Research Focus

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Volume 2 • 2013

Alzheimer's Disease: Amyloid Cascade and Beyond

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Alzheimer's disease (AD), the principal cause of senile dementia, is characterized by regional neuronal degeneration, synaptic loss, and the presence of neurofibrillary tangles (NFTs) and senile plaques. NFTs are aggregates of hyperphosphorylated microtubular Tau protein, whereas senile plaques are complex extracellular lesions composed of a β-amyloid (Aβ)-containing core that is surrounded by activated microglia, fibrillary astrocytes, and dystrophic neurites.

A decade of research has established that reactive oxygen species (ROS) contribute extensively to the neuronal damage in AD. Oxidative damage is one of the early markers of neuronal dysfunction in AD. With advancing age, there is increased production of ROS and diminished capacity to protect against ROS, leading to an increasingly oxidizing cellular environment. A strong correlation exists between the extent of free radical generation by Aβ and neurotoxicity. In addition to its direct neurotoxic effects, Aβ may also fragment into free radical peptides (containing 25-35 amino acids) that act as potent initiators of lipid peroxidation.

The Amyloid Cascade

Deposition of Aβ is an early event in the pathogenesis of AD that precedes the formation of Tau-positive paired helical filaments (PHFs) in NFTs. AD is also characterized by a progressive deposition of the Aβ peptide in senile plaques. In normal healthy individuals, Aβ peptides are present only in small quantities as soluble monomers that circulate in the cerebrospinal fluid and blood. In AD patients, however, their levels increase significantly and they begin to accumulate as insoluble, fibrillar plaques. The Aβ in senile plaques vary in length from 40 to 43 amino acids, however, Aβ1-42 occurs more frequently and forms fibrillar aggregates far more readily than the Aβ1-40 peptide. Aβ peptides originate from the proteolytic cleavage of the amyloid precursor protein (APP). The β-amyloid gene, located on chromosome 21, encodes the transmembrane APP. APP occurs in three common isoforms, APP695, APP751, and APP770. The APP695 is expressed exclusively in neurons, whereas APP751 and APP770 are present in both neural and non-neural cells. The primary structure of APP contains a small signal sequence, a large extramembranous N-terminal region, a single transmembrane domain, and a cytoplasmic C-terminal tail.

Processing of APP *in vivo* occurs by two major pathways (Figure 1). Cleavage of APP at the N-terminus of the Aβ region by β-secretase and at the C-terminus by γ-secretase represents the amyloidogenic pathway for processing of APP. The β-secretase cleaves APP between residues Met671 and Asp672 and yields sAPPβ and C99. The β-secretase has also been identified as an aspartyl protease (BACE or Asp2) of unusual nature. It has a C-terminal transmembrane domain and two active site motifs located in the luminal domain. Newly synthesized BACE contains a pro-peptide domain, which is cleaved at residue Glu46 to produce the mature enzyme. The active site of BACE and the β-secretase cleavage site of APP are in precise topological orientation for endoproteinases. Following the β-secretase cleavage, a second cleavage occurs at the C-terminus of Aβ peptide that releases Aβ from C99. This cleavage occurs in the vicinity of residue 712 of the C-terminus. The γ-secretase can cleave the C-terminal region at either Val711 or Ile713 to produce the shorter Aβ peptide (Aβ1-40) or the longer Aβ peptide (Aβ1-42). The predominant form of Aβ found in the cerebrospinal fluid is the shorter Aβ1-40 peptide. Despite its lower rate of synthesis, Aβ1-42 is the peptide that is initially deposited within the extracellular plaques of AD patients. In addition, Aβ1-42 is more hydrophobic and aggregates at much lower concentration than the Aβ1-40 form.

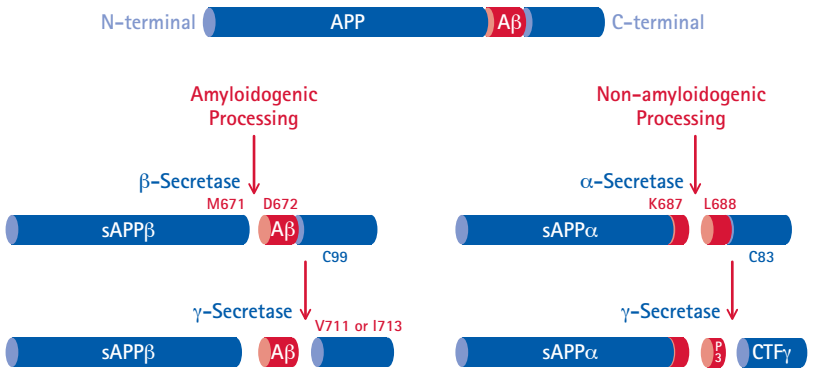

Figure 1.

Amyloidogenic and nonamyloidogenic pathways for proteolytic processing of amyloid precursor protein, APP.

APP can also be processed, via the nonamyloidogenic pathway, by α-secretase, which cleaves within the Aβ domain between Lys687 and Leu688, to produce a large soluble α-APP domain and the C-terminal fragment containing P3 (C83). The latter can then be cleaved by γ-secretase at residue 711 or 713 to release the P3 fragment. This pathway does not yield Aβ peptide. Hence, shunting APP towards the α-secretase pathway may have a beneficial effect in lowering Aβ peptide levels. It is reported that α-secretase shares many of its properties with the secretase that cleaves angiotensin-converting enzyme and is believed to be a zinc metalloproteinase of the ADAMs family. Muscarinic agonists (M1 and M3) and some PKC activators are reported to enhance α-secretase activity and are under consideration for their therapeutic value as AD treatment tools.

Neuronal toxicity caused by Aβ occurs via several different mechanisms, of which free radical-induced damage appears to the most prominent one. Aβ can activate inflammatory pathways by enhancing the microglial secretion of inflammatory cytokines, such as IL-1 and IL-6. Additionally, it can trigger the production of ROS, nitrogen intermediates and TNF-α from microglia. Aβ also increases the accumulation of H_2O_2 in a Cu^{2+}/Zn^{2+}-dependent manner, which can lead to lipid peroxidation and cell death. *In vitro*, Aβ1-42 is shown to induce apoptosis in cultured cortical neurons, possibly through alterations of cellular calcium homeostasis. Interaction between Aβ and ApoE3 or E4 is considered to be an important determinant of amyloidosis. ApoE3 is shown to inhibit Aβ aggregation *in vitro* by decreasing Aβ multimers, whereas ApoE4 is reported to accelerate the rate of amyloid fibril formation (Aβ1-42 > Aβ1-40).

Presenilin Mutations

Another set of proteins, known as presenilins (PS1 and PS2), is also reported to play an important role in APP processing. PS1 and PS2 share about 62% amino acid identity. They are involved in the maintenance of cortical activity and their loss can lead to neuronal atrophy, astrogliosis, caspase-3-mediated apoptosis, and hyperphosphorylation of Tau. PS1 and PS2 are expressed throughout most peripheral tissues and in all regions of the brain. In newborn mice, PS1 mRNA levels are shown to be about three-fold higher than that of PS2. Proteolytic processing of PS1 results in a 27-28 kDa N-terminal fragment (NTF) and a 16-17 kDa C-terminal fragment (CTF). Similarly, PS2 cleavage generates a 35 kDa NTF and 20 kDa CTF. Their processing sites are identified as Asp345/Ser346 in PS1 and Asp329/Ser330 in PS2. Also, it has been reported that PS1 is phosphorylated by GSK-3β at the Ser353 and Ser357 residues in its cytoplasmic loop, which may enhance its activity as a Ca^{2+} leak channel and can influence the activity and substrate specificity of

γ-secretase. PS1 is suggested to have either an inherent γ-secretase activity or act as a co-factor for γ-secretase. Li et al. (2000) have reported that the active site of γ-secretase is shared between the NTF and CTF fragments of presenilin. Cells obtained from PS1/PS2 double knockout mice do not show any γ-secretase activity. Presenilins are also known to be involved in the regulation of Notch signaling, which is important in framing cell destiny during embryogenesis, hematopoiesis, and neural stem cell differentiation. PS1 is also reported to play an important role in the formation of the axial skeleton, neurogenesis, and in the survival of progenitor cells and neurons in specific brain regions.

Over 150 mutations in PS1 and 10 mutations in PS2 genes have been reported. These mutations enhance amyloid deposition and are the main cause of familial type of AD (FAD). Most PS1 mutations are of the missense type, involving a single amino acid substitution. However, more severe mutations, such as donor-acceptor splice mutations, can result in two amino acid substitutions. PS1 and PS2 deficiency leads to reduced Aβ generation, whereas FAD-linked PS1 and PS2 mutations lead to misregulation of γ-secretase activity that results in a substantial increase in the ratio of Aβ1-42 to Aβ1-40. It has been suggested that mutant PS1 proteins alter the proteolytic processing of APP at the C-terminus of Aβ and favor the deposition of Aβ1–42 peptide. A FAD-linked PS1 mutation involving M146V can result in the inhibition of store-operated Ca^{2+} (SOC) entry into neurons. This can result in acquisition of spontaneous activity of SOC driven by stromal interaction molecule 2 (STIM2). PS1 and PS2 are also involved in several additional γ-secretase-independent functions in neurons, including Wnt and Akt signaling, membrane trafficking, ion channel regulation and cell junction organization. Aberrant splicing events in PS1 gene are also reported in other neurological diseases besides AD; for example, the G183V mutation is seen in patients with Pick type Tauopathy.

Mutations in Familial Alzheimer's Disease

Most cases of FAD are reported to result from mutations in one of the three genes, APP, PS1 and PS2. Mutations in these genes can result in elevated levels of Aβ peptide. Mutations in the APP gene, located on chromosome 21, account for about 2% of all cases of FAD and approximately 5 to 20% of early-onset FAD. A substitution of Glu to Gln at codon 693 of APP is termed the "Dutch mutation," which is responsible for hereditary cerebral hemorrhage with amyloidosis (Dutch type). Here, amyloid deposits containing the Aβ peptide are found in cerebral vessel walls with diffuse plaques in the brain parenchyma. Another mutation, known as "Flemish mutation," occurs at codon 692, where Ala is replaced by Gly. It causes an intermediate phenotype between congophilic angiopathy and AD. A well-studied mutation, the "Swedish mutation," results from the replacement of Lys and Met by Asn and Leu at codons 670 and 671, respectively. The Swedish mutation does not lie within the Aβ peptide region, but instead lies in the proximity of the β-secretase cleavage site and affects mainly the production of soluble Aβ1-40 peptide. Fibroblast cell lines transfected with APP bearing the Swedish mutation are shown to produce elevated levels of the soluble form of Aβ peptide. Recently, Jonsson et al. (2012) reported a mutation at site 673, where Ala is replaced by Thr. This mutation in the APP gene protects against Alzheimer's disease and cognitive decline in the elderly. This substitution is shown to be adjacent to the aspartyl protease β-site in APP, and results in an about 40% reduction in the formation of amyloidogenic peptides. It increases sAPPα production and reduces sAPPβ production.

Hyperphosphorylation of Tau Proteins:

The localization of Tau protein in the AD brain is markedly abnormal and may contribute to neuronal dysfunction. Tau is a neuronal protein located mostly in the axon and, to a lesser extent, in cell bodies, but is almost absent from dendrites. In AD, normal soluble cytoskeletal elements, such as Tau and neurofilaments, are transformed into insoluble paired helical filaments (PHFs). This is linked to the post-translational change in Tau, primarily its hyperphosphorylation by a number of protein kinases. In its non-phosphorylated state, Tau promotes rapid and extensive microtubule (MT) polymerization; however, upon phosphorylation, its ability to promote MT assembly is diminished. Tau phosphorylation is intimately tied to oxidative stress response via the MAP kinase pathway and through activation of NF-κB. Pyramidal neurons of the hippocampus undergoing degeneration are reported to show higher levels of free carbonyls, lipid peroxide adduction, and nitrotyrosine.

In vitro, Tau is a substrate for a multitude of protein kinases including CaM kinase II, casein kinase II, PKA, ERK2, and GSK-3. Cyclin-dependent kinase 5 (Cdk5), in conjunction with its neuron-specific activator p35 (cdk5/p35), is another protein kinase implicated in Tau hyperphosphorylation. Proteolytic cleavage of the regulatory unit p35 by calpain produces p25, which accumulates in the AD brain. This cleavage is reported to be induced by Aβ in cortical neurons. Another protein kinase that has been implicated in Tau phosphorylation in AD is MARK (microtubule regulating kinase), which preferentially phosphorylates KXGS motif in the microtubule affinity binding domains. It predominantly phosphorylates Tau on Ser262, although Ser293, Ser324, and Ser356 are also reported to be phosphorylated.

In fact it has been suggested that phosphorylation of Ser262 in AD may be a primary event contributing to Tau dysfunction and, eventually, PHF and NFT formation. PHF-Tau is reported to be at least partially phosphorylated at 19 sites, of which 9 sites have a Ser/Thr-Pro motif. It is believed that the phosphorylations at specific sites, rather than the overall extent of phosphorylation, are important in modulating the ability of Tau to bind MTs.

A significant consequence of Tau hyperphosphorylation in AD is a reduction in its ability to bind microtubules and promote microtubule assembly (Figure 2). Hyperphosphorylated Tau may contribute to a destabilized microtubule network, impaired axonal transport, and ultimately result in NFT formation and neuronal death. Phosphorylation of Tau at only a few sites within the microtubule binding regions (Ser262, Ser356, and to a lesser extent Ser293 and Ser324) is sufficient to diminish its ability to bind microtubules. Another interesting fact to note is that hyperphosphorylated Tau is far more resistant to degradation by calpain, a calcium-activated protease. This may be the result of the Tau self-association that occurs throughout microtubule-binding domains, thereby reducing the accessibility of these sites to calpain. Self-association of Tau is potentiated in an oxidizing environment. Another significant outcome of increased Tau aggregation in an oxidizing environment is glycation, or the non-enzymatic addition of a reducing sugar to a protein. This often occurs on a lysine residue and may result in the formation of Schiff bases. PHF Tau, which is both glycated and hyperphosphorylated, shows a greater reduction in microtubule-binding capacity compared to the soluble Tau from AD brain, which is hyperphosphorylated but not glycated. Oxidative crosslinking also makes proteins more resistant to proteolytic removal by inhibiting the activity of proteasomes. Therefore, oxidative crosslinking may be a significant contributor to the accumulation of ubiquitin conjugates in NFTs. Higher levels of ubiquitin have been reported in several neurodegenerative diseases.

