TIMELINE

The Immune Tolerance Network at 10 years: tolerance research at the bedside

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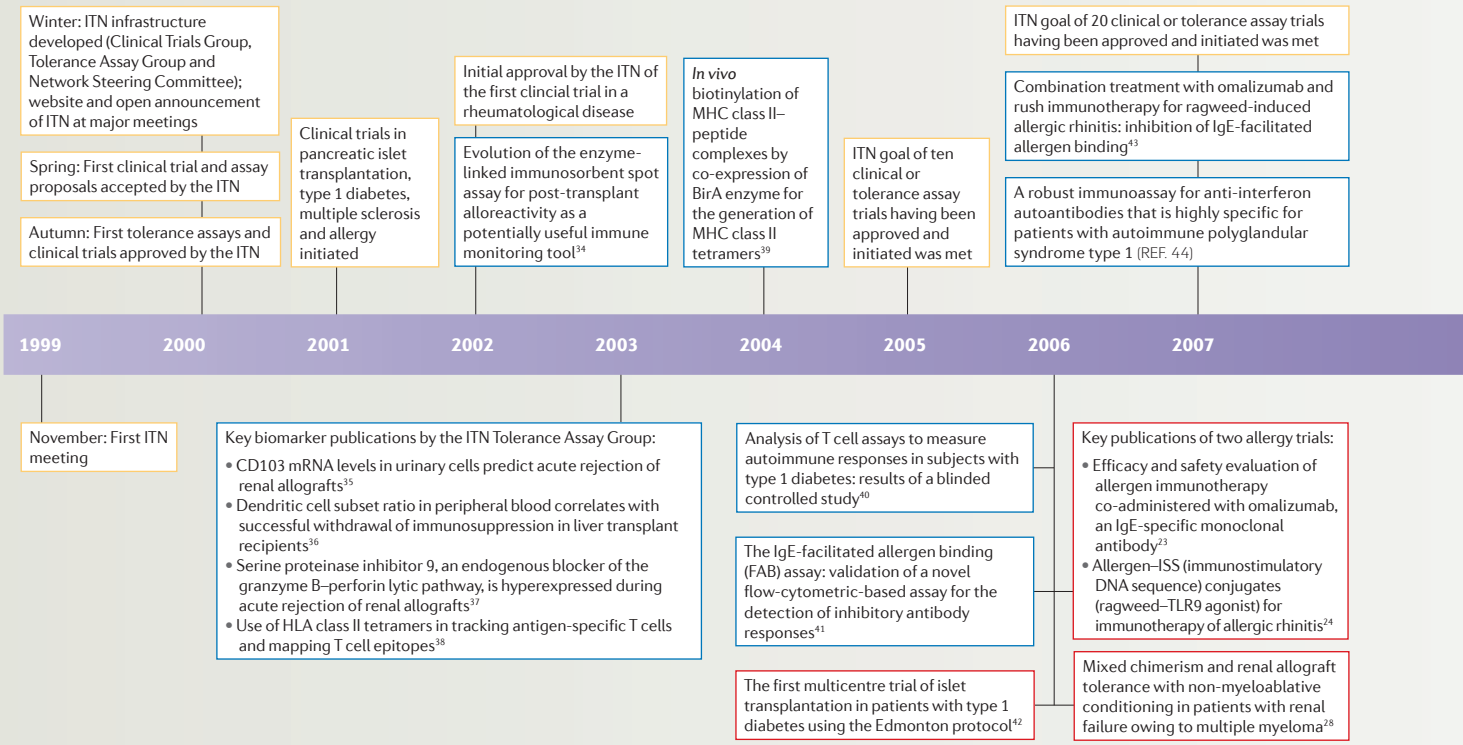
Abstract | Immune tolerance-inducing therapies reprogramme immune cells to eliminate pathogenic immune responses while preserving protective immunity. The Immune Tolerance Network (ITN), sponsored by the US National Institutes of Health, was established in 1999 to evaluate new tolerance-inducing therapies and carry out mechanistic studies using a unique interactive approach in partnership with industry, academia and foundations. Ten years later, the ITN has carried out approximately 36 clinical trials and tolerance studies examining innovative tolerogenic approaches in the settings of allergy, autoimmune diseases and organ transplantation. ITN investigators have published more than 80 original research papers based on this work. This Timeline article summarizes the progress and challenges of clinical research in the ITN.

