ADAM COOPER

Up Close With

Kevin Tracey

NEUROSURGEON, IMMUNOLOGIST

"Doing science is just addictive. It is more like a hobby than a job."

SPECIAL MOMENT

Meeting the Dalai Lama

MOTTO

Carpe Diem (Seize the Day)

FAVORITE WEEKEND ACTIVITY

Cheering for his daughters at their soccer games

HOBBIES

Woodworking, deep sea fishing

WHO WOULD PLAY HIM IN A MOVIE

Harrison Ford

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For Janice: Legacy of a Short Life

BY EMILY CARLSON

After 4 years of medical school and 2 years of training to be a brain surgeon, Kevin Tracey had learned to control the emotions he felt for his patients. But everything changed on May 3, 1985, when he met Janice.

As part of his training, Tracey was working in the emergency room at Cornell University's hospital in New York City. At 6:45 p.m., paramedics brought in an 11-month-old female with severe burns. Tracey examined her and noted: burns on 75 percent of her body, no broken bones, no other injuries.

As he focused on his patient's needs, Tracey held back tears. Janice, who arrived wrapped in a teddy bear blanket, now writhed and sobbed on a metal gurney. Her once-soft skin was seared and peeling from her arms, legs and back. She had a 25 percent chance of surviving.

Just an hour before, Janice had been giggling on the kitchen floor while her grandma cooked spaghetti. When the grandma turned to drain a 10-quart pot of boiling noodles, she tripped and spilled the 212-degree water all over the baby. Sweet chuckles turned to inconsolable screams.

For the next 3 weeks, Tracey and others watched Janice ride a rollercoaster of recoveries and setbacks.

First, she went into a 5-hour surgery, where Tracey and his colleagues removed scalded skin and replaced it with thin layers shaved from Janice's bottom—an area that had been protected by her diaper. Everyone—her family and her medical team—sighed with relief once Janice opened her eyes and smiled.

The next night, though, her blood pressure dropped dangerously low, starving her brain, kidneys, lungs and other vital systems of much-needed oxygen. Her body was in septic shock. Tracey immediately pumped fluids and drugs into her veins to raise her blood pressure and prevent permanent tissue damage.

Despite these measures, Janice drifted into a coma. The next day, her organs began working again and she awoke.

But then she spiked a fever and her body swelled. Her kidneys—and soon her liver and other organs—stopped working. Janice was experiencing wide-spread inflammation, a life-threatening condition called sepsis. As before,

Her immune system had begun to destroy the

Tracey's infusion brought her back to life.

On May 28, Tracey celebrated with her family as Janice turned 1 year old. Instead of machines and monitors, balloons and streamers now filled her room.

But the very next day, Janice's heart stopped. This time, no medical feat could bring her back.

A New Path

Stunned by her sudden, unexpected death, Tracey set out to understand what caused it and to prevent the same thing from happening to anyone else.

During the next 2 years, he put his neurosurgery career on hold and focused on medical research.

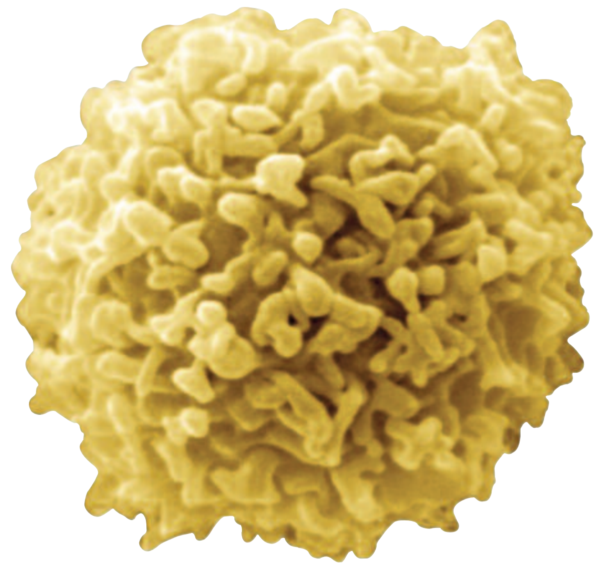
"Most doctors have a patient who affects their lives, who they really wish they could have done something more for," says Tracey. "Janice is my patient, and she has a lot to do with the path I've been on ever since."

Tracey was particularly curious to figure out why Janice's blood pressure had dropped so low. He knew her condition stemmed from septic shock, when the body's immune system reacts violently to a bacterial infection. But he had run all sorts of blood tests to locate an infection and had never found one.

If there was no infection, then what caused her immune system to rage out of control? The answer could overturn centuries of thinking about what makes us sick (see "Cytokine Theory of Disease," page 14).

