Lysogene's gene therapy in Sanfilippo syndrome

Karen Aiach
Lysogene
CEO & Founder
Member of IRDiRC executive and interdisciplinary scientific committees

Lysogene background

"There is an urgent need to improve the health status of patients suffering from incurable life threatening disorders. Our mission is to develop and deliver cutting edge gene therapy solutions for CNS disease"

- Founded in 2009 with a focused scientific development plan, pragmatic approach and bold mission.
- 2011: first gene therapy clinical trial in Sanfilippo syndrome (Mucopolysaccharidosis IIIA)
- 2014: raised €16,5 million
- Small team using strong collaborative network of world leaders in gene therapy research and development

Karen AIACH, M.Sc./MBA
Founder, CEO

Olivier DANOS, Ph.D.
Co-founder,
Senior Scientific Advisor

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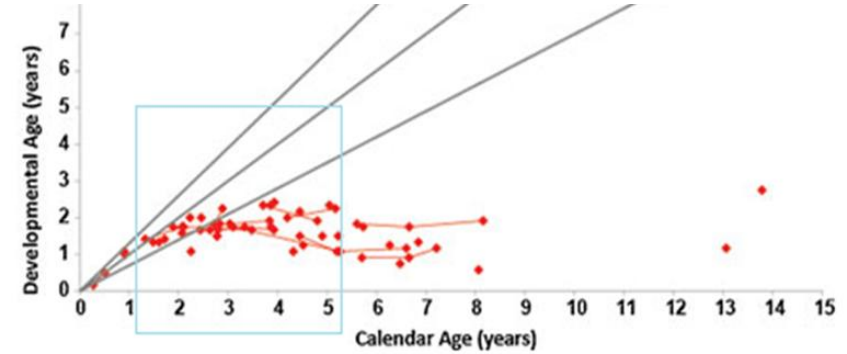
Mucopolysaccharidosis type IIIA disease

- Rare (live birth incidence approx 1:50,000 – 100,000) severely debilitating neurodegenerative lysosomal storage disease
- Enzyme defect causes accumulation of heparin sulfate
- Primary block triggers a pathological cascade of CNS manifestations: severe mental retardation with behavioural problems and only mild somatic disease –CNS+++
- Age at diagnosis 1-3 years
- Median life expectancy is 15-18 years
- No treatment available



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Adapted from Buhrman et al. (2013). Natural history of MPSIIIA. J Inherit Metab Dis

- video

Therapeutic development challenges

- Therapies delivered to the vascular system do not cross the Blood Brain Barrier
- Treatment should be initiated early as damage to the brain will be irreversible
- Lack of objective, validated evidence detailing the neurocognitive development, hyperactivity, sleeping disorders and quality of life
- No single centre/country has a sufficient number of patients to conduct the clinical research
- New developments in the treatment are on-going (gene therapy, enzyme replacement therapy, haemopoetic stem cell gene therapy) → trial recruitment issues, duplication of natural history studies…
- The development of gene therapy poses specific challenges for health technology assessment

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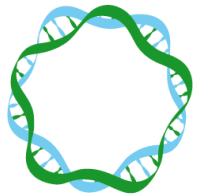
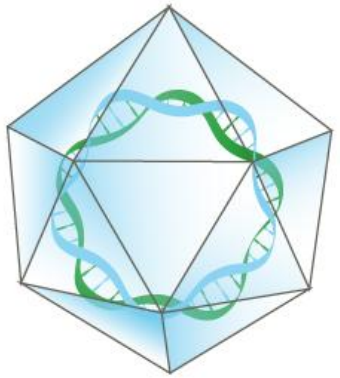
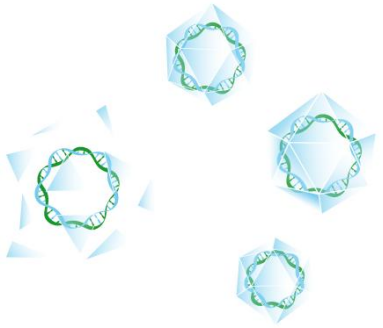
Lysogene's Lead Product: AAVrh10.hSGSH

