Semmelweis Symposium 2018
8th-9th November, 2018

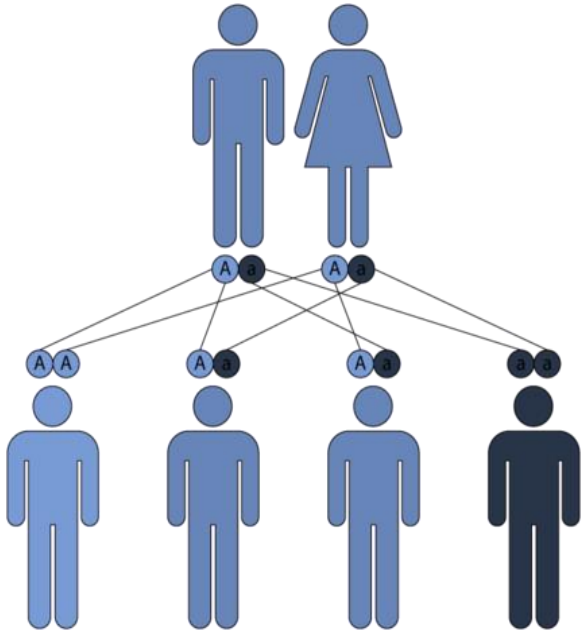
Enzyme Replacement Therapies for Lysosomal Storage Diseases

Maria Francisca Coutinho

Lysosomal Storage Disorders Group
Research & Development Unit,
Department of Human Genetics,
INSA

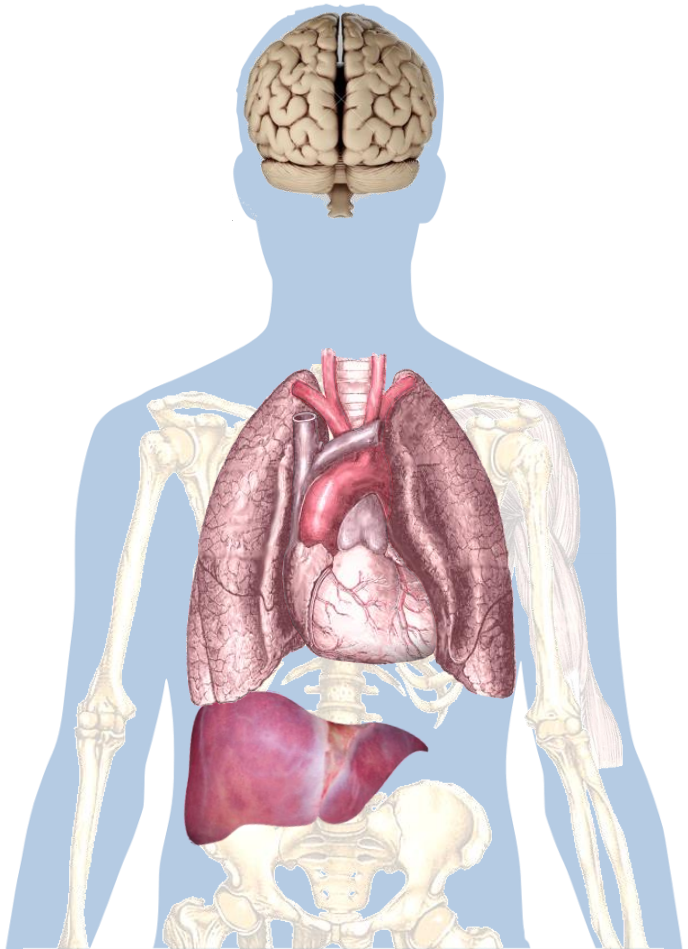
Lysosomal Storage Disorders (LSDs)

- Genetic
- Rare
- Autosomal recessive (majority)
  - Portugal - 1/4000
  - Almost 70!



Lysosomal Storage Disorders (LSDs)

- Chronic
- Progressive
- Large spectrum of severity & symptoms



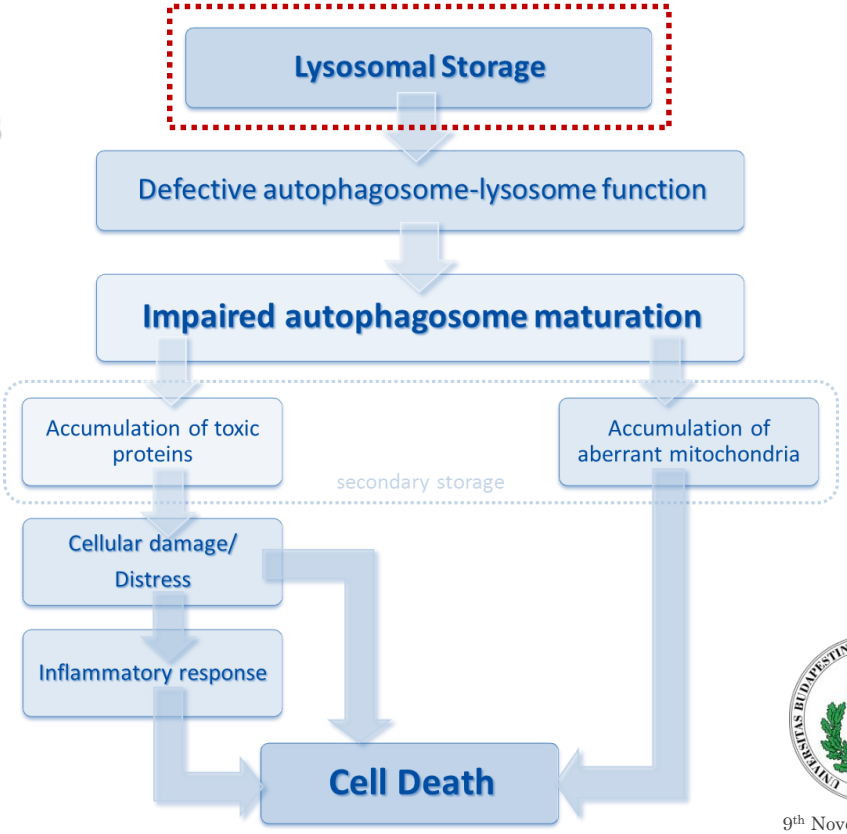
CNS pathology is a common hallmark of LSDs

