

NEWS

Putting Tolerance to the Test

A disparate group of researchers banded together in 1999 to explore novel therapies in immunology. Five years later, the Immune Tolerance Network has "turned the corner" on management problems, leaders say, and clinical results are starting to appear

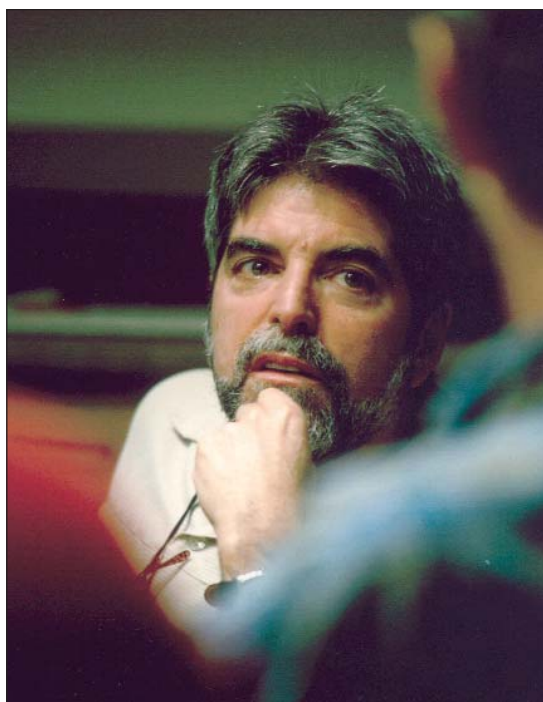
It was touch and go when immunologist Jeffrey Bluestone finally handed off his precious cargo 5 years ago: an 800-page tome he hoped would transform medicine. An overnight courier drove up to his Chicago doorstep at 2 a.m. and collected the massive application, to airlift it to the National Institutes of Health (NIH) in Bethesda, Maryland, before the day's end.

Racing to meet the deadline, Bluestone was certain he knew what he was getting into: "I thought I was going to be the head of a think tank, a brain trust, come up with some cool ideas and let other people test them," he says of his proposal to run a \$144 million, 7-year clinical research network. The application reached Bethesda on time, and Bluestone beat out his competitors. But little else in the Immune Tolerance Network (ITN), which Bluestone now directs from the University of California, San Francisco (UCSF), has worked out quite as planned.

ITN was a tall order from the start. Its several dozen members—leaders in transplant medicine, autoimmune diseases, and allergy—would oversee a collection of ambitious and potentially risky clinical trials. The goal was to find therapies that could retrain the immune system—instead of bluntly suppressing it with drugs—thereby teaching the body to tolerate tissue that it might otherwise attack. Because immunosuppressant drugs have potent side effects and often must be taken for life, researchers hoped to discover experimental therapies that could be given briefly and then withdrawn. Their objectives included curtailing the use of bone-damaging steroids in kidney transplant patients, for example, and treating or even curing some devastating autoimmune diseases such as multiple sclerosis.

But ITN has also been a radical experiment in management. Few of the academic scientists running it had ever designed multisite clinical trials before. And the branch of immunology they were charging into was relatively new. To succeed, ITN

needed basic and clinical researchers from a host of specialties—surgery, endocrinology, immunology, rheumatology, pediatrics—and it had to coax them to cooperate. Many didn't speak the same medical language, let alone agree on what level of risk was acceptable for these ethically complex, unprecedented clinical trials. "We really had to



Juggling act. ITN director Jeffrey Bluestone acknowledges that the complex trial network got off to a slow start.

invent ourselves," says Larry Turka, chief of the renal division at the University of Pennsylvania in Philadelphia and a member of ITN's executive committee.

The ride has been rocky, and ITN has amassed critics along the way. They charge that an unwieldy bureaucracy and endless debates on trial protocols have slowed promising studies. Some even suggest that the network is failing to fulfill its mission of testing immune tolerance in human beings. To date, the network has approved 23 clinical trials. A dozen are ongoing, including two that are near completion. And 11 are under development, on hold for safety reasons, or cancelled.

Despite the setbacks and frustrations,

though, many immune tolerance researchers say ITN deserves great credit for launching clinical trials that wouldn't have begun otherwise. "What the ITN is doing is something of a different spirit, which is very important for medical progress," says Jean-François Bach, an immunologist at the Necker Hospital for Sick Children in Paris, who's not directly involved with the organization. Bluestone admits there have been problems but says he's committed to fixing them—and that he and other leaders have already taken steps to accelerate trial development.

