Stanford MEDICINE | News Center

Study finds first possible drug treatment for lymphedema

Collaboration between two Stanford labs has resulted in the discovery of a molecular cause for lymphedema and the first possible drug treatment for it.

MAY 10
2017

Tracey Campbell has lived for seven years with lymphedema, a chronic condition that causes unsightly swelling in her left leg.

The disease, which stems from a damaged lymphatic system, can lead to infections, disfigurement, debilitating pain and disability. There is no cure. The only available treatment is to wear compression garments or use massage to suppress the swelling, which can occur throughout the body in some cases.

Tracey Campbell suffers from lymphedema and is participating in a clinical trial of a drug to determine whether it can treat the painful condition.
Mark Williams

Campbell — who had two quarts of excess water in her left leg by the time she was diagnosed — has for years worn restrictive garments 24 hours a day and has spent an hour each night massaging the lymph fluid out of her leg.

Lymphedema is uncomfortable, exhausting and dangerous if left uncontrolled. As many as 10 million Americans and hundreds of millions of people worldwide suffer from the condition, many from the after-effects of cancer therapy treatments.

“There’s this extra layer of emotional burden,” said Campbell, who added that she has to be constantly vigilant to protect against infection. “All you want to be is normal.”

Now there’s new hope for a possible pharmaceutical treatment for patients like Campbell. A study led by scientists at the Stanford University School of Medicine has uncovered for the first time the molecular mechanism responsible for triggering lymphedema, as well as a drug with the potential for inhibiting that process.

The study was published May 10 in *Science Translational Medicine*.

“We figured out that the biology behind what has been historically deemed the irreversible process of lymphedema is, in fact, reversible if you can turn the molecular machinery around,” said Stanley Rockson, MD, professor of cardiovascular medicine and the Allan and Tina Neill Professor of Lymphatic Research and Medicine at Stanford. Rockson shares senior authorship of the study with Mark Nicolls, MD, professor of pulmonary and critical care medicine. Stanford research scientists Wen “Amy” Tian, PhD, and Xinguo Jiang, MD, PhD, share lead authorship of the study and are also affiliated with the Veterans Affairs Palo Alto Health Care System.

‘Fundamental new discovery’

“This is a fundamental new discovery,” said Nicolls, who is also a researcher at the VA Palo Alto.

Stanley Rockson

The researchers found that the buildup of lymph fluid is actually an inflammatory response within the tissue of the skin, not merely a “plumbing” problem within the lymphatic system, as previously thought.

Working in the lab, scientists discovered that a naturally occurring inflammatory substance known as leukotriene B4, or LTB4, is elevated in both animal models of lymphedema and in humans with the disease, and that at elevated levels it causes tissue inflammation and impaired lymphatic function.

Further research in mice showed that by using pharmacological agents to target LTB4, scientists were able to induce lymphatic repair and reversal of the disease processes.

“There is currently no drug treatment for lymphedema,” Tian said. Based on results of the study, the drug bestatin, which is not approved for use in the United States but which has been used for decades in Japan to treat cancer, was found to work well as an LTB4 inhibitor, with no side effects, she said.

Based on the research, bestatin (also known as ubenimex), is being tested in a clinical trial that started in May 2016 — known as ULTRA — as a treatment for secondary lymphedema, which occurs because of damage to the lymphatic system from surgery, radiation therapy, trauma or infection. Primary lymphedema, on the other hand, is hereditary. The results of the research pertain to both types.

Rockson is principal investigator for this multisite phase-2 clinical trial.

“The cool thing about this story — which you almost never see — is that a clinical trial testing the therapy has already started before the basic research was even published,” Nicolls said. “This is the first pharmaceutical company-sponsored trial for a medical treatment of lymphedema, a condition that affects millions.”

Nicolls and Tian are co-founders of Eiccose LLC. Eiccose is now part of Eiger BioPharmaceuticals, which gets the drug from Nippon Kayaku in Japan. Eiger is sponsoring the clinical trial. Nicolls and Rockson are both scientific advisers to the company.

Two labs, two diseases

The study, which got underway about four years ago, began somewhat uniquely as a collaboration between two labs that were studying two completely different diseases. At the time, the Nicolls lab, where Tian works, was studying pulmonary hypertension. The Rockson lab was conducting lymphedema research.

The two teams met through SPARK, a Stanford program designed to help scientists translate biomedical research into treatments for patients.

“I was in a privileged position of seeing two faculty conducting important research and recognizing the possible link in causality,” said Kevin Grimes, MD, associate professor of chemical and systems biology and co-founder of SPARK. “It occurred to me that both diseases affected vascular tissues and had strong inflammatory components.”

Mark Nicolls

“He blind-dated us,” Nicolls said. “When Amy Tian and I looked at the data from Stan’s research, Amy said, ‘It looks like it could be the same molecular process.’”

“It was an arranged marriage between us and Stan which worked out great,” Tian said.

