



Neuro61 and Neuro77 Biomarker Panels

Anand Sethuraman, PhD*; Chuck Herbert*;
Tony Wyss-Coray, PhD**; Markus Britschgi**, PhD;
Lynn Kozma* PhD

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* Satoris Inc., Menlo Park, CA

** Stanford University, Stanford, CA

Satoris Neuro61 and Neuro77 Biomarker Panels

The Satoris Neuro61 and Neuro77 Biomarker Panels are configured for use in clinical research in neurodegenerative diseases, in particular Alzheimer's disease and dementia. These products are offered as a service exclusively through Satoris with sample processing provided by Rules-Based Medicine.

Abstract

Many proteins have been proposed as biomarkers for neurodegenerative disorders and for dementias in particular. We have examined more than 120 proteins detectable in plasma samples from more than 500 human subjects (Alzheimer's disease, control, other dementias) using Rules-Based Medicine HumanMAP® panels and have selected two panel sets of proteins that showed utility in distinguishing the diagnosis classes from one another. The two assays are the Neuro61 Biomarker Panel and the Neuro77 Biomarker Panel. Common to both assays are 61 biomarkers which have been identified in multiple studies of over 3300 subjects using antibody arrays, ELISA assays and Rules-Based Medicine HumanMAP® panels. The majority of these markers were identified on nitrocellulose filters as described in Nature Medicine (Ray et al). The Neuro77 Biomarker Panel contains an additional 16 biomarker proteins that have been associated with Alzheimer's disease based on literature citations.

Introduction

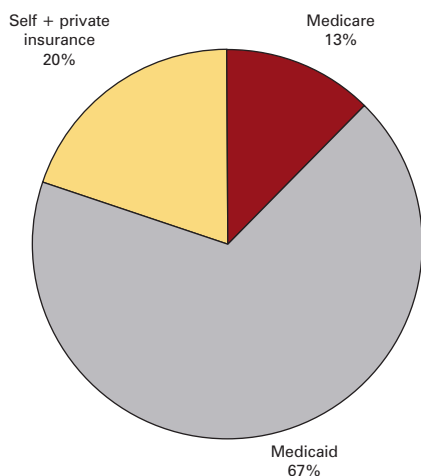
There are more than 70 conditions that produce clinical dementia in humans, of which Alzheimer's disease (AD), and Frontotemporal Lobar Degeneration (FTLD) are the most common. The epidemiological findings of the Rochester, Minnesota study (Knopman et al) for incidences (per 100,000) within the USA in the early 1990s are summarized in the table below.

Disease	Incidence per 100,000 ages 40-49	Incidence per 100,000 ages 50-59	Incidence per 100,000 ages 60-69
Alzheimer's Disease	0.0	3.3	88.9
FTD	2.2	3.3	8.9

Table 1: Dementia prevalence within the USA in the early 1990s.

It is estimated that the prevalence of AD in the USA is at least 5.3 million people predicted to increase to 11–16 million people by 2050 in the absence of the discovery of preventative treatments. AD accounts for roughly 85% of dementias in the USA (Mandavilli). FTLD is thought to account for >12% of dementias in the USA.

Currently, the societal cost of AD to the U.S. is \$148 billion per year, including \$61 billion born by U.S. businesses. AD is currently the sixth highest cause of death in the US and ranks fifth in those individuals over 65. Neither Medicare nor most private health insurance covers the long-term care most patients need.

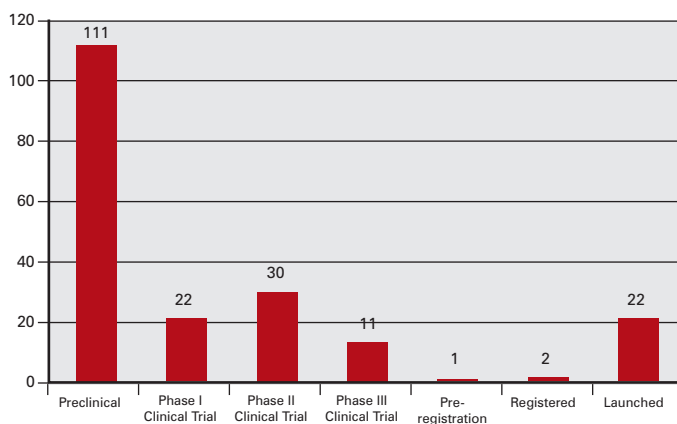


Source: Halteras Consulting

Figure 1: USA payers of nursing home care.

These economic estimates do not include the unpaid hours from family members. In 2008, it is estimated that 9.9 million family members, friends and neighbors provided unpaid care for a person with Alzheimer’s disease or other dementia.

There are currently more than 20 drugs on the market for the treatment of AD (Delagarza) but all have drawbacks. Most are thought to treat the symptoms, rather than being truly disease-modifying. Many have high non-responder rates. Many demonstrate reduced efficacy over time. Many are associated with side effects, often severe. Clearly there is room for improvement in the development and commercialization of novel therapeutics to meet this growing medical need. Currently there are more than 100 compounds at various stages of development in several pharmaceutical companies (see Figure 2).



Source: Halteras Consulting

Figure 2: Drugs for treatment of Alzheimer's Disease.

There are numerous other compounds targeting other dementia and other neurodegenerative diseases. For most of the compounds currently in development, the molecular target is known, representing more than 30 unique protein targets. However, clinical trials for novel therapeutics for AD continue to be hampered by the lack of a clear, objective, and highly accurate diagnostic test for the disease. Also lacking are adequate tools for monitoring the progress and responsiveness of patients undergoing treatment, adding considerably to the cost of such trials. The identification of

biomarkers for specific forms of dementia, including AD, as well as the identification of biomarkers indicative of disease progression, or therapeutic effectiveness can be of utility to the development of novel therapeutics at a number of stages in the drug development process, as illustrated in Figure 3.

