Sociedade Portuguesa de Doenças Metabólicas
14th International Symposium
15th-17th March, 2018

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 **MPS**s;

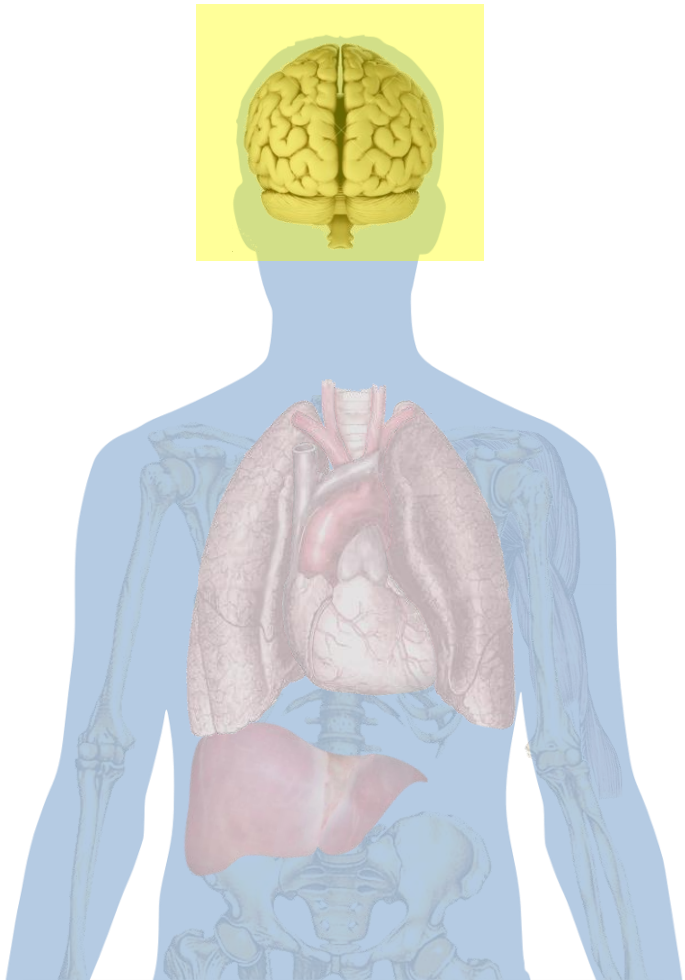
    glycosaminoglycans (GAGs)
  - Accumulated substrate: **heparan sulphate**

- 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 promissing results

Available Therapies

- None!

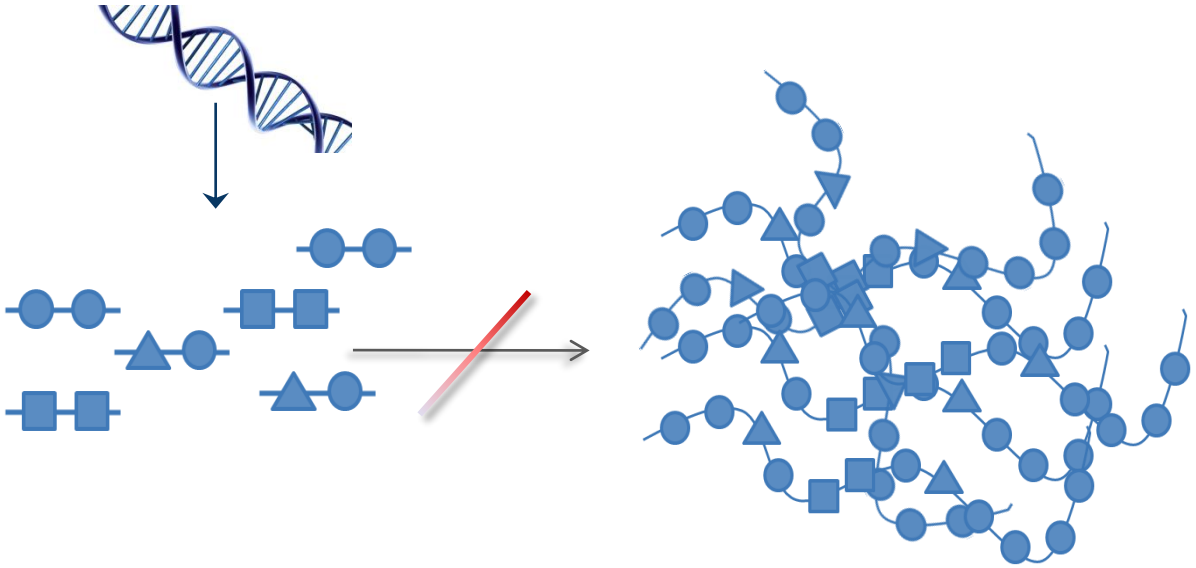
...only symptomatic!

