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SHORT STORIES OF SUCCESS



Immune
Tolerance
Network



01.

COMMUNITY LEADERSHIP THROUGH COMMUNITY INPUT

FORMED IN RESPONSE TO THE NIH'S 1998 "EXPERT PANEL ON IMMUNE TOLERANCE," the ITN was born from the collective vision of the community of tolerance researchers - a key mandate was that it must reflect the needs and priorities of the tolerance research community as a whole. Today, the ITN maintains an important leadership role within this scientific community. In addition to being led by a steering committee comprised of a diverse group of world-leaders in tolerance, an extensive network of academic advisors help steer ITN scientific direction through its annual strategic reviews. The centerpiece of the ITN's community outreach, however, is our always-open call for proposals that enables all researchers the opportunity to participate in the ITN. Employing a unique, interactive review process where applicants meet their reviewers face-to-face to discuss their proposal before rendering a decision, the ITN has received and reviewed over 225 concept proposals to date, with an average response time of just 6 weeks from receipt.

02.

BRIDGING THE GAP BETWEEN ACADEMIA AND INDUSTRY

THE ITN WAS ALWAYS MEANT TO OCCUPY A UNIQUE NICHE in the research world, acting as a bridge between academia and industry, engaging the biotechnology and pharmaceutical industries in collaborations to propel tolerance forward. By offering an open and flexible partnership model that addresses many of the common barriers to true academic-industry cooperation, the ITN has formed clinical collaborations with a wide range of companies, from industry leaders like Genentech, to up-and-coming biotechs like Dynavax Technologies; pharmaceutical companies such as Roche, Bristol Myers-Squibb and Fujisawa have donated drugs for our trials, while biomedical firms like Nikon and Lifescan have supplied medical devices needed for our research efforts. What's more, our core facilities and assays capitalize on state-of-the-art technologies and methods through collaborations with such accomplished companies as Becton Dickenson, Beckman-Coulter and Affymetrix.

03.

NO IMMUNOSUPPRESSION IS GOOD IMMUNOSUPPRESSION

WHILE IMMUNOSUPPRESSIVE DRUGS HAVE BECOME increasingly effective in preventing organ transplant rejection, they are far from an ideal solution to the problem. Because they require lifelong treatment, they are not only expensive, but leave patients at increased risk of serious infections and certain types of cancer – risks that are aggravated in childhood transplant recipients. Importantly, getting patients off immunosuppressive drugs safely has been one of the ITN's key objectives and complete immunosuppressive withdrawal is a goal of all ITN transplant trials. In all, ITN transplant trials now have a total of 10 patients who are completely free from immunosuppression, with an additional 18 tapering their doses under the watchful eye of ITN investigators. As our trials progress, these numbers will continue to grow, allowing more transplant recipients the chance of living free from the burden of immunosuppression, while providing exciting opportunities to observe tolerance in humans as it happens.

04.

TWO IMMUNE SYSTEMS ARE BETTER THAN ONE

WHEN THE ITN WAS FOUNDED IN 1999, results in small and large animal models of transplantation indicated combined renal and bone marrow transplants from the same donor could induce renal allograft tolerance in the transplant recipient. The mixed chimerism model was believed to promote central tolerance, primarily acting through the thymus. However, in humans, rates of rejection had shown no improvement using the technique. Since that time, two separate ITN pilot studies have established mixed chimerism as a viable and promising means of promoting immune tolerance to transplanted kidneys. To date, 5 patients in these trials have maintained stable kidney allograft function despite discontinuing all immunosuppression; some subjects have now been immunosuppression-free for as long as 4 years. Importantly, these studies have also challenged conventional wisdom, providing evidence that peripheral regulation, in addition to central mechanisms, plays an important role in tolerance induction by this treatment.

**“GETTING PATIENTS
OFF IMMUNOSUP-
PRESSIVE DRUGS
SAFELY IS A KEY
OBJECTIVE OF
ITN TRANSPLANT
TRIALS.”**

05.

A SHORT-TERM ALLERGY TREATMENT WITH A LONG-TERM EFFECT

ALTHOUGH TRADITIONAL IMMUNOTHERAPY CAN BE VERY EFFECTIVE as a long-term treatment for seasonal allergies, it is terribly inconvenient. A typical course of immunotherapy requires subcutaneous injections of allergen extracts every other week for several years. For many allergy sufferers, such a commitment is often difficult or impossible to keep, leaving many without a viable treatment option. A recent ITN study, however, provided proof of concept that a novel DNA-based drug could affect similar levels of symptom reduction as immunotherapy, but in a dramatically reduced period of time. Just a 6 week course of Dynavax's "AIC", a DNA immunostimulatory sequence linked to the major ragweed pollen, was shown to significantly improve ragweed allergy symptoms, even 2 years and 2 allergy seasons after this short treatment. DNA immunostimulatory sequences are now gaining attention in other allergic conditions, including asthma.

