

TAUOPATHIES

A Center for Strategic Philanthropy
Giving Smarter Guide



MILKEN INSTITUTE

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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.



PHILANTHROPIST FORWARD

Our family's journey into tau-related neurodegenerative disorders began unexpectedly in 2009. At the time, Richard Rainwater was a vibrant and healthy man in his sixties, enjoying all the rewards of being one of the era's most successful investors. He was deeply grateful for everything life had given him, and he still loved going to work every day.

Then the mysterious symptoms started. An otherwise athletic man, he experienced a few falls. He began to shuffle a bit.

We were blessed to have access to the best doctors in the world, but that didn't do much to soften the shock of Richard's diagnosis. Over the course of the next few days, we learned that progressive supranuclear palsy (PSP) was a form of frontotemporal dementia that afflicted about 20,000 Americans. It was poorly understood, but researchers believed that it involved the toxic build-up of a protein called "tau" in the brain. The only certainties were that it would progress quickly, and there were no effective treatments on the horizon.

Our family was devastated by this news, but we were also committed to doing something positive in response. We immediately expanded the scope of our foundation, already active in education philanthropy, to include funding for neurodegenerative disease research. We brought together an all-star team of neurologists and scientists, and the Tau Consortium was born.

The Tau Consortium commissions world-class basic research, drug discovery, and related efforts to accelerate the development of new treatments for PSP, Alzheimer's disease, and other neurodegenerative disorders involving the tau protein. We seek to achieve this mission by ensuring that our funded researchers work collaboratively and also by actively engaging with partners who can accelerate our progress. In everything we do, we act with urgency for the benefit of patients and families. Our goal is to systematically develop and guide novel treatments into human trials.

PHILANTHROPIST FORWARD

Since 2009, we've invested nearly \$100 million in the Tau Consortium. This represents about 65 percent of all U.S. philanthropic funding for tau research in the last decade, and the consortium's approach has had some success. In just a few short years, Tau Consortium researchers have identified a key risk gene involved in tauopathies, discovered novel disease mechanisms, and developed stem cell and animal models to enable drug discovery efforts.

Most importantly, we've helped to build a pipeline of nearly two dozen potential new treatments, including eight in various stages of human clinical trials. Richard Rainwater's courageous and inspiring battle with PSP came to an end in 2015, but he left behind a legacy of progress and hope for other patients and families.

This Giving Smarter Guide builds directly on that legacy. The Rainwater family remains committed to doing whatever we can to accelerate progress toward treatments and ultimately a cure, but we know that we can't do it alone. Getting there will require even closer collaboration and more efficient resource allocation by us and our partners. Government funders, philanthropies, individual donors, industry players, and the patient community each have an important role to play. We hope this guide will help us all to better navigate the path forward. We are deeply grateful to the Milken Institute and the many subject matter experts who generously contributed their valuable time and insights to the development of this report.

Finally, to the patients and families who are currently battling a tau-related disorder, I want you to know that you're not alone. Thousands of people like you are getting involved in clinical trials and advocacy work to help us beat these diseases. I hope you will think about getting involved, too. But in any case, please know that there are some incredibly talented and dedicated scientists who are working very hard every day to help families like yours. There is hope.

Todd Rainwater
Chair of the Board of Trustees
Rainwater Charitable Foundation

DISEASE OVERVIEW

Tauopathies are a class of neurodegenerative diseases associated with the aggregation of tau protein. These diseases include Alzheimer's disease, Progressive Supranuclear Palsy, and more than 20 others including several forms of fronto-temporal dementia. Across the tauopathies, the tau protein aggregates within cells, forming structures known as tangles. Although tau aggregation is a common feature of these diseases, it is not clear how the aggregation of this protein is linked to cellular dysfunction or neuronal death.

Tauopathies appear to share common mechanisms that lead to cell death; however, the symptoms experienced by patients vary and have led to a range of distinct diagnoses. Primary symptoms are classified according to the physiological system affected and include motor, cognitive, behavioral, and language. Current understanding of these diseases suggests that the dysfunction at the cellular level is likely similar across diseases, but the regions of the brain and specific cell types affected may be distinct and driving the differences in diagnosis.

Although the individual tauopathies are typically studied in terms of each unique disease, this report discusses the diseases and their underlying science as a whole because the tau protein appears to play an integral role across all of them.

To provide more clarity on how individual diseases manifest symptomatically, the following common tauopathies are primarily discussed below. We also reference a few others that may be particularly important for clinical and scientific study of tauopathies and neurodegeneration more broadly:

- Progressive Supranuclear Palsy (PSP)
- Corticobasal Degeneration (CBD)
- Alzheimer's Disease (AD)
- Behavioral Variant Frontotemporal Degeneration (bvFTD)
- Chronic Traumatic Encephalopathy (CTE)

BIOLOGY REFRESHER

Proteins are large molecules within organisms that carry out a vast array of cellular functions including metabolism, transport, and DNA replication. Proteins consist of amino acids, the sequence of which is determined by RNA. Finally, proteins fold in specific ways as determined by the characteristics of the specific amino acids. The folding of a protein determines the protein's function, and misfolded proteins typically lose their function or gain spurious activity, which can be harmful to the organism.

DISEASE OVERVIEW

PROGRESSIVE SUPRANUCLEAR PALSY (PSP)

PSP is a neurological disease that causes progressive movement, balance, and vision problems. Beyond motor symptoms, patients experience changes in mood, behavior, sleep, and cognition.

Many PSP symptoms overlap with those of Parkinson's disease, often resulting in misdiagnosis. In fact, PSP was originally thought to be a cause of atypical parkinsonism but is now recognized as a unique disease based on tau pathology. A key distinction between the two diseases is that PSP progresses more rapidly than Parkinson's. PSP typically leads to severe disability within three to five years, whereas Parkinson's patients can thwart severe disability for four to seven years with Levodopa treatment and proper medical care. Although PSP patients may initially respond to Levodopa, because of rapid progression the treatment does not provide long-term relief comparable to its effect in Parkinson's patients.

Another distinction between the two diseases is that PSP brains show tau aggregates at autopsy, while the brains of some Parkinson's patients show tau aggregation, but overall a different pattern of protein aggregation with a different misfolded protein seeming to play a greater role.

It is estimated that 20,000 Americans have this disease. PSP symptoms typically begin after age 60. Finally, although PSP typically leads to severe disability within three to five years, individuals can live for a decade or more after the first symptoms appear with proper medical care.

For more detailed information, we recommend the National Institute of Neurological Disorders and Stroke (NINDS)'s [Progressive Supranuclear Palsy Fact Sheet](#) and CurePSP's [Patient Guide](#).

20,000
Americans living
with PSP

60+
Typical age onset

7 years
Disease duration

DISEASE OVERVIEW

CORTICOBASAL DEGENERATION (CBD)

Like patients with PSP, patients with CBD experience slowing movement, stiffness, tremor, falls, shuffling of the feet, and changes in memory and thinking. However, in the clinic, CBD is distinguished by the initial presentation of symptoms on one side of the body. Additionally, people with CBD may be unable to voluntarily control their limbs. For example, an arm on the affected side might move on its own, which is known as alien limb syndrome.

CBD brains show distinct patterns of tau aggregation in different brain cell populations, some of which resemble PSP and others that do not. This interesting distinction suggests that a unique cell type is affected in CBD patients, although the protein aggregation type may be highly similar between the patient populations.

CBD is rare, affecting approximately 3,000 patients in the United States. Patients typically begin to show symptoms around age 60 and progressive symptomatic decline for five to 10 years.

3,000
Americans living
with CBD

50-70
Typical age onset

6 years
Disease duration

BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA (bvFTD)

Patients with bvFTD experience gradual changes in behavior and language while memory functions are typically preserved. As the disease progresses, patients struggle to function in typical social situations (such as work settings) and increasingly struggle to plan or organize activities. Approximately 50 percent of bvFTD patients have tau aggregates in their brains. However, at present, physicians are not able to distinguish which bvFTD cases are driven by tau or another aggregating protein.

The typical age of disease onset is 45 to 64 years, and the mean length of disease progression is seven to 13 years. Because onset occurs at a younger age than a more typical dementia (such as Alzheimer's) and involves behavioral symptoms, it is often initially misdiagnosed as a psychiatric disorder because patients are typically considered "too young" for a dementia diagnosis.

50,000
Americans living
with bvFTD

45-64
Typical age onset

8 years
Disease duration

DISEASE OVERVIEW

bvFTD is thought to represent between 10 and 20 percent of all dementia cases, which is an estimated 50,000-60,000 Americans. Worldwide, the prevalence of bvFTD in 45- to 64- year-olds is estimated at 15-22 per 100,000.

The Association for Frontotemporal Degeneration provides [patient materials](#) and a very comprehensive overview of the disease. We recommend accessing its materials for further patient, physician, and caregiver information.

ALZHEIMER'S DISEASE (AD)

AD differs from the other tauopathies discussed in that another protein (amyloid-beta) aggregates in the brain as well as tau. At present, it is not known what specific, and potentially unique, roles amyloid-beta and tau play in disease progression. However, characterization of the role of tau in dementia will likely lead to a greater understanding of AD and accelerated therapeutic development.