Immune-mediated diseases are prevalent, debilitating and costly. These diseases — including autoimmune diseases such as type 1 diabetes mellitus, rheumatoid arthritis and multiple sclerosis, and more than 80 other autoimmune diseases — affect tens of millions of Americans and result in annual health-care costs of more than US$100 billion in the United States and at least double that worldwide. In addition, immune-mediated organ graft rejection is an ongoing challenge for the estimated 250,000 Americans who are recipients of solid organ transplants. Add to this the tens of millions of individuals who suffer from asthma and various allergic conditions and it becomes clear that immune-mediated diseases affect nearly every US household. Although traditional immunosuppressive therapies, such as corticosteroids, methotrexate, calcineurin inhibitors, azathioprine, mycophenolate mofetil and cyclophosphamide, have greatly improved the lives of organ transplant recipients and patients with immune disorders, such therapies require life-long treatment and function to non-specifically suppress the entire immune system, thereby exposing patients to considerably higher risks of opportunistic infections and cancer. Even the newer therapies that target T and B cells, interfere with cell–cell interactions regulating the immune response or neutralize potent inflammatory mediators, such as tumour necrosis factor (adalimumab (HUMIRA; Abbott)), interleukin-1 (IL-1) (anakinra (Kineret; Biovitrum)) or IL-6 (tocilizumab (Actemra; Roche)), have not led to a cure for immune-mediated diseases. Clearly, there is room for improvement and a paradigm shift in our thinking about the optimal treatment approach. In essence, the challenge is to replace chronic treatments with their associated toxicities, costs and long-term complications with new therapies that can be used briefly to induce a state of specific immune tolerance characterized by long-term, drug-free existence and immune competence.

The concept of a large clinical trials 'network' devoted to the study of new therapies to induce immune tolerance first attracted attention in the mid-1990s (TIMELINE). Tolerance-inducing therapies would be a radically new approach for the treatment of human immune-mediated diseases, offering the exciting possibility of short-term treatment followed by long-term or even permanent remission off immunosuppressive drugs. A series of promising results in small and large animal models showed that short-term treatment with drugs, cells or combination interventions designed to induce tolerance could lead to robust long-term organ graft survival[1], remission from autoimmunity[2] and abrogation of allergic reactions[3]. Such striking achievements raised hopes that these related fields of transplantation, autoimmunity and allergy might be poised for major clinical breakthroughs and indicated that new strategies to induce immune tolerance might be evaluated in humans relatively soon thereafter. To facilitate these efforts, in the mid to late 1990s, the US National Institute of Allergy and Infectious Diseases (NIAID) solicited advice from experts in immune tolerance, which culminated in 1998 with a broad-based, long-range plan entitled 'NIAID Plan for Research on Immune Tolerance'. In addition to other activities, the Plan called for the evaluation of promising tolerogenic approaches in the clinic through partnerships between academia, industry, patient advocacy groups and government, organized around a network that would bridge these various communities and multiple scientific disciplines.

As a result, the Immune Tolerance Network (ITN) was founded in 1999 — a new clinical research programme to develop novel therapeutic interventions that would permanently alter the specific reactivity of the immune system[4]. The scientific objectives of the ITN were clear: to carry out clinical trials to determine the safety, toxicity and efficacy of promising tolerogenic strategies in kidney and pancreatic islet transplantation, allergy and asthma, and autoimmune diseases; to investigate the basic mechanisms of immune tolerance in these diseases as an integral part of clinical trials; and to develop, refine and validate immune assays to monitor the induction, maintenance and loss of tolerance in these disorders.

Timeline | **The Immune Tolerance Network: milestones, biomarker studies and clinical trials**