Defense, Defense, Defense

The immune system is the body's natural defense against viruses, bacteria and other invaders. Its army is made up of more than 15 different types of white blood cells that produce molecules to defend and protect our bodies.



White blood cells, part of the immune system, protect us from viruses, bacteria and other invaders.

IMAGE COURTESY JIM EHRMAN, DIGITAL MICROSCOPY FACILITY, MOUNT ALLISON UNIVERSITY

Some white blood cells produce proteins called antibodies that bind to particular invaders and disable their actions. Others make proteins called cytokines that, when released into an infected area, help heal wounds and repair damaged tissue.

You can tell when your immune system is working because you get a fever, swollen lymph nodes in your neck, redness around a wound or even a rash or hives. These are the hallmarks of inflammation, an immune response designed to kill foreign invaders.

But for Janice, it had a different effect. Her immune system had begun to destroy the very thing it was supposed to protect. Tracey set out to discover why and how.

Cytokine Cures

Tracey's mentor and others had just identified a type of cytokine abbreviated TNF. Their research in mice suggested that TNF might play a role in infection.

Wondering whether TNF had been involved in Janice's case, Tracey injected rats with the cytokine. Almost immediately, their blood pressure plummeted and they went into septic shock.

Like Janice, the rats had a high white blood cell count, suggesting infection. But again, there was no bacterial infection—just an excess of TNF.

These experiments convinced Tracey that too much TNF can cause septic shock in rats. He further reasoned that, since rats and people are biologically similar, TNF probably does the same thing in humans.

Committed to finding a better treatment for patients, Tracey and his team created an antibody that could latch onto and immobilize TNF. It worked in laboratory dishes, but could it soak up excess TNF in living organisms? Could it stop septic shock, preventing harm to healthy organs and tissues?

very thing it was supposed to protect.

To find out, the scientists tested the antibody in baboons whose bloodstreams were filled with live bacteria, a condition known to cause septic shock.

Bingo! The antibody protected the animals.

While the anti-TNF antibody was never developed into a drug, other scientists built on Tracey's work and soon developed anti-TNF medicines that are now used to treat inflammation-triggered arthritis in millions of people.

Ulf Andersson, a doctor in Sweden, says he had been waiting decades for a medicine like this. He treats kids with inflammatory conditions like juvenile arthritis. When they come to him, many of his patients ache from inflamed joints in their arms and legs, making it difficult for them to move and even grow. The drug can dramatically improve the quality of their lives, Andersson reports.

"I have children who have been in wheelchairs for years who now play soccer again."

Compassion Cures

Andersson describes Tracey not only as a scientific collaborator but also as a close friend.

"I admire his human character as much as his genius," Andersson says.

After Andersson's wife died, Tracey flew from New York to Sweden to cheer up his friend. In the dead of winter, they put on special long skates and glided across parts of the Baltic Sea. Tracey's comfort and support, says Andersson, brought him back to life.

Andersson returns the favor twice a year, spending a week with Tracey, his wife and their four daughters.

"It is really amazing how he finds the time to perform first-class science and manage to be the best father and husband I have ever seen," says Andersson, who admits to copying some of his friend's family skills with his own children.

Tracey attends each of his daughters' soccer games and says he would attend every single practice if he could. He wants them to have fun, follow their passions and gain confidence in all that they do.

"Kevin is at his peak performance when he runs along the sidelines providing advice about how to play," says Andersson. "As an American, his understanding of soccer equals his lack of skill on the skates," he jokes.

When the weather is warm, Tracey packs up his family and heads into Long Island Sound to fish. Being a scientist, he studies the water and weather to find the best spot to drop the line. The family throws back most of what they catch.

"We all like being on the water," Tracey says. "A couple of hours feel like 2 days off."

The Octopus and the O.R.

Tracey decided on a career path when he was just 5 years old, right after his mother died. Sitting on his grandpa's lap, he asked what had

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FIND MORE @

Play the Immune System Defender game (very basic) at http://nobelprize.org/educational/medicine/immunity or Immune Attack (more advanced and requires download) at http://www.immuneattack.org

Scientists who determined the 3-D structure of a flu protein suggest a way to make better anti-flu medicines.

A New View of the Flu

If you've ever gotten the flu, you know that we don't have many drugs to treat it. New information from scientists studying one anti-flu medicine, amantadine, may pave the way for designing more such drugs.

Biophysicists Mei Hong at Iowa State University and William DeGrado at the University of Pennsylvania discovered how amantadine interacts with a flu protein called M2. This protein launches infection by creating a channel between the flu virus and a healthy cell.

