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SUBSTRATE REDUCTION THERAPY for LYSOSOMAL STORAGE DISORDERS

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Research & Development Unit,
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INSA

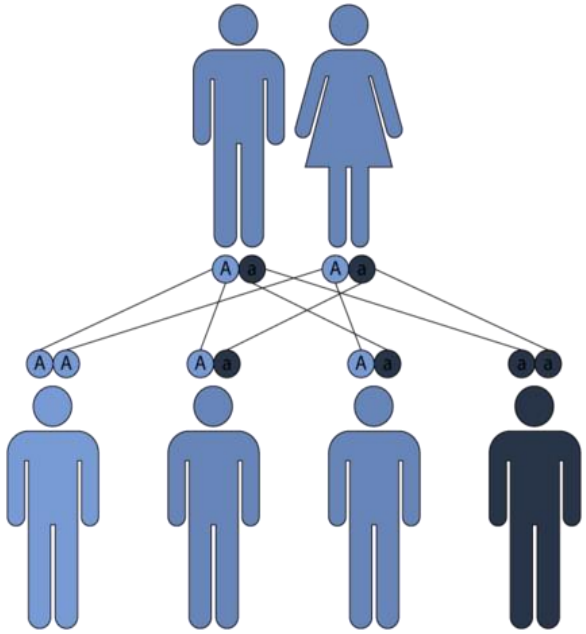
REPÚBLICA PORTUGUESA SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

Instituto Nacional de Saúde Doutor Ricardo Jorge

Lysosomal Storage Disorders

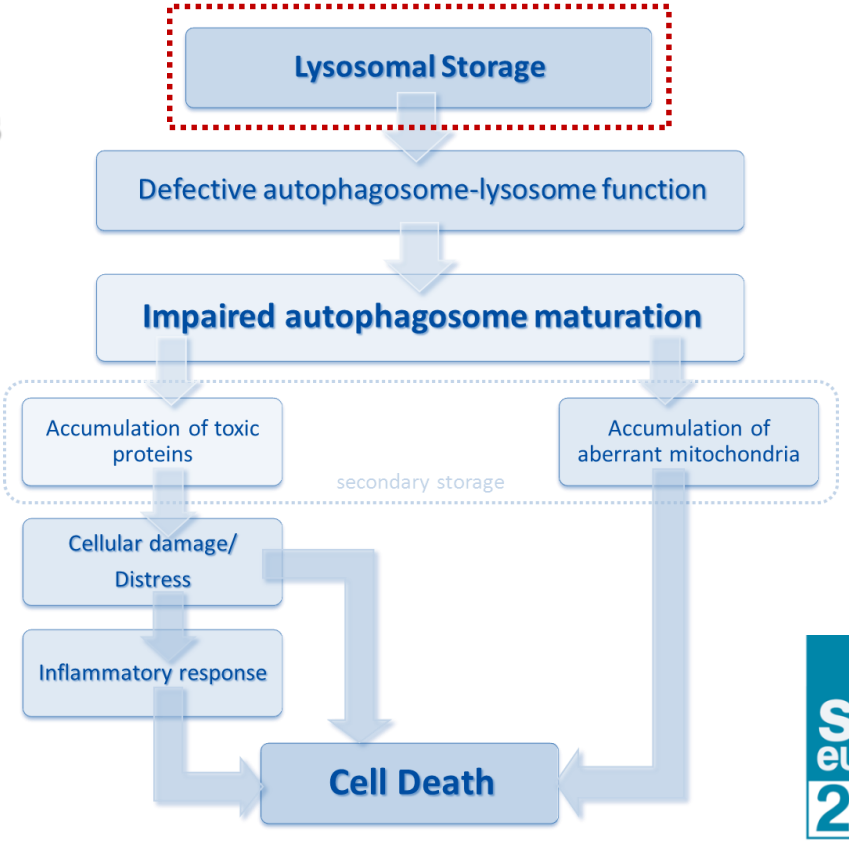
- Genetic
- Rare
- Autosomal recessive (majority)
  - Portugal - 1/4000
  - Almost 60!



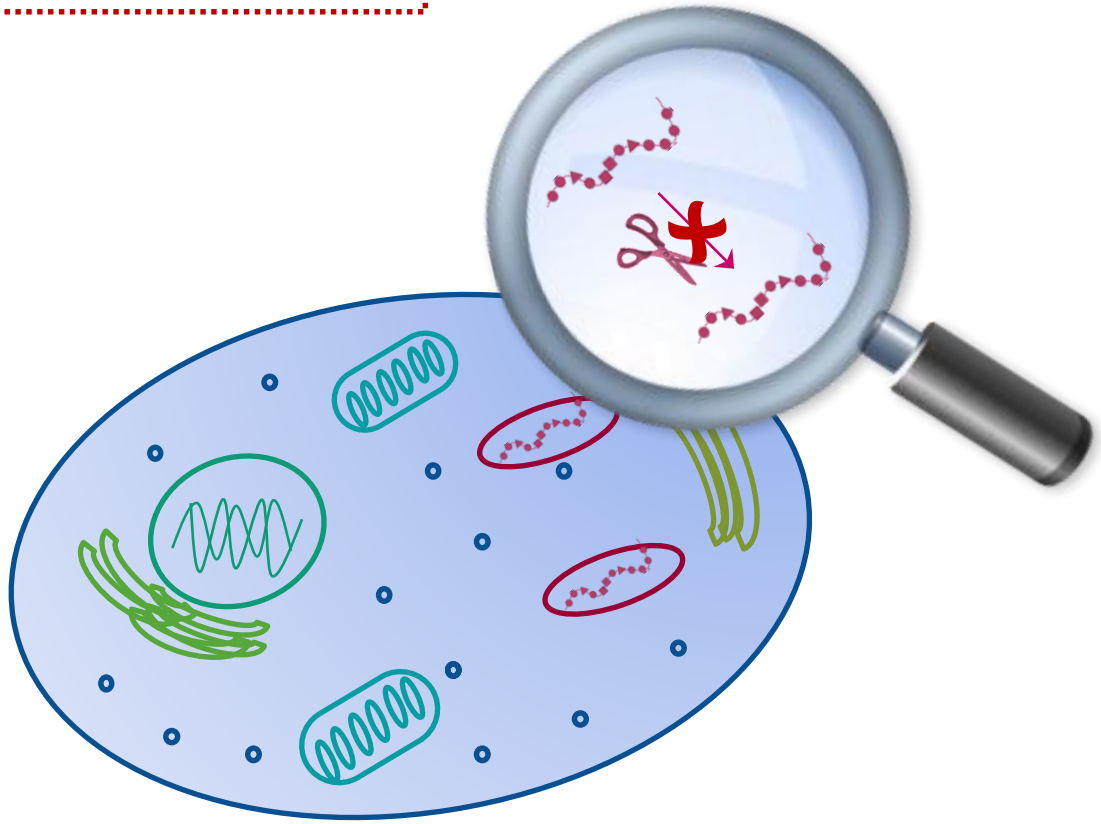
Lysosomal Storage Disorders (LSDs)

- Chronic
- Progressive
- Large spectrum of severity & symptoms

- Pathophysiology *still unknown!*



LYSOSOMAL STORAGE DISORDERS (LSDs)

