PIONEERING GENE THERAPIES FOR RARE CNS DISEASES

LYSOGENE

Pioneering gene therapies for CNS disorders

Advanced Therapies – Opportunities and Challenges
14th November, London

Michaël Hocquemiller

Disclosure Information

Michael Hocquemiller, PhD is a full time employee and shareholder of LYSOGENE.

The investigational use of AAVrh10-SGSH gene therapy for MPS IIIA will be presented.

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LYSOGENE FOCUS

- Lysogene was founded in 2009 by Karen Aiach, the parent of an MPS IIIA (Sanfilippo A) child
- Co-founded with the world-leading gene therapy expertise of Olivier Danos
- Lead product candidate (LYS-SAF302) is entering a pivotal phase 2/3 trial in MPS IIIA patients.

Karen Aiach | MBA
Founder,
Chief Executive Officer
Board Member
*European Medicines Agency (PDCO)**
Arthur Andersen
Consultancy Boutique (founder)
Ethics committee

Olivier Danos | PhD
Co-Founder
Scientific Advisor, Board Member,
Chief Scientific Officer RegenX Bio.
Biogen ,Kadmon, UCL, Genethon, Pasteur Institute

INDICATION	PROGRAM	VECTOR	ENZYME	DEVELOPMENT STAGE: PRE-CLINICAL / PHASE I/II* / PIVOTAL	COMMENTS
Sanfilippo A (MPS IIIA)	**LYS-SAF302**	AAVrh10	N-sulfoglycosamine sulphohydrolase	*Non clinical regulatory studies*	▫ Pivotal trial to begin by H1 2018 (FPI**)
GM1 Gangliosidosis	**LYS-GM101**	AAVrh10	Beta-galactosidase-1		▫ Phase I/II trial to begin in 2019 (FPI**)

**MPS IIIA Phase I/II: LYS-SAF301, first generation program*
*** FPI : « First Patient In », treatment of the first patient*

MPS IIIA (MUCOPOLYSACCHARIDOSIS TYPE IIIA /SANFILIPPO SYNDROME TYPE A)

