Analyzing Eosinophilic Esophagitis and Allergic Disorder Pathways and Potential Drug Solutions

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Outline

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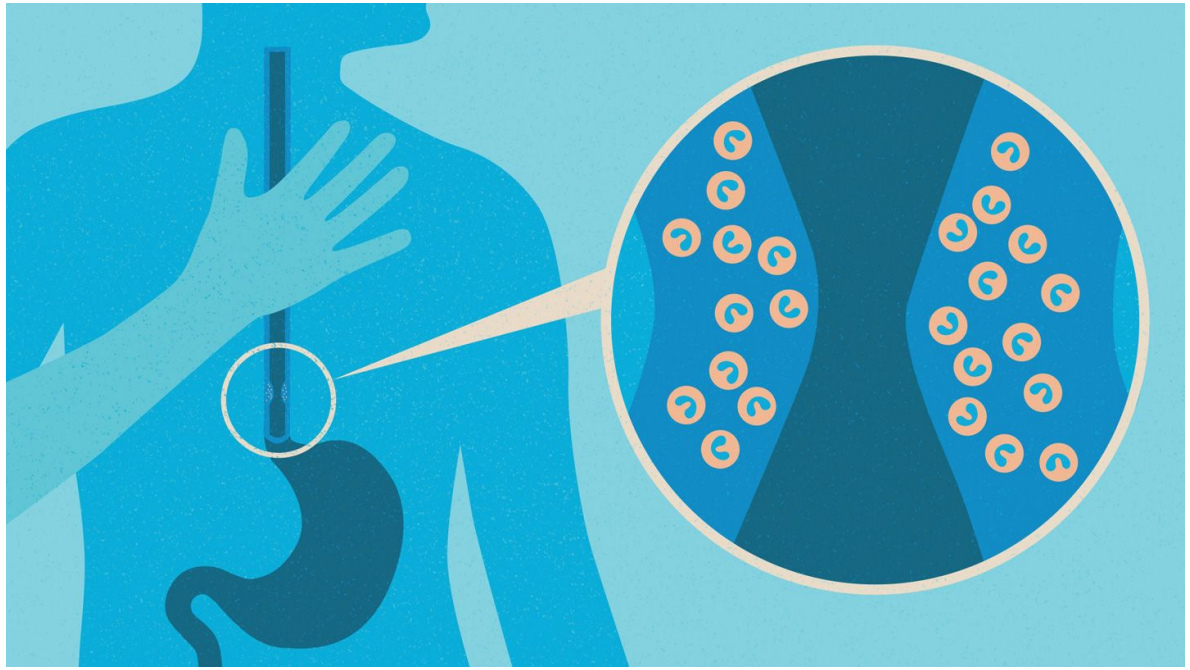
Objective

- Analyze the genetics of EoE while finding potential repurposed drug options for patients with EoE and similar allergic conditions
- Investigate the two common pathways in EoE and other allergic disorders: Th2 Immune Response and Epithelial Barrier Dysfunction Pathways
- Look at current drug options and potential drug design plans



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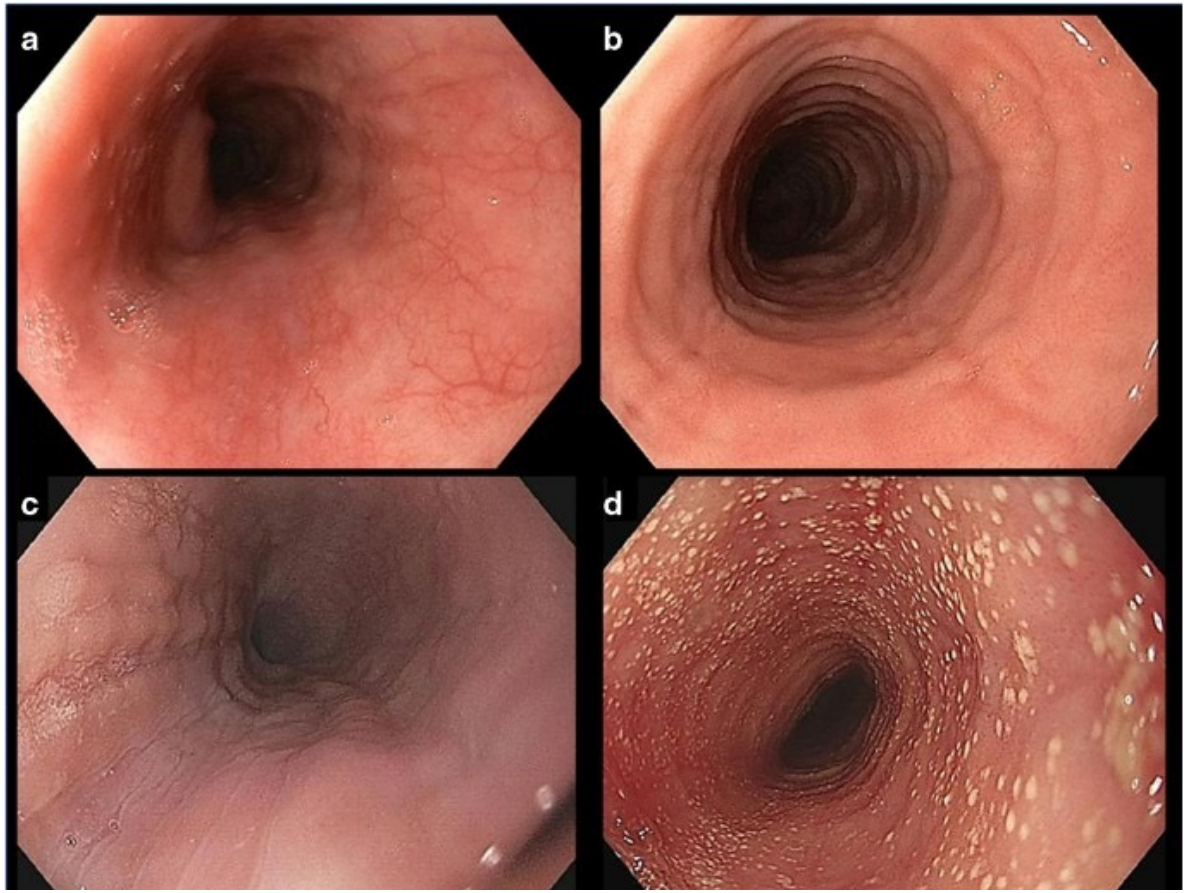
Introduction to Eosinophilic Esophagitis

