Drug blocks mosquito-borne viruses in cell cultures, researchers discover

By Sarah C.P. Williams

If there was a Mafia crime family of the virus world, it might be flaviviruses. Dengue, Zika, West Nile and yellow fever virus — to name the more infamous public health gangsters of this clan — are all mosquito-borne flaviviruses, and they’re notoriously hard to take out. Researchers struggle to find drugs to combat just a single flavivirus at a time.

Now, researchers at the School of Medicine have discovered a way to block a handful of members of the family at once. The approach, rather than killing the viruses directly, is akin to cutting off a crime family’s bank accounts: It re-routes around inhibiting access to a complex of proteins in mammalian cells on which the viruses rely when they invade.

“Generally, when you destroy a region in the brain — the habenula, for example — your entire body tradeoff is changed,” said Jacek Jan Carette, PhD, associate professor of microbiology and immunology and senior author of the paper, which was published Dec. 12 in Cell Reports. “There’s a next step in the brain’s reward circuitry, which evolved...”

Brain zap saps destructive urges

By Bruce Goldman

School of Medicine investigators have identified the smoking gun of a “moment of weakness”: a signature pattern of electrical activity in a small, deep-brain region just a second or two before a burst of impulsive behavior.

The Stanford scientists discovered similar patterns in mice that had learned to binge-eat fatty food and in a human subject anticipating a large cash reward.

The researchers also showed, in mice, that supplying a small electrical pulse to the brain region in question, called the nucleus accumbens, as soon as the electrical signature manifested prevented the mice from overindulging in fatty food, while not affecting their intake of normal food, their social behavior or other physical activity.

The findings were published online Dec. 18 in the Proceedings of the National Academies of Sciences.

“We’ve identified a real-time biomarker for impulsive behavior,” said Casey Halpern, MD, assistant professor of neurosurgery and the study’s senior author. Postdoctoral scholar Hemmings Wu, PhD, and neurosurgery resident Kai Miller, MD, PhD, share lead authorship. “Interruptions are normal and absolutely necessary for survival,” Halpern explained. “They convert our feelings about what’s rewarding into concrete actions to obtain food, sex, sleep and defenses against rivals or predators.”

Good impulses gone bad

But in some contexts, impulsive behavior can be pathological, manifesting as a marked tendency to make poor decisions and act on them. One need look no further than the recent rash of reports of sexual predators perched in powerful positions in Hollywood, the media, finance and politics to see examples of a fundamentally unhealthy drive — sexual appetite — taken to a pathological level.

The nucleus accumbens is the hub of the brain’s reward circuitry, which evolution has engineered to reinforce survival-promoting actions. See IMPULSIVE, page 7
Stanford innovator, imaging expert Juergen Willmann dies at 45

By Hanae Armitage

Juergen Willmann, MD, a professor of radiology at the School of Medicine, died Jan. 8 in a car accident near Palo Alto. He was 45.

Willmann honed an imaging tool known as targeted contrast microbubbles that, in combination with ultrasound, could be used to detect early tumors and target the delivery of drugs. Over a decade at the School of Medicine, his lab advanced the microbubble work from the bench to animals, all the way to the first clinical imaging trials in humans, in which microbubbles were used to detect breast and ovarian cancer.

Described as both a brilliant clinician and a compassionate family man, Willmann was known for his boundless energy and approachable empathy. He loved music, played four instruments, was an accomplished pianist and considered becoming a professional musician before deciding on a medical career.

“He was as spectacular a person as he was a scientist. He just radiated this magnetism,” said Brooke Jeffrey, MD, professor of radiology at Stanford. “He was never arrogant, never showed hubris, and he was always interested in you and your family were doing — it was a compass that’s rare to find in someone who’s so accomplished.”

Native of Germany

Born in Germany, on May 24, 1972, Willmann earned his medical degree, summa cum laude, just 15 months after his medical school classmate in Bavaria, at Albert Ludwig University of Freiburg, Willmann traveled between California and Zurich, training in medical imaging at the University of California-San Francisco and in surgery at a teaching hospital of the University of Zurich as part of his education. He completed his residency at the University of Zurich along with his wife Amelia Larson, MD, whom he met in medical school. Luzi is currently an assistant professor of radiology at Stanford. After completing his residency, Willmann became an assistant professor and clinical attending physician at the University of Zurich in 2003. He received tenure two years later. In 2008, Luzi was granted funding from the Swiss government to take a two-year leave and travel to Stanford for a research fellowship — quite a stroke of fate, considering both brothers applied and were considered based on their independent merit. The two ended up together in the lab of Sanjiv Sam Gambhir, MD, PhD, professor and chair of radiology, where they worked on multimodality molecular imaging technologies and early cancer detection.

