Shifting the treatment paradigm: the promise of gene therapy for neurodegenerative diseases

The health challenge of neurodegenerative diseases

Conditions affecting the nervous system are prevalent in approximately 43.1% of the global population.[1] Stroke, neonatal encephalopathy, migraine, Alzheimer's disease and other dementias, diabetic neuropathy, meningitis, epilepsy, neurological complications due to preterm birth, autism spectrum disorder, and nervous system cancer contribute the highest disability adjusted life-years (DALYs).[1]

Most therapies for neurodegenerative diseases are focused on managing symptoms and slowing progression.[2] Neurodegeneration refers to the progressive damage or loss of neurons and/or their function.[3] Neurodegenerative diseases are a broad and heterogenous group, typically affecting the central nervous system (CNS) and can involve all bodily functions. Examples of these diseases include spinal muscular atrophy, Alzheimer's disease, Parkinson's disease, and Huntington's disease.[3, 4]

Finding effective and safe disease-modifying treatments for neurodegenerative diseases is critical to improving and extending the lives of patients. One such potential treatment option is gene therapy, which involves delivering DNA- or RNA-altering systems to cells to turn genes off, on, down, or up, or to correct a gene so that a defective protein can become functional (Figure 1 and Table 1).
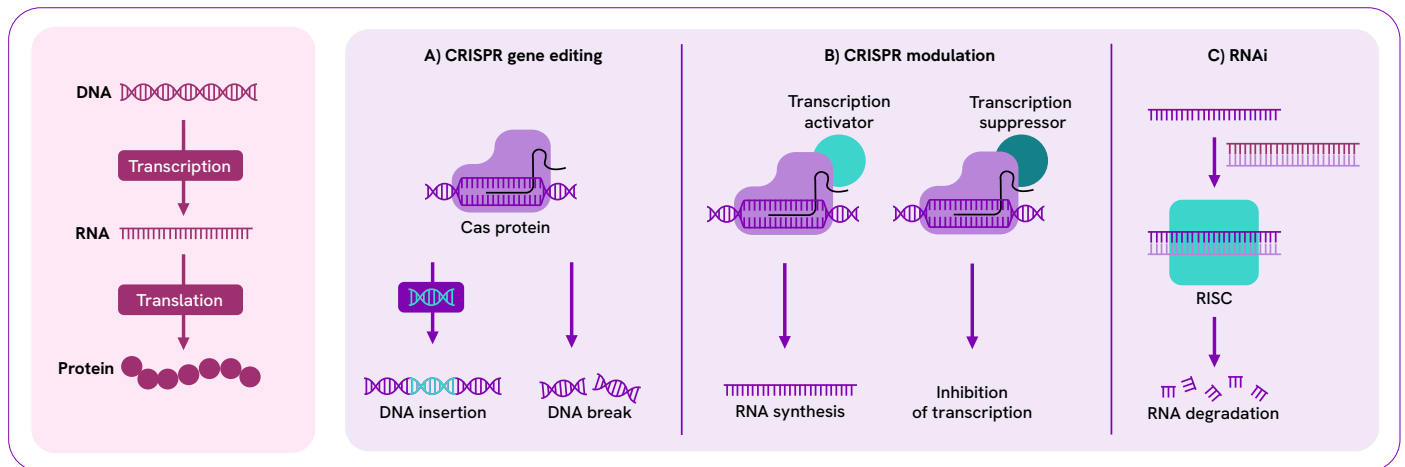

Figure 1. Overview of protein synthesis (left) and potential gene modulation and modification approaches that could be used in gene therapy (right), including: A) CRISPR (clustered regularly interspaced short palindromic repeats) gene editing, such as inserting DNA at target site; B) CRISPR modulation, where transcription activators and suppressors can activare or suppress transcription of target site; and C) RNA inteference (RNAi), such as siRNA (small intefering RNA).

