CNS Klotho™ NEUROSCIENCES

Novel Cell and Gene Therapies Targeting Neurodegenerative Diseases and Aging

Dr. Joseph Sinkule
CEO and Chairman

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Corporate Profile

Klotho is focused on the development of innovative, disease-modifying gene therapies using our patented secreted form of the anti-aging Klotho gene (**s-KL**) to transform the treatment of neurodegenerative and age-related disorders, such as ALS, Alzheimer's, and Parkinson's disease.

- Anew Medical, Inc., the predecessor company founded by Dr. Joseph Sinkule, licensed platform technologies to commercialize several early-stage and late-stage assets.
- Corporate Headquarters: Omaha, NE
- NASDAQ: KLTO
- Website: https://www.klothoneuro.com
- Sector: Healthcare – Pharmaceutical and Biotechnology

Our Mission:

*"To pioneer the development of innovative, disease-modifying cell and gene therapies using a patented secreted form of the anti-aging Klotho gene (**s-KL**) to transform the treatment of neurodegenerative and age-related disorders such as ALS, Alzheimer's, and Parkinson's disease."*

Our Vision:

"To lead the advancement of gene therapy in the fight against neurodegenerative and age-related diseases, bringing hope and improved quality of life to patients by unlocking the potential of the Klotho gene."

Recent News

Dr. Robert Langer, Co-Founder of Moderna, Joins Scientific Advisory Board of Klotho Neurosciences, Inc. (KLTO)

Renowned Biotech Leader to Contribute Expertise in Neuroscience and Therapeutics Development

NEW YORK, Sept. 30, 2024 (GLOBE NEWSWIR
developing innovative therapies for neuro
co-founder of Moderna, has joined its Scie
strategic direction, this also signals Dr. Lar

ANEW MEDICAL, Inc. Announces Name Change to Klotho Neurosciences, Inc.

Strategic Rebranding Reflects Focus on Neurodegenerative Therapies and Healthy Longevity

NEW YORK, Sept. 17, 2024 (GLOBE NEWSWIRE) -- The Board of ANEW MEDICAL, INC. (NASDAQ: WENA), today announced a name and ticker symbol change to Klotho Neurosciences, Inc. (NASDAQ: KLTO), and has launched a new website, www.klothoneuro.com . The name and ticker change will have no
there is no action required on their part.

ANEW MEDICAL, INC. Strengthens Intellectual Property Protection with U.S. Patent Issuance for Its Secreted RNA Splice Variant of the Human Klotho Gene Used for the Treatment of Neurodegenerative and Age-Related Diseases

Issuance of the Klotho gene-therapy patent will be instrumental in protecting ANEW's IP for dev commercialization in the U.S.

NEW YORK, Aug. 15, 2024 (GLOBE NEWSWIRE) -- ANEW MEDICAL, INC. ("ANEW" or "the Company") (NASDAQ: WENA) a U.S. -based bio focused on developing cell and gene-based treatments for aging, and age-related diseases, today announced the grant and i No. 12,036,268 ("the 268 patent") covering the secreted RNA splice variant of the human Klotho gene, referred to as "s-KL", for the t and neurodegenerative diseases.

ANEW MEDICAL, INC. Appoints New CFO

NEW YORK, Aug. 19, 2024 (GLOBE NEWSWIRE) -- ANEW MEDICAL, INC. ("ANEW" or "the Company") (NASDAQ: WENA) a U.S.-based biotechnology company focused on developing cell and gene-based treatments for aging, and age-related diseases, today announced the appointment of Jeffrey LeBlanc as the company's Chief Financial Officer (CFO), replacing the interim CFO, Edward Cong Wang who was the former CFO of Redwoods Acquisition Corp into which ANEW merged.

ANEW MEDICAL Forms Strategic Partnership with Japan's Okinawa Research Center for Longevity Science (ORCLS) to Study Klotho Gene

Collaboration focuses on research and development of ANEW's patented Klotho gene therapy in enhancing longevity and reducing age-related diseases

ANEW's mission is to deliver transformative protein, cell, and gene therapies in areas of high unmet medical needs, particularly targeting highly prevalent neurodegenerative diseases and age-related disorders

NEW YORK, June 27, 2024 (GLOBE NEWSWIRE) -- ANEW MEDICAL, INC. (Nasdaq: WENA), a biopharmaceutical company specializing in the advancement of novel disease-modifying therapies for neurological and age-related disorders and specialty diagnostics, announces a strategic partnership with Drs. Makoto Suzuki, Craig and Bradley Willcox, Richard Allsopp, and Michio Shimabukuro of Japan's Okinawa Research Center for Longevity Science

ANEW MEDICAL, INC. Achieves Debt-Free Status, Boosts Financial Flexibility

Successful Conversion Eliminates Over $4 Million in Long-Term Debt

NEW YORK, Aug. 26, 2024 (GLOBE NEWSWIRE) -- ANEW MEDICAL, INC. (NASDAQ: WENA), a leading U.S. biotechnology company pioneering cell and gene-based treatments for aging and age-related diseases, announces the successful conversion of its convertible promissory notes by investors. This strategic move significantly strengthens ANEW's balance sheet by eliminating over $4 million in long-term debt.

Leadership

Dr. Joseph Sinkule
CEO & Chairman

- 40+ Years of drug, biologic, and medical device experience
- Serial Biotech Founder & CEO
- Immunex / Quintiles
- FDA Approvals: 8 Biologicals, 5 Med Device, and 8 in vitro Diagnostics
- University of Nebraska Medical Center

Peter Moriarty
Chief Operating Officer

- Co-founder of Shire Pharmaceuticals and other healthcare companies
- Extensive Senior Management and Board experience
- Various leadership positions ex-US in global pharmaceutical company

Dr. Brad Navia
Chief Medical Advisor

- Clinical Dev and Regulatory Affairs;
- FDA and EMA approvals for KYNMOBI
- Internal Medicine and Neurology;
- Associate Professor Tufts Medical School;
- Professorships at Boston U and Brown;
- M.D. from Columbia University College
- Ph.D. in Neuroscience / Genetics from Harvard University,

Jeffrey LeBlanc
Chief Financial Officer

- 20+ years finance/entrepreneurship
- Co-founder, Winvest Acquisition Corp
- Co-founder, Out of Print (acquired)
- Co-founder, Litsy (acquired)
- Investment Analyst, Greenlight Capital
- Associate, GE Capital
- BS in Chem Eng, MIT
- MBA Harvard Business School

Eric Boyd
Chief IR/PR Officer

- Institutional and corporate finance
- Experience in IPO financing
- Founder - Financial Consulting
- Successfully raised capital for major companies
- Known for versatility, adaptability, and entrepreneurial spirit

Jim Self
Corporate Development

- 30+ years Pharma Bus Dev
- Founder ProBioPharm
- Global Bus Dev Leader @ Merck
- Various Mfg, BD and Operational roles
- MBA Wharton, University of Penn
- BS Engineering, NCSU

Dr. Miguel Chillon
Chief Scientific Advisor

- Head of Gene Therapy in Neurodegenerative Diseases Laboratory, Universitat Autònoma de Barcelona
- 11 patents generated in viral vectors for gene therapy, 80 scientific papers published in peer-review international journals.

Dr. Assumpcio Bosch
Chief Scientific Advisor

- Gene Therapy
- Full Professor, Department of Biochemistry and Molecular Biology at Universitat Autònoma de Barcelona
- Post Doc – Pasteur Institute
- Post Doc – University of Iowa

Board of Directors

Dr. Joseph Sinkule
Founder, CEO, Chairman

Dr. Sinkule is the company's Chief Executive Officer (CEO), Founder, and the Chairman of the Board of Directors. He has over 40 years of drug, biologic, and medical device R&D and commercialization experience. This serial entrepreneur is the founder and driving force behind the Company, its growing product portfolio, and its financing strategies. He has personally managed over 8 drug and biotech products successfully through FDA approval to market, 5 medical devices and 8 in vitro diagnostics. He has hired and managed both small and large teams of experienced people in pharma and biotech organizations, and managed contract research organizations ("CROs") and contract development and manufacturing companies ("CDMOs"), working for large and small clients. After serving in academics and then in industry, Dr. Sinkule has evolved into a successful businessman and entrepreneur. He serves on the Board of two companies, and routinely consults for venture capitalist firms, investment banks, as well as both large and early-stage pharmaceutical and biotech companies.

