MECHANISTIC ASSAYS ON STORED SAMPLES FROM THE GRASS TRIAL

The Immune Tolerance Network (ITN) is an international clinical research consortium supported by the National Institute of Allergy and Infectious Diseases, NIH with the mission to accelerate the clinical development of immune tolerance therapies through a unique collaborative model.

The ITN develops, implements, and conducts trials of novel immune tolerance therapeutics in solid organ and islet transplantation, autoimmune diseases, and allergy & asthma. ITN trials look beyond the traditional endpoints of safety and efficacy, actively investigating the mechanisms of tolerance induction and maintenance by integrating hypothesis-driven, mechanism-based research into all our clinical trials. The overarching goals are to establish tolerance in the human clinical setting, to improve our understanding of the underlying mechanisms of immune tolerance, and to develop new biomarkers of tolerance in human disease.

The Gauging Response in Allergic Rhinitis to Sublingual and Subcutaneous Immunotherapy (GRASS) trial is a single-center, randomized, double-blind, double-dummy, placebo-controlled, three-arm study comparing SLIT, SCIT and placebo (randomized 1:1:1) of 106 participants over 3 years' duration. Participants received 2 years of immunotherapy or placebo followed by a 1-year observation period. Clinical response and mechanistic outcomes were measured following nasal allergen challenge at several timepoints. Desensitization and sustained unresponsiveness were determined using total nasal symptom score after a nasal allergen challenge at 2 and 3 years, respectively.

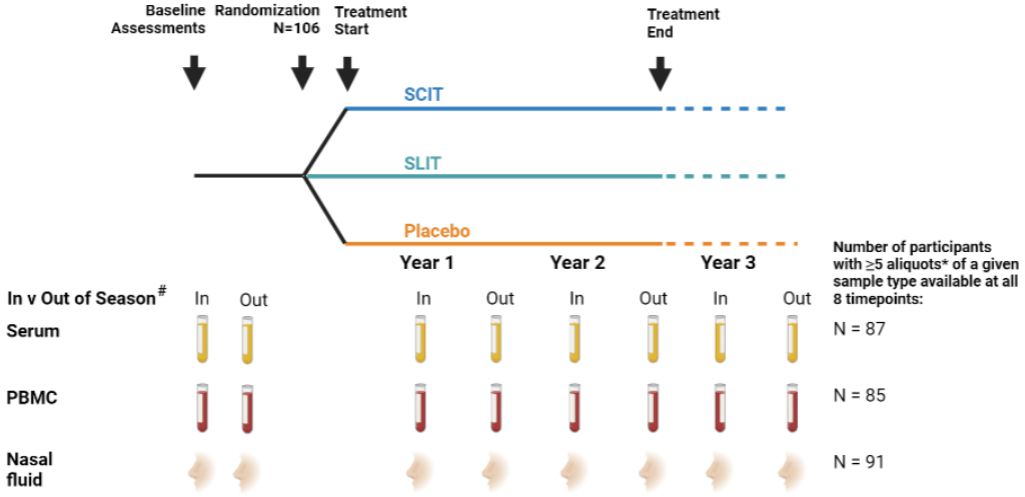
Both SCIT and SLIT, when compared to placebo, were successful in inducing desensitization at year 2. There was a broad range of sustained unresponsiveness (year 3) although not significantly different for either treatment group compared to placebo.

Some of the key mechanistic findings resulting from this trial are:

- Grass pollen-specific Th2 cells paralleled the clinical response to SCIT and SLIT with a decrease during years 1 and 2 and a return to pre-treatment levels following withdrawal of treatment.
- Participants receiving SCIT or SLIT had decreased Th2 cytokines in their nasal fluid and improved nasal epithelial barrier function at year 2 compared to those who received placebo.
- The mechanisms of SCIT and SLIT appeared to differ in their pattern of 'blocking' antibody responses. SCIT was associated with a ten-fold greater increase in allergen Specific IgG4 compared to SLIT whereas SLIT resulted in a 5-fold greater increase in allergen-Specific IgA compared to SCIT. These differences in antibody concentrations were apparent in both serum and in local nasal fluid.

Banked serum, PBMC, and nasal fluid (as outlined in the schematic below) from over 80 participants are available for supplementary mechanistic analyses. Most of these participants have all sample types available at all study time points allowing for both longitudinal and cross-sectional analyses.

Along with demographic and disease-specific information, the participant cohort in this study is extremely well characterized. The detailed demographic information, and clinical and mechanistic trial data are available to the public on our website, TrialShare.



*** Aliquots are defined as follows:**
Serum: 1,000 to 1,250 µL volume
PBMCs: 5-10 million cells, collected in Lithium Heparin tube, cryopreserved
Nasal fluid: variable volume of up to 75µL per aliquot

 # Out of season samples were collected the same day that nasal allergen challenges (NACs) were performed
Serum & PBMCs were collected prior to NAC.
Nasal fluid was collected immediately after the NAC.

The ITN is currently seeking short proposals for novel mechanistic studies using our banked samples from well-characterized GRASS study participants. While we consider that these samples are ideal for studies that examine the differences between SLIT and SCIT and/or to understand why desensitization but not sustained unresponsiveness might occur, ITN is also open to making samples available for other validated mechanistic analyses.

The ideal proposal will be supported by preliminary data and the laboratory should have a strong publication record for the assay proposed to be used in this study. The proposal should state the hypothesis to be tested and include any preliminary data, and should indicate how the new findings will be integrated with the existing clinical findings and lab assessments. A power calculation that justifies the requested sample size should be included, along with the minimum sample volume (serum and/or nasal fluid) or cell number (PBMCs) of each type required for the proposed studies. Please indicate whether funding is, or will, be available to support the proposed studies. This request for proposals is primarily intended to make GRASS samples available; and although funding for the experiments may be available for collaborative projects, funding is not promised.

Proposals should be brief, no more than 5-pages. The proposal review process will focus on evaluating the conceptual framework of the proposed mechanistic study and its significance and suitability for further development. Responses to this RFP will be evaluated upon receipt and the RFP will remain open until the samples have been allocated.

GRASS Study Publications:

Differential Induction of Allergen-specific IgA Responses following Timothy Grass Subcutaneous and Sublingual Immunotherapy (2021). Shamji et al. J Allergy Clin Immunol, S0091-6749 (21), 00552-2. http://dx.doi.org/10.1016/j.jaci.2021.03.030, PMID: 33819508

Synchronous Immune Alterations Mirror Clinical Response During Allergen Immunotherapy (2018). Shamji et al. J Allergy Clin Immunol. , J Allergy Clin Immunol, 2018 May;141(5):1750-1760.e1. doi: 10.1016/j.jaci.2017.09.041

Effect of 2 Years of Treatment With Sublingual Grass Pollen Immunotherapy on Nasal Response to Allergen Challenge at 3 Years Among Patients With Moderate to Severe Seasonal Allergic Rhinitis: The GRASS Randomized Clinical Trial (2017) Scadding et al. JAMA, 317 (6), 615-625. http://dx.doi.org/10.1001/jama.2016.21040, PMID: 28196255

Please direct all proposal inquiries and submissions to Philip Bernstein, PhD: pbernstein@immunetolerance.org.