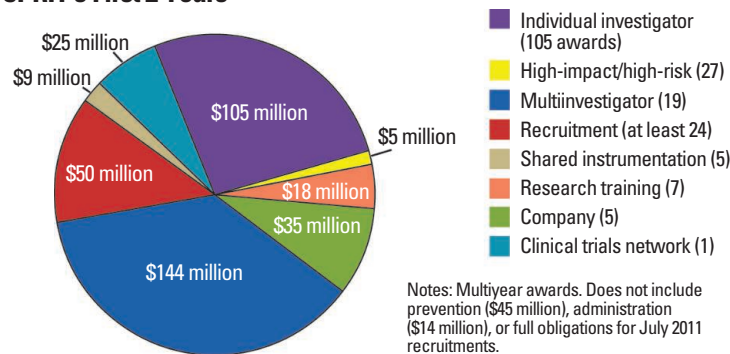


award will provide “a springboard,” says Onuchic. Quips Levine: “People are asking, ‘How can you move from San Diego to Texas?’ The answer is that science comes first at the end of the day; weather comes second.” (The five “superstar” recruitments won’t be official until CPRIT’s board approves them in July, Gilman says.)

Now that CPRIT has proved itself, Gilman expects the legislature to approve the full \$600 million for the next 2 years. One question is whether the state will reach a “saturation” point where all Texas labs with worthy proposals have won a grant, Kaelin says. But Gilman says another 10 to

CPRIT's First 2 Years



Notes: Multiyear awards. Does not include prevention (\$45 million), administration (\$14 million), or full obligations for July 2011 recruitments.

20 recruits each year will help keep up the demand for grants. In addition, the fund will soon begin supporting clinical trials through CTNeT, a state clinical trials network that aims to avoid problems with NCI’s creaky

Spreading the wealth. CPRIT is spending its first \$450 million on a variety of programs.

cooperative groups. “It will be streamlined from the get-go,” with genetic analysis of tumors and high-quality tissue banking, says network steering committee chair and UT Southwestern oncologist David Johnson, whom CPRIT recruited from Vanderbilt University last year.

Gilman says CPRIT has plenty left to do: “It’s tough to figure out exactly where the steady state will be, but I think it will work out pretty well.”

—JOCELYN KAISER

IMMUNOLOGY

Regulatory T Cells Get Their Chance to Shine

Like a heavily recruited high school basketball star, regulatory T cells (T regs) carry a hefty burden of expectations. The cells naturally rein in immune attacks, and infusing T regs into mice curbs the rejection of transplanted organs and halts, or even reverses, the progression of autoimmune diseases. Whether T regs can duplicate such feats in people is now the question.

Researchers are encouraged by results from initial T reg safety trials, in which the cells were given to patients vulnerable to graft-versus-host disease (GVHD), a sometimes lethal complication of transplants of bone marrow and blood-making stem cells that occurs when mature immune cells in the transplant turn on their new host. The first

clinical trial to pit T regs against an autoimmune disease, type 1 diabetes, has also recently begun. And European scientists are starting a study of the cells’ ability to forestall rejection of transplanted kidneys. “It’s a terrific, exciting time in the field,” says immunologist Alexander Rudensky of the Memorial Sloan-Kettering Cancer Center in New York City.

Once known as suppressor T cells before they fell out of favor decades ago, T regs have made a comeback over the past 15 years as researchers have found better ways to identify and study these cells (*Science*, 6 August 2004, p. 772). Still, immunologist Ethan Shevach of the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, and other scientists

caution that most of the practical questions about the cells—which varieties of T regs to use in a treatment, how many to transfer, how long their effects last—remain unanswered. And as three papers (<http://scim.ag/human-treg>, <http://scim.ag/funclional-treg>, and <http://scim.ag/exvivo-treg>) published last week in *Science Translational Medicine (STM)* reveal, researchers are still

hunting for the best method to obtain clinically useful quantities of the rare, hard-to-grow cells. Leading the way on T regs are scientists searching for new ways to forestall GVHD. For example, transplant immunologist Bruce Blazar of the University of Minnesota, Twin

“It’s a terrific, exciting time in the field.”

