

BEAR DOWNING ON PARKINSON'S

Are scientists at last closing in on a drug to stop the progress of this disease?

By Robert Langreth Illustration by Kensuke Koike





Randy Schekman, a cell biologist at the University of California at Berkeley, won the 2013 Nobel Prize in medicine for his insights into how yeast cells transport proteins to where they're needed. Some of that work helped lead to biotech breakthroughs, including new ways to produce insulin and hepatitis vaccines.

Despite his brilliance, and his access to other brilliant scientists and doctors, Schekman sometimes felt helpless after his wife, Nancy Walls, was diagnosed with Parkinson's disease in the late 1990s. Many of her symptoms were controlled by dopamine-boosting drugs, and later a surgically implanted pacemakerlike device, but that didn't stop the disease from progressing. By the time Schekman won the Nobel, Walls had developed Parkinson's-related dementia. In her final months she was often in a zombielike state. She died in her sleep in 2017 at age 68.

"There was nothing I could do to help her and nothing I could do to prepare, because the disease progresses in ways that are quite different," Schekman recalls. "There is no way to plan ahead." So when a representative from the family office of Google co-founder Sergey Brin called on him shortly after his wife's death to see if he was interested in helping establish a vast program to find the cause of Parkinson's, it resonated. Now Schekman and molecular biologist Ekemini Riley are helping lead a new Brin-sponsored initiative called Aligning Science Across Parkinson's, or ASAP. Started quietly

right before the pandemic, it's become one of the biggest funders of Parkinson's research in the world. The organization is working hand in hand with the Michael J. Fox Foundation for Parkinson's Research, named after the *Back to the Future* actor with the disease.

Brin has one of the most common Parkinson's risk mutations, in a gene called LRRK2, and he's been a heavy funder of research for years. He and his family foundation have donated almost \$1.3 billion to the cause and are the biggest donor to the Michael J. Fox Foundation. "The family has been very good to us," says Fox in an interview at his office on New York's Upper East Side. Together the two groups are now putting more than \$350 million a year into Parkinson's research, more than the National Institutes of Health, with hundreds of millions of dollars more likely over the next several years.

The goal is to develop disease-slowng therapies and tests that can detect Parkinson's before the development of obvious symptoms, when the disease may be more easily treatable. ASAP can be thought of as the basic science arm of the effort, building teams to help find genetic clues and come up with new ideas for drugs and diagnostics. The Fox Foundation proper is more focused on applied research, devising the tools that companies can use in the near to medium term to develop therapies.

It's all badly needed. Parkinson's is the second most common neurodegenerative disease after Alzheimer's. Worldwide, 8.5 million people suffer from Parkinson's, and its prevalence has doubled in the past 25 years as the population has aged. Most people first develop symptoms after age 60. The disease causes cells that produce dopamine to die, leading to stiffness, slowness, tremors and a bewildering variety of other symptoms including loss of smell, sleep disturbances, depression, psychosis and dementia. Exactly what triggers Parkinson's remains mysterious, though many clues point to defects in cellular waste removal and debris buildup inside delicate neurons.

US regulators gave full approval to the first disease-slowng agent for Alzheimer's, Eisai Co.'s Leqembi, in July; approval of a second is expected in early 2024. No such medicines exist for Parkinson's. It's been 60 years since scientists discovered the effects of L-Dopa, the symptom-alleviating drug featured in *Awakenings*, a movie about patients with a rare Parkinson's-like encephalitis. But as effective as dopamine-boosting drugs are in easing motor symptoms, they don't arrest or slow the death of brain cells, and they cause

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long-term side effects. The implanted device that Walls received, an electrical deep-brain stimulator, provides substantial relief but doesn’t slow neuronal death.

The alliance of a brainy tech mogul and a high school dropout actor has already found new leads and largely avoided the scientific infighting that’s plagued the Alzheimer’s field. In April researchers at the Fox Foundation, the University of Pennsylvania and elsewhere confirmed that a spinal fluid test can accurately spot a toxic protein called alpha-synuclein, which builds up inside the neurons of Parkinson’s patients; this advance could pave the way for new tests to monitor disease progression at its earliest stages. In August, ASAP-funded researchers in Nigeria, the UK and the US found a gene variant that increases risk of the disease 3.5-fold in people of West African descent, in one of the first big studies of the genetic risk of Parkinson’s in that population. And in drug development, ASAP “has revolutionized the research,” says Dario Alessi, a biochemist at the University of Dundee in Scotland who used to work on cancer but now focuses exclusively on Parkinson’s. With Fox Foundation funding, he’s designed laboratory tests that drug companies use to search for treatments blocking the LRRK2 protein that is overactive in people like Brin.

