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TAUOPATHIES

Executive Summary

TARGETING TAU—OUR HOPE TO SOLVING THE DEMENTIA CRISIS. In our systems-based review of the biomedical landscape supporting research of a cellular protein called tau—a common culprit in a number of neurodegenerative diseases—we make the case that focused strategic investment in tau research and the category of neurodegenerative diseases called tauopathies, could have a transformative impact on the landscape of neurodegenerative diseases writ large. We have identified specific areas where carefully targeted funding, particularly philanthropic capital, could have an outsized impact on the field.

Cells in our brains die over time, which is a natural part of aging. However, several neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, accelerate this process, thereby wreaking havoc on patients by taking away their memory, dramatically altering their personality, and diminishing bodily control. For many of these diseases, no treatments exist that can reverse or even halt disease progression. A cellular protein called tau is a key culprit in many neurodegenerative diseases. Over time this protein misbehaves in the cells and begins to stick together to form tangles. These tangles disrupt the function of brain cells—particularly neurons—which leads to cellular dysfunction and death. While we know that tau is a key miscreant in the development of a number of neurodegenerative diseases (referred to as tauopathies), the mechanism by which it causes damage remains poorly understood. By intensively studying tauopathies, particularly those where tau is the sole culprit (such as Progressive Supranuclear Palsy (PSP)), we have an opportunity to unlock the mystery of the mechanism by which this protein interacts with itself, other proteins, and neurons to create the devastation that accompanies rapid neurodegeneration.

TAUOPATHIES ARE OFTEN MISDIAGNOSED, ADDING TO THE SUFFERING OF PATIENTS

Among the various neurodegenerative diseases that are categorized as tauopathies, Alzheimer's disease has absorbed the majority of mainstream attention in recent decades. Others are not as well known, such as Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), behavioral variant Frontotemporal Degeneration (bvFTD), and Chronic Traumatic Encephalopathy (CTE). CTE has recently gained traction in the news because it is linked to repetitive head trauma associated with sports, as well as traumatic brain injuries sustained from accidents or combat. Because tau is a common thread, these diseases are often misdiagnosed as they are mistaken for one of the more "mainstream" neurodegenerative diseases, such as Alzheimer's or Parkinson's. Although several diagnoses are classified as tauopathies, the individual diseases differ based on the location of tau clumps in the brain, the brain cells affected, and whether tau aggregates with itself or other protein partners. Currently, imaging scans are the best way to distinguish between tauopathies; however, because these tests are expensive and the equipment is not universally available at all medical institutions, patients are not routinely diagnosed using imaging. As a result, many patients go misdiagnosed for years, and some are even enrolled in clinical trials for forms of tauopathies that they do not have, which contributes to the high failure rate of these trials.

Because we do not understand the biological underpinnings of individual neurodegenerative diseases, many neurodegeneration drugs fail in late-stage clinical trials. A recent study shows that for Alzheimer's alone, 99.5 percent of clinical trials fail. We need a different approach—now.

Philanthropic capital holds a unique place in the biomedical landscape. Unlike federal or corporate research dollars, philanthropic dollars are nimble and able to de-risk new ideas.

PHILANTHROPIC OPPORTUNITIES

In collaboration with the Rainwater Charitable Foundation, Association for Frontotemporal Degeneration, Alzheimer's Association, and CurePSP, the Milken Institute Center for Strategic Philanthropy brought together 30 experts in tauopathies and other neurodegenerative diseases to identify priority areas where philanthropic investment could have a tremendous impact on the field.

Support Basic Research

Insufficient understanding of the molecular underpinnings of the tauopathies is a critical barrier to developing novel therapeutic approaches for Alzheimer's, PSP, CTE, and others. It is imperative to invest in basic research that will fill in knowledge gaps as to how tau mediates neurodegeneration, which could lead to the identification of new therapeutic targets.

Focus on Diagnostic Tools

Investing in enhanced tools that will enable early and distinct diagnosis amongst the tauopathies would be game-changing. Although there are no cures or disease modifying treatments for tauopathies, there are interventions that help to slow or mitigate symptoms. Furthermore, early and accurate diagnosis would improve stratification of patients into clinical trials such that there is a higher certainty that the patient has the specific tauopathy under investigation in the study. Minimizing patient heterogeneity in trials will help to illuminate the distinct biological underpinnings of each disease, as well as differences in disease progression and treatment responses to new therapies. Currently most efforts are focused on developing Alzheimer's diagnostics using imaging modalities. Philanthropic support should build on these efforts to diversify into other diseases and new modalities to provide clinicians with a robust toolkit.

Increase Access to Patient Samples

In order to understand the range and variation of disease, researchers need access to both postmortem patient brain tissue, as well as biospecimens from living patients. Age-matched control (normal) tissue is also necessary to understand the differences between diseased and normal tissue. These samples are used to identify biomarkers, understand progression, and test novel therapeutics. Philanthropists can support local infrastructure within institutions to gather and maintain patient tissues. Additionally, there is great value in supporting researchers to run large-scale analyses on these tissues, which could be used by many labs through openly sharing the resulting data. This approach minimizes the likelihood of researchers running duplicative studies on these limited resources of tissue samples.

Facilitate Data Sharing

Big data often brings big insights in complex diseases. However, sharing and collaboratively using large data sets requires careful data management, curation, and infrastructure. As neurodegenerative disease research continues to move toward big data approaches and multicenter collaborations, data sharing will be necessary and will lead to reduced duplication of efforts. Philanthropists can contribute to this change by including public data-sharing requirements in the funding agreements and, in some cases, providing funding for curation and infrastructure efforts.

Form a Streamlined Collaborative

Neurodegenerative disease clinical trials have shown very low success rates. Pure tauopathies provide a promising avenue to test tau-based therapeutic approaches because they are specifically characterized by tau aggregation rather than a mix of protein aggregates present in other diseases. However, unique challenges are likely because the pure tauopathies are rare diseases. The development of a collaborative initiative in oncology between pharmaceutical companies, the U.S. Food and Drug Administration (FDA), the National Institutes of Health (NIH), and relevant nonprofits to standardize and centralize clinical trials led to streamlining and reduced cost. A similar effort could provide transformative change for neurodegenerative diseases and could be facilitated through philanthropic support.