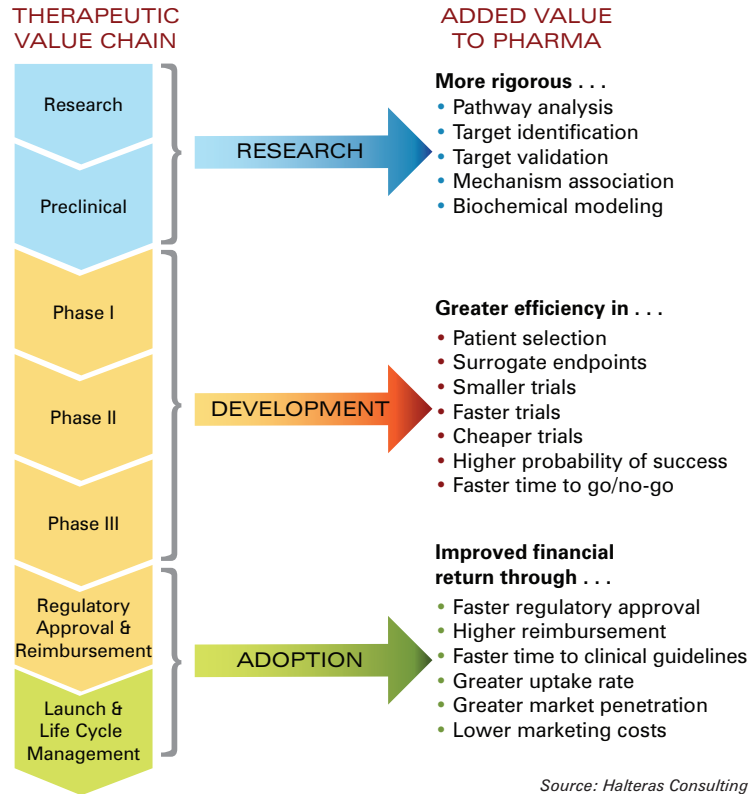


Figure 3: Added value of biomarker-based tests for Alzheimer's Disease.

We have previously demonstrated that peripheral signaling proteins may also be useful as biomarkers for AD (Ray et al). This was based on the hypothesis that changes in the extracellular milieu within the brain in response to the disease state of the patient would be reflected in the periphery and, therefore, measurable in the blood. A growing body of literature supports the notion that there are perturbations in the immune and/or inflammatory mechanisms associated with Alzheimer's disease within the brain itself, and also measurable in the periphery.

Current methods of monitoring of patients actively undergoing treatment for AD and other dementias currently relies heavily on cognitive assessment tests, none of which seems to be entirely satisfactory (Raetz and Luft, Cummings et al). Patients could benefit greatly should a biochemical diagnostic test become available that would provide an additional objective assessment of the clinical profile.

Recognizing the potential utility of a broad but dementia-focused panel of biomarkers to the research community and to pharmaceutical companies, we have designed two panels enriched for dementia-focused markers for the detection and quantitation of these plasma proteins. We identified more than 40 signaling molecules present in human plasma that demonstrated significant differences between Alzheimer's disease and non-demented controls (Ray et al.) Work was completed to migrate these initial findings onto a platform more amenable to high throughput. Testing and analysis was completed on Rules-Based Medicine HumanMAP® panels on several hundred additional samples, including those from patients with other forms of dementia. Based on the results, we were able to assess over 150 markers.

Selection of Neuro61 and Neuro77 Biomarker Panels

The biomarker panels were selected from three sources. For each panel, custom multiplex assays were developed by Rules-Based Medicine utilizing their HumanMAP® assay platform:

1. Ray et al. (2007) identified 40–50 markers in over 2800 samples (tested using nitrocellulose filter based antibody panels) that were statistically significantly different between classes (AD = Alzheimer’s, OD = Other Dementia)
2. An additional 500 samples (including an expanded representation of other dementias) were tested in two batches using the Rules-Based Medicine HumanMAP® panels containing ~150 markers. The descriptive statistics for these samples are shown in the two tables below.
3. Biologically associated markers as established in the peer review literature were also added. These 16 supplementary biomarkers were added to the existing content of the Neuro61 panel and are designated as the Neuro77 Biomarker Panel.

The selection of content for each panel is illustrated in Figure 4:

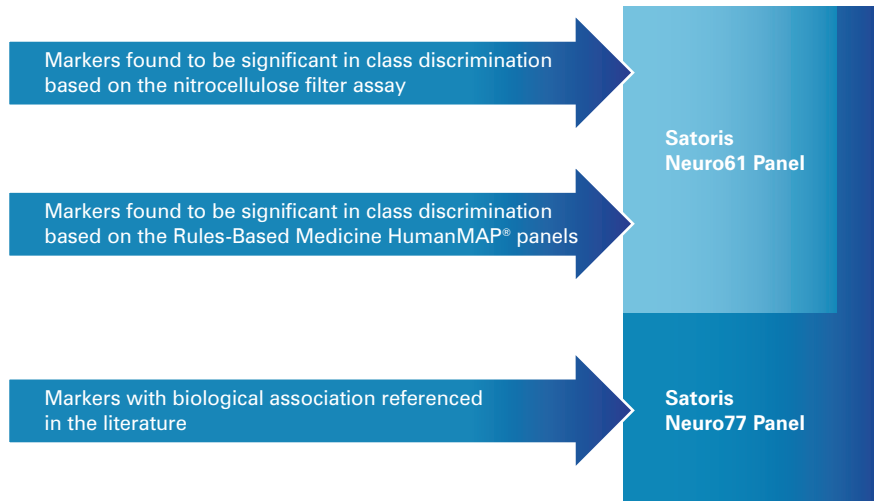


Figure 4: Added value of biomarker-based tests for Alzheimer’s Disease.

Neuro61 Biomarker Panel Content

The final list of markers for the Neuro61 Biomarker Panel with associated p-values (t-test) or q-values (SAM) is shown below for the main panel of markers. Please note: p values are presented for markers which were determined to be significant ($p < 0.05$). These results are based on samples analyzed with the Rules-Based Medicine HumanMAP® panels.

Neuro61 Biomarker Panel Content			
Marker Name	AD/NDC	AD/OD	OD/NDC
Adiponectin		p=0.011	p=0.008
Agouti-related Protein (AgRP)	q= <0.05		
Angiotensin 2	p=0.0013		
AXL	q= <0.05		
B Lymphocyte Chemoattractant		p=0.001	p=0.018
BDNF	p=0.0095		

Satoris Neuro61 and Neuro77 Biomarker Panels

Neuro61 Biomarker Panel Content, <i>continued</i>			
Marker Name	AD/NDC	AD/OD	OD/NDC
Betacellulin (BTC)	q= <0.05		
BMP-6	p=0.0035		
Ciliary Neurotrophic Factor (CNTF)	q= <0.05		
EGF	p=0.0009		
ENA-78	p=0.05	p=0.035	p=E-5
Eotaxin-3	q= <0.05		
FAS	q= <0.05		
FAS Ligand			
FGF-4	p=0.015		p=0.017
FGF basic			
G-CSF	q= <0.05		
GM-CSF			
GRO		p=0.006	p=E-6
HCC-4			
HGF	p=0.0001		
I-309			
ICAM-1	p=E-5		
IGF-1			
IGFBP2	p=E-7		
IL-1 alpha	q= <0.05		
IL-1 beta	q=0.344		
IL-2			
IL-3	q= <0.05		
IL-4	q=0.67		
IL-5	p=0.046		
IL-6			
IL-7			
IL-8	p=0.0007		
IL-10	p=0.0052		
IL-12p40	q= <0.05		
IL-12p70		p=0.004	p=0.003
IL-13			
IL-15			
IL-16	p=0.05	p=0.0144	p=0.0019
Insulin			
Lymphotactin			
MCP-1			p=0.019
MCP-3	p=0.05		p=0.0001
M-CSF	p=0.0002		
MDC	q=0.67		
MIF	p=0.01	p=E-5	p=E-8
MIP-1 alpha			

