CNS Klotho™ NEUROSCIENCES

Novel Cell and Gene Therapies Targeting Neurodegenerative Diseases and Aging

Dr. Joseph Sinkule
CEO and Chairman

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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."*

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
Investor Relations Advisor

- 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 Pennsylvania
- BS Engineering, NCSU

Dr. Miguel Chillon
Chief Scientific Advisor

- 30 years gene therapy in nervous system
- Head of Gene Therapy in Neurodegenerative Diseases Laboratory, Universitat de Barcelona
- 14 patents in viral vectors for gene therapy
- 85 scientific papers in peer reviewed journals
- Cofounder of NanoTherapix SL and Klogene

Dr. Assumpcio Bosch
Chief Scientific Advisor

- 30 years gene therapy in nervous system
- 10 years' experience on ALS gene therapy
- Full Professor of Biochemistry & Molecular Biology, Universitat de Barcelona
- Head of the Gene Therapy for Neurometabolic Diseases at the Neurosciences Institute, UAB
- Over 80 papers in peer reviewed journals, 7 patents, cofounder of 2 biotech companies.

Board of Directors

Dr. Joseph Sinkule
Founder, CEO, Chairman

A serial entrepreneur, graduate of University of Nebraska Medical Center

- Over 45 years of drug, biologic, and medical device R&D and commercialization experience
- 8 years academic medicine, industry, a successful businessman and entrepreneur
- He serves on the Board of two other companies

Riad El-Dada
Independent Director

Senior life science executive with global operating experience

- President, Merck USA (retired)
- President, NBB Consulting
- MKG Group – Board of Directors
- Mallinckrodt Pharmaceuticals - former Board of Directors
- McKinsey Consultant
- MS - Georgetown University
- BA - Cornell University

Dr. Shalom Hirshman
Medical Advisor & Director

Preeminent research physician, clinical medical expert, and entrepreneur

- He is a key medical consulting advisor to the Company
- Intern and resident in medicine at Mass General and Harvard Medical School, then at NIH
- Mount Sinai School of Medicine/Mount Sinai Hospital in NYC, Vice-Chairman and Chairman of the Department of Medicine at Mount Sinai, where he remained for three decades

Mr. Jon McGarity
Independent Director

Senior life science executive with global operating experience

- CEO of EthiX Associates
- COO of MiClimate, Inc.
- Co-Founder NeuroEM Therapeutics
- Advisor, Biodesign Institute at Arizona State University and member of the Arizona Biosciences Roadmap
- Senior management positions with GlaxoSmithKline, Bristol Myers Squibb and Novartis (Sandoz Pharmaceuticals), launching over 40 products and completing numerous business development deals

Dr. Samuel Zentman
Independent Director

Senior business executive with global experience

- CFO and then CEO of Manhattan Textile Corporation
- Board member of several Tech and Medical start-ups
- Serves as the Chairman of the Board of several national non-profit organizations devoted to education in the U.S. and abroad
- Director of Corporate Computer Center of American Motors Corporation
- BS/BA from Wayne State University MS University of Michigan, and Ph.D. from Wayne State University in Complex Analysis

Scientific Advisory Board

Merit Cudkowicz, MD, MSC

Dr. Merit Cudkowicz is a renowned neurologist and neuroscientist specializing in ALS research and treatment. She holds key positions at Harvard Medical School and Massachusetts General Hospital, including Director of the Sean M. Healey & AMG Center for ALS. Dr. Cudkowicz co-founded the Northeast ALS Consortium and has led numerous clinical trials for novel ALS treatments. Her groundbreaking work includes developing the first ALS treatment discovery pipeline and the HEALEY ALS Platform Trial. She has made significant contributions to understanding ALS pathogenesis, exploring the role of immune and glial cells in disease progression. Dr. Cudkowicz's innovative approaches have accelerated therapy development and earned her recognition in the field.

Makoto Kuro-o, M.D., Ph.D.

Makoto Kuro-o, M.D., Ph.D., is a distinguished physician-scientist and pioneer in aging research, renowned for identifying the klotho gene, often called the "anti-aging gene." His 1997 discovery revealed the gene's critical role in regulating aging, showing that its absence accelerates aging while its overexpression extends lifespan. Dr. Kuro-o received his M.D. and Ph.D. from the University of Tokyo and has held prestigious academic positions, including Professor at Jichi Medical University and UT Southwestern Medical Center. With over 175 peer-reviewed publications, his research focuses on the roles of Klotho proteins, endocrine FGFs, and their impact on metabolism and aging.