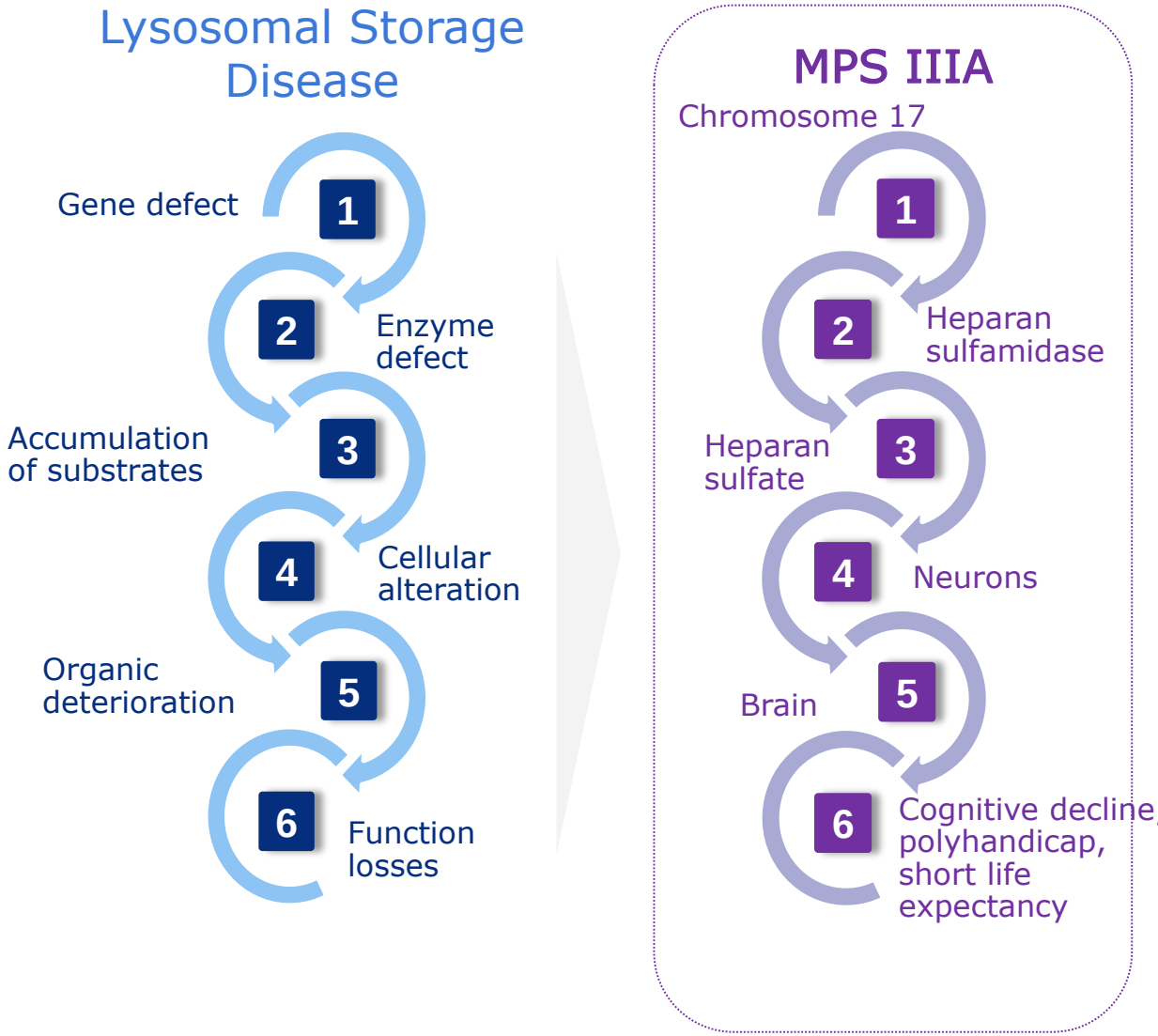
Inheritance
Autosomal recessive lysosomal storage disease

Symptoms
First clinical symptoms occurring early in life
Severe behavioral, sleep and cognitive deficiencies and progressive loss of functions such as talking, eating, walking
Less than 15% patients survive beyond their teens

Population
Incidence: 0.5-1.2 / 100,000 live births (1)
Point prevalence worldwide: 3000 (2)

Burden of disease
Extremely deteriorating quality of life, devastating for patients and families (3)
Massive social/economic costs

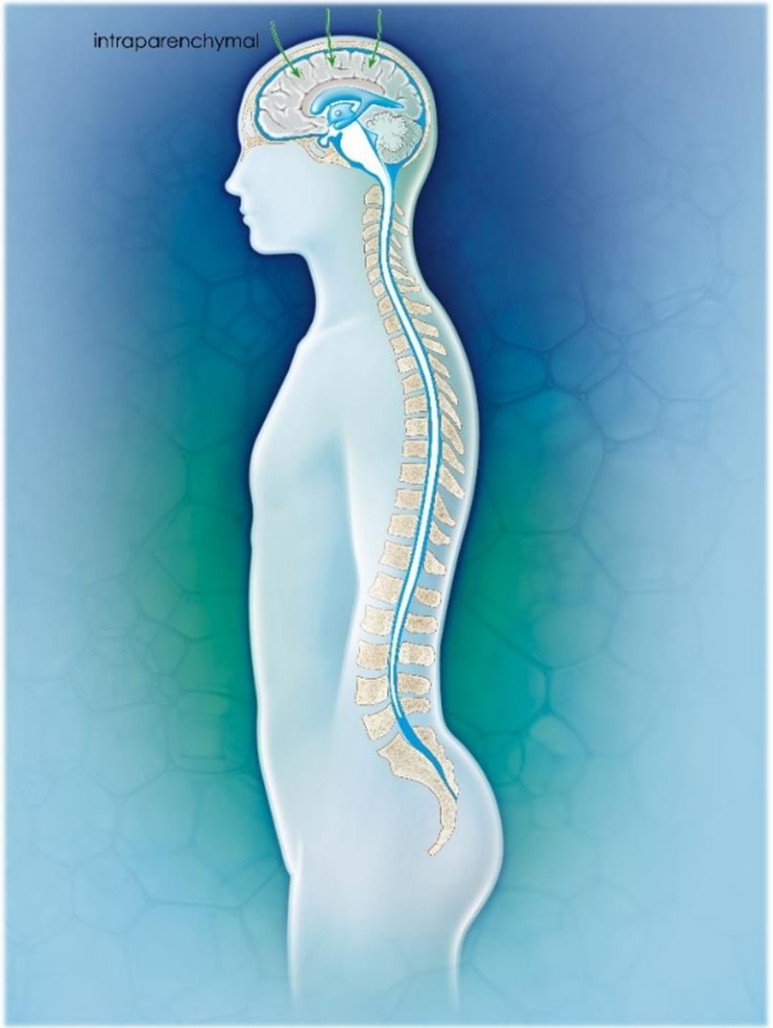
Treatment
No approved or curative treatments



