There are approximately 170 billion cells in the human brain — a quantity that is within the range of the estimated number of stars in the Milky Way. When some of these cells deteriorate and die, the reduction in the chemical they produce (dopamine) leads to a loss of motor coordination and control that is characteristic of Parkinson's disease (PD). Abnormal clumps of a protein called alpha-synuclein also begin to cluster in PD patients' brains.

But these broad clinical descriptions do not explain why most of the 10 million people alive today with PD have the disease, or how quickly their disease will progress. Different genes and environmental exposures mold each person’s billions of brain cells to behave differently from the next person’s — a lack of pathological uniformity that precludes a one-size-fits-all treatment.

Researchers at the Brigham are examining this challenge from multiple perspectives. They are collecting vast amounts of longitudinal data from thousands of human patients and replicating specific genetic and cellular mechanisms in both human stem-cell and animal models to pinpoint where brain circuitry becomes faulty, ultimately hoping to determine how to treat PD patients according to their unique situations.

A Center for Precision Neurology

For Clemens Scherzer, MD, founding director of the Center for Advanced Parkinson Research and the Precision Neurology Program, understanding the heterogeneity of PD and identifying a full range of possible therapies starts with mapping genome function in patients and patient brain cells. Instead of treating patients as if they were all the same, Scherzer is on a mission to predict and target the specific disease-drivers in each patient.
Faithful Human Models

Like Scherzer, Vikram Khurana, MD, PhD, MBBS, chief of the Division of Movement Disorders at the Brigham and a principal faculty member of the Harvard Stem Cell Institute, sees individualized treatments as the future for Parkinson’s disease. But whereas Scherzer decodes patients’ brain cells to gain more insight into the nature of the disease, Khurana is focused on growing them himself.

Khurana’s laboratory, based in the Ann Romney Center for Neurologic Diseases, is able to take mature cells — like those in a skin sample or strand of hair — from genetically diverse patients and reprogram them into stem cells that can develop into the different types of brain cells implicated in PD.

“Ultimately, if you have a faithful model of your own patients’ brain cells or even ‘mini-brains’ in a dish, when they’re alive, then you can use that as a model for therapeutic intervention,” said Khurana, noting that neurologists, unlike cancer researchers, are otherwise unable to procure live tissue samples from their patients given the nature of the human brain.

In particular, Khurana closely examines the misfolding of the alpha-synuclein protein, which forms clusters in the brain cells of PD patients. In 2013, he led a seminal study that showed that PD patient-derived brain cells could be used to identify new candidate drugs. In 2017, Scherzer led a study analyzing the pharmaceutical records of over 4 million people, identifying a commonly used asthma drug, called a beta-2 adrenoreceptor agonist, that may be effective in targeting a regulator of the alpha-synuclein gene. He collaborated with Khurana’s team to verify these findings in human stem-cell models, and clinical trials of the drug are now underway.

“What you see overall in the Ann Romney Center is colleagues working in close contact with each other, which motivates a new understanding of the biology of the disease,” Khurana said. “Ultimately, if someone has a potential therapy for Parkinson’s in our department, we want to find out who the best candidates are, and that’s where the human stem cell model is extremely powerful.”

He adds that these models can also play a key role in understanding how an individual’s genetic composition and environmental exposures can contribute to that specific individual’s disease. Khurana, a co-investigator of another project recently awarded an ASAP grant, is using this funding in addition to federal grants to advance discovery in these important areas.

Modeling PD in Mice

In the laboratory of Silke Nuber, PhD, of the Ann Romney Center, research is focused on novel mice with a trembling gait that closely resembles PD’s motor disabilities. Unlike PD researchers using stem-cell models, scientists working with animal models can study how, for example, mutations in the human alpha-synuclein gene affect phenotypes and behaviors that are indicative of alterations in the animal’s brain. Many of these models, however, fail to reproduce PD symptoms in all of their intricacy. Without accurate animal models, identifying the pathologies in brain neurons leading to disease is much more difficult, as is evaluating the efficacy of drugs in preclinical trials.

Recently, Scherzer and colleagues who are part of an initiative known as the PD5D Consortium were awarded a $9 million grant to map the integrated cell circuits of PD. The Aligning Science Across Parkinson’s (ASAP) initiative funded five laboratories, including three at the Brigham, to analyze 645,000 human brain cells. PD researchers will investigate how glitches in the genetic code cause specific brain cells to falter across five dimensions, including brain cell types, brain space and disease progression.

Transforming these data into cures requires the expertise of researchers from across disciplines. With one of the nation’s eight Centers for Advanced Research supported by the American Parkinson Disease Association, the Brigham is well-positioned to break down the silos separating disciplines. Scherzer, its director, describes it as “a center without walls” — a place where physicians, scientists, and engineers collaborate to bring discoveries to the patient’s bedside.