Robert S. Langer, Sc. D.

Robert S. Langer, an Institute Professor at MIT, is a pioneering biotechnologist, engineer, and inventor who has revolutionized drug delivery systems and tissue engineering. With over 1,500 patents, 1,600 articles, and 438,200 citations, he is the most cited engineer in history. Langer's groundbreaking work includes developing controlled-release drug delivery, creating artificial organs, and founding over 40 biotech companies, including Moderna. His research has led to life-saving treatments for cancer, heart disease, and other ailments. Langer has received numerous prestigious awards, including the National Medal of Science, the National Medal of Technology and Innovation, and the $3 million Breakthrough Prize in Life Sciences.

Scientific Advisory Board

Richard Allsopp, PhD

Richard Allsopp, PhD, is a Professor at the John A. Burns School of Medicine, University of Hawaii, and a member of the Okinawa Research Center for Longevity Research. Internationally recognized for his work on telomeres, stem cells, and aging, he has led NIH-funded studies, co-directing the COBRE Aging Research grant. His research revealed the FOXO3 gene's role in protecting telomeres and combating age-related diseases. A frequent keynote speaker, Dr. Allsopp is a leader in aging and longevity science.

Craig Wilcox, MHSc, PhD, FGSA

Craig Willcox, MHSc, PhD, FGSA, is a leading expert in aging research, Co-Principal Investigator of the Okinawa Centenarian Study, and Professor at Okinawa International University. With over 20 years of experience, he has uncovered longevity-related gene variants and authored best-selling books on healthy aging. Dr. Willcox is a Fellow of the Gerontological Society of America and contributes as Associate Editor for leading aging research journals. His work highlights the genetic and lifestyle factors influencing longevity.

Bradley J. Willcox MD, MSc, FGSA, FRSM

Dr. Bradley J. Willcox is a renowned expert in healthy aging research, serving as Professor and Director of Research at the University of Hawaii's Department of Geriatric Medicine. He leads the NIH-funded Hawaii LIFESPAN and HEALTHSPAN Studies and co-leads the Okinawa Centenarian Study. Trained at prestigious institutions like Mayo Clinic and Harvard, Dr. Willcox has made significant contributions to understanding longevity factors. A New York Times bestselling author, he has received numerous awards for his work, including the Dorothy Dillon Eweson Award. His research has been featured in major media outlets worldwide.

Dr. Michio Shimabukuro

Dr. Michio Shimabukuro is a distinguished researcher in healthy aging and longevity, collaborating with the Okinawa Research Center for Longevity Science for two decades. A graduate of the University of the Ryukyus School of Medicine, he completed fellowships in Endocrinology and Cardiology. Dr. Shimabukuro's work with Dr. Roger H. Unger at UT Southwestern Medical Center led to the proposal of the lipotoxicity theory. He has held professorships at the University of the Ryukyus, University of Tokushima, and currently serves as a full Professor at Fukushima Medical University since 2016.

Klotho Proprietary Technology Platform

Klotho – “The Anti-Aging Gene”

Klotho SM
NEUROSCIENCES

The Human Klotho Gene

Dr. Makoto Kuro-O

In 1997, Dr. Makoto Kuro-O showed that elimination of a gene ("knock-out") in mice resulted in a significantly reduced life-span and premature muscular, vascular, and CNS aging, including memory deficits, alterations in axonal transport, reduced numbers of brain synapses in the hippocampus, hippocampal degeneration, neuroinflammation, and problems in myelin production.

Kuro-O named the gene "Klotho", after the Greek Goddess "Clotho", daughter of Zeus, who "Spins the Thread of Life" – later referred to as the "Anti-Aging Gene".

