Long Ago pocketknife. The 550-year-old Canadian iceman kept his knife in this pouch.

will last. "We should be out there with 10 helicopters every summer, because these places may go fast," says Gordon Jarrell, curator of the frozen-tissue collection at the University of Alaska, Fairbanks, where many of the Yukon finds are stored. He says that flesh starts rotting within hours of exposure—and ravens and other alert scavengers may not mind eating even 8000-year-old meat.

To get ahead of the curve, scientists are now trying to pinpoint good prospecting spots. "We know things melt out, but the real problem is predicting exactly where they'll appear," says archaeologist James Dixon of the University of Colorado Institute of Arctic and Alpine Research (INSTAAR).

Dixon and glaciologist William Manley, also of INSTAAR, have spent the last 3 years assembling a Global Information System model to map potentially fruitful areas in Alaska, which they hope to apply to other areas of the world. Their charts overlay glaciologic data, such as the altitudes below which particular glaciers are melting, with information such as trade routes, ancient stone quarries, mineral licks, and other places where people and animals may have been.

Last summer Dixon and Manley tested their model in Alaska's Wrangell-St. Elias Park—and hit the jackpot. Landing by helicopter and ski plane, they found 36 sites with a mind-boggling array of melted-out material. In addition to the ever-present feces, they found fleshy remains of Dall sheep, caribou, assorted carnivores, many birds, and even a complete, perfectly preserved fish, perhaps hauled in by a human. Other leavings of people included an antler projectile lying near a punctured caribou scapula, a piece of cut wood, and a pile of horse-hoof rinds (the part of the toenail cut off to reshoe the horse) with rusty nails still attached. Dixon assumes these last are from a 1902 gold rush in which prospectors foolishly tried crossing the glaciers.

"The organic content of glaciers is amazing, and it has profound implications for everything from paleontology to water quality," says Dixon. Water quality? "Yes," he says, pointing out that many glaciers provide drinking water. One small example: A hotel near his Colorado home has a drinking fountain labeled: PURE WATER DIRECTLY FROM ARAPAHOE GLACIER. "I wince, thinking about what's probably in there."

–KEVIN KRAJICK

Kevin Krajick is the author of *Barren Lands: An Epic Search for Diamonds in the North American Arctic*. He lives in New York City.

IMMUNOLOGY

Gently Soothing a Savage Immune System

Autoimmune disease and transplant researchers are teaming up in their search for ways to make the immune system tolerate tissue it's attacking

The immune system is a shifty character, displaying the faces of Dr. Jekyll and Mr. Hyde. Most people encounter only its benevolent side, charged with protecting against disease. But in others, the immune system bares its teeth. For organ transplant recipients, efforts to quash a beastly, overactive immune system have defined treatment for a generation. That may be about to change, as researchers search for ways to tame the immune system without obstructing it entirely.

The new approach, called immune tolerance as opposed to immune suppression, is driven by work in the transplant field, but experts in autoimmune diseases such as multiple sclerosis (MS) and type I diabetes are also getting into the game—in their case to modulate attacks on the patient's own tissue. Results from animal studies have generated promising findings, such as mice cured of diabetes and off all medication and monkeys with new kidneys who don't need immunosuppressants. Spurred on by such successes, dozens of clinical trials are now under way or gearing up.

"I'm very optimistic that [immune tolerance] is going to be a big step forward," says Fritz Bach, a transplant surgeon at Harvard Medical School in Boston. "I've been in this a long time, [and] I've never taken this view before."

But in humans, the work remains highly experimental. Along with some promising preliminary results, a handful of trials have screeched to a halt due to deadly adverse effects—a reminder of how exquisitely sensitive the immune system can be, and how much about it is left to learn.

Friendly fire

Transplant surgeons have been battling host rejection for decades with drugs such as cyclosporine, which massively suppresses the immune system. This approach has allowed an impressive 90% to 95% of organ transplant recipients to retain their new organ for at least 1 year. But rejection numbers rise sharply with time. Despite continued use of immunosuppressants—patients must take them for life—by 10 years after transplant, the immune systems of roughly 50% of patients have rejected the organ. Even when