“Juergen was very interested in early cancer detection because he understood the value of long-term research and how impactful early cancer detection could be to humanity when eventually successful,” Gambhir said. “He was exceptionally intelligent, highly driven, supremely organized and a wonderful leader, mentor, father and husband. I could not be more proud of anyone who had the opportunity to work with and learn from him.”

In 2008, shortly after the fellowship ended, Willmann and Luzi made a permanent move to the United States, and he became an assistant professor of radiology in the School of Medicine. In 2015, Willmann was promoted to the rank of professor. "Though his life was tragically cut short, Dr. Willmann had already made extraordinary contributions to his field and touched countless lives through his warmth, leadership and compassion,” said Lloyd Minor, MD, dean of the School of Medicine. “His death is a profound loss for the entire Stanford Medicine community.”

‘Just a dynamo’

Throughout his career, Willmann was generous in sharing his time and expertise with doctoral students in his lab, and did so in a way that fostered what many deemed a family environment, Jeffrey said.

Outside of research, he assumed several administrative roles in the Department of Radiology, including clinical division chief of body imaging and executive vice chair of strategy, outreach and clinical trials. Jeffrey, the former clinical division chief, said that when he stepped down, Willmann was the unanimous choice. “In addition to his big脑子里 accomplishments and his truly remarkable emotional intelligence, he was a real leader,” he said. “His management style was very inclusive, low-key and effective at all levels.”

Willmann’s investigation into cancer detection and imaging technologies earned him the 2017 Distinquished Investigator Award from the Academy for Radiology & Biomedical Imaging Research. ‘He was just a dynamo — people have used the term ‘superstar’ to describe him, and they’re not wrong,’ Jeffrey said.

‘He was a larger-than-life kind of person,’ Gambhir said. Willmann was an elected fellow of the Society of Abdominal Radiology and of the American Institute for Medical and Biological Engineering.

He is survived by his wife and their two children, Alexander and Juliana Willmann; his parents, Elisabeth and Karl Willmann; and sister Sabine Willmann. Arrangements for a memorial service are pending.

By Sarah C.P. Williams

In the last few decades, dozens of new breast cancer drugs — from chemotherapy to targeted compounds — have become available, for example, since mammogram technology has gone from film to digital. But are the changes making a difference these advances are making?

The answer to that question is a resounding yes, according to a multi-institutional network of researchers who have modeled the effect of breast cancer screening and treatment on mortality rates.

The researchers’ models showed that screening and treatment reduced breast cancer mortality by 49 percent in 2012, compared with 37 percent in 2000.

“These numbers represent very positive news for breast cancer patients,” said Sylvia Plevritis, PhD, professor of radiology and of biomedical data science at the School of Medicine and lead author of the paper, which was published Jan. 9 in JAMA. “Advances in screening and treatment are saving patients’ lives, and this paperquantifies just how much of a difference those advances are making.”

An international effort

In 2005, Plevritis and her colleagues in the Cancer Intervention and Surveillance Modeling Network used data from 1975 through 2000 to reveal the relative contributions of screening and treatment to reductions in breast cancer mortality rates. Using knowledge of how breast cancer advances, they developed models representing how many women would die of the cancer with no screening and no treatments, then simulated the effect of screening and treatment on those mortality numbers.

The decrease in mortality from the modeled baseline, they found, was about 50 percent due to screening and 50 percent due to treatment.

“Now, over 18 years later, a lot has happened in the field,” said Plevritis, who leads the Stanford Cancer Center for Molecular Imaging Biology. “We’ve seen advances from film-based mammography to digital; there are new molecularly targeted treatments and new types of chemotherapy regimens. We wondered whether these advances had changed the relative contributions of treatment and screening on breast cancer mortality.

So researchers in the network updated their models to reflect molecular subtypes of breast cancer. Six independent research teams — including researchers at Stanford, the Dana-Farber Cancer Institute, Erasmus Medical Center, the University of Zurich, the University Medical Center, Albert Einstein College of Medicine, the University of Wisconsin, Harvard Medical School and MD Anderson Comprehensive Cancer Center — put together models representing the effect of current treatment and screening.

The group added new data — spanning 2000 to 2012 — to the existing data and compared the conclusions of each 52 researchers to determine how mortality of screening and of treatments, including chemotherapy, hormone therapy and drug treatments, had changed over time. One of the models includes microbubbles used to detect breast and ovarian cancer.

“Microbubbles are so useful because they allow us to look at molecular subtypes because not all breast cancers are the same as a whole, but on molecular subtypes of breast cancer, such as those that are ER and HER2 positive, meaning that they grow in response to the hormone estrogen.

