

Research Push

Anxious for Cures, Grant Givers Turn More Demanding

To Speed Discovery Process,
Scientists Must Share Data
As Condition for Funding

An Ex-CEO Tackles His Illness

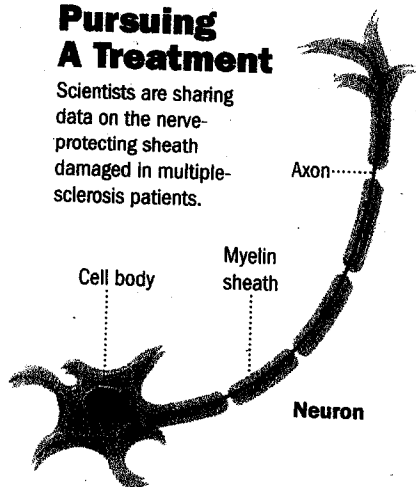
By SHARON BEGLEY

Trent Watkins had just made an extraordinary discovery. The young graduate student had identified a rogue enzyme that could be a key to treating multiple sclerosis, the neurological disease that can leave victims blind and unable to walk.

If Mr. Watkins had been conducting science-as-usual, no outsider would have learned of his "eureka" for years, as it wended its way through scientific review to publication in a top journal. Instead, within days of the finding, his lab shared the data with four research groups at

Pursuing A Treatment

Scientists are sharing data on the nerve-protecting sheath damaged in multiple-sclerosis patients.



Source: Myelin Repair Foundation

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"My heart almost stopped, it's so against how we usually do things," says Ben Barres, a Stanford University neurobiologist and head of the lab where Mr. Watkins is pursuing his doctorate. "Normally, the kind of work we do would go for seven or eight years before moving to an animal model, which would take several more years before moving to human tissue."

The Stanford group reached out to other scientists for one reason: It was a condition of a grant from a new research foundation that is supporting the lab's work. Without assurance that Prof. Barres and his colleagues would quickly share important findings with other scientists, the foundation wouldn't have written the check.

The requirement reflects a growing movement among patient-advocacy and other private funding organizations—ranging from the powerhouse Juvenile Diabetes Research Foundation to newcomers like the Michael J. Fox Foundation for Parkinson's Research—to shake up the structure and culture of biomedical research. Fed up with the glacial pace at which new discoveries become medical treatments, the groups are insisting that the scientists they fund swear off secrecy in favor of collaboration.

Traditionally, academic biomedical researchers get federal grants and tenure by working largely alone toward basic discoveries, usually collaborating only with colleagues in their own labs. Now some are calling that model flawed. Despite the flood of new knowledge in the biosciences, there has been "a slowdown instead of an expected acceleration in innovative medical therapies reaching patients," says Janet Woodcock, an acting deputy commissioner at the Food and Drug Administration.

What's needed, many agree, is more "translational" research to turn fundamental discoveries into practical treatments. And funding organizations are realizing that translational research is by its nature collaborative. A lone genius might find a disease-causing gene, for example, but turning that into a cure requires biologists to figure out what the

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gene does and chemists to work with them designing drugs to block that action.

Even the National Institutes of Health, the primary funder of basic biomedical research in the U.S., is beginning to put more weight on translational research as part of a "road map" unveiled in September 2003. In addition to funding projects scientists dream up on their own, the NIH is setting more of its own big goals and directing scientists to work toward them.

There isn't any assurance that the new strategy will work. It may not shorten the time required for clinical trials of new drugs or devices, for instance, which typically take a decade or more. Many scientists say the traditional system is working fine. Siphoning money—public or private—away from basic research and setting direction from above could choke off discoveries that underpin every treatment and drug now in use, they say. It could also stifle the independent spirit that leads talented people to academia in the first place.

But funders say they're tired of writing checks for research that doesn't lead anywhere. Five years after the juvenile-diabetes foundation raised and distributed millions of dollars for basic-science research in a 1990s campaign called "The Only Remedy Is a Cure," it had no real clinical progress to show for the money. In one instance, a foundation-supported scientist discovered a gene that increases the risk of developing juvenile diabetes. All well and good, says Richard Insel, the foundation's executive vice president for research, "but then the scientist, being a geneticist, went and looked for another risk gene." The first discovery just sat there in a scientific paper.

"We used to leave it to chance that someone would pick up on the discovery and advance it," says Dr. Insel. That has seldom happened. The foundation distributes more than \$100 million a year in research grants but the scientists it funds haven't found a cure for an illness that afflicts at least 1.3 million adults and children in the U.S. and 5.3 million worldwide.

An Active Role

This spring, the foundation began taking a much more active role in some of the research it supports. It listed steps deemed crucial to treating or curing juvenile diabetes, such as coaxing the body's insulin-making cells, which are destroyed in the disease, to regenerate. Then it invited scientists to propose experiments toward achieving those steps. It also began requiring that scientists seeking its money either hook up with researchers from other disciplines or let the foundation play matchmaker—or look for funding elsewhere.

Left on their own, says Dr. Insel, "academics aren't skilled at translating discoveries into cures. It's incumbent on us to figure out how to do that, and it's only going to work if we take a hands-on approach."

The Fox Foundation for Parkinson's disease, only four years old, also started out the old-fashioned way, inviting scientists to propose studies that promised a better understanding of Parkinson's. "But then we looked around and asked how we could have the biggest impact," says Katie Hood, director of the group's research programs.



Scott Johnson

Scott Johnson, a longtime Silicon Valley executive who started the Myelin Repair Foundation, decided to go even further. In 1976, when he was 20, he was diagnosed with multiple sclerosis. In this disease, the immune system attacks the fatty sheath that coats axons, the long cables that carry electrical transmissions from one neuron to the next. Without this sheath, called myelin coating, electrical current leaks and the neuronal signal peters out before it reaches its target. As a result, patients can suffer extreme fatigue, blindness, loss of balance, slurred speech and problems with cognition.