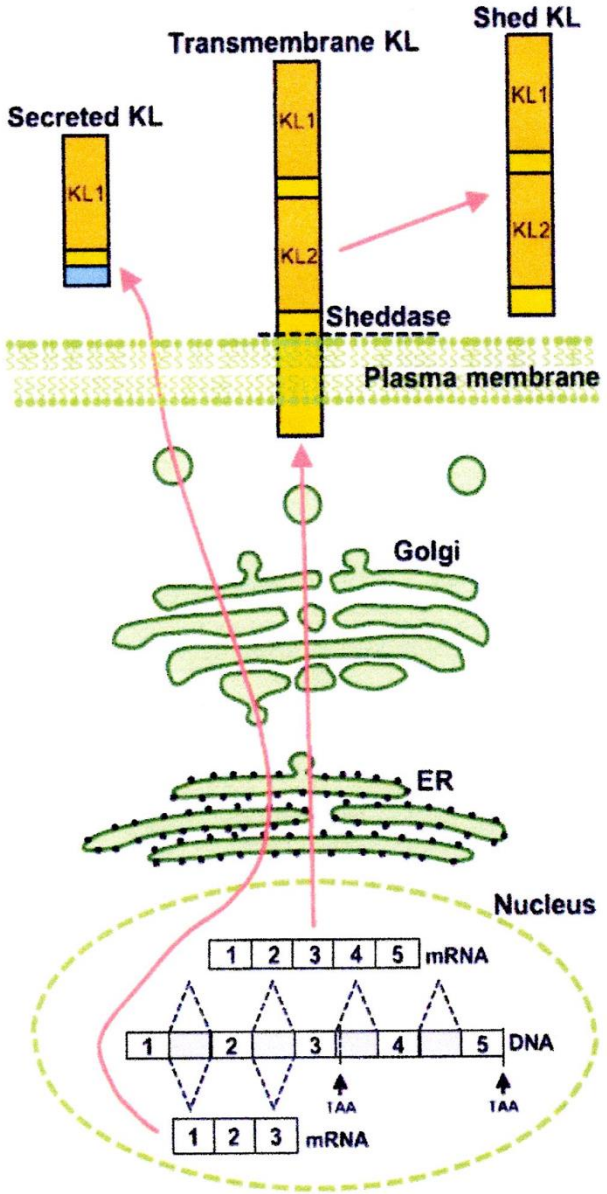
Significance of the Klotho Gene

The α-Klotho gene (a 5 exon gene found in all mammals) transcribes two proteins:

- A 140KDa protein (m=KL) that binds FGF-21/FGF-23 and regulates Phosphate ion homeostasis; and
- A 63KDa protein RNA splice variant (s-KL) that provides
  - neuroprotection against oxidative stress, decreases neuroinflammation, increases autophagy, increases synaptic plasticity, increases myelination, increases axonal transport, stimulates neurogenesis and
  - results in improvements in cognition, memory , myelination, and motor neuron function.

Secreted Klotho Isoform (s-KL)

- Produced mainly by neurons in the brain and throughout CNS.
- Suppression of oxidative stress & mitochondrial redox.
- Stimulates neurogenesis and myelin production.
- Inhibition of insulin and IGF-1 mediated signaling (diabetes, obesity and longevity)



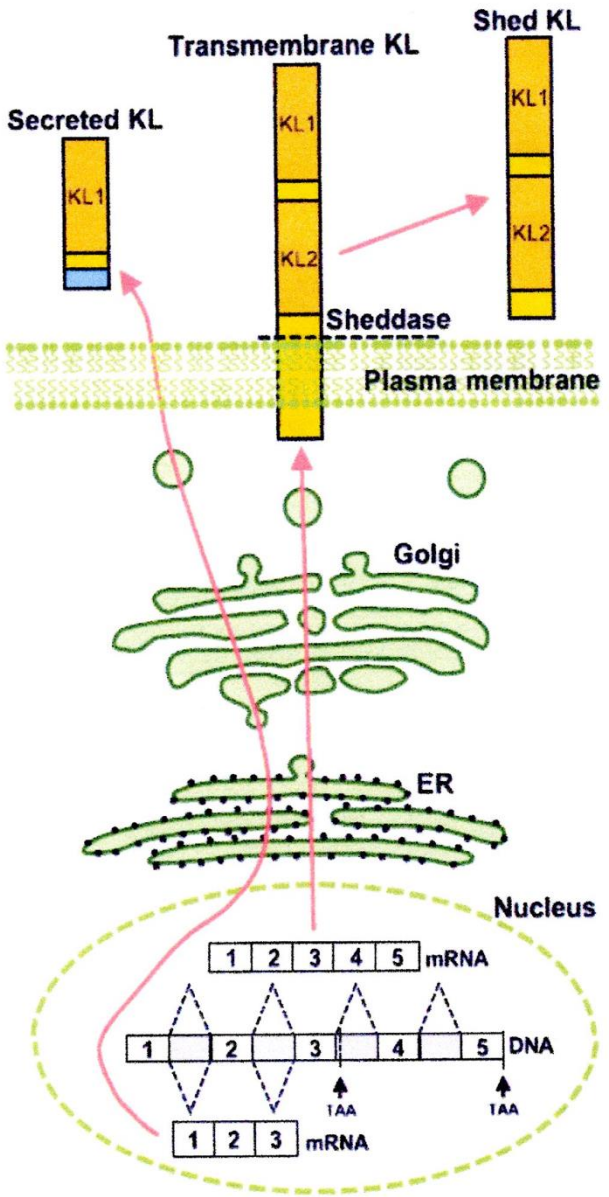
- Suppresses neuroinflammation (cytokine reduction).
- Autophagy activator (clearance of cell debris like amyloid and tau).
- Regulates autophagy lysosomal protein (ALP) pathway.