At the time, Rockson had begun to suspect that lymphedema was an inflammatory disease. This led to his team’s discovery that the anti-inflammatory drug ketoprofen successfully helped to relieve lymphedema symptoms, although it wasn’t a perfect drug; side effects were a concern, and it remained unclear how the drug worked at the molecular level.

Meanwhile, the Nicolls lab had discovered that LTB4 was part of the cycle of inflammation and injury that keeps pulmonary hypertension progressing. When researchers blocked LTB4 in rats with the disease, their symptoms lessened and blood vessels became less clogged, lowering blood pressure in the lungs.

“When we became aware of Mark’s work, we began to realize that we were both possibly dealing with the activation of steps downstream of the 5-LO [5-lipoxygenase] *pathway,” Rockson said*. “This became intriguing and formed the basis of our relationship.”

Joining forces

The two teams joined forces to figure out the mechanism that triggered lymphedema, hopefully revealing a target for drug treatment in humans. After determining that ketoprofen was primarily working on the 5-LO pathway, the researchers began blocking the various endpoint pathways after 5-LO activation in mouse models of lymphedema, Rockson said.

“It turned out that, in fact, we were both dealing with the same branch, which is LTB4,” Rockson said.

> *“When all of the sudden one of your limbs begins to swell, you want to understand what the heck is going on.”*

“So now it became clear we really were dealing with a very similar biological process in two different diseases,” he said. “Because of Mark’s work in pulmonary hypertension, we knew that we had an ideal form of therapy that we could try in lymphedema as well.”

The Nicolls lab had used the drug bestatin, which blocks the enzyme that generates LTB4, to reverse pulmonary hypertension disease processes. When researchers tested bestatin in the mouse lymphedema model, it worked to reverse symptoms of that disease.

“I’m still in awe,” Rockson said. “There are few situations where you take a problem at the bedside, and go into the lab, and then take discoveries back to the bedside. It’s amazingly gratifying.”

Campbell, who is now participating in the double-blinded, placebo-controlled bestatin trial at Stanford, remains hopeful.

“When all of the sudden one of your limbs begins to swell, you want to understand what the heck is going on,” she said. “It’s a tough condition that few people seem to care about, even though millions and millions suffer with it. We’re hoping for something that gives some relief.”

Other Stanford authors are research associate Jeanna Kim; former medical students Adrian Begaye, MD, and Abdullah Feroze, MD; Roham Zamanian, MD, associate professor of medicine and director of the Adult Pulmonary Hypertension Service; Gundeep Dhillon, MD, associate professor of medicine and medical director of the Stanford Lung Transplant Program; and research assistants Eric Shuffle and Allen Tu. Shuffle and Tu are affiliated with both Stanford and the VA Palo Alto.

Researchers at the Georgia Institute of Technology, Virginia Commonwealth University, the University of Michigan Health Systems and the University of Illinois at Chicago are also co-authors.

Eiger BioPharmaceuticals has licensed intellectual property developed by Tian, Rockson, Jiang, Kim and Nicolls involving the targeting of LTB4 for the treatment of lymphedema.

Stanford’s Department of Medicine supported the work.

By

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Stanford MEDICINE | News Center

In northern humans, evolution favored shorter bones — but with a painful trade-off

Humans in Europe and Asia evolved to have shorter bones and an increased risk of osteoarthritis, a trade-off that may have helped them in colder climates, Stanford researchers say.

JUL 3
2017

A single genetic change linked both to a reduction in human height and an increase in osteoarthritis risk might seem like it would quickly be kicked to the evolutionary curb. After all, how could it be an advantage to be both shorter and less mobile in the cutthroat competition for scarce resources and fickle mates? Darwin's finches would be appalled.

David Kingsley

Now, researchers at the Stanford University School of Medicine and at Harvard University have shown that, despite its association with the painful joint disease, this genetic variant was repeatedly favored as humans migrated out of Africa and into colder northern climates. At least half of Europeans and Asians harbor the gene variant, which is relatively rare in African populations.

"Because it's been positively selected, this gene variant is present in billions of people," said David Kingsley, PhD, professor of developmental biology at Stanford. "So even though it only increases each person's risk by less than twofold, it's likely responsible for millions of cases of arthritis around the globe. This study highlights the intersection between evolution and medicine in really interesting ways, and could help researchers learn more about the molecular causes of arthritis."

A more compact body structure due to shorter bones could have helped our ancestors better withstand frostbite and reduce the risk of bone fracture from falling, the researchers speculate. These advantages in dealing with chilly temperatures and icy surfaces may have outweighed the threat of osteoarthritis, which usually occurs after prime reproductive age.

Cold may have selected for gene variant

"The gene we are studying shows strong signatures of positive selection in many human populations," said Kingsley, who is also a Howard Hughes Medical Institute investigator and a member of Stanford Bio-X. "It's possible that climbing around in cold environments was enough of a risk factor to select for a protective variant even if it brought along an increase likelihood of an age-related disease like arthritis, which typically doesn't develop until late in life."