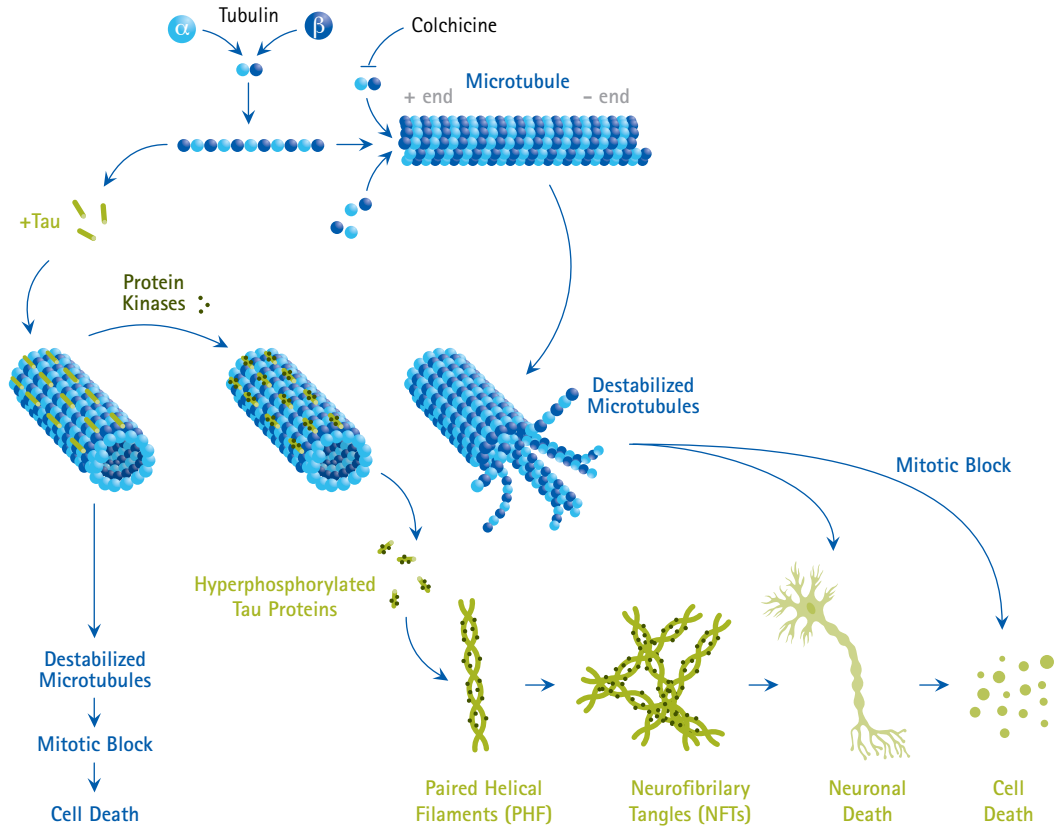

Figure 2.

Hyperphosphorylated Tau proteins destabilize microtubules and also form NFTs, both resulting in neuronal death in AD.

Endoplasmic Reticulum–Mitochondrial Cross-talk in Alzheimer's Disease:

Although the Aβ hypothesis for AD is well accepted, a few questions have been raised recently about the contribution of mitochondrial dysfunction, altered cholesterol and fatty acid metabolism, and aberrant Ca^{2+} homeostasis that precede accumulation of Aβ and NFTs. Hence, researchers have begun to look into endoplasmic reticulum (ER) and mitochondria for answers. Studies have shown that several regions of ER are in actual physical contact with the mitochondria. These regions, known as mitochondria-associated ER membranes (MAMs), exhibit lipid raft-like properties and are shown to be detergent-resistant. About 75 different proteins are reported to be associated with MAMs, which are involved in Ca^{2+} homeostasis, cholesterol and phospholipid metabolism, and apoptotic signaling. Area-Gomez, et al. (2012) have shown that PS1, PS2, APP and γ-secretase activity are enriched in MAMs regions and any mutation in these can perturb MAM function. Higher levels of ER–mitochondria connectivity are detected in human fibroblasts from FAD patients with mutations in PS1, PS2, or APP, as well as in a neuroblastoma cell line containing a familial PS2 mutation. This increase is evident even before any signs of Aβ accumulation. In addition, upregulated MAM-associated proteins are found in the post-mortem AD brains and in murine models of AD. Hippocampal neurons exhibit elevated contact points between ER and mitochondria following exposure to Aβ peptides, leading to increased ER-to-mitochondria Ca^{2+} transfer via the low-affinity mitochondrial uniporter. Higher levels of Ca^{2+} can perturb normal mitochondrial metabolism and lead to changes in transmembrane potential and subsequent apoptotic cell death. Increased intracellular calcium due to MAM dysfunction may activate Ca^{2+}-regulated kinases, which can lead to hyperphosphorylation of Tau. Although mutations in Tau are not reported in any case of FAD, a P301L mutation observed in familial fronto-temporal dementia (FTD) has been shown to increase the association between ER and mitochondria in a transgenic mouse model of FTD.

microRNAs (miRNAs) in Alzheimer's Disease–selected examples:

Thus far, over 1,000 miRNAs have been reported in the literature, and each miRNA is capable of binding to multiple mRNA targets that affect the production of hundreds of proteins in the cell. It is believed that the miRNA system regulates over 60% of all protein-coding genes from development to death. Also, it has been suggested that about 70% of all miRNAs are expressed in various regions of the brain. Abnormalities in expression and function of miRNAs have been reported in Alzheimer's disease by several researchers. Lukiw et al. (2008) showed that miRNA-9, miRNA-128, and miRNA-146a are upregulated in the hippocampus of AD brains. Their studies indicated that miRNA-146a expression is regulated via NF-κB, and, since AD brains exhibit higher NF-κB activity, it can also lead to an increase in complement factor H and IRAK1, resulting in sustained neuroinflammation. NF-κB activation inhibitors, such as caffeic acid phenethyl ester (CAPE), are shown to block miRNA-146a activity.

β-secretase-1, the rate-limiting enzyme in Aβ production, is a target of miRNA-107. Significantly reduced levels of miRNA-107 have been reported in the temporal cortex of AD patients and in those with mild cognitive impairment, an early sign of AD. Likewise, greatly reduced levels of miRNA-298 and miRNA-328, which also target β-secretase-1, have also been reported in the hippocampus of aged APPswe/PS1 transgenic mice with the A246E mutation. These studies indicate that repressed levels of selected miRNAs may lead to overexpression of β-secretase and increased production of Aβ peptides. Interestingly, Aβ42 is shown to downregulate levels of several miRNAs (miRNA-9, 20b, 21, 30b, 125b, 137, 148b, 181, 187, 433, and 664) in the hippocampus.

miRNA-34c, a negative constraint of memory consolidation, is shown to be significantly elevated in the hippocampus of AD patients and in APPPS1-21 mice, and impairs memory and learning. Zovoilis et al. (2011) have shown that injecting miRNA-34c mimics into normal mice and subjecting them to fear conditioning increases their hippocampal levels of miRNA-34c and impairs learning. This upregulation also reduced levels of SIRT1. On the other hand, significant improvements in learning and memory and increases in SIRT1 were observed when APPPS1-21 mice were injected with miRNA-34c seed inhibitors.

Concluding Remarks: Therapeutic Strategies

An important question that arises is whether reducing oxidative stress has any therapeutic value in minimizing the pathogenesis of AD. Agents that inhibit free radical formation have been shown to reduce the incidence and progression of AD. Addition of antioxidants, such as propyl gallate, vitamin E, and spin traps, such as N-tert-butyl-α-phenylnitrone, reduces neurotoxicity in cultured cells exposed to Aβ. Vitamin E has been reported to promote hippocampal neuronal survival *in vitro* and restore hypofunctioning cholinergic neurons in rats.

Another approach to minimize neuronal damage appears to be reducing or preventing the release of Aβ from APP. The characterization of secretases has spurred the development of therapeutic strategies that may limit the buildup of Aβ peptides in the brain and eliminate or delay the pathological effects of AD. Inhibiting the activity of β- or γ-secretase is therapeutically attractive, because clinical intervention at this step affects the early events that lead to plaque formation and neuronal death. Small molecules that inhibit β- and/or γ-secretase would therefore be expected to decrease production of Aβ and retard the progression of AD. Passive anti-amyloid immunotherapy with short sequence antigens has gained some traction in recent years. Several earlier vaccines developed with longer peptide sequences had failed in clinical trials.

A major focus in neurodegeneration research is to identify more genetic and environmental factors responsible for Aβ buildup in nerve cells, in AD and other disorders. Although Aβ peptides were long considered to be causative factors in AD alone, they have recently attracted attention in multiple sclerosis, where Aβ42 is shown to be upregulated in brain lesions. Grant et al. (2013) showed that intraperitoneal administration of Aβ40 or Aβ42 in experimental autoimmune encephalomyelitis (EAE) mice results in reduced motor paralysis, brain inflammation, and lymphocyte activation. In addition, there was a lack of Aβ plaque deposition in EAE mice following Aβ treatment. These studies may generate more interest in regulation of the dynamic efflux of Aβ peptides between the central nervous system and plasma.

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Antibodies for Secretases

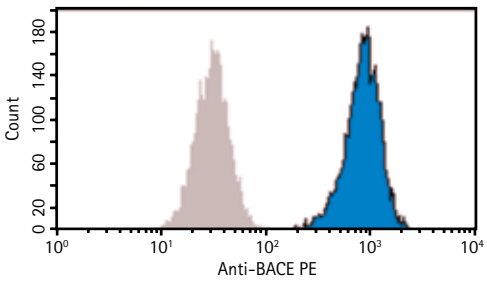
Description	Species Reactivity*	Applications**	Qty/Pk	Catalogue No.
Anti-BACE (487-501) Rabbit Antibody	Hu, Hmst	IP, WB	100 µL	195102
Anti-BACE (Ab-2) (485-501) Rabbit Antibody	Hu, Ms	WB	100 µg	PC529
Anti-BACE Antibody, C-terminus	Hu	IHC, WB	100 µg	AB5940
Anti-BACE Antibody, C-terminus, clone 61-3E7	Hu, Ms, Rt, Prim	IP, WB	100 µg	MAB5308
Anti-BACE Antibody	Hu, Ms	WB	100 µg	AB5832
Anti-BACE1 Antibody, C-Terminal (485-501) Rabbit	Hu, Ms, Rt	IF, IHC, IP, RIA, WB	100 µL	195111
Anti-BACE2 Antibody	Hu, Ms, Rt	IP, WB	100 µL	AB9574
Anti-TACE (807 | 823) Rabbit Antibody	Hu, Ms, Rt	WB	100 µL	PC491

Species: Hu=Human, Ms=Mouse, Rt=Rat, Bov=Bovine, Prim=Primate, Ham=Hamster, Chk=Chicken
Applications: IHC=Immunohistochemistry, IF=Immunofluorescence, IP=Immunoprecipitation, WB=Western Blotting, RIA=Radioimmunoassay

Milli-Mark® Anti-BACE, C-terminus-PE, clone 61-3E7

(Catalogue No. FCMAB410PE)

Purified mouse monoclonal IgG_1 conjugated to PE in PBS with 0.1% sodium azide and 15 mg/mL BSA. Recognizes multiple isoforms for BACE, calculated molecular weights ranging from 48 to 55 kDa. Specially designed for flow cytometry.



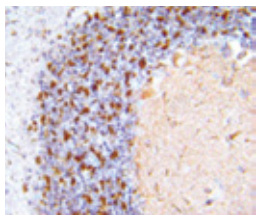
Flow cytometric analysis of U251 cells stained with either anti-BACE PE (blue) antibody or PE Mouse IgG_{1k} isotype control (gray).

BACE Proteins Investigator Minipack

(Catalogue No. 15-206)

3 individual tubes containing:

- AB5940SP Anti-BACE
- AB9574SP Anti-BACE2
- MAB5308SP Anti-BACE, C-terminus, clone 61-3E7



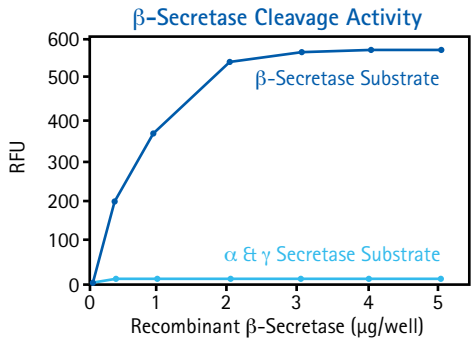
BACE staining of Human Cerebellum, tissue Pretreated with citrate buffer, pH 6.0. pAb at 5.0 µg/mL, IHC-Select Detection with HRP-DAB. Immunoreactivity is restricted to small neurons in the inner granular layer.

Secretase Activity Assays

β-Secretase Activity Assay Kit, Fluorogenic

(Catalogue No. 565785)

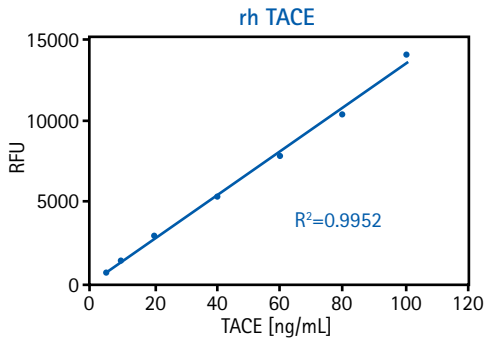
Suitable for measuring the β-secretase (BACE) activity in cell lysates, tissue extracts, or purified enzyme preparations in a 96-well format, this assay uses a secretase-specific peptide conjugated to EDANS and DABCYL. When the substrate is intact (uncleaved), the fluorescence from EDANS is effectively quenched by the DABCYL moiety. Cleavage of the peptide by β-secretase physically separates EDANS and DABCYL, allowing the emission of the fluorescence signal. The increase in fluorescence is measured at an excitation wavelength of 335-355 nm and an emission wavelength of 495-510 nm.