7 Roig-Soriano, et al. 2023

Secreted Klotho Isoform (s-KL)

Transmembrane Klotho m-KL isoform

- Produced mainly in the kidneys.
- Obligatory coreceptor of factor FGF-23 and FGF-21.
- Binds FGF-23 and FGF-21 and regulates the concentration of phosphate and calcium in plasma.



- Produces the active form of vitamin D (prominent role in calcium metabolism).
- Overexpression causes hypocalcemia and hypophosphatemia.
- Dimer can be metabolized to KL1 and KL2 monomers that circulate systemically but don't cross the BBB.

7 Roig-Soriano, et al. 2023

α-Klotho: Targeting Multiple Pathways and Indications

Secreted α-Klotho s-KL and Aging: Multiple Potential Therapeutic Mechanisms

Anti-Aging Properties

Protects Neurons from Death

- Oxidative stress
- Mitochondrial redox
- Neuroinflammation

Mitigate Neuroinflammation

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

Autophagy Lysosomal Activator

- Binds APP & protects CNS against amyloid toxicity
- Autophagy clearance of amyloid & tau tangles (cell debris)
- Regulates ALP pathway, cellular homeostasis & Organ protection via “ALP”

Enhance Cognition

Increases:

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

Motor Neuron Activities

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

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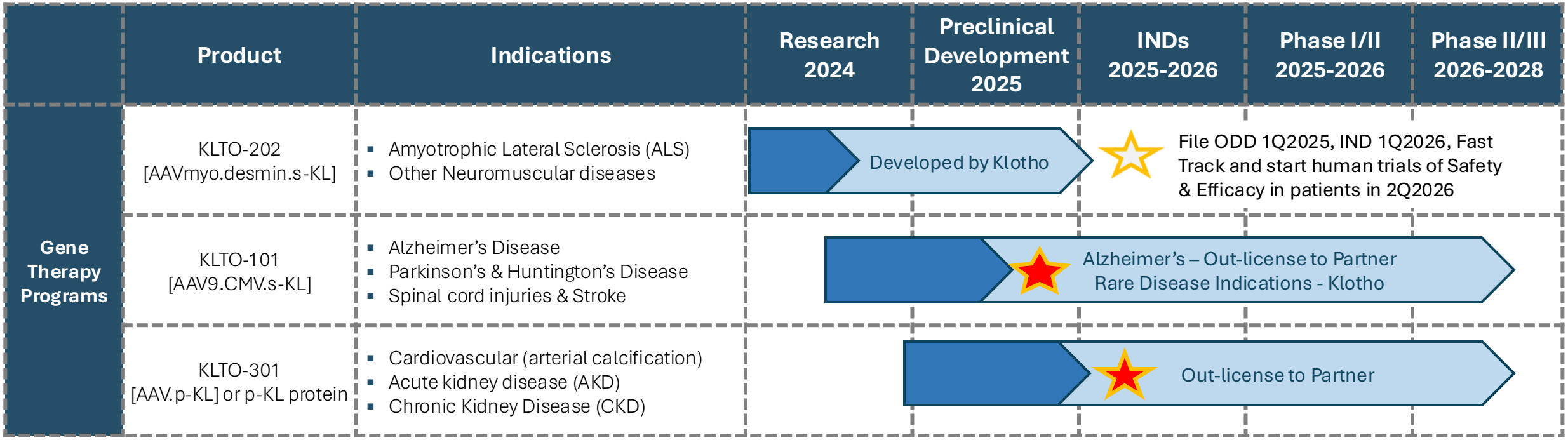
Intellectual Property & Know How

- 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 agreement with Okinawa Research Center for Longevity Research and the Klotho and Foxo3 genes as related to healthy lifespan extension and longevity.
- Sponsored Research Agreement with the Okinawa Research Center for Longevity, analyzing stored blood and serum samples collected over 30+ years from Okinawa residents living long and healthy lives (many 100+ years). Research focuses on investigating Klotho levels.