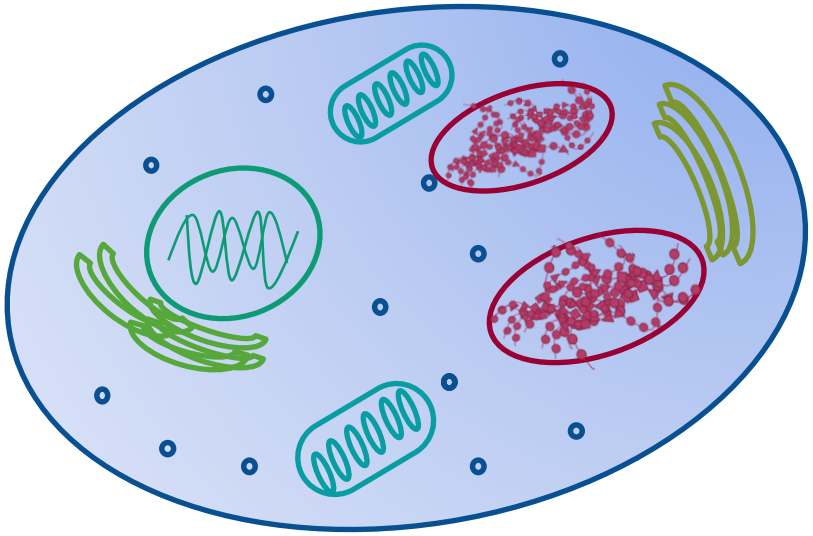


Lysosomal Storage Disorders (LSDs)

- Progressive accumulation

  ⇓

  DISEASE



THE ENZYME AS A DRUG?

- 1969
- Elizabeth Neufeld

THE DEFECT IN HURLER AND HUNTER SYNDROMES,
II. DEFICIENCY OF SPECIFIC FACTORS INVOLVED IN MUCOPOLYSACCHARIDE DEGRADATION

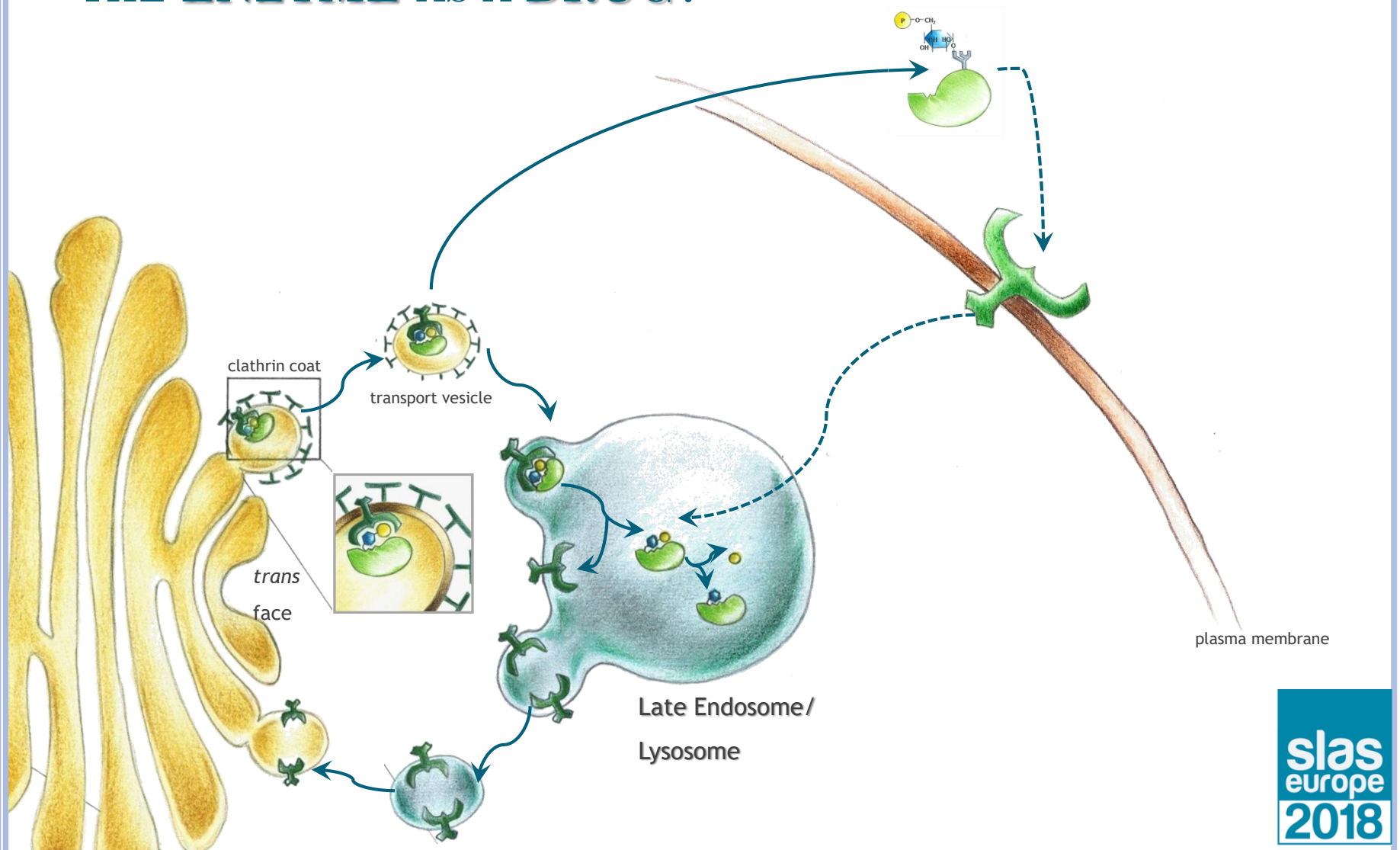
By Joseph C. Fratantoni, Clara W. Hall, and Elizabeth F. Neufeld

