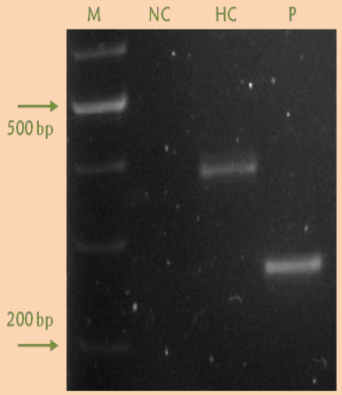
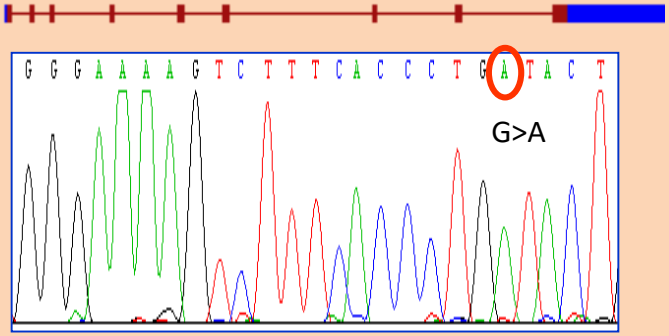
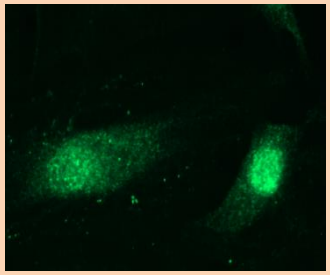
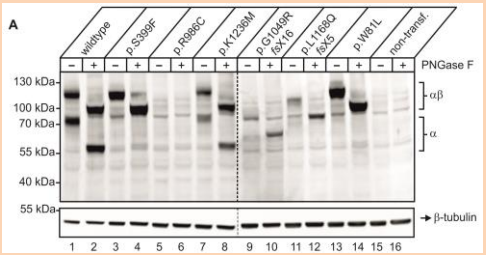






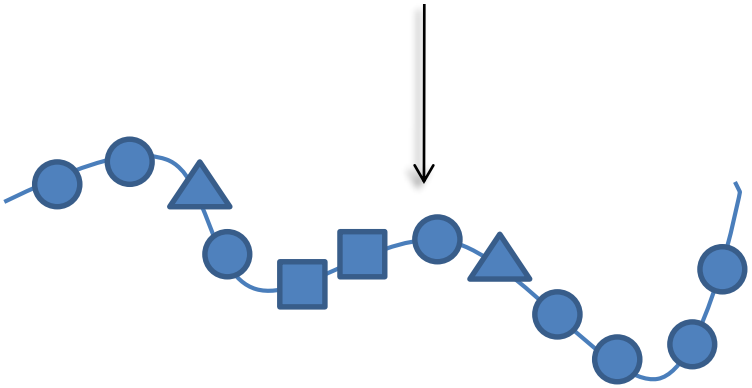
Um olhar sobre a investigação das MPS em Portugal |A look over MPS research in Portugal

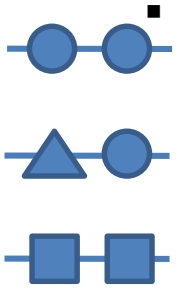


Sandra Alves - INSA

Mucopolysaccharidoses (MPS)

- LSD sub-group– 11 diseases;
- Accumulated substrate(s) : glycosaminoglycans (GAGs)





Sociedade Portuguesa de Doenças Metabólicas

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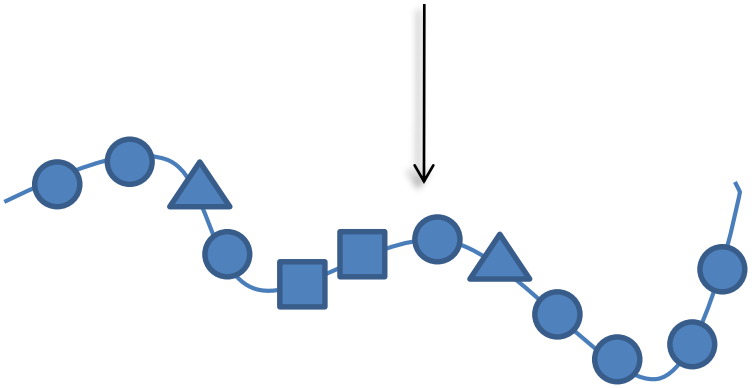

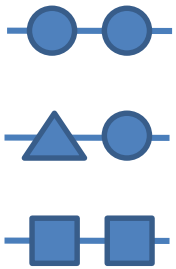

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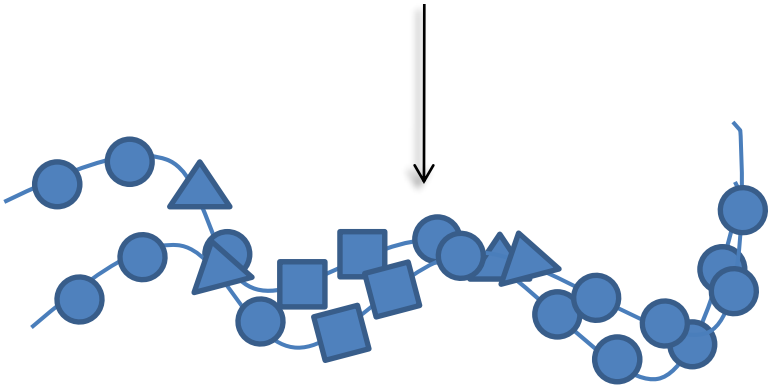

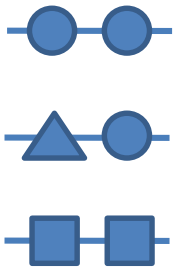

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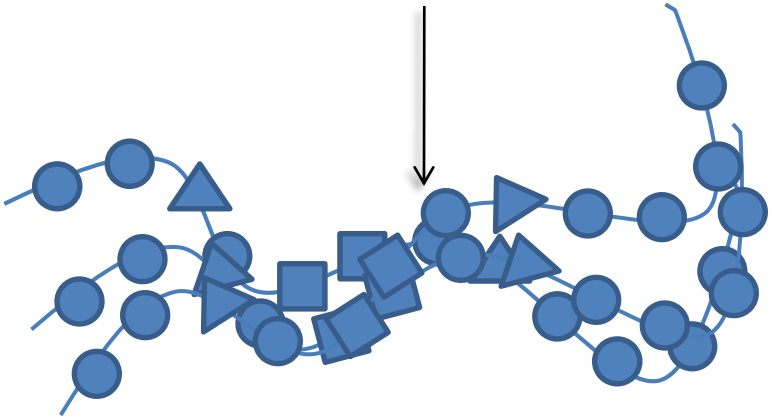

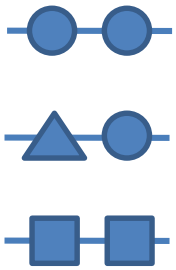

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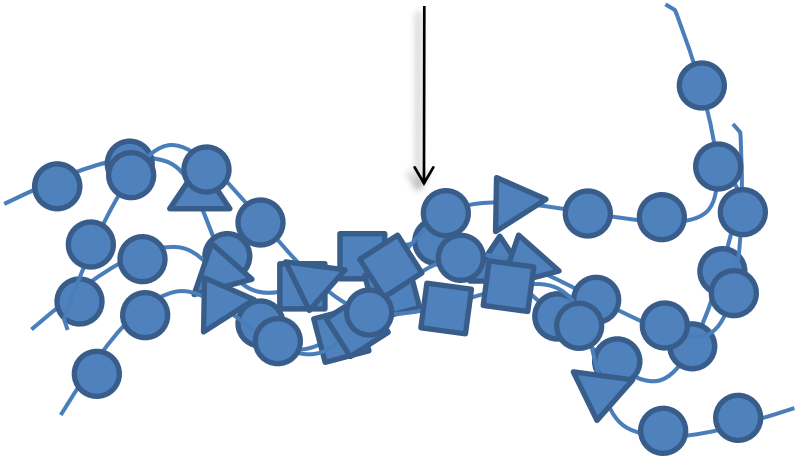

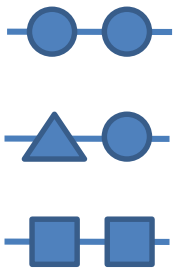

Sociedade Portuguesa de Doenças Metabólicas

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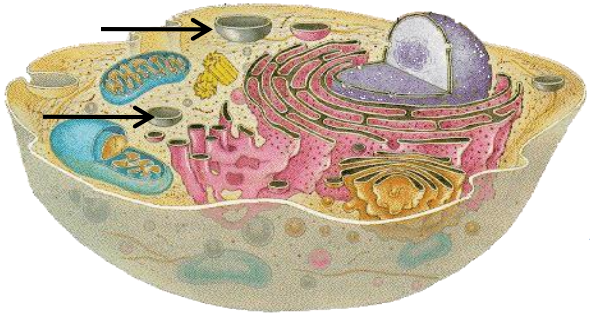

