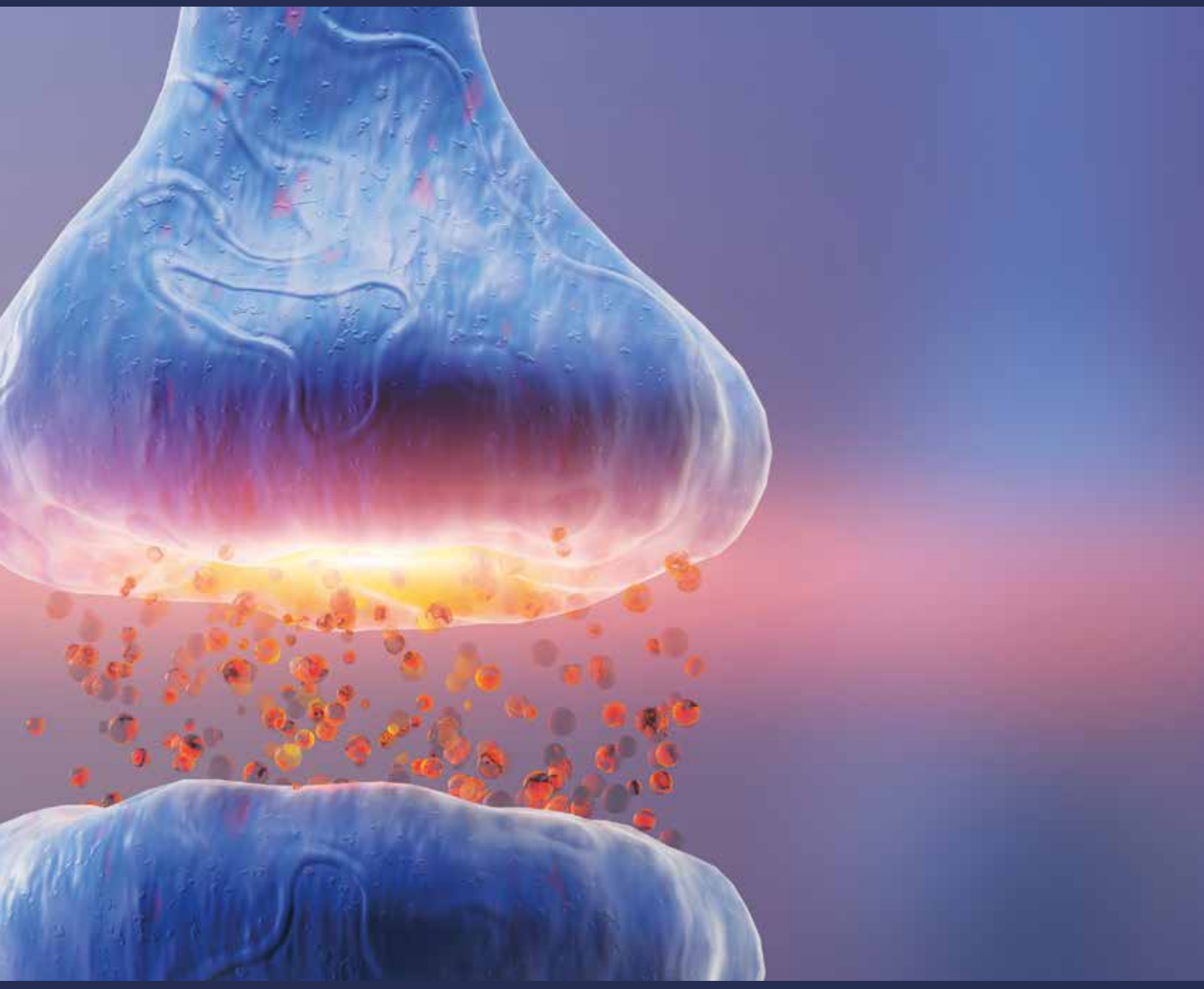
StressMarq Biosciences INC.

Neuroscience



www.stressmarq.com | info@stressmarq.com

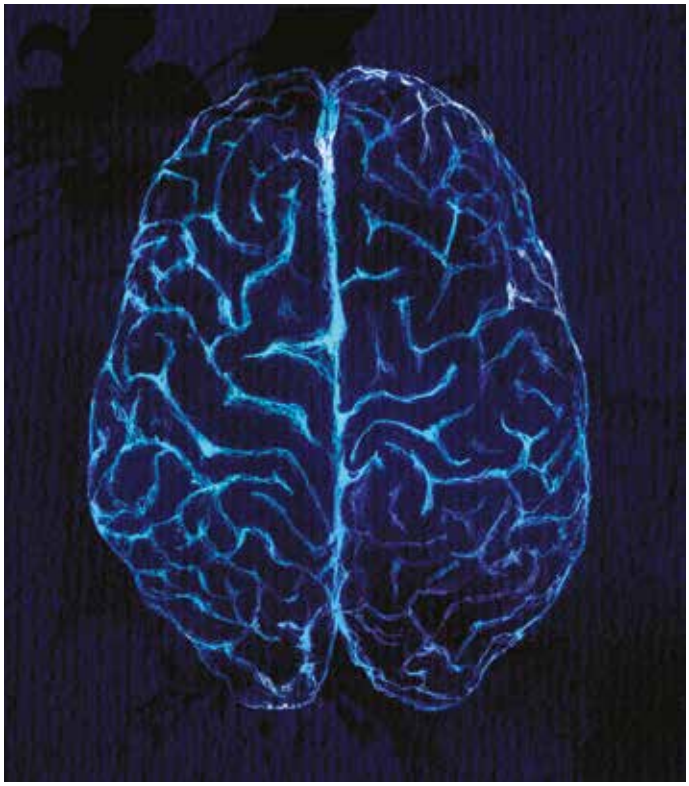
Neuroscience

Neuroscience is an interdisciplinary science devoted to the study of the nervous system's structure and function, which involves:

- Cognitive neuroscience, focusing on the neural substrates of mental processes.
- Cellular and molecular biology.
- Psychology, the study of conscious and unconscious phenomena, including feelings and thoughts.
- Pharmacology, which concerns drug-induced changes of the neural cells.