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland

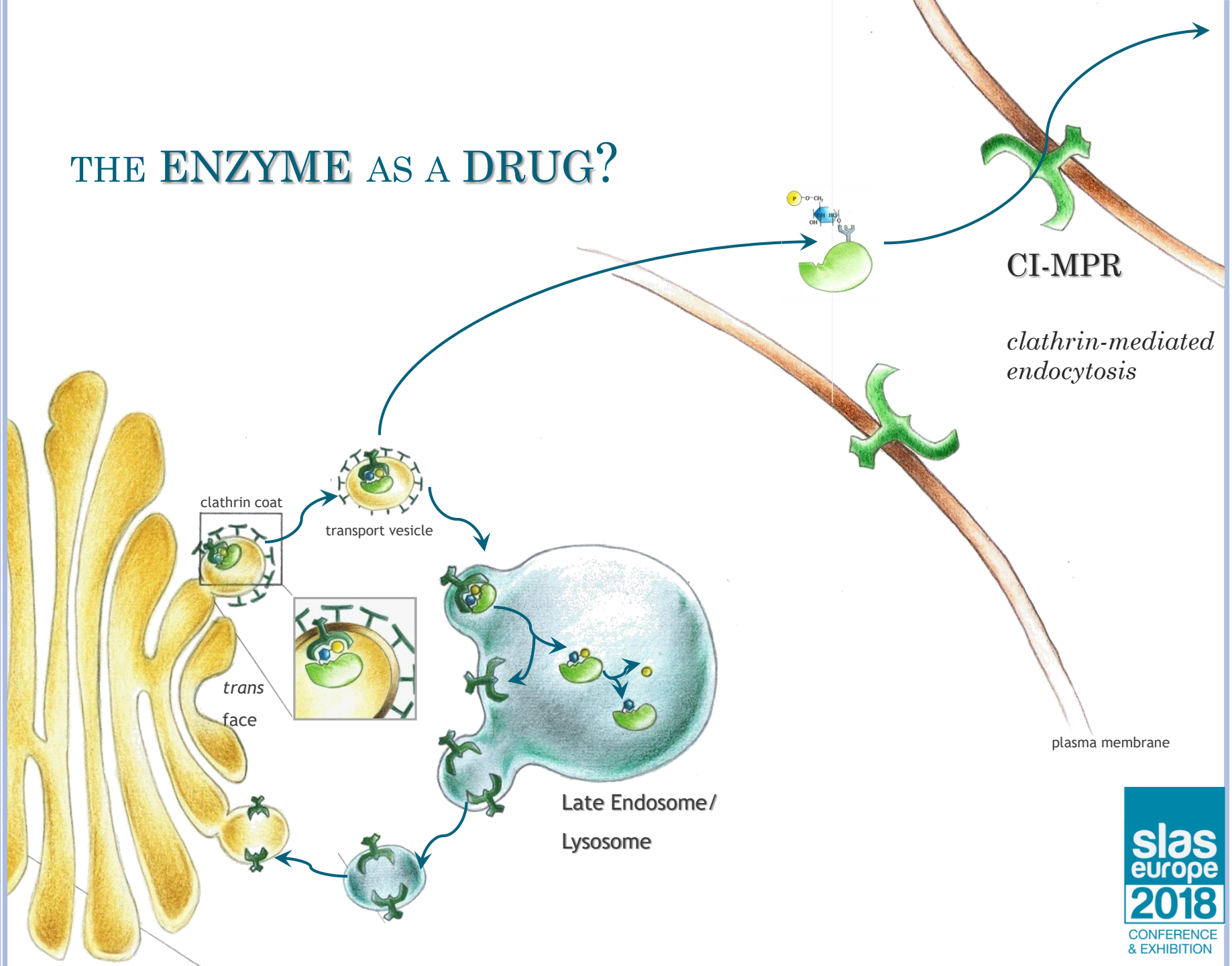
Communicated by Christian B. Anfinsen, July 9, 1969

Abstract.—Cultured fibroblasts, derived from patients with the Hurler and Hunter syndromes, show defective degradation of sulfated mucopolysaccharide. The aberrant metabolism of Hurler cells can be corrected by secretions of fibroblasts of genotype other than Hurler, and similarly, the defect of Hunter cells can be corrected by secretions of fibroblasts of genotype other than Hunter. The active factors in these secretions, which are heat labile and associated with macromolecules, accelerate the degradation of mucopolysaccharide.

THE ENZYME AS A DRUG?



THE ENZYME AS A DRUG?



Proof of Principle…

- **Gaucher Disease** (GD)
- Deficient enzyme: β-glucocerebrosidase
- Gene: *GBA* (1q21)

- Most frequent LSD

genzyme
A SANOFI COMPANY

Original illustration by Marcos Bernardino for Cristiana Petriz´s "*Gigi e a Doença de Gaucher*", 2010

Proof of Principle…

- **Gaucher Disease** (GD)
- Deficient enzyme: **β-glucocerebrosidase**
- Gene: *GBA* (1q21)

- Intravenous injections of the **recombinant enzyme**
- Excellent results in **systemic** disease

Original illustration by Marcos Bernardino for Cristiana Petriz´s "*Gigi e a Doença de Gaucher*", 2010

genzyme
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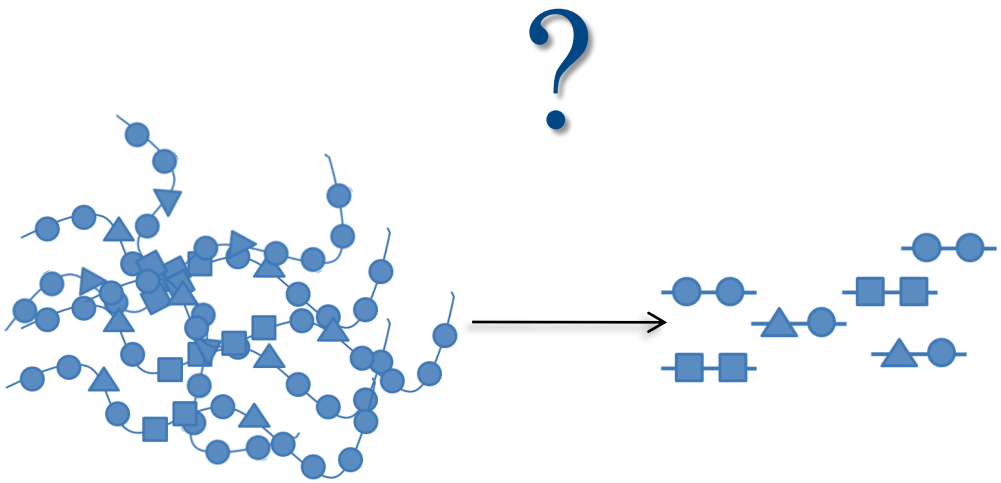
THE ENZYME AS A DRUG?

Pathology	Available ERT		
Gaucher	Cerezyme® (Imiglucerase; Genzyme)	VPRIV® (Velaglucerase alfa; Shire)	Elelyso® (Taliglucerase alfa; Pfizer)
Fabry	Replagal® (Agalsidase alfa; Shire)	Fabrazyme® (Algalsidase beta; Genzyme)	
MPS I	Aldurazyme® (Laronidase; Genzyme)		
MPS II	Elaprase® (Idursulfase; Shire)		
MPS IV A	Vimizim® (Elosulfase alfa; Biomarin)		
MPS VI	Naglazyme® (Galsulfase; Biomarin)		
Pompe	Myozyme® (Lumizyme, Alglucosidase alfa; Genzyme)		
LAL deficiency	Kanuma® (Sebelipase alfa; Alexion)		

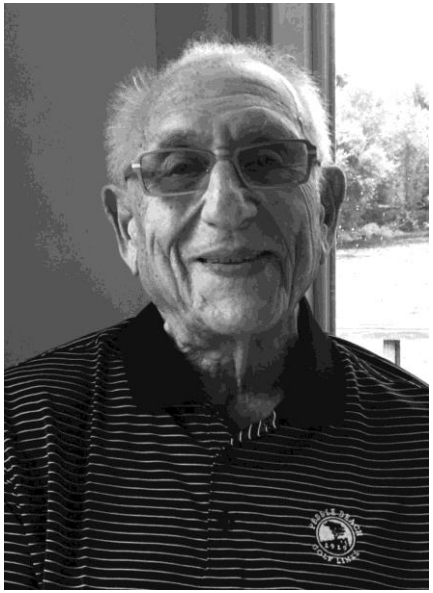
THE ENZYME AS A DRUG?



enzyme replacement

THE ENZYME AS A DRUG?

