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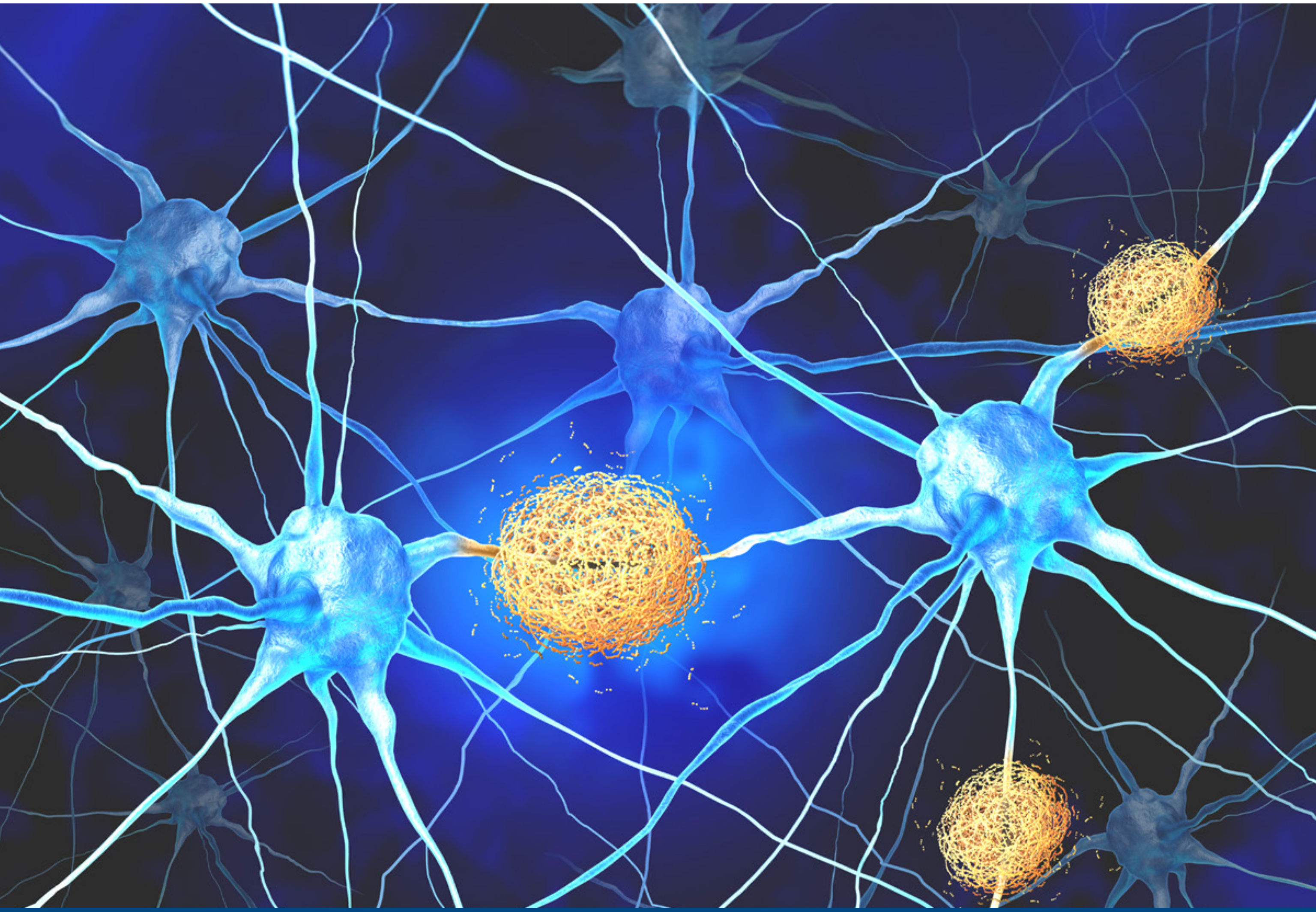
NEURODEGENERATIVE DISEASE MARKERS AND DETECTION METHODS