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Table 1: Summary of gene and RNA editing and modulation approaches.[5]

	CRISPR Editing	CRISPR Modulation	RNAi
Level of operation	Transcription	Transcription	Translation
Down regulation	CRISPRko	CRISPRi	siRNA, shRNA, miRNA
Up regulation	Gene insertion via HDR knock-in	CRISPRa	cDNA/ORF
Benefits	Specific and efficient programmable gene editing	CRISPR-level specificity without cutting DNA	Simplest knockdown/ overexpression workflows
Ideal applications	Cell line engineering; making permanent changes to the genome	Exploring essential gene knockdown, endogenous gene activation	Transient knockdown assays (siRNA), inducible knockdown for essential genes (shRNA), rescue experiments (cDNA/ORF)

Here we review the currently approved gene therapies specifically for neurodegenerative diseases, comparing their mechanism of action, delivery modality and editing system being used, and provide our insights into the future of gene therapies in treating neurodegenerative diseases.

Approved gene therapies for neurodegenerative disease

As of mid-2024, there are four approved gene therapies for neurodegenerative disease: three for spinal muscular atrophy (SMA) and one for amyotrophic lateral sclerosis (ALS).

Spinal muscular atrophy (SMA)

Pathology

SMA is caused by a lack of sufficient SMA protein – a neuroprotectant – which leads to degeneration of alpha motor neurons in the spinal cord, resulting in progressive muscle atrophy.[6] The incidence rate is approximately 10 per 100,000 live births.[7] SMA is caused by a reduction in the survival motor neuron (SMN) protein due to loss of the SMN1 gene. SMA often presents in newborns as muscle weakness and, besides gene therapies, treatment consists of physical therapy, occupational therapy, speech therapy, and eventually feeding tubes and ventilation.[8] SMA is usually diagnosed by the detection of mutations or deletions in the SMN1 gene from a blood sample. Revvity offers SMA diagnosis by qPCR on its Eonis Q system (from a dried blood spot card)[9] and through its Revvity Omics global newborn screening service labs.

Genetic cause

SMA is caused by homozygous deletion or mutation of the SMN1 gene, which encodes the SMN protein.[6,20] The incidence of carriers of autosomal recessive mutations is 1 in 40 to 1 in 60.[10]

Gene therapy approach

A naturally occurring backup gene, SMN2, can also generate functional SMN protein but can only compensate for approximately 10% of the functionality of the SMN1-encoded SMN protein. This reduced function is due to alternate splicing – which largely excludes exon 7 from the RNA transcript – creating a truncated protein.[11] SMA disease severity is linked to the number of copies of the SMN2 gene—where patients with higher copy numbers tend to have later disease onset and milder symptoms. Gene therapies have been designed to reintroduce a functional SMN1 gene or create full length proteins from the SMN2 gene.

Approved SMA molecular therapies and their mechanisms of action

To date, three genetic therapies for SMA have been approved by the U.S. Food and Drug Administration (FDA):[11-13] Spinraza® and Evrysdi®. Both therapies interfere with splicing of mRNA derived from the SMN2 gene, allowing the creation of full length SMN protein. Zolgensma is a gene therapy that introduces a fully functional new copy of the SMN1 gene.

1. Nusinersen (Spinraza)[14, 15] — a modified antisense oligonucleotide (ASO) that interferes with exon 7 excision during SMN2 mRNA splicing and allows the full length SMN protein to be produced from the SMN2 gene. It binds to pre-mRNA downstream of exon 7 in an intronic silencing sequence that regulates splicing and inhibits binding of hnRNP, preventing the removal of exon 7 from

the mature mRNA. Spinraza is directly delivered into the CNS through intrathecal administration since it is not able to cross the blood–brain barrier. It is used to treat symptomatic children and adults and is administered initially as four consecutive doses, then three times per year.

2. Risdiplam (Evrysdi)[16] — an SMN2 splicing modifier that promotes exon 7 inclusion during SMN2 splicing to create a full length SMN protein in motor neurons. The exact mechanism of action is unknown, but it is possible that Spinraza and Evrysdi might work in a complementary way. It is used to treat symptomatic children and adults and requires daily oral administration.