- Name of the active substance:
  - ✓ Adenovirus Associated Viral vector serotype 10 carrying the human N-sulfoglycosamine sulphohydrolase
- Mechanism of action
  - ✓ Stable establishment into the cell of DNA molecule encoding SGSH protein
  - ✓ Cascade: Correction of metabolic defect / Reduction/Reversal of toxic storage Reduction / Reversal of Pathology / Improvement of functions / Improvement of Health Status and Quality of Life of patients and their families







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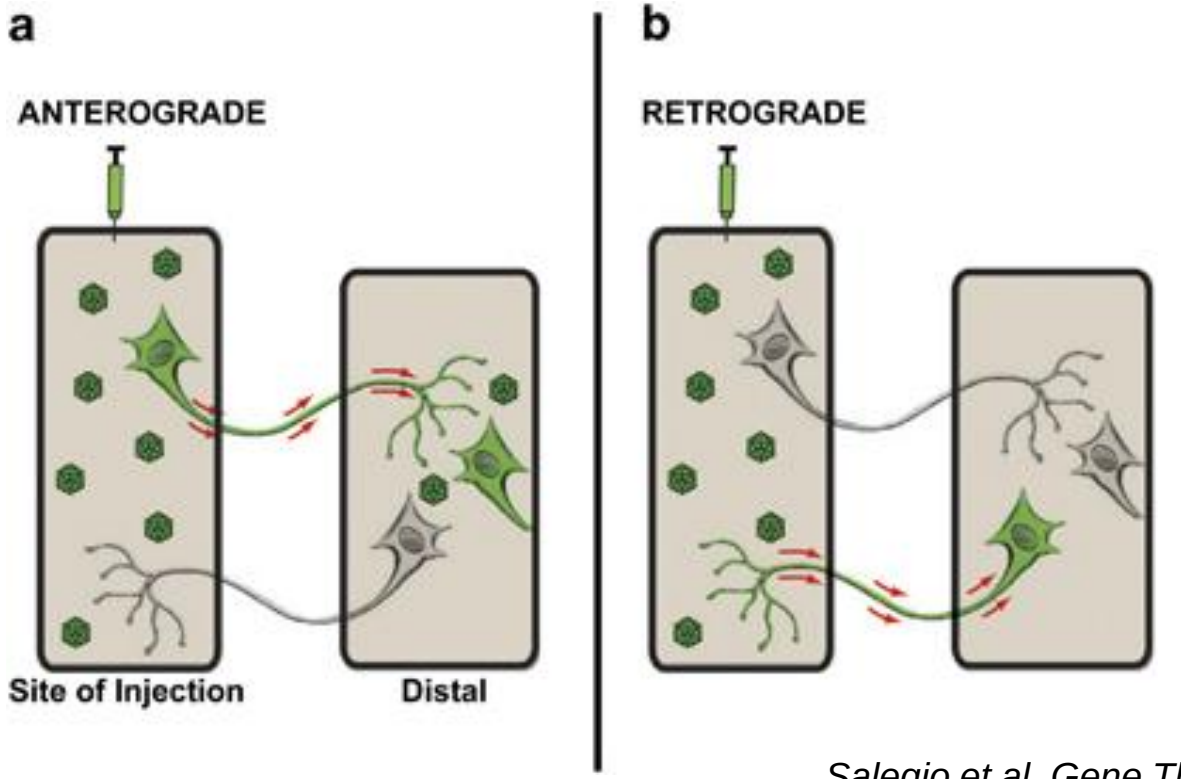
AAV neuronal transportation properties



Salegio et al. Gene Therapy, 2012

Vectors, especially AAV, can be transported along neuronal connections to distal location of injections sites