Sensitive, Selective, and Specific Measurements



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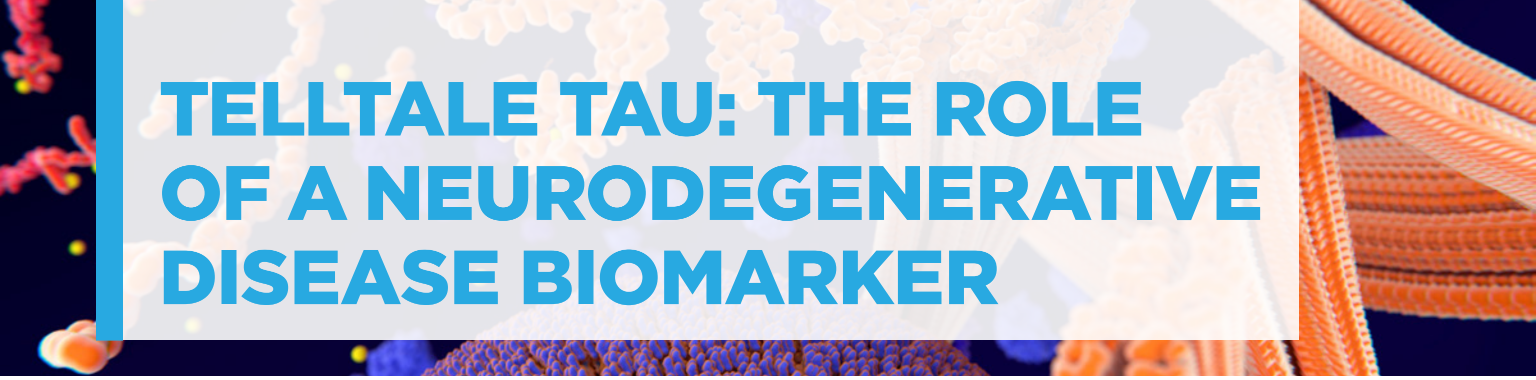

TELLTALE TAU: THE ROLE OF A NEURODEGENERATIVE DISEASE BIOMARKER

Neurodegenerative conditions affect millions of people worldwide, collectively representing the leading cause of physical and cognitive disability. Over 20 types of neurological conditions are tauopathies, linked to pathological accumulation of the tau protein in the brain.[1] Researchers investigate tauopathy mechanisms and turn to tau detection methods to help improve health care outcomes and lower the economic burden of these diseases.

What Is Tau?

Tau is a microtubule-associated protein that researchers first discovered in 1975.[2,3] It is encoded by the microtubule associated protein tau (*MAPT*) gene located on chromosome 17q21.3, and there are six tau isoforms found in the adult human brain.[2] Depending on N-terminal exon splicing and the presence of three or four microtubule binding domain repeats in each isoform, tau proteins are classified as 3R0N, 3R1N, 3R2N, 4R0N, 4R1N, or 4R2N tau, with 3R and 4R expression levels occurring at a roughly equal ratio in the healthy human brain.[2,3]

Brain aggregates or inclusion bodies comprised of different isoform ratios accumulate in neurodegenerative conditions called tauopathies.[2] Importantly, each tauopathy is characterized by unique tau behaviors. For example, mutations that increase 4R tau isoforms and exacerbate tau-microtubule interactions in the brain can cause familial forms of frontotemporal lobar degenerative (FTLD) conditions.[3]

Tauopathies are usually classified based on the predominant aggregate isoforms: 3R tauopathies are majority 3R isoforms, 4R tauopathies mainly have 4R, and 3R/4R tauopathies have approximately equal ratios.[2] Alzheimer's disease (AD)—one of the most common and thoroughly studied tauopathies—is a 3R/4R tauopathy linked to hyperphosphorylated tau aggregates present in neurofibrillary tangles (NFTs).[1,3,4] These abnormal and hyperphosphorylated tau aggregates disrupt microtubule assembly and are critical in disease diagnostics.[2] Total and phosphorylated tau aggregation in the brain are key pathological AD hallmarks that were first reported in 1986, and continue to be of great research interest today.[1,3]

AD is a secondary tauopathy because tau aggregation is often considered a response to other pathological proteins or events, such as beta amyloid (Aβ) plaque formation. In primary tauopathies such as Pick's disease (PiD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and argyrophilic grain disease (AGD), tau is the major pathological component that scientists detect in inclusion bodies.[2]

Where and How Is Tau Detected?