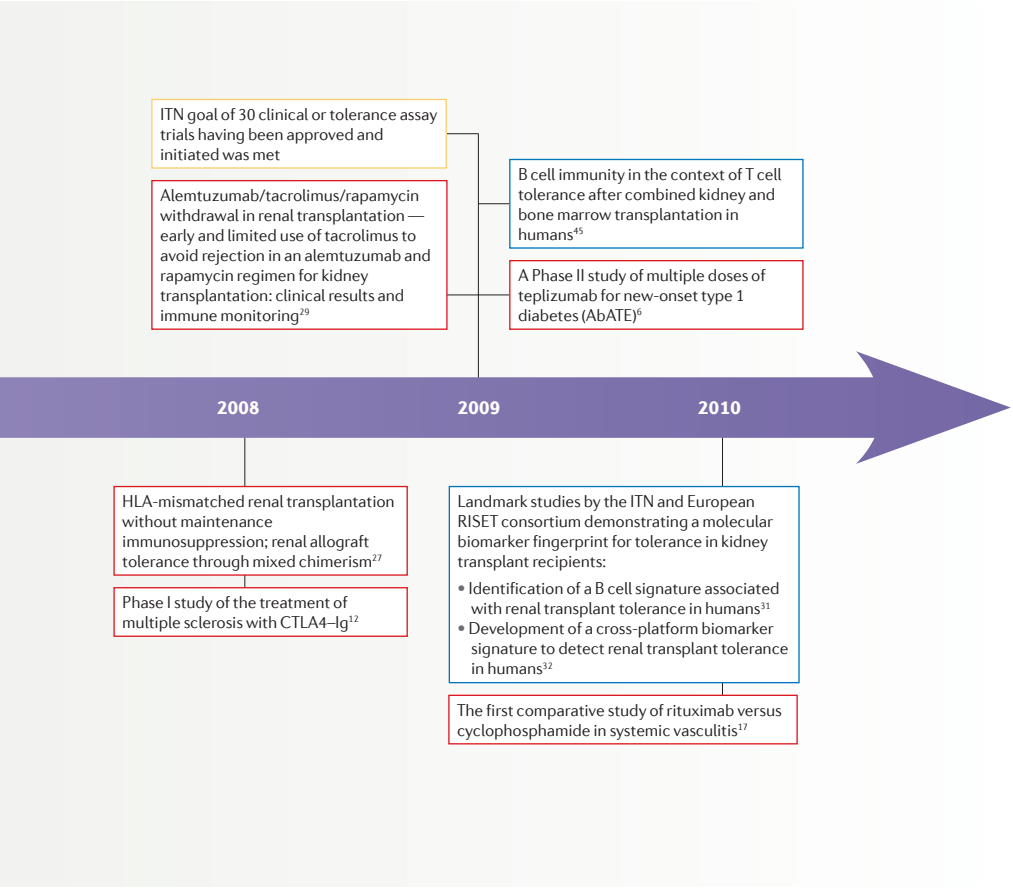


Milestones, yellow; biomarker studies, blue; clinical trials, red. CTLA4–Ig, cytotoxic T lymphocyte antigen 4–immunoglobulin; RISET, Reprogramming the Immune System for Establishment of Tolerance; TLR9, Toll-like receptor 9.

The ITN is not the only organization that carries out research in the field of immune tolerance. Another example is the multinational European project 'Reprogramming the Immune System for Establishment of Tolerance' (RISET), which is financed by the European Commission and focuses on the translation of advances in basic research into clinical practice in organ transplantation. However, to our knowledge, the ITN is the only organization that is not focused on a single disease area. Moreover, the research carried out by the ITN is limited to human studies. Unlike most funding streams of the US National Institutes of Health (NIH), the ITN is explicitly international, and it has funded trials and mechanistic studies in Europe and elsewhere. This is a significant advantage for such a complex effort, and the ITN has supported many of the best groups in the field worldwide. With an approximately US$25 million a year budget allocated for distribution by the University of California, San Francisco — which is comparable to the budget of other NIH-funded networks, such as the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored Type 1 Diabetes TrialNet, the National Cancer Institute (NCI)-sponsored cancer networks or the six NIAID-sponsored HIV/AIDS clinical networks — the ITN can develop and carry out complicated clinical trials and mechanistic studies to advance our understanding of and drug development for many disease areas.

The ITN adopted a five-part strategy to accomplish its goals. First, the ITN would assemble a team of academics to identify and review grant proposals but maintain an objective and inclusive approach that allows any investigator to suggest a potential tolerogenic protocol. Second, the ITN would operate in an efficient manner to allow quick turn-around of submitted proposals to meet the needs of companies and academics. Third, the ITN would be flexible and cost effective, such that it can adapt quickly to address emerging information and technologies. Fourth, the ITN would create an integrated clinical research organization with capabilities to develop clinical trial protocols, gain regulatory and ethical approvals, and carry out and monitor studies, including state-of-the-art mechanistic assays, as a component of the clinical research agenda. Fifth, and most importantly, the ITN would be centred on scientific concepts, rather than a particular disease or medical discipline, such that the clinical research carried out by the ITN, in terms of both clinical trials and mechanistic studies, is devoted to testing scientific hypotheses. This last strategy was unique in that it brought together experts from distinct disease areas — from allergy to autoimmunity to organ transplantation — in a new forum for interdisciplinary clinical research efforts.

This year, the ITN celebrates its 10th anniversary, with the ongoing primary support of NIAID and partnering organizations including NIDDK, the Juvenile Diabetes Research Foundation (JDRF), the Food Allergy Initiative (FAI) and more than 30 companies. Although it has been challenging to meet all of its original aspirations, the ITN has developed and carried out more than 25 clinical trials, published more than 80 primary research papers and created an open model of translational research whereby scientists throughout the world can request ITN resources to support cutting-edge clinical studies. These trials have led to the



testing of new immunotherapies that have resulted in clinically durable tolerance in some patients and a requirement for only minimal immunosuppression in many others. Importantly, clinical and basic-science researchers, working with the ITN Mechanistic Studies group, have begun to determine the molecular and cellular 'fingerprints' of immune tolerance (the unique molecular or cellular signatures that would enable the identification of tolerant individuals). With more than one third of a million patient samples available for future analyses, a large clinical database and new tools for data visualization, the ITN has the potential to break new ground in the study of the tolerant phenotype.