AD is the most common form of dementia and is characterized by progressive memory loss. Early in the disease, patients experience difficulty remembering newly learned information. However, as the disease progresses, severe memory problems become more common, as well as disorientation, mood changes, and confusion. In late-stage AD, patients can experience difficulty walking, speaking, and swallowing, as well as severe memory and mood problems.

Because AD is the most common tauopathy, it has been the most extensively studied in terms of societal and economic impact. According to the Alzheimer's Association, nearly 5.7 million Americans are living with AD. It is also estimated that, without a therapeutic or prevention strategy, 14 million Americans could be living with AD in 2050. Furthermore, over 16 million Americans currently provide unpaid care to a person living with AD or a related dementia. The opportunity cost of this time is valued at \$232 billion

Figure 1. Healthy vs. AD postmortem brain structure

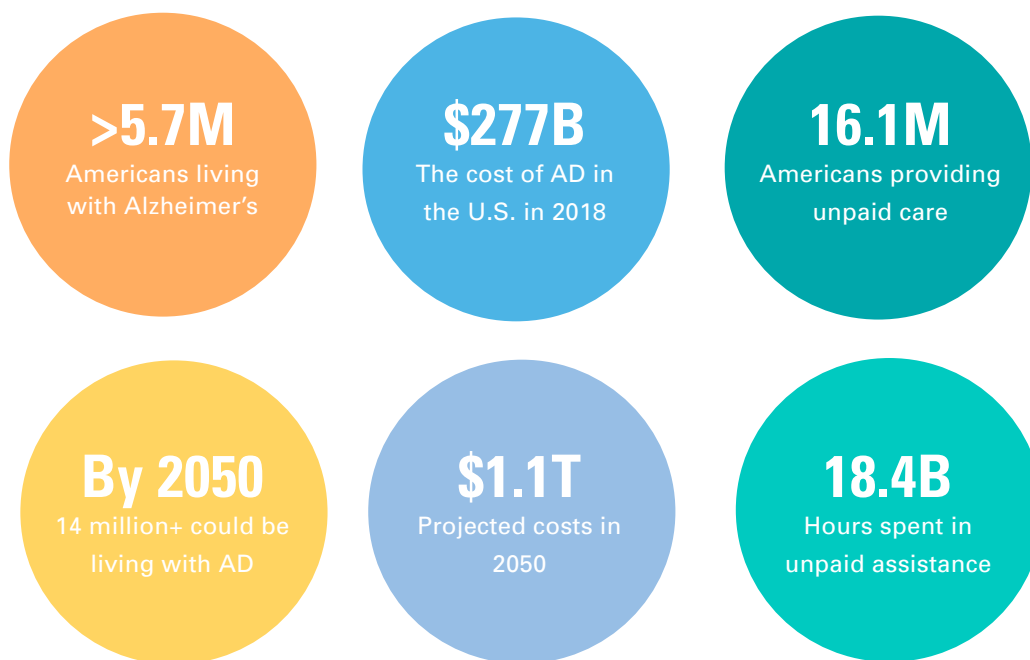


Source: [National Institutes of Health](#).

DISEASE OVERVIEW

annually, while the 2018 projected annual cost for AD and related dementias is \$277 billion.

The Alzheimer's Association has created [specific information for patients, physicians, and caregivers](#) to explain the disease and provide insight into treatment options and care. We recommend accessing these resources for additional information.



CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE)

CTE is the only known tauopathy thought to be caused by injury. CTE is the result of repeated brain trauma, including both concussive and sub-concussive hits to the head. Over time, tau accumulates in neurons and supporting cells around the crevasses of the brain and near blood vessels. As the disease progresses, the frontal lobes of the brain begin to degenerate. CTE is thought to largely affect professional athletes in contact sports and military personnel but has also been observed in domestic violence victims. Symptoms include memory loss, impaired judgment, impulse control problems, and aggression. These symptoms typically appear years after injury occurs; however, the average age of onset is younger than those of other tauopathies, with early symptoms typically occurring in one's

DISEASE OVERVIEW

30s and cognitive symptoms appearing in one's 40s. As is the case with other tauopathies, definitive diagnosis occurs only upon examination of postmortem brain tissue.

DIAGNOSIS

Across the tauopathies, no single test can determine the diagnosis or the specific type of tauopathy driving symptoms. Instead, clinicians use a variety of assessment tools such as a physical examination, laboratory tests, and medical history to make a diagnosis. Because the tauopathies show complex patterns of motor and cognitive decline, assessments of these symptomatic domains are the most common.

For AD, neuroimaging is becoming increasingly used in patients. Functional imaging technologies, such as positron emission tomography (PET), are used in a variety of ways to diagnose AD. PET tracers identify the presence of amyloid, an aggregated protein indicative of AD. Additionally, physicians can use surrogate measures of neural activity and detect changes in affected regions. Finally, scientists have noted that structural imaging technologies, such as magnetic resonance imaging (MRI), reveal a shrinkage of affected brain regions in patients with AD. However, standardized criteria have not yet been developed to make this assessment widely utilized.

There has been a substantial effort to develop tau tracers to characterize all tauopathy patient populations. Currently, the pharmaceutical company Avid Radiopharmaceuticals has developed the most commonly used PET tracer for tau, which shows utility in AD (18F-AV-1451). Unfortunately, the Avid tracer does not seem to provide as much diagnostic utility in the pure tauopathies, such as PSP and CBD. Ongoing work to develop tau tracers for all tauopathy populations is under way, but in need of continued support.

MAJOR UNMET NEED: DIAGNOSTIC TOOLS

Objective diagnostic tools would allow patients to receive accurate and timely disease diagnoses. This innovation could improve patient care and clinical trial patient pools because incorrectly diagnosed patients would no longer be included. Better clinical trials will be important to allow effective therapeutics to reach patients. Finally, an ideal diagnostic tool could identify the presence of disease and distinguish between the diseases much earlier before symptoms reflect irreversible damage to brain tissue.

DIAGNOSIS

HEALTH CARE ACCESS

Because tauopathies are rare and we lack definitive diagnostic tools, it is suspected that patients receiving care outside of major research centers may be less likely to receive the correct diagnosis. Therefore, these patients likely do not have access to appropriate care information or treatment. This reality highlights the need for improved clinician education and robust diagnostic tools.

THREE SYMPTOMATIC DOMAINS OF TAUOPATHIES

- 1. Motor symptoms:** Common changes in motor control, associated with tauopathies, include difficulty walking, difficulty maintaining balance, increased falls, shuffling of feet, tremor, and difficulty controlling eye movements.
- 2. Cognitive decline:** Tauopathy patients may experience memory problems and changes in judgment and problem solving.
- 3. Changes in mood:** Depression is common in PSP, CBD, FTD, and AD. Additionally, patients often experience apathy, which describes a generalized lack of care about anything.

While the symptom domains overlap across tauopathies, the specific symptoms vary by disease and individual.



SYMPTOMATIC INTERVENTIONS

At present, no disease-modifying therapies for the pure tauopathies exist; however, the number of interventions to provide symptomatic relief is growing. Researchers are working to develop effective therapeutic agents, which include approaches such as decreasing the amount of tau within the brain.

MOVEMENT SYMPTOMS

Patients experiencing motor symptoms are often prescribed the dopamine-enhancing drug, Levodopa. Levodopa is commonly prescribed for Parkinson's disease. However, patients who are actually suffering from a tauopathy, such as PSP, can see benefit from the therapy for two to three years. Levodopa is often prescribed with Carbidopa to relieve commonly associated nausea symptoms. Sinemet is the most commonly prescribed generic form of Levodopa and Carbidopa.

Physical and occupational therapy are critical aspects of patient care for the diseases that involve motor symptoms. A physical therapist can help a patient learn to use assistive devices and help caregivers make the patient's home safer by installing handrails and removing trip hazards. The occupational therapist will help patients and caregivers devise strategies for daily living, including navigating mobility problems, managing falls, and independent eating.

DEPRESSION

A variety of antidepressants have been effective in patients with PSP, CBD, and bvFTD and who experience depression. For PSP, clinicians have reported that there appears to be no difference in the effectiveness of the older tricyclic antidepressants when compared to the newer serotonin reuptake inhibitor therapeutics.

SYMPTOMATIC INTERVENTIONS

INVOLUNTARY EYE CLOSURE

Blepharospasm describes involuntary closure of the eyes. This symptom leads to patients with PSP experiencing difficulties with sight. A neurologist can administer Botox injections into the eyelid to temporarily relieve the symptom.

DEMENTIA

Although a few drugs have been developed for dementia associated with AD, currently, no drugs provide clinical improvement for PSP or bvFTD.