—ALEXANDER RUDENSKY,
MEMORIAL SLOAN-KETTERING
CANCER CENTER

Cities, and colleagues recently conducted a phase 1 trial in which they transferred T regs into 23 leukemia and lymphoma patients who had just undergone transplants of cord blood, which contains blood-generating stem cells. Almost simultaneously, a group led by hematologist Mauro Di Ianni of the University of L’Aquila in Italy was administering T regs to 28 lymphoma and leukemia patients who had gotten replacement blood-forming stem cells.

Neither team has found any obvious safety concerns. A potential hazard was that the added T regs would scupper immune defenses against microbes, but Blazar and colleagues reported online in October in *Blood* that the cancer patients receiving T regs and cord blood didn’t suffer more infections, compared with historical controls, suggesting that the cells didn’t impair overall immunity. The results also hinted that T regs didn’t affect how long the patients

Regulatory T Cells Enter the Clinic

Target	Source of T regs	Type of trial	Status
Graft-versus-host disease (GVHD)	Cord blood	Phase I	Completed
GVHD	Peripheral blood	Phase I	Completed
Type 1 diabetes	Autologous	Phase I	Recruiting patients
Kidney transplant rejection	Autologous	Phase I	Received funding
GVHD	Induced in patient by interleukin-2	Phase II	Recruiting patients

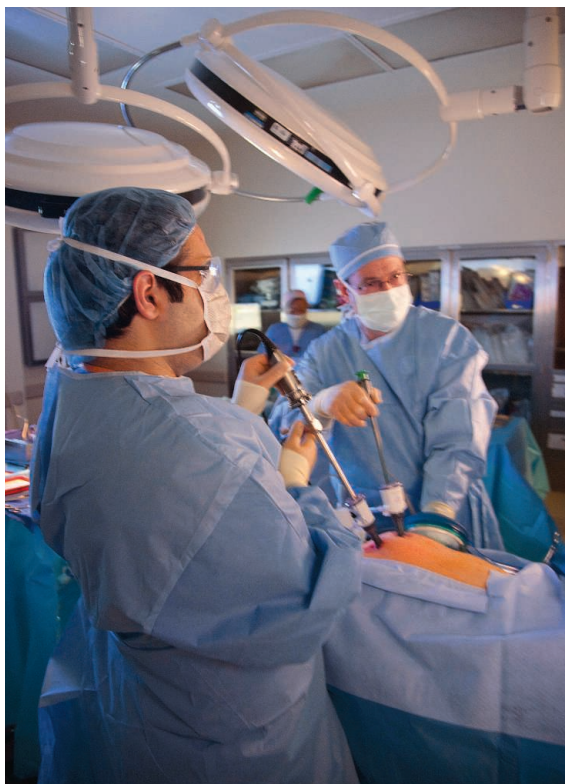
remained alive and free of cancer.

Although the studies primarily addressed the safety of the treatment, both found evidence that it hinders GVHD. (Di Ianni's team reported its findings online in February in *Blood*.) For example, Blazar's team documented that just 43% of the T reg recipients developed the acute form of GVHD, which usually strikes in the first 3 months after the procedure. Typically, 61% of patients suffer from the complication. Blazar suggests that his group might have seen an even stronger protective effect if they'd been able to isolate more T regs to infuse: The researchers describe a new technique for cultivating large numbers of T regs in one of the *STM* papers.

The T regs in these GVHD studies share a drawback: They are third-party cells, meaning they didn't come from the intended recipients or from the same source as the bone marrow or stem cells being transplanted. (Blazar's group isolated T regs from umbilical cord blood, the other group from freshly donated blood.) The immune system could treat third-party T regs as invaders, unleashing an attack that could annihilate the cells or sicken the recipients. So in a recently launched diabetes trial, immunologist Jeffrey Bluestone of the University of California, San Francisco (UCSF), and colleagues instead plan to isolate T regs from each participant's blood, expand their numbers in the lab, and return them to that patient. The initial target population for this so-called autologous T reg therapy consists of young adults newly diagnosed with type 1 diabetes, in which the immune system devastates the insulin-making beta cells in the pancreas.