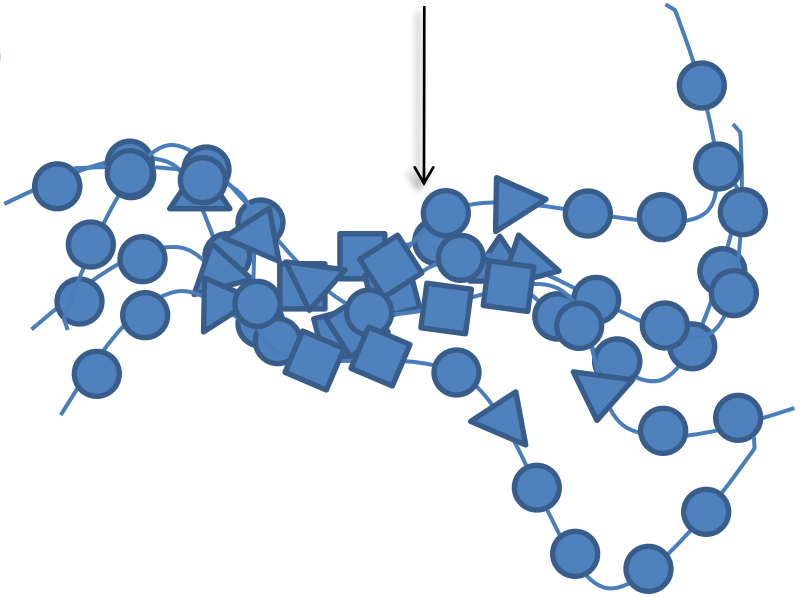

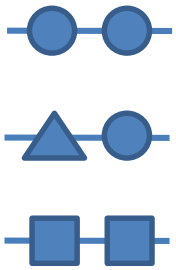

sdm Sociedade Portuguesa de Doenças Metabólicas

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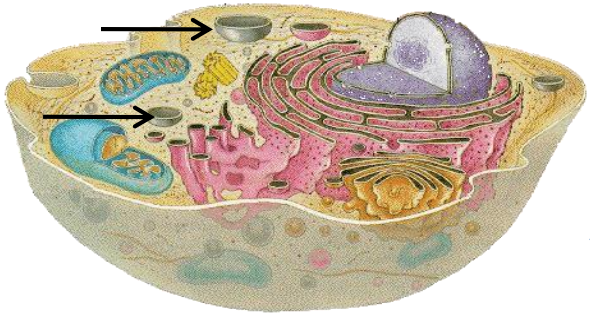

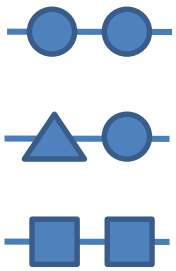

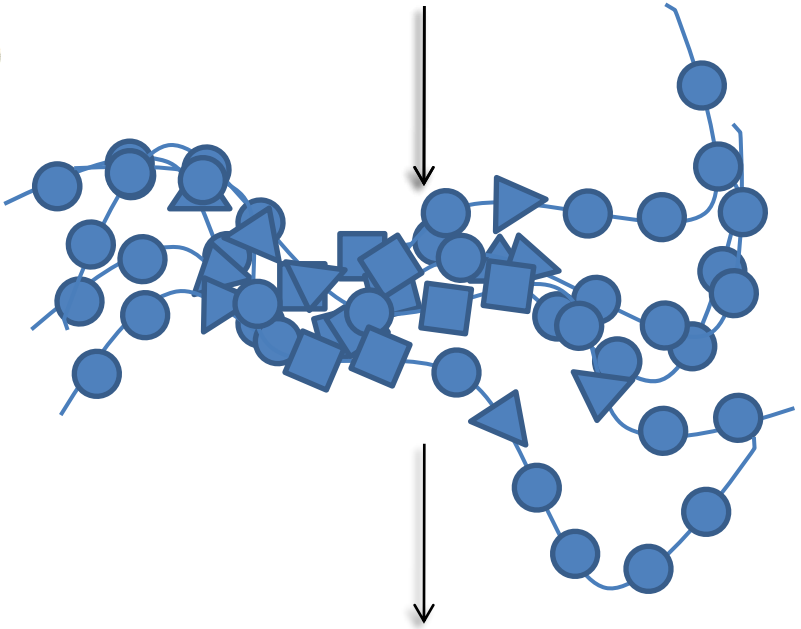

Excess: DISEASE

Sociedade Portuguesa de Doenças Metabólicas

Mucopolysaccharidoses (MPS)

- Chronic
- Progressive
- Large spectrum of severity & symptoms

Sociedade Portuguesa de Doenças Metabólicas

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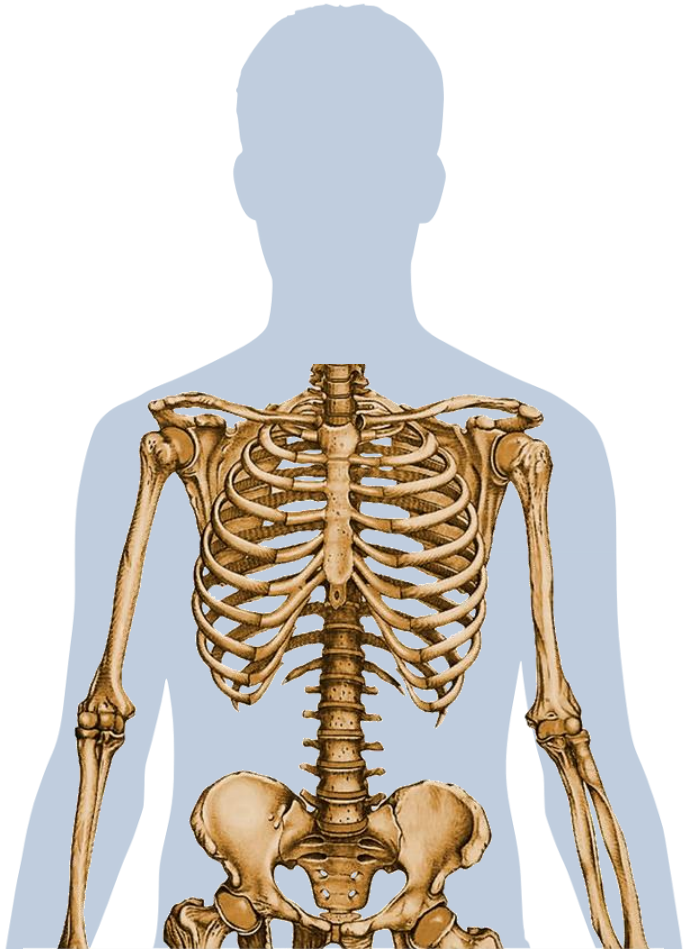

Sociedade Portuguesa de Doenças Metabólicas

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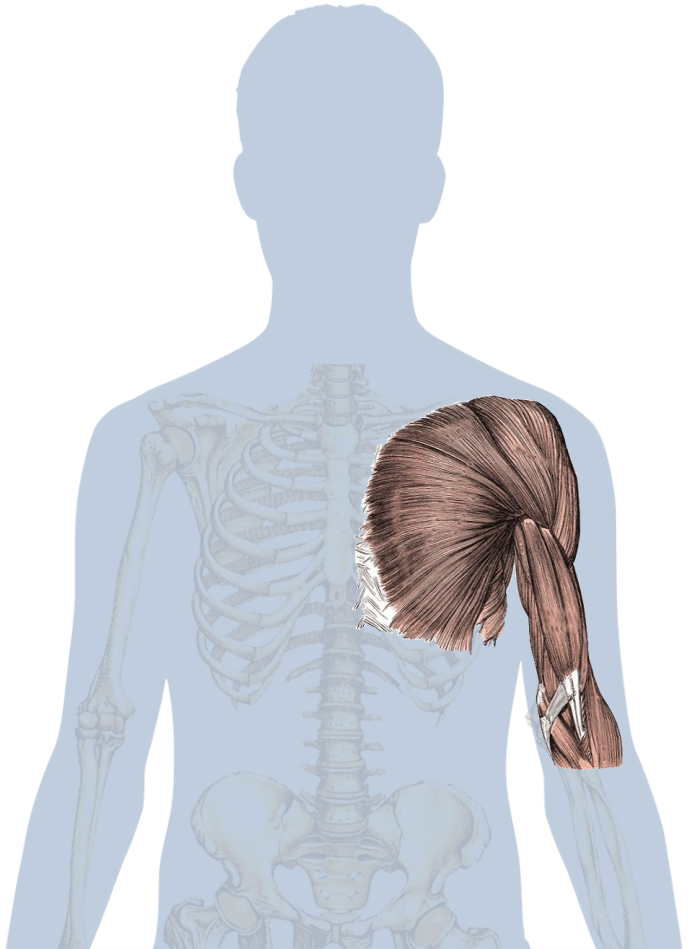

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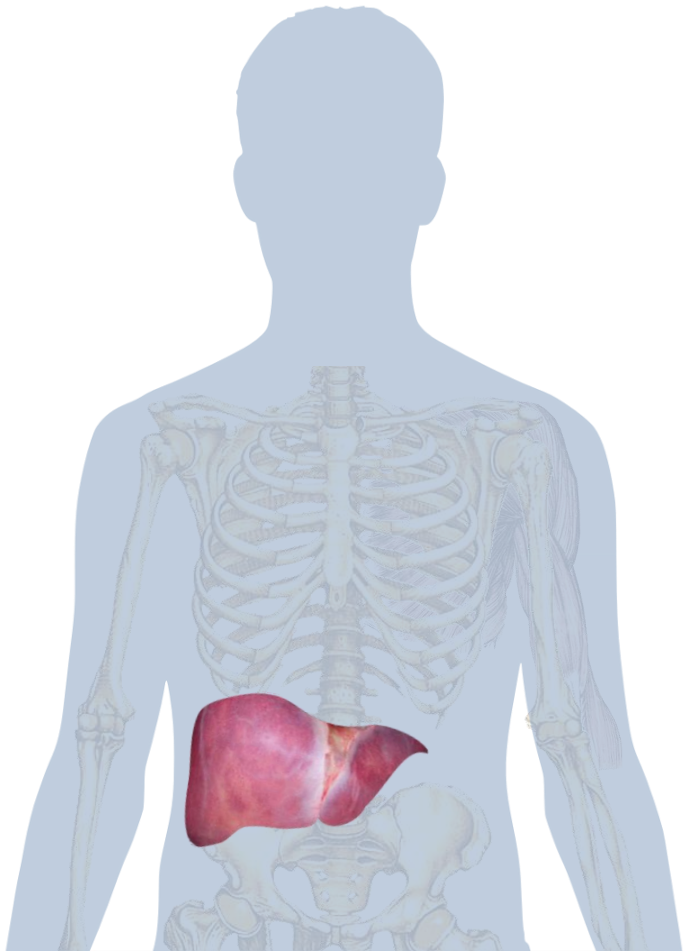