3. AVXS-101 or onasemnogene abeparvovec (Zolgensma®)[17] — an AAV9-based therapeutic that delivers functional SMN1 to neurons. Zolgensma is delivered intravenously, crossing the blood–brain barrier to access the motor neurons. The AAV transports self-complementary DNA encoding a functional copy of the SMN1 gene under the control of a continuous promoter to motor neurons. Once delivered to the nucleus, the scDNA (self-complementary single-stranded DNA) forms a circular episome, enabling the constitutive expression of the new SMN1 gene and an accumulation of SMA protein in these cells, thus preserving motor neuron function. The AAV is non-replicating and the neurons are non-dividing. It is used to treat presymptomatic children less than two years of age and is administered as 1.1e14vg per kg body weight. Presymptomatic children treated with SMA achieved age-appropriate motor milestones, including sitting, standing, and walking; did not need ventilatory or nutritional support; and had no serious treatment-related adverse events.[18, 19]

Amyotrophic lateral sclerosis (ALS)

Pathology

ALS, also known as Lou Gehrig's disease, is a severe neurodegenerative disease that affects motor neurons in the brain and spinal cord, leading to the death of these cells and, eventually, paralysis.[20, 21] The cause of ALS remains unknown, but it is the most prevalent neurodegenerative disease, with an incidence ranging from 0.26 per 100,000 person years up to 23.46 per 100,000 person years.[22] While 90% of cases are sporadic with no known genetic cause or familial history, a small proportion cases are linked to genetics.[23] The disease usually presents in people aged 40–70 years and is diagnosed by the onset of a range of

nerve symptoms, including twitching, cramping, and loss of motor control.[24] Current therapies outside of gene therapy include physical, occupational, speech, respiratory, and nutritional therapies to manage symptoms.[24] The rate of progress of the disease varies between individuals, ranging from months to years.[24]

Genetic cause

Mutations in more than 40 different genes have been linked to ALS.[25] The first gene identified in this list was SOD1, which encodes superoxide dismutase 1 protein. The functional SOD1 protein attaches to copper and zinc molecules to break down toxic byproducts of normal cellular function.[25] A large number of mutations within the SOD1 gene cause the protein to misfold and clump, effectively reducing its function.[21, 25-28]

Approved ALS gene therapy and its mechanism of action

In 2023, Qalsody® (tofersen) received accelerated FDA approval for the treatment of ALS caused by mutations in the SOD1 gene. Tofersen is an ASO that causes SOD1 mRNA degradation through RNase H.[21] Whilst there was no statistically significant decrease in disease progression compared to placebo, the therapy has been approved based on an observed reduction in CSF SOD1 protein and plasma neurofilament light chain (NfL).[29-31] NfL is released from nerve cells when they are damaged or destroyed, so a reduction in NfL suggests less nerve damage is occurring.[29]

Future gene therapy strategies for neurodegenerative diseases

There is rapid progress in the field of gene therapy. Newer DNA and RNA editing methods, novel multi-target therapeutic approaches, and more specific delivery systems will enable the development of a range of neurodegenerative disease gene therapies.

Advances in gene editing systems

DNA and RNA editing technologies are rapidly advancing. Whilst the early neurodegenerative disease gene therapies act by altering gene transcription or introducing exogenous copies of functional genes, the more recent methods are focused on correcting disease-causing mutations at the DNA or RNA level. These methods include CRISPR-Cas9 and the newer approaches of base editing and prime editing. A technical description of these methods and the differences

| Table 2: Summary of FDA approved gene therapies for neurodegenerative diseases |

Drug	FDA Approval Date	Manufacturer	Delivery Method	Editing System	Mechanism of Action
Nusinersen	December, 2016	Biogen	Intrathecal (local)	ASO	Stops exon 7 excision from SMN2 to create full length SMN protein. Exact mechanism unclear
Evrysdi	August, 2020	Genentech	Oral	Small molecule	Promotes SMN2 exon 7 inclusion to create full length SMN protein
Zolgensma	May, 2019	Novartis	IV-administered neuron-targeting AAV9	Gene insertion	Introduces a new copy of the SMN1 gene
Tofersen	April, 2023	Biogen	Intrathecal (local)	ASO	Promotes mRNA degradation encoding the SOD1 protein

between them is available in a separate Revvity application note.