LSDs are the commonest cause of paediatric neurodegenerative disease

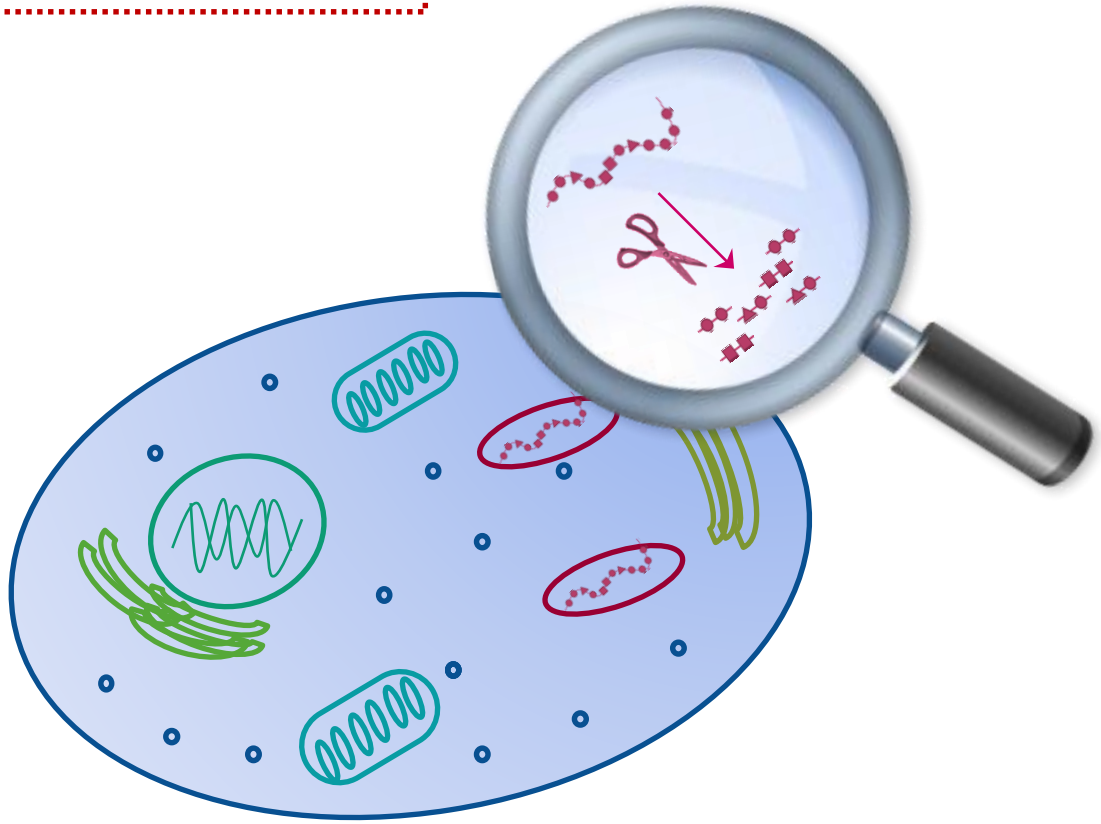
Lysosomal Storage Disorders (LSDs)

- Chronic
- Progressive
- Large spectrum of severity & symptoms

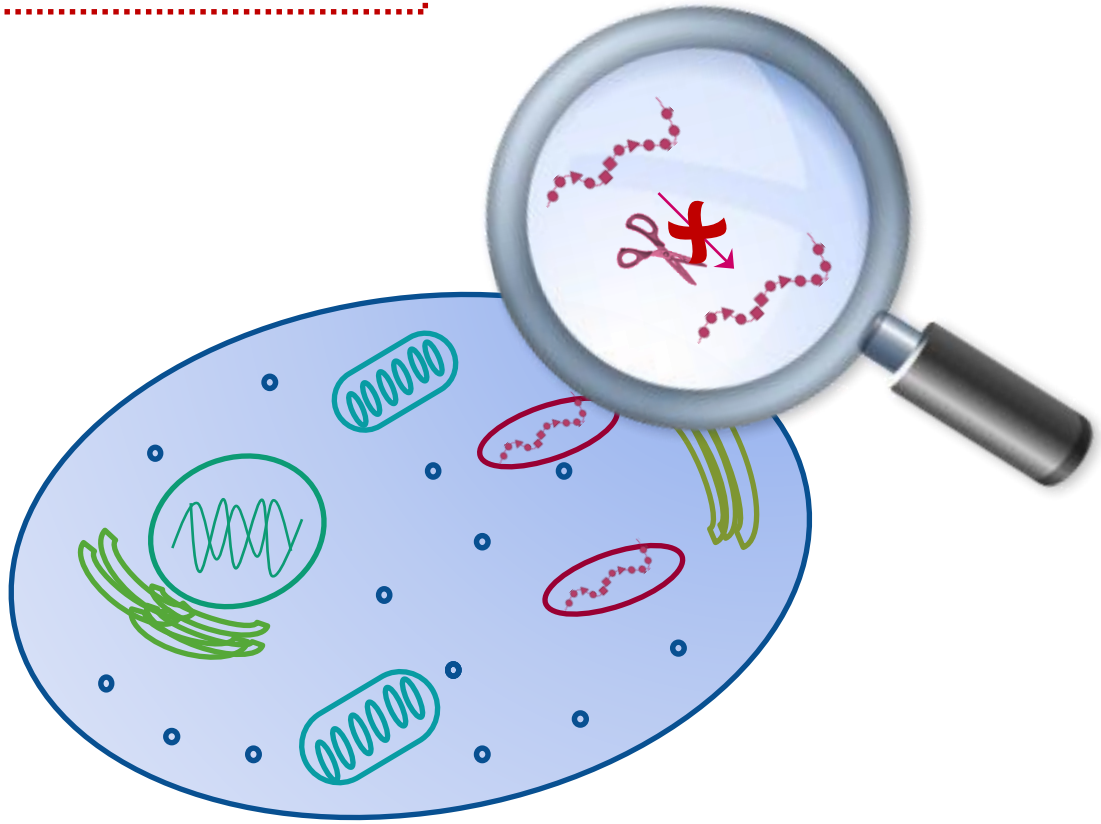
- Pathophysiology *still unknown!*



LYSOSOMAL STORAGE DISORDERS (LSDs)

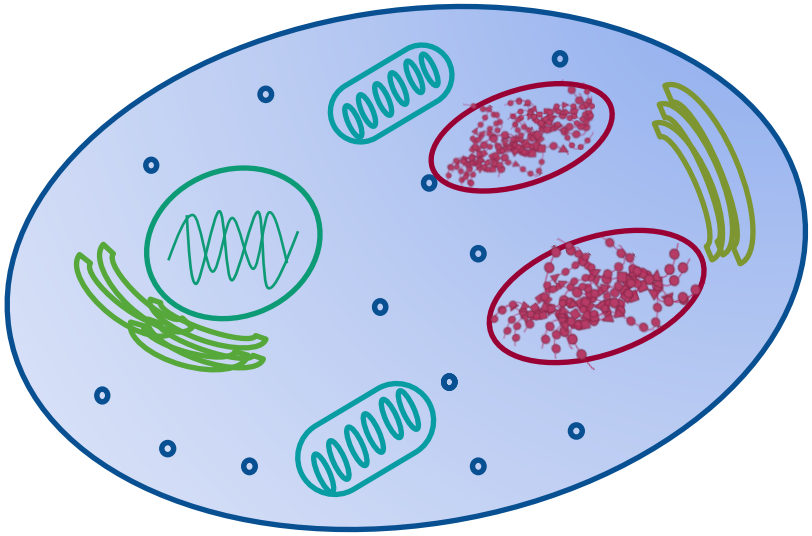


LYSOSOMAL STORAGE DISORDERS (LSDs)



