NANOBIO EUROPE

Development of molecular imaging strategies for in vivo animal model phenotyping of human pathologies. Translational extension to patients

Jesus Santamaría

Ana Paula Candiota

Barcelona, 9-13th June 2008

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Centro Investigación Biomédica en Red
Bioingeniería, Biomateriales y Nanomedicina

nanobio europe
Barcelona (Spain)
June 9-13, 2008

MINISTERIO DE SANIDAD Y CONSUMO

Instituto de Salud Carlos III

Objectives of the IMAFEN project:

To develop preclinical strategies in order to achieve MR-based non invasive phenotyping of tumoural and neurodegenerative (Alzheimer) pathology of the brain.

- For this we will develop *funcionalized nanoparticles* in order to obtain specific contrast enhancement with MRI.
- We will also investigate the *endogenous contrast* caused by reversible perturbation of the metabolomic pattern of the tissue and its detection by magnetic resonance spectroscopy (MRS) maintaining the spatial information (*Chemical Shift Imaging*, CSI).

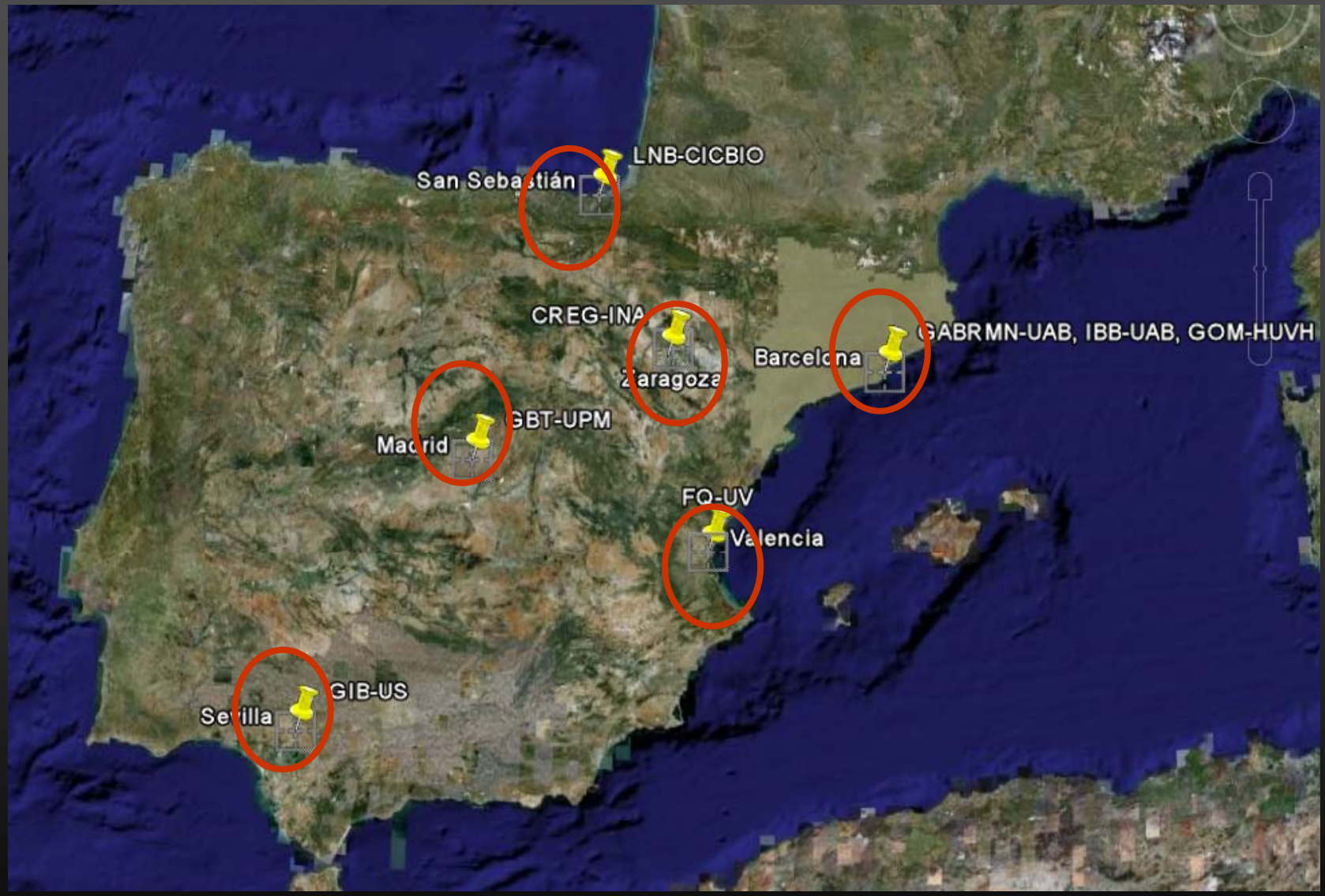
CIBER groups involved in IMAFEN:

PROJECT COORDINATOR : GABRMN-UAB, CIBER06-01-0010, PI : Carles Arús (GABRMN-UAB)

OTHER GROUPS:

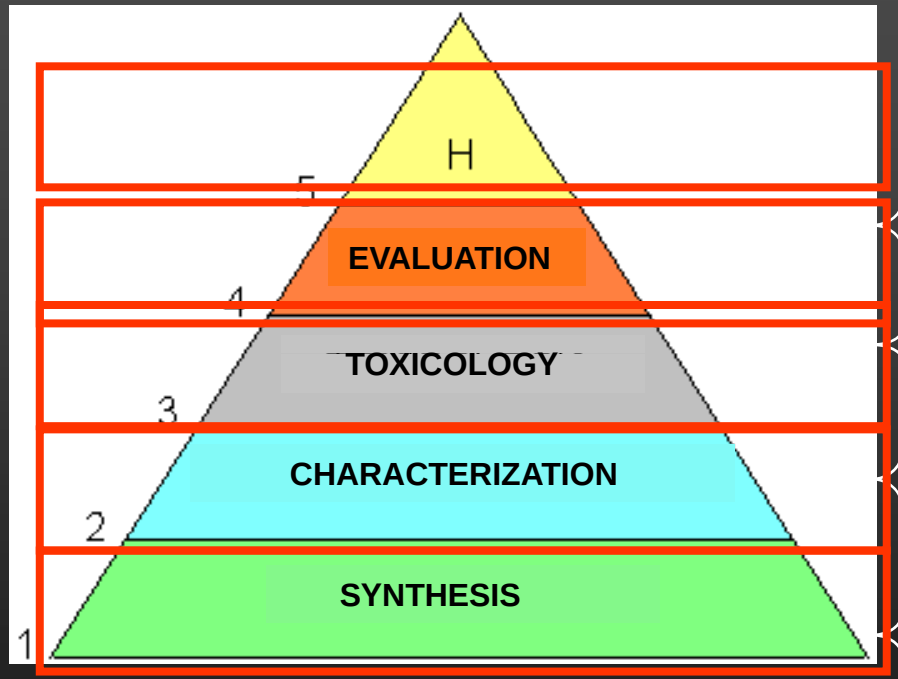
GROUP:	CB06-01-0004	PI: Soledad Penades	(LNB-CICBIO)
GROUP :	CB06-01-0012	PI: Simó Schwartz	(GOM-HUVH)
GROUP :	CB06-01-0014	PI: Antoni Villaverde	(IBB-UAB)
GROUP :	CB06-01-0022	PI: Laura Roa	(GIB-US)
GROUP :	CB06-01-0026	PI: Jesús Santamaría	(CREG-INA)
GROUP :	CB06-01-0029	PI: Bernardo Celda	(FQ-UV)
GROUP :	CB06-01-0051	PI: Francisco del Pozo	(GBT-UPM)

Geographic location of the IMAFEN partners



IMAFEN

Summary of the steps in the research of new contrast agents and antitumoral agents based in nanoparticles