Dr. Shalom Hirshman
Medical Advisor & Director

Dr. Shalom Hirschman, M.D. is a preeminent research physician, a clinical medical expert, and entrepreneur in infectious diseases, oncology, and cancer supportive care. He is a key consulting advisor to the Company. As a young man, he served as an intern and resident in medicine at the Massachusetts General Hospital and Harvard Medical School, and then went on to a career in molecular biology and virology research at the National Institute of Health (NIH). During his career in medical research, he interacted closely with several Nobel Prize winners including Drs. Berson and Yalow (Nobel Prize for development of radioimmunoassays). He was recruited to The Mount Sinai School of Medicine and The Mount Sinai Hospital in New York City as Head of the Department of Infectious Diseases, and eventually he also became Vice-Chairman and Chairman of the Department of Medicine at Mount Sinai, where he remained for three decades. He still is asked to consult on difficult diagnostic dilemmas like the recent COVID-19 pandemic.

Dr. Samuel Zentman
Independent Director

Dr. Zentman graduated from Wayne State University and the University of Michigan and holds a Ph.D. doctorate in Complex Analysis. He was a Mathematics professor at several divisions of the University of Detroit. And worked as a systems analyst, manager of Engineering Computer Center, and director of the Corporate Computer Center of American Motors Corporation. Dr. Zentman was the CFO and then CEO of Manhattan Textile Corporation, a privately held export firm in New York city. He was a Board member of several Tech and Medical start-ups including: Neuromedical Systems Inc., Amplification Technologies, Inc., Power Safe Technology Corp, and Hinson Hale Medical Technologies Inc. Sam is currently a Board member of Acorn Energy where he has serv3ed for over the past 15 years, and is the Chairman of the Audit Committee, and member of the Nominating Committee and Compensation Committee. Sam has extensive experience in dealing with early stage medical and technology companies. He also serves as the Chairman of the Board of several national non-profits organizations devoted to the quality of education in the U.S. and abroad.

Mr. Jon McGarity
Independent Director

Mr. McGarity is the President & CEO of EthiX Associates, which he founded in February 1996 and is a consultancy business serving the business needs of the healthcare industry with a focus on pharmaceuticals and biotechnology. In addition, he has been the Chief Operating Officer of MiClimate, Inc. since 2022 which has developed the first body temperature regulation device resulting in a change in the way people manage individual temperature sensitivities. He co- founded NeuroEM Therapeutics, Inc., which is currently evaluating transcranial electromagnetic therapy (TEMT) for the treatment of cognitive functioning in Alzheimer's disease patients, and served as the founding CEO & Board Chairman and most recently as its Chief Business Officer until 2023. In addition he currently is an Advisor to the Biodesign Institute at Arizona State University. He is an original and current member of the Arizona Biosciences Roadmap Committee which provides strategic direction to the biosciences industry in Arizona. His pharmaceutical experience includes senior management positions with GlaxoSmithKline, Bristol Myers Squibb and Novartis (Sandoz Pharmaceuticals). Mr. McGarity has launched over 40 products as well as completing numerous business development deals involving product acquisitions, licensing, co-marketing and promotional arrangements.

Technology Platform

Klotho – “The Anti-Aging Gene”

Klotho℠ NEUROSCIENCES

Advancing α-Klotho-based Therapies

Klotho Neuroscience's focus is to bring to market groundbreaking α-Klotho gene and cellular therapies, utilizing novel methods of gene and protein delivery for aging-related diseases and neurologic disorders.

- The α-Klotho (Klotho) gene was discovered in 1997 by Dr. Kuro-O at University of Texas-Southwestern who identified its unique mechanisms of action in the brain, CNS, and peripheral nervous system.
- Increased Klotho levels are associated with heathy aging and longevity while reduced levels are associated with age-related disorders including those involving the brain.
- Eliminating Klotho in gene knock-out mice results in remarkably reduced life-span and premature muscular, vascular, and CNS aging, including memory deficits, alterations in axonal transport, reduced brain synapses in the hippocampus, hippocampal degeneration, neuroinflammation, and problems in myelin production.
- Overexpression of the α-Klotho gene product is associated with neuroprotection against oxidative stress, decreased neuroinflammation, increased synaptic plasticity, increased myelination, increased axonal transport, neurogenesis and associated improvements in cognition, memory and motor neuron function.
- Secreted Klotho isoform(s-KL) is almost exclusively produced in the brain; expression levels correlate with brain health and healthy aging.
- Klotho Neurosciences is focused on **s-KL** - develop and commercialize gene and protein diagnostics and therapies for amyotrophic lateral sclerosis (ALS), Alzheimer's, Parkinson's and other neurodegenerative diseases.

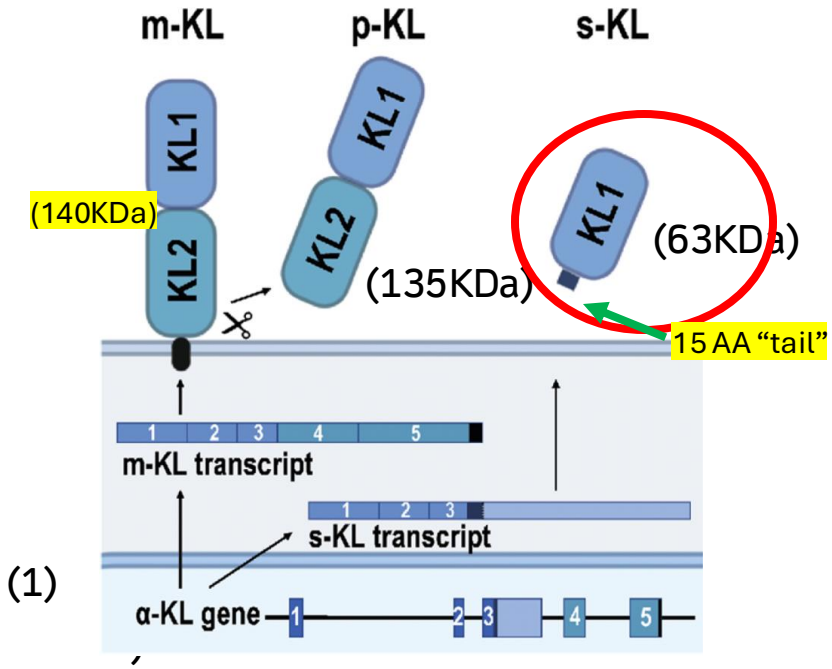
The Unique Secreted Klotho Isoform (s-KL)

The 5 exon Klotho (KL) gene on human chromosome 13 produces 2 different Klotho protein transcripts:

1. A transmembrane Klotho (m-KL), which may be metabolized further to a dimer termed processed Klotho (p-KL) … and
2. A secreted-KL (s-KL), which is produced directly as a RNA splice variant isoform and is the predominant biologically active form in the CNS..
   The s-KL (63 KDa) is our proprietary form of the gene and protein, with minor changes (C-terminal amino acid tail) to the natural-occurring hormone.

Transmembrane m-KL isoform

- Obligatory coreceptor of factor FGF-23.
- Binds FGF-23 and regulates the concentration of phosphate in plasma
- Produces the active form of vitamin D (prominent role in calcium metabolism).
- Overexpression causes hypocalcemia and hypophosphatemia.