Notes:
(1) Heron (2011); Poorthuis (1999)
(2) Average life expectancy: 15 years;
(3) Grant (2012)

LYSOGENE'S APPROACH TO MPS IIIA

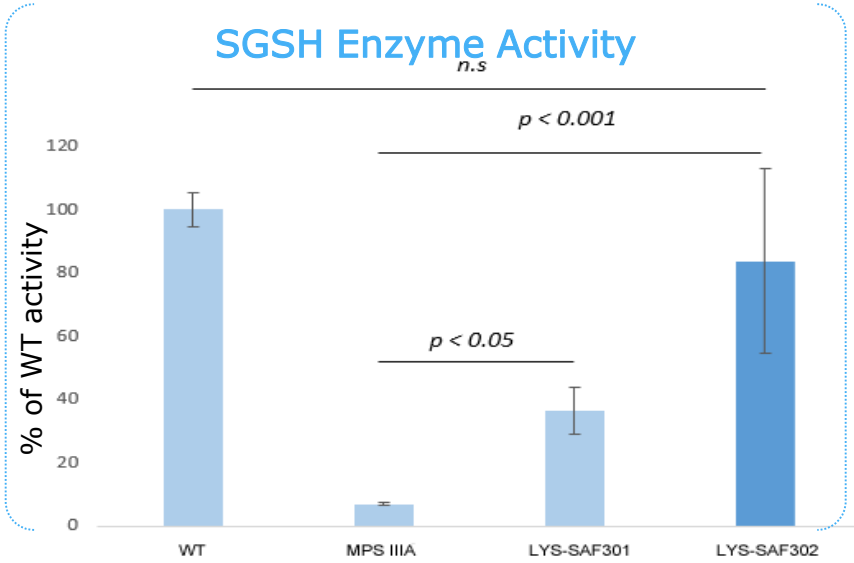
- To overcome the blood brain barrier hurdle, therapy must get **to the CNS** with a broad distribution throughout the brain so that the missing enzyme is **sustainably** produced where it is most needed
- SGSH is a secreted enzyme and can therefore have an effect on cells distant from transfected cells via cross correction
- AAV-mediated transfection of neurons is expected to express the transgene, SGSH, long-term, as supported by existing brain expression data e.g., *long-term transgene expression (AAV2-NRTN) has been shown up to 11.5 years in human Parkinson patients (R. Bartus, personal communication)*
- Lysogene has a unique expertise in gene therapy in MPS IIIA with 5 years safety data with LYS-SAF301 (1st generation product)
- Intense program optimization performed since the early Phase 1/2 LYS-SAF301 Study to support a Pivotal LYS-SAF302 Study



