

## TAKING THE GUESSWORK OUT OF CANCER SURGERY

In 2016, nearly 1.7 million people in the United States alone will be diagnosed with cancer. For many of these people, treatment will involve surgery to remove the cancer. However, because it's very difficult for the naked eye to distinguish between normal tissue and cancerous tissue, standard protocol requires doctors to remove the tumor as well as some surrounding tissue. If this tissue is found to contain cancer cells, which can happen in as high as 40 percent of cases, the patient often faces a second round of surgery. Samuel Achilefu and his research team at Washington University in St. Louis have developed a simple, but powerful solution that might significantly improve these odds. Their cancer goggles, used with a special imaging dye also developed by Achilefu, illuminate cancer cells and make it easier for surgeons to remove all of the cancer the first time around.

Dr. Achilefu, the Michel M. Ter-Pogossian Professor of Radiology at Washington University School of Medicine, explains that dye injected into the patient binds to the cancer cells and emits a light undetectable by the human eye. With the goggles on and an infrared light shining on the tumor, the only light a surgeon sees is that emitted from the cancer cells, clearly illuminating the tissue that needs to be removed. This system also enables doctors to see cancerous cells in places beyond the target tumor — cells that would have been overlooked because they are too small to have been identified by traditional imaging techniques prior to surgery.

Improving cancer treatment, relieving patient anxiety, and reducing health care costs here in the United States, are clear potential



## CANCER SURGERY

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benefits of the cancer goggles. However, the Nigerian native also has his eye on improving treatment options for people in less developed parts of the world. “One of my biggest joys would be to see this technology go to people who cannot afford good health care. The beauty of our system is that it can be used in the most advanced centers like Washington University in St. Louis, and it can be used in the most rural areas of the world.”

The cancer goggles have been successfully used in a pilot study at Washington University’s Siteman Cancer Center on patients with breast, skin and liver cancers. As of September 2016, Dr. Achilefu is awaiting U.S. Food and Drug Administration (FDA) approval to allow other institutions to evaluate the technology in clinical trials. He also is in the process of submitting an investigational new drug (IND) application to the FDA for the imaging dye.

Funding for Dr. Achilefu’s work has come from a variety of public and private sources. However, he says that funding from the National Institutes of Health and other federal agencies has been absolutely essential to moving his cancer goggles from concept to reality. Moreover, he says that it’s only through continued federal funding of research that future innovations will evolve.

PHOTOS COURTESY OF ROBERT BOSTON, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE IN ST. LOUIS



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## A FATHER'S MISSION TO DEVELOP A BIONIC PANCREAS

For the 1.25 million American adults and children with type 1 diabetes, managing blood-sugar levels is a 24/7 affair that involves sticking their fingers many times a day and either manually injecting insulin as needed or wearing an insulin pump. Blood glucose management is an inexact science, with levels too high or too low having dangerous consequences. Even a small overdose of insulin can be deadly. Boston University bioengineering Professor Ed Damiano's involvement with type 1 diabetes began in May 2000 on a highly personal note when his son David was diagnosed at just 11-months old.

In caring for his infant son, Dr. Damiano learned quickly that the more fastidious he and his wife were in maintaining David's glucose levels, the better the results. As a biomedical engineer, this hard-earned realization got him thinking. Could he create a completely automated device capable of keeping blood sugar levels in check? If so, the result would revolutionize diabetes care and indefinitely stave off the long-term health complications facing people like his son.

Looking back on it now, Damiano readily admits a practical dual-hormone pocket-sized system to automate blood sugar control was highly premature 16 years ago. Several technologies had to fall into place first. Among other things, back in 2000 a reliable and accurate continuous glucose monitoring system wasn't even available, and neither was a stable, pumpable form of glucagon. As these necessary technologies matured, Damiano and his research team began to develop and test the all-important algorithms that would ultimately form the backbone of their bionic pancreas.



## A FATHER'S MISSION CONTINUED

After about 15 years of research and development, testing and clinical trials, of fine-tuning and evolving from a laptop-based technology to a pocket-sized mobile device, Damiano's dream for his son, and everyone with type 1 diabetes, is on the cusp of becoming a reality. Securing licenses to the intellectual property from Boston University in late 2015, he and his team formed a public benefit corporation called Beta Bionics to produce, test and seek regulatory approval to market their bionic pancreas, the iLet.



