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# ALLERGOONCOLOGY: IGE/ALLERGEN COMPLEXES FOR SOLID TUMORS

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## ABSTRACT

AllergoOncology is an emerging field that investigates the use of immunoglobulin E (IgE) antibodies as innovative agents in cancer immunotherapy. This review evaluates the therapeutic potential of preformed humanized IgE/folate receptor alpha (FRα) complexes (IgE-AC) to stimulate the immune system and inhibit solid tumors overexpressing FRα. The mechanistic focus is on how IgE-ACs activate agranulocytes and engage CD23-mediated Facilitated Antigen Presentation (FAP), ultimately inducing the production of FRα-specific IgE autoantibodies. These autoantibodies are designed to inhibit aggressive FRα-overexpressing solid tumors, including epithelial ovarian, non-small cell lung, endometrial, and triple-negative breast cancers. IgE-AC immunotherapy offers a promising pathway for durable and selective immune activation, with the potential to improve long-term outcomes by reducing the incidence and recurrence of FRα-positive tumors. Limitations such as hypersensitivity risk, patient selection, and the need for further clinical validation are also discussed, highlighting the importance of ongoing research to realize the full potential of this strategy.

**Keywords:** AllergoOncology; Folate Receptor Alpha (FRα); Humanized IgE/Allergen Complexes (IgE-AC); Facilitated Antigen Presentation (FAP); Immune Memory; Autoantibodies

## 1 INTRODUCTION

The search for innovative and effective immunotherapies for solid tumors has become a focal point in cancer research, driven by the persistent challenges of tumor recurrence and treatment resistance. Among solid tumors, those overexpressing folate receptor alpha (FRα)—including epithelial ovarian, triple-negative breast, and lung adenocarcinomas—stand out due to their aggressive clinical course and high rates of relapse and mortality. Traditional IgG1-based therapies, particularly antibody-drug conjugates, have provided important advances but are limited by off-target toxicities and immune evasion mechanisms.

In response, the emerging field of AllergoOncology is exploring the therapeutic potential of immunoglobulin E (IgE) antibodies as next-generation immunotherapeutic agents. Unlike IgG, IgE antibodies can engage distinct immune effector pathways and elicit potent, localized anti-tumor responses. Notably, humanized IgE monoclonal antibodies such as Mov18 IgE target FRα-positive tumors and have demonstrated the ability to overcome the immunosuppressive tumor microenvironment. However, the lack of durable immune memory limits their long-term efficacy.

This review examines the development of preformed humanized IgE/FRα complexes (IgE-AC), a novel approach designed to induce tumor-specific IgE autoantibody responses and robust immunological memory. By leveraging mechanisms such as CD23-mediated FAP, IgE-AC therapy seeks to bridge innate and adaptive immunity, providing a sustained anti-tumor effect. The advantages, limitations, and prospects of IgE-AC immunotherapy are discussed, with a focus on its transformative potential for patients with FRα-expressing solid tumors.

## 2 DISCUSSION

Folate Receptor alpha (FRα) positive solid tumors—particularly epithelial ovarian cancer, triple-negative breast cancer, and lung adenocarcinomas—are associated with aggressive disease progression, high recurrence rates, and elevated morbidity and mortality [1,2,3].

Fully human IgG1 antibodies have been used to inhibit FRα-overexpressed solid tumors. This approach works especially well when the antibody is paired with a toxic drug as an antibody-drug conjugate, which enters the cancer cell and releases its payload to destroy the tumor [4]. While using a fully human or humanized IgG1-ADC provides excellent therapeutic precision against Folate Receptor-alpha (FRα)- positive solid tumors, this class of treatment carries several notable drawbacks. These limitations stem primarily from off-target "payload-driven" toxicities and biological resistance mechanisms [5,6].

Recent advances in antibody engineering have shifted the focus beyond the conventional IgG class to unlock more powerful immune activation strategies. Mov18 IgE, a next-generation monoclonal antibody, utilizes the IgE isotype to selectively inhibit FRα-positive tumor cells. Through high-affinity binding to immune effector cells such as macrophages and monocytes, Mov18 IgE triggers a robust and highly localized antitumor response, even at low concentrations. This approach effectively counteracts the immunosuppressive tumor microenvironment and induces potent local tumor destruction. However, a significant limitation remains: Mov18 IgE does not establish durable, systemic adaptive immune memory, leaving patients vulnerable to tumor recurrence. Despite its strong engagement of tissue-resident innate immune cells, Mov18 IgE lacks prolonged lymphatic surveillance and T-cell memory integration characteristic of traditional IgG-based therapies [7].