Perfect Target
for
Substrate Reduction Approaches!

ERT for
introdu

Still, it's being attempted with some promissing results

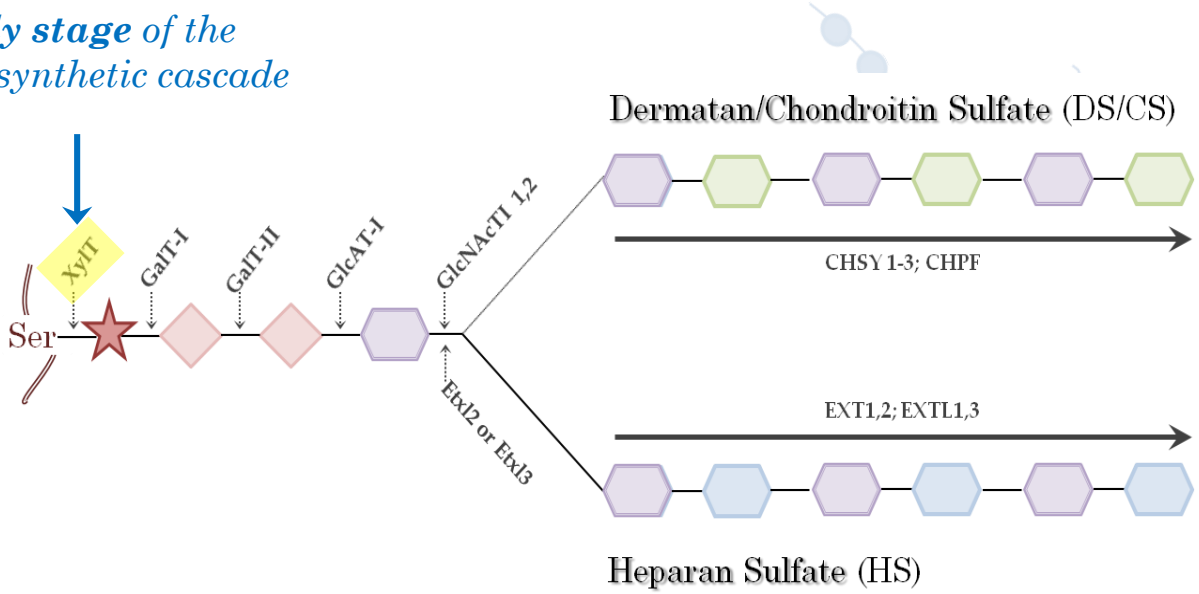
gSRT for MucoPolySaccharidosis type III



genetic substrate reduction

gSRT for MucoPolySaccharidosis type III

early stage *of the*
HS biosynthetic cascade