MONIT_IM

CIBER06-01-0010 Carles Arús

CB06-01-0029 Bernardo Celda

CB06-01-0022 Laura Roa

CB06-01-0012 Simó Schwartz

CB06-01-0051 Francisco del Pozo

CB06-01-0014 Antoni Villaverde

CB06-01-0026 Jesús Santamaría

NANOMAG

CB06-01-0004 Soledad Penades

CB06-01-0051 Francisco del Pozo

CIBER06-01-0010 Carles Arús

CB06-01-0026 Jesús Santamaría

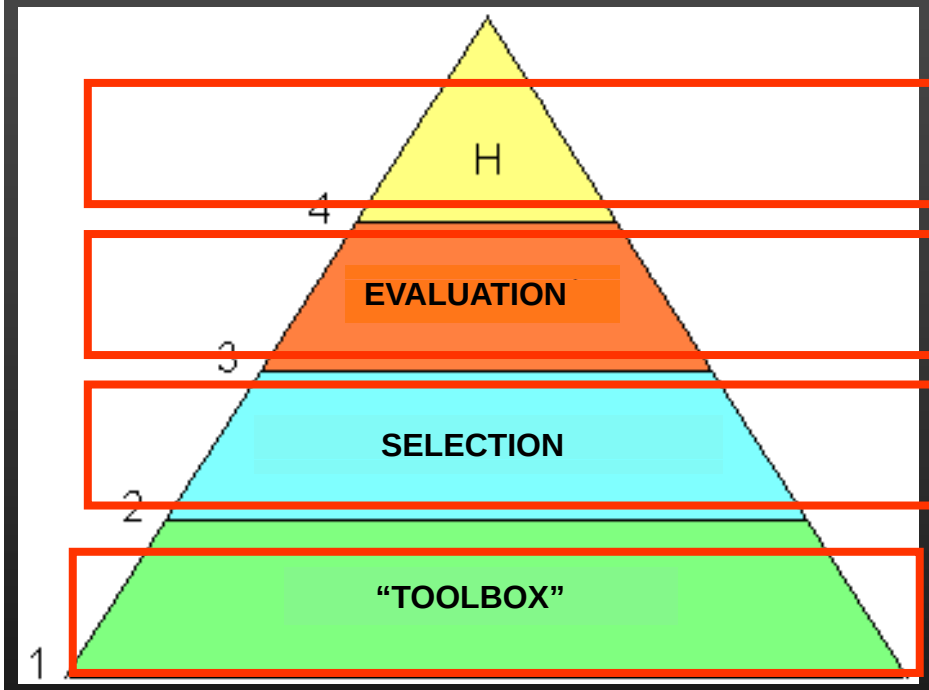
CB06-01-0004 Soledad Penades

NANOMAG

MONIT_IM

IMAFEN

Summary of the steps in the research of reversible perturbation of spectral pattern



Translational Studies

CIBER06-01-0010 Carles Arús

CB06-01-0029 Bernardo Celda

CB06-01-0051 Francisco del Pozo

CB06-01-0022 Laura Roa

CIBER06-01-0010 Carles Arús

CIBER06-01-0010 Carles Arús

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IMAFEN
Nanoparticles and contrast type: which one?
SYNTHESIS

T1 contrast agents

↓

Paramagnetic GNP
(Gd incorporation)

↓

Enhance signal in T1-weighted images
"positive contrast"

↓

LNB-CICBIO

T2 contrast agents

↓

Magnetic nanoparticles
Fe or Fe+Au (core)

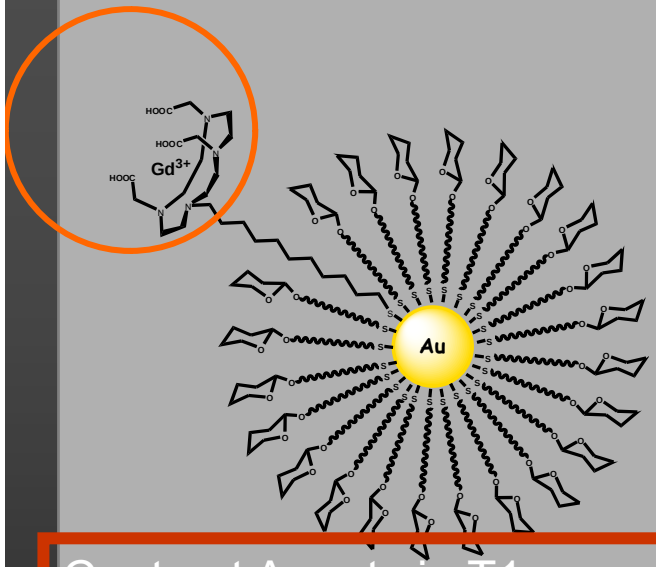
↓

Signal drop in T2-weighted images
"negative contrast"