After years of consulting and running start-ups, among them a company that developed technology to destroy air pollutants, Mr. Johnson found it more and more difficult to function with his MS. Today, his right hand is virtually useless and he walks with a cane. Three years ago, he decided to pursue a cure full-time.

A Handful of Scientists

In February 2002 he attended a research conference in Ventura, Calif., on myelin. While Mr. Johnson found the studies presented in formal sessions interesting, he hit paydirt chatting up the scientists in hallways and at the bar of the Ventura Beach Hotel. If you had to choose just a handful of scientists to receive funding for research on MS, he asked about 30 of them, whom would you pick? The names of the same five scientists came up again and again.

Mr. Johnson invited the quintet to a meeting over Memorial Day weekend 2002. In the boardroom of Silicon Valley Bank in Santa Clara, Calif., he presented his vision. Repairing myelin, he said, is a "finite and definable" goal for MS therapy. He was prepared to raise significant sums for such research, but there was one condition.

Mr. Johnson had come to realize that scientists typically keep their discoveries secret for years, the time it takes to methodically repeat an experiment to make sure the results are sound, write up a description of the methods and results, submit the manuscript to a scientific journal, wait for it to be critiqued, make the requested revisions, resubmit it, and wait some more until the journal publishes it. In the kind of research he was prepared to bankroll, the scientists had to agree to work as a team to develop and execute a coordinated research plan. Anyone who made a discovery had to share it with the other four labs right away.

That flew in the face of the culture of academic biomedicine and its reward system. Scientists earn prestige, tenure and more grants by making basic discoveries, and by doing it first. Being part of a collaboration can dilute prestige. As a result, scientists typically do not share their hunches or plans with people outside their own research group. Although studies may list a dozen authors from several institutions, in many cases the scientists did not actually work together. They just supplied materials (anything from lab mice to biochemicals), for instance, or did a statistical analysis of the data.

"Can you send me your reagent and I'll put your name on the paper?"—that's what counts as collaboration in the usual model," says neurobiologist Robert Miller of Case Western, one of the five scientists invited to Santa Clara by Mr. Johnson. "It was very hard to get used to this way of doing things."

Laying Out a Plan

Despite some qualms, all five scientists Mr. Johnson recruited decided to take the plunge. They agreed on what should be accomplished by the end of the first year, "and from that we laid out a business plan," says Mr. Johnson, who holds a masters in business administration from the University of California, Berkeley. He and the scientists spent the next six months refining that plan, scheduling monthly teleconferences and four-month reviews where the researchers would share results. Starting with a \$1 million donation in March from Scott Cook, co-founder of software publisher Intuit Inc., Mr. Johnson established the Myelin Repair Foundation. It has raised about \$2 million toward its five-year goal of \$25 million.

The five universities employing the scientists in the collaboration have all signed intellectual property agreements under which any royalties from discoveries funded by MRF will be shared 50-50 with the foundation, which would plow the earnings back into more research grants.

Last November, when the five foundation scientists met in Chicago, Stanford's Prof. Barres shared his lab's latest discovery. He explained how Mr. Watkins, the graduate student, was examining rodent brain cells growing in lab dishes when he saw something striking. Usually, special cells in the nervous system called oligodendrocytes slather myelin on axons, which is exactly what MS patients would love to happen in their own bodies. But when a certain enzyme is present, Mr. Watkins noticed, these special cells fail to do their job. They sit right next to axons that need myelin but don't do anything about it. The Stanford group figured that blocking the enzyme might unleash myelination and maybe heal MS patients.

If he had held back the discovery until it could be published in a scientific journal, says Prof. Barres, "it would have been years and years before anyone got around to the next logical step"—seeing what happens in lab mice in which the myelination-blocking enzyme is knocked out—"and only years after that would anyone get to doing this with human tissue."

Instead, revealing the unpublished discovery was like shooting off a starter's pistol. A molecular geneticist at the University of Chicago said he had mice with an MS-like disease and would see what happened when he blocked the rogue enzyme. Case Western's Prof. Miller said he had human brain tissue from MS patients that he would test. "You wouldn't hear this stuff anywhere else," says Prof. Miller. "We're thinking about it immediately, which has probably saved us two years."

Since then, the Stanford scientists have gone on to identify a molecule that knocks out the myelination-blocking enzyme and are preparing to file for at least one patent on it, in the hope that it might be the basis for a new myelin-repair drug.

On the Trail

At the most recent meeting of the five teams of Myelin Repair Foundation scientists, ideas flew through the air. Neuroscientist Brian Popko of the University of Chicago described another molecule that seems to knock out the myelin-making oligodendrocytes. Now the foundation's team is on the trail of ways to sideline that molecule.

Prof. Miller unveiled unpublished discoveries about ways to manipulate precursor cells in ways that make them develop into oligodendrocytes. "The brain and spinal cord contain these precursor cells, so why don't they turn into oligodendrocytes?" he asked. Whenever a precursor cell interacts with a certain molecule, it seems to develop into a kind of cell that is no good at myelination. By tying up the molecule, precursor cells might take the path to becoming oligos.

The scientists' goal is to identify a drug target and find a promising compound by 2009—10 years to 15 years faster, they say, than the traditional approach. Even then it would take a decade or more to test the new drug. And only 8% of compounds that enter human trials become approved drugs.

Mr. Johnson is convinced that the hard-driving style he used at his startups is the way to cure the disease that is crippling him. "To make progress against this disease," he says, "you have to do things differently."