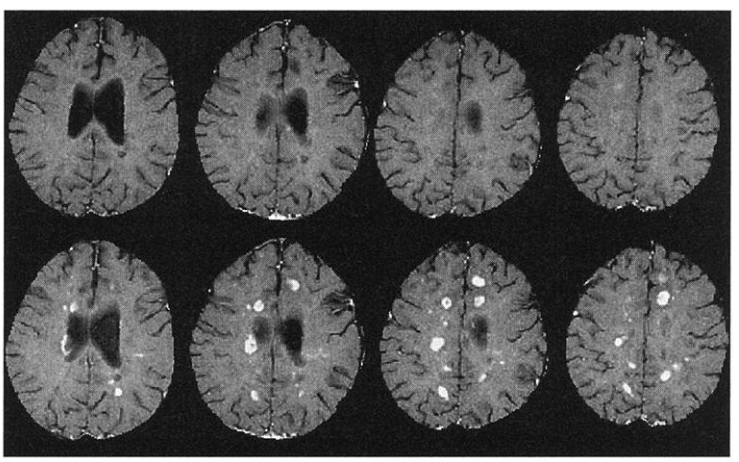
Mix and match. Immunologist Megan Sykes adds elements of an organ donor's immune system to a recipient's, aiming to overcome the need for immunosuppressants.

CREDITS: (TOP TO BOTTOM) CORBIS; M. SYKES

immunosuppressants keep working, they can have harmful side effects, including infections and cancer.

If immune suppression is a sledgehammer approach, immune tolerance is more akin to a massage. By coaxing subtle shifts, researchers hope to train the system to accept tissue it's trying to destroy. Strategies vary. In some cases, researchers administer experimental drugs to suppress only those immune system cells causing problems. Other approaches put patients through risky stem cell transplants, which usually require toxic chemotherapy. The hope is that those transplants will destroy renegade immune cells or mingle a patient's immune system with a donor's so that the body accepts the donated organ. Research is showing that tissue rejection mechanisms can be quite similar, whether in autoimmune diseases or transplants, and some of the same drugs are being tested in both types of patients.

So far, tolerance treatment has helped a subset of individuals on whom it's been tested; they can get by on lower drug doses or respond to standard treatments they once resisted. But very few have met the strictest test of tolerance: an immune system that no longer recognizes tissue from the donor or, in the case of autoimmune diseases, their own tissue as foreign once drugs are withdrawn.



Backfired. Images of a multiple sclerosis patient's brain before (*top row*) and after (*bottom row*) experimental treatment show an increased number of lesions after the drug was given.

CREDIT: J. A. FRANK AND N. RICHERT/LABORATORY OF DIAGNOSTIC RADIOLOGY RESEARCH, CLINICAL CENTER, NIH

In with the new

One way to revamp an immune system is with a bone marrow or stem cell transplant. It can come from a matched donor such as a sibling or from cells taken from the patient and later reintroduced. Commonly used to treat life-threatening blood disorders and leukemias, such transplants are performed after large doses of chemotherapy and radiation destroy existing marrow. The marrow contains infection fighters such as T cells as well as other immune cells and the stem cells that produce them. Once the marrow is gone, doctors infuse a new dose of bone marrow extracted from the donor's hip or stem cells taken from the blood. If all goes well, the new cells will churn out blood and marrow free of disease.

But such treatments carry serious risks. Chemotherapy and radiation regimens are toxic enough to kill. If the patients survive, their new marrow may attack their bodies, a sometimes deadly complication called graft-versus-host disease (GVHD). Still, researchers have improved the technique substantially in recent years, and some believe that the potential benefits of stem cell transplants outweigh their risks and justify extending the treatment to those with autoimmune disease or transplants.

At Stanford University 18 months ago, immunologist Samuel Strober began combining stem cell and kidney transplants in humans. Years of lab research had convinced him that a mix, or chimera, of a patient's immune system cells and the donor's could prevent organ rejection. He crafted a low-toxicity regimen that includes drugs and radiation and destroys some cells in the bone marrow to make room for new ones.

Four patients have signed on, receiving cells that should generate T cells identical to the donor's; the patients also retain some of their own T cell–producing stem cells. The volunteers will be allowed to stop taking immunosuppressants if they exhibit chimerism, no rejection, and blood markers of tolerance to the donor. The first patient went off medication after 1 year. Strober will present an update at meetings of the American Association of Immunologists and the American Society of Transplantation this month.