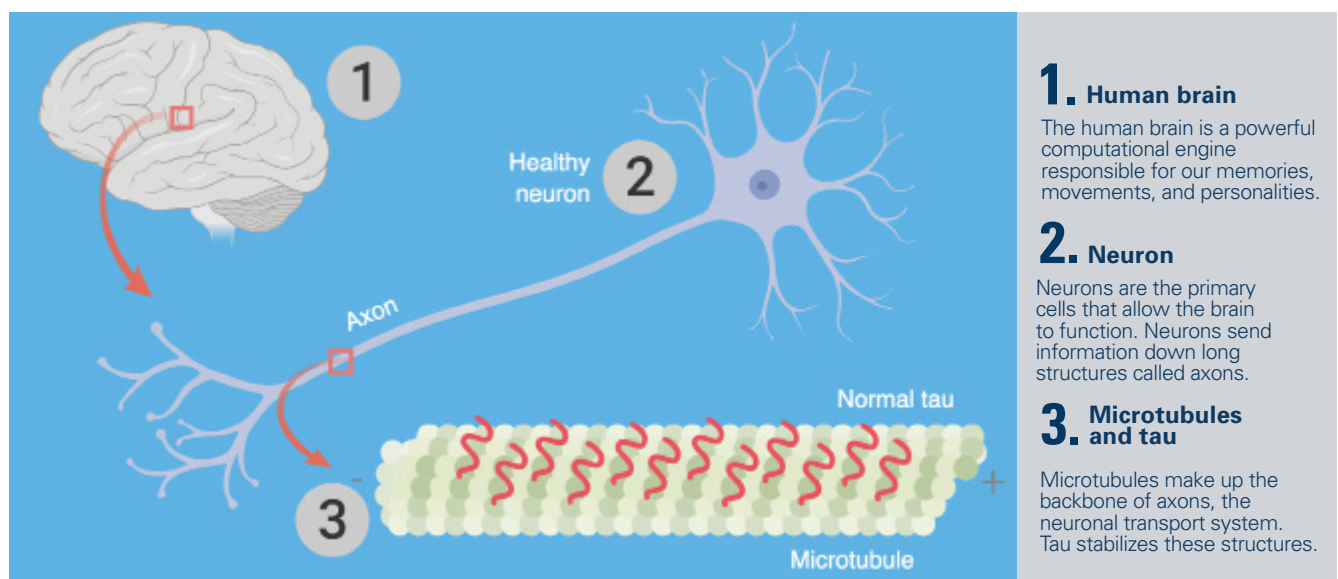
BIOLOGY AND POTENTIAL THERAPEUTIC APPROACHES

Tau-related neurodegeneration is characterized by tau aggregation, loss of neuronal function, and progressive death of neurons. Although the link between aggregated tau and neuronal loss is not well understood, scientists and clinicians have begun to reveal many functions of tau within normal cells and to identify the ways tau is different in diseased cells.

TAU IN A HEALTHY NEURON

The healthy brain consists of nearly 86 billion neurons that store memories, plan our motor movements, and guide decision-making. The shape and structure of individual neurons is critical to their function, allowing them to carry information across long distances. Specifically, neurons carry information signals down long axons to communicate with other distant neurons. Inside of the axons, microtubules play an important role in both structurally supporting the long axons, as well as providing “roadways” to transport nutrients to the neuron terminals, known as synapses. Tau associates with the microtubules and seems to play a key role in stabilizing the microtubules, making tau an important protein for *neuronal health and communication*.

Figure 2. Tau in a healthy neuron

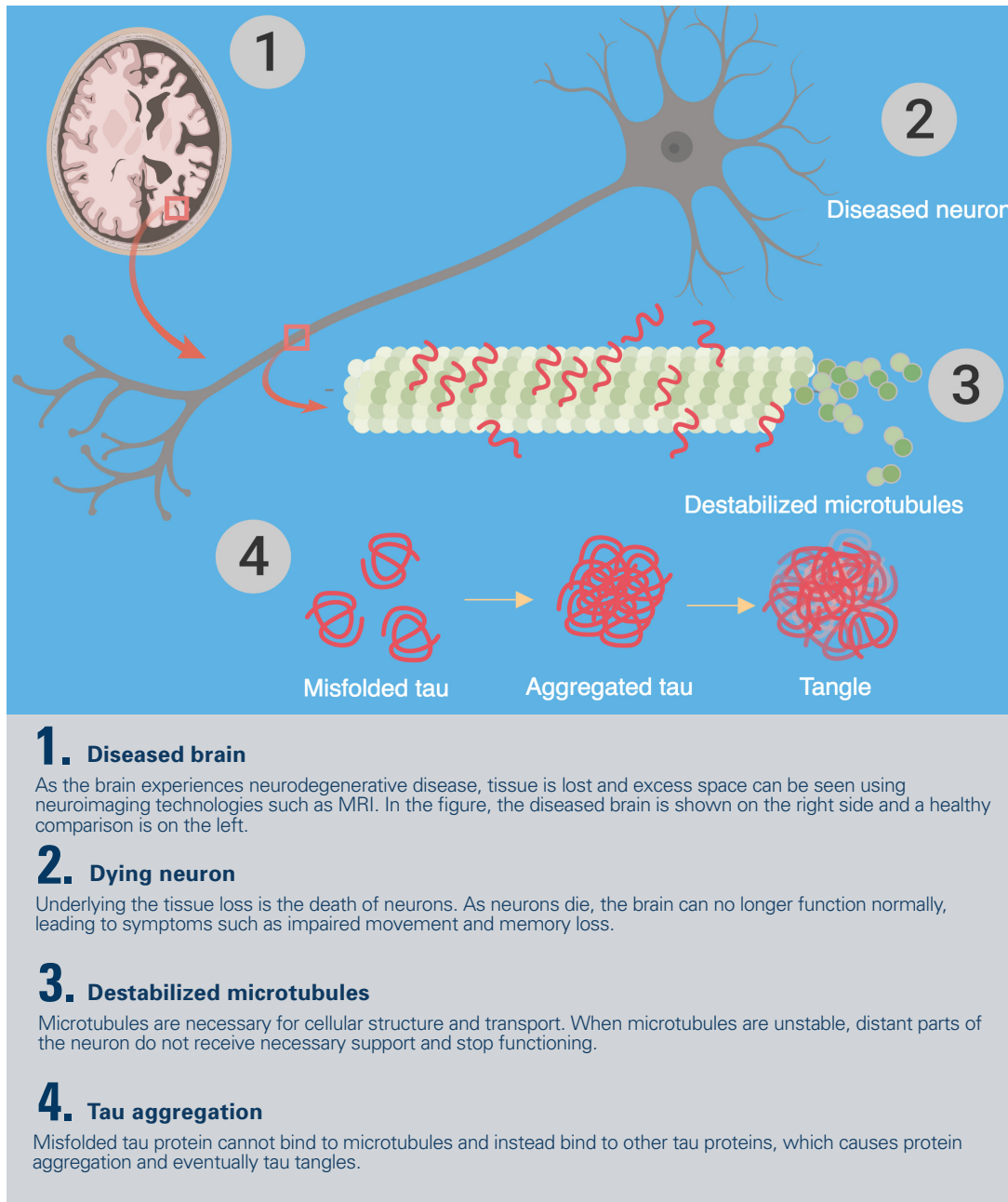


TAU IN NEURODEGENERATION

The brains of patients with neurodegenerative disease show abnormal loss of neurons, leading to measurable loss of brain mass. In diseased areas of the brain, the remaining neurons show distinct changes that provide insight into the cause of neuronal death. Specifically, axonal microtubules are destabilized and broken down. Additionally, tau, which normally binds to microtubules, is misfolded and aggregated in clumps known as tangles. In fact, misfolded tau is hypothesized to be a driving factor of disease, because once tau misfolds, it can no longer stabilize microtubules and appears to facilitate the further misfolding of other tau proteins, leading to larger tangles.

Finally, misfolded tau appears to spread in a progressive fashion, suggesting that it, or an intermediate factor, can cause further misfolded tau in neurons that are downstream within the communication network. This spread model suggests that tau accumulation in one part of the brain can infect other parts of the brain over time and may explain the progressive nature of the diseases.

Figure 3. Tau in neurodegeneration



1. Diseased brain

As the brain experiences neurodegenerative disease, tissue is lost and excess space can be seen using neuroimaging technologies such as MRI. In the figure, the diseased brain is shown on the right side and a healthy comparison is on the left.

2. Dying neuron

Underlying the tissue loss is the death of neurons. As neurons die, the brain can no longer function normally, leading to symptoms such as impaired movement and memory loss.

3. Destabilized microtubules

Microtubules are necessary for cellular structure and transport. When microtubules are unstable, distant parts of the neuron do not receive necessary support and stop functioning.

4. Tau aggregation

Misfolded tau protein cannot bind to microtubules and instead bind to other tau proteins, which causes protein aggregation and eventually tau tangles.