InnoZyme™ TACE Activity Kit

(Catalogue No. CBA042)

Designed to measure human TACE activity in cell lysates and biological samples in a 96-well format, this assay may also be used for screening enzyme inhibitors. The plate is pre-coated with a monoclonal antibody specific for human TACE that captures the enzyme. Unbound material is discarded, the plate is washed, and the activity of captured TACE is measured using an internally quenched fluorescent substrate, MCA-KPLGL-Dpa-AR-NH_2. Cleavage of the scissile amide bond, G-L, releases the fluorophore from the quenching molecule, Dpa, resulting in an increase in fluorescence. Fluorescence of the cleaved product, MCA-KPLG, is measured at an excitation wavelength of ~324 nm and emission wavelength of ~400 nm.



Purified Secretase Enzymes

BACE1, His•Tag®, Human, Recombinant, NSO Cells

(Catalogue No. PF125)

Recombinant, human BACE-1 (amino acids 1-460) fused at the C-terminus to a His•Tag® sequence and expressed in NSO cells. Supplied as a mixture of the ~68-70 kDa proenzyme and the ~65-67 kDa mature enzyme. Specific activity: ≥1 pmol/min/µg protein.
Purity: ≥90% by SDS-PAGE.

TACE, His•Tag®, Human, Recombinant, *T. ni.*

(Catalogue No. PF133)

Recombinant, human TACE (amino acids 1-671) His•Tag® sequence and expressed in *T. ni.* insect cells. The major form of the purified protein corresponds to the mature form with an apparent molecular mass of ~70 kDa.
Purity: ≥90% by SDS-PAGE.

Secretase Inhibitors

Description	Catalogue No.	Comments	Size
Amyloid Precursor Protein β-Secretase Inhibitor (KTEETSEVN(stat)VAEF)	171601	A potent inhibitor of the amyloid precursor protein β-secretase (IC_{50} = 30 nM).	500 µg
β-Secretase Inhibitor II (Z-VLL-CHO)	565749	A cell-permeable, potent, and reversible inhibitor of β-secretase (Aβ total: IC_{50} = 700 nM; and Aβ1-42 (IC_{50} = 2.5 µM).	1 mg 5 mg
β-Secretase Inhibitor III (H-EVNstatineVAEF-NH_2)	565780	A substrate analog inhibitor of β-secretase that completely blocks the proteolytic activity (at 5 µM) in solubilized membrane fractions from BACE transfected MDCK cells.	500 µg
β-Secretase Inhibitor IV (N-(1S, 2R)-1-Benzyl-3-(cyclopropyl-amino)-2-hydroxypropyl)-5-(methyl (methylsulfonyl)amino-N'-((1R)-1-phenylethyl)isophthalamide)	565788	A cell-permeable, potent inhibitor that binds to BACE-1 active site and blocks its proteolytic activity (IC_{50} = 15 nM for BACE-1, human).	1 mg
InSolution™ β-Secretase Inhibitor IV (N-(1S, 2R)-1-Benzyl-3-(cyclopropyl-amino)-2-hydroxypropyl)-5-(methyl (methylsulfonyl)amino-N'-((1R)-1-phenylethyl)isophthalamide)	565794	A cell-permeable inhibitor that binds to BACE-1 active site and blocks its proteolytic activity (IC_{50} = 15 nM for BACE-1, human).	500 µg
γ40-Secretase Inhibitor I (t-3,5-DMC-IL-CHO)	565765	Potent, cell-permeable, reversible γ-secretase inhibitor that preferentially appears to inhibit the secretion of Aß1-40 (>90%) over Aβ1-42 (~15%) (Aβ total IC_{50} ~ 15 µM; Aβ1-40 IC_{50} ~ 22 µM; Aβ1-42 IC_{50} > 50 µM)	1 mg
γ-Secretase Inhibitor I (Z-LLNle-CHO)	565750	A cell-permeable inhibitor of γ-secretase that also acts as an inhibitor of proteasome activity.	1 mg
γ-Secretase Inhibitor II (MW167)	565755	A cell-permeable, reversible and selective peptidomimetic inhibitor of γ-secretase (IC_{50} = 13 µM).	1 mg
γ-Secretase Inhibitor IV (2-Naphthoyl-VF-CHO) stably transfected with the APP Swedish mutants.	565761	A cell-permeable, reversible inhibitor of γ-secretase. Equipotently inhibits the release of Aβ1-40 (ED_{50} = 2.6 µM) and Aβ1-42 (ED_{50} = 2.7 µM) in HEK293 cells	1 mg
γ-Secretase Inhibitor VI (1-(S)-endo-N-(1,3,3)-Trimethyl-bicyclo[2.2.1] hept-2-yl)-4-fluorophenyl Sulfonamide)	565763	A cell-permeable, potent inhibitor of γ-secretase that blocks the formation of Aβ42 (IC_{50} = 1.8 µM).	5 mg
γ-Secretase Inhibitor IX (DAPT)	565770	A cell-permeable dipeptide that suppresses Aß production by blocking γ-secretase (Aβ total IC_{50} = 115 nM; Aβ42 IC_{50} = 200 nM).	5 mg 10 mg
InSolution™ γ–Secretase Inhibitor IX (DAPT)	565784	A cell-permeable dipeptide that inhibits γ-secretase activity and suppresses Aβ production (Aβ total IC_{50} = 115 nM; Aβ42 IC_{50} = 200 nM).	5 mg 10 mg
InSolution™ γ-Secretase Inhibitor X (L-685,458)	565771	A cell-permeable, potent, and highly specific inhibitor of γ-secretase (Aβ total IC_{50} = 17 nM; Aβ40 IC_{50} = 48 nM; and Aβ42 IC_{50} = 67 nM in SH-SY5Y cells over-expressing spβA4CTF). Binds to presenilin and blocks Notch intracellular domain production.	250 µg 500 µg
γ-Secretase Inhibitor XI (JLK6; 7-Amino-4-chloro-3-methoxyisocoumarin)	565772	A cell-permeable, active site-directed, irreversible serine protease inhibitor. Acts as a potent and selective inhibitor of γ-secretase. Blocks the production of both Aβ40 and Aβ42 (IC_{50} = <100 mM) in HEK293 cells expressing wild-type and Swedish-mutant β-APP.	5 mg
γ-Secretase Inhibitor XII (Z-IL-CHO)	565773	A cell-permeable, reversible inhibitor of γ-secretase activity *in vitro* (Aβ40 IC_{50} = 7.9 µM; Aβ42 IC_{50} = 7.6 µM) and in cultured CHO 2b-7 cells that stably over-express APP695 (Aβ40 IC_{50} = 11.5 µM; Aβ42 IC_{50} = 8.3 µM).	5 mg

Secretase Inhibitors (continued)

Description	Catalogue No.	Comments	Size
γ-Secretase Inhibitor XVI (DAPM)	565777	A cell-permeable γ-secretase inhibitor (IC_{50} ~10 nM in 7PA2 cells (CHO cell line stably transfected with APP751 containing V717F familial Alzheimer's disease mutation). Also exhibits anti-aggregation properties and selectively blocks Aβ dimer and trimer formation.	5 mg
γ-Secretase Inhibitor XX ((S,S)-2-[2-(3,5-Difluorophenyl) acetylamino]-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl) propionamide) (IC_{50} = 1.7 nM in SupT1 cells).	565789	A cell-permeable, potent inhibitor of γ-secretase that lowers both brain and plasma Aβ40 levels by ~72% in Tg2576 mutant APP transgenic mouse model (100 µmol/kg, b.i.d). Also potently inhibits Notch processing	500 µg 1 mg
γ-Secretase Inhibitor XXI, Compound E ((S,S)-2-[2-(3,5-Difluorophenyl)-acetylamino]-N-(1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-propionamide)	565790	A cell-permeable, potent, selective, non-transition-state analog inhibitor of γ-secretase and Notch processing (IC_{50} = 300 pM for Aβ40 in CHO cells over-expressing wild type βAPP; 240 pM for Aβ40, 370 pM for Aβ42, and 320 pM for NICD, respectively, in HEK293 cells stably transfected with βAPP695 and mNotchDE(M1727V).	500 µg 1 mg
γ-Secretase Inhibitor XXII, Aβ42-Selective, CS-1 (3,3′-(3,4,5-Trifluorophenyl) methylenebis-(4-hydroxycoumarin))	565791	A cell-permeable dicoumarin compound that selectively inhibits γ-secretase-mediated production of Aβ42 over Aβ38, Aβ40, and Notch1, both in cell-free APP cleavage assays (IC_{50} = 70 nM; 710 nM, 310 nM, and 1.77 µM, respectively).	10 mg
γ-Secretase Inhibitor XXIII, Aβ42-Selective	565792	A cell-permeable purine compound that acts as a highly potent and selective inhibitor against γ-secretase-mediated production of Aβ42 over Aβ40 (IC_{50} = 21 and 350 nM, respectively). Crosses the blood-brain barrier.	5 mg
γ-Secretase Inhibitor XXIV, BMS299897 (4-(2-((1R)-1-(((4-Chlorophenyl)sulfonyl)-2,5-difluoro anilino)ethyl)-5-fluorophenyl) butanoic acid)	565793	A cell-permeable sulfonamide compound that preferentially inhibits γ-secretase activity toward APP CTF over Notch-1 (IC_{50} = 7.1 and 105.9 nM against APPSW CTF and murine ΔE-Notch processing, respectively, in HEK293 cells). Shown to be orally available and readily cross the blood-brain-barrier.	5 mg

Secretase Substrates

Description	Catalogue No.	Comments	Size
α-Secretase Substrate II, Fluorogenic (Ac-RE(EDANS)-VHHQKLVF-K(DABCYL)-R-OH)	565751	An internally quenched fluorogenic peptide substrate that contains the α-secretase cleavage site of β-APP. The cleavage has been shown to occur at the Lys-Leu bond. Excitation max: ~340 nm; emission max: ~490 nm.	1 mg
β-Secretase Substrate IV, Fluorogenic (FS-1; H-RE(EDANS) EVNLDAEFK(DABCYL)R-OH)	565758	A highly sensitive FRET peptide substrate based on the GVNLDAEF sequence derived from the β-secretase site of the Swedish mutation of APP. Hydrolysis of the substrate at Leu-Asp bond results in enhanced fluorescence. Excitation max.: ~350 nm; emission max.: ~490.	1 mg
β-Secretase Substrate VI, Fluorogenic (H-K(DABSYL)-SEVNLDAEFRQ(LY))	565781	A highly selective, FRET peptide substrate for β-secretase (pH ~4.0, kcat = 0.02 sec-1; Km = 9 µM). Derived from the Swedish mutant APP β-cleavage site (-NL ↓ DA-). Useful for high throughput screening of β-secretase inhibitors. Excitation max.: ~430 nm; emission max.: ~520 nm.	500 µg
γ-Secretase Substrate, Fluorogenic (NMA-GGVVIATVK(DNP)-DRDRDR-NH_2)	565764	An internally quenched fluorogenic peptide substrate containing the C-terminal β-APP amino acid sequence that is cleaved by γ-secretase. The proteolysis at the Aβ40-, Aβ42-, and Aβ43-generating cleavage sites results in enhanced fluorescence. Excitation max.: ~355 nm; emission max.: ~440 nm.	1 mg

Antibodies for Presenilin and Related Proteins

Description	Species Reactivity*	Applications**	Qty/Pk	Catalogue No.
Anti-APH-1 Antibody	Ms	WB	100 µL	AB9214
Anti-PEN2	Ms, Rt	IF, IHC, WB	100 µg	ABN489
Anti-Presenilin-1 Antibody, loop, a.a. 263-378, C-terminus, clone PS1-Loop	Hu, Ms, Rt, Prim	ICC, IH(P), IP, WB	100 µL	MAB5232
Anti-Presenilin 1 Antibody	Hu, Ms, Rt	ELISA, WB	100 µg	AB5757
Anti-Presenilin-1 Antibody, a.a. 14-33, N-terminus	Hu	ELISA, IH(P), WB	200 µL	AB1575
Anti-Presenilin-1 Antibody, N-terminus, clone hPS1-NT	Hu	ELISA, IHC, IP, WB	100 µL	AB1563
Anti-Presenilin-1 Antibody, loop, a.a. 275-367, C-terminus	Hu, Hmst, Ms, Mky	ICC, IP, WB	100 µL	AB5308
Anti-Presenilin-1, N-terminus, a.a. 14-23	Hu, Mky	ICC	100 µL	AB5310
Anti-Presenilin 1 Antibody, N-Terminal (1-65) Rabbit	Hu, Mky, Ms, Rt	IF, IP, WB	100 µL	529591
Anti-Presenilin Antibody, shared sequence	Hu	ELISA, IH(P)	200 µL	AB5984
Anti-Presenilin-2 Antibody	Hu, Ms, Rat	ELISA, WB	100 µg	AB5759

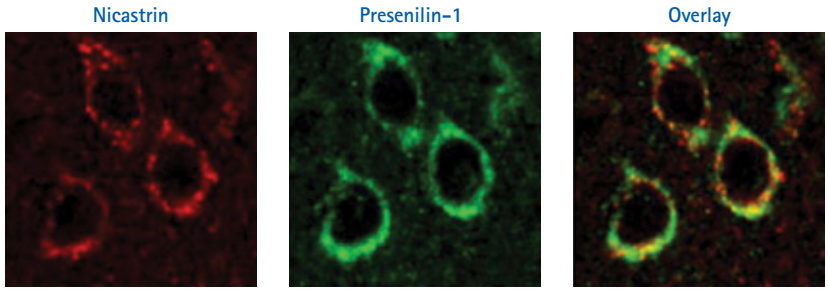
Species: Hu=Human, Ms=Mouse, Rt=Rat, Mky=Monkey, Prim=Primate, Hmst=Hamster
Applications: FC=Flow Cytometry, ICC=Immunocytochemistry, IHC=Immunohistochemistry, IH(P)=Immunohistochemistry (Paraffin), IF=Immunofluorescence, IP=Immunoprecipitation, WB=Western Blotting, ELISA=Enzyme Immunoassay, CS=Cell Sorting

Antibodies to Nicastrin

Anti-Nicastrin (Rat, expected to react with Human)

(Catalogue No. AB5890)

Preferentially labels cell bodies in the hippocampal formation, cerebral cortex, thalamic nuclei, Purkinje cells of the cerebellum, motor neurons in the brainstem and spinal cord. The staining pattern for the immunoreactive cell bodies obtained with the nicastrin antiserum corresponds to the pattern described using antibodies to presenilin-1. Suitable for immunohistochemistry and Western blotting.