Immunologist Megan Sykes and colleagues at Massachusetts General Hospital (MGH) in Boston have pioneered additional chimerism protocols. Sykes has performed transplants on three people with both bone marrow cancer and kidney failure who were not eligible for standard kidney transplants; two are off immunosuppressants. She's also experimenting in animals with adding antibodies to the mix. The antibodies would in theory disable T cells in the patient, doing some of the work of radiation and chemotherapy without their side effects; they also attack T cells from the donor, reducing the risk of GVHD. Both the MGH and Stanford groups have used living organ donors, although both say it's possible to extract stem cells along with organs from cadavers.

Tolerance treatment has also been tried in autoimmune patients. European scientists are tracking about 400 patients in Europe, Asia, and Australia who suffer from diseases such as rheumatoid arthritis and MS and have received stem cell transplants. By administering chemotherapy before the transplant, researchers such as Alan Tyndall, a rheumatologist at the University of Basel in Switzerland, and Richard Nash, an oncologist at the Fred Hutchinson Cancer Research Center in Seattle, believe they are reducing the number of overactive T cells, B cells, and other immune cells. Then the patients receive an infusion of stem cells previously extracted from their own blood. That way, the theory goes, the immune system can "turn back the clock," as the stem cells produce new cells that haven't yet gone bad.

Early results found that a majority of patients initially stabilized or improved after the transplant, but between 20% and 70%, depending on the disease, of the European cohort later relapsed. Many of them, though, continue to respond far better to standard treatments they once resisted, says Tyndall, who's coordinating the study, run by the European Group for Blood and Marrow Transplantation and the European League Against Rheumatism.

About half of the U.S. transplants for autoimmune patients are overseen by doctors at the Fred Hutchinson Cancer Research Center, who are coordinating a multicenter trial on more than 50 people with MS and scleroderma. For scleroderma, severity on average has been reduced 50%, says Daniel Furst, a rheumatologist at the University of California, Los Angeles. "In any other studies, the max is 20%," he says.

Promise aside, these treatments—like all stem cell and bone marrow transplants—carry a risk of death. In the European studies, 28 autoimmune patients have died from transplant-related complications, as have four in the Hutchinson protocol. Although researchers initially performed transplants on the sickest patients, they found that too many succumbed to the rigors of the transplant. The teams have since shifted to patients with poor prognoses—in the Hutchinson protocol, the scleroderma patients are deemed to have a 50% chance of living 3 to 5 years—but relatively good health currently. "If it's done in the right patients, it gives them the best chance," says Tyndall.

Still, such transplants remain a drastic treatment for both organ recipients and

autoimmune patients. Their toxicity and their reliance, so far, on living donors has prompted questions about how widespread the treatment can become.

Divide and conquer

Another way to thwart immune cells is to isolate them. A strategy called co-stimulatory blockade stops communication between specific immune receptors, which stud the surface of all sorts of immune cells and help govern their behavior, and the T cells on which particular receptors reside. Ideally, this prevents a defined subset of T cells from causing inflammation, while leaving everything else untouched. MGH's Sykes co-opted this approach when she added antibodies to her chimerism approach, but it can also be used alone.

One co-stimulatory blockade drug is anti-CD3, which interferes with so-called CD3 receptors and alters their ability to signal to T cells. The drug inactivates a subset of helper T cells thought to be involved in type I diabetes. These T cells apparently destroy insulin-producing islet cells in the pancreas. French scientists, led by Lucienne Chatenoud at the Necker Hospital in Paris, reported in 1997 that giving mice anti-CD3 cured diabetes, even after the drug was stopped. Now Kevan Herold of Columbia University, Jeff Bluestone of the University of California, San Francisco, and others are testing it in newly diagnosed diabetic patients, with the hope that such patients may still have islet cells left to save. Other antibodies are being explored for diseases ranging from psoriasis to MS to rheumatoid arthritis as well as kidney transplants.

Discouraging works

For tolerance researchers, safety issues loom large. In the past few years, a handful of trials have caused enough harm to be halted, and others, such as stem cell transplants on autoimmune patients, have recorded higher-than-expected mortality rates for reasons not understood, says Roland Martin, chief of the cellular immunology section at the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland.

