Machine Learning Approach to Predict responder and non-responder in Allergen-Specific Immunotherapy (AIT)

What is an Allergen-Specific Immunotherapy (AIT) is and why it is relevant to predict responsiveness early in the treatment?

1.1 Allergen specific immunotherapy (AIT)

Allergen-specific immunotherapy (AIT) stands as a successful immune modifying therapeutic approach for established allergies (IgE -mediated hypersensitivity). The aim of AIT is to initiate and endure the state of immunotolerance toward an allergen and to thereby reduce allergic symptoms.

AIT involves the administration of allergen extracts, either monthly subcutaneously (SCIT) or daily sublingually (SLIT), in gradually increasing doses over a period of 3-5 years. It is reported that those immunological changes persist even after a long time of discontinuation of immunotherapy and have the ability to reduce the progression in asthma [1].

Other therapeutic approaches to tackle allergic disease are allergen avoidance and conventional pharmacotherapy. During pharmacotherapy various anti-mediator and anti-inflammatory agents, like the prominent anti-histamines and corticosteroids, are used to reduce allergic symptoms. However, only AIT is operating on the root cause of allergy: inducing immunotolerance, and thus provides tong-term improvement [2].

Successful AIT orchestrates the regulation and initiation of peripheral immune tolerance to a specific allergen.

Despite the potential of AIT, several challenges remain. Long treatment duration and the resulting the inconvenience of AIT results in poor patient compliance and treatment refusal as reported in patient surveys., in which **only 58.7% completed the SCIT and only 11.6% finished the SLIT treatments** [3]. Furthermore, side effects can range from mild local reaction to severe systematic anaphylactic reactions, also resulting in treatment refusal.

The lack of a commonly used definition of AIT responders and non-responders makes it very difficult to accurately say whether a patient will respond positively to therapy. The only way for patients to know if they will respond or not is to go through it.

The **identification of responder and non-responder** is needed for the assessment which patients are likely to benefit from AIT and which are not, thereby avoiding the risk and cost of treatment. Therefore,

due to the heterogeneous response of patients to AIT, well described standardized validated biomarkers are urgently needed to determine successful treatment response.

My thesis aims to establish a standardized data analysis approach to identify responders and non-responders in patients treated with birch pollen AIT, based on early humoral biomarkers.