In healthy brains, tau is typically present in axons, whereas tauopathies often involve abnormal tau protein deposits in dendrites and the neuron cell body.[5] Additionally, tau is secreted from healthy and disease neurons and present in the cerebrospinal fluid (CSF) and blood.[5]

Different tauopathies and disease stages have distinct clinical presentations and tau aggregating patterns, including build up in separate brain regions, cell types, and subcellular regions.[1] For example, tau aggregation in the brainstem and entorhinal cortex is the earliest histopathological finding in AD brains, and aggregates spread to other brain regions as the disease progresses.[1]

Researchers have historically faced challenges investigating tau protein in living systems because the brain is a difficult organ to study noninvasively. Recent advances in tau-sensitive positron emission tomography (PET) imaging, mass spectrometry, and CSF and blood-based immunoassay detection methods hold immense potential for scientists seeking and developing diagnostic and research tools to evaluate neurological diseases.[2]

The Importance of Detecting Tau

There is a growing research interest in tau-directed therapeutics and diagnostics.[2] Total tau levels in CSF correlate with AD neurodegeneration, making it an excellent liquid-based biomarker that can be detected by molecular methods and immunoassays such as enzyme-linked immunosorbent assay (ELISA) and immunoblotting.[5] However, CSF samples are often limited in volume, making it challenging to detect CSF tau protein on a nanoscale.[2,5] Additionally, despite advances in blood-based detection, the accuracy of plasma biomarkers is affected by sample dilution and other alterations that influence sensitivity and selectivity.[2] Finally, although tau-related biomarkers have been explored more thoroughly in AD, many non-AD tauopathies still lack established biomarkers.[2]

Tauopathies remain untreatable and early diagnosis continues to be challenging. For example, researchers showed that in the absence of reliable biomarkers, incorrect AD diagnoses were common in young-onset atypical presentations (53%) compared with patients with typical presentations (4%).[6] Scientists need improved tools and methods for tau detection to elucidate pathological characteristics, capture biomarkers, and enable translational breakthroughs.[2]

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DETECTING DISEASE BIOMARKERS: BRAIN, BLOOD, AND BEYOND

In recent decades, biomarkers have become increasingly important in the neurology field, particularly to meet the clinical need of a substantial neurodegenerative disease burden globally. There is research demand for reliable, highly specific reagents for sensitive biomarker detection and tools that selectively measure disease-related post-translationally modified biomarker states, particularly phosphorylated tau (pTau). While mechanisms and etiologies differ between neurodegenerative disorders, many share the benefit of detectable fluid biomarkers, which aid disease characterization and offer opportunities for new therapeutically-relevant discoveries.[1]

What Makes a Good Biomarker and Detection Method?

Good biomarkers are specific, accessible, and detectable. Until recently, researchers and clinicians relied on surgically collected brain tissue samples to investigate and measure neurodegenerative disease biomarkers.[2] Widespread efforts to identify markers in circulating biological fluids, such as cerebrospinal fluid (CSF) and serum, have enabled quicker, inexpensive, and less invasive identification, screening, and staging of neurological conditions in the laboratory and clinic.[2]

Given the prevalence of neurodegenerative diseases, there is also a significant need for new and ideal biomarker detection methods. Regardless of the research focus, reliable biomarker testing should be sensitive and specific to the target analyte, easy to measure with reproducible results, and reflective of disease progression. Additionally, detection in different sample types is challenging but crucial for new screening methods, especially in clinical biomarker testing. Molecular biomarkers measured in the CSF or blood typically include nucleic acids such as microRNA and proteins such as pTau, beta amyloid (Aβ), or alpha-synuclein.[1,2]