“Our unique, interdisciplinary set-up allows us to find disease drivers and then go back to Parkinson’s patients with precision medicine trials,” Scherzer said. “Building on the rich Brigham ecosystem, we are focused on creating health care models for the future.”
Silke Nuber

normal four-unit-structure (tetramer) of the alpha-synuclein protein to disassemble into single units. These units then form aggregates similar to those seen in PD patient brain.

“The advantages of this approach are very compelling,” Nuber said. “You can see just by looking at the mouse with this genetic variation that it has motor dysfunction, a body tremor that develops as early as three months, and one can see aggregates in the mouse brain sections already at six months.”

The rapid onset of these symptoms, which developed in many single-mutant PD mouse models over the course of more than 14 months with less phenotypic subtlety, makes it possible for researchers to test treatments more effectively. In collaboration with her colleagues including Selkoe, Ulf Dettmer, PhD, and Saranna Fanning, PhD, both of the Ann Romney Center, Nuber undertook a trial of a drug called enzyme stearoyl-CoA desaturase (SCD) in mice with PD phenotypes. The group’s insight into the chemical interactions between the disassembled alpha-synuclein proteins and the lipid membranes to which they bind led to an investigation of whether SCD, which changes the saturation of these membrane lipids, could improve Parkinson’s disease phenotypes.

“After four months of treatment, we found fewer lipid-rich aggregates, higher dopamine levels, lesser tremors and better gait balance,” Nuber said. The findings bolster support for a clinical trial of SCD inhibitors in human patients.

Lessons from a Fruit Fly

Nuber and Khurana’s intersecting work on SCD inhibitors is just one example of how Brigham laboratories with robust animal models of Parkinson’s disease contribute to the search for new therapies.

In 2000, Mel Feany, MD, PhD, of the Department of Pathology, helped create the first Drosophila (fruit fly) model of PD. Feany, Khurana’s former mentor and a co-principal investigator of the PD5D initiative alongside Scherzer, is now guiding other Brigham researchers as they adapt this model for novel research.

Abby Olsen, MD, PhD, of the Movement Disorders Division, is working to systematically knock out genes in Drosophila glia, another type of brain cell that may play a role in disease progression. Olsen is beginning with genes that are already targets of therapies approved by the U.S. Food and Drug Administration. If “erasing” a gene improves the functioning of the PD fly, then the protein it produces may be an easy therapeutic target.

“What’s really effective about the fly model is that it’s in vivo, but it’s more manipulatable than a rodent model of Parkinson’s disease, in which I could never do this high-throughput analysis on the same scale,” Olsen said. “I’m finding novel pathways that we didn’t know were important for Parkinson’s pathogenesis, but that when we target them in glia, can improve Parkinson’s symptoms in the fly.”

She will soon be publishing her findings that the LRRK2 and GAK genes, which are already well-established to play a role in the neurons of PD patients, also exert some of their influence in glia. She suggests that their role is more complex than was previously appreciated, calling into question theories on how to target them therapeutically.

“We’re all bringing something to the table with different model systems,” Olsen said. “These are all pieces in the puzzle. It’s through the fly, the stem cells, the mouse, and the human samples that we’re going to really learn things about this disease.”

Rounding Back to the Patient

While neurodegeneration researchers at the Brigham may spend many of their days each week in a lab, they also spend time at the bedside, listening to the experiences of patients who are currently struggling with the disease. For many PD experts, the roles of doctor and researcher are deeply intertwined, each informing the other.

“As a physician-scientist, you see what’s important to people,” Olsen said. “You see what this disease really looks like on a regular basis for people, which lends insight into better ways to model the disease in animals.”

One example of a commonly reported symptom in humans that has been largely overlooked by researchers working with animal models is constipation, which often predate the onset of many other PD symptoms and can severely impact patients’ quality of life. Olsen, who sees this frequently with her patients, has begun monitoring the rate at which Drosophila are able to process their food, an easy task given their transparent abdomens. Constipation in a fruit fly is not only indicative of a faithful model but also allows Olsen to better understand the science behind it and explore treatments for patients.

This patient-centered ethos is at the core of the major PD initiatives being conducted at the Brigham. “The Brigham is one of the leaders, if not the leader, in precision medicine for Parkinson’s disease,” Scherzer said. “Parkinson’s disease research starts with the patient and ends with the patient.”
As an example, he cites the recent finding based on genetic sequencing of patients that clarified the role of the glucocerebrosidase (GBA) gene in regulating the speed of PD progression, with samples from the HBS biobank revealing biomarkers for this pathway. The Brigham has partnered with the drug company Sanofi to advance gene-targeted drug trials for the GBA pathway.

Physicians like Olsen are acutely aware of the importance of patient participation in that process. "I'm so grateful to our patient population," she said. "On the whole, our patient population has been so willing to participate in research that often doesn't benefit them directly. They're really doing it out of the goodness of their hearts, knowing that it's going to benefit other people in the long run."