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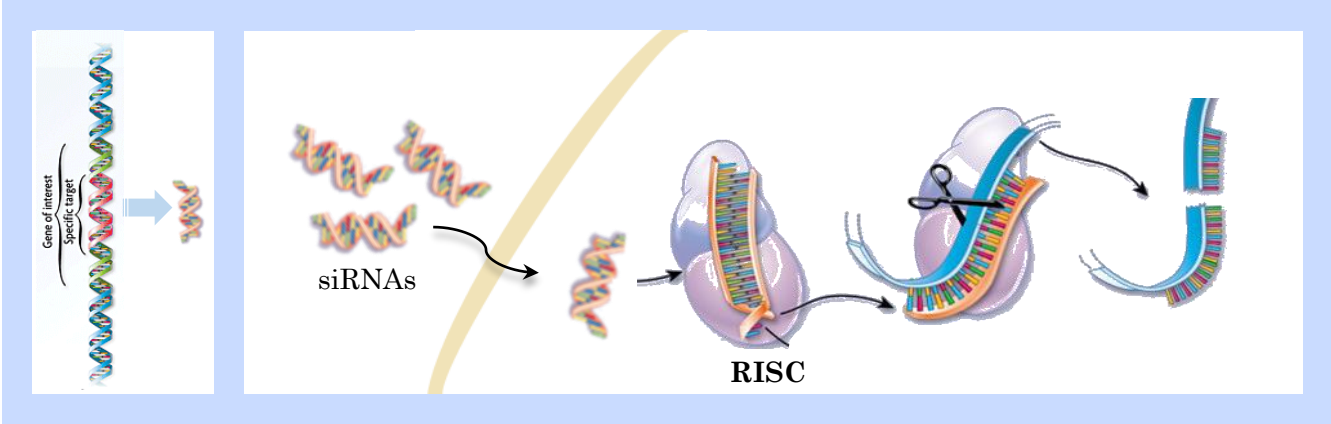
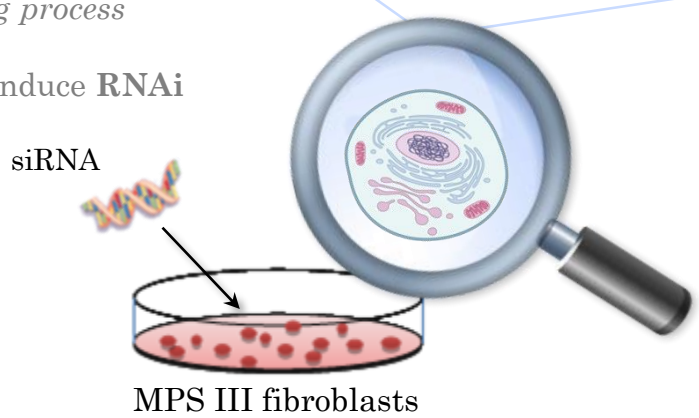


naturally occurring post-ranscriptional gene silencing process

Designed to induce **RNAi**



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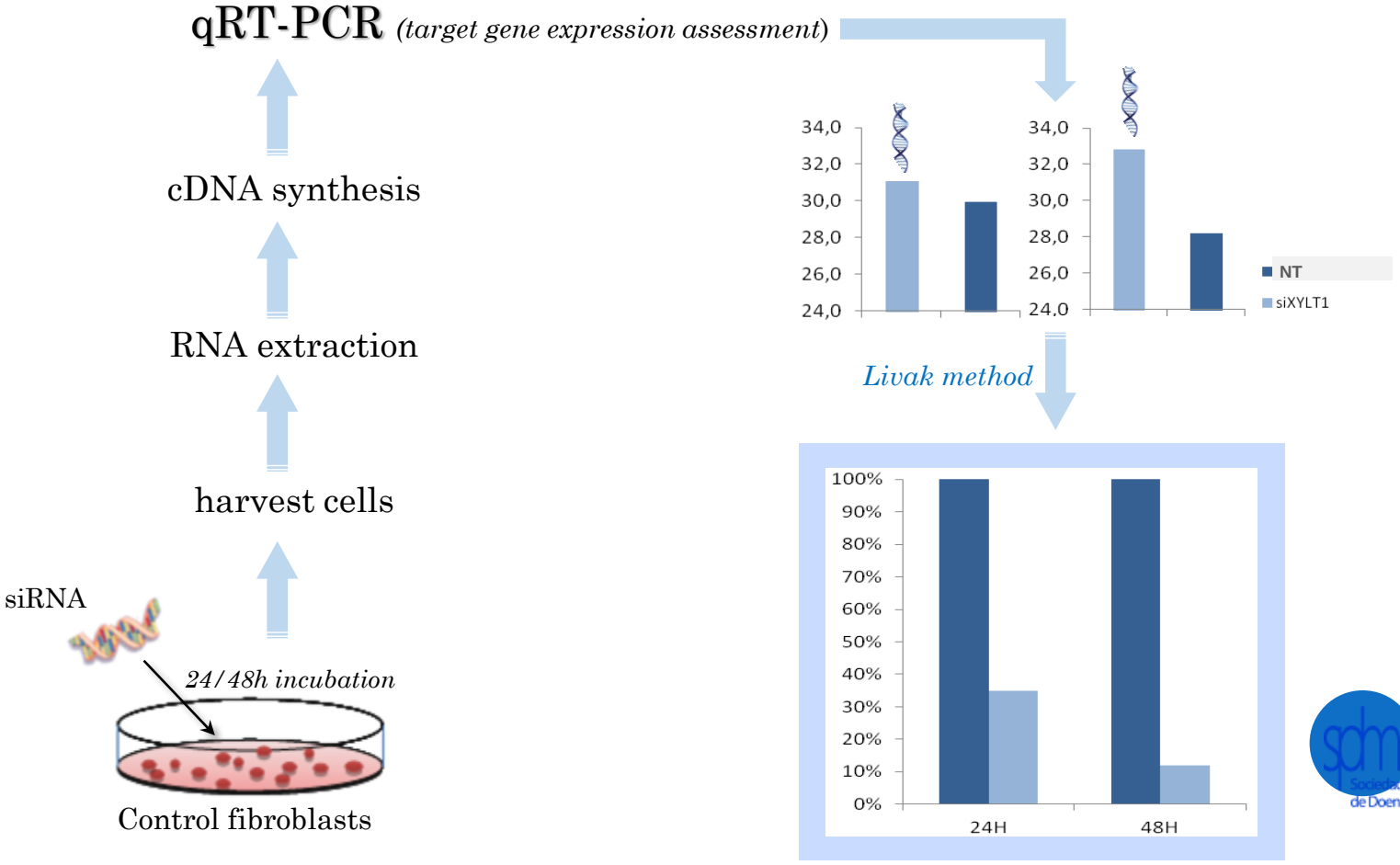