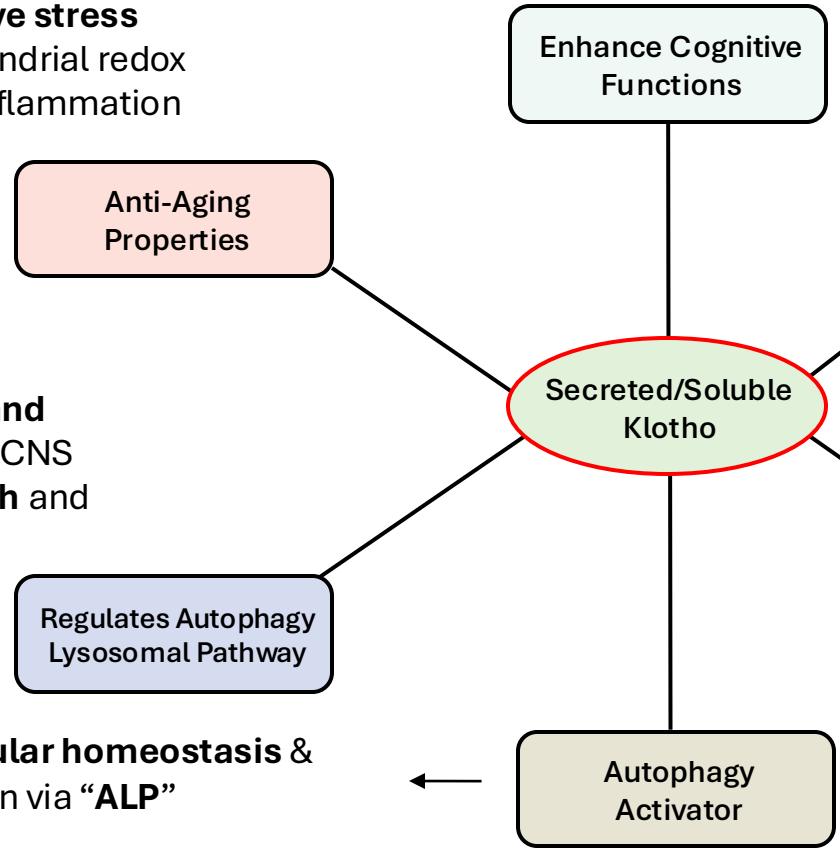
Isoforms in plasma (p-KL and s-KL)

- Regulation of nitric oxide production and protection against endothelial dysfunction (antioxidant).
- Regulation of calcium channels.
- Inhibition of insulin and IGF-1 mediated signaling (diabetes & obesity)
- Suppression of oxidative stress.
- Suppression of Wnt-mediated cellsignaling suppresses cancer cells.
- s-KL produced by neurons in the brain.
- s-KL – Shows no interference with calcium & phosphate homeostasis.

7 Roig-Soriano, et al. 2023

α-Klotho –Multiple Mechanisms of Action Targeting Multiple Pathways and Indications

Secreted α-Klotho s-KL and Aging – Multiple Potential Therapeutic Indications



Increases
- Synaptic GluN2B and NMDA receptors.
- Maturation of oligodendritic cells.
- Axonal transport, Neuron plasticity, and **Neurogenesis (growth of new neurons).**

Protects Neurons from Death
- **Oxidative stress**
- Mitochondrial redox
- Neuroinflammation

- **Inhibits inflammatory cytokines** in brain & CNS.
- Promotes anti-inflammatory cytokines.

- Increases integrity of Myelin
- **Increases motor neurons and neuronal activity** in brain & CNS
- **Increase in muscle strength** and electrophysiologic activity

- Binds APP & protects CNS against amyloid toxicity.
- **Autophagy clearance of amyloid & tau tangles** (cell debris).

Regulates cellular homeostasis & Organ protection via "**ALP**"

Activates Autophagy-Lysosomal Protein (**ALP**) the "master regulator", Transcription Factor EB for cell death "clean-up"

UAB and Klotho: Pioneers in Gene Therapy

Our Barcelona team has over 28 years of experience selectively manipulating levels of therapeutic proteins like s-KL and m-KL in vivo by using gene therapy strategies.

OPEN

Molecular Psychiatry (2017) 00, 1–11
www.nature.com/mp

ORIGINAL ARTICLE

Secreted αKlotho isoform protects against age-dependent memory deficits

A Massó[1], A Sánchez[1,2], A Bosch[1,2,3], L Giménez-Llort[2,4] and M Chillón[1,2,5,6]

αKlotho is a gene regulator of aging, increasing life expectancy when overexpressed and accelerating the development of aging phenotypes when inhibited. In mice, expression levels of the secreted isoform Klotho (s-KL) are very high in the brain, suggesting that s-KL activity may have an important role in the nervous system. Here we study the functional relevance at behavioural level of

PLOS ONE

RESEARCH ARTICLE

Secreted and Transmembrane αKlotho Isoforms Have Different Spatio-Temporal Profiles in the Brain during Aging and Alzheimer's Disease Progression

Anna Massó[1,2], Angela Sánchez[1,2], Lydia Gimenez-Llort[3,4], Jose Miguel Lizcano[1,3], Manuel Cañete[1,2], Belen García[1,2], Virginia Torres-Lista[3,4], Meritxell Puig[1,2], Assumpció Bosch[1,2], Miguel Chillon[1,2,5]*

1 Departament Bioquímica i Biologia Molecular, Universitat Autònoma Barcelona, Bellaterra, Spain,
2 Center of Animal Biotechnology and Gene Therapy (CBATEG), Universitat Autònoma Barcelona

Received: 3 June 2021 | Revised: 9 February 2022 | Accepted: 20 February 2022

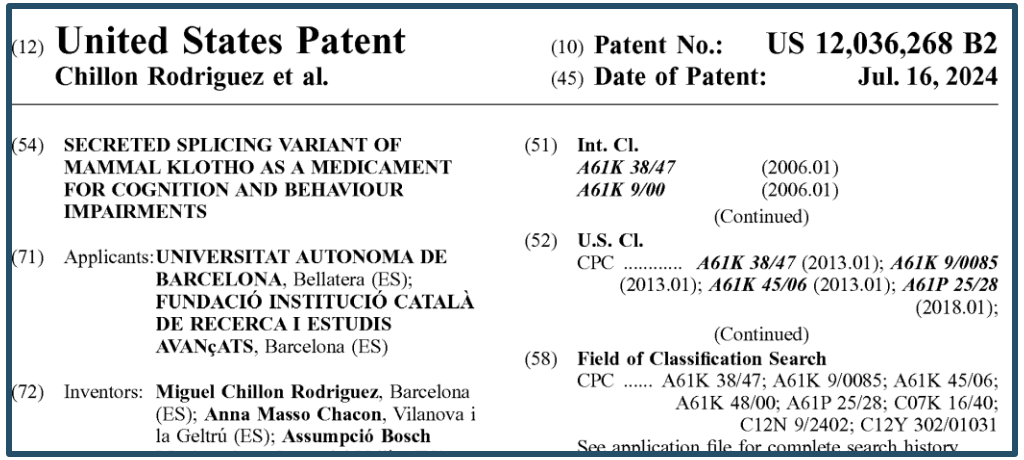
DOI: 10.1111/acel.13581

RESEARCH ARTICLE

Aging Cell WILEY

AAV-mediated expression of secreted and transmembrane αKlotho isoforms rescues relevant aging hallmarks in senescent SAMP8 mice

J. Roig-Soriano[1] | C. Griñán-Ferré[2] | J. F. Espinosa-Parrilla[1] | C. R. Abraham[3] | A. Bosch[1,4,5,6] | M. Pallàs[2] | Miguel Chillón[1,4,5,7]



(12) **United States Patent**
Chillon Rodriguez et al.