Klotho Neurosciences – Our Path Forward

- Secreted Klotho isoform (s-KL) is almost exclusively produced in the brain (choroid plexus and hippocampus).
- Leverage these findings to develop protein, cell and gene therapy products that improve neurologic function in humans by targeting neurodegenerative diseases.
- Develop genomic and proteomic assays to predict "high risk" subjects to monitor more closely and treat earlier in the course of the disease.
- Klotho Neurosciences' lead project, KLTO-202, is focused on utilizing our s-KL gene and protein therapies for amyotrophic lateral sclerosis (ALS).
- Other near-term clinical targets – Alzheimer's, Parkinson's, Huntington's disease, Multiple Sclerosis (demyelination), Spinocerebellar Ataxia, Spinal Muscular Atrophy.

Pipeline – α-Klotho RNA Splice Variant s-KL



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

Amyotrophic Lateral Sclerosis

KLTO-202 for ALS

Product Profile

Klotho SM NEUROSCIENCES

Amyotrophic Lateral Sclerosis - ALS

Rare Disease with Limited Treatment Options

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.

ALS is a rare disease, affecting approximately 5 out of every 100,000 people.

Patients typically die within 2-3 years of initial diagnosis due to respiratory failure.

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):

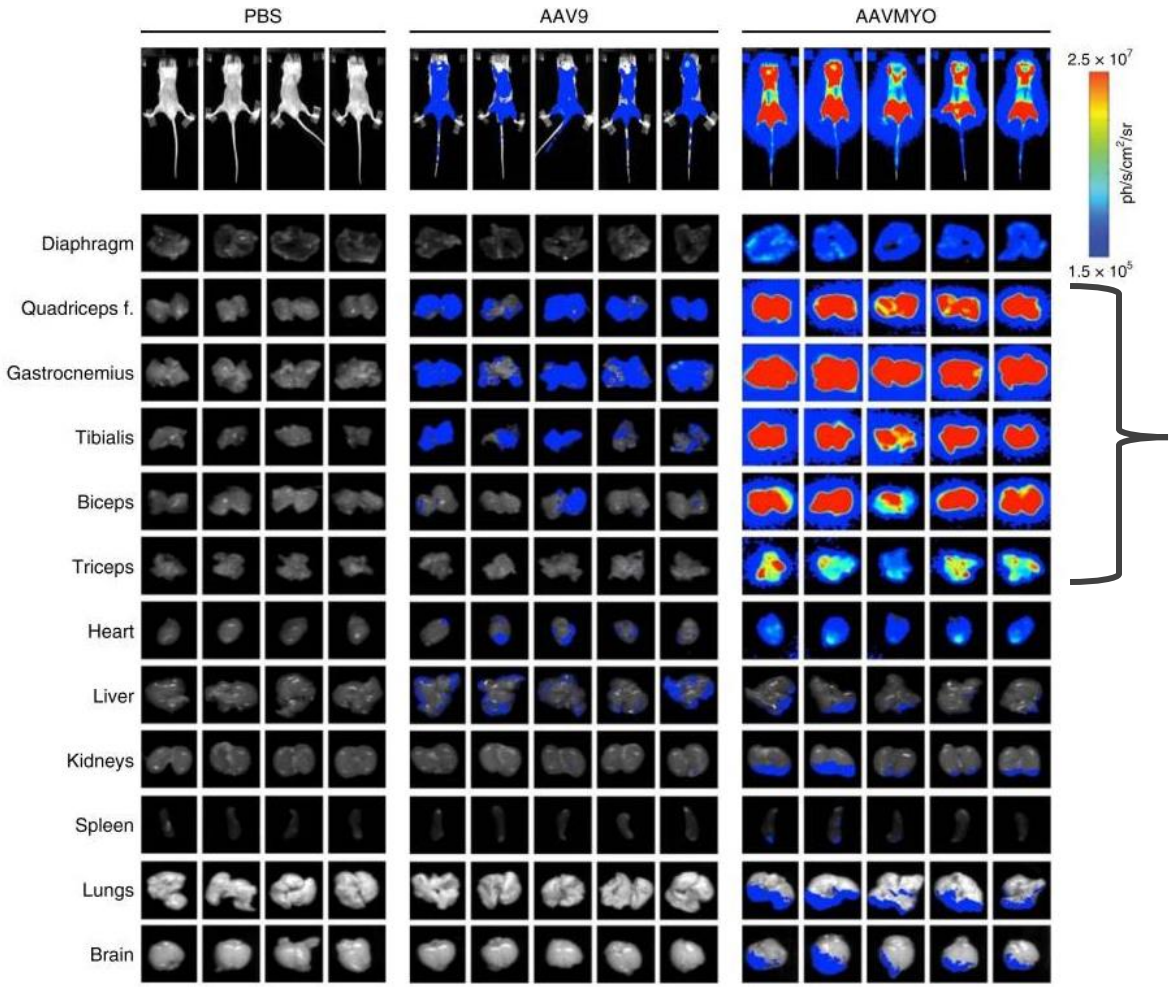
- Initially administered intravenously and later in an oral form (Radicava ORS).
- It is thought to act as an antioxidant, helping to slow the decline in physical function.
- Shown to have a modest effect on slowing disease progression in certain patients.