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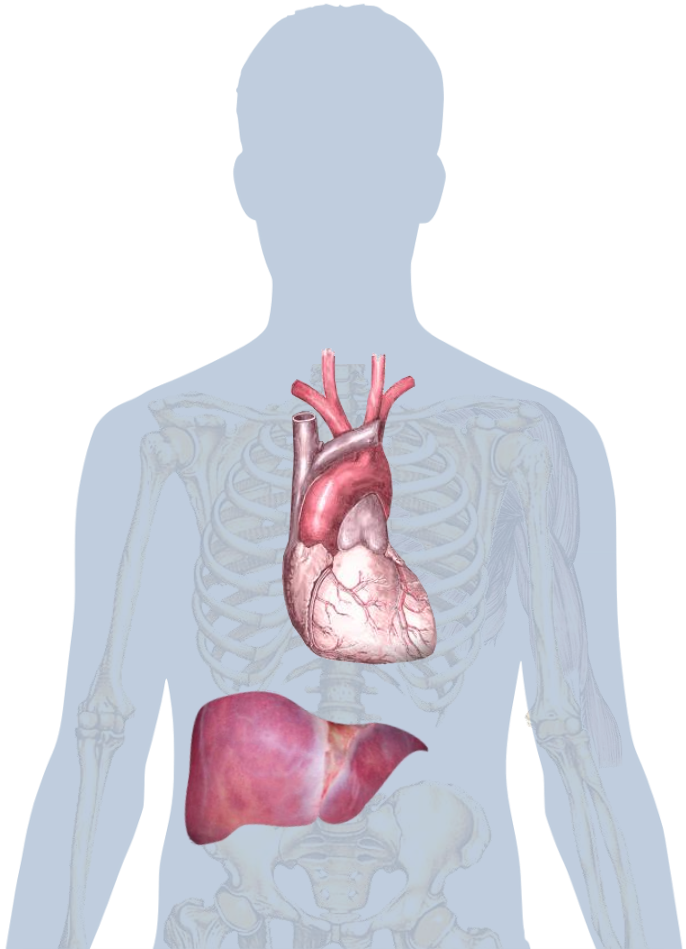

Sociedade Portuguesa de Doenças Metabólicas

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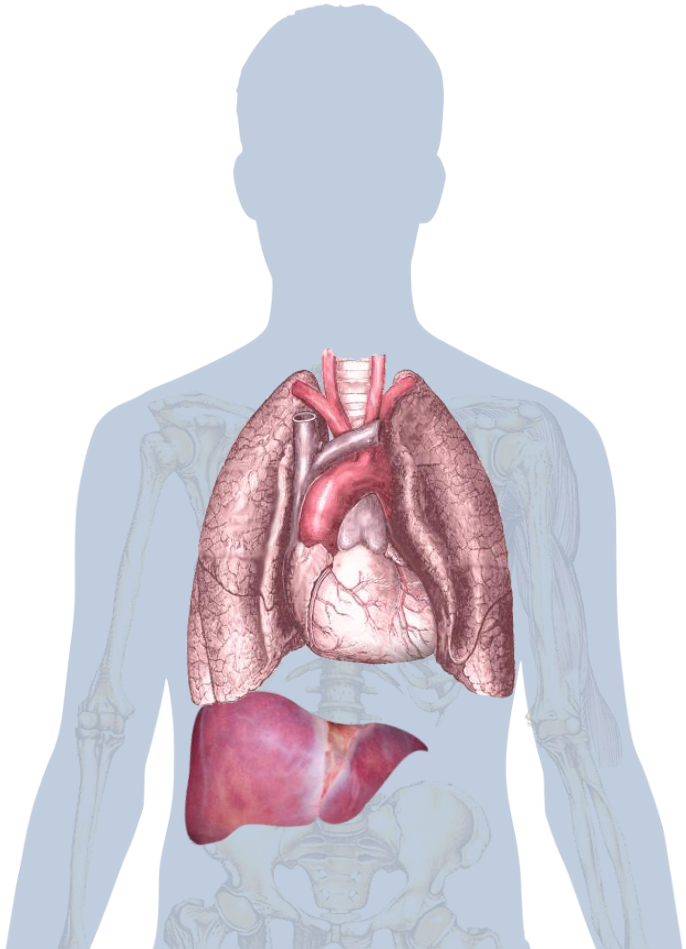

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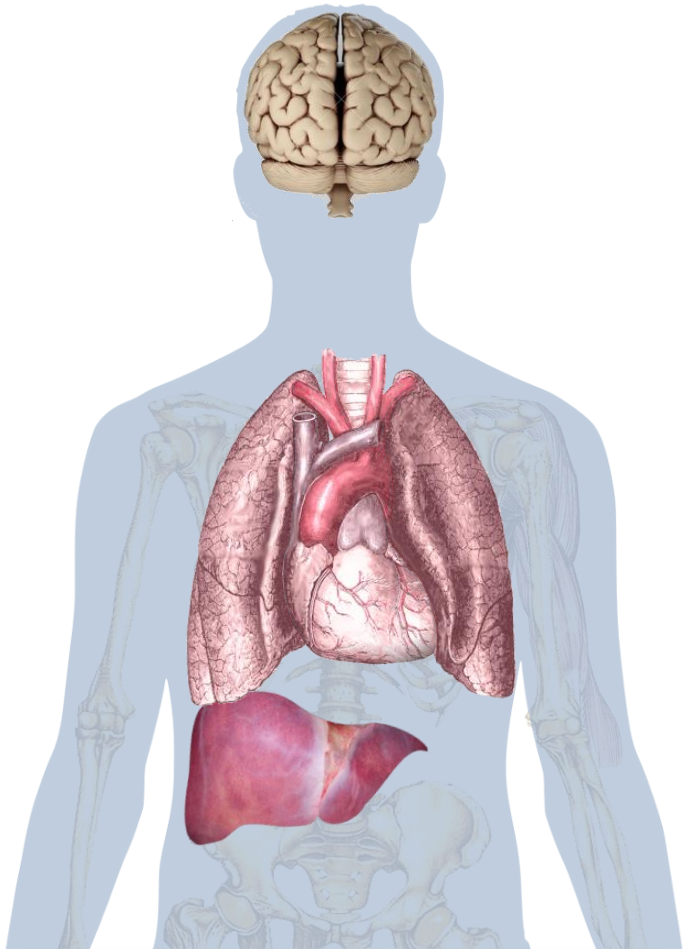
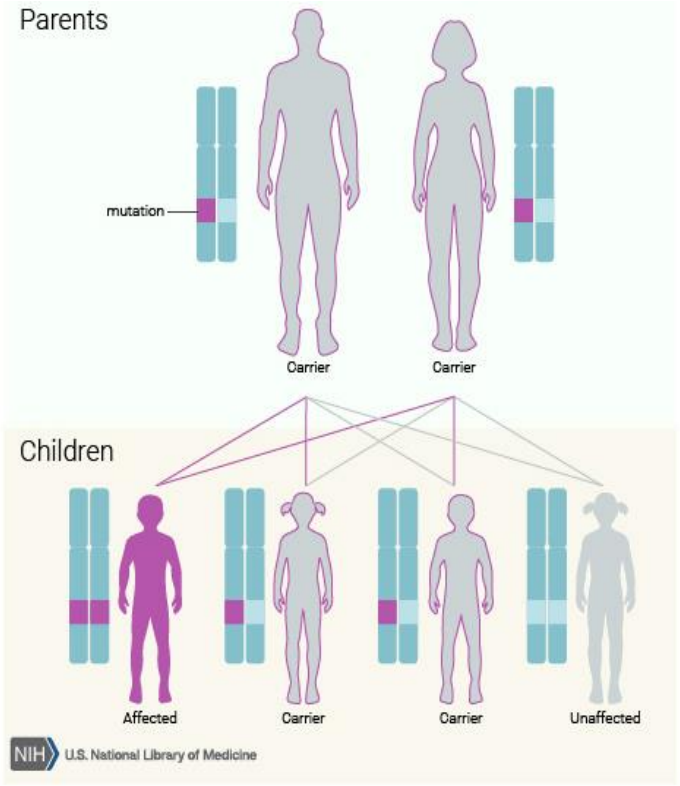


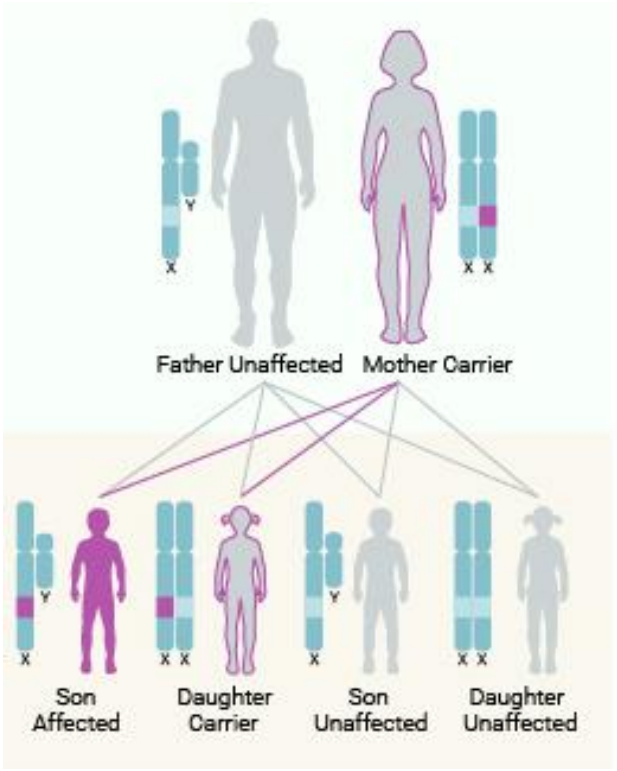
Sociedade Portuguesa de Doenças Metabólicas

Mode of Inheriteance

Autosomal recessive



X-linked recessive (only MPS II)