↓

CREG-INA
GBT-UPM

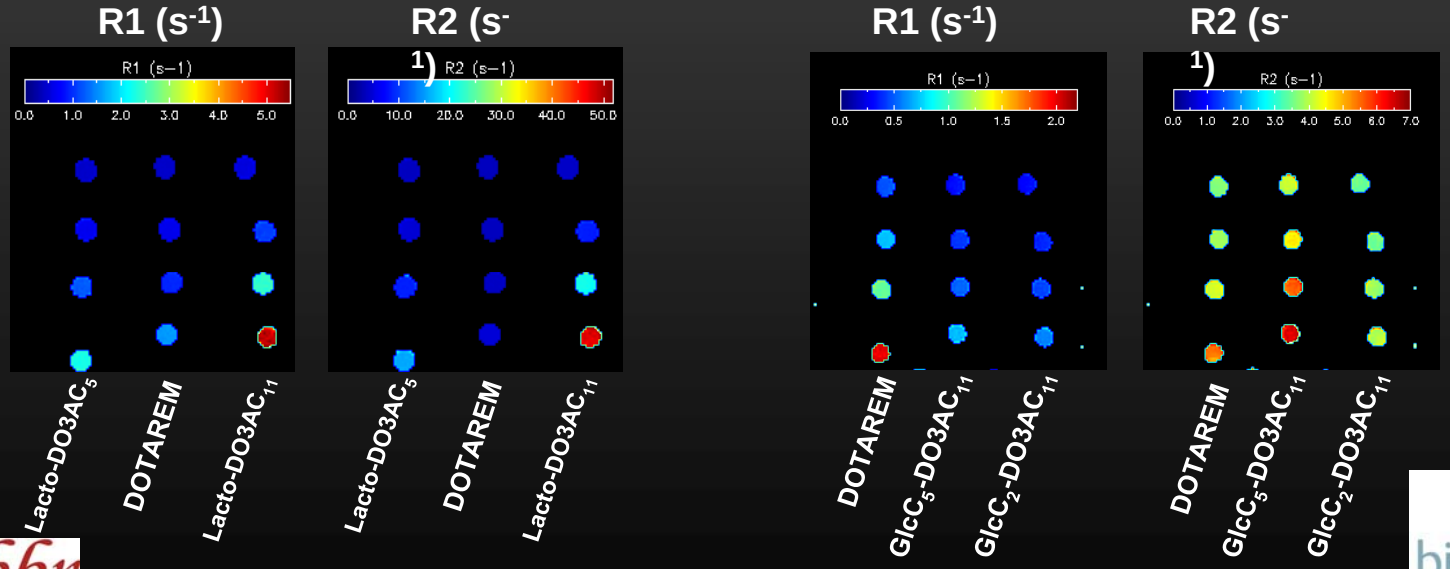
Paramagnetic Gold Glyconanoparticles



Contrast Agents in T1w sequences

Relaxivity Values r_1 (longitudinal) and r_2 (transversal)

GNPs and Commercial Contrast Agents	r_1 [$s^{-1}mM^{-1}$]	r_2 [$s^{-1}mM^{-1}$]
$GlcC_2S$-Au-$SC_{11}DO3A$-Gd^{3+}	1.4	2.1
$GlcC_5S$-Au-$SC_{11}DO3A$-Gd^{3+}	3.1	5.3
$LactoC_5S$-Au-$SC_{11}DO3A$-Gd^{3+}	25.2	40.7
$GlcC_2S$-Au-SC_5DO3A-Gd^{3+}	5.3	7.6
$GlcC_5S$-Au-SC_5DO3A-Gd^{3+}	2.1	4.5
$LactoC_5S$-Au-SC_5DO3A-Gd^{3+}	14.3	22.5
Magnevist®	3.4	3.8
Dotarem®	3.1	3.7



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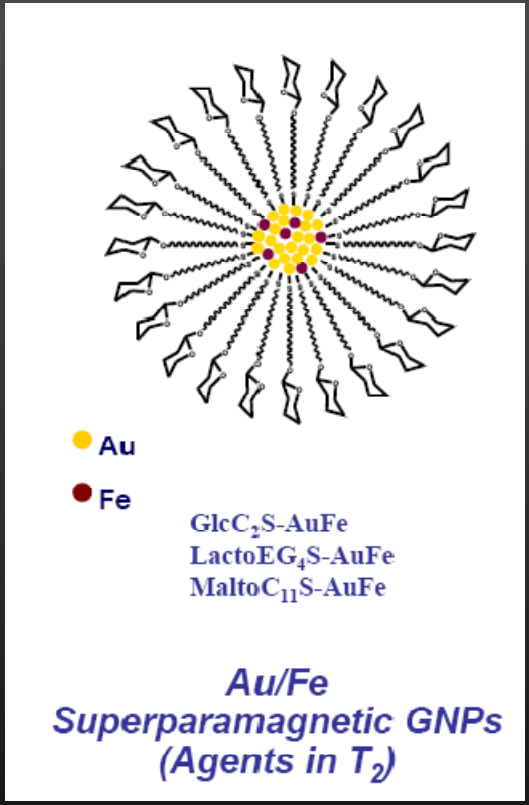
Laboratory of GlycoNanotechnology (*LNBT- CICBIO*)

CIC biomaGUNE
Biomaterialetako Ikerkuntza Kooperatiboko Zentroa
Centro de Investigación Cooperativa en Biomateriales