* 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.

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.

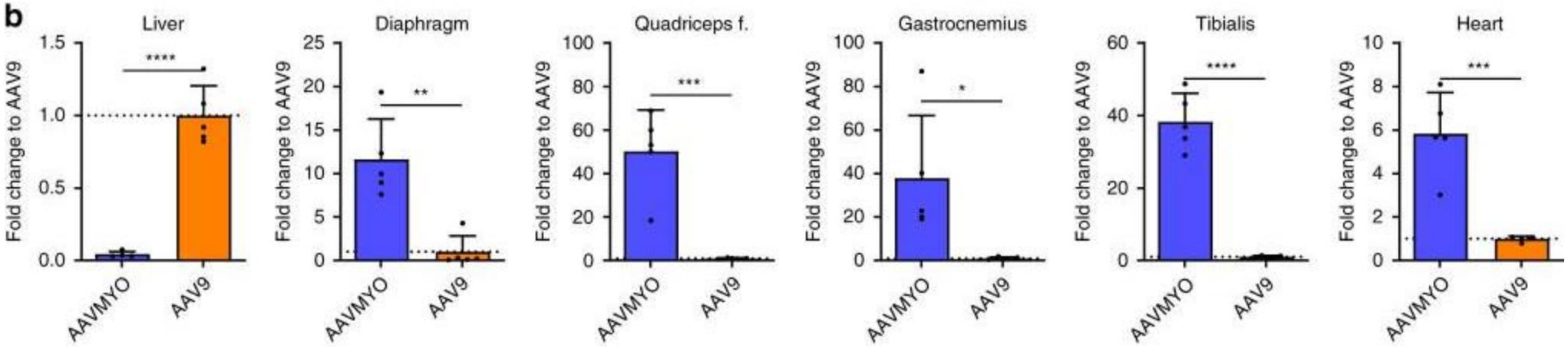


Very high concentrations of AAV.myo in major muscles in both mice and non-human primates (NHP).

[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.



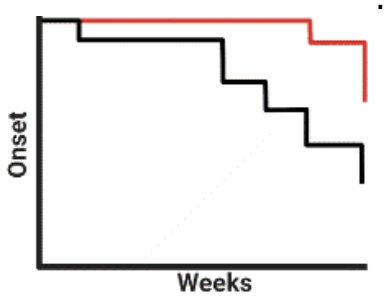
"Regular" AAV is high in liver compared to our licensed AAV.myo vector.

[14] Grimm, *et al*. 2020

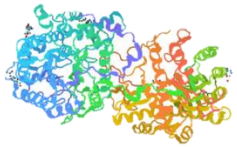
Results - Murine ALS/Neuromuscular Disease Model