BIOMARKER SPECIFICITY

Disease heterogeneity within and between conditions drives the need for accurate and specific biomarkers in neurodegenerative disorder research. Currently, several fluid biomarkers can differentiate neurodegenerative diseases, and there is great interest in establishing biomarkers that may differentiate normal aging from pathological cognitive decline.[1]

For example, there are three CSF biomarkers included in the diagnostic criteria for Alzheimer's disease (AD): Aβ, total tau protein, and pTau.[2] In conjunction with other markers, elevated total tau in circulation reflects molecular differences between AD and age-matched healthy individuals. Hyperphosphorylated tau species are the major component of the neurofibrillary tangles (NFTs) that are characteristically present in AD brains. Certain pTau variants are also specific to AD and may help differentiate AD from frontotemporal dementia.[1] Additionally, increased pTau at threonine positions 181, 217, and 231 in either the CSF or blood can be used alongside Aβ biomarkers to monitor AD onset and progression.[2,3]

SENSITIVE AND SELECTIVE SAMPLE DETECTION

Although brain imaging and CSF samples yield highly accurate and validated biomarkers that have been widely used in research settings, blood-based tests are increasingly adopted in the field of neurology.[3] Recent techniques and optimized detection tools allow researchers to measure serum analytes at very low concentrations, providing scientists with sensitive detection and less invasive sample options.[4]

At the same time, reported variations in biomarker performance for different plasma pTau species highlight the importance of using selective reagents for detecting modified protein states. For example, pTau217 reflects abnormal CSF and PET biomarker status with higher accuracy than pTau181, and it better differentiates AD from other neurodegenerative disorders.[3]

Reliable Biomarker Immunoassays

Several immunoassays have been developed to detect different pTau species in tissue, cells, CSF, and plasma. However, scientists must thoughtfully choose immunoassay components such as antibodies, reagents, and detection systems, as each component may affect the reliability of biomarker measurements. For instance, studies comparing commercially-available plasma pTau immunoassays have revealed a certain degree of performance variability for pTau species, including pTau217 and pTau181.[3] It is critical that researchers use validated and reliable immunoassays to ensure that they measure the desired and most informative biomarker species.

Neurology biomarker detection, discovery, and implementation is steadily increasing in laboratories and clinical settings, driven by technological advancements that enhance precision and sensitivity, as well as insights gained from various disease subfields. This growth is expected to continue as measurement capabilities improve and more specific, selective, and reliable biomarkers emerge through optimized, targeted assays.[4]

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ELISA KITS FOR EASY MEASUREMENTS AND SENSITIVE DETECTION

Researchers often turn to the enzyme-linked immunosorbent assay (ELISA) to measure and quantify biomarkers in biofluid samples, including cell lysate, CSF, and plasma-based neurodegenerative markers.[1]

ELISA Workflows

ELISA is a plate-based immunoassay technique that was first described in the 1970s for detecting proteins of interest. Generally, researchers use this assay to immobilize a target antigen on a microplate and complex it with an antibody linked to a reporter enzyme.[2]

One common ELISA format is the sandwich ELISA, which uses a plate-bound antibody to capture a specific target and an enzyme-labeled detection antibody that converts the assay substrate into a colored product for plate reader measurements. Other ELISA workflows include direct ELISA, which uses an antigen-coated plate that directly binds reporter antibodies; indirect ELISA, which uses an antigen coated plate, a target analyte antibody or antigen, and a secondary reporter antibody; and competitive ELISA, which screens for targets in serum through reporter antibody competition.[2,3] Recent progress in ultra-sensitive detection techniques such as digital ELISA has further improved research on circulating brain-specific proteins.[4]

Factors that may interfere with ELISA workflows include the quality and integrity of the assay plate, coating buffer, capture and detection antibodies, blocking and wash buffers, target antigen, enzyme conjugate and substrate, sample matrix, and signal detection method.[2]

