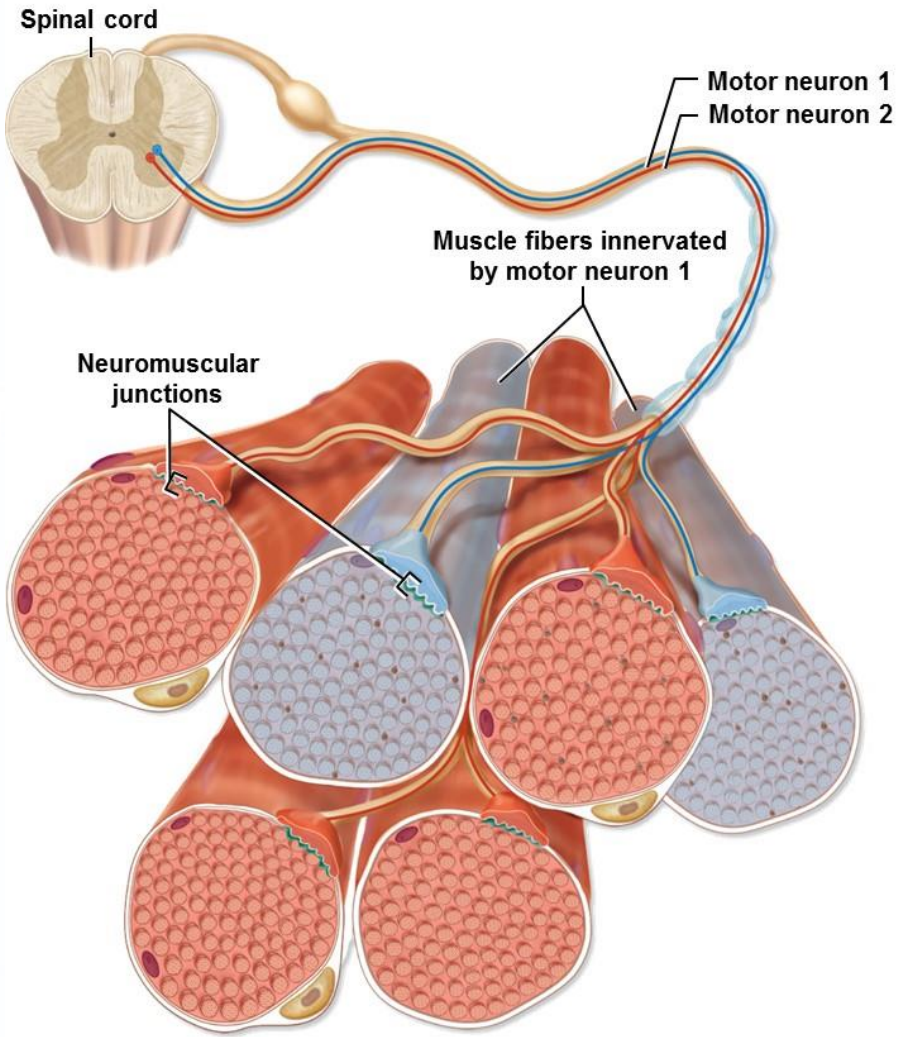
Matrix Metalloproteinase Inhibitor for the Treatment of Amyotrophic Lateral Sclerosis (ALS).

Non-Confidential Presentation

Amyotrophic Lateral Sclerosis (ALS)