LYS-SAF302: AN OPTIMIZED SECOND-GENERATION PROGRAM

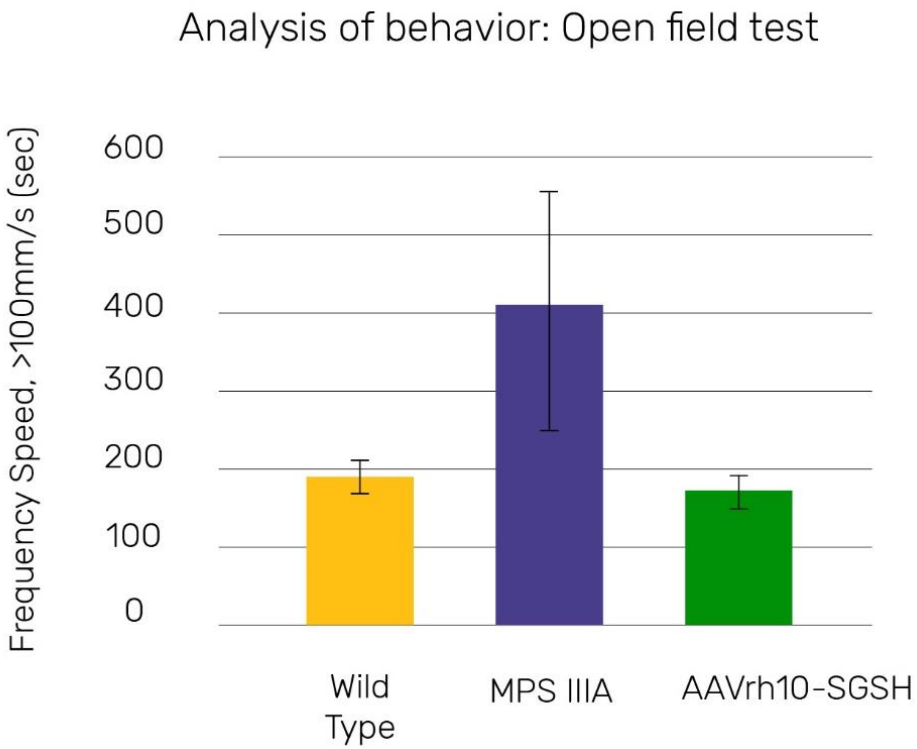
Product Candidate	LYS-SAF301	LYS-SAF302
Promotor	mPGK	CAG
Transgenes	SGSH cDNA & SUMF-1 cDNA	SGSH cDNA
Manufacture	Academic centres: Weill Cornell, University College London	Commercial CMO: Novasep, process development & optimization
Delivery	Physician-assembled device	Commercial device