- 1996
- Norman Radin



Glycoconjugate Journal (1996) **13:** 153–157

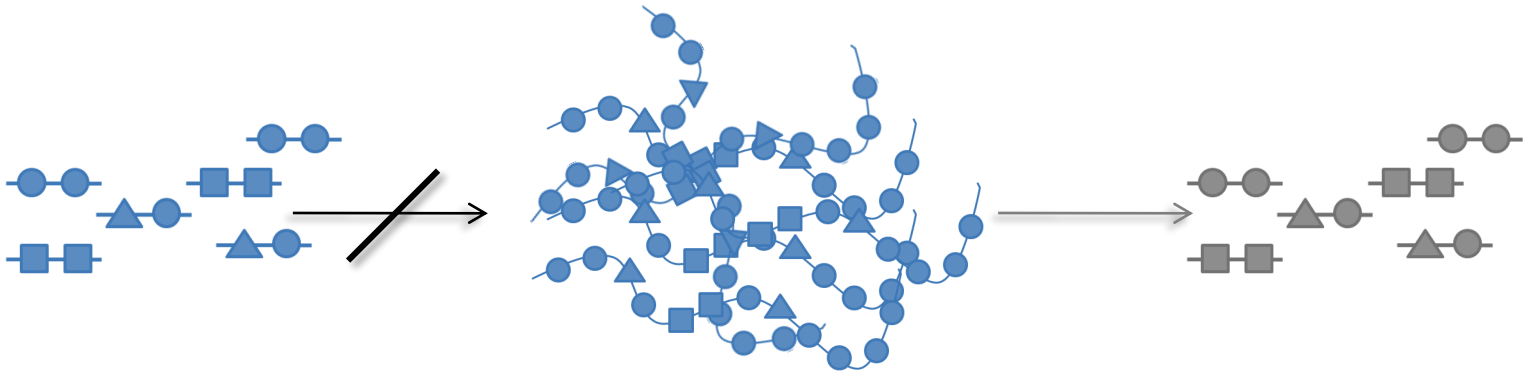
Treatment of Gaucher disease with an enzyme inhibitor

NORMAN S. RADIN

Mental Health Research Institute and Division of Nephrology MSRBII, University of Michigan, 1550 W. Medical Centre Drive Ann Arbor, MI 48109-0676, USA

Received 23 May 1995, revised 20 June 1995

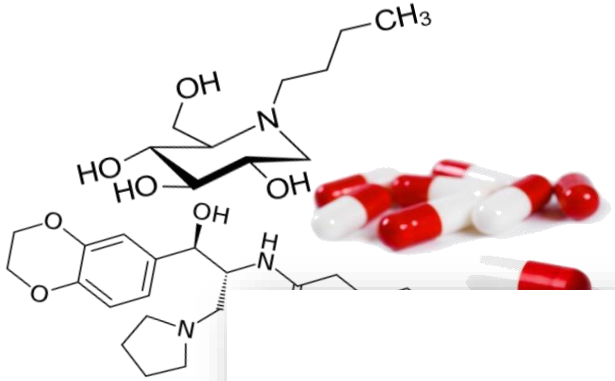
The hypothesis is offered predicting that Gaucher patients could be treated with a drug that slows the synthesis of glucosylceramide, the lipid that accumulates in this disorder. The present therapeutic approach involves augmenting the defective enzyme, glucosylceramide β-glucosidase, with exogenous β-glucosidase isolated from human tissue. This spectacularly expensive mode of treatment should be replaceable with a suitable enzyme inhibitor that simply slows formation of the lipid and matches the rate of synthesis with the rate of the defective, slowly working β-glucosidase. Several drugs that possess this ability are available, the best known of which is 1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP), a designer inhibitor that resembles the synthase's substrate and product. PDMP has been found to be effective in mice, rats, fish, and a wide variety of cultured cells. Its use, at suitable dosages, seems to be harmless, although long-term tests have not been made. The lack of suitable animal models of Gaucher disease has made it difficult to test the hypothesis adequately, but PDMP does rapidly lower the levels of glucosylceramide in normal animal tissues and the animals evidently do well with the lowered levels of glucosylceramide and its more complex glycolipid metabolites.



substrate reduction

enzyme replacement

SUBSTRATE REDUCTION THERAPY (SRT)



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Printed in U.S.A.

N-Butyldeoxynojirimycin Is a Novel Inhibitor of Glycolipid Biosynthesis*

(Received for publication, October 1, 1993, and in revised form, November 15, 1993)

Frances M. Platt‡§, Gabrielle R. Neises¶, Raymond A. Dwek‡, and Terry D. Butters‡

From the ‡Glycobiology Institute, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, United Kingdom and the ¶Monsanto Company, St. Louis, Missouri 63198

Safety, Tolerability, and Pharmacokinetics of Eliglustat Tartrate (Genz-112638) After Single Doses, Multiple Doses, and Food in Healthy Volunteers

M. Judith Peterschmitt, MD, MMsc, Amy Burke, MPH, Larry Blankstein, PhD, Sharon E. Smith, MD, Ana Cristina Puga, MD, PhD, William G. Kramer, PhD, James A. Harris, BSc, MRSC, David Mathews, MD, and Peter L. Bonate, PhD

Three phase 1 studies of eliglustat tartrate (Genz-112638), an oral inhibitor of glucosylceramide synthase under development for treating Gaucher disease type 1 (GD1), evaluated the safety, tolerability, and pharmacokinetics in healthy volunteers after escalating single doses (n = 99), escalating multiple doses (n = 36), and food (n = 24). Eliglustat tartrate was well tolerated at single doses ≤20 mg/kg and multiple doses ≤200 mg bid, with 50 mg bid producing plasma concentrations in the predicted thera-

~2 hours, followed by a monophasic decline with a ~6-hour terminal half-life. Unchanged drug in 8-hour urine collections was <1.5% of administered doses. Food did not significantly affect the rate or extent of absorption. Multiple-dose pharmacokinetics was nonlinear, showing higher than expected plasma drug concentrations. Steady state was reached ~60 hours after bid dosing. Higher drug exposure occurred in slower CYP2D6 metabolizers. Based on favorable results in healthy participants, a phase 2 trial

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SUBSTRATE REDUCTION THERAPY (SRT)

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

SUBSTRATE REDUCTION THERAPY (SRT)

1. NAME OF THE MEDICINAL PRODUCT

Zavesca 100 mg hard capsules

4.4 Special warnings and precautions for

Tremor

Approximately 37% of patients in clinical trial
clinical trial in Niemann-Pick type C disease re
these tremors were described as an exaggerated
began within the first month, and in many case
3 months. Dose reduction may ameliorate the t
treatment may sometimes be required.

Gastrointestinal disturbances

Gastrointestinal events, mainly diarrhoea, have
the outset of treatment or intermittently during
likely inhibition of intestinal disaccharidases su
leading to reduced absorption of dietary disacc
gastrointestinal events have been observed to r
reduction of sucrose, lactose and other carbohy
to anti-diarrhoeal medicinal products such as loperamide. In some patients, temporary dose reduction
may be necessary. Patients with chronic diar
not respond to these interventions should be
not been evaluated in patients with a history
inflammatory bowel disease.

Effects on spermatogenesis

Male patients should maintain reliable contra
have shown that miglustat adversely affects s
fertility (see sections 4.6 and 5.3). Until furt
male patients should cease Zavesca and mair
3 months.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/39261/2015
EMEA/H/C/003724

EPAR summary for the public

Cerdelga

eliglustat

What are the risks associated with Cerdelga?

The most common side effect seen with Cerdelga (which may affect more than 1 in 10 people) is diarrhoea, in approximately 6 out of 100 patients. The majority of side effects are mild and transient. For the full list of all side effects reported for Cerdelga, see the package leaflet.

Cerdelga must not be taken together with certain medicines that can interfere with the ability of the body to break down the medicine, which may affect the levels of Cerdelga in blood. For the full list of restrictions, see the package leaflet.