In the rest of this article, we highlight selected clinical and mechanistic accomplishments of the ITN, as well as some of the challenges we have experienced in achieving tolerance in the clinical setting. We also discuss future directions of the ITN and opportunities to realize the original goals set forth in our mission statement, "…to achieve in patients a robust state of immune tolerance in the absence of ongoing immunotherapy while maintaining a competent immune system".

Targeting cell subsets and pathways

One of the main targets for tolerogenic therapies is T cells, the activation of which initiates a cascade of cellular and cytokine responses that can destroy self and foreign tissues. So, it is not surprising that many ITN trials have focused on T cell-specific agents (see the ITN website for a complete list of clinical trials and publications). Such agents have greater cellular specificity than generalized immunosuppressive therapies and hold the promise of creating a tolerogenic environment that would limit the need for continuous treatment. In one set of trials, a novel Fc receptor non-binding CD3-specific monoclonal antibody (teplizumab) was evaluated for the treatment of patients with type 1 diabetes[5,6] or psoriatic arthritis[7]. Previous animal studies had shown that this bivalent form of a CD3-specific antibody delivers altered biochemical signals to T cells that selectively deplete effector T cells, stabilize regulatory T (T_{Reg}) cells[8,9] and induce a state of immune tolerance. The clinical studies in patients with type 1 diabetes showed that short-term treatment with teplizumab produced long-term benefits, including the preservation of pancreatic beta cell function and an improvement in the control of blood sugar levels[5,6] (ClinicalTrials.gov identifier: NCT00129259). In a recent randomized, open-label trial, treatment with teplizumab for only two weeks at disease onset prolonged beta cell function in some patients with type 1 diabetes for up to 5 years after treatment. These results led to a follow-up ITN trial that included a second course of teplizumab treatment at 1 year after disease onset and they stimulated two pivotal industry-sponsored Phase III trials in patients with type 1 diabetes (sponsored by MacroGenics/Lilly (NCT00920582) and Tolerx/GlaxoSmithKline (NCT01123083)). Another tolerogenic T cell-targeted therapy — a polyclonal rabbit thymocyte-specific antibody preparation (Thymoglobulin; Genzyme) — is also being tested in an ITN trial (NCT00515099). This therapy is also thought to deplete activated effector T cells while promoting T_{Reg} cell survival and/or proliferation.

The activation of T cells requires a signal through the T cell receptor plus additional co-stimulatory signals[10]. Several candidate co-stimulatory molecules have been targeted for T cell tolerance induction. Early on, the ITN sought to study the effect of an antibody specific for the co-stimulatory molecule CD154 (also known as CD40L), produced by Biogen Idec, in patients with multiple sclerosis. However, problems with the antibody in another disease setting (thrombotic events in patients with systemic lupus erythematosus) halted the drug development programme[11]. The ITN has since been able to work with other co-stimulation antagonists, including the cytotoxic T lymphocyte antigen 4 (CTLA4)–immunoglobulin fusion protein abatacept (Orencia; Bristol-Myers Squibb), which has been approved for the treatment of rheumatoid arthritis. A similar drug (CTLA4–Ig; RepliGen) was shown to be safe and well-tolerated in an ITN-led Phase I trial involving patients with multiple sclerosis[12]; the efficacy of tolerance induction using abatacept is currently being tested in follow-up Phase II trials in patients with multiple sclerosis (under development) or with lupus nephritis (NCT00774852). It is interesting to note that immunological assessment of the patients with multiple sclerosis in the Phase I trial showed that after two months of CTLA4–Ig treatment, there was a decrease in myelin basic protein (MBP)-stimulated T cell proliferation and decreased interferon-γ production by MBP-specific T cells.

One of the more innovative Phase I trials in this category combines IL-2 and rapamycin (also known as sirolimus) therapy in patients with type 1 diabetes. IL-2 — aldesleukin (Proleukin; Prometheus) — is a cytokine that has been shown to expand T cell populations through the activation of signal transducer and activator of transcription 5 (STAT5). Rapamycin (Rapamune; Wyeth), an immunosuppressant drug that is used to prevent rejection after organ transplantation, blocks signalling through mammalian target of rapamycin (mTOR), thereby inhibiting effector T cell function. Previous mouse studies have shown that IL-2 treatment markedly increases the proliferation and survival of $CD4^+CD25^+$Forkhead box P3 $(FOXP3)^+$ T_{Reg} cells[13,14], and that rapamycin stabilizes FOXP3 protein expression and inhibits effector T cell signalling[15]. Therefore, the ITN has been examining the combination of IL-2 and rapamycin for safety and biological activity with the intention of carrying out an efficacy trial to follow. We hypothesize that this combination will expand the T_{Reg} cell population in the peripheral blood and that antigen-specific T_{Reg} cells will selectively traffic to the sites of inflammation, as predicted by the results of animal studies[13,14].