Improved construct increases enzyme activity
MPS IIIA Mouse model



4 weeks post injection

NORMALIZATION OF BEHAVIOR IN MPS IIIA MOUSE MODEL

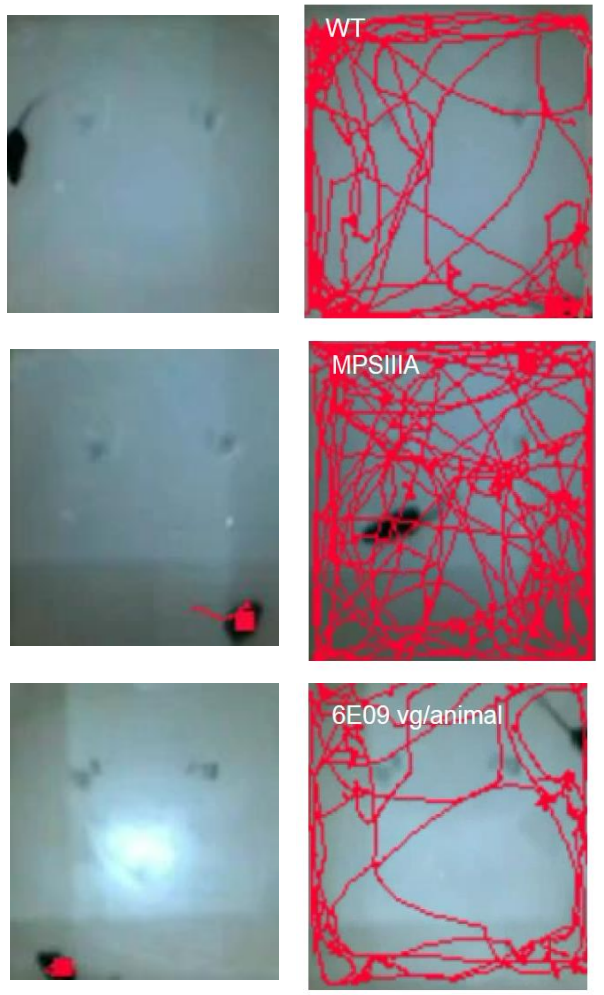


Shown as frequency of rapid exploration - 16wks post-injection

Wild Type

MPS IIIA untreated

MPS IIIA treated



Rostro-Caudal spread of Gadolinium, Vector and SGSH activity in Dog Brain Mapped onto Child's Brain

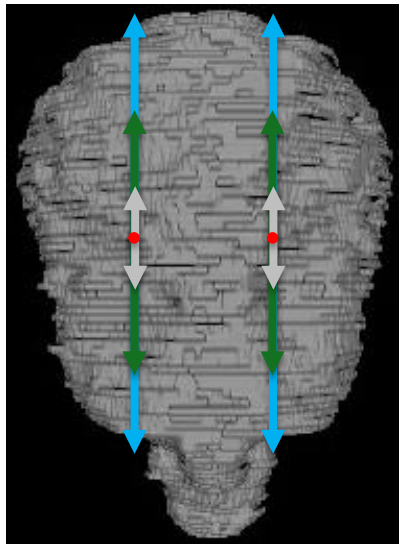
Injection sites

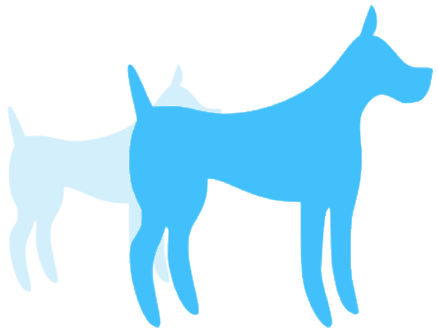
Slab with gadolinium signal

Slab with punches
> 0,1 vector copies per cell

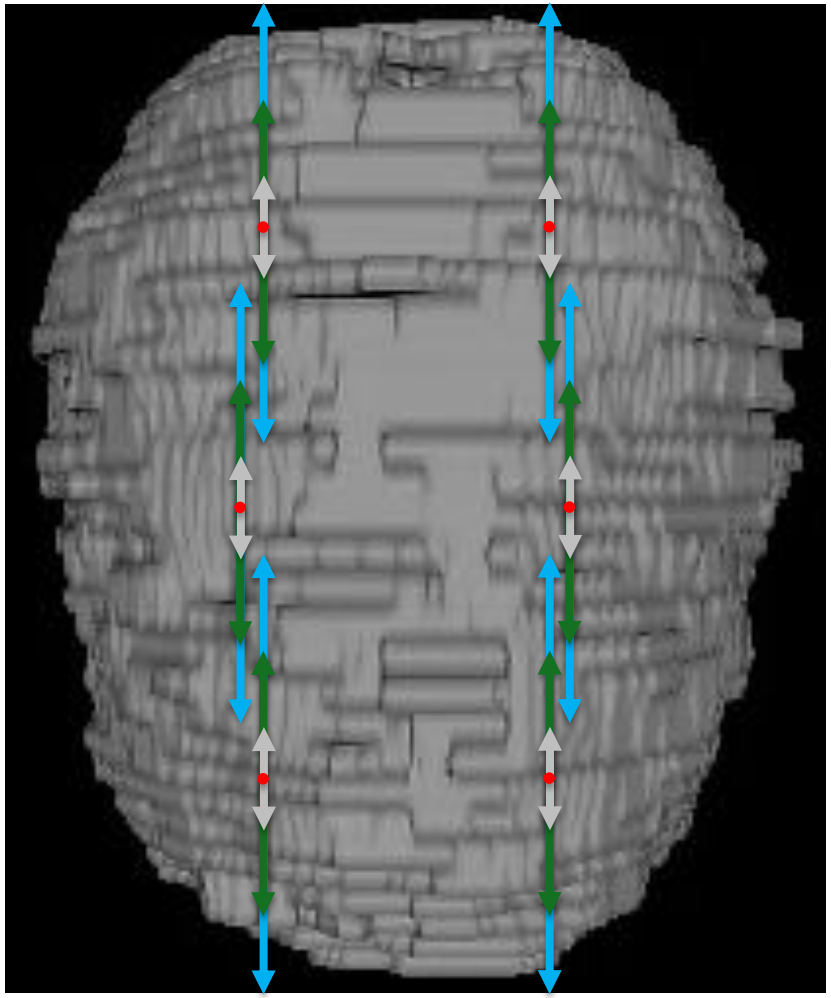
Slab with punches
> 10% enzymatic increase

