NANOBIOFAR Group, School of Pharmacy
University of Santiago de Compostela, Spain

Nanosciences, nanotechnologies, Materials and new Production technologies – NMP
Large EU projects

NEW ORAL NANOMEDICINES: TRANSPORTING THERAPEUTIC MACROMOLECULES ACROSS THE INTESTINAL BARRIER

"TRANSINT"

Maria José Alonso

INNOVATION IN NANOMEDICINES AND EU FUNDING

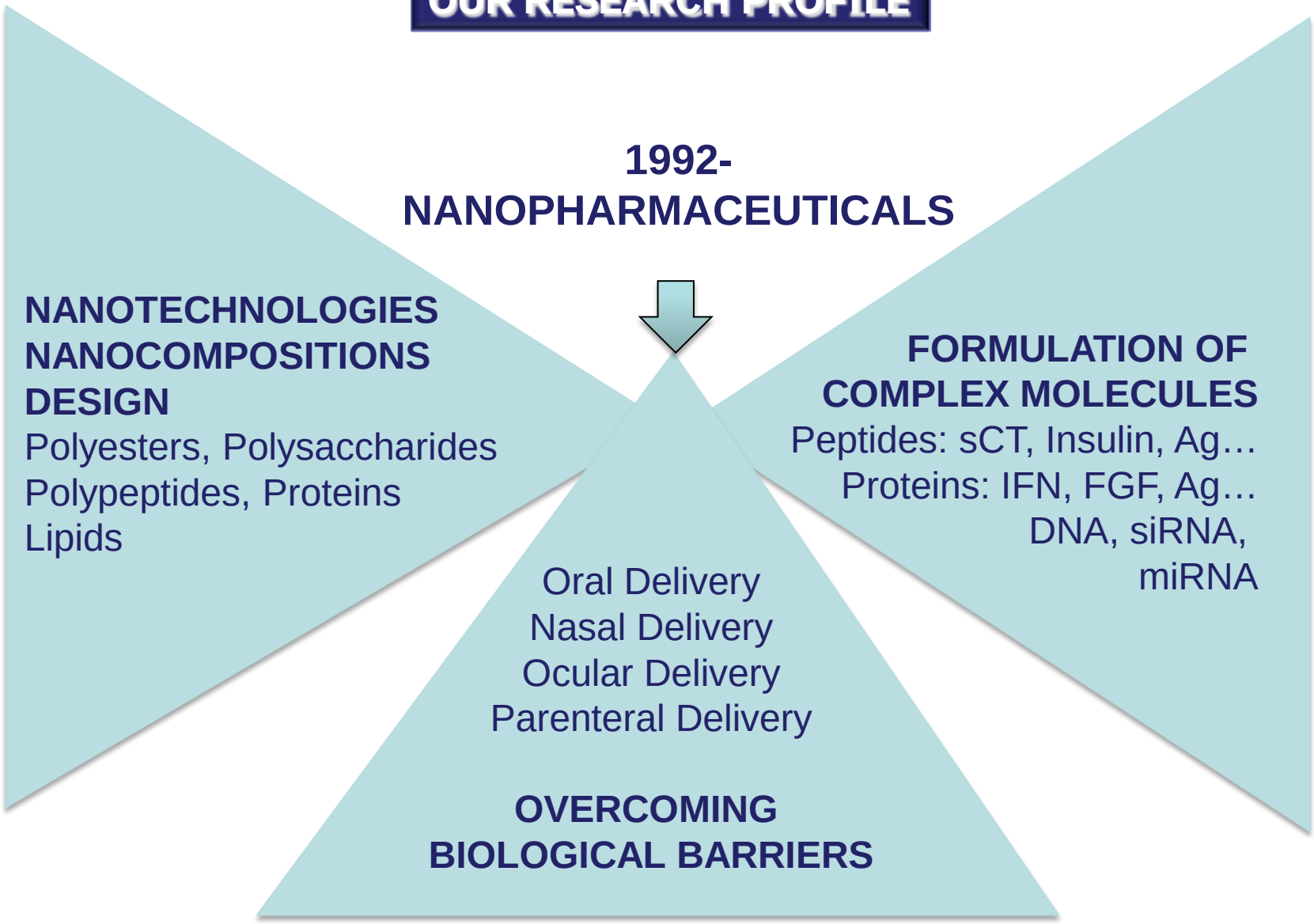
VI Conferencia de Plataformas Tecnológicas y de Investigación Biomédica, Madrid 2013

How the TRANSINT project started…

- Research profile and background
- View of valorization models in therapeutics
- The key elements of the TRANSINT consortium

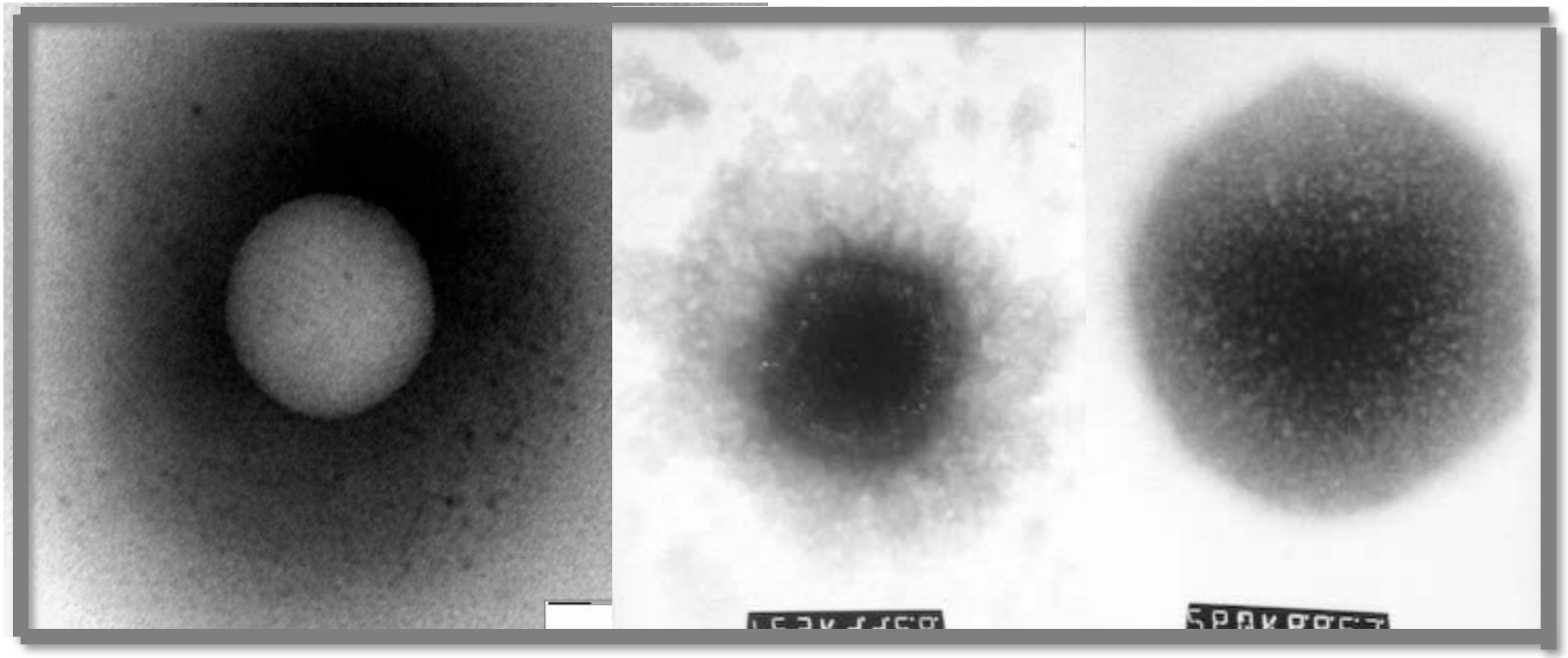
Where we are now…

OUR RESEARCH PROFILE



OUR RESEARCH PROFILE

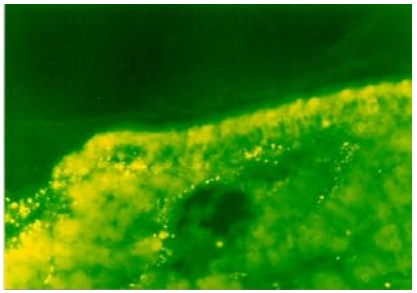
Technology-driven goal:
The rational design of delivery systems for helping complex molecules to overcome biological barriers



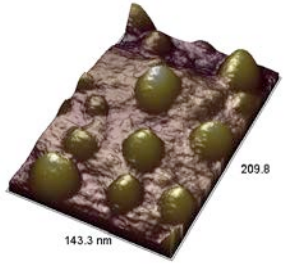
OUR RESEARCH PROFILE

OVERALL GOAL: the translation of ideas from the university through novel pharmaceutical nanotechnology.

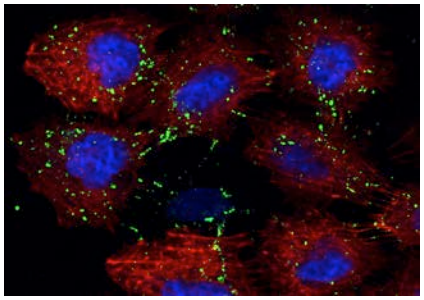
Oral/Nasal peptide Delivery



Brain Delivery

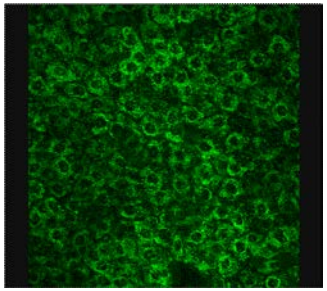


Cancer
Targeted therapies
Immunomodulation
Gene therapies

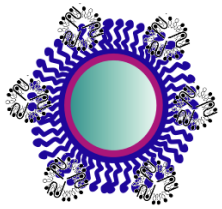


Transdermal Drug Delivery

Ocular Drug delivery



Nanovaccines
Adjuvants
Needle-free vaccination



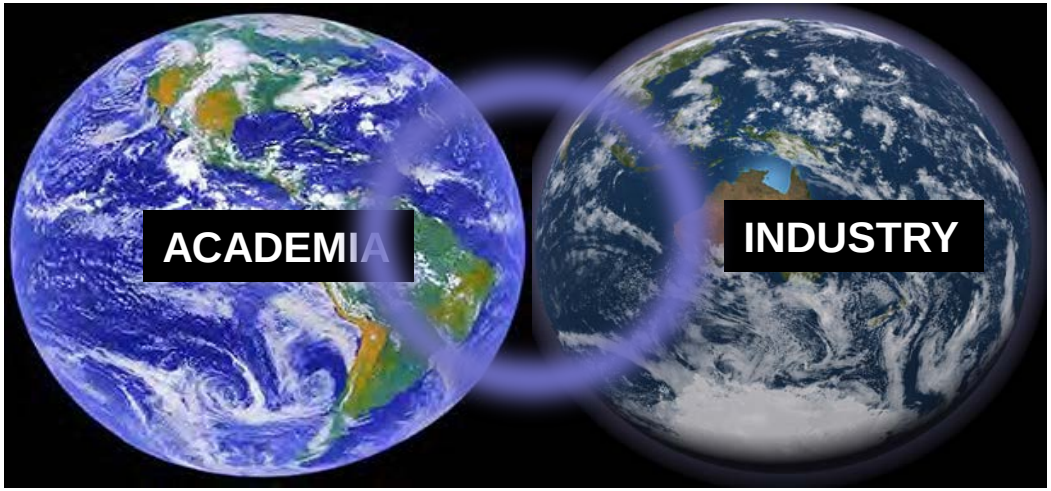
http://www. webspersoais.usc.es/

OUR RESEARCH PROFILE

OVERALL GOAL: the translation of ideas from the university through novel pharmaceutical nanotechnology.

VALORIZATION MODELS IN THERAPEUTICS

IDEAS → KNOWLEDGE → VALUE



BARRIERS IN THE TRASLATION/VALORIZATION PATH

Strategic view

IDEA

Visibility

Patent, Paper Institution

Feasibility

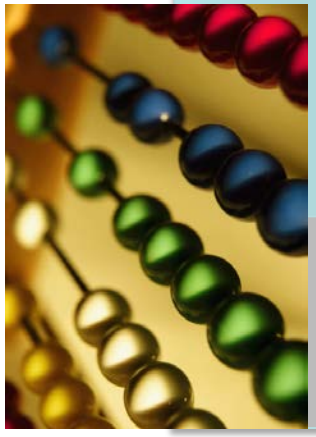
PRODUCT

INDUSTRY-ACADEMIA COLLABORATIVE MODELS

THE PAST: PASIVE MODEL → **THE PRESENT:** ACTIVE MODEL

SUBCONTRACTING ACTIVITIES

Industry => Academy (desmotivation)



LICENCING IP
Academia => Industry (limited industry input)
Restricted

UNIVERSITY SPIN-OFFs
(restricted)

THE SINERGISTIC MODEL

THE CONSORTIA MODEL:

US model enlight biosciences

EU model

Ej. TRANSINT

ACADEMIA

START-UPS

BIG PHARMA

THE KEY ELEMENTS OF THE TRANSINT CONSORTIUM

1. The call:

WORK Program COOPERATION-THEME 4-NMP
NMP.2011.1.2-2 New targeted therapy using nanotechnology for transport of macromolecules across biological barriers

2. The industry needs

New complex molecules, i.e. peptides
Oral Drug Delivery?

3. The adequate partners selection

Best pharmaceutical nanotech
Complementary expertise

THE INDUSTRY NEED: ORAL PEPTIDE DELIVERY STRATEGIES (18)

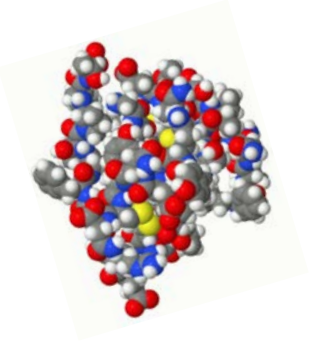
Company	Technology	Phase
UNIGENE/Tarsa Therapeutics (USA) **UNIGENE/GSK**	**Enteripep™:** solid dosage oral delivery formulation containing a protease inhibitor (coated citric acid), an absorption enhancer (lauroyl carnitine), a non ionic polymer) and an enteric coat (Eudragit L30 D-55)	**CALCITONIN** (OSTORA™): **sucessfull Phase III trials** (NDA and MAA submissions to FDA and EMA in process) **PTH analog:** Phase II (2011-2012, unpublished results)
ORAMED (Israe	Formulations containing protease inhibitors*, Omega-3 fatty acids,… encapsulated in soft-gel enteric capsules *SBTI (a soybean extract trypsin inhibitor) and Aprotinin	**INSULIN:** FDA-approved **Phase II Trial in the U.S.** IND FDA application, 2012. **GLP1 analog (EXENATIDE): Phase Ib/IIa**
MERRION Pharma (Ireland)/ Novo Nordisk (Denmark)	**GIPET®**: oral tablet/capsule formulations of API and patented absorption enhancers (medium chain fatty acids or derivatives*) + a DAC inhibitor *e.g. C10 fatty acid caprate, FDA/FAO/ WHO approved GRAS additive	**GLP-1 Analogue** (NN9926): successful **Phase I** trial, October, 2012 **INSULIN (NN1953):** successful **Phase I** trial, February, 2012
OSHADI DRUG ADM LTD. (Israel)	Silica nanoparticles having a hydrophobic surface, a polysaccharide, and insulin	**INSULIN**: Phase I (February, 2011), undisclosed results

Company	Technology	Phase
EMISPHERE (USA)/ NOVARTIS   **EMISPHERE/NOVO NORDISK** 	**Eligen™ Technology:** proprietary delivery agents. Most of them are **amido acids.** *** e.g. SNAC** (Sodium N-[8-(2-hydroxybenzoyl)amino]caprylate), achieved GRAS status in the US	**CALCITONIN:** 3 **Phase III** trials in 2011, failure efficacy endpoints **PTH: Phase I** (2010), failure clinical endpoints **rhGH: successful Phase I**, discont **INSULIN:** Development and license agreement (2010). **GLP-1 receptor agonists:** currently in **Phase I**
Bone Medical **Dial** 	**Axcess Oral Delivery Tech.:** use of aromatic alcohols (GRAS listed) as absorption enhancers	**CALCITONIN, PHT: Phase II** **INSULIN** (Capsulin™): Phase II (2008, discontinued)
Biocon (India)  	Oligomer linked PEG units attached to peptide	**INSULIN: Phase III** clinical trials in India. Nov. 2012: agreement with Bristol-Myers Squibb, new clinical trials tol be conducted.
Chiasma (Israel) 	**Transient Permeability Enhancer tech. (TPE):** C8 fatty acids (GRAS) in an oily suspension.	**OCTREOTIDE: Phase III** (acromegaly) and **Phase II** (neuroendocrine tumor)
Zydus Cadilla Research Center	**Novel orally bioavailable peptidomimetics**	**GLP-1 analog:** early phase clinical studies **PTHR1 receptor agonist: Phase I**

THE INDUSTRY NEED: ORAL PEPTIDE DELIVERY STRATEGIES

Company	Technology	Phase
NOD Pharmaceuticals (USA)	**Nanoparticle oral delivery (NOD) :** bioadhesive nanoparticles	**INSULIN** (Nodlin): currently **Phase I** in China
Tamarisk Technologies (USA)	**Serum-Specific Nano-Encapsulate particles (SSNe):** polymeric vehicles of alginate and a transmucosal enhancer covalently conjugated (Coenzyme Q10, geraniol, vit A and E, etc)	**INSULIN:** attempting **Phase III** Other peptides Bioavailability > 90%
Access Pharmaceuticals (USA)	**Cobalamin™ Oral nanoparticles:** attachment of Cobalamin to drugs, polymers containing drugs ot nanoparticles	**INSULIN and hGH:** Preclinical
Transgene Biotek (India)	**TrabiOral ™**: A polymerized solid lipid nanoparticle system comprising lipids and long chain fatty acids, a therapeutic protein or peptide, a lectin and at least one polymer	**INSULIN:** Preclinical (good results, 2012) Other peptides
NanoMega Medical Co.	**Chitosan/Gamma poly glutamic acid nanoparticles**	**INSULIN:** Preclinical, leading to initial human clinicals

THE INDUSTRY NEED:
ORAL PEPTIDE DELIVERY



Insulin

IDENTIFICATION OF THE PROJECT:

- >1000 peptides are marketed or under clinical evaluation, 2 (cyclosporin A and desmopresine) are administered orally.

THE DIFFICULTIES:

-Several oral insulin formulation developed on the last decades (hundreds of papers)
- Several products in clinical development

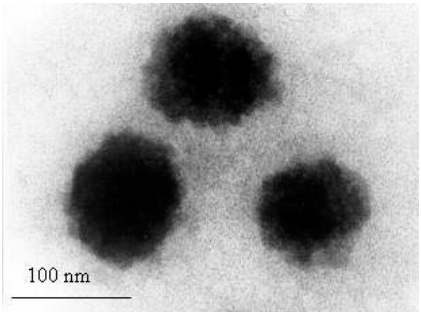
THE POTENTIAL OF NANOCARRIERS:

- Scarce and scattered knowledge about the mechanistic issues and toxicological aspects => limited rational design.

- Most nanocarriers disclosed have little chance to reach clinical development as they are made of expensive materials with a non-proved safety record.

TRANSINT aims to generate integrative multidisciplinary knowledge and to apply it to the rational development of oral peptide nnaopharmaceuticals.

TRANSINT CONCEPT:



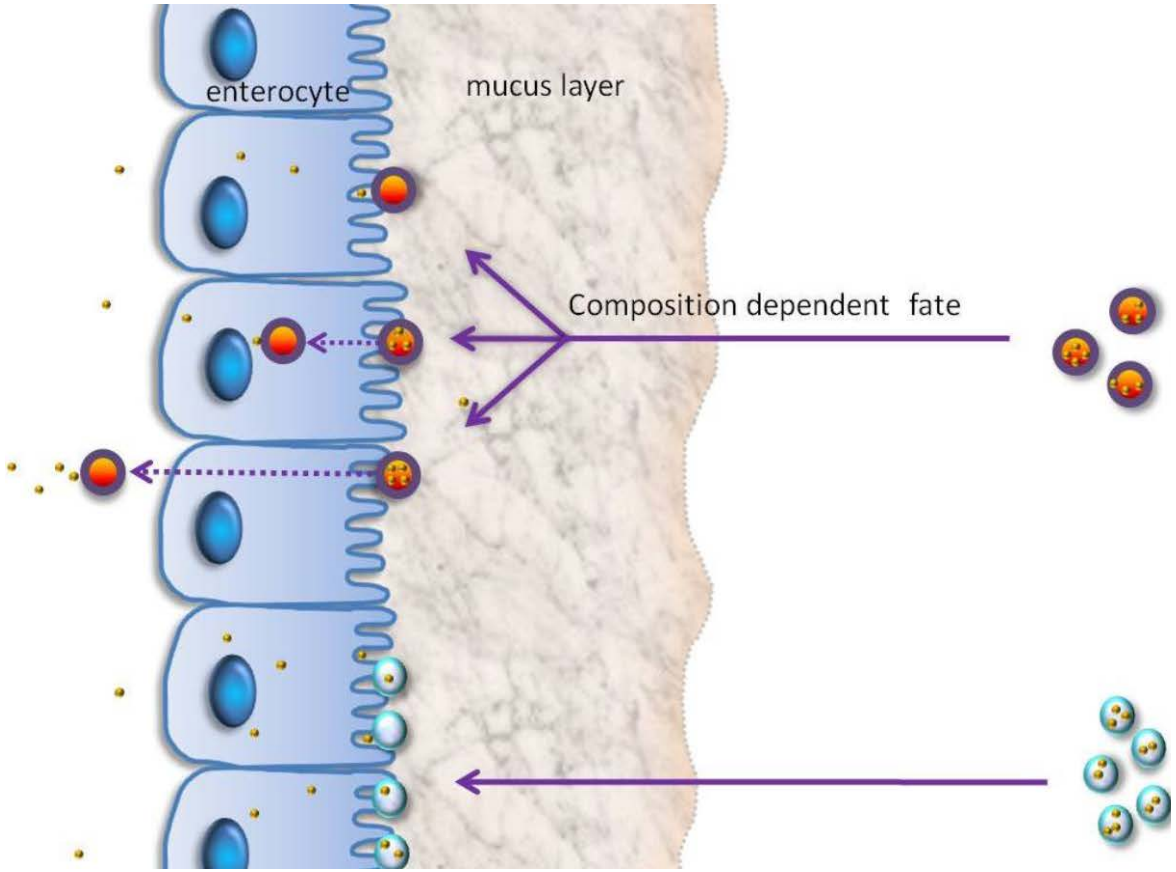
THE DESIGN OF NANOCARRIERS:

- Biopharmaceutical mechanistic criteria (knowledge of the nanomaterial-biological barrier interaction)
- Safety issues (materials on the market or in clinical evaluation)
- Pharmaceutical technology criteria (drug loading, stability and scalability).

Targeted molecules could be anti-obesity/diabetes peptides

TRANS-INT motto:
"Understand the barrier; understand the carrier"

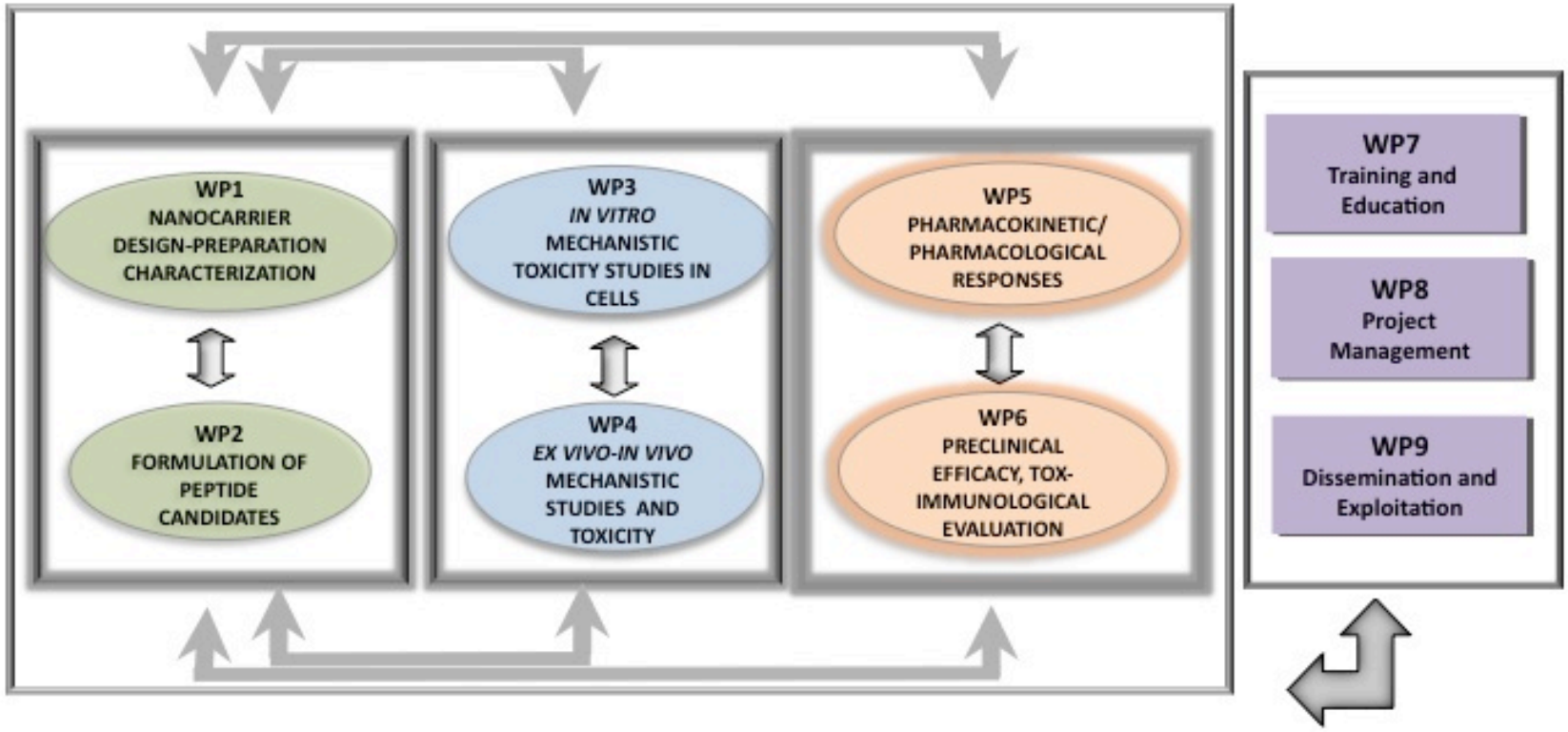
TRANSINT CONCEPT: BIOLOGICAL BARRIERS



- STABILITY IN GI FLUIDS
- MUCUS INTERACTION
- MUCUS DIFUSION
- EPITHELIUM INTERACTION
  A) ADHESION
  B) PENETRATION
  C) TRANSLOCATION
- DRUG RELEASE
- DRUG ABSORPTION

TRANSINT ORGANIZATION

The relationship between the different WPs



TRANSINT ORGANIZATION

ACADEMIC INSTITUTIONS (13)

BIG PHARMA: Sanofi

Nanotechnologists (4)

Tox/Immunology (3)

SMEs: Seroscience Sigmoid

Chemical biology (1)

Barriers biology (4)

Nanocarriers design and assessment

Peptides
Preclinical evaluation

THE CONSORTIUM DEFINITION: TRANSINT PARTNERS

Coordinator: **Maria José Alonso** (USC, Spain)

Deputee coordinator: **David Brayden** (UCD, Ireland)

Academic partners:

Caitriona O'Driscoll (Irish Drug Delivery Network, Ireland)

Andreas Schatzlein/Ijeoma Uchegbu (UL, London School of Pharmacy, UK)

Jean Pierre Benoit (UA, Université d'Angers, France)

Veronique Préat (UCL, Université Catholique de Lovaine, Belgium)

Ernest Giralt (UB, University of Barcelona)

Vicenzo Bronte (IOV-UNIPD, Uni. of Padova, Italy)

Jürgen Borlak (Hannover University, Germany)

Aloïse Mabondzo (CEA, France)

Per Arturson (Uppsala University , Sweden)

Lisa Bregoli (Veneto Nanotech, Italy)

THE CONSORTIUM DEFINITION: TRANSINT PARTNERS

SMEs:

Sigmoid Pharma, Dublin (Oral Drug Delivery)

Delivery platform for oral peptides

SeroScience Ltd, Hungary (Immo-tox studies)

Preclinical Immunological evaluation

LARGE PHARMAs: peptides

Sanofi

ADVICERS:

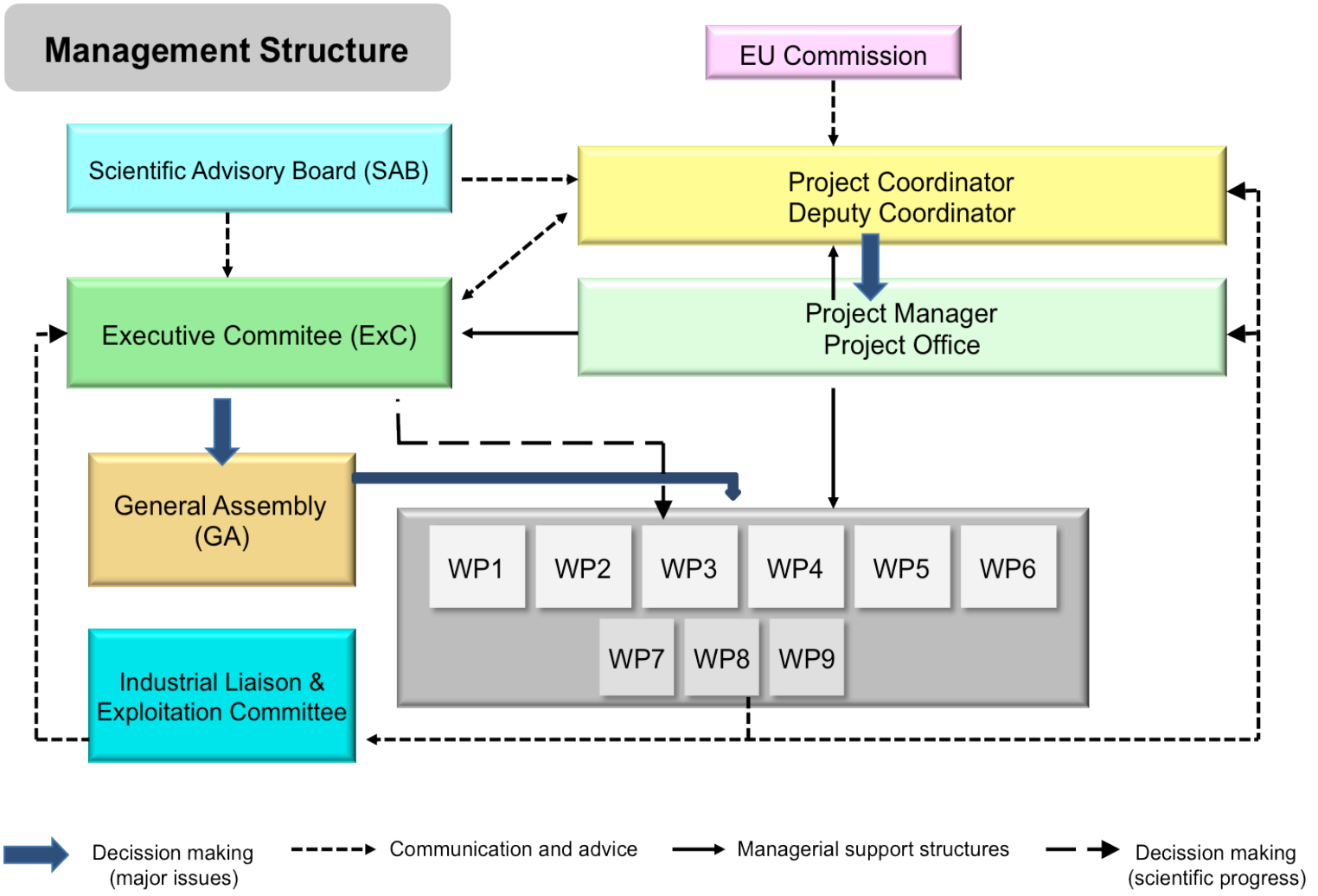
Scientific and regulatory issues:

Robert Langer
Patrick Couvreur
Randall Mrsny
Rogerio Gaspar
Ruth Duncan

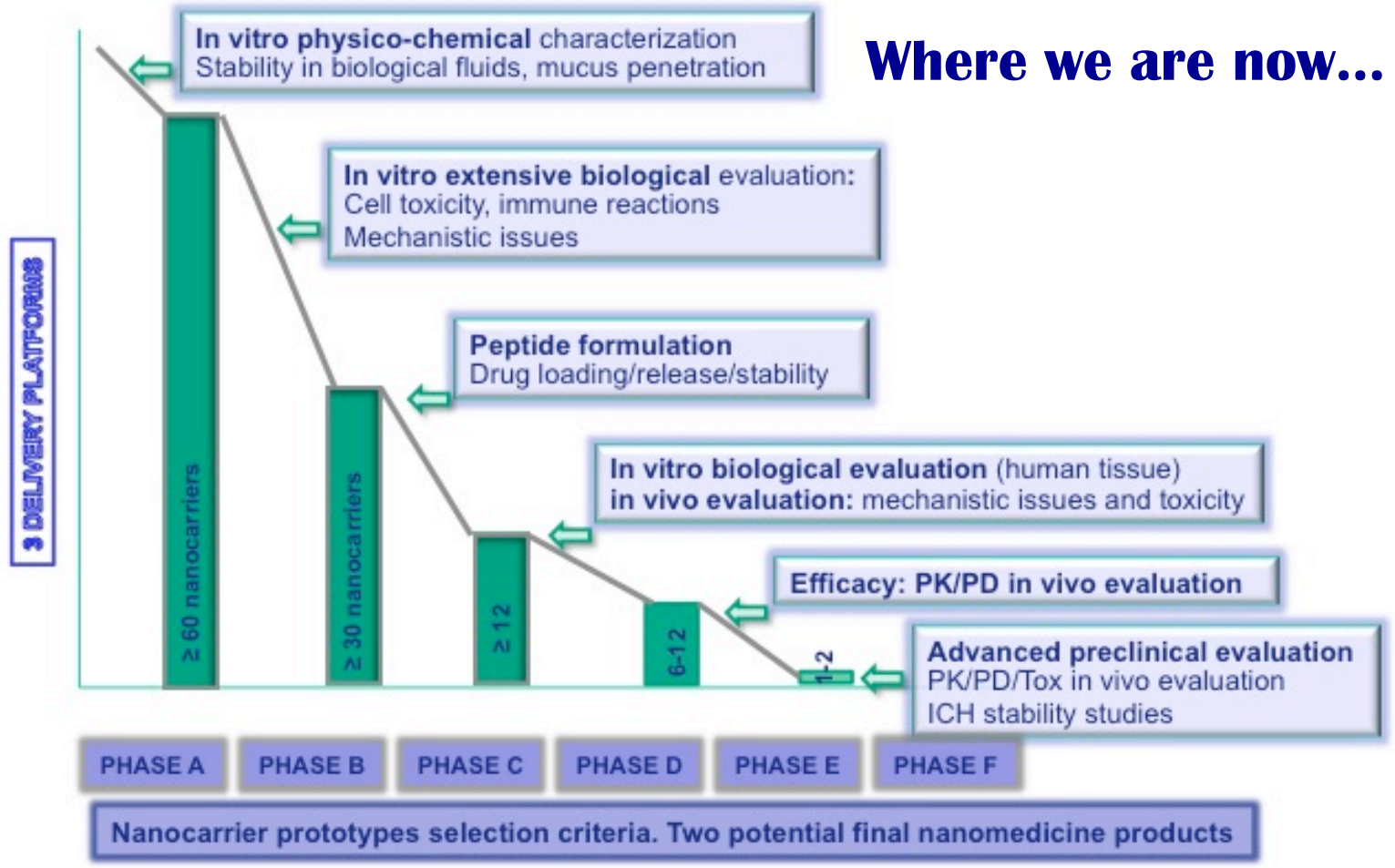
Clinical issues:

Stephen Gough
Michael Nouck
Felipe Casanueva

TRANSINT ORGANIZATION: MANAGEMENT STRUCTURE



THE TRANSINT DECISION MAKING PROCESS



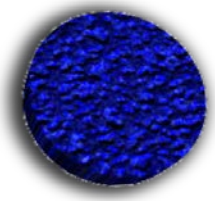
Where we are now…

THE STRATEGY OF TRANSINT NANOCARRIERS DESIGN

NANOCARRIERS PROPERTIES:
- Adequate stability in the Gastrointestinal fluids
- Favored interaction with the IB
- Controlled DD

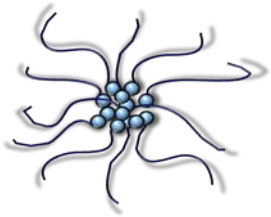
- Biomaterials: lipids, polysaccharides, polypeptides..(safety record)
- Architectural organization
- Adequate size and surface composition

Nanoparticle

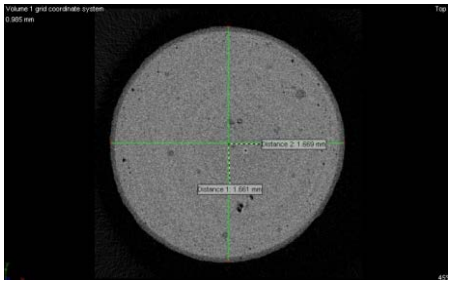


Nanocapsule

Micelle



SmPill™ technology



And easy to scale-up using mild technologies!!!

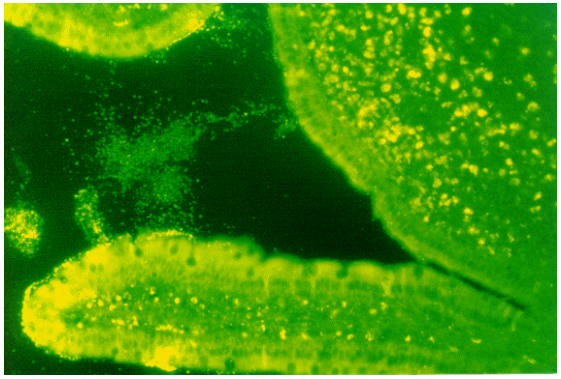
GRACIAS

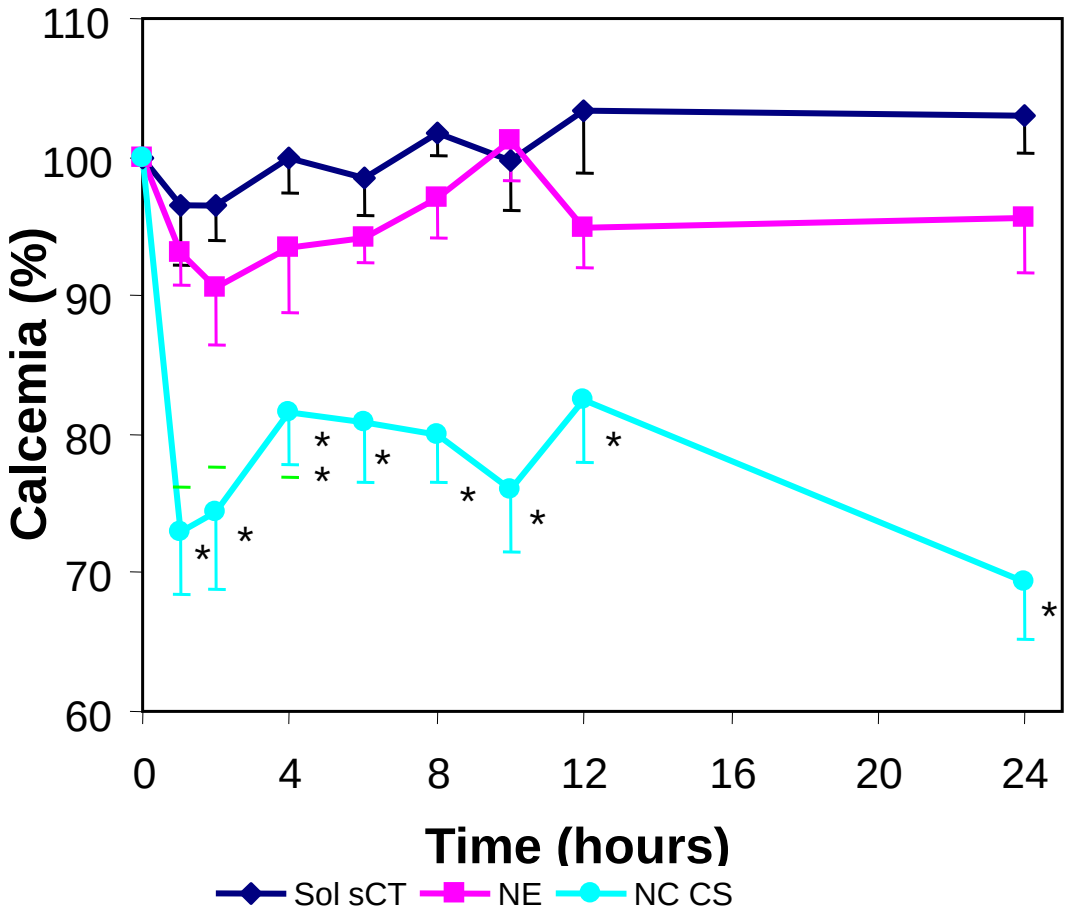
Financial support: “Gates Foundation”, European Commission, Ministry of Spain, Galicia Regional Government (Feder Founds), Advancell, Pharmamar

KEY ACHIVEMENTS

Nanoparticles as carriers for oral sCT delivey

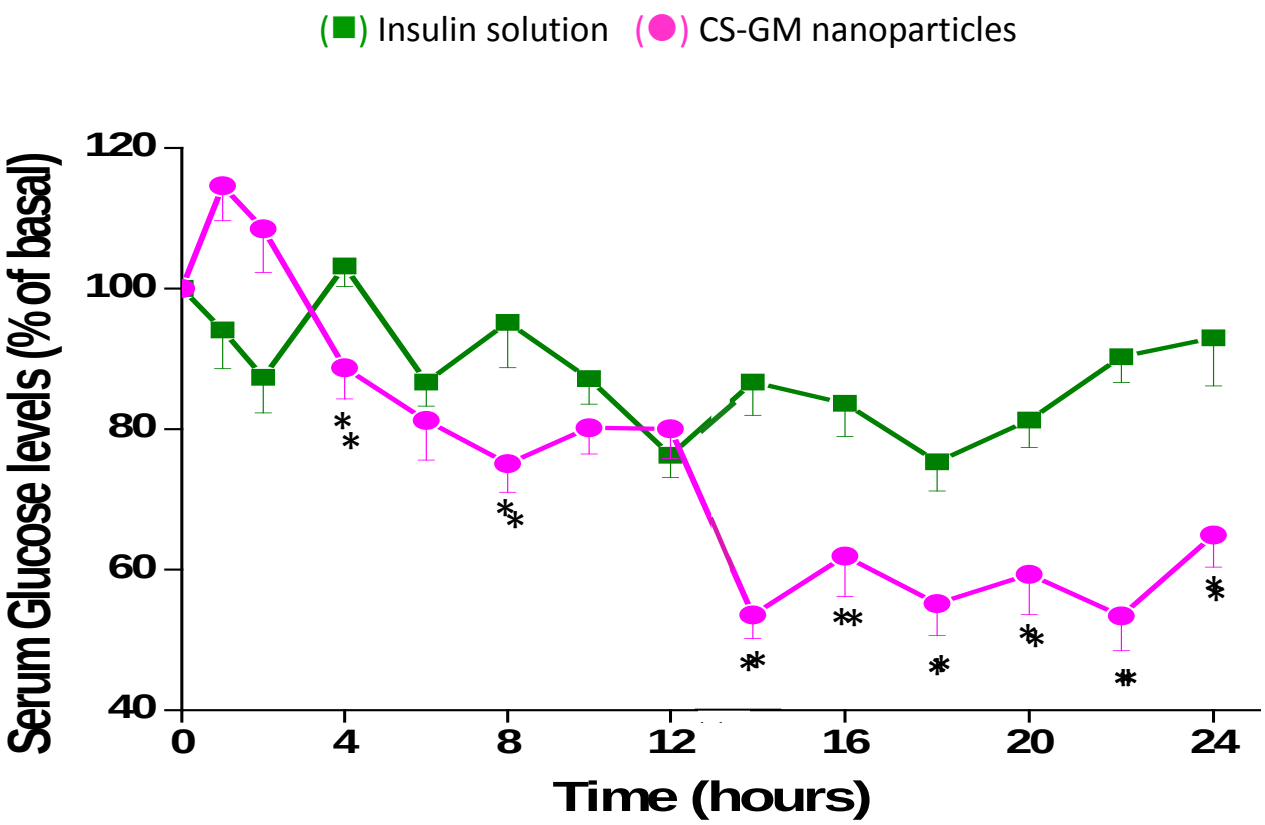
Oral administration of sCT-loaded chitosan nanocapsules

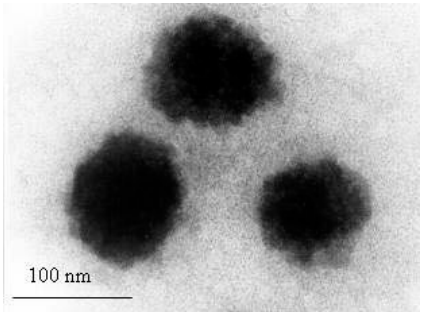




Nanoparticles as carriers for oral insulin delivey

Oral administration of insulin loaded chitosan-glucomannan nanoparticles (50 UI/kg)





TEM image of
CS-GM nanoparticles

M. Alonso and Carmen Remuñan