Neurodegenerative Disease Research Applications

There is significant interest in creating specific, sensitive, and practical tools to accurately detect different neurodegenerative conditions, including Alzheimer's disease (AD) and other dementias. ELISA is the most accepted method for biomarker validation research; it can measure many samples at once with low variation and it is accessible for all laboratories because it does not require specialized expertise or technology. Sandwich ELISA, known for its high specificity and sensitivity, is the most commonly used format in biomarker analysis.[5]

For example, sensitive ELISA kits have allowed researchers to detect increased tau protein levels in serum samples from individuals with different neurological conditions. Scientists used ELISA to measure total tau in plasma and found significant differences between individuals with normal cognitive function, mild cognitive impairment, and AD.[1] Thus, ELISA is a suitable method for detecting changes in plasma total tau levels and may help scientists elucidate AD's pathological mechanisms from pre-onset to progression.[1]

Validated ELISA Kits for Biomarker Research

Developing and optimizing an ELISA involves careful design, as factors such as antibody specificity and reagent concentration can influence results. A meticulous design and validation process can reduce development costs and improve the accuracy of biomarker analysis for researchers investigating neurodegenerative diseases.[5]

Although in-house ELISA development is possible, many researchers buy validated ELISA kits to simplify their workflows, improve biomarker measurement reliability, and readily adapt their studies for a range of targets and applications.[5] Aviva Systems Biology ELISA kits deliver high specificity and sensitivity detection of neurodegenerative disease biomarkers, including measuring total tau and phosphorylated tau by sandwich ELISA for a range of neurodegenerative disorders, including tauopathies such as AD, Pick's disease, frontotemporal dementia, cortico-basal degeneration, and progressive supranuclear palsy.[6,7]

With over 18,000 ELISA kits across nearly 7,000 targets and Custom ELISA Development services, Aviva Systems Biology supports scientists searching for novel and common targets. An established expertise in protein and antibody assays enables rapid, high quality standardized development and validation of ELISA approaches that researchers tap into for sensitive, selective, and specific biomarker detection. Whether a researcher is on the hunt for the perfect ELISA kit, optimizing an existing workflow, or starting from scratch in biomarker discovery, Aviva produces assays for exceptional reagent control and target detection from start to finish.[6-8]

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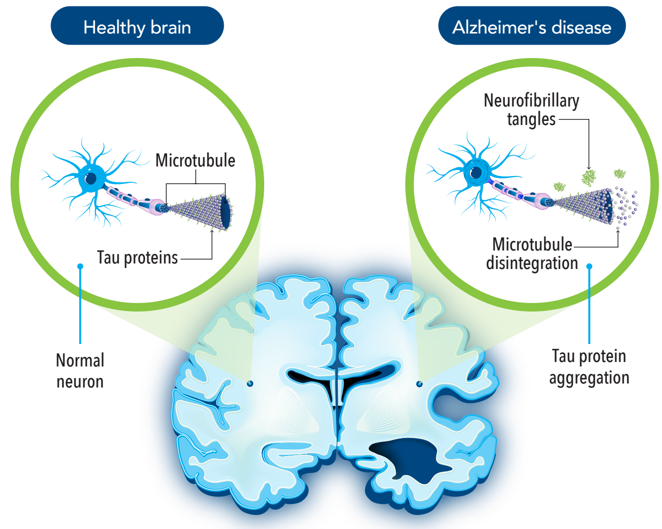
Tracking Down Tau: Immunoassay Measurement Methods

All about Tau

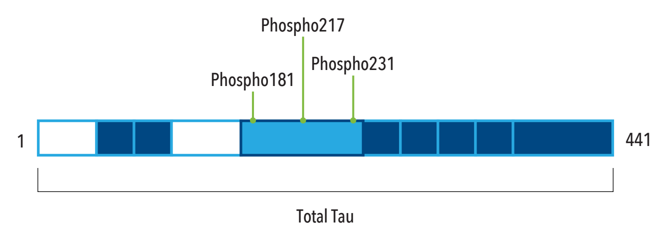
Tau is a microtubule-associated protein encoded by the *MAPT* gene, which is commonly implicated in neurodegenerative conditions called tauopathies. There are six tau isoforms expressed at specific levels in the axons of healthy human neurons, but in tauopathies such as Alzheimer's disease (AD), abnormal and hyperphosphorylated tau aggregates build up and disrupt microtubule assembly in different brain regions, cell types, and subcellular deposits.[1]