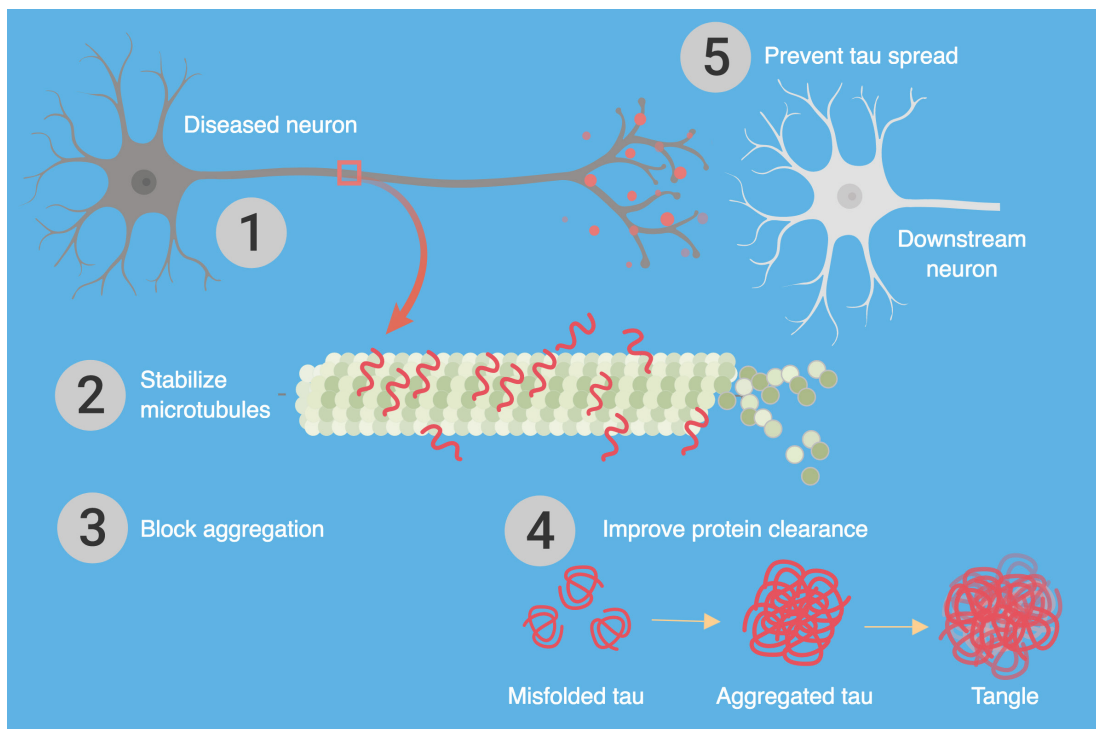
Source: Milken Institute.

BIOLOGY AND POTENTIAL THERAPEUTIC APPROACHES

TAUOPATHY THERAPEUTIC STRATEGIES

Although no effective therapeutics to prevent or slow disease progression in tauopathies exist, new approaches are being studied in the lab and clinical trials. These approaches intersect with the molecular underpinnings of the disease in an effort to halt or slow disease development. Five example approaches are outlined in figure 4.

Figure 4. Tau in therapeutics



1. Modulate tau modifications

This approach hinges on findings that identify specific changes to the normal tau protein that seem to precede misfolding and aggregation.

2. Stabilize microtubules

Because tau plays a key role in stabilizing microtubules, some research groups have explored whether microtubules can be stabilized using alternative methods so that misfolded tau is less detrimental to the cell.

3. Block aggregation

Based on the hypothesis that aggregated tau causes cellular damage, the aggregation of tau can be blocked by using molecules that reduce the electrostatic attraction between the misfolded tau proteins.

4. Improving protein clearance

Research has shown that the cells' ability to remove unnecessary and damaged proteins decreases as we age, which could lead to increased tau accumulation. Therapeutic approaches, which improve protein clearance, have the potential to slow or prevent protein aggregation across neurodegenerative diseases.

5. Prevent tau spread

Tau antibodies target tau outside of the cell (extracellular) that may be leading to the spread of misfolded tau between neurons. Reducing extracellular tau has the potential to prevent the progression of the disease.

BIOLOGY AND POTENTIAL THERAPEUTIC APPROACHES

This list is not intended to be exhaustive. There are many other approaches that are not shown in figure 4, such as the use of RNA interference or antisense oligonucleotides to reduce the total amount of tau produced. By reducing tau levels, aggregated tau may also be diminished.

BIOLOGY REFRESHER

Ribonucleic acid (RNA) plays a central role in the flow of genetic information in cells from deoxyribonucleic acid (DNA) to proteins. DNA is often thought of as the cellular blueprint, storing the genetic information for the cell. When a cell needs to produce a protein, the relevant DNA is copied into RNA in the form of messenger RNA (mRNA) and then the mRNA is translated into proteins. As RNA carries the genetic signal to make proteins, it provides a potential target to reduce specific protein production.

RESEARCH FUNDING ANALYSIS

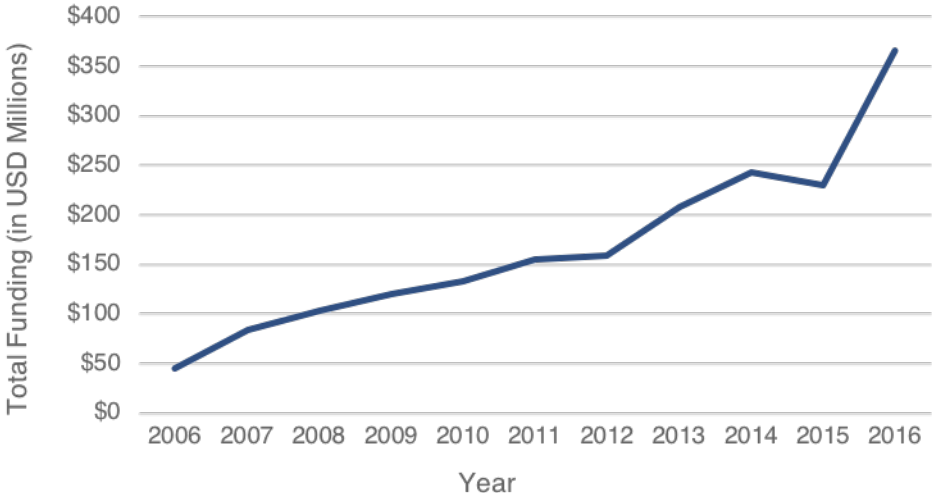
To assess the research funding trends, we collated funding data from 58 unique funders across 24 countries into a single database. These grants were classified based on their topic area, disease focus, and research phase (i.e., basic, translational, clinical). This analysis showed that public and private funding entities differentially allocate tau-relevant research dollars across disease and scientific areas, thus highlighting the unique value of philanthropy. For example, philanthropic research dollars provided a large portion of funding for the rare tauopathies and provided disproportionately more funding for drug discovery efforts when compared to public research funds.

Overall, we found that annual tau research funding has dramatically increased over the past decade; however, this funding has become increasingly concentrated in AD. Additional key findings from this analysis are presented below.

GLOBAL TRENDS

From 2006 to 2016, \$1.85 billion supported tau-relevant research, and the field has shown consistent growth in funding throughout this period. Approximately 90 percent of tau research funding was supported by U.S. public funding, predominantly from NIH.

Figure 5. Global annual tau funding

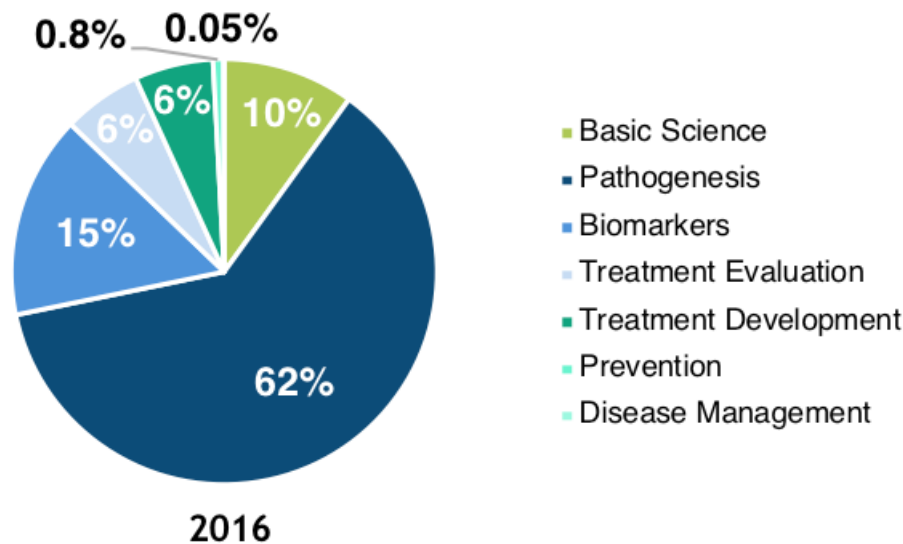


RESEARCH FUNDING ANALYSIS

Summary of tau research funding by scientific area

A majority of grants fall into the study of “Pathogenesis of Disease,” covering approximately 60 percent of all funding. However, basic science research as a proportion of total tau research decreased by 38 percent from 2006 to 2016, while biomarker development as a proportion of total research grew by 300 percent in the same period.