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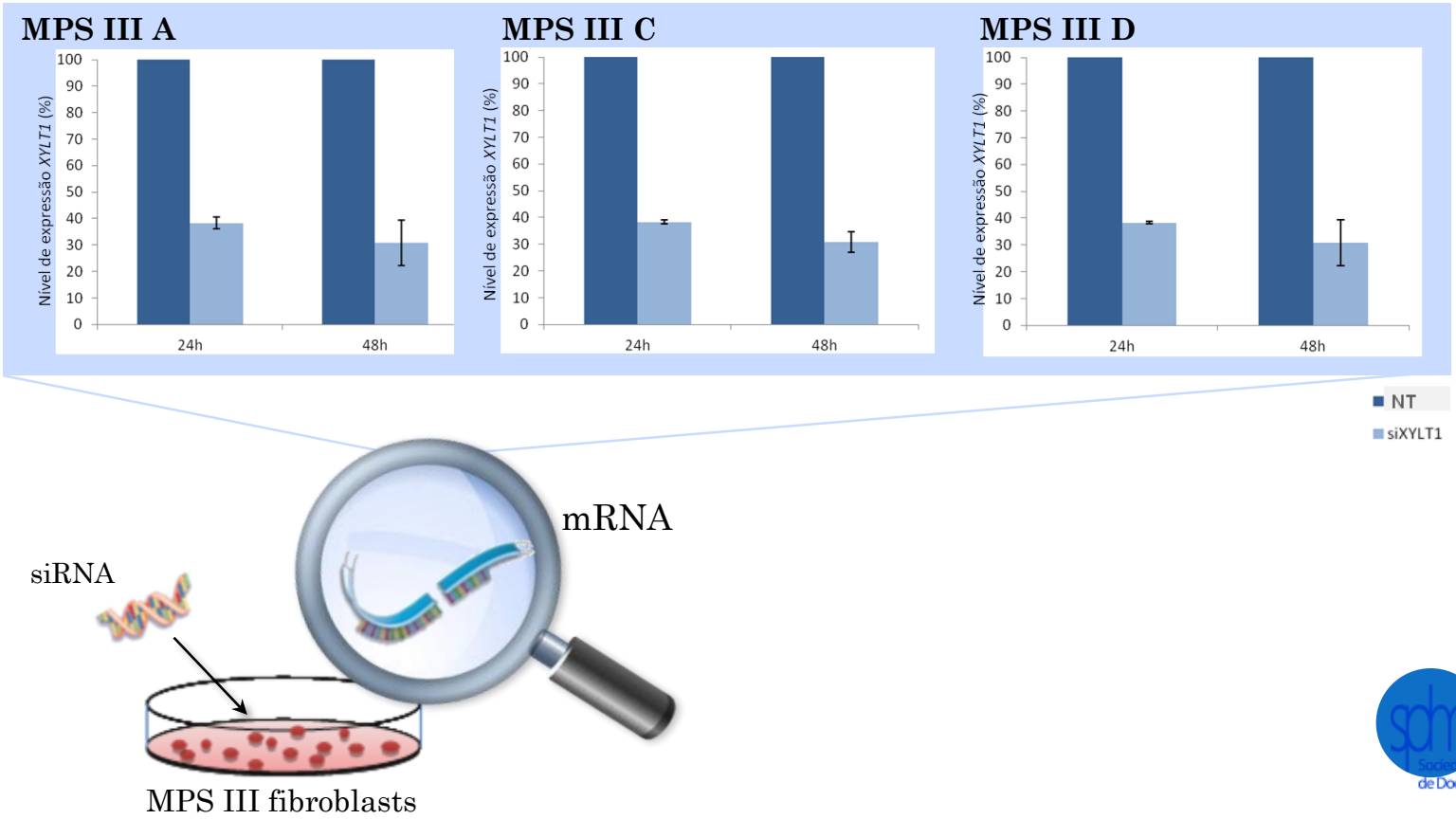