Martin still does not understand exactly what went wrong in his MS trial, supported by Novartis in Basel, Switzerland, and the biotech firm Neurocrine Biosciences in San Diego, California. It ended disastrously in 2000, after three of the eight volunteers suffered exacerbated MS symptoms apparently linked to the peptide-targeting drug supposed to temper immune attacks. One patient began the trial with a few brain lesions and ended up with 91, and another exhibited large tumorlike lesions he'd never had before. It's still not clear what caused the lesions—which were successfully treated with standard MS drugs—although Martin theorizes that the dosing may have been too high, somehow sending immune cells into overdrive instead of quelling their activity.

"[Immune tolerance] is a matter of tipping the balance," says Elaine Collier, chief of the autoimmunity section at the National Institute of Allergy and Infectious Diseases in Bethesda. "We may be tipping one set of regulatory cells the way we want, and another set the way we don't want."

Fine distinctions in the immune system or among different diseases may help explain the startling variations in response to treatments, says Tyndall. Clues to what distinguishes subsets of patients could come from the tiny number of transplant patients who stopped taking immunosuppressants but somehow kept their organ. Kenneth Newell, a kidney and pancreas surgeon at Emory University in Atlanta, Georgia, is hoping to identify roughly 40 kidney patients in the United States and Europe who fit the bill; a group at the University of Pittsburgh in Pennsylvania is doing the same for liver recipients.

Fully "curing" disease by inducing true tolerance without the help of drugs remains the holy grail of the field. But those involved say that, given the mysteries that still surround the human immune system and the devastation it can produce, a more realistic, short-term goal may fall somewhere between broad immune suppression and total tolerance.

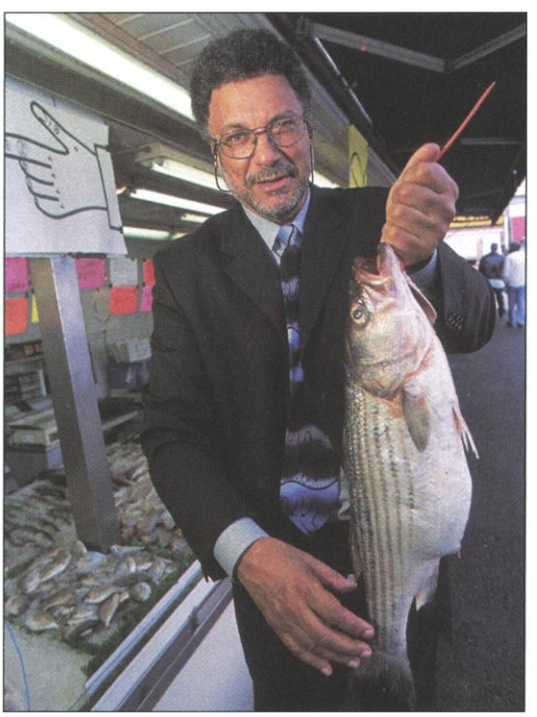
–JENNIFER COUZIN

PROFILE DANIEL PAULY

Going to the Edge to Protect the Sea

Fisheries biologist Daniel Pauly has carved out a colorful—and controversial—career with fresh and frank insights into marine fisheries

Daniel Pauly still remembers his youthful encounter 30 years ago with what he calls "the living papers." A graduate student in Germany, Pauly watched the field's royalty with awe at his first major fisheries conference. "Names I knew only from the literature were suddenly parading before me like kings," he recalls. "I was terrified."



Earning his stripes. Daniel Pauly displays a professional interest in a Washington, D.C., fish market.

CREDIT: RICK KOZAK

These days, the 55-year-old Pauly—tall and graying—is a bit of a living paper himself. A professor at the University of British Columbia (UBC) in Vancouver, he is arguably the world's most prolific and widely cited living fisheries scientist, with recent headline-grabbing papers in *Science* and *Nature*. He's also an architect of a leading fish database and a popular ecological modeling program.

Despite these accomplishments, Pauly remains something of an outsider. His offbeat approach to the science is part of the reason. Whereas colleagues have built careers by using complex mathematics to crunch massive data sets, Pauly has worked mostly in data-deprived developing nations, and he says he can't stomach "enormous equations."

His irreverence is another factor. In a field marked by caution, Pauly has become an outspoken and often controversial critic of modern fishing practices. He's suggested that marine fishers will leave little but jellyfish for future generations to eat, and he has blamed the Chinese government for inflating fish catch statistics and helping obscure a global overfishing crisis. The industry, he says in a sonorous accent that hints at a globe-trotting life, "has acted like a terrible tenant who trashes their rental." Some colleagues are also uneasy about his close ties to