Parkinson's disease research spawns Novato stem-cell startup

Xianmin Zeng founded Novato-based XCell Science six years ago to develop lines of stem cells and neurons. (James Dunn / North Bay Business Journal, May 2016)

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Stem cells

Scientists start with adult somatic or embryonic stem cells, which can differentiate into cell types including muscle, skin and bone. In adults, stem cells remain quiescent until disease or injury activates them. Stem cells can be cultured to divide and replicate into a stem-cell line of identical stem cells, then stimulated to specialize. Embryonic stem cells can differentiate into more cell types than adult

A scientist and company founder at the Buck Institute for Research on Aging in Novato has developed stem cell lines from patients with Parkinson's disease that will accelerate research on the motor disorder which results from death of brain cells that generate dopamine, a crucial neurotransmitter. Dopamine controls the human brain's regulation of movement and emotions, including response to reward and pleasure.

Xianmin Zeng, a faculty member at the Buck Institute, published her findings May 18 in the Public Library of Science. Zeng derived 10 lines of pluripotent stem cells from tissue donated by Parkinson's patients. These stem cells can differentiate into many human cell types, especially to replace dopamine-producing neurons lost in the disease that affects nearly a million Americans and 7 million people worldwide.

Humans have far more dopamine than most species. High dopamine levels are associated with aggression and competitiveness (business ambition), as well as intense sexual feelings, euphoria and control of impulses. Low dopamine levels are found in people with Parkinson's, Alzheimer's, depression, binge eating, drug and gambling addiction, schizophrenia, bipolar disorder and attention-deficit disorder.

Canadian actor Michael J. Fox, who acquired Parkinson's at age 30 and turns 55 on June 9, poured resources into propelling research into the disease. About 4 percent of people with the disorder develop it before age 50. Parkinson's disease causes tremors, muscle stiffness, lack of facial

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stem cells.

Totipotent: Able to differentiate into all cell types, such as zygotes, formed at egg fertilization and first few divisions thereafter, can produce entire organism.

Pluripotent: Able to differentiate into most cell types, such as embryonic stem cells and those formed in early embryonic cell differentiation.

Multipotent: Able to differentiate into closely related family of cells, such as hematopoietic adult stem cells that become red or white blood cells or platelets.

Oligopotent: Able to differentiate into a few cells, such as adult lymphoid or myeloid stem cells.

Unipotent: Able to reproduce only their own type of cell or to self-renew, such as adult muscle stem cells.

Total estimated cells in human body: 37 trillion (37,000,000,000,000)

Neural stem cells: Differentiate into nerve cells (neurons), astrocytes and oligodendrocytes.

Transdifferentiation: Reprogramming stem cells to produce cell types not of the stem cells' lineage, such as neural stem cells differentiating into muscle cells.

Induced pluripotent stem cell: Adult cells genetically reprogrammed to resemble embryonic stem cells by being forced to express particular genes or factors. First created in 2007 in humans, useful for drug development, disease modeling and transplantation. Viruses used to introduce reprogramming factors into adult cells.

Countries that distribute XCell Science products

Belgium, Luxembourg and Netherlands: Sanbio

Denmark, Finland, France, Germany, Italy, Norway, Spain and Sweden: tebu-bio

Japan: Veritas Corp.

Commonly mutated genes implicated in Parkinson's

expression, speech impairment, and loss of balance and coordination. There is no cure yet, but Zeng's work holds huge promise.

About six years ago, Zeng founded XCell Science, a Novato-based company that sells nearly 80 products including 20 engineered lines of induced pluripotent stem cells, neural cells, and models to promote gene-editing research on diseases of the central nervous system: Parkinson's, Alzheimer's, amyotrophic lateral sclerosis, Huntington's Disease, schizophrenia and autism.

AVOIDED VENTURE CAPITAL

XCell Science, which has six employees in addition to Zeng, also does gene cloning, toxicity screening, drug testing and contract research. The company is funded with private money, Zeng said in an interview with the Business Journal. She avoided venture capital investors because they usually exert major control over a startup company's growth and focus. "I was very uncomfortable — if they tell me that another area is hotter," she said, VC funds could jump to another venture.