(10) **Patent No.: US 12,036,268 B2**
(45) **Date of Patent: Jul. 16, 2024**

(54) **SECRETED SPLICING VARIANT OF MAMMAL KLOTHO AS A MEDICAMENT FOR COGNITION AND BEHAVIOUR IMPAIRMENTS**

(71) Applicants: **UNIVERSITAT AUTONOMA DE BARCELONA**, Bellatera (ES); **FUNDACIÓ INSTITUCIÓ CATALÀ DE RECERCA I ESTUDIS AVANÇATS**, Barcelona (ES)

(72) Inventors: **Miguel Chillon Rodriguez**, Barcelona (ES); **Anna Masso Chacon**, Vilanova i la Geltrú (ES); **Assumpció Bosch**

(51) **Int. Cl.**
A61K 38/47 (2006.01)
A61K 9/00 (2006.01)
(Continued)

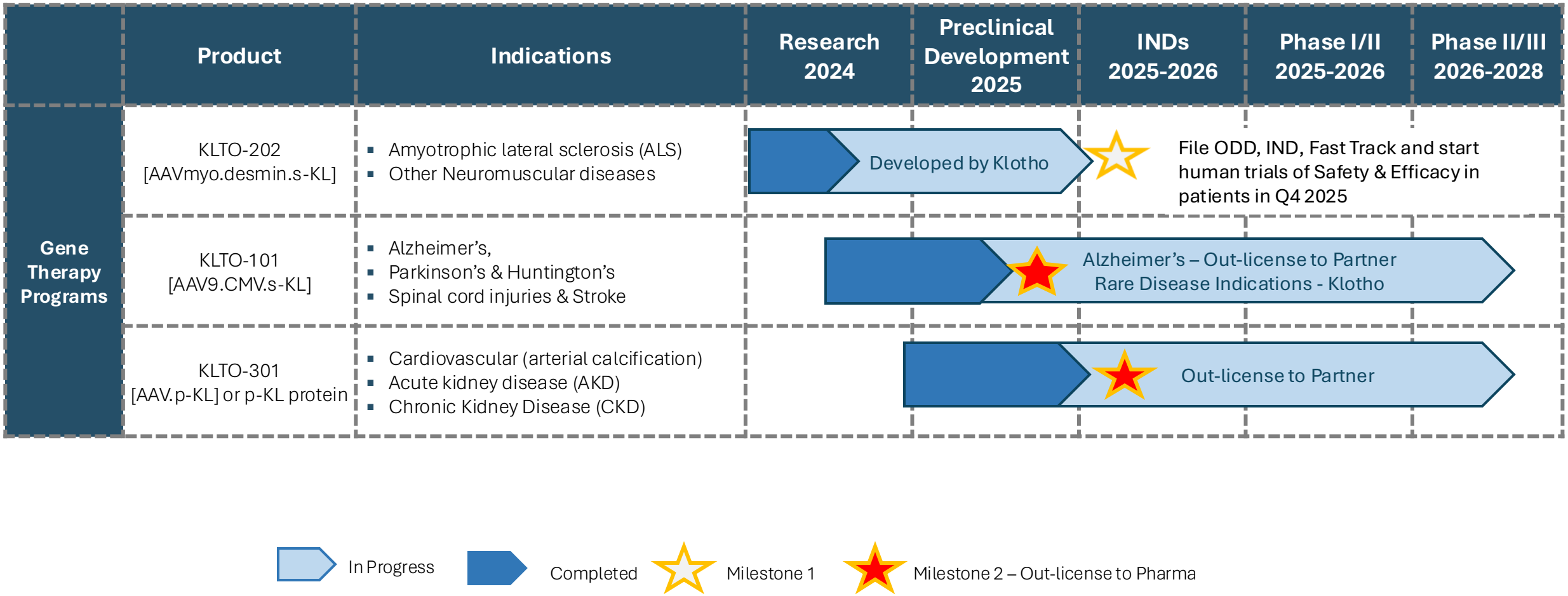
(52) **U.S. Cl.**
CPC ***A61K 38/47*** (2013.01); ***A61K 9/0085*** (2013.01); ***A61K 45/06*** (2013.01); ***A61P 25/28*** (2018.01);
(Continued)

(58) **Field of Classification Search**
CPC A61K 38/47; A61K 9/0085; A61K 45/06; A61K 48/00; A61P 25/28; C07K 16/40; C12N 9/2402; C12Y 302/01031
See application file for complete search history

Intellectual Property & Know How

- USPTO patent no. 12,036,268, application no.: 15/777,456; filed: May 18, 2018. Title: secreted splicing variant of mammalian klotho as a medicament for cognition and behavior impairments. [Alzheimer's and neurodegenerative diseases]
- USPTO application no.: 18/299,989: filed: April 13, 2023. Title: treatment of neuromuscular diseases via gene therapy that expresses klotho protein. [ALS, MS and other neuromuscular diseases]
- USPTO application no. 17/051,123; University of Heidelberg. Pct/er2019/060790 filed: April 26, 2019. Title: Modified AAV capsid polypeptides for treatment of muscular diseases. [Als and other neuromuscular diseases]
- Exclusive Licenses to develop and commercialize therapeutics derived from know-how and IP from the UAB Laboratories of Assumpcio Bosch Merino and Dr. Miguel Chillon Rodriguez in the areas of neurodegenerative diseases (exclusive) and aging, and aav vectors by Dirk Grimm at University of Heidelberg (non-exclusive).
- Sponsored research agreements ("sra") with the UAB Laboratories to investigate neurodegenerative diseases and age-related diseases – e.G., osteoporosis, sarcopenia, cancer, chronic kidney disease and heart disease.
- Sponsored research agreement with Okinawa Center of Longevity Research and the Klotho and Foxo3 genes as related to healthy lifespan extension and longevity.

Pipeline – α-Klotho RNA Splice Variant s-KL



Amyotrophic Lateral Sclerosis

Disease State and Competitive Landscape

Klotho SM NEUROSCIENCES

Amyotrophic Lateral Sclerosis - ALS

Amyotrophic Lateral Sclerosis, or Lou Gehrig's disease, is a terminal neurodegenerative disorder that results in the progressive loss of both upper and lower motor neurons that normally control voluntary muscle contraction. Patients typically die within 2-3 years of initial diagnosis due to respiratory failure.

- ALS is a rare disease, with global prevalence ranging from 4 to 6 people per 100,000.
- Approximately 450,000 people worldwide are living with ALS at any given time
- ALS incidence rates vary slightly across different regions, but they are generally consistent across ethnic and geographic populations, with slightly higher rates in Europe and North America.

U.S. Prevalence & Incidence:

- ALS affects approximately 5 out of every 100,000 people.
- The CDC estimates that 20,000 to 30,000 people in the U.S. currently living with ALS
- Each year, about 5,000 new cases of ALS are diagnosed in the U.S.

FDA Approved Treatments

Riluzole (Rilutek, Tiglutik, Exservan):

- The first drug approved for ALS, Riluzole helps reduce damage to motor neurons by decreasing glutamate levels.
- It can extend survival by a few months and may delay the need for a ventilator.

Edaravone (Radicava/Radicava ORS):

- Initially administered intravenously and later in an oral form (Radicava ORS).
- It is thought to act as an antioxidant, helping to slow the decline in physical function.
- Shown to have a modest effect on slowing disease progression in certain patients.

AMX0035 (Relyvrio):

- A combination of sodium phenylbutyrate and taurursodiol, originally Fast Tracked and Approved by the FDA in 2022.
- Phase 3 Trial failed to confirm clinical benefit. Amylyx pulled Relyvrio from market April 2024 – Not Effective.