- Eosinophilic esophagitis (EoE) is a chronic disorder of the esophagus caused by an accumulation of eosinophils in the esophageal lining
- EoE affects patients from birth to adulthood with symptoms including inflammation, esophagus narrowing, difficulty swallowing, nausea, and chest pain
- Initially viewed as a manifestation of gastroesophageal reflux disease (GERD)



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Diagnosis and Treatment

- Diagnosis of EoE typically involves endoscopy with biopsy
- Treatment options:
  - Dietary therapy
    - Top-8 allergen elimination diets
    - Food trialing
    - Elemental-formula diets
  - Proton pump inhibitors
  - Topical corticosteroids
  - Biologics

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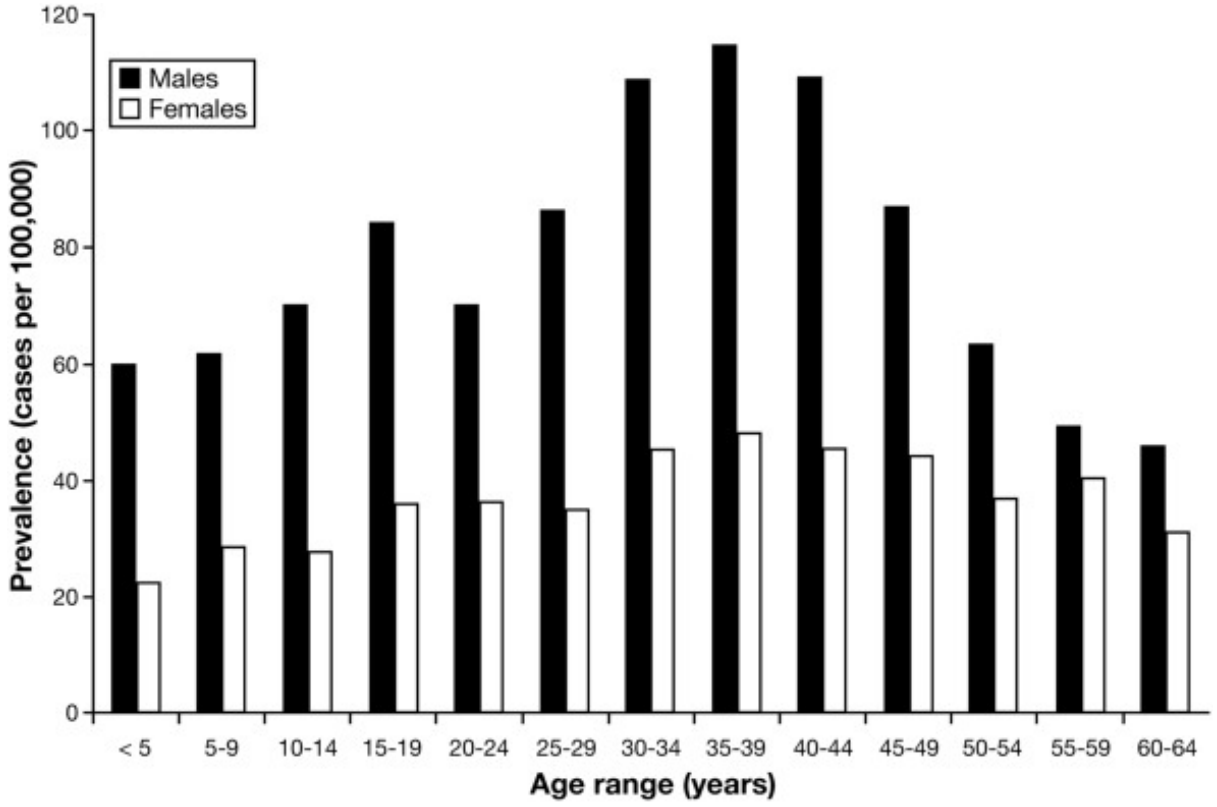
Populations and Demographics