Finally, the ITN is also investigating other co-stimulation antagonists. For example, a trial in patients with new-onset type 1 diabetes will be initiated in 2010, in collaboration with Astellas Pharma, to test the effects of alefacept (Amerive), a soluble CD2 antagonist that blocks the co-stimulatory LFA3–CD2 interaction; alefacept has been approved for the treatment of psoriasis and has been shown to promote tolerance after organ transplantation[16]. The mechanism of action of this therapy remains unclear, but it is thought to function by inducing the apoptosis of effector-memory T cells, thereby re-establishing immune homeostasis and perhaps tolerance. Mechanistic studies will be designed to determine the basis of immune modulation by this therapy and its potential as a tolerogenic treatment.

Although a large proportion of ITN tolerance trials have targeted T cells, compelling data in animal models indicate that other cell types, such as B cells and dendritic cells, are also likely to be important, by controlling the presentation of auto and/or alloantigens for T cell activation, by immune regulation of cytokine production or through direct cell–cell interactions. The ITN has just completed a seminal Phase II study directly comparing rituximab (Rituxan/Mabthera; Genentech/Roche/Biogen Idec) — a CD20-specific antibody that depletes B cells, which has been approved for the treatment of rheumatoid arthritis and certain types of lymphoma — with the standard of care, cyclophosphamide, for the treatment of severe cases of systemic vasculitis associated with neutrophil-specific cytoplasmic antibodies, such as Wegener's granulomatosis and microscopic polyangiitis (NCT00104299). This study was supported in part by Genentech. The results of the trial showed that rituximab is as effective as cyclophosphamide in inducing clinical remission at 6 months after therapy[17]; the 18-month follow-up data are being analysed. We are keen to determine to what extent tolerance is induced in the rituximab-treated patients and if we can identify biomarkers that are predictive of successful therapy.

The ITN has provided an opportunity for investigators to propose 'out-of-the-box' approaches to immune modulation using drugs that have been approved for completely different purposes. Several years ago, the lipid-lowering drug atorvastatin (Lipitor; Pfizer) was shown to be effective in treating experimental autoimmune encephalomyelitis in mice[18]. These animal studies formed the scientific rationale for a randomized, placebo-controlled, double-blind trial of atorvastatin therapy for patients with early-stage multiple sclerosis, referred to as clinically isolated syndrome. In this small study, the investigators found that atorvastatin treatment did not significantly decrease the number or size of brain lesions as shown by magnetic resonance imaging (MRI) activity compared with placebo, although more patients in the atorvastatin treatment group had no new MRI lesions in the brain[19].

Imatinib (Gleevec; Novartis), a breakpoint cluster region (BCR)–ABL1 antagonist that has been approved for the treatment of chronic myelogenous leukaemia, targets several receptor tyrosine kinases in addition to ABL1 and has been shown to reverse diabetes in the spontaneous non-obese diabetic (NOD) mouse model[20]. The ITN has designed a randomized, placebo-controlled trial to determine if short-term imatinib therapy (6 months) of patients with type 1 diabetes will have any ameliorating effects on beta cell function and/or survival or the autoimmune abnormalities that are associated with disease. Another clinical study in patients with type 1 diabetes will test the efficacy and safety of α1-antitrypsin (AAT), a protease inhibitor that is approved for the treatment of AAT deficiency in children. This drug has been shown to inhibit IL-1 signalling, leading to reversal of disease in diabetic NOD mice[21]. As it is probable that combinations of therapeutics will be more efficacious at altering multiple immunological pathways, the ITN is actively exploring such strategies using the above agents, and others.