This review highlights the transformative potential of immunoglobulin E (IgE)-based immunotherapies for inhibiting folate receptor alpha (FRα)-positive solid tumors. IgE monoclonal antibodies, exemplified by Mov18 IgE [8,9,10,11], can harness tissue-resident innate immune cells, disrupt the immunosuppressive tumor microenvironment, and elicit robust, localized tumor cell destruction. Unlike traditional IgG-based strategies, IgE-based therapies offer the advantage of potent immune activation with reduced reliance on cytotoxic payloads, thereby potentially minimizing off-target toxicities and circumventing common resistance mechanisms. Importantly, these findings position IgE immunotherapy as a compelling alternative in the oncology landscape, with the capacity to address the unmet needs associated with FRα-overexpressing tumors.

Despite these advantages, IgE-based therapies present several notable limitations and challenges. Chief among them is the current inability to induce durable, systemic adaptive immune memory—a limitation that renders patients vulnerable to cancer recurrence. The absence of prolonged lymphatic surveillance and T-cell memory integration, features typically observed with IgG-based immunotherapies, continues to impede the achievement of lasting clinical benefit. Furthermore, safety concerns—such as the potential for hypersensitivity reactions—and the necessity for rigorous, biomarker-driven patient selection remain critical factors to address as the field advances toward clinical translation.

To address these obstacles, emerging approaches leverage novel strategies such as preformed IgE/allergen complexes (IgE-ACs) to stimulate FRα-specific IgE autoantibody production and promote long-term immune surveillance. This cancer immunotherapy mechanism utilizes preformed IgE-allergen complexes to activate CD23-mediated FAP, breaking self-tolerance to induce FRα-IgE autoantibodies. The process triggers CD23-mediated endocytosis of the complex in B cells, resulting in MHC-II antigen presentation to CD4+ T-helper cells, subsequently driving Class-Switch Recombination and long-term memory plasma cell differentiation to form FRα-specific IgE autoantibodies.

Preformed IgE/allergen complex example: MOv18 IgE is a standard Y-shaped monomeric antibody possessing two identical antigen-binding sites (Fab fragments), allowing it to bind to two separate FRα molecules simultaneously. The simultaneous attachment to two FRα on a cell surface is called bivalent binding (or homobivalent). Membrane-bound CD23 forms a stable trimer that structurally facilitates and favors multivalent interactions, including homobivalent and trivalent binding with its symmetrical ligand, IgE. Cooperative avidity effects via multiple lectin-like heads significantly enhance the overall binding stability [12].

IgE-ACs mechanisms involving CD23-mediated FAP and class-switch recombination may be particularly promising for generating lasting adaptive responses and reducing solid tumor recurrence. Moving forward, research should prioritize optimizing IgE autoantibody memory induction, integrating with complementary immunomodulatory agents, and refining patient selection through advanced biomarker discovery. Addressing these areas will be key to realizing the full therapeutic impact of IgE immunotherapy against FRα-expressing solid tumors.

*Limitations of Preformed Humanized IgE/ FRα Complexes (IgE-AC)*

- Risk of Hypersensitivity Reactions: Because IgE plays a key role in allergic responses, administration of IgE-AC may provoke immediate hypersensitivity or anaphylactic reactions, necessitating careful monitoring and risk mitigation.
- Limited Clinical Data: Most findings are based on preclinical studies; there is limited evidence from human clinical trials regarding efficacy, safety, optimal dosing, and long-term outcomes.
- Tumor Heterogeneity and Antigen Escape: Solid tumors may express variable levels of folate receptor alpha (FRα), and antigen downregulation or mutation may lead to therapeutic resistance and reduced effectiveness.
- Potential for Off-Target Effects: Non-specific activation of immune effector cells by IgE-AC could result in inflammation or damage to healthy tissues.
- Manufacturing Complexity: Large-scale production of consistent, GMP-grade humanized IgE antibodies and complexes is technically challenging and may impact accessibility.
- Patient Selection: Identification of appropriate biomarkers and selection criteria for patients likely to benefit from IgE-AC therapy remain under development.