ALS – Current Clinical Trials

Drug Name	Clinical Phase	Originator	Type of Drug
Tofersen	Phase 3	Biogen	Antisense Oligonucleotide
Masitinib	Phase 3	AB Science	Tyrosine Kinase Inhibitor
Verdiperstat	Phase 3	Biohaven Pharmaceuticals	Myeloperoxidase Inhibitor
NurOwn	Phase 3	BrainStorm Cell Therapeutics	Stem Cell Therapy
Pridopidine	Phase 2/3	Prilenia Therapeutics	Sigma-1 Receptor Agonist
Arimoclomol	Phase 3	Orphazyme	Heat Shock Protein Amplifier
ANX005	Phase 2	Annexon Biosciences	Complement C1q Inhibitor
Ibudilast	Phase 2	MediciNova	Phosphodiesterase Inhibitor
Trehalose	Phase 2	Seelos Therapeutics	Autophagy Enhancer

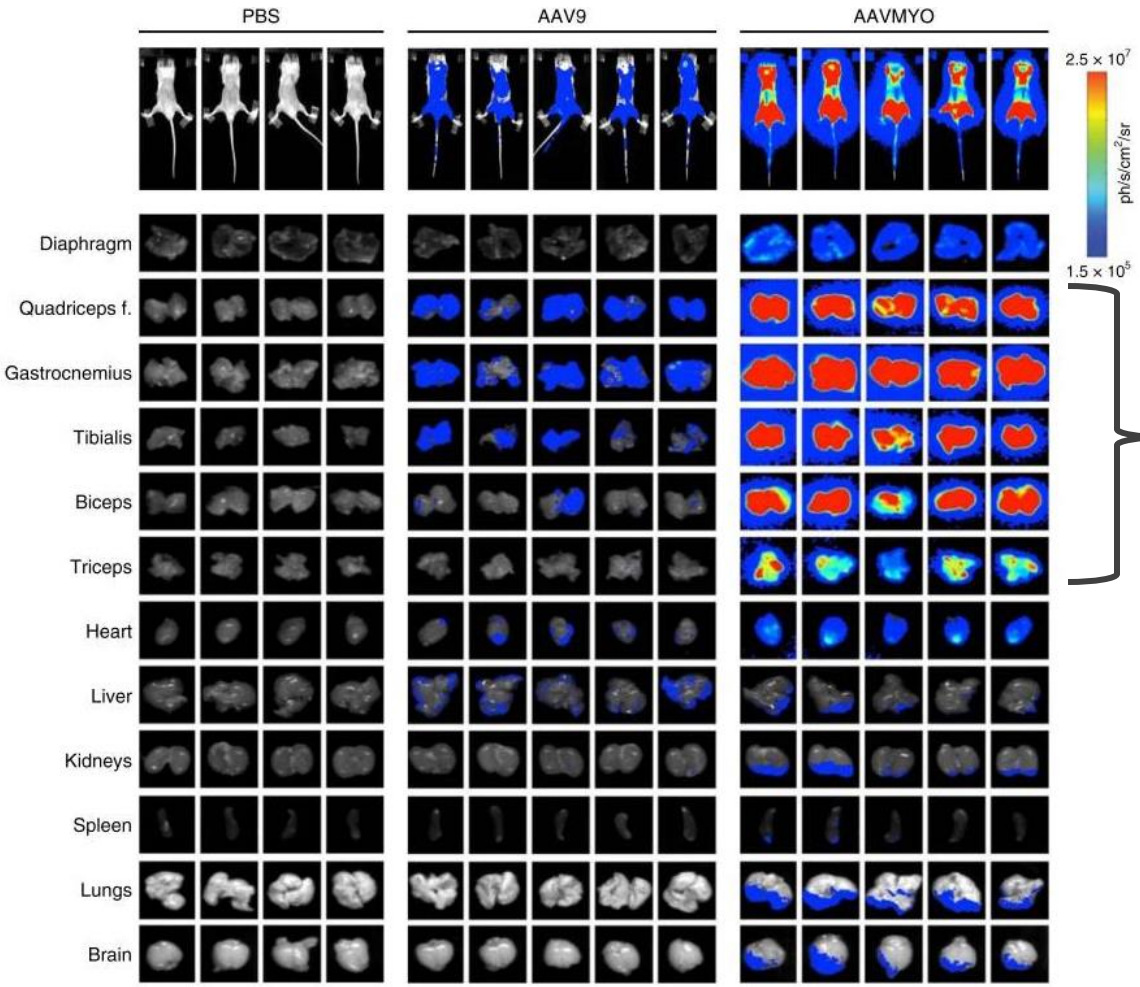
KLTO-202 for ALS

Product Profile

Klotho SM NEUROSCIENCES

AAV.myo Concentrates in Muscle Tissue[14]

Klotho Neurosciences licensed this AAV.myo vector for the delivery of our payload to human muscle tissue and the neuromuscular junction for ALS treatment.

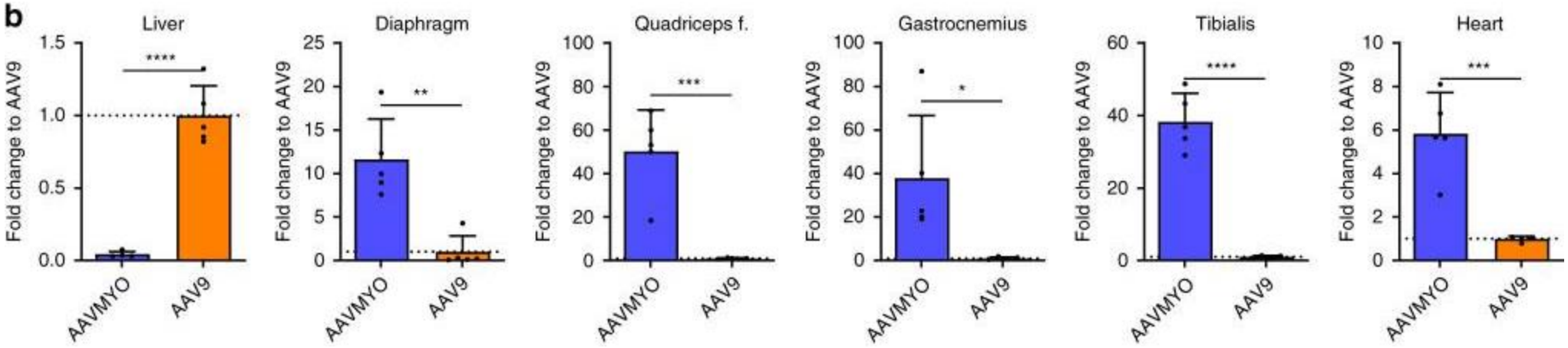


Very high concentrations of AAV.myo in major muscles in both mice and non-human primates (NHP).

[14] Grimm, *et al*. 2020

AAV.myo in Mouse Muscle Tissue[14]

Klotho Neurosciences licensed this proprietary AAV.myo vector for the delivery of our **s-KL** sequence and tissue-specific promoter payload to muscle tissue and the neuromuscular junction for ALS treatment.



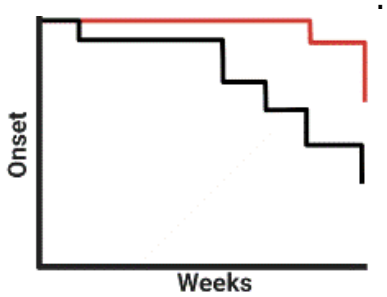
"Regular" AAV is high in liver compared to our licensed AAV.myo vector.