06.

IMPROVING THE SAFETY OF ALLERGY IMMUNOTHERAPY

ALLERGY IMMUNOTHERAPY IS NOT ONLY TIME CONSUMING, but patients who do manage to commit to its multi-year schedule are at risk of developing a severe and sometimes fatal allergic reaction known as anaphylaxis. Because anaphylaxis, like other allergic responses, depends upon the IgE immunoglobulin, Dr. Tom Casale of Creighton University hypothesized that interrupting this pathway during immunotherapy could reduce the anaphylaxis risk and increase the effectiveness of immunotherapy. Testing this hypothesis in an ITN clinical trial performed in collaboration with leading biotechnology firm, Genentech, Casale was proved correct. Ragweed immunotherapy patients pretreated with Genentech's anti-IgE antibody (omalizumab) showed significantly fewer side effects from immunotherapy, including fewer instances of anaphylaxis. Using an accelerated or "rush" immunotherapy protocol, anti-IgE pretreatment also appears to allow more rapid and higher doses of allergen, which, in the future, may reduce treatment time and increase overall efficacy.



**“ IMMUNE TOLERANCE
IS THE KEY TO A SAFE,
DRUG-FREE EXISTENCE
FOR TYPE 1 DIABETES
SUFFERERS.”**

07.

A LONGER HONEYMOON FOR TYPE 1 DIABETES SUFFERERS

GENERALLY, AT THE TIME OF DIAGNOSIS, BETWEEN **60-85%** of a type 1 diabetes patient's pancreatic beta cells have already been destroyed by the ongoing autoimmune attack. Protecting the remaining 15-40% of these cells to preserve what insulin production remains is paramount, as even small amounts of natural insulin production can lead to greatly improved control of blood glucose. An ITN pilot study led by Harvard's Tihamer Orban tested the efficacy and safety of vaccination with an insulin-B chain peptide for this purpose. The vaccine was well-tolerated, and evidence of both a humoral and antigen-specific cellular response to the vaccine have provided an impetus for a second, phase II study. The ITN is also leading the way with clinical studies of the promising anti-CD3 monoclonal antibody, hOKT3 γ 1 (Ala-Ala), which has been shown to prolong the insulin "honeymoon" phase for up to two years in recently diagnosed type 1 diabetes.

08.

PREPARING ISLET TRANSPLANTATION FOR THE FUTURE

SINCE 1999, WHEN RESEARCHERS IN EDMONTON, CANADA SHOCKED THE WORLD with news that islet transplantation had rendered 7 of 7 patients insulin-free, islet transplantation has become one of our greatest hopes for a cure to type 1 diabetes. One year later, in collaboration with the Edmonton team, the ITN began the world's first multicenter clinical trial of islet transplantation, at 9 clinical centers in 5 countries. The study was designed to investigate the feasibility and practical difficulties of standardizing an islet transplantation protocol across multiple centers. The results, published in the New England Journal of Medicine in 2006, showed that even those individuals with partial islet function who lost, or did not become "insulin-free" displayed improved post-transplant glycemic control, potentially redefining the utility of islet transplantation in the future. The study was a critical element in advancing islet transplantation research forward into a new era.

09.

SPECIMEN MANAGEMENT MADE SIMPLE

WITH SO MANY CLINICAL TRIALS EACH COLLECTING NUMEROUS CLINICAL SPECIMENS, and a large number of different assays performed on each, the task of collecting specimens and getting them to a the specimen repository to be aliquotted and distributed to core facilities for assay is a monumental task. To accomplish this complex task, the ITN has created “ImmunoTrak,” a specimen management system that not only handles specimen logistics and routing, but also maintains inventories of specimen volumes and permits detailed annotation to help validate and explain data exceptions during analysis. Using barcode and scanner technology, ImmunoTrak enforces predefined, study-specific workflows and specimen collection processes, while keeping specimens blinded at all steps during processing.

10.

BANKING ON THE FUTURE

WHILE EACH ITN CLINICAL TRIAL INTEGRATES WIDE-RANGING MECHANISTIC STUDIES designed to investigate the mechanisms of tolerance and identify new biomarkers, it is not always clear which assays will produce the most important information. In fact, many assays we might want to apply may not even be invented yet. For this reason, the ITN banks a portion of each specimen for future use - over 125,000 are currently stored in the ITN repository. The ITN has also future-proofed its data storage system by invoking flexible data storage and transfer routines that can be easily adapted to specialized data formats of new assays. The ITN “Data Warehouse,” a massive relational database, holds every single piece of mechanistic data collected by the ITN – over 18 million individual data points so far. Heavily annotated, it is the largest repository of clinical tolerance data in the world. Soon, the ITN will open both the specimen repository and data warehouse to the community for data mining proposals.



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LONG RANGE BINOCULARS
1. DROP COIN IN SLOT.
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3. TO CLEAR VISION - TURN RED
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