What Fox, Brin and Schekman don’t have is a breakthrough treatment that can stop or even slow Parkinson’s. A variety of companies, including Biogen, Roche, Novartis and startup Neuron23, have begun human trials with agents targeting potential molecular causes of Parkinson’s. But most of these drugs are in the early to middle stages of testing, and results won’t start to roll in until the end of 2024 or later. At age 62, Fox has lived with the ailment for half his life, and his disease is progressing: He falls more often—including an onstage fall at a fan expo in June—and has uncontrolled movements from years of taking dopamine-producing drugs. Brin recently turned 50 and, like millions of others with Parkinson’s risk mutations, faces a substantial likelihood of developing symptoms in the coming years.

PARKINSON’S-SLOWING AGENTS: WHERE THEY STAND

Phase of trials	Company	Molecular target
Phase II (initial efficacy)	Biogen/Denali	LRRK2
	Roche	Alpha-synuclein
	UCB/Novartis	Alpha-synuclein
Phase I (safety)	Neuron23	LRRK2
Preclinical	AbbVie	PINK1

In 1817 a British surgeon named James Parkinson described six people with a strange slow-moving disease he called “the shaking palsy.” It usually started with trembling in the hands or feet, he noted in a 66-page essay, and progressed over years until patients had trouble walking, speaking intelligibly, sleeping or even feeding themselves. Efforts to understand the disease proceeded in fits and starts over the next century and a half. In the 1870s the French neurologist Jean-Martin Charcot refined the description, noting that profound slowness was a central feature, and renamed it Parkinson’s disease. Over the next 50 years, researchers showed that damage to a structure deep inside the brain called the substantia nigra is what causes Parkinson’s.

It wasn’t until the late 1960s, after dopamine was shown to be a neurotransmitter produced in that part of the brain, that a highly effective therapy was discovered: levodopa, or L-Dopa. It and numerous other drugs that boost or modulate dopamine levels have remained the mainstay of therapy for decades. But none of these treatments solve the central problem, says Dimitri Krainc, a neurologist at Northwestern University: “You feel better with L-Dopa, but your neurons are still dying.”

Fox was diagnosed in 1991, at the age of 29, and founded his nonprofit in 2000. The Parkinson’s drug development field had begun to stagnate, and Fox wanted to do something aggressive about drug development. He picked an energetic former Goldman Sachs Group Inc. ►executive

◀ with limited nonprofit experience, Deborah Brooks, to run the organization.

Fox and Brooks say it was an advantage to come into the field without any biases or preconceived notions about what might work. “I am an expert in frigging Parkinson’s,” Fox says. “I have had it for 30 years. You can be a Nobel Prize winner, and I can tell you stuff you don’t know.” In his office, an honorary Academy Award given to him for his charity work faces a giant black-and-white print of him and the late boxer Muhammad Ali, who suffered for years from Parkinson’s.

His sense from the beginning, Fox says, was that “the science was ahead of the money.” His foundation aimed to give out grants faster and with less paperwork than government funders while forcing scientists, who can be highly competitive, to share data. It focused on blue-sky research but also funded applied science that could lead to drugs and diagnostics, including eventually providing money directly to companies. Fox says his instructions at the first board meeting were “I would like you to help me go out of business.”

Well into the 1990s, Parkinson’s researchers remained focused on environmental causes and, in particular, pesticides, says John Hardy, a geneticist at University College London. “Everybody was taught that Parkinson’s was not a genetic disease,” he says. That started to change in 1997, when researchers at the National Institutes of Health found the first genetic link to Parkinson’s, a rare mutation in the alpha-synuclein gene. Since then, around 15 other Parkinson’s-promoting gene mutations have been found. Although most Parkinson’s patients don’t have these mutations, they still provide drug hunters important clues to the molecular causes of the disease.

In 2004, Brooks heard through a contact that Eugenia Brin, Sergey’s mother, had Parkinson’s. Through former Intel Corp. Chief Executive Officer Andrew Grove, a Parkinson’s sufferer and an early adviser to the Fox Foundation, Brooks was able to set up an introductory dinner with Sergey Brin and Grove, leading to Brin’s first large donation in early 2005. Brin “really wants to see this happen,” Fox says. “He is exciting to work with because you’ll literally tell him something and he’ll go, ‘Let’s do it.’” Around this time, researchers at the NIH and elsewhere discovered LRRK2 mutations, found in roughly 2% to 4% of cases. The mutations produced an overactive enzyme that could, in theory, be blocked with a drug to reduce their activity. It was the same class of enzyme that’s been successfully targeted to create many cancer drugs.