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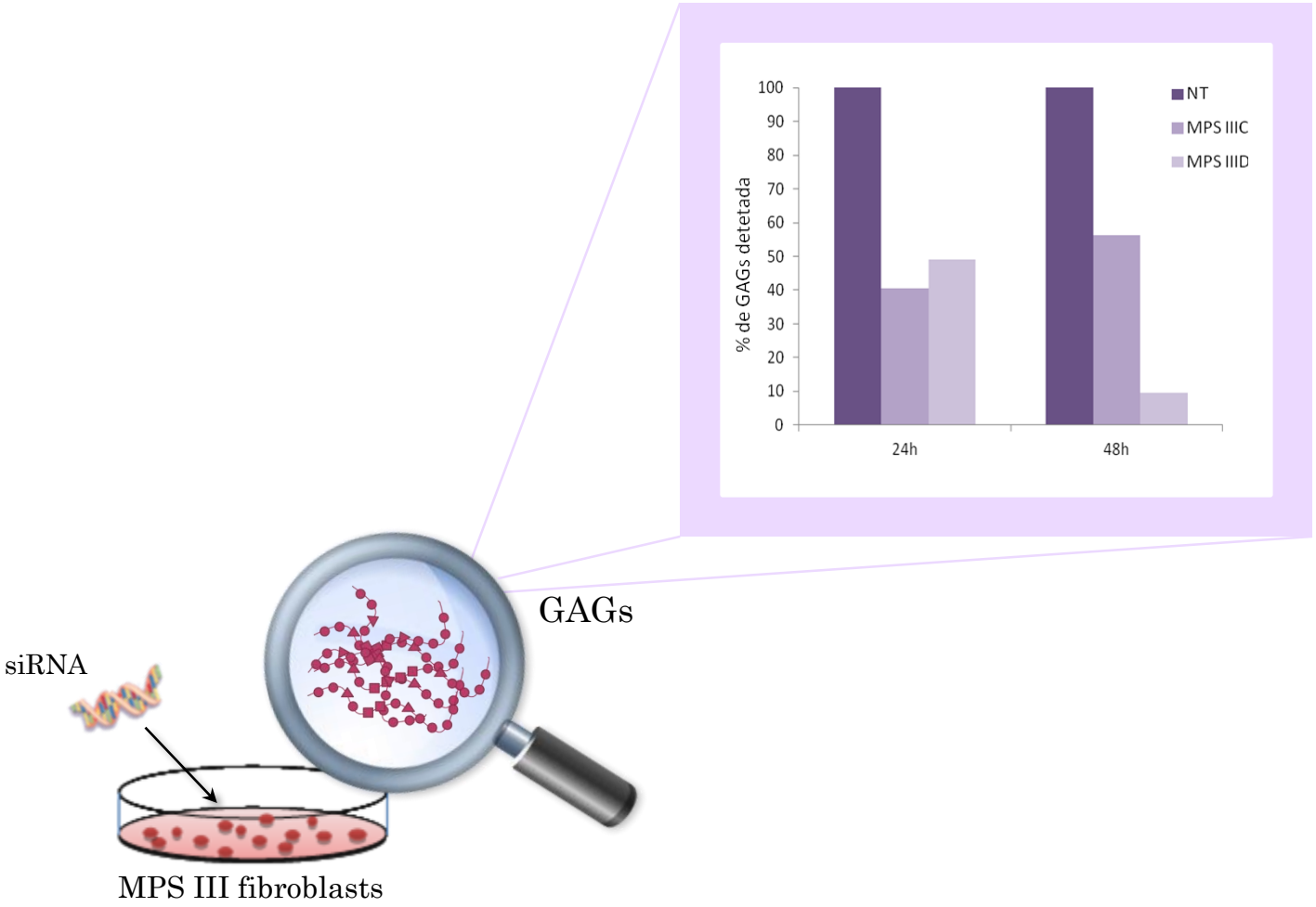
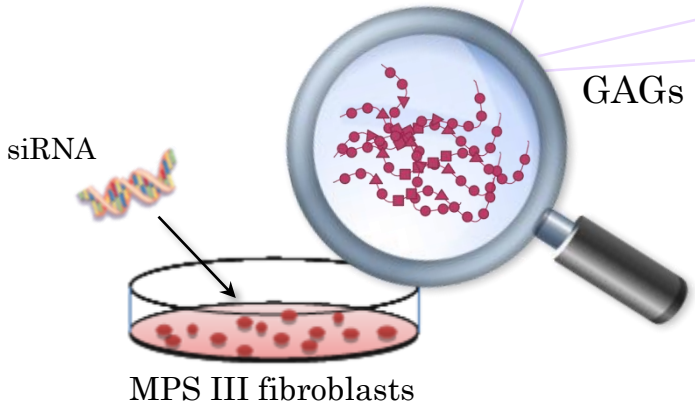


