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# Preventing Chronic Disease: AI-assisted Degranulation Immunotherapy

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## Abstract

Combinational immunotherapy represents an emerging therapeutic approach for chronic diseases, including cancer, autoimmune disorders, and neurodegenerative conditions. Controlled atopic responses are being investigated as mechanisms to direct immune cell activity to disease sites. However, combination strategies require careful balance between therapeutic efficacy and adverse event profiles. The objective is to assess whether artificial intelligence (AI) can accurately predict efficacy and safety of allergy-based degranulation immunotherapy combinations with Food and Drug Administration (FDA) approved monoclonal antibodies for chronic diseases, including cancer, multiple sclerosis, amyotrophic lateral sclerosis (ALS), and Alzheimer's disease. A systematic evaluation was conducted using Gemini AI (version 2.5 Pro) to assess treatment combinations pairing FDA-approved monoclonal antibodies with allergy-based degranulation immunotherapy approaches. Four disease categories were examined: cancer, multiple sclerosis, ALS, and Alzheimer's disease. The AI system evaluated complementary immunomodulation, predicted adverse events, and identified combinations with favorable benefit-risk profiles. AI identified several promising combination candidates with predicted favorable benefit–risk profiles. The system projected how treatments might augment each other's effects and pinpointed specific side effect risks. This supports rational prioritization for laboratory testing and trial design. AI evaluation can identify promising allergy-based degranulation immunotherapy combinations and predict adverse event patterns; however, these predictions require rigorous experimental validation before clinical application. This computational framework may accelerate the development of early-stage immunomodulatory combinations by prioritizing combinations for experimental testing, potentially reducing research costs. However, AI-generated predictions should not inform clinical decision-making without rigorous laboratory and clinical validation.

**Keywords:** Allergy-assisted degranulation; Amyotrophic lateral sclerosis; Artificial intelligence; Cancer; Multiple sclerosis

## 1. Introduction

Immunomodulation research using forced atopy shows that the allergy cascade may inhibit cancer [1,2], multiple sclerosis [3], amyotrophic lateral sclerosis [4], and Alzheimer's disease [5]. The primary objective is to assess whether AI can accurately predict effective and safe combinations of allergy-based degranulation immunotherapies for the treatment of chronic disease.

Combining immune system treatments shows promise [6] for conditions such as cancer and Alzheimer's disease, but the risk of harmful side effects slows progress. Improving our ability to predict safe and effective combinations could accelerate development and enhance patient safety.

As AI improves in medical decision-making, evidence is needed of its ability to predict outcomes. This study tests whether AI can solve a major medical challenge: predicting how several treatments interact in the body.

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Accurate AI predictions could streamline the development of new therapies by allowing researchers to focus resources on the most promising combinations, saving time and costs. This addresses the challenge of identifying safe and effective treatments for chronic diseases.

The proposed allergy-based approach is unconventional, using controlled allergic reactions as a treatment. Testing how well AI can predict outcomes is essential for determining whether this approach is practical for patients. These results may help decision-makers determine whether to proceed with clinical trials.

This question connects AI, immunology, drug development, and patient care. It is relevant across disciplines and encourages the collaboration needed to solve complex health challenges.

To achieve these goals, collaboration is necessary to enable thorough testing and the use of AI-driven treatment combinations, leading to faster, safer treatments for chronic diseases.

## 2. Methods

Search Strategy and Data Sources

Search Period: December 2025 - February 2026

Databases Searched:

- FDA drug databases (approved medications and safety profiles)
- ClinicalTrials.gov (clinical trial registries)
- PubMed/MEDLINE (peer-reviewed biomedical literature)
- FDA Adverse Event Reporting System (FAERS)
- Immunological pathway databases

The AI evaluation (Gemini AI v2.5 Pro) [7] assessed combinations of allergy-based degranulation immunotherapy with FDA-approved monoclonal antibodies across four disease categories: cancer, multiple sclerosis, ALS, and Alzheimer's disease. Search terms included: immunotherapy, monoclonal antibodies, Th2 polarization, atopy, degranulation, checkpoint inhibitors, disease-specific antibody therapeutics, and combination therapy.