Neuro61 Biomarker Panel Content, <i>continued</i>			
Marker Name	AD/NDC	AD/OD	OD/NDC
MIP-1 beta			
PARC	p=0.0003		p=0.0005
RANTES		p=0.029	p=0.0041
SGOT		p=E-6	p=E-6
Stem Cell Factor			
Thymus-Expressed Chemokine (TECK)			
TIMP-1	p=E-5	p=0.0048	p=0.011
TIMP-2			
TGF beta 3			
TNF beta			
TPO	q=<0.05		
TRAIL R3	p=0.03		
VEGF	p=0.044		

Neuro77 Biomarker Panel

Additional review of the literature identified 16 additional markers that were found to associated with AD . These supplementary markers from the literature have been incorporated in to the Neuro77 Biomarker panel in addition to those found on the Neuro61 Biomarker Panel.

The list of these additional markers with associated p values is shown below. A small number of these markers were found to be significant in our assessment, although most of the markers were not tested.

Additional Biomarkers included in Neuro77 Biomarker Panel			
Marker Name	AD/NDC	AD/OD	OD/NDC
Apo B		p=E-9	p=E-8
Apo D			
Apo E		p=0.043	p=E-4
Apo J			
CD5L			
CgA			
Complement Factor H			
Fetuin A			
NGFb			
NrCAM			
Protein S			
S100b			
SOD-1			
Sortilin			
sRAGE			
Vitronectin			

Summary

The Satoris Neuro61 and Neuro77 Biomarker Panels are offered as a service-based test for human plasma*¹ or serum. These panels were developed in collaboration with Rules-Based Medicine, our test provider, who have optimized the multiplex biomarker test panels. Sample reports and analysis of results are provided from Satoris. The sample reports include the concentration of each of the biomarkers represented, and if sample class identification is provided, include fold change and t-test.

As this service is intended for research use only, it is not recommended for use in diagnostic procedures for patient diagnosis or patient management.

The Neuro61 and Neuro77 Biomarker Panels represent a supplementary method for the detection and quantitation of biomarker proteins associated with dementia. These panels are configured for use in clinical research of neurodegenerative diseases, in particular Alzheimer's disease and dementia and represent an additional tool for use in pharmaceutical development and subject stratification.

¹ Satoris performance is based on EDTA plasma samples. Performance on other sample types has not been established

Appendix A – Neuro61 Biomarker Content Reference

Marker Name	Swiss -Prot Accession Number	Description	Neurobiological Association	Reference
Adiponectin	O15848	Adiponectin is an adipokine involved in the control of fat metabolism and insulin sensitivity, with direct anti-diabetic, anti-atherogenic and anti-inflammatory activities. Binding to its receptor stimulates AMPK phosphorylation and activation in the liver and the skeletal muscle, enhancing glucose utilization and fatty-acid combustion. It antagonizes TNF-alpha by negatively regulating its expression in various tissues such as liver and macrophages, and also by counteracting its effects. It inhibits endothelial NF-kappa-B signaling through a cAMP-dependent pathway. It may also play a role in cell growth, angiogenesis and tissue remodeling by binding and sequestering various growth factors with distinct binding affinities, depending on the type of complex, low, medium or high molecular weight	AD	Giordano et al
Agouti-related Protein	O00253	AgRP plays a role in weight homeostasis and may play a role in the regulation of melanocortin receptors within the hypothalamus and adrenal gland, and therefore in the central control of feeding.		
Angiopoietin 2	O15123	Angiopoietin 2 (ANG-2) binds to TIE2 receptors and counteracts blood vessel maturation and stability mediated by ANG-1. In the absence of angiogenic inducers such as VEGF, ANG-2-mediated loosening of cell matrix contacts may induce endothelial cell apoptosis with consequent vascular regression. In concert with VEGF, it may facilitate endothelial cell migration and proliferation, thus serving as a permissive angiogenic signal.	AD	Thirumangalakudi et al
AXL	P30530	AXL may function as a signal transducer between specific cell types of mesodermal origin. In case of filovirus infection, it seems to function as a cell entry factor. It is a tyrosine kinase receptor	AD	Allison
BDNF	P23560	BDNF is a protein found in the neurons of the nervous system where it helps to support the survival of existing neurons, and encourage the growth of new neurons and synapses. Various studies have shown possible links between low levels of BDNF and conditions such as depression, obsessive-compulsive disorder, Alzheimer's disease (AD) or senile dementia of Alzheimer's type which is a disorder or loss of mental functions resulting from brain tissue changes.	HD AD PD	Strand et al Leyhe et al, Laske et al 2006, Zhang et al Zhang et al, Sawada et al
B Lymphocyte Chemoattractant (BLC)	O43927	BLC, also known as CXCL13, is chemotactic for B-lymphocytes but not for T-lymphocytes, monocytes and neutrophils. It does not induce calcium release in B-lymphocytes. It binds to BLR1/CXCR5.	MS LNB	Corcione et al Ljostad et al
Betacellulin	P35070	Betacellulin (BTC) is a potent mitogen for retinal pigment epithelial cells and vascular smooth muscle cells. The effects of betacellulin are probably mediated by the EGF receptor and other related receptors. Betacellulin from beta cells could play a role in the vascular complications associated with diabetes.		