In 2008, Brin revealed in a blog post that he had G2019S, a common LRRK2 mutation, and that he’d gotten it from his mother. At a meeting that year at Google headquarters, Brooks says, she proposed a Manhattan Project to speed research into LRRK2 to help pave the way for treatments. At the time researchers knew little about what LRRK2 mutations do in the body or how they might contribute to Parkinson’s risk. Within the next few years, numerous drug companies started researching LRRK2. By 2011 the Fox Foundation, supported by Brin, was funding 30 teams of academic scientists to understand what the mutations did. It also created an industry advisory board to find ways to share resources

to push the research ahead.

The Fox Foundation has spread its bets widely. In 2010 it funded Neuropore Therapies Inc. to research a drug targeting alpha-synuclein. That helped lead to a compound now in Phase II trials at Belgian drugmaker UCB SA and its partner Novartis AG. It also funded early research at the University of California at San Francisco that paved the way for a drug candidate against a third Parkinson’s risk protein, called PINK1. In October, AbbVie Inc. acquired the biotech company based on the UCSF technology for \$110 million. It could lead to the first human trials for a drug targeting this protein.

In 2017, at a dinner with Fox and a group of Fox Foundation donors, Brin told attendees that he never expected to be working with the actor who played Marty McFly, but he was impressed by the quality of his foundation’s work. “Many other disease categories would love to have an equivalent organization,” he said.

By that point, Brin’s family foundation was quietly planning for a massive expansion of his Parkinson’s efforts. In 2015 it had started working with the Milken Institute Center for Strategic Philanthropy to identify gaps in research. Riley, who was then at the Milken Institute, set up a series of meetings with top neuroscience researchers to determine the major deficiencies that could be addressed if money were no object. “We’d gotten the signal from the foundation that they were really interested in doing something big,” Riley says. The assignment was “if you wanted to increase it and do something bigger, what would you do?”

Around that time, Schekman started talking with George Pavlov, a former venture capitalist who heads Brin’s family office. Pavlov had heard about Walls’ diagnosis and wanted his advice on how one might deploy significant resources to move the science forward, Schekman says. By that point, Walls’ dementia was advanced. She would sometimes open her mouth to talk and not say a word, having already lost the thought. She didn’t know who the president was. On the plane ride home from the 2013 Nobel Prize ceremony, she had forgotten the reason for the trip.

A few months after Walls’ death, Pavlov invited Schekman to chair a planning committee for Brin’s new initiative, held during a big annual gathering of brain scientists. “I came away from that meeting thinking, ‘I have to do this, whatever is involved,’” Schekman says. He and Riley started working closely together to develop the program that became ASAP. It was introduced in October 2019, with Riley as the day-to-day leader and Schekman as the head of the scientific advisory board. It isn’t a separate charity but funds and administers its programs through the Fox Foundation. Schekman maintains his lab at UC Berkeley, which is working on Parkinson’s. On a bulletin board in his office, he’s tacked a faded snapshot of his wife before she was sick.

A cornerstone of ASAP is a \$290 million collaborative research network that funds 35 teams from normally competitive labs to get a handle on numerous potential causes of the disease. Schekman has long been frustrated with incentives in academia that can discourage collaboration and data sharing between labs. “The way industry works, it is a team effort,” he says. “In academic science, the reward ▶



FOX IN HIS
NEW YORK OFFICE

◀ structure favors the individual.” To counteract this tendency, Schekman and Riley require that teams include scientists from multiple institutions and assign a doctoral-level project manager to each team to make sure those institutions continue to work together.

Alessi, the researcher in Scotland, is working with Stanford University on one team to figure out how LRRK2 mutations damage neurons. Another team, led by Memorial Sloan Kettering Cancer Center stem cell biologist Lorenz Studer, is using stem cells to better understand the multiple risk factors for the disease. A third team is exploring whether Parkinson’s starts in odor-sensing neurons before spreading to other parts of the brain. For many patients, including Schekman’s late wife, a poor sense of smell is the first symptom.

“The idea is to have lots of shots on goal” and not get fixated on any one therapeutic strategy, Schekman says. He contrasts ASAP’s broad approach with the Alzheimer’s field, which, despite its recent success at creating disease-slowing drugs, has often been criticized for focusing too heavily on one cause of the disease, amyloid plaques. In Schekman’s view, that narrow approach has diverted attention away from alternative avenues for developing treatments, something he doesn’t want to see happen with Parkinson’s research.