A paper describing the research was published online July 3 in *Nature Genetics*. Kingsley is the senior author. Harvard graduate student Jiaxue Cao and former Stanford postdoctoral scholars Terence Capellini, PhD, and Hao Chen, PhD, share lead authorship. Capellini is now an associate professor of human evolutionary biology at Harvard, and Chen is an associate clinical scientist at Genentech Inc.

> *"Many people think of osteoarthritis as a kind of wear-and-tear disease, but there's clearly a genetic component at work here as well."*

The researchers were studying a gene called GDF5 that Kingsley's laboratory first linked to skeletal growth in the early 1990s. GDF5 is involved in bone growth and joint formation, and mutations in the coding portion of the gene have been shown to cause malformations in leg-bone structure in mice. In humans, GDF5 mutations are associated with shorter stature and joint problems; in particular, two nucleotide changes immediately upstream of the gene have been strongly associated with a 1.2- to 1.8-fold increase in the risk of osteoarthritis.

In the new study, the researchers were interested in learning more about how the DNA sequences surrounding GDF5 might affect the gene's expression. Often, these noncoding sequences contain key regulatory regions known as promoters and enhancers. Capellini, Chen and Cao were able to identify a previously unknown enhancer region they termed GROW1, which is several thousand nucleotides downstream of GDF5.

When the researchers analyzed the sequence of GROW1 in the 1,000 Genomes Project database, which collects and compares sequences from many human populations around the globe, they identified a single nucleotide change that is highly prevalent in Europeans and Asians but that rarely occurs in Africans. When they introduced this nucleotide change into laboratory mice, they found that it decreased the activity of GDF5 in the growth plates of the long bones of fetal mice.

A common thread

Further research showed that this nucleotide change has been repeatedly favored during human evolution. Modern humans migrated from Africa between 50,000 and 100,000 years ago. But they weren't the first to leave the continent. Neanderthals and Denisovans moved north into Europe and Asia about 600,000 years ago. Interestingly, the researchers found that the same GROW1 variant was found in the DNA of both ancient and modern humans in Europe and Asia.

However, there's a dark side to this stocky, hardy body type: The GDF5 variant that reduces bone length comes hand-in-hand with the two upstream nucleotide changes known to confer an increased risk for osteoarthritis.

"It's clear that the genetic machinery around a gene can have a dramatic impact on how it works," said Capellini. "The variant that decreases height is lowering the activity of GDF5 in the growth plates of the bone. Interestingly, the region that harbors this variant is closely linked to other mutations that affect GDF5 activity in the joints, increasing the risk of osteoarthritis in the knee and hip."

"The potential medical impact of the finding is very interesting because so many people are affected," said Kingsley. "This is an incredibly prevalent, and ancient, variant. Many people think of osteoarthritis as a kind of wear-and-tear disease, but there's clearly a genetic component at work here as well. Now we've shown that positive evolutionary selection has given rise to one of the most common height variants and arthritis risk factors known in human populations."

A researcher from the University of Waterloo in Ontario, Canada, also contributed to the study.

The research was supported by the National Sciences and Engineering Research Council of Canada, the Arthritis Foundation, the National Institutes of Health (grant AR42236), the Howard Hughes Medical Institute, the Milton Fund of Harvard, the China Scholarship Council and the Jason S. Bailey Fund of Harvard.

Stanford's Department of Developmental Biology also supported the work.

By

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Small drop in measles vaccinations would have outsized effect

A 5 percent drop in childhood measles vaccination levels would cause annual measles cases to triple, according to researchers at Stanford and Baylor.

JUL 24
2017

Small reductions in childhood measles vaccinations in the United States would produce disproportionately large increases in the number of measles cases and in related public health costs, according to a new study by researchers at the Stanford University School of Medicine and Baylor College of Medicine.

Researchers constructed a mathematical model that indicates a 5 percent drop in vaccination rates among U.S. children ages 2 to 11 would triple the number of measles cases in the age group.
Shutterstock

A 5 percent drop in the number of children ages 2 to 11 inoculated against the measles, mumps and rubella would triple the number of annual measles cases in this age group, the study found. The MMR vaccine is an inoculation against the three diseases.

The additional measles cases would increase annual public health expenditures by at least $2.1 million, or $20,000 per case of measles.

The study was published July 24 in *JAMA Pediatrics.*

“We focused on measles as a case example of the effects of declining vaccine coverage because it is highly infectious,” said Nathan Lo, the study’s lead author and an MD-PhD student at Stanford. “It’s likely to be the first infectious disease causing outbreaks if vaccination declines.”

Lo said he hopes the findings will be considered by state legislators making decisions about vaccination policy.

“I think our study is a wake-up call for what we can expect in the coming months and years as vaccine coverage rates continue to decline in the 18 states that now allow non-medical or philosophical belief exemptions,” said senior author Peter Hotez, MD, PhD, dean of the National School of Tropical Medicine at Baylor.

Across the country, several regions are near the threshold of 90 to 95 percent vaccine coverage needed to prevent measles outbreaks. The new study predicts a sharp rise in measles cases if vaccination further declines.