- EoE affects 4 in every 10,000 people worldwide
- Increased prevalence for men
- More common in Western countries
- Affects all ages, but increased prevalence in adults



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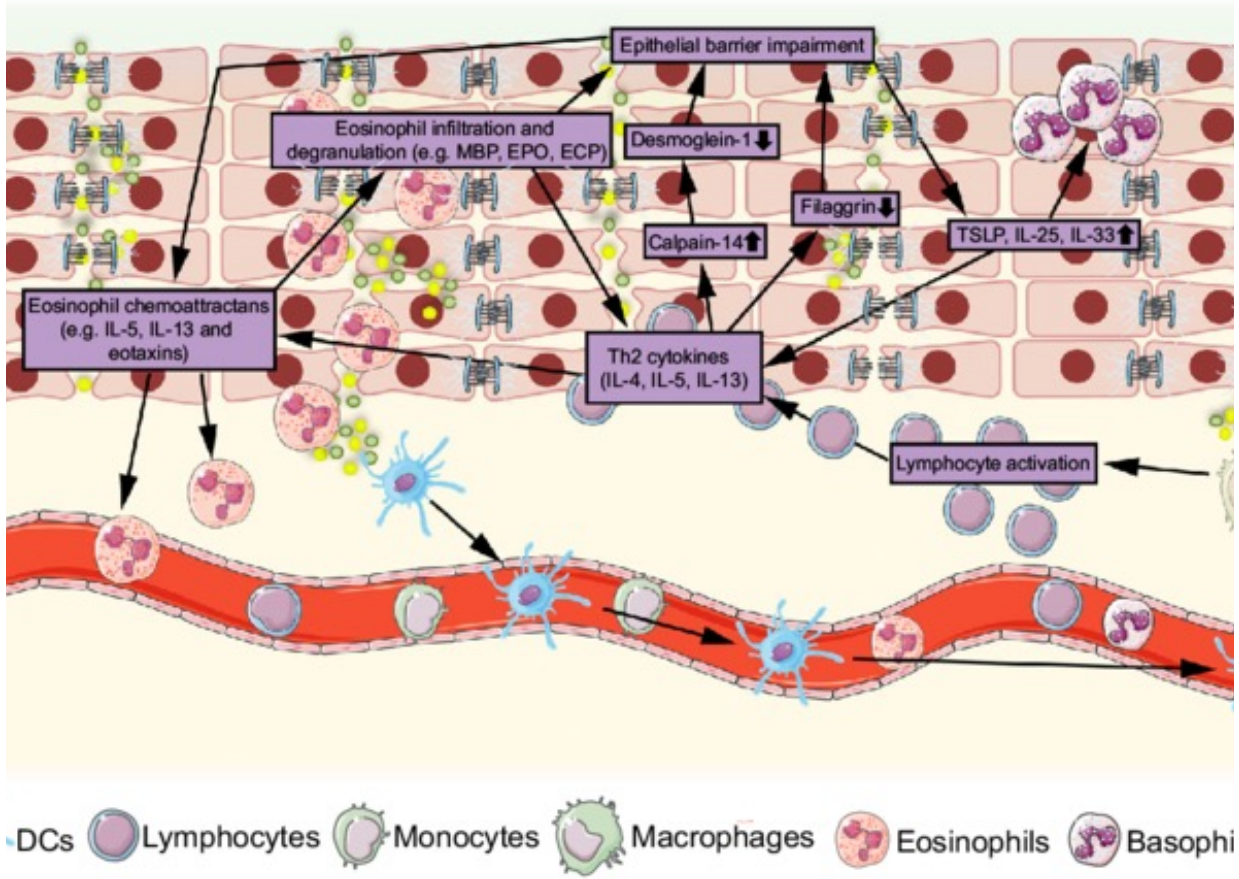
Th2 Response Pathway