### 2.1 Side Effects of Preformed Humanized IgE/FRα Complexes (IgE-AC)

- Allergic Reactions and Anaphylaxis: The most significant risk is the induction of severe allergic reactions, including anaphylaxis, due to IgE-mediated immune activation.
- Cytokine Release Syndrome: Potent immune cell activation may lead to systemic cytokine release, causing fever, chills, hypotension, and other inflammatory symptoms.
- Infusion or Injection Site Reactions: Localized pain, redness, swelling, or systemic symptoms may occur at the site of administration.
- Potential Autoimmunity: Breaking immune tolerance to self-antigens may theoretically increase the risk of autoimmune reactions, though this risk is not yet well characterized in clinical settings.
- Off-Target Immune Activation: Unintended activation of mast cells, basophils, or other immune cells could result in tissue inflammation or damage outside the tumor microenvironment.

In summary, IgE-based immunotherapies represent an exciting frontier in the treatment of aggressive FRα-positive solid tumors. Continued innovation, collaborative research, and rigorous clinical evaluation will be essential to overcome current challenges, optimize safety and efficacy, and fully unlock the transformative potential of these therapies for patients in need.

### 2.2 Prophetic Example: Clinical Application of Preformed Humanized IgE/FRα Complexes (IgE-AC)

For instance, a patient is diagnosed with recurrent, platinum-resistant epithelial ovarian cancer characterized by high-level expression of folate receptor alpha (FRα). Having exhausted conventional therapies, the patient is enrolled in an advanced immunotherapy protocol employing IgE-AC (e.g., Mov18 IgE, FRα).

Prior to treatment, comprehensive allergen screening and immune profiling are conducted to minimize the risk of hypersensitivity reactions. The patient receives a controlled intravenous infusion of IgE-AC under close clinical supervision, with premedication protocols in place. Premedication protocols for intravenous (IV) monoclonal antibody and immunoglobulin therapy typically combine an antipyretic, antihistamine, and sometimes a corticosteroid given 30 to 60 minutes prior to the infusion to prevent infusion-related reactions. Hopefully, the patient reports no mild infusion reactions, and tests show no evidence of severe allergies or autoimmune complications. The IgE-AC binds to CD23 receptors on B cells, triggering FAP and breaking immune tolerance to induce tumor-specific IgE autoantibody responses.

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If successful, within weeks laboratory monitoring reveals a robust expansion of FRα-specific IgE autoantibodies in the patient's serum, accompanied by the emergence of memory plasma cells and FRα-specific T-helper cells. Ideally, radiographic imaging demonstrates a marked reduction in tumor burden, and biopsies confirm increased infiltration of activated macrophages and eosinophils within the tumor microenvironment.

When successful, the patient's solid tumor status shows regression over the following year. Additionally, serial assessments show persistent FRα-specific IgE autoantibodies and a vigilant memory immune repertoire. Long-term follow-up suggests that IgE-AC immunotherapy not only mediates tumor regression but also establishes durable immune surveillance, substantially reducing the risk of recurrence compared to historical controls.

This prophetic example illustrates the potential for IgE-AC therapy to deliver adaptive and sustained antitumor immunity in patients with FRα-positive solid tumors, suggesting a new immunotherapy in precision oncology.

## 3 CONCLUSION

Preformed humanized IgE/FRα complexes (IgE-ACs) signal a new era in AllergoOncology by offering an active immunotherapeutic strategy that bridges both innate and adaptive immunity. Through CD23 engagement and FAP, IgE-AC therapy uniquely stimulates the generation of durable, FRα-specific IgE autoantibody responses and lasting immunological memory, potentially overcoming the recurring challenge of tumor relapse. While this approach addresses key limitations of passive IgE therapies, including inadequate immune surveillance, it also introduces new challenges such as hypersensitivity risk and the need for robust patient selection. As the field advances, sustained investment in preclinical and clinical research will be crucial to optimizing safety, efficacy, and accessibility. Ultimately, IgE-ACs immunotherapy holds the promise of not only improving clinical outcomes but also redefining the standard of care for patients with FRα-positive solid tumors.

## STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Grammarly was used for grammar, spelling, and punctuation throughout the preparation of the review article. The tool (Grammarly, version 14.1271.0, Grammarly Inc., San Francisco, CA) was used to review and edit the entire article for grammatical accuracy, clarity, and readability. Grammarly's AI-powered writing assistant provided suggestions on sentence structure, word choice, and tone consistency, which the author reviewed and selectively incorporated. The tool was not used to generate original scientific content, data analysis, or research conclusions. The author takes full responsibility for the integrity of all content generated and presented in this review article.

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Michael John Dochniak has authored several books on Alzheimer's disease, Artificial Intelligence, Autism Spectrum Disorders, and Climate Change through Cambridge Scholars Publishing and Nova Science Publishers.

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