Guinea Pig anti-Nicastrin (Catalog Number AB5890) and Mouse anti-Presenilin-1 (Catalog Number MAB5232) localization of Nicastrin (red) with Presenilin-1 (green) in rat cerebral cortex.

Anti-Nicastrin Antibody

(Catalogue No. MAB5556)

The antibody recognizes a doublet of ~100-110 kDa. Due to sequence similarity, it is expected that the antibody will react with most mammals. Suitable for immunocytochemistry, immunoprecipitation, and Western blotting.

Glycogen Synthase Kinase-3 (GSK-3) Inhibitors

Description	Catalogue No.	Comments	Size
GSK-3β Peptide Inhibitor, Cell-permeable (L803-mts, Myr-N-GKEAPPA PPQSpP-NH_2)	361546	A cell-permeable myristoylated form of GSK-3β Peptide Inhibitor with a glycine spacer. Acts as a selective, substrate-specific, competitive inhibitor of GSK-3β (IC_{50} = 40 µM).	1 mg
GSK-3β Inhibitor I (4-Benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione)	361540	A cell-permeable, thiadiazolidinone analog that acts as a highly selective, non-ATP-competitive inhibitor of GSK-3β (IC_{50} = 2 µM).	5 mg
GSK-3β Inhibitor II (2-Thio(3-iodobenzyl)-5-(1-pyridyl)-[1,3,4]-oxadiazole)	361541	A potent inhibitor of glycogen synthase kinase-3b (IC_{50} = 390 nM).	5 mg
GSK-3 Inhibitor IV, SB-216763	361566	A cell-permeable maleimide compound that acts as a potent, selective, ATP-competitive inhibitor of GSK-3 activity (K_i = 9.1 nM for GSK-3α).	10 mg
GSK-3β Inhibitor VI (2-Chloro-1-(4,5-dibromo-thiophen-2-yl)-ethanone)	361547	A cell-permeable, and non-ATP competitive inhibitor of GSK-3β (IC_{50} = 1 µM).	5 mg
GSK-3β Inhibitor VII (α-4-Dibromoacetophenone)	361548	A cell-permeable, selective, and non-ATP competitive inhibitor of GSK-3β (IC_{50} = 500 nM).	5 mg
GSK-3β Inhibitor VIII (AR-A014418, N-(4-Methoxy benzyl)-N′-(5-nitro-1,3-thiazol-2-yl)urea)	361549	A cell-permeable, potent inhibitor of GSK-3β (IC_{50} = 104 nM). Inhibition is competitive with respect to ATP (K_i = 38 nM).	5 mg
InSolution™ GSK-3β Inhibitor VIII	361557	A cell-permeable, potent inhibitor of GSK-3β (IC_{50} = 104 nM). Inhibition is competitive with respect to ATP (K_i = 38 nM).	5 mg
GSK-3 Inhibitor IX (BIO, (2′Z,3′E)-6-Bromo indirubin-3′-oxime)	361550	A cell-permeable, highly potent, selective, reversible, ATP-competitive inhibitor of GSK-3α/β (IC_{50} = 5 nM). Maintains self-renewal in human and mouse embryonic stem cells.	1 mg 10 mg
GSK-3 Inhibitor IX, Control, MeBIO (1-Methyl-BIO)	361556	A cell-permeable N-methylated analog of GSK-3 Inhibitor IX, BIO that serves as an inactive control for Cdk1/cyclin B, Cdk5/p25, and GSK-3α/β (IC_{50} >92 µM for Cdk1/cyclin B, >100 µM for Cdk5/p25, and GSK-3α/β).	1 mg
InSolution™ GSK-3 Inhibitor IX	361552	A cell-permeable, highly potent, selective, reversible, and ATP-competitive inhibitor of GSK-3α/β (IC_{50} = 5 nM). Sustains pluripotency of human and murine embryonic stem cells	500 µg
GSK-3 Inhibitor X ((2′Z,3′E)-6-Bromoindirubin-3′-acetoxime, BIO-Acetoxime)	361551	An acetoxime analog of BIO, GSK-3 Inhibitor IX (Cat. No. 361550) that exhibits greater selectivity for GSK-3α/β (IC_{50} = 10 nM) over Cdk5/p25, Cdk2/cyclin A, and Cdk1/cyclin B (IC_{50} = 2.4 µM, 4.3 µM, and 63 µM, respectively).	1 mg
GSK-3β Inhibitor XI (3-(1-(3-Hydroxypropyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-4-pyrazin-2-yl-pyrrole-2,5-dione)	361553	A cell-permeable, potent, specific, ATP-competitive inhibitor of GSK-3β (K_i = 25 nM). Shown to increase intracellular glycogen synthase activity in HEK293 cells (EC_{50} = 32 nM).	1 mg
GSK-3β Inhibitor XII, TWS119	361554	A cell-permeable, potent inhibitor of GSK-3β (IC_{50} = 30 nM). Selectively induce neuronal differentiation in both pluripotent murine embryonal carcinoma cells (P19; 30-40% at 1 µM) and embryonic stem cells (D3; 50-60% at 400 nM).	1 mg 5 mg
GSK-3 Inhibitor XIII ((5-Methyl-1H-pyrazol-3-yl)-(2-phenylquinazolin-4-yl)amine)	361555	A potent and ATP-competitive inhibitor of GSK-3 (K_i = 24 nM).	1 mg 5 mg
GSK-3 Inhibitor XV	361558	The racemic mixture of a cell-permeable pyridocarbazolo-cyclopentadienyl Ruthenium complex. Acts as a reversible, ATP-competitive, and highly potent inhibitor of GSK-3 (IC_{50} = 400 and 600 nM for GSK-3α and GSK-3β, respectively).	1 mg

Glycogen Synthase Kinase-3 (GSK-3) Inhibitors (continued)

Description	Catalogue No.	Comments	Size
GSK-3 Inhibitor XVI (CHIR99021)	361559	A cell-permeable aminopyrimidine compound that acts as potent, ATP-competitive, and highly selective GSK-3 inhibitor (IC_{50} = 10 and 6.7 nM against GSK-3α and β, respectively).	5 mg
InSolution™ GSK-3 Inhibitor XVI, CHIR99021	361571	A cell-permeable, potent, ATP-competitive, and highly selective GSK-3 inhibitor (IC_{50} = 10 and 6.7 nM against GSK-3α and GSK-3β, respectively).	5 mg
GSK-3β Inhibitor XVIII (2-(Chloro-4-(4-thiophen-2-yl-pyrimidin-2-ylamino)-phenyl)-(4-methyl-pierazin-1-yl)-methanone)	361562	A cell-permeable thienylpyrimidine compound that acts as a potent and selective GSK-3β inhibitor (IC_{50} = 64 nM),	5 mg
GSK-3 Inhibitor XXII, Compound A (6-Methyl-N-[3-[[3-(1-methyl ethoxy)propyl]carbamoyl]-1H-pyrazol-4-yl]pyridine-3-carboxamide)	361563	A cell-permeable, potent inhibitor of both GSK-3α and GSK-3β (IC_{50} = 2.3 and 2 nM, respectively).Shown to selectively inhibit the phosphorylation of cellular Tau on GSK-specific serine/threonine residues, but not those targeted by non-GSK kinases.	5 mg
GSK-3 Inhibitor XXIII, 3F8 (5-Ethyl-7,8-dimethoxy-1H-pyrrolo [3,4-c]-isoquinoline-1,3-(2H)-dione)	361564	A cell-permeable, potent, reversible, and ATP-competitive inhibitor of GSK-3β (IC_{50} = 34, 67 and 304 nM in the presence of 10, 30 and 100 µM ATP, respectively).	10 mg
GSK-3β Inhibitor XXIV (2-Methyl-5-(3-[4-(methylsulfinyl) phenyl)-1-benzofuran-5-yl)-1,3,4-oxadiazole, Racemic)	361567	The racemic mixture of a cell-permeable oxadiazolo-benzofuranylphenylsulfoxide that inhibits GSK-3β (IC_{50} = 35, 34, and 140 nM using the racemate, the (S), and the (R) enantiomer, respectively).	5 mg
GSK-3β Inhibitor XXV (M SEW00923SC)	361568	A blood brain barrier permeable oxadiazole compound that acts as a potent, reversible and ATP-competitive inhibitor of GSK-3β activity (IC_{50} = 17.1 nM) with excellent selectivity over Cdk2 (22% inhibition at 10 µM).	10 mg
GSK-3β Inhibitor XXVI	361569	A cell-permeable, pyrazolone GSK-3β inhibitor (IC_{50} = 34 nM, in an enzymatic assay) that is highly selective among a panel of 40 kinases.	5 mg
GSK-3β Inhibitor XXVII (3-Amino-6-(4-((4-methylpiperazin-1-yl) sulfonyl) phenyl)-N-(pyridin-3-yl) pyrazine-2-carboxamide, HCl)	361570	A cell-permeable, highly potent, reversible, and ATP-competitive inhibitor of GSK-3β (K_i = 4.9 nM) with ~110-fold greater selectivity over Cdk2 (K_i = 540 nM).	10 mg

Active Glycogen Synthase Kinase-3

GSK-3β, His•Tag®, Human, Recombinant, *E. coli*

(Catalogue No. 361524)

Recombinant, human GSK-3β fused at the N-terminus to a His•Tag® sequence and expressed in *E. coli*. Biological activity: 1 µg GSK-3β maximally phosphorylates 100 ng Tau protein in 30 min in an *in vitro* kinase assay at 30°C, pH 7.5. **Purity**: ≥90% by SDS-PAGE.

GSK-3β, Rabbit Skeletal Muscle, Recombinant, *E. coli*

(Catalogue No. 361526)

Recombinant, rabbit glycogen synthase kinase 3β expressed in *E. coli*. **Specific activity**: ≥5,000,000 units/mg protein.

GSK3β, Active, Rat

(Catalogue No. 14-538)

An N-terminal GST-tagged rat GSK3β fusion protein expressed in *E. coli* and purified by glutathione agarose chromatography.

GSK3β, Active

(Catalogue No. 14-306)

An N-terminal His-tagged recombinant GSK-3β residues 2 -end with H350L mutation. Expressed in baculovirus Sf21 insect cells and purified using Ni^{2+}/NTA agarose.
Purity: >90% by SDS-PAGE.

GSK-3 Peptides and Substrates

GSK3 Substrate Peptide
(Catalogue No. 12-533)

Synthetic peptide (RRRPASVPPSPSLS RHS(pS)HQRR) based on muscle glycogen synthase 1, where (pS) corresponds to phosphorylated serine. **Purity**: >90% by HPLC.

Phospho-Glycogen Synthase Peptide-2
(Catalogue No. 12-241)

The peptide is similar to skeletal muscle glycogen synthase; it contains sites 3b, 3c and phosphorylated site 4 from glycogen synthase. The sequence of the peptide is: YRRAAVPPSPSLSRHSSPHQ(pS)EDEEE.
Purity: >90% by HPLC.

Glycogen Synthase Peptide-2 (Ala21)
(Catalogue No. 12-242)

Serves as a negative control for other GSK3 substrates. The peptide is similar to skeletal muscle glycogen synthase; it contains sites 3b and 3c. Site 4, however, serine is replaced with alanine. The sequence of the peptide is: YRRAAVPPSPSLSRHSSPHQAEDEEE. **Purity**: >97% by HPLC.

