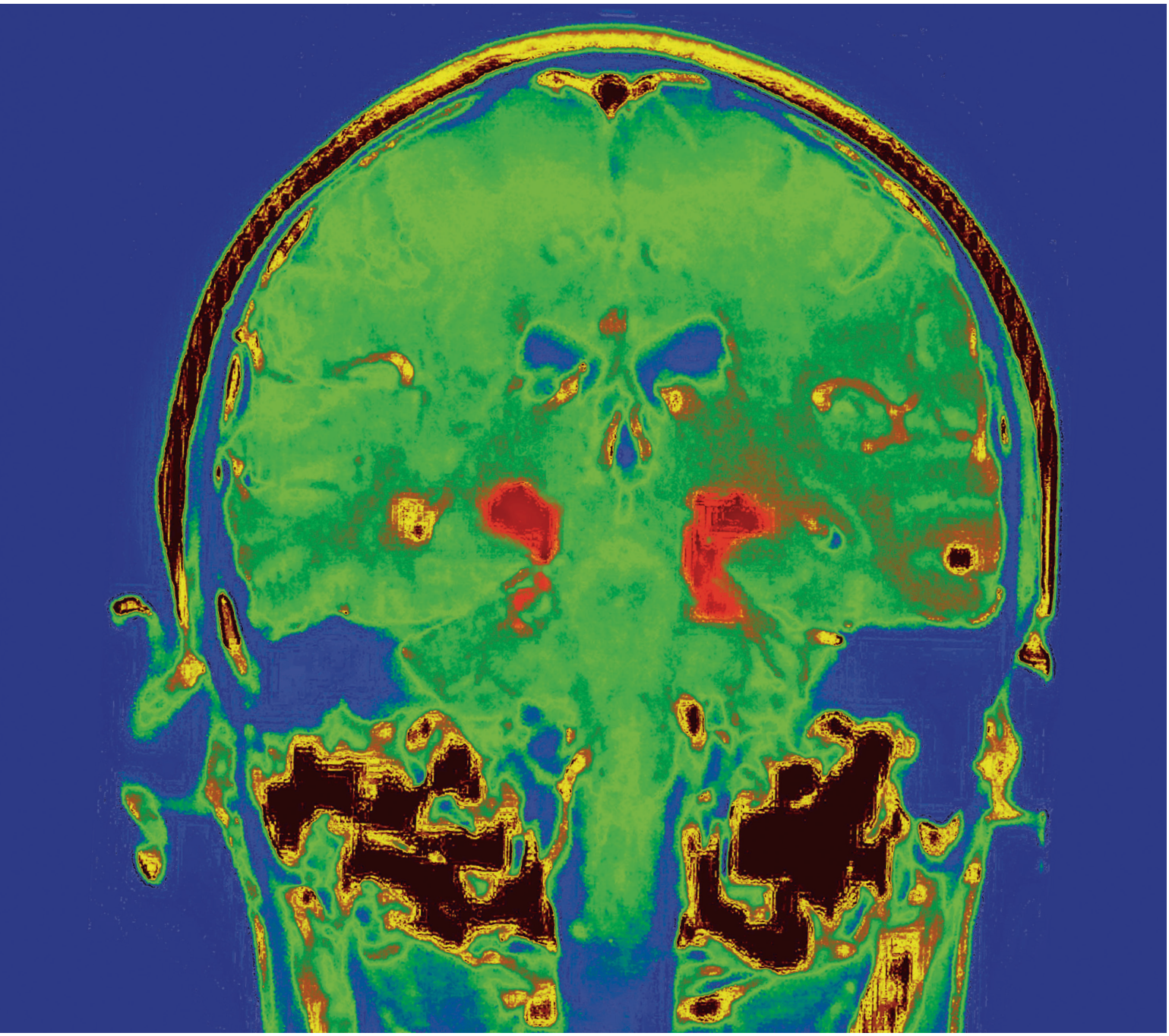
Stanford | MEDICINE



Parkinson's Disease

A THERAPEUTIC PIPELINE TO TRANSLATE DISCOVERIES INTO PERSONALIZED INTERVENTIONS

Parkinson's disease disrupts the motor function, cognition, and even autonomic function of millions of individuals. It will also exact a grievous toll on their loved ones and society as a whole. As our population ages, these human costs will only grow higher—unless we act now. Current interventions can relieve some motor symptoms of Parkinson's disease, but none slow disease progression, and none are effective against the cognitive aspects of Parkinson's that are critical to gait and balance, thinking, and planning.