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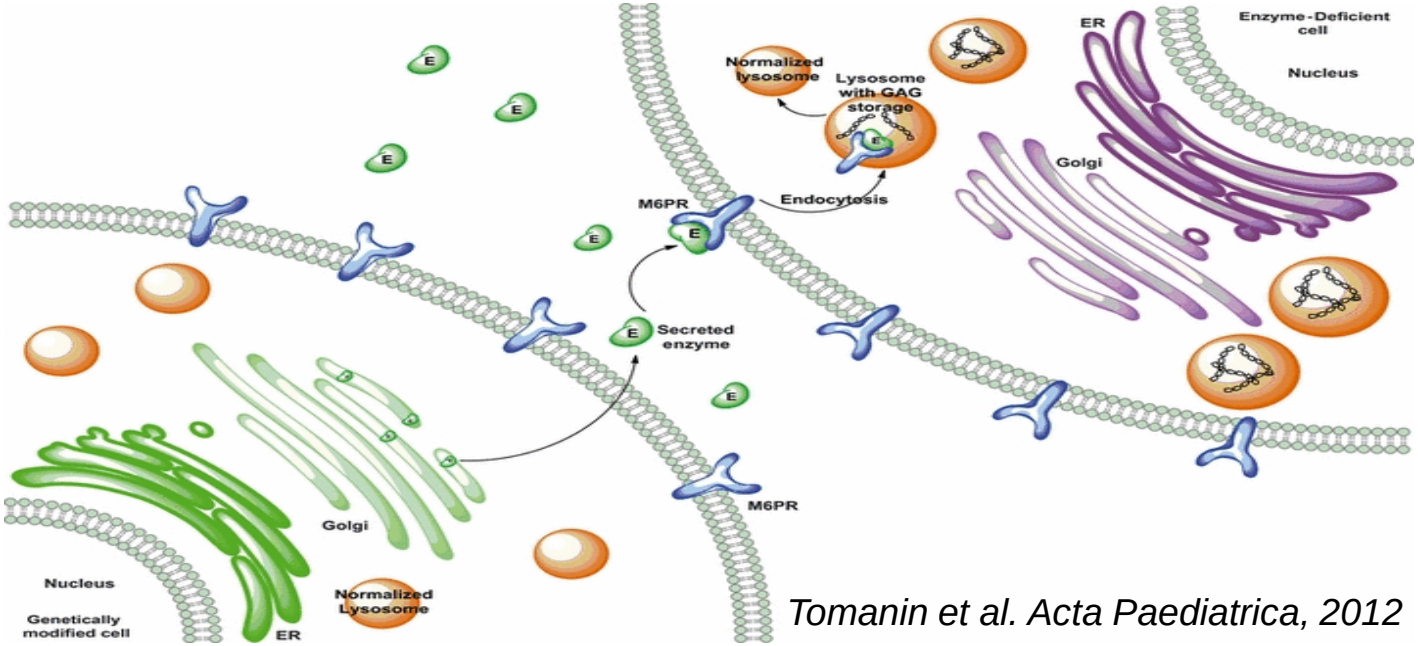
Lysosomal enzyme properties



Tomanin et al. Acta Paediatrica, 2012

- **Lysosomal enzymes cross-correction mechanism: once administered, newly synthesized lysosomal enzymes are secreted and available for adjacent and distant cells that transport them through the M6P receptor**

- **10-12% of normal level of enzymatic activity restauration are sufficient for a normal phenotype**

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AAV Serotypes in CNS

- To date, most CNS clinical studies have been conducted with AAV 2 serotype vectors, but within the last years, a number of other AAV serotypes have been characterized especially AAV5 and AAVrh10.
- AAVrh10 vector
  - ✓ Transduces a much larger area of the CNS and provides a higher level of transgene expression than AAV5, which is better than the commonly used AAV2 vector
    - ✓ AAV9 and rh10 mediate strong neuronal transduction in the dog brain (Swain GP, Prociuk M, Bagel JH, O'Donnell P, Berger K, Drobatz K, Gurda BL, Haskins ME, Sands MS, Vite CH., Gene Ther. 2013 Oct 17. doi: 10.1038/gt.2013.54.)
  - ✓ Reduces probability of attenuated gene transfer owing to pre-existing immunity (30% to 80% of humans have antibodies against the common human AAV serotypes 2 and 5) (Chirmule, Propert et al. 1999) and (Halbert, Miller et al. 2006)
  - ✓ For clinical applications, AAVrh10 is to be preferred to the preclinical stage AAV9 due to its favorable immunogenicity profile (Recombinant Advisory Committee, US, RAC Meeting June 2013)