MPS IVB
Wolman
Pycnodysostosis
Beta-mannosidosis
Metachromatic
Danon
Sandhoff
leukodystrophy
MPS IVA
Tay–Sachs
Mucopolysaccharidosis
Fucosidosis
Mucolipidosis
type I
Fabry
type II
Gaucher
Farber
MPS II
Niemann-Pick
Pompe
type C
ML III
MPS IIIC
Multiple sulfatase
Sialidosis
deficiency
MPS IIIA
MPS IIIB
Alpha-
Krabbe
mannosidosis
Galactosialidosis
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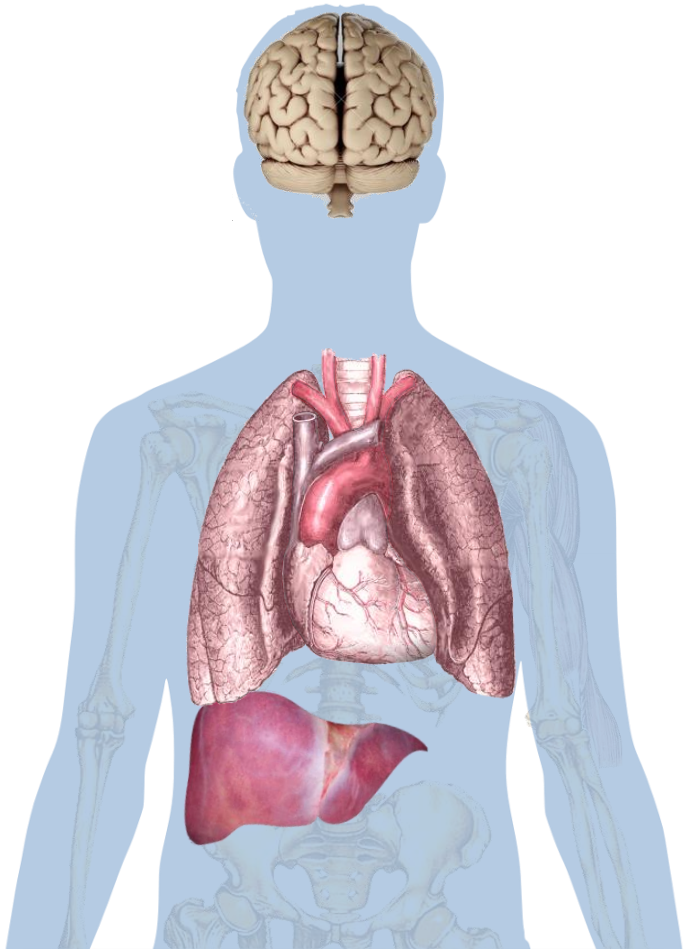
MUCOPOLYSACCHARIDOSES (MPS)

- Chronic
- Progressive
- Large spectrum of severity
  & symptoms



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MUCOPOLYSACCHARIDOSES (MPS)

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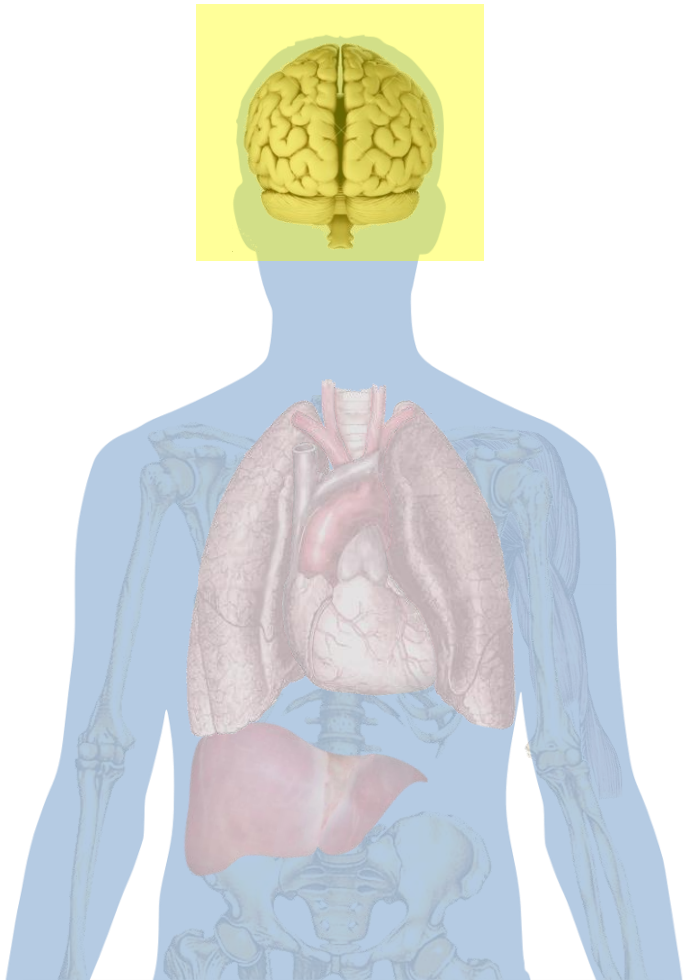


MPS III

(= Sanfilippo Syndrome)

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

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!

Available Therapies

- None!

…only symptomatic!

ameliorate symptoms
support disabled patients

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

⇓

Still, it's being attempted with some promissing results

Available Therapies

- None!

...only symptomatic!

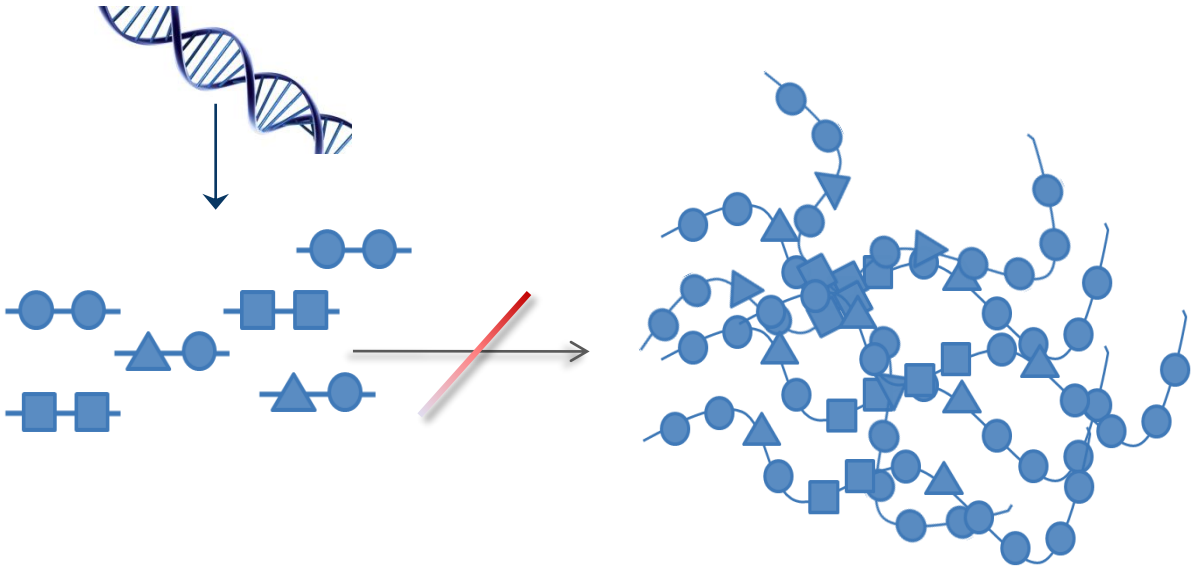
Perfect Target
for
Substrate Reduction Approaches!