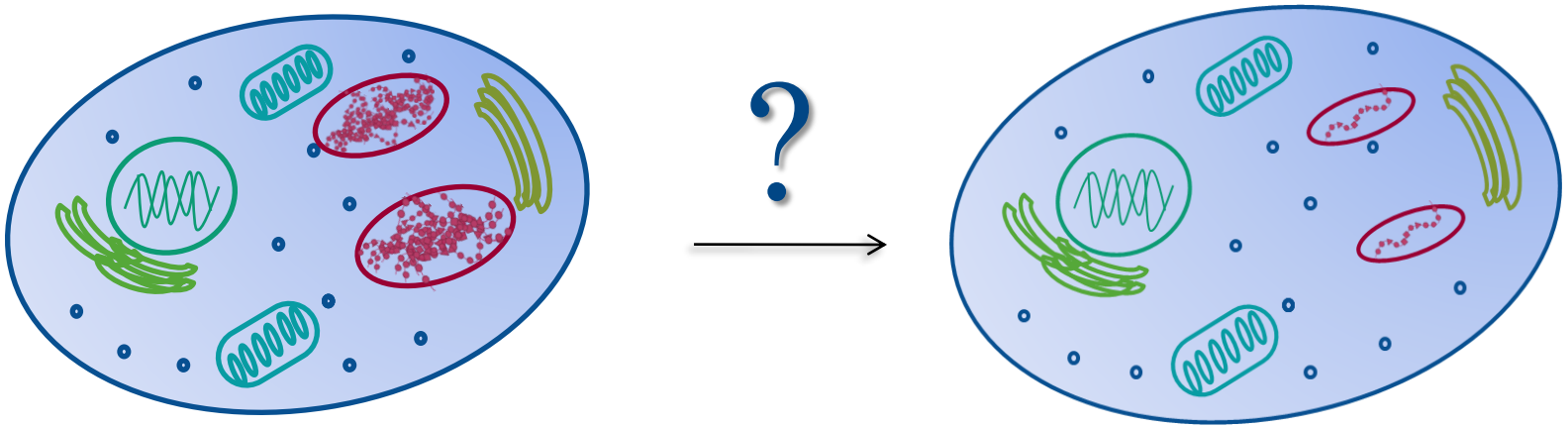
Lysosomal Storage Disorders (LSDs)

- Progressive accumulation



Lysosomal Storage Disorders (LSDs)

- Progressive accumulation



THE ENZYME AS A DRUG?

- 1969
- Elizabeth Neufeld

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

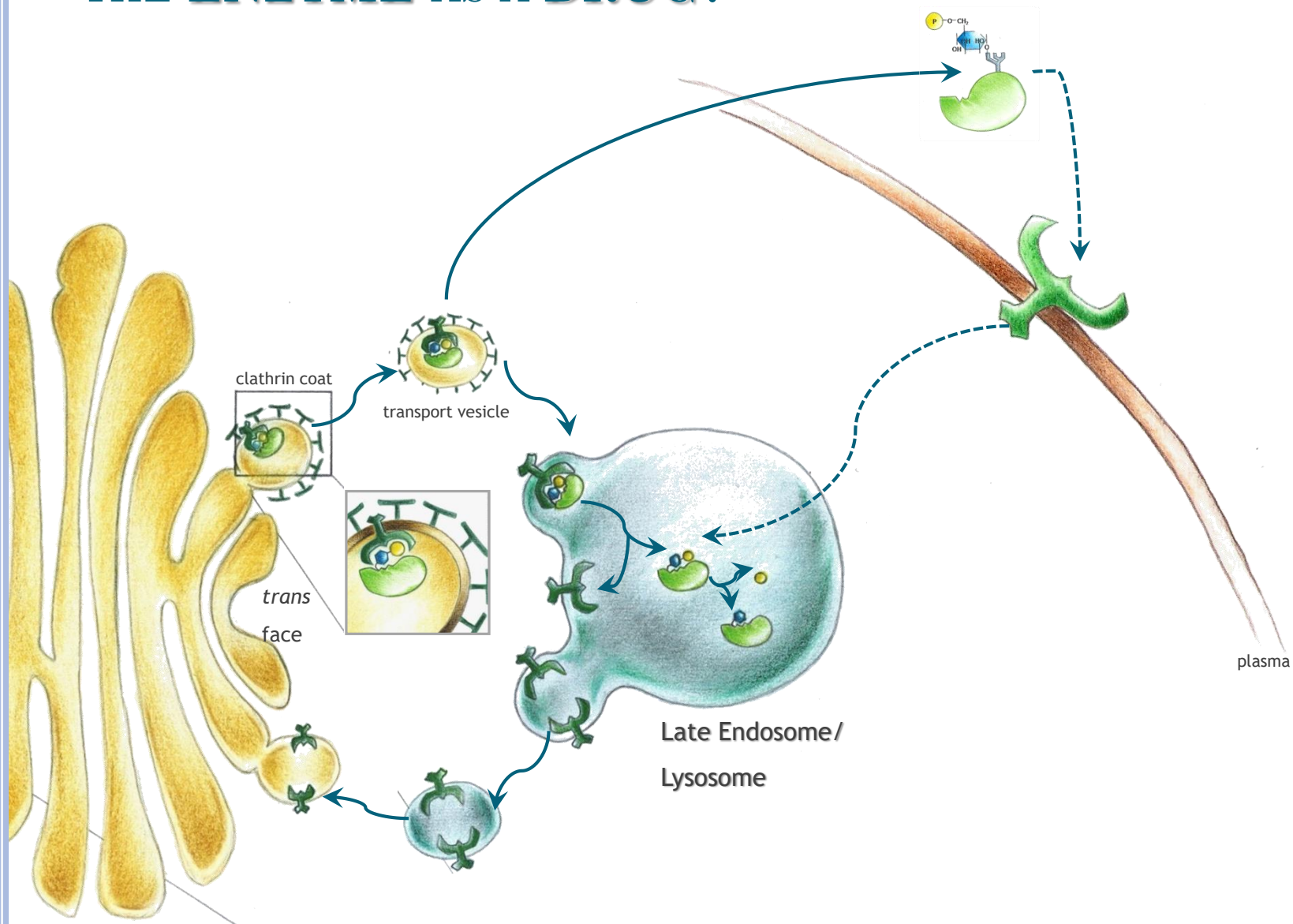
By Joseph C. Fratantoni, Clara W. Hall, and Elizabeth F. Neufeld