The nervous system is divided into two different structures:

- The Central Nervous System (CNS) consists of the brain and spinal cord. The brain is further divided into the cerebral cortex, cerebellum, and brain stem.
- The Peripheral Nervous System (PNS)



The main function of the Central Nervous System (CNS) is to gather all the sensory neurons, process the information, and send out responses through motor neurons. This structure is responsible for regulating and maintaining homeostasis through its receptors. The cerebral cortex is responsible for integrating sensory impulses, directing motor activity, and controlling higher intellectual functions. The cerebellum helps in movement coordination and regulates temperature. Most limbic pathologies affect this part of the brain.

The brainstem connects the brain to the spinal cord and controls balance, coordination, and reflexes. The Peripheral Nervous System (PNS) consists of nerves that connect the CNS to the rest of the body. These nerves, which are aggregates of neuron processes, can be categorized as cranial nerves (sensory, motor, or mixed), and spinal nerves. The PNS controls voluntary and involuntary bodily functions and regulates the glands.

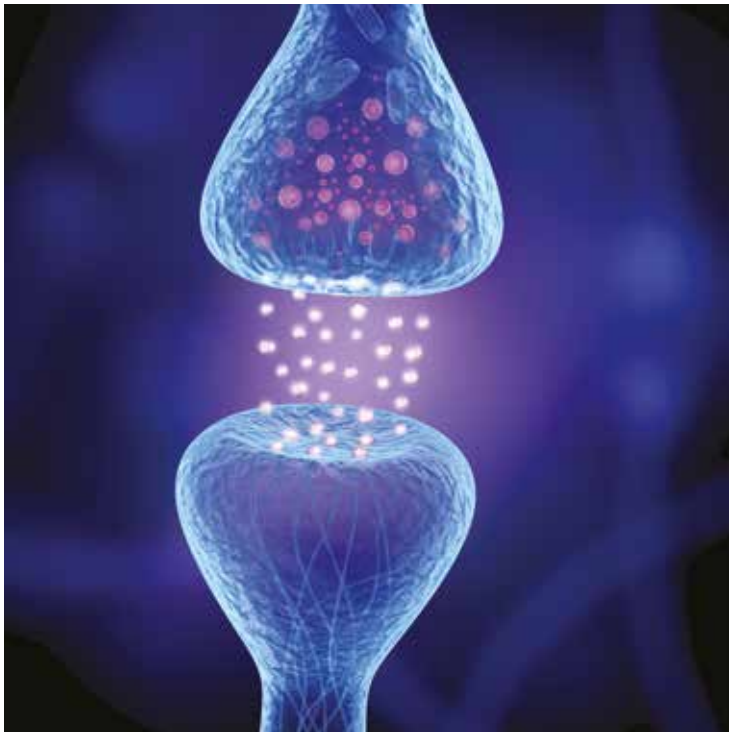
Conditions affecting the nervous system are defined as neurological diseases:

- Parkinson's disease (PD)
- Alzheimer's disease (AD)
- Multiple Sclerosis (MS)
- Amyotrophic Lateral Sclerosis (ALS)
- Friedreich's ataxia
- Huntington's disease (HD)
- Lewy body dementia (LBD)
- Motor neuron diseases (MND)
- Prion disease
- Spinocerebellar ataxia (SCA)
- Spinal muscular atrophy (SMA)

These neurodegenerative diseases are marked by the progressive degeneration of the structure and function of the central or peripheral nervous system. Neuroscience research requires a good range of life science products to study new methods for diagnosis and treatment. **At StressMarq Biosciences, we are devoted to providing cutting-edge research products to assist in the study of neurodegeneration, including antibodies, proteins, immunoassays, small molecules, and a range of monomeric, fibrilized (pre-formed fibrils/PFFs) and oligomeric protein preparations.**

The main targets for the study of these pathologies have been identified through the generation of toxic proteins and their accumulation into aggregates in the form of extracellular plaques, intracellular neurofibrillary tangles, and cytoplasmic or intranuclear inclusions. A few examples are as follows:

- Amyloid-beta 1–42 accumulates in senile Alzheimer's disease.
- Filamentous tau inclusions are a common feature in sporadic disorders and frontotemporal dementia.
- The protein alpha-synuclein is found in inclusions called Lewy bodies in PD14.
- Mutant SOD1 is found in intraneuronal inclusions in some forms of familial Amyotrophic Lateral Sclerosis (ALS).
- For polyglutamine expansion disorders, Huntington's disease is the prototypical example, and mutant huntingtin protein is found sequestered in cytoplasmic and nuclear inclusions within affected cortical pyramidal neurons of the brain.



The scientific research on these conditions involves the use of a range of fibrillar and oligomeric protein preparations, such as alpha-synuclein, tau, amyloid-beta and more. Alpha-synuclein is a distinctive hallmark of Parkinson's disease and therefore has a potential application in the diagnosis and treatment of it. Tau is a microtubule-associated protein involved in axonal transport which, under pathological conditions, forms anomalous assembly into insoluble aggregates. This leads to synaptic dysfunction and neural cell death and is mainly related to Alzheimer's. Amyloid beta-peptide (Amyloid beta) is generated by protease cleavage of amyloid precursor protein (APP), which aggregates into oligomers, protofibrils, fibrils, and ultimately plaques. The accumulation of amyloid-beta plaques in the brain is considered another distinct hallmark of Alzheimer's disease (AD). Another popular target is SOD1, a pathological hallmark of familial ALS causing mitochondrial dysfunction, leading to motor neuron pathology and death. Mutant SOD1 accumulates inside the intermembrane space (IMS), and misfolded SOD1 deposits onto the outer mitochondrial membrane (OMM), clumping the transport across mitochondrial membranes and engaging mitochondrial-dependent cell apoptosis. Finally, transthyretin (TTR) is an amyloid binding protein with a neuroprotective role in Alzheimer's.