When the researchers determined the detailed, 3-D structure of amantadine bound to M2, they revealed that the drug plugs this channel, preventing infection. They also noticed that amantadine fits loosely inside M2, possibly leaving room for altered versions of the protein to wiggle free and go on to infect a cell. If virus particles containing this version of M2 multiplied, they could lead to a drug-resistant strain.

Already, many strains of the flu resist treatment by amantadine. The biophysicists think that designing drugs that fit into M2 more tightly than amantadine does could provide an effective treatment for the flu that is more difficult for the virus to resist. —*Kirstie Saltsman*

Cytokine Theory of Disease

When Kevin Tracey showed that our own immune systems produce molecules that can harm and even kill us (see main story), he called it the "cytokine theory of disease." This added a new chapter to the 2,000-year story about what makes us sick.

Prints depicting two of the four humors (choleric and sanguine) by Virgil Solis (1514–1562).

Dating back to the ancient Greeks, people and doctors alike believed that all human diseases, ailments and moods stemmed from an imbalance of the "four humors": blood, yellow bile, black bile and phlegm. Too much phlegm was thought to make a person tired and apathetic, while too much black bile caused delusions and depression.

This idea persisted in Western medicine until the 19th century. After showing that microscopic organisms can spoil food, French chemist Louis Pasteur hypothesized that the same organisms could cause diseases in animals and people. Building on this work, British surgeon Joseph Lister showed that sterilizing surgical tools reduced the number of postoperative infections. Finally, in 1890, the German doctor Robert Koch proved the "germ theory of disease."

Up until the 1980s, the majority of researchers focused on further demonstrating Pasteur's germ theory that viruses and bacteria make people sick and that our immune systems work to prevent this. Most weren't thinking about how the immune system itself could cause severe diseases. But as Tracey went on to show, the overproduction of cytokines can cause disabling and even life-threatening illnesses like arthritis and septic shock.

Tracey notes that his cytokine theory of disease actually echoes a key idea of the ancient Greeks' humoral theory of disease: Human illnesses aren't always caused by outside contagions—sometimes they stem from imbalances within.—*E.C.*

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happened to her and why. His grandpa said she had a tumor that, like an octopus, had spread its tentacles throughout her brain, making it impossible to remove. Right then, Tracey said he wanted to be a scientist so other kids didn't have to suffer like him.

He also liked caring for people, which steered him toward medicine.

Eventually, he decided to become a neurosurgeon—a specialty that allowed him to split his time between the operating room and the research lab. This dual career, he says, made him both a better doctor and a better scientist.

"Being a doctor is gratifying in part because of the experience that comes from helping one person at a time," he says. "But I was always excited about the possibility of discovering something that could help many, many people."

Also, he says, "Doing science is just addictive. It is more like a hobby than a job."

"For every 100 questions, there are another 100 questions. The churning of these questions and the development of new ideas are what drive scientific progress."

Surprise in the Lab

In 2000, Tracey left his medical practice to devote all his energy to the lab. He turned his attention again to creating an anti-TNF drug.

He and his team developed a chemical called CNI-1493. This compound, which could switch off TNF production, had the potential to treat cytokine-related disorders from sepsis and arthritis to stroke and digestive diseases.

Tracey knew the substance targeted immune cells. What surprised him was that it had an even more powerful effect on brain cells.

For every 100 questions, there are another 100 questions.

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For Tracey and coworkers, lively discussions often lead to new questions to explore and answer.

That's weird, Tracey thought. Why would something designed to target the immune system have an effect in the nervous system?

He discovered that CNI-1493 tells brain cells to activate a particular nerve, called the vagus nerve. Once activated, the nerve turns down TNF production.

The Wanderer

We know that the nervous system controls many important functions—from moving muscles to forming thoughts. But until quite recently, scientists believed that the immune system functioned independently.

Now it's clear that the brain and other parts of the nervous system—probably a whole lot of nerves, Tracey suspects—help direct our immune responses.

Tracey focused on the vagus nerve. This nerve, which means "wandering" in Latin, regulates our heart rate, digestion and other essential functions.

It meanders from the brain stem, across the neck and chest, down into the abdomen and ends up in our internal organs, including the spleen. Like the appendix, the spleen is an organ you probably think little about. But it's actually a major player in the immune system.

"Most of our circulating [white blood] cells pass through the spleen every 5 minutes," says Tracey.

The brain communicates with these white blood cells via the vagus. Electrical signals from the brain zip down the nerve and trigger its endings to release a molecule called acetylcholine into the spleen. When acetylcholine binds to special receptors on white blood cells, the cells stop making TNF. Less TNF means less inflammation.