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

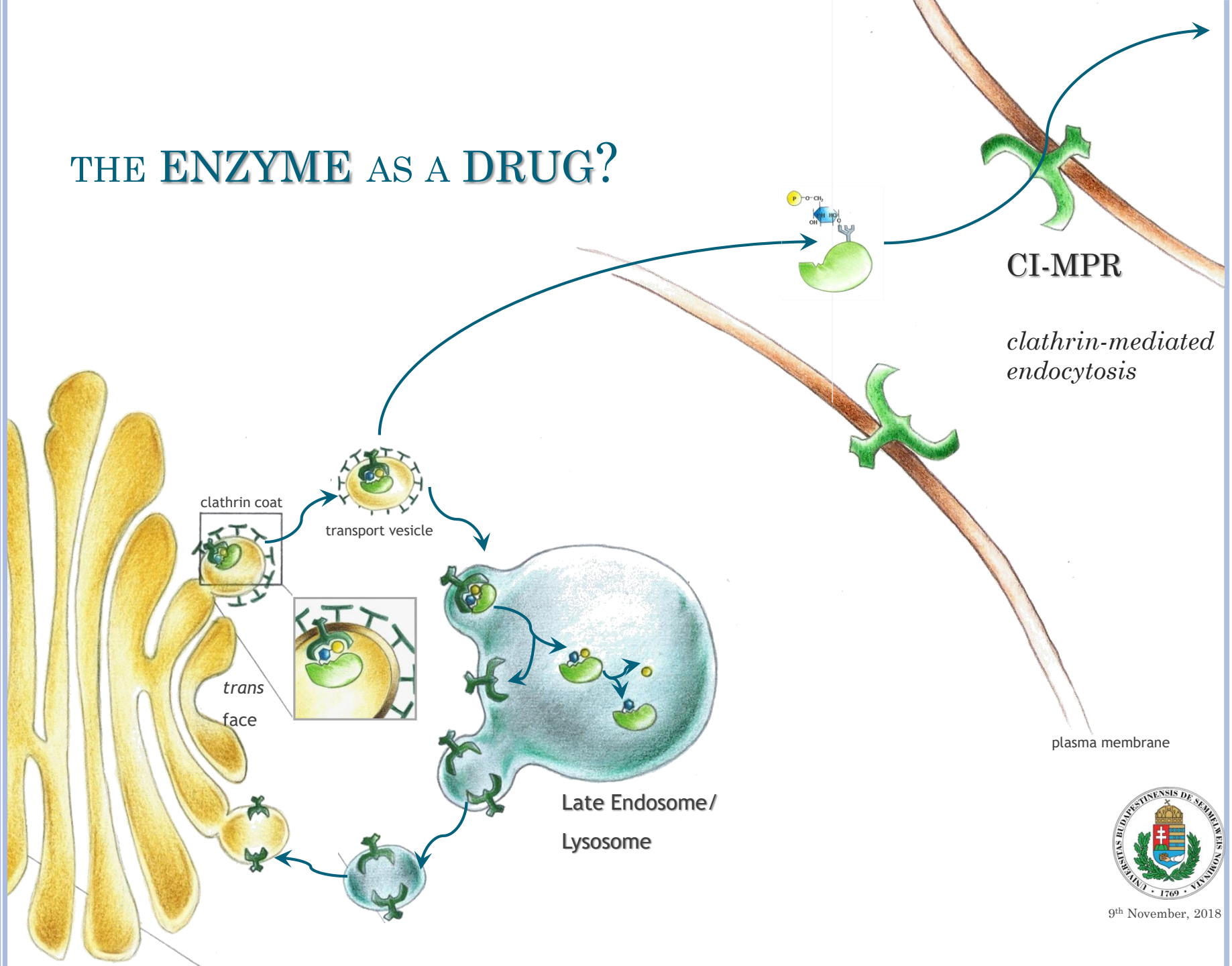
Communicated by Christian B. Anfinsen, July 9, 1969

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.

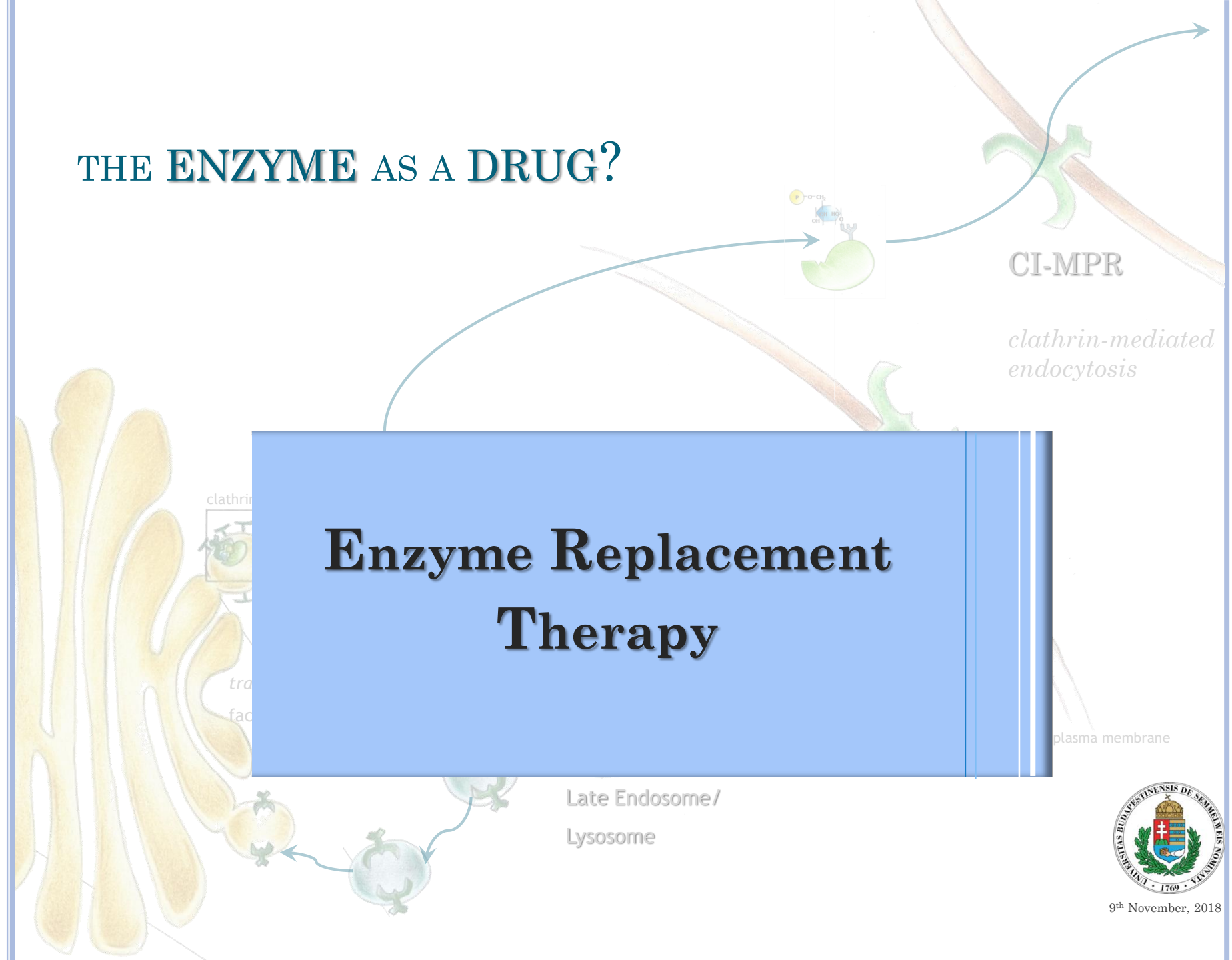
THE ENZYME AS A DRUG?



THE ENZYME AS A DRUG?



THE ENZYME AS A DRUG?