Elevated total tau protein in circulation is a biomarker that reflects molecular differences between AD and age-matched healthy individuals. Certain phosphorylated tau species are also specific to AD and may help differentiate AD from other tauopathies. *MAPT* polymorphisms have also been strongly linked to other proteinopathies, suggesting that tau may play an important role in neurological health beyond tauopathy research.[1]



Measurement Methods

As biomarkers, total tau and phosphorylated tau can be detected in brain tissue, cell lysates, cerebrospinal fluid (CSF), and blood samples. Increased phosphorylation at clinically relevant threonine (Thr) positions, such as 181, 217, and 231 in either the CSF or blood can be used alongside other biomarkers to monitor AD onset and progression. Several immunoassays have been developed to detect different phosphorylated tau species, but scientists must thoughtfully choose validated immunoassay components such as antibodies, reagents, and detection systems. The enzyme-linked immunosorbent assay (ELISA) is widely accepted for biomarker research validation due to its ability to handle multiple samples simultaneously with minimal variation. Among the different ELISA types, sandwich ELISA is the most used for biomarker analysis because of its high specificity, sensitivity, ease of use, and rapid results.[2,3]



**Threonine 181, 217, and 231 are three known clinically relevant sites among the 85 putative phosphorylation sites in the tau protein.*

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Tau Measurement FAQ

What is tau?

Tau is a microtubule binding protein that aggregates in neurodegenerative conditions like Alzheimer's disease.[1]

How do you measure tau?

Researchers typically measure tau protein levels with immunoassays, such as ELISA or immunoblotting, or by mass spectrometry.[2]

What are the benefits of quantifying tau proteins for research and diagnosis?

Researchers measure tau to elucidate tauopathy mechanisms; quantifying biomarkers such as tau in biofluids has made identifying and staging neurological conditions quicker, cheaper, and less invasive.[1,2]

How do Aviva's ELISAs improve tau detection?

Aviva Systems Biology ELISA kits simplify workflows, improve reliability, and deliver high specificity and sensitivity detection of neurodegenerative disease biomarkers, including total tau and pTau, for a range of neurodegenerative disorders.[4,5]

See References on Page 7

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Infographic: Tracking Down Tau: Immunoassay Measurement Methods

