Revealing the Mechanisms of Tolerance
AN INTERVIEW WITH THE IMMUNE TOLERANCE NETWORK’S JEFFREY BLEUSTONE, PhD

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In the late 1970s, when “the whole field of cancer immunology was exploding,” Jeffrey Bluestone, PhD, says he was an immunology graduate student stuck in a laboratory, “working on just mice and yet watching all these patients every day come in and suffer.” While Dr. Bluestone was not interested in becoming a clinician, he wanted a direct connection between his research and the difference that research might one day make in patient treatment. “I respect tremendously the people who have defined the alphabet of biology or defined the words of biology,” he says. “I wanted to create some of the prose out of those letters and words that really can make a difference in people’s lives.”

In the three decades since he received his doctorate from the Sloan-Kettering division of the Weill Cornell Graduate School of Medical Sciences in New York, NY, Dr. Bluestone has thrown himself into the kind of work that does just that, never more so than in his founding and directing of the Immune Tolerance Network (ITN) (www.immunetolerance.org), an organization that fosters collaboration between researchers across the globe to identify new therapies for diseases of the immune system. A nonprofit, the ITN is sponsored by a branch of the National Institutes of Health (NIH)—the National Institute of Allergy and Infectious Diseases (NIAID)—and the Juvenile Diabetes Research Foundation (JDRF), and receives additional funding from the NIH’s National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The consortium focuses on clinical trials of treatments intended to address autoimmune conditions, allergies, and asthma and to prevent the rejection of transplanted organs. An integral part of every ITN clinical trial is basic laboratory research that investigates the treatment’s cellular and genetic effects.

Shifting the Paradigm
The ITN’s genesis began in the mid-1990s, when there was an increasingly acknowledged need for an entity that would test the therapies that might help patients with immune disorders but would also focus on understanding the underlying mechanisms that made those therapies effective or not. The NIH and others feared that exciting animal studies in immunologic pathways would not be translated to the human body without a concerted effort. As Dr. Bluestone observes, a “paradigm shift [was] necessary to get pharmaceutical and biotech companies to invest in ‘drugs that could permanently alter the immune system and allow people to stop taking immunosuppressive drugs,” therapies that patients might otherwise continue for the rest of their lives.

The NIH stepped in to fill the void, and Dr. Bluestone assembled a team of 75 academics that won the contract to be the review arm of the nascent ITN. In the organization’s first year, it became clear that the clinical research organization (CRO) intended to implement the proposals Dr. Bluestone’s team reviewed could not perform the complex trials required, and Dr. Bluestone and his colleagues at NIAID transitioned to running the full operation. As he explains, the very point was to facilitate “very high-level, cutting-edge mechanistic studies so that, whether or not the drug treatment succeeded or failed in terms of clinical outcome, we could learn something about mechanisms of drug action, mechanisms of disease, and fundamentals of human immunology . . .”

More than a decade after its 1999 launch, the ITN comprises eight divisions and employs almost 90 people. With the help of two deputy directors, Drs. Larry Turka and Bill St. Clair, and the NIAID program officers, Dr. Bluestone oversees a full range of activities, from administrative and information technology functions to data analysis, bioinformatics, and clinical trial development. The integrated nature of the organization means that Dr. Bluestone is heavily involved with the data, the proposal reviews, and the efficient and ethical operation of the clinical trials themselves.

Understanding Tolerance
Those clinical trials can be grouped into three broad categories, the most immediately important being the kind of clinical trial that has the potential to change clinical care in the near future. To illustrate, Dr. Bluestone cites a trial directly comparing Rituximab, an antibody working against the protein CD20, with Cyclophosphamide, a drug commonly used in chemotherapy, in treating forms of vasculitis such as ANCA-positive vasculitis and Wegener’s granulomatosis. Supported in part by Genentech, which is involved in marketing Rituximab and wanted a clinical trial large enough to be presented to the FDA, the trial revealed that Rituximab was as effective or better than Cyclophosphamide in inducing remission in this patient population and did not have some of the serious side effects associated with the latter, a finding that Dr. Bluestone believes will “fundamentally change how patients with this disease are treated.”

Clinical trials in a second ITN category ask how tolerance could be induced in settings where none currently exists, a question pursued most aggressively through the ITN’s transplant portfolio. Those studies are, Dr. Bluestone says, “proof-of-principle small trials to try to convince the community that tolerance is achievable, durable, and healthy for the patient.” In one such effort, ITN colleagues in Boston have conducted trials with patients who received bone marrow transplants as part of the treatment for a kidney transplant. The small but impressive result, Dr. Bluestone reports, is that 12 or 13 patients have quit all immunosuppressive drugs “with very high durability and success.”

The ITN’s third kind of trial focuses on the basic processes of tolerance. One study investigated 25 kidney transplant patients

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has embarked upon research into diabetes "self-therapies that were not taking immunosuppressive drugs and yet did not reject their donated kidney. Having found a genetic signature that identifies uniquely tolerant patients, the researchers now seek patients in other ITN trials who may also have that signature. Another group working to get pediatric liver recipients off their drugs has illustrated the frequent ability of young patients to accept transplanted organs without the need for 70 years of immunosuppressive drug therapy.