MPS patients' needs/problems

Diagnosis

Therapy

Molecular study of Portuguese patients

MPS II

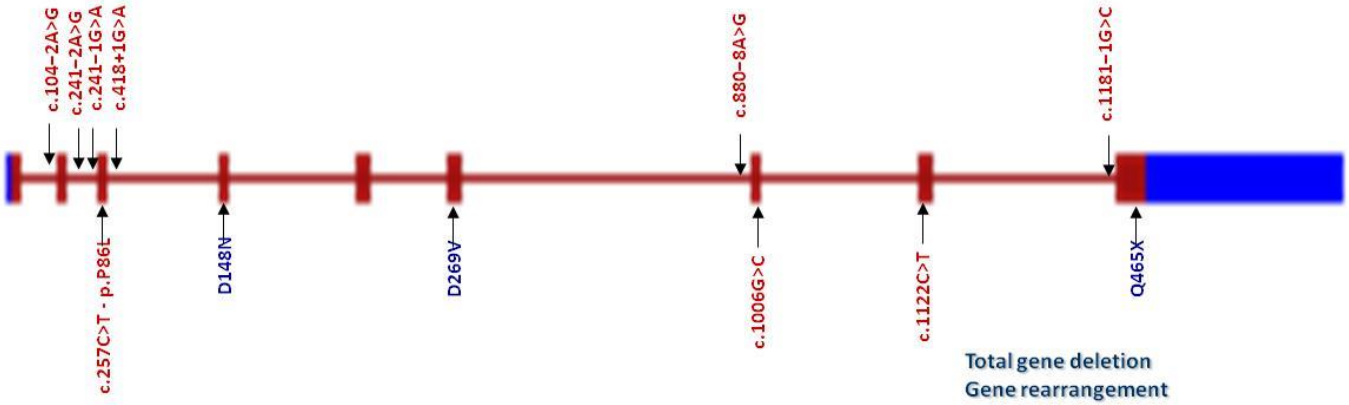
J Inherit Metab Dis (2006) 29:743–754
DOI 10.1007/s10545-006-0403-z

ORIGINAL ARTICLE

Molecular characterization of Portuguese patients with mucopolysaccharidosis type II shows evidence that the *IDS* gene is prone to splicing mutations

S. Alves · M. Mangas · M. J. Prata · G. Ribeiro · L. Lopes · H. Ribeiro · J. Pinto-Basto · M. Reis Lima · L. Lacerda

16 unrelated Portuguese patients;
15 different mutations;



Molecular study of Portuguese patients

MPS IIIA and IIIB

Clin Genet 2008: 73: 251–256
Printed in Singapore. All rights reserved

CLINICAL GENETICS
doi: 10.1111/j.1399-0004.2007.00951.x

Short Report

Molecular analysis of mucopolysaccharidosis type IIIB in Portugal: evidence of a single origin for a common mutation (R234C) in the Iberian Peninsula

11 Portuguese patients;
5 novel mutations.

Frequent mutation: R234C (also in Spanish patients)

Molecular study of Portuguese patients

MPS IIIC

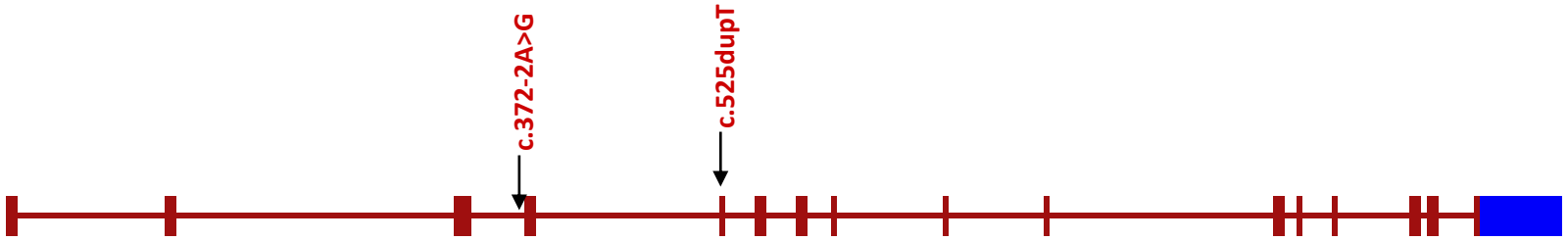
Clin Genet 2008: 74: 194–195
Printed in Singapore. All rights reserved

CLINICAL GENETICS
doi: 10.1111/j.1399-0004.2008.01040.x

Letter to the Editor

Molecular characterization of Portuguese patients with mucopolysaccharidosis IIIC: two novel mutations in the *HGSNAT* gene

3 patients;
2 novel mutations.



Molecular study of Tunisian patients

Update of the spectrum of mucopolysaccharidoses type III in Tunisia: identification of three novel mutations and *in silico* structural analysis of the missense mutations

Souad Ouesleti, Maria Francisca Coutinho, Isaura Ribeiro, Abdehedi Miled, Dalila Saidane Mosbahi, Sandra Alves
Porto, Portugal

Original article

Background: Mucopolysaccharidoses type III (MPS III) are a group of autosomal recessive lysosomal storage diseases, caused by mutations in genes that code for enzymes involved in the lysosomal degradation of heparan sulphate: heparan sulfate sulfamidase (*SGSH*), α-N-acetylglucosaminidase (*NAGLU*), heparan sulfate acetyl-CoA: α-glucosaminide N-acetyltransferase (*HGSNAT*), and N-acetylglucosamine-6-sulfatase (*GNS*).

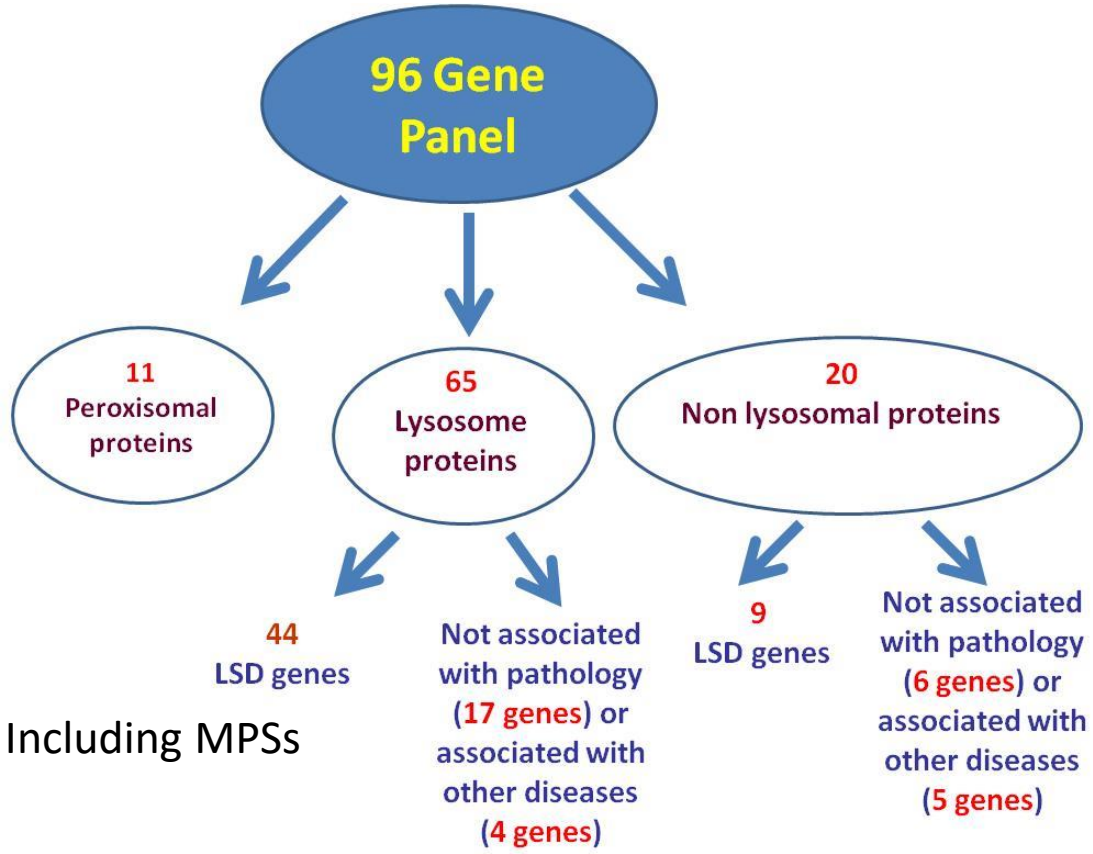
the hypothesis of its peri Mediterranean origin. With the exception of the c.234+1G>A mutation, that was identified in two unrelated MPS IIIC families, the other identified mutations were family-specific and were always found in homozygosity in the patients studied, thus reflecting the existence of consanguinity in MPS III Tunisian families.

Conclusions: Three novel mutations are reported here,

Molecular study of Portuguese patients

Next-generation-sequencing (NGS) as an approach for the diagnosis of LSDs

Our current NGS-based workflow gene panel seems to be a valid tool for the genetic analysis of the classical LSDs associated genes.



Including MPSs

Aparentemente saudáveis!

PROJECTO **find**

A IMPORTÂNCIA DE UM DIAGNÓSTICO

A maioria das crianças com MPS não apresentam sintomas ao nascimento e o fenótipo progride com o tempo. O diagnóstico atempado deste tipo de doenças é essencial para modificar a sua evolução e poder proporcionar aconselhamento genético familiar.

Se suspeitar

Solicite **GRATUITAMENTE** um KIT de diagnóstico por e-mail para:

projecto.find@gmail.com

Parceria científica:

SPP SOCIEDADE PORTUGUESA DE PEDIATRIA
SECÇÃO DE DOENÇAS HEREDITÁRIAS DO METABOLISMO

Parceria laboratorial:

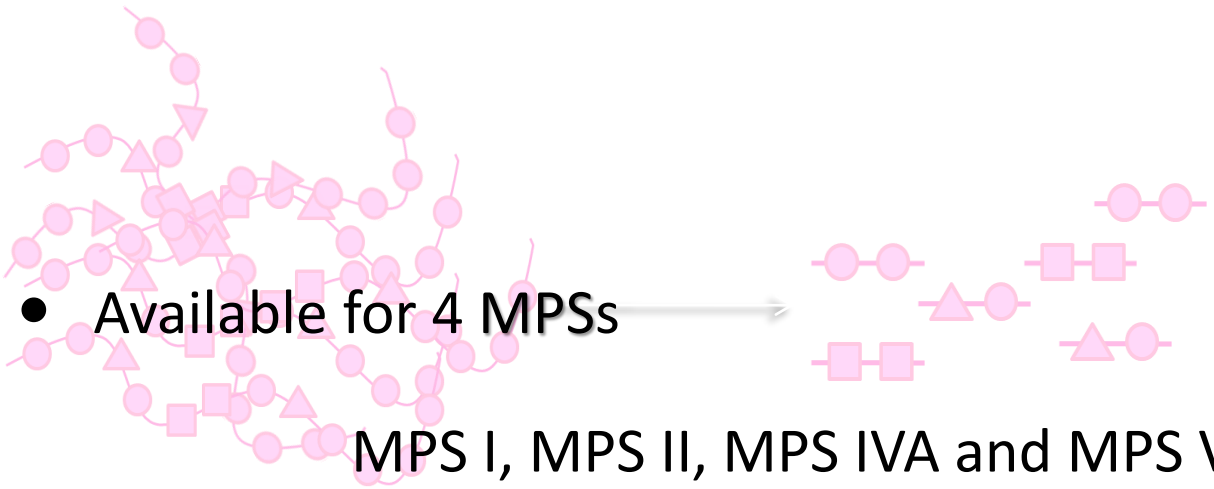
Instituto Nacional de Saúde Doutor Ricardo Jorge
Unidade de Rastreio Neonatal
Metabolismo e Genética
Departamento de Genética Humana