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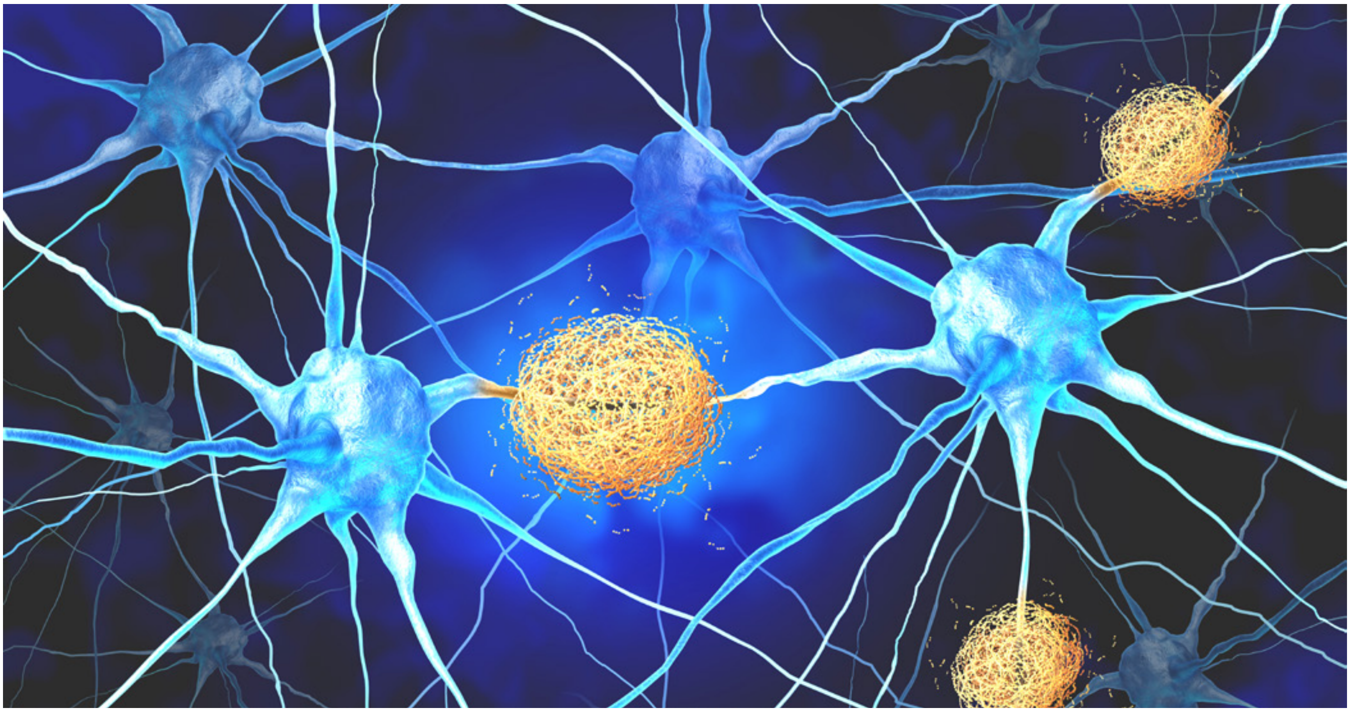

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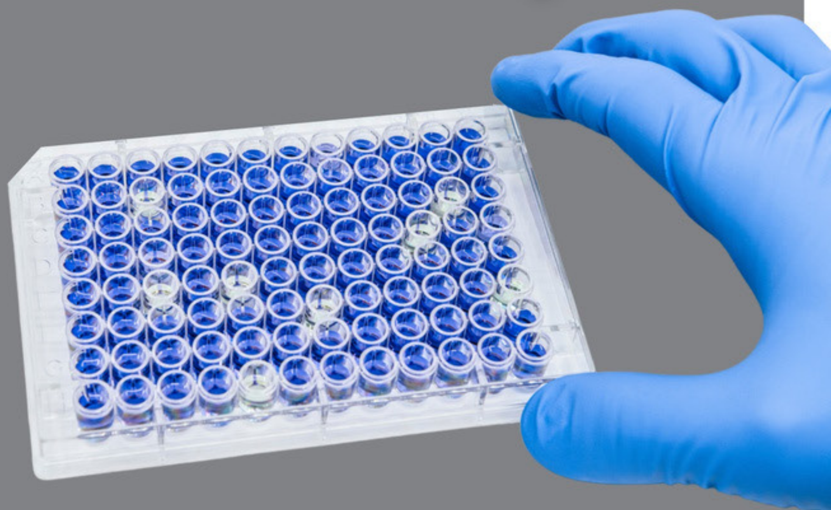
Leading the Way in
High-Precision Tau Assays

Aviva Systems Biology offers a comprehensive suite of Tau ELISA assays designed to advance research in Alzheimer's disease and other tauopathies.

Our assays offer unparalleled accuracy and sensitivity for detecting these crucial biomarkers in a variety of biological samples.



Target Specific PTMs

< 2pg/mL Sensitivity

Blood, Serum, CSF Detection

Total and Phospho-Tau ELISA Kits

TOTAL TAU ELISA **OKGD00201**

Detection Range: 7.81 – 500 pg/mL

PHOSPHO-TAU (THR181) ELISA **OKGD00202**

Detection Range: 15.6 – 1000 pg/mL

PHOSPHO-TAU (THR231) ELISA **OKGD00203**

Detection Range: 9.38 – 600 pg/mL

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