Yet another study builds upon the Nobel Prize-winning research of Sir Peter Medawar, who in the 1950s demonstrated the ease with which animals could be neonatally tolerized to potential foreign antigens. In spite of Medawar's findings, Dr. Bluestone notes that over the past five decades the conventional wisdom has come to be that "exposure of babies to foreign proteins is in fact why we have a higher incidence of allergy." The ITN is now testing the question in a clinical trial in the United Kingdom, where researchers will see if hundreds of babies can be tolerized to peanuts. "Will that change the world?" Dr. Bluestone asks. "Probably not... But it is to the core essence of the whole ITN: can we understand processes that are critical for the tolerance paradigm and start to make insights in humans so we can understand the biology of tolerance in that setting?"

Making the Research Personal

The curiosity that motivates these questions has guided Dr. Bluestone through an interesting and varied career. At the end of his graduate work in cancer immunology, he decided to leave basic cancer research for work at the NIH in organ transplantation, research that ultimately led to the development of an anti-CD3 monoclonal antibody that is now in Phase III trials as a therapy for Type 1 diabetes and, potentially, islet transplantation, psoriatic arthritis, and other autoimmune diseases. In his later years at the NIH and during his time at the Ben May Institute for Cancer Research at the University of Chicago, Dr. Bluestone's personal research interests began turning more toward a disease that was affecting his family: in 2001, he donated a kidney to his father, who was suffering from the ravages of diabetes. Dr. Bluestone explains, "I just felt at that point in my life that I could take all of the stuff that I had done and why not move it towards the field that I was most personally impacted by."

That focus has resulted, in addition to other appointments and honors, in his current position as the Director of the Diabetes Center at the University of California at San Francisco (UCSF) (www.diabetes.ucsf.edu). In contrast to his many hands-on activities at the ITN, at UCSF's Diabetes Center, Dr. Bluestone views himself primarily as a "cheerleader", someone who, with the help of a "number of absolutely superb administrators," provides the center's faculty members "what they need for success—a good home, good space, good support—and then [lets] them take their great talents and put them to good use."

As UCSF's A. W. and Mary Margaret Clausen Distinguished Professor of Metabolism and Endocrinology, Dr. Bluestone also carves out time for his laboratory work. He explains that his team has embarked upon research into diabetes "self-therapies that will promote tolerance by putting certain types of cells back into patients with Type 1 diabetes." A recently published paper on the subject of regulatory T cells and a clinical trial scheduled for spring 2010 pursue a potential therapy in this area while also delving into the underlying causes of autoimmune disease.

Bridging the Gap

In his work as researcher and administrator, but especially in his ITN role, Dr. Bluestone feels strongly that the answer to the challenge of translational medicine lies in teamwork and reaching across traditional boundaries separating the clinic from the lab and academia from industry. He says the ITN has served as a model "for partnering with industry to get access to drugs and to work across diseases," adding, "I think the ITN broke some barriers in the immunology community because it's perceived as being academics trying to bridge that gap."

Getting the two camps to interface is important because each brings with it its own strengths. Industry, Dr. Bluestone says, "is far better at the team-oriented research effort," but the scope of industry has often been too limited, focusing on the financial costs and benefits of drug development sometimes to the exclusion of "the basic understanding of what the drug did or why it did it." On the other hand, academic traditions may unintentionally discourage the collaboration essential to translating research discoveries to patient care. Dr. Bluestone observes, "Our whole academic system is skewed, not towards team approaches, not towards the kind of thing that makes translational research really possible, but much more towards individualized research efforts."

There is also in academia some skepticism that investments in large-scale efforts like the ITN are appropriate. Periodically, Dr. Bluestone receives implicit criticism of the organization from those who believe the significant financial contribution that launched the ITN could have been used more productively to fund many smaller-scale, individual projects. Dr. Bluestone remains open to those questions as a means to evaluate the ITN's efforts: "Is this a good use of our money? Or isn't this industry's job... to do these proof-of-principle studies? What have you really learned at the end of the day that you wouldn't have learned had you just plowed it into the mouse work?" As he admits, clinical research is difficult, expensive, and "hard to reward. As much as we're trying, I think there needs to be a better system to foster it, at least in academia."

As for the middle ground between bench and bedside, while firmly based in the lab, Dr. Bluestone has forged collaborations that have brought those two realms closer together. "I've been fortunate to have spent so much of my career being able to interface and partner with really great clinicians." The willingness to work together is crucial, he says. "I'm a firm believer in the idea that it's very difficult today for a physician scientist to do it all, to be the great educator, the great clinician, and the great researcher. If we can build bridges between the PhD research community and the clinical research community... the partnership can be very effective." With and beyond the ITN, Dr. Bluestone and his colleagues collaborate and influence each other's work in ways that continue to promote Dr. Bluestone's and the ITN's missions to improve patient care.