“This time around, it was important to look at molecular subtypes because more women are being treated based on the molecular subtype of their tumor,” Plevritis said.

The researchers found that in 2012, screening and treatment together reduced breast cancer mortality by 49 percent. For all breast cancers together, 57 percent of that reduction was due to screening, and 63 percent was due to treatment.

Subtype matters

However, when they looked at some molecular subtypes of can-

Treatment that targets specific characteristics of cancer, the numbers varied. For ER-positive/HER2-positive breast cancer, the number was 52 percent; for HER2-negative breast cancer, the number was 48 percent. For the greatest number of new targeted treatments available, only 51 percent of the mortality decline was associated with screening, with 69 percent associated with treatment. For ER-negative/HER2-negative breast cancer, which has fewer treatment options, 48 percent of the mortality decline was associated with screening and 52 percent was associated with the treatment, similar to results from 2000.

“Newer drugs, particularly ones that are molecularly targeted, are associated with a greater reduction in breast cancer mortality than screening,” said Jeanne Mandelblatt, MD, MPH, professor of Oncology and of Medicine at George-town University and a senior author of the paper, “However, screening is still having a significant effect in reducing breast cancer deaths.”

The work is an example of Stanford Medicine’s focus on understanding the goal of which is to anticipate and prevent disease, as well as to precisely diagnose and treat.

The study was funded by the National Institutes of Health. Data used in this study was supported by the National Cancer Institute.
By Bruce Goldman

Ben Barres, who identified crucial role of brain’s glial cells, dies

Kurian is the lead author of the study, which was published online Dec. 11 in the Journal of the National Cancer Institute. Steven Katz, MD, MPH, professor of medicine and of health management and policy at the University of Michigan, and co-author of the study, said, “Our study shows how breast cancer is a model for how doctors have driven advances in personalized medi- cine not just in the breast cancer, but also in other classes.”

Barres, who had held the position from 2008 until then, was first diagnosed with cancer in 2005, and people had thought he was glau- gria were mere passive participants in maintaining brain function. Ben’s own involvement in researching the brain’s glial cells transformed this view entirely,” said Kurian. “When Barres first began studying this pathological state, those whose name comes from the Greek word for glue, were thought to be not much more than scaffolding, supplying positional stability and various nutrients to the brain’s much more talented neurons.

But Barres and the nu-

mous biologists who cycled through his lab showed otherwise.

Glial cells, they prove, are critical to maintaining 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.

Born Sept. 13, 1954, grew up in West Orange, New Jersey, one of four children. His mother was a nurse who got her first taste of science in the West Orange Public Library, developed an affinity for microscopes and chemistry as a child, and entered Princeton University as a high school senior. Attending the Massachusetts Insti- tute of Technology on a scholarship, he earned bachelor’s and master’s degrees in life science there in 1976 and headed to medical school at Dartmouth, where he ob- tained an MD in 1979.

Motivated by a mystery

During his subsequent internship and residency in clinical neurology at Cornell, Barres grew increasingly frustra- ted at physicians’ inability to provide cure or even relief. He discovered the cause of neuronal degeneration. He was struck by the observation, in patholo- gists’ specimens of degenerating brain tissue, of irregular-appearing glial cells’ ubiquitous presence near the lesions. He decided that he, alone among his trainees, would see what could be done.

Barres changed course. He returned to aca- demia, enrolling in a graduate program in Harvard Medical School’s neurosci- ence, enrolling in a graduate program for maintaining circuit function throughout our lives,” said Thomas Clandinin, PhD, professor of neurobi- ology, who assumed the role of department chair in April 2016 when Barres,

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 pioneered the idea that glia play a central role in sculpting the wired- in brain and therefore crucial for maintaining circuit function throughout our lives,” said Thomas Clandinin, PhD, professor of neurobi- ology, who assumed the role of department chair in April 2016 when Barres,

By Krista Conger

A study of nearly 3,000 women with early stage breast cancer indicates a recent, significant decline in the use of chemotherapy despite the lack of any change in mortality rates, according to researchers at the School of Medicine and the University of Michigan.

“The growing acknowledgement by oncologists and patients that for some women, the harms of chemotherapy may outweigh its potential ben- efits, the study also revealed that physicians are more likely to be considering what Barres expresses a treatment preference that doesn’t match his physi- cian’s recommendations.

Kurian is the lead author of the study, which was published online Dec. 11 in the Journal of the National Cancer Institute. Steven Katz, MD, MPH, professor of medicine and of health management and policy at the University of Michigan, and co-author of the study, said, “Our study shows how breast cancer is a model for how doctors have driven advances in personalized medi- cine not just in the breast cancer, but also in other classes.”