gSRT for MucoPolySaccharidosis type III

Further validation:

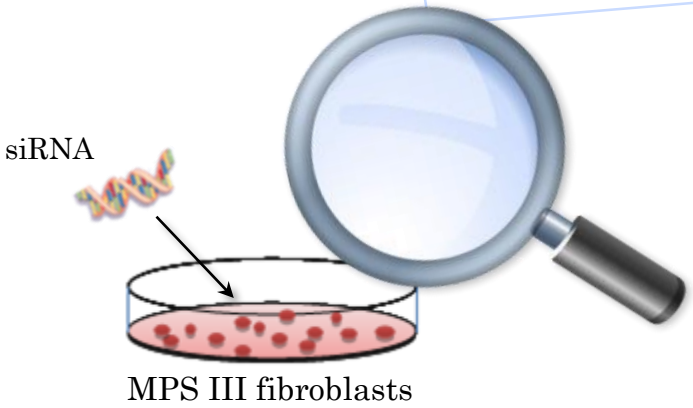
- ↑ nr of experiments;
- immunocytochemistry
  (anti-HS antibody)
- + tests in **MPS IIIB**



gSRT for MucoPolySaccharidosis type III

Promising results!

Reasons to keep studying...



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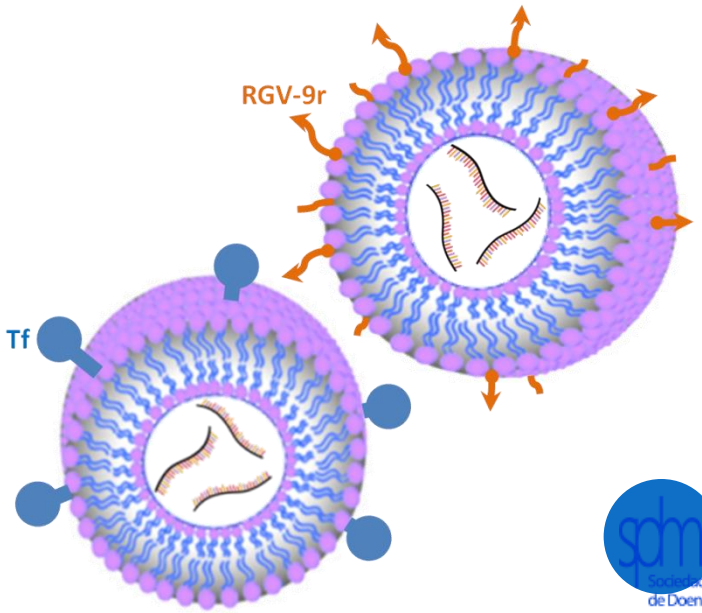
A LOOK FORWARD…