Neuro61 Biomarker Content Reference, <i>continued</i>			Neurobiological Association	Reference
Marker Name	Swiss -Prot Accession Number	Description		
BMP-6	P22004	Bone morphogenic protein 6 (BMP-6) induces cartilage and bone formation.	Neuro protection	Du et al, Yabe et al
Ciliary Neurotrophic Factor (CNTF)	P26441	Ciliary Neurotrophic Factor (CNTF) is a survival factor for various neuronal cell types. It seems to prevent the degeneration of motor axons after axotomy.	MS	Dutta et al
			HD	Bloch et al, Emerich and Thanos
ENA-78	P42830	Also known as CXCL5, ENA-78 is secreted from peripheral blood monocytes and is involved in neutrophil activation. The N-terminal cleavage products (8-78) and (9-78) show 3-fold higher chemotactic activity for neutrophil granulocytes.	ALS	Jiang et al, Ilzecka
Eotaxin-3	Q9Y258	Eotaxin-3 has been renamed CCL26. It is chemotactic for eosinophils and basophils and binds to CCR3.	NMO	Correale and Fiol
Epidermal Growth Factor (EGF)	P01133	EGF is a small protein that promotes cell growth and differentiation, is essential in embryogenesis, and is important in wound healing. It is produced by many normal cell types and is made in large amounts by some tumors.	AD	Gomez Ravetti et al, Ray et al
FAS	P25445	FAS is known as Tumor necrosis factor receptor superfamily member 6. It is the receptor for TNFSF6/FASLG. The adapter molecule FADD recruits caspase-8 to the activated receptor. The resulting death-inducing signaling complex (DISC) performs caspase-8 proteolytic activation which initiates the subsequent cascade of caspases (aspartate-specific cysteine proteases) mediating apoptosis. FAS-mediated apoptosis may have a role in the induction of peripheral tolerance, in the antigen-stimulated suicide of mature T-cells, or both. The secreted isoforms 2 to 6 block apoptosis (in vitro).	MS	Fainardi et al, Grossman et al, Lopatinskaya et al, Sofo et al
FAS Ligand	Q53Z1	FAS Ligand is also known as TNFSF6 and binds FAS. The adapter molecule FADD recruits caspase-8 to the activated receptor. The resulting death-inducing signaling complex (DISC) performs caspase-8 proteolytic activation which initiates the subsequent cascade of caspases (aspartate-specific cysteine proteases) mediating apoptosis. FAS-mediated apoptosis may have a role in the induction of peripheral tolerance, in the antigen-stimulated suicide of mature T-cells, or both.	MS	Lopatinskaya et al, Sofo et al
FGF-4	P08620	FGF-4 is a member of the heparin-binding growth factor family. It is a mitogenic protein found in human stomach tumors and in Kaposi's sarcomas.		
FGF basic	P09038	FGF basic is also called Heparin-binding growth factor 2. The heparin-binding growth factors are angiogenic agents in vivo and are potent mitogens for a variety of cell types in vitro.	CJD	Albrecht et al
			AD	Bellucci et al
			MS	Su et al
			HD	Haque and Isacson

Neuro61 Biomarker Content Reference, <i>continued</i>		Neurobiological Association		Reference
Marker Name	Swiss -Prot Accession Number	Description		
G-CSF	P09919	Granulocyte/macrophage colony-stimulating factors are cytokines that act in hematopoiesis by controlling the production, differentiation, and function of 2 related white cell populations of the blood, the granulocytes and the monocytes-macrophages. This CSF induces granulocytes. Pharmacologically, it is used to treat neutropenia (a disorder characterized by an extremely low number of neutrophils in blood).	AD	Ray et al, Ravetti and Moscato
			ALS	Cashman et al, Tanaka et al
GM-CSF	P04141	Granulocyte-macrophage colony-stimulating factor is a cytokine that stimulates the growth and differentiation of hematopoietic precursor cells from various lineages, including granulocytes, macrophages, eosinophils and erythrocytes. Pharmacologically, it is used in myeloid reconstitution following bone marrow transplant, bone marrow transplant engraftment failure or delay, mobilization and following transplantation of autologous peripheral blood progenitor cells, and following induction chemotherapy in older adults with acute myelogenous leukemia.	AD	Volmar et al
GRO	P09341	GRO (CXCL-1) has chemotactic activity for neutrophils and may play a role in inflammation. It exerts its effects on endothelial cells in an autocrine fashion. In vitro, the processed forms GRO-alpha(4-73), GRO-alpha(5-73) and GRO-alpha(6-73) show a 30-fold higher chemotactic activity.	AD	Parachikova et al
HCC-4	O15467	HCC-4 is known as CCL16. This chemokine displays chemotactic activity for lymphocytes and monocytes but not neutrophils. It also has potent myelosuppressive activity, suppresses proliferation of myeloid progenitor cells. Recombinant SCYA16 shows chemotactic activity for monocytes and THP-1 monocytes, but not for resting lymphocytes and neutrophils. Binding to its receptor induces a calcium flux in THP-1 cells that were desensitized by prior exposure to RANTES. It is induced by IL-10.		
HGF	P14210	Hepatocyte Growth Factor (HGF) is a potent mitogen for mature parenchymal hepatocyte cells, seems to be an hepatotrophic factor, and acts as growth factor for a broad spectrum of tissues and cell types. It has no detectable protease activity.	AD	Tsuboi et al, Fenton et al
I-309	P22362	I-309 is also known as CCL1. It is a cytokine that is chemotactic for monocytes but not for neutrophils. It acts by binding to CCR8.		
ICAM-1	P05362	ICAM-1 is a cell surface receptor molecule that is implicated in a number of cellular processes including inflammation, cardiovascular disease, diabetes, and metastasis of cancer. Its soluble form is a product of cleavage at the cell surface and this form may have either positive or negative feedback functions as found in the blood.	AD	Janciauskiene et al, Rentzos et al (2005), Nielsen et al (<i>Neurobiol Dis</i> 2007)
			MS	Trojano et al
			ALS	Rentzos et al (2005)
			DLB	Nielsen et al (<i>Neuro</i> 2007)