Magnetic Glyconanoparticles as Contrast Agents in MRI

Gold Core Modification



D. Alcántara, J. de la Fuente, 2003

Contrast agents in T2w sequences

Magnetic nanoparticles as Contrast Agents in MRI

SiO_2
Drug delivery
Gene Therapy

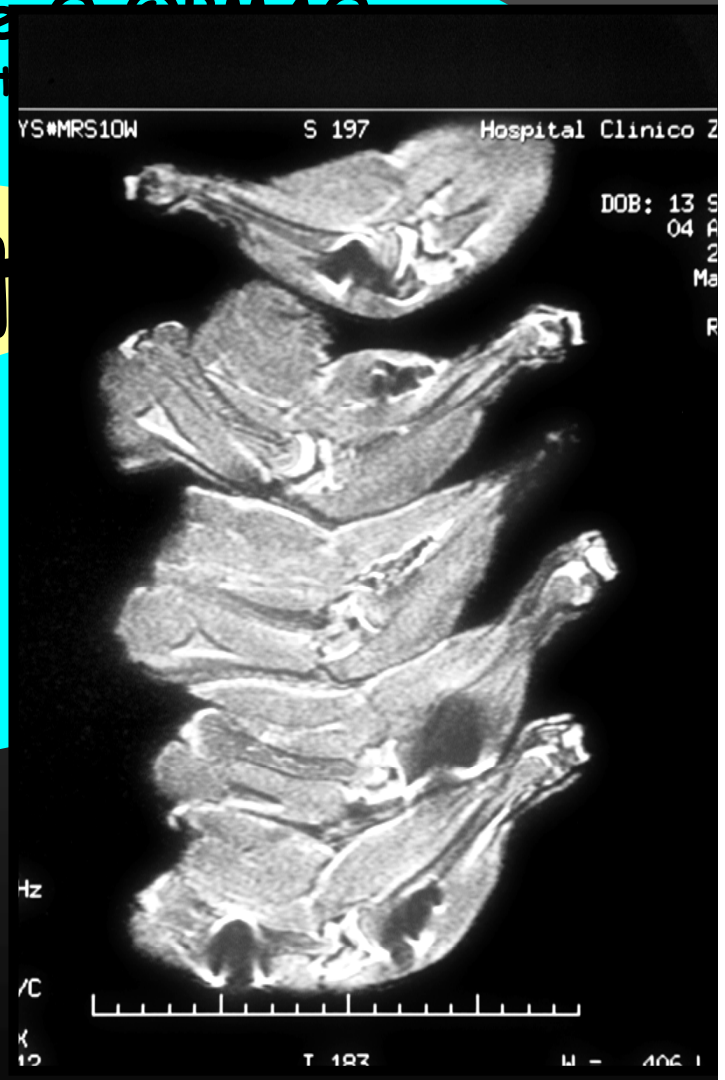
Fe
Ant

Vectorizat

Fe_3O_4@Au
Antibody conjugation
hyperthermia
MRI

Fe_3O_4@SiO_2
Antibody conjugation
hyperthermia

Contrast agents in T2w sequences



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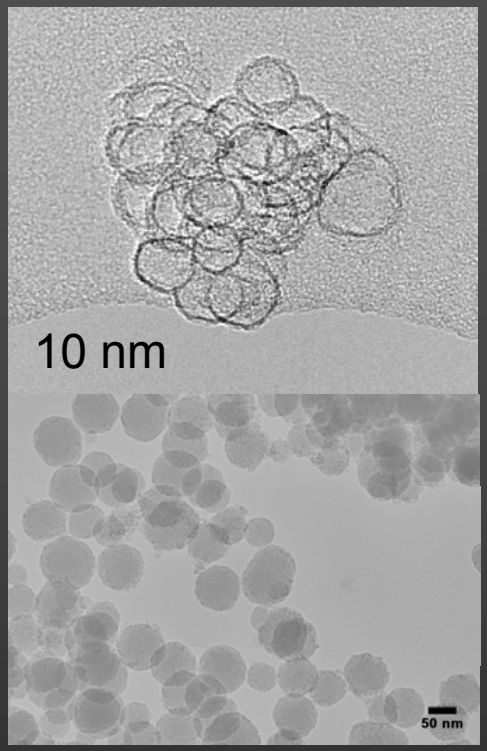
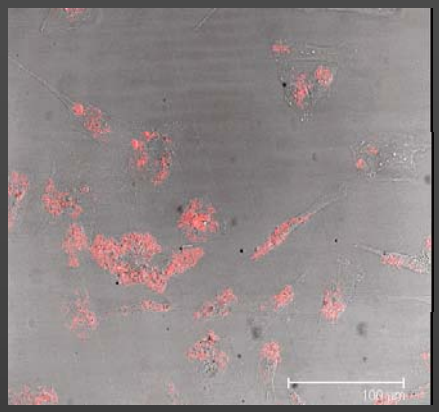
SiO_2