Surveying women, oncologists

The researchers surveyed 5,080 women treated for early stage breast cancer between 2013 and 2015 in Georgia and Los Angeles. Among them, 2,526 had lymph node involvement and who, without any lymph node involvement declined from 26.6 percent to 14.1 percent; in patients with lymph node involvement, it de- clined from 81.1 percent to 64.2 percent.

Finally, 67.4 percent of oncologists surveyed indi- cated they would order tumor genomic testing to es- timate a lymph node-positive woman’s risk of cancer if they were to agree with their patient’s recommenda- tion to receive chemotherapy. In contrast, only 17.5 percent would order the test if the patient chose to Weiss. It might be that the people who started them were already understood to wrap themselves around neurons’ lengthy projec- tions, process called my- elinisation, providing electrical insulation and vastly increasing speed and reliabil- ity of neuronal impulses. But 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 Uni- versity College London to the department of immunology at Stanford University’s School of Medicine, where he was promoted to his current position as a full professor in 1998, and to a full professor in 2001. At Stanford, Barres turned his at- tention to a second avenue of interest, the study of tumors. Working with colleagues, he discovered that they are common cells in the human brain, out- numbering 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 these cells are crucial to the physical formation of syn- apses, as well as to those synapses’ function. 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 early postnatal development, thus serving brain circuitry that’s proven it-self to perform legitimate activities and clearing out the dead wood.

Barres showed, among other things, that electrical activity in neurons was necessary for neurons’ myelination.

Barres described these findings as “the most important discovery my lab has ever made. If you took the Barres lab out of the field of glial studies, there would be no work.”

But Barres and the nu-}

tions and to spare patients toxicity when possible,” said Kurian. “As personalized medicine becomes more widespread, people are thinking more about their preferences and wishes, especially their trainees. We were his kids.”

Kurian is the lead author of the study, which was published online Dec. 11 in the Journal of the National Cancer Institute. Steven Katz, MD, MPH, professor of medicine and of health management and policy at the University of Michigan, and co-author of the study, said, “Our study shows how breast cancer is a model for how doctors have driven advances in personalized medi-
New device can quickly select healthy sperm, researchers say

By Hanae Armitage

A device the size of your business card can separate the strong, healthy sperm cells from the duds, and it does so in about 10 minutes, according to a new study led by researchers at the School of Medicine and the Worcester Polytechnic Institute.

The sperm-sorting tool is called the Simple Periodic Array for Trapping and Isolation, or SPARTAN. It filters semen through rows and rows of pillars fitted for healthy sperm.

SPARTAN is not the only device of its kind, but its creators say it yields higher-quality sperm more efficiently and effectively than others and hence could improve infertility treatments.

"SPARTAN picks out the healthiest sperm, but it also allows us to ask deeper questions in the setting of terms of how much sperm selection really matters for infertility treatments," Demirci said. "Many infertility treatments, like IVF, focus on finding a healthy egg, the quality of the sperm cell is often secondary. But sperm carry critical heritable genetic elements, just like the egg does, and Demirci said sperm selection does play a big role in the quality of the embryo, so it warrants more careful selection. "Maybe SPARTAN can help change the paradigm in the field," he said.

He said sperm selection does play a big role in the quality of the embryo, so it warrants more careful selection. "Maybe SPARTAN can help change the paradigm in the field," he said.

"SPARTAN offers a lot more advantages in terms of speed of sorting and fitness of the cells," Demirci said. "And I believe it will be easier to regulate these types of devices replace the current centrifuge-based methods used in embryology labs."
By Erin Digitale

A randomized, controlled phase-2 clinical trial, an asthma medication increased the speed and safety of a protocol used to treat multiple food allergies at once, according to a study by researchers at the School of Medicine. The study was published online Dec. 11 in The Lancet Gastroenterology & Hepatology.

About 30 percent of people who have food allergies also have more than one food. Doctors tell them never to eat foods that trigger their allergies — the consequences can be deadly — but this requires constant vigilance.

"Patients find it very hard to live with multiple food allergies," said the study’s senior author, Sharon Chinthrajah, MD, director of the Clinical Translational Research Unit at the Sean N. Parker Center for Allergy and Asthma Research at Stanford University. "It puts a huge social and economic burden on families." The trial was conducted at the Parker Center.

"Having food allergies separates you from everyone else," said Kristen Geller, the mother of 14-year-old Joshua Geller, who participated in the trial. Before Joshua enrolled in the trial, ordinary childhood activities, such as birthday parties and restaurant meals, were a constant source of anxiety for the Geller family.

The new trial examined oral immunotherapy, an allergy treatment in which patients are dosed daily with tiny amounts of the foods that cause their allergic reactions. Over time, the dose is gradually increased until the patient can tolerate normal quantities of the food. The drug used in the trial was combined with omalizumab, an antibody medication that ramps down the immune response.