Figure 6. Breakdown of tau research by scientific area



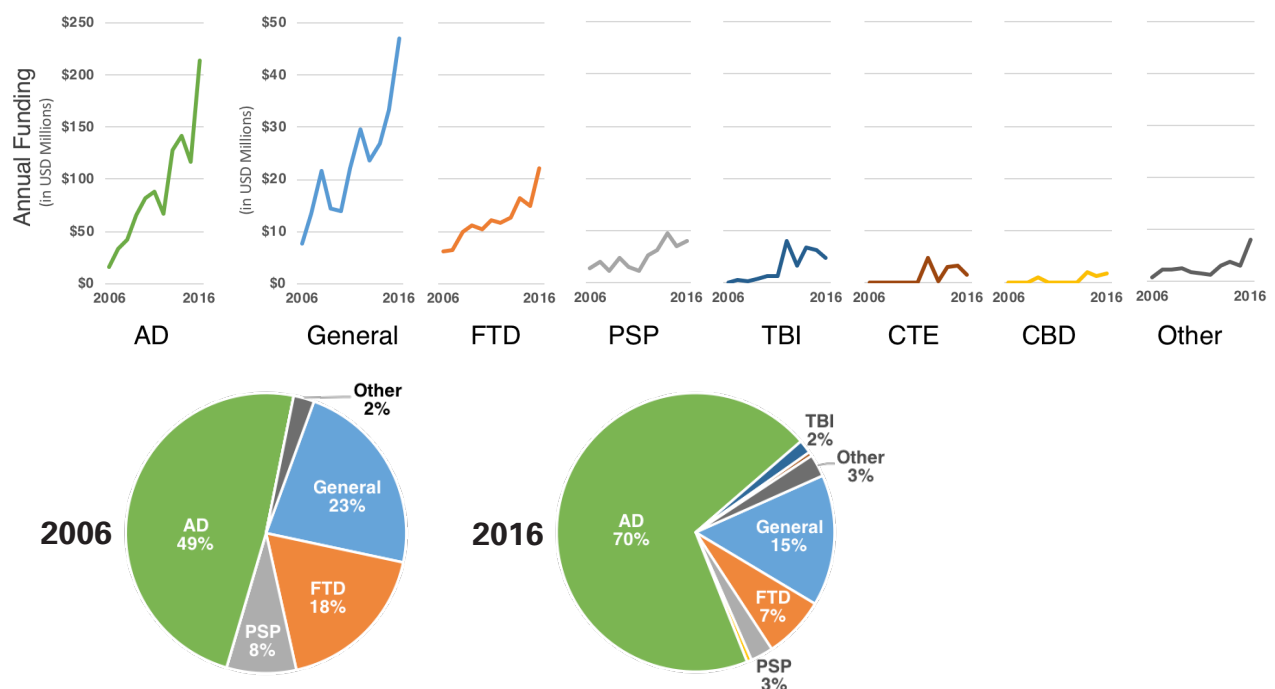
Treatment development is a critical phase of research because it represents the steps by which key findings are translated into potential therapeutics, and then those therapeutics are optimized for clinical studies (treatment evaluation). Treatment development comprised a relatively small proportion of funding throughout the period. In 2006, no recorded funding was allocated to treatment development. From 2007 to 2016, allocations to treatment development equaled 5-10 percent. Treatment development and treatment evaluation are likely underestimated in this analysis because private company activities are not captured unless they were funded by a grant maker, such as NIH.

RESEARCH FUNDING ANALYSIS

Summary of tau research funding by disease

Research funding grew across the distinct tauopathy diseases; however, the proportion of funding devoted to specific diseases changed dramatically over the 11-year time period. In this time span, funding specific to AD increased from 48 to 70 percent of the total tau funding, while funding specific to PSP decreased from 8 to 3 percent and funding specific to FTD decreased from 18 to 7 percent. The overall increase in research dollars suggests that these proportion changes are likely driven by the increased interest in studying tau in the context of AD, rather than a decreased interest in diseases such as PSP and FTD. While the increased funding of tau research will likely benefit many neurodegenerative diseases, researchers have outlined specific reasons that the study of diseases with less heterogeneity of protein aggregates would be more beneficial than those with increased complexity. In a recent discussion of PSP, researchers speculated that tau therapeutics developed for this specific disease would likely be generalizable to AD and CTE (Boxer 2017). In summary, the study of pure tauopathies such as PSP may provide key insight into the mechanism of tau in neurodegeneration.

Figure 7. Tau funding across individual tauopathies



RESEARCH FUNDING ANALYSIS

Additional insights gained from tau funding database

In the NIH grant coding system, standard research grants, program grants, training fellowships, and focused grants can be distinguished from one another. Analysis of these grant types over time revealed that program and center grants are being used with less frequency, while focused grants (RF and UF) are being used with increased frequency. The standard R series grant was the most common grant type in this research space.

The patterns of grant size have also changed within the field in the studied time range. In 2007, 17 percent of all grants ranged from \$200,000 to \$300,000, while in 2016 only 10 percent of grants fell within this range. In 2007, only 2 percent of grants deployed exceeded \$1 million; however, in 2016 approximately 7 percent of grants fell into this category.

Finally, analysis of the number of funded principal investigators (PIs) each year showed that the field has grown from fewer than 100 PIs in 2006 to nearly 450 PIs in 2016. In total, 1,060 unique PIs were identified in the funding database for the 11-year period. This finding suggests that the tau research field has more than quadrupled within the past decade, which is in part due to early philanthropic support.

OVERVIEW OF GRANT TYPES

R01 (Investigator initiated) grants are the most typical academic research grant funded by NIH. They provide sufficient funding for a single lab to pursue a research program.

Focused grants are typically similar in size to the R01 grants, but the research area or topic is identified by the grant maker.

Program grants allow multiple research investigators to apply together to work on a series of research questions that are interrelated.

KEY FUNDERS

The funding analysis identified 58 unique funders that invested in tau-focused research. However, several funders were identified as being particularly impactful because of funding amount, priority areas, or both.

NATIONAL INSTITUTES OF HEALTH

The National Institutes of Health (NIH) is the largest public funder of biomedical research in the United States. Twenty-seven separate institutes and centers each focus on a specific physiological system, disease class, or research phase. Within NIH, two primary institutes fund tauopathy research:

- The **National Institute of Aging (NIA)** leads a broad scientific effort to understand aging and to extend the healthy years of life. Importantly, this institute is the primary funder of AD research for the U.S. federal government.
- The **National Institute of Neurological Disorders and Stroke (NINDS)** seeks to develop fundamental knowledge about the brain and to reduce the burden of neurological disease. NINDS plays a key role in the implementation of the National Alzheimer's Project Act (NAPA), which was signed into law in 2011. Based on this plan, NINDS supports research on AD and the related dementias, specifically funding FTD research.

RAINWATER CHARITABLE FOUNDATION

The Rainwater Charitable Foundation is the primary funder of the [Tau Consortium](#), which operates an invitation-based consortium of tauopathy-focused researchers. There are approximately 40 members of the consortium. Although the consortium has funded research spanning the scientific areas, approximately 40 percent of its funds have supported therapeutic development. Furthermore, the consortium supported 30 percent of all PSP research globally in 2016.

KEY FUNDERS

CUREPSP

CurePSP is a research and patient advocacy nonprofit focused on the pure tauopathies PSP and CBD. Although it has provided grants of all sizes, its signature program is the “Venture Grant Program,” which provides \$100,000 to nascent and highly innovative ideas with the goal of allowing researchers to test novel concepts and gather preliminary data for more sustained funding. CurePSP also works with patients to provide information and connection to relevant clinical trials.

ALZHEIMER’S ASSOCIATION

The Alzheimer’s Association is the largest nonprofit funder of AD research globally. It awards research grants to identify new treatment strategies, improve care, and provide more information about brain health and disease prevention. Since 1982, it has awarded \$405 million in research funds. Beyond its research activities, the organization supports education, advocacy, and broader field-wide organization to promote advancement in AD and related dementias.

ASSOCIATION FOR FRONTOTEMPORAL DEGENERATION (AFTD)

The AFTD has worked to bring awareness and specific focus on the FTDs. Beyond work to support and advocate for patients, it specifically funds research to understand, diagnose, and treat FTD. It also works to raise awareness of the disorders in public forums, among clinicians, and within government to drive comprehensive change in FTD care.

BRIGHTFOCUS FOUNDATION

BrightFocus Foundation is a nonprofit funder focused on Alzheimer’s disease, related dementias, macular degeneration, and glaucoma. The organization currently funds nearly 200 research projects globally. BrightFocus’ Alzheimer’s Disease Research (ADR) program has awarded nearly \$110 million to support promising research in fields ranging from molecular biology and biomarkers to drug discovery and clinical studies. ADR is currently supporting 99 neurodegenerative disease projects, including those led by postdoctoral fellows and early-career investigators.

KEY INITIATIVES

TAU CONSORTIUM

The Tau Consortium is an innovative medical research program that is operated under the auspices of the Rainwater Charitable Foundation. The Consortium commissions research at approximately two dozen top universities, with the goal of finding new treatments for all tauopathies. The Tau Consortium ensures that its members work collaboratively and engage with partners who can accelerate their progress. Since founding the Tau Consortium in 2009, the Rainwater Charitable Foundation has committed nearly \$100 million to the program. This represents about 65 percent of all U.S. private funding for tau research over the last decade.

LONGITUDINAL EVALUATION OF FAMILIAL FRONTOTEMPORAL DEMENTIA SUBJECTS (LEFFTDS)

The [LEFFTDS project](#) is funded by NIH (NIA and NINDS) to longitudinally follow 300 frontotemporal degeneration patients or family members who have mutations in a known genetic risk factor (progranulin, C9ORF72 or tau). One-third of patients will be mutation carriers experiencing symptoms of FTD, one-third of patients will be mutation carriers with no FTD symptoms, and one-third will be non-carriers with no symptoms. Participants are enrolled starting in their 30s and are evaluated annually through clinical evaluation, neuropsychological measures, biofluid collection, and neuroimaging (although not tau PET). This study will provide insight into how specific underlying proteinopathy leads to disease.