Techniques such as Western Blot, ICC, Flow Cytometry, ELISA, and IHC have all been used extensively to characterize key neuronal targets, not only supporting the investigation of neuronal physiology but also providing insight into these neurological disorders.

StressMarq Biosciences offers a broad range of products to support neuroscience research, including high-quality antibodies for:

- Cell structure and Neurogenesis
- Neurotransmitters
- Transporters and Ion Channels
- Neurodegeneration

Cell Structure and Neurogenesis

The nervous system is composed of two main cell types: Glial cells and Neurons.

The glial cells comprise astrocytes, oligodendrocytes, microglia, and ependymal cells in the central nervous system, and satellite and Schwann cells in the peripheral nervous system. Their main functions include synaptic ion and pH homeostasis, blood-brain barrier maintenance, and structural support to neurons.

Neurons are the main type of cell in the nervous system that generate and transmit electrochemical signals. They primarily communicate with each other using neurotransmitters at specific junctions called synapses. Neurons come in many shapes that often relate to their function, but most share three main structures: axons and dendrites extending out from a cell body.

Neurogenesis is the process of neural development from the neural stem cells during embryonic development and adulthood. Neural stem cells divide and develop into mature neurons during neurogenesis.

StressMarq is committed to supplying high-quality antibodies to support research on different neural cell structures and neurogenesis.

Please contact us for a list of our neuroscience antibodies or visit: stressmarq.com/research/neuroscience.

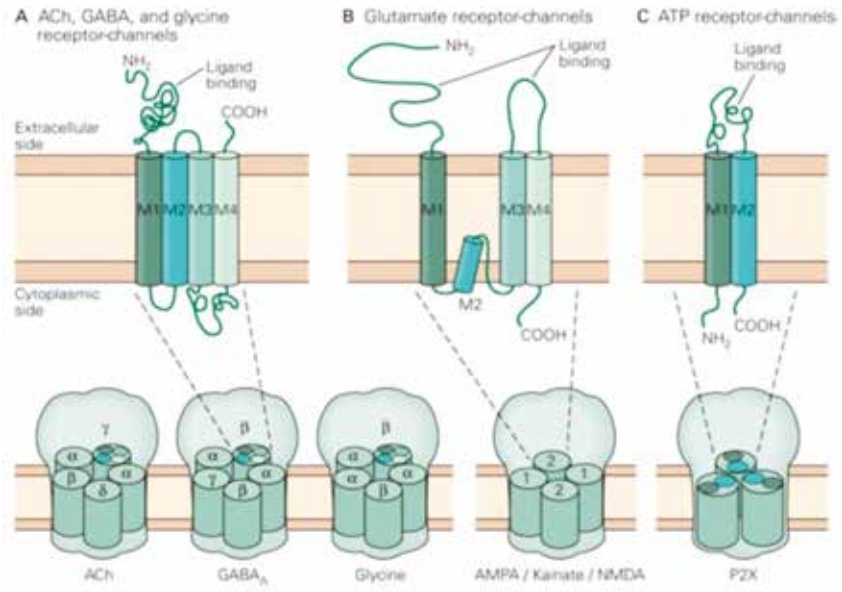
Neurotransmitters

Neurotransmitters are chemical messengers that transmit a message from a nerve cell across the synapse to a target cell. The target can be a nerve cell, a muscle cell, or a gland cell. They are released by the axon terminal of a neuron (the pre-synaptic neuron) and bind to and react with the receptors on the dendrites of another neuron. Neurotransmitters allow the impulse to cross a synapse (excitatory) or stop the impulse and prevent it from crossing a synapse (inhibitory).

Neurotransmitters are themselves affected by agonists which amplify their effect and antagonists which reduce their effect.

There are two types of receptors:
1 - Ionotropic receptors (Ligand-gated receptors) bind ionic ligands such as K+, Na+, Cl–, and Ca2+. Examples are the Cysteine loop family (nAch-R, GABA-R, Glycine-R, 5HT-R), Glutamate-R, and Purine-R.

Figure 1 (Kandel E.R., 2014).

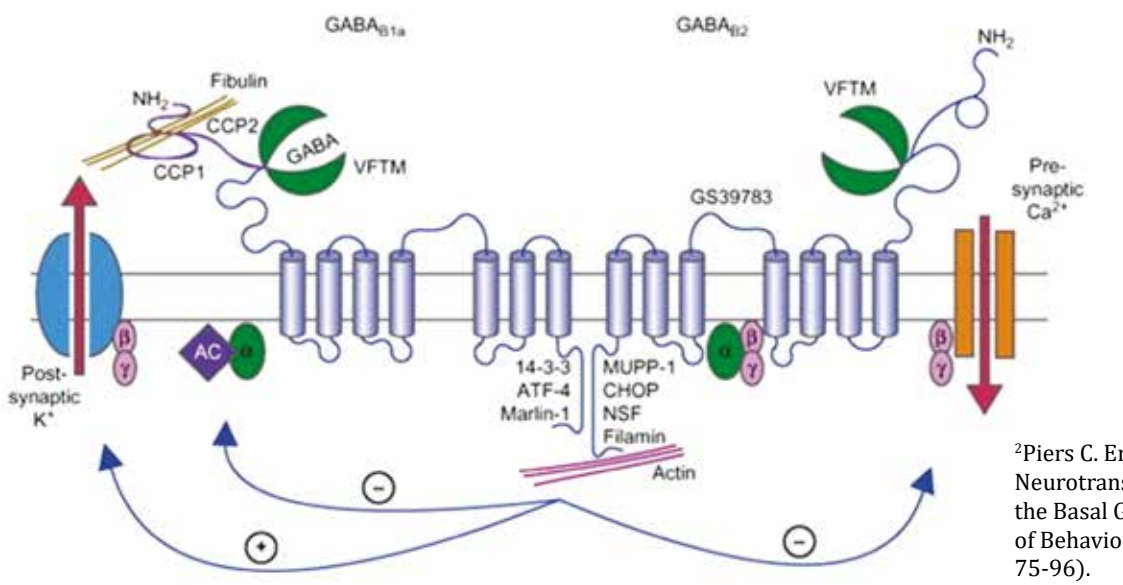


[1]Kandel E.R., &. S. (2014). Synaptic integration in the central nervous system. In M. Hill, Principles of Neural Science, Fifth Edition

2 - Metabotropic receptors (G-protein coupled receptors) bind non-ionic ligands such as chemical receptors or G protein-coupled receptors, which are single polypeptides with 7 transmembrane helixes. For example, Dopamine receptors, GABAB receptors, Glutamate receptors, and Histamine receptors. They use signal transduction mechanisms, often G proteins, to activate a series of intracellular events using second messenger chemicals.