Enzyme Replacement Therapy

Proof of Principle…

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

- Most frequent LSD

genzyme
A SANOFI COMPANY

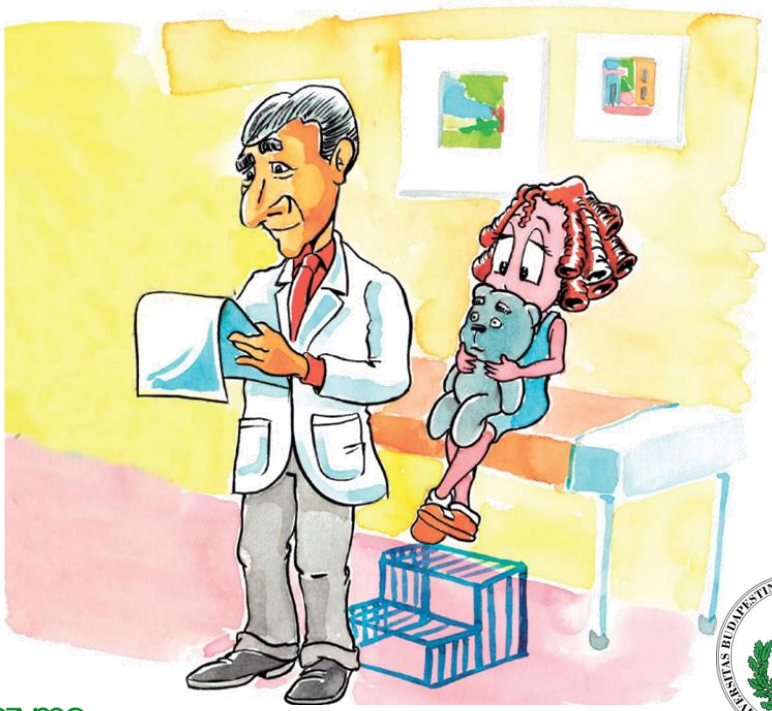
Original illustration by Marcos Bernardino for Cristiana Petriz´s "*Gigi e a Doença de Gaucher*", 2010

Proof of Principle…

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

- Missing enzyme
  - ↳ isolated from human placentae
- IV injection into patients
- **extraordinary results**

in blood tests!



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**

genzyme
A SANOFI COMPANY

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

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?

- Several limitations

  - Cost
  - Lifelong dependance
  - **Ineffective** for the **CNS manifestations**

…antibodies?

…secondary effects?