ADVANCING RESEARCH AND TREATMENT FOR FRONTOTEMPORAL LOBAR DEGENERATION (ARTFL)

The ARTFL consortium is an integrated group of 14 academic medical centers in the United States and Canada, partnered with patient support organizations and dedicated to conducting clinical

KEY INITIATIVES

research in sporadic and familial frontotemporal lobar degeneration (FTLD) syndromes. ARTFL is funded by NIH and is part of the Rare Diseases Clinical Research Network.

The [ARTFL project](#) will establish a large cohort (roughly 1,500) of patients with FTD (PSP, CBD, bvFTD, svPPA, nvPPA, and FTD-ALS) and healthy family members of patients with genetic causes of the disorders. Participants will undergo onsite evaluations that include medical exams, clinical assessments of cognition and functioning, questionnaires, surveys, and biological specimen collection. All participants will be followed longitudinally. The data resulting from this longitudinal cohort study will allow scientists to further understand the class of disorders and has the potential to help identify new methods of diagnosing individual disorders.

TAU CENTERS WITHOUT WALLS

[Tau Centers Without Walls](#) is a multi-center NIH-funded program to bring together scientists across disciplines to understand the mechanisms of tau-driven neurotoxicity. These centers will focus on understanding the pathophysiological events by which tau leads to neuronal dysfunction and death. Additionally, the program has emphasized the acquisition, curation, and open sharing of tau-relevant data sets with the broader research community.

FTD BIOMARKERS INITIATIVE

The Association for Frontotemporal Degeneration has committed up to \$5 million to support innovative approaches to biomarker development. This [initiative](#) prioritizes biomarkers that can differentiate FTDs from other neurodegenerative diseases, discriminate subtypes of FTD, identify the molecular pathology, confirm pharmacodynamic modulation of the disease pathways, and track disease progression.

KEY INITIATIVES

FTD DISORDERS REGISTRY

The [FTD Disorders Registry](#) is a contact and research registry bringing together patients with FTD into a single platform. The registry is an important step in identifying and recruiting patients for clinical trials, as well as providing unique insight to researchers and clinicians.

PSP GENETICS CONSORTIUM

The [PSP Genetics Consortium](#) is a joint initiative funded by CurePSP and the Tau Consortium/Rainwater Charitable Foundation. The Consortium consists of neurologists, geneticists, and neuroscientists to characterize the underlying genetics of PSP. This research initiative is working toward genetic sequencing and analysis of 2,000 genomes.

PSP RESEARCH ROUNDTABLE

The [PSP Research Roundtable](#) is a precompetitive collaboration including industry leaders, academia, and patient advocacy organizations. The group is working to accelerate the development of new treatments for PSP and other primary tauopathies. The group is convened by CurePSP and the Tau Consortium and currently includes academic researchers, industry leaders, nonprofits, and representatives from key government agencies.

THE MODELING ALLIANCE OF SYSTEMS PHARMACOLOGY IN TAUOPATHIES (MAPTA)

Cohen Veterans Bioscience has partnered with In Silico Biosciences to form the [MAPTA Alliance](#) to drive efforts in developing predictive models of tauopathies. This will be achieved by building mechanistic models based on Quantitative Systems Pharmacology (QSP) approaches and by integrating Causal Knowledge Base models.

KEY INITIATIVES

CONCUSSION LEGACY BRAIN BANK

The [Concussion Legacy Foundation](#) has partnered with Boston University and the U.S. Department of Veteran Affairs to collect and facilitate the study of brains from individuals with a history of head injury. The brains are analyzed for evidence of all known brain diseases, including chronic traumatic encephalopathy.

CurePSP BRAIN DONATION PROGRAM

The [Mayo Clinic Brain Bank](#), supported by CurePSP, aids scientists in finding the cause and cure for progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA), and related prime of life brain diseases. The examination of brain tissue is vital to research and provides families with a sure postmortem diagnosis to confirm or further elucidate clinical findings. CurePSP reimburses families for the costs of brain donation.

GENETIC FTD INITIATIVE (GENFI)

The Genetic Frontotemporal dementia Initiative ([GENFI](#)) is a group of research centers across Europe and Canada with expertise in familial FTD. The aim of the study is to understand more about genetic FTD, particularly in those who have mutations in the progranulin (GRN), microtubule-associated protein tau (MAPT), and chromosome 9 open reading frame 72 (C9ORF72) genes. The key objective of GENFI is to develop markers which help identify the disease at its earliest stage and track the progression of the disease.

PET IMAGING CONSORTIUM

The Michael J. Fox Foundation and the Rainwater Charitable Foundation have partnered to co-fund a team to develop imaging tracers for alpha-synuclein and tau in the living brain. This initiative seeks to bring in additional support from other neurodegenerative disease focused non-profits and industry players to allow collaborative PET tracer development across neurodegenerative diseases.

KEY INITIATIVES

TAU CONSORTIUM DRUG DISCOVERY OUTSOURCING SERVICE

The Tau Consortium has established an innovative drug discovery outsourcing service that helps academic researchers to translate their discoveries into new treatments for tauopathies. Academic researchers who are accepted into this program receive ongoing guidance from drug discovery experts with extensive industry experience. Where needed, the Consortium also pays for outsourced drug discovery work via a pre-negotiated agreement with one of the world's largest contract research organizations. By providing these services, the Tau Consortium seeks to expand and accelerate the pipeline of new treatments moving toward human trials.

KEY UNMET NEEDS IMPEDING TAUOPATHY RESEARCH PROGRESS

Tauopathies are an extremely complex class of brain disorders that are difficult to study, diagnose, and treat. In November 2017, the Milken Institute Center for Strategic Philanthropy convened world-renowned tauopathy and neurodegeneration experts to discuss the state of the science and the greatest hurdles to research and therapeutic development. The goal of this retreat was to identify impactful and actionable solutions where philanthropic investment could accelerate progress in tauopathy research. In total, five key barriers were identified and then used to frame the most impactful solutions. These five barriers are:

- Insufficient understanding of fundamental tau biology
- Lack of data sharing
- Difficult access to biospecimens
- Lack of diagnostic tools
- Poor clinical trial design and implementation

FUNDAMENTAL TAU BIOLOGY

There is a great need for an increased scientific understanding of the role of tau in neurodegeneration. Researchers and drug developers emphasized the lack of fundamental knowledge about tau in the cell and its action in neurodegeneration.

Through the discussions about the biggest open questions, we have identified five key questions that have the greatest potential to accelerate progress in the field of tauopathies.

KEY UNMET NEEDS IMPEDING TAUOPATHY RESEARCH PROGRESS

What is the role of tau in normal cellular physiology?	The role of tau and its modifications, in normal cellular physiology, is vital for understanding potential mechanisms of disease, additional drug targets, and potential on-target drug effects.
What is the link between tau mutations, aggregation, and neuronal loss?	All of the studied human tau mutations result in tau aggregation in the brain. Additionally, the tau aggregation patterns have been shown to correspond to impairment and cell loss. However, these observational correlations do not provide the mechanistic insight that is needed to understand the role of tau in disease.
What forms of tau are associated with toxicity?	A diversity of tau variants (final protein sequence and fold) likely play a role in normal tau function, as well as in tau pathology. Each variant is differentially expressed in a cell type-specific manner and has unique modifications. Furthermore, the tau variants appear to aggregate in a disease-specific manner. It is unclear how these factors interact to promote aggregation and tau spreading.
What is the tau interactome in healthy cells and in pathology?	There is great need to understand the interactions between tau and other proteins within the cell as a key way to identify potential tau modulators and additional therapeutic targets beyond tau. As an additional step to this inquiry, analysis of cell type-specific differences in this interactome could define the basis for differences in cellular vulnerability to disease.
Is there a fundamental mechanism of neurodegenerative disease?	Although tauopathies manifest in the aggregation of tau, the tauopathies are part of a larger class of neurodegenerative diseases. A hallmark of each neurodegenerative disease is the accumulation of protein aggregates and associated cellular loss. By understanding the tau network of activity, accelerated understanding of neurodegeneration more broadly could be achieved.

DIAGNOSTIC TOOLS

A major linchpin identified throughout many discussions during and after the retreat was the need for robust tools to diagnose tauopathies and to provide a window into disease state and progression. PET tracers were identified as one important avenue; however, many individuals discussed specificity problems with currently available tracers, and more broadly, with the limited

KEY UNMET NEEDS IMPEDING TAUOPATHY RESEARCH PROGRESS

access and prohibitive cost of available tracers. Furthermore, PET imaging is relatively expensive and is therefore typically only available at major clinical research institutions. This method also exposes individuals to radiation that can create additional health problems in the long-term. This discussion highlighted the need for more diagnostic tools, with prioritization of biofluid-based methods (e.g., blood, cerebrospinal fluid [CSF]) or MRI-based methodologies.