ERT for

introdu

Still, it's being attempted with some promissing results

gSRT for MucoPolySaccharidosis type III



genetic substrate reduction

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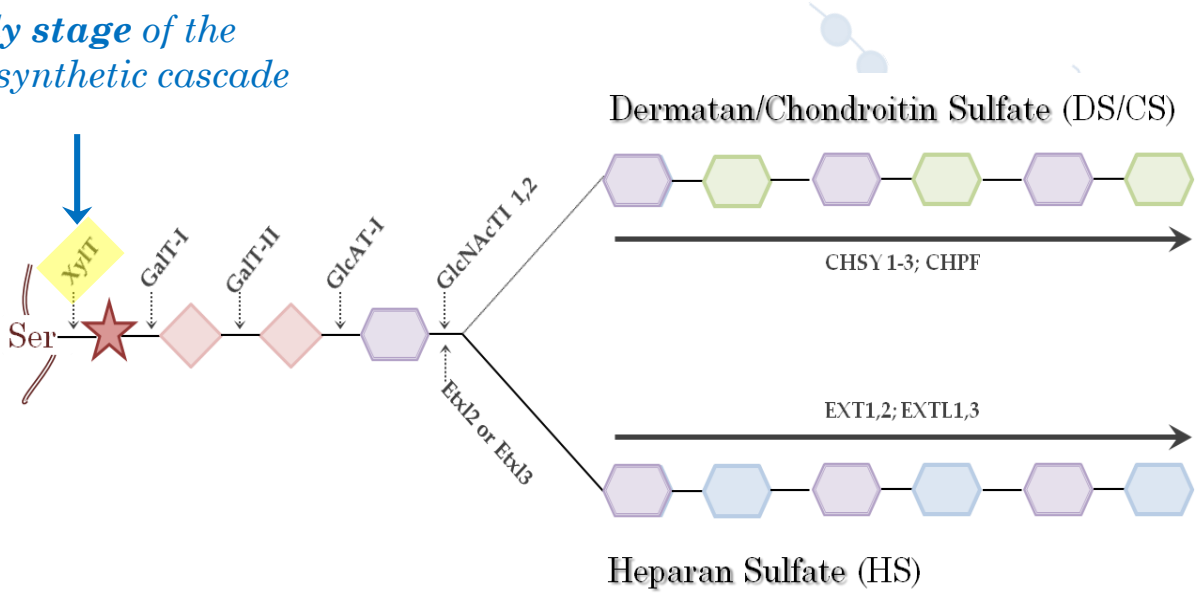
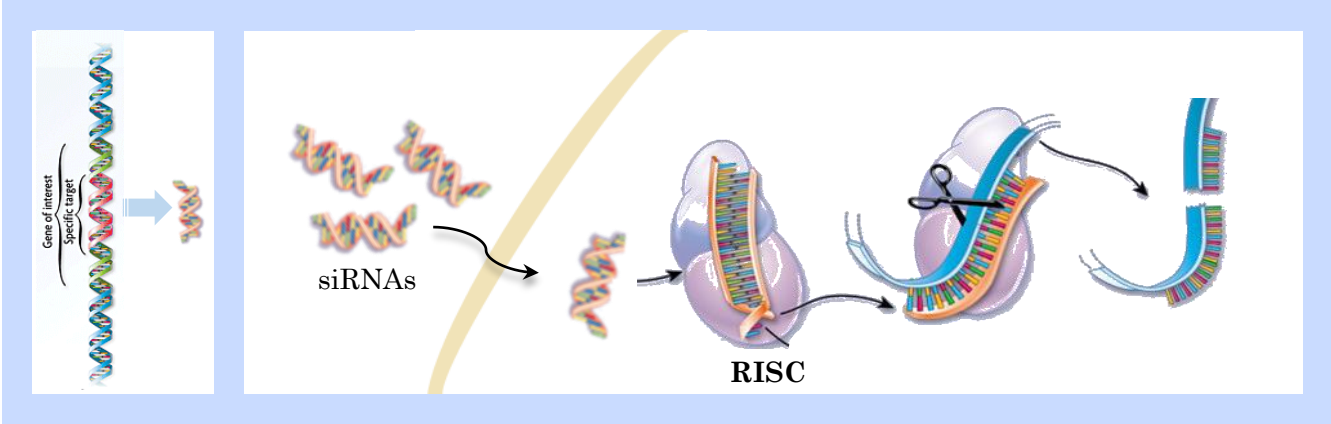
gSRT for MucoPolySaccharidosis type III