"It's a company based on technology developed in my lab," Zeng said of XCell. "I just got a small-business-innovation grant" from the National Institutes of Health, awarded on March 1. "That provided $1.5 million." She brings scientific direction for the company "and business strategy," as well as "executive decisions," she said. "I don't run daily operations. I make sure they have enough business."

She recruited an executive who worked for a large biotech company to take the reins of XCell at the end of the summer. Zeng won't disclose his name.

"Eventually my goal is to develop and sell therapy," Zeng said. "That's why I spun out the company. It needs to have a commercial entity." The Buck Institute is an academic institution. XCell was one of the first private companies to emerge there.

LABS AS CUSTOMERS

Hundreds of laboratories in the United States and worldwide study Parkinson's disease and other diseases of aging, and these laboratories are potential customers for products developed at XCell Science, which has distributors in Europe and Japan. A one-milliliter vial of induced pluripotent stem cells costs an estimated $5,000. Pluripotent stem cells can differentiate into nearly any type of human tissue, including dopamine-producing neurons lost in Parkinson's.

The brain has roughly 100 billion neurons, but only about 20,000 make dopamine. Those cells are located in the midbrain —the substantia nigra and ventral tegmental areas.

"The first time I was given two frozen vials of embryonic stem cells," Zeng said, "each vial cost $5,000. My boss said, grow them."

That was 10 years ago. Her experience evoked the entrepreneurial urges that led to XCell Science. "Now look at my lab," Zeng said. "We grow these cells routinely."

$140 BILLION MARKET

The potential market for treating Parkinson's patients is enormous. Prescription drugs and other treatment cost an estimated $20,000 per Parkinson's patient per year, according to a 2012 study by the National Institutes of Health. With a million patients in the U.S., total annual treatment is about $20 billion a year. Worldwide, with 7 million patients, the market could hit $140 billion a year.

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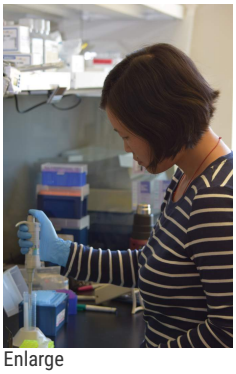
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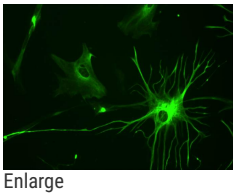
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So far, the best-selling products at XCell are neural cells, according to Ying Pei, associate director of research and development at XCell Science. She previously worked as a post-doctoral researcher at the Buck Institute. XCell also produces the medium in which to grow cells — another popular product. “We also sell them as a kit,” Pei said.

Neurons and astrocytes are sold in one-milliliter vials, Pei said, each priced at about $500. Astrocytes —star-shaped cells — are non-neuronal glial cells that surround neurons and are derived from stem cells. Astrocytes are essential to the central nervous system, providing structure and support for neurons, and in healing brain injuries.

“We guarantee one million live cells per vial,” Pei said. “When we are freezing down cells, we do very small volume. When you sort them out, you don’t want the time to be too long,” she said. “That will kill the cells.”

Induced pluripotent stem-cell lines are “much more expensive,” Pei said, several thousand dollars per vial, and are ordered by labs researching diseases such as Parkinson’s. “A lot of customers are also interested in the neuronal products of these lines,” Pei said. “Instead of getting the iPSC and doing the experiments themselves, they’d rather buy the product. A lot of these are linked to Alzheimer’s or Parkinson’s.” Two or three employees work in production for XCell Science.

SINGLE GENE MUTATION

Zeng acquired cells donated from Parkinson’s patients with a form of the disease caused by a single gene mutation then derived 10 induced pluripotent stem-cell lines. “This is the largest collection of patient-derived lines generated at an academic institute,” she said. Eight of the 10 patient lines were able to generate neural stem cells; all the neural stem-cell lines could be coaxed into dopaminergic neurons. She has studied Parkinson’s for about 15 years, including 11 years at the Buck Institute.

Overall gene expression patterns in healthy cell lines resembled those in diseased cell lines, Zeng said. Her team stressed cells by treating them with MPTP, a drug that causes Parkinson’s-like symptoms in people. MPTP caused changes in gene expression related to mitochondrial function and cell death. Mitochondria are organelles that produce energy, and are found in most cells.