‘A tenuous handle on measles’

“We have a tenuous handle on measles disease now. It’s all dependent on very small increments of vaccination,” said Yvonne Maldonado, MD, professor of pediatric infectious diseases at Stanford. Maldonado, an expert on vaccination, was not involved in the study. “We really need to focus on making sure that all children are vaccinated to eliminate this disease from the face of the Earth,” she added.

Nathan Lo

Although vaccination has been successful at controlling measles in the United States, a few dozen to a few hundred cases occur here every year, usually when U.S. citizens travel abroad and unknowingly bring the virus home. Infected people can spread the virus by sneezing and coughing for four days before they show symptoms. Measles lingers in the air and remains infectious for up to two hours, an unusually long time for an airborne virus, and a high percentage of unvaccinated people exposed to the infected air become sick themselves.

All 50 states require the MMR vaccine and other childhood vaccinations prior to enrollment in elementary school or day care. In all states, children can be exempted from vaccination for medical reasons. All but three states also allow parents to decline vaccination for religious reasons, and 18 states have exemptions for personal beliefs. (Notably, California eliminated its religious and personal-belief exemptions in 2015 following a large measles outbreak that originated at Disneyland.)

Lo analyzed MMR vaccination data from the U.S. Centers for Disease Control and Prevention. He constructed a mathematical model from the data to predict the effects of declining vaccination rates in children ages 2 to 11, simulating about 10,000 scenarios that could occur as measles is introduced by returning travelers into different locations around the country at a rate similar to that of recent years. They also estimated the cost of declining vaccination rates if children younger than 2 were included in the models — a scenario that increased the predicted public health costs by another $400,000 per year beyond the $2.1 million cost for older children. (Infants are not eligible for their first dose of the MMR vaccine until they’re 1, making them especially vulnerable to measles.)

The public-health costs estimated in the new paper from declining vaccination rates are conservative, Lo said. The costs are for measles alone, and do not include other infectious diseases that may rise with lower vaccination coverage, such as mumps and pertussis. The costs include some health care expenditures and outbreak-containment tasks, such as tracking and vaccinating those whom infected people contacted, but not the costs of hospitalization or days of work missed by parents of ill children. Children ages 2 to 11 now account for about 30 percent of U.S. measles cases, meaning that the impact of declining vaccination rates would be significantly larger than the figures predicted in this study if all age groups were considered.

Geographic hotspots

Unvaccinated people tend to cluster in certain geographic areas, and introducing measles in these areas would cause significant outbreaks, the researchers noted. Such outbreaks took place in 2014, when 383 measles cases occurred in unvaccinated Amish communities in Ohio, and this spring among an under-vaccinated community of Somali immigrants in Minnesota.

“Even in states with a high level of vaccine coverage, there can be very large differences within the state, including poorly vaccinated pockets of communities that may be masked,” Lo said. If travelers bring home measles to well-vaccinated communities, the number of cases is much lower than if they come home to a poorly vaccinated region. The study capped the outbreak size in the researchers’ calculations at 100 cases, although individual outbreaks can become larger, especially with declining vaccine coverage.

The study was also conservative in the level of infectiousness it built into its calculations, Maldonado noted. “They used the lowest possible level of infectiousness that is reasonable for measles and still found substantial public-health and medical consequences to not getting vaccinated,” she said.

Lo hopes state lawmakers will consider the study’s findings as they contemplate vaccination policies, especially non-medical personal belief exemptions to childhood vaccination requirements. “Every year, an increasing number of states are debating non-medical exemptions, which are a critical driver of vaccination coverage,” he said. “This study quantifies the consequences of a rise in measles cases and state dollars that will be spent if personal belief exemptions that can reduce vaccine coverage are in place.”

Lo is supported by the Medical Scientist Training Program at the Stanford School of Medicine. Stanford’s Department of Health Research and Policy also supported the work.

By

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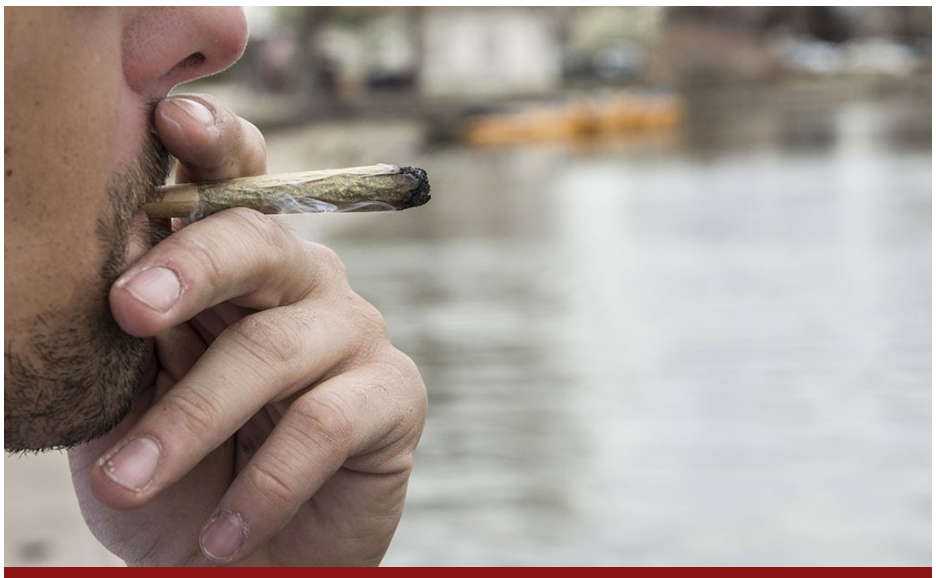
Regular marijuana use linked to more sex

The first study to examine the relationship between marijuana use and frequency of sexual intercourse at the population level in the United States shows a positive correlation between the two.