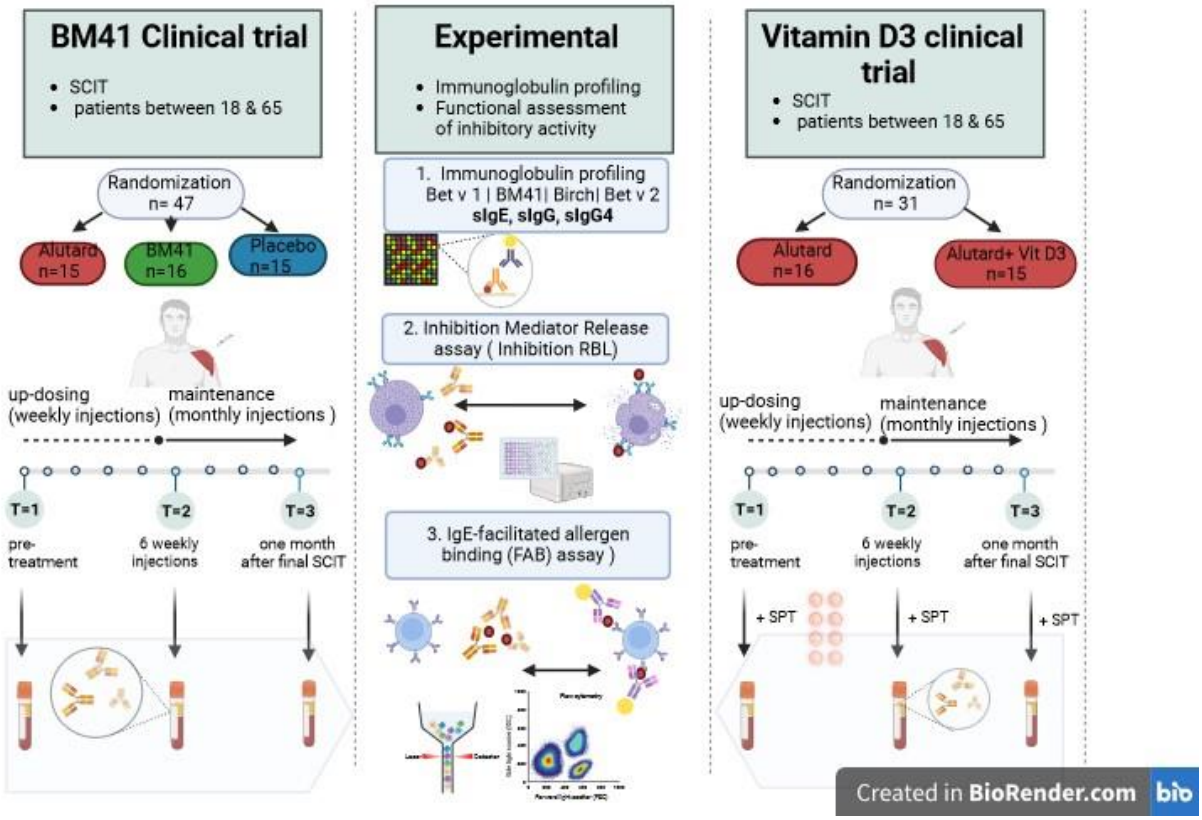

Figure 1 Study Methodology; Datasets study design and experimental study overview created with BioRender.com.

We analyzed clinical trial data of patients treated with two types of subcutaneous AIT active treatments (recombinant hypoallergen BM41 with n=16 and Alutard SQ extract with n=15) and a placebo group (n=15). The patients' **humoral immune responses** were assessed at three timepoints: pre-treatment, 2 months, and 6 months after the initial dose. We measured **allergen-specific** (Bet v 1) **Antibodies:** serum IgE, IgG, and IgG4 levels, as well as serum inhibitory activity for IgE using the IgE-facilitated allergen binding inhibition assay (FAB) and the mediator release assay.

The key pillar is that in allergic disease mainly IgE (Antibodies) are produces as result of the misguided immune response, which recognizes a harmless intruder as harmful and reacted with an immune pathway that leads to allergic systems (TH2 pathway). On the other hand, during AIT IgG Antibodies are produced against the Allergen, which is due to a different (TH1) immune pathway.

We comprehensively analyzed the resulting data following three main strategies: exploratory data analysis using techniques such as **Principal Component Analysis (PCA)** and **unsupervised machine learning (K-means clustering)**, predictive analysis with **Receiver Operating Characteristics (ROC)** and **correlations, and validation analysis by correlating** results with the clinical gold standard (skin prick tests) in an independent cohort. Let me guide you through the findings from the first part of the analysis.

1.2 Explorative analysis of the immune response to AIT

The first step of the data analysis was to analyze and visualize the modulation of the humoral immune response during early Allergen immunotherapy (AIT). Figure 2 shows a heatmap illustrating the entire BM41 clinical trial dataset in a concise manner. Patients are shown on the rows, while the columns represent measurements of **serological parameters at three different time points during treatment.**

This suggests that a treatment response is associated with higher values of the measured parameters, Birch, r Bet v 1 and BM41 s IgG and IgG4 as well as high expression in the three serum inhibitor assays Inhibition RBL, Competition FAB, and Inhibition FAB.