Promise

ITN was born after the heady summer of 1999, when results from two studies in rhesus monkeys electrified researchers. Both used an experimental drug that appeared to reset the animals' immune systems and cure them of disease.

The studies tested a drug called anti-CD154 that disrupts signals flying between certain cells in the immune system. In one study, monkeys received a new kidney; in the other, animals without a pancreas got an infusion of insulin-producing islet cells from a donor pancreas. Type I diabetes arises from attacks on the pancreas, which destroy its islet cells and stop insulin production; the islet cell transplants were a test of what many consider the best shot at a cure. Without standard immunosuppressants, the body would normally reject both foreign islet cells and kidneys. But with anti-CD154 treatment, all 15 monkeys stayed healthy. And all discontinued anti-CD154 without ill effects.

The results seemed to confirm promising work in mice, so NIH decided to press forward with tests in human patients. It teamed up with the Juvenile Diabetes Research Foundation (JDRF), which has made islet cell research one of its top priorities. The foundation offered \$6 million to augment NIH's plan. Together, NIH and JDRF assembled a panel of several dozen experts and asked them to parcel out funds over 7 years to make immune tolerance a reality.

By early 2000, ITN was moving full steam ahead. But soon after, exuberance over the monkey trials began to fade. Over the course of several years, all the monkeys eventually rejected their new kidneys and islet cells. "It looked like it was too good to be true, and it turned out to be," says Allan Kirk, chief of the transplantation branch at the National Institute of Diabetes and Di-

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gestive and Kidney Diseases in Bethesda, who participated in both monkey studies.

Uncertainty

What plagued the monkey trials and still confounds human studies is the befuddling nature of immune tolerance. Immunologists know how to define it clinically: It is the absence of disease along with the absence of therapy. But they don't have a coherent picture of how it works at the cellular or molecular level.

with a similar study in liver transplant patients that ITN is just beginning, will help scientists match clinical symptoms with molecular patterns in the immune system.

As it attempts to define tolerance, ITN continues to debate which trials fall under its mandate. For example, some ITN committee members question whether it makes sense to include studies of islet cell transplantation, because these currently require the use of immunosuppressants and aren't striving for pure tolerance. The network is also divided

results in June at the American Diabetes Association annual meeting in Orlando, Florida, reporting that 19 of the 36 participants no longer need insulin shots up to 1 year after their transplant. All receive a three-drug immunosuppressant regimen that doesn't include steroids; two must be taken indefinitely.

Early on, Shapiro's trial stirred up "a lot of argument" within ITN, recalls Kevan Herold, an endocrinologist at Columbia University in New York City who's running a separate ITN diabetes trial. Some saw the islet-cell study as too removed from the network's focus. But JDRF, an ITN backer, favored it; as Chief Scientific Officer Robert Goldstein says, "We have to do a few things" that may be considered partial steps before attaining the goal of pure tolerance. Furthermore, Shapiro's interest in diabetes dovetails with ITN's agenda, Shapiro explains. "We'd like to be in a position where we can offer a child who walks in the door, who's diagnosed with diabetes, the option of a transplant," he says, which requires tolerance. It's for this reason, explain ITN leaders, that traditional islet-cell transplant trials were supported by the network to begin with. Shapiro

says future islet-cell trials—his own and others—will attempt to do transplants without standard immunosuppressants.

Ongoing Network Trials

Disease	Lead investigator	Approved	Launched
Type I diabetes	James Shapiro, University of Alberta	2000	2001
Kidney transplant	Megan Sykes, Harvard University	2000	2001
Kidney transplant	David Sachs, Massachusetts General Hospital	2000	2002
Type I diabetes	Kevan Herold, Columbia University	2000	2002
Psoriatic arthritis	Marcus Clark, University of Chicago	2000	2004
Allergies	Peter Creticos, Johns Hopkins University	2001	2002
Type I diabetes	Tihamer Orban, Joslin Diabetes Center	2001	2002
Multiple sclerosis	Samia Khoury, Brigham and Women's Hospital	2001	2003
Kidney transplant	Stuart Knechtle, University of Wisconsin	2001	2004
Type I diabetes	Bernhard Hering, University of Minnesota	2001	2004
Allergies	Thomas Casale, Creighton University	2002	2003
Kidney transplant	Kenneth Newell, Emory University	2002	2004