The odds that the first generation of gene-targeted

Parkinson’s drugs will succeed in trials are probably low. With Alzheimer’s it took more than 20 years of failed drug trials until the first big success in 2022. Parkinson’s progresses slowly, with effective symptom-masking drugs, making testing potential disease-slowing agents in people a particularly long and difficult endeavor.

Over the years, at least a dozen drugs attempting to slow Parkinson’s have failed in trials. In 2020 a Roche Holding AG antibody against alpha-synuclein generated mixed results in a Phase II trial, missing its main efficacy goal; the company is now running a second big trial. In February 2021, Biogen Inc. canceled research into its own alpha-synuclein antibody after a Phase II trial showed no benefit. The same month, Sanofi said its experimental drug venglustat failed to slow Parkinson’s in a Phase II trial of people with a specific genetic form of the disease.

The many uncertainties may be making some drug executives hesitate before moving prototype drugs into costly human trials—a reality that Brin’s billions of dollars can’t easily counteract. “A lot of them are sitting on the fence,” Alessi says. “They have been burnt before, so maybe their strategy is to wait and see what happens before they decide what to do.”

In the case of drugs that aim at LRRK2 mutations, several of the companies that started researching them years ago have not moved into human trials. GSK Plc worked on LRRK2 drugs for at least six years, with early funding from the Fox Foundation, and in 2018 it said the program had the potential to move into human trials. Since then, the company has made a business decision to focus on other disease areas, according to a spokesperson. And while Merck & Co. and Eli Lilly & Co. are looking into LRRK2, neither has started human efficacy trials.

Some patient advocates worry whether drugs against any of the genetic targets will make much of a difference in people who already have symptoms. Benjamin Stecher of Toronto was diagnosed with Parkinson’s at 29 years old, the same age as Fox when he received his diagnosis. He’s now 39 and says he’s grown skeptical of the Fox Foundation’s focus. In particular he’s not convinced the gene-based approach to developing drugs will pay off.

Although Stecher has one of the Parkinson’s-promoting mutations that drugmakers are targeting, called GBA1, it’s far from clear that a drug that counteracts it could make a difference at his stage in the disease. “I don’t think going after the genetics of the disease will translate into treatments



“Now we can measure it in life and don’t have to wait for someone to die”

for patients like me, ever,” he says. In his view the foundation should put more emphasis on developing digital tools that could customize symptomatic treatments for existing patients and do more work on improving existing electrical stimulation therapies.

By the time Stecher, Fox and Eugenia Brin were diagnosed with Parkinson’s, they likely had already lost about 50% of their dopamine-producing brain cells. That’s the best estimate doctors have, based on autopsy studies of patients who died at various stages of the disease. In a living patient, it’s hard to tell for sure, because there are few tests that can peer inside the brain to determine how the pathology is progressing in real time.

In Alzheimer’s, the advent of specialized brain scans to detect buildup of amyloid has aided the testing of disease-slowng drugs. A way to measure Parkinson’s pathology early in the course of the disease with a scan or blood test could undoubtedly speed the testing of disease-slowng drugs, but Parkinson’s still lacks a way to quantitatively measure alpha-synuclein pathology in living patients, making drug studies much harder.

But researchers are getting closer. The recent study from the University of Pennsylvania and Fox Foundation, reported in *Lancet Neurology*, found that a spinal fluid test can accurately detect alpha-synuclein pathology in about 90% of Parkinson’s patients. (The test is available, but insurance may not cover it.) “For 100 years, we have known that synuclein was a key pathology in Parkinson’s disease,” says Kenneth Marek, a neurologist at the Institute for Neurodegenerative Disorders and a senior author on the study. “Now we can measure it in life and don’t have to wait for someone to die.”

Fox hopes that advances like this can eventually help to treat people when more neurons are intact and there’s still a chance of preserving them. Toward this end, the Fox Foundation plans to soon start working with multiple drug companies on trials aimed at disease prevention. Such trials are likely to be long and expensive, and it’s not clear how many drug companies would be willing to do it on their own. The foundation plans to take some of the risk off the table by partially subsidizing the trials and providing a giant cohort of at-risk people who’ve already agreed to be in a study. It says it’s received letters of interest from numerous drug companies, though no deal has been finalized.

Fox says he’s not expecting anything his foundation is doing will generate cures for himself. He’s too far along in the progression of the disease for many treatment trials. “I don’t think about that,” he says. Nonetheless he sometimes gets impatient that progress can’t happen faster. Schekman says his own goal is to generate lots of new leads for drugs and devices over the next five years. “If we could find a drug that was designed to mitigate or relieve the progression in one genetic, one familial form of Parkinson’s,” he says, “that would be a tremendous victory.” **B**