PARKINSON’S IN A DISH

Because Parkinson’s is complex, research is needed with additional patient lines. Zeng’s work can “enable researchers to model Parkinson’s disease in a dish,” said Brian Kennedy, Buck Institute’s CEO, and “dissect how genes interact with each other to cause Parkinson’s.”

Zeng’s research at the Buck Institute garnered grants totaling $12.4 million from California Institute for Regenerative Medicine, starting in 2007, and including a $5 million grant for Parkinson’s research awarded in 2016, entitled: “Banking transplant-ready dopaminergic neurons using a scalable process.”

California’s stem-cell agency, founded in 2004 by passage of Proposition 71, channels $3 billion in public funds in California to support stem-cell research. Litigation to challenge Prop. 71 ended in 2007 when the Supreme Court of California upheld lower-court decisions permitting funding of stem-cell research.

“Human pluripotent stem cells may offer a potentially unlimited source of the right kind of cell required for cell-replacement therapy,” said Zeng, who earned a Ph.D. in molecular biology in Denmark. “We have optimized a step-wise scalable process for generating authentic dopaminergic neurons in defined media from human pluripotent stem

cells, and have determined the time point at which dopaminergic neurons can be frozen, shipped, thawed and transplanted without compromising their ability to mature," she said.

"I want to develop a human model system to study developmental neurobiology," Zeng said. "The best model is to use stem cells." She came into the field when human embryonic stem cells had just been derived. Zeng did research for the NIH based in Maryland.

REPLACE DYING NEURONS

Initially, scientists considered direct cell-replacement therapy to hold the best promise in treating Parkinson's. "We know which cells are primarily affected," Zeng said, "neurons producing dopamine, the most important neurotransmitter." She uses embryonic stem cells to make dopaminergic neurons."

In Parkinson's, "dopamine neurons are dying. We don't know why," Zeng said. When about 60 percent of these cells die, a patient begins to show symptoms. "If you know that a long time before" symptoms appear, she said, "you can prevent that."

Dopaminergic neurons placed inside a patient's brain must function. "If you can do that, theoretically you have a cure," she said. "New neurons are doing the job they are supposed to do."

Researchers in Sweden and the United States tried that approach with three clinical trials in the late 1990s and early 2000s, using dopamine neurons harvested from aborted tissue. "It's very difficult," Zeng said. "You have to get (cells from) four to six aborted fetuses to give to one patient. That's crazy. Plus, you cannot get pure cells through all the transplantation. You maybe get one percent of the right type of cells. The 99 percent may give you side effects," and transplantation surgery poses risks to the patient.

Some patients showed significant improvement with cell-replacement therapy and did not need levodopa or other drugs used to ease Parkinson's symptoms. "Cell-replacement therapy in theory can work," Zeng said.

Technology for making induced pluripotent stem cells was invented by Nobel prize-winner Shinya Yamanaka in 2006; he reprogrammed adult specialized cells into stem cells. Yamanaka added four genes to skin cells from a mouse, converting them to pluripotent stem cells in two or three weeks.

Induced pluripotent stem cells divide and reproduce indefinitely, like embryonic stem cells. Zeng purchased 15 skin-biopsy samples from Parkinson's patients, obtained by the NIH, and reprogrammed them into induced pluripotent stem cells of the neuron type affected by Parkinson's. These neurons have the same genetic make-up as the patient's cells — in re-creating that patient's Parkinson's in a dish.

"When you buy it, you get a vial of those frozen cells," a million per vial, Zeng said. She picked which gene mutations she wanted to study. When she started, the NIH had fewer than 100 samples. "You can grow them" into stem cells. "It's a very complicated process, and not everyone can do it," she said. The study took five years.

In 2013, XCell landed a contract with the NIH to produce 20 lines of induced pluripotent stem cells in a year. The company produces stem-cell lines from patients with Parkinson's, Alzheimer's, ALS, schizophrenia and other neurodegenerative diseases.

The NIH has a repository of many more samples of cells donated by patients. Now cells are donated by drawing blood. "You can make them

into stem cells. You have to do the reprogramming," Zeng said.