New delivery methods for neurodegenerative disease gene therapy

In addition to newer gene editing systems, a variety of viral and nonviral strategies are being used for delivering gene therapy cargo to the CNS. Viral vectors, such as AAVs, offer a promising strategy for delivering genes into the CNS, a target area that can be particularly difficult for therapeutics to efficiently reach due to the blood–brain barrier.[12] Several viral vectors – including AAV9, AAV4, and AAV5ch – have been found capable of crossing the blood–brain barrier, making them suitable systems to be administered intravenously for neurodegenerative disease. While there are other viral capsids available, AAVs are the most common viral vectors being used in neurodegenerative disease therapeutics due to their low immunogenicity and inability to integrate, cause disease, or replicate by themselves.[31, 32]

Next generation AAVs are offering an improved ability to target the CNS when delivered intravenously.[33, 34] For example, AAV vectors with a VHH domain insertion in the capsid have demonstrated high delivery precision and efficiency.[35, 36] These vectors are promising tools for direct cerebrospinal fluid (CSF) administration routes, such as intraparenchymal, intracerebroventricular, and intrathecal administration.[3] The choice of delivery route can depend on several factors, such as the gene therapy cargo/vector and disease or region of interest. Intravenous delivery can also face other challenges, such as the presence of anti-AAV antibodies that can neutralise AAV-based gene therapeutics.[33]

While non-viral vectors, such as lipid nanoparticles, can offer advantages – such as the ability to re-administer

treatment due to their low immunogenicity – these methods typically require high therapeutic doses to work effectively. This comes with liver toxicity risks and can require repeated administration due to having only transient effects.[32] Consequently, viral vectors are currently more commonly used in gene therapy.[12]

Indicators of disease progression and measuring the efficacy of gene therapy in neurodegenerative diseases

With neurodegenerative diseases encompassing a heterogenous group of disorders, a broad range of physiological and biochemical indicators could be monitored to determine the efficacy of a new therapy – which can also act as targets for therapies (Figure 4) – such as:[33]

- Endoplasmic reticulum (ER) — many neurodegenerative diseases involve misfolded protein aggregates that can cause ER stress and disrupt systems that manage proteostasis (such as unfolded protein response signaling). For example, tau accumulation has been found to impair ER-associated protein degradation and activate unfolded protein response signalling.[37] Targeting systems that alleviate ER stress and restore proteostasis may help treat neurodegenerative diseases.[33]

- Mitochondria — multiple neurodegenerative diseases are associated with mitochondrial dysfunction. As healthy mitochondrial functioning is needed for neuron function and survival, mitochondrial defects can lead to disease.[38] For example, mitochondrial complex I can be impaired in Parkinson's disease, which can lead to high levels of reactive oxygen species during respiration.[39]

- Autophagy — as mentioned above, many neurodegenerative diseases exhibit aggregates of misfolded proteins. As autophagy clears misfolded

proteins, impaired autophagy can disrupt protein homeostasis and lead to disease. For example, suppressed transcripts of Beclin1 – a protein needed for autophagosome generation – have been reported in Alzheimer's disease.[40]

- Epigenetic regulation — epigenetic regulatory mechanisms, such as histone acetylation, are critical to neuron function and survival. Impaired epigenetic regulatory mechanisms can therefore lead to neurodegenerative disease. For example, CREB-binding protein (histone acetyltransferase) has been found to mislocalize to polyglutamine aggregates in Huntington's disease.[41]

- Mammalian target of rapamycin (mTOR) signaling — mTOR signaling is involved with a variety of cellular processes, such as cell survival and metabolism. Impaired mTOR signaling can consequently lead to neurodegenerative disease.[42] For example, upregulation of mTOR signaling has been linked to elevated hyperphosphorylation of Tau proteins.[43]

