

OF MICE & PAC-MEN



In the brains of mice, a voracious little immune cell can gobble and destroy one of the key attributes of Alzheimer's. A Cedars-Sinai researcher's stunning discovery could open the door to a treatment for this devastating brain disorder.



Late one December night in 2006, Terrence Town, PhD, sat alone in his Yale University lab, poring over his Alzheimer's disease research. On his bench sat a pile of data to bore through like archeological strata. After 20 long months in the lab, he was becoming more perplexed by the day: His experiments were producing results that were the opposite of what he expected. Town was eager for a sign, a glimmer of hope, for *something* to happen.

It was a few minutes before 9 p.m. when Town looked through his laser scanning confocal microscope at the brain of a laboratory mouse and saw something he had never seen before: a proliferation of perfectly round immune cells. The young researcher rose from his bench and took a deep breath. "That was the moment," Town recalls, "when I realized this was going to be a really interesting discovery."

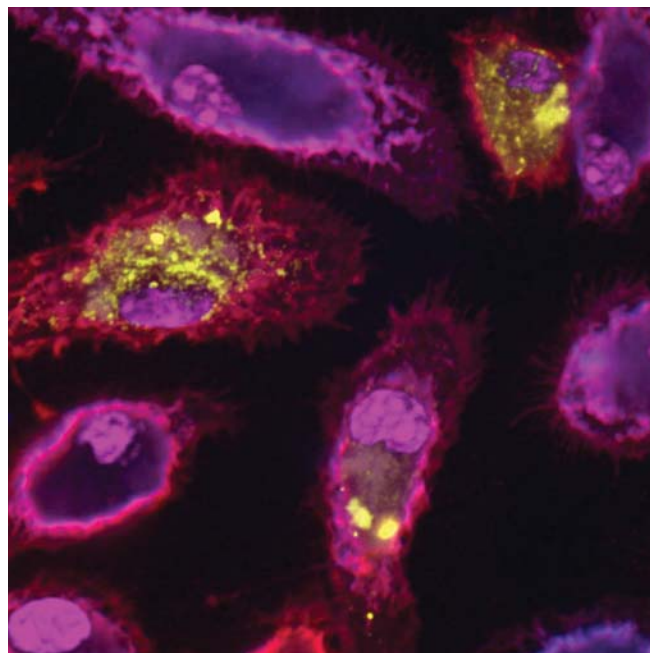
The game changer

Today, Dr. Terrence Town is an associate professor in the Department of Neurosurgery and the Department of Biomedical Sciences at Cedars-Sinai. His work is opening the door for a promising new strategy: an immune-based approach to treating Alzheimer's disease. Dr. Town found

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that certain immune cells could be coaxed into the brains of laboratory mice programmed to develop Alzheimer's-like disease. There, the cells attacked the damaging sticky plaque buildup that is a defining feature of Alzheimer's disease. Town recently published his findings in the prestigious journal *Nature Medicine*.

The plaques in question—amyloid plaques—are thought to damage the brain's nerve cells and inflame nearby cells. Could Alzheimer's be treated by somehow preventing or removing the plaque buildup and calming



Photograph taken from a laser-scanning confocal microscope showing cultured macrophages in magenta gobbling up amyloid plaque in yellow (reproduced from Town et al., *Nat. Med.* 2008, 14:681-687).

the inflammation? In 2004, Town started by looking at the brain's immune-inflammatory response and its role in the progression of neurodegenerative disease.

"We took mice deficient in a molecule known to promote immune response and inflammation, and crossed them with mice programmed to develop Alzheimer's-like disease," says Dr. Town. "We were surprised to see a big reduction in amyloid plaques in these crossed mice. We determined that the brain's inflammatory response was important in the progression of the disease. We began investigating additional molecules, one by one, to determine which were important for neuroimmunity." He stopped when he got to TGF- β .

This immunosuppressive molecule is increased in abundance in the brains of patients with Alzheimer's disease. These increased levels may represent the brain's attempt to return to normalcy by quieting the immune response around the amyloid plaques. Town and his colleagues turned to genetically engineered mice whose TGF- β molecule on immune cells outside the brain had been blocked, or deactivated. "We hypothesized that shutting off this key anti-inflammatory signal would cause a rampant inflammatory response, which would damage

sensitive neurons and worsen Alzheimer's development," he says. This is akin to expecting more burglars to rob a bank if the alarm is not turned on.

The upside of guessing wrong

Surprisingly, the results were the opposite of what he had expected. "We thought our mice would do worse in behavioral tests of learning and memory, but they were doing better. We had no idea why. It was really perplexing," says Town. Upon conducting further analysis at the molecular and cellular levels, they found an explanation: the amyloid plaques in these mice were dramatically reduced, more than the researchers had ever seen following other experimental interventions.