By the time people learn they have type 1 diabetes, they typically retain only 15% to 40% of their beta cells, says pediatric endocrinologist Stephen Gitelman of UCSF, who is working with Bluestone on the trial. But even at this stage, they can usually keep their blood glucose under control with insulin doses and other measures. The ultimate goal, Gitelman says, is to determine whether T regs can "preserve the honeymoon," allowing people with manageable diabetes to remain at this stage by curbing the loss of beta cells.

Organ transplant recipients, who now require lifelong courses of drugs that knock down the immune system to prevent rejection of the transplant, are also about to receive T regs. Six European institutions are collaborating on the ONE Study, a 5-year project to test whether T regs can prevent rejection of kidney transplants. "There's a huge need to improve immunosuppression in [organ] transplants," says Andrew Bushell, a transplant immunologist at the University of



Cellular help. Kidneys are often rejected by a recipient after a transplant operation (above), but administering regulatory T cells may prevent this.

Oxford in the United Kingdom, which is part of the project.

The ONE Study and Bluestone's type 1 diabetes trial will dose patients with polyclonal T regs, which turn down immune responses relatively broadly. The alternative is so-called antigen-specific T regs, which block attacks by other T cells that target a particular antigen, such as a characteristic protein on the cells in a transplanted organ. In theory, antigen-specific T regs shouldn't provoke general immune suppression that might undermine antipathogen defenses and even lead to cancer. "We really believe that antigen specificity is the future of any successful T reg therapy," says transplant immunologist and ONE Study collaborator Giovanna Lombardi of King's College London. Bluestone says that future diabetes trials will also probably switch to antigen-specific T cells.

Researchers can obtain antigen-specific human T regs that suppress immune responses to, say, a skin graft by exposing the T regs to cells from the graft's donor. But generating specific T regs to treat type 1 diabetes is tricky, Bluestone says, because

researchers don't know which antigen they should protect in order to spare beta cells. Another limitation is that the techniques for producing antigen-specific T regs are less efficient than those for making the polyclonal variety. Two of the *STM* papers published last week address this problem. Bushell and colleagues showed that a drug prescribed for vascular inflammation could spur generalist human T cells to specialize into T regs that, when injected into mice, prevented rejection of human artery grafts. Meanwhile, Lombardi and her group found that they could hike the yield of antigen-specific human T regs in culture by sorting the cells based on two surface proteins that mark activated T regs.

Although the initial GVHD trials revealed no obvious safety risks, immunologist Christophe Benoist of Harvard Medical School in Boston notes that it remains a contentious issue whether T regs can convert into cells that attack rather than sup-

press. "In that case, antigen-specific T regs could be harmful," he says, because the treatment might introduce a large number of potentially destructive cells into the body.

Therapies that involve growing T regs in the lab face some big challenges. For one thing, Rudensky says, they are expensive. Blazar says that his cord-blood treatment cost nearly \$40,000 per patient. Lombardi puts the cost of generating polyclonal T regs for the ONE Study at \$32,000 to \$48,000 per recipient.

Because of the technical challenges of producing ample T regs and the related high costs, some immunologists favor alternative approaches, such as identifying drugs that spur T regs to multiply within the body.

For example, researchers at Baylor College of Medicine in Houston, Texas, and colleagues have begun a clinical trial to test whether injections of interleukin-2, an immune system messenger, boost T reg numbers and prevent GVHD. Still, other researchers are confident that transplanted T regs will have a medical role. "Yes, we are going to see these cells in the clinic," Bushell predicts. **—MITCH LESLIE**

"Yes, we are going to see these cells in the clinic."

**—ANDREW BUSHELL,
UNIVERSITY OF OXFORD**