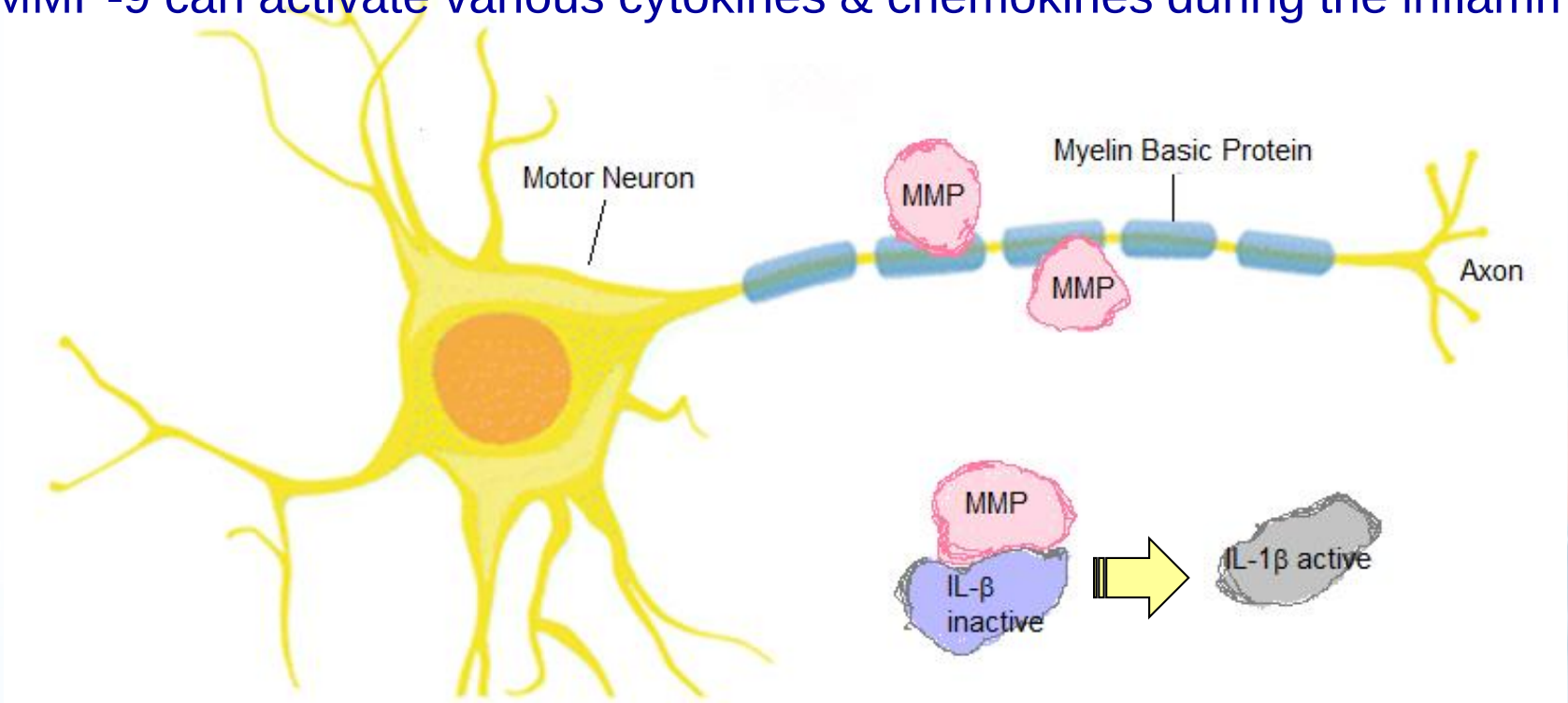
- A progressive neurodegenerative disease.
- 5600 new US cases per year, 40-70 y/o.
- Sporadic - 90 to 95% of all cases.
- Familial - accounts for 5 to 10% of all cases.
- The average life expectancy after diagnosis is two to five years.
- The disease affects fast-twitch fatigable (FF) motor neurons “the cells that control voluntary muscle activity such as speaking, skeletal muscle movement, breathing & swallowing” but leave slow-twitch (S) motor neurons alone ‘the cells that control eye movement.”

Matrix Metalloproteinases (MMPs)

- The MMP family consists of 24 members of zinc dependent proteinases that are responsible for digesting the various structural components of the extracellular matrix.

- MMP-2 and MMP-9 are a subset of MMPs that can breakdown myelin basic protein (MBP) which is a key component of the myelin sheath of motor neurons.

- MMP-2 and MMP-9 can activate various cytokines & chemokines during the inflammatory process.