- EoE caused by adverse immune responses to a variety of foods
- T-helper type 2 (Th2) mediated disorder
- Interleukin (IL) 4 is responsible for initiating the Th2 response through the differentiation of naive T helper cells into Th2-type cells
- Starts when antigenic proteins such as casein in milk, or ovalbumin in eggs, produce cytokines such as interleukin (IL) 5 and IL-13
  - IL-5: Key cytokine that regulates the survival, activation, and trafficking of eosinophils to the esophagus
  - IL-13: Triggers esophageal epithelial cells to produce proteins such as eotaxin 3 (recruits eosinophils from peripheral blood into the tissue)
- The CCR3 receptor receives signals from Th2 cells, increases expression, correlating positively with Eotaxin 3 frequency and eosinophil number
- Recruited eosinophils express antigen-4 and P-selectin glycoprotein ligand-1, which bind to vascular cell adhesion molecule-1 and P-selectin, and migrate into the tissue
- Eosinophils in EoE patients have increased expression of proteins such as eotaxin and interleukins 4, 5, and 13

Epithelial Barrier Dysfunction Pathway

- Epithelial barrier dysfunction pathway is another pathway that plays a crucial role in developing an EoE response
- Significant factor in a variety of IgE allergic conditions, including EoE (many EoE patients have IgE-mediated conditions)
- Refers to the loss of integrity of the protective barrier that lines the esophagus and allows Eosinophils to penetrate the tissues underneath
- After allergen exposure, mast cells activated by crosslinking of IgE receptors on the surface
- Leads to the activation of a signaling pathway that involves the tyrosine kinase Syk and the adaptor protein LAT releasing mediators that contribute to the symptoms of EoE
- Release of mediators from mast cells and proteins from eosinophils cause alterations in the disrupt tight junctions, desmosomes, adherens junctions, and other barrier proteins



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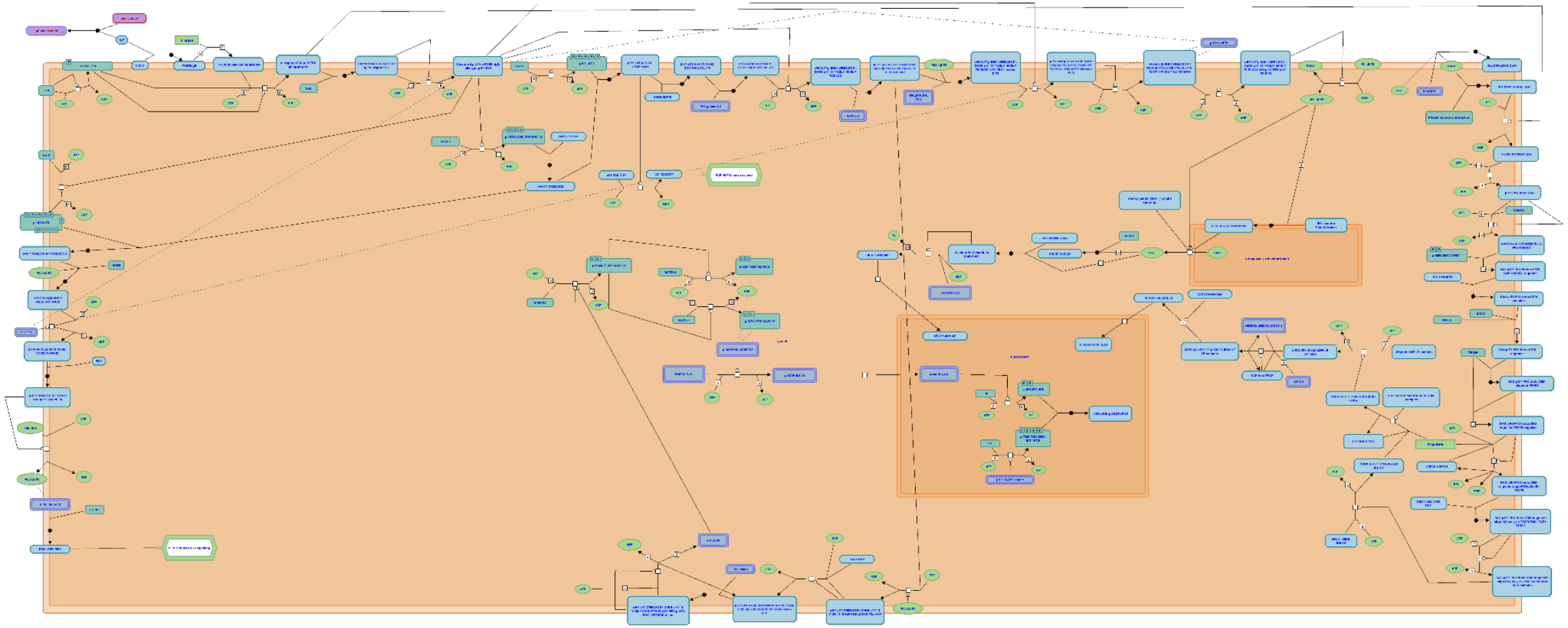
FCER1 Receptor and FCER1A Gene