"It completely changed our lives."

The study found that in women who don’t have a history of living with food allergies, using oral immunotherapy and omalizumab reduced the risk of giving birth to a child with a congenital heart defect, by 8 percent for every increase of 10 milligrams per deciliter in blood glucose levels in the early stages of pregnancy. The next step in the research is to conduct a prospective study that follows a large group of women through pregnancy to see if the results are confirmed, Priest said. If researchers see the same relationship, it may be helpful to measure glucose early in pregnancy in all pregnant women to help determine which individuals are at greater risk for having a baby with a heart defect, he said.

"We could use blood glucose information to select women for whom a screening of the fetal heart could be helpful," Priest said, adding that modern prenatal imaging allows for detailed diagnoses of many congenital heart defects before birth. "Knowing about defects prenatally improves outcomes because mothers can receive specialized care that increases their babies’ chances of being healthier after birth." The work is an example of Stanford Medicine’s focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

The research was funded by the National Heart, Lung, and Blood Institute, the American Heart Association, and the Food Allergy Research and Education Institute. The Parker Center; National Institutes of Health; the Myra Reinhard Foundation; the Myron and Marilyn Warren Parker Foundation; the Stanford’s departments of Pediatrics and of Pathology also supported the work.
heart. Using Shumway’s surgical tech- 
tique, Barnard forever cemented himself into 
the annals of history as the first to 
transplant an adult human heart. Wash- 
kansky lived 18 days.

Shock to the program
It was a shock to the Stanford pro-
gram. Everyone knew Shumway was
way to be the first. But work at Stanford
continued, and on Jan. 5, 1968, both a
donor and a transplant recipient were
found.

At 2 p.m. Jan. 5, Kasperak had a mas-
sive heart attack at his home in East Palo
Alto, Calif. The emergency call went out
for several years, and the prognosis wasn’t
good.

“Had he been referred to me,” said
Don Harrison, MD, a Stanford cardi-
ologist. “He had end-stage heart disease
and was not going to live very long. I
remember talking to his wife about this
transplant surgery. I explained to her
that this was a new procedure that had only
been done once in the world before. I
had to explain to her that her husband
was terminally ill, and there was noth-

Just four hours after Kasperak’s heart
attack and 7 miles west of his home, an-
other woman also walked into Shum-
way’s office at the pediatric ICU. Her
husband, Virgina White, a 43-year-old
housewife and mother of two from Mountain
View, suffered a brain hemorrhage that left her
in a coma at nearby El Camino Hospi-
tal. Physicians had confirmed that she
was brain-dead by the time they placed
her on a respirator, which pumped air in
driver, the first man to get a heart trans-
plant in the United States.

The operation, which took place
Jan. 6, 1968, sparked a flurry of heart
transplantations worldwide, but most
institutions and cardiac surgeons
quickly desisted because of the high
cost of post-operative deaths. Shum-
way and his team at Stanford persevered,
however, ultimately leading to the
success of the operation today.

Radical innovation
Norman Shumway not only in-
troduced a lifesaving procedure but
also made sure that the operation be-
came widespread practice,” said
Lloyd Minor, MD, dean of the School of
Medicine. “We are honored to cel-
brate the anniversary of this un-
precedented and extraordinary male in
Stanford Medicine’s history, and to recog-
nize Dr. Shumway’s radical innovation and
perseverance.

For nearly a decade following that
first surgery, Stanford was virtually the
only major institution moving ahead
with heart transplant research and
continuing to perform operations. The
radical innovation, led by Shumway,
drug cyclosporine to help prevent the
body’s rejection of a donor heart, and
to an innovative biopsy technique that
helps doctors assess whether a heart
transplant is failing before it’s too late.
These advances greatly improved pa-
tient survival rates.

In 1981, Shumway and Bruce
Reitz, MD, who is now a professor emeritus of cardiothoracic surgery,
performed the world’s first heart-lung
transplant at Stanford.

Shumway died in 2006 at the age of
25 minutes, the new heart faintly pulsed
and then grew stronger. “We were elated,”

A ‘three-ring circus’
Downstairs, all hell broke loose. Fifty
or so journalists had arrived even
before surgery began, according to an
article in Stanford Report by Spyros An-
dropoulos, director of the medical
center’s news office at the time. He
had converted two classrooms into an
im-promptu press room.

Shumway (left) and cardiologist Ed Harrison spoke to the media after the historic transplant surgery.

The next morning, Shumway, with
Harrison by his side, stood with arms
folded over a wrinkled, white lab coat
and faced the crowd of several hun-
dred reporters at an impromptu news
conference.