OCT 27
2017

The jury's still out on rock 'n' roll. But the link between sex and at least one drug, marijuana, has been confirmed.

A study by investigators at the Stanford University School of Medicine indicates that, despite concerns among physicians and scientists that frequent marijuana use may impair sexual desire or performance, the opposite appears more likely to be the case.



Stanford researchers analyzed data and found a positive association between frequency of marijuana use and frequency of sexual intercourse.
Mitch M/Shutterstock

The findings, published online Oct. 27 in the *Journal of Sexual Medicine*, are based on an analysis of more than 50,000 Americans ages 25-45. And they're unambiguous.

"Frequent marijuana use doesn't seem to impair sexual motivation or performance. If anything, it's associated with increased coital frequency," said the study's senior author, Michael Eisenberg, MD, assistant professor of urology. The lead author is Andrew Sun, MD, a resident in urology.

Hint of a causal connection

The study does not establish a causal connection between marijuana use and sexual activity, Eisenberg noted. But the results hint at it, he added. "The overall trend we saw applied to people of both sexes and all races, ages, education levels, income groups and religions, every health status, whether they were married or single and whether or not they had kids."

The study is the first to examine the relationship between marijuana use and frequency of sexual intercourse at the population level in the United States.

"Marijuana use is very common, but its large-scale use and association with sexual frequency hasn't been studied much in a scientific way," Eisenberg said.

Michael Eisenberg

According to the National Institute on Drug Abuse, more than 20 million adult Americans are current marijuana users. With the drug's legalization for medical or recreational use in 29 states, that number is climbing. But despite marijuana's growing status as a recreational drug, its status as a procreational drug remains ambiguous: On one hand, there are reports of erectile dysfunction in heavy users, and rigorous studies have found reduced sperm counts in men who smoke it; on the other hand, experiments conducted in animal models and humans indicate that marijuana stimulates activity in brain regions involved in sexual arousal and activity.

Looking at survey responses

To arrive at an accurate determination of marijuana's effect on intercourse frequency, Eisenberg and Sun turned to the National Survey of Family Growth, sponsored by the federal Centers for Disease Control and Prevention. The survey, which provides data pertaining to family structures, sexual practices and childbearing, reflects the overall demographic features of the U.S. population. Originally conducted at regular intervals, the survey is now carried out on an annual basis. It explicitly queries respondents on how many times they've had intercourse with a member of the opposite sex in the past four weeks, and how frequently they've smoked marijuana over the past 12 months.

> *"It doesn't say if you smoke more marijuana, you'll have more sex."*

The investigators compiled answers to those questions for all years since 2002, when the survey first began collecting data on men as well as women. They included data from respondents ages 25-45 and excluded a small percentage (fewer than 3 percent) of respondents who had failed to answer one or more relevant questions.

In all, Eisenberg and Sun obtained data on 28,176 women averaging 29.9 years of age and 22,943 men whose average age was 29.5. They assessed these individuals' self-reported patterns of marijuana use over the previous year and their self-reported frequency of heterosexual intercourse over the previous four weeks.

Some 24.5 percent of men and 14.5 percent of women in the analysis reported having used marijuana, and there was a positive association between the frequency of marijuana use and the frequency of sexual intercourse. This relationship applied to both sexes: Women denying marijuana use in the past year, for example, had sex on average 6.0 times during the previous four weeks, whereas that number was 7.1 for daily pot users. Among men, the corresponding figure was 5.6 for nonusers and 6.9 for daily users.

In other words, pot users are having about 20 percent more sex than pot abstainers, Eisenberg noted.

Positive association is universal

Moreover, Eisenberg said, the positive association between marijuana use and coital frequency was independent of demographic, health, marital or parental status.

In addition, the trend remained even after accounting for subjects' use of other drugs, such as cocaine or alcohol. This, Eisenberg said, suggests that marijuana's positive correlation with sexual activity doesn't merely reflect some general tendency of less-inhibited types, who may be more inclined to use drugs, to also be more likely to have sex. In addition, coital frequency rose steadily with increasing marijuana use, a dose-dependent relationship supporting a possible active role for marijuana in fostering sexual activity.

Nevertheless, Eisenberg cautioned, the study shouldn't be misinterpreted as having proven a causal link. "It doesn't say if you smoke more marijuana, you'll have more sex," he said.