- FCER1 receptor: Specific upstream receptor involved in mast cell activation in EoE
- Binds to IgE, and signaling proteins Syk and LAT
- Genetic variations in EoE that affect the expression or function of FCER1 leading to increased sensitivity to allergens and heightened immune response
- FCER1A: Cell surface receptor protein and component of the FCER1 receptor complex
- Found on the surface of mast cells and basophils that triggers an immune response when cross-linked by IgE molecules bound to allergens
- One study shows monoclonal antibodies binding to this receptor to prevent a downstream response

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4114087/

Signaling Pathway



Fc epsilon receptor (FCERI) signaling

reactome

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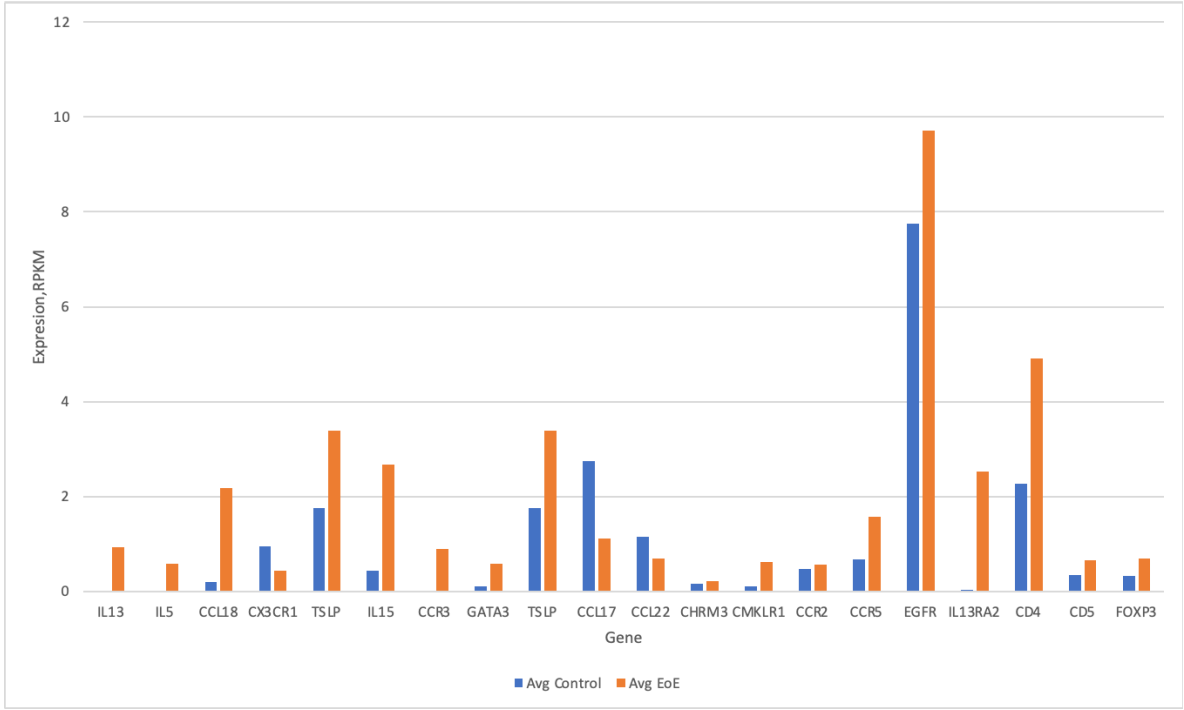
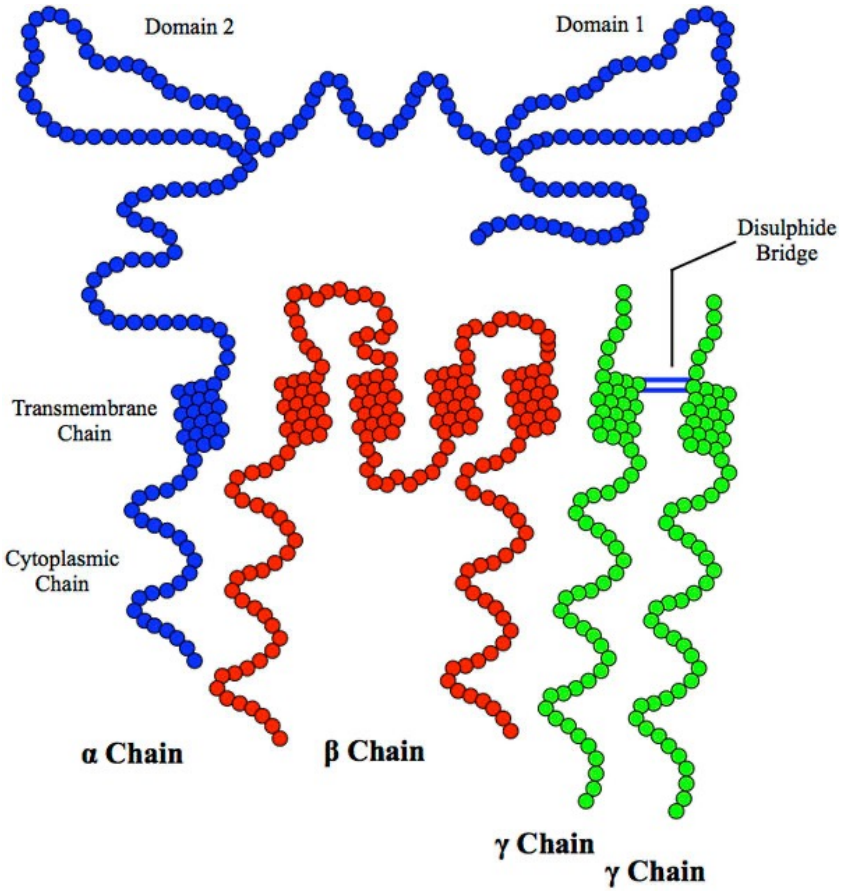
Methods: Phase 1