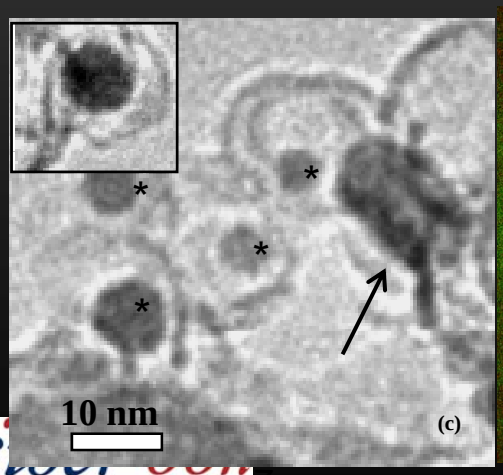
Drug delivery

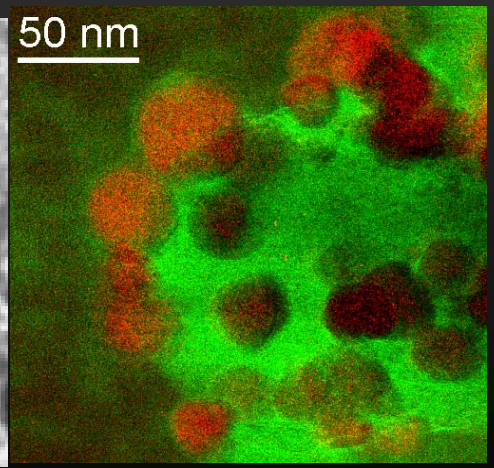
Gene Therapy





in collaboration with N. Villaboa





$Fe_3O_4@SiO_2$

Antibody conjugation

hyperthermia

MRI

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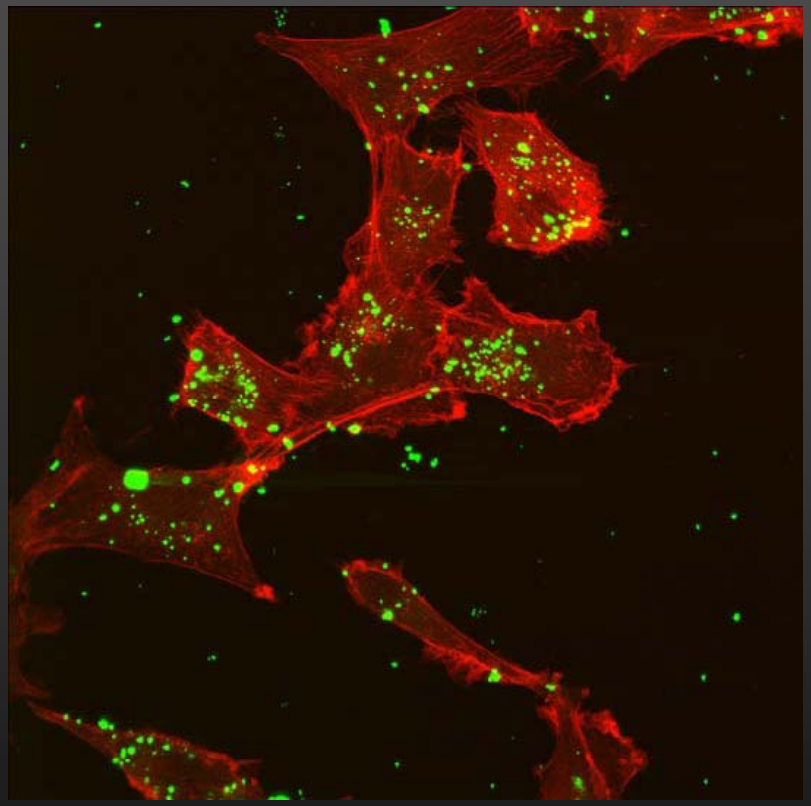
Magnetic nanoparticles as Contrast Agents in MRI
Initial studies



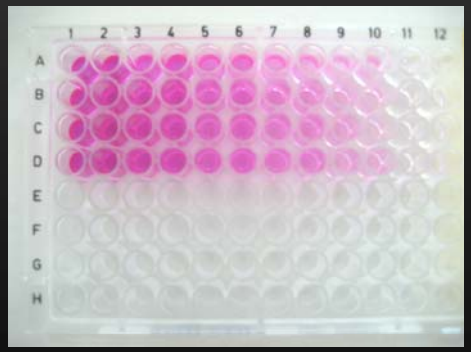
- *Magnetic nanoparticles (50nm, dextran coated)*
- *Using 1321n1 cell line (human brain glioma) → log phase*
- *100 µg NP /ml culture media*
- *Endocytosis of the MNP*