StressMarq supplies a range of antibodies for neuronal markers and synaptic markers. We also offer antibodies and small molecules to study ion channels.

Figure 2: (Piers C. Emson, 2010)



[2]Piers C. Emson, H. J. (2010). Neurotransmitter Receptors in the Basal Ganglia. In Handbook of Behavioral Neuroscience (pp. 75-96).

Transporters and Ion Channels

The release of neurotransmitters such as GABA and Glutamate during synapse causes the activation of transmembrane proteins which move the ions against the concentration gradient across the membrane, thereby recycling the neurotransmitter and maintaining a low extracellular concentration of it. These are mainly powered by the Na+ gradient across the plasma membrane and this process is electrogenic, as it moves net charges across the plasma membrane due to the movement of ions accompanying the movement of the neurotransmitter.

Neurotransmitter transporters are of great clinical interest. They are the pharmacological target of many drugs in the treatment of depression (for example serotonin-noradrenalin reuptake inhibitors (SNRIs)), epilepsy, and schizophrenia. In addition, narcotics such as cocaine exert their effects through actions on this class of transporters.

Transporters and Ion Channels

Transporters and ion channels are classified based on the way they transport ions, either actively or passively:

- Ion pumps actively transport ions against a concentration gradient.

- Ion channels passively transport ions down their concentration gradient.

Ion pumps are further classified into two types:

- Primary active transporters are usually transmembrane ATPases, that hydrolyze ATP to produce energy to transport ions against their concentration gradient.

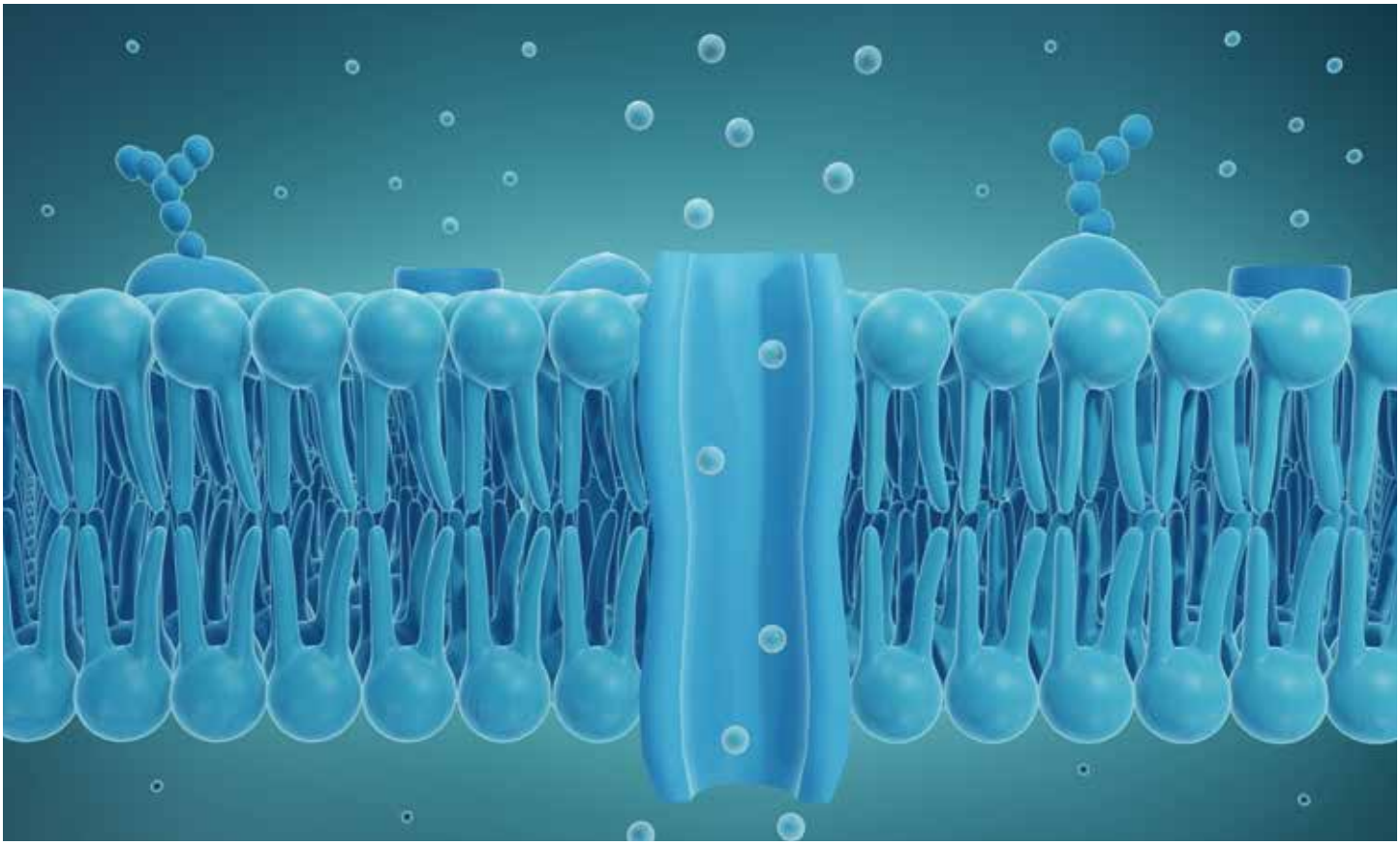
- Secondary active transporters pump ions against the concentration gradient by using the electro chemical gradient created across the membrane to pump ions in or out of the cell.