The iLet is — as envisioned — a portable, wearable electronic device, which is not much larger than the original 2007 iPhone, that takes blood-sugar readings every five minutes, and, depending on levels, either releases insulin to bring blood sugar down or glucagon to bring it back up. Damiano's goal is to have an insulin-only version of the iLet on the market by the time David enters his sophomore year of college in 2018.

Ed Damiano and his research team have received funding from a variety of sources. Of the \$18 million raised through Boston University to fund his program over the past decade, half has come from the National Institutes of Health.

PHOTOS COURTESY OF BOSTON UNIVERSITY AND BETA BIONICS

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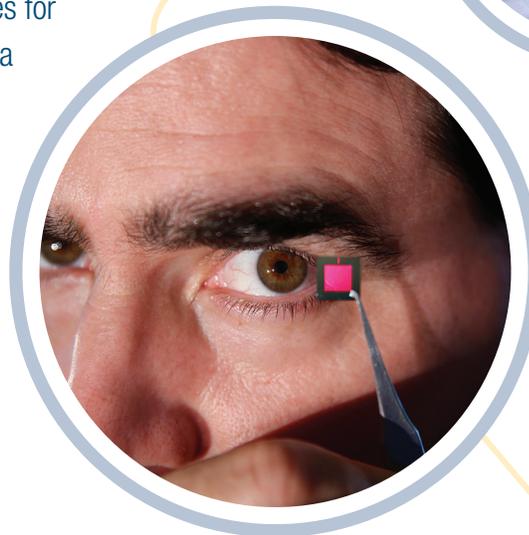
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## GIVING KIDNEY PATIENTS THEIR QUALITY OF LIFE BACK

More than 460,000 Americans have end stage renal disease. While transplant of a human kidney is the best treatment for kidney failure, there simply aren't enough donor kidneys to go around, leaving the vast majority of these patients tied to dialysis machines for the rest of their lives. Every day 13 people die waiting for a kidney. Vanderbilt University Medical Center nephrologist and associate professor of medicine Dr. William H. Fissell IV and his colleague Dr. Shuvo Roy at the University of California, San Francisco have spent the better part of two decades working on a technology solution to this problem of supply and demand. And now, in 2016, they are closing in on what he calls the "Holy Grail" for people with kidney disease: An implantable artificial kidney.

Their bio-hybrid device, built from microchip filters and living kidney cells, would be powered by the patient's own heart and be about the size of a soda can, freeing kidney patients from dialysis and reducing the need for kidney transplants. While treatment options for those suffering from kidney disease haven't changed in decades, advances in two key areas of science — nanotechnology and regenerative medicine — have come together to make this 'bioartificial' kidney possible.

Inspired by nature, the artificial kidney has the same division of labor as a real kidney: filters and a bioreactor of living cells. In this case, the filters are made from silicon nanotechnology. They filter the blood and send the remaining fluid to the tubule. The bioreactor processes the filtered fluid by either adding or removing water and chemicals



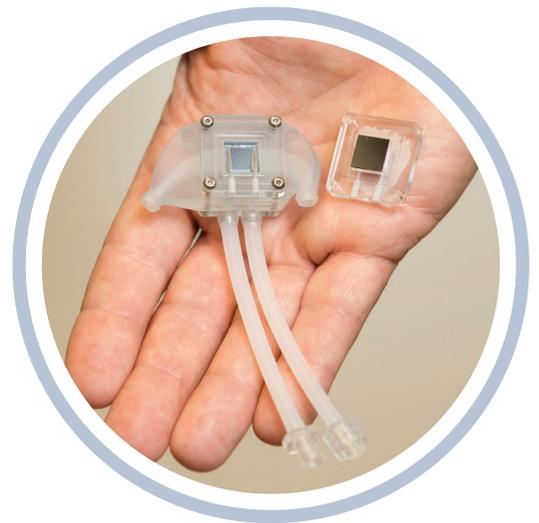
## QUALITY OF LIFE

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according to the body's needs, and ultimately, producing urine. While growing the filters in the lab at this time is not feasible, kidney tubule cells do grow well in the lab. These cells can use the body's chemical energy to regulate fluid and electrolyte balance, and excrete wastes, eliminating the need for dialysate.