Targeting antigen-specific immunity

Human allergy is an informative setting in which to explore the mechanisms and clinical effects of antigen-specific tolerance induction owing to our ability to quantify the history of allergen exposure and recent increases in our knowledge of the fine structures of stimulating allergens. Allergen immunotherapy has been known for nearly 100 years to have some clinical efficacy. The immunological changes that occur after insect sting immunotherapy, which we now recognize as hallmarks of immunological tolerance, were first shown in 1990 (REF. 22) and it was first suggested that immunological tolerance was induced by allergen immunotherapy in 1999 (REF. 3) Rush immunotherapy (RIT) — a form of immunotherapy in which patients are administered an allergen extract on a rapid dose-escalating titration schedule that greatly decreases the time it takes to reach maintenance doses — has the goals of rapidly 'desensitizing' patients to the allergen and quickly attaining maintenance dosing with only a modest increase (as compared with traditional allergen immunotherapy) in the risk of serious side effects, which leads to earlier therapeutic benefits. In an ITN trial, RIT for ragweed allergy was carried out after patients were administered an IgE-specific monoclonal antibody, omalizumab (Xolair; Genentech/Novartis). Compared with placebo, pretreatment with omalizumab resulted in marked protection from serious allergic reactions after RIT[23]. Pretreatment with omalizumab before RIT also led to an improvement in symptom scores during the ensuing ragweed season, although the overall effect was small and there was substantial site-to-site variability. With further investigation, the appropriate dosing and timing of omalizumab pretreatment might ultimately lead to safer and more tolerogenic allergen immunotherapies.

In another ITN study, a DNA–ragweed allergen conjugate (Amb a1 immunostimulatory complex (AIC); Dynavax) was tested in a randomized, placebo-controlled study of patients with ragweed-induced allergic rhinitis[24]. The CpG DNA component of the conjugate, a Toll-like receptor 9 (TLR9) agonist, was hypothesized to promote tolerance to Amb a1 (the major ragweed allergen) by

shifting the allergen-specific T helper (T_H) cell response from a pro-allergic T_H2 cell response to a T_H1 cell response, as well as to improve the safety profile of the ragweed allergen component through steric hindrance of the IgE-binding sites on Amb a1. During the ensuing ragweed season, the AIC treatment group had decreased peak-season rhinitis scores and increased mid-season overall quality-of-life scores compared with the placebo group. More significantly, the clinical benefits of AIC treatment persisted through the second ragweed season one year later. The seasonal Amb a1-specific IgE antibody response was decreased in both seasons in the AIC treatment group, together with an AIC-induced transient increase in levels of Amb a1-specific IgG antibody. There was also a decrease in the number of IL-4$^+$ basophils in AIC-treated patients, which correlated with decreased rhinitis scores. Of particular interest, the conjugate seemed to be strongly pro-tolerogenic in that the clinical and laboratory effects of AIC required only six injections in the first year, compared with the typical 2-year course of standard ragweed immunotherapy.

Another ITN study that is underway in the allergy field builds upon strong epidemiological evidence and the Nobel Prize-winning research of Sir Peter Medawar, who in the 1950s showed that animals could be tolerized to transplantation antigens if they were introduced very early in life[25]. Until recently, the conventional wisdom has been that parents of infants who are at high risk of developing food allergies — for example, as determined by family history, genetics, prior sensitization or concomitant eczema or other food allergies — should delay early childhood exposure to common allergenic foods as a way of avoiding sensitization and therefore the emergence of clinical allergy. However, carefully conducted epidemiological studies have indicated that Israeli children, who typically consume peanut-containing snacks at an early age, have an approximately tenfold lower incidence of peanut allergy compared with children in the United Kingdom or United States[26]. An ITN open-label, controlled study that builds on these findings is looking to determine if infants who consume peanut-containing snacks beginning at 4–11 months of age will have a lower incidence of peanut allergy by 5 years of age compared with children who are randomly assigned to a peanut avoidance group. The results of this study, if positive, could have a major impact on public health policies in the United States and other countries and on the design of prevention studies for other childhood allergies.

Antigen-specific therapies are also being tested in the autoimmune setting, where putative autoantigens are being used in various forms as tolerogens. We can normally only speculate about the initiating antigens responsible for organ-specific autoimmune diseases and often by the time that a patient comes to the clinic with signs and symptoms of disease, the pathogenic response has diversified to target multiple autoantigens. However, it might be possible to use an antigen-specific approach regardless of whether or not the tolerogenic antigen is the disease-driving antigen if presentation of the autoantigen in a tolerizing context elicits the desired regulatory effects in the inflamed tissue and draining lymph nodes.

> “Achieving tolerance is a huge challenge — success will probably be incremental and expectations need to be appropriately scaled.”