- Microglia — microglia are macrophages found in the CNS where they perform a number of roles, such as repairing CNS injuries and clearing misfolded proteins. Microglial activation has been linked to a number of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and multiple system atrophy.[44]
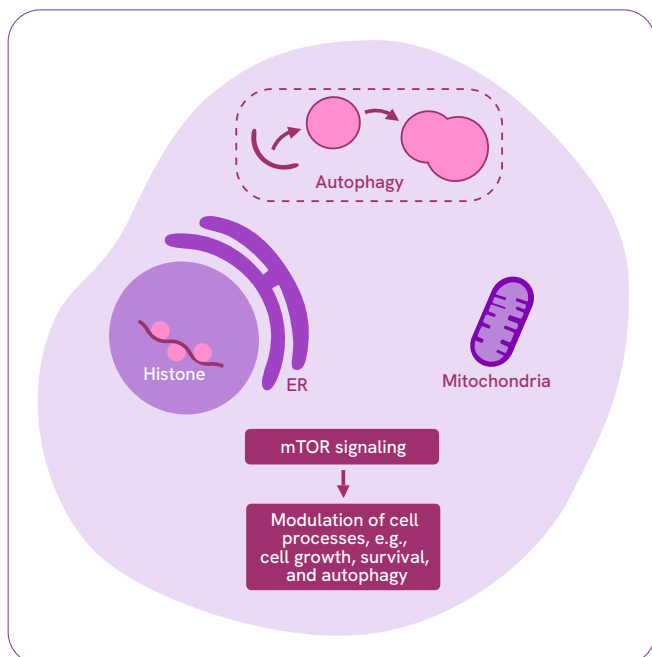

Figure 2. Overview of example or potential gene therapy cellular targets for neurodegenerative diseases.

How Revvity is enabling neurodegenerative disease research and the development of gene therapies

Revvity provides a range of solutions to drive the development of gene therapy products for neurodegenerative diseases.

AAV capsid analysis

AAV capsid analysis detection and analysis in immunoassay and capillary electrophoresis formats (Table 3; Figures 3–4) that can quantify viral titre, characterize capsid composition, and determine empty/full ratios.

Table 3: AAV titer immunoassays.

Capsid Detection Kit	AlphaLISA™ 500 Assay Points*	HTRF™
AAV1	AL3181C	64AAV1PEG
AAV2	AL3177C	64AAV2PEG
AAV3B	AL3187C	64AAV3PEG
AAV5	AL3183C	64AAV5PEG
AAV6	AL3186C	64AAV6PEG
AAV8	AL3180C	64AAV8PEG
AAV9	AL3182C	64AAV9PEG

*also available in other pack sizes.

Microfluidic characterization of viral DNA and protein

The LabChip™ GX II Touch System (CLS138160) offers an array of assay kits that enable the characterization of viral genome and VP1, 2, and 3 capsid proteins. The electrophoretic separation allows for the sizing, purity assessment, and quantification for both the viral DNA and protein using a DNA chip (CLS157607) and a protein chip (CLS- 157612), respectively. See Table 4 for additional products.

