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SPECIAL ARTICLE

What impact will the immune tolerance network have on the future treatment of allergic diseases?

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Summary

The immune tolerance network (ITN) plans to capitalize on the current state of understanding of immunologic science to solicit, design and implement human trails designed to 'cure' allergic diseases. While the ITN can bring tremendous resources to bear, it is actively looking for the participation of innovative physician–scientists worldwide in order to optimize the changes of success and thereby have a major impact on the future treatment of allergic diseases.

I firmly believe and will try to convince you that immune tolerance network (ITN) will have a major impact on the future treatment of allergic diseases by engaging in and supporting novel interventions aimed at prevention and cure of allergic disease. While advances in pharmacotherapy have greatly improved the health and quality of life for the majority of patients with allergic diseases, in truth, there remain only two specific treatments available to the allergy patient – allergen avoidance and allergen-specific immunotherapy (IT). And IT is far from ideal: it is a cumbersome treatment, generally non-standardized in application and requires several years of treatment, while exposing patients to considerable risk of adverse reactions. Furthermore, despite its widespread application, the mechanisms of IT remain poorly understood. It is clear then, that safer, more robust, short-term, preventative therapies based upon well-understood immunologic mechanisms are the allergist's real desired end point for our patients.

But how is this best achieved, considering the vast spectrum that makes up allergic disease and the financial constraints of replacing long-term therapies with short-term treatments? I believe it is precisely through the establishment of the ITN and similar organizations.

The ITN is an international research consortium whose goal is to accelerate the clinical development of immune tolerance therapies in (a) allergy and asthma, (b) kidney, liver and islet transplantation, and (c) autoimmune diseases. It does so by providing funding and support for highly novel clinical trials and clinically based mechanistic studies of tolerance that are proposed by the community in a year-round call for proposals. While sponsored by the National Institutes of Health (NIH), it is important to emphasize that the ITN is *not* the NIH – it does not fund basic research, animal studies or generally even phase 1 clinical trials. It is also not simply a funding agency. In addition to providing subcontracted research funds, the ITN provides investigators with: (i) the advice of a group of fully engaged colleagues whose charge is to assist the investigator in developing an optimal research plan that maximizes the resulting knowledge; (ii) start-to-finish clinical operations (CRO) support for protocol development, regulatory, study monitoring and data analysis; (iii) expertise and access to a startling array of cutting-edge technologies and tools via its integrated network of core facilities that perform diagnostic and research-based assays to help investigators get the most from their research, whether it is academic or industry-initiated. An overview of the structure and the resources of ITN are given in Fig. 1.

But why is the ITN so well positioned to advance the treatment of allergic disease? Foremost, as opposed to organizations whose agenda is to improve the pharmacologic *management* of disease, the ITN's mandate is to study relatively short-term interventions that lead to long-term improvement even though the treatment has been stopped (this, in fact, is the working definition of tolerance). This is a critical distinction. The ITN will consider supporting all forms of interventions that may lead to long-term allergic tolerance. Treatment could involve a controlled allergen exposure (vaccine) approach, a combination of controlled or natural allergen exposure plus an immunomodulatory product, e.g. Toll-like receptor agonists, or the use of an immunomodulatory treatment alone, e.g. anti-IL-4. Whatever the approach, the plan must be to stop the treatment and have achieved a new and healthier immune homeostasis in the subjects. The ITN's position also means that in selecting research to pursue, it is motivated purely by potential therapeutic benefit and knowledge gained, unconcerned with the potential to recoup the significant investment required for early-stage clinical research. In addition, as a non-profit organization, the ITN has no propriety interest in any one approach. Thus it retains a considerable breadth in the research it may conduct. This is apparent in that ITN support is open to any investigator worldwide with a good idea, be they academic, government or industry-based – it already has numerous active partnerships with biotech and pharmaceutical companies. By studying a range of only the best opportunities, the ITN optimizes the chances of success, as in all science; it is not possible to predict which of the many good ideas out there will ultimately work. Finally, as one of the largest contracts in NIH history, the ITN has the financial