As mucopolissacaridoses (MPS) são doenças de sobrecarga multissistémicas e progressivas que costumam AFECTAR:

- **SISTEMA NERVOSO** (atraso psicomotor, deteriorização cognitiva, alterações do comportamento)
- **SISTEMA MÚSCULO-ESQUELÉTICO** (disostose múltipla, contracturas, síndrome do túnel cárpico, cifoescoliose)
- **ORGANOMEGALIAS**
- **SISTEMA RESPIRATÓRIO** (constipações e otites recorrentes, hipoacusia, síndrome de apneia obstrutiva do sono)
- **OLHOS** (opacidade da córnea, retinopatia)
- **CORAÇÃO** (valvulopatia, miocardiopatia)
- **TECIDO CONJUNTIVO** (hérnias)
- **ROSTO** (fácies grosseiras)

Available Therapies

Enzyme Replacement Therapy



- Available for 4 MPSs

MPS I, MPS II, MPS IVA and MPS VI

Current limitations

- Cost
- Lifelong dependance
- Ineffective for the CNS manifestations

"With research, possibilities are limitless"…

- 'Broader' approaches

  i.e. 1 therapy ⇔ 1 disease

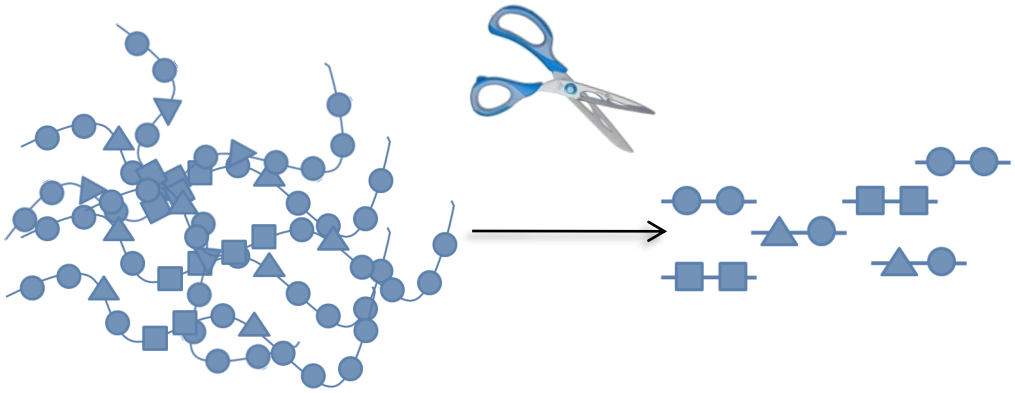
  (or even more!)

- 'Personalized' approaches

  i.e. 1 therapy for each mutation/
  type of mutation

"With research, possibilities are limitless"…

- 'Broader' approaches



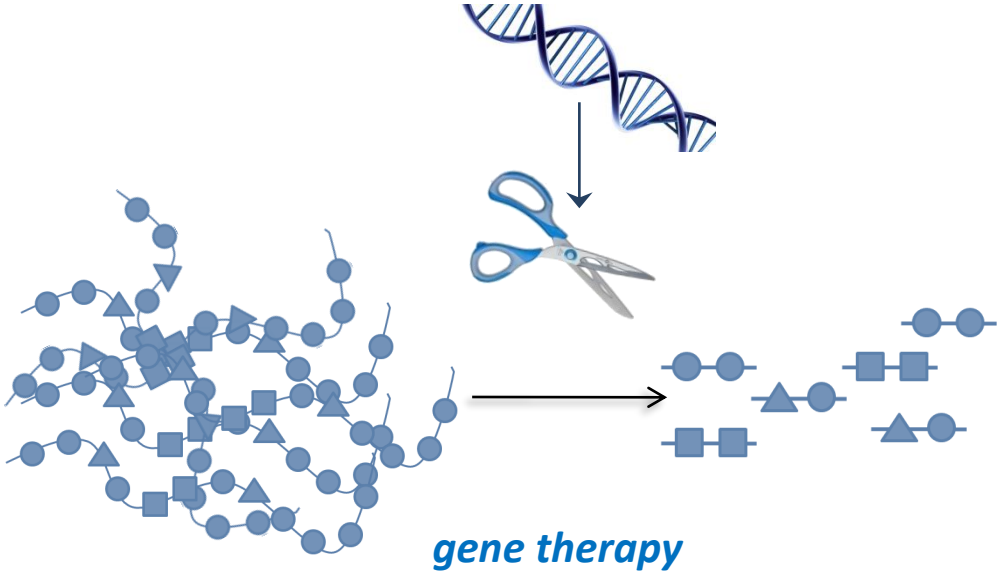
enzyme replacement therapies

more effective

able to cross the BBB

"With research, possibilities are limitless"…

- 'Broader' approaches

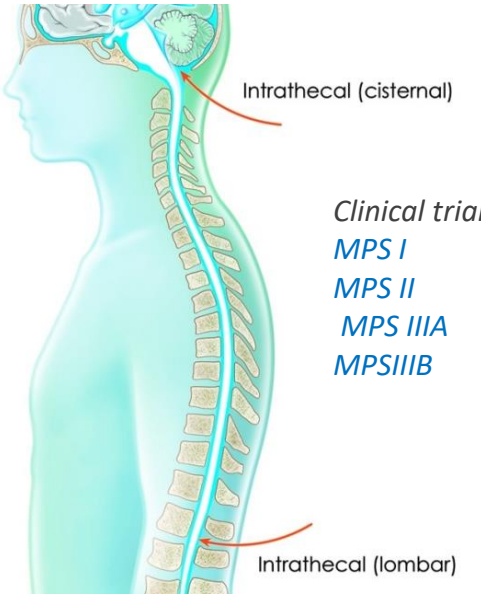


Clinical trials:

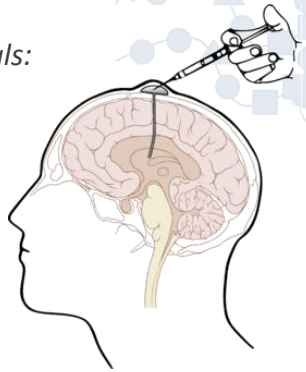
Metachromatic leukodystrophy

"With research, possibilities are limitless"…

- 'Broader' approaches
  Final goal: brain
  How?



Clinical trials:
MPS I
MPS II
MPS IIIA
MPSIIIB



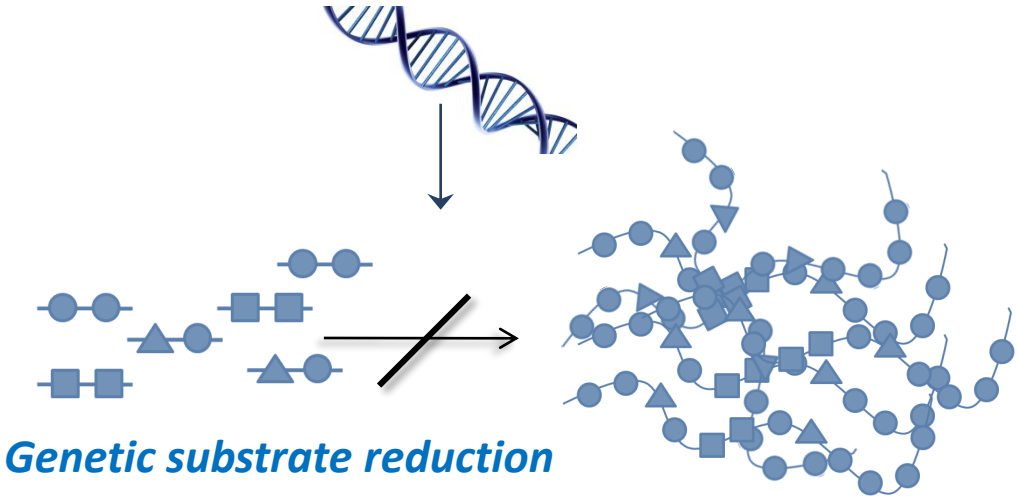
intracerebroventricular injections

Better vectors
Modified viruses (non-pathogenic)

**retrovirusess (RNA)*
Lentiviruses
**adenoviruses (DNA)*
'adeno-associated' viruses (AAV)

"With research, possibilities are limitless"…

- 'Broader' approaches



Genetic substrate reduction

Gaucher	**Zavesca®** (Miglustat; Actelion) **Cerdelga®** (Eliglustat tartrate; Genzyme)
Niemann-Pick C	Zavesca® (Miglustat; Actelion)

"With research, possibilities are limitless"…

- 'Personalized' approaches

  Final goal:

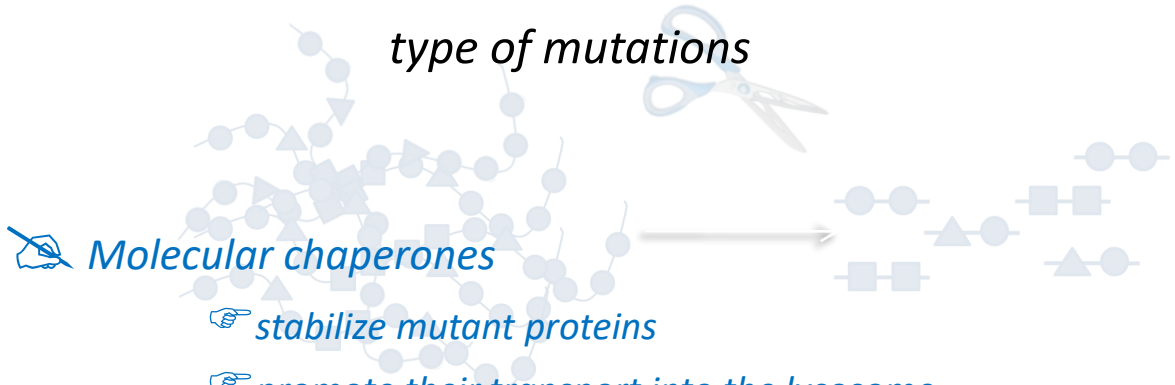
  correction/amellioration of 1 mutation in particular type of mutations

  How?