Stanford's Department of Urology supported the work.

By

BRUCE GOLDMAN

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Neuroscientist Ben Barres, who identified crucial role of glial cells, dies at 63

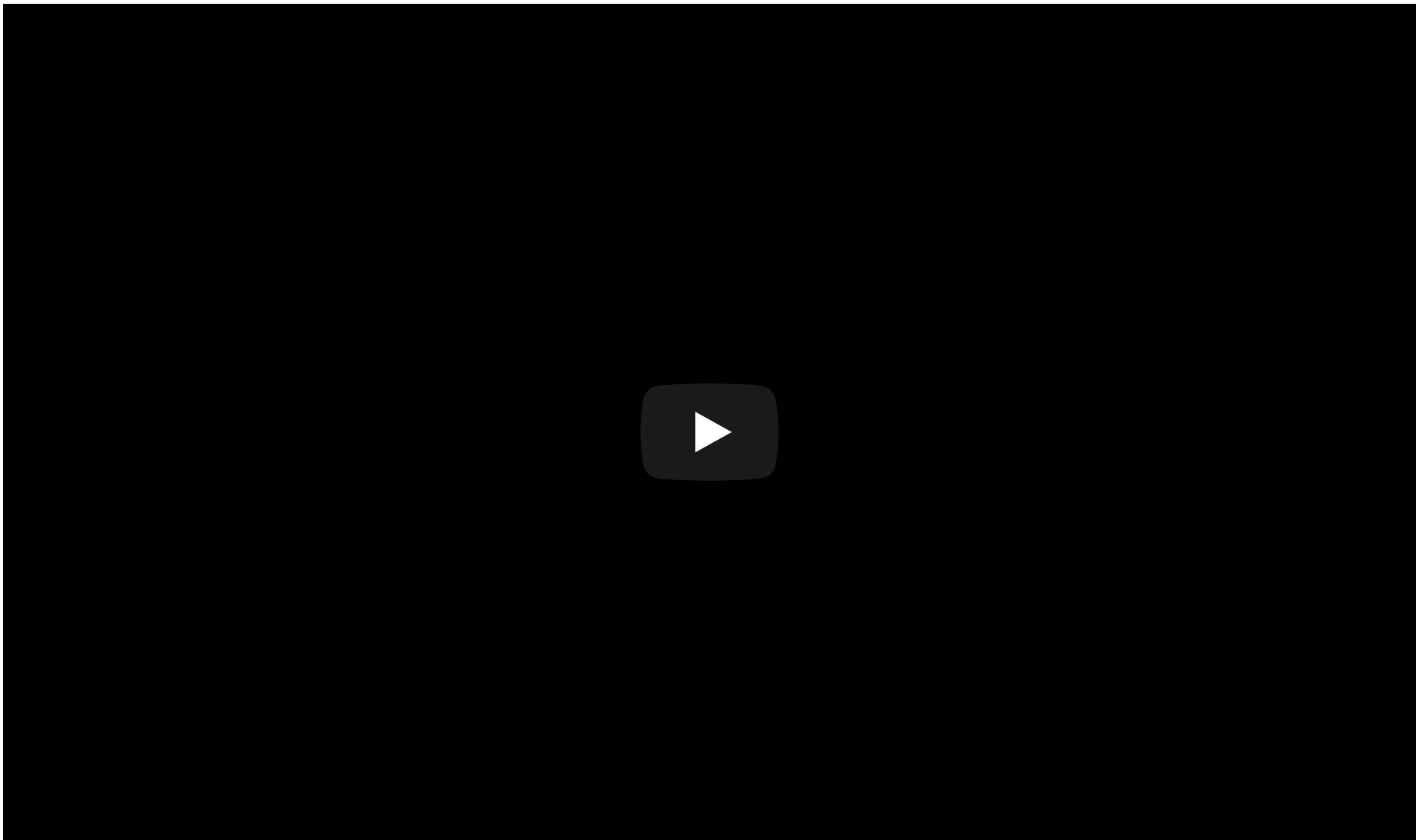
The Stanford neuroscientist's research focused on the cells in the brain that aren't nerve cells. Collectively called glia, these "other" cells play a central role in sculpting and maintaining the brain's wiring diagram.

DEC 27
2017

Acclaimed Stanford neuroscientist Ben Barres, MD, PhD, died on Dec. 27, 20 months after being diagnosed with pancreatic cancer. He was 63.

Barres' path-breaking discoveries of the crucial roles played by glial cells — the unsung majority of brain cells, which aren't nerve cells — revolutionized the field of neuroscience.

Barres was incontestably visionary yet, ironically, face-blind — he suffered from prosopagnosia, an inability to distinguish faces, and relied on voices or visual cues such as hats and hairstyles to identify even people he knew well. And there were many of them.



A professor of neurobiology, of developmental biology and of neurology, Barres was widely praised as a stellar and passionate scientist whose methodologic rigor was matched only by his energy and enthusiasm. He was devoted to his scholarly pursuits and to his trainees, advocating unrelentingly on their behalf. He especially championed the cause of women in the sciences, with whom he empathized; he was transgender.