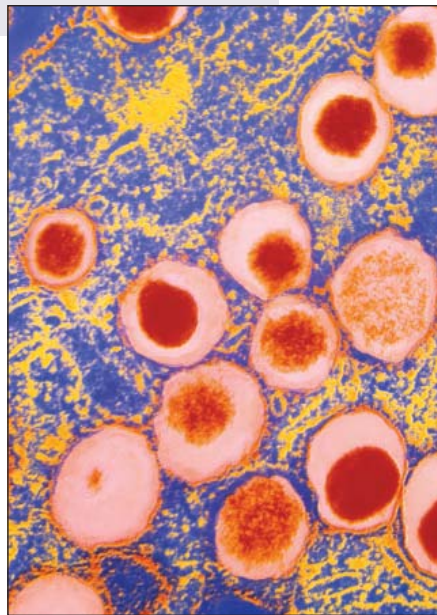
One way to pin down tolerance, ITN resolved early on, is to crack a puzzling phenomenon long familiar to transplant surgeons, in which an expected immune attack fails to occur. For example, patients who receive new organs sometimes get fed up with the high cost and side effects of immunosuppressants—infections, weight gain, and tremors—and stop taking the drugs. Surprisingly, a handful do just fine without them.

Kenneth Newell, a kidney and pancreas surgeon at Emory University in Atlanta, Georgia, applied for ITN funding to track down and gather data from these individuals. He planned to use assays developed by ITN scientists and others that measure levels of different immune cells, in an attempt to determine the biological basis of tolerance.

After 3 years of preparation, Newell began enrolling the first of 240 volunteers in May. He still wonders, though, whether anyone knows enough about the combination of cells that sustain tolerance to predict which ones need monitoring. "If you said, 'OK, Ken, what assay even correlates with the existence of tolerance?'" he says, his answer would be straightforward: "None." Yet Newell believes that it is time to start assembling a database. He and other members of ITN hope that the kidney registry, along

on trials that minimize immunosuppressant doses but don't discard them. Withholding these drugs can be risky, raising tough ethical questions and making it difficult to find volunteers.

To lessen the hazards and skirt the unknowns, ITN is running a number of studies that many—including ITN supporters—agree are not strictly focused on tolerance. Indeed, one of ITN's most prominent—and most controversial—trials is a \$6 million, multisite islet-cell transplant study led by James Shapiro, director of the clinical islet-cell center at the University of Alberta in Edmonton, Canada. It was the first ITN trial to enroll patients and is nearly complete. Shapiro's team presented



Part of ITN's mission? Whether to fund transplants of islet cells such as these engendered heated debate.

munosuppressant, rather than the usual multi-ingredient cocktail. There was a risk: Patients might lose the kidney they'd waited and wished for, sending them back on dialysis and the transplant waiting list. But if the experiment worked, the volun-

Exasperation

Twenty-five hundred kilometers from the Alberta plains is another physician who pinned his hopes on ITN, transplant surgeon Stuart Knechtle of the University of Wisconsin, Madison. Knechtle planned an audacious experiment: He wanted to stitch new kidneys into patients suffering from renal failure, offering them therapy that included an experimental drug and just a single im-

teers would end up with a rejiggered immune system that embraced their new organ—and no ravaging drug side effects.

What Knechtle hadn't banked on was ITN's glacial review process. After much debate over whether to support a trial that included some standard immunosuppression, ITN gave Knechtle a green light for a study in early 2001; it was expected to cost about \$2 million. Soon after, with the help of ITN members, he began writing the protocol. And then he waited. The study wended its way from the ITN executive committee to the ethics committee to NIH and back. Frustrated, Knechtle eventually reapplied for funding directly from NIH. He quickly got his money, enrolled his 29 transplant subjects, ran the study, and published it a year ago. Most patients did well, although eight suffered some rejection, and one lost the kidney.

Three years ago, ITN agreed to fund a second study of kidney transplantation by Knechtle, again at \$2 million. He's still waiting for those funds, too, but began recruiting patients recently "on good faith."

Knechtle's experience isn't unique. Jack Antel, a neurologist at McGill University in Montreal, is running an experimental drug study in multiple sclerosis (MS) patients. Around the time ITN was born, Antel learned that Neurocrine Biosciences in San Diego, California, was developing an experimental MS drug called altered peptide ligand (APL). It targets only immune cells thought to be involved in MS, and a preliminary study hinted that APL might reduce brain lesions, whereas another suggested it might aggravate them. One of Antel's aims was to resolve this apparent paradox.