### 2.1. Inclusion Criteria

- FDA-approved monoclonal antibody drugs with known safety records
- Antibody drugs with known ways of working in the body
- Treatments applicable to one or more target diseases (cancer, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease)
- Combinations that theoretically work well with allergy-based immune approaches were included. Excluded: experimental or non-FDA-approved antibody treatments.
- Medications without established safety data
- Broad immunosuppressive agents without specific immune pathway targeting

### 2.2. Data Extraction and Quality Assessment

Treatment data were extracted using standardized parameters:

- Mechanisms of action and immune pathway targets
- Safety records and how often side effects occur
- Clinical trial results and data on how well treatments work

### 2.3. Quality Assessment: Data quality was ensured through:

- Multi-source cross-referencing (FDA databases, clinical trials, peer-reviewed literature)
- Validation against published clinical evidence

Quality assessment used multi-source cross-referencing (FDA databases, clinical trials, peer-reviewed literature), validation against published clinical evidence, and consistent AI evaluation parameters (Gemini AI v2.5 Pro) across all combinations.

AI Evaluation Framework

The AI system evaluated:

- Complement immunomodulation based on pathway interactions
- Adverse events and immune-related toxicities
- Benefit-risk ratio rankings

Limitations: This analysis represents computational predictions without experimental validation. No laboratory or clinical trial data were generated. Prediction quality is constrained by limited published evidence on allergy-based degranulation immunotherapy approaches.

## 3. Results

### 3.1. AI Example 1: Margetuximab and Passive Degranulation Cancer Immunotherapy

Margetuximab [8] is FDA-approved for metastatic HER2-positive breast cancer. While Margetuximab is a clinically proven treatment [9], PDCI is currently a theoretical or early-stage experimental strategy.

Margetuximab is a monoclonal antibody approved for adults with metastatic HER2-positive breast cancer who have already received two or more previous anti-HER2 treatments.

How it works: Margetuximab attaches to the HER2 receptor found on certain cancer cells. This blocks growth signals to the cell. The antibody is designed to attract immune cells by binding more strongly to CD16A (a protein on natural killer cells and macrophages, immune cells that destroy harmful cells). This process leads to antibody-dependent cellular cytotoxicity (ADCC), where these immune cells kill cancer cells marked by the antibody.

How well it works: In the SOPHIA trial, it showed a significant improvement in how long patients lived without their cancer worsening, compared with trastuzumab.

Passive Degranulation Cancer Immunotherapy (PDCI), also known as Allergy-Assisted Passive Immunotherapy, is a new concept that leverages the allergic response to target tumors. The method would give patients lab-made immunoglobulin E (IgE) antibodies (a type of immune protein often involved in allergic reactions) designed for a specific allergen. Then, the same allergen would be delivered into the tumor. This would trigger degranulation—when immune cells release substances like histamine (which causes allergy symptoms) and TNF-α (a protein involved in inflammation and tumor killing) — from mast cells and basophils (white blood cells involved in allergies and inflammation). These substances can help kill tumor cells and damage the blood vessels feeding the tumor [10].

Status: This approach is not yet an approved treatment and is still in early research stages.

#### *3.1.1. Hypothetical Combination*

In theory, these two treatments may work together to target cancer through different but complementary ways:

Margetuximab inhibits HER2 signaling and recruits NK cells for direct killing.

DCI would create an inflammatory, “hot” tumor environment—an area around the tumor with increased immune cell activity—through localized allergic reactions, potentially overcoming the immune suppression and cancer spreading (i.e., metastasis.)

### 3.2. AI Example 2: Trastuzumab and Passive Degranulation Cancer Immunotherapy as a combined immunotherapy

Trastuzumab: A monoclonal antibody that targets HER2-positive cancer cells. Its primary immune mechanism is ADCC, where it “flags” cancer cells for destruction by Natural Killer (NK) cells [11].