Neuronal ion channels are gated pores whose opening and closing are usually regulated by factors such as voltage or ligands. They are often selectively permeable to ions such as sodium, potassium, calcium, or non-selective cation channels. Rapid signaling in neurons requires fast voltage-sensitive mechanisms for closing and opening the pore. Anything that interferes with the membrane voltage can alter the channel opening and even small changes in the gating properties of a channel can have profound effects.

They can either be:

- Voltage-gated channels respond to the membrane potential to control the flow of ions through the channel.

- Ligand-gated channels open in response to the binding of a specific ligand to the receptor protein located in the extracellular space.



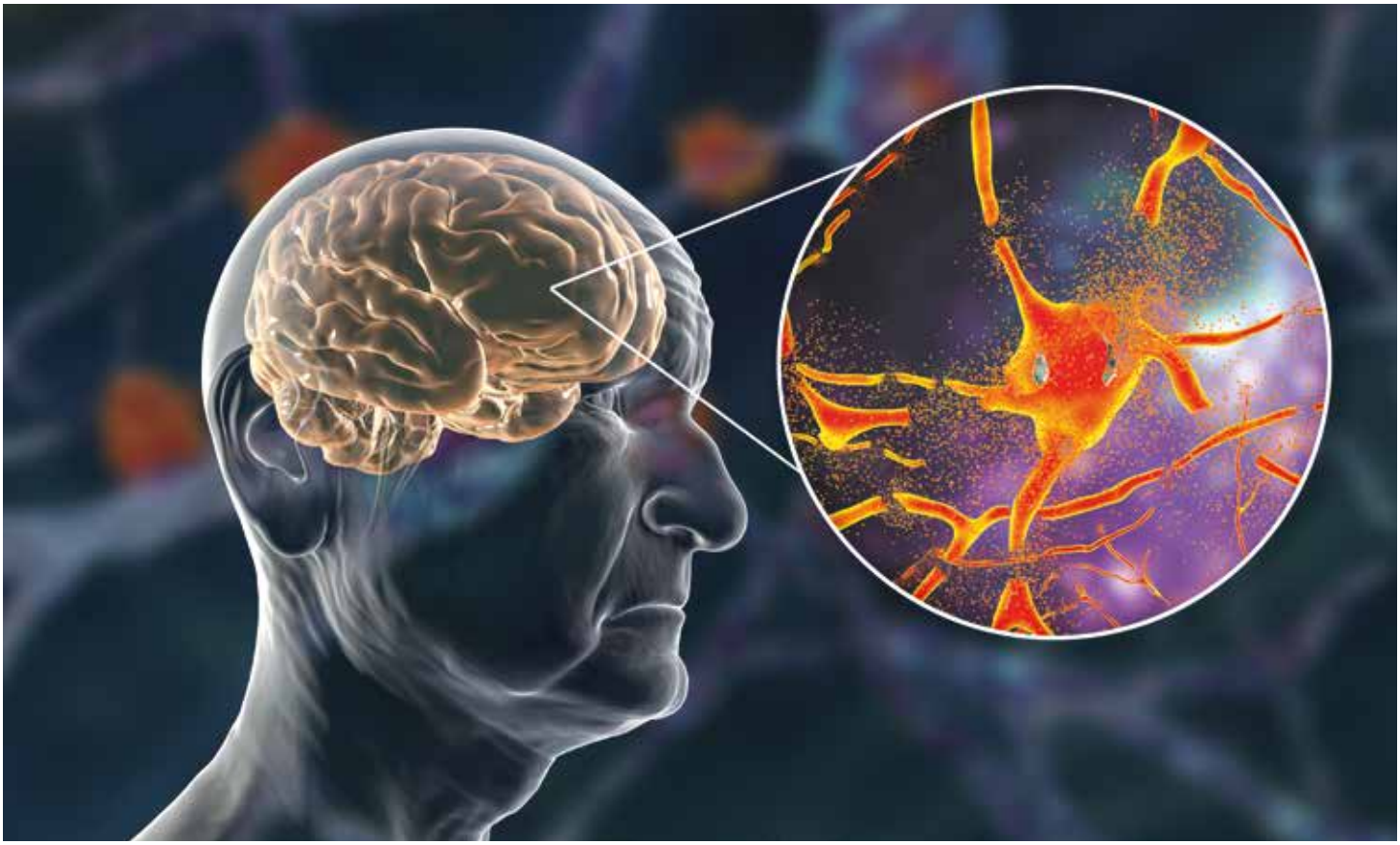
Neurodegeneration

Neurodegeneration is a slow and progressive loss of neuronal cells in specified regions of the brain and is the main pathologic feature of Alzheimer's disease and Parkinson's disease, causing dementia (loss of cognitive functioning) or ataxia (impaired movement), respectively. The underlying pathophysiology of neurodegenerative diseases is believed to be the oxidative stress caused by protein misfolding and aggregation, insufficient protein clearance, dysfunctional mitochondria, altered energy metabolism, disrupted axonal transport, neuroinflammation, or RNA-mediated toxicity. Pathological inclusions and the associated toxicity appear to spread through the nervous system in a characteristic pattern during the progression of the disease.

Therapeutic targeting of protein misfolding has created unique challenges for drug discovery and development for several reasons, including:

- The dynamic nature of the protein species involved.
- Uncertainty about which forms of a given disease protein (monomers, oligomers, or insoluble aggre gates) are primarily responsible for cellular toxicity.
- Lack of well-validated biomarkers for clinical trials.

StressMarq Biosciences has developed a range of monomeric, fibrilized and oligomeric protein preperations for use in neurodegenerative disease research including alpha synuclein, beta synuclein, gamma synuclein, tau, amyloid beta, SOD1 and TTR.