“Ben was a remarkable person. He will be remembered as a brilliant scientist who transformed our understanding of glial cells and as a tireless advocate who promoted equity and diversity at every turn,” said Marc Tessier-Lavigne, PhD, president of Stanford University. “He was also a beloved mentor to students and trainees, a dear friend to many in our community and a champion for the fundamental dignity of us all.” (Read Tessier-Lavigne's tribute to Barres.)

Added Lloyd Minor, MD, dean of the School of Medicine, “Through courage and determination, Ben not only changed the course of neuroscience, he touched many lives. He was an inspiration, and I, like so many others, am a better person for having known him.”

Nine of every 10 brain cells

Barres’ research focused on the nine of every 10 cells in the human brain that aren’t nerve cells, or neurons. They’re called glial cells or, collectively, glia.

Ben Barres

“Ben pioneered the idea that glia play a central role in sculpting the wiring diagram of our brain and are integral for maintaining circuit function throughout our lives,” said Thomas Clandinin, PhD, professor of neurobiology, who assumed the role of departmental chair in April 2016 when Barres, who had held the position from 2008 until then, was first diagnosed with pancreatic cancer. “People had thought glia were mere passive participants in maintaining neural function. Ben’s own work and that of his trainees transformed this view entirely.”

When Barres first began studying them, glia, whose name comes from the Greek word for glue, were thought to be not much more than packing peanuts, supplying positional stability and various nutrients to the brain’s much more talented neurons.

But Barres and the numerous trainees who cycled through his lab showed otherwise.

Glial cells, they proved, are critical to sustaining the overall architecture of the brain’s constellation of synapses, through which neurons pass signals to one another. Recent evidence from Barres’ lab indicates that glia gone wrong may be to blame for many of the neurodegenerative disorders that vex humanity.

“Ben placed a big career bet on the possibility that there was gold in glia,” said neurobiology professor William Newsome, PhD, the Vincent V. C. Woo Director of the Stanford Neurosciences Institute. “And he started by solving a big problem: No one had been able to grow glial cells in isolation.”

Burning the midnight oil

Intent on determining exactly how glia influence brain function and dysfunction, Barres typically worked until midnight or later throughout his career. Early on, he generated tools that allowed each of the three distinct types of glial cells to be purified and cultured in a way that retained all of their functionality, so they could be studied in a dish with a previously unobtainable acuity. Rather than jealously guard his methods and reagents, Barres took pains to make them widely available to others just as, later on, he did with the voluminous data his lab was able to generate with them.

“He had a selfless, outward-looking focus,” Clandinin said. “I’ve gone a lot of places in the months since Ben was diagnosed, and I haven’t gone anywhere yet where someone hasn’t come up to me and asked me about how Ben was doing. Every one of them has a story about how he helped them in their career.”

In doing so, Barres seeded an entire field of scientists studying glia, said Andrew Huberman, PhD, an associate professor of neurobiology at Stanford who was Barres’ postdoctoral advisee from 2005 through 2010.

“He didn’t have these normal territorial issues all of us have,” Huberman said. “He always gave more than he took. If ever there was an example of a purpose-driven life, it’s Ben. His passion was for science. His obsession was glia. His mission was to bring equality to how people are treated and promoted in science.”

Born Sept. 13, 1954, Barres grew up in West Orange, New Jersey, one of four children in a not well-to-do family. He got his first taste of science in the West Orange Public Library, developed an affinity for microscopes and chemistry sets, and became a high school math star. Attending the Massachusetts Institute of Technology on a scholarship, he earned a bachelor’s degree in life science there in 1976 and headed to medical school at Dartmouth, where he obtained an MD in 1979.

Motivated by a mystery

During his subsequent internship and residency in clinical neurology at Cornell, Barres grew increasingly frustrated at physicians’ inability to provide cures or even to understand the causes of neuronal degeneration. He was struck by the observation, in pathologists’ specimens of degenerating brain tissue, of irregular-appearing glial cells’ ubiquitous presence near the lesions.

Bent on finding out why, Barres changed course. He returned to academia, enrolling in a graduate program in Harvard Medical School’s neuroscience program in 1983, and published several research papers by the time he received his PhD in neurobiology in 1990. Then he embarked on a postdoctoral fellowship in the lab of Martin Raff, MD, a professor of biology at University College London who was using immunological techniques to tease apart the three classes of glial cells.

Working under Raff, Barres pushed forward and unearthed new insights concerning the best-known glial class: oligodendrocytes, cells stuffed with a fatty substance called myelin. These fat-filled cells were already understood to wrap themselves around neurons’ lengthy projections, a process called myelination, providing electrical insulation and vastly increasing the transmission speed and reliability of neuronal impulses. Barres showed, among other things, that electrical activity in neurons was necessary for neurons’ myelination.

Barres would routinely work in the lab until 2 or 3 a.m., said Raff. “He slept on the floor of my small office. Every morning when I arrived and opened the door, it would whack him in the head — he eventually learned to sleep facing the opposite direction.”