MPS IVB

Wolman

Beta-mannosidosis

Pycnodysostosis

Sandhoff

Metachromatic leukodystrophy

Danon

MPS IVA

Tay

dosis

Mucoli

cosidosis

type II

r

Niema

II

type C

ML III

MPS IIIC

Multiple sulfatase deficiency

Sialidosis

MPS IIIA

MPS IIIB

Alpha-mannosidosis

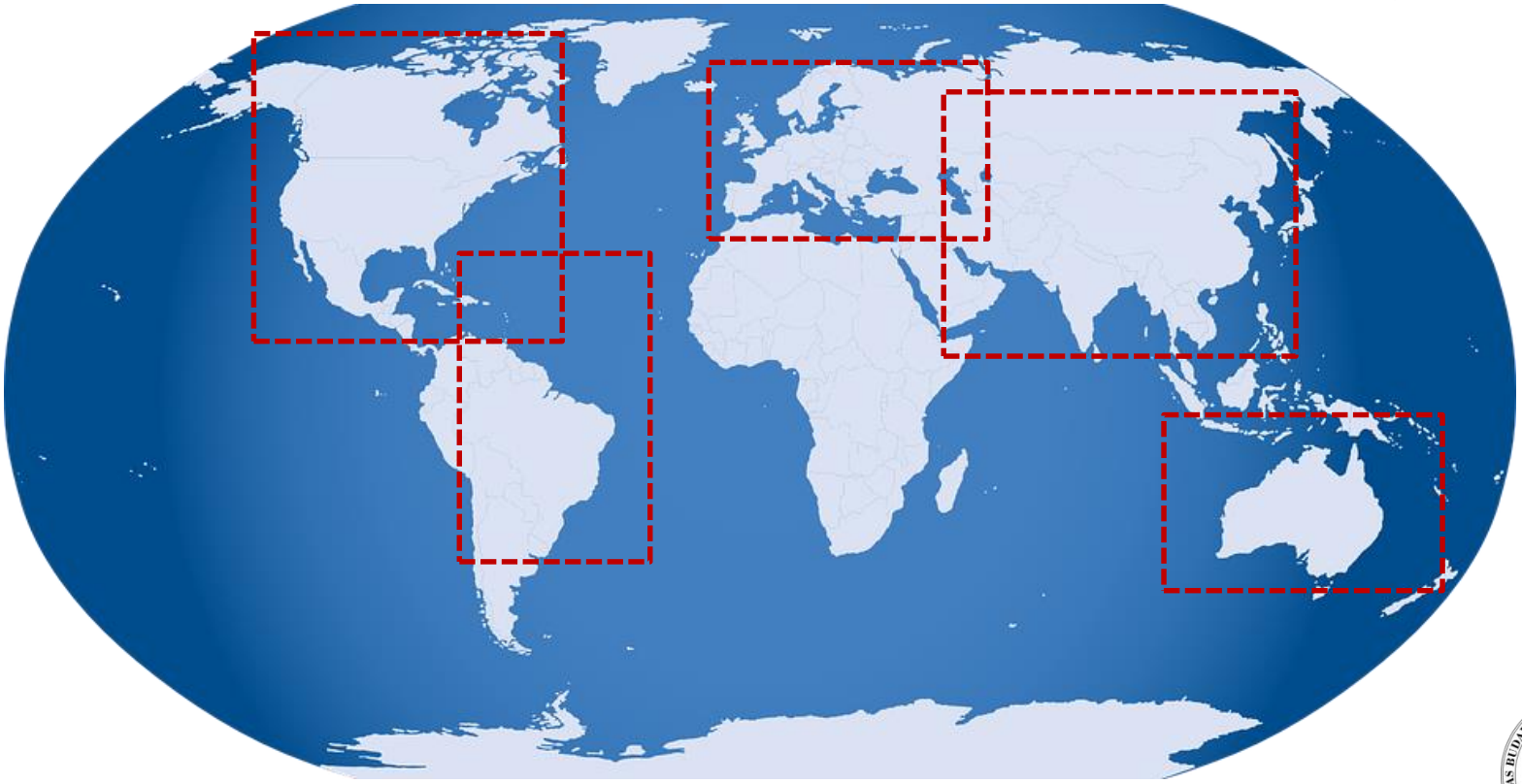
Krabbe

Galactosialidosis

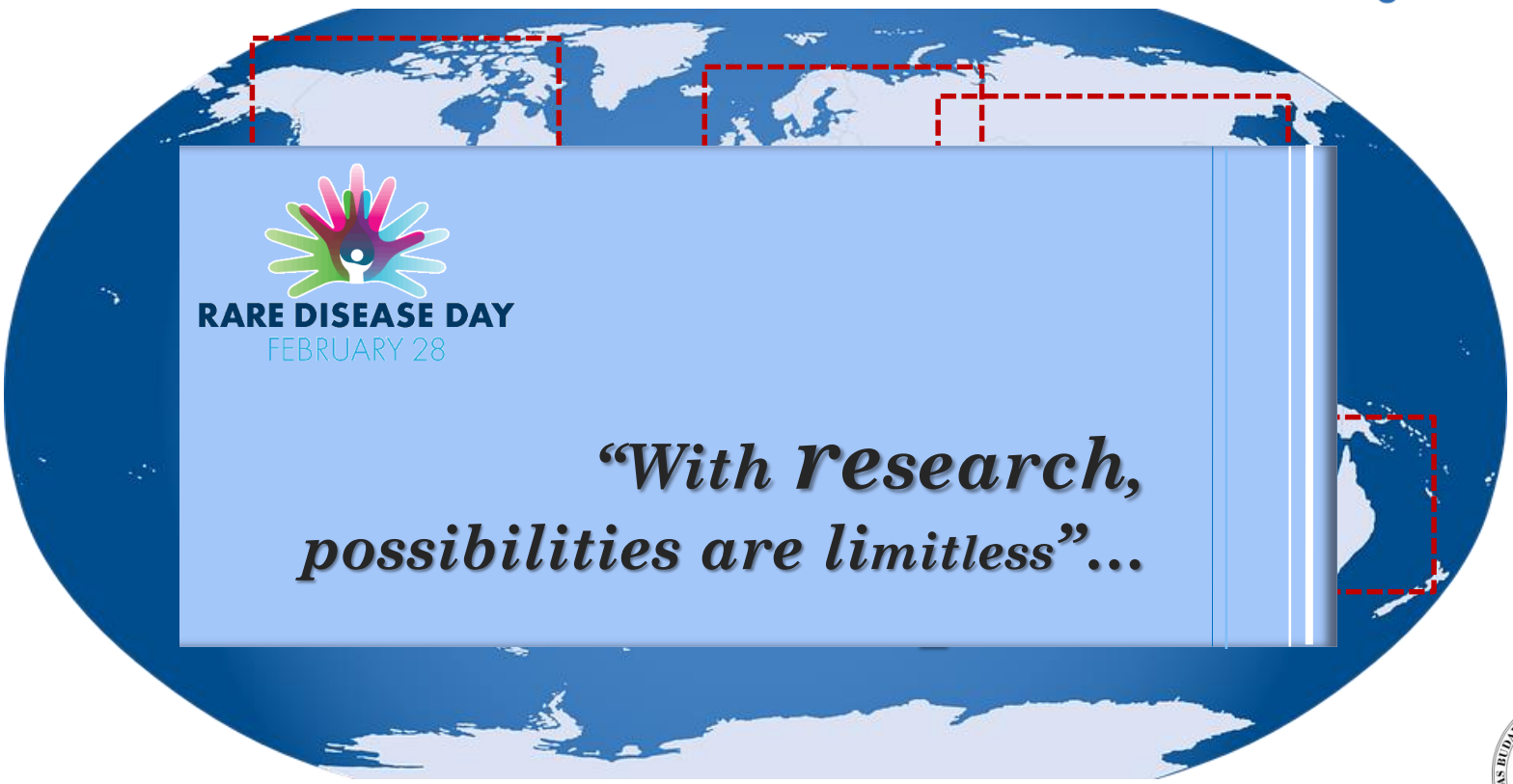
+ 70 diseases

most has no treatment!

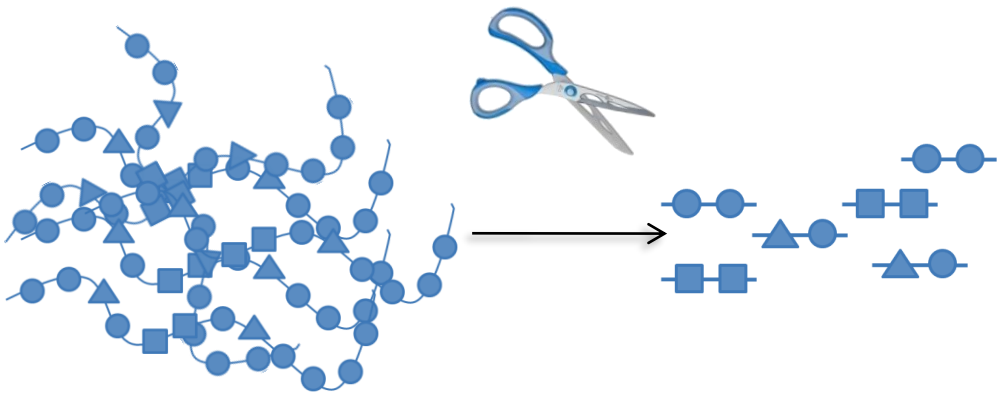
STILL SO MUCH TO DO…



STILL SO MUCH TO DO…



"WITH RESEARCH, POSSIBILITIES ARE LIMITLESS"…



enzyme replacement therapies

more effective

able to cross the BBB

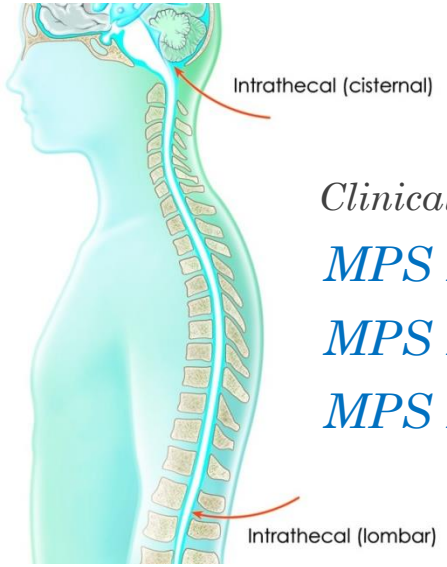
"WITH RESEARCH, POSSIBILITIES ARE LIMITLESS"…

- *Final goal:* ***brain***

  How?

✍ *intrathecal injection*

(into the spinal canal/subarachnoid space so that it reaches the cerebrospinal fluid (CSF))



Clinical trials:

MPS I

MPS II

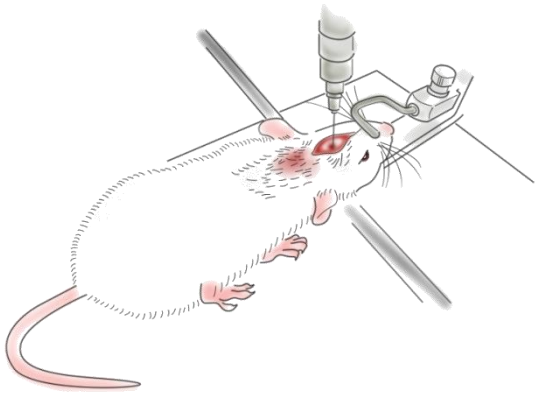
MPS IIIA

"WITH RESEARCH, POSSIBILITIES ARE LIMITLESS"…

- *Final goal:* ***brain***

  How?

✍ *intracerebroventricular injections*

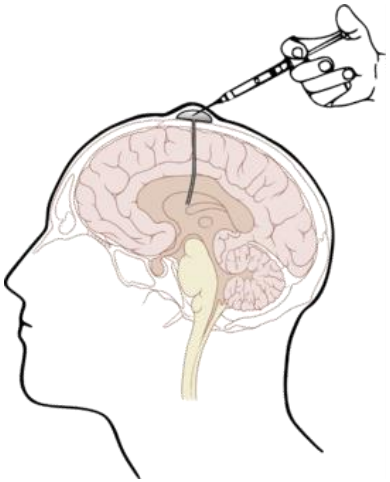


"WITH RESEARCH, POSSIBILITIES ARE LIMITLESS"…

- *Final goal:* ***brain***

  How?

✍ *intracerebroventricular injections*



Clinical trials:

MPS IIIB

9th November, 2018

"WITH RESEARCH, POSSIBILITIES ARE LIMITLESS"…

- *Final goal:* ***brain***

  How?

✍ *intracerebroventricular injections*

intrathecal

Associated risks!

👎 *infections*

👎 *cirurgical procedures*

"WITH RESEARCH, POSSIBILITIES ARE LIMITLESS"…

- *Final goal:* ***brain***

  How?

✍ *Better vectors*

Modified viruses (non-pathogenic)

retrovirusess (RNA)

adenoviruses (DNA)

lentiviruses

'adeno-associated' viruses(AAV)

"WITH RESEARCH, POSSIBILITIES ARE LIMITLESS"…

- *Final goal:* ***brain***

  How?