Treatment of SOD1^{G93A} mouse model of ALS

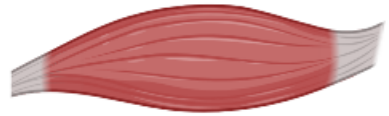
Early Treatment Delayed disease onset

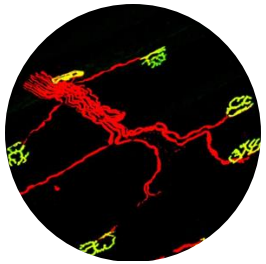


KLTO-202 Secreted α-Klotho
Desmin=s-KL-AAV.myo

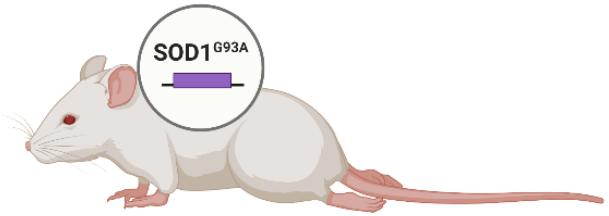


Increased muscle mass and strength



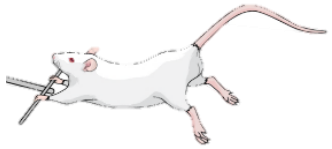


Promoted muscle end-plates reinnervation at the neuromuscular junction

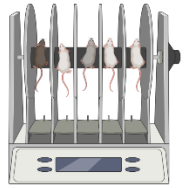


↑Amplitude of the muscle action potentials

Improved the connectivity between cortex and spinal motor neurons



Improved grip strength testing

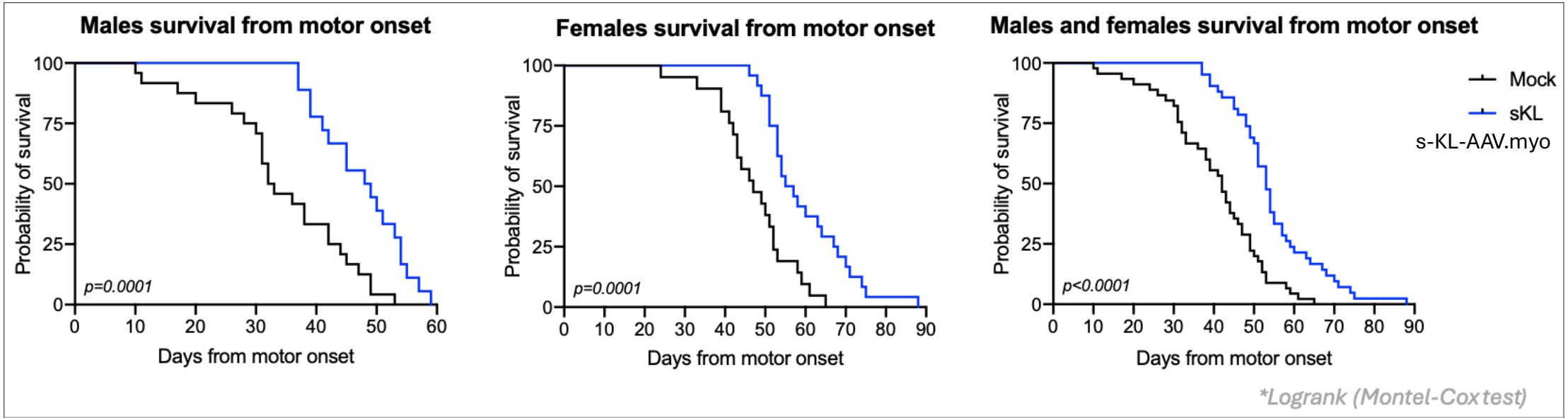


Enhanced motor coordination and balance

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

KLTO-202 for ALS: Clinical & Regulatory Strategy

- 1Q 2025 - Submit application for Orphan Drug Designation (ODD) 1Q 2025
- 2Q- 3Q 2025 - Pharmacology, Toxicology PK and PD studies, and assemble CMC dossier
- 4Q 2025 - IND for Phase 1B/2A trial in early ALS with Fast Track Designation

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 1Q2025, IND 1Q2026, Fast Track and start human trials of Safety & Efficacy in patients in 2Q2026		

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

Orphan Drug Designation

ALS affects less than 200,000 people in the U.S., and 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.

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.

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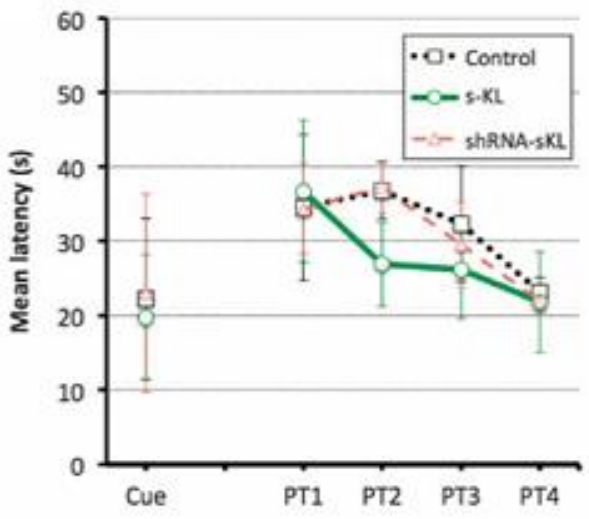
Alzheimer's Disease (AD)

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.