[14] Grimm, *et al*. 2020

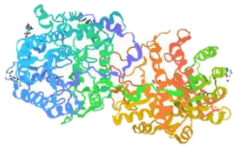
Results - Murine ALS/Neuromuscular Disease Model

Treatment of SOD1^{G93A} mouse model of ALS

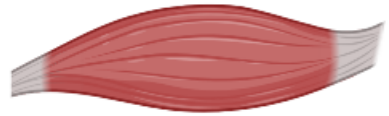
Early Treatment Delayed disease onset

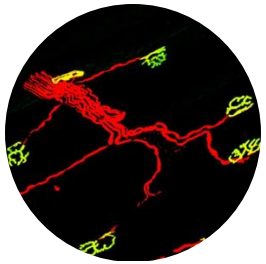


KLTO-202 Secreted α-Klotho
Desmin=s-KL-AAV.myo

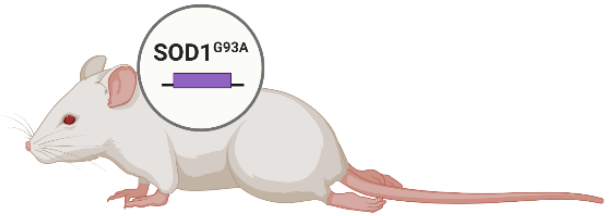


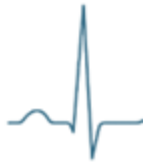
Increased muscle mass and strength





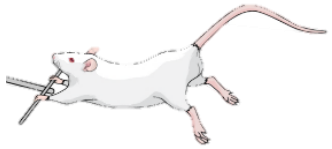
Promoted muscle end-plates reinnervation at the neuromuscular junction



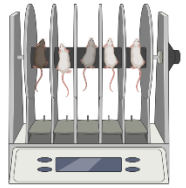


↑Amplitude of the muscle action potentials

Improved the connectivity between cortex and spinal motor neurons



Improved grip strength testing

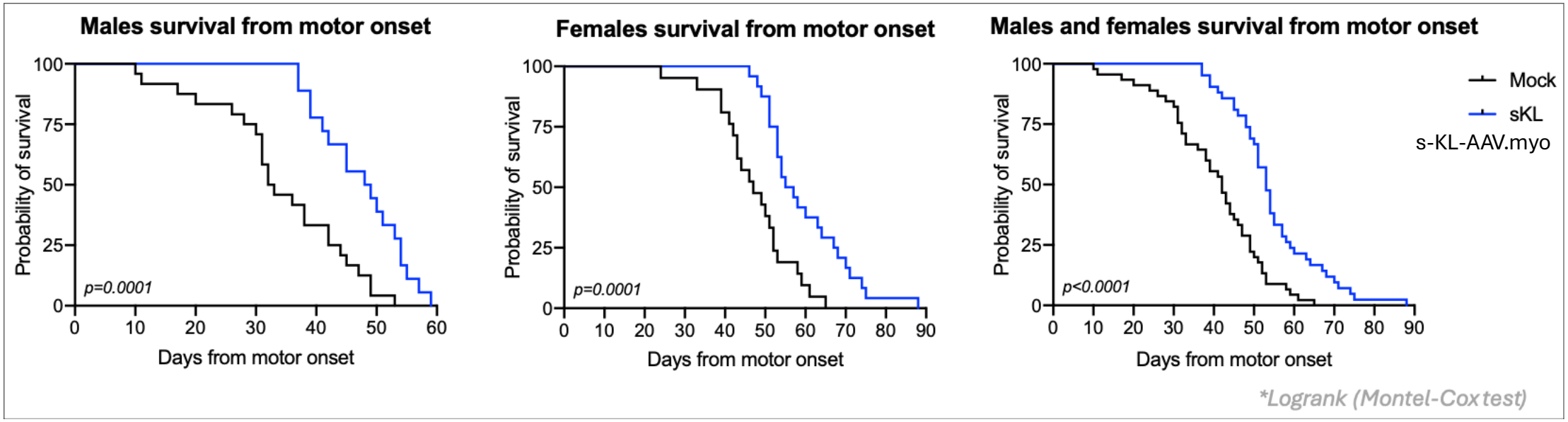


Enhanced motor coordination and balance

Improved Disease-Free Survival - in ALS/SOD1 Model

KLTO-202 - Survival Study of SOD1^{G93A} mouse model of ALS

Single Dose Treated After Disease Onset



Death - Control v. KLTO-202
- 10 days v. 40 days (400%)
- LD50 35 days v. 54 days

Death - Control v. KLTO-202
- 22 days v. 45 days (200%)
- LD50 45 days v. 62 days

Avg Death - Control v. KLTO-202
- 10 days v. 40 days (400%)
- LD50 40 days v. 60 days

ALS KLTO-202: Summary of Preclinical Results

- Amyotrophic Lateral Sclerosis (ALS) is a progressive neurologic disorder characterized by the degeneration of cortical and spinal motor neurons, resulting in debilitating loss of motor function, muscle atrophy, respiratory failure and eventual death.
- ALS is mainly due to oxidative stress, neuroinflammation, excitotoxicity and mitochondrial dysfunction….dysfunctions that are mitigated and improved by s-KL protein transcribed by the gene sequence.
- Preclinical results in the ALS mouse model (SOD) show that overexpression of s-KL gene in muscles and CNS mediated by our AAV.myo.s-KL vector enhances motor function, delays disease onset of disease, yields higher number of innervated neuromuscular junctions, higher muscle action potential of major muscle groups, stronger muscle strength overall and improves survival versus controls.

ALS KLTO-202: Clinical & Regulatory Strategy

- Submit application for Orphan Drug Designation (ODD) 1Q 2025
- IND for Phase 1B/2A trial in early ALS with Fast Track Designation for KTLO-202 for the treatment of ALS, 3/4Q 2025
- Proposed clinical trial – Randomized placebo-controlled trial to evaluate the safety and efficacy of KLTO-202 in approximately 50 patients with early ALS, randomized 2:1, active to placebo; primary endpoint: change in ALSFRS-R at 6 months; secondary/exploratory endpoints – change in plasma NFL levels, change in muscle strength, change in vital capacity, time to death or ventilatory support, ALS Quality of Life measures.

	Product	Indications	Research 2024	Preclinical Development 2025	INDs 2025-2026	Phase I/II 2025-2026	Phase II/III 2026-2028
Gene Therapy Programs	KLTO-202 [AAVmyo.desmin.s-KL]	▪ Amyotrophic lateral sclerosis (ALS) ▪ Multiple Sclerosis (MS) ▪ Other Neuromuscular diseases	Developed by Klotho		File ODD, IND, Fast Track and start human trials of Safety & Efficacy in patients in Q4 2025-1Q 2026		

In Progress Completed Milestone 1 Milestone 2 – Out-license to Pharma

Orphan Drug Designation

Because ALS affects less than 200,000 people in the U.S., a new ALS drug may be eligible for FDA Orphan Drug Designation (ODD)

Benefits of Orphan Drug Designation

- 7 Years of Market Exclusivity: No other company can market the same drug for the same indication during this period.
- Tax Credits: Up to 25% of clinical trial costs can be claimed as tax credits.
- Waiver of FDA Fees: Application fees for FDA review are waived, saving companies millions of dollars. Grants and Funding: Access to grants to support clinical trial costs.
- Assistance in Drug Development: Companies receive FDA guidance on the clinical trials and approval process.