- 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



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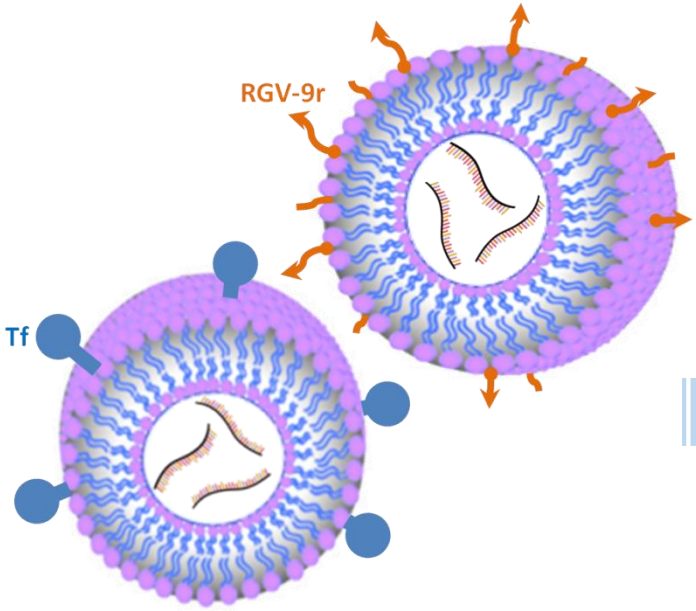
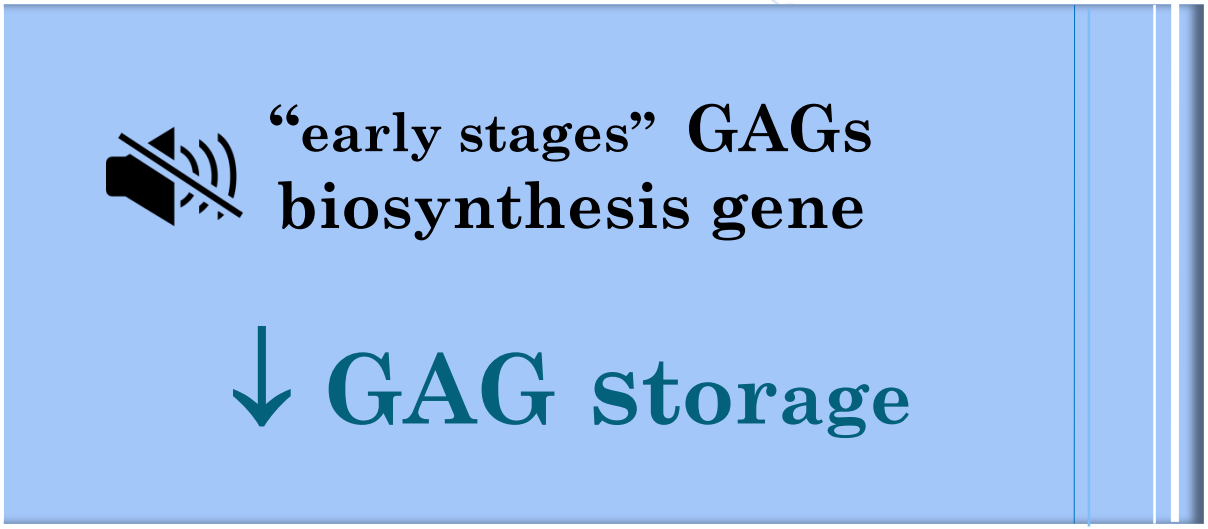


in vivo studies

gSRT for MucoPolySaccharidosis type III

SUMMARY



gSRT for MucoPolySaccharidosis type III

SUMMARY

"early stages" GAGs biosynthesis gene

Therapeutic use ✓

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gSRT for MucoPolySaccharidosis type III

SUMMARY

"early stages" GAGs biosynthesis gene

Holds potential to benefit virtually all MPS!

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Acknowledgments

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Sanfilippo Portugal

Jonah's Just Begun
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Sanfilippo Sud

António Reis ♥

Thank You!