  ✍ *Molecular chaperones*

  ☞ *stabilize mutant proteins*

  ☞ *promote their transport into the lysosome*



"With research, possibilities are limitless"…

- 'Personalized' approaches

Final goal:

correction/amellioration of 1 mutation in particular type of mutations

How?

Molecular chaperones

Galafold™

(Migalastat; Amicus Therapeutics)

"With research, possibilities are limitless"…

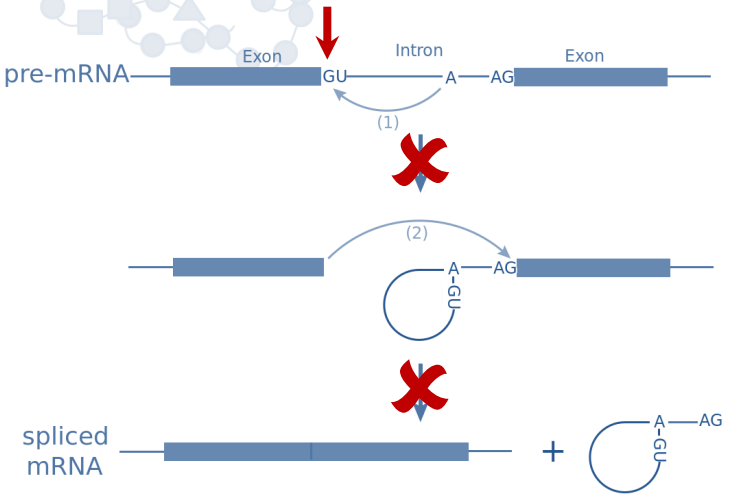
- 'Personalized' approaches

Final goal:

correction/amellioration of 1 mutation in particular type of mutations

How?

Correction of splicing mutations



Our work at INSA…

- ‘Broader’ approaches
  - gSRT for MPS

- ‘Personalized’ approaches
  - correction of *splicing* mutations in different LSDs

Common denominator:

Genetic-based therapies

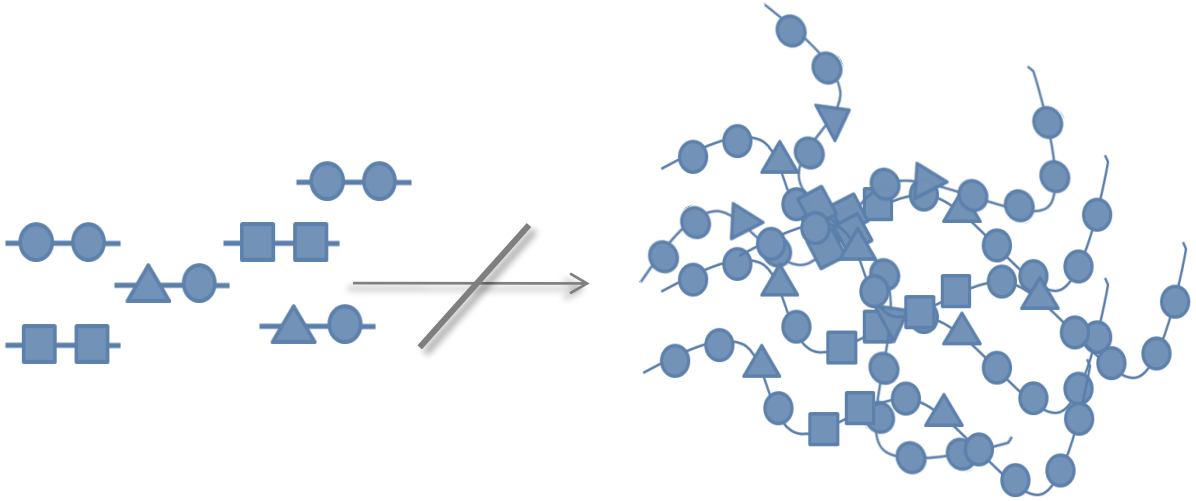
RNA-based

‘Easy’ to test at a cellular level – 1st stage

gSRT for MucoPoliSacharidoses

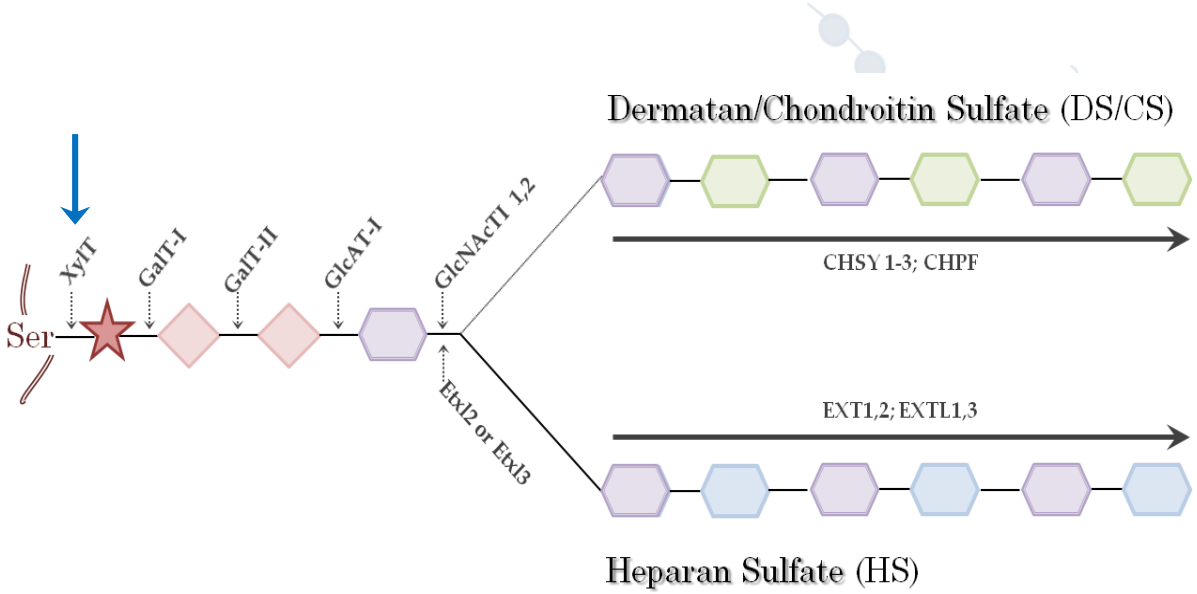
- ‘Broader’ approach

- Targets: *genes from the GAGs biosynthetic pathway*



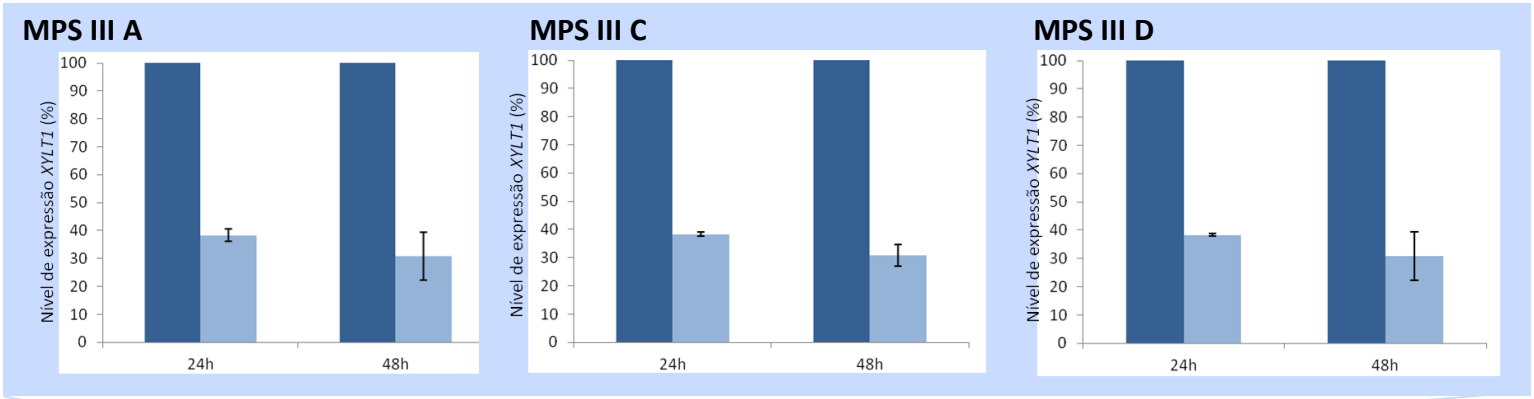
gSRT for MucoPoliSacharidoses

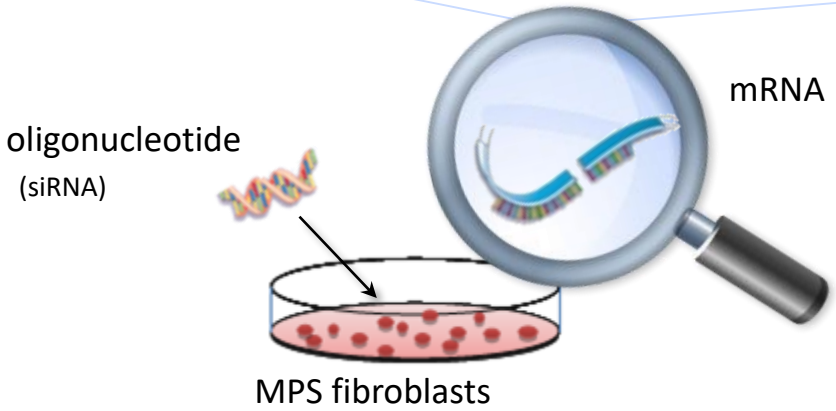
- ‘Broader’ approach
- Targets: *genes from the GAGs biosynthetic pathway*