DATA SHARING

Many researchers shared that not only is it difficult to access data within institutions, but also, perhaps more importantly, there is no centralized or standardized method to share data across institutions. By comparison, other disease-oriented fields have standardized data collection and centralized data storage around key initiatives, indicating the feasibility of this endeavor.

The specific scientific area affected most is the sharing of genomic and phenotypic data (patient data). These data are of particular importance because sequencing and phenotyping are costly. Additionally, genetic association studies require large populations and become more informative as more patients and phenotypes are included, something that can be accomplished through increased sharing.

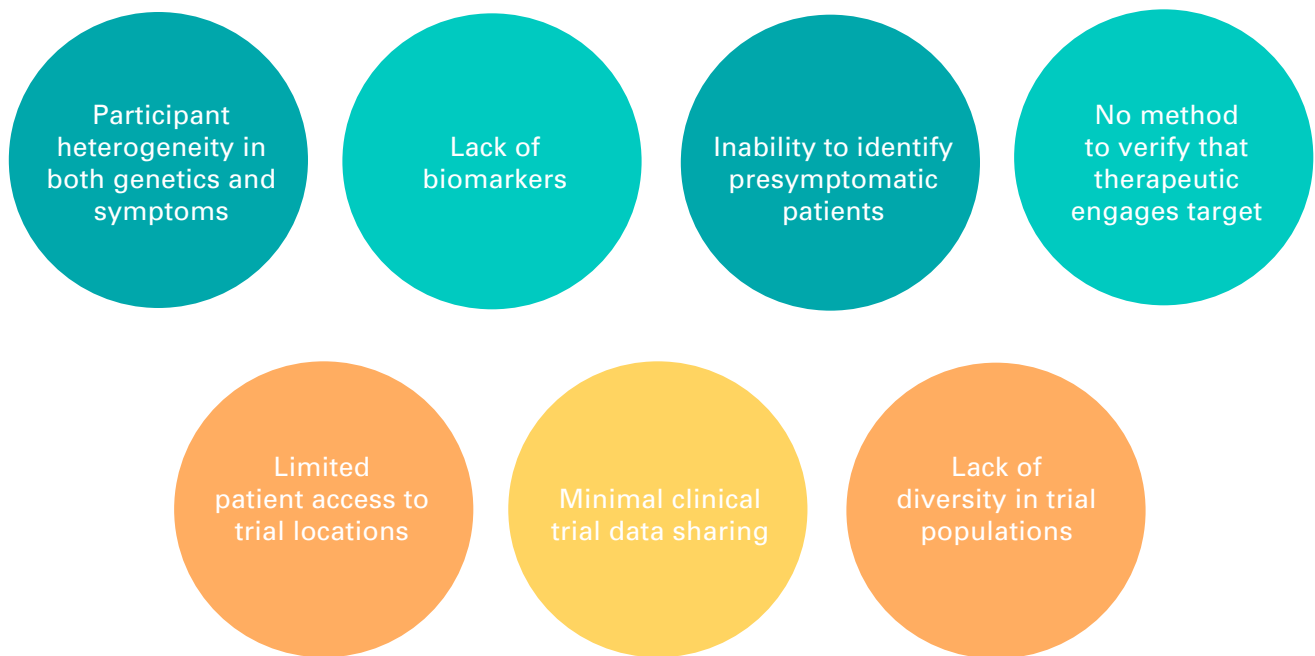
BIOSPECIMEN ACCESS

Many researchers discussed the difficulty accessing patient tissue samples with accompanying longitudinal data. However, the specific tissue of interest and the degree of the problem varied by institution. Broadly, it was noted that researchers affiliated with a robust clinical program have easier access to brain tissue of patients, while researchers outside of a few top institutions struggle to access quality tissue. Furthermore, all researchers identified age-matched controls as a key research gap. Another issue is access to high-quality patient and control CSF and plasma. For CSF, this seems to be driven by a low rate of investigators willing to include the procedure in their studies, and potentially patients' unwillingness to undergo lumbar puncture.

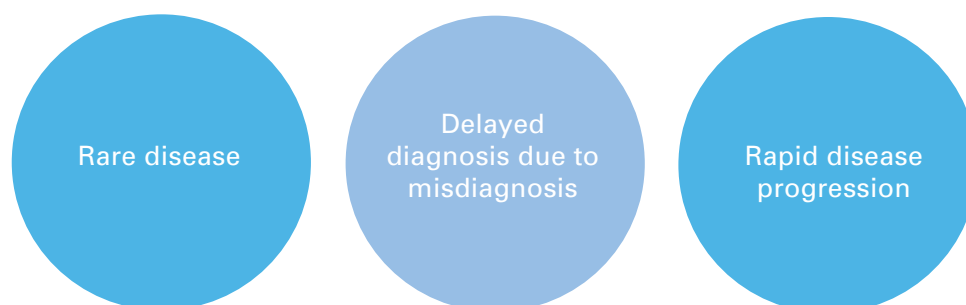
KEY UNMET NEEDS IMPEDING TAUOPATHY RESEARCH PROGRESS

CLINICAL TRIALS

A unique difficulty in research of neurodegenerative diseases, including the tauopathies, is clinical trial design and implementation because of the general issues listed below:



Additionally, unique barriers to clinical trials supporting pure tauopathies are as follows:



KEY UNMET NEEDS IMPEDING TAUOPATHY RESEARCH PROGRESS

Furthermore, potential attributes of the PSP population for clinical trials were discussed, namely:

1. PSP and CBD patients show specific rather than general protein aggregation, allowing for potentially more straightforward therapeutic targeting.
2. PSP progression is accelerated compared to Parkinson's or AD, which allows for greater potential difference between treatment and control groups observed in a shorter time window.
3. The recognized relevance of tau to more common diseases such as AD could provide additional incentive to investigate promising tau therapeutics in a PSP population initially.
4. PSP designation as a rare disease would allow a drug manufacturer to participate in the U.S. Food and Drug Administration (FDA) Rare Disease Program, which could allow accelerated approval of tau-relevant therapeutics.

Finally, there is currently a world-wide need of approximately 800 patients for PSP clinical trials. However, clinical researchers in the field expect this number to grow to several thousand within a five-year time horizon due to an increased number of clinical trials in the population.



PHILANTHROPIC OPPORTUNITIES

Throughout this systems-based research process, we collected ideas from researchers and key opinion leaders about how to overcome the identified barriers. For each identified barrier, we have provided potential ways that philanthropists and funders can target the identified gaps.

SUPPORT BASIC RESEARCH

The role of tau in neurodegeneration is poorly understood, and there is a paucity of potential targets and candidate therapeutics for pure tauopathies. Furthermore, analysis of the funding landscape shows that, at present, tau is predominantly studied in the context of Alzheimer's disease, which may not be representative of tau pathology in other diseases. The funding analysis also indicated that a smaller percentage of research funding has been devoted to more basic studies of tau, which is likely necessary to ultimately foster growth in the therapeutic pipeline for tauopathies.

Based on these findings, we recommend fostering research to understand the fundamental roles of tau in both healthy cells (within the context of aging) and in disease through **the following areas of research:**

1. Genetic studies of pure tauopathy patients to understand the risk associated with specific tau mutations and non-tau mutations in the eventual development of the disease.
2. Analysis of the tau interactome based on disease, cell type, age, and tau isoform.
3. Structural analysis of tau aggregates and oligomers to understand the key domains of tau which may drive disease or be targetable for imaging tracers or therapeutics.

PHILANTHROPIC OPPORTUNITIES

4. Continued development of experimental models to understand the cellular mechanisms of tau, the effects of specific mutations on physiology, and improved preclinical testing.
5. Targeted translational studies to assess the potential of moving basic findings to clinical trials.

Finally, **we recommend the following activities** to foster a more robust tau-focused research field:

1. Incubate new ideas through funding “pre-NIH” or pilot projects to allow investigators to collect preliminary data.
2. Expand the talent pool by funding early career (new faculty) investigators and “cross-disciplinary” projects.
3. Evaluate rigor and reproducibility within the grant review process.
4. Create an inclusive tau-focused research community by holding a recurring meeting with open attendance.
5. Build out a translational platform for tauopathies to foster the rapid translation of discovery to clinical-trial-ready therapeutics.

PHILANTHROPIC HIGHLIGHT: THE POWER OF SUPPORTING YOUNG SCIENTISTS

Private scientific funding plays an important role in the biomedical research pipeline by allowing researchers to explore and test innovative ideas. Although NIH is a very important funder of biomedical research, a majority of its budget is devoted to more mature research ideas and investigators. If well supported, more nascent science and scientists (early-career investigators or new entrants in a field) can collect preliminary data and become more competitive in the traditional NIH review process, creating a very strong return on the philanthropic investment.

PHILANTHROPIC OPPORTUNITIES

PROMOTE THE DEVELOPMENT OF DIVERSE DIAGNOSTIC TOOLS

Experts identified the lack of tauopathy biomarkers as the greatest barrier to developing a therapeutic. Biomarkers would allow more reliable diagnosis, which would improve time to a correct diagnosis. Additionally, some biomarkers can provide insight into therapeutic efficacy during a clinical trial. PET tracers were highlighted for their potential to track disease progression and to link regional tau aggregation to clinical symptoms, although limited access and the cost were cited as major problems. Tissue-based and MRI biomarkers were highlighted because they are more accessible than PET and would allow for earlier screening of at-risk patients. In addition, the field should consider quantitative *behavioral-* or *data-* based assessments as diagnostic tools.