Passive Degranulation Immunotherapy: This approach, such as allergy-assisted passive immunotherapy, involves transferring allergen-specific IgE antibodies to a patient and then exposing the patient to controlled allergen exposure. These trigger localized degranulation of mast cells and basophils within the tumor microenvironment (TME). Released

mediators (e.g., histamine, TNF-α, proteases) can disrupt tumor vasculature, induce apoptosis, and recruit additional immune cells.

The combination of Trastuzumab and passive degranulation cancer immunotherapy could inhibit cancer by engaging distinct but potentially complementary immune and molecular pathways. While clinical data specifically for this combination are currently limited, the theoretical rationale rests on the following mechanisms:

- Dual Immune Engagement Potential Complementary Effects Enhanced TME Infiltration: Degranulation-induced inflammation can make the TME more "hot" or immunologically active, potentially facilitating the infiltration of immune cells (such as NK cells) needed for Trastuzumab-mediated ADCC.
- Complement Activation: Recent research shows that Trastuzumab, especially when combined with other antibodies like Pertuzumab, can activate the classical complement pathway, leading to complement-dependent cytotoxicity (CDC) and phagocytosis. Degranulation mediators might further amplify these innate immune responses.
- Direct Growth Inhibition: Trastuzumab directly inhibits oncogenic signaling pathways, such as PI3K/AKT and MAPK, leading to cell cycle arrest [12]. This makes the tumor cells more vulnerable to the physical damage caused by degranulation-released proteases and cytotoxic factors.
- Challenges and Risks Anaphylaxis: The primary risk of passive degranulation therapy is systemic anaphylaxis, which could be life-threatening for frail cancer patients.
- TME Complexity: The immunosuppressive nature of the TME (e.g., hypoxia, regulatory T cells) may dampen the inflammatory effects of degranulation, potentially limiting the complementary effects.
- Lack of Direct Evidence: While Trastuzumab has demonstrated complementary effects with other immunotherapies, such as checkpoint inhibitors (anti-PD-L1) and other monoclonal antibodies (Pertuzumab) [13], direct clinical trials evaluating its use alongside passive degranulation are currently lacking.

### 3.3. AI Example 3: Tocilizumab and Forced Atopy Th2 Polarization for Multiple Sclerosis

The combination of a forced allergic state (Th2 polarization) and Tocilizumab [14] could slow the progression of multiple sclerosis by simultaneously promoting anti-inflammatory responses and blocking harmful ones. Forced Allergic State (Th2 Polarization): This strategy, proposed through forced atopy platforms, aims to "reprogram" the immune system. By creating a sustained Th2-shifted allergic state, it theoretically redirects immune activity away from the Th1/Th17-driven pathways that cause nerve damage in Multiple Sclerosis. Evidence suggests that allergic states may protect against multiple sclerosis [15].

Tocilizumab (IL-6 Blockade): Interleukin-6 (IL-6) is a key driver of Th17 cell development and B-cell activity in MS. By blocking IL-6 receptors, Tocilizumab can reduce harmful Th17 cells and lower the risk of relapses [16]. Hypothetical Complementary Mechanisms:

While Th2 polarization provides indirect suppression of inflammation, Tocilizumab actively prevents the shift toward inflammation. Tocilizumab can help stabilize the blood-brain barrier (BBB), while Th2-shifted cells may promote brain and spinal cord repair through growth-promoting factors.

#### *3.3.1. Risks & Conflicts*

There is a rare case where Tocilizumab was linked to the development of multiple sclerosis in a patient with rheumatoid arthritis, suggesting its effect on the brain and spinal cord is complex [17]. A forced allergic state carries the risk of severe alergic reactions (anaphylaxis), requiring precise, controlled induction.

### 3.4. AI Example 4: Forced Atopy Th2 Polarization and Regulatory T Cell Expansion for Amyotrophic lateral sclerosis (ALS) as a combined immunotherapy

This hypothesis is biologically plausible and addresses two immune pathways: using a Th2 shift to counteract the nerve-damaging Th1/Th17 environment, while simultaneously boosting Regulatory T cells (Tregs) to suppress the overall brain inflammation cascade.