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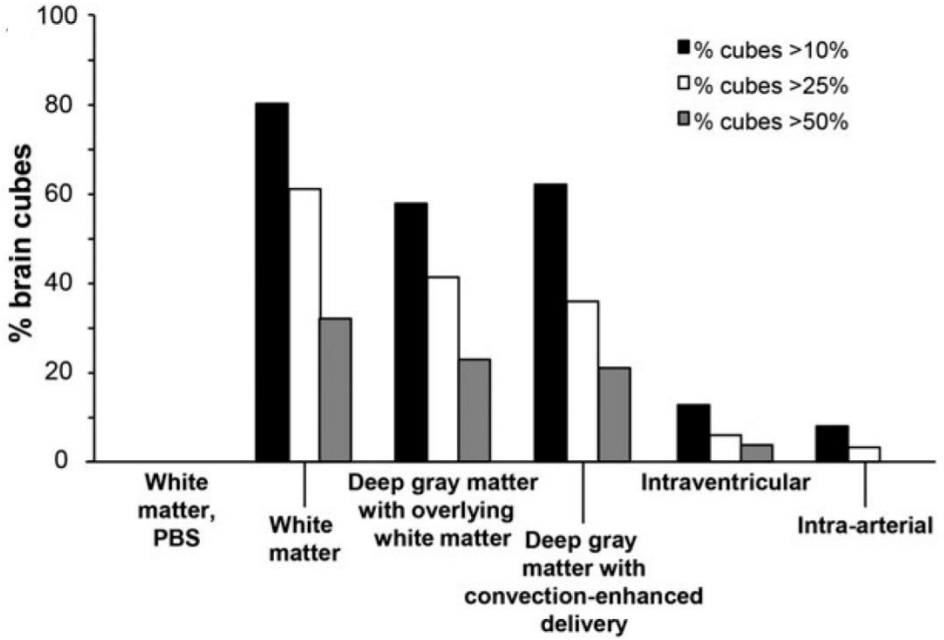
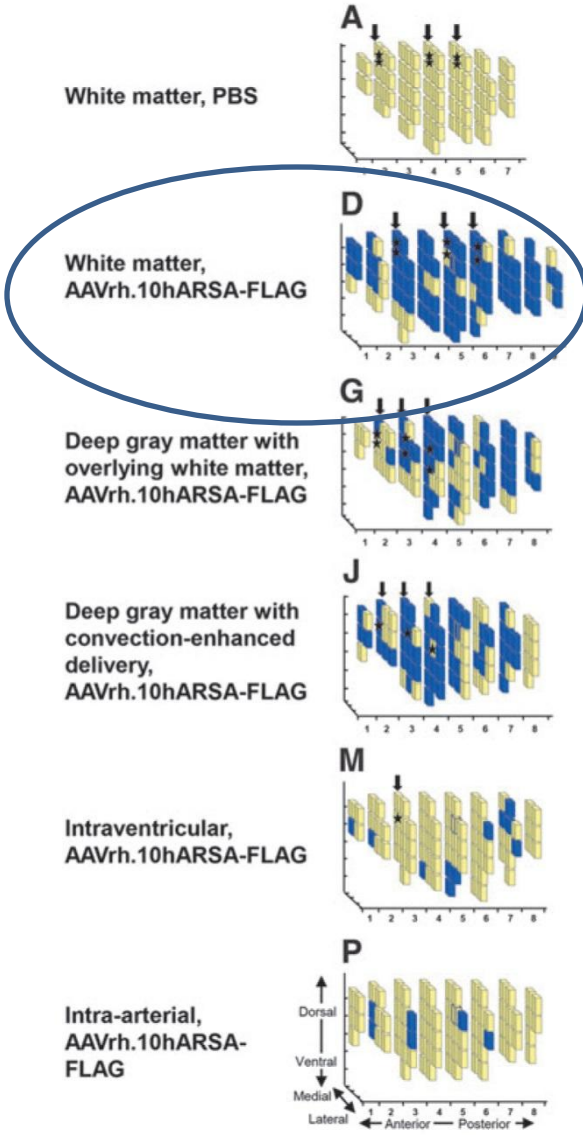
Intracerebral administration

- CNS administration into the white matter using frameless stereotaxic guidance
- Intracerebral administered gene therapy is the most advanced and proven strategy in humans:
  - Batten (Souweidane et al. J Neur Ped 2010)
  - Canavan trials (Leone et al. Sci Transl Med 2012)
  - Metachromatic Leukodystrophy (ClinicalTrials.gov number: NCT01801709)
  - Sanfilippo A (Tardieu et al. 2013)
  - Sanfilippo B (Institut Pasteur)

Comparative study of multiple routes of direct AAVrh10 CNS administration

- Objective: to assess the optimal CNS delivery route of an AAVrh.10 vector encoding ARSA in a large animal model for broadest distribution of ARSA enzyme.
- ➢ Of the five routes studied, administration to the white matter generated the broadest distribution of ARSA, with 80% of the brain displaying more than 10% increase in ARSA activity above PBS controls.





