Compassionate Care, Pioneering Research

Alzheimer’s disease and related dementias are among the top 10 causes of death and debility in the United States, and the number of deaths attributed to Alzheimer’s disease is expected to triple by 2050, when it is estimated that more than 135 million people worldwide will be afflicted.

Without dramatic improvements in our ability to treat or prevent these illnesses, dementia will likely overwhelm health care budgets worldwide. Still, research into the causes and treatment of these dementias does not receive support commensurate with their devastating impact. For example, when compared to the health and economic costs of cancer and heart disease, the National Institutes of Health provides manyfold fewer dollars for dementia.

Mount Sinai is leading efforts to study Alzheimer’s disease and other dementias, as well as chronic traumatic encephalopathies, which are caused by repeated traumas—even concussions—resulting in similar syndromes with shared pathological mechanisms. The recently established Ronald M. Loeb Center for Alzheimer’s Disease joins Mount Sinai’s longstanding National Institute on Aging-funded Alzheimer’s Disease Research Center and our Center for Cognitive Health in driving efforts to better understand dementing illnesses, developing better ways at diagnosing and treating them, and working toward ultimate cures and preventive measures.

New Loeb Center Targets Alzheimer’s Disease And Other Degenerative Disorders

With the recent launch of the Ronald M. Loeb Center for Alzheimer’s Disease, Mount Sinai is further expanding its commitment to develop major research and clinical breakthroughs for this devastating illness. The Loeb Center was established with a $15 million gift from Daniel S. and Margaret Loeb and is named after Mr. Loeb’s father, who succumbed to Alzheimer’s disease. Alison M. Goate, DPhil, world-renowned for her work on the genetic causes of dementia, was recruited to Mount Sinai to direct the new Center (see page 3). The Loeb Center will advance basic research and compassionate clinical care, and drive the development of transformative new therapeutics.

Two scientific themes will guide research carried out by the Loeb Center. Many degenerative brain disorders—including Alzheimer’s disease; several types of related dementias, such as frontotemporal dementia and progressive supranuclear palsy; as well as Parkinson’s disease and amyotrophic lateral sclerosis (ALS)—are characterized by the accumulation of abnormal protein aggregates in the brain, leading to the death of specific types of nerve cells. Some of the same proteins may even be involved across these syndromes, such as β-amyloid, tau, and α-synuclein. Genetic studies in humans with each of these diseases, as well as research on animal models, have demonstrated that this protein aggregation is causal in disease pathogenesis. These findings suggest there are common mechanistic principles shared across these disorders that may be exploited to develop fundamentally new treatments.

A second focus of researchers is to better understand nature’s own protective mechanisms against these illnesses. It has long been understood that some people carrying known genetic risk factors remain healthy, and recent research has begun to uncover genetic factors in these individuals that appear protective. Identification of such protective genes, and understanding how they counteract pathogenic mechanisms, is driving highly novel approaches to therapeutics aimed at developing drugs that prevent or delay the onset of disease.

The Loeb Center will build upon substantial existing strengths at Mount Sinai (see related stories on pages 2 and 3), helping to strengthen collaborative efforts among innovative scientists and physicians with a goal to discover the fundamental mechanisms underlying disease and bring new treatments to the patient.

To learn more, visit www.mountsinai.org/loebcenter.
Advancing the Understanding of Cognitive Loss and Dementia at Mount Sinai’s Alzheimer’s Disease Research Center

Mount Sinai’s Alzheimer’s Disease Research Center (ADRC), a nationally renowned program established in 1984, conducts clinical and basic research dedicated to understanding both normal aging and Alzheimer’s disease (AD). The Center’s goals are to develop techniques to detect the progression from normal aging to the earliest signs of cognitive loss and dementia, and to develop therapies to stop this deterioration and to treat cognitive loss and other symptoms. Directed by Mary Sano, PhD, the Center is one of 14 ADRCs supported by the National Institute on Aging (NIA).

Recent focus has been on clinical and molecular endophenotyping. This includes characterizing the associations among AD neuropathology, hypertension, diabetes, renal disease, depression, and cognitive decline. The Center has also pioneered cognitive assessment with technologies that capture subtle deficits using home-based and audio-recorded testing, and provided normative data for Spanish-speaking populations. Basic laboratory projects have specifically focused on γ-secretase-related mechanisms and efforts that may point to the development of new vasculotropic drugs.

Over the next five years, the team, including Sam Gandy, MD, PhD, expects to define the mechanisms that link type 2 diabetes and insulin resistance to cognitive impairment and dementia with clinical characterization using both AD- and diabetes-related biomarkers. Investigators intend to generate human skin fibroblasts and induced pluripotent stem cells from individuals—representing a full range of insulin resistance and cognitive function—to enable unique tools for understanding the overlap and the biology of these interrelated diseases.

The ADRC provides critical resources to support dementia-related research across the Mount Sinai Health System by offering expertise in clinical characterization and maintaining cohorts of aging individuals. Mount Sinai researchers can share access to national datasets of clinical populations and, in some cases, biological samples. The Mount Sinai ADRC works closely with the NIA Alzheimer’s Disease Neuroimaging Initiative, as well as the NIA Alzheimer’s Disease Cooperative Study, the main federal entity responsible for conducting human clinical trials of promising new drugs.

To learn more, visit icahn.mssm.edu/adrc.

Mary Sano, PhD
Director, Alzheimer’s Disease Research Center; Associate Dean, Clinical Research; and Professor of Psychiatry

New Collaborative Programs Awarded

The National Institute on Aging (NIA) recently created a new generation of Alzheimer’s disease (AD) centers to be known as NIA Alzheimer’s Disease Translational Centers for Predictive Drug Development (ADCPD).