Alzheimer's Disease

Alzheimer's disease (AD) is a major form of dementia, and accounts for up to 70% of cases of dementia all over the world. Aging is the most important risk factor for this disease, which can be inherited as an autosomal dominant disorder with nearly complete penetrance in the case of early-onset. As the disease progresses, loss of synapses is observed in association with tau (microtubule-associated proteins) and amyloid beta pathology (deposition of amyloid protein); neuronal loss occurs in the most affected areas, causing cognitive deficits such as language difficulties and disorientation.

Featured Products

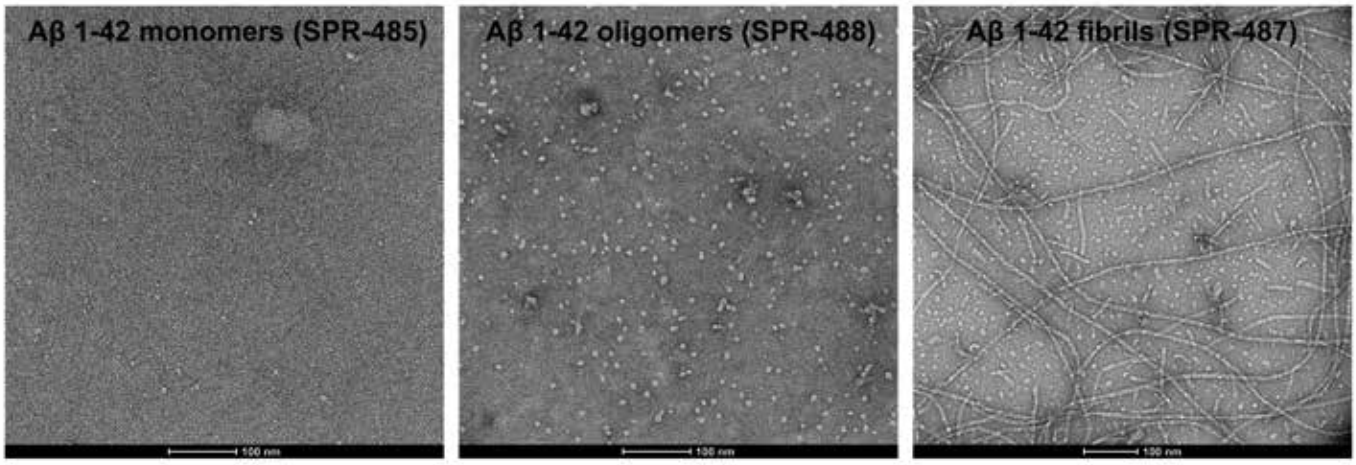
TAU	
Monomer	
Product Description	Catalog #
Tau-441 (2N4R) Wild-Type Monomers (human)	SPR-479
Tau-441 (2N4R) P301S Mutant Monomers (human)	SPR-327
Tau-430 (2N4R) P290S Mutant Monomers (mouse)	SPR-474
Tau-441 (2N4R) P301S Mutant Monomers (human)	SPR-473
Tau Truncated Fragment (AA297-391) (dGAE) Monomers (human)	SPR-444
Tau Truncated Fragment (AA297-391) (dGAE C322A) Monomers (human)	SPR-445
Tau (K18) P301L Mutant Monomers (human)	SPR-328
Tau (K18) Delta K280 Mutant Monomers (human)	SPR-476
Pre-formed Fibrils (PFFs)	
Product Description	Catalog #
Tau-441 (2N4R) Wild-Type Pre-formed Fibrils (human)	SPR-480
Tau-441 (2N4R) P301S Mutant Pre-formed Fibrils (human)	SPR-329
Tau-441 (2N4R) P301S Mutant Pre-formed Fibrils: ATTO 488 (human)	SPR-329-A488
Tau-441 (2N4R) P301S Mutant Pre-formed Fibrils (human)	SPR-471
Tau-430 (2N4R) P290S Mutant Pre-formed Fibrils (mouse)	SPR-475
Tau-441 (2N4R) P301S Mutant Filaments (human)	SPR-463
Tau Truncated Fragment (AA297-391) (dGAE) Pre-formed Fibrils (human)	SPR-461
Tau Truncated (AA297-391) (dGAE C322A) Pre-formed Fibrils (human)	SPR-462
Tau (K18) P301L Mutant Pre-formed Fibrils (human)	SPR-330
Tau (K18) Delta K280 Mutant Pre-formed Fibrils (human)	SPR-477

The characteristics of AD neuropathology include accumulations of intracellular and extracellular protein aggregates. Abnormally phosphorylated tau assembles into paired helical filaments (PHFs) that aggregate into neurofibrillary tangles (NFTs) in the neuronal perikarya (cell soma, non-process portion of a neuron) and dystrophic neurites (abnormal neuronal processes). The second pathological hallmark of this condition is the extracellular deposition of beta-pleated assemblies of amyloid-beta peptides, forming diffuse senile plaques. The cleavage of amyloid precursor protein (APP) results in the formation of amyloid-beta fibrils. Despite the critical roles of amyloid-beta and tau in AD pathology, drugs targeting amyloid-beta or tau have so far reached limited success.

Featured Products

AMYLOID-BETA	
Monomer	
Product Description	**Catalog #**
Amyloid-Beta 1-42 Peptide (HFIP, monomeric) (human)	SPR-485
Oligomers	
Product Description	**Catalog #**
Amyloid-Beta 1-42 Oligomers (human)	SPR-488
Pre-formed Fibrils (PFFs)	
Product Description	**Catalog #**
Amyloid-Beta 1-42 Pre-formed Fibrils (PFFs) (human)	SPR-487

StressMarq manufactures products to assist researchers find novel genetic risk factors, research disease mechanisms, identify candidate biomarkers for early diagnosis and potential drug targets. StressMarq also produces a range of antibodies to various forms of Tau including phosphorylated Tau, total Tau, and the dGAE truncated form of Tau.