Rosenberg et al. 2014

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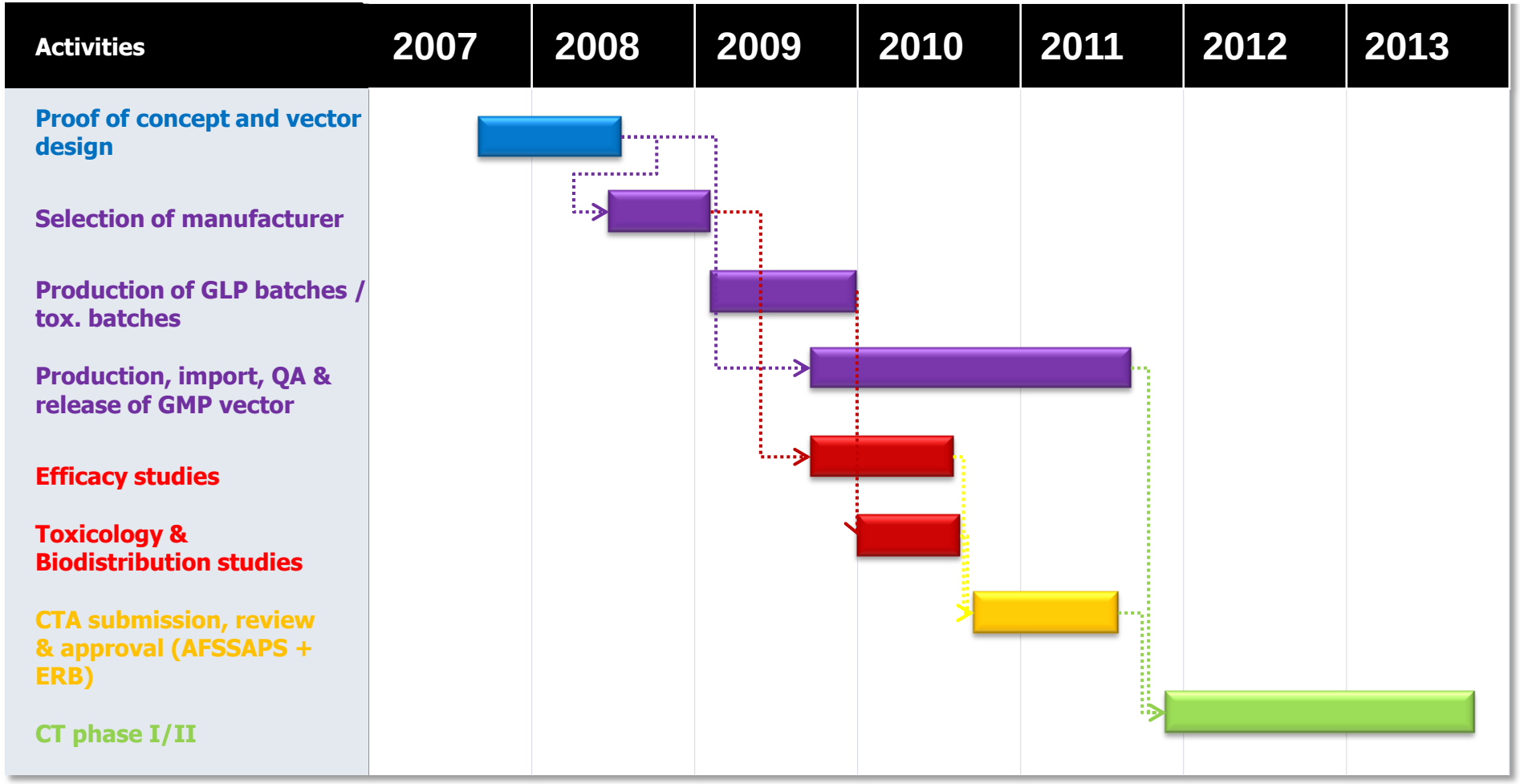
AAVrh10h.SGSH – translation from bench to bedside in < 5 YEARS