gSRT for MucoPoliSacharidoses

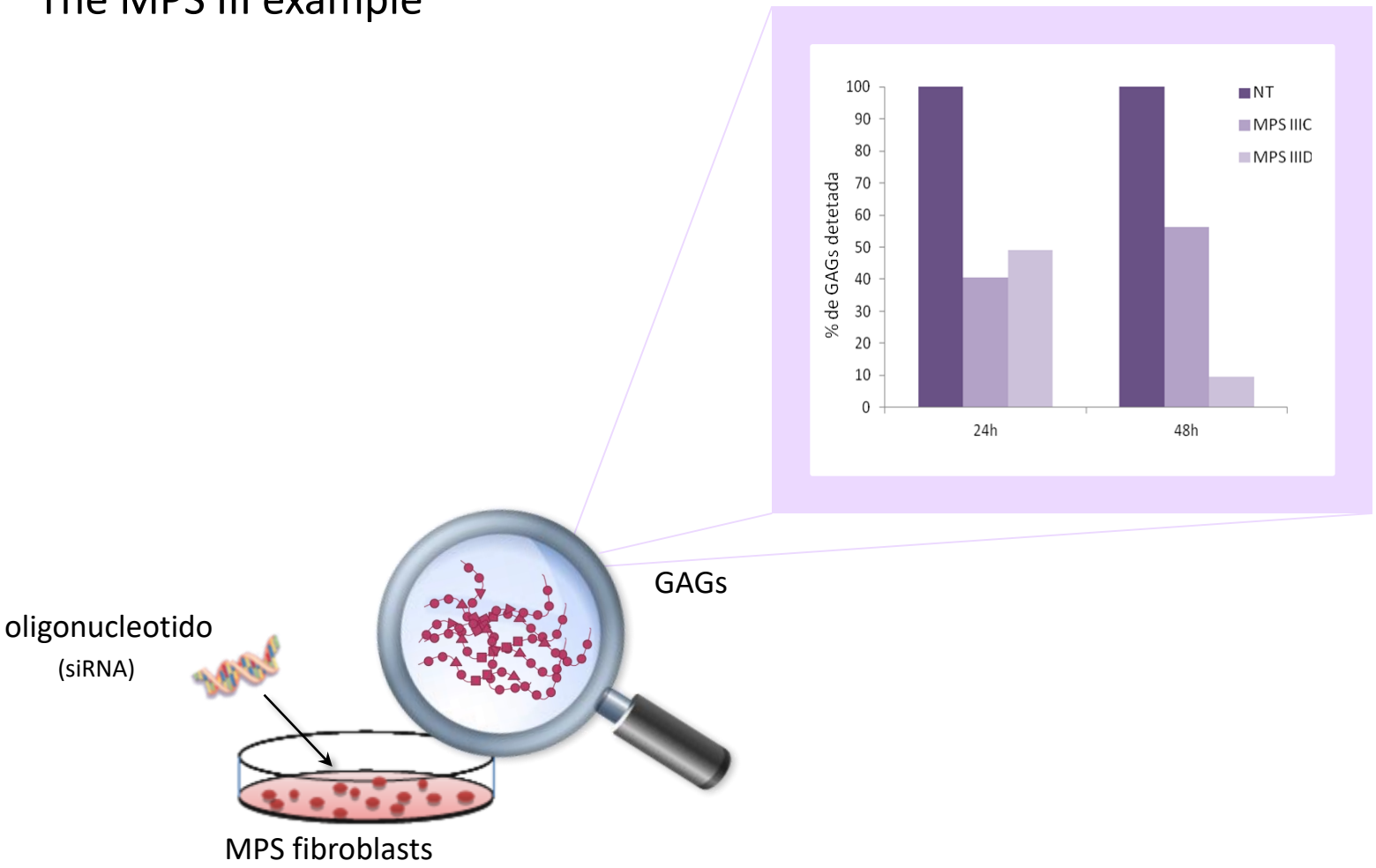
- The MPS III example





gSRT for MucoPoliSacharidoses

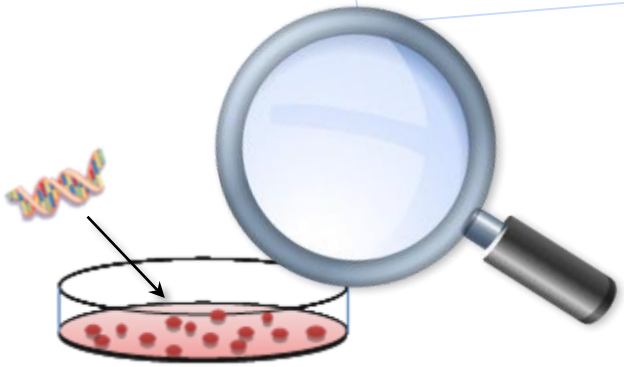
- The MPS III example



gSRT for MucoPolySaccharidosis type III

Promising results!

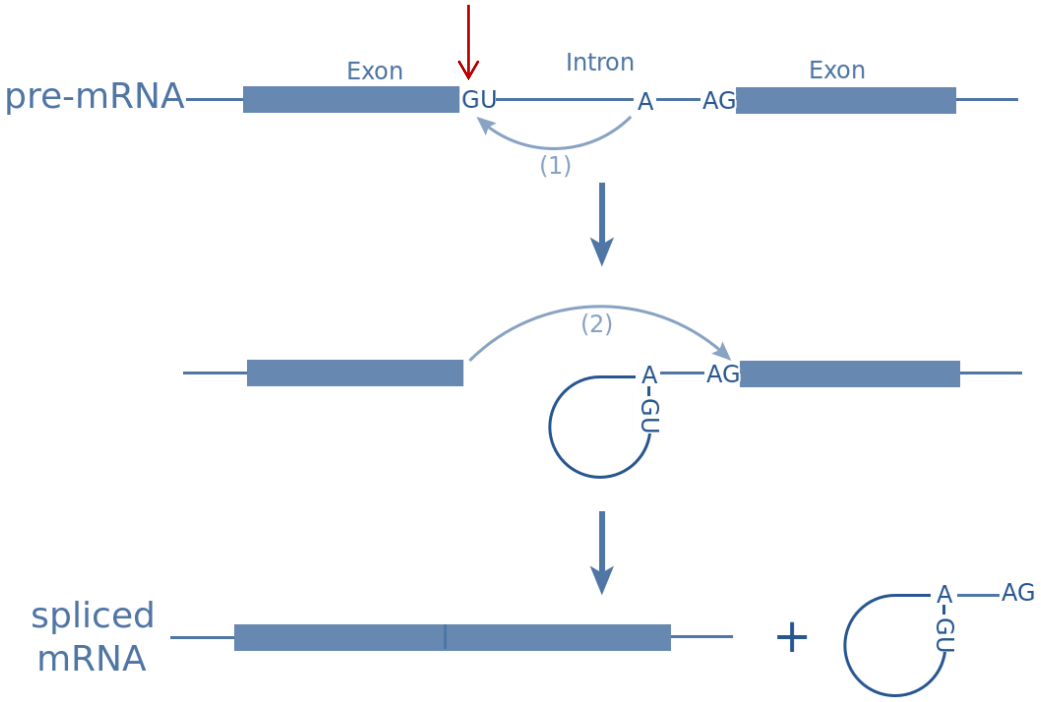
Reasons to keep studying...



Sociedade Portuguesa de Doenças Metabólicas

Splicing Therapies for LSD

- ‘Personalized’ approach



Splicing Therapies for LSD

- The MPS example

- MPS III C
  - *Splicing* mutations → frequent (~20%)

↳ 1 quite frequente in

Portuguese
Spanish
Morrocan
} patients

↓

c.234+1G>A

↓

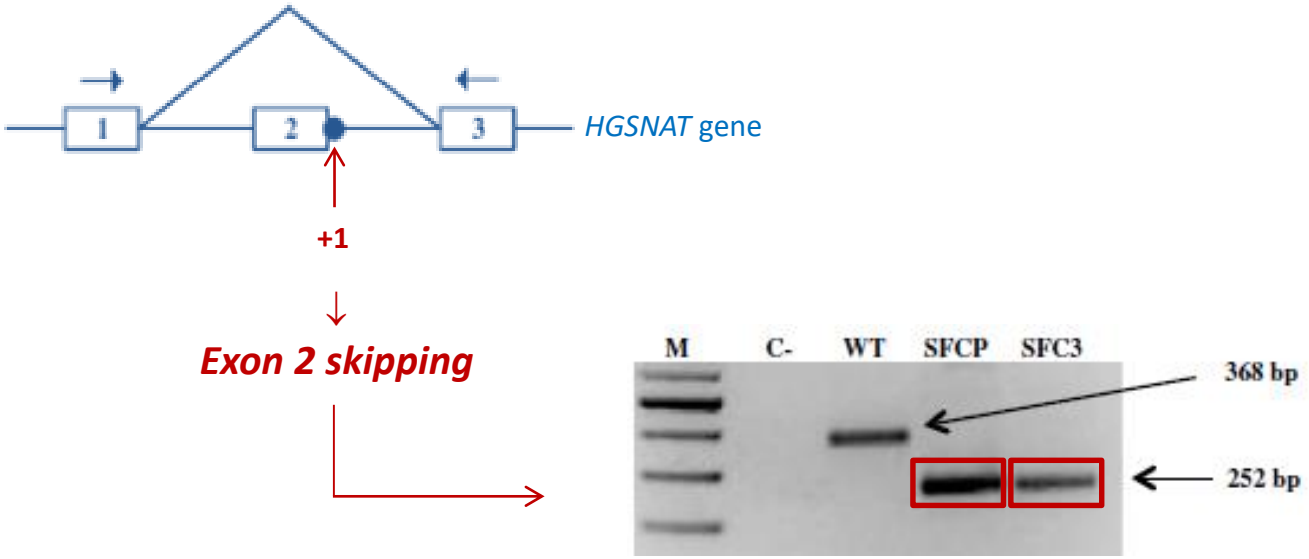
good motifs to attempt splicing correction as a therapeutic approach!