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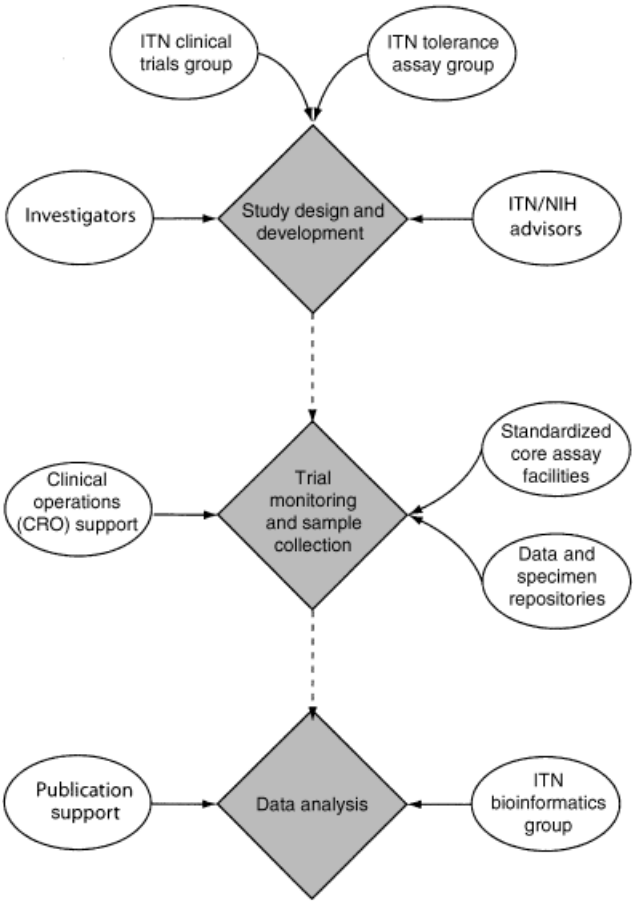

Fig. 1. Schematic of the key components of the Immune Tolerance Network and their interactions in achieving optimal clinical trial performance and outcome.

strength to do the robust translational clinical trials needed to establish clinical efficacy of such therapies. Now, at just over four years since its mandate began, the ITN model is already showing that it can and will carry out unique, important trials.

For instance, one major way the ITN will impact allergic disease is by supporting active primary prevention studies ('active' meaning to provide a 'therapeutic' as opposed to avoidance intervention) with 'high-dose antigen' early in life. A newly approved study will test the hypothesis that high-dose sublingual/oral antigen administration in very young children who have atopic dermatitis and food allergy can prevent future allergic sensitization to respiratory allergens and asthma. The ITN is also entertaining an analogous approach of early-in-life high-dose allergen exposure for the prevention of severe food allergy in high-risk children. Certainly, if high-dose allergen exposure very early in life can prevent future allergic sensitization and the development of allergic rhinitis, asthma and/or severe food allergies, those discoveries will have a major impact on the way allergy is managed in the future. Such studies underscore the ITN's unique position, as the financial returns of such therapies are likely insufficient for early investment by 'big Pharma' and the complexity of the studies are ill suited to traditional R01-style NIH funding.

Lest one believe that the ITN plans to 'do it alone,' it must be emphasized that the ITN is developing a strong track record of working *with* industry to achieve its goals. Case and point is a study of the effects of rush ragweed immunotherapy with or without anti-IgE coverage that is being performed in collaboration with Genentech. The study is testing the hypothesis that anti-IgE can improve the safety of rush IT such that the dose escalation phase may be avoided. The results of this study also have the potential to radically change the way allergen IT is administered and would have the added advantage of being able to be used with all forms of IT, including those with large numbers of antigens.

The ITN is also actively pursuing studies aimed at improving the nature of allergen-specific desensitization and plans to broaden its portfolio in this regard. A pilot trial of Immunostimulatory Sequences (that bind Toll-like receptor 9) coupled to ragweed (in an ITN-industry partnership with Dynavax Technologies) has already been completed, demonstrating a positive clinical benefit in the first allergy season and a greater positive benefit in the second season, more than a year after the therapy had been given [1]. The entire course of therapy lasted only 6 weeks. Dynavax is using the results of this study as the basis for next-stage clinical trials of immune stimulatory sequence.

