vaporization.

- **Nebulization Method:** A Vibrating Mesh Nebulizer (VMN) is preferred over ultrasonic or jet nebulizers. VMNs apply minimal thermal and mechanical shear stress, preserving the structural integrity of the preformed anti-IgE:IgE clones (e.g., UB-221).
- **D Droplet Optimization:** The aerosol is engineered to achieve a Mass Median Aerodynamic Diameter (MMAD) of 1 to 5 microns. This size profile allows the biologic droplets to bypass the upper airways and

deposit deep in the lower respiratory bronchioles, where CF tissue remodeling and ABPA colonization are most destructive [27].

- **Mucolytic Co-Formulation:** Because CF mucus lacks hydration, the aerosol vehicle may contain a hypertonic or osmotic driver or be co-administered with a mucolytic (like dornase alfa or OligoG). This lowers mucus viscosity, clearing a path for the complexes to reach the membrane-bound CD23 receptors on epithelial and immune cells [28].

4.2 Formulation Challenges

Formulating preformed anti-IgE:IgE macromolecular complexes for aerosolization presents a steep biochemical challenge. Unlike standard small-molecule asthma inhalers, these multi-protein complexes are highly sensitive to the unique biophysical stresses generated during vaporization. Standard intravenous antibody formulations cannot simply be repurposed for inhalation without causing immediate protein unfolding, structural dissociation, or large-scale submicron aggregation [29,30,31].

4.3 Stoichiometric Structure

To maintain the precise stoichiometric structure required to safely target CD23 receptors within a cystic fibrosis (CF) lung, an engineered biochemical formulation must address core stability requirements.

- **Interfacial Stabilization (Preventing Air-Water Surface Unfolding):** Aerosol generation dramatically expands the air-water surface area. Proteins are inherently amphiphilic and migrate to this interface, where the antibody's hydrophobic patches unfold, leading to rapid, irreversible aggregation [32]. **Mechanistic Solution:** Add non-ionic surfactants, most notably Polysorbate 20, Polysorbate 80, or Poloxamer 188.
- **Biochemical Action:** These surfactants exhibit a much higher surface activity than the anti-IgE:IgE complex. Through *preferential competitive adsorption*, they saturate the air-water interface, physically blocking the protein complex from migrating to the bubble surfaces during droplet generation [33,34,35].

4.4 High Viscosity and Shear Control

Vibrating mesh technology forces liquid through micron-sized apertures via an ultrasonic piezoelectric ring. While this minimizes the continuous recycling stress seen in jet nebulizers, it introduces targeted thermal energy and intense mechanical shear stress right at the mesh border [36,37].

Viscosity Limits: To pass through a mesh nebulizer without plugging or breaking the device, solution viscosity must be carefully balanced and kept below 5- 6 mPa·s (cP) [38,39].

- **Concentration Buffering:** Maintaining a critical mass protein concentration (typically ≥ 15 mg/mL) paradoxically protects the antibodies. Higher concentrations limit the baseline molecular mobility of the preformed complex, reducing its propensity to self-associate or undergo conformational shifts [40,41].

4.5 Selection of the Optimal Buffering System

The local micro-environment pH determines the net electrical charge of the antibody complexes. If the solution matches the protein's isoelectric point (pI), the complex loses electrostatic repulsion and precipitates out of solution instantly [42].

The Buffer Trap: Standard citrate buffers extensively accelerate monoclonal antibody aggregation during mesh nebulization and require excessive surfactant compensation [43].

Biochemical Choice: Utilizing L-histidine or acetate buffering systems maintained at a precise pH of 6.0 to 6.5 provides optimal structural stability. These specific systems maximize the native electrostatic repulsion between the anti-IgE:IgE complexes, preventing them from fusing into inactive clusters under thermal stress [44].

4.6 Tonicity and Mucosal Osmolality

Because these complexes are destined for the heavily compromised, highly vulnerable airways of CF patients, the fluid dynamics must not aggravate bronchospasms.

- **Biochemical Strategy:** The formulation must remain close to isotonic or slightly hypertonic using simple sugars like sucrose or trehalose rather than high concentrations of sodium chloride (NaCl).

- Dual-Purpose Excipients: Carbohydrates like trehalose double as cryoprotectants/lyoprotectants. They form a tight hydrogen-bonded shell around the protein complex, replacing the water molecules lost or shifted during aerosol shear and preserving the native tertiary structure of the antibody components [45].