Amyotrophic Lateral Sclerosis

Market Opportunity

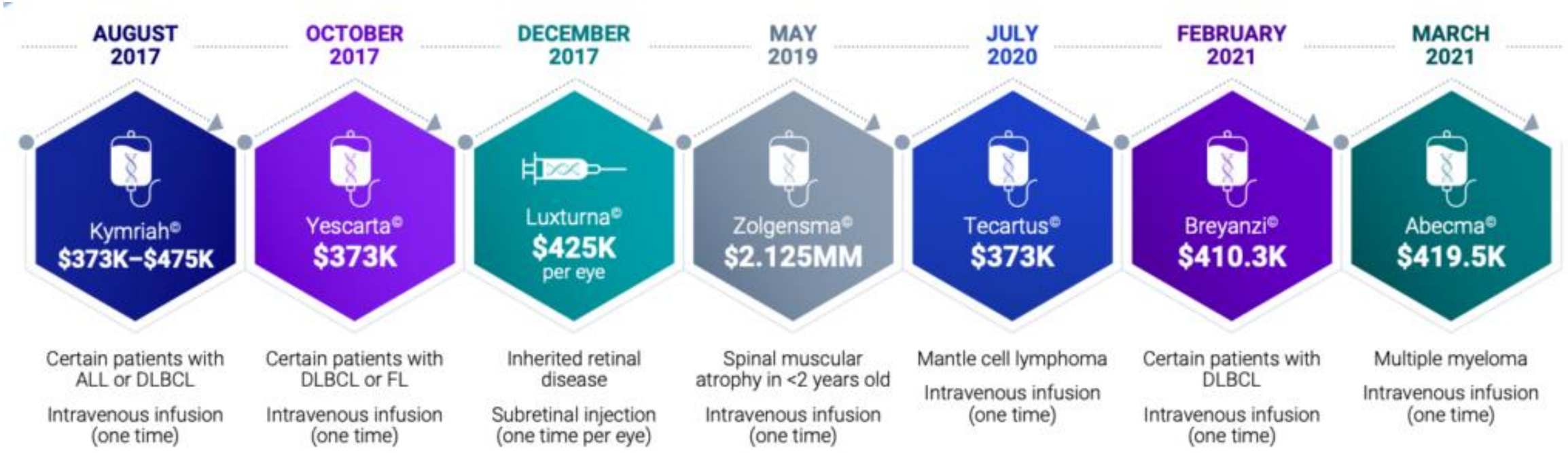
Klotho SM NEUROSCIENCES

FDA Approved ALS Drugs

Drug Name	Originator	FDA Approval	Generic Status	Patent Expiry	US Sales 2023 (Million USD)	Global Sales 2023 (Million USD)
Riluzole (Rilutek, Tiglutik, Exservan)	Sanofi	Dec 1995	Generic	Expired	$150	$250
Edaravone (Radicava, Radicava ORS)	Mitsubishi Tanabe Pharma Corporation	May 2017	Not Generic	2028-2030 (estimated)	$300	$400

FDA Approved Gene Therapies

2024 Estimated Sales of $11.1 Billion



https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

truveris

Market Potential

- Product Profile: Gene therapy drug for ALS that improves survival by 6 months and slows motor decline
- ALS Patient Population
  - US: Approximately 20,000-30,000 people live with ALS at any given time.
  - Worldwide: Estimates suggest there are around 450,000-500,000 ALS patients globally.
- Annual Incidence
  - US: About 5,000 new cases of ALS are diagnosed each year.
  - Worldwide: The annual incidence is around 2 per 100,000 people, leading to roughly 120,000 new cases per year globally.
- Potential Market Size Based on Uptake
  - US Market: 20% uptake: 4,000 to 6,000 patients
  - Global Market: 5% uptake: 22,500 to 25,000 patients
- Estimated Cost per Treatment
  - Gene therapies are typically expensive, with recent approved gene therapies costing between $500,000 to $2.5 million per treatment. Assumed cost:
  - US Average Cost per Treatment: $1 million
  - Ex-US Avg Cost per Treatment: $500,000 (50% discount)

US Market Estimate*
$5.0 Billion

Ex-US Market Estimate*
At $22.5 Billion

*** Disclaimer:** The figures presented are preliminary estimates based on available data and assumptions. A formal market forecast will be conducted to validate these projections. Estimates are subject to change as more detailed information becomes available.

Alzheimer's Disease

Secreted Klotho Isoform s-KL (KLTO-101)

- A single AAV-vectored treatment to the brain/CNS.
- Multiple pharmacologic pathways for treating AD that have not yet been explored.
- Treatment with a naturally-occurring s-KL protein should be safe and effective.

Klotho℠ NEUROSCIENCES

Alzheimer's Disease (AD)

Alzheimer's Disease is a progressive, age-related neurodegenerative disease affecting memory, cognition, and behavior. It is the most common cause of dementia, accounting for 60-80% of cases.

- Global Statistics:
  - Over 50 million people worldwide are living with dementia, with Alzheimer's constituting the majority of these cases. By 2050, 138 million people are projected to have AD or related disorders.
- U.S. Statistics:
  - Over 6 million Americans are living with Alzheimer's.
  - By 2050, this number is expected to reach nearly 13 million.

Current Disease Modifying Treatments

Disease modifying treatments (DMTs) target the biological processes underlying Alzheimer's, particularly amyloid plaques and tau tangles.

- Aducanumab (Aduhelm): Approved in 2021, removes amyloid-beta plaques in the brain. Yet its effectiveness remains unclear, and it is recommended for early-stage Alzheimer's (BioMed Central).
- Lecanemab (Leqembi): Approved in 2023, this monoclonal antibody also targets amyloid plaques and has shown modest efficacy in slowing cognitive decline despite marked reductions in amyloid burden (MedPage Today).
- Donanemab (Kisunla): Approved in 2024, it has demonstrated significant yet modest slowing of disease progression, especially if administered early in the disease (BrightFocus).
- Current DMTs are associated with safety risks due to the occurrence of brain hemorrhages and/or rain swelling in 20-30 % of patients, especially among carriers of the ApoE4 gene.

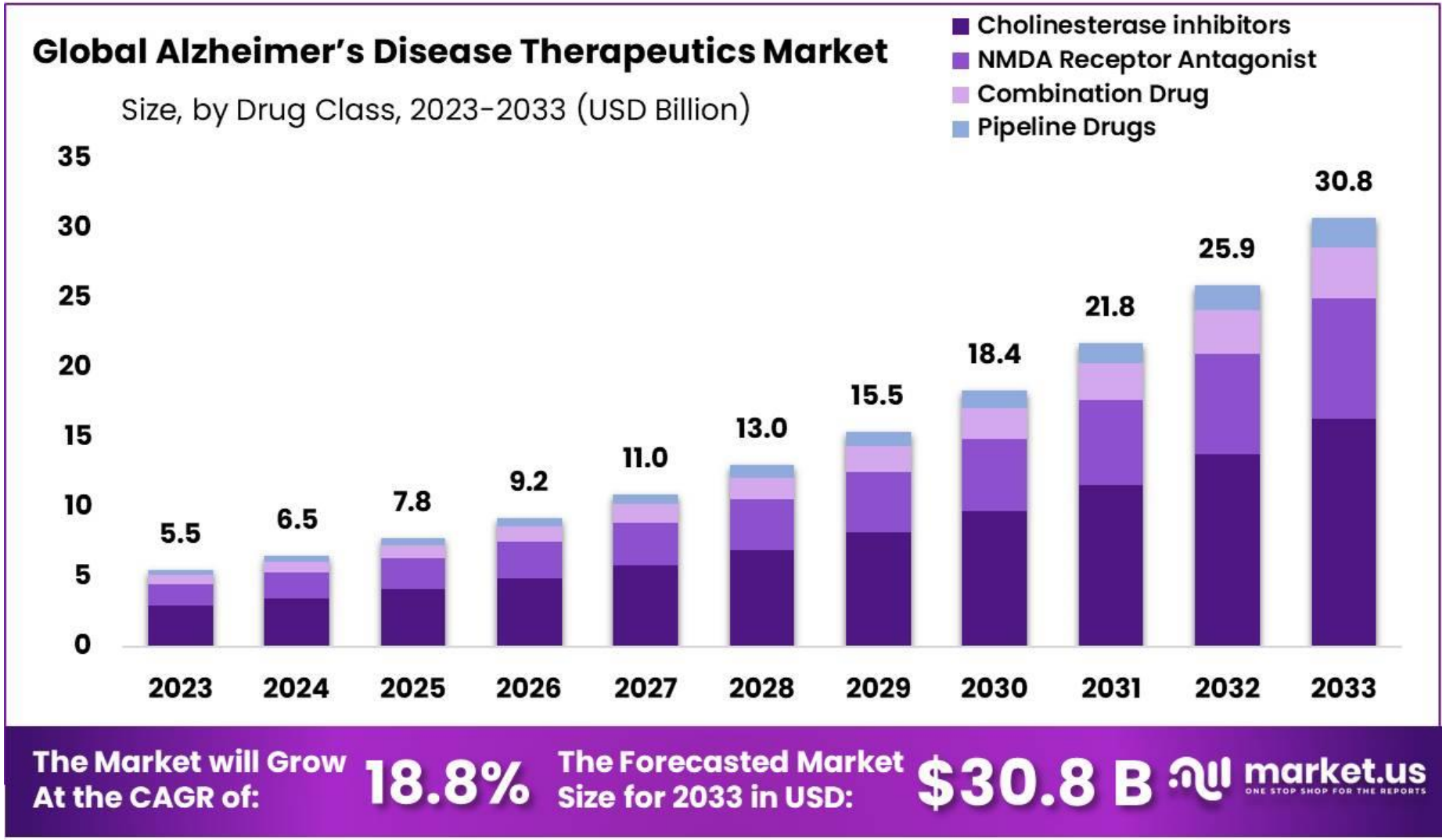
Novel treatments used alone or in combination for significant unmet medical needs.