early stage *of the*
HS biosynthetic cascade

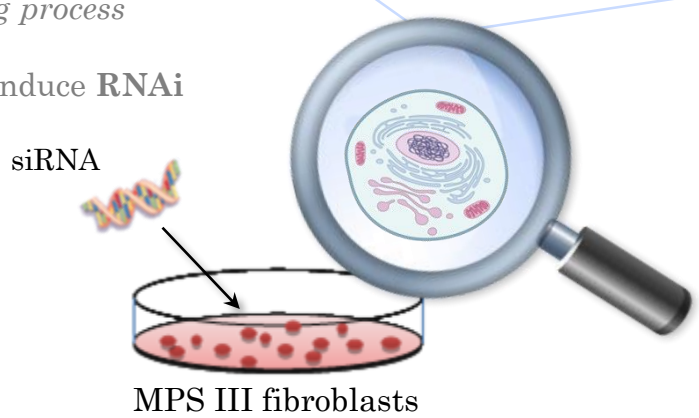


gSRT for MucoPolySaccharidosis type III



naturally occurring post-transcriptional gene silencing process

Designed to induce **RNAi**



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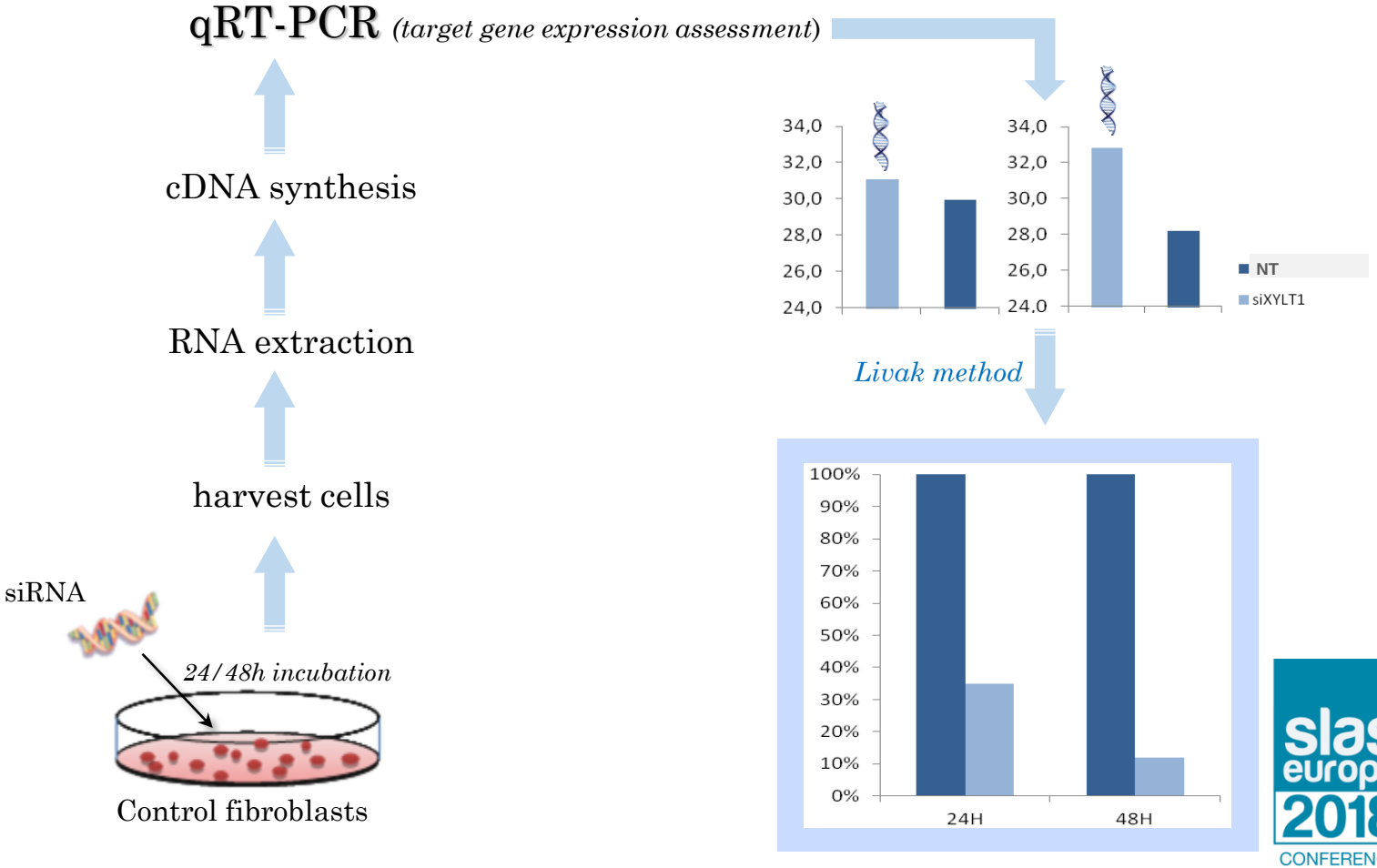

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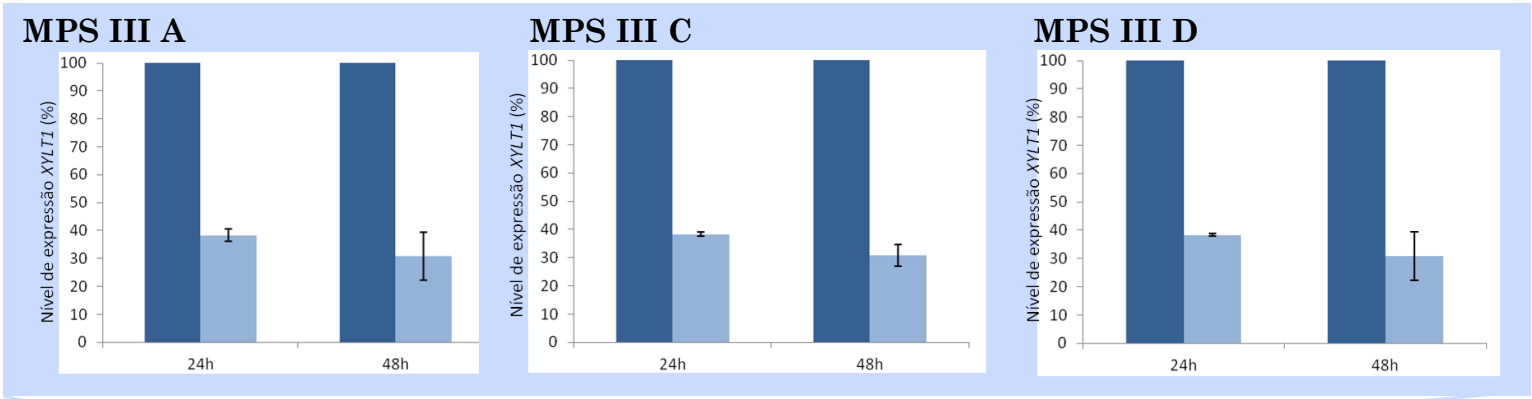