Clearly, the value of such studies is enormous – short courses of high-dose ISS-allergen, if indeed safer and more effective than regular IT, will fundamentally alter the playing field in allergy. This form of tailor-made IT holds great promise in other specific situations such as grass allergy, severe food allergy, etc., where the number of antigens/allergens is relatively limited. The ITN is also looking at other potential methodologies to deviate the immune response by selective triggering of the innate immune system employing either co-administration of or natural exposure to allergens.

The ITN has also committed funding for a trial peptide therapy in cat allergy based on board major histocompatibility complex (MHC)II binding [2, 3]. The concept of peptide therapy in allergy using different peptides than proposed for the ITN trial was effectively abandoned by 'Pharma' because after a single trial, late airway reactions felt to be based on T cell reactivity were noted [4]. This willingness of the ITN to fully investigate a good idea is another example of how the ITN stands out from the norm and is positioned to impact the future treatment of allergy disease.

There are many other approaches beyond allergen-specific vaccination strategies that the ITN is interested in pursuing. In general the ITN is seeking approaches that can establish functional tolerance to allergens – relatively short-term therapies with long-term immunologic consequences, as opposed to immunosuppressive strategies that require continuous therapy. For instance, allergens genetically modified to remove the IgE binding sites would be an interesting proposition. The ITN is also very interested in working with Pharma to redirect some of their efforts from drugs for 'treatment' of allergy and asthma into drugs for induction of tolerance. Drugs such as IL-4 or IL-4/13 antagonists may not prove to be useful treatments for asthma, but they may well have important immunologic effects in the setting of allergen immunotherapy such that improved outcomes result [5].

Of course, not all of these approaches will prove successful. Even so, the knowledge alone that will be generated by the ITN in conducting such a unique set of trials stands to

revolutionize our understanding of the disease and plant the seeds of the next generation of allergy therapies. Already, the state of immunological science is ripe for major advances. The ITN has strong financial resources, a fresh approach that emphasizes concurrent clinical and mechanistic evaluations, an expanding high-quality infrastructure of facilities and resources to support these studies and a highly motivated, experienced group of individuals dedicated to making it happen.

Therefore, my answer to the question posed in the title of this article, then, is that the ITN will surely have a significant impact on the future treatment of allergic disease. The ITN will increase the odds of developing safe and effective treatments that lead to long-term allergy tolerance by providing (a) money, (b) scientific expertise, and (c) technical and administrative support. However significant and in exactly what way, however, is up to you as investigators with 'good ideas' are the life-blood of any research endeavour, and the ITN is no exception. Thus, in Fig. 1, the block marked 'investigators' does not represent a cadre of appointed people but rather is an open invitation to those who want to work with the ITN to achieve its stated goals. At the ITN, investigators good ideas are welcomed year-round with no deadline, in the form of a short, three-page 'concept proposal'. Visit www.immunetolerance.org for more information and for online proposal submission.

References

1 Creticos PS, Lighvani SS, Bieneman AP et al. Enhanced IL10 secretion by PBMC during the ragweed season: effects of AIC immunotherapy vs placebo. J Allergy Clin Immunol 2003; 111: S201 (530) (presented at 60th Meeting AAAAI, Denver, CO, 3–7 March 2003 abstract 530).

2 Haselden BM, Kay AB, Larché M. Immunoglobin E-independent major histocompatibility complex-restricted T cell peptide epitope-induced late asthmatic reactions. J Exp Med 1999; 189:1885–94.

3 Oldfield WL, Larché M, Kay AB. Effect of T-cell peptides derived from Fel d 1 on allergic reactions and cytokine production in patients sensitive to cats: a randomised controlled trial. Lancet 2002; 360:47–53.

4 Maguire P, Nicodemus C, Robinson D, Aaronson D, Umetsu DT. The safety and efficacy of ALLERVAX CAT in cat allergic patients. Clin Immunol 1999; 93:222–31.

5 Izuhara K, Arima K, Yasunaga S. IL-4 and IL-13: their pathological roles in allergic diseases and their potential in developing new therapies. Curr Drug Targets Inflammat Allergy 2002; 1:263–9.