Target protein quantification

Many proteins are part of the cellular processes that shape neurodegenerative disease, such as mutant huntingtin in Huntington's disease and ataxin-2 in ALS. Revvity offers a variety of HTRF and Alpha detection assays to quantify target proteins in neurodegenerative disease research samples (Table 5).
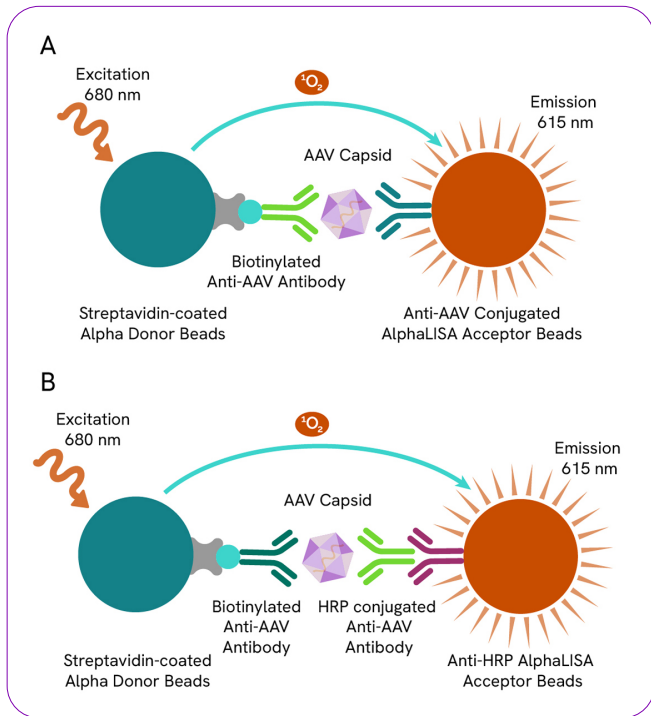
Figure 3. A) canonical AlphaLISA AAV capsid detection kit bead chemistry. B) AlphaLISA AAV1 and AAV6 capsid detection kit bead chemistry.
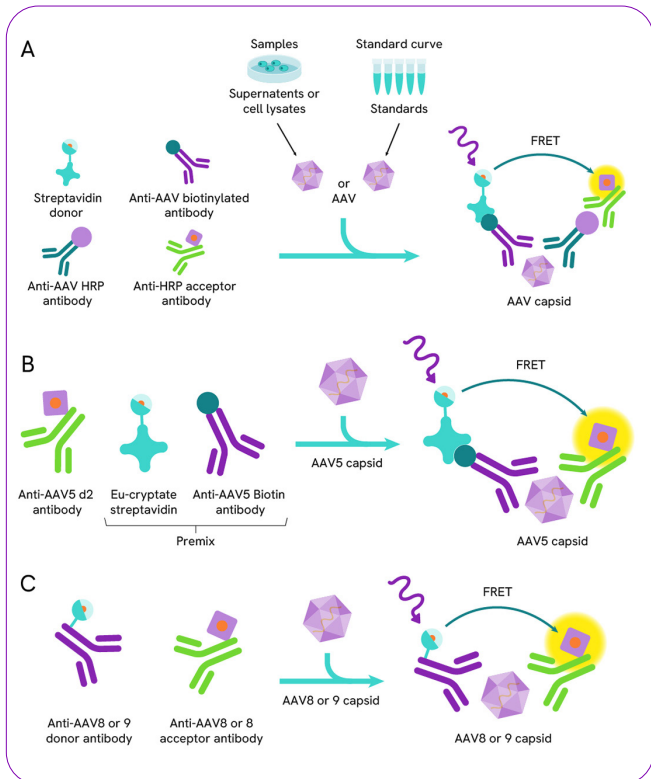

Figure 4. Detection of the AAV capsid using HTRF AAV capsid detection kits: A) assay scheme for HTRF AAV1, AAV2, AAV3B, and AAV6 capsid detection kits; B) assay scheme for HTRF AAV5 capsid detection kit; and C) assay scheme for HTRF AAV8 and AAV9 capsid detection kits.

Table 4: LabChip AAV products.

LabChip AAV Product	Application	Product Number
LabChip AAV DN DNA Analysis Kit	ssDNA analysis	CLS159488
LabChip AAV Pico Protein Analysis kit	AAV protein analysis	CLS159517
LabChip AAV8 standard	Standard for use with LabChip AAV Empty/Full Assays.	CLS157467

Host cell protein contaminant detection

Contaminants in samples can impact laboratory research and cause adverse events when found in therapeutics, including triggering immunogenicity. Revvity offers a host cell protein contamination kit that can detect and quantify contaminants stemming from vector production (Table 6).

Creation of the next generation of gene therapies

Revvity also outlicenses proprietary gene editing and delivery technologies for therapeutic use.

Revvity's Pin-point™ base editing platform

Revvity offers proprietary base editing research-grade reagents, cell line engineering services, and tiled screening services to accelerate gene therapy discovery. Base editing offers precise and efficient DNA editing at the single base resolution.