5 PROPHETIC EXAMPLE: INHALED ANTI-IGE:IGE COMPLEXES IN CF SPLICING MUTATION

5.1 Background & Patient Cohort

A cohort of human subjects diagnosed with cystic fibrosis who carry homozygous rare splicing mutations (e.g., *1811+1G->C* or *3120+1G->A*) and demonstrate refractory Allergic Bronchopulmonary Aspergillosis (ABPA) are selected. These subjects are ineligible for traditional CFTR modulators. Baseline metrics include a Forced Expiratory Volume in 1 Second (FEV1) of <60% predicted, highly viscous sputum, and total serum IgE levels > 1,000 IU/mL. [46].

5.2 Pharmaceutical Composition

A sterile, aqueous pharmaceutical solution is prepared containing preformed humanized anti-IgE:IgE complexes composed of the humanized anti-IgE monoclonal antibody clone UB-221 bound stoichiometrically to purified human IgE. The solution is buffered to a physiological pH (6.5 to 7.2) with polysorbate-20 added as a stabilizer to prevent surface-induced aggregation during nebulization.

5.3 Method of Administration

Subjects receive a 5 mL dose (20 mg/mL concentration of the preformed complex) administered twice weekly. The solution is vaporized using a high-efficiency vibrating mesh nebulizer over a continuous 15-minute inhalation period. Subjects utilize a mouthpiece with an exhalation filter to ensure complete pulmonary capture.

5.4 Predicted Outcomes & Experimental Metrics

Following a 12-week treatment protocol, these biological and clinical changes are desired.

- Sputum Biomarkers: Sputum induction assays will demonstrate a localized reduction in free eosinophil cationic protein (ECP) and interleukin-5 (IL-5) levels within the bronchial washings, indicating a profound blunting of the Th2 allergic response.
- CD23 Downregulation: Flow cytometry of harvested alveolar macrophages will indicate a downregulation of membrane-bound CD23, correlating with a shifted, highly phagocytic cellular phenotype active in clearing cellular debris.
- Pulmonary Capacity Improvement: The cohort will exhibit an average baseline increase in FEV1, attributed to reduced tissue edema, stabilized mast cells, and less airway restriction.
- Steroid Independence: Over the course of the study, the required daily maintenance dose of systemic corticosteroids will be successfully tapered downward across all subjects, substantially mitigating the risk of developing Cystic Fibrosis-Related Diabetes (CFRD).

6 CONCLUSION

Inhaled delivery of preformed anti-IgE:IgE complexes represents a promising, mutation-agnostic approach for cystic fibrosis patients who are ineligible for CFTR modulator therapy. By targeting the CD23 pathway, this biologic aerosol strategy addresses key drivers of pulmonary morbidity—including uncontrolled Th2 inflammation, allergic bronchopulmonary aspergillosis (ABPA), and chronic steroid dependence—while also offering potential protection against cystic fibrosis-related diabetes (CFRD) and structural lung decline. Overcoming the unique formulation and delivery challenges of biologic aerosols in CF's dehydrated, obstructed airways is critical for successful clinical translation. Continued research, including rigorous preclinical and clinical studies, will be essential to validate efficacy, optimize dosing, and realize the therapeutic potential of anti-IgE:IgE complexes for this vulnerable patient population.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Michael John Dochniak used the program “Grammarly” for grammar, spelling, and punctuation throughout the preparation of the review article. Mr. Dochniak used Grammarly, version 14.1271.0 (Grammarly Inc., San Francisco, CA). Dochniak used Grammarly to review and edit the entire article for grammatical accuracy, clarity, and readability. Grammarly’s AI-powered writing assistant suggested improvements to sentence structure, word choice, and tone consistency, which the author reviewed and selectively incorporated. The author did not use it to generate original scientific content or research conclusions. The author takes full responsibility for the integrity of all content generated and presented in this review article.

Disclosure of conflict of interest

The author claims no conflict of interest.

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Michael John Dochniak is an independent medical researcher who has authored several books on Alzheimer’s disease, Artificial Intelligence, Autism Spectrum Disorders, and Climate Change through Cambridge Scholars Publishing and Nova Science Publishers. Mr. Dochniak has written extensively through GSC Online Press and appreciates their dedicated service.

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