Neuro61 Biomarker Content Reference, <i>continued</i>		Description	Neurobiological Association	Reference
Marker Name	Swiss -Prot Accession Number			
IGF-1	P01343	Insulin-like growth factor IA. The insulin-like growth factors, isolated from plasma, are structurally and functionally related to insulin but have a much higher growth-promoting activity. Defects in IGF1 are the cause of insulin-like growth factor I deficiency (IGF1 deficiency). IGF1 deficiency is an autosomal recessive disorder characterized by growth retardation, sensorineural deafness and mental retardation.	Neuroprotection AD	Morselli et al Burgos-Ramos et al, Vardy et al
IGFBP-2	P18065	IGF-binding proteins prolong the half-life of the IGFs and have been shown to either inhibit or stimulate the growth promoting effects of the IGFs on cell culture. They alter the interaction of IGFs with their cell surface receptors.	AD Neuro-degeneration	Tham et al Busiguina et al
IL-1 alpha	P01583	Interleukin-1 alpha is produced by activated macrophages. IL-1 stimulates thymocyte proliferation by inducing IL-2 release, B-cell maturation and proliferation, and fibroblast growth factor activity. IL-1 proteins are involved in the inflammatory response, being identified as endogenous pyrogens, and are reported to stimulate the release of prostaglandin and collagenase from synovial cells.	MS PD	Sarial et al Imamura et al
IL-1 beta	P01584	Interleukin-1 beta is produced by activated macrophages. IL-1 stimulates thymocyte proliferation by inducing IL-2 release, B-cell maturation and proliferation, and fibroblast growth factor activity. IL-1 proteins are involved in the inflammatory response, being identified as endogenous pyrogens, and are reported to stimulate the release of prostaglandin and collagenase from synovial cells.	Dementia PD MS	Angelopoulos et al Reale et al (2009), Imamura et al Sarial et al, Ysrraelit et al
IL-2	P60568	Interleukin 2 (IL-2) is produced by T-cells in response to antigenic or mitogenic stimulation. This protein is required for T-cell proliferation and other activities crucial to regulation of the immune response. It can stimulate B-cells, monocytes, lymphokine-activated killer cells, natural killer cells, and glioma cells.	AD	Deniz-Naranjo et al, Kong et al, Gambi et al
IL-3	P08700	Interleukin-3 (IL-3) is one of the Granulocyte/macrophage colony-stimulating factors. These are cytokines that act in hematopoiesis by controlling the production, differentiation, and function of 2 related white cell populations of the blood, the granulocytes and the monocytes-macrophages. This CSF induces granulocytes, macrophages, mast cells, stem cells, erythroid cells, eosinophils and megakaryocytes.	Neuroprotection MS	Beloosesky et al, Angelopoulos et al Rojo et al Baranzini et al

Neuro61 Biomarker Content Reference, <i>continued</i>		Neurobiological Association		Reference
Marker Name	Swiss -Prot Accession Number	Description		
IL-4	P05112	Interleukin 4 (IL-4) participates in at least several B-cell activation processes as well as of other cell types. It is a costimulator of DNA-synthesis. It induces the expression of class II MHC molecules on resting B-cells. It enhances both secretion and cell surface expression of IgE and IgG1. It also regulates the expression of the low affinity Fc receptor for IgE (CD23) on both lymphocytes and monocytes. Genetic variations in IL4 may be a cause of susceptibility to ischemic stroke.	AD CJD	Gambi et al, Reale et al (2008) Stoock et al, Iwasaki et al
IL-5	P05113	Interleukin 5 (IL-5) is produced by T-cells. It is a specific hematopoietic growth factor that is responsible for the growth and differentiation of eosinophils. It also promotes the generation of cytotoxic T-cells from thymocytes.	MS	Baranzini et al
IL-6	P05231	Interleukin-6 (IL-6) is a cytokine with a wide variety of biological functions: it plays an essential role in the final differentiation of B-cells into Ig-secreting cells, it induces myeloma and plasmacytoma growth, it induces nerve cells differentiation, in hepatocytes it induces acute phase reactants. Genetic variations in IL6 may be correlated with bone mineral density (BMD). Low BMD is a risk factor for osteoporotic fracture. Genetic variations in IL6 are associated with susceptibility to systemic juvenile rheumatoid arthritis. Systemic juvenile rheumatoid arthritis is juvenile chronic arthritis associated with severe, debilitating, extraarticular features, and occasionally fatal complications. Despite medical treatment, many children still experience early joint destruction, necessitating surgical replacement. At least 1 polymorphism in the IL6 gene renders HIV-infected men susceptible to Kaposi sarcoma. Kaposi sarcoma is a sarcoma of spindle cells mixed with angiomatous tissue. It is a relatively rare malignant skin tumor that results in multifocal purplish colored papules or plaques that eventually form nodules most commonly seen in patients who suffer from AIDS.	VAD AD PD dementia MS	Mulugeta et al Paradowski et al Brodacki et al, Imamura et al Angelopoulos et al Baranzini et al, Ysrraelit et al
IL-7	P13232	Interleukin 7 (IL-7) stimulates the proliferation of pre-B and pro-B-cells without affecting their differentiation. It also selectively supports the maturation of megakaryocytes. In human peripheral monocytes, IL-7 induces the synthesis of some inflammatory mediators such as IL-1, IL-6 and. It also enhances the expression and secretion of IL-3 and GM-CSF in activated human T-cells. IL-7 down-regulates expression of TGF-beta in macrophages which has been suggested as an inhibitor of the antitumor immune response.	MS	Traggiai et al
IL-8	P10145	Interleukin 8 (IL-8) may be of clinical relevance in psoriasis and rheumatoid arthritis. Elevated concentrations are observed in psoriatic scales and this may explain the high proliferation rate observed in these cells. It may also be a marker of different inflammatory processes and probably plays a role in the pathogenesis of chronic polyarthritis since excessive amounts of this factor are found in synovial fluids.	HAD ALS PD	Albright et al Kuhle et al Reale et al (2009)

Neuro61 Biomarker Content Reference, <i>continued</i>			Neurobiological Association	Reference
Marker Name	Swiss -Prot Accession Number	Description		
IL-10	P22301	Interleukin 10 (IL-10) is produced by, and down-regulates the function of, Th1 and Th2 cells. In human monocytes, IFN-gamma and IL-10 antagonize each other's production and function and has been shown to be a physiologic antagonist of IL-12. Studies suggest that IL-10 indirectly suppresses tumor growth of certain tumors by inhibiting infiltration of macrophages which may provide tumor growth promoting activity. It has been detected in the sera of a subgroup of patients with active non-Hodgkin's lymphoma, and it appears to correlate with a poor survival in patients with intermediate or high-grade non-Hodgkin's lymphoma.	HAD MS PD CJD AD	Sasseville et al Wiesemann et al Brodacki et al Stoeck et al, Iwasaki et al Maier et al
IL-12p40	P29460	Interleukin 12p40 (IL-12p40) is also called Interleukin-12 subunit beta. It is a cytokine that can act as a growth factor for activated T and NK cells, enhance the lytic activity of NK/lymphokine-activated killer cells, and stimulate the production of IFN-gamma by resting PBMC. It associates with IL23A to form the IL-23 interleukin, an heterodimeric cytokine which functions in innate and adaptive immunity. IL-23 may constitute with IL-17 an acute response to infection in peripheral tissues. IL-23 binds to an heterodimeric receptor complex composed of IL12RB1 and IL23R, activates the Jak-Stat signaling cascade, stimulates memory rather than naive T-cells and promotes production of proinflammatory cytokines. IL-23 induces autoimmune inflammation and thus may be responsible for autoimmune inflammatory diseases and may be important for tumorigenesis. Defects in IL12B are a cause of mendelian susceptibility to mycobacterial disease (MSMD) also known as familial disseminated atypical mycobacterial infection.	MS	Braitch et al, Brahmachari and Pahan
IL-12p70	P29459	Interleukin 12p70 (IL-12p70) is a cytokine that can act as a growth factor for activated T and NK cells, enhance the lytic activity of NK/lymphokine-activated Killer cells, and stimulate the production of IFN-gamma by resting PBMC.		
IL-13	P35225	Interleukin-13 (IL-13) is a cytokine that acts to inhibit inflammatory cytokine production. It synergizes with IL2 in regulating interferon-gamma synthesis and may be critical in regulating inflammatory and immune responses. Mutation at Gln-130 is a significant risk factor for asthma development. Gln/Gln at position 130 is associated with higher levels of serum total IgE than Arg/Arg in Chinese allergic rhinitis patients.	ALS	Shi et al
IL-15	P40933	Interleukin-15 (IL-15) is a cytokine that stimulates the proliferation of T-lymphocytes. Stimulation by IL-15 requires interaction of IL-15 with components of IL-2R, including IL-2R beta and probably IL-2R gamma but not IL-2R alpha.	MS AD	Rentzos et al (<i>J Neuro Sci</i> 2006) Rentzos et al (<i>JGPN</i> 2006)