- First part of my research phase was finding proteins involved in the Th2 pathway that were either significantly upregulated or downregulated in patients with EoE
- I used patient RNA Sequencing data from EGIDExpress to identify these proteins and gather more information about each one
- In the graph below, upregulated genes and their expressions (RPKM) were plotted for healthy controls and EoE patients
- As expected, many interleukins and proteins discussed in the Th2 pathway section of the introduction were upregulated
- Lack of sample size



Methods: Phase 2

- While this data was beneficial for confirming the mechanisms of the Th2 pathway, the goal of this project was to investigate a gene that could prevent the downstream reaction cascade
- After doing research using previous studies and LeMeDISCO, I found the epithelial barrier dysfunction pathway, the FCER1 receptor, and the corresponding FCER1A protein
- As mentioned earlier, cross-linkage with this receptor caused the downstream immune response, so I focused on finding molecules using FINDSITE that could prevent this pathway from starting in the first place



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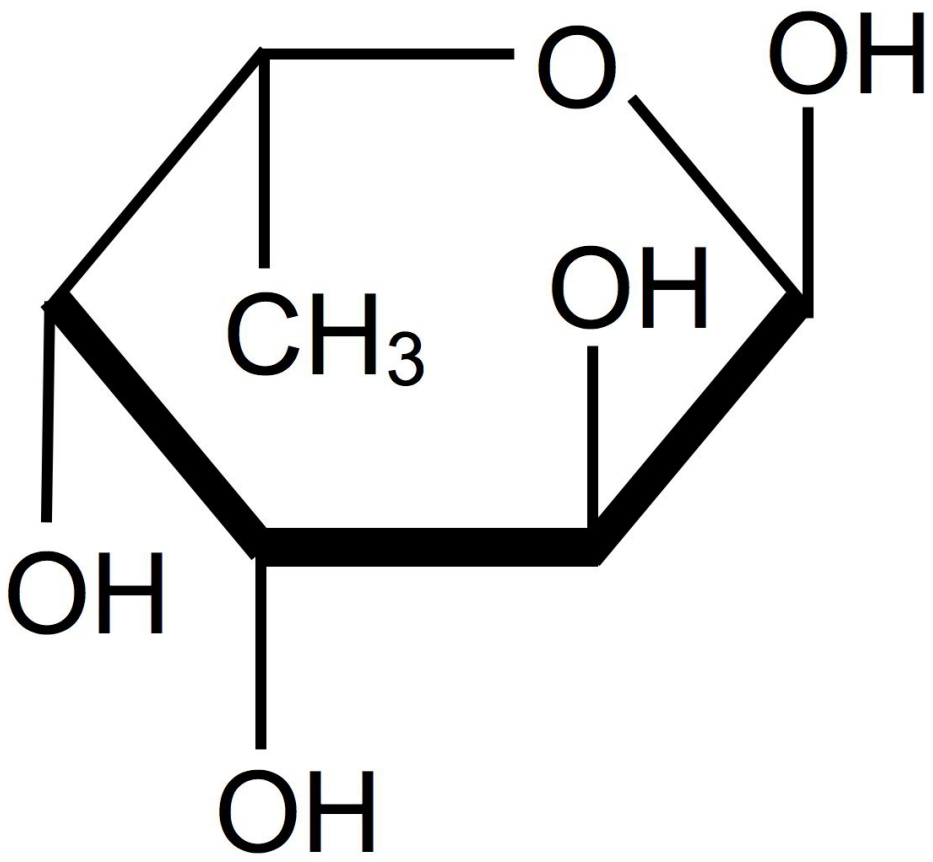
Results