Contrast agents in T2w sequences

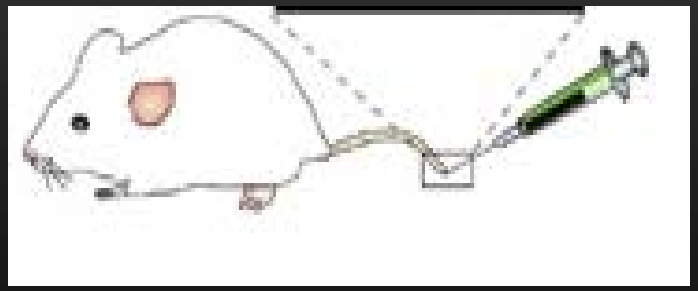
IMAFEN
CHARACTERIZATION, TOXICOLOGY

- Characterization: in vitro relaxativity, solubility, aggregation…
- Ex vivo testing: mouse brain tissue
- Toxicology tests previous to in vivo testing

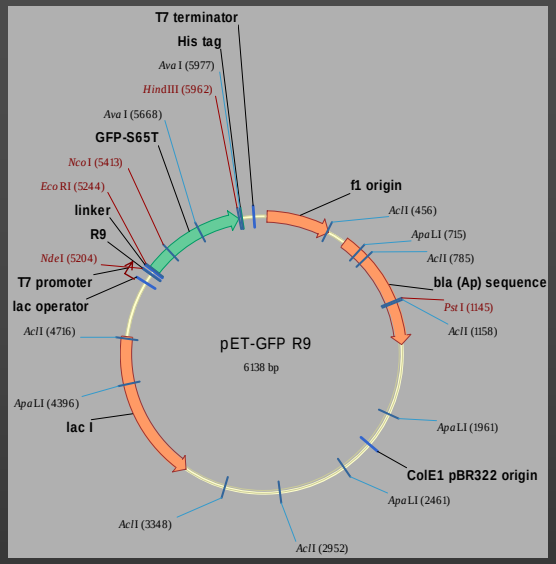
In vitro toxicity

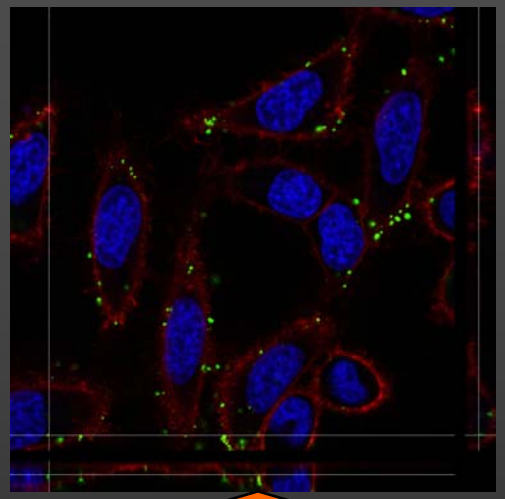


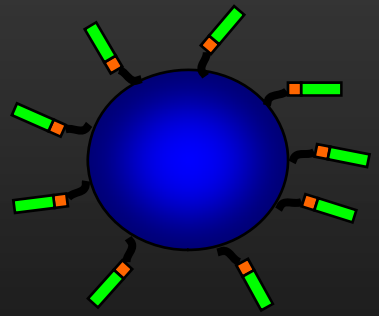
In vivo toxicity



IMAFEN
CROSSING INTACT BBB







New strategy #1: ***use of D-arginines***
(Wender, P.A. et al PNAS 97(24): 13003-13008, 2000

New strategy #2: ***use of Myristoylated arginines***
(Pham W. et al Neuroimage 28: 287-292, 2005

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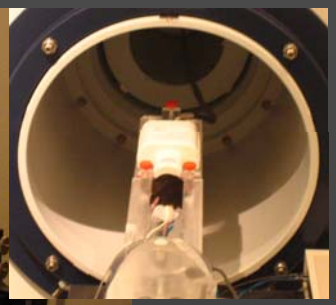
Laboratori de Microbiologia Aplicada
IBB-UAB IP: Antonio Villaverde