Neuro61 Biomarker Content Reference, <i>continued</i>			Neurobiological Association	Reference
Marker Name	Swiss -Prot Accession Number	Description		
IL-16	Q14005	Interleukin 16 (IL-16) was described originally as Lymphocyte chemoattractant factor (LCF), which acts as a chemoattractant for CD4 (+) T-cells, macrophages, and eosinophils. The protein is produced by lymphocytes, eosinophils, mast cells, and lung epithelium. Fibroblasts from several tissues can express IL-16. Very high levels are produced in response to IL-1-beta.	AD	Motta et al
Insulin	P01308	Insulin decreases blood glucose concentration. It increases cell permeability to monosaccharides, amino acids and fatty acids. It accelerates glycolysis, the pentose phosphate cycle, and glycogen synthesis in liver.	PD AD	Wilhelm et al Vepsalainen et al
Lymphotactin	P47992	Lymphotactin (XCL1) has chemotactic activity for lymphocytes but not for monocytes or neutrophils.	HAD	Kim et al
MCP-1	P13500	Monocyte chemotactic protein-1 plays a role in the recruitment of monocytes to sites of injury and infection. MCP-1 has been found in the joints of people with rheumatoid arthritis where it may serve to recruit macrophages and perpetuate the inflammation in the joints. MCP-1 has also been found elevated in the urine of people with lupus as a sign warning of inflammation of the kidney. MCP-1 has also been called small inducible cytokine A2 (SCYA2) and monocyte chemotactic and activating factor (MCAF).	AD HAD PD	Reale et al (2008), Galimberti et al Albright et al, Kim et al Reale et al (2009)
MCP-3	P80098	Monocyte chemotactic protein 3 (MCP-3) is also known as CCL7. It is a chemotactic factor that attracts monocytes and eosinophils, but not neutrophils. It augments monocyte anti-tumor activity. It also induces the release of gelatinase B. This protein can bind heparin and binds to CCR1, CCR2 and CCR3.	ALS MS VAD HAD	Tanaka et al, Kuhle et al Baranzini et al Mulugeta et al Sasseville et al
M-CSF	P09603	Granulocyte/macrophage colony-stimulating factors are cytokines that act in hematopoiesis by controlling the production, differentiation, and function of 2 related white cell populations of the blood, the granulocytes and the monocytes-macrophages. CSF-1 induces cells of the monocyte/macrophage lineage. It plays a role in immunological defenses, bone metabolism, lipoproteins clearance, fertility and pregnancy.	AD MS	Kong et al Werner et al

Neuro61 Biomarker Content Reference, <i>continued</i>		Description	Neurobiological Association	Reference
Marker Name	Swiss -Prot Accession Number			
MDC	O00626	This macrophage-derived chemokine, also known as CCL22, may play a role in the trafficking of activated/effector T-lymphocytes to inflammatory sites and other aspects of activated T-lymphocyte physiology. It is chemotactic for monocytes, dendritic cells and natural killer cells. It is a mild chemoattractant for primary activated T-lymphocytes and a potent chemoattractant for chronically activated T-lymphocytes but has no chemoattractant activity for neutrophils, eosinophils, and resting T-lymphocytes. It binds to CCR4. The processed forms MDC(3-69), MDC(5-69) and MDC(7-69) seem not be active.	MS	Galimberti et al (<i>Neuro Sci</i> 2008), Galimberti et al (<i>Mult Scler</i> 2008)
MIF	P14174	Macrophage migratory inhibitory factor (MIF) is expressed at sites of inflammation suggesting a role for the mediator in regulating the function of macrophage in host defense. It also acts as a phenylpyruvate tautomerase.	Neuro regeneration	Nishio et al
MIP-1 alpha	P10147	MIP-1 alpha is also called CCL3. It is a monokine with inflammatory and chemokinetic properties. It binds to CCR1, CCR4 and CCR5. It is one of the major HIV-suppressive factors produced by CD8+ T-cells. Recombinant MIP-1-alpha induces a dose-dependent inhibition of different strains of HIV-1, HIV-2, and simian immunodeficiency virus (SIV).	PD	Reale et al (2009)
			MS	Miyagishi et al, Baranzini et al
			HAD	Kim et al
MIP-1 beta	P13236	Macrophage inflammatory protein 1-beta (MIP-1 beta) is also known as CCL4. It is a monokine with inflammatory and chemokinetic properties. It binds to CCR5 and is one of the major HIV-suppressive factors produced by CD8+ T-cells. Recombinant MIP-1-beta induces a dose-dependent inhibition of different strains of HIV-1, HIV-2, and simian immunodeficiency virus (SIV). The processed form MIP-1-beta(3-69) retains the abilities to induce down-modulation of surface expression of the chemokine receptor CCR5 and to inhibit the CCR5-mediated entry of HIV-1 in T-cells. MIP-1-beta(3-69) is also a ligand for CCR1 and CCR2 isoform B	AD	Li et al, Tripathy et al
			HAD	Kim et al
PARC	P55774	Pulmonary and activation-regulated chemokine (PARC) has been renamed to CCL18. It is a chemotactic factor that attracts lymphocytes but not monocytes or granulocytes and may be involved in B-cell migration into B-cell follicles in lymph nodes. CCL18 attracts naive T-lymphocytes toward dendritic cells and activated macrophages in lymph nodes, has chemotactic activity for naive T-cells, CD4+ and CD8+ T-cells and thus may play a role in both humoral and cell-mediated immunity responses. It is specifically induced in macrophages by IL-4, IL-13, and IL-10. Its expression is inhibited by IFN-gamma while glucocorticoids exert a slightly positive synergistic effect in combination with IL-4	AD	Ray et al