Arriving at Stanford

In 1993, Barres moved from University College London to an assistant professorship in Stanford's Department of Neurobiology. He was promoted to associate professor of neurobiology and of developmental biology in 1998, and to a full professorship in 2001. In 2008, he became chair of neurobiology. From 2005 on, he was the director of the Masters of Science in Medicine Degree Program for PhD students, which he had created.

At Stanford, Barres turned his attention to a second class of glial cells known as astrocytes. These are the most common cells in the human brain, outnumbering neurons by a factor of four or so. Before Barres began focusing on them, nobody really had understood what astrocytes do for a living. With his colleagues, he discovered that they are crucial to the physical formation of synapses, as well as to those synapses' functional activation. He and his colleagues also discovered that astrocytes cooperate with microglia — a third glial-cell type that's become the object of much recent attention in Barres' lab — in pruning away excess synapses during fetal and neonatal development, in essence preserving brain circuitry that's proven itself to perform legitimate activities and clearing out the dead wood.

Beth Stevens, PhD, then a postdoctoral scholar in Barres' lab, led a 2007 study showing that the cooperation of astrocytes and microglia in synaptic pruning involves the coordinated secretion of molecules previously thought to be exclusive to the body's immune system. Stevens continues to focus on this phenomenon as an associate professor of neurology at Harvard Medical School.

"When I left Stanford for my new job," she said, "Ben told me, 'Take this work with you to your new lab, Beth. Nobody can do it better than you.' Mentors aren't always so generous about ceding areas of research initiated in their lab to trainees headed elsewhere. But Ben was a very special person. Not only was he an incredible scientist, but he also cared deeply about other people, especially his trainees. We were his kids."

Never losing sight of goal

Barres never lost sight of his original goal: to figure out the molecular and cellular causes of the brain tissue degeneration seen in Alzheimer's, Parkinson's and Huntington's diseases; multiple sclerosis; amyotrophic lateral sclerosis, or Lou Gehrig's disease; and glaucoma, an optic-nerve degenerative disease. Research in Barres' lab has strongly implicated inflamed or "reactive" astrocytes and microglia as drivers in all of these neurodegenerative disorders — most recently, in a 2017 *Nature* paper describing how certain reactive astrocytes secrete something that kills stressed or injured neurons.

In an interview about this study, Barres described these findings as "the most important discovery my lab has ever made."

"Wherever we look in degenerating cortical tissue, we find reactive astrocytes," said the study's lead author, Shane Liddelow, PhD, a postdoctoral scholar in Barres' lab. "And now we've learned that a subset of these reactive astrocytes not only fail to execute their synapse-building and -pruning tasks but also secrete a factor, or combination of them, that's toxic to damaged neurons, and that these astrocytes become malevolent only when stimulated by yet other factors secreted by microglia that are themselves in an inflammatory state."

Postdoctoral scholar Mariko Bennett, PhD, who will receive a medical degree in June, identified those microglia-derived factors, and graduate student Kevin Guttenplan is working on identifying and characterizing the astrocyte-generated toxin. In 2011, Barres co-founded a biotechnology company, Annexon Biosciences, to translate these findings into drugs that could someday succeed in retarding or preventing the progression of neurodegenerative disorders.

'Just so I could work with him'

Liddelow hadn't initially intended to study glia. In 2010, he was a graduate student in Australia, focused on another research area. "I met Ben at a meeting, and we hit it off. I switched fields in a heartbeat, just so I could work with him."

Liddelow sat next to Barres during the meeting. “He was happily handing me one after another peanut butter and jelly sandwich,” Liddelow recalled. “I didn’t like peanut butter. But I think I ate three sandwiches. I just wanted him to like me.”

Barres was an outspoken advocate for gender equity in the sciences, not infrequently digressing for a few minutes during his scientific talks to point out the differences he’d personally experienced in how other scientists treated him when they perceived him as a woman versus as a man.

Barres spent his last days and final hours making sure that the letters of recommendation he had written for others were ready. “In what time remains to me that will be my highest priority,” he assured trainees in a letter he sent to them in early November.

Over the course of his career, Barres’ published 167 peer-reviewed papers, organized and chaired numerous meetings, won many awards and served on the editorial boards of *Science*, *Neuron*, the *Journal of Neuroscience*, the *Journal of Cell Biology*, *Glia*, *Current Biology* and more. He was elected to membership in the American Association for the Advancement of Science, the American Academy of Arts and Sciences, the National Academy of Sciences and the National Academy of Medicine.

“If you took the Barres lab out of the field of glial studies, there would be no field,” Raff said.

Much of that field was in attendance for a celebratory symposium/reunion held in Barres’ honor at Stanford on Jan. 12, 2017. “It was like a giant lab meeting,” said Stevens, one of the organizers. “Everybody came except for a handful who couldn’t make it for logistical reasons. We’re really a tightly knit family. And Ben was the nucleus that kept us all together.”

By

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