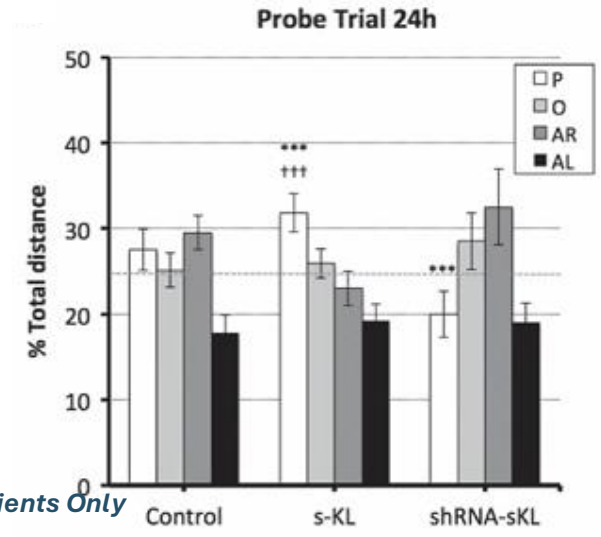
- Global Statistics:
  - Over 50 million people worldwide are living with dementia, with Alzheimer's constituting the majority of these cases. By 2050, 138 million people are projected to have AD or related disorders.
- U.S. Statistics:
  - Over 6 million Americans are living with Alzheimer's
  - Cost of Care for those patients is over $350 billion
  - By 2050, this number is expected to reach nearly 13 million.

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 effects 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 in 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

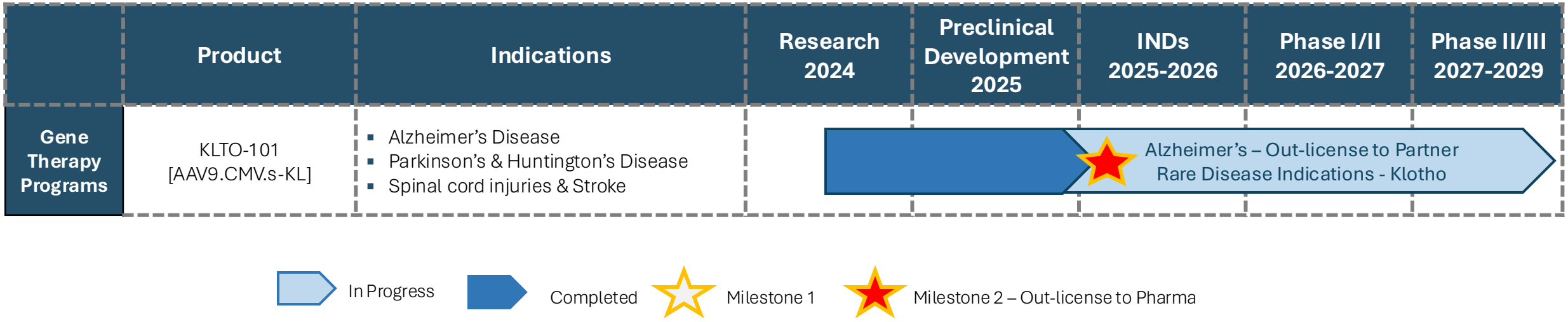


The group overexpressing s-KL showed better long-term memory. Shown by its significantly higher preference for the platform (P) quadrant as compared to the control group. Inhibition of s-KL had the opposite effect.

[11] Masso, *et al*. 2017

AD KLTO-101 Clinical & Regulatory Pathway

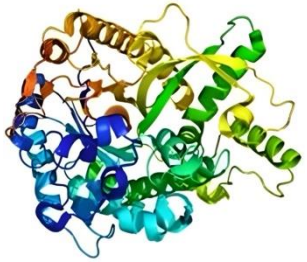
- Submit IND for Phase 1B/2A in patients with early AD and Fast Track application, 4Q,2025
- Initiate trial 1Q 2026
- Proposed clinical trial – Randomized placebo-controlled trial to evaluate the safety and efficacy of KLTO-101 in approximately 100-200 patients with early AD, randomized 1:1; AD pathology 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 is focused on the development of innovative, disease-modifying cell and gene therapies.
- The Klotho gene (s-KL) holds the promise to transform the treatment of neurodegenerative and age-related disorders, such as ALS, Alzheimer's and Parkinson's disease.

- Intellectual Property – patented isoform of Klotho gene produced primarily in the CNS
- Clinical Pipeline targets disease states with high unmet medical needs
- Pioneering proprietary protein, cell, and gene therapeutics
- Seasoned Executive Team
- World Class Scientific and Strategic Advisors



Thank You!

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Klotho SM NEUROSCIENCES