AD: Current Clinical Trials

- As of January 1, 2024, there were 164 trials for AD evaluating 127 drugs.
- Most of these are small molecules and biologics, including vaccines, and 96 were DMTs, targeting single proteins or pathways (amyloid, tau, neuroinflammation, oxidative stress or lipid metabolism).
- It is widely recognized that AD is a heterogeneous, multifactorial disorder implicating multiple pathogenic pathways.
- New treatment regimens will likely include combination therapies or drugs that can target multiple pathways.
- **s-KL** (secreted Klotho) has been shown to have anti-aging, cognitive enhancing, antioxidative and anti-inflammatory properties and could offer a promising novel therapeutic approach to treat or prevent this devastating disease.

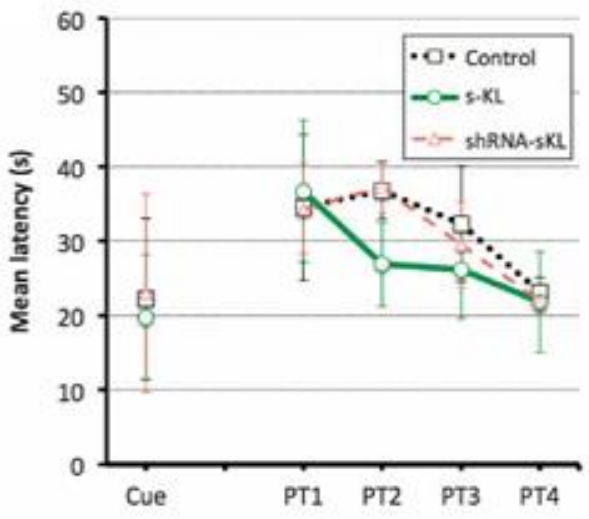
Cummings J et al, 2024

Alzheimer's Market

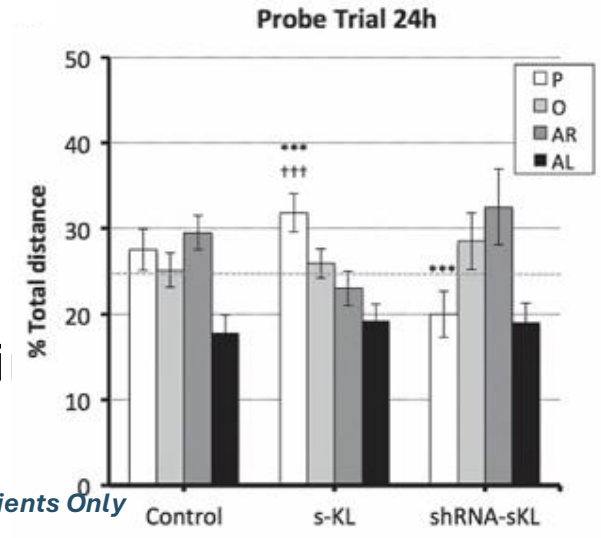


Data – Aging and Alzheimer's Cognition Models

- The secreted Klotho isoform (s-KL) is almost exclusively (>90%) found in the brain and high expression levels of s-KL corelate with brain health and healthy aging.
- We have leveraged AAV-based vectors to target the CNS leading to in vivo expression of s-KL in the brain and spinal fluid after i.v. administration in mice models of Alzheimer's and aging.
- A single i.v. dose of AAV-expressing s-KL had long-term effect and protected memory decline in mouse models of normal aging.
- Also, a single i.v. dose of AAV-expressing s-KL protected against memory decline in mouse models of accelerated aging.
- s-KL reverses senescence epigenome in accelerated aging, rejuvenating the epigenetic profile of memory and cognition i mouse models of aging.



All groups showed the capacity to learn the task, reflected by the gradual reduction in time to perform it, though s-KL-treated animals learned it faster

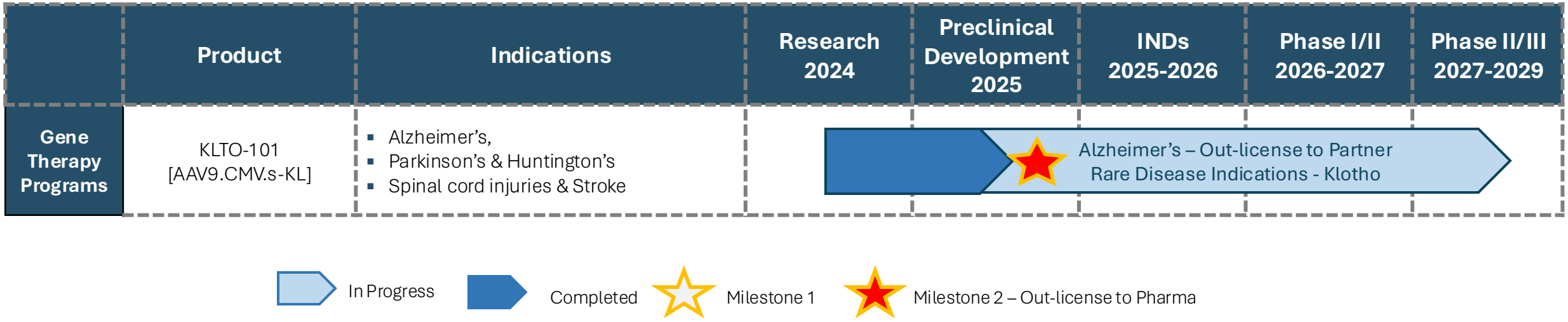


The group overexpressing s-KL showed better long-term memory. Shown by its significantly higher preference for the platform (P) quadrant as compared to the control group. Inhibition of s-KL had the opposite effect.

[11] Masso, *et al*. 2017

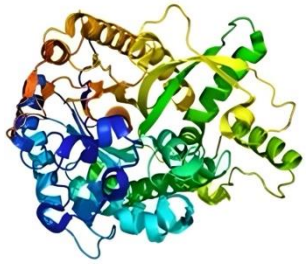
AD KLTO-101 Clinical & Regulatory Pathway

- Submit IND for Phase 1B/2A in patients with early AD and Fast Track application, 4Q,2025
- Initiate trial 1Q 2026
- Proposed clinical trial – Randomized placebo-controlled trial to evaluate the safety and efficacy of KLTO-101 in approximately 100-200 patients with early AD, randomized 1:1; AD pathology confirmed with fluid or imaging biomarkers; primary endpoint at 12 months in the CDR-SB; secondary: ADAScog -14, ADCS-ADL-MCI; MRI; plasma total tau, tau-181, plasma A-beta 42 and 40, and GFAP.



Conclusions

- Klotho Neurosciences, Inc. is focused on the development of innovative, disease-modifying gene therapies using our novel, patented secreted form of the anti-aging Klotho gene (s-KL) to transform and improve the treatment options for neurodegenerative and age-related disorders, such as ALS, Alzheimer's and Parkinson's disease.
- We have a robust and growing Intellectual Property Portfolio.
- The clinical Pipeline is targeting high value, critical, unmet medical needs.
- Recruited a seasoned Executive Team and World Class Advisors.
- We are Pioneering proprietary protein, cell, and gene therapeutics.



Thank You!

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Klotho SM NEUROSCIENCES