“Knowing that she is helping another
sufferer is a great gift,” said Bill White,
according to news reports. “I’ve got two of
those. I want you all to know that.”

Stafford Medical History Center

Celebration planned for 50th anniversary of the first U.S. adult heart transplant
By Tracie White
Fifty years ago, Norman Shumway,
MD, performed the first suc-
cessful human heart transplant in the
United States at Stanford Hospital.
To celebrate that landmark event,
a daylong conference is set for Jan. 22
at the Li Ka Shing Center for Learning and
Innovation. Experts from Stanford and other
institutions will speak, including Shum-
way’s daughter, Sue Shumway, MD, a pro-
fessor of surgery and vice chief of car-
diothoracic surgery at the University
of Minnesota; and Edward Stinson,
MD, professor emeritus of surgery at
Stanford, who assisted Shumway dur-
ing the operation.

The operation, which took place
Jan. 6, 1968, sparked a flurry of heart
transplantation

The operation began.

Washkansky was awake, confident,

radical innovation

“The tip actually came from a re-
porter from the San Jose Mercury News
who was at a wedding reception with
members of the transplant team,” An-
dropoulos wrote. “When they received
information was available at: http://
med.stanford.edu/csurgery/shum-
way-50th-anniversary.html

“I remember thinking they were go-
ing to break their necks!” said Stinson,
who saw them climbing when he stepped
outside. Kasperak’s nurses, though,
were quick to close the curtains, prevent-
ing any photos, and the defeated reporters
climbed back down.

The next morning, Shumway, with
Harrison by his side, stood in the med-
icenter’s news office at the time. He
had converted two classrooms into an
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Shumway (left) and cardiologist Ed Harrison spoke to the media after the historic transplant surgery.

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Harrison by his side, stood with arms
folded over a wrinkled, white lab coat
and faced the crowd of several hun-
dred reporters at an impromptu news
conference.
**Viruses**

stranded RNA viruses which, combined, are responsible for widespread morbidity and mortality throughout the world. Some flaviviruses, including dengue, Zika, West Nile and yellow fever viruses, are among the most prevalent and widespread of all viruses, spread by ticks. Existing drugs that work against flaviviruses often target the viruses’ RNA polymerase. Carette and his colleagues, however, study the components of host cells—cells which viruses infect, such as human cells—that flaviviruses depend on. In a previous study, they found that the viruses are especially dependent on their host cell’s OST complex, which is normally responsible for adding sugar molecules, called glycans, to proteins. Glycans help the incorrectly engineered cells to lack OST, which is made up of multiple protein subunits, the cell could no longer be infected by flaviviruses.

In the new work, Carette and lead author Andreas Puschnik, a former Stanford student who worked at the Chan Zuckerberg Biohub, teamed up with Yale University researchers who had just completed a virtual chemical screen of the activity of the OST complex. While high concentrations of NGI-1 stopped OST activity by targeting it and halting its normal function, the group found that much lower concentrations of NGI-1 were needed to block flaviviruses from replicating inside the cells. Therefore, low concentrations of the drug could be used to block the viruses without harming the host.

When Carette and Puschnik treated Zika- or dengue-infected cells with NGI-1 immediately after infection, they saw a 99 percent decrease in infection; when the treatment was administered 24 hours after initial infection, the decrease was 95 percent. Animal experiments showed antiviral activity against all four dengue types and multiple strains of Zika, as well as against West Nile and yellow fever virus.

The researchers went on to show that viruses implanted with NGI-1 showed less resistance to NGI-1 because it would require four specific and separate changes to the virus.

“When you target a host function rather than a viral protein, it’s usually much more difficult for a virus to develop resistance,” said Carette.

A better antiviral

To understand exactly what makes NGI-1 such an effective and broad antivi-

rural property associated with these findings. Further experiments compared responsive neurostimulation delivery to non-responsive delivery. As with the mice, once the participant got accustomed to the near-certainty of receiving a reward upon completing the task, a receiver to which the impulsive electrical leads were temporarily hooked was able to detect the characteristic “high-delta” electrical signature in his nuclei accumbens just before he committed the “task fail”.

“The fact that we saw a similar signal prior to two different behaviors, both intended to obtain rewards—food in the case of mice, money in the case of the human subject—to which the individuals had become hypersensitized by their repeated exposure suggests that this signal may be common to many impulsive behaviors, making them amenable to treatment along similar lines,” said Halpern.

Unlike newer parts of the brain, such as the cerebral cortex, which is responsible for memory, emotions and reasoning, the nuclei accumbens have largely been conserved among vertebrates. So Halpern thinks the behavior-altering results his team observed in mice are likely to apply to humans, although further study will be needed to confirm these findings in a single human subject.