The costs to society of kidney disease are significant. Each year, the Centers for Medicare and Medicaid Services (CMS) spends around \$35 billion to care for people with end-stage renal failure — more than the entire budget of the National Institutes of Health. Bringing down health care costs will be an enormous benefit of the bioartificial kidney, but not the only one. “If we can move people off thrice-weekly dialysis and let them get their quality of life back — that’s the big offering. Patients can become who they want to be again. That’s the gift of transplant and that’s what we are trying to accomplish with our device,” says Fissell. Pilot studies of the silicon filters could start in patients by the end of 2017.

Sustained funding from the NIH, and the National Institutes of Biomedical Imaging and Bioengineering (NIBIB) in particular, has been essential to the work of Fissell and Roy and development of their artificial kidney.



PHOTOS COURTESY OF VANDERBILT UNIVERSITY MEDICAL CENTER

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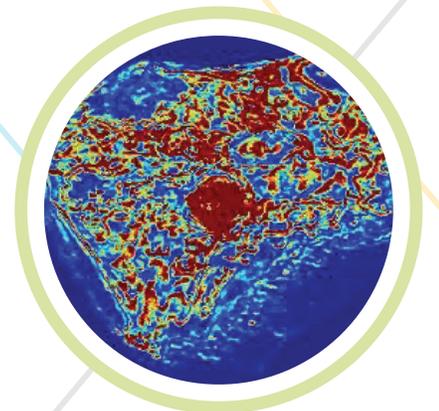
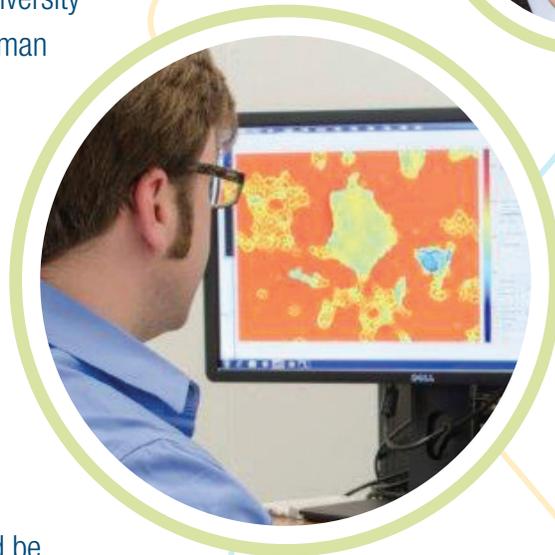
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## DETECTING CANCER AT ITS EARLIEST STAGES

What if you could detect cancer at its earliest stages — before there are any symptoms that would send you to a doctor? What if such a diagnostic tool existed and it was low-cost, minimally invasive and easy to use? The impact would be huge. Northwestern University professor of bioengineering and biophotonics Vadim Backman is closing in on this goal. By the end of 2017 he expects that the first of a series of cancer pre-screening tests will be available for use by physicians.

Backman and a team of researchers at Northwestern University have developed a way to identify and measure changes to a cell's genome at the nanoscale. This means identifying the signs of cancer before a tumor even develops. Cancer doesn't develop from a single rogue cell, but rather from a series of alterations at the molecular level. Thus, at its earliest stages, you should be able to see alterations in any cell from within the field of cancer. For instance, in the case of lung cancer, a swab from a patient's cheek can provide the needed cell sample to determine if cancer is present.

The challenge was developing the technology capable of working at such a small scale — a few orders of magnitude greater than existing techniques. The key, they determined was the difference between measuring such small structures and attempting to visualize them. Backman's technology doesn't try to visualize changes in the cell's chromatin, but rather detect and measure them using a combination of spectroscopy and microscopic sensing. He likens it to radar for air traffic control: Radar doesn't need to image every aspect of an aircraft to detect its presence.



## DETECTING CANCER EARLY

### CONTINUED

While the technological aspect of their work is impressive, what really excites Backman is the potential human impact of what they've accomplished. "You are detecting disease at the very earliest stages when it is most treatable." Moreover, treatment at this state is often less traumatic and lower cost. Physicians can incorporate this type of test into annual physicals, it can be done in settings like Walgreens or CVS, and it could even be done at home. A positive report from the lab would identify exactly who should have more comprehensive, costly and invasive diagnostic tests. Since more than \$100 billion is spent each year on cancer care in the United States, the potential economic impact is significant.