Antibodies for Glycogen Synthase Kinase-3

Description	Species Reactivity*	Applications**	Qty/Pk	Catalogue No.
Anti-GSK-3β Rabbit Antibody	Hu, Ms, Rt	IHC, WB	100 µg	PK1111
Anti-GSK3 Antibody, clone 4G-1E	Hu, Ms, Rt, Dictyostelium, Vertebrates	ICC, WB	100 µg	05-412
Anti-GSK3α/β Antibody	Hu, Ms, Rt	IP, WB	100 µL	04-903
Anti-GSK3α/β Antibody	Hu, Ms, Rt	IP, WB	100 µL	04-903
Anti-GSK3α/β Antibody	Hu, Ms,	IP, WB	100 µL	05-903
Anti-GSK3α Antibody	Hu, Rt	IP, WB	200 µg	07-389
Anti-GSK3α Antibody, clone EP793Y, Rabbit Monoclonal	Hu, Ms, Rt	ICC, IH(P), IP, WB	100 µL	04-360
Anti-GSK-3β Antibody, a.a. 335-349	Bov, Hu, Ms, Rt	IH(P), IP, WB	50 µg	07-1413
Anti-GSK-3 α/β Antibody, clone 12B11.1	Hu	ICC, WB	100 µL	MABS77
Anti-GSK3 Antibody, clone Y174, Rabbit Monoclonal	Hu, Ms, Rt	ICC, IH(P), WB	100 µL	04-361
PhosphoDetect™ Anti-GSK3β (pSer9) Mouse (2D3) Antibody (positive control included)	Hu, Ms	ELISA, WB	1 set	361527
Anti-phospho-GSK3 β (Ser9) Antibody, clone EPR2286Y, Rabbit	Hu	ICC, IH(P), WB	100 µL	04-1075
PhosphoDetect™ Anti-GSK-3α/β (pTyr279/216) Rabbit Antibody	Hu, Ms, Rt	DB, ELISA, ICC, WB	10 Tests	ST1013
Anti-phospho-GSK3 (Tyr279/ Tyr216) Antibody, clone 5G-2F	Hu, Ms, Rt, Dictyostelium, Yeast	WB	200 µg	05-413
Anti-phospho GSK3β-(Ser389)	Ms, Rt	WB	200 µL	07-2275
Anti-phospho GSK3β (Thr390) Antibody	Hu	WB	100 µL	AB537
Anti-phospho-Glycogen Synthase (Ser641/Ser645) Antibody	Hu, Ms	WB	100 µL	07-817

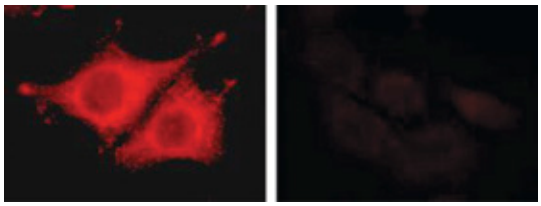
Species: Hu=Human, Ms=Mouse, Rt=Rat, Bov=Bovine
Applications: ICC=Immunocytochemistry, IHC=Immunohistochemistry, IH(P)=Immunohistochemistry (Paraffin), IF=Immunofluorescence, IP=Immunoprecipitation, WB=Western Blotting, ChIP=Chromatin IP, ELISA=Enzyme Immunoassay, DB=Dot Blot

Antibodies for Presenilin and Related Proteins (continued)

Anti-GSK3, clone 4G-1E, Alexa Fluor® 555 conjugate

(Catalogue No. 16-260)

Raised against amino acids 203-219 derived from a region of the catalytic domain (between subdomain VII and VIII) of the Drosophila GSK3/shaggy enzyme, coupled to ovalbumin. Clone 4G-1E. Suitable for flow cytometry, immunocytochemistry, immunofluorescence, and Western blotting in a variety of species.

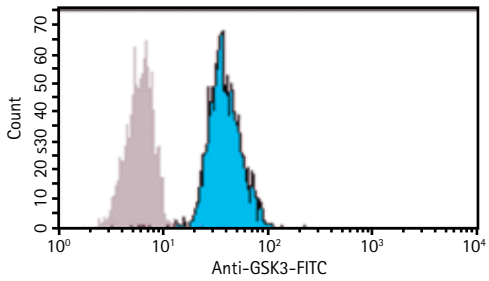


L6 cells were stained with 2 µg/mL of Anti-GSK3, clone 4G-1E, Alexa Fluor® 555 (left panel) or Normal Mouse IgG, Alexa Fluor® 555 conjugate (Cat. No.16-239; right panel) and analyzed by immunocytochemistry.

Milli-Mark® Anti-GSK3-FITC Antibody, clone 4G-1E

(Catalogue No. FCMAB386F)

Designed for use in flow cytometry. Raised against a peptide derived from a region of the catalytic domain of the Drosophila GSK3/shaggy enzyme, coupled to ovalbumin.



Flow cytometric analysis of Jurkat cells stained with Anti-GSK3, clone 4G-1E,-FITC conjugated. Cells were stained with the antibody (blue) or stained with an isotype control (gray).

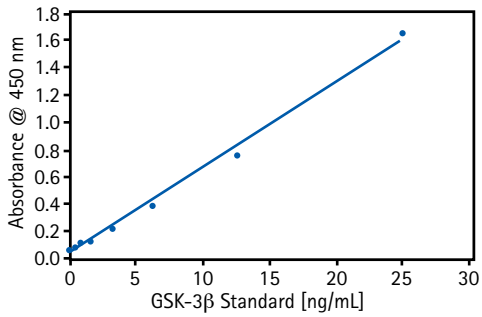
GSK-3β STAR ELISA Kit

(Catalogue No. 17-471)

STAR ELISAs are solid phase sandwich enzyme linked immunosorbent assays that provides a fast, sensitive method to detect specific levels of signaling targets in whole cell extracts. The GSK-3β plate is coated with a specific mouse monoclonal anti-GSK-3β capture antibody on the microwells of the 96-well clear plate. Suitable for use with Human, mouse and rat samples.

Sensitivity: 0.4 ng/mL.

Range of Detection: 0.4 to 25 ng/mL

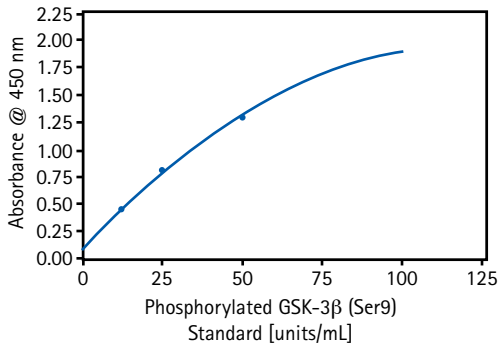


A standard curve for GSK-3β was established by assaying 100 µL of progressive 2 fold dilutions of the GSK-3β standard.

Phospho-GSK-3β (Ser9) STAR ELISA Kit

(Catalogue No. 17-472)

STAR ELISAs are solid phase sandwich enzyme linked immunosorbent assays that provides a fast, sensitive method to detect specific levels of signaling targets in whole cell extracts. The GSK-3β plate is coated with a specific mouse monoclonal GSK-3β capture antibody in the microwells of the 96-well clear plate. Can be used with human, mouse, and rat samples. **Sensitivity**: 1.6 Units/mL; **Range of Detection**: 1.6 to 100 Units/mL.



A standard curve for phospho-GSK-3β was established by assaying 50 µL of progressive 2-fold dilutions of the phosphorylated GSK-3β (Ser9) standard.

Tau Protein and Tauopathies

Tau, a highly asymmetric and heat-stable protein, is expressed mainly in the brain, where it regulates the stability and orientation of microtubules in neurons, astrocytes, and oligodendrocytes. Tau is highly enriched in the axon where it is involved in anterograde transport. The major function of Tau is to stabilize microtubules and to bundle microtubules in the axon. The Tau protein is reported to be the predominant component of the paired helical filaments (PHFs) and neurofibrillary tangles (NFTs) that are characteristic of pathological brain lesions in the Alzheimer's disease.

The dephosphorylated Tau promotes rapid and extensive microtubule polymerization, while increasing its phosphorylation state of reduces its ability to promote microtubule assembly. The Tau protein, especially in Alzheimer's brains, is found to be phosphorylated at many different sites. *In vitro* studies have shown that Tau is a substrate for a multitude of protein kinases, including CaM kinase II, casein kinase II, protein kinase A (PKA), MAP kinase (ERK2), cdk5/p35, and glycogen synthase kinase 3 (GSK3). It is believed that the phosphorylation of specific sites, rather than the overall extent of phosphorylation, is important in modulating the ability of Tau to bind microtubules and promote microtubule assembly. For example, phosphorylation of Tau by PKA decreases tubulin binding, while phosphorylation by CaM kinase II does not appear to alter this. Tau is extensively phosphorylated by ERK2 *in vitro*, and this phosphorylation reduces its affinity for paclitaxel-stabilized microbutules. Phosphorylation of Tau at Ser262 and Ser356, within the microtubule-binding regions, by p110mark (MARK) virtually abolishes the ability of Tau to bind microtubules. The role of protein phosphatases in Tau phosphorylation state has also gained significance in recent years. Phosphorylated Tau is shown to be dephosphorylated by protein phosphatase 1 (PP1), protein phosphatase 2A (PP2A) and protein phosphatase 2B (PP2B). Upon dephosphorylation the ability of Tau to bind microtubules and promote microtubule assembly is significantly increased.

A significant consequence of Tau hyperphosphorylation in Alzheimer's disease is a reduction in its ability to bind microtubules and promote microtubule assembly. In Alzheimer's disease brain, PHFs exist in an insoluble state as a component of the NFTs. *In vitro* studies have shown that the ability of insoluble PHFs to bind microtubules is significantly reduced and can be restored upon dephosphorylation of PHF-Tau. The hyperphosphorylated PHF-Tau is highly resistant to degradation by calpain.

It is believed that the hyperphosphorylation of Tau alone is not sufficient to induce PHF formation *in vivo*. A decrease in redox potential and the resulting oxidizing environment also plays an important role in the Tau-associated pathology in Alzheimer's disease. Self-association of Tau proteins is reported to be much higher in an oxidizing environment. Tau-Tau dimer formation is depended upon the intermolecular disulfide linkages. Increased Tau aggregation due to a more oxidizing environment also results in Tau glycation. Proteins susceptible to glycation are usually long-lived and often have high lysine content; Tau has 44 lysine residues. PHF-Tau from the temporal cortex of Alzheimer's disease patients is shown to be glycated, while normal control Tau, or soluble Tau from Alzheimer's disease brains, is not glycated. PHF-Tau, which is both glycated and hyperphosphorylated, exhibits a greater reduction in microtubule binding compared to soluble Tau from Alzheimer's brain, which is only hyperphosphorylated, but not glycated.

Tau Proteins Investigator Antibody Mini-Pack

(Qty: 3 vial/pk, Catalogue No. 15-208)

- AB9668SP Anti-Tau phospho Threonine 231; 30 µL
- MAB361SP Anti-Tau, a.a. 210-241, clone Tau-5; 30 µL
- MAB5430SP Anti-Tau, Caspase Cleaved (truncated at Asp421); 30 µL

Alzheimer's Disease I - Tauopathy Investigator Antibody Mini-Pack

(Qty: 3 vial/pk, Catalogue No. 15-202)

- AB9560SP Anti-WWOX; 30 µg
- AB9668SP Anti-Tau phospho Threonine 231; 30 µL
- MAB3420SP Anti-Tau-1, clone PC1C6; 30 µg

Antibodies for Tau Proteins

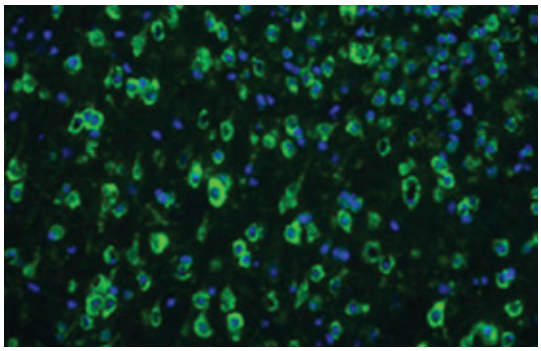
Description	Species Reactivity*	Applications**	Qty/Pk	Catalogue No.
Anti-Tau-1 Antibody, clone PC1C6	Bov, Hu, Rt	IHC, WB	100 µg	MAB3420
Anti-Tau Antibody, clone Tau-2	Bov, Hu, Feline	IHC	100 mL	MAB375
Anti-Tau Antibody, clone Tau 7	Hu, Ms	WB	100 µg	MAB2239
Anti-Tau Antibody, clone Tau 12	Hu	WB	100 µg	MAB2241
Anti-Tau Antibody, clone 5E2	Bov, Hu, Ms, Rt, Rb	IHC, WB	200 µg	AB9686
Anti-Tau-1 Antibody, prediluted, clone PC1C6	Bov, Hu, Rt	IH(P)	6 mL	IHCR1015-6
Anti-Tau Antibody, clone 46.1	Hu, Ms	IHC, WB	200 µL	05-838
Anti-Tau Antibody, a.a. 210-241, clone Tau-5	Bov, Hu, Ms, Rt	IHC, WB	100 µL	MAB361
Anti-Tau, a.a. 210-241 Antibody, clone Tau-5	Bov, Rt	WB	100 µg	MABN162
Anti-Tau Mouse (TAU-5) Antibody	Hu, Ms, Rt, Sheep	IHC, IH(P), IP, WB	100 µg	577801
Anti-Tau Antibody, PAD, clone TNT-1	Hu, Ms, Rt	DB, ELISA,IF, IHC, WB	100 µg	MABN471
Anti-cleaved-Tau (Asp421) Antibody, clone C3	Hu, Ms, Rt	IHC, IP, WB	100 µL	36-017
Anti-Tau Antibody, Caspase Cleaved (truncated at Asp421)	Hu	ELISA, IHC, WB	100 µg	MAB5430
Anti-Tau (3-repeat isoform RD3) Antibody, clone 8E6/C11	Hu	IHC, WB	200 µL	05-803
Anti-Tau (4-repeat isoform RD4) Antibody, clone 1E1/A6	Bov, Hu, Ms, Rt	IHC, WB	200 µL	05-804
Anti-Tau Antibody, nitrated, clone n847	Hu	ICC, IHC, IH(P), WB	100 µg	MAB5711
Anti-Nitrated Tau (Tyr18) Antibody, clone Tau-nY18	Hu	WB	100 µg	MAB2242
Anti-Nitrated Tau (Tyr29) Antibody, clone Tau-nY29	Hu	IHC, WB	100 µg	MAB2244
Anti-Tau phospho Serine 199 Antibody	Hu	WB	100 µL	AB9652
Anti-Tau phospho Serine 199/202 Antibody	Hu	WB	100 µL	AB9674
Anti-Tau phospho Threonine 205 Antibody	Hu	WB	100 µL	AB9676
PhosphoDetect™ Anti-Tau (pThr212) Rabbit Antibody	Hu	WB	10 Tests	577810
Anti-Tau phospho Threonine 212 Antibody	Hu	WB	100 µL	AB9688
Anti-Tau phospho Serine 214 Antibody	Hu	WB	100 µL	AB9672
Anti-Tau phospho Threonine 231 Antibody	Hu	WB	100 µL	AB9668
Anti-Tau Antibody, phosphoThreonine 231, clone PHF-6	Hu	ELISA, WB	100 µL	MAB5450
Anti-Tau phospho Serine 262 Antibody	Hu	WB	100 µL	AB9656
PhosphoDetect™ Anti-Tau (pSer262) Rabbit Antibody	Hu, Ms, Rt	WB	10 Tests	577814
Anti-Tau phospho Serine 396 Antibody	Hu	WB	100 µL	AB9658
Anti-phospho-Tau (Ser396) Antibody, clone PHF13	Hu, Rt	WB	100 µL	05-885
PhosphoDetect™ Anti-Tau (pSer396) Rabbit Antibody	Hu	WB	10 Tests	577815
Anti-Tau phospho Serine 404 Antibody	Hu	WB	100 µL	AB9660
Anti-Tau phospho Serine 409 Antibody	Hu	WB	100 µL	AB9662
Anti-Tau phospho Serine 422 Antibody	Hu	WB	100 µL	AB9664
PhosphoDetect™ Anti-Tau (pSer422) Rabbit Antibody	Hu	WB	10 Tests	577817

Species: Hu=Human, Ms=Mouse, Rt=Rat, Bov=Bovine, Can=Canine, Prim=Primate, Por= Porcine
Applications: FC=Flow Cytometry, ICC=Immunocytochemistry, IHC=Immunohistochemistry, IH(P)=Immunohistochemistry (Paraffin), IF=Immunofluorescence, IP=Immunoprecipitation, WB=Western Blotting, ELISA=Enzyme Immunoassay, DB=Dot Blot

Anti-Tau-1 Antibody, clone PC1C6, Alexa Fluor® 488 Conjugate

(Catalogue No. MAB3420A4)

This antibody binds to all known electrophoretic species of Tau in human, rat, and bovine brain. Suitable for immunocytochemistry and immunohistochemistry.

