GENETICALLY MODULATED SUBSTRATE REDUCTION THERAPY for SANFILIPPO SYNDROME – proof of principle

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Mucopolysaccharidosis (MPS) Type III

- Autosomal recessive
- Lysosomal Storage Disorders
  - Sub-type of MPSs; glycosaminoglycans (GAGs)
  - Accumulated substrate: heparan sulphate

- 4 different diseases:
  - III A
  - III B
  - III C
  - III D

depending on the defective enzyme
Mucopolysaccharidoses (MPS)

- Chronic
- Progressive
- Large spectrum of severity & symptoms

MPS III
(= Sanfilippo Syndrome)
Available Therapies

- None!

...only symptomatic!

ameliorate symptoms
support disabled patients

ERT for neurodegenerative MPS would require the introduction of active enzyme into the CNS

extra difficulties!
Still, it’s being attempted with some promising results
Available Therapies

None!

...only symptomatic!

ERT for neurodegenerative MPS would require the introduction of active enzyme into the CNS.

Still, it’s being attempted with some promising results.

Perfect Target for Substrate Reduction Approaches!
gSRT for MucopolySaccharidosis Type III

*genetic substrate reduction*
gSRT FOR MucoPolySaccharidosis TYPE III

early stage of the HS biosynthetic cascade

![Diagram showing the early stage of the HS biosynthetic cascade with enzymes and molecules involved in the pathway of Dermatan/Chondroitin Sulfate (DS/CS) and Heparan Sulfate (HS).]
gSRT FOR MUCOPOLYSACCHARIDOSIS TYPE III

naturally occurring post-transcriptional gene silencing process

Designed to induce RNAi

siRNA

MPS III fibroblasts
gSRT FOR MucoPolySaccharidosis type III

- Control fibroblasts
- 24/48h incubation
- siRNA
- Harvest cells
- RNA extraction
- cDNA synthesis
- qRT-PCR (target gene expression assessment)

Livak method

Graphs showing gene expression changes over time.
gSRT for MucoPolySaccharidosis Type III

MPS III A

MPS III C

MPS III D

siRNA

mRNA

MPS III fibroblasts

NT

siXYLT1
gSRT FOR MucoPolySaccharidosis Type III

MPS III fibroblasts

siRNA

GAGs

% de GAGs detetada

NT
MPS IIIC
MPS IIIIC

24h
48h
gSRT for MucoPolySaccharidosis type III

Further validation:

- ↑ nr of experiments;
- immunocytochemistry (anti-HS antibody)
- + tests in MPS IIIB
gSRT FOR MucOPolySaccharidosis TYPE III

Promising results!

Reasons to keep studying...

siRNA

MPS III fibroblasts
A LOOK FORWARD…

- Vector design & siRNA encapsulation into liposomes
  - ↑ bioavailability of siRNAs;
  - protection from degradation
  - control of
    - circulation time
    - release rate

- Coupling of specific ligands to siRNA-carrying liposomes
  - Transferrin (Tf)
  - Rabies virus peptide derivative (RGV-2r)

- Efficiency assessment + Targeting of brain cells
A LOOK FORWARD…

in vivo studies
gSRT for MucopolySaccharidosis Type III

SUMMARY

“early stages” GAGs biosynthesis gene

↓ GAG Storage
gSRT for Mucopolysaccharidosis Type III

Summary

“early stages” GAGs biosynthesis gene

Therapeutic use ✓
gSRT FOR MucoPolySaccharidosis TYPE III

SUMMARY

“early stages” GAGs biosynthesis gene

Holds potential to benefit virtually all MPS!
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THANK YOU!