Antel applied for ITN funding to test APL in a broader group of patients and got a thumbs-up for \$1 million. "The fun was getting the grant," he says. That was over 2 years ago; he's still waiting for the money. The trial is up and running with funds from Neurocrine, even though none of the 24 hospitals involved is getting reimbursed by ITN. "ITN's filling a void conceptually," he says. But "logistically, it's very hard to work with."

Multitasking

Bluestone, ITN's director, leads the elaborate juggling act of setting up and coordinating its nearly two dozen clinical trials. He devotes up to 30 hours a week to his ITN job; the rest of the time he runs an immunology and diabetes research lab at UCSF. Bluestone readily agrees that the network has had its share of stumbles. Getting money out the door has been "very, very tough." He says that's partly because NIH provides the funds through a

closely watched contract. It required that every expenditure over \$50 be cataloged—an approach the government uses in unexplored medical territory to better oversee research, says Daniel Rotrosen, director of allergy, immunology, and transplantation at NIH's National Institute of Allergy and Infectious Diseases and a top NIH official on ITN.

Bluestone says his move from the University of Chicago to UCSF in 2000 put the



In the queue. Transplant surgeon Stuart Knechtle discovered that getting an ITN trial launched can take years.

brakes on ITN reviews, as the massive contract was transferred. He adds that UCSF administrators, fearful of being audited, wanted to track ITN spending almost dollar by dollar and "know what every syringe would cost."

But some difficulties have little to do with the network, notes Bluestone. Designing multisite clinical trials takes time, often years, and the protocols must be reviewed not only by the funders but by local institutional review boards, the Food and Drug Administration (FDA), and others. Many of the holdups on ITN trials come from non-ITN committees.

Complaints about ITN's procedures grew so loud, however, that NIH decided to take a closer look. After an internal ITN assessment last fall, Bluestone, NIH officials, and others convened at UCSF in January to try to fix a problem-filled funding model. Bluestone thinks they've succeeded, at least in part: easing up on the stringent budget requirements and shrinking from 6 months to 3 months or fewer the

time it takes ITN to assess a study's budget before passing it to NIH. In the last few months, Bluestone feels that ITN has "turned the corner." NIH's contract with UCSF expires in 2006; Bluestone and other ITN members hope NIH will continue it.

Members of ITN say that the network has also matured—even blossomed—in its relations with drug and biotechnology companies, on whom its success heavily depends. A growing number of companies have agreed to supply experimental treatments and help fund trials. Earlier this year, Bristol-Myers Squibb agreed to support a drug-withdrawal study in kidney transplant patients; the company will help fund tests of its experimental treatment, called LEA29Y, that volunteers will receive for a year or two before they're weaned off it.

"Initially, there was skepticism from the drug companies," says Hugh Auchincloss, a transplant surgeon at Harvard Medical School in Boston and the recently named deputy director of ITN. But he feels the situation has improved, particularly in the past year.

The companies are sometimes skittish, though, about new therapies that come with potentially large risks. Lloyd Kaspar and Randy Noelle of Dartmouth College in Hanover, New Hampshire, ran into problems with their MS trial of an anti-CD154 compound—the drug that spawned such hope when it was tested in monkeys. A different version of the drug caused blood clots in volunteers, and FDA halted the studies. Although the agency has allowed trials to resume with the modified compound Kaspar and Noelle planned to use, the manufacturer got cold feet. Biogen in Cambridge, Massachusetts, which merged with the drug's original developer, has sent the drug back to its labs to assuage its concerns, declining, for now, to supply it for the ITN trial. "It's horribly disappointing," says Noelle, who believes that this version of the drug is safe.

Safety issues are to be expected, ITN researchers say, because many trials include very sick patients, and the therapies are novel and potentially risky. "The ITN tends to push the envelope," says Columbia's Herold.

Five years after launching ITN, Bluestone says he's upbeat but still impatient with the pace of progress. "Sometimes I get very depressed that we haven't fixed this yet," that tolerance in humans remains a goal on the horizon—visible, but remote. "Many of my colleagues in the research community ask me all the time, 'Is this a good use of our money?'" says Bluestone, of ITN funds. But "somebody," he adds, "has got to push this thing forward."

—JENNIFER COUZIN

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