USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

SCHOOL OF PHARMACY

idis

CiMUS

CAMPUS VIDA UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

NANO-DRUG DELIVERY

María José Alonso

http://webspersoais.usc.es/mariaj.alonso

THE ORIGIN OF NANOPHARMACEUTICALS

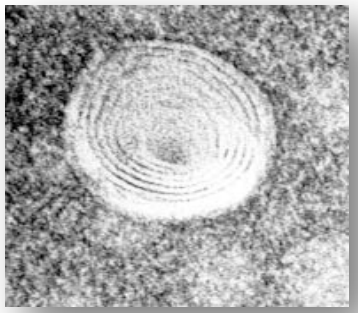
DRUG DELIVERY

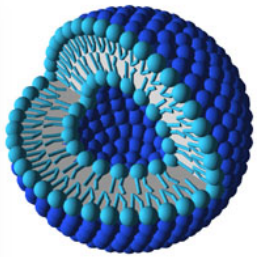
1960---

J. Folkman

A. Bangham

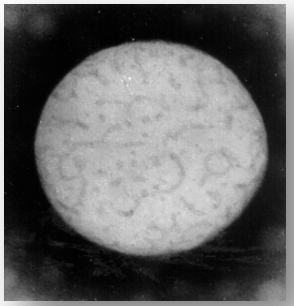
LIPOSOMES

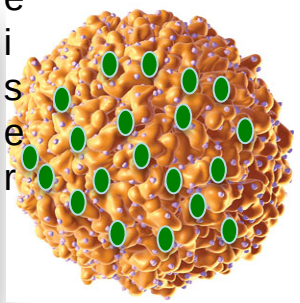




NANOPARTICLES

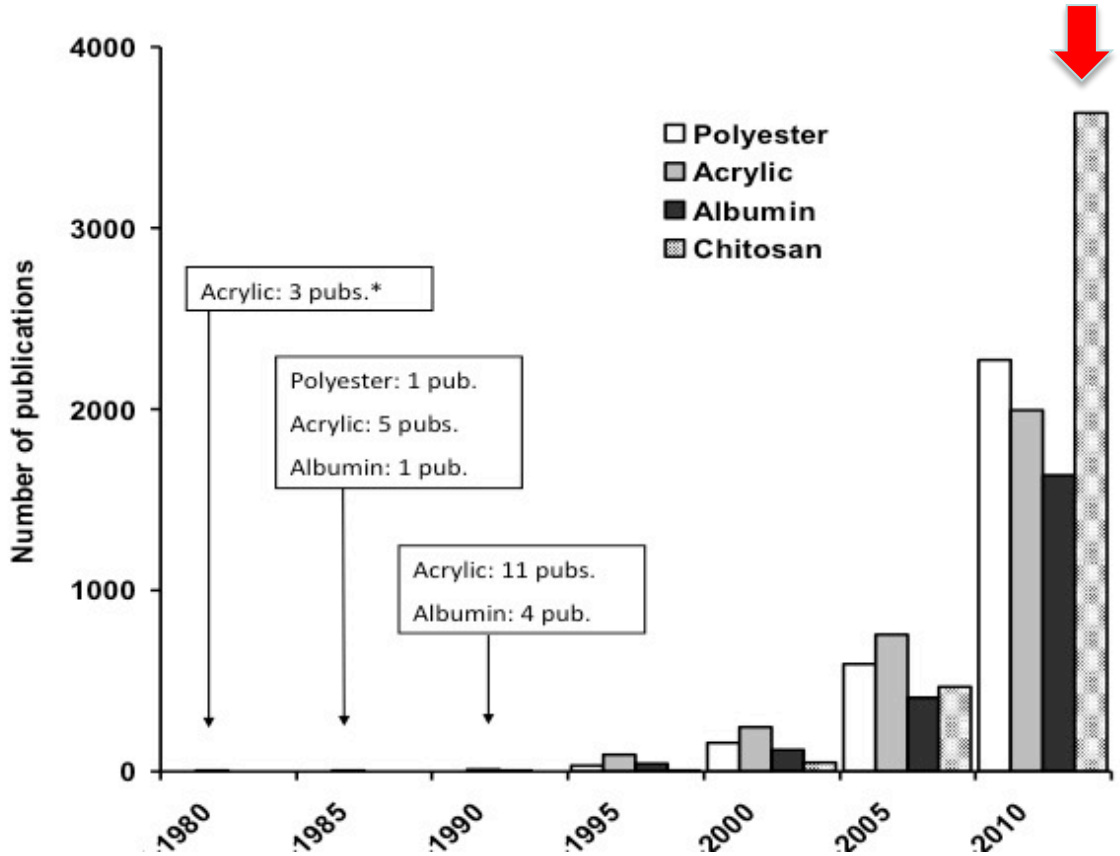
P. Speiser





RESEARCH ACTIVITY ON POLYMER NANOPARTICLES AS DRUG CARRIERS

OUR WORK



THE CURRENT STATUS OF NANOPHARMACEUTICALS

More than 40 Nano-drug delivery products

NANOCARRIERS

12 liposomes/virosomes

10 nanocrystal formulations

8 Polymer conjugates

3 polymer micelles (PLA-PEG, PGA-PEG, protein)

3 nanoparticles (albumin, phosphate, lipid NP)

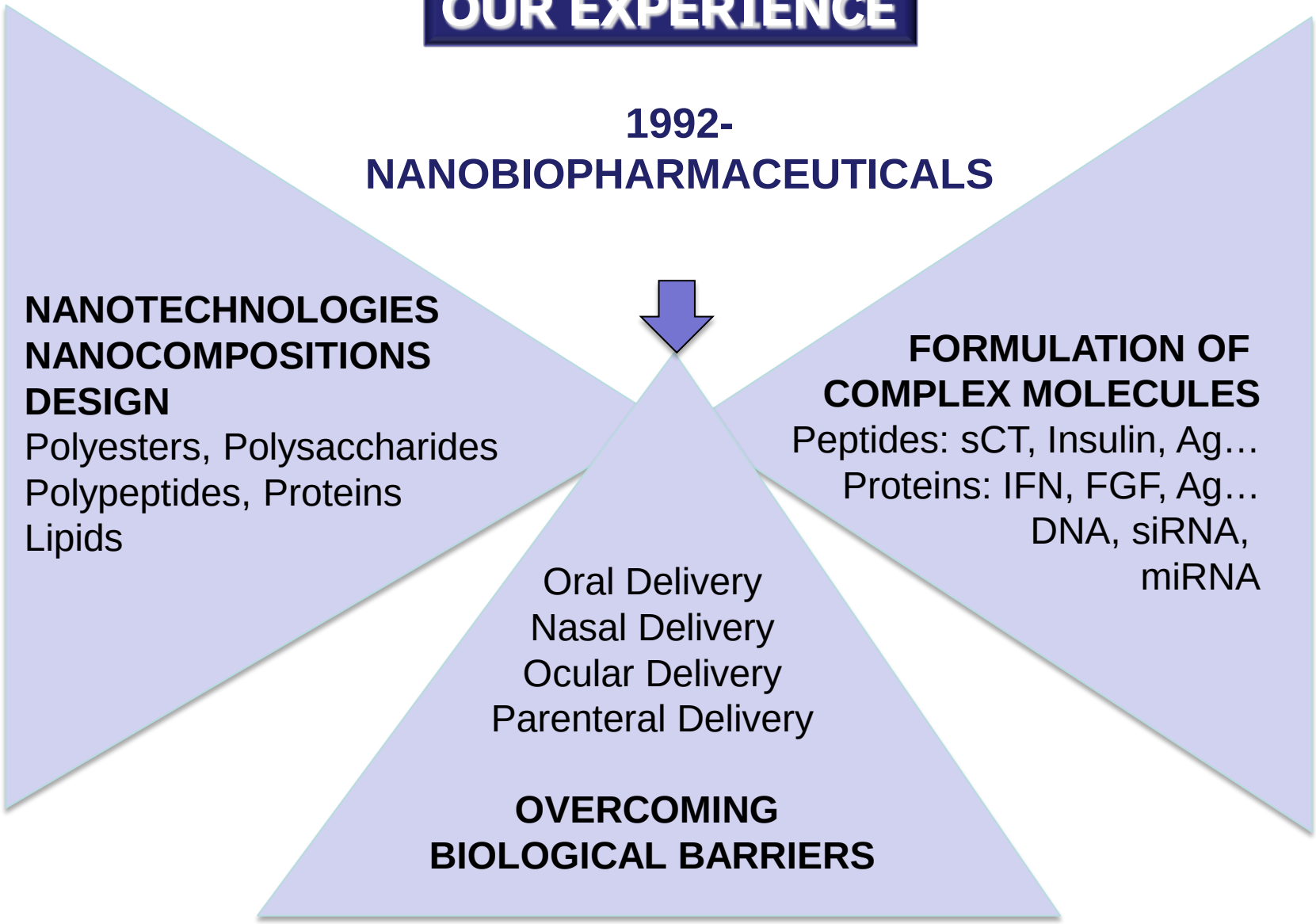
.....

INDICATIONS

Cancer
Infectious diseases
Pain
Autoimmune diseases
Acromegalia
Ocular disease
.....

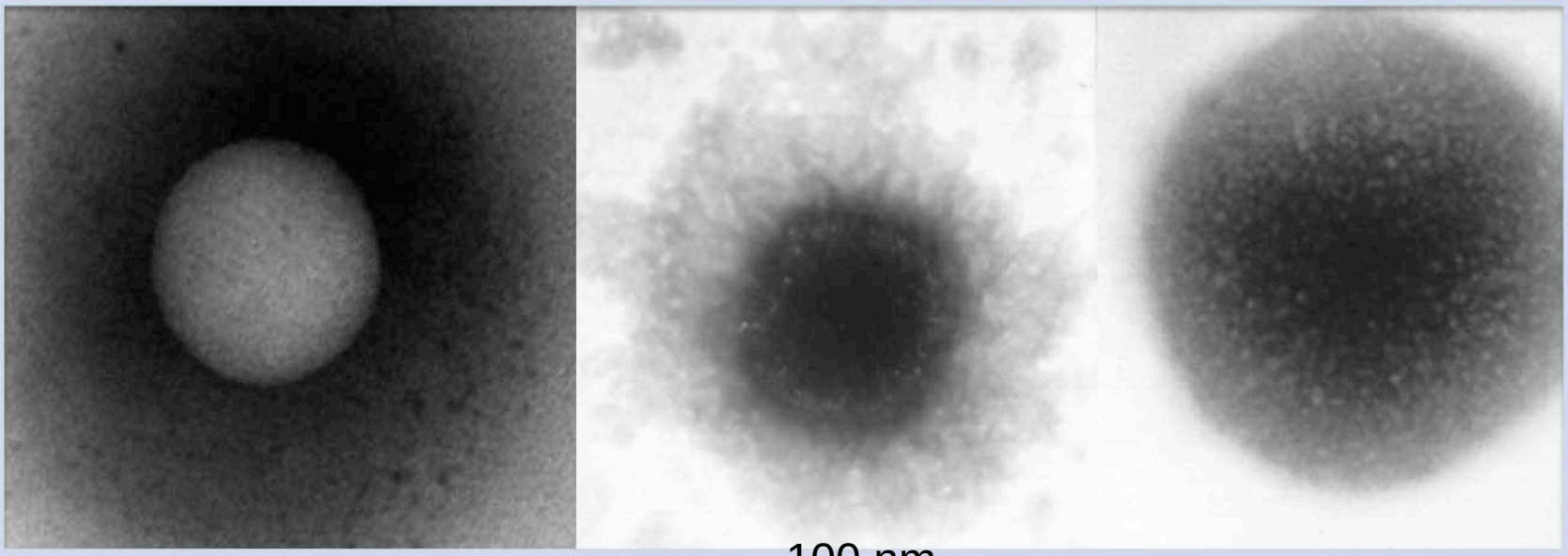
OUR EXPERIENCE

1992-
NANOBIOPHARMACEUTICALS



OUR EXPERIENCE AT THE USC

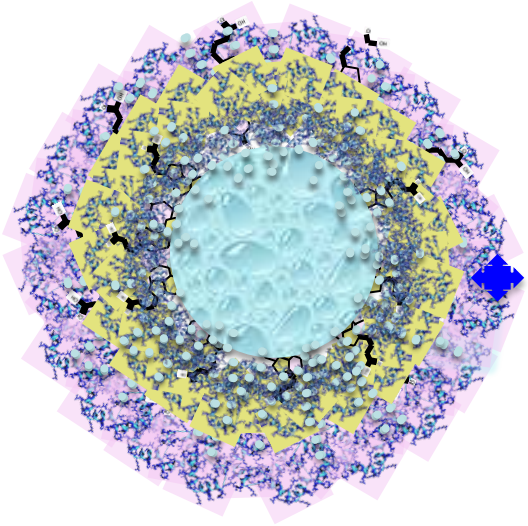
The rational design of delivery systems for complex molecules



MATERIALS: Polysaccharides, polypeptides, surfactants, oils

KEY ACHIVEMENTS

LATEST TECHNOLOGIES



THE KEY FEATURES:

Small size: 50-300 nm

Multiple layers

Functionalized surface

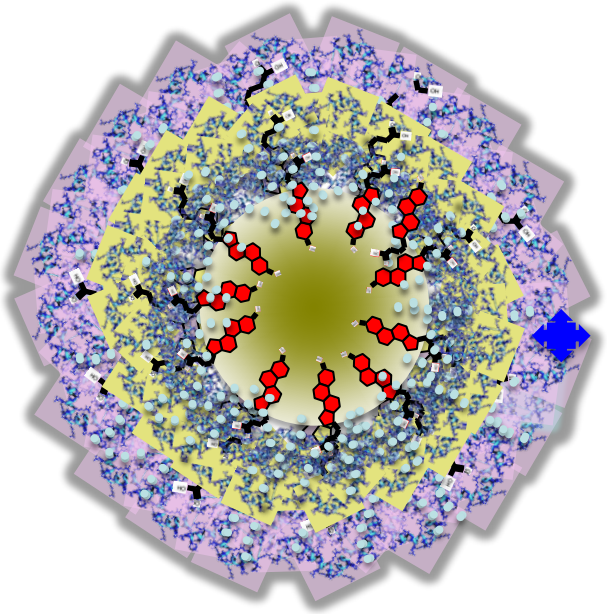
Negative/positive surface charge

Hydrophobic/hydrophilic core

TOOL-BOX FLEXIBILITY

One or more drugs
Protective agents
Controlling agents
Targeting agents

MULTI-LAYER POLYMER NANOCAPSULES



BIOMATERIALS:
Polyglutamic acid
Polyasparagine
Polyarginine
Hyaluronic acid…

THE KEY:

POLYMER/SURFACTANT/OIL

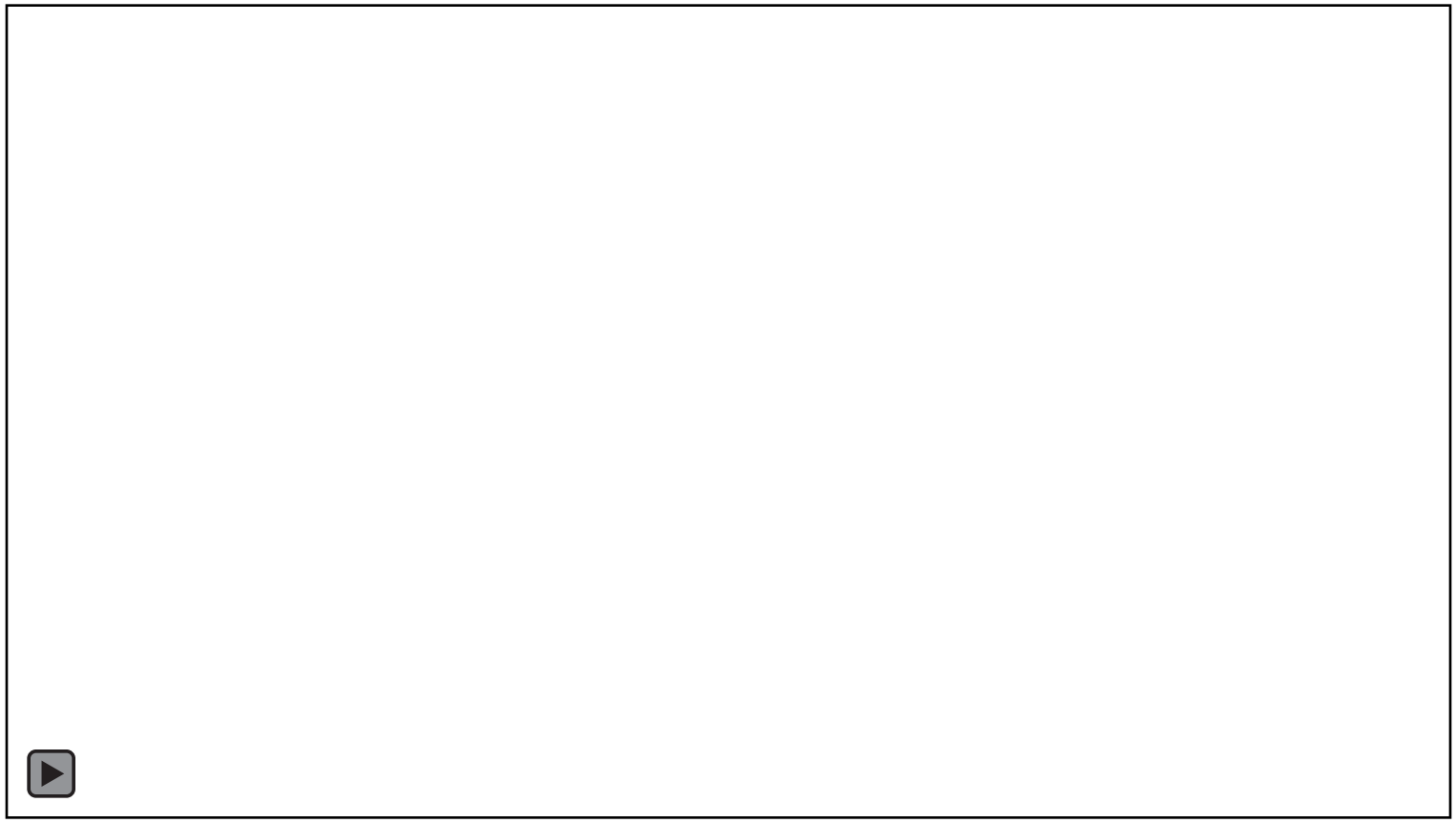
Self-assembling

Ionic/ hydrophobic…forces

EASY SCALABLE TECHNOLOGIES

- **Solvent displacement**
- **Self-emulsification**

SELF-EMULSIFICATION TECHNIQUE



Simple, mild and easy to scale-up

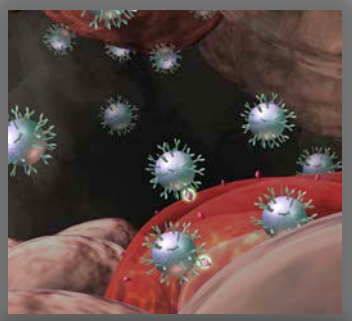
The goal: helping drugs overcoming barriers and reaching their targets

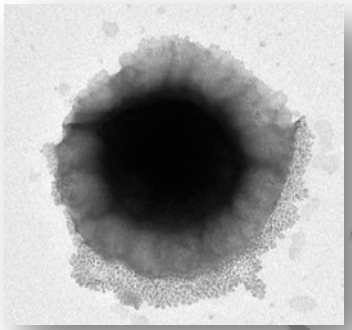
Systemic barriers

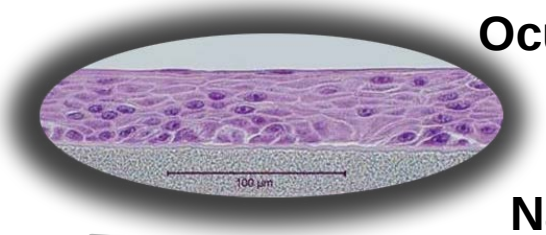
Ocular

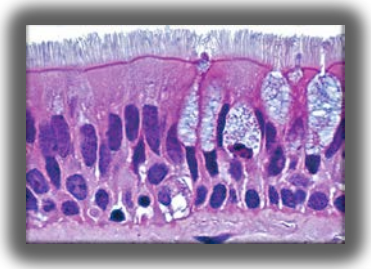
Targeting

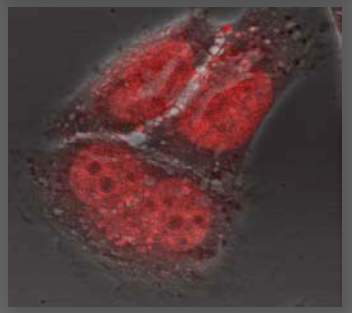
Nasal

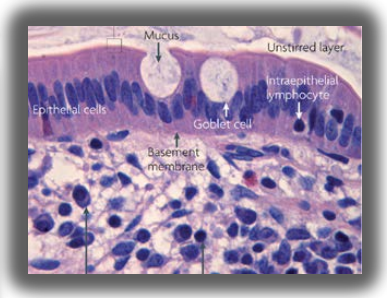












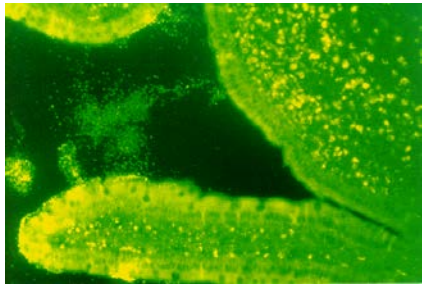
Skin

Cellular barriers

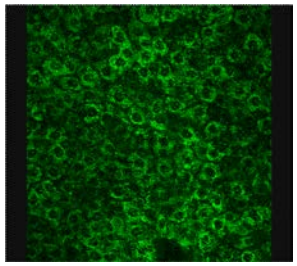
Intestinal

CURRENT APPLICATIONS

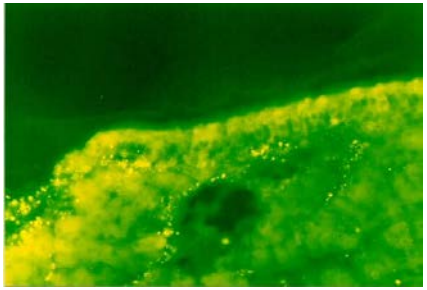
ORAL PEPTIDE DELIVERY
TRANS-INT-eu



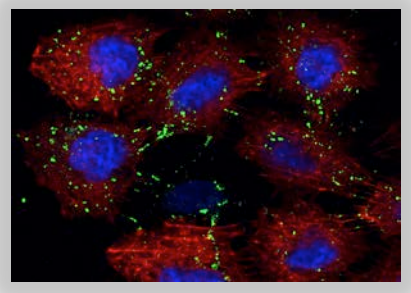
OCULAR DRUD DELIVERY
SURFEye, NABBA
Dry eye, corneal healing



NASAL
VACCINE/PEPTIDE
DELIVERY- NIH



CANCER
NICHE, NANOFAR, WORLDWIDE
Immunotherapies



CURRENT APPLICATIONS

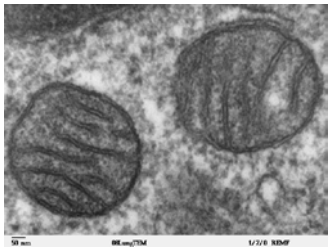
TOPICAL APPLICATION: Psoriasis

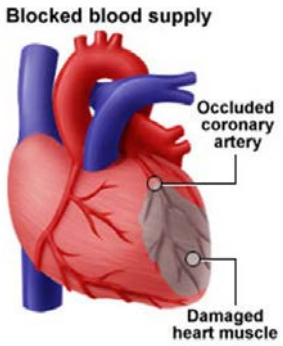
LYMPHATIC TARGETING: THERAPEUTIC VACCINES
Auto-immuno diseases

Multiple esclerosis

Diabetes

CARDIO- DRUG DELIVERY
Cardiac ischemia





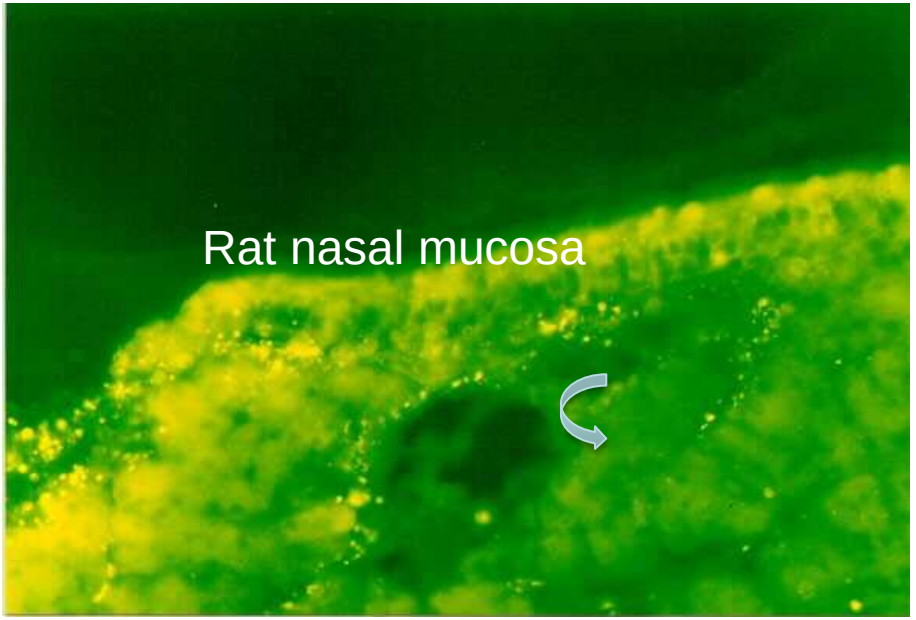
KEY ACHIVEMENTS: APPLICATIONS

NASAL/ORAL DRUG/GENE/ANTIGEN DELIVERY

Enhancement of systemic absorption of complex drugs

Drugs:
Insulin
sCalcitonin

Antigens:
Tetanus Toxoid, DT
Hepatitis B, HIV



Tobío M. et al. **Pharm. Res.,** 15, 270 (1998)

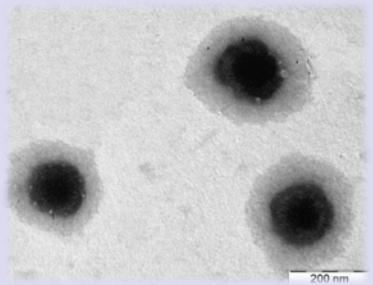
NASAL VACCINE DELIVERY

BILL & MELINDA GATES foundation

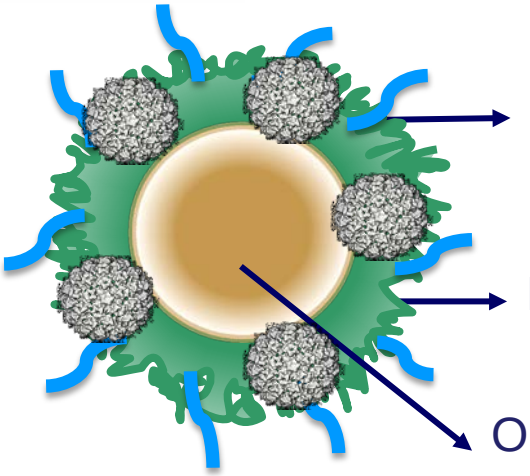
Grand Challenges in Global Health

Needle-free vaccine delivery systems
Thermostable vaccines

MULTIFUNCTIONAL POLYMER NANOCAPSULES



Protection
Presentation
Multi-adjuvant



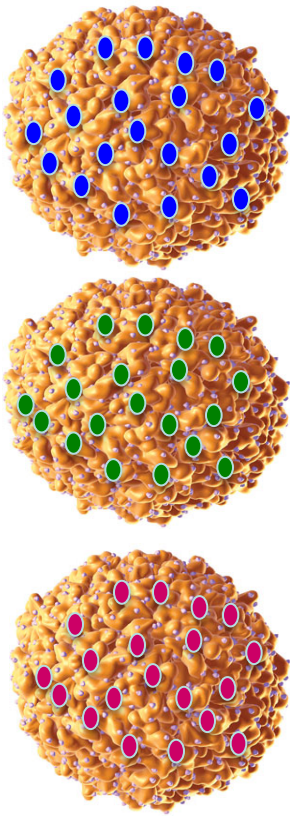
Antigen (capsomer/protein/peptide)
(encapsulation/adsorption/ chemical linking)

Polymer/ Immunomodulator (poly(I:C)

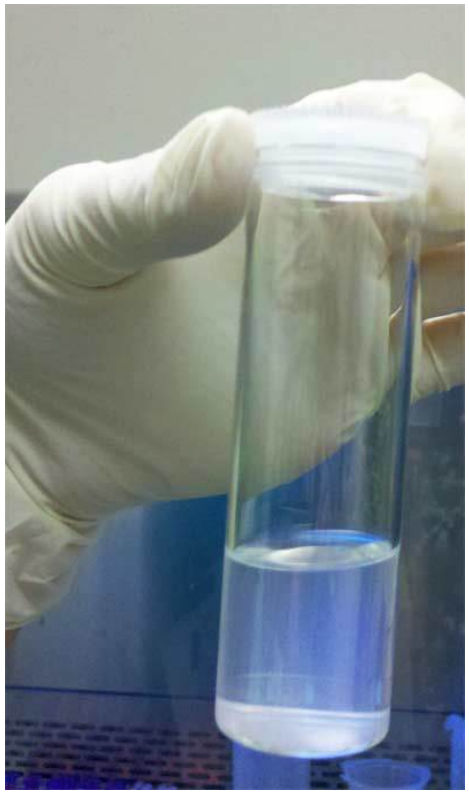
Oily core (Imiquimod)

S. Vicente et al. JCR, 2014

A novel HIV vaccine: packaging of 12 antigen peptides into nanoparticles



…12 PCS peptides



A cocktail of 12 nanopackaged peptides

J. C. Pinto, Collaboration with University of Manitoba

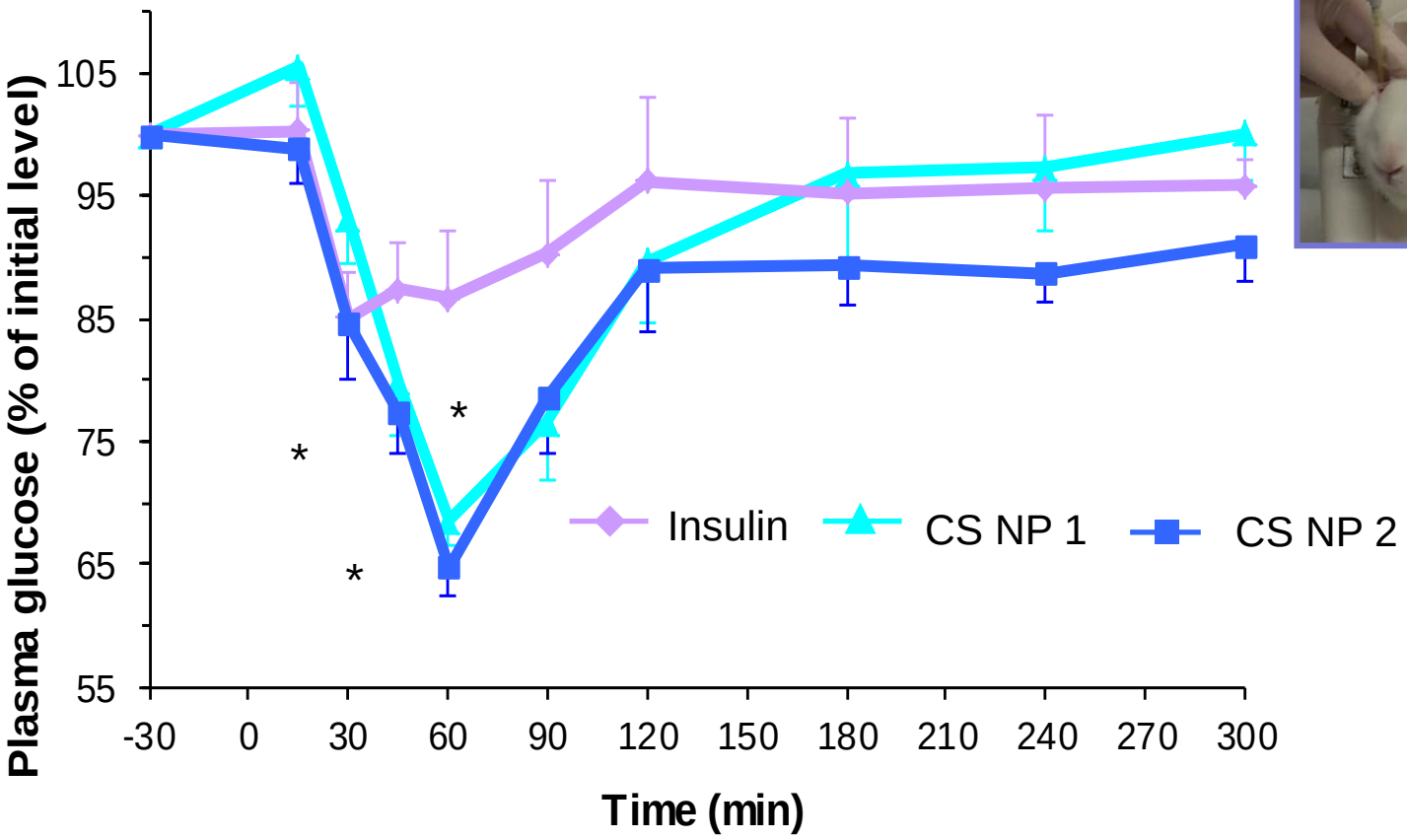
NASAL NANOPACKAGED SIV PEPTIDE ANTIGENS

SIV challenges

INN

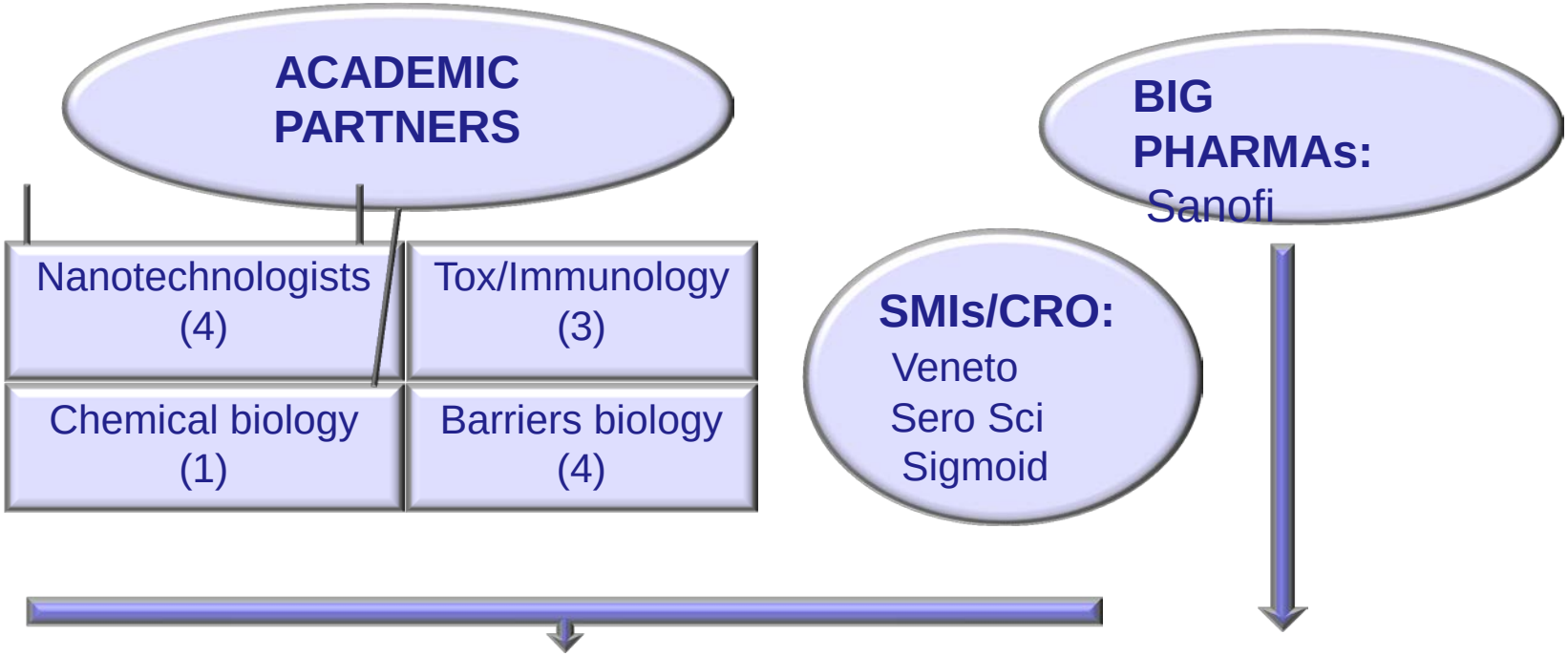
Collaboration with University of Manitoba

CHITOSAN-BASED NANOPARTICLES FOR NASAL INSULIN DELIVERY



Teijeiro-Osorio et al. *Biomacromolecules* 10, 243 (2009)

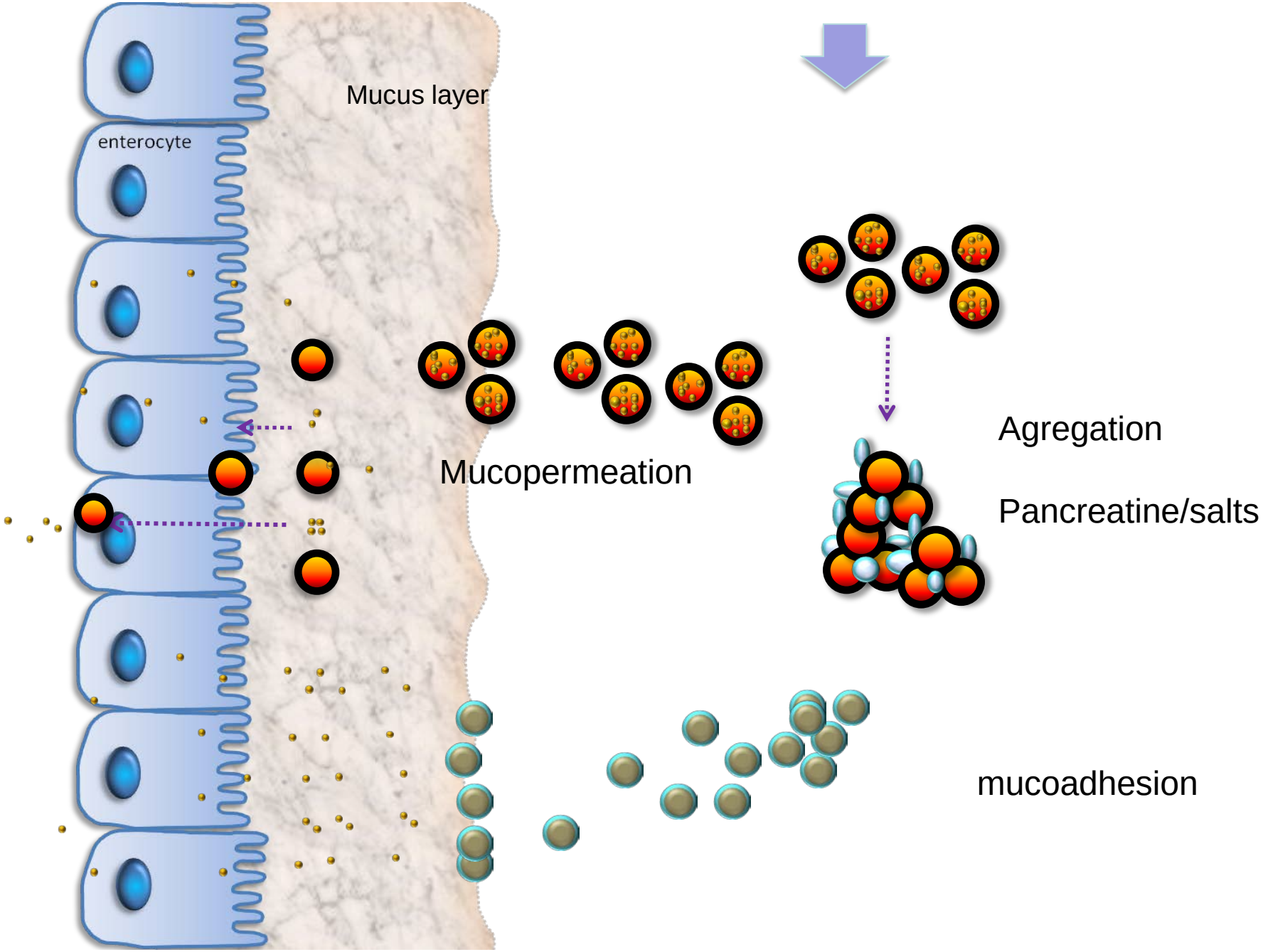
CHITOSAN-BASED NANOPARTICLES FOR ORAL INSULIN DELIVERY



Nanocarriers design, development and assessment of formulations

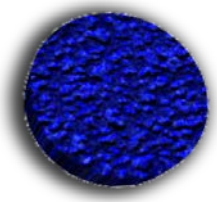
Peptides
Preclinical evaluation

www.TRANS-INT.EU


Mucus layer
enterocyte
Mucopermeation
Agregation
Pancreatine/salts
mucoadhesion

TRANS INT

Nanoparticle



Nanocapsule

Micelle

Easy to scale-up, mild technologies!!!

More than 1,000 prototypes

4 peptides

12

Mechanistic issues

PK/PD analysis

FINAL DOSAGE FORM

MULTI-TARGET ONCOLOGICAL THERAPIES

Passive/Active targeting: THE TARGET CELLs

QUIMIOTHERAPY

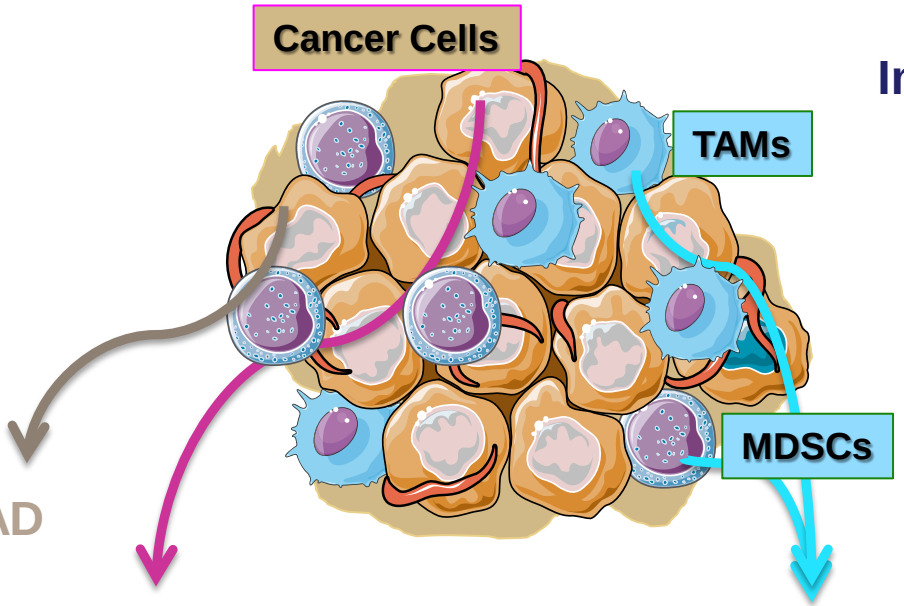
Cytotoxic drugs

IMMUNOTHERAPY

mAb

siRNA/miRNA

Immuno-modulators



CELL DEAD

IMMUNOGENIC CELL DEAD

IMMUNOACTIVATION

MULTI-LAYER NANOCAPSULES: MULTITARGET ONCOLOGICAL THERAPIES

THE « LYMPHOTARG » EUROPEAN CONSORTIUM

THE « NICHE » EUROPEAN CONSORTIUM

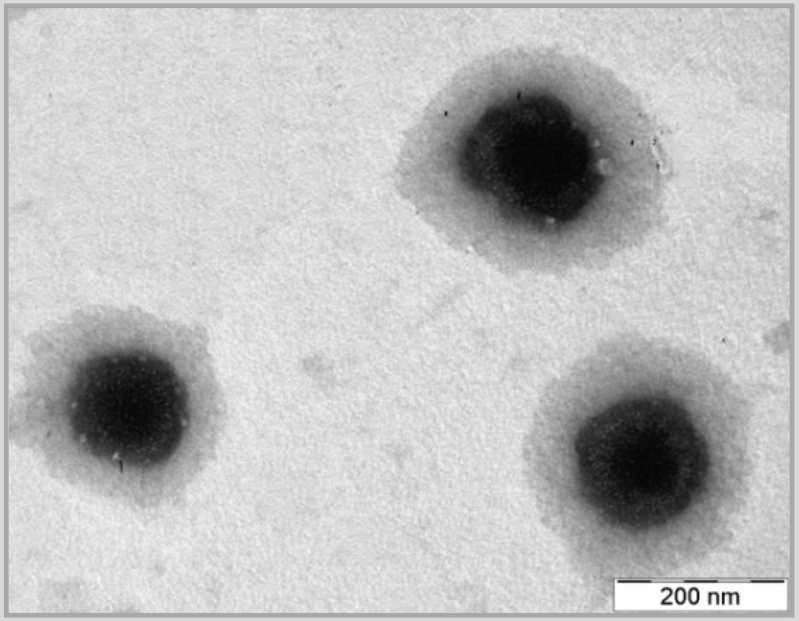
THE WORLDWIDE CANCER RESEARCH CONSORTIUM

Bioactive molecules:

Cytotoxic drugs: Plitidepsin
Docetaxel
Curcumine
Gemcitabine
mAb

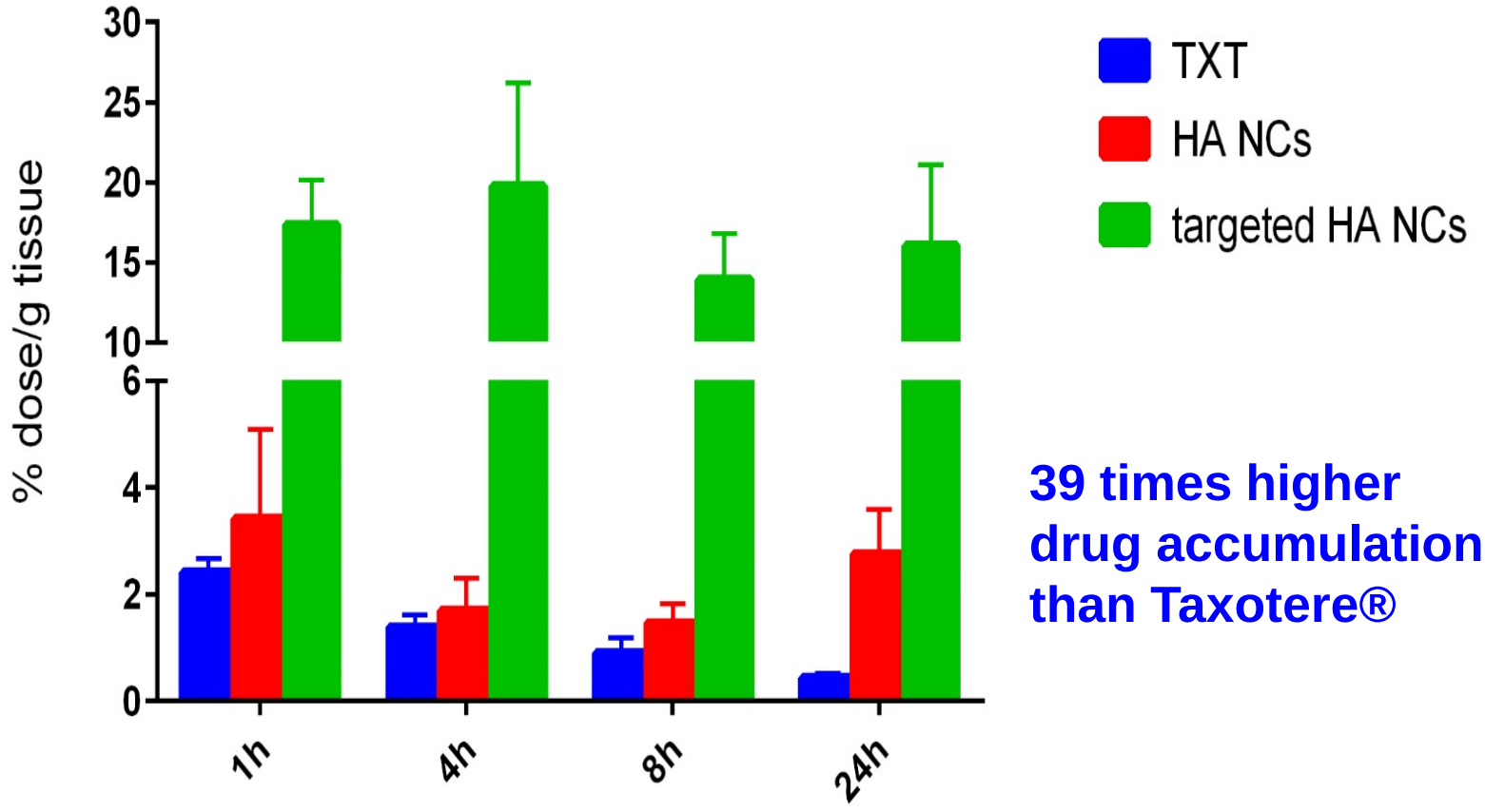
Immunomodulators: Imiquimod
Poly(I:C)

Polynucleotides: miRNA/siRNA



PK analysis: Nanocapsules improve Docetaxel tumour accumulation, compared to Taxotere®,

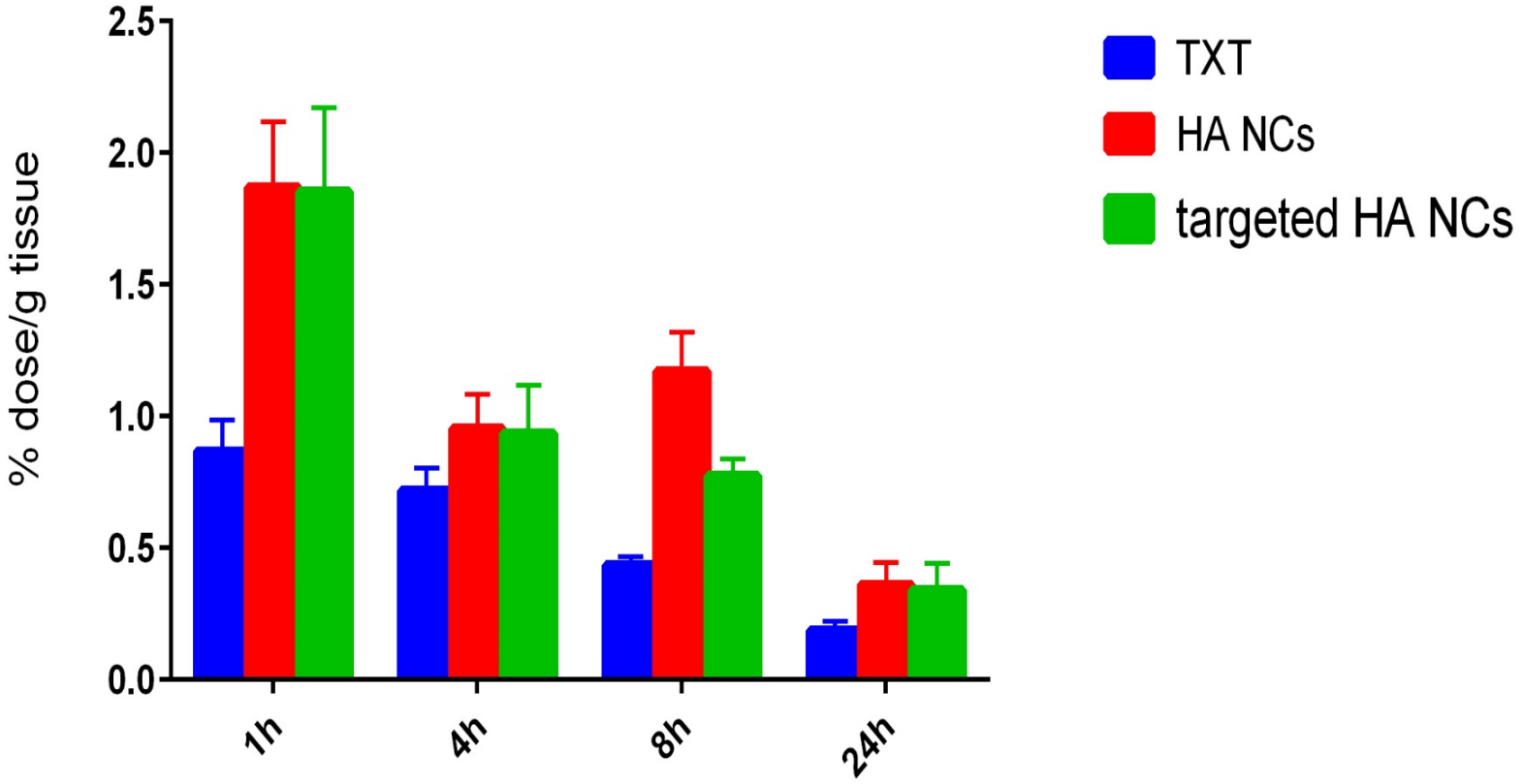
(Orthotopic lung cancer model)



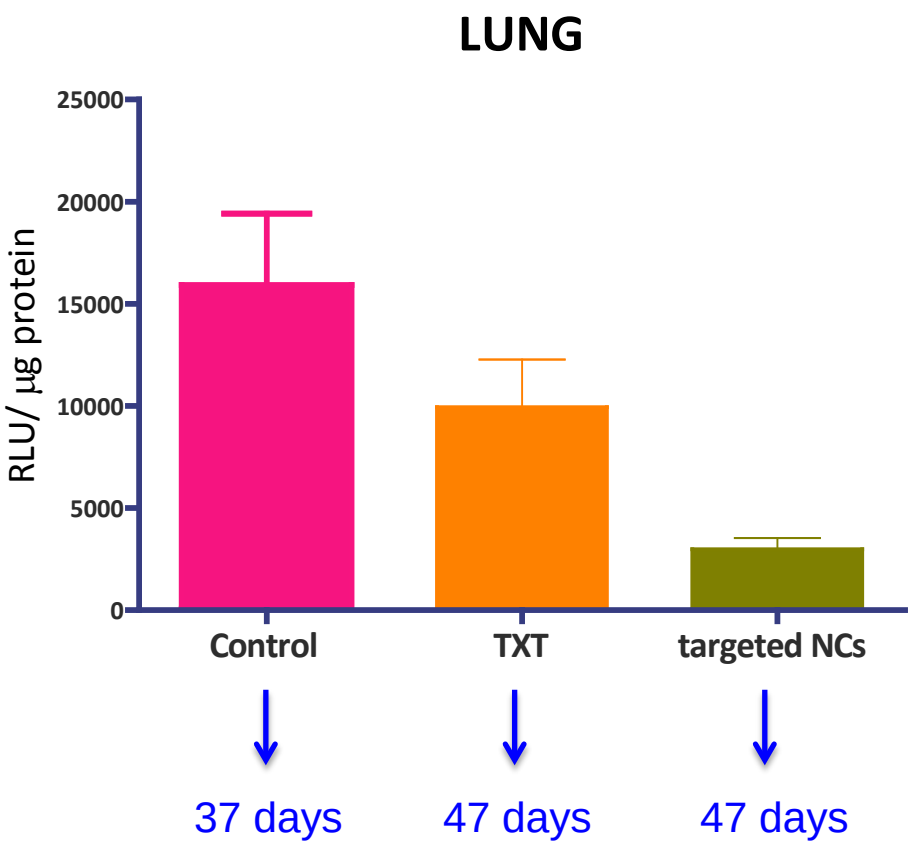
39 times higher drug accumulation than Taxotere®

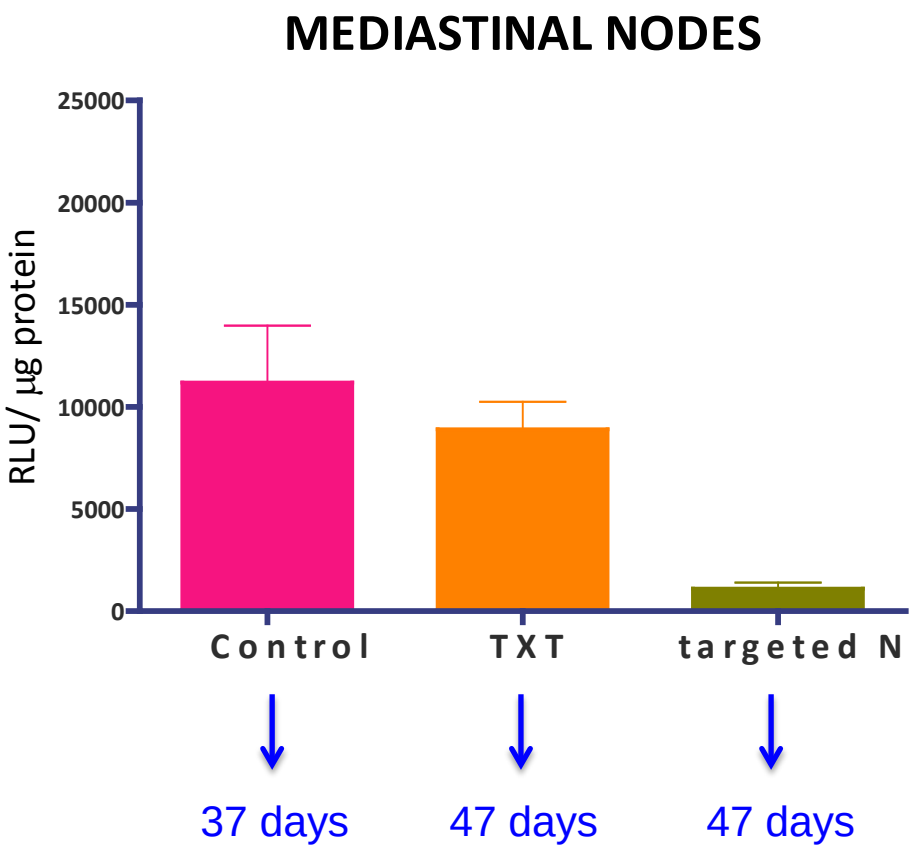
Nanocapsules increases docetaxel lymphatics accumulation, compared to Taxotere®

(Orthotopic lung cancer model)

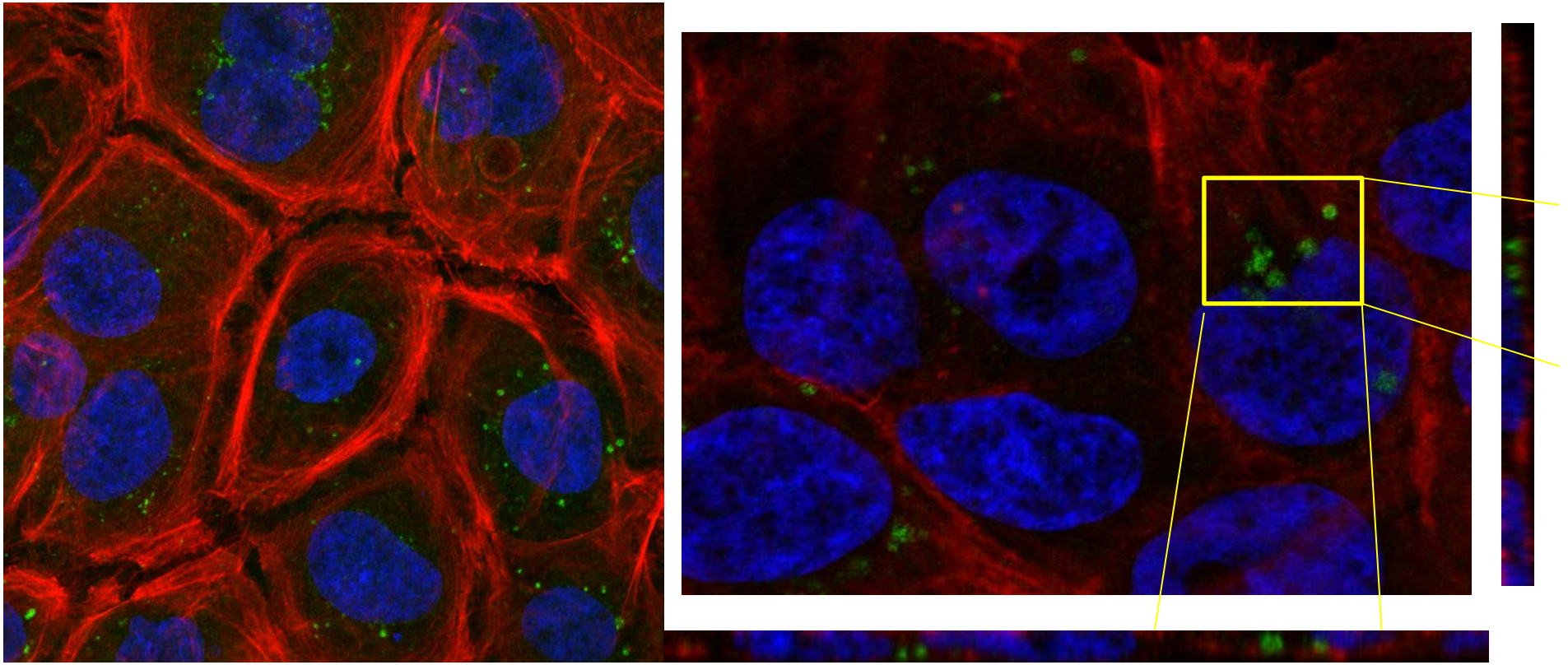


Docetaxel-loaded Targeted HA Nanocapsules: the only treatment capable of reducing metastasis





Internalization of mAb-loaded nanoparticles



BLUE: DAPI RED: FALOIDIN GREEN: MONOCLONAL ANTIBODY

Collaboration with Ana Cadete, Dolores Torres and Gema Moreno

THE FUTURE

- Advances in material sciences and engineering
- Advances in pharmaceutical technology
- Advances in cell and molecular biology

Listening to industry

Listening to clinicians

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SCHOOL OF PHARMACY

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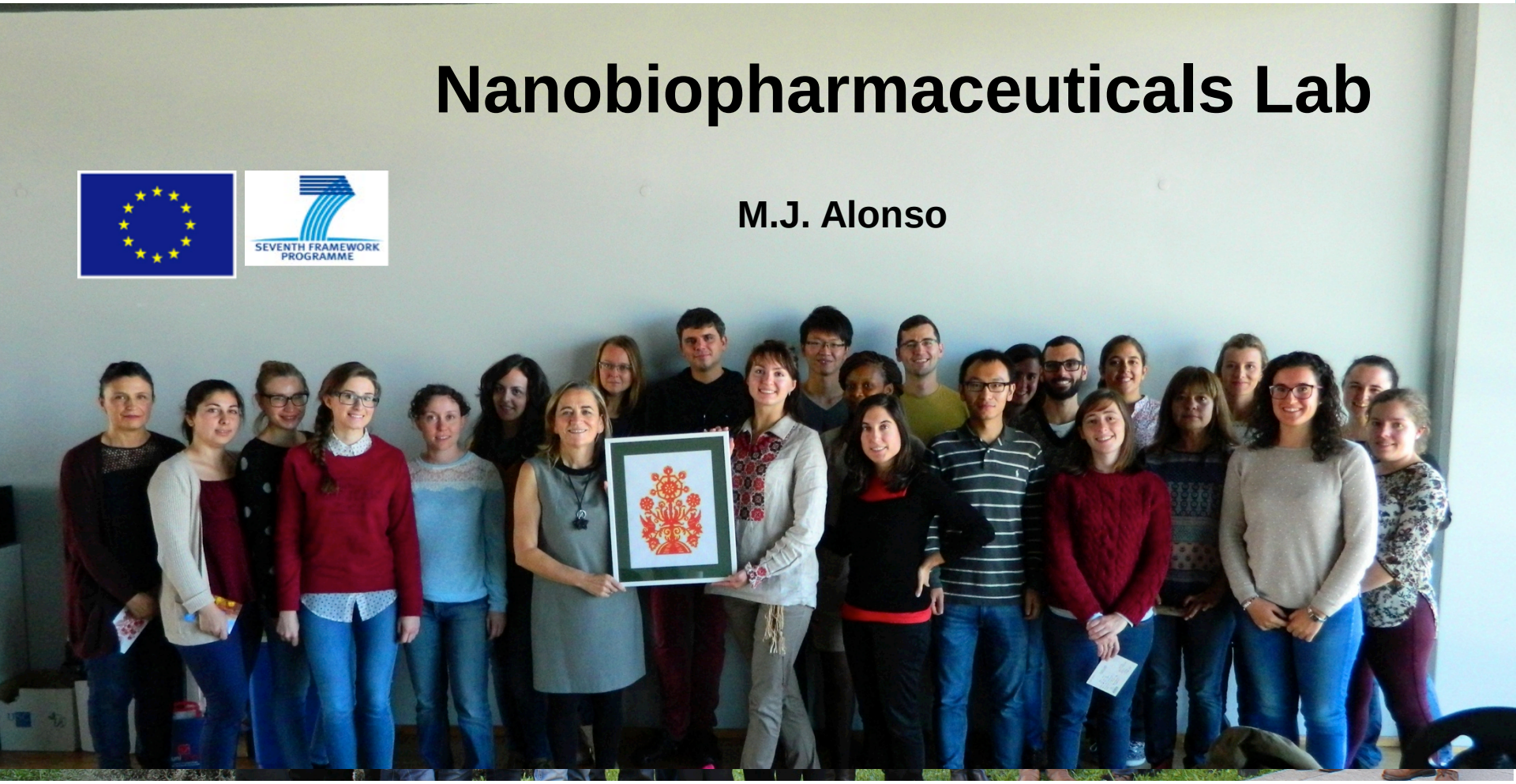
Nanobiopharmaceuticals Lab

SEVENTH FRAMEWORK PROGRAMME

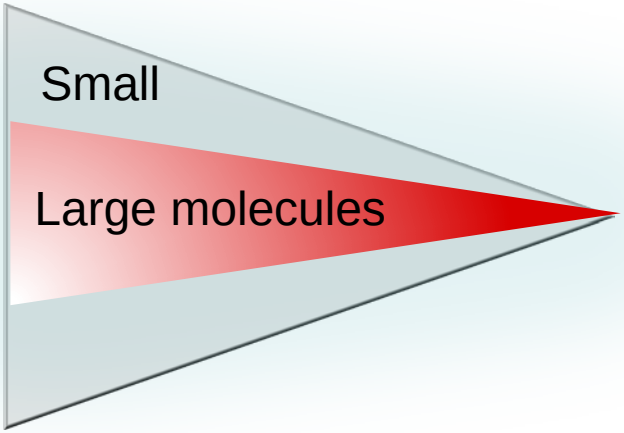
M.J. Alonso



"Bill & Melinda Gates Foundation", National Institutes of Health, European Commission, Ministerio de Economía y Competividad, Xunta de Galicia

THERAPEUTIC POTENTIAL OF PEPTIDE DRUGS AND ANTIGENS

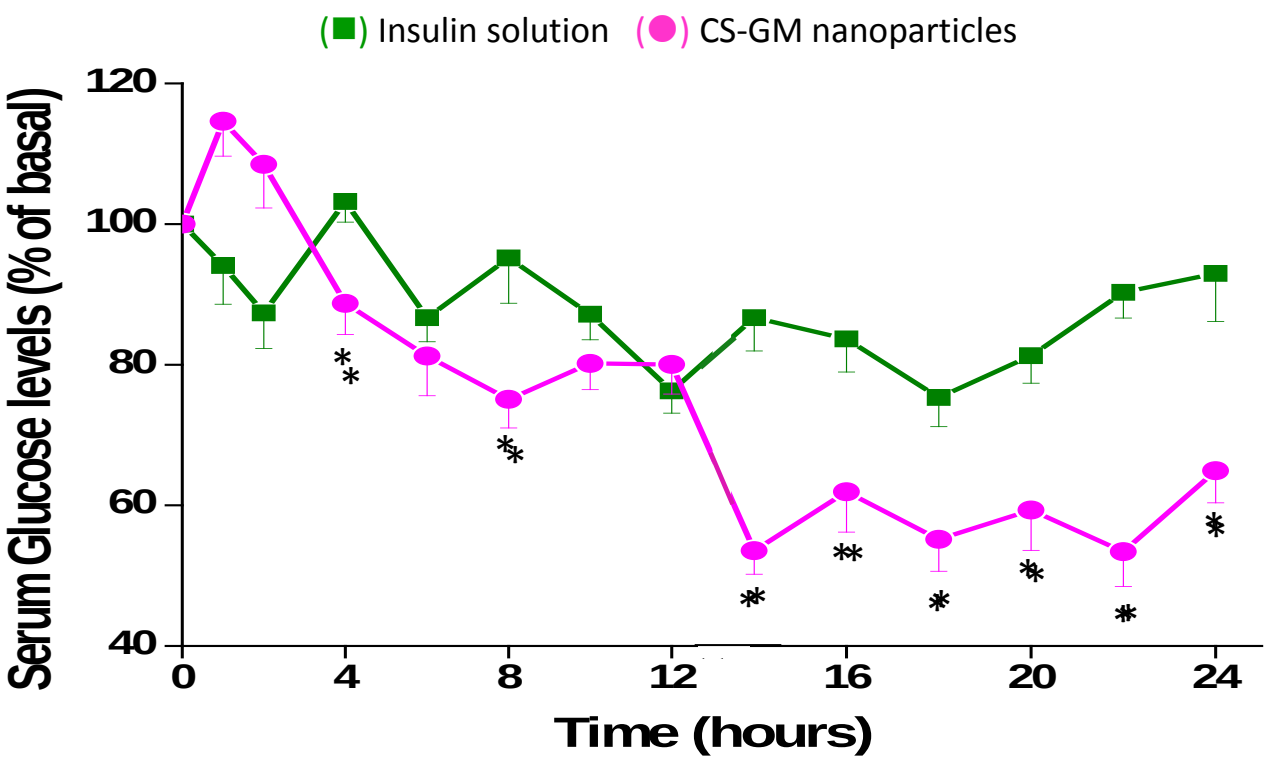
	Preclinical	Phase I	Phase II	Phase III
Small molecules	**2%**	**4%**	**10%**	**50%**
Large molecules	**10%**	**15%**	**25%**	**60%**

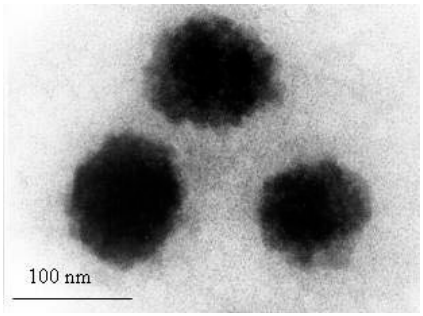


10 times higher success of large molecules!

Hay M. et al.: Nat. Biotech. 32, 40-51, 2014

ORAL INSULIN DELIVERY





Maria Alonso et al. (non published results)

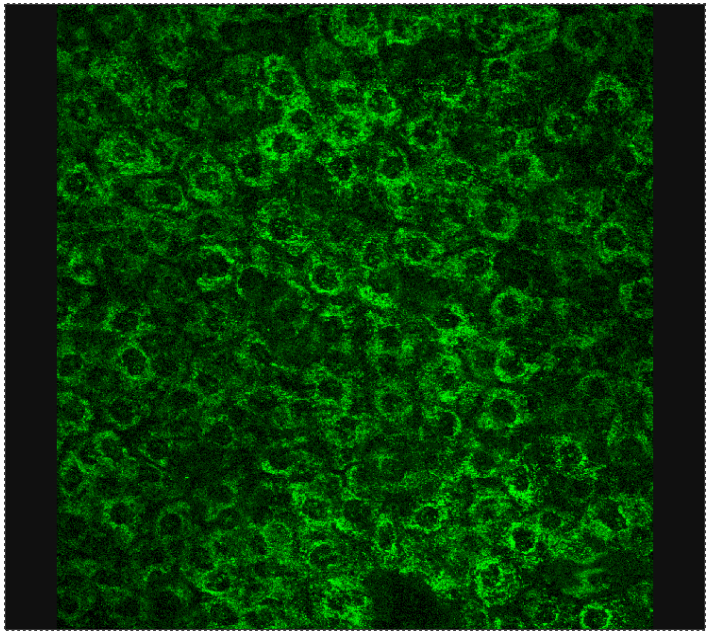
KEY ACHIVEMENTS: APPLICATIONS

OCULAR DRUG/GENE DELIVERY

1. To facilitate the penetration of complex drugs across the cornea

2. To target and deliver drugs to the back of the eye

Peptides, proteins, nucleic acids



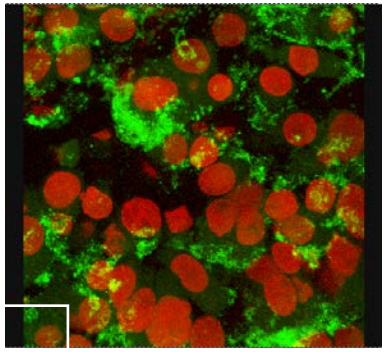
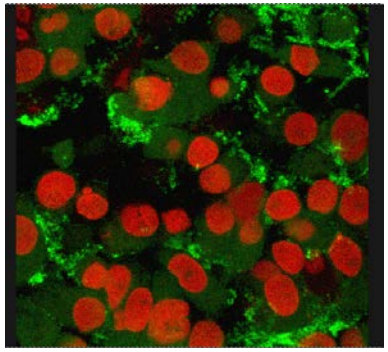
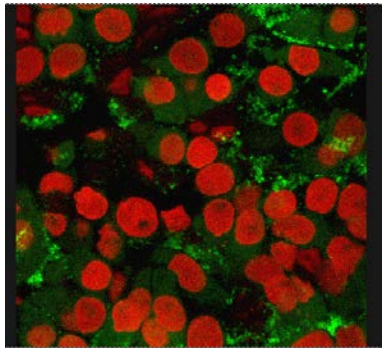
Cornea transfected for 5 days →

Colaboration with C. Pastor, M. Calonge, J. Merayo

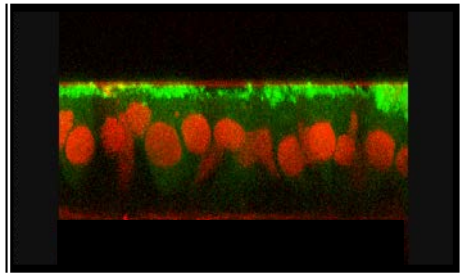
NASAL PEPTIDE DELIVERY

Do the nanoparticles enter epithelia?

Calu-3 differentiated cells:

	Epithelium surface	5 μm depth	10 μm depth
CS/**SBE-β-CD** nanoparticles			

y-sections



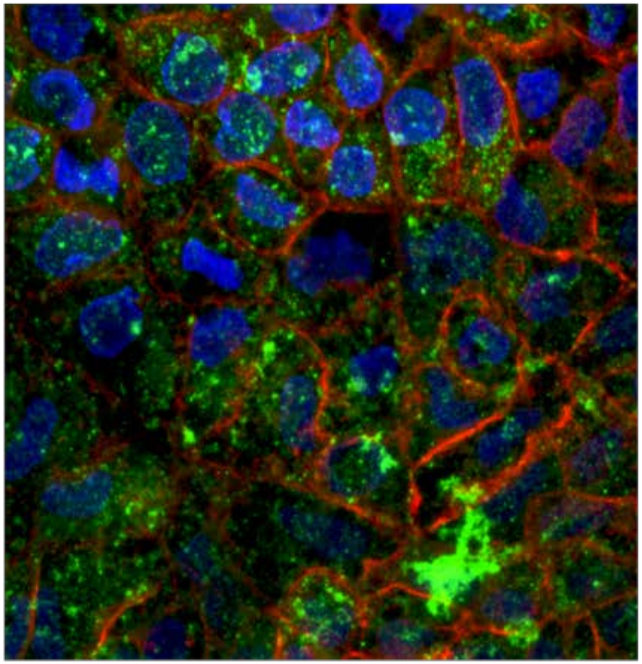
z-section

ORAL PEPTIDE/PROTEIN DELIVERY

Do the nanoparticles enter epithelia?

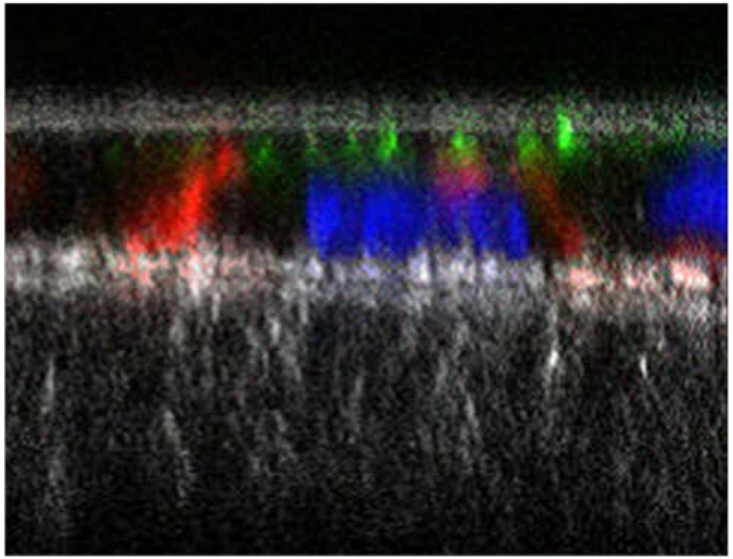
Study of CS Nanocapsules in Caco-2 cells

X-y cross section



X-z cross section

Apical side



Basolateral side

44 marketed Nano-delivery products

Product	Generic	Formulation	Indication	Manufacturer
Abraxane	Paclitaxel	Polymeric nanoparticles	Cancer chemotherapy	Celgene
Abelcet	Amphotericin B	Liposomal formulation	Fungal infections	Elan/Alkermes, Enzon, Cephalon
Adagen	Adenosine deaminase	PEGylation	Enzyme replacement therapy	Enzon, Sigma-Tau
AmBisome	Amphotericin B	Liposomal Formulation	Oral and perioral infections	Astellas/Gilead Sciences
Amphotec	Amphotericin B	Liposomal Formula	Oral and perioral	Three Rivers aceuticals/ALZA
Avinza	Morphine sulphate	nanocry formulat		lkermes, Pfizer
Copaxone	Glatiramer acetate	Copolyn acid, lal and l-lys		Pharmaceuticals
Curosurf	Poractant alfa	Liposom		
DaunoXome	Daunorubicin	PEGylat Formula		
DepoCyt	Cytarabine	Sustaine Liposom		
Depodur	Morphine sulphate	Liposom		
Diprivan	Propofol	Liposom		
Doxil/CaelyX	Doxorubicin	PEGylated liposome Formulation	Cancer chemotherapy	
Elestrin	Elestrin Estradiol gel	Phosphate nanoparticles	Menopausal symptoms	
Elyzol	Metronidazole	Dental gel	Parodontitis Camuru	
Emend	Aprepitant	Nanocrystal Formulation	Anti-emetic	
Epaxal	Hepatitis A vaccine	Virosome technology	Prevention of Hepatitis A infection	
Episil	Bioadhesive barrier	Fluidcrystal	Oral pain	
Estrasorb	Estradiol gel	Micellar Nanoparticles	Menopausal symptoms	
Focalin XR	Dexmethylphenidate hcl	Nanocrystals	ADHD	
Fosrenol	Lanthanum carbonate	Inorganic Nanoparticles	End-stage renal disease	Shire
Genexal PM	Paclitaxel	Polymeric micelles	Cancers	Samyang

Product	Generic	Formulation	Indication	Manufacturer
Indaflex	Indomethacin	Solid/lipid nanoparticles	Osteoarthritis	AlphaRx
Inflexal V	Subunit influenza vaccine	Virosome	Influenza prophylaxis	Crucell
Invega Sustenna	Paliperidone	Nanocrystal	Antipsychotic	Janssen
Macugen	Pegaptanib	Pegylated anti-vegf aptamer	Age-related macular degeneration	OSI Pharmaceuticals/ Pfizer
Myocet	Doxorubicin citrate complex	Liposome encapsulated	Cancer chemotherapy	Cephalon/Zeneus Pharma/ Sopherion Therapeutics
Megace ES	Megestrol acet			Elan/Alkermes+Par+Bristol-Myers Squibb
			xers	Access Pharma
				Elan/Alkermes
			py	Dabur Pharma
				Amgen
				Enzon/Schering-Plough
			s C	Roche/Nektar
				Schering-Plough
				Wyeth Élan/Alkermes
			in	Genzyme
		quid		Xerostomia
		er protein conjugate		Acromegaly
		tile release crystal formulation		ADHD
		ome encapsulated		Neonatal respiratory distress
		crystal formulation		Lipid reduction
		crystal formulation		Abbott Élan/Alkermes
				SkyePharma/ First Horizon Pharmaceuticals/Sciele Pharma
Verelan/ Verelan PM	Verapamil	Elan's SODAS Multiparticulate technology	Hypertension	Elan/Alkermes Schwarz

Source BCC Research

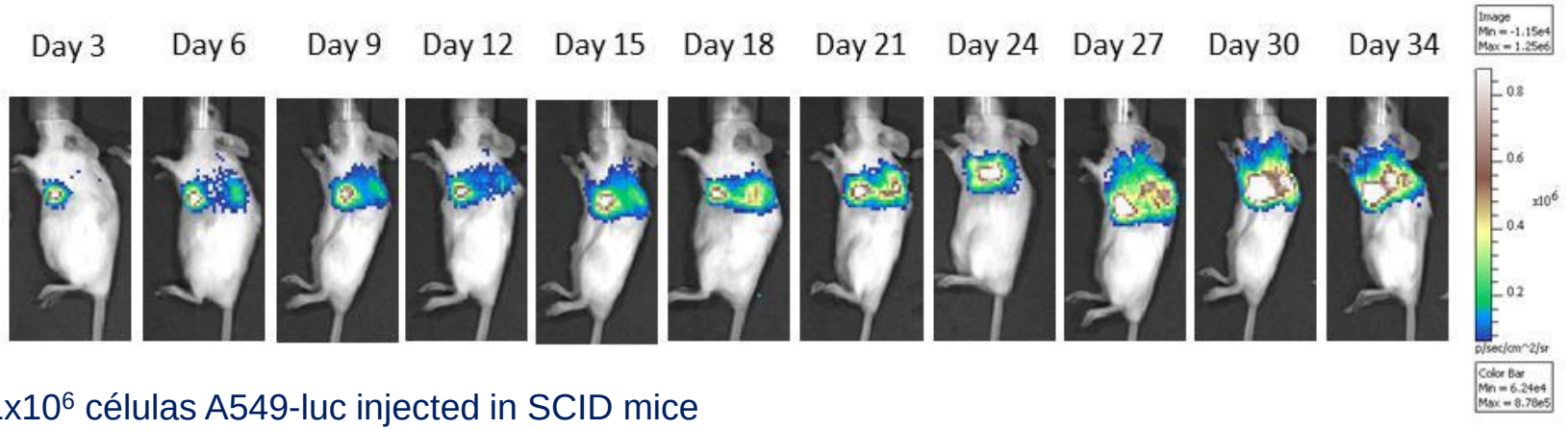
>70 Nanomedical Products in Clinical trials

Cardiovascular Diseases	Endocrinology	Hematology	Immunology Infectious Diseases	Musculoskeletal	Neurology	Oncology
NCE [redacted]; AstraZeneca; For the reduction of thrombotic events in patients with acute coronary syndrome, Approved July 2011	NCE [redacted]; Novartis; For the treatment of advanced pancreatic neuroendocrine tumors, Approved May 2011	NANO [redacted]; Seattle Genetics; For the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma, Approved August 2011	NCE [redacted]; Novartis; For the treatment of airflow obstruction resulting from chronic obstructive pulmonary disease, Approved July 2011	AB [redacted]; Genentech; For the treatment of systemic juvenile idiopathic arthritis, Approved April 2011	NCE [redacted]; ProStrakan; For the treatment of breakthrough cancer pain in opioid-tolerant patients, Approved January 2011	NCE [redacted]; ProStrakan; For the treatment of breakthrough cancer pain in opioid-tolerant patients, Approved January 2011
NCE [redacted]; Takeda; For the treatment of hypertension, Approved February 2011	NCE [redacted]; Merck; For the treatment of type II diabetes, Approved October 2011	NCE [redacted]; Apotex; For the treatment of transfusional iron overload due to thalassemia, Approved October 2011	AB [redacted]; Human Genome Sciences; For the treatment of systemic lupus erythematosus, Approved March 2011	NCE [redacted]; Horizon Pharma; For the relief of rheumatoid arthritis and osteoarthritis and prevention of gastric ulcers, Approved April 2011	NCE [redacted]; Abbott; For the treatment of postherpetic neuralgia, Approved February 2011	NANO [redacted]; Seattle Genetics; For the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma, Approved August 2011
NCE [redacted]; Bayer; For the prophylaxis of deep vein thrombosis during knee or hip replacement surgery, Approved July 2011	NCE [redacted]; Pfizer ; For the treatment of pancreatic neuroendocrine tumors, Approved May 2011	AB [redacted]; Alexion; For the treatment of atypical hemolytic uremic syndrome, Approved September 2011	NCE [redacted]; Gilead; For the treatment of HIV-1 in treatment-naive adults, Approved August of 2011	**Nephrology Urology**	NCE [redacted]; GlaxoSmithKline; For the treatment of restless legs syndrome, Approved April 2011	NCE [redacted]; Novartis; For the treatment of advanced pancreatic neuroendocrine tumors, Approved May 2011
Dermatology Plastic Surgery	NCE [redacted]; Boehringer Ingelheim; For the treatment of type II diabetes, Approved May 2011	NCE [redacted]; Bayer; For the prophylaxis of deep vein thrombosis during knee or hip replacement surgery, Approved July 2011	NCE [redacted]; Forest Pharmaceuticals; For the treatment of chronic obstructive pulmonary disease, Approved February 2011	NBE [redacted]; Bristol-Myers Squibb; For the prevention of organ rejection following kidney transplant, Approved June 2011	NCE [redacted]; Archimedes; For the management of breakthrough cancer pain, Approved June 2011	NCE [redacted]; Archimedes; For the management of breakthrough cancer pain, Approved June 2011
peptide [redacted]; Shire; For the treatment of acute attacks of hereditary angioedema, Approved August of 2011	**Gastroenterology**	**Otolaryngology**	NCE [redacted]; Optimer Pharmaceuticals; For the treatment of Clostridium difficile-associated diarrhea, Approved May 2011	AB [redacted]; Alexion; For the treatment of atypical hemolytic uremic syndrome, Approved September 2011	NCE [redacted]; Lundbeck; For the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome, Approved October 2011	NCE [redacted]; Pfizer; For the treatment of pancreatic neuroendocrine tumors, Approved May 2011
NCE [redacted]; Abbott; For the treatment of postherpetic neuralgia, Approved February 2011	NCE [redacted]; Novartis; For the treatment of advanced pancreatic neuroendocrine tumors, Approved May 2011	NCE [redacted]; Astra Zeneca; For the treatment of thyroid cancer, Approved April 2011	NCE [redacted]; Tibotec; For the treatment of HIV-1, Approved May 2011	**Pharmacology Toxicology**	NCE [redacted]; Pfizer; For the management of acute and chronic moderate to severe pain, Approved June 2011	NANO [redacted]; Merck; For the treatment of melanoma, Approved April 2011
CELL [redacted]; Fibrocell Science; For the improvement of nasolabial fold wrinkles in adults, Approved June 2011	NCE [redacted]; Optimer Pharmaceuticals; For the treatment of Clostridium difficile-associated diarrhea, Approved May 2011	**Pulmonary Respiratory Diseases**	Peptide [redacted]; Shire; For the treatment of acute attacks of hereditary angioedema, Approved August of 2011	NCE [redacted]; Pfizer; For the management of acute and chronic moderate to severe pain, Approved June 2011	NCE [redacted]; Valeant Pharmaceuticals; For the treatment of partial-onset seizures, Approved June 2011	NCE [redacted]; Astra Zeneca; For the treatment of thyroid cancer, Approved April 2011
NANO [redacted]; Merck; For the treatment of melanoma, Approved April 2011	NCE [redacted]; Horizon Pharma; For the relief of rheumatoid arthritis and osteoarthritis and prevention of gastric ulcers, Approved April 2011	NCE [redacted]; Novartis; For the treatment of airflow obstruction resulting from chronic obstructive pulmonary disease, Approved July 2011	NCE [redacted]; Abbott; For the treatment of postherpetic neuralgia, Approved February 2011	**Rheumatology**	NCE [redacted]; Clinical Data; For the treatment of major depressive disorder, Approved January 2011	NCE [redacted]; Pfizer; For the treatment of ALK+ non-small cell lung cancer, Approved August of 2011
antibody [redacted]; Bristol-Myers Squibb; For the treatment of metastatic melanoma, Approved March 2011	17 NCE [redacted]; Vertex; For the treatment of genotype 1 chronic hepatitis C, Approved May 2011	NCE [redacted]; Forest Pharmaceuticals; For the treatment of chronic obstructive pulmonary disease, Approved February 2011	NCE [redacted]; Vertex; For the treatment of genotype 1 chronic hepatitis C, Approved May 2011	AB [redacted]; Genentech; For the treatment of systemic juvenile idiopathic arthritis, Approved April 2011	**Pediatrics Neonatology**	AB [redacted]; Bristol-Myers Squibb; For the treatment of metastatic melanoma, Approved March 2011
NCE [redacted]; Roche; For the treatment of BRAF + melanoma, Approved August of 2011	NCE [redacted]; ProStrakan; For the treatment of chronic anal fissure, Approved June 2011	NCE [redacted]; Pfizer; For the treatment of ALK+ non-small cell lung cancer, Approved August of 2011	[redacted]; Bristol-Myers Squibb; For the prevention of organ rejection following kidney transplant, Approved June 2011	NCE [redacted]; Horizon Pharma; For the relief of rheumatoid arthritis and osteoarthritis and prevention of gastric ulcers, Approved April 2011	AB [redacted]; Genentech; For the treatment of systemic juvenile idiopathic arthritis, Approved April 2011	NCE [redacted]; Roche; For the treatment of BRAF + melanoma, Approved August of 2011
Obstetrics Gynecology	NCE [redacted]; Pfizer; For the treatment of pancreatic neuroendocrine tumors, Approved May 2011	**Pharmacology Toxicology**	NCE [redacted]; Merck; For the treatment of chronic hepatitis C genotype 1, Approved May 2011		NCE [redacted]; Forest Pharmaceuticals; For the treatment of chronic obstructive pulmonary disease, Approved February 2011	NCE [redacted]; Centocor Ortho Biotech; For the treatment of prostate cancer, Approved May 2011
NCE [redacted]; Hologic; For the prevention of risk of preterm birth, Approved February 2011	NCE [redacted]; Merck; For the treatment of chronic hepatitis C genotype 1, Approved May 2011	NCE [redacted]; Pfizer; For the management of acute and chronic moderate to severe pain, Approved June 2011			NCE [redacted]; Lundbeck; For the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome, Approved October 2011	

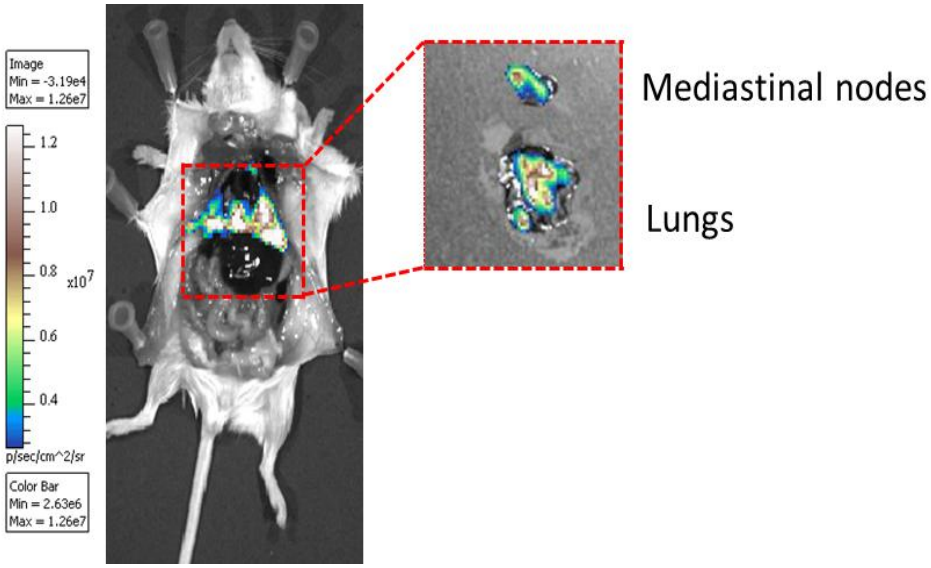
http://www.centerwatch.com/drug information/fda approvals/drug areas.aspx?mp=empty

Orthotopic methastatic lung cancer model

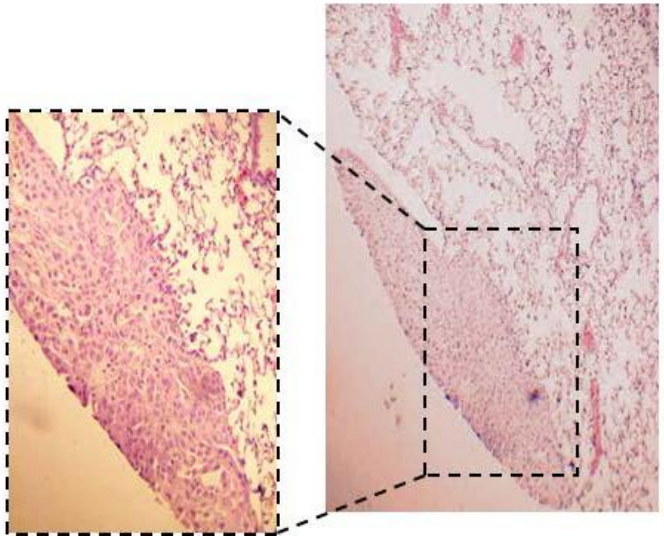
Intercostal space left lung



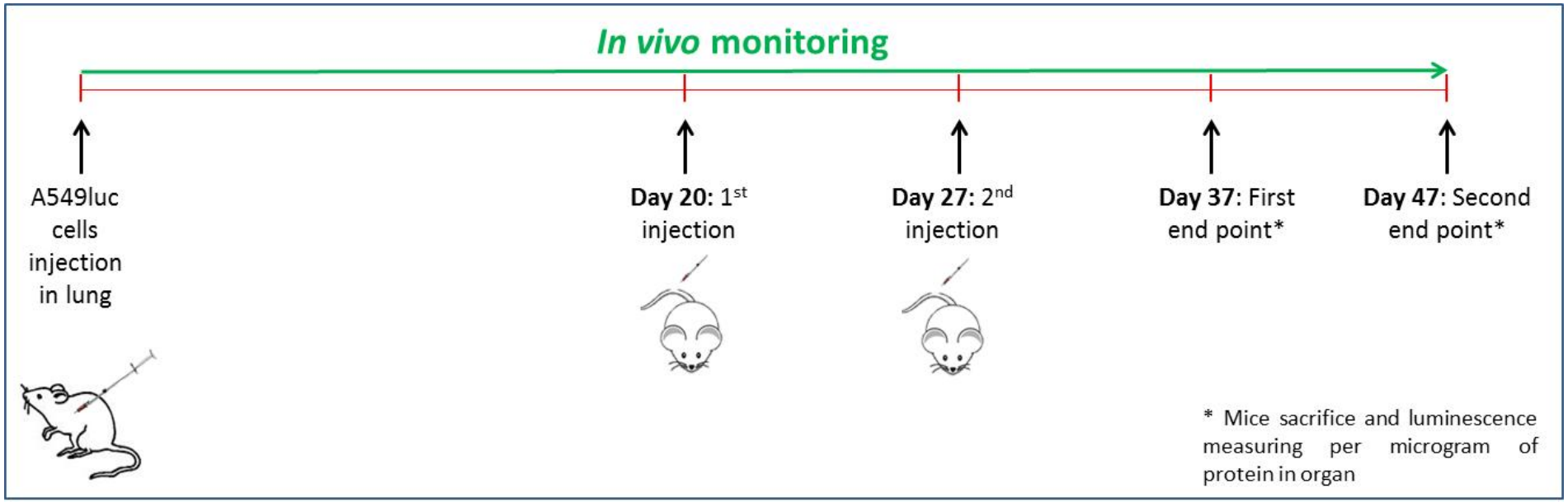
1x10^6 células A549-luc injected in SCID mice



H&E Orthotopic implants (24 days post-injection)



Antitumor efficacy in orthotopic methastatic lung cancer model

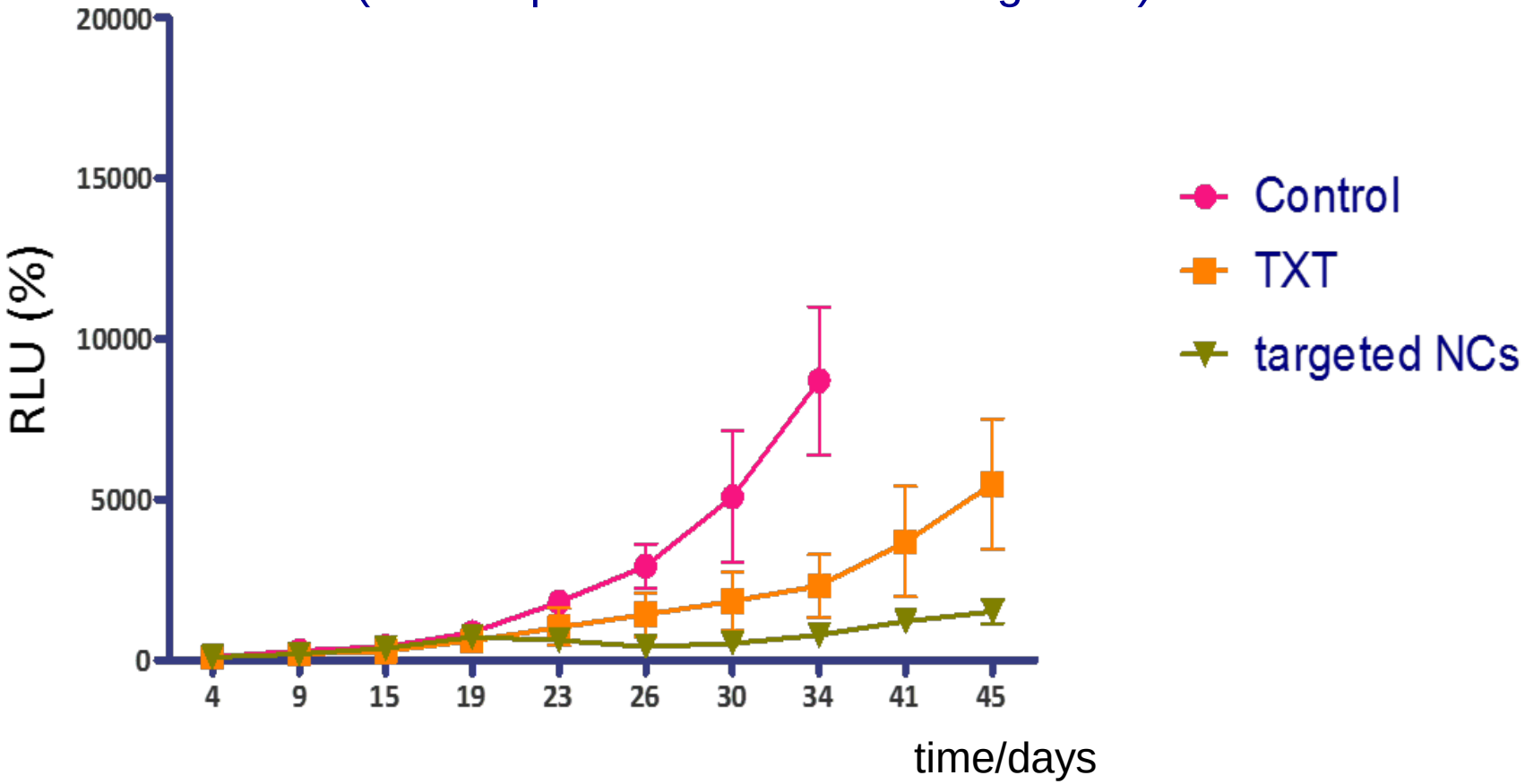


Experimental groups:
- 5 control mice without treatment
- 5 mice iv. Taxotere® 10 mg/kg
- 5 mice i.v. Taxotere® 20 mg/kg
- 5 mice i.v. NCs PGA-PEG DCX 10 mg/kg
- 5 mice i.v. NCs PGA-PEG DCX 20 mg/kg

E. Borrajo. colaboration with A. Vidal and M. Garcia-Fuentes

Antitumor efficacy in methastatic orthotopic lung cancer model

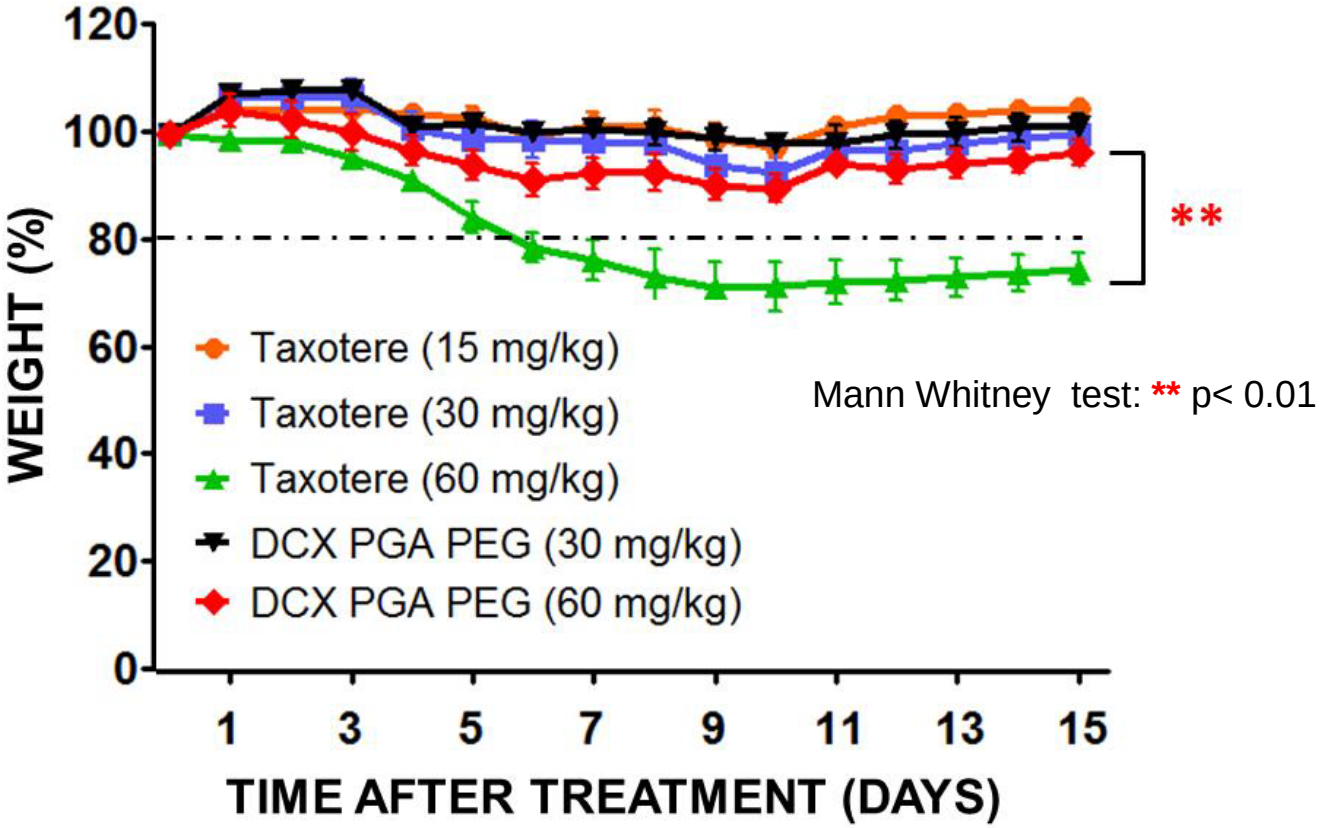
(Orthotopic A549-tumor bearing mice)



E. Borrajo. collaboration with A. Vidal and M. Garcia-Fuentes

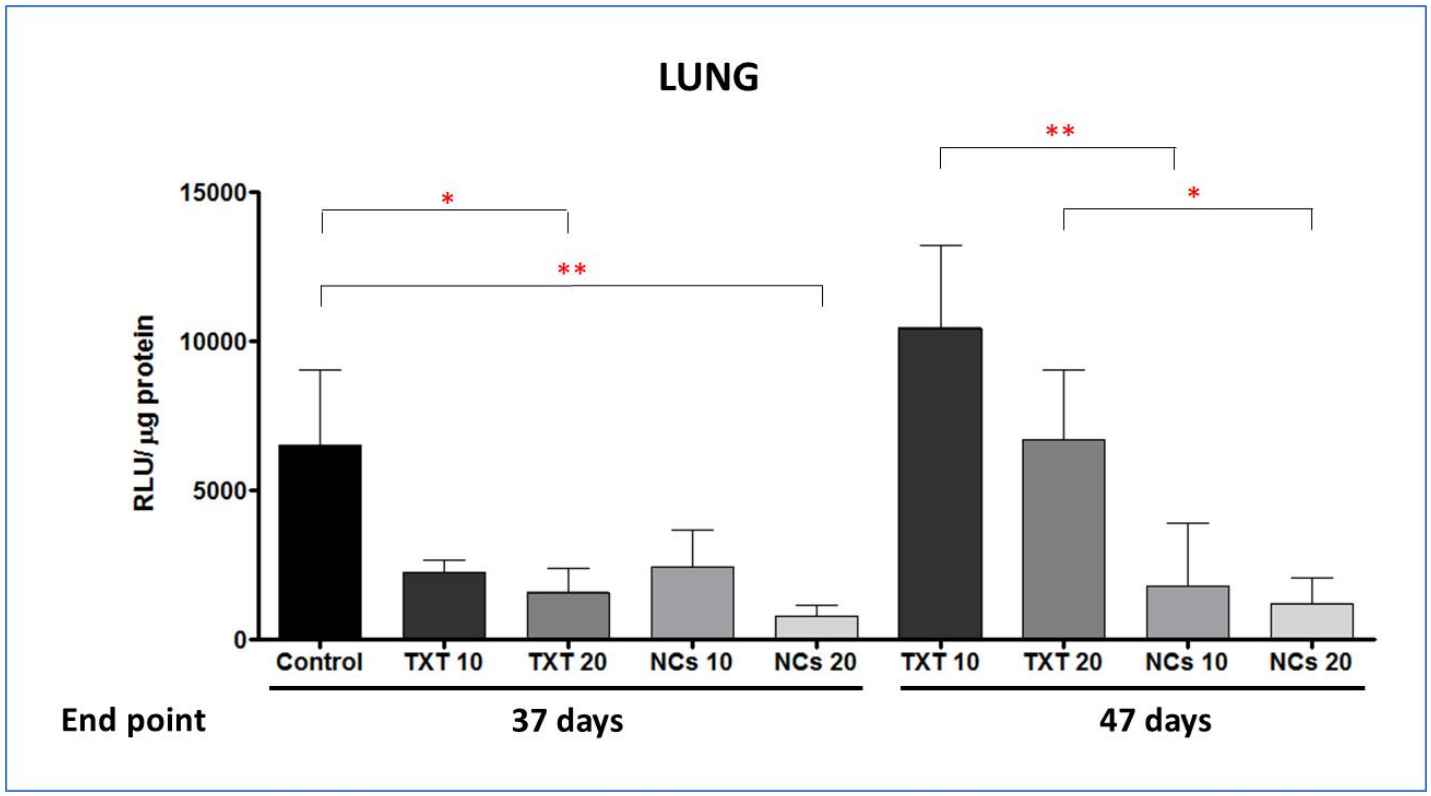
Docetaxel-loaded PGA-PEG Nanocapsules are less toxic than Taxotere®

(SCID non tumor-bearing mice)



E. Borrajo. colaboration with A. Vidal and M. Garcia-Fuentes

Docetaxel-loaded PGA-PEG Nanocapsules inhibit tumor growth as compared to Taxotere®



Mann Whitney test: * p< 0.05, ** p< 0.01

Measurement of luciferase activity

CONTROL

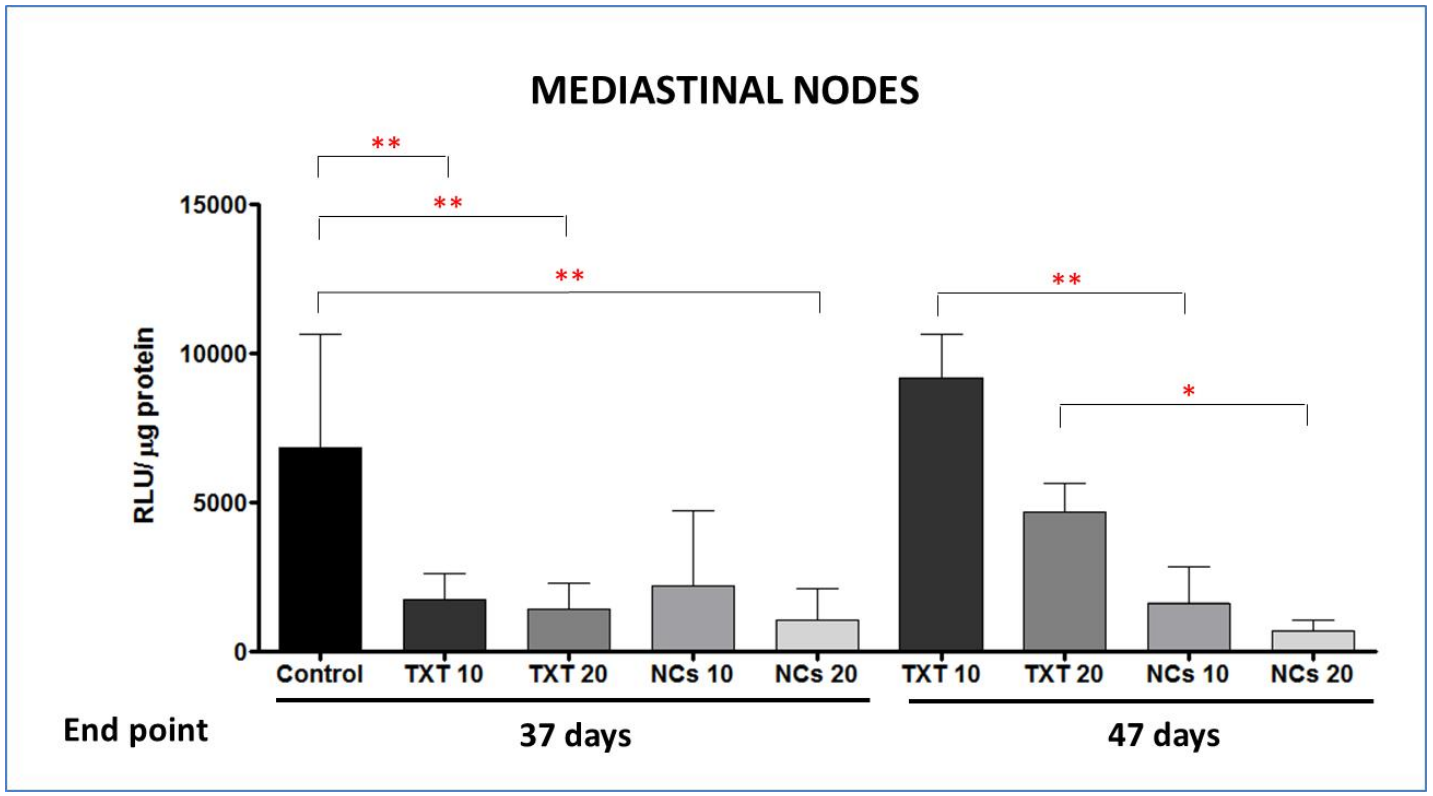
TAXOTERE 10 mg/kg

TAXOTERE 20 mg/kg

NCs PGA-PEG DCX 10 mg/kg

NCs PGA-PEG DCX 20 mg/kg

Docetaxel-loaded PGA-PEG Nanocapsules inhibit metastasis as compared to Taxotere®



Mann Whitney test: * p< 0.05, ** p< 0.01

CONTROL

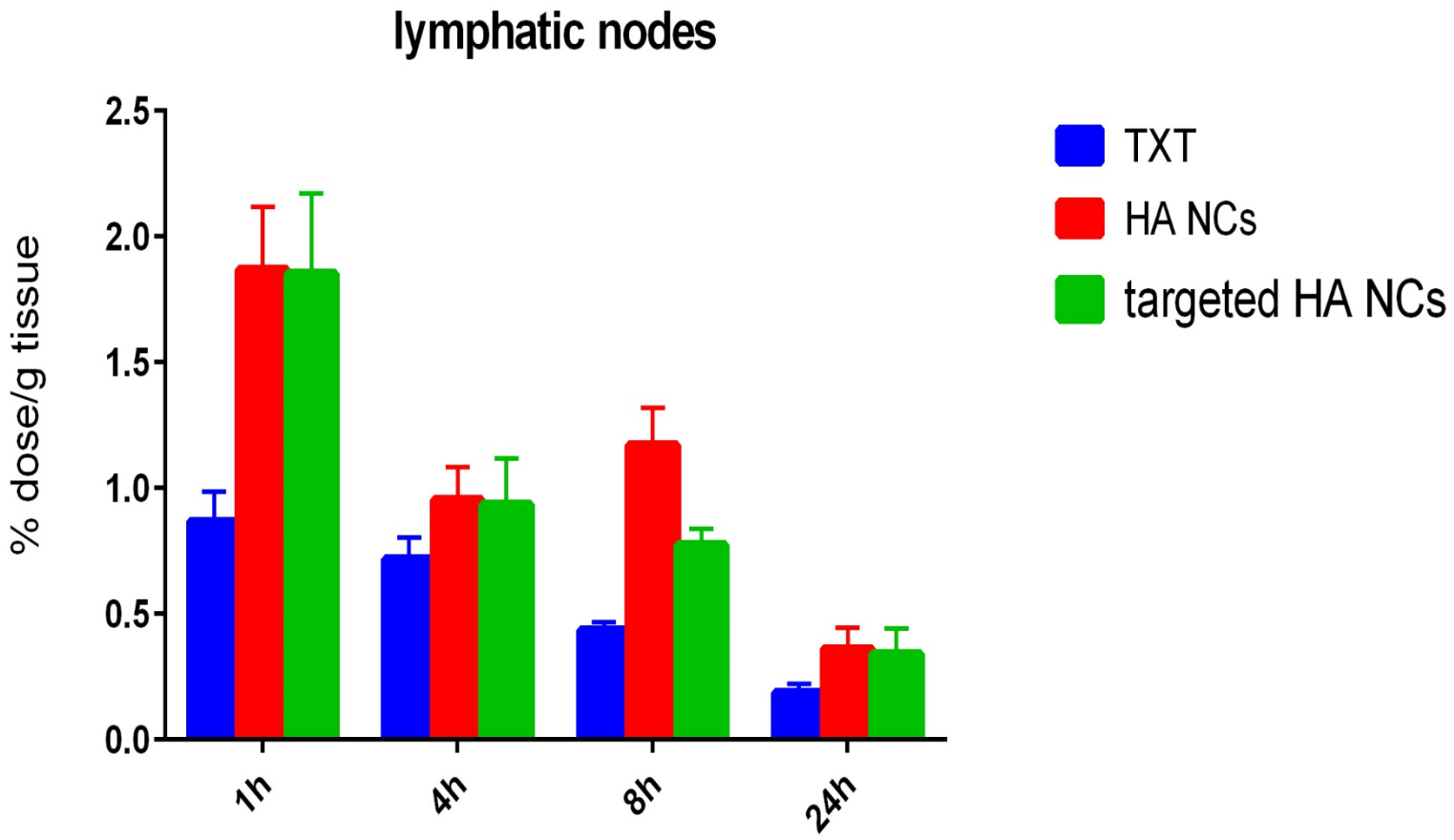
TAXOTERE 10 mg/kg

TAXOTERE 20 mg/kg

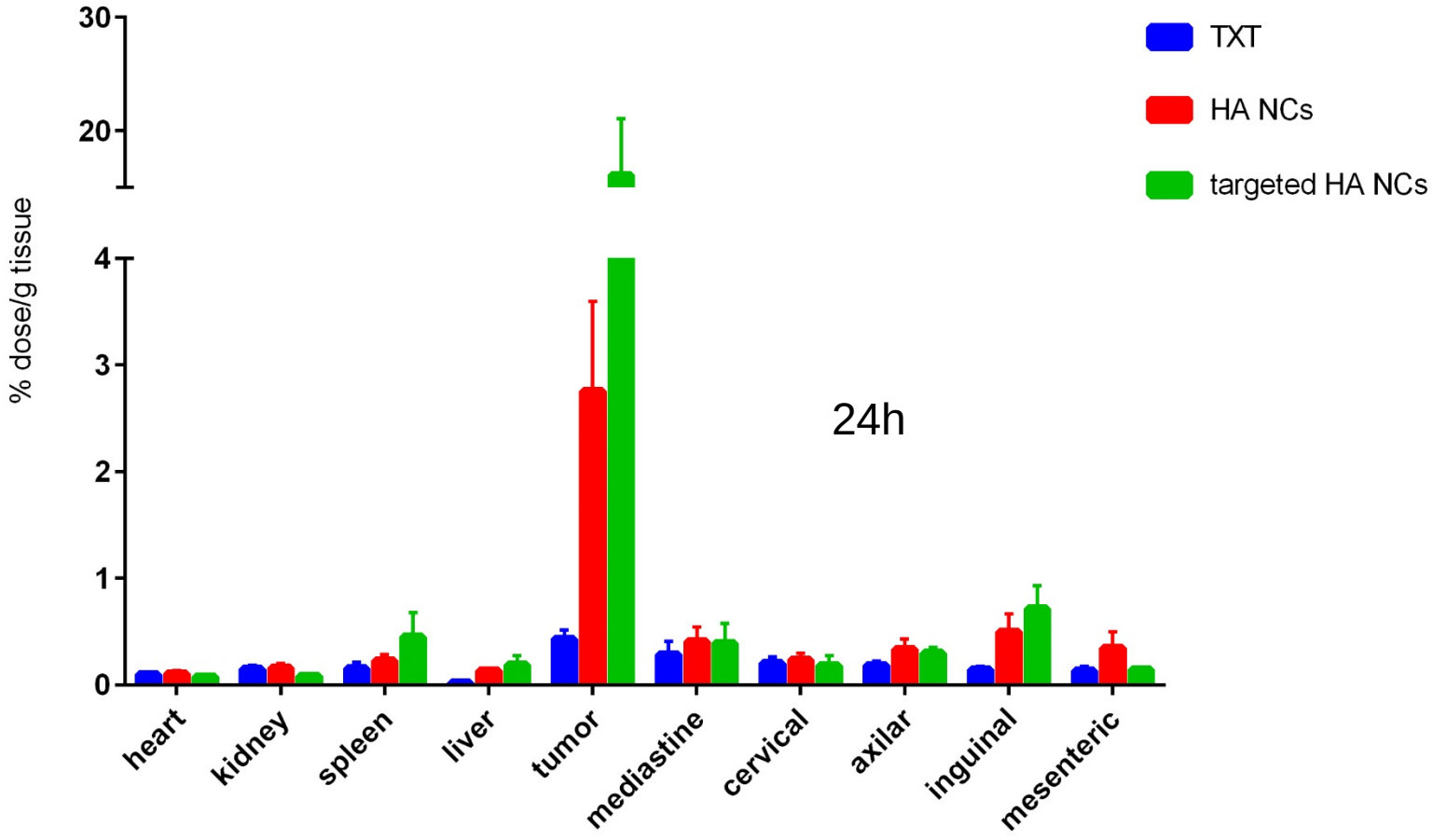
NCs PGA-PEG DCX 10 mg/kg

NCs PGA-PEG DCX 20 mg/kg

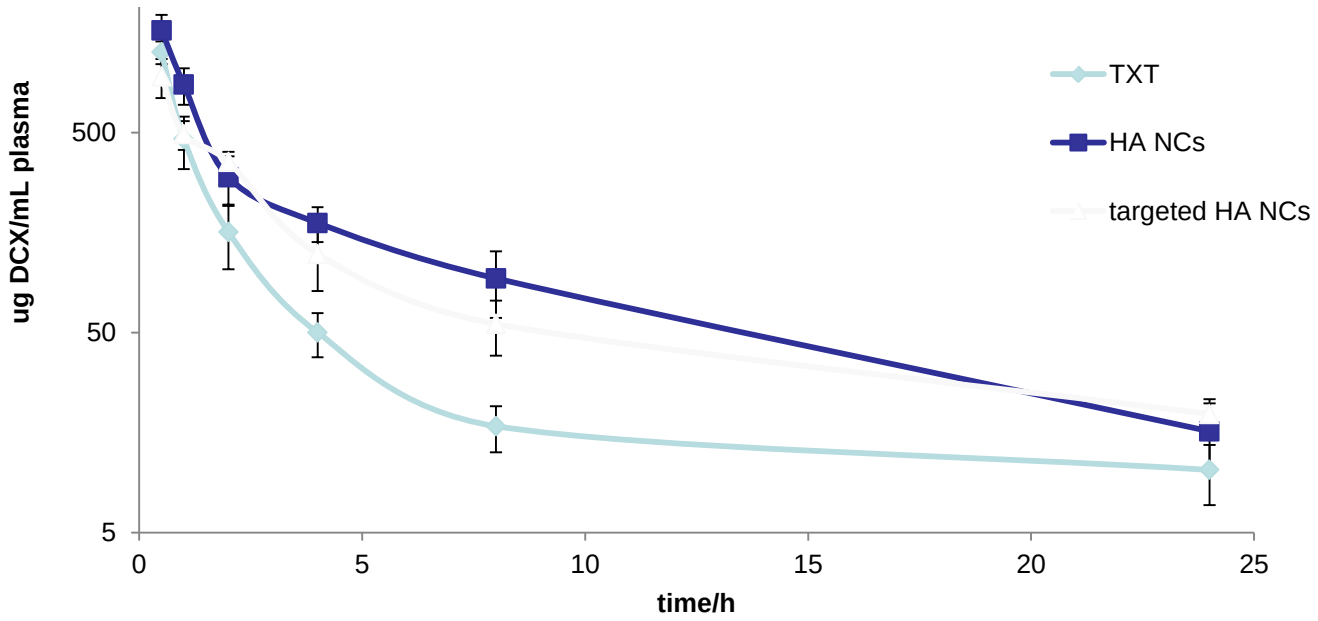
Docetaxel-loaded Nanocapsules (NCs) increases lymphatics accumulation, as compared to Taxotere® (TXT), in orthotopic lung cancer model



Docetaxel-loaded Nanocapsules (NCs) exhibit the same accumulation as Taxotere® (TXT) in heart, kidney, spleen and liver.
No detectable levels were found in brain tissue.



Docetaxel-loaded Nanocapsules (NCs9 shows increased blood circulation time, as compared to Taxotere® (TCT), in orthotopic lung cancer model



Pharmacokinetic parameters using a non compartimental model

	t1/2 (h)	AUC 0-inf obs ((mg/L).h)	Cl_obs (L/kg.h)	MRT 0-inf_obs (h)	VdB (L/kg)
TXT	5,40±1,27	2576,15 ± 346,71	0,0039±0,00053	2,89±0,2420	0,0113±0,00060
HA NCs	5,75±0,55	4400,45 ± 1110,96	0,0024±0,00062	4,25±0,5017	0,0099±0,00137
Targeted HA NCs	8,43±0,91	3162,72 ± 707,1	0,0033±0,00075	6,33±0,4195	0,0209±0,00619