Upon resuspension in DMSO/dH2O, Amyloid beta 42 presents as a monomeric peptide without fibrils, Amyloid beta 42 oligomers present as globular oligomers and have a unique dimer/trimer and oligomer signal, and Amyloid beta 42 PFFs present as long strands when observed under TEM, AFM and on a Western Blot with an anti-amyloid beta antibody.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a prototypical neurodegenerative disease that is characterized by the progressive degeneration of motor neurons in the brain and spinal cord. Its clinical hallmark is the degeneration of both upper and lower motor neurons, leading to progressive muscle atrophy, weakness, and paralysis.

Although the cause is still unknown, several genetic and molecular pathways are involved in the development and progression of ALS. These mechanisms include altered RNA processing leading to prion-like self-aggregation, Superoxide Dismutase type 1 (SOD1) mutations leading to free radical toxicity, cascading inflammatory responses, excessive concentrations of glutamate, mitochondrial dysfunction, and disruption of axonal transport processes. The recently identified hexanucleotide repeat expansion in the noncoding region of the chromosome 9 open reading frame 72 gene (c9orf72RE) is another common genetic cause of ALS spectrum disorder (Todd, 2016).

At StressMarq Biosciences, we supply a range of tools to investigate potential ALS causes, to help the development of clinical trials and drug discovery.

Featured Products

SOD1	
Product Description	**Catalog #**
Superoxide Dismutase Monomers (human)	SPR-435
Superoxide Dismutase Pre-Formed Fibrils (human)	SPR-470
Mn SOD Protein (rat)	SPR-130
Mn SOD Protein (human)	SPR-131

StressMarq Biosciences produces a range of antibodies to various forms of SOD. Please contact us for further information.

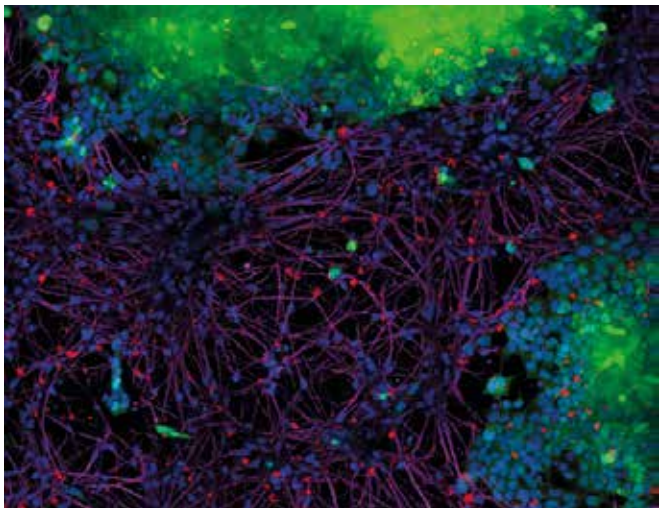
TTR	
Monomer	
Product Description	**Catalog #**
Transthyretin L55P Variant Monomers (human)	SPR-451
Transthyretin Y78F Variant Monomers (human)	SPR-452
Filaments	
Product Description	**Catalog #**
Transthyretin L55P Variant Filaments (human)	SPR-464
Transthyretin Y78F Variant Filaments (human)	SPR-465

Parkinson's Disease

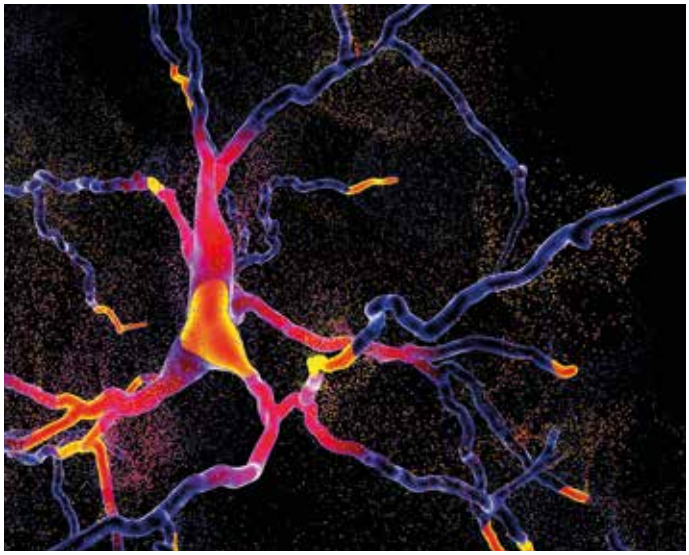
Parkinson's disease (PD) is a common progressive bradykinetic disorder (reduced or slow movement), characterized by the loss of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies (abnormal deposits of alpha-synuclein). One of its main features is the severe loss of pars-compacta nigral-cell, and the accumulation of alpha-synuclein aggregations in the brain stem, spinal cord, and cortical regions. Like other neurodegenerative diseases, aging is the major risk factor. This disease commonly causes symptoms like the impairment of motor areas, difficulty in walking, shaking, or, less commonly, a slight dragging of one foot.

The primary pathogenesis of Parkinson's disease appears to be the accumulation of alpha-synuclein in various parts of the brain, primarily the substantia nigra, leading to degeneration and subsequent loss of dopamine in the basal ganglia that control muscle tone and movement. An abnormal, post-translationally modified, and aggregated form of the presynaptic protein alpha-synuclein is the main component of Lewy bodies.

Mutations in the mitochondrial localized PTEN-induced putative kinase 1 (PINK1) have been shown to cause autosomal recessive Parkinson's disease 6 (PARK6). PINK1 mutations lead to a build-up of improperly folded proteins and the inability to protect neurons from cellular stress and apoptosis. A point mutation in Ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCHL1) has been seen to cause the autosomal dominant Parkinson's disease 5 (PARK5). Additionally, a polymorphism in UCHL1, which increases antioxidant activity, may protect against early-onset Parkinson's disease.



Cell to cell transmission of alpha synuclein PFFs (catalog# SPR-322). Pre-formed Fibrils (red) were shown to be taken up by SH-SY5Y cells and transmitted to neural iPSCs within 14 days.