✍ *Molecular 'Trojan-horses'*

\+ *signal-peptides*

↳ *'receptor-mediated transport'*

☞ *insulin*

☞ *apolipoprotein*

☞ …

"WITH RESEARCH, POSSIBILITIES ARE LIMITLESS"…

- 'Broader' approaches

  i.e. 1 therapy ⇔ 1 disease

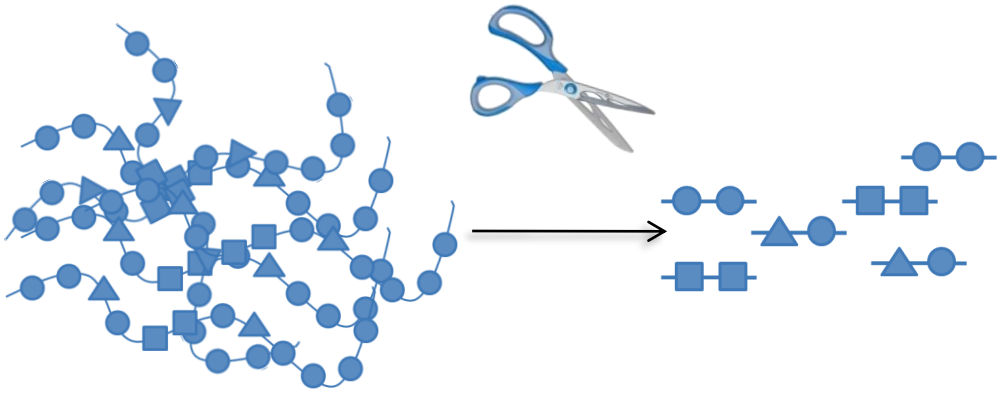
  (or even more!)

- 'Personalized' approaches

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

"*WITH RESEARCH, POSSIBILITIES ARE LIMITLESS*"…

- 'Broader' approaches



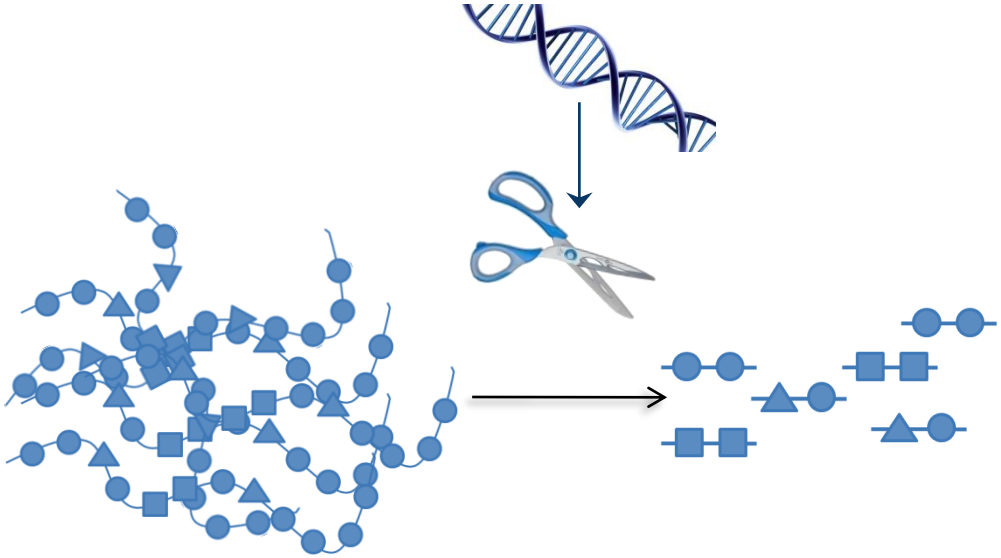
enzyme replacement therapies

more effective

able to cross the BBB

"*WITH RESEARCH, POSSIBILITIES ARE LIMITLESS*"…

- 'Broader' approaches



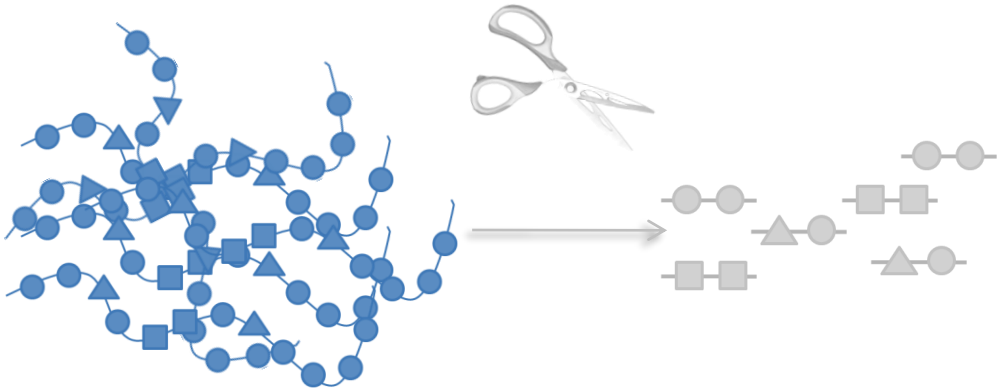
gene therapy

Clinical trials:

Metachromatic leukodystrophy

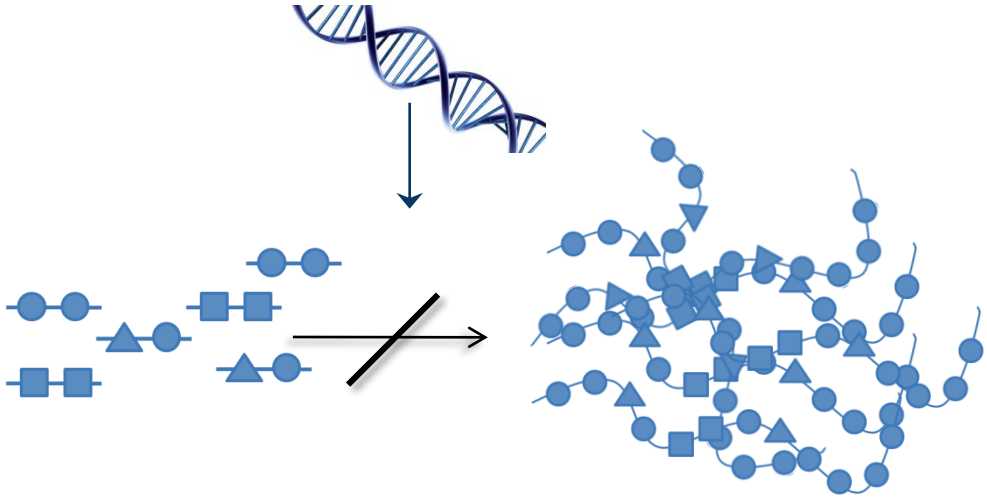
"*WITH RESEARCH, POSSIBILITIES ARE LIMITLESS*"…

- 'Broader' approaches



"*WITH RESEARCH, POSSIBILITIES ARE LIMITLESS*"…

- 'Broader' approaches



Genetic substrate reduction

"*WITH RESEARCH, POSSIBILITIES ARE LIMITLESS*"…

- 'Personalized' approaches

  Final goal:

  correction / amellioration of 1 | *mutation* / *type of mutations* | *in particular*

  How?