Neuro61 Biomarker Content Reference, <i>continued</i>		Neurobiological Association		Reference
Marker Name	Swiss -Prot Accession Number	Description		
RANTES	P13501	This factor has been renamed CCL5. RANTES is chemotactic for T-cells, human eosinophils and basophils and plays an active role in recruiting leukocytes into inflammatory sites. It also activates eosinophils to release, for example, eosinophilic cationic protein. It changes the density of eosinophils and makes them hypodense, which is thought to represent a state of generalized cell activation and is associated most often with diseases such as asthma and allergic rhinitis.	AD PD MS HAD	Reale et al (2008) Reale et al (2009) Baranzini et al Sasseville et al, Kim et al
SGOT	P17174	SGOT is an enzyme that is normally present in liver and heart cells. SGOT is released into blood when the liver or heart is damaged. The blood SGOT levels are thus elevated with liver damage or with an insult to the heart. Some medications can also raise SGOT levels. SGOT is also called aspartate aminotransferase (AST). It is an acute phase reactant suggestive of inflammation.	PD AD	Steur et al Tapiola et al, Yavuz et al
Stem Cell Factor	P21583	SCF is a stromal cell-derived cytokine synthesized by fibroblasts and other cell types. It is a glycoprotein that plays a key role in hematopoiesis acting both as a positive and negative regulator, often in synergy with other cytokines. It also plays a key role in mast cell development, gametogenesis, and melanogenesis.	AD	Laske et al (2008)
Thymus-Expressed Chemokine (TECK)	O15444	Thymus-expressed chemokine (TECK) is also called CCL25. It may be involved in T-cell development. The recombinant protein shows chemotactic activity on thymocytes, macrophages, THP-1 cells, and dendritic cells but is inactive on peripheral blood lymphocytes and neutrophils. It binds to CCR9.		
TIMP-1	P01033	Metalloproteinases (MMP) of the extracellular matrix are a family of secreted proteolytic enzymes that are involved in the biosynthesis of connective tissue. The synthesis and secretion of matrix metalloproteinases (MMPs) is induced in various cell types by a number of cytokines. Metalloproteinases degrade constituents of the basal membrane and the extracellular matrix, including collagens, proteoglycans, gelatin, fibronectin, laminin, and elastin, under physiological and pathological conditions. The biological activities of the proteases are subject to a complex regulation also involving specific inhibitors, called TIMP (Tissue inhibitor of metalloproteinases). Many proforms of these metalloproteinases form complexes with these inhibitors. TIMP 1 is a major regulator of extracellular matrix synthesis and degradation. A certain balance of MMPs and TIMPs is essential for tumor growth and health.	HAD MS AD ALS	Albright et al Lee et al 1999 Aviolo et al, Comabella et al Lorenzi et al (2003),
TIMP-2	P16035	Metalloproteinase inhibitor 2 complexes with metalloproteinases (such as collagenases) and irreversibly inactivates them. TIMP-2 is known to act on MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-13, MMP-14, MMP-15, MMP-16 and MMP-19.	FTD	Lorenzi et al (2008)

Neuro61 Biomarker Content Reference, <i>continued</i>		Neurobiological Association	Reference
Marker Name	Swiss -Prot Accession Number	Description	
TGF-beta-3	P10600	Transforming growth factor beta-3 is involved in embryogenesis and cell differentiation. Defects in TGFB3 are a cause of familial arrhythmic right ventricular dysplasia 1 (ARVD1) also known as arrhythmic right ventricular cardiomyopathy 1 (ARVC1). ARVD is an autosomal dominant disease characterized by partial degeneration of the myocardium of the right ventricle, electrical instability, and sudden death. It is clinically defined by electrocardiographic and angiographic criteria; pathologic findings, replacement of ventricular myocardium with fatty and fibrous elements, preferentially involve the right ventricular free wall.	PD Imamura et al
TNF-beta	P01374	TNF-beta is also known as lymphotoxin A. It is a cytokine that in its homotrimeric form binds to TNFRSF1A/TNFR1, TNFRSF1B/TNFR and TNFRSF14/HVEM. In its heterotrimeric form with LTB binds to TNFRSF3/LTBR. Lymphotoxin is produced by lymphocytes and cytotoxic for a wide range of tumor cells in vitro and in vivo	
TPO	P40225	Thrombopoietin (TPO) is a lineage-specific cytokine affecting the proliferation and maturation of megakaryocytes from their committed progenitor cells. It acts at a late stage of megakaryocyte development. It may be the major physiological regulator of circulating platelets. Defects in THPO are a cause of essential thrombocythemia (ET). ET is inherited as an autosomal dominant trait which is characterized by elevated platelet levels due to sustained proliferation of megakaryocytes, and frequently lead to thrombotic and haemorrhagic complications.	
TRAIL R3	O14798	TRAIL R3 is known as Tumor necrosis factor receptor superfamily member 10C. It is a receptor for the cytotoxic ligand TRAIL that lacks a cytoplasmic death domain and hence is not capable of inducing apoptosis. It may protect cells against TRAIL mediated apoptosis by competing with TRAIL-R1 and R2 for binding to the ligand.	
VEGF	P15692	VEGF is important in the pathophysiology of neuronal and other tumors, probably functioning as a potent promoter of angiogenesis. It may be involved also in altering blood-brain-barrier functions under normal and pathological conditions. VEGF secreted from the stromal cells may be responsible for the endothelial cell proliferation in capillary hemangioblastomas which are composed of abundant microvasculature and primitive angiogenic elements represented by stromal cells.	AD MS Thirumangalakudi et al, Mateo et al Su et al

Appendix B – Listing of 16 Supplemental Markers Contained on the Neuro77 Biomarker Panel.