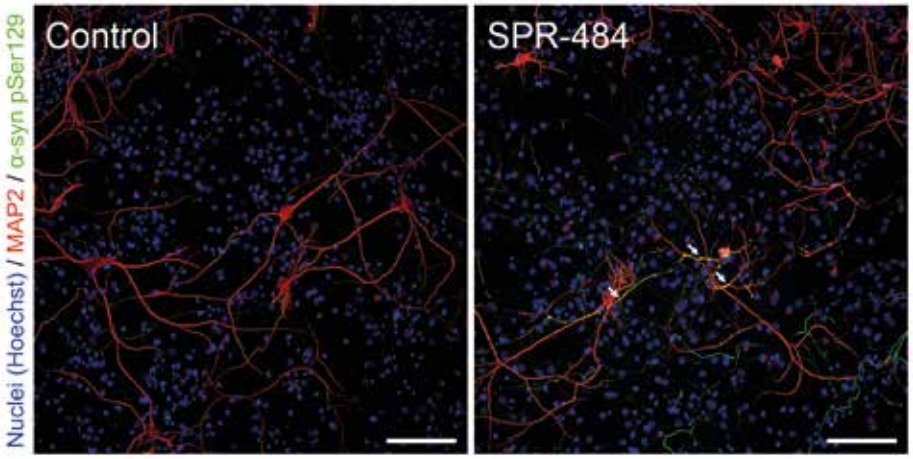


Featured Products

ALPHA SYNUCLEIN	
Monomer	
Product Description	**Catalog #**
Alpha-Synuclein Monomers (Type 1) (human)	SPR-321
Alpha-Synuclein Monomers (Type 2) (human)	SPR-316
Alpha-Synuclein Monomers (Type 1) (mouse)	SPR-323
Alpha-Synuclein A53T Mutant Monomers (Type 1) (human)	SPR-325
Alpha-Synuclein N-Terminal Acetylated Monomers (Type 1) (human)	SPR-331
Alpha-Synuclein Monomers (rat)	SPR-481

ALPHA SYNUCLEIN	
Oligomers	
Product Description	**Catalog #**
Alpha-Synuclein Oligomers (Kinetically Stable) (human)	SPR-484
Alpha-Synuclein Oligomers (Dopamine HCl Stabilized) (human)	SPR-466
Alpha-Synuclein Oligomers (EGCG Stabilized) (human)	SPR-469

StressMarq has developed a range of monomeric, fibrilized and oligomeric protein preparations for use in neurodegenerative disease research including alpha synuclein, beta synuclein, gamma synuclein, tau, amyloid beta, SOD1 and TTR.



Parkinson's-associated pSer129 pathology induced in rat primary dopaminergic cells by kinetically stable alpha synuclein oligomers (catalog# SPR-484) in MAP2 positive neurons. Arrows emphasize several regions of strong pathology.

ALPHA SYNUCLEIN

Pre-formed Fibrils (PFFs)

Product Description	Catalog #
Alpha-Synuclein Pre-formed Fibrils (Type 1) (human)	SPR-322
Alpha-Synuclein Pre-formed Fibrils (ATTO 594 conjugated, Type 1) (human)	SPR-322-A594
Alpha-Synuclein Pre-formed Fibrils (Type 1) (mouse)	SPR-324
Alpha-Synuclein Pre-formed Fibrils (Type 2) (human)	SPR-317
Alpha-Synuclein N-Terminal Acetylated Pre-Formed Fibrils (Type 1) (human)	SPR-332
Alpha-Synuclein A53T Mutant Pre-formed Fibrils (Type 1) (human)	SPR-326
Alpha-Synuclein Pre-formed Fibrils (rat)	SPR-482
Alpha-Synuclein Pre-formed Fibrils (Type 3) (human)	SPR-448
Alpha-Synuclein Filaments (Immature Fibrils) (human)	SPR-450

BETA SYNUCLEIN

Monomer

Product Description	Catalog #
Beta Synuclein Monomers (human)	SPR-405
Beta Synuclein Monomers (mouse)	SPR-406

Pre-formed Fibrils (PFFs)

Product Description	Catalog #
Beta Synuclein Pre-Formed Fibrils (Type 1) (human)	SPR-457

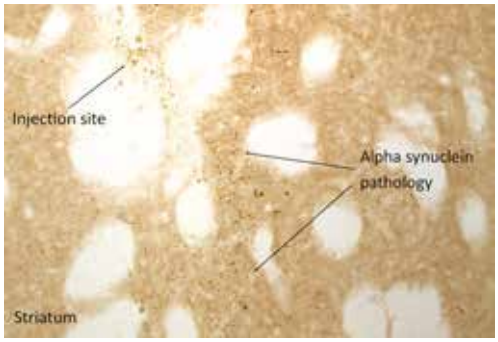
GAMMA SYNUCLEIN

Monomer

Product Description	Catalog #
Gamma Synuclein Monomers (human)	SPR-407
Gamma Synuclein Monomers (mouse)	SPR-408

Pre-formed Fibrils (PFFs)

Product Description	Catalog #
Gamma Synuclein Pre-formed Fibrils (Type 1) (human)	SPR-459
Gamma Synuclein Pre-formed Fibrils (Type 1) (mouse)	SPR-460



Immunohistochemistry analysis of rat brain injected with Type 1 human alpha synuclein PFFs (catalog# SPR-322).

StressMarq Biosciences INC.

Specializing in Fibrilized & Oligomeric Proteins for Neurodegenerative Disease Research

Products in Development

(please inquire)

Alpha Synuclein

- C-terminally AVI- tagged & biotinylated monomers & fibrils (human)
- C-terminally cleaved (deleted to AA114) monomers & fibrils
- E114C fibrils conjugated to Atto488
- pSer129 monomers & fibrils

Tau

- Tau 2N4R wild-type (Baculovirus/Sf9) monomers & fibrils (human)
- Tau dGAE 297-391 wild-type (Baculovirus/Sf9) monomers & fibrils (human)
- Tau dGAE 297-391 (E. coli) fibrils (human)

Mixed Fibrils

- 2N3R Tau/Alpha Synuclein mixed fibrils (human)
- 0N3R Tau/Alpha Synuclein mixed fibrils (human)

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