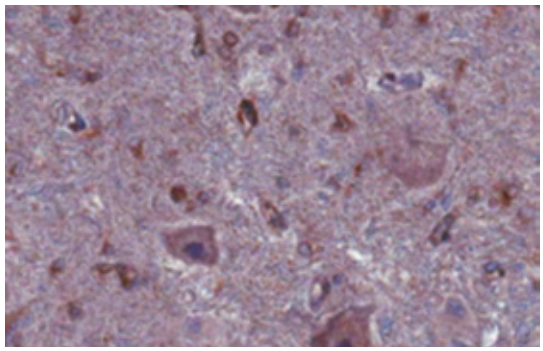


Fluorescent IHC staining of adult mouse brain (8 µm coronal cryosections) with Anti-Tau-1-Alexa Fluor® 488 Conjugate (green) at a 1:100 dilution. Immunoreactivity is seen as cytoplasmic and axonal staining of neurons in the cerebral cortex. Hoechst 33342 (blue) staining of nuclei is also shown.

Anti-Tau-Tubulin Kinase 2 (TTBK2) Antibody

(Catalogue No. ABN103)

Recognizes all three isoforms of Tau-tubulin kinase 2. Reacts witih human, mouse, and rat samples. Suitable for use in dot blot, immunohistochemistry, and Western blotting.

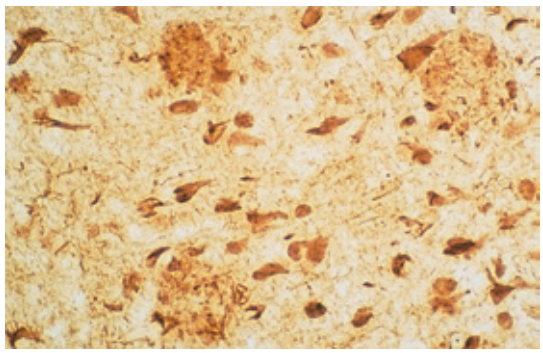


Formalin Fixed Paraffin Embedded (FFPE) human substantia nigra tissue was probed using heat-induced epitope retrieval (HIER). Immunostaining was performed using a 1:500 dilution of Cat. No. ABN103, Anti-Tau-tubulin kinase 2 (TTBK2). Reactivity was detected using an Anti-Rabbit secondary antibody and HRP-DAB. Positive staining was observed in human neurons.

Anti-Neurofibrillary Tangles Antibody

(Catalogue No. AB1518)

Specifically stains neurofibrillary tangles and degenerating plaque neurites in cases of Alzheimer's disease, Down's Syndrome and normal aged individuals. Suitable for ELISA, immunohistochemistry, and Western blotting. Reacts with human samples.



Rabbit Anti-Neurofibrillary Tangles (AB1518) staining of tangles and senile plaques in Alzheimer's brain

MILLIPLEX® MAP Multiplex Bead-Based Assay Kits for Neurodegenerative Disease Research

Abnormalities in signaling networks contribute to neurodegenerative and neurological disorders. Specific markers for these abnormalities can be quantified simultaneously in each of your precious samples. Measure multiple biomarkers in a single, small sample with MILLIPLEX® MAP panels and gain precise quantitation.

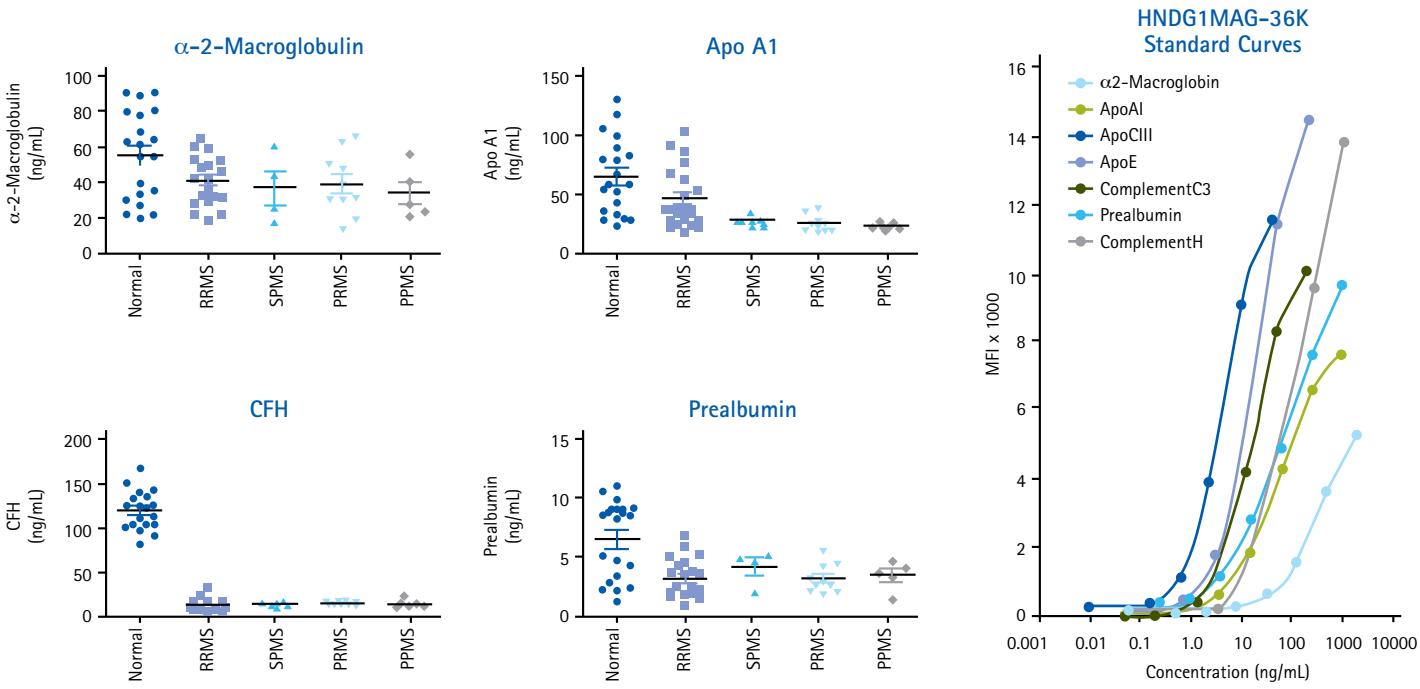
MILLIPLEX® MAP Human Neurodegenerative Disease Magnetic Bead Panel 1

(Catalogue No. HNDG1MAG-36K)

Based on Luminex xMAP®-technology, this kit is suitable for the simultaneous quantification of the following 7 analytes in any combination:

- α-2-Macroglobulin
- Apo AI
- Apo CIII
- Apo E
- Complement C3
- Complement Factor H (CFH)
- Prealbumin

This kit may be used for the analysis of all above analytes in human serum, plasma, and cerebrospinal fluid samples. No cross-reactivity between the antibodies and any of the other analytes is observed. This assay requires 25 µL of 1:40,000 diluted serum/plasma or 1:400 diluted CSF per well.



Using the MILLIPLEX ® MAP Human Neurodegenerative Disease Magnetic Bead Panel 1 (HNDG1MAG-36K), 4 out of 7 plasma biomarkers were found to be significantly up- or down-regulated in MS plasma samples compared to the normal controls using the Student t-test ($p<0.05$).

Key to MS Subtypes: RRMS=relapsing remitting MS; SPMS=secondary progressive MS; PPMS=primary progressive MS; PRMS=progressive relapsing MS

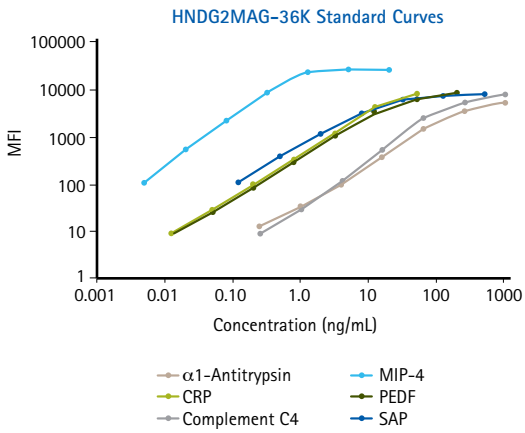
MILLIPLEX® MAP Human Neurodegenerative Disease Magnetic Bead Panel 2

(Catalogue No. HNDG2MAG-36K)

Based on Luminex xMAP® technology, this kit is suitable for simultaneous quantification of the following 6 analytes in any combination:

- α-1-Antitrypsin
- Complement C4
- CRP
- MIP-4
- PEDF
- SAP

This kit may be used for the analysis of all above analytes in human serum, plasma, and cerebrospinal fluid samples. This assay requires 25 µL of 1:2,000 diluted serum/plasma or 1:20 diluted CSF per well.



Standard curves show assay dynamic range and sensitivity of detection for all analytes.

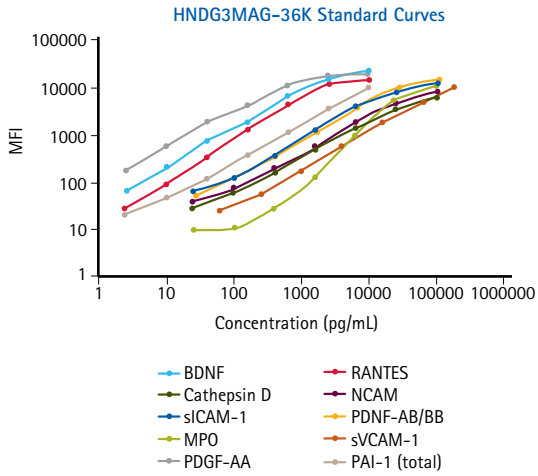
MILLIPLEX® MAP Human Neurodegenerative Disease Magnetic Bead Panel 3

(Catalogue No. HNDG3MAG-36K)

Based on Luminex xMAP® technology, this kit is suitable for the simultaneous quantification of the following 10 analytes in any combination:

- BDNF
- Cathepsin D
- MPO
- PAI-1 (total)
- PDGF-AA
- PDGF-AB/BB
- RANTES
- sICAM-1
- sNCAM
- sVCAM-1

This kit may be used for the analysis of all above analytes in human serum, plasma, and cerebrospinal fluid samples. This assay requires 25 µL of 1:100 diluted serum/plasma or neat CSF per well.



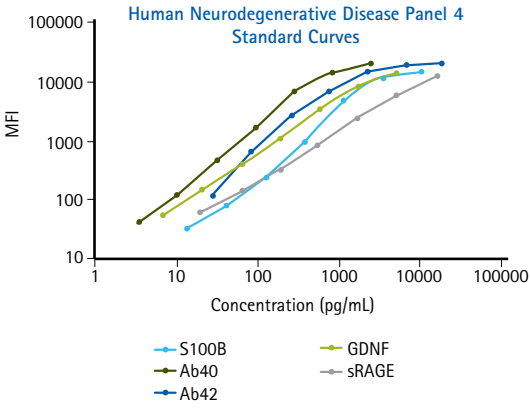
Standard curves show assay dynamic range and sensitivity of detection for all analytes.

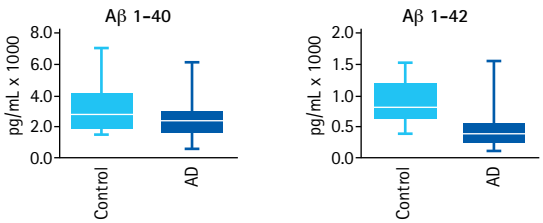
MILLIPLEX® MAP Human Neurodegenerative Disease Magnetic Bead Panel 4

(Catalogue No. HNDG4MAG-36K)

Based on Luminex xMAP® technology, this kit is suitable for the simultaneous quantification of the following 5 analytes in any combination in human cerebrospinal fluid (CSF). This kit is not validated for testing serum or cell culture supernatants. This assay requires 25 µL of 1:3 diluted CSF per well.

- Amyloid β40 (Aβ1-40)
- Amyloid β42 (Aβ1-42)
- GDNF
- S100B
- sRAGE





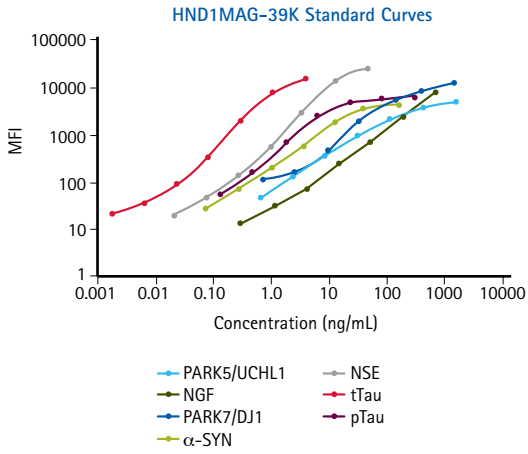
Levels of Aβ 1-40 and 1-42 in CSF obtained from AD patients and age-matched controls using MILLIPLEX® MAP Neurodegenerative Disease Panel 4. Aβ (1-40 and 1-42) values were determined using 16 AD and 16 age-matched control CSF samples.