Matos *et al*. Orphanet Journal of Rare Diseases, 2014

Splicing Therapies for LSD

- The MPS example

- MPS III C



Matos *et al*. Orphanet Journal of Rare Diseases, 2014

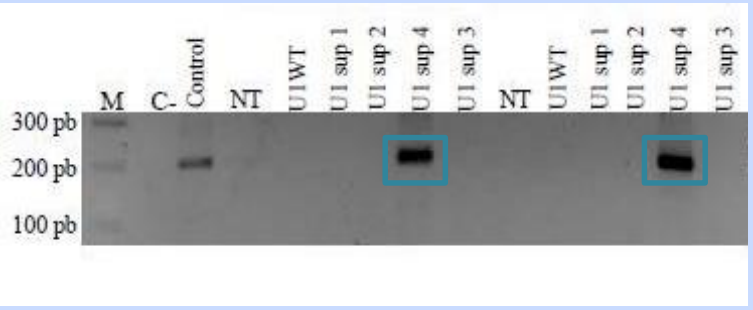
Splicing Therapies for LSD

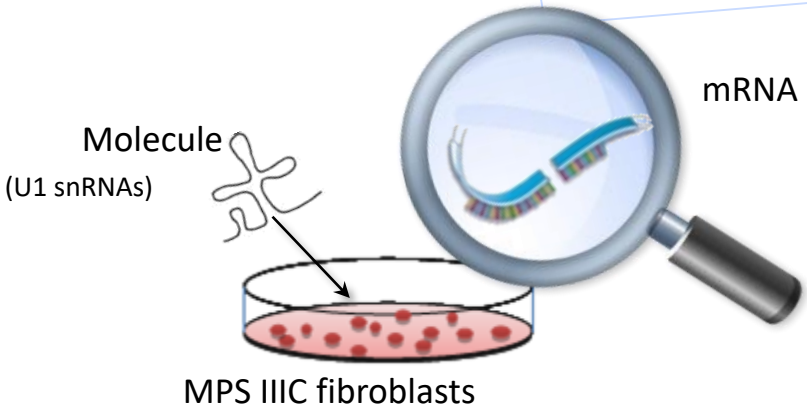
- The MPS example
- MPS III C

4 ≠ oligos

1-4

↗ comp.





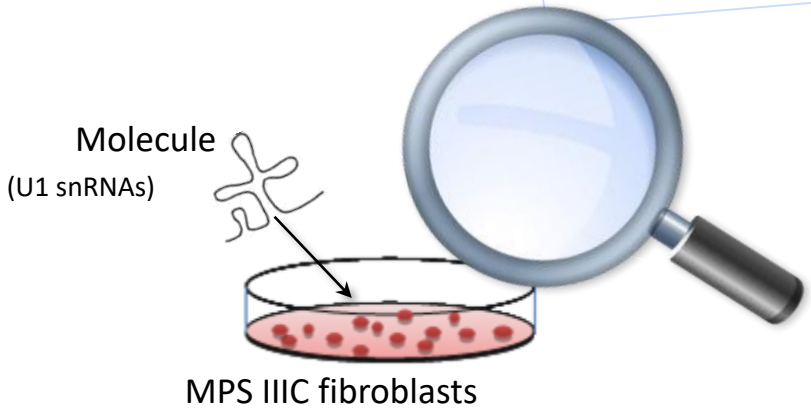
Matos *et al*. Orphanet Journal of Rare Diseases, 2014

Splicing Therapies for LSD

- The MPS example
- MPS III C

Promising results!

Reasons to keep studying...



Matos *et al*. Orphanet Journal of Rare Diseases, 2014

A look forward…

- *in vivo* studies

A look forward…

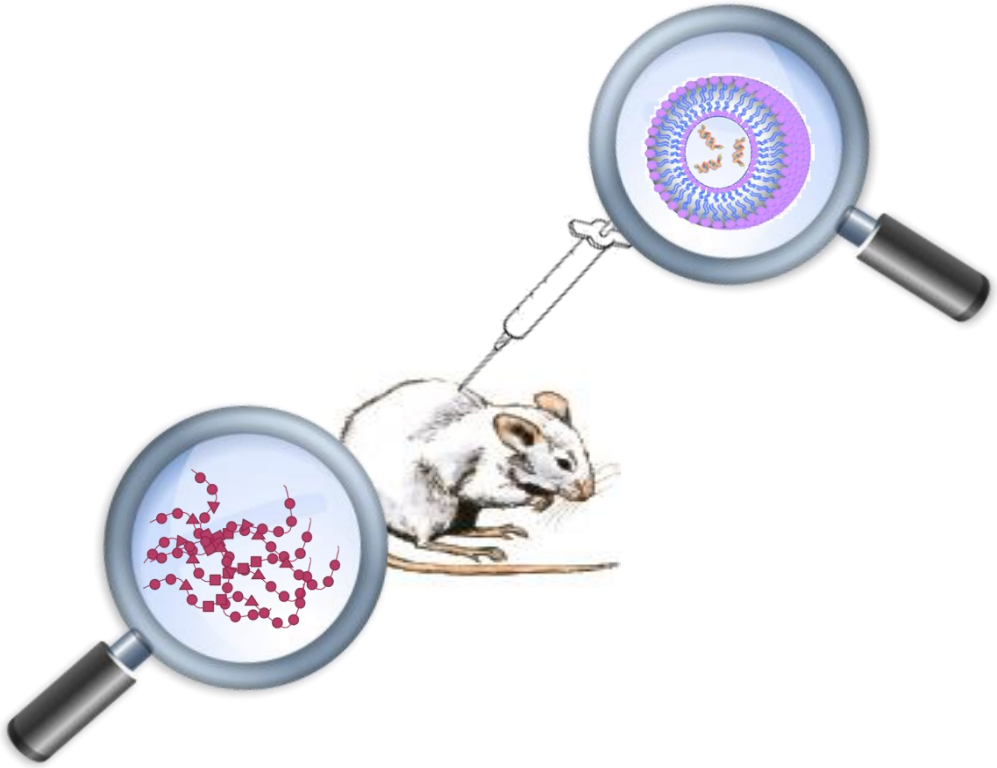
- *in vivo* studies

A look forward…

- *in vivo* studies

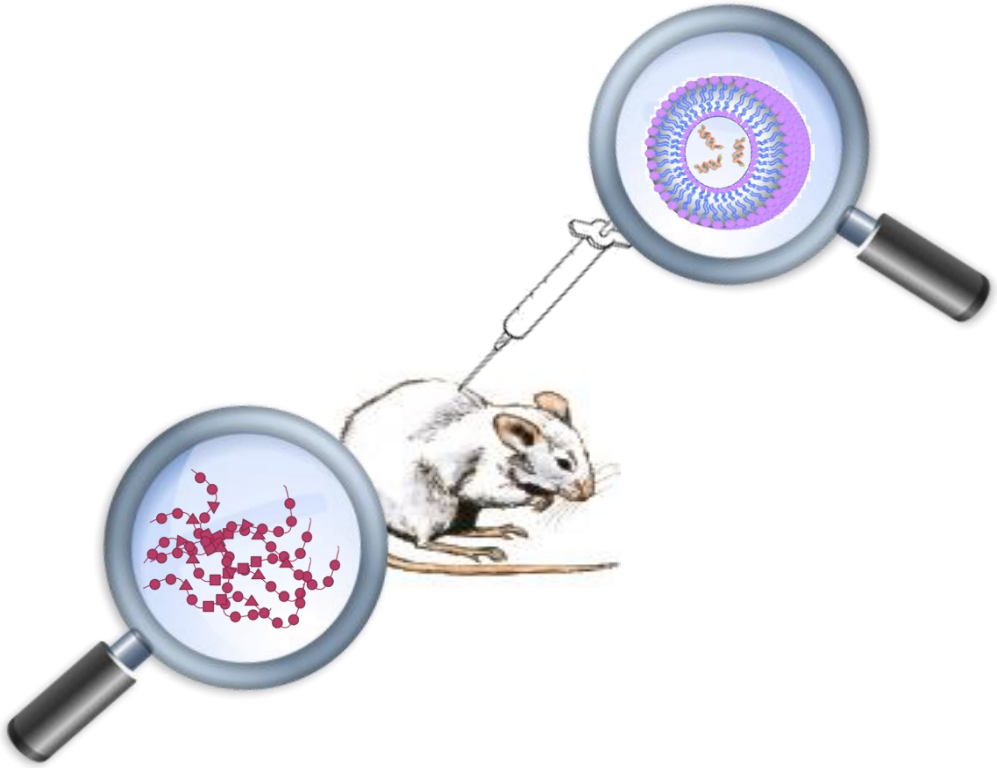
A look forward…

- *in vivo* studies



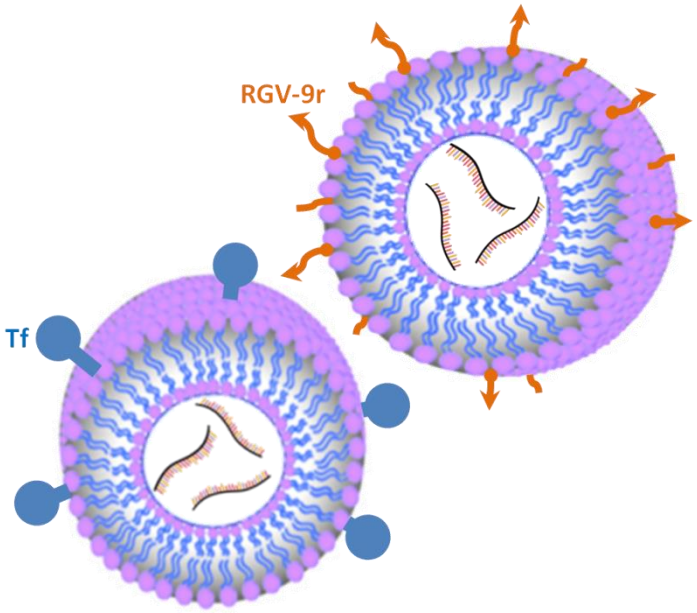
A look forward…

- *in vivo studies*



A look forward…

- Design a proper siRNA delivery strategy for therapeutic purposes



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

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