In terms of transplantation, antigen-specific immunotherapy is best achieved by exposing transplant recipients to donor alloantigens. Several proof-of-principle studies have shown that tolerance can be achieved in this way. Non-myeloablative conditioning followed by donor bone marrow infusion as part of a kidney transplant protocol has resulted in more than ten patients being free of immunosuppressive drugs[27,28]. Another, less invasive protocol incorporating treatment with the CD52-specific antibody alemtuzumab (MabCampath; Genzyme), which is a potent lymphocyte-depleting antibody, and rapamycin has resulted in nine renal transplant recipients who are currently only on rapamycin monotherapy[29]. Interestingly, the patients in this study have done so well that none has been willing to stop immunosuppressive drug therapy completely for fear of graft rejection. This point illustrates one of the complex ethical issues that arises when carrying out clinical tolerance trials. Finally, in a trial of drug withdrawal after paediatric liver transplantation, we have learned through an ITN study that the majority (more than 70%; $n = 20$) of children who have received a live donor (parent) liver transplant at a very young age (<2–5 years of age) can be successfully withdrawn from immunosuppressive drugs[30]. This last result raises several key questions about the role of the thymus, education of the young immune system and the potential of the immune system to adapt to the presence of foreign tissue over several years as a child.

Dissecting the tolerance phenotype

The ITN is fundamentally interested in developing a better understanding of the basic processes of tolerance, in studies ranging from autoimmunity to allergy to organ transplantation. Therefore, the ITN has engaged in multiple studies that aim to determine if there is a specific phenotype indicative of tolerance. One landmark study examined 25 kidney transplant recipients from throughout the United States who had not rejected their graft despite stopping all of their immunosuppressive drugs, which is an unusual clinical scenario[31]. The genetic and cellular signature of these patients, which was independently verified by a European group, showed that B cells uniquely mark the tolerant state[32]. In the European study, there was also a FOXP3 expression signature in the tolerant patients, not unlike that which has been seen in several of the ITN trials using CD3-specific antibodies and Thymoglobulin, which supports a possible role for T_{Reg} cells in tolerance[31]. Of course, the identification of B cells or T_{Reg} cells as a biomarker of tolerance does not establish causality, but this does not necessarily decrease the potentially utility of the biomarker as a clinical management tool.

The challenge now is to confirm and extend these results. First, the ITN will study a large cohort of renal transplant recipients on various immunosuppressive therapies to determine if any of the patients have this tolerance ‘fingerprint’ and therefore might be candidates for drug withdrawal. Although it remains to be seen if patients who are stable on minimal immunosuppression will, in fact, decide to terminate therapy, the identification of a tolerance signature will help to inform evidenced-based decisions about drug withdrawal, as has recently been instituted by the liver transplant group in Barcelona, Spain[33]. Second, the ITN will look to find similar tolerance ‘fingerprints’ in patients with other immune-mediated diseases. Finally, the ITN will determine if kidney and liver transplant recipients who have been withdrawn from immunosuppressive drugs acquire these biomarkers. The patient populations and sample collections from these and other ITN studies provide a rich resource not only for evaluating tolerance signatures as predictive biomarkers, but also for exploring diverse cell populations and phenotypes associated with therapeutic effects.

Box 1 | **The Immune Tolerance Network: lessons learned and future challenges**

- Clinical research is difficult: it's expensive; it's hard to reward; it takes infrastructure; it takes time. The efforts of the Immune Tolerance Network (ITN) to maintain a cadre of experienced clinical investigators and qualified sites for specific diseases, in addition to as much centralization of the ITN as possible, will reduce costs, start-up efforts and recruitment times for future clinical trials. Owing to the breadth of its mission, these efforts are a particular challenge for the ITN relative to other clinical research networks that typically focus on a single disease or medical discipline.
- One of the biggest challenges in translational medicine is the need for teamwork that reaches across traditional boundaries separating the clinic from the laboratory, and separating academia from industry. Success in this venture depends on academic institutions being willing to reward participants in clinical trials for team efforts in terms of publications, appointments and promotions, and training.
- The immunological disciplines of transplantation, allergy and autoimmunity have a lot to learn from each other, and making strategic choices to pursue some agents or biomarker assays in one discipline instead of another is likely to accelerate the pace of therapeutic development. For example, the pioneering advances in the use of rituximab in patients with autoimmunity have led to use of the drug in organ transplant recipients, where the role of B cells has been underappreciated. This lesson is being exploited in other consortiums tackling the development of new vaccines in cancer and the treatment of other immune-mediated inflammatory diseases, where multidisciplinary efforts can lead to new insights in clinical research and biomarker discovery.
- Radical ideas in immunotherapeutics need a thoughtful incubator, where the broad immunological community can assess, improve and innovate. The ability of the ITN to carry out early proof-of-concept trials, particularly in indications that are not routinely looked at by industry, provides opportunities to study disease mechanisms in novel ways. Proof-of-mechanism and proof-of-concept studies carried out by academic institutions will be the gateway to innovative therapies and biomarker identification.
- It is possible to achieve immunological tolerance, but a better understanding of disease and treatment mechanisms will be crucial to reliably predict and induce tolerance in the clinic. Moving forward, complete withdrawal from immunosuppressive drugs, particularly in the organ transplant setting, is likely to depend on a set of predictive markers that increase the chance of success.