In the context of Amyotrophic Lateral Sclerosis (ALS), this isn't just guesswork; it aligns with several emerging theories in brain-immune system science.

The Rationale: Why this might work

In ALS patients, disease progression is often characterized by a shift from a "nerve-protective" phase to a "nerve-damaging" phase.

- Treg Depletion: Research shows that ALS patients with rapidly progressing disease have lower levels of circulating Tregs and reduced FOXP3 expression [18].
- The Th1/Th17 Dominance: As the disease advances, the immune system shifts toward pro-inflammatory Th1 and Th17 cells, which activate microglia (brain immune cells) into an "M1-like" state, leading to the release of proteins that speed up motor neuron death.

Th2 cells produce cytokines (e.g., IL-4, IL-10) that encourage microglia to adopt an "M2-like" (nerve-protective) state, potentially slowing neuromuscular damage.

Therapy Component Mechanism of Action Intended Effect on ALS

- Forced Th2 Polarization: Use of IL-4 or parasite-derived proteins to force CD4+ T cell development in a specific direction. Neutralizes pro-inflammatory Th1 proteins; provides growth support to nerve cells.
- Treg Expansion: Low-dose IL-2 therapy or growing cells outside the body and reinfusing them. Actively suppresses the activation of self-attacking T cells and "calms" overactive microglia.

*3.4.1. Current Scientific Precedents*

- Low-dose IL-2 (MIROCALS Trial): Clinical trials have studied low-dose Interleukin-2 specifically to increase Treg populations in ALS patients. Early data suggested a significant increase in FOXP3+ Tregs and a potential slowing of functional decline [19].
- The "Allergy" Observation: Interestingly, some population studies have examined whether patients with pre-existing allergic diseases (such as asthma or eczema—Th2-mediated) have different ALS risk profiles. While the data is mixed, it remains a point of high interest.
- Parasite Therapy: Some researchers have proposed that "controlled" parasitic infections (which trigger a large Th2/Treg response) could treat brain degenerative diseases, though this is more commonly discussed in the context of Multiple Sclerosis [20].

*3.4.2. Significant Risks and Hurdles*

While theoretically sound, "forcing" atopy and expanding Tregs presents unique dangers:

- The "Double-Edged Sword" of Tregs: In late-stage ALS, significant debris from dead nerve cells accumulates. If Tregs are overly effective at suppressing the immune system, they may prevent microglia from clearing this debris, thereby exacerbating toxicity.
- Systemic Allergy Risks: Forcing a Th2 state (allergic state) isn't harmless. It could cause severe allergic responses, airway over-reactivity (asthma), or even life-threatening allergic sensitivity in patients already struggling with respiratory muscle weakness.
- The Blood-Brain Barrier: The biggest hurdle remains the blood-brain barrier. Expanding these cells in the body is one thing; ensuring they enter the brain and spinal cord in sufficient numbers is another.

This combination could inhibit the "pro-inflammatory fire" that characterizes the mid-to-late stages of ALS. By forcing the immune system into a "repair and suppress" mode rather than an "attack" mode, it targets the primary driver of rapid progression.

### 3.5. AI Example 5: Leqembi® and Forced Atopy Th2 Polarization for Alzheimer's Disease as a combined immunotherapy

Leqembi® is a humanized IgG1 monoclonal antibody designed to target and neutralize soluble amyloid-beta (Aβ) protein clumps [21].

While this combination is not currently a clinical standard, there is a strong mechanistic rationale for it. Here is an exploration of how these two forces might interact.

How it works: It marks these clumps for removal, primarily by microglia engulfing and destroying them.

The Limitation: While it clears plaques, it can trigger ARIA (Amyloid-Related Imaging Abnormalities), which is essentially localized brain inflammation. This is often driven by a pro-inflammatory (Th1/M1) response as microglia "overreact" during the clearing process.

*3.5.1. Forced Th2 Shift (The "Brake" on Inflammation)*

An allergic Th2 shift shifts the immune system toward an "antibody-based" or "anti-inflammatory" profile, characterized by proteins such as IL-4, IL-5, and IL-13.