The Pin-point base editing platform is also licensable for use in therapeutic development. The Pin-point base editing platform has demonstrated an improved safety profile over traditional CRISPR-Cas9 editing because the technology avoids introducing double-stranded DNA breaks, which can lead to cytotoxicity and genomic aberrations. The platform is modular in design, meaning that it can be configured and optimized with a variety of nuclease and deaminase components to specifically and effectively edit genes for a variety of applications. This modularity also allows the use of ultra-compact nucleases, to enable single AAV *in vivo* delivery of a base editing system.

Pin-point™ base editing reagents are available for research use only and are not for diagnostic use or direct administration into humans or animals. The Pin-point™ base editing platform technology is available for clinical or

| Table 5: Target protein quantification products.

Protein	AlphaLISA™ 500 Assay Points*	HTRF™	Gene Therapy Applications
HTT Mutant		64HTTMPEG	Huntington's disease
HTT, Total		64HTTTPEG	Huntington's disease
Ataxin 2 Mutant	AL3197C	64ATA2MPEG	spinocerebellar ataxia type 2 and ALS
Ataxin 2, Total	AL3193C	64ATA2PEG	spinocerebellar ataxia type 2 and ALS
mTOR, Phospho	ALSU-PMTOR-C500	64TORPEG	Autophagy
p62/STSQM1, Phospho-Ser351/403	ALSU-PSQSTM-A500	64P62S4PEG	Autophagy
ULK1, Phospho	ALSU-PULK1-A500	64ULKPEG	Autophagy
AMPK, Phospho-Thr172	ALSU-PAMPK-A500	64MPKPET	Autophagy
LC3B & LC3B-II	AL306C	64LC3B2PEG	Autophagy
ATG16L1, Phospho-Ser278	ALSU-PATG-A500	64ATG16S8PEG	Autophagy
ATG16L1, Total	ALSU-TATG-A500	64ATG16TPEG	Autophagy
ATG14, Phospho-Ser29		64ATG14S9PEG	Autophagy
ATG14, Total		64ATG14TPEG	Autophagy
Ubiquitin, Phospho-Ser65	ALSU-PUBI-A500	64UBIS65PEG	Mitophagy
Parkin, Phospho-Ser65	ALSU-PPARK-A500		Mitophagy
Parkin, Total	ALSU-TPARK-A500		Mitophagy
PINK1, Total	ALSU-TPINK-A500	64PINKTPEG	Mitophagy
TREM2, Total	ALSU-TTREM2-A500	64ADK099PEG	Neuroinflammation
TREM2 Aggregate	ALSU-ATREM2-A500		Neuroinflammation
TREM2/DAP12 complex	ALSU-TTRMDP-A500		Neuroinflammation
SYK, Phospho-Tyr525/526	ALSU-PSYK-A500	64SYKY525PEG	Neuroinflammation
SYK, Total	ALSU-TSYK-A500	64SYKTPEG	Neuroinflammation
p62/SQSTM1, Phospho-Ser403	ALSU-PSQSTM-A500	64P62S4PEG	Autophagy
p62/SQSTM1, Total	ALSU-TSQSTM-A500	64N62PEG	Autophagy

*also available in other pack sizes.

I Table 6: Host cell protein kits

Host Cell Protein Kits	AlphaLISA™ 500 Assay Points*
HEK293 host cell protein detection	AL3198C

*also available in other pack sizes.

diagnostic study and commercialization under a commercial license from Revvity with further development from the licensee.

Revvity's AAV evolution and VHH-AAV platform

Revvity developed a range of evolved AAV vectors for clinical use to treat retinal disorders and pursues rapid evolution of AAV by biopanning and monitoring biodistribution of AAV vectors each expressing a barcode *in vivo*. The newest generation of direct targeted AAV vectors displays a VHH domain on the vector and enables highly specific and efficient gene delivery.

Conclusions

Devastating neurodegenerative diseases encompass a broad range of heterogeneous conditions, often without traditional therapies. Gene therapy is emerging as a potential treatment strategy, as highlighted by the approval of several therapies for SMA and ALS, with many more disease-modifying treatment options in the clinic. Advances in gene editing and delivery systems will increase their specificity and efficacy. Revvity is committed to providing the technologies needed to rapidly advance this new treatment modality and support the creation of novel therapies for these devastating diseases.

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