MMPs & ALS

- Elevated levels of MMP-2 & MMP-9 have been reported in the skin, CSF and blood of people with ALS (PALS).[1,2]
- Microarray profiling studies in SOD1 mice have shown that MMP-9 is one of a few genes that are selectively expressed >10 fold in FF motor neurons as compared to S motor neurons[3]
- MMP-9 knockout of SOD-1 mice extend animal survivability by 25% as compared to wild-type and significantly alter gene expression of many phsiological processess.[3]

1) Fang, L.; et al. Linking neuron and skin: matrix metalloproteinases in amyotrophic lateral sclerosis (ALS), J. Neurol Sci., 285(1-2), 62-66, (2009).

2) Demestre, M.; et al. The pro and the active form of matrix metalloproteinase-9 is increased in serum of patients with amyotrophic lateral sclerosis, Journal of Neuroimmunology, 159, 146-154, (2005).10

3) Kaplan, A; et al., Neuronal matrix metalloproteinase-9 is a determinant of selective neurodegeneration, Neuron, **81**, 333-348, (2014).

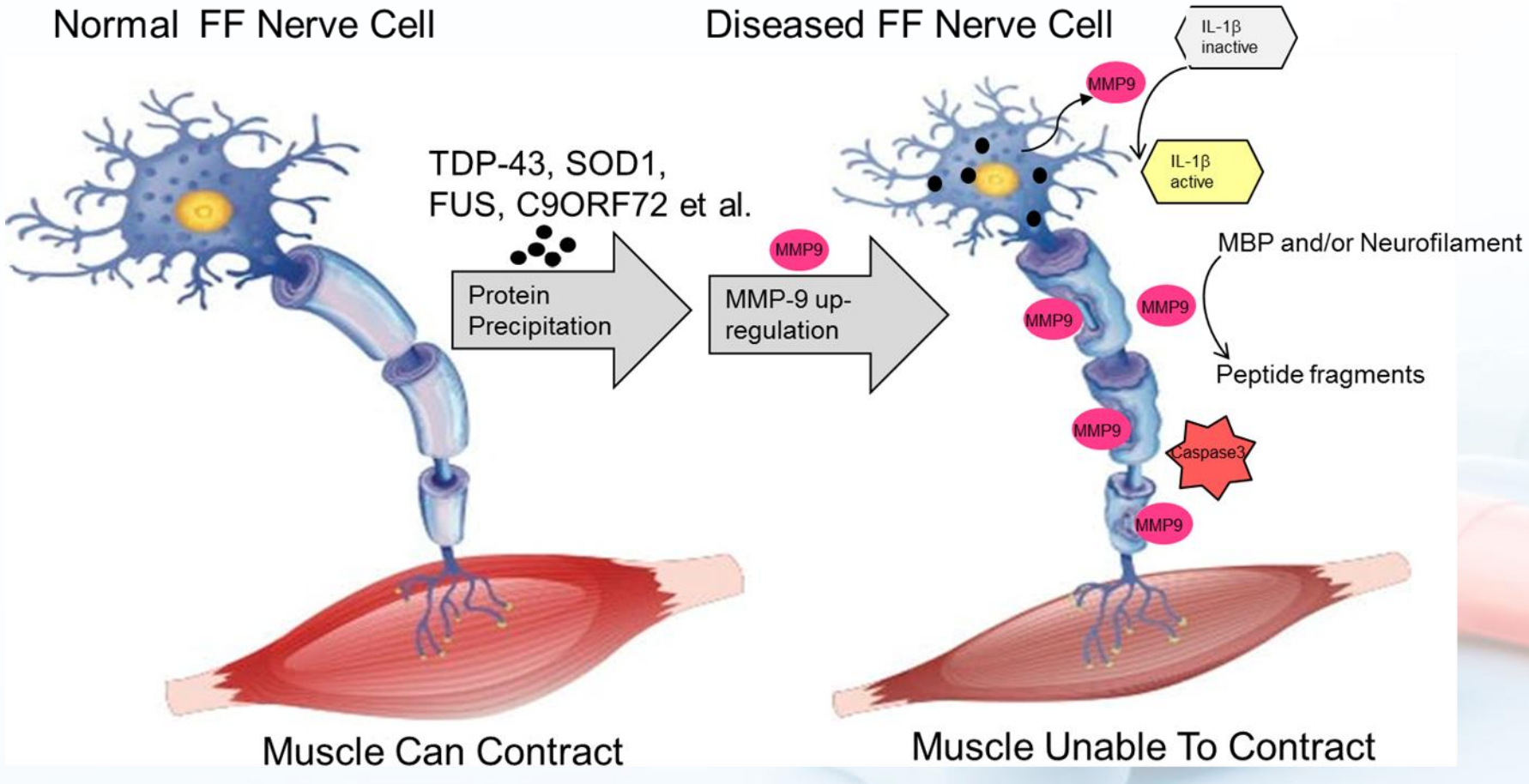
ALS & Human Biomarkers

- Aquilus tested the blood of a group of people with ALS (PALS) (n=30) and found a 7.5-fold higher (**650%)** mean MMP-9 protein level as compared to healthy, aged matched controls.