Sketching Out an Idea

Since TNF causes septic shock, Tracey wondered how the brain limits production of the cytokine. To work out the answer, he turned to a trick he often uses to capture his thoughts: sketching.

When he first examined Janice, he diagrammed her burns and their severity. When he planned to build his daughters a two-story playhouse, he drew a blueprint on the back of a grocery bag. When he talked to middle school students about being a brain surgeon, he went to the blackboard and drew a drill with a spring to help the kids figure out how to bore through the skull without nicking the brain.

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KEVIN TRACEY

Tracey designed and built this two-story playhouse for his daughters.

FIND MORE

Watch a video of Tracey talking about his research at http://publications.nigms.nih.gov/multimedia/captions/tracey-captions.html

Her short life had a big impact.

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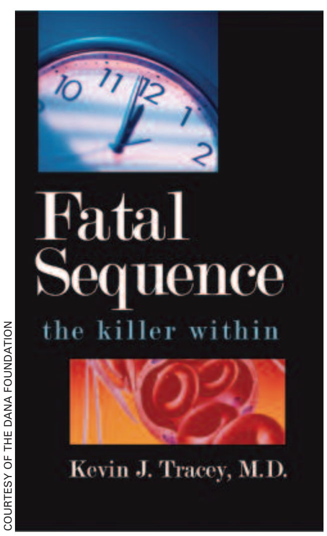
Now using a whiteboard in his lab, Tracey sketched the brain, the spleen and the vagus nerve running between them.

The next day, he set up an experiment to see if, by stimulating the vagus nerve, he could dampen TNF production. He used an electrical device to activate the vagus nerve of rats. Within seconds, the animals produced less TNF.

Since then, he has shown that in animals, stimulating the vagus nerve can block arthritis, sepsis, shock, heart failure and inflammation of the colon and pancreas.

"The groundwork is being laid to try some of these approaches in humans, perhaps within the next year," he says.



COURTESY OF THE DANA FOUNDATION

Tracey's book describes Janice's life and what he and others have learned about septic shock.

Legacy of Life

When Janice died, Tracey didn't know exactly what happened or why.

"I had no good explanation for what the molecules in her body were doing," he says. "I know a tremendous amount more now."

He suspects that the baby's injury impaired her nervous system, which not only led to an overproduction of TNF but also to her heart failure. He also thinks that too much HMGB1—another type of cytokine discovered in his lab—likely triggered her sepsis.

More than 25 years later, Janice's story still influences Tracey every day.

"I tell everyone who will listen never to take anything out of the microwave with a baby in their arms," he says. "Never put hot food on a tablecloth that a child could pull down."

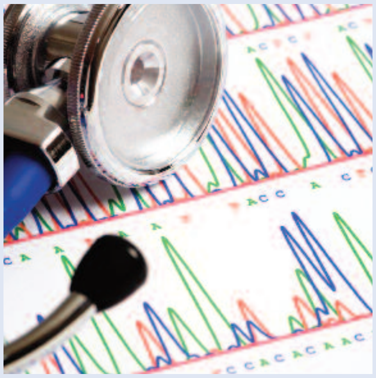
He created an invisible triangle that fills the space between his kitchen sink, stove and refrigerator. From an early age, his girls—now 7 to 15 years old—knew not to step inside it when unsupervised.

He even wrote a book called *Fatal Sequence: The Killer Within*. The title refers to septic shock caused by the immune system. The book describes Janice's life, how she changed Tracey's life and what he and others have learned—and applied to help patients—because of her.

Although she didn't live to see it, her short life had a big impact, says Tracey. "The people who receive drugs based either directly or indirectly on knowledge that came [because of] her—they're her legacy."

FIND MORE

Read about a veterinarian who studies sepsis at http://publications.nigms.nih.gov/findings/mar07/dogging.html



A person's complete genome sequence can yield clinically useful information.

Rx: Genome Sequence

You've probably heard that scientists have sequenced the entire human genome. But what does this mean for you? If your doctors knew the identity and order of all 3 billion letters in your genome, what could it tell them?

That's what researchers wanted to know. One of them, bioengineer Stephen Quake at Stanford University, volunteered his genome sequence for the study.

He and his colleagues used computer searches to find disease-related gene variants. They then analyzed his medical and family history. They even factored in statistical disease risks.

After all the number crunching, they found he had a higher-than-average risk for developing a handful of conditions, including heart attacks, thyroid disease, iron overload and certain cancers. Some of these run in his family and some don't. Also, he might respond poorly to certain heart medications—something good to know since he's at increased risk for heart problems.

With this study, the researchers have shown that a person's complete genome sequence can yield clinically useful information. But many challenges remain, including understanding the influence of a person's environment, which can change over time.
—*Alisa Zapp Machalek*