"That was, again, somewhat perplexing," shares Town. "It was as if the plaques had miraculously been removed." Closer examination revealed the presence of large white blood cells—called macrophages—that are key players in the immune response to foreign invaders. The macrophages had infiltrated the brains of the crossed animals in massive numbers, homed to the plaques, and devoured them, substantially reducing brain plaque "burden" by 80 to 90 percent. "By knocking out TGF- β signaling in these macrophages, we had somehow stumbled onto a way to recruit these amyloid-clearing cells into the brain, where they removed the plaques like miniature vacuum cleaners, eating them up like Pac-Man eats dots," says Town, referring to the classic arcade game.

That was what his microscope revealed on that December night. "I saw immune cells that actually contained amyloid in them; they had been eating the sticky plaque, munching on it," he says, his excitement still palpable. "This tied it all together and explained everything we had seen so far that did not make sense." It was "a eureka moment," as Town calls it, and they don't happen often in the life of a scientist. Town adds: "The curtain had been lifted to expose a fascinating piece of biology."

From plaque to promise

Fascinating, and potentially revolutionary. This discovery quite simply opens up the possibility of a new, much-needed approach to treating Alzheimer's—a disease

A Healing Legacy

Dr. Terrence Town is the inaugural holder of the Ben Winters Endowed Chair in Regenerative Medicine—named in memory of Ben Winters, who became a member of the Mount Sinai Hospital board in 1954 and was instrumental in bringing together Cedars of Lebanon and Mount Sinai hospitals to form Cedars-Sinai Medical Center in 1961. When he passed away from Lou Gehrig's disease (ALS), his family and friends wanted to show their gratitude for the care he received at Cedars-Sinai by raising funds in his name to support research in degenerative diseases and regenerative medicine.

"Research is a natural result of inquiry and education," says Elaine Winters, Ben's widow. "This endowment in Ben's name is a natural fit; the fact that Dr. Town is so young would have pleased him immeasurably. He believed in our youth."

The leadership of a single gifted scientist can yield incalculable benefits. Mindful of this, Cedars-Sinai philanthropists support chair holders who are advancing the understanding and treatment of a wide spectrum of diseases, including atherosclerosis, cancer and brain tumors, hypertension, diabetes, inflammatory bowel disorders, schizophrenia, and others.

An Endowed Chair is created with a philanthropic gift of at least \$2,000,000. The principal remains untouched, generating continuing resources to support the chair holder's research and teaching efforts.



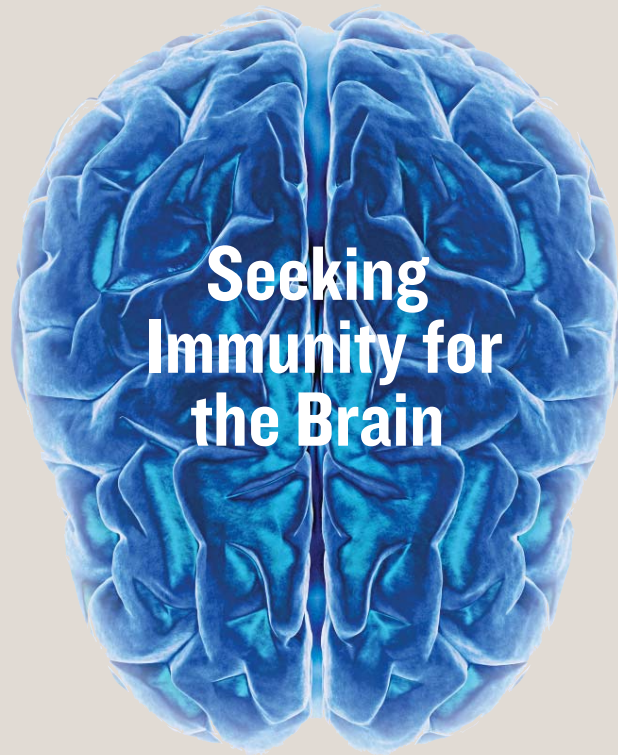
Ben Winters illustration by Tom Root

for which there is currently no cure. According to a 2009 report from the Alzheimer's Association, as many as 5.3 million people in the United States are living with Alzheimer's; someone develops the disease every 70 seconds. The direct and indirect costs of Alzheimer's and other dementias to Medicare, Medicaid, and businesses amount to more than \$148 billion each year, making finding a cure a priority for legislators, patients, and researchers alike.

"It's really exciting when you get a result that's the exact opposite of what you expect," says Town, "because it means that you missed something, and that's an opportunity to learn even more. If results from our study are supported by studies in humans, we may be able to develop a drug that could be introduced into the bloodstream to cause peripheral immune cells to target a key aspect of Alzheimer's disease."