Halpern, Wu and study co-author Robert Maikala, MA, a PhD candidate at Stanford Medicine, have co-authored a patent file that is now available in both Stanford's Office of Technology Licensing and the Life Science Technology Office.

**Impulsive**

by inducing pleasure in anticipation or performance of those actions. The study's findings offer the promise, Harrington said, that by understanding the electrical signals that regulate the nucleus accumbens for the telltale signal preced ing a burst of impulsivity and immediately delivering a measured amount of stimulating current, doctors might be able to prevent impulsive and sometimes life-threatening actions by high-risk people for whom all noninvasive therapies have failed.

The findings could also lead to less invasive metho ds of countering obesity, substance-abuse disorders, pathological gambling, sexual addiction or intermittent explosive disorder, a psychiatric condition marked by outbursts of inappropriate ferocity.

"Imagine if you could predict and prevent a suicide attempt, or a binge aliment, a burst of binge eating or an alcohol intake, or a sudden bout of uncontrollable rage," Halpern said.

Clinically, Halpern focuses on deep-brain stimulation, a procedure that delivers electrical pulses to targeted brain regions in which they’ve been implanted. DBS is now approved by the Food and Drug Administration for treating symptoms of Parkinson's disease and essential tremor, and is currently in clinical trials for depression, obsessive-compulsive disorder and multiple other disorders of the brain.

But the tens of thousands of DBS devices in current use are inflexible in the timing, duration and intensity of the pulses they deliver; they simply fire away on a preprogrammed basis, 24/7. New-generation devices can respond to feedback from the brain region they target, or even a distant one, so pulses get delivered only when the brain's electrical signals cross a so-called rational threshold. So-called responsive neurostimulation devices have so far been approved for partial-onset epilepsy. Because they fire on the basis of nearby brain activity, these devices, in principle, may actually deliver as little as five minutes per day of total stimulation, which neuroscientists such as Halpern view as greatly advantageous from the standpoint of avoiding side effects and optimizing the behav ioral specificity of the treatment.

There’s no available responsive neurostimulation intervention for dangerous impulsive behavior yet, because until now no one’s been able to document a characteristic signature in the brain that could be used for triggering pulse delivery by the device," he said.

From mouse to man

The Stanford scientists discovered this signature in experiments with mice. Typically, laboratory mice are fed pellets of a standard chow that's nutritious but not appetizing. If the mice were instead provided with special high-fat food pellets for one hour every day for 10 days. During that time, they were allowed to eat as much as they wanted.

The novel food took some getting used to, by day 10 the mice became habituated to it and pretty much ate it nonstop. The researchers had implanted electrode arrays in the mice's brains in order to monitor electrical activity in the nucleus accumbens, where a range of behavioral tasks, including the restriction of rewards, a particular low-frequency band called delta — emerged immediately prior to binge-eating, peaking about one second before a mouse took a bit of the high-fat food pellet. Notably, this uptick didn’t occur when that mouse was about to bite into standard lab chow. Nor was it seen in other typically rewarding activities, such as interactions with younger mice.

Halpern and his colleagues then programmed their electrode arrays to deliver 10-second pulses of electrical current whenever a characteristic delta wave emerged in the participant’s nucleus accumbens but prior to either random or DBS delivery, despite delivering far fewer electrical pulses daily than DBS.

When the scientists implanted a DBS device, researchers worked to de velop a drug that can more specifically target the viruses. One is a specific anti-viral compound known as NGI-1, said Puschnik. “We hope this leads to a new generation of antiviral drugs,” he sai d.

**Transplant**

held in one of the medical school’s annual traditions. It’s never a bad thing to speak, but our work is just beginning,” Stinson said.

The Stanford heart transplant patient, Mike Kasperak, awakened in satisfactory condition.” Harrison, the patient’s cardiologist, presented diagrams of cardiac functioning and rated the patient “outstanding.” Shumway said, cameras clicking. “The patient, Mike Kasperak, 54 years old, was reported to be awake and alert and walking around five days after surgery. He was "able to walk a first visit with his wife yesterday evening and slept through the day. He was followed up with,” said. “Mr. Kasperak managed to acribe to love you love and hate, done with this.” For the first few days post-surgery, Kasperak’s condition remained hopeful, but then he slipped into a semi-comatose state. Extreme bloating of the stomach

led to worries that his liver and kidneys had been too severely damaged by years with disease to bring him alive.

“ln retrospect, he was too ill at the time of surgery,” Stinson said. “His kidneys, liver, and brain were functioning well. His body didn’t tolerate the stress of the operation well.” Fifteen days after the surgery, Kasperak entered severe hemorhaging. Stinson, making certain he was given enough morphine that he was never in pain, was there by his side.