Backman's research benefitted from substantial support from the National Institutes of Health, and the National Cancer Institute in particular, as well as the National Science Foundation. He says there is no other way to do this type of work without grant support from the NIH.

Backman and colleagues have formed a company, Preora Diagnostics, to commercialize their technology and bring it to market. The first test to be rolled out will be for lung cancer, with tests for other cancers to follow. The anticipated cost of a test is approximately \$150.

PHOTOS COURTESY OF NORTHWESTERN UNIVERSITY AND PREORA DIAGNOSTICS



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## REPAIRING THE GENES THAT CAUSE DUCHENNE MUSCULAR DYSTROPHY

Thousands of diseases are rooted in our genes, occurring when something goes wrong during cell multiplication and causes a mutation in the gene's DNA sequence. This is why researchers the world over heralded the 2012 revelation of the CRISPR-Cas9 system, a groundbreaking tool for editing faulty genes. CRISPR-Cas9 allows scientists with relative ease and precision to snip out a segment of mutated or damaged DNA, correcting genes that are disease-causing and opening the door to potential treatments for diseases where there currently are none.

Duchenne muscular dystrophy (DMD) is one of those diseases. Dr. Amy Wagers of the Harvard Stem Cell Institute has been looking at ways to use stem cells to treat DMD. Duchenne results from mutations in the gene on the X chromosome that encodes for a protein called dystrophin, which is necessary for proper muscle function and regeneration. Duchenne is a particularly debilitating and rapidly progressive form of muscular dystrophy affecting about 1 in every 3,500 male births worldwide. Most patients are confined to a wheelchair by their teens, and few survive to age 30.

Stem cells are unique in that they don't yet have a specific function in the body. Rather, they are what make it possible for us to recover after injury and repair and replace cells that are lost. Several years ago Wager's lab began looking at using stem cells to provide the missing dystrophin protein to muscle affected by Duchenne muscular dystrophy, essentially by transplanting cells from healthy muscle into diseased muscle. While promising, this approach requires finding a way to get enough muscle stem cells to treat all of the affected muscles and then getting those cells to all of the muscles in the body. Another way to achieve the same end is to edit the mutated dystrophin-encoding gene so that when stem cells replicate, the edited version of the gene is reproduced. Enter CRISPR-Cas9.



## REPAIRING GENES

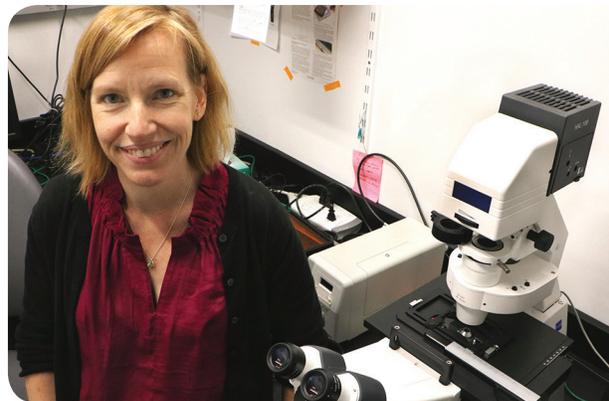
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Building on previous work in the muscular dystrophy community demonstrating that the dystrophin protein can function with pieces of its middle missing, Wager's team used the new gene editing tool on mice bred with Duchenne muscular dystrophy. They wanted to see if simply cutting out the mutation that caused the loss of the dystrophin protein could restore expression of the DMD gene and production of the muscle-building protein; their experiment worked. They found that, despite missing a small chunk in the middle, the gene was still partially functional, and now had an improved capacity for protection against muscle damage.

While much work remains — studies in mice are not proof of effectiveness in humans — the findings by Wagers and her team are a momentous first step toward her goal of providing hope to patients and families affected by this devastating disease. "All you have to do is meet someone with the disease to understand that this is something worth dedicating your energy and your efforts to fighting," she said.