Adult Dog: 65 cm^3





IIIA child 6 year old: 1003 cm^3



3 injections/hemisphere planned in clinical trial

LYS-SAF302: PIVOTAL STUDY DISCUSSED WITH FDA & EMA

Primary objective	✓	Assess the efficacy of direct to CNS delivery of LYS-SAF302 in improving or stabilizing the neurodevelopmental status of severe MPS IIIA patients after 12 months, compared with the natural history Powered to demonstrate disease stabilization using Development Quotient as PEP(1)
Endpoints	✓	Primary endpoints: Neurocognitive and motor development (Development quotient) Secondary endpoints: Behavior, sleep, QOL(2) , MRI(3), Biomarkers (CSF, blood, urine)
Sample size and sites	✓	N=20 patients • US: sites • EU: sites
First patient enrolled	✓	By Q2-2018
Study duration	✓	12-24 months (efficacy analysis) Study extension of additional 4 years, with secondary efficacy analysis at 24 months

(1): DQ= Development Age/Calendar age ;(2): QOL= Quality Of Life; (3): MRI= Magnetic Resonance Imaging

GM1 GANGLIOSIDOSIS

Inheritance

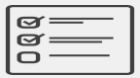
Lysosomal disease caused by mutations in the GLB1 gene, which encodes the β-galactosidase enzyme

Symptoms

Four clinical subtypes based on age of symptom onset and disease severity: early infantile, late infantile, juvenile and adult.
Severe neurodegeneration, seizures, coarse facial features.
100% lethal

Population[(1)]

Incidence: 1/200 000 to 1/100 000 live births
Prevalence: 2,000



Burden of disease

Extremely deteriorating quality of life, devastating for patients, and families

Treatment

No approved or curative treatments

Notes
(1): Pinto (2004), Poorthuis (1999), Meikle (1999), Severini (1999)

LYS-GM101: TRANSFORMATIONAL IMPROVEMENT OF SEVERE MOTOR DISTURBANCE AFTER TREATMENT WITH DIRECT TO BRAIN AAV GENE THERAPY

Direct to brain injections of an AAV prototype in GM1 cat model

6-7 month-old GM1 cat

5 year-old AAV-treated GM1 cat

Research Collaborations

Source: Douglas R. Martin lab, Scott-Ritchey Center at Auburn University School of Veterinary Medicine

CONCLUSION

- Intracerebral injection of AAV vector provides a durable therapeutic protein via a single administration.
- AAV serotype and route of administration choices are crucial and need to be supported by efficacy data in animal disease models of the disease and biodistribution studies in larger animals.
- Concerted efforts are required for gene therapy development to accelerate research through collaborations between academia, industry and patient organizations.

Thank you

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