NanobioEurope
Barcelona, 9 – 13th June 2008

NMR facility for in vivo/ex vivo studies at UAB



Avance 600

ARX400 HRMAS

Biospec 7T

Avance 500
+ crioprobe

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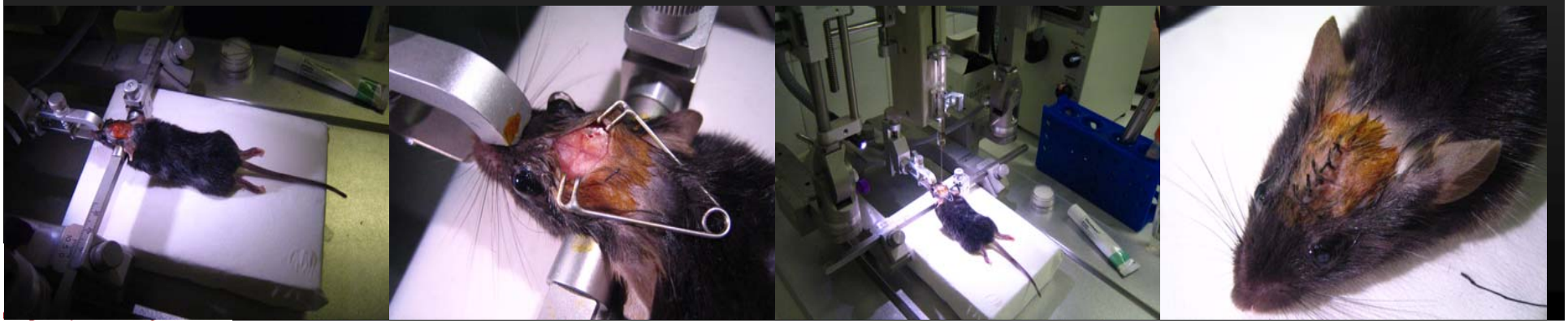
Animal models of cerebral tumours (UAB)

GEM colonies at SE-UAB

- *Nf1-Trp53*$^{(+/-)}$ **N**
  Astrocitoma (high incidence)
- *GFAP-v-src* **G**
  Astrocitoma (low incidence)
- *s100β-v-erbB* **S**
  Oligodendroglioma (low grade)
- *s100β -v-erbB / InK4a-Arf(+/-)* **S**
  Oligodendroglioma (high grade)

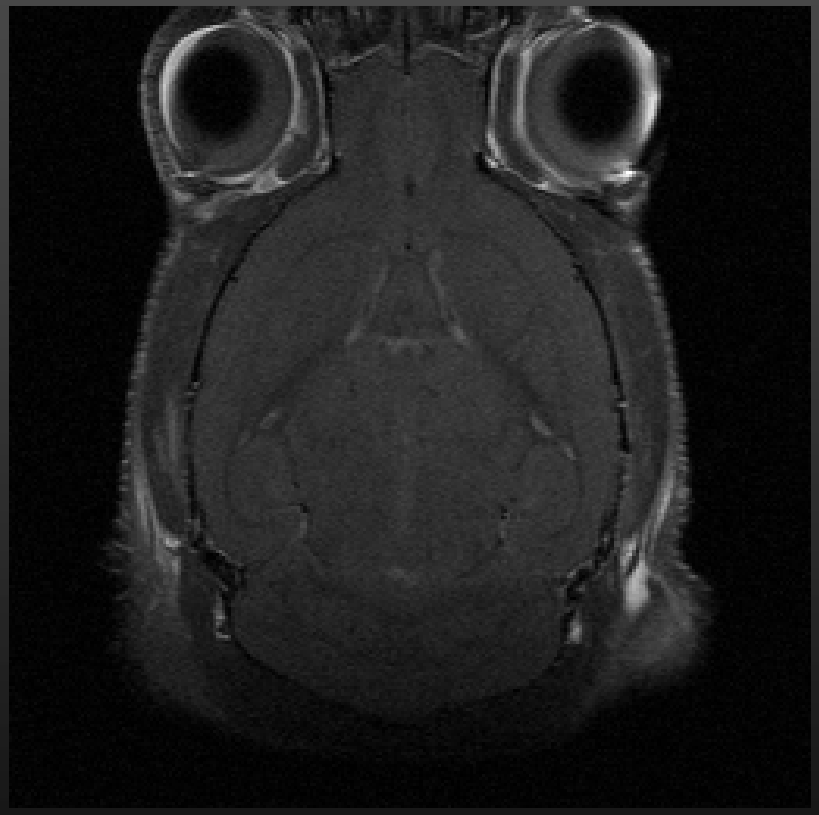
Low grade ↓ High grade

Intracerebral injection of GL261 cells