"Now you have a cell source that is renewable," Zeng said. "They can proliferate forever. You make the right type of cells using a manufacturing process we have already defined. You can give 10 patients exactly the same thing," eliminating unknowns of varying fetal tissue. "We know exactly which cell types are there," she said. "You don't need to go through the embryo," Zeng said. "Now we can do all this in a petri dish. We can make exactly the type of neurons" that succumb to Parkinson's.

Even more promising than cell-replacement therapy is use of induced pluripotent stem cells to test or discover new drugs. "If you can find a drug that can prevent (cell) deaths, then you don't need to do" cell replacement, she said. "Even if cells start dying, if you can hold it at 60 percent, then the disease is very much manageable with levodopa."

PERSONALIZED MEDICINE

Use of induced pluripotent stem cells to test hundreds or even thousands of new drugs in the laboratory could vastly speed up development of treatments for Parkinson's and other diseases. Some drugs might help one patient who has a particular genetic background more than another. "It's personalized medicine. You can do this. Before, you could just talk about it," Zeng said.

She scans literature about new drugs in development to identify molecules she wants to test, such as those that appear to protect dopamine neurons from death in mouse models. "We chose 45 or 46 drugs," she said, "and we tested them in a petri dish. We found that only a third to half of them protect the death of human dopaminergic neurons," even though they might have worked in mice.

With pluripotent cell lines derived from cells donated by Parkinson's patients, "we have the patient's history," she said. "We know exactly what mutation it is" that triggered Parkinson's.

The cells can be used to do pre-clinical studies, trying drugs on a particular form of Parkinson's without posing any risk to the person with the disease. "We have to prove that the cells are safe," Zeng said, in Phase I clinical trials. Efficacy studies show that a drug works on a disease in animals before trying it in humans.

Particularly intriguing is "repurposing" of drugs already approved by the FDA for other applications, she said. Such applications could reduce time to market by many years.

"If you think about neurodegeneration in the brain," Zeng said, "and Parkinson's disease, very often it affects mitochondria" as well. Alzheimer's disease has also been linked to impaired mitochondria functioning. "If you find a drug that can affect the mitochondria, you can maybe treat multiple diseases," she said.

Cell therapy for Parkinson's and other diseases is a few years away, Zeng said, and represents a frontier of science. "It has not been tried before," she said. "It's very exciting."

Last year Zeng met with the FDA to discuss the prospect of clinical trials for her work, and an investigational new drug application. "Where I am is to manufacture the cells in the CGMP (Current Good Manufacturing Practice of the FDA)," she said. "It's very expensive."

Pre-clinical studies and testing in mice would take about two years, and a Phase I clinical trial could be three years away. That trial would take roughly two more years, followed by Phase II and III trials.

GENE EDITING

A third research approach is to attempt editing of specific genes typically mutated in Parkinson's patients, such as SNCA, PARK2, LRRK2 and GBA.

Zeng's team compares genes from Parkinson's patients with those from healthy people, analyzing them at the molecular level. "You can maybe use some specific drug that" affects a particular genetic pathway. "We have done this with the patient line," Zeng said.

She also has taken healthy control cells and created mutations identical to those in Parkinson's patients. "I make a specific mutation that is linked to Parkinson's disease," she said. "Then I compare this to isogenic cells — identical genetic background." Such research provides highly detailed information about how drug molecules affect cells.

Another strategy is to take cells with particular genetic mutations and correct those mutations, "what we call genome editing," she said. "This is one of my interests, to develop genome-editing technology. Then you can see if the phenotype (physical expression of genetic mutation) is rescued or not. This can also help predict a drug's effect. Would it work for this patient or not — personalized medicine," she said. "Today we can do genome editing relatively easily."

The potential to help millions of Parkinson's patients and their families through groundbreaking science is a potent motivator for her research and related business enterprise. "I love work in this field," Zeng said. "This new technology can benefit human health. In the end, I want to develop a therapy — if I can make a difference, no matter how small, that's my goal. Think about — if I can prevent them from getting sick." The impact could be gigantic.

Though Zeng doesn't directly treat Parkinson's patients, "I understand their pain," she said. "I see how they struggle."

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