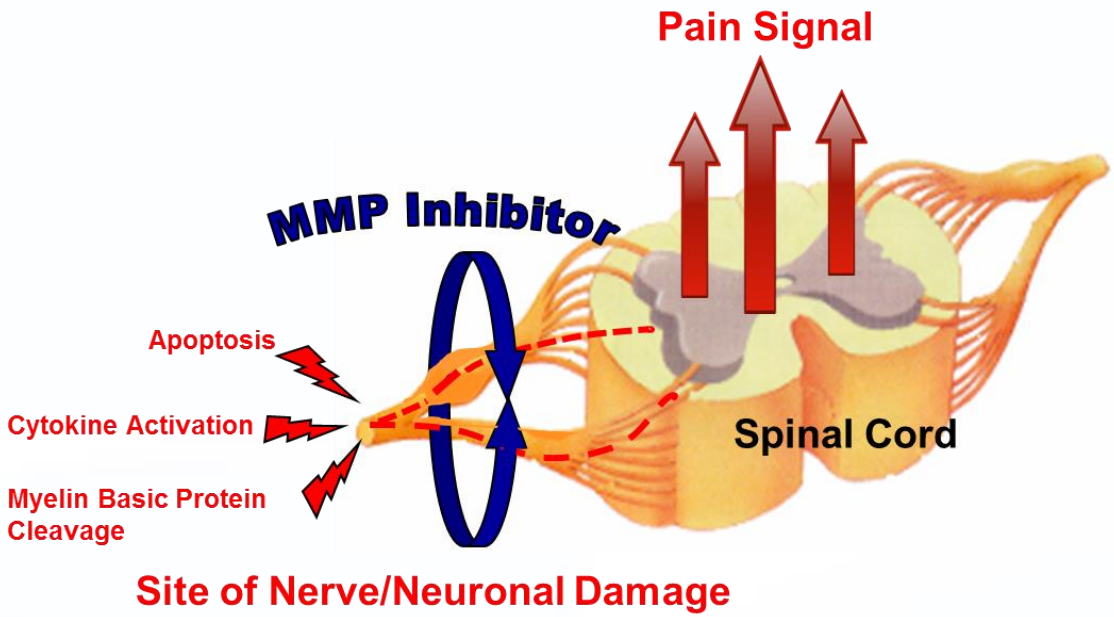
- Aquilus tested the blood of a group of aged matched, diabetics clinically diagnosed with peripheral diabetic neuropathy (n=124) and found the PALS group exhibited a 5-fold higher mean MMP-9 protein level over that of the aged matched diabetics.

Oral Dosing With a MMP Inhibitor to Reduce Inflammatory Processes Leading to Motor Neuron Cell Death

- Aquilus believes that ALS is a result of systemic inflammatory processes initiated through various known (SOD1 or TDP-43, et al.) gene mutations that trigger overproduction of MMP-9 in FF motor neurons. MMP-9 then degrades the BBB, MBP and neurofilament, activates various cytokines and upregulates caspase levels, all leading to neuronal cell death.



AQU-118 : A Safe & Orally Bioavailable MMP-2/-9 Inhibitor



➢ AQU-118 is a potent, small molecule inhibitor of MMP-2 and MMP-9 which when given orally has been found to significantly reduce nerve damage in several different rodent animal models of neuropathic pain & nerve injury*

*Henry, M.A.; et al.. Effect of a novel, orally active matrix metalloproteinease-2 and-9 inhibitor in spinal and trigeminal rat models of neuropathic pain. *J. Oral Fac. Pain Headache* **2015**, *29*, 286–296.