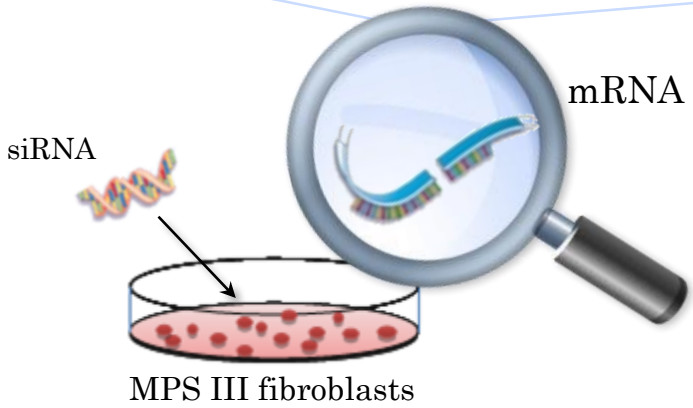

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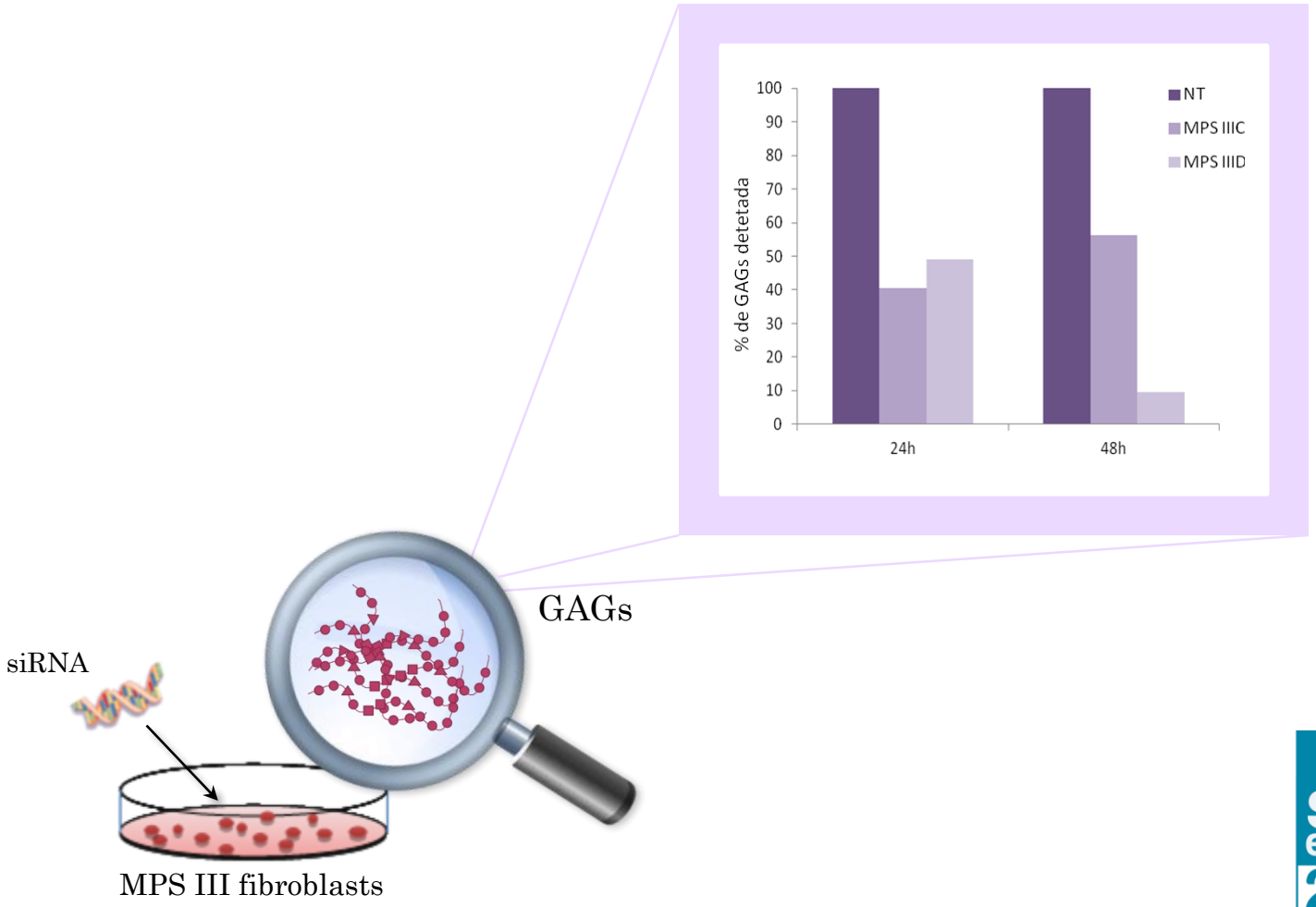
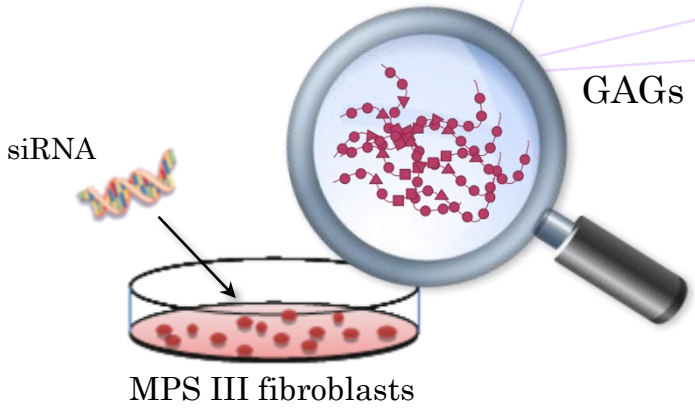
gSRT for MucoPolySaccharidosis type III



gSRT for MucoPolySaccharidosis type III

Further validation:

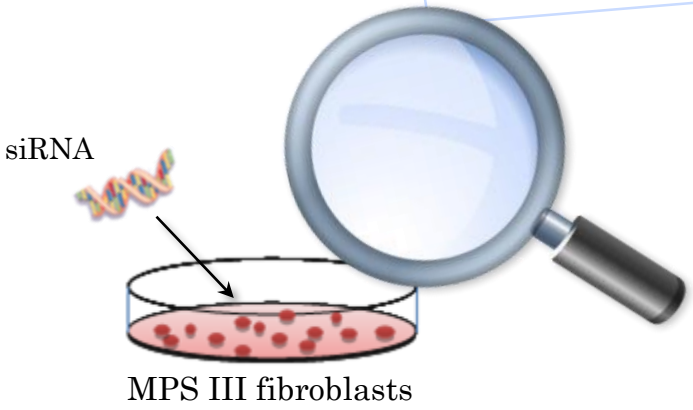
- ↑ nr of experiments;
- immunocytochemistry
  (anti-HS antibody)
- + tests in **MPS IIIB**



gSRT for MucoPolySaccharidosis type III

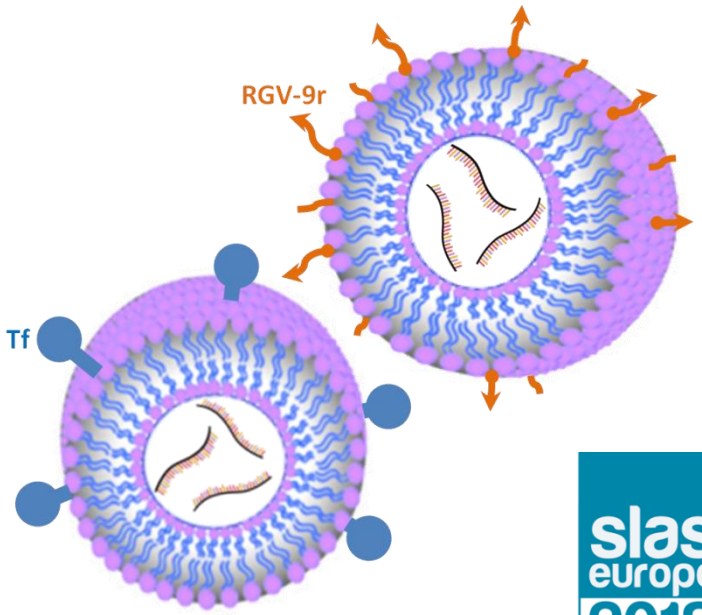
Promising results!

Reasons to keep studying...

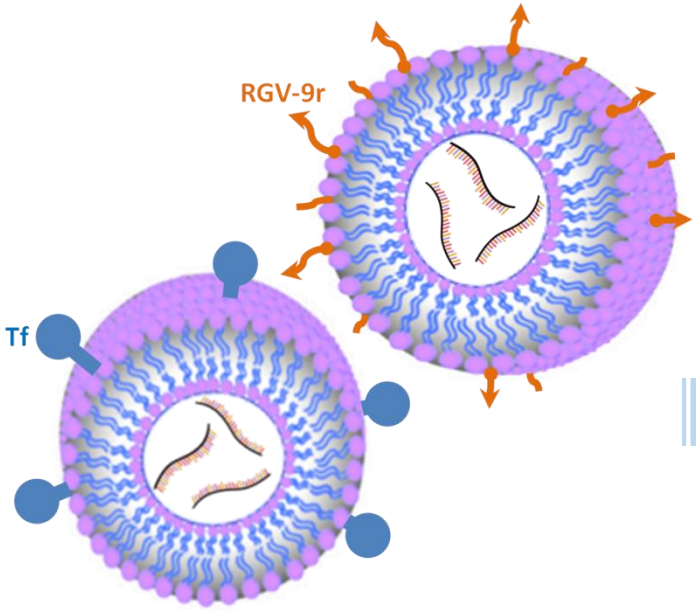


A LOOK FORWARD…

- 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

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gSRT for MucoPolySaccharidosis type III

SUMMARY

"early stages" GAGs biosynthesis gene

↓ GAG storage

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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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Paulo Gaspar

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SFRH/BD/124372/2016

Fundação Millennium bcp
bcp/LIM/DGH/Dz2015

Sanfilippo Portugal

Jonah's Just Begun
jonahsjustbegun.org

Iluminemos a los niños, digámosle SI a la vida

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE
PRÉFET DE TARN-ET-GARONNE

Sanfilippo Sud

António Reis ♥

Thank You!

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