  ✍ *Molecular chaperones*

  ☞ *stabilize mutant proteins*

  ☞ *promote their transport into the lysosome*

As possibilidades (ilimitadas) da Investigação…

- ‘Personalized’ approaches

  Final goal:

  correction / amellioration of 1 | *mutation* / *type of mutations* | *in particular*

  How?

  - *Molecular chaperones*

    Galafold™

    (Migalastat; **Amicus Therapeutics**)

"*WITH RESEARCH, POSSIBILITIES ARE LIMITLESS*"…

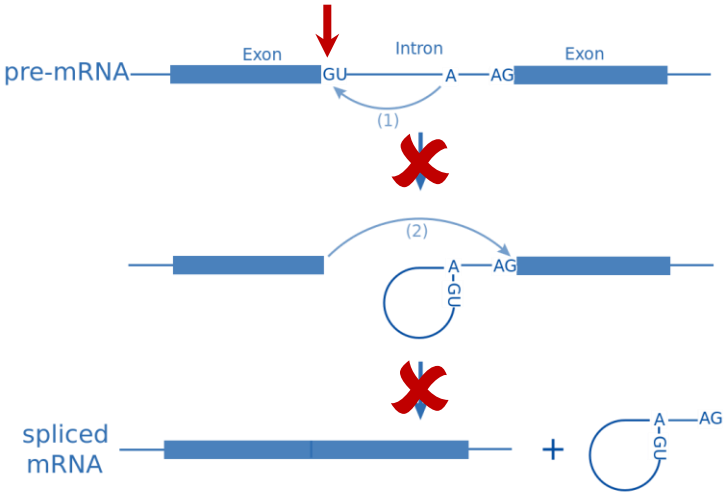
- 'Personalized' approaches

  Final goal:

  correction / amellioration of 1 | *mutation* / *type of mutations* | *in particular*

  How?

✍ *Correction of splicing mutations*



Our work at PT National Institute of Health…

- ‘Broader’ approaches
  - gSRT for MPS

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

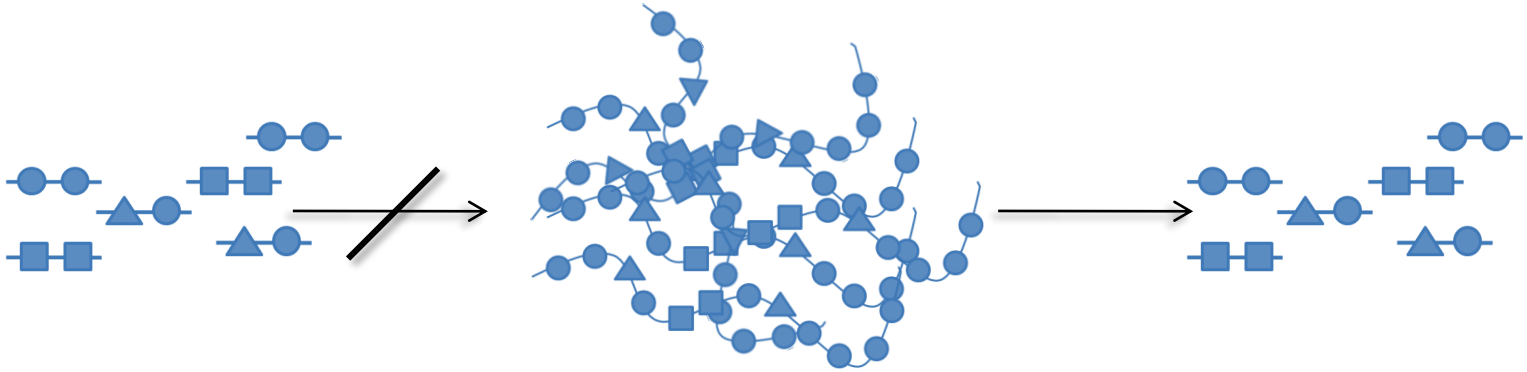
Common denominator:

Genetic-based therapies

RNA-based

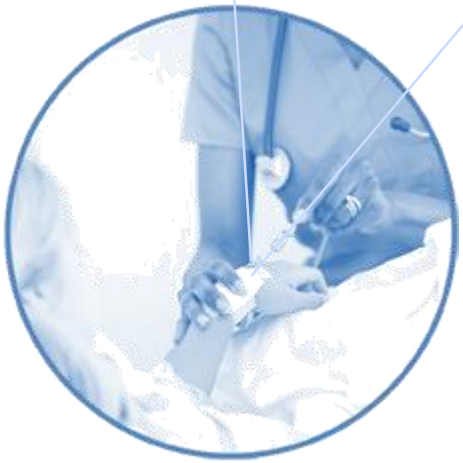
‘Easy’ to test at a cellular level – 1st stage

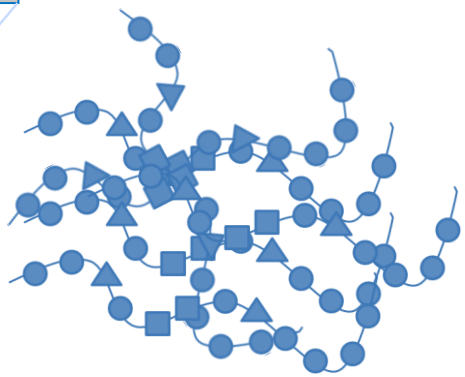
THE FUTURE(S)…

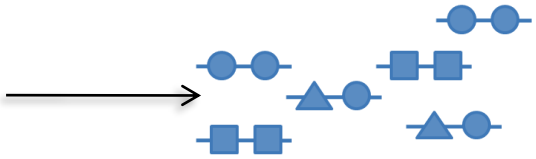


gSRT + enzyme replacement therapy

The Future(s)…

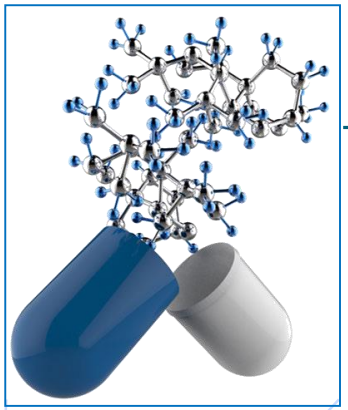


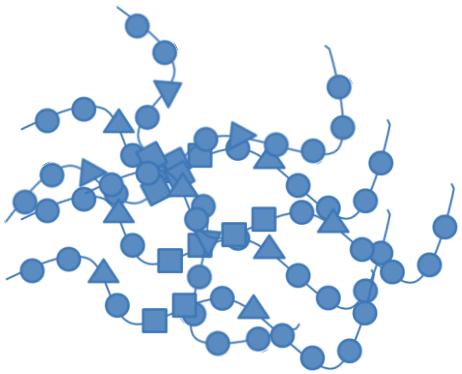


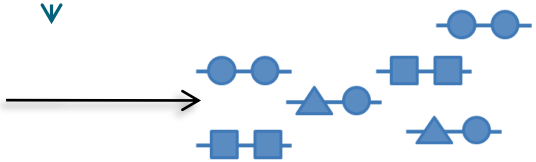


gene therapy

The Future(s)…







Personalized therapies

Acknowledgments

Dr. Sandra Alves

Prof. Mª João Prata

Juliana Inês Santos

Paulo Gaspar

Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, INOVAÇÃO E DO ENSINO SUPERIOR

SFRH/BPD/101965/2014
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!