Wagers has received significant support from the National Institutes of Health throughout her career, including funding for the most recent mouse study. She credits an NIH "New Innovator" award early in her career as having had a "catalytic effect" on the direction of her work.

PHOTOS COURTESY OF AMY WAGERS



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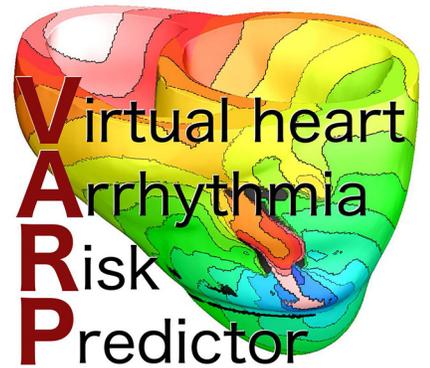
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## USING A PERSONALIZED, VIRTUAL HEART TO PREVENT SUDDEN CARDIAC DEATH

More than 350,000 people each year will experience an out of hospital cardiac arrest. Cardiac arrest is an extremely dangerous circumstance that requires immediate treatment. In cardiac arrest, death results when the heart suddenly stops working properly. This may be caused by abnormal, or irregular, heart rhythms (called arrhythmias). Since prior heart attack, or myocardia infarction, is a major risk factor for arrhythmia, these patients are prime candidates for surgically implanted defibrillators, which monitor heart rhythm and deliver an electric shock if needed to keep the heart beating regularly.

The current tools for assessing whether a patient is likely to actually suffer an arrhythmia and therefore benefit most from the defibrillator (which carries its own risks) are not highly predictive. Dr. Natalia Trayanova, the Murray B. Sachs Professor of Biomedical Engineering and Medicine at Johns Hopkins University, and a team of researchers are working to change this. They have developed a computational model for predicting which heart patients are at greatest risk for arrhythmia. Called VARP, for virtual arrhythmia risk predictor, Dr. Trayanova's virtual heart uses MRI and other patient-specific cardiac data to create a personalized geometrical model of the heart. The model incorporates not just the wall of the heart, but also all the structural remodeling that occurs after a heart attack. That computer model, coupled with mathematical equations that express the dynamics of the human cells of the heart, is then stressed in a variety of different ways and locations to see if a patient is at risk for sudden cardiac death due to arrhythmia.

A groundbreaking retrospective [study](#) published in *Nature Communications* in May 2016 demonstrated the accuracy of the VARP model. In this study, Dr. Trayanova and her team looked at 41



# PREVENTING CARDIAC DEATH CONTINUED

patients who had received a defibrillator because they were deemed at risk for arrhythmia based on current clinical predictors. Using their virtual replica of each patient's heart, they then set out to predict which patients were at highest risk and eventually compared their predictions to the defibrillator recipients' post-implantation records. Patients who tested positive for arrhythmia risk by VARP were four times more likely to develop arrhythmia than those who tested negative. VARP also predicted arrhythmia occurrence in patients four to five times better than existing clinical predictors.

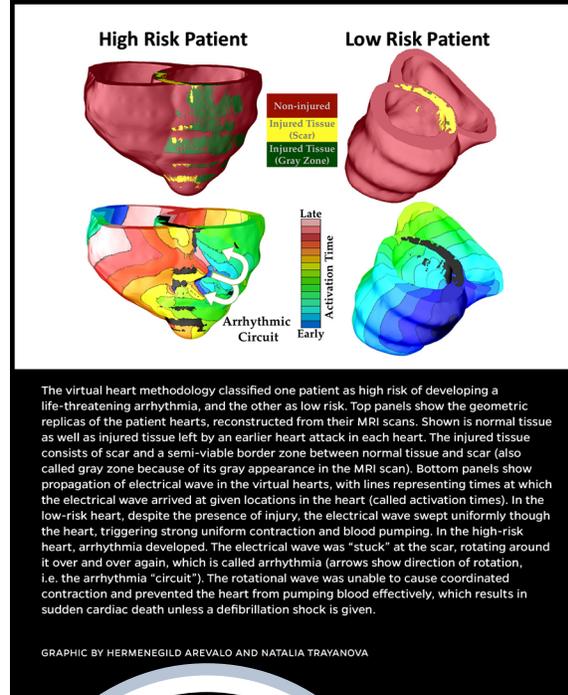
This study provided important proof of concept for VARP. Although more study is needed before VARP reaches the clinic, Dr. Trayanova is excited about the possibility it represents to save lives and direct healthcare intervention and spending to where they will have the greatest impact.