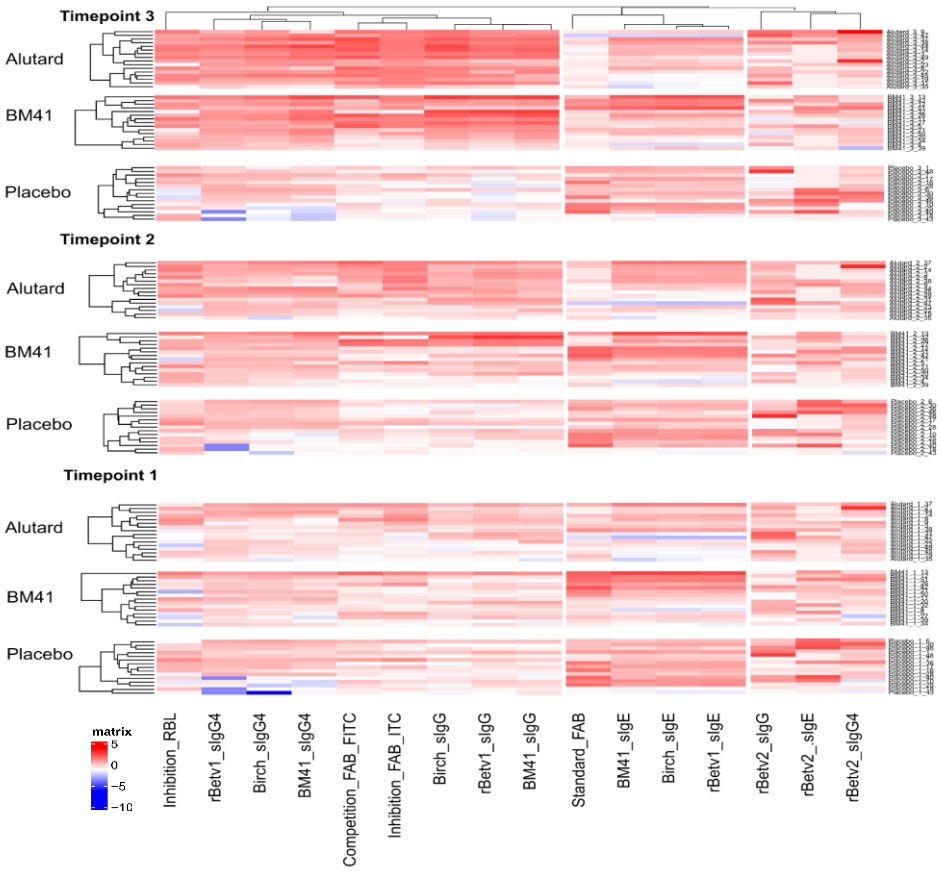

Figure 2 BM41 clinical trial Heatmap facetted by treatment group and timepoint, summarizing the humoral immune modulations taking place in the different patients and treatment groups.

Allergen specific immunotherapy has shown to alter the course of immune response to specific allergens, by inducing peripheral immune tolerance mechanisms. In the context of a responder vs. non-responder approach, there is a lack of biomarkers for early prediction of AIT efficacy. To that end, we applied a bioinformatical approach to investigate the predictive potential of 16 humoral measurements in a randomized, -double-blinded, placebo-controlled Bet v 1 mutant (BM41) and birch pollen AIT clinical trial. **We observed a clear association between the expression of blocking antibodies rBet v 1 specific IgG (1,2,3,4 combined) and the treatment response,** in both birch pollen extract and BM41, revealing comparable treatment effect patterns. This pattern also emerged when measuring sIgG4 separately.

References:

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[2] U. Wahn, C. Bachert, J. Heinrich, H. Richter, S. Zielen, Real-world benefits of allergen immunotherapy for birch pollen-associated allergic rhinitis and asthma, Allergy 74 (2019) 594-604. 10.1111/all.13598.

[3] F. Musa, M. Al-Ahmad, N. Arifhodzic, W. Al-Herz, Compliance with allergen immunotherapy and factors affecting compliance among patients with respiratory allergies, Hum Vaccin Immunother 13 (2017) 514-517. 10.1080/21645515.2016.1243632.