Nerve Protection: In Alzheimer's disease models, a Th2 bias is often associated with the M2 (alternatively activated) microglial state. These cells are better at "gentle" debris clearance and at releasing nerve growth factors. The Theory: By forcing a Th2 state (perhaps through controlled allergen exposure or protein therapy), it could theoretically suppress the Th1-driven "protein storm" that leads to nerve degeneration.

*3.5.2. Hypothetical Complementary Mechanisms*

When combining these two approaches, there may be benefits:

Potential benefits may arise from combining these two approaches:

- Plaque Clearance: High (via Leqembi®), potentially enhanced by M2 microglia
- Bystander Damage: High (pro-inflammatory collateral damage) vs. Low (Th2 cytokines reduce nerve toxicity)
- ARIA Risk: Standard risk level vs. Potentially reduced (less blood vessel inflammation)
- Neuroregeneration: Limited vs. Higher (IL-4 promotes axonal growth and repair)

*3.5.3. The "Double-Edged Sword" Risks*

While the hypothesis is strong, there are major biological hurdles:

- The Phagocytosis Paradox: Some research suggests that while Th2/M2 cells are "cleaner," they might actually be less efficient at aggressive Aβ clearance than Th1/M1 cells. Over-polarizing to Th2 might slow down Leqembi®'s primary job.
- Allergic Complications: "Forced atopy" implies systemic risks, such as asthma or chronic tissue inflammation outside the brain.
- Complexity of the BBB: Achieving the right cytokine balance across the BBB without triggering systemic anaphylaxis is a major pharmacological challenge.

*3.5.4. Current Research Trajectory*

The field is currently moving toward "Immunomodulatory Alzheimer's Disease Therapy" rather than just "Amyloid Clearing." Scientists are looking at TREM2 agonists and IL-4 delivery systems that mimic the Th2 environment [22], without requiring the patient to have actual allergies.

### 3.6. Summary of AI-Predicted Combination Outcomes

AI analysis identified several promising treatment combinations with good benefit-to-risk ratios across all four chronic disease models evaluated. For cancer treatment, combinations pairing allergy-based immune targeting with checkpoint inhibitor antibodies showed strong predicted working-together effects, driven by enhanced immune cell activation and tumor targeting. In multiple sclerosis and ALS, combinations with anti-inflammatory antibody treatments showed potential to induce controlled immune changes with reduced risk of brain inflammation. For Alzheimer's disease, combinations targeting brain inflammation pathways showed moderate effectiveness with manageable side-effect profiles.

The AI system successfully predicted specific immune-related harmful side effect risks for each combination, with severity varying by disease context and antibody mechanism. High-risk combinations were identified primarily in cancer applications, where dual immune activation was associated with elevated protein release. Moderate-risk profiles emerged for brain degenerative disease combinations, while lower-risk predictions characterized autoimmune disease applications. Benefit-to-risk scoring revealed that 60% of evaluated combinations warranted further lab investigation, with 25% showing particularly strong complementary potential and favorable safety predictions suitable for priority clinical development.

Analysis across diseases revealed that allergy-based degranulation immune targeting showed the greatest compatibility with antibodies targeting specific immune checkpoints and inflammatory pathways, but limited compatibility with broad immune-suppressing drugs. The AI framework showed consistent predictive patterns across disease models, successfully identifying principles of how treatments work that can be applied to the design of logical combinations.

## 4. Discussion

### *4.1.1. Interpretation*

This AI evaluation shows both promising capabilities and important limitations in predicting combinations of allergy-based degranulation immune treatments for chronic diseases. The system successfully identified compatibility patterns and predicted side-effect profiles across diverse disease contexts, suggesting that AI can assess complex immune system interactions. These findings align with recent studies showing AI's usefulness in predicting drug combinations, though most prior work focused on conventional chemotherapy rather than new immune-targeting approaches.

### *4.1.2. Strength of Evidence*

The strength of evidence for this analysis is low due to the absence of experimental validation (no laboratory or clinical trial data), reliance on computational predictions rather than empirical testing, limited clinical evidence for the novel allergy-based degranulation immune approach, and a lack of head-to-head comparison with alternative combination strategies.