Marker Name	Swiss -Prot Accession Number	Description	Neurobiological Association	Reference
Apolipoprotein B	P04114	Apo B is a constituent of chylomicrons, LDL, and VLDL particles. It functions as a recognition signal for the cellular binding and internalization of LDL particles by apoB/E receptors. Mild defects at the gene level result in hypobetalipoproteinemia. Severe genetic defects result in hypercholesterolemia and an increased risk of coronary artery disease	AD	Caramelli et al, Namba et al
			VAD	Urakami et al
Apolipoprotein D	P05090	Agrp plays a role in weight homeostasis and may play a role in the regulation of melanocortin receptors within the hypothalamus and adrenal gland, and therefore in the central control of feeding.	AD	Kalmar et al, Beloir et al, and Thomas et al
Apolipoprotein E	P02649	Apo E mediates the binding, internalization, and catabolism of lipoprotein particles. It can serve as a ligand for the LDL (apo B/E) receptor and for the specific apo-E receptor (chylomicron remnant) of hepatic tissues. Three common APOE alleles have been identified: APOE 2, APOE 3, and APOE 4. The corresponding three major isoforms, E2, E3, and E4, are recognized according to their relative position after isoelectric focusing. Different mutations causing the same migration pattern after isoelectric focusing define different isoform subtypes. The most common isoform is E3 and is present in 40-90% of the population. Common APOE variants influence lipoprotein metabolism in healthy individuals. The APOE 4 allele is associated with late onset Alzheimer disease. The APOE 4 allele is genetically associated with the common late onset familial and sporadic forms of Alzheimer disease (AD). Risk for AD increased from 20% to 90% and mean age at onset decreased from 84 to 68 years with increasing number of APOE 4 alleles in 42 families with late onset AD. Thus APOE 4 gene dose is a major risk factor for late onset AD and, in these families, homozygosity for APOE 4 was virtually sufficient to cause AD by age 80. The mechanism by which APOE 4 participates in pathogenesis is not known.	AD	Thomas et al, Wada, Zhang et al
			PD	Zhang et al
Apolipoprotein J	P10909	Also known as clusterin, it is known to be expressed in a variety of tissues and it seems to be able to bind to cells, membranes and hydrophobic proteins. It has been associated with programmed cell death (apoptosis)	AD	McGeer et al (1992, 1994), Calero et al
CD5L	O43866		CJD	Freixes et al
			PD	Sasaki et al
			DLB	Sasaki et al
CgA	P10645	Chromogranin A may play a role in the regulation of the immune system. It seems to play a role as an inhibitor of apoptosis. Chromogranin A is a pancreastatin that strongly inhibits glucose induced insulin release from the pancreas.	AD	Lechner et al, Simonsen et al
			ALS	Obayashi et al

Supplemental Markers Contained on the Neuro77 Biomarker Panel, <i>continued</i>			
Marker Name	Swiss -Prot Accession Number	Description	Reference
Complement Factor H	P08603	Factor H functions as a cofactor in the inactivation of C3b by factor I and also increases the rate of dissociation of the C3bBb complex (C3 convertase) and the (C3b)NBB complex (C5 convertase) in the alternative complement pathway.	Hye et al, Zetterberg et al, Akuffo et al
Fetuin A	P02765	Fetuin A is also known as Alpha-2-HS-glycoprotein. It promotes endocytosis, possesses opsonic properties and influences the mineral phase of bone. It shows affinity for calcium and barium ions.	Geroldi et al
NGFb	P01138	Nerve growth factor is important for the development and maintenance of the sympathetic and sensory nervous systems. It stimulates division and differentiation of sympathetic and embryonic sensory neurons.	Al-Shawi et al
NrCAM	Q92823	Neuronal cell adhesion molecule (NrCAM) functions in cell adhesion. It is an ankyrin-binding protein involved in neuron-neuron adhesion and may play a role in the molecular assembly of the nodes of Ranvier.	Cuello et al, Schulte-Herbruggen et al, Marksteiner et al
Protein S	P07225	Also known as vitamin K-dependent protein S, it functions as an anticoagulant plasma protein; it is a cofactor to activated protein C in the degradation of coagulation factors Va and VIIIa. It helps to prevent coagulation and stimulating fibrinolysis.	
S100b	P04271	Weakly binds calcium but binds zinc very tightly-distinct binding sites with different affinities exist for both ions on each monomer. Physiological concentrations of potassium ion antagonize the binding of both divalent cations, especially affecting high-affinity calcium-binding sites. Binds to and initiates the activation of STK38 by releasing autoinhibitory intramolecular interactions within the kinase.	Edwards and Robinson, Gruden et al
SOD-1	P00441	Superoxide dismutase Destroys radicals which are normally produced within the cells and which are toxic to biological systems	Chen et al, Bayer et al
			ALS
			Mackenzie et al

Supplemental Markers Contained on the Neuro77 Biomarker Panel, continued			Neurobiological Association	Reference
Marker Name	Swiss -Prot Accession Number	Description		
Sortilin	Q99523	Sortilin functions as a sorting receptor in the Golgi compartment and as a clearance receptor on the cell surface. It is required for protein transport from the Golgi apparatus to the lysosomes by a pathway that is independent of the mannose-6-phosphate receptor (M6PR). Also, it is required for protein transport from the Golgi apparatus to the endosomes. It promotes neuronal apoptosis by mediating endocytosis of the proapoptotic precursor forms of BDNF (proBDNF) and NGFB (proNGFB). It also acts as a receptor for neurotensin. It may promote mineralization of the extracellular matrix during osteogenic differentiation by scavenging extracellular LPL. It is probably required in adipocytes for the formation of specialized storage vesicles containing the glucose transporter SLC2A4/GLUT4 (GLUT4 storage vesicles, or GSVs). These vesicles provide a stable pool of SLC2A4 and confer increased responsiveness to insulin. It may also mediate transport from the endoplasmic reticulum to the Golgi.	Neuro degeneration	Al-Shawi et al
sRAGE	Q15109	Soluble advanced glycosylation end product-specific receptor (sRAGE) mediates interactions of advanced glycosylation end products (AGE). These are nonenzymatically glycosylated proteins which accumulate in vascular tissue in aging and at an accelerated rate in diabetes. It serves as the receptor for amyloid beta peptide.	AD VAD	Emanuele et al Toth et al
Vitronectin	P04004	Vitronectin is a cell adhesion and spreading factor found in serum and tissues. Vitronectin interacts with glycosaminoglycans and proteoglycans. It is recognized by certain members of the integrin family and serves as a cell-to-substrate adhesion molecule. It functions as an inhibitor of the membrane-damaging effect of the terminal cytolytic complement pathway. Also known as Somatomedin-B, it is a growth hormone-dependent serum factor with protease-inhibiting activity.	AD	Akiyama et al, McGeer et al (1992, 1994)

Abbreviations: Alzheimer's disease (AD), vascular dementia (VAD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), dementia with Lewy bodies (DLB), Creutzfeldt-Jakobs disease (CJD).

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