Challenges and opportunities for the ITN

Fundamental principles of immunological tolerance that cross disciplines from allergy to transplantation to autoimmunity ultimately present the best therapeutic opportunities, and the ITN is poised to explore these possible breakthroughs in caring for patients with immune-mediated diseases. However, the advances made so far have not been without setbacks and unexpected challenges (BOX 1). The ITN has learned that success in inducing robust clinical tolerance is an incremental journey. Humans are not mice. Indeed, we have only a limited understanding of what drives an abnormal immune response in humans. The biology of human disease is complex and systems biology is just beginning to provide insights into the fine regulation of pathways and mediators. Experimental manipulations in humans take a long time (several years) and are limited for safety and ethical reasons that cannot be underestimated. A few ITN studies have been stopped early for failure to recruit, others have been put on clinical hold and in some cases the ITN has faced lengthy delays identifying industry support for a particular trial or negotiating clinical trial agreements.

In the past few years, the ITN and NIAID have learned crucial lessons about gauging industry interest in a project and communicating with decision-makers in these companies. The incorporation of an extensive feasibility assessment, after a trial proposal has been approved by the ITN, increases the chance of success in discussions with potential industry partners and quickly reveals scientifically and/or mechanistically interesting projects that have a clear corporate commitment. This integrated approach for priority setting by the ITN enhances the selection and conduct of ITN-funded trials and ensures the continued support of industry in the development pathway. Another outcome of these assessments has been concerted efforts to forge long-standing partnerships between industry and academia (such as those with Genentech and Bristol-Myers Squibb) that place the ITN in an ideal position to carry out innovative studies that combine drugs from multiple commercial sources. Advances in innovative clinical trial design and infrastructure, as well as improving institutional support, should fuel more rapid progress in the next phase of the ITN's life.

However, it is essential that as a community we continue to challenge our assumptions. Will the ITN create enough clinical value from the research it funds to justify the investment? There is no doubt that clinical research is expensive and takes a long time. To gain the most from its funding, the ITN must focus on testing therapeutic interventions that have the potential to impact clinical care in a major way. This 'game-changing' mentality has increasingly guided the decision-making process of the ITN, but it is clearly a high-risk, high-reward strategy. Some negative trials are inevitable with this approach. Will patients, physicians and industry support full drug withdrawal in the organ transplant setting at the risk of graft rejection in the absence of definitive biomarkers of tolerance? To mitigate such risks, the ITN works closely with NIAID medical and regulatory officers, its Statistical and Coordinating Center and a community of scholars to ensure that studies are carefully designed, are practically feasible, can enroll the study population of interest and meet the rigorous standards of ethical research.

What are the metrics of success that should be applied to ITN trials? One typical metric of success is the development of therapies that alter clinical care and eliminate many of the problems associated with current immunosuppressive drug treatment. Another important metric of success is the demonstration of crucial scientific insights into human biology. Although a clinical trial might fail to meet its primary clinical endpoint, it should nevertheless provide a rich source of data and samples that can inform future research efforts.

Lastly, does the pace of progress of the ITN meet the needs of the community and compete effectively with industry-sponsored trials? We believe that the ITN, given its focus on mechanism-based understanding of both treatment successes and treatment failures, is distinct from many traditional industry-sponsored efforts and should be judged against a different timeline. Moreover, the ability of the ITN to involve multiple research and clinical centres enhances the ability of discovery scientists to see their efforts translated into potential clinical interventions.

Achieving tolerance is a huge challenge — success will probably be incremental and expectations need to be appropriately scaled. The ability to remove immunosuppressive drug therapy from almost 70% of pediatric liver transplant recipients[30] and to support a tolerance protocol in

kidney transplant recipients[27] are the most clear examples of success, but the ITN has also stopped or substantially slowed the progress of established autoimmunity in patients with type 1 diabetes[6] and it has almost certainly achieved some degree of clinical, two-season tolerance in patients with ragweed allergy[24]. Ultimately, the efforts of the ITN to impact the clinical immunology framework will be judged on clinical outcomes, and the ITN hopes that academic and industry colleagues with similar goals will participate in this quest to improve the lives of patients with immune-mediated diseases. By maintaining an open and inclusive structure, while implementing a strategic approach that fills gaps in current approaches to immunotherapy based on state-of-the-art mechanistic rationale, we believe that the ITN can realize its goals and demonstrate its value to the community.

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Competing interests statement
J.A.B. declares competing financial interests: see web version for details.

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