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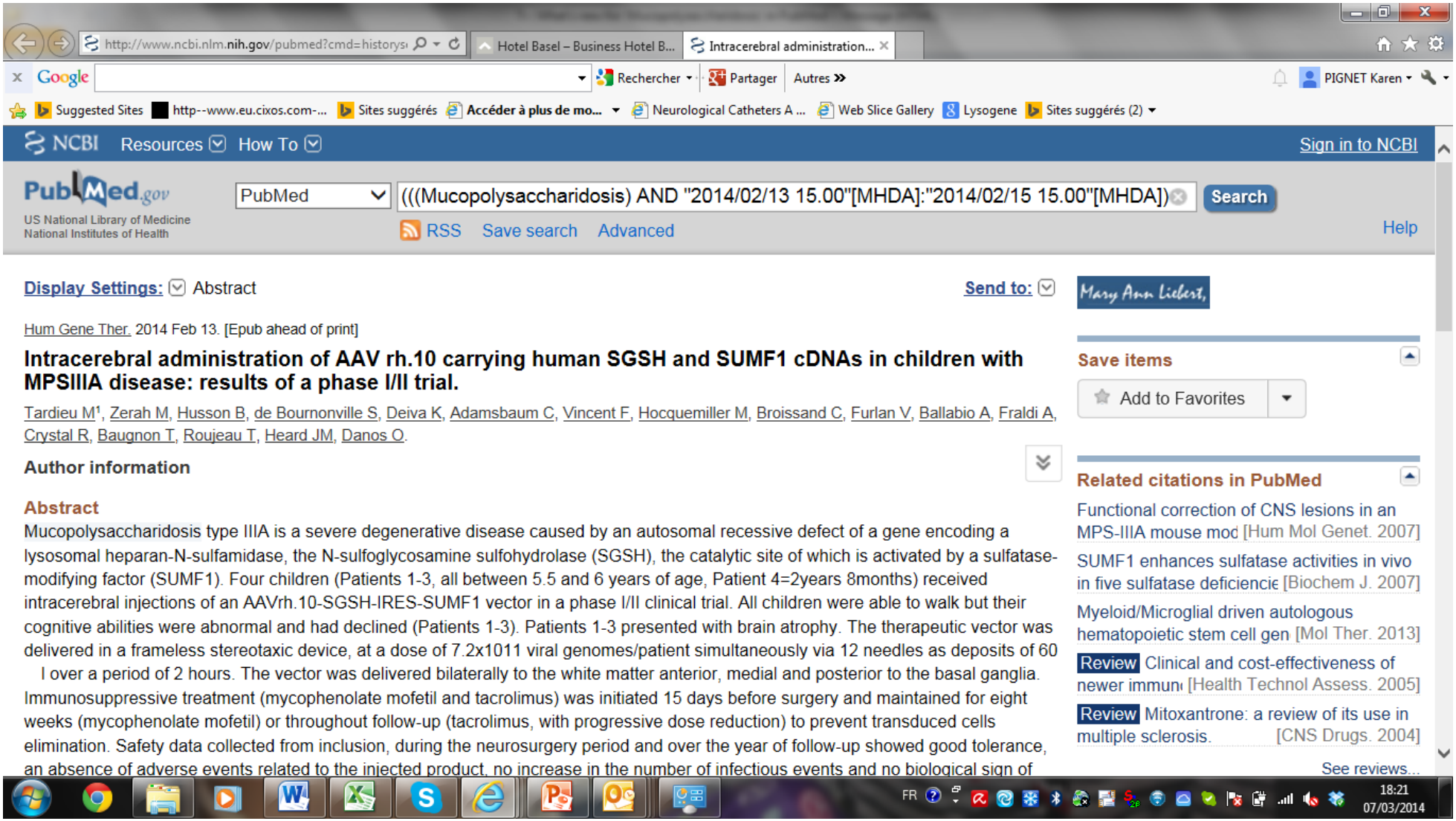
Tardieu et al., 2014 (HGT)



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(((Mucopolysaccharidosis) AND "2014/02/13 15.00"[MHDA]:"2014/02/15 15.00"[MHDA])

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Hum Gene Ther. 2014 Feb 13. [Epub ahead of print]

Intracerebral administration of AAV rh.10 carrying human SGSH and SUMF1 cDNAs in children with MPSIIIA disease: results of a phase I/II trial.