Based on these factors, **we recommend the following activities:**

1. Support research to develop non-PET tau biomarkers, with a specific focus on biomarkers that could be accessible to a broad population.
2. Promote the development of biomarkers that could provide valuable data to a clinical trial such as target engagement and disease progression.
3. Support the development of diverse tau PET tracers and consider the intellectual property agreements to allow negotiated pricing and access for academic research and clinical trials within the funding agreement.
4. Assess the use of consumer-grade health technologies (i.e., Fitbit or mobile phone apps) to identify preclinical changes linked to tauopathies or to track disease progression in diagnosed patients.

PHILANTHROPIC HIGHLIGHT: BIOMARKERS

Today, no tools allow clinicians to objectively determine whether a patient is suffering from a tauopathy and, if so, which one. The lack of objective diagnostic tools affect patient care and hinders progress in therapeutic development. Additionally, the field will not need a single diagnostic tool but rather a “panel” of tests that can determine whether a patient is suffering from neurodegenerative diseases, and which one, and provide information about the disease stage, prognosis, and effectiveness of therapeutics. Tactical investment in these tools can make a large impact on a specific disease as well as the greater field of neurodegeneration.

PHILANTHROPIC OPPORTUNITIES

FACILITATE DATA SHARING

Although data sharing was one of the most cited hurdles in tauopathy research, it was very clear that the major funder in the field (NIH) is actively working to address the issue. Nonetheless, this theme is shared across neurodegenerative research and may be worth further investigation. The following ideas emerged in the discussion:

1. Data stored in a cloud-based system or within a centralized storage system is more easily shared (compared to intra-lab hard drive-based storage). These data are also theoretically better protected from loss.
2. Sharing robust genomic and associated phenotypic data from patients is extremely valuable. Aligning the data collection, ontology, and storage across neurodegenerative or even motor disorders would allow for further analysis of common genetic variants.

We recommend the following activities to facilitate data sharing within the tau research community:

1. Specify in funding agreements what types of data should be shared and on which data platforms.
2. Provide specific funds earmarked to enable data curation, analysis, storage, and sharing.
3. Consider collaborating with a data platform with a focus on biomedical or neuro-specific data to provide a common location for data sharing focused on tau research.
4. Partner with the Parkinson's Progressive Marker Initiative (PPMI) to intentionally include PSP patients in the project because these patients are often confused with "atypical" Parkinson's disease and may already be present within the data set.

PHILANTHROPIC OPPORTUNITIES

INCREASE ACCESS TO BIOSPECIMENS

In both our study of tauopathies and other neurodegenerative disease areas such as Parkinson's disease and AD, access to human tissue was identified as a key barrier. Furthermore, researchers cited a great need for control tissue and the associated patient data when using brain tissue.

Therefore, **we recommend the following activities:**

1. Support neuropathologists at institutions with neurodegenerative disease clinical programs.
2. Support standardized -omics analysis on a set of tissue with the intention of creating a shared data resource for the field.
3. Develop a public outreach campaign aimed at increasing brain donation across diverse populations and support a broader advocacy effort to expand the organ donation program to include brains.

SUPPORT COORDINATION OF CLINICAL TRIAL RECRUITMENT, DESIGN, AND REPORTING

Throughout this project, key opinion leaders discussed the magnitude of failed neurodegenerative disease clinical trials. The cited reasons for failure were many and included heterogeneous patient and control populations, variable and slow disease progression, treatment too late in disease progression, incorrect therapeutic dose, no assessment of therapeutic target engagement, and crude symptomatic evaluation scales. However, several researchers have postulated that the pure tauopathies would be better populations in which to assess tau-based therapies, which could then be translated to other related neurodegenerative diseases such as AD. These reasons included faster disease progression, rare disease designation, and more predictable and homogeneous protein aggregates.

PHILANTHROPIC OPPORTUNITIES

Based on the uniqueness and potential importance of the pure tauopathies in clinical research, **we recommend the following activities:**

1. Develop a master clinical trial protocol in collaboration with industry leaders, government agencies, and nonprofits. A similar effort in the oncology clinical trial space won the support of NIH and FDA and led to a streamlining of the drug-approval process. This protocol will streamline patient screening and selection for clinical trials. Novel therapies could thus be tested with lower investment, while also having a reduced time for patient recruitment and a “fit-based” clinical trial model. Additionally, the master protocol could provide both the structure and incentive necessary to persuade independent companies to share patient data from clinical trials.
2. Develop educational materials and a clinician outreach program to increase physician awareness of the pure tauopathies. This could facilitate higher rates of correct diagnoses and shortened timelines to the correct diagnosis.
3. Increase global patient recruitment through patient outreach and education efforts.

PUBLIC, PRIVATE, AND PHILANTHROPIC COLLABORATION

Several of the recommendations developed in this document lend themselves to a large, more collaborative initiative. In the two opportunities outlined below, philanthropic support could be used to promote a larger public-private partnership to increase the impact on the field.

Accelerating Medicines Partnership (AMP)

Analysis of the tau interactome and targeted translational studies are identified as pathways to building a greater understanding of the biology and function of tau in healthy cells and in disease. The AMP

PHILANTHROPIC OPPORTUNITIES

initiative is a partnership between NIH, 10 biopharmaceutical companies, and relevant nonprofit organizations managed by the Foundation for the NIH (FNIH). AMP programs have been established in Alzheimer's and Parkinson's disease with a general structure of using unbiased approaches to understand the basic biology and to identify the key cellular components involved in disease. The pharmaceutical companies then use the data to develop potential therapeutics. This approach is novel because the data are made accessible to the scientific community and the work is done in a precompetitive space.

Although Alzheimer's and Parkinson's are related diseases, they are characterized by a mix of protein aggregates. Conversely, PSP patients show only tau aggregation, making this a better model to understand the individual mechanism of tau-mediated neurotoxicity. Because PSP could provide increased leverage to understand the other neurodegenerative diseases, the non-biased approaches, such as those followed by the AMP programs, could provide insight into the current AMP programs as well as the pure tauopathies.

Philanthropic leaders can play a unique role in helping to bring together organizations and to help define priorities. Additionally, the AMP programs have nonprofit partners that could be specifically supported with philanthropic funds.

Master Clinical Trial Protocol

A master clinical trial protocol is an alternative to standard clinical trial protocol design. This type of protocol allows for the simultaneous testing of multiple drug candidates and the matching of patients to the most appropriate therapeutic. Although it requires collaboration among competitive entities, it also reduces the overall cost of running a trial, increases the efficiency of recruiting patients, and provides consistent data to patient groups.

PHILANTHROPIC HIGHLIGHT: COLLABORATIVE CLINICAL TRIALS

During the past decade, hundreds of clinical trials for neurodegenerative disease have been conducted. However, these trials are costly and have not led to disease-modifying therapeutics. Rethinking the standard approach could be extremely impactful. Philanthropic investment can promote collaborative trials, where control patients are shared and participants are matched to experimental therapeutics. This approach also lowers the financial barriers to entry, allowing for a variety of approaches and participation of smaller companies.

PHILANTHROPIC OPPORTUNITIES

In standard drug development, each potential new therapy for a specific disease is tested independently from other therapies seeking to treat the same condition. Each new trial protocol requires an independent review by the regulatory and oversight entities (i.e., Institutional Review Board, FDA) to verify that the study design is feasible, ethical, and scientifically sound. It can take years to move from initial trial design to patient recruitment. Additionally, as trials increasingly rely on screening and biomarker-based criteria, patients will be increasingly turned away from individual trials because of lack of fit with the selection criteria. Individuals working in neurodegenerative disease and other fields have noted that patients who are rejected from a clinical trial rarely seek participation in another trial. Overall the traditional approach is slow, costly, and strains the patient population.

Approximately five years ago, Friends of Cancer Research developed an alternative approach to clinical trials. It developed a multi-arm protocol and received a Master-Investigational New Drug Application (Master-IND), which is held by a foundation rather than a private company. This Master-IND eliminates the need for a new protocol each time a new compound is ready for clinical trial testing. The multi-arm protocol allows for testing of five drugs simultaneously and for the addition of new drugs as existing drugs complete testing. Additionally, the one control arm is used across experimental groups, dramatically reducing the number of required patients. Finally, all patients, regardless of study site, undergo the same screening protocol, which is used to determine their study group. This not only increases the ability to compare data across studies, but also allows for better assignment of patients to therapeutic groups and thereby reduces patient attrition.

Because the Master Clinical Trial Protocol requires buy-in from clinicians, study sites, regulatory bodies, and the drug manufacturers, an independent arbiter of the protocol is most likely to be successful. In this example, the protocol registration was held

PHILANTHROPIC OPPORTUNITIES

by a neutral third party, and therapeutic inclusion criteria were determined prior to the study initiation. Friends of Cancer Research brought together all key parties to determine the protocol design, gauge industry interest, and navigate the standardization of procedures across institutions. We imagine that a similar structure would be required within the tauopathy clinical trial space as well, and is a key area where philanthropic investment could catalyze a new direction for the field.

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