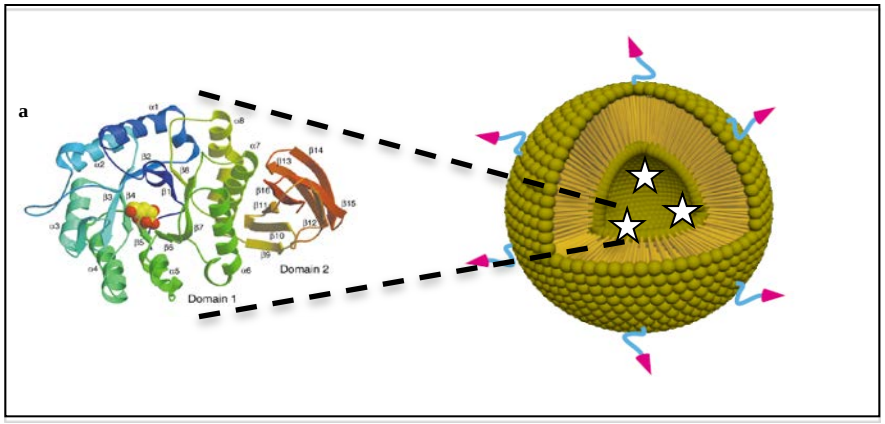
IX Conferencia anual de las Plataformas Tecnológicas de Investigación Biomédica

Barcelona, 15 y 16 de Marzo de 2016

"Nanoformulación de enzimas para el tratamiento de enfermedades lisosomales"



Nora Ventosa

ICMAB

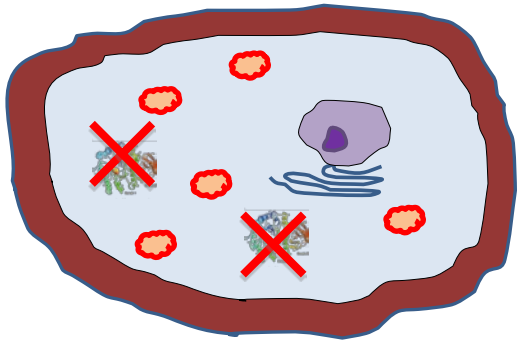
CSIC

NANOMOL

ciber-bbn
Centro Investigación Biomédica en Red
Bioingeniería, Biomateriales y Nanomedicina

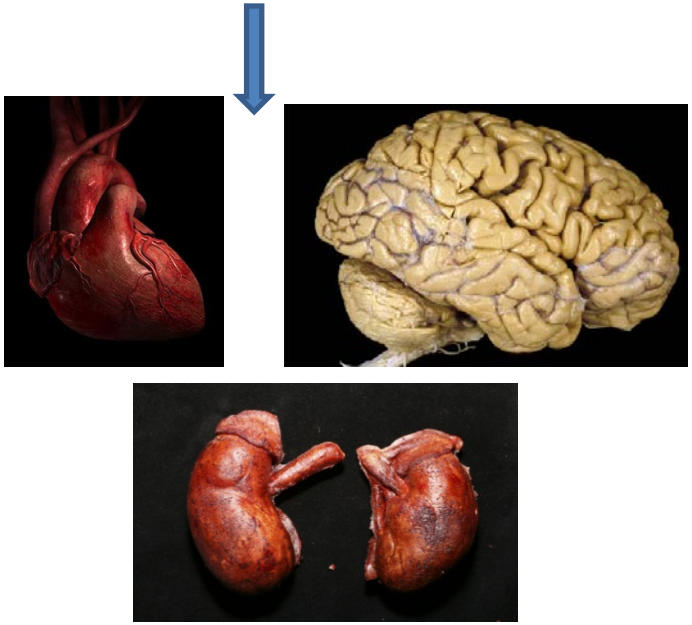
FABRY DISEASE: lack of α-galactosidase (GLA) enzyme

Lysosomal hereditary disorder



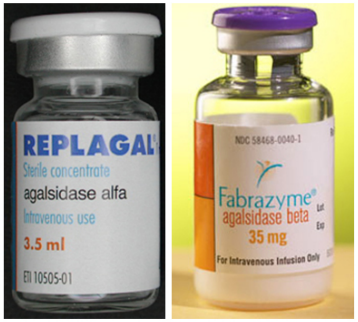
- **Estimated incidence: 1 per 117 000 live birth**
- **Without treatment patients die before 45 years**

The lack of α-galactosidase (GLA) enzyme produces Globotriaosylceramide (Gb3) accumulation



Multi-systemic clinical symptoms

Treatment: Enzyme replacement therapy (ERT)



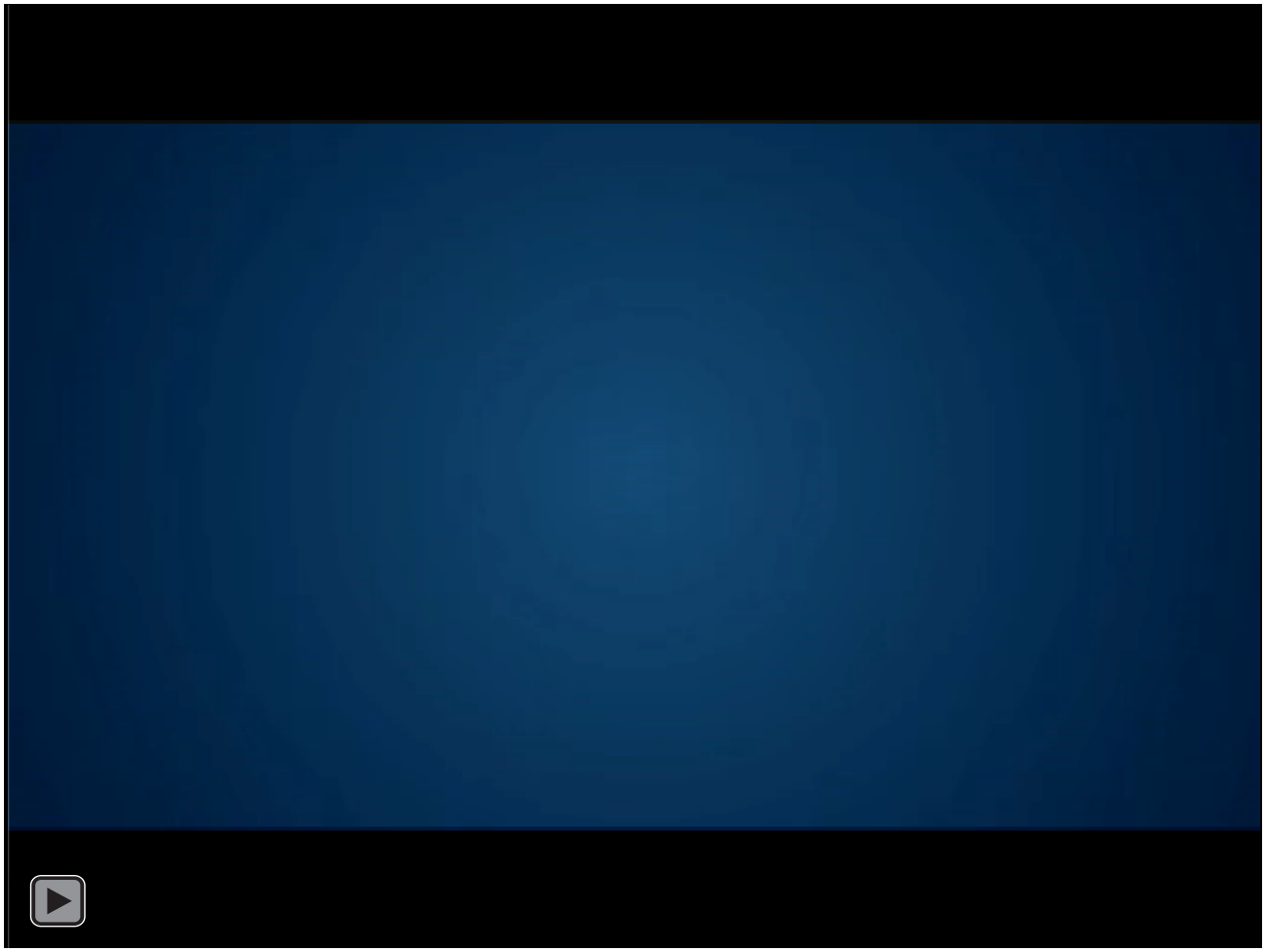
GLA-based medicines

Drawbacks of enzyme replacement therapy (ERT)

- Limited efficacy in an advance stage of the disease
- Enzyme degradation
- Enzyme small circulating half-life
- Deficient biological membranes penetration of enzyme
- High immunogenicity
- Expensive (> 280.000 €/year)

Nanotechnology : promising opportunity to overcome drawbacks for biological actives delivery

Micro- and Nanoparticulate Drug Delivery Systems



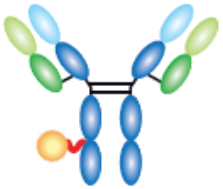
Hubbell, *J.A. Science* ***2003,*** 300, 595

FABRY PROJECT (2009/IP: Simó Schwartz (HVH)): Development of different nanoestructures to encapsulate GLA enzyme

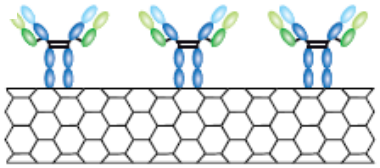
Collaboration

ciber-bbn
Centro Investigación Biomédica en Red
Bioingenieria, Biomateriales y Nanomedicina

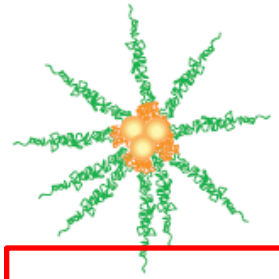
Immuno-toxin/drug fusion protein



Carbon nanotube



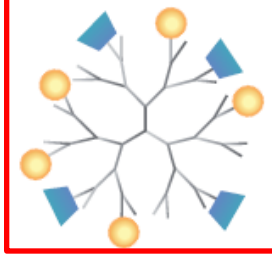
Micelles

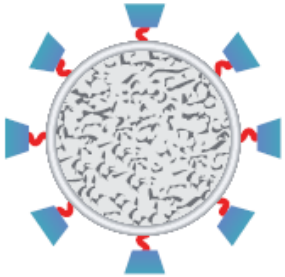


Polymer-conjugate drug/protein

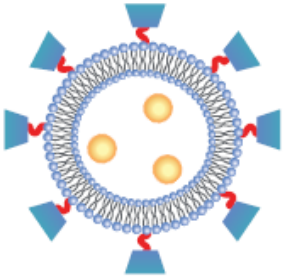
Nanocarriers

Dendrimers

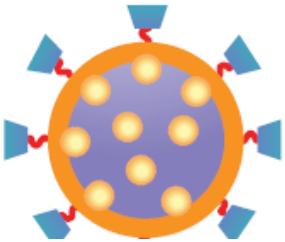




Nanoshells



Vesicles



Polymeric carriers

Nanovesicles for the protection and intravenous delivery of GLA enzyme

NANOMOL

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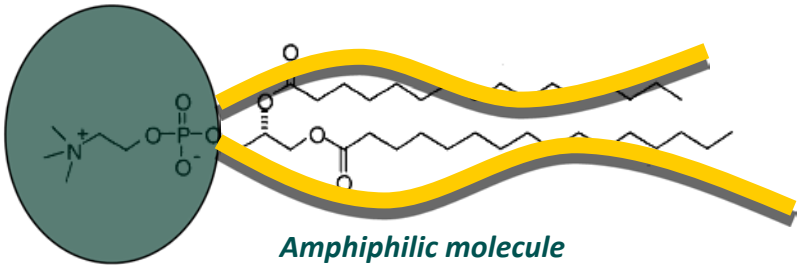
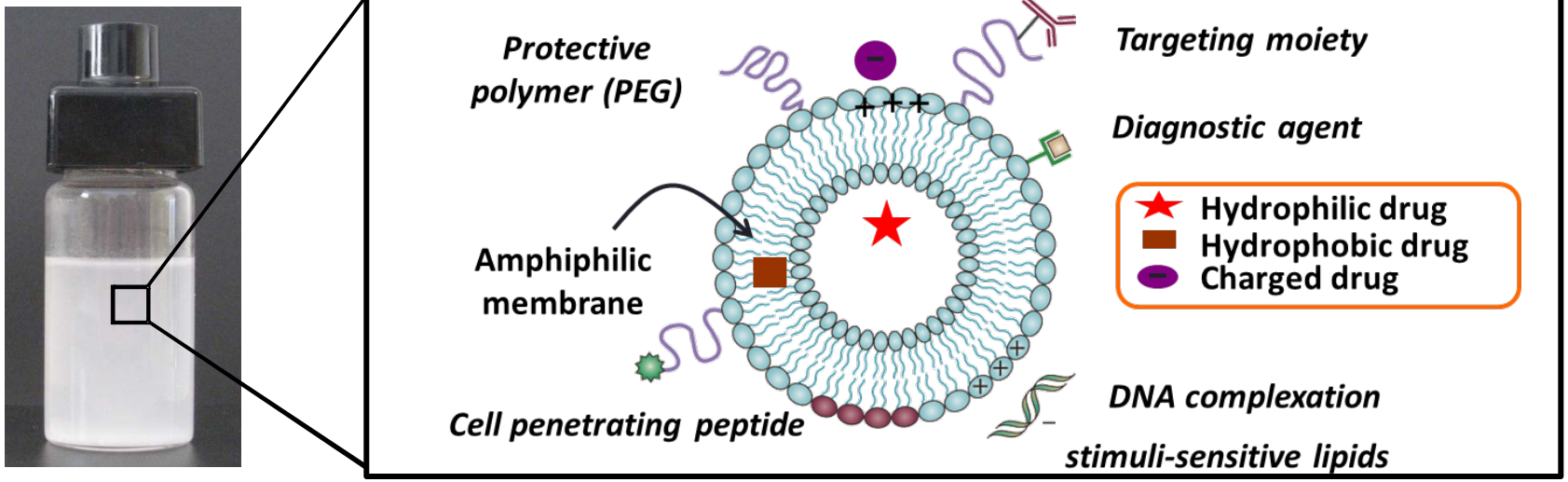




Self-assembling of amphiphilic molecules through non-covalent weak interactions

V.P. Torchilin et al., *Nature Reviews Drug Discovery,* 2005, *4*, 145-159

New peptide targeted nanoliposomes for intracellular drug delivery

Collaboration

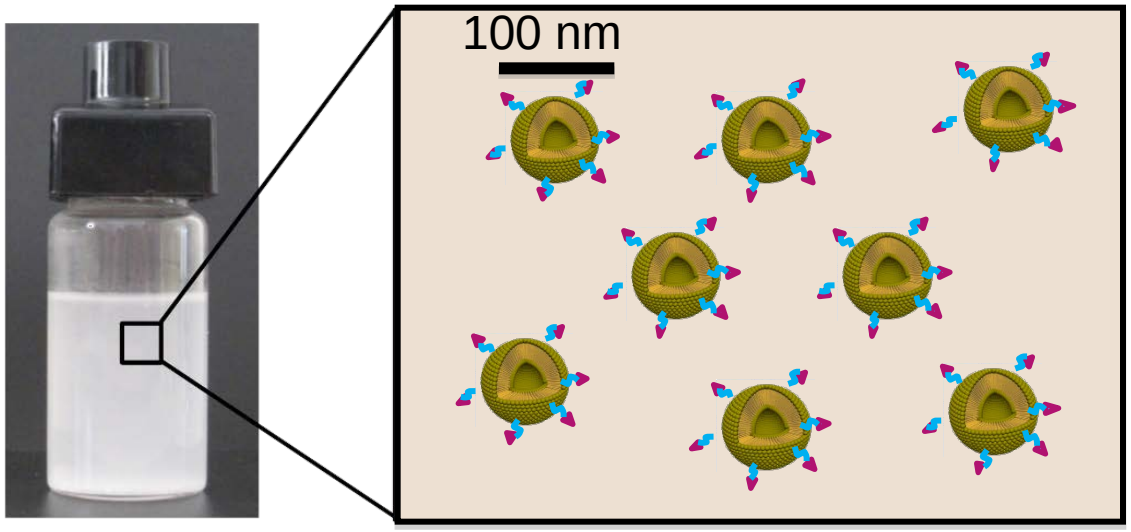
NANOMOL

CSIC

Dr. Miriam Royo

UQC

U B Parc Científic de Barcelona

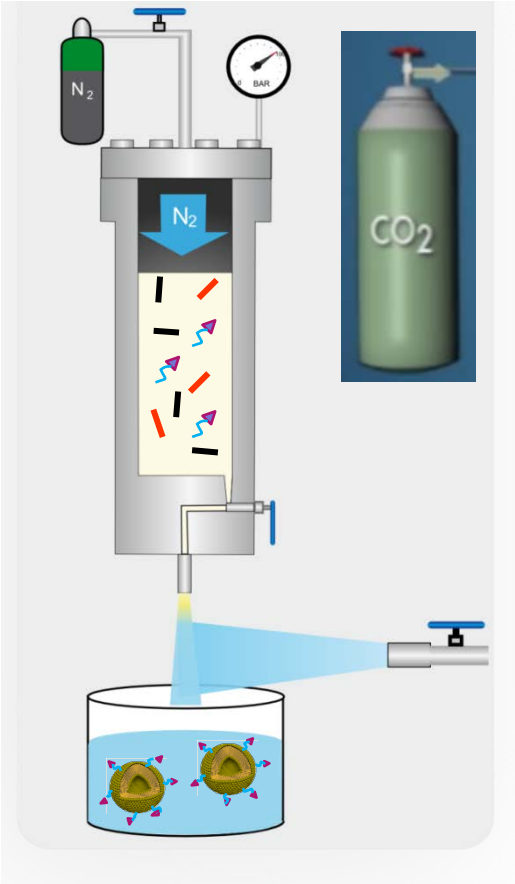


Patent Application WO2014/001509

Physico-chemical characteristics and quality of peptide targeted nanoliposomes given by an innovative preparation route

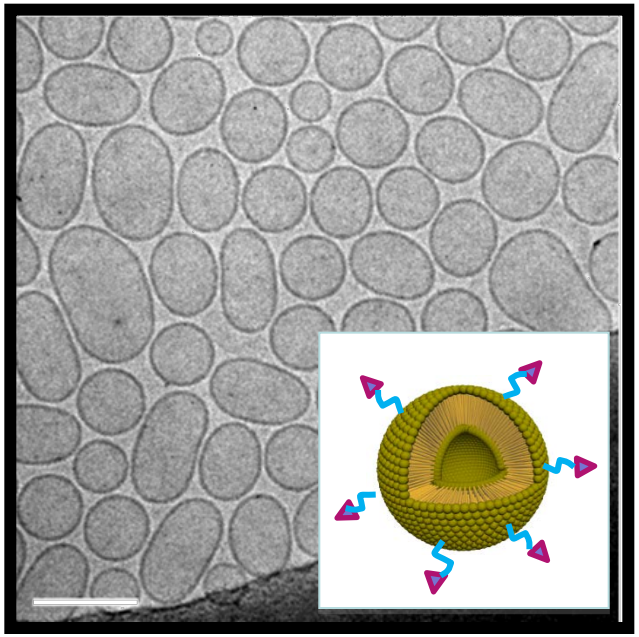
One-step procedure

DELOS-SUSP platform



Start-up creation

Nanoliposomes with high homogeneity in size and morphology

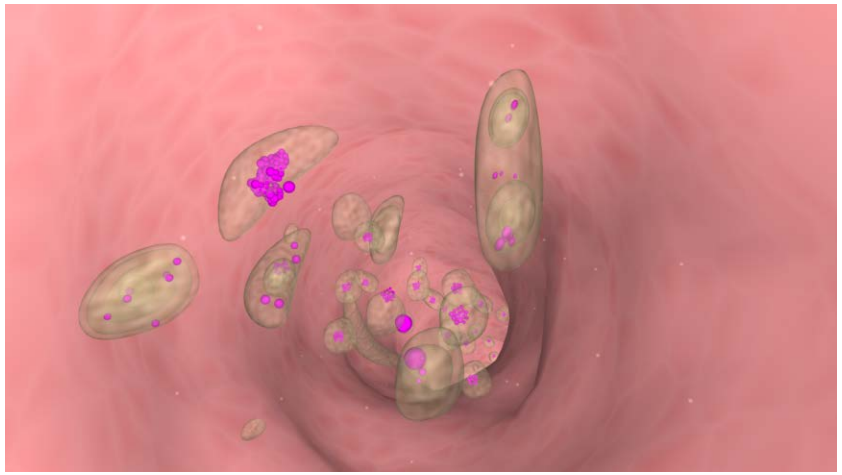


nanomol Technologies

Granted patents: WO2006079889; EP 1843836 ; US2007259971 ; CA 2566960

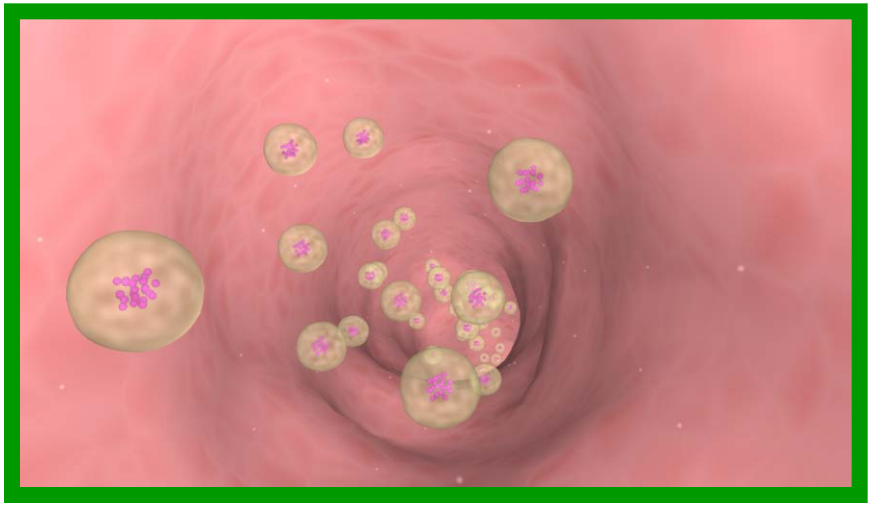
Pharmaceutical quality in nanoformulations is determined by structural attributes at the nanoscale

Heterogeneous nanoliposomes



Poor pharmaceutical quality

Homogeneous nanoliposomes

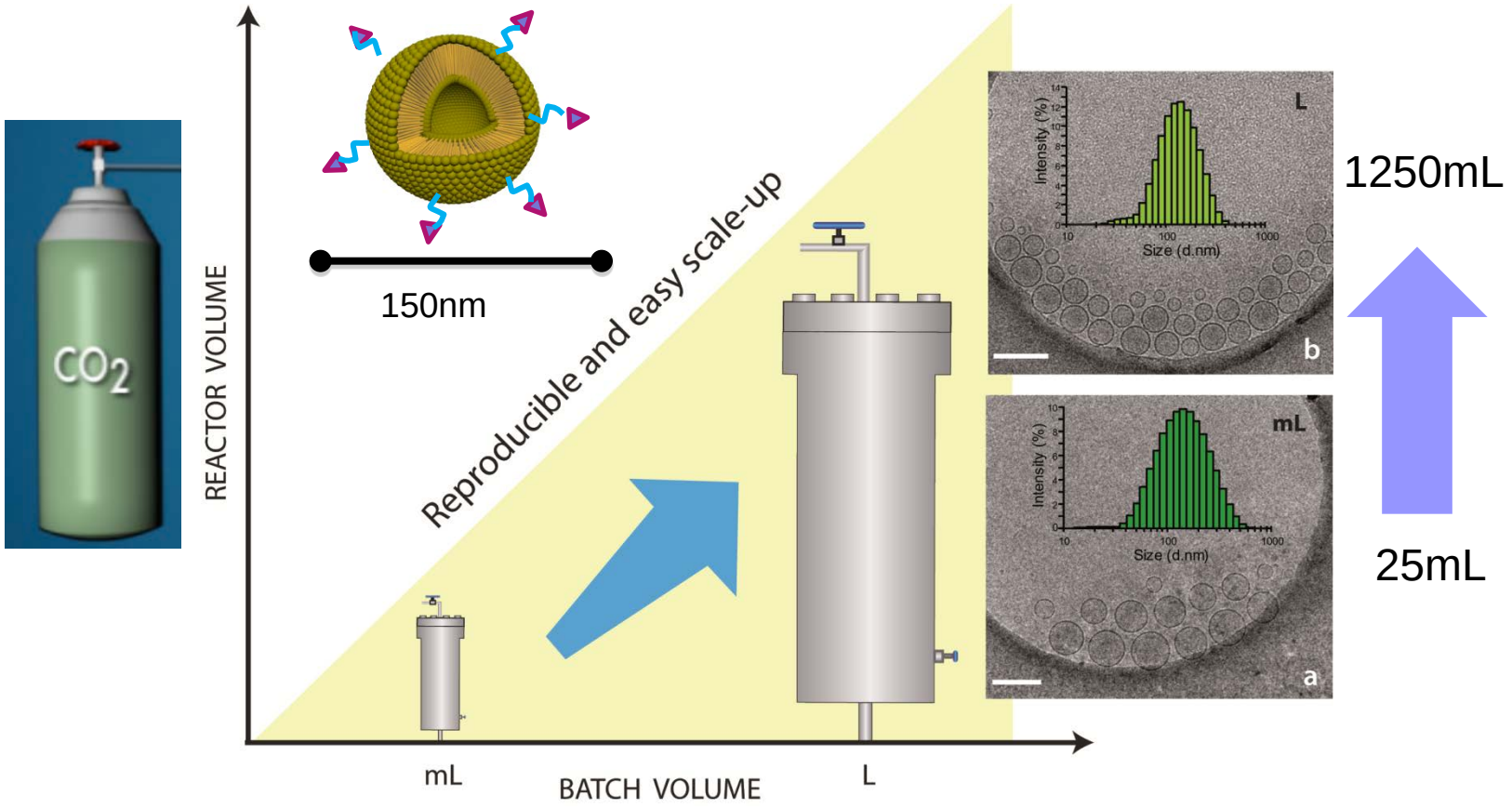


High pharmaceutical quality

European Medicine Agency, Reflection Paper, CHMP, 806058, February 2013

Keys: characterization and preparation at the nanoscale

Well-defined and scalable manufacturing process



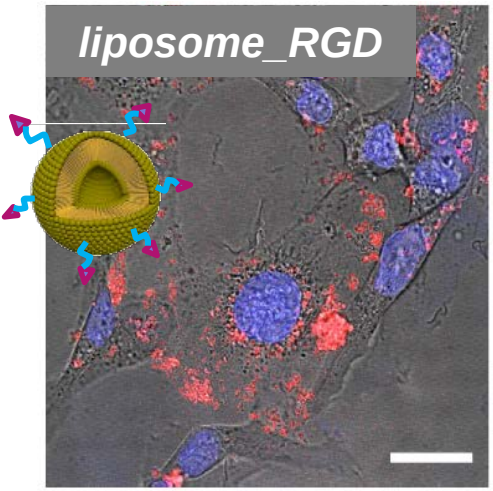
GMP compatibility positively evaluated

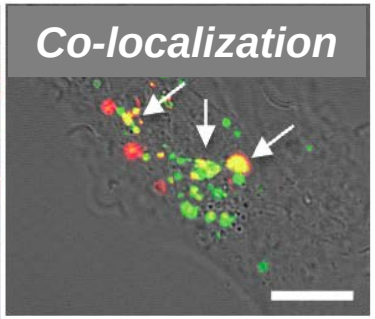
I. Cabrera et al, *Nano Letters*, 2013, *13*, 3766

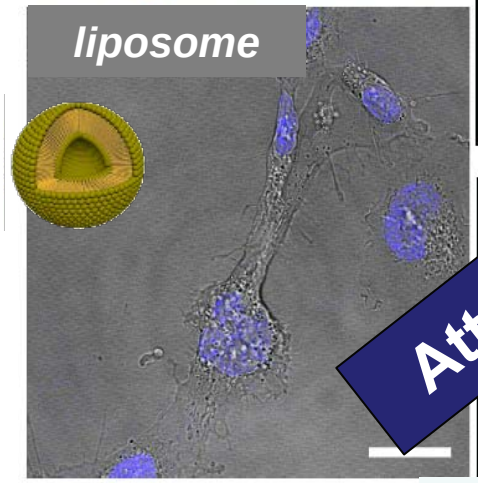
Praxis Pharmaceutical

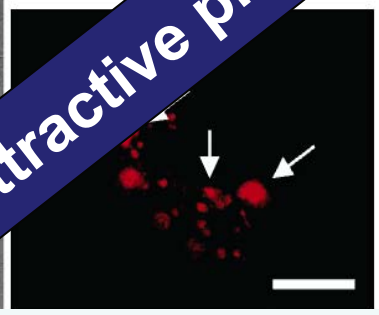
nanomol Technologies

Cell uptake of new peptide targeted nanoliposomes 30-fold higher than plain nanoliposmomes



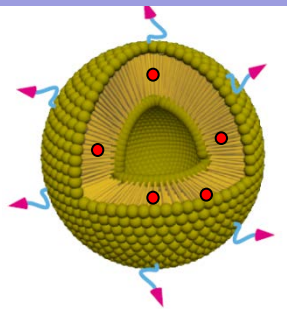


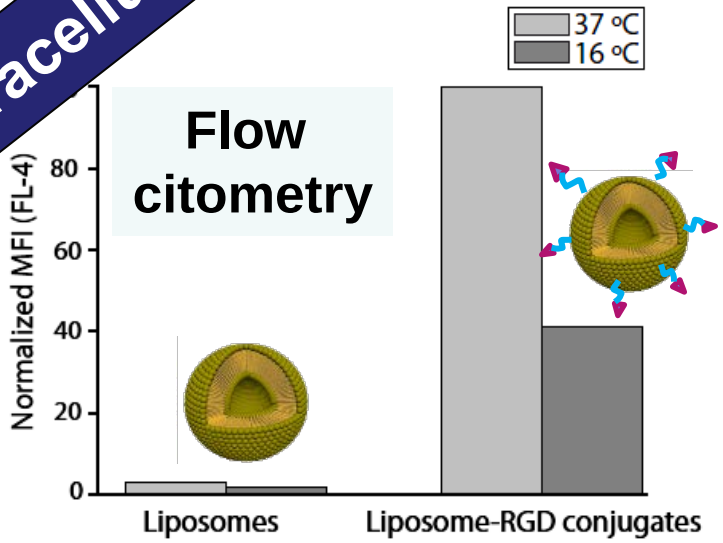




Attractive platform for intracellular delivery

DiD labelled liposom
Nucleus
Lysosom





Flow citometry

Scale bars are 10 µm.

Confocal microscopy

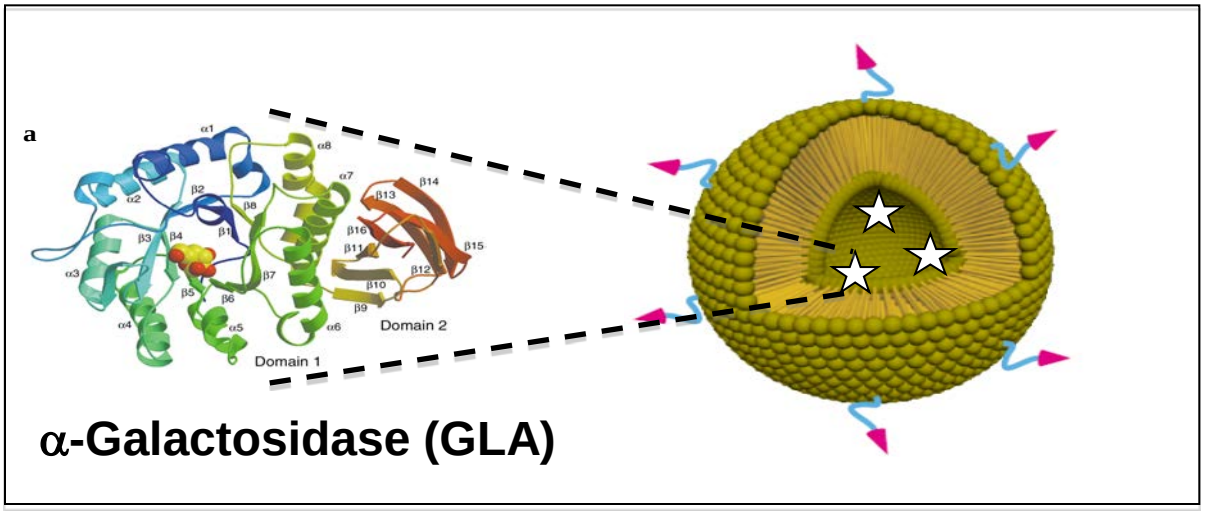
In collaboration with group of Prof. Maria F. García-Parajo (ICFO)

NANOFABRY PROJECT: GLA loaded peptide targeted-nanoliposomes for the treatment of Fabry's disease

NANOFABRY

La Marató 3

IP: S. Schwartz (HVH) (2011-2014)



Vall d'Hebron Hospital

CSIC

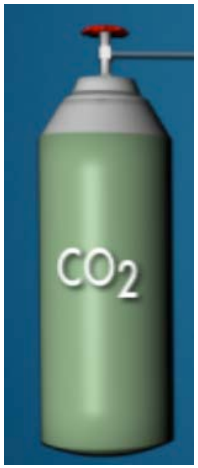
ibb
Institut de Biotecnologia i de Biomedicina

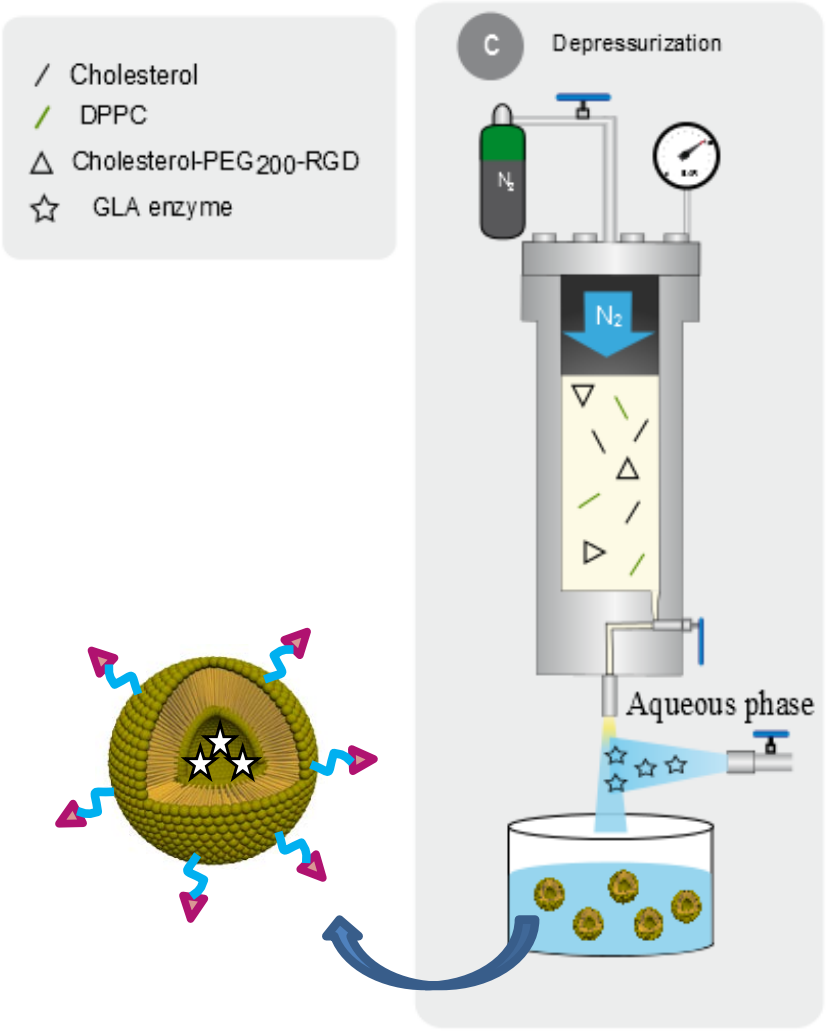
Parc Científic de Barcelona

ICFO
The Institute of Photonic Sciences

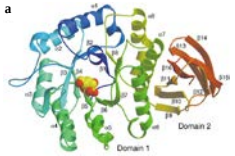
ciber-bbn
Centro Investigación Biomédica en Red
Bioingeniería, Biomateriales y Nanomedicina

One-step and easy scalable production platform for the GLA nanoformulation in peptide targeted nanoliposomes





☆ **α-Gal**



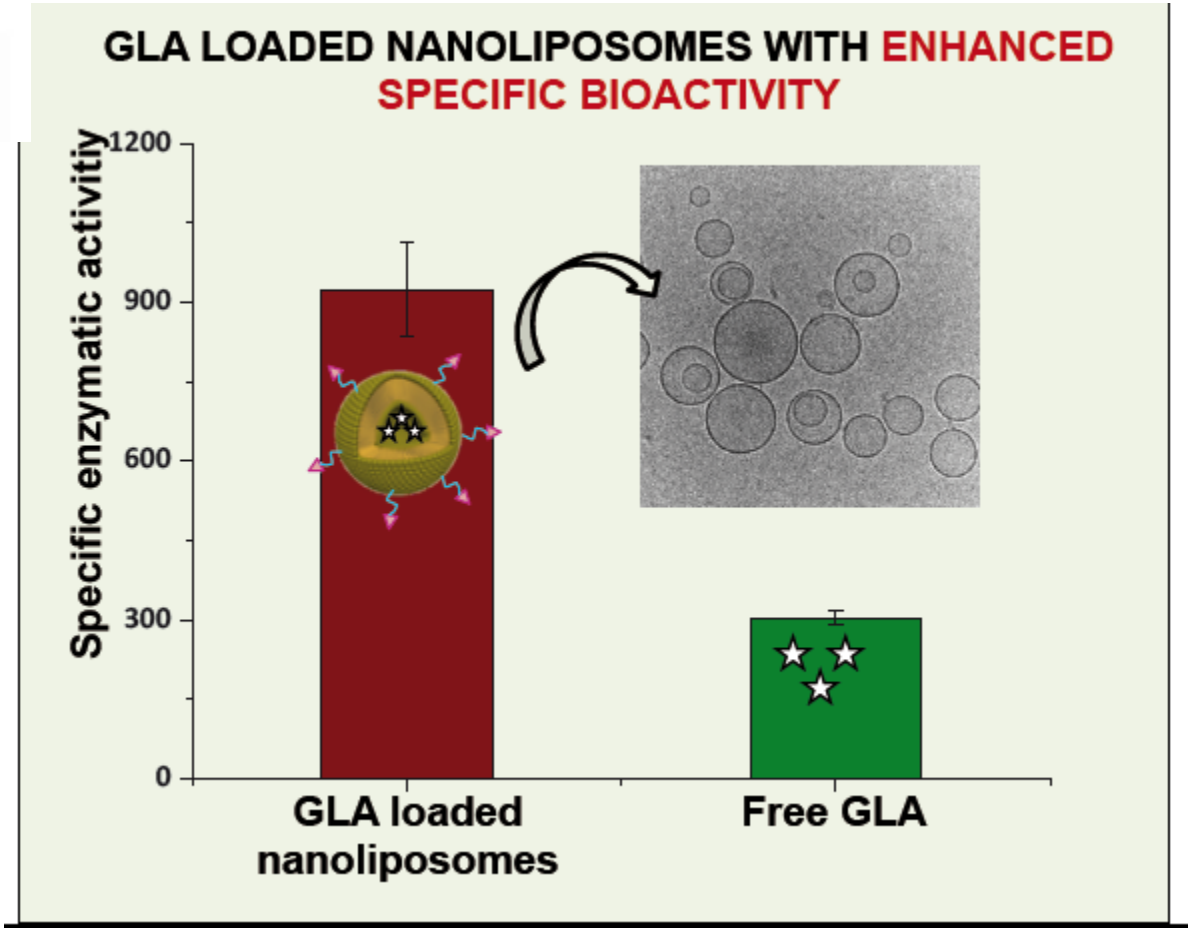
Patent Application WO2014/001509

Enhanced enzymatic activity of GLA loaded in peptide targeted nanoliposomes in relation to free enzyme

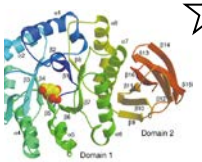
Collaboration

Dr. I. Abasolo

Vall d'Hebron Hospital



α-Gal

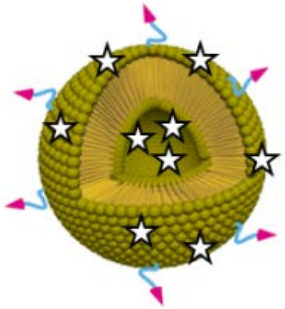


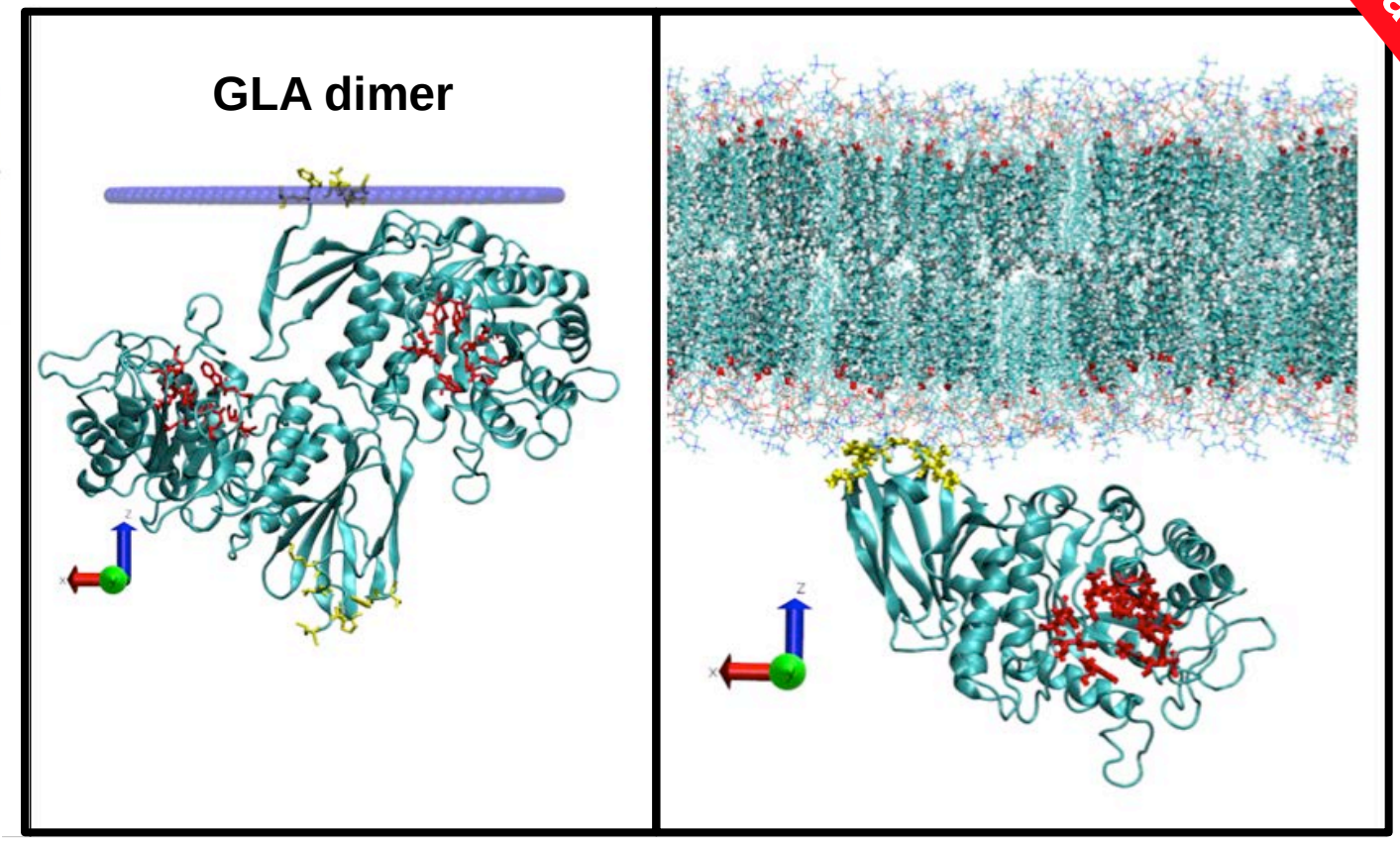
Patent Application WO2014/001509

I. Cabrera et al, *Advanced Healthcare Materials*, 2016

Active site of GLA enzyme exposed towards the aqueous phase (opposite to the bilayer)

Collaboration



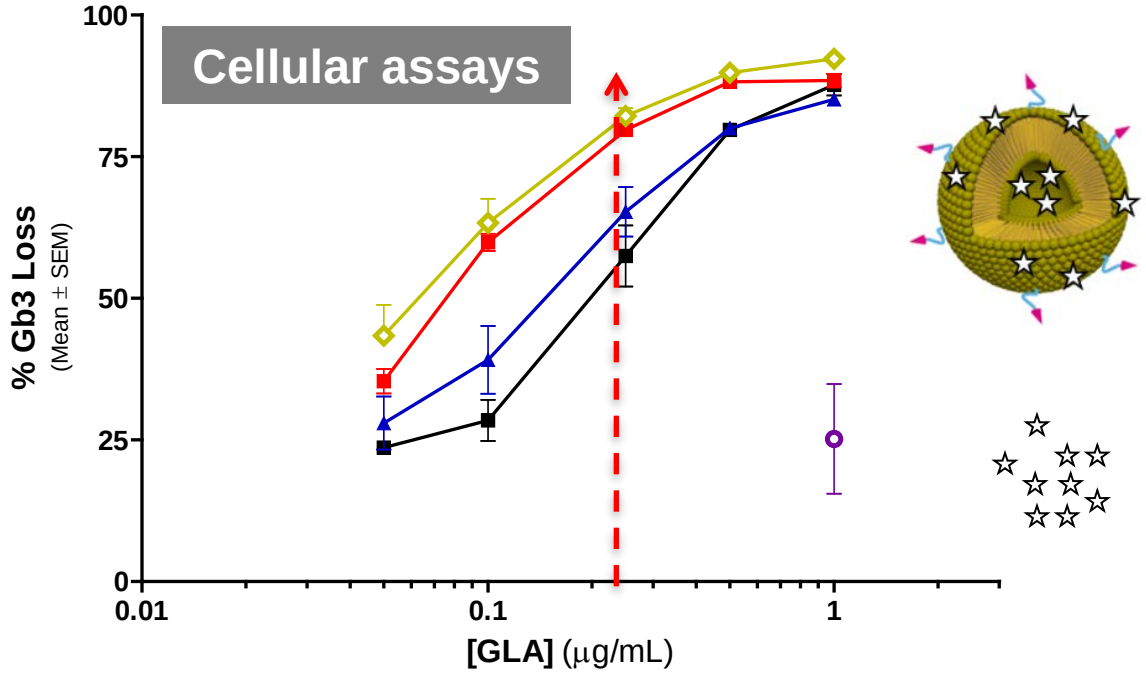


Large-scale molecular dynamics simulations

Dr. J. Faraudo

ICMAB CSIC

Higher reduction of undesired intracellular accumulation of glycosphingolipid Gb3 by encapsulated GLA



GLA loaded in peptide targeted nanoliposomes

Free GLA

Collaboration

I. **Nanoliposomes are uptaken by GLA deficient cells.**

II. **Nanoconjugates reach the lysosomal compartment.**

III. **GLA is efficiently released so that the GLA activity in the cells is restored.**

Dr. I. Abasolo

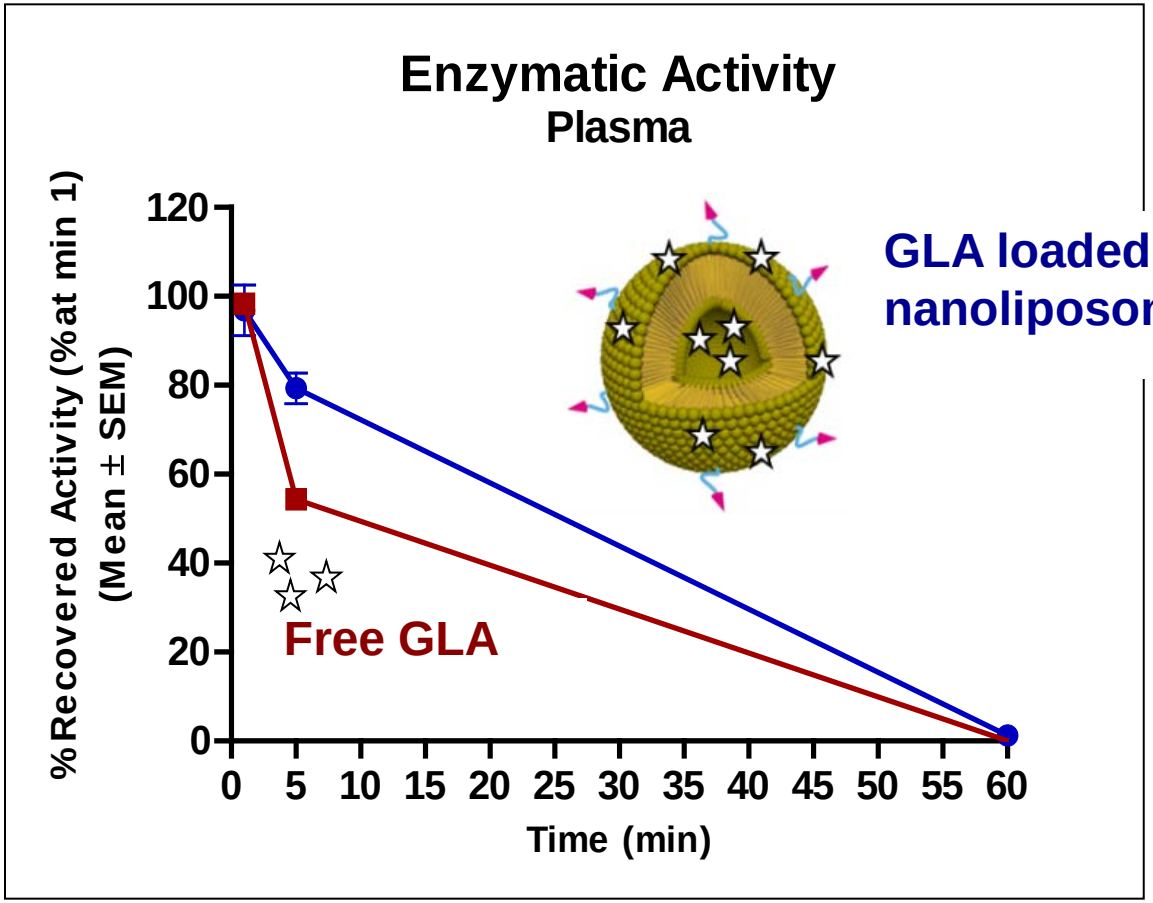
Vall d'Hebron Hospital

Patent Application WO2014/001509; **I. Cabrera et al,** ***Advanced Healthcare Materials*****, 2016**

Preliminary promising in-vivo pharmacokinetic studies in animal models.

Collaboration

In-vivo pharmacokinetic studies in KO Fabry mice



Dr. I. Abasolo

Vall d'Hebron Hospital

2014: CIBER-BBN licensed to BioPraxis Research the nanoliposomal platform for the encapsulation of enzymes

LIPOCELL PROJECT

Praxis Pharmaceutical

ciber-bbn
Centro Investigación Biomédica en Red
Bioingeniería, Biomateriales y Nanomedicina

IP: N. Ventosa (CSIC)
(2015-2016)

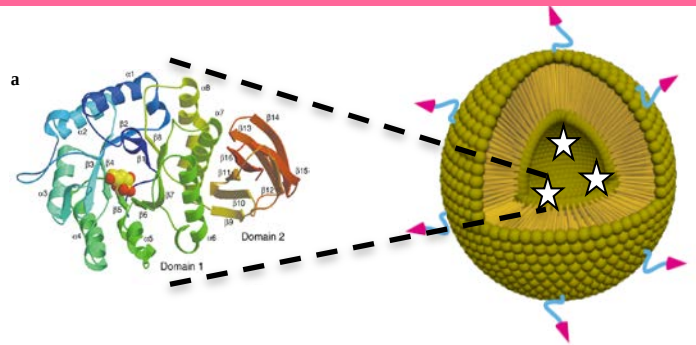
TERARMET PROJECT

UNIÓN EUROPEA
FONDO EUROPEO DE DESARROLLO REGIONAL
"Una manera de hacer Europa"

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMIA Y COMPETITIVIDAD

IP: E. Gainza (BioPraxis Research)
(2015-2017)

<u>Bring the new nanoformulation of GLA to the end of the pre-clinical regulatory stage</u>



Project presented to Nanomedicine Translation Advisory Board (TAB)

1st round : October 2015

Strengths

- **Flexible interdisciplinary and translational research team**
- ***Praxis as industrial partner open to further agreements with other industrial partners***

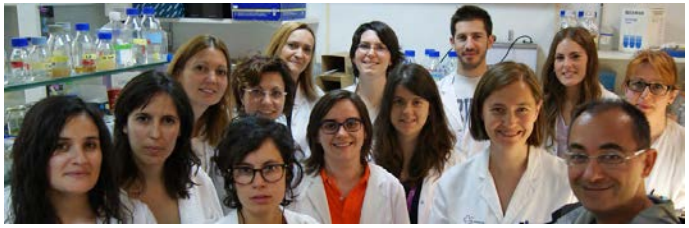
Recommendations

- **Involvement of Fabry industrial player into the project (Shire, Sanofi (Genzyme) or Protalix)**
- ***Application of the nanolipsomal platform for the delivery of other therapeutic enzymes and to cross BBB***

Functionalized nanoliposomes for the development of therapies for intracellular-based diseases. Application to Fabry Disease.

Nanomol Group.
Instituto de Ciencia de Materiales de Barcelona
Coordinator of the project: Nora Ventosa

Nanoparticle and Peptide Chemical Group
Parc Científic de Barcelona
Miriam Royo



Drug Delivery and Targeting Group
Hospital Universitari Vall d'Hebron. Institut de recerca
Simó Schwartz Navarro & Ibane Abasolo

Nanobiotechnology Group
Instituto de Biotecnología y Biomedicina
José Luis Corchero

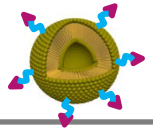
ciber-bbn

Praxis Pharmaceutical
Eusebio Gainza & Ángel del Pozo

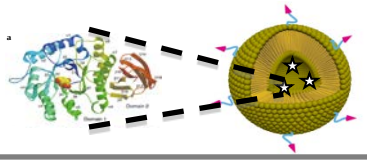
Praxis Pharmaceutical

Objectives

1. **Optimization of the Liposomal Intracellular Transport Platform**



2. **Development of New Fabry Nano-conjugate**



Gantt Diagram

Work Packages	M1-M3	M4-M6	M7–M9	M10–M12	M13–M15	M16–M18	M19–M21	M22–M24
WP1: Definition of the specifications of the drug product for the non-regulatory preclinical phase	Start: 18/11/2014			Deadline: 18/11/2015				
WP2: "in-vitro" and "in-vivo" pharmacology studies.	Start: 18/11/2014							Deadline: 18/11/2016
WP3: Plant Design and Process Development for Fabrication of the final galenic prototype under quasi GMP conditions					Start: 18/12/2015			Deadline: 18/11/2016
WP4: Regulatory			Start: 18/08/2015					Deadline: 18/11/2016
WP5: Proof of concept of new nanoliposome-active conjugates			Start: 18/08/2015					Deadline: 18/11/2016
WP6: Licensing and Marketing plans					Start: 18/12/2015			Deadline: 18/11/2016