Dr. Trayanova's research has been supported by the National Institutes of Health and other organizations. She particularly credits receipt of an NIH Director's Pioneer Award for giving her the freedom to pursue an idea that some might have thought unworkable, but which has turned out to be potentially transformative, as having the greatest impact on her academic career.

PHOTOS COURTESY OF DR. NATALIA TRAYANOVA/JOHNS HOPKINS UNIVERSITY

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## The Virtual Heart Arrhythmia Risk Prediction for Two Patients



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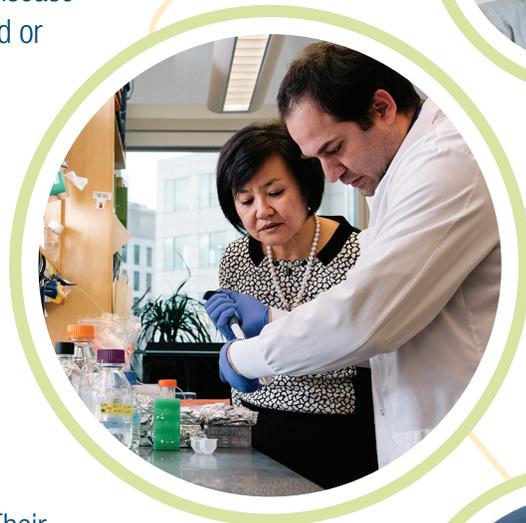
## A RAY OF HOPE IN THE SEARCH FOR A TREATMENT FOR ALZHEIMER'S DISEASE

The statistics on Alzheimer's disease are daunting. More than five million Americans are living with the disease and by 2050 this number could be as high as 16 million. Alzheimer's is the sixth leading cause of death in the United States, but the only disease among the top ten killers that cannot be prevented, slowed or cured. In fact, Alzheimer's disease drug candidates have one of the highest [failure rates](#) of any disease area. The resulting human and economic tolls are significant: in 2017, Alzheimer's and other dementias will [cost the nation](#) \$259 billion.

Yet, there is a potential, flickering light at the end of the tunnel. Dr. Li-Huei Tsai, Picower Professor of Neuroscience at MIT, and her team of researchers have [discovered](#) that LED lights, flickering at a specific frequency, substantially reduce the beta amyloid plaques seen in Alzheimer's disease, in the visual cortex of mice. Their work was published in the journal *Nature* in December 2016. If this finding bears out in humans, it is a game-changer.

Amyloid plaques accumulate in the brains of patients with Alzheimer's and are considered the "culprit of the disease," Dr. Tsai explains. However, the buildup of amyloid begins two decades before other pathological symptoms occur. During this time, the brain structure changes, cells die, and brain function slowly deteriorates to the point that medical help is sought. This fact led Dr. Tsai and her team to look at Alzheimer's disease as a "system-level failure" and to try to figure out what happens to the brain's circuits and networks during that two-decade period of amyloid buildup.

They began to look at brain waves and specifically gamma waves, which are associated with higher order brain functions like sensory perception, attention, decision making and working memory. They knew that others had found that gamma waves are disrupted in people with Alzheimer's disease and they wondered whether the



## RAY OF HOPE

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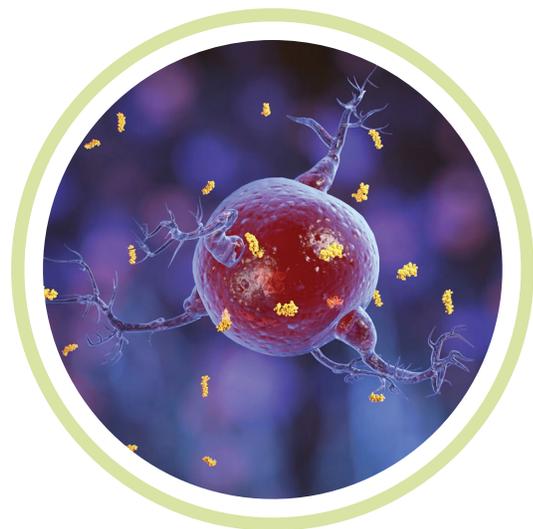
compromised gamma waves contributed to the development of the disease.