Mount Sinai received a planning award for one of these new Centers under the direction of Joel Dudley, PhD, and Sam Gandy, MD, PhD, and also involving Eric Schadt, PhD, and Alison Goate, DPhil. The new ADCPD will partner Mount Sinai with individuals at General Electric and the New York Stem Cell Foundation.

The Mount Sinai ADCPD would also expand the work of the Accelerating Medicines Partnership (AMP), a new effort led by Dr. Schadt and seven other principal investigators, supported by the National Institutes of Health and several pharmaceutical firms aimed at developing computational approaches for a number of common conditions, such as type 2 diabetes and Alzheimer’s disease.

The Icahn School of Medicine at Mount Sinai is one of only five sites across the nation selected to focus on Alzheimer’s disease, specifically, the transcriptomic analysis of brains from early stage AD patients from its Alzheimer’s Disease Research Center (ADRC) Brain Bank. This new approach will take investigators from Mount Sinai and its collaborators in Japan, New York, and Boston, beyond the discovery of gene network hubs and drivers, and allow them to merge molecular pathway data with the universe of knowledge about existing drugs.

Thus, well-studied compounds can be repurposed without the need for extensive preclinical testing. To complete the circle, the clinical trials unit of the ADRC will be tasked with assessing a number of these repurposed drugs for the specific treatment and prevention of AD.

Joel Dudley, PhD
Assistant Professor, Genetics and Genomic Sciences, and Population Health Science and Policy

Eric Schadt, PhD
Director, Icahn Institute for Genomics and Multiscale Biology; Chair, Genetics and Genomic Sciences; and Jean C. and James W. Crystal Professor of Genomics
PET scan with florbetaben reveals accumulation of β-amyloid in the brain of a patient with Alzheimer’s disease (AD). In contrast, β-amyloid accumulation is not detectable in a normal control subject (HC) or in a patient with frontotemporal dementia (FTD), which is associated with accumulation of tau instead. 

Collaboration Drives Dementia Science and Care Delivery

The Center for Cognitive Health (CCH) and the National Football League Neurological Center (NFLNC) are at the crossroads of dementia science and care delivery. Its leadership includes Director Sam Gandy, MD, PhD, who also serves as an Associate Director of the National Institute on Aging-designated Alzheimer’s Disease Research Center (ADRC); Martin Goldstein, MD, who oversees the clinical care division; and Mary Sano, PhD, ADRC Director, who heads the research division.

The CCH reflects a collaborative effort across the departments of Neurology, Psychiatry, Rehabilitation Medicine, and Geriatrics. Some Center physicians are doubly certified in both neurology and psychiatry and are especially skilled at managing patients of all ages with both cognitive and behavioral symptoms. The Center’s staff also includes several neuropsychologists to evaluate a patient’s cognitive function, and social workers and psychologists to provide counseling and social support. The NFLNC is one of five such centers nationwide and provides complete and standardized neurological, neuropsychological, and neuroradiological assessment to former National Football League players approved and referred by the league.

An area of particular interest within both Centers is the development of innovative brain imaging tests to diagnose Alzheimer’s disease, other forms of dementia, and chronic traumatic encephalopathy (CTE). Mount Sinai was the first institution in New York City to offer patients amyloid brain scans, which can detect, for the first time, the deposition of β-amyloid in the brains of living patients. Research is now under way to similarly scan for pathological forms of tau and for evidence of abnormal inflammatory activity in the brain. This work is being performed in collaboration with Lale Kostakoglu, MD, Chief, Division of Nuclear Medicine, in the Department of Radiology. Additionally, in collaboration with Mount Sinai Heart, there is an active interest in vascular factors that cause dementia.

To learn more, visit www.mountsinai.org/cch.

APPOINTMENT

Alison M. Goate, DPhil, Joins Mount Sinai

Alison M. Goate, DPhil, the Director of Mount Sinai’s new Ronald M. Loeb Center for Alzheimer’s Disease, is a world leader in neurogenetics who has studied the genetic causes of Alzheimer’s disease (AD), other dementias, and neuropsychiatric conditions for more than 27 years.

A native of the United Kingdom, Dr. Goate completed her doctoral degree at the University of Oxford where she studied the cellular pathology of intermediate filaments and came to the United States for postdoctoral training on somatic cell genetics under the mentorship of Theodore T. Puck, PhD, the founding director of the Eleanor Roosevelt Institute in Denver. She returned to the UK as a postdoc at the Institute of Neurology in London with Louis Lim, PhD, where she studied the molecular mechanisms of Down Syndrome, and later joined Imperial College where she worked on AD as the lead geneticist for the research team headed by John Hardy, PhD.

In 1991, Drs. Goate and Hardy reported the first genetic mutations causing AD, a groundbreaking discovery that transformed research by enabling the development of cellular and animal models of AD. Most of the drugs currently in clinical trials for the treatment of AD are anti-amyloid drugs that trace their genesis to these seminal discoveries. She continued to be at the forefront of dementia genetics for many years at Washington University, St. Louis, where she served as Professor of Psychiatry, Neurology, and Genetics, and Director of the Hope Center for Neurological Disorders, before joining Mount Sinai.
Multiplexing Immunofluorescence in the Neocortex in Severe Alzheimer’s Disease

The six imaging channels shown here reveal neuronal, glial, immunity, and pathological markers of the disease.

Courtesy of Dan Meyer, PhD, Senior Scientist, GE Global Research, Niskayuna, N.Y.; and Patrick R. Hof, MD, Irving and Dorothy Regenstrief Research Professor of Neuroscience and Vice Chair of the Department of Neuroscience, and Dara L. Dickstein, PhD, Assistant Professor of Neuroscience, and Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai