PRON01, pharmacological chaperone as treatment to GM1 and Morquio B lysosomal diseases

Pronacera Therapeutics

Showing R&D results

Barcelona, 20 de octubre de 2015

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1. The Institution

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Spin-off (2014)

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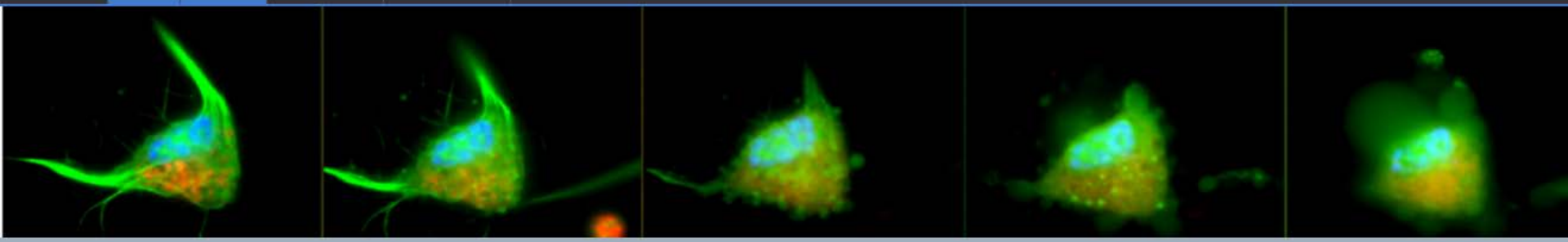
PRONACERA THERAPEUTICS S.L.

Empresa Biotecnológica en Sevilla

Búsqueda...

INICIO | SERVICIOS | PRODUCTOS



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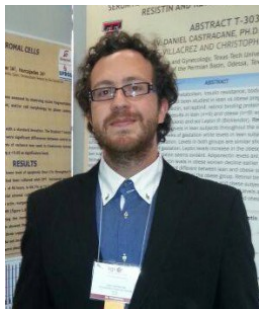
CEO

CSO

PM



CRM

ADVISORS

1. The Institution

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Pronacera Therapeutics is focused on
rare diseases

→ **Diagnostic:** CarrierMap Recombine kit

Very specific clinical determinations

Personalized medicine

→ **Treatment:** Extracorporeal photopheresis optimization

Therapeutic approximation to NBIA

Pharmacological chaperone in LDS

2. The Product

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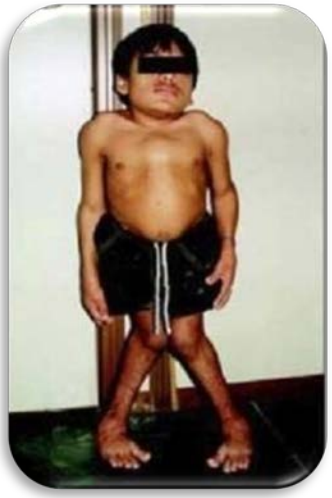
PRON01: Pharmacological chaperone as treatment to *GM1* and *Morquio B* lysosomal diseases.

a) Target Indications **GM1- gangliosidosis and Morquio B disease (MPS IV)**

Disorders caused by deficient activity lysosomal β-galactosidase (*β Gal, GLB1*)

The **GM1 gangliosidosis** is a widespread disease that occurs mainly neurosomatic in early childhood, and rarely in childhood or young adulthood.

Morquio B disease is mucopolysaccharidosis (MPS-IV), a rare bone disease without involvement of the central nervous system.



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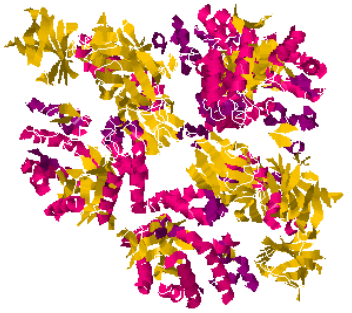
PRON01: Pharmacological chaperone as treatment to *GM1* and *Morquio B* lysosomal diseases.

a) Target Indications

GM1- gangliosidosis and Morquio B disease (MPS IV)

GLB1 gene encoding the protein β-Gal: 677 amino acids. 88 kDa precursor is transported to lysosomes where it passes its mature form of 64 kDa.



To date, over **160 mutations** has been described causing defects in protein folding during translation in the endoplasmic reticulum which reduces the transport of the enzyme to the lysosome (cell mediated degradation of quality control machinery).

There are 5 common mutations associated with different ethnic prevalence: **R208C** in *US* patients with infantile GM1; **R482H** in *Italian* patients with infantile GM1; **R201C** in *Japanese* patients with GM1 Youth; **I51T** in *Japanese* patients with GM1 Adult; **W273L** in *Caucasians* patients with MPS-IVB.

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PRON01: Pharmacological chaperone as treatment to *GM1* and *Morquio B* lysosomal diseases.

a) Target Indications

GM1- gangliosidosis and Morquio B disease (MPS IV)

Currently there are only symptomatic therapies available for these patients, differing therapeutic approaches:

- **Substrate reduction therapy (SRT)** based inhibiting production substrate using inhibitors of enzymes involved in their biosynthesis.
- **Enzyme replacement therapy (ERT)**, based on exogenous administration of recombinant active enzymes without effectiveness due to impossibility to cross blood brain barrier.
- **Gene therapy,** promising but requires a lot more research and is currently not available.

Currently, for these patients, there is not available treatment that stops the course of these disease.

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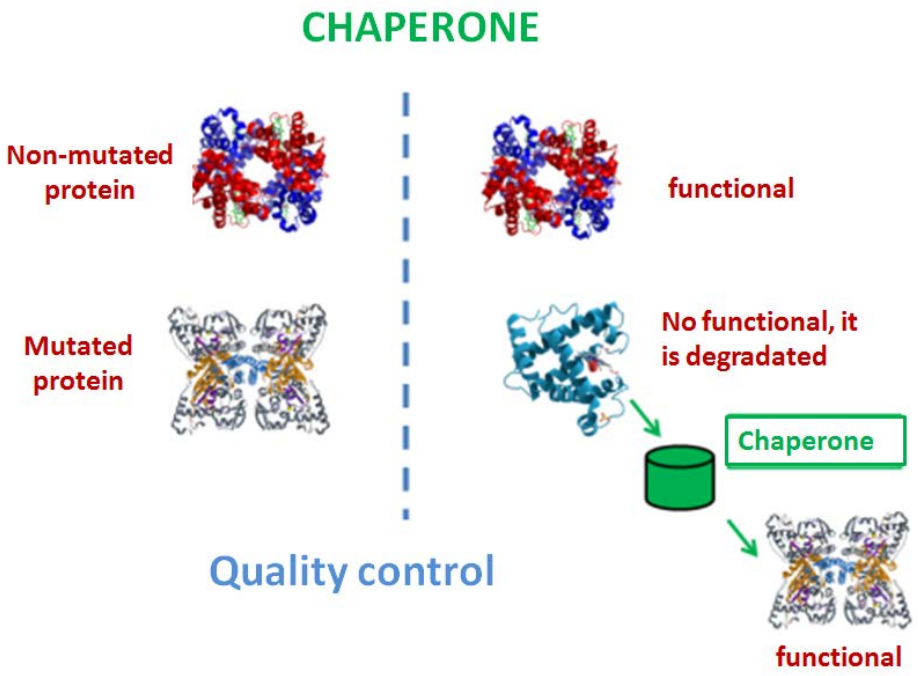
PRON01: Pharmacological chaperone as treatment to *GM1* and *Morquio B* lysosomal diseases.

b) Innovative mechanisms of action

Pharmacological chaperones (PC)
Innovative drugs consisting of small molecules able to reach the CNS and act via stabilization of unstable proteins.

*This type of treatment is **specific to some mutations** affecting protein folding within each disease.*



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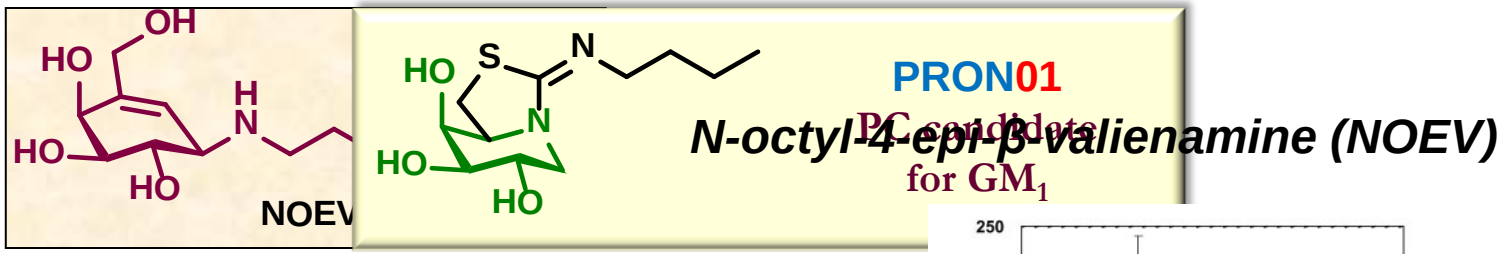
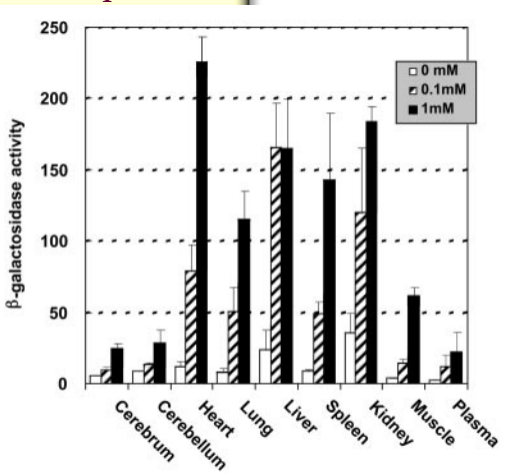
b) Innovative mechanisms of action



NOEV has presented *in vitro* and *in vivo* promising properties, but:

(I) the range of mutations for that is active is relatively small,

(II) its synthesis is extremely difficult to scale up.



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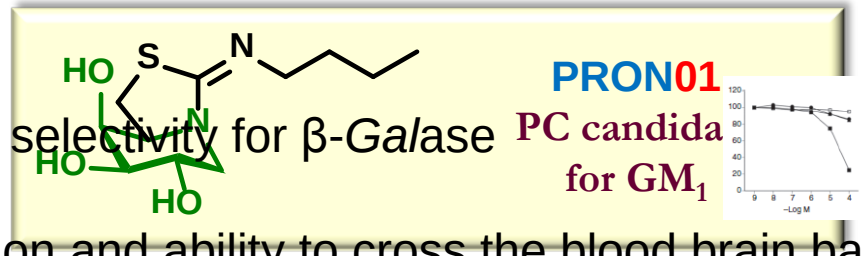
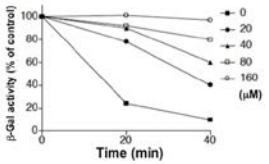
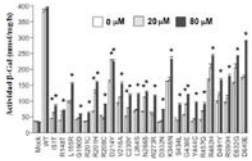
b) Innovative mechanisms of action



- ✓ High affinity and selectivity for β-*Gal*ase
- ✓ Oral administration and ability to cross the blood brain barrier
- ✓ Increased stability to degradation
- ✓ It shows no toxicity at concentrations studied (up to 640 µM).
- ✓ Wide mutational spectrum(24/88)

5*N,6S-(N'-butiliminometiliden)-6-tio-1-desoxigalactonojirimicina*
(**6S-NBI-DGJ**)





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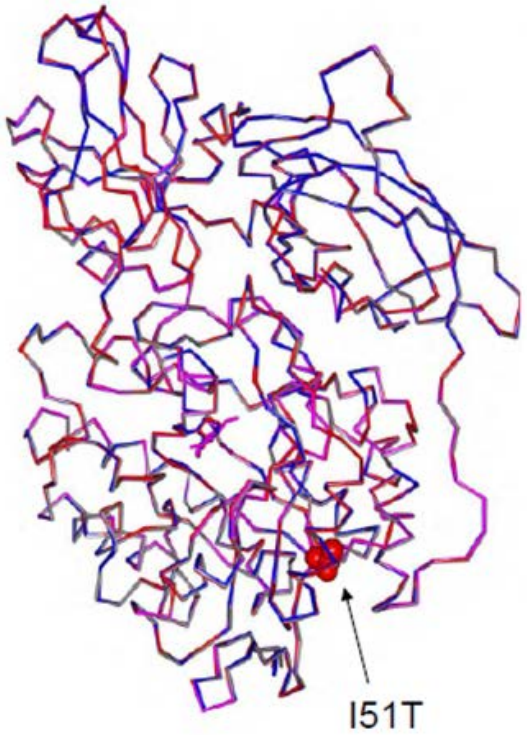
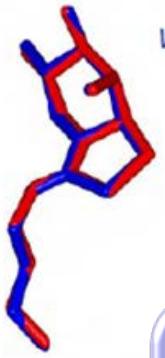
b) Innovative mechanisms of action





Wild type + **MTD118**

I51T + **MTD118**

Wild type + **galactosa**

I51T + **galactosa**

Crystallographic structures superposition of β-Gal complexed with PRON01 or D-galactose showed no significant differences either in the disposition of the iminosugars or in their interaction with the enzyme

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Showing R&D results

PRON01: Pharmacological chaperone as treatment to *GM1* and *Morquio B* lysosomal diseases.

c) Differential features facing the market

minoryx therapeutics

Passion for challenges

Status at Minoryx

Through its proprietary technological platform (SEE-Tx), Minoryx has identified a novel series of non-competitive pharmacological chaperones which are able to stabilize GLB1 and restore its enzymatic activity.

These compounds are binding on a novel site identified through SEE-Tx and contrary to pharmacological chaperones targeting the active site, they do not inhibit GLB1. Also, Minoryx has established collaborations with many of the academic groups leading research on this field.

Currently the project is at lead optimization and a development candidate is expected in the following months. Such compound would be a first-in-class drug for the treatment of GM1-glangliosidosis and/or Morquio B diseases.

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Pronacera Therapeutics

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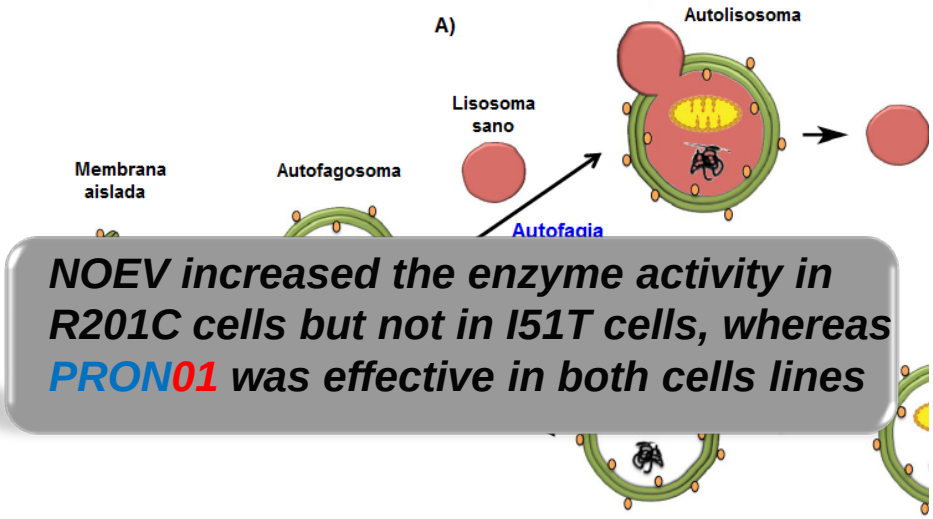
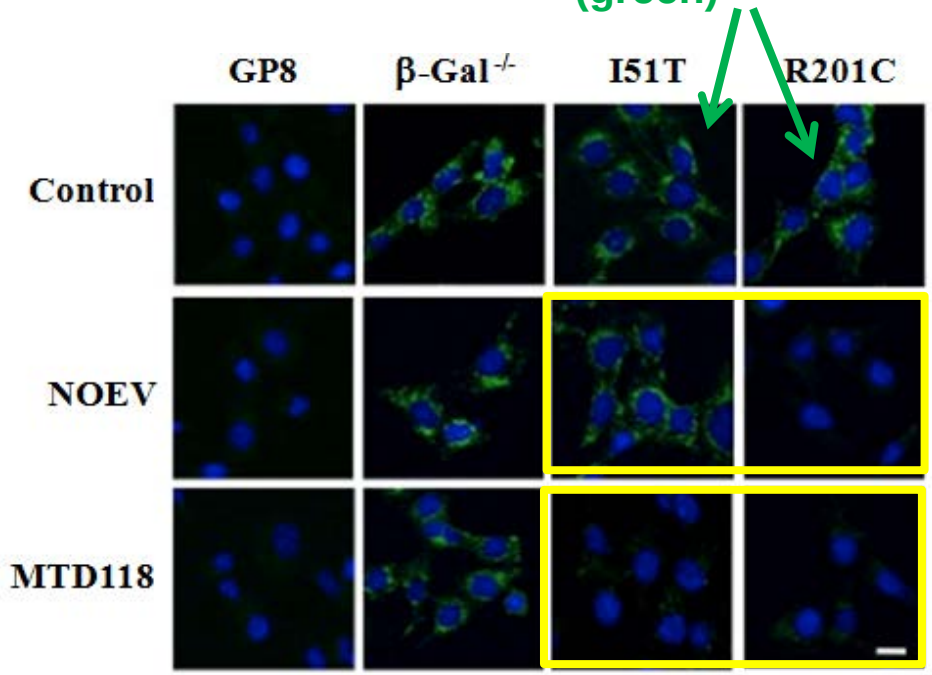
PRON01: Pharmacological chaperone as treatment to *GM1* and *Morquio B* lysosomal diseases.

d) Current status of development



NOEV increased the enzyme activity in R201C cells but not in I51T cells, whereas PRON01 was effective in both cells lines

Ganglioside accumulation (green)



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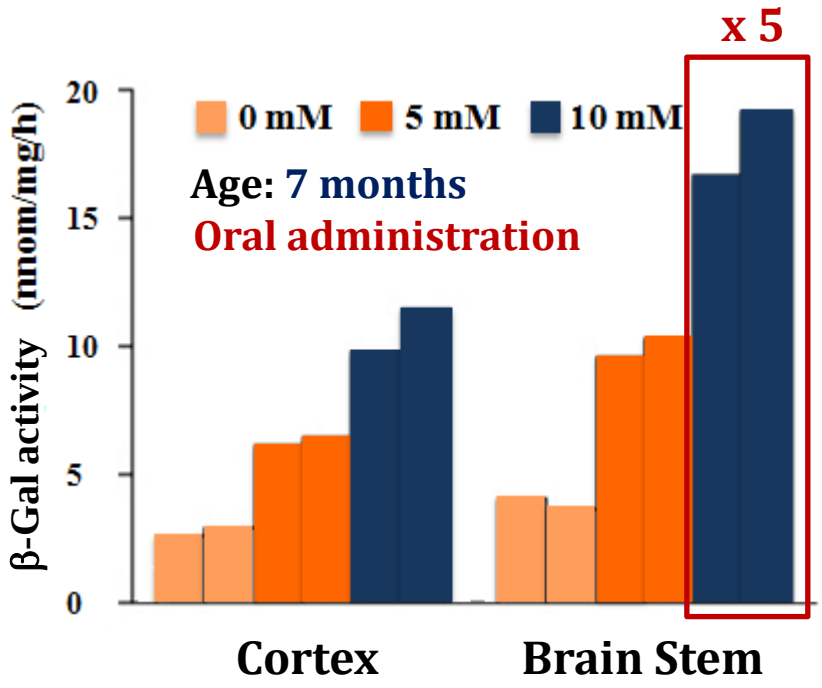

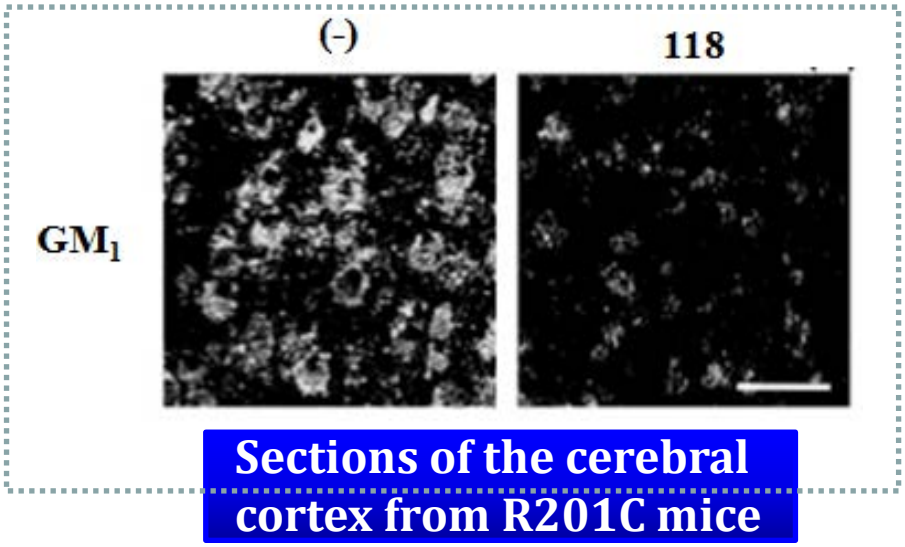

Reduction of lysosomal accumulation of GM_1 in the cortical sections of treated mice

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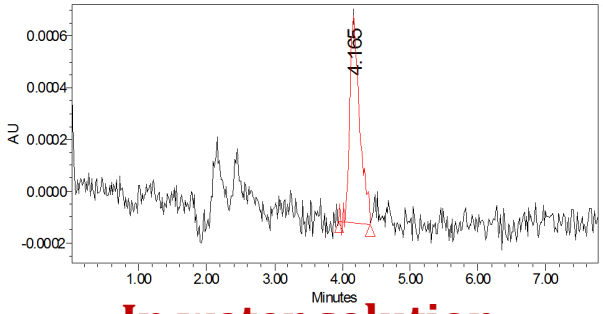
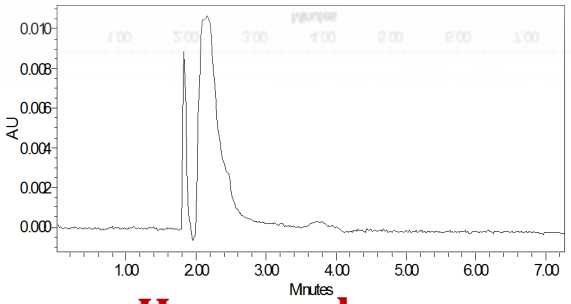
d) Current status of development

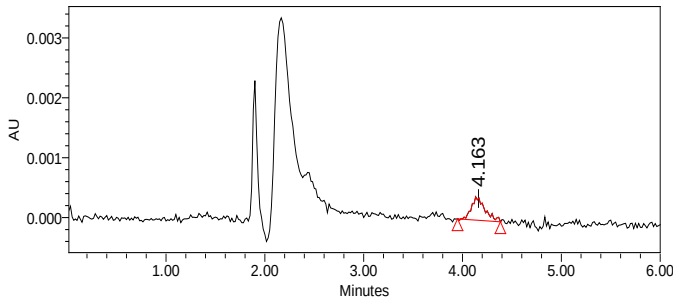


In water solution



Human plasma

PRON01 Determination in Biological Samples by HPLC



Human plasma

+

10 ppm PRON01

2. The Product

PRON01: Pharmacological chaperone as treatment to *GM1* and *Morquio B* lysosomal diseases.

e) IPR protection

Production and application of PRON01 is protected under number patent **P201232024**:

"UTILIZACIÓN DE DERIVADOS BICÍCLICOS DE 1-DESOXIGALACTONOJIRIMICINA EN LA PREPARACIÓN DE UN MEDICAMENTO PARA EL TRATAMIENTO DE ENFERMEDADES RELACIONADAS CON BETA-ENZIMAS GALACTOSIDASAS LISOSÓMICAS MUTANTES HUMANAS".

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f) Pitfalls & Risks to be considered

3. Partnering Opportunities

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PRON01: Pharmacological chaperone as treatment to *GM1* and *Morquio B* lysosomal diseases.

Currently, the company is seeking partners to finalize the pre-clinical phase and continue the development of the lysosomal pharmacological chaperone under a cooperative model of co-development or returnable investment.

Danke

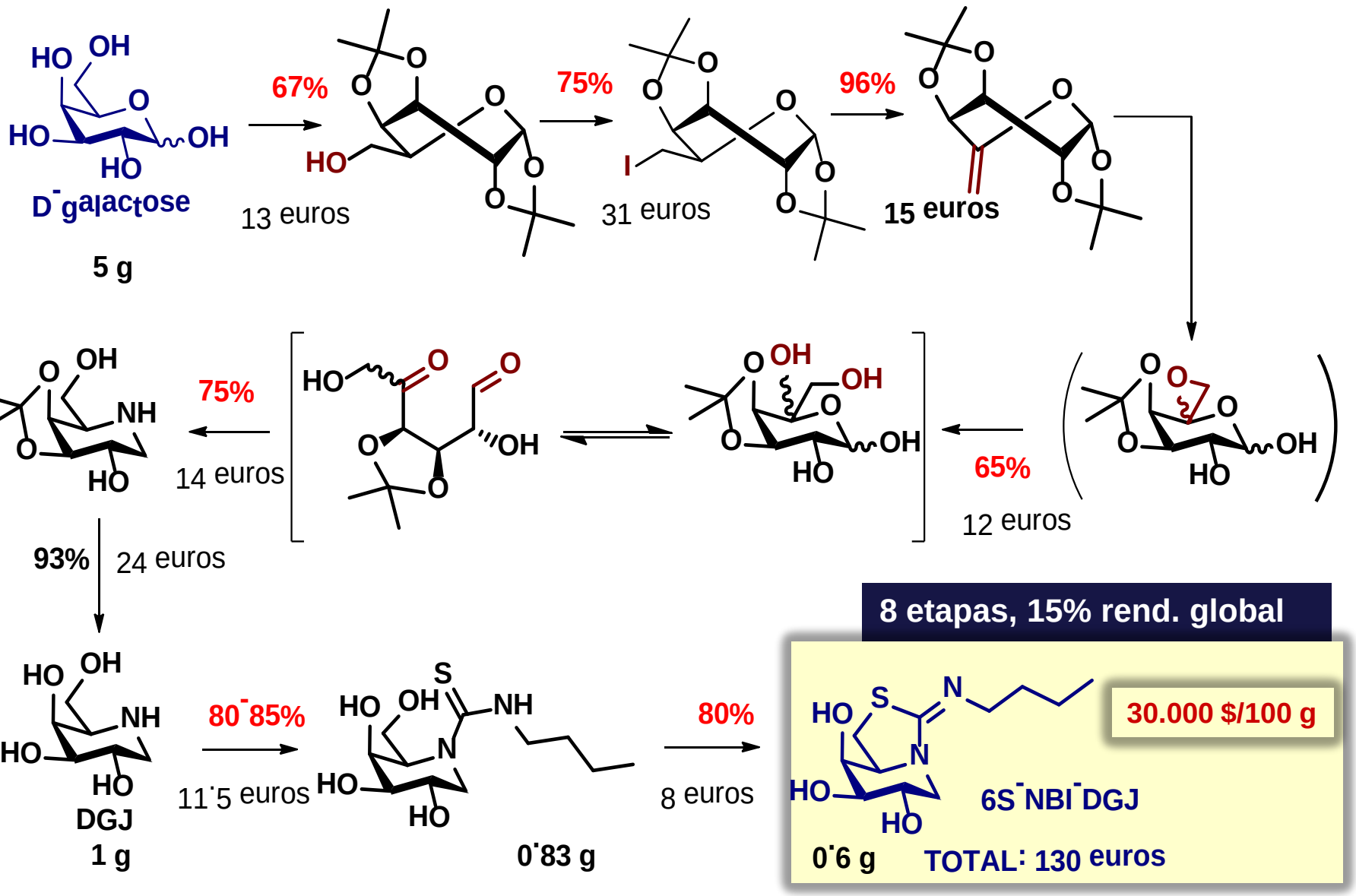
Thank you

Gracies

d.cotan@pronacera.com

ESCALADO DE PREPARACIÓN (100 g)

PRON01



ADDITIONAL MATERIAL

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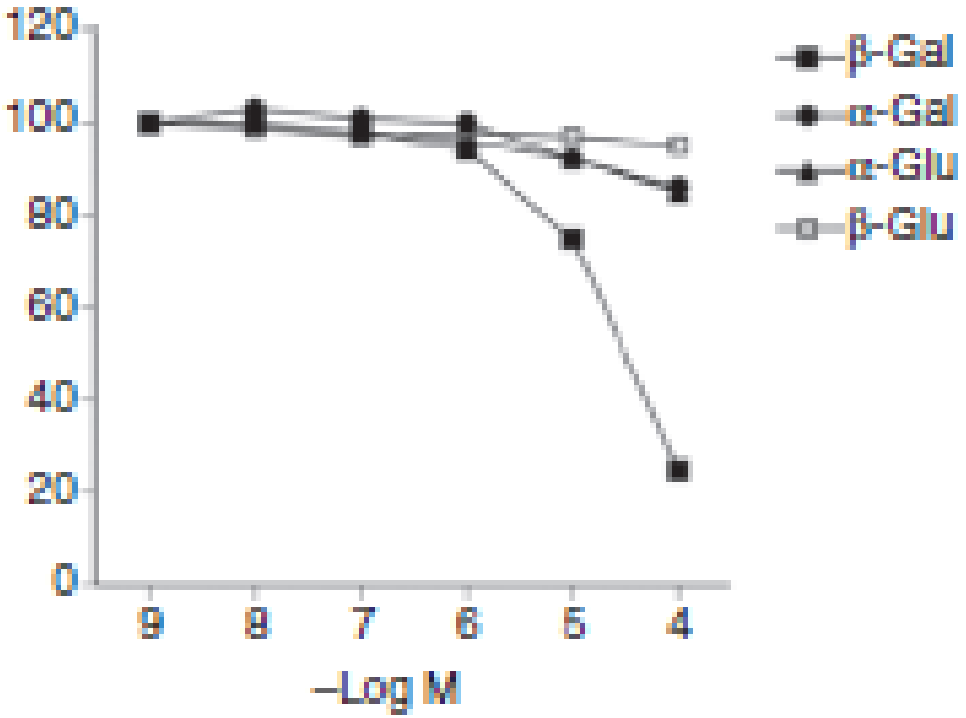
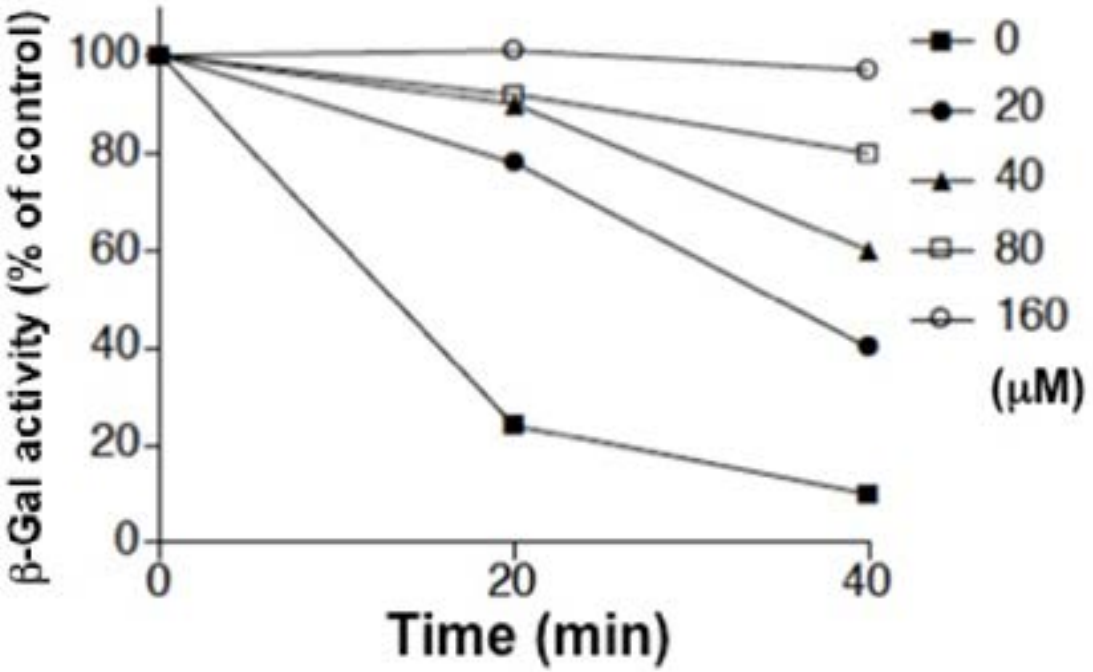
Inhibitory activities of PRON01 on lysosomal enzymes in lysates from normal human fibroblasts



Selectivity and **specific** for human β-*Gal*ase

Protection of human β-Gal from heat-induced degradation



PRON01 prevents heat-induced degradation of human β-Gal *in vitro*

Screening of chaperone effects on recombinant human β-Gal mutants

Up to 24 over 88 mutant types of human β-Gal mutants expressed in COS7 cells responded to PRON01