Tardieu M[1], Zerah M, Husson B, de Bournonville S, Deiva K, Adamsbaum C, Vincent F, Hocquemiller M, Broissand C, Furlan V, Ballabio A, Fraldi A, Crystal R, Baugnon T, Roujeau T, Heard JM, Danos O.

Author information

Abstract

Mucopolysaccharidosis type IIIA is a severe degenerative disease caused by an autosomal recessive defect of a gene encoding a lysosomal heparan-N-sulfamidase, the N-sulfoglycosamine sulfohydrolase (SGSH), the catalytic site of which is activated by a sulfatase-modifying factor (SUMF1). Four children (Patients 1-3, all between 5.5 and 6 years of age, Patient 4=2years 8months) received intracerebral injections of an AAVrh.10-SGSH-IRES-SUMF1 vector in a phase I/II clinical trial. All children were able to walk but their cognitive abilities were abnormal and had declined (Patients 1-3). Patients 1-3 presented with brain atrophy. The therapeutic vector was delivered in a frameless stereotaxic device, at a dose of 7.2x1011 viral genomes/patient simultaneously via 12 needles as deposits of 60 l over a period of 2 hours. The vector was delivered bilaterally to the white matter anterior, medial and posterior to the basal ganglia. Immunosuppressive treatment (mycophenolate mofetil and tacrolimus) was initiated 15 days before surgery and maintained for eight weeks (mycophenolate mofetil) or throughout follow-up (tacrolimus, with progressive dose reduction) to prevent transduced cells elimination. Safety data collected from inclusion, during the neurosurgery period and over the year of follow-up showed good tolerance, an absence of adverse events related to the injected product, no increase in the number of infectious events and no biological sign of

Mary Ann Liebert,

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Related citations in PubMed

Functional correction of CNS lesions in an MPS-IIIA mouse mod [Hum Mol Genet. 2007]

SUMF1 enhances sulfatase activities in vivo in five sulfatase deficiencie [Biochem J. 2007]

Myeloid/Microglial driven autologous hematopoietic stem cell gen [Mol Ther. 2013]

Review Clinical and cost-effectiveness of newer immun [Health Technol Assess. 2005]

Review Mitoxantrone: a review of its use in multiple sclerosis. [CNS Drugs. 2004]

See reviews...

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Phase I/II results

Safety (primary endpoint)

- Good tolerance
- Neurosurgery itself was uneventful
- Absence of adverse events related to the injected product
- No increase in the number of infectious events
- No biological sign of toxicity related to immunosuppressive drugs

Efficacy (secondary endpoint)

- Neuropsychological evaluations suggested improvement, although moderate, in behaviour and attention in the 3 older patients who showed cognitive decline at inclusion.
- Neurocognitive benefit was more marked in the youngest patient
- Improvement in behavioural disorders, hyperactivity and sleep, reported by the parents (without symptomatic medications)

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Lysogene looking forward

Phase II/III trial

Open label, single arm, multi-centric, phase II/III clinical study of intracerebral administration of AAVrh10 carrying the human SGSH cDNA for the treatment of MPSIIIA

Anticipate two to three clinical trial sites in Europe & US

Minimum of 12 patients

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Natural history study

- Several natural history studies (Buhrman (2013), Delaney (2013), Delgadillo (2013), Guffon (2011), Héron (2010) Muschol (2004), Rumsey (2014), Valstar (2008); but
- No satisfactory natural history study that can be used in monitoring response to therapeutic interventions
- Commercial registries exist for numerous LSD but the data is not shared and collects data relevant to one specific study
- Primary objective: to collect data into a multicentre observational study to provide comparative data for clinical trial
- Secondary objective: design standard protocols and assessment tools for MPSIIIA
- Core data sets made available to the research community via RD-Connect

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Parent reported outcome data

- Mixed method approach to fully appreciate: burden of disease on families and treatment benefits
  - Children's Sleep Habits Questionnaire
  - Child behaviour checklist
  - Quality of life
  - Qualitative semi-structured interviews