- After using the amino acid sequence for the FCER1A to do a FINDSITE search, I found a variety of compounds for further investigation
- I will give an overview of these molecules alongside two other drugs that have relevance for patients with EoE and other IgE-related allergic conditions
- Ligand screening for the FCER1A protein. Found two related molecules that could be used for potential drug repurposing

Molecule 1: alpha-L-fucose

- Ranked first in the ligand screen match with an mTC score of 0.969
- Type of sugar molecule that is commonly found in plants and other organisms
- Associated in humans with cell-to-cell communication, immune function, and inflammation
- Important component of complex carbohydrates such as glycoproteins and glycolipids
- Can be obtained from dietary sources such as fruits and vegetables or synthesized in the body



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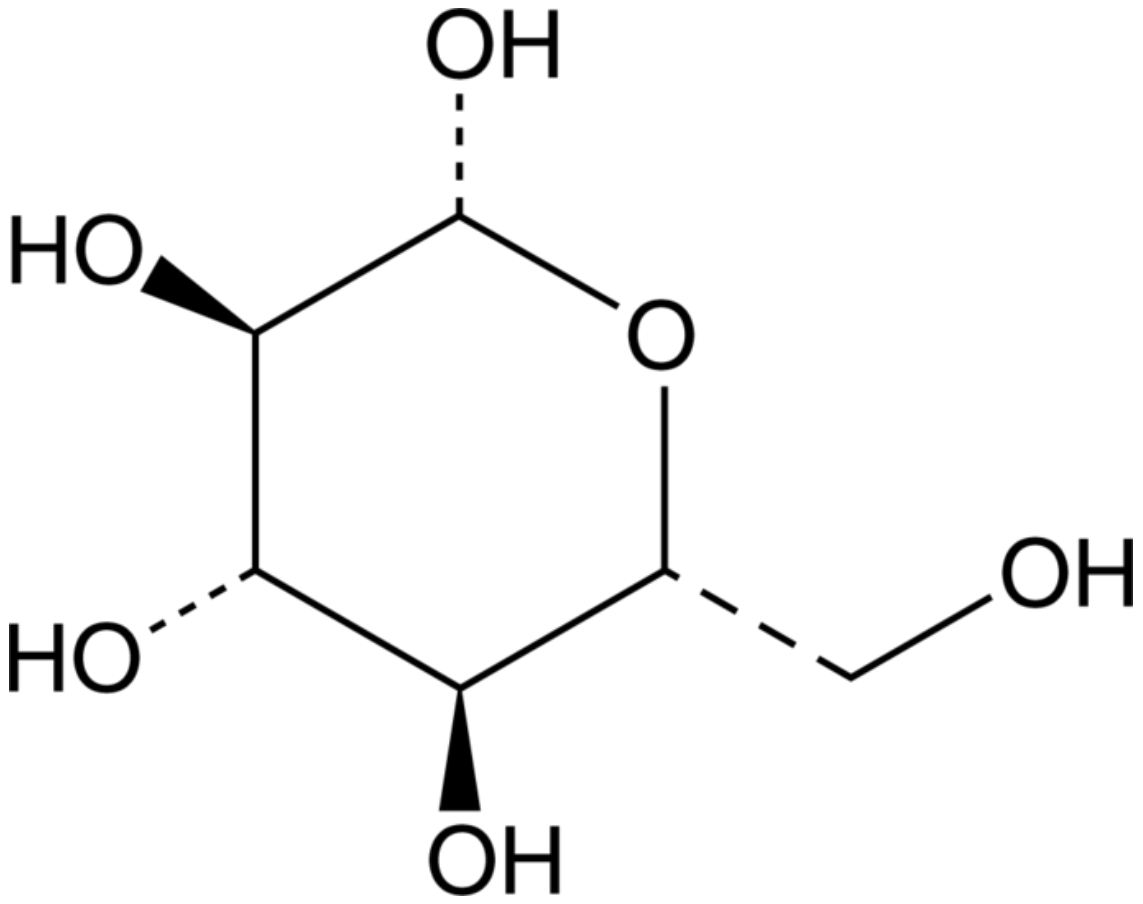
Molecule 2: beta-D-glucose

- Ranked first in the ligand screen match with an mTC score of 0.969
- Involved in cell signaling and immune recognition
- Beta-D-glucose is a monosaccharide and one of the most common forms of glucose found in nature.
- Important source of energy for living organisms and is a key component of many biomolecules, including starch, glycogen, and cellulose.
- Beta-D-glucose has a six-membered ring structure with an oxygen atom bridging two carbon atoms, and its molecular formula is C6H12O6.