MILLIPLEX® MAP Human Neurological Disorders Magnetic Bead Panel 1

(Catalogue No. HND1MAG-39K)

Based on Luminex xMAP® technology, this kit is suitable for the simultaneous quantification of the following 7 analytes in any combination in human cerebrospinal fluid (CSF). Cross-reactivity between the antibodies and any of the other analytes in this panel is non-detectable or negligible. This assay requires 25 µL of neat CSF per well.

- α-Synuclein
- NGFβ
- Neuron-Specific Enolase (NSE)
- PARK5/UCHL1 (Parkinson Disease Protein 5)
- PARK7/DJ1 (Parkinson Disease Protein 7)
- Tau (Thr231) (Phosphorylated Neurofibrillary Tangle Protein)
- Tau (total)



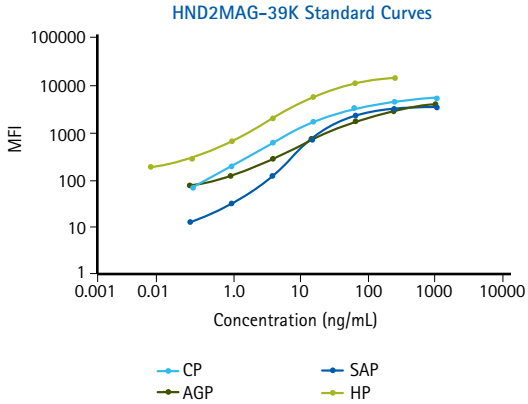
Standard curves show assay dynamic range and sensitivity of detection for all analytes.

MILLIPLEX® MAP Human Neurological Disorders Magnetic Bead Panel 2

(Catalogue No. HND2MAG-39K)

Based on Luminex xMAP® technology, this kit is suitable for the simultaneous quantification of the following 4 analytes in any combination in human serum, plasma and cerebrospinal fluid (CSF). This assay requires 25 µL of 1:25,000 diluted serum/plasma or 1:50 diluted CSF per well.

- AGP (α-1-Acid Glycoprotein)
- CP (Ceruloplasmin)
- HP (Haptoglobin)
- SAP (Serum Amyloid P component)



Standard curves show assay dynamic range and sensitivity of detection for all analytes.

Fibrillogenesis Inhibitors

Description	Catalogue No.	Comments	Size
Aβ42 Fibrillogenesis Inhibitor III (Ac-Leu-Pro-Phe-Phe-Asp-NH_2)	171588	Crosses the blood/brain barrier and acts as a β-sheet breaker. Increases neuronal survival with a concomitant reduction in brain inflammation by reducing Aβ deposition (in a transgenic mouse model of Alzheimer's disease). Displays greater stability against proteolytic degradation ($t_{1/2}$ > 24 h in human plasma and cerebrospinal fluid; ~37 min in blood).	5 mg
β-Amyloid Oligomer Inhibitor, K01-162	200487	A cell permeable, fluorene compound that destabilizes the aggregation state of β-amyloid oligomers (AβO) by directly targeting AβO and inhibiting AβO binding to synapses. Displays full MC65 protection (at ~125 nM) and reduces intraneuronal AβO in primary neuronal culture.	10 mg
Clioquinol (5-Chloro-7-iodo-8-hydroxyquinoline)	233165	A metal ion chelator that crosses the blood-brain barrier and dissolves senile plaques. Reduces amyloid's ability to clump together, apparently by trapping the Cu^{2+} and Zn^{2+} that reduces the build-up of these deposits.	1 g
Diclofenac Sodium (2-[(2,6-Dichlorophenyl)amino] benzeneacetic Acid, Na)	287840	A potent non-steroidal anti-inflammatory drug that inhibits both COX-1 (IC_{50} = 76 nM) and COX-2 (IC_{50} = 26 nM) activities. Strongly inhibits insoluble transthyretin (TTR) amyloid fibril formation.	1 g
Flurbiprofen ((±)-2-Fluoro-α-methyl[1,1′-biphenyl]-4-acetic Acid, U-27182)	344079	A cell-permeable mixture of S(+) and R(-) enantiomers. that acts as a potent COX inhibitor (IC_{50} = 5 nM for LPS-induced COX in human peripheral blood cells). Reduces Aβ loads and Congo Red staining in APP+PS1 transgenic mice	100 mg

Amyloid-Related Proteins and Peptides

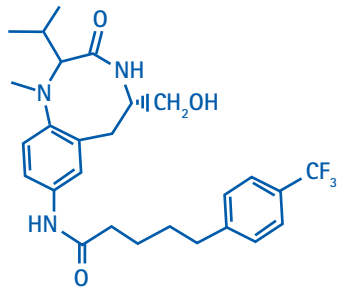
Description	Qty/Pk	Catalogue No.
β Amyloid 1-40, aβ, ultra pure, NaOH, Recombinant Human Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val	1 mg	AG964
β Amyloid 1-40, aβ, ultra pure, TFA, Recombinant Human Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val	1 mg	AG910
β Amyloid 1-40, aβ, F4W, TFA, Recombinant Human Asp-Ala-Glu-Trp-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val	1 mg	AG918
β Amyloid 1-40, aβ, Y10W, TFA, Recombinant Human Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Trp-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val	1 mg	AG920
β Amyloid 1-40, aβ, D23N, TFA, Recombinant Human Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asn-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val	1 mg	AG922
β Amyloid 1-40, aβ, ultra pure, HFIP, Recombinant Human Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val	1 mg	AG962
β Amyloid 11-40, human Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val	500 µg	AG544
β Amyloid 11-40, Rat and Mouse Glu-Val-Arg-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val	500 µg	AG546
β-Amyloid Peptide (1-42), Human H-Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala-OH	250 µg	PP69
β-Amyloid Peptide (1-42), Rat H-Asp-Ala-Glu-Phe-Gly-His-Asp-Ser-Gly-Phe-Glu-Val-Arg-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala-OH	250 µg	171596
β Amyloid 1-42, Rat and Mouse Asp-Ala-Glu-Phe-Gly-His-Asp-Ser-Gly-Phe-Glu-Val-Arg-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val- Ile-Ala	500 µg	AG542
β Amyloid (1-42), mutant, Y10A, TFA Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Ala-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala	500 µg 1 mg	AG928
β Amyloid 1-42, aβ, ultra pure, HFIP, Recombinant Human H-Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala-OH	1 µg	AG968
β Amyloid 1-42, aβ, ultra pure, NaOH, Recombinant Human Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala	500 µg 1 mg	AG970
β Amyloid 1-42, aβ, ultra pure, TFA, Recombinant Human H-Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe- Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala-OH	1 mg	AG912
β Amyloid 1-42, aβ, scrambled, TFA, Recombinant *E. coli* Lys-Val-Lys-Gly-Leu-Ile-Asp-Gly-Asp-His-Ile-Gly-Asp-Leu-Val-Tyr-Glu-Phe-Met-Ala-Ser-Asn-Ser-Ala-Ile-Phe-Arg-Glu-Gly-Val-Gly-Ala-Gly-His-Val-His-Val-Ala-Gln-Val-Glu-Phe	500 µg	AG916
β Amyloid 1-42, aβ, ultra pure, HCl, Recombinant Human H-Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala-OH	500 µg 1 mg	AG972
β Amyloid 1-43, aβ, ultra pure, TFA, recombinant human H-Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala-Thr-OH	500 µg 1 mg	AG974

α-Amyloid Precursor Protein Modulator

(Catalogue No. 565740-1MG)

(2S,5S)-(E,E)-8-(5-(4-(Trifluoromethyl)phenyl)-2,4-pentadienoyl amino)benzolactam).

A cell-permeable PKC activator (K_i = 11.9 nM for PKCα) that efficiently enhances non-amyloidogenic α-processing of amyloid precursor protein (APP) but lacks any tumor promoting activity.



Antibodies to Amyloid Related Proteins and Peptides

Description	Species Reactivity*	Applications**	Qty/Pk	Catalogue No.
Anti-β-Amyloid Antibody, C-Terminal Mouse (6G12)	Hu	ELISA, ICC, WB	100 µg	171607
Anti-Amyloid βA4 protein Antibody	Most Mammalian Species	IHC, WB	100 µg	AB2500
Anti-Amyloid βA4 protein Antibody, clone MM26-2.1.3	Hu, Ms, Rt	ELISA, ICC, IHC, WB	100 µg	MAB8768
Anti-Amyloid βA4 protein Antibody	Most Mammalian Species	IHC, WB	100 µg	AB2500
Anti-Amyloid β Antibody, clone W0-2	Hu, Ms	ELISA, IHC, WB	50 µg	MABN10
Anti-Amyloid β peptide (MOAB-2), pan Antibody, clone 6C3	Hu	DB, IF, IH(P), IP, WB	100 µg	MABN254
Anti-Amyloid Antibody, β, aa1-14 h β-amyloid	Hu	IHC, WB	100 µL	AB1510
Anti-Amyloid Antibody, β 1-16, clone DE2	Bov, Hu, Mky	ELISA, IH(P), WB	2 mL	MAB5206
Anti-Amyloid Antibody, β 1-16, clone AB10	Bov, Hu, Mky	ELISA, ICC, IHC, IP, WB	100 µg	MAB5208
Anti-Amyloid Antibody, β 1-40	Hu, Ms	ELISA, IHC, WB	50 µg	AB5074P
Anti-Amyloid, β 1-40, aβ Antibody	Hu	ELISA, IH(P), WB	100 µL	ABN240
Anti-Amyloid β40 Antibody, clone G2-10	Hu, Ms	ELISA, IHC, WB	50 µg	MABN11
Anti-Amyloid Antibody, β 1-40, clone OM16	Hu	ELISA, WB	100 µg	MAB5226
Anti-β-Amyloid40 (FCA3340) Rabbit Antibody	Can, Hu, Lemur, Ms	ELISA, IF, IH(P), IP, WB	50 µL	171608
Anti-Amyloid Antibody, β 1-40, aβ	Hu	ELISA	100 µg	AB5737
Anti-Amyloid β (Aβ)x-40 Antibody, clone 11A5-B10	Hu, Ms	IHC, WB	100 µL	05-799
Anti-Amyloid, β 20-40, aβ	Hu	IH(P)	100 µL	AB5304
Anti-Amyloid, β 20-40, aβ	Hu	IH(P)	100 µL	AB5304
Anti-Amyloid Antibody, β 37-42, aβ	Hu	ELISA, IH(P)	100 µL	AB5306
Anti-Amyloid Antibody, β 1-40/42	Hu, Ms	ELISA, IHC, WB	50 µg	AB5076
Anti-β-Amyloid 1-42 Antibody	Chk, Hu, Ms	ELISA, IHC, IH(P), WB	50 µg	AB5078P
Anti-Amyloid β (Ab) x-42 Antibody, clone 12F4	Hu	ELISA, IHC	100 µL	05-831-I
Anti-β-Amyloid (1-42) Rabbit Antibody	Hu	DB, ELISA, RIA	25 µg	PC150
Anti-Amyloid β42 Antibody, clone G2-11	Hu, Ms	ELISA, IHC, WB	50 µg	MABN12
Anti-Amyloid β42 Antibody, clone G2-13	Hu, Ms	ELISA, IHC, WB	50 µg	MABN13
Anti-β-Amyloid42 (FCA3542) Rabbit Antibody	Can, Hu, Lemur, Ms	ELISA, IF, IH(P), IP, WB	50 µL	171609
Anti-Amyloid β peptide (MOAB-2), pan Antibody, clone 6C3	Hu	DB, IF, IH(P), IP, WB	100 µg	MABN254

Species: Hu=Human, Ms=Mouse, Rt=Rat, Bov=Bovine, Can=Canine
Applications: ICC=Immunocytochemistry, IHC=Immunohistochemistry, IH(P)=Immunohistochemistry (Paraffin), IF=Immunofluorescence, IP=Immunoprecipitation, WB=Western Blotting, ELISA=Enzyme Immunoassay, DB=Dot Blot, PIA=Peptide Inhibition Assay

Antibodies to Amyloid Precursor Proteins

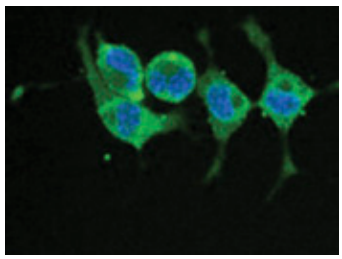
Description	Species Reactivity*	Applications**	Qty/Pk	Catalogue No.
Anti-APP Antibody	Hu, Ms, Rt	IP, WB	100 µL	07-667
Anti-APP A4 Antibody, a.a. 66-81 of APP {N-terminus}, clone 22C11	Most Mammalian Species	IF, IHC, IH(P),WB	50 µg	MAB348
Anti-Alzheimer Precursor Protein A4 Antibody, clone 22C11, Biotin Conj	Most Mammalian Species	ICC, IHC	100 µL	MAB348B
Anti-APP-C99 Antibody, clone mC99(1-7)	Hu, Ms	ICC, IHC, IP, WB	100 µL	MABN381
Anti-APP-C99 Antibody, clone mC99 (70-80)	Hu, Ms	ICC, IHC, IP, WB	100 µL	MABN380
Anti-Alzheimer Precursor Protein A4 Antibody, clone 22C11, Alexa® 488 Conj.	Most Mammalian Species	ICC, IHC		
Anti-APP A4 Antibody, a.a. 66-81 (N-terminus), Prediluted, clone 22C11	Most Mammalian Species	IH(P)	6 mL	IHCR1002-6
Anti-Amyloid Precursor Protein Antibody, a.a. 44-63	Hu	ELISA, IF, IHC, IH(P), WB	100 µL	AB1593
Anti-Amyloid Precursor Protein Antibody, Secretory, clone OM84	Hu	ELISA, WB	100 µg	MAB5228
Anti-Amyloid Precursor Protein Antibody, C-terminus	Hu, Mky	ICC, IHC, IP, WB	100 µL	AB5352
Anti-Amyloid β Precursor Protein Antibody, KPI domain, clone 4.1	Hu	ELISA, IHC, WB	100 µg	MAB5354
Anti-Amyloid Precursor Protein Antibody, A4(695), clone 1.D5	Hu, Rt	WB	100 µg	MAB349
Anti-Amyloid Precursor Protein Antibody, Domain 770	Hu, Mky	ICC, IHC, IP, WB	100 µg	AB5588P
Anti-Amyloid Precursor Protein Antibody, universal	Hu, Ms, Mky	IP, WB	100 µL	AB5300
Anti-Amyloid Precursor Protein, Caspase Cleaved	Hu, Rt	IHC, WB	100 µg	AB5942
Anti-Amyloid Precursor Protein Antibody, C-Terminal (751-770) Rabbit	Hu	IF, IHC, IP, WB	50 µL	171610

Species: Hu=Human, Ms=Mouse, Rt=Rat, Mky=Monkey
Applications: ICC=Immunocytochemistry, IHC=Immunohistochemistry, IH(P)=Immunohistochemistry (Paraffin), IF=Immunofluorescence, IP=Immunoprecipitation, WB=Western Blotting, ELISA=Enzyme Immunoassay

Anti-Alzheimer Precursor Protein A4 Antibody, clone 22C11

(Catalogue No. MAB348A4)

Reacts with pre-A4. The unconjugated antibody (MAB348) recognizes all three isoforms of APP, immature ~110kDa, sAPP ~120kDa, and mature ~130kDa. Suitable for immunocytochemistry and immunohistochemistry. Reacts with most mammalian species.