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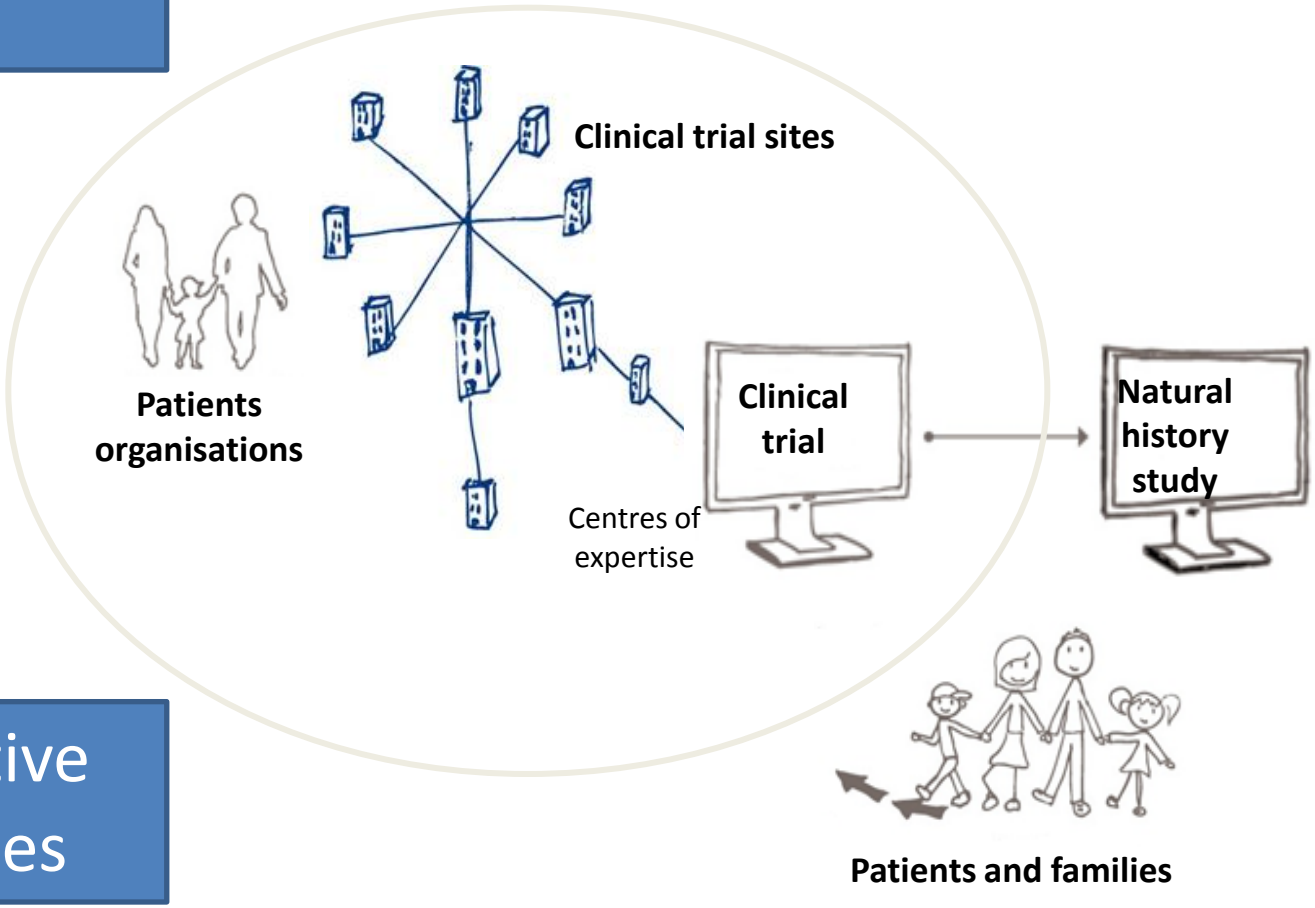
Patient access to the phase II/III trial

Equal access to patients Europe-wide

Collaboration with MPS family groups for dissemination, support and logistics

Impartial, non-directive information to families



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Contribution towards IRDiRC objectives

- ✓ First safe and efficient therapy for MPSIIIA
- ✓ Linkages with biobanks, natural history and clinical trials
- ✓ Defining data access structures
- ✓ Substantial patient representation in development programme
- ✓ Applying and validating IRDiRC models, systems and tools
- ✓ Potential to push additional boundaries in ethical & legal aspects of rare diseases, paediatrics and gene therapy

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Thank you

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