To attempt to answer that question they ran a series of experiments on mouse models of Alzheimer's disease using a system of flickering lights to mimic a specific gamma pattern and recording brain activity during the light treatment. What they saw was initially unbelievable — that inducing the gamma waves drastically reduced beta-amyloid in the brain. Further study bore out that finding and more. It wasn't just that light therapy reduced the production of amyloid, but that it actually stimulated the destruction of it. The brain's immune cells, microglia, which become very impaired with Alzheimer's, became active again as a result of exposure to the gamma wave-mimicking light and were actually getting rid of the amyloid.

Dr. Tsai is quick to caution that often what is observed in mouse models doesn't translate to humans. This is why she and a research partner formed Cognito Therapeutics in 2016 to pursue testing of their flickering light therapy in humans. If successful, she is very excited about the widespread availability and ease of access such a therapy could offer people with Alzheimer's.

Dr. Tsai's work was funded by the National Institutes of Health (NIH). This type of federal investment is essential because of the long-term and unpredictable nature of biomedical research, she says, adding that the payback can be extraordinary.

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## RESTORING VISION IN PEOPLE WITH BLINDING DISEASES

In December 2017 the U.S. Food and Drug Administration (FDA) announced [approval](#) of a novel gene therapy, Luxturna, to treat patients with a rare form of inherited vision loss. It is the first gene therapy approved in the United States to target a disease caused by mutations in a specific gene. In this case, the RPE65 gene, which affects vision. For [Dr. Jean Bennett](#), the physician scientist behind this medical breakthrough, being able to change the prognosis for people who are blind or losing their vision — and to see the profound impact that this has on their life — has been a career well spent.

Luxturna works by delivering a normal copy of the RPE65 gene directly to retinal cells. These retinal cells then produce the normal protein that converts light to an electrical signal in the retina to restore a patient's vision loss. Luxturna uses a naturally occurring adeno-associated virus, which has been modified using recombinant DNA techniques, as a vehicle to deliver the normal human RPE65 gene to the retinal cells to restore vision.

Dr. Bennett, the F.M. Kirby Professor of Ophthalmology at the University of Pennsylvania, describes the factors that enable this particular gene therapy to work as a perfect storm: “We’ve got this Trojan horse (the recombinant virus) essentially delivering the normal copy of the DNA that is missing in the target cells; we’ve got tissue (the retina) that does not reject foreign antigens; and we have a tightly enclosed space (the eye) where we can deliver these new genes very, very efficiently and under direct visualization to the target cells. And then we can monitor the function of those cells without causing any discomfort or pain to the patient.”

However, just like a perfect storm involves a rare combination of circumstances, the basic science that led to this treatment for blinding diseases required the convergence of decades of work by Dr. Bennett, a massive international effort to map the human genome, and enormous advances in biomedicine. All of which, involved the National Institutes of Health.



## RESTORING VISION

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During a post-doctoral fellowship Dr. Bennett worked with a researcher at NIH who was seeing children in his lab with various genetic disorders and her interest in developing gene therapies really took off. However, getting from point A to point B required learning more about these diseases and going to medical school. It was at Harvard Medical School that she met her husband and their focus on the retina took root: his studies in neuroscience morphed into studies of the retina and she gained further expertise in genetic engineering and genetics. While they discussed gene therapy for the eye back then, no one knew — in the 1980s — which genes caused retinal diseases.

But then came the 1990s and the [Human Genome Project](#). While Dr. Bennett was focused on developing the methods to manipulate genes and deliver them safely and with good duration — the tools needed for gene therapy — the Human Genome Project was enabling the identification of genes, that when mutated, caused different genetic diseases, including the RPE65 gene and its role in blindness.

It still took another 20 years to fully deliver on her goal: a gene therapy to treat blindness. And along the way the NIH was a constant presence. Dr. Bennett credits the NIH for not only supporting her work, but for shaping her career.



PHOTOS COURTESY OF DR. JEAN BENNETT/UNIVERSITY OF PENNSYLVANIA

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