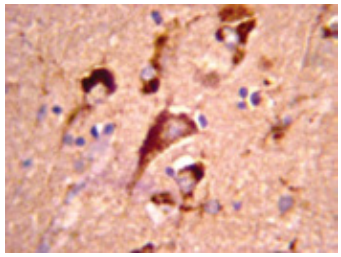


Confocal fluorescent analysis of mouse N1E-115 neuroblastoma cells using Anti-Alzheimer Precursor Protein A4, clone 22C11, Alexa® 488 Conj. (green). Positive staining of N1E-115 cells was observed. Cell nuclei were counterstained with DAPI (blue).

Amyloid β Precursor Proteins Explorer Antibody MiniPack

(Catalogue No. 15-205)

- MAB348SP Anti-Alzheimer Precursor Protein A4, clone 22C11: 15 µg
- MAB343SP Anti-Alzheimer Precursor Protein, APP 643-695 C-terminal fragment, Clone 2.F2.19B4; 30 µL
- AB5352SP Anti-Amyloid Precursor Protein, C-terminus; 30 µL



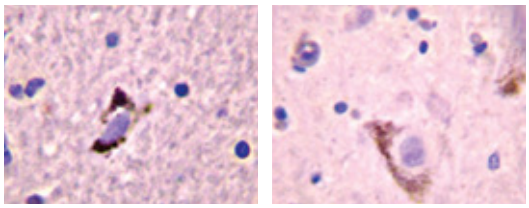
APP was detected in AD human brain by immunohistochemistry using anti-APP (C-terminus, 1:100).

Alzheimer's Disease II – Amyloidosis Investigator Antibody Mini-Pack

(Catalogue No. 15-203)

Contains one vial each of:

- MAB348SP - Anti-Amyloid Precursor Protein, clone A4; 15 µg
- AB9732SP - Anti-14-3-3-ε C-terminus; 30 µL
- AB9890SP - Anti-AGE (Advanced Glycation Endproducts); 60 µL



Human AD brain tissue section was stained with anti-AGE (1:100) and analyzed using immunohistochemistry.

Human Amyloid β42 Brain ELISA

(Catalogue No. EZBRAIN42)

The Amyloid β42 ELISA uses monoclonal anti-Aβ antibodies with high selectivity for human Aβ. The capture antibody recognizes the C-terminal end of Amyloid β1-42, which causes a high selectivity for Aβ42. The cross-reactivity of the antibodies used in this kit to other Amyloid peptides was tested by ELISA and surface plasmon resonance, and showed no significant cross-reactivity to Aβ1-38, Aβ1-39, Aβ1-42, Aβ1-43 and Aβ1-44.

Human Amyloid β40 Brain ELISA

(Catalogue. No EZBRAIN40)

The Amyloid β40 ELISA uses monoclonal anti-Aβ antibodies with high selectivity for human Aβ. The capture antibody recognizes the C-terminal end of Amyloid β1-40, which causes a high selectivity for Aβ 40. The cross-reactivity of the antibodies used in this kit to other Amyloid peptides was tested by ELISA and surface plasmon resonance, and showed no significant cross-reactivity to Aβ1-38, Aβ1-39, Aβ1-42, Aβ1-43 and Aβ1-44.

High Sensitivity Human Amyloid β42 ELISA

(Catalogue No. EZHS42)

The Amyloid β42 ELISA (HS) uses monoclonal anti-Aβ antibodies with high selectivity for human Aβ. The capture antibody recognizes the C-terminal end of Amyloid β1-42, which causes a high selectivity for Aβ42. The cross-reactivity of the antibodies used in this kit to other Amyloid peptides was tested by ELISA and surface plasmon resonance, and showed no significant cross-reactivity to Aβ1-38, Aβ1-39, Aβ1-40, Aβ1-43 and Aβ1-44.
Sensitivity: 8 pg/mL

High Sensitivity Human Amyloid β40 ELISA

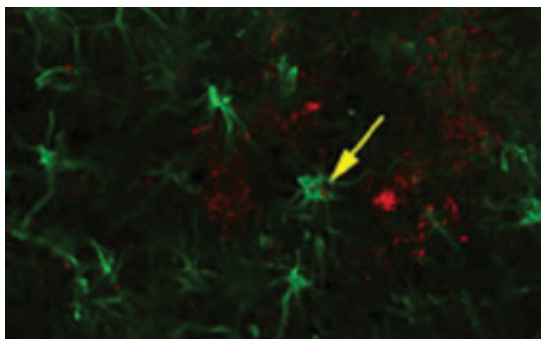
(Catalogue No. EZHS40)

The Amyloid β40 ELISA (HS) uses monoclonal anti-Aβ antibodies with high selectivity for human Aβ. The capture antibody recognizes the C-terminal end of Amyloid β1-40, which causes a high selectivity for Aβ 40. The cross-reactivity of the antibodies used in this kit to other Amyloid peptides was tested by ELISA and surface plasmon resonance, and showed no significant cross-reactivity to Aβ1-38, Aβ1-39, Aβ1-42, Aβ1-43 and Aβ1-44.
Sensitivity: 6 pg/mL.

Anti-Amyloid Oligomer Antibody, αβ, oligomeric

(Catalogue No. AB9324)

Recognize a peptide backbone epitope that is common to all amyloid oligomers, but is not found in native proteins, amyloidogenic monomer or mature amyloid fibrils. Suitable for ELISA, immunofluorescence, immunohistochemistry, immunoprecipitation, and Western blotting. Reacts with human, mouse, and rat samples.



Immunofluorescence: Rabbit anti-Amyloid β, micellar (oligomeric) (AB9234). Immunolocalization of oligomeric β amyloid (red) in human Alzheimer's Disease Brain Tissue.

MicroRNAs in Alzheimer's Disease

MicroRNAs (miRNAs) are small noncoding RNAs that play a vital role in regulating translational repression of their target mRNAs. About 70% of all miRNAs identified thus far are known to be expressed in the brain where they control and regulate the expression of a variety of molecules in a spatial and temporal manner. These miRNAs regulate neuronal and glial development, neuronal differentiation and proliferation, and neuronal death by apoptosis. Since a single miRNA can concurrently affect hundreds of target mRNAs, even a small change in its expression could deleteriously affect a wide range of signaling pathways leading to abnormalities associated with Alzheimer's disease. Microarray-based miRNA expression profiling studies have shown that abnormal repression and expression of several miRNAs can accelerate amyloid β peptide production via over-expression of β-secretase (BACE1). miRNAs are believed to have a neuroprotective function and any diminution in their level may result in neurodegeneration. Treatment of mouse primary neurons with Aβ42 is shown to downregulate several miRNAs and activate miRNA-specific nucleases, such as XRN-2.

References:
Alexandrov , P.N., et al. 2012. Int. J. Biochem. Mol. Biol. 3, 365-373.
Satoh, J. 2012. Exp. Neurol. 235, 436-446.
Schonrock, N., et al. 2010. PLoS One 5, e11070.
Maes, O.C., et al. 2009. Curr. Genomics 10, 154-168

Monitoring RNA within intact cells is challenging and involves multistep isolation of RNA. Merck Millipore's SmartFlare™ RNA detection probes can be used to detect and quantify RNA in live cells without using any transfection reagents. This technology is based upon an oligonucleotide gold nanoparticle conjugate that can detect mRNA and miRNA levels in intact living cells. The probe enter the cell via endocytosis and binds to the complementary target RNA sequence and releases a fluorescent signal (flare) that can be detected on one of the commonly used fluorescence platforms. This technology offers superior advantages, because SmartFlare™ does not harm or alter the cells biology and those same cells can be used for immunodetection of proteins or other studies following SmartFlare™ detection.

Description	Catalogue No.	Comments	No. of Reactions
miR-9-3p Hu-Cy5 SmartFlare™ Probe	SF-715	Down-regulated by amyloid peptides. Activated by NF-κB.	250
miR-9-5p Hu-Cy3 SmartFlare™ RNA Probe	SF-1091	Down-regulated by amyloid peptides. Activated by NF-κB.	250
miR-9-5p Hu-Cy5 SmartFlare™ RNA Probe	SF-497	Down-regulated by amyloid peptides. Activated by NF-κB.	250
miR-15a-5p Hu-Cy3 SmartFlare™ Probe	SF-159	Down regulated in Alzheimer's disease brain cortex. Targets ERK1 and APP.	250
miR-15a-5p Hu-Cy5 SmartFlare™ Probe	SF-430	Down regulated in Alzheimer's disease brain cortex. Targets ERK1 and APP.	250
miR-21-5p Hu-Cy3 SmartFlare™ Probe	SF-471	Downregulated by Aβ peptides in Alzheimer's disease.	250
miR-29a-3p Hu-Cy3 SmartFlare™ Probe	SF-177	Downregulated in Alzheimer's disease brain. Correlates with increased BACE1 expression.	250
miR-29a-3p Hu-Cy5 SmartFlare™ Probe	SF-424	Downregulated in Alzheimer's disease brain. Correlates with increased BACE1expression.	250
miR-29b-3p Hu-Cy3 SmartFlare™ Probe	SF-425	Downregulated in Alzheimer's disease brain. Correlates with increased BACE1 expression.	250
miR-30a-5p Hu-Cy5 SmartFlare™ Probe	SF-1131	Higher levels are found in the cerebrospinal fluid from Alzheimer's disease subjects.	250
miR-30c-5p Hu-Cy3 SmartFlare™ Probe	SF-441	Higher levels of Aβ peptides down-regulate miRNA 30c.	250
miR-30c-5p Hu-Cy5 SmartFlare™ Probe	SF-457	Higher levels of Aβ peptides down-regulate miRNA 30c.	250
miR-101-3p Hu-Cy5 SmartFlare™ Probe	SF-403	Downregulated in Alzheimer's disease brain. Targets amyloid precursor protein.	250
miR-106b-5p Hu-Cy5 SmartFlare™ Probe	SF-436	Downregulated in Alzheimer's disease brain. Targets amyloid precursor protein.	250
miR-106b-5p Hu-Cy3 SmartFlare™ Probe	SF-1285	Downregulated in Alzheimer's disease brain. Targets amyloid precursor protein.	250
miR-124-3p Ms-Cy3 SmartFlare™ Probe	SF-1095	Downregulated in Alzheimer's disease brain. Targets PTBP1.	250
miR-125b-5p Hu-Cy3 SmartFlare™ Probe	SF-1096	Upregulated in Alzheimer's disease brain. Activated by NF-κB.	250
miR-125b-5p Hu-Cy5 SmartFlare™ Probe	SF-467	Upregulated in Alzheimer's disease brain. Activated by NF-κB.	250
miR-130a-3p Hu-Cy3 SmartFlare™ Probe	SF-810	Upregulated in hippocampus region in Alzheimer's disease.	250
miR-130a-3p Hu-Cy5 SmartFlare™ Probe	SF-809	Upregulated in hippocampus region in Alzheimer's disease.	250
miR-132-3p Hu-Cy3 SmartFlare™ Probe	SF-428	Downregulated in Alzheimer's disease. Targets ARHGAP32 Rho GTPase activating protein 32.	250
miR-132-3p Hu-Cy5 SmartFlare™ Probe	SF-452	Downregulated in Alzheimer's disease. Targets ARHGAP32 Rho GTPase activating protein 32.	250
miR-146a-5p Hu-Cy5 SmartFlare™ Probe	SF-500	Upregulated in Alzheimer's disease brain. An NF-κB-sensitive miRNA.Targets IRAK1.	250
miR 146b-5p Cys SmartFlare™ Probe	SF-479	Upregulated in Alzheimer's disease brain. An NF-κB-sensitive miRNA.Targets IRAK1.	250
miR-197-3p Hu-Cy5 SmartFlare™ Probe	SF-1126	Upregulated in brain cortex in Alzheimer's disease.	250
miR-320-3p Ms-Cy5 SmartFlare™ Probe	SF-1101	Upregulated in brain cortex in Alzheimer's disease.	250
miR-328 Hu-Cy3 SmartFlare™ Probe	SF-850	Downregulated in Alzheimer's disease. Believed to target BACE1/β-secretase.	250
miR-338-3p Hu-Cy5 SmartFlare™ Probe	SF-853	Low levels are found in CSF of AD patients.	250

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