Dr. Town's work is funded by the National Institutes of Health and the Alzheimer's Association, and has led to numerous publications in peer-reviewed journals. Of the approximately 75 research papers Town has published, half of them have been related to his Alzheimer's disease research. With the Ben Winters Endowed Chair in Regenerative Medicine (see insert) he became, at 34, Cedars-Sinai's youngest chair holder. On his desk, next to a picture of him holding his newborn son, Town keeps a replica of the symbolic chair representing the millennium of medicine. In the corner of his tiny office, on top of various books and papers, is a minuscule white children's chair inscribed "IKEA Chair" and "Congratulations, Terrence!" in black marker. The chair is covered with signatures, a fun and heartfelt gift to the accomplished scientist from his colleagues at Cedars-Sinai. "There's actually a photograph somewhere in the building of me sitting on it," he laughs.

For Dr. Town and his team, the pharmacotherapy approach is next. They are working with a group of colleagues at Yale to devise a carrying device to bring the now-illustrious TGF- β pathway blocker molecules into the brain. According to Town, if all goes well, early developmental clinical trials in humans could begin in three to five years. "I see this as one of the most promising therapeutic avenues for the treatment of Alzheimer's disease." ●



Researchers are working to harness the potential of the immune system's defense mechanisms to seek out, destroy, and even prevent diseases of the brain.

The immune system is a complex network of cells and chemicals that forms the body's defense against foreign invaders. If the concept of immune response could be applied to the brain, some of our most dreaded diseases would become manageable, even curable.

But until recently this simple scenario had one fatal flaw: the blood-brain barrier, a roadblock of high-density cells that prevented infiltration of substances, including immune cells, from the bloodstream into the brain. This left the brain without an arsenal to fight off neurological diseases, like Alzheimer's, Parkinson's, and ALS, as well as spinal cord injury.

A SWAT team of researchers working in the Department of Neurosurgery laboratories of Keith Black, MD, is intently focused on clarifying the relationship between the immune system and the brain and studying the

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effect of immune aging on the central nervous system.

According to Dr. Black, glioblastoma multiforme (GBM, the most common and aggressive form of brain tumor) led researchers to take this approach. “Brain tumors see the immune system as a natural enemy,” says Dr. Black. “If we can find ways of enhancing the body’s immune response, we can have better weapons to fight the tumor.”

Dr. Black’s early research focused on designing ways to open the blood-brain barrier, making it possible for chemotherapy to be delivered directly to the tumor site. This led to the design of a vaccine—now in phase II clinical trials—that prompts the immune system to dispatch killer T-cells to the tumor.

“The brain’s immune response is very different from what we see in the rest of the body,” says Christopher Wheeler, PhD, a research scientist and principal investigator in the immunology program. “In the brain, it operates at a low level, so we are trying to upgrade it.”

That upgrade, or boosting of the brain’s muted immune response, involves taking immune cells from a patient, activating them with the patient’s own tumor cells, and injecting them back into the system. “We see an increased immune activation in up to 60 percent of patients we treat,” Wheeler says.

While Dr. Wheeler is studying the immune response at the cellular level, Dwain Morris-Irvin, PhD, is testing another theory to further boost the vaccine’s effectiveness.

“I am adding a synthetic compound to the core vaccine, to further energize immune cells,” he says. Patients who were given this “boosted” vaccine showed a stronger immune response and lived significantly longer.

“Immunotherapy has only been studied in conjunction with glioblastoma for a decade or so,” says Dr. Morris-Irvin.

“This is a very new, exciting field that is opening doors to designing better treatments for this disease.”

Michal Schwartz, PhD, a member of the Weizmann Institute of Science in Israel, is internationally recognized for her work in neuroimmunology and has made groundbreaking discoveries about the role the immune system plays in maintaining the brain in health and disease. Dr. Schwartz hypothesized that neurodegenerative diseases emerge just at the point when the immune system deteriorates, or when the disease becomes stronger than the opposing immune response.

“As we age and more risk factors, such as oxidants, are accumulated, our immune system grows weaker. We become more vulnerable to disease,” she says. Dr. Schwartz is now applying her theories to a wide range of neurological conditions, including Alzheimer’s disease, Parkinson’s disease, stroke, spinal cord injury, glaucoma, and even the overall decline of mental faculties associated with normal aging. “We know we can’t apply the same therapy to all disorders of the central nervous system,” she says. “But they all share a common factor: the failure of the immune system to cope with the disease; thus, the diseases share a common target.”

Can we slow down the aging process of our immune system? Can immune cells be rejuvenated? “In some ways, our efforts to increase the body’s ability to fight neurological disorders are doing just that,” says Dr. Black. “I think neuroimmunology is one of the most promising approaches I’ve seen, and we have a critical mass of top research in place to push this field forward.”

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