In the aftermath of the Stanford transplant, the world hit near-hystera in its acceptance of a donor with heart, lung and liver transplants. Nearly 1000 medical institutions jumped in to attempt the operation. The surgery itself was fairly simple, but “The real challenge was to prevent recipients’ bodies from rejecting foreign organs quickly led to alarming rejection rates. Sensitivity was increased, and some of these operations appeared in newspapers like the National Enquirer. One paper ran with this headline: ‘Does give her a man’s heart — now she puff s stogies and rants and ravels at TV wrestlers.”

In 1970, on the third anniversary of Banting and Best’s work, a London newspaper by this near-madness and frightened by the soaring death rates, the medical establishment, led by the American Heart Association, called for a moratorium on heart transplants. All major institutions complied, except for one: Stanford.

**Refining the work**

The Stanford physicians-statisticians continue to publish scientific papers and conduct heart transplants, slowly establishing new protocols for the surgery and improving the odds of success and for treating rejection.

Today, Stanford Medicine’s reputation as the clinic of choice is not just the result of early success. It is also the result of the clinic’s commitment to responsible to leading to the thousands of successful transplants carried out an national level. Since that historic moment when the surgery remains a magical moment, for Stinson at least, and an essential one, along the journey toward making heart transplantation a standard operation.
Novel technique could reveal immunotherapy targets, researchers find

By Hanae Armitage

Researchers at the School of Medicine and their colleagues have developed a way to pinpoint potential targets for cancer therapies that rely on the body's immune system.

Custom antigens are targets molecules called antigens, which appear on the surface of tumor cells and other malignant or damaged cells. Antigens are chemically similar to normal tissue antigens but are modified in a way that the immune system recognizes them as foreign.

The researchers exploited years of structural and protein engineering studies by the Team of Two, led by Nobel laureate Christopher Garcia, PhD, professor of molecular and cellular physiology and of structural biology, to better understand how the immune system's "sees" antigens. Based on this knowledge, they developed a technique to identify them. What's more, the technique could serve to identify potential antigens relevant to other immunotherapies, such as those that combat autoimmune or infectious diseases.

A paper describing the work was published online Dec. 21 in Cell. Stanford graduate student Marvin Gee and postdoctoral scholar Alan Hon, MD, PhD, share lead authorship of the paper. Garcia, who holds the Younger Family Professorship, is the senior author. The study's approach depends on immune cells recognizing specific antigens on tumor cells. That's because the basis of the process is whether antigens are shared self-antigens, and the implications are that if you screen many more T cells, you'll likely find a lot of shared antigens, Garcia said. "So in theory, you could have one immunotherapy that targets this antigen, and it'd be effective for multiple patients.

By Stacey McCutcheon

Paul Yock, MD, professor of medicine and bioengineering at Stanford and the founder and director of the Stanford Byers Center for Biodesign, has been named the National Academy of Engineering's 2018 Bernard M. Gordon Prize for Innovation and Engineering Education.

The academy said Yock was chosen for "the development and global dissemination of a medical innovation training program that creates leaders and innovators that benefit patients." That program, the Stanford Biodesign Program and the Center, are the "best of the best," according to the academy.

Gordon Prize winner

"He has inspired generations of students to an academic career in innovation by creating a mentorship program that exclusively to the design and development of medical devices, and was retooled on nearly every front, including identifying and characterizing important, unmet clinical needs as the essential first step in successful inventing. They have developed a way to pinpoint potential targets for cancer therapies that rely on the body's immune system.

"There are different innovation processes that make sense for different technology domains," said Yock. "Unlike the situation for consumer products, health care has a complex landscape of stakeholders — from doctors and patients to payers and insurers — all of whom have a say in whether a new technology is adopted or not.

"Not only do innovators need to satisfy all these stakeholders, but given the enormous variation in costs, they're required to develop, test and obtain regulatory approval for a new device, which is an essential that innovators get it right the first time. This is why our trainees spend three to four months screening needs and understanding the problem they ultimately choose to solve before they even invent anything," Yock said.

Doctors, engineers work together

Stanford Biodesign was also among the first academic training programs to formalize the mechanism for bringing together talented engineers and physicians to collaborate on project-based learning experiences.\n
Christopher Garcia

BY HANAE ARMITAGE

Researchers at the School of Medicine and their colleagues have developed a way to pinpoint potential targets for cancer therapies that rely on the body's immune system.

Novel technique could reveal immunotherapy targets, researchers find

"The screen is a completely unbiased way of taking a random T cell receptor that's infiltrated a tumor and interrogating it to find out exactly what antigen it is recognizing," said Garcia, who is a Howard Hughes Medical Institute Investigator.