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Uganda Study

- Discovered that reactivity to specific cross-reactive carbohydrate determinants (CCD) moieties, including core beta-D-glucose and alpha-L-fucose, was positively associated with sensitization to extracts and Schistosoma mansoni infection
- Not with skin reactivity to extracts or sensitization to their major allergenic components
- Reactivity to a subset of alpha-L-fucose-carrying N-glycans was inversely associated with asthma, suggesting a potential protective effect of certain environmental exposures against asthma

https://onlinelibrary.wiley.com/doi/10.1111/all.14469

Dupilumab (Dupixent)

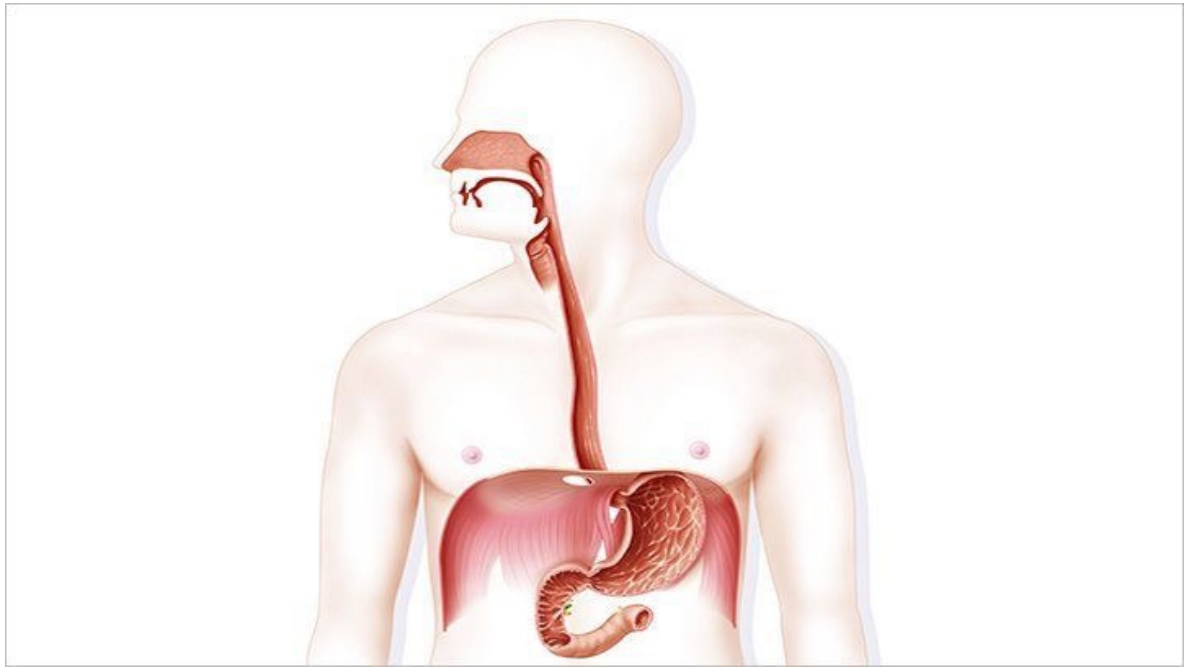
- Biologic that blocks the IL-4 and IL-13 signaling pathways
- Specifically targets the IL-4 receptor alpha subunit to prevent the release of proinflammatory cytokines, chemokines, and immunoglobulin E
- Multiple studies have shown that Dupixent can reduce IL-4, IL-13, and eotaxin-3 expression
- Led to its use in treating conditions such as asthma, eczema, and eosinophilic esophagitis with great success (including myself)
- Risk of immunosuppression and off-target effects on other parts of the immune system
- Minor side effects including body aches, chills, and coughing
- Trials have shown that Dupixent demonstrates efficacy in blocking the Th2 pathway and reducing biomarker expression

Omalizumab and Monoclonal Antibodies

- Use of monoclonal antibodies (mAbs) to target IgE
- Difficulty identifying agents that can block reactions without cross-linking of IgE and FCER1
- Omalizumab: Anti-IgE monoclonal antibody
  - Effective in reducing IgE responses (especially asthma) without causing an anaphylactic reaction
  - Has been used to treat severe allergic asthma in adults and children over the age of 12 years
- Binds to the FCER1 receptor to prevent the epithelial barrier dysfunction pathway from starting
- Side effects include blood vessel inflammation (rare), fever, rash, and muscle aches
- QGE031 is another more potent monoclonal antibody that is creating further opportunities for anti-IgE therapy
  - Used for severe cases of asthma, atopic dermatitis, and food allergy conditions
- Further research into monoclonal antibodies can lead to drugs that can positively impact varying severity levels of IgE-mediated conditions

Conclusion

- More investigation into solutions that impact an upstream area of pathways is necessary
- To continue this experiment:
  - Gather a group of patients aged 12 and above with EoE and similar conditions
  - Trial drugs such as dupilumab, omalizumab, stronger monoclonal antibodies, and repurposed compounds containing alpha-L-fucose and beta-D-glucose
  - Obersve the impact of each drug on various stages of the Th2 and epithelial barrier dysfunction pathways



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