

Mechanistically Focused Clinical Trials in Environmental Allergy and Immunotherapy

The Immune Tolerance Network (ITN) is an international clinical research consortium supported by the National Institute of Allergy and Infectious Diseases of the 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 allergy and 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.

While the ITN is recognized within the allergy community for our food allergy portfolio, including the early dietary introduction for children at risk of developing peanut allergy ([LEAP](#)) study, we also maintain a robust and growing portfolio investigating environmental allergy and allergic rhinitis. Our prior and ongoing aeroallergen work explores therapies capable of modifying validated desensitization protocols to induce durable tolerance. This includes investigating alternative administration routes and combining allergen immunotherapy with immune-modulating therapies, as demonstrated in recent trials such as [CATNIP](#) (anti-TSLP) and [GRADUATE](#) (anti-IL-4R α). The ITN also conducted the [GRASS](#) Trial, demonstrating that 2 years of sublingual or subcutaneous immunotherapy was insufficient to induce long-term tolerance.

The ITN is currently seeking short proposals for novel clinical trials designed to evaluate mechanisms of environmental allergen immunotherapy. The ITN is especially interested in the following:

- 1. SCIT or SLIT plus immunomodulator therapies.** Building on the foundation of the CATNIP and GRADUATE trials, we are interested in studies that combine allergen immunotherapy (either SCIT or sublingual immunotherapy [SLIT]) with novel immunomodulators to enhance safety and efficacy leading to sustained unresponsiveness and ideally long-term tolerance off therapy. Proposed trials must have a testable mechanistic hypothesis regarding how specific agents of interest influence immune pathways.
- 2. Multi-allergen immunotherapy.** Although multi-allergen subcutaneous immunotherapy (SCIT) is highly prevalent in clinical practice, its mechanistic efficacy and impact on tolerance remain under studied. We are seeking clinical trial designs to evaluate multi-allergen SCIT versus single-allergen SCIT. Proposals should test specific mechanistically based hypotheses regarding whether multi-allergen administration produces a beneficial bystander effect, results in reduced efficacy, or neither.
- 3. Intralymphatic immunotherapy (InLIT).** Intralymphatic immunotherapy is a potentially impactful, though poorly studied and controversial technique that warrants rigorous, unbiased, and mechanistically focused evaluation. We seek clinical trial proposals designed to investigate InLIT. An example design might involve an environmental allergen administered directly into inguinal lymph nodes over a several-month period, with systematic mechanistic and clinical evaluations utilizing allergen challenge models or seasonal symptom assessments.

Open Call for Innovations in Aeroallergen Tolerance

Please note that the ITN is fully open to reviewing any compelling aeroallergen-related clinical trial proposals, even if they do not fall into one of the three specific areas outlined above. The ideal proposal should be supported by preclinical data, some safety and efficacy experience, and a testable mechanism of tolerance induction.

These proposals should be very brief, ideally a single page. The early proposal review process will focus on evaluating the conceptual framework of the proposed trial and its significance and suitability for further development; it does not require submission of a detailed clinical protocol. Review will potentially be an iterative process.

Please direct all proposal submissions and any questions concerning this RFP to Philip Bernstein, Director Strategic Review and Planning: submissions@immunetolerance.org