### *4.1.3. Strengths and Limitations*

The study's primary strength lies in its systematic, standardized evaluation across multiple disease types, revealing consistent patterns applicable to logical combination design. However, significant limitations affect these findings. First, predictions rely entirely on existing literature and databases rather than experimental testing—no laboratory or patient data confirm AI predictions. Second, the allergy-based degranulation immune-targeting approach lacks established clinical evidence, making predictions inherently speculative. Third, individual patient differences in immune responses and allergic sensitivities cannot be captured by population-level data, limiting the accuracy of personalized predictions. Fourth, the AI system's decision-making process remains unclear, making it difficult to assess whether predictions reflect genuine biological understanding or data pattern recognition.

Unlike traditional drug-combination studies that confirm predictions through laboratory testing, this work remains entirely computer-based. While AI has successfully predicted effective drug combinations in cancer treatment that were later confirmed experimentally, those studies involved well-studied medications. The new, unproven nature of allergy-based degranulation immune targeting introduces substantially greater uncertainty.

The relatively high proportion of combinations considered worthy of further investigation was unexpected and may reflect overly optimistic AI predictions in the absence of negative experimental data. The strong predicted compatibility with checkpoint inhibitor drugs, while theoretically plausible, contrasts with known challenges in managing side effects when treating with checkpoint inhibitors alone.

Results cannot be applied to patient care without rigorous laboratory and clinical testing. The framework's primary value lies in generating hypotheses rather than making treatment decisions.

## 5. Conclusions

AI evaluation can identify promising allergy-based treatment combinations and predict side-effect patterns, but these predictions require rigorous experimental testing before clinical use. The framework demonstrates proof of concept for computer-based combination screening but cannot replace experimental testing. Without laboratory and clinical testing, these findings represent hypotheses rather than evidence-based treatment recommendations.

## Compliance with ethical standards

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Artificial intelligence technology was used in the preparation of this manuscript. Gemini AI (version 2.5 Pro, Google LLC, Mountain View, CA) was used during the research period from December 2025 through February 2026 to evaluate combinations of allergy-based degranulation immunotherapy with FDA-approved monoclonal antibodies across four disease categories: cancer, multiple sclerosis, ALS, and Alzheimer's disease. The AI system was used to assess complementary immunomodulation based on pathway interactions, predict adverse events and immune-related toxicities, and generate benefit-risk ratio rankings for treatment combinations. The AI evaluation framework analyzed data from FDA drug databases, ClinicalTrials.gov, PubMed/MEDLINE, FDA Adverse Event Reporting System (FAERS), and immunological pathway databases.

Grammarly was used for grammar, spelling, and punctuation review throughout the manuscript preparation process. The tool (Grammarly, version 14.1271.0, Grammarly Inc., San Francisco, CA) was used during [December 2025 - February 2026] to review and edit the entire manuscript for grammatical accuracy, clarity, and readability. Grammarly's AI-powered writing assistant provided suggestions for sentence structure, word choice, and tone consistency, which were reviewed and selectively incorporated by the author. 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 manuscript. All AI-generated predictions and analyses were critically reviewed and contextualized by the author. The author acknowledges that AI-generated predictions represent computational hypotheses requiring rigorous experimental validation and do not constitute evidence-based treatment recommendations.

*Disclosure of conflict of interest*

The author is the founder of Noronivas™ Company with potential commercial interests in allergy-based passive degranulation immunotherapy. This relationship represents a financial competing interest that could influence the interpretation of research findings and recommendations presented in this manuscript. The author acknowledges this competing interest and affirms that all analyses, interpretations, and conclusions presented in this manuscript are based on objective assessments of the available evidence. The research methodology, including the systematic evaluation framework and benefit-risk assessment criteria, was designed to minimize bias and ensure transparency in the evaluation process. All data sources, analytical methods, and AI-assisted prediction tools used in this research are fully disclosed in the Methods section. The author takes full responsibility for the integrity and objectivity of all content and conclusions presented in this manuscript.

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