*Kwan, M.Y.; et al. Biomarker analysis of orally dosed, dual active, matrix metalloproteinase (MMP)-2 and MMP-9 inhibitor, AQU-118, in the spinal nerve ligation (SNL) rat model of neuropathic pain. *Int. J. Mol. Sci*. **2019**, *20*, 811.

AQU-118 Project Status for IND Submission for the Treatment of ALS

TASK	Completed	12-months
In-vitro tox including hERG	✓	
Non-GLP pharmacokinetics	✓	
Preclinical efficacy observed in animal pain models	✓	
Off-target screening	✓	
GMP synthesis & API stability studies*	✓	
GLP rat tox (MTD & 28 day) & Irwin (CNS)	✓	
GLP dog tox (MTD), respiratory & cardiovascular	✓	
Pre-IND meeting	✓	
Formulation stability testing of drug product		✓
GLP 28-day dog tox and rat micronucleous Study		✓
IND submission		✓

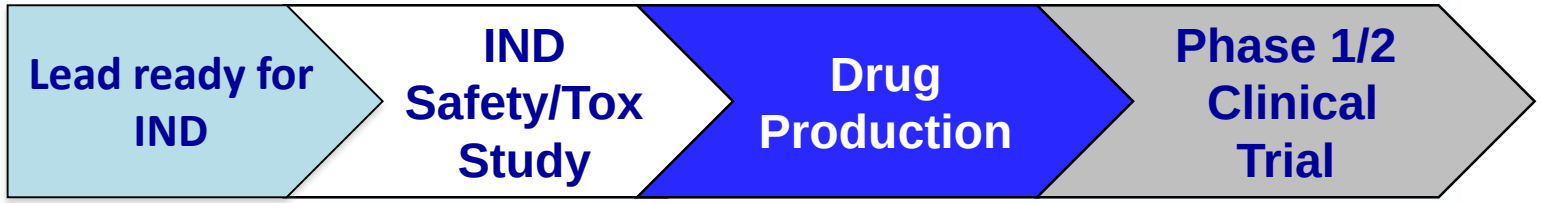
*Sufficient GMP AQU-118 has been produced for both IND studies and early clinical development.

AQU-118 Is Fully Protected By Global Patents

➢ Fully issued patents for composition of matter and method of use in the following countries:

United States	Germany	Israel
Mexico	Spain	Australia
England	Italy	China
Ireland	Russia	Korea
France	Japan	

Cash Flow Diagram & AQU-118 Trial Time-Line



Timeline	2022	2023
Cost	Fully Funded*	Needing to Raise
Milestones	Complete remaining IND enabling safety studies & preclinical formulation stability study.	Phase 1/2 ALS Biomarker Clinical Trial of orally dosed AQU-118 in people with ALS (PALS) (includes biomarker analysis, PK & physical exam).*

*Aquilus has received funds through a Lawrence and Isabel Barnett Drug Development grant award sponsored by the ALS Association and a grant award from the Department of Defense (DOD) that will allow Aquilus to fully complete all of the remaining IND enabling studies.

Management

Irving Sucholeiki, Ph.D., President & CEO

-24 years industrial experience as a medicinal chemist (Eli Lilly, MDS Proteomics, Alantos Pharmaceuticals).

Darrell J. Nix, Ph.D., Vice President of R & D

-18 years industrial experience as a pharmacologist.

-Development team for VELCADE™ CTD, Nutropin Depot® and the recently approved, ISTODAX®

Dr. Roy Sucholeiki, M.D. Vice President of Clinical Development & CMO

-Neurologist / Neurophysiologist, Division of Neurosciences - Northwestern Medicine - Central Dupage Hospital.

Consultants/Scientific Collaborators

Professor Robert Bowser, Chairman, Department of Neurobiology, Barrow Neurological Institute

Professor Rita Sattler, Associate Professor, Barrow Neurological Institute.

Professor Daniela Zarnescu, Professor of Molecular & Cellular Biology, University of Arizona

Professor Peter Noakes, Professor, School of Biomedical Sciences, The University of Queensland

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