Safe and effective interventions to cure Parkinson's disease—or at least delay its onset and slow its progression—are needed desperately. Offering patients real solutions requires a dedicated therapeutic pipeline that spans basic research to clinical trials, which in turn requires a focused intellectual and financial commitment. This therapeutic pipeline is a focused, coordinated, step-by-step approach directed by Thomas Montine, MD, PhD, a physician-scientist known widely for his seminal work untangling the molecular and structural causes of brain aging and neurodegeneration. The founding director of one of only seven national Udall Centers for Parkinson's disease research, Dr. Montine will lead an unparalleled team of experts in neurobiology, neurology, neuropathology, stem cell medicine, genetics, medicinal chemistry, engineering, and molecular and cellular physiology from across Stanford. Together, these scientists will drive progress at every stage of the pipeline, with an intense focus on early detection and molecularly-tailored interventions.

Leveraging the scientific powerhouses on our campus, including the Stanford Neurosciences Institute, the Institute for Stem Cell Biology and Regenerative Medicine, Chemistry, Engineering & Medicine for Human Health (ChEM-H), the multidisciplinary research incubator Bio-X, and the SLAC National Acclerator Laboratory, will uniquely enable our success. So will our outstanding clinical enterprise, including the new $2 billion Stanford Hospital and the new state-of-the-art Stanford Neuroscience Health Center. Stanford has all these resources on a single campus where researchers and clinicians can collaborate easily. Additionally, the Stanford Alliance for Innovative Medicines (AIM), a partnership with Takeda Pharmaceuticals, will help bridge the "valley of death" between fundamental Parkinson's research and the development and approval of new therapies.

Stanford Medicine's location in the heart of Silicon Valley offers further advantages. Not only does it allow us to leverage strong connections with leading pharmaceutical and biotech companies to advance innovations to clinical trials quickly, it also gives us our most valuable asset of all—our culture. Stanford is imbued with an entrepreneurial research ethos unique in academia. From our seven Nobel laureates in the biosciences (one of whom will lead a critical stage of the pipeline), to our first-year grad students, researchers here are encouraged to take intellectual risks and ignore traditional academic boundaries in pursuit of their most creative and innovative work. The result is an ecosystem where bold endeavors like this can thrive and succeed like nowhere else.

The team's immediate objective is to advance at least two novel interventions to biomarker-based learning-phase clinical trials over the next five years. But our ultimate goal is to discover, innovate, and implement solutions until each person afflicted with Parkinson's disease can be diagnosed early and offered a personalized treatment plan that prevents or stops the disease. With your philanthropic partnership, we'll finally make safe and effective interventions for Parkinson's disease a reality.

Parkinson's Pipeline at Stanford

Each stage, as outlined at right, will have specific objectives and faculty leaders with proven track records. From unraveling genetic risk and molecular mechanisms through finding novel biomarkers to guide clinical trials, these leaders will drive progress at all five stages of the pipeline simultaneously. The result will be a robust system for creating new methods for early detection and effective intervention.

Stage 1: Genetic Risk

Identifying genes that drive disease initiation and progression, and understanding how their expression is controlled, is crucial to finding new diagnostics and molecular mechanisms. The genes MAPT *and* SNCA *have been identified as the major risk genes for Parkinson's disease over the last decade. More recent studies conducted at Stanford have determined that the genes* APOE *and* GBA *are also major risk variants for the impairment of motor and cognitive function in Parkinson's patients.*

Howard Chang, MD, PhD, and Ryan Corces, PhD, will lead this first stage. Co-inventor of the widely-used ATAC-seq epigenomic profiling assay, Howard has also developed Omni-ATAC, a version of this technology that is optimized for human brain samples. His team is using this groundbreaking assay to map the regulatory landscape of risk genes in the regions of the brain affected by Parkinson's disease.

Stage 2: Molecular Mechanisms

Although genetic studies can identify risk genes, they do not clarify what roles are played by their protein products. Understanding the molecular mechanisms that initiate or promote disease is necessary for us to discover therapeutic targets.

Nobel laureate Thomas Südhof, MD, PhD, brings his vast experience in determining how risk gene products promote neurodegeneration to this stage of the pipeline. He and his team are working to unravel the molecular mechanisms of protein products in Parkinson's disease.

Stage 3: Candidate Therapeutics

The next stage is transforming knowledge about molecular mechanisms into candidate therapeutics. Success here not only requires broad expertise in medicinal chemistry, engineering, and stem cell biology, but also close collaboration between basic scientists and clinicians. This stage will focus on three approaches:

***Neuron energetics** – Chaitan Khosla, PhD, director of ChEM-H, and Mark Smith, PhD, are working with Tom Montine, MD, PhD, to develop novel agents to support the high energy needs of neurons affected by Parkinson's disease.*

***Neurotrophic Therapeutics** – Frank Longo, MD, PhD, and his team have developed agents that suppress tau pathology in the brain in animal models and are working to optimize them for Parkinson's disease.*

***Cell-Based Therapies** – Maria Grazia Roncarolo, MD, co-director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, and her team are working to repurpose cell-based treatments for Gaucher's disease to fight Parkinson's disease. Both share* GBA*, the most common risk gene for Parkinson's.*

Stage 4: Pre-Clinical Development

Success in taking discoveries from the laboratory to clinical application requires experimental models that accurately reflect human biology and predict efficacy in people. Reprogramming cells in culture enables us to produce human brain cells (neurons and glia) from skin fibroblasts obtained by biopsy.

Marius Wernig, MD, who pioneered the direct reprogramming of human fibroblasts into neurons, will use this method to create neuronal or glial cell lines from each Parkinson's patient enrolled at Stanford who consents to skin biopsy. We will establish a repository of cells that reflects the entire spectrum of Parkinsonian diseases, use it to test promising candidates, and share this invaluable resource with investigators around the world.

Aaron Gitler, PhD, will then optimize dose and timing for penetration into the brain by testing candidates in transgenic mice. This graded approach of testing in cultured cell lines for relevance to humans and then in transgenic mice for optimal delivery to the brain will provide the pre-clinical evidence to move forward with clinical trials.

Stage 5: Clinical Trials

As promising candidates emerge, customized biochemical assays will assess target engagement. (Patho)physiologic impact will be evaluated with molecular neuroimaging.

This includes kinematic measures of gait and balance like those pioneered by Dr. Helen Bronte-Stewart, novel PET tracers, including one recently developed for neuroinflammation by the lab of Michelle James, PhD, and functional MRI led by Kathleen Poston, MD, MS, who is also the director of the Udall Center Clinical Core at Stanford.

Together, these experts and technologies will confirm target engagement, determine efficacy, and accelerate clinical trials at Stanford.

For a complete listing of clinical trials at Stanford visit clinicaltrials.stanford.edu.

Parkinson's Pipeline Team

TEAM LEADER

Thomas Montine, MD, PhD
Stanford Medicine Endowed Professor in Pathology
Chair, Department of Pathology
Director, Pacific Udall Center

STAGE 1 | GENETIC RISK

Howard Chang, MD, PhD
Virginia and D. K. Ludwig Professor of Cancer Genomics
Director, NIH Center of Excellence in Genomic Science: Center for Personal Dynamic Regulome

Ryan Corces, MD, PhD
Post-Doctoral Fellow
Chang Lab

STAGE 2 | MOLECULAR MECHANISMS

Thomas Südof, MD, PhD
Avram Goldstein Professor in the School of Medicine
Nobel laureate, Physiology and Medicine, 2013

STAGE 3 | CANDIDATE THERAPEUTICS

Chaitan Khosla, PhD
Wells H. Rauser and Harold M. Petiprin Professor in the School of Engineering
Professor of Chemistry and, by courtesy, of Biochemistry
Director, Stanford ChEM-H (Chemistry, Engineering & Medicine for Human Health)

Mark Smith, PhD
Senior Research Scientist, Stanford ChEM-H

Frank Longo, MD, PhD
George and Lucy Becker Professor in Medicine
Chair, Department of Neurology and Neurological Sciences

Maria Grazia Roncarolo, MD
Professor of Pediatrics and of Medicine
Co-Director, Stanford Institute for Stem Cell Biology and Regenerative Medicine

STAGE 4 | PRE-CLINICAL DEVELOPMENT

Marius Wernig, MD
Associate Professor of Pathology and, by courtesy, of Chemical and Systems Biology

Aaron Gitler, PhD
Professor of Genetics

STAGE 5 | CLINICAL TRIALS

Helen Bronte-Stewart, MD, MSE
The John E. Cahill Family Professor
Director, Stanford Movement Disorders Center
Department of Neurology and Neurological Sciences

Michelle James, PhD
Assistant Professor of Radiology and of Neurology

Kathleen Poston, MD, MS
Associate Professor of Neurology and, by courtesy, of Neurosurgery
Director, Udall Center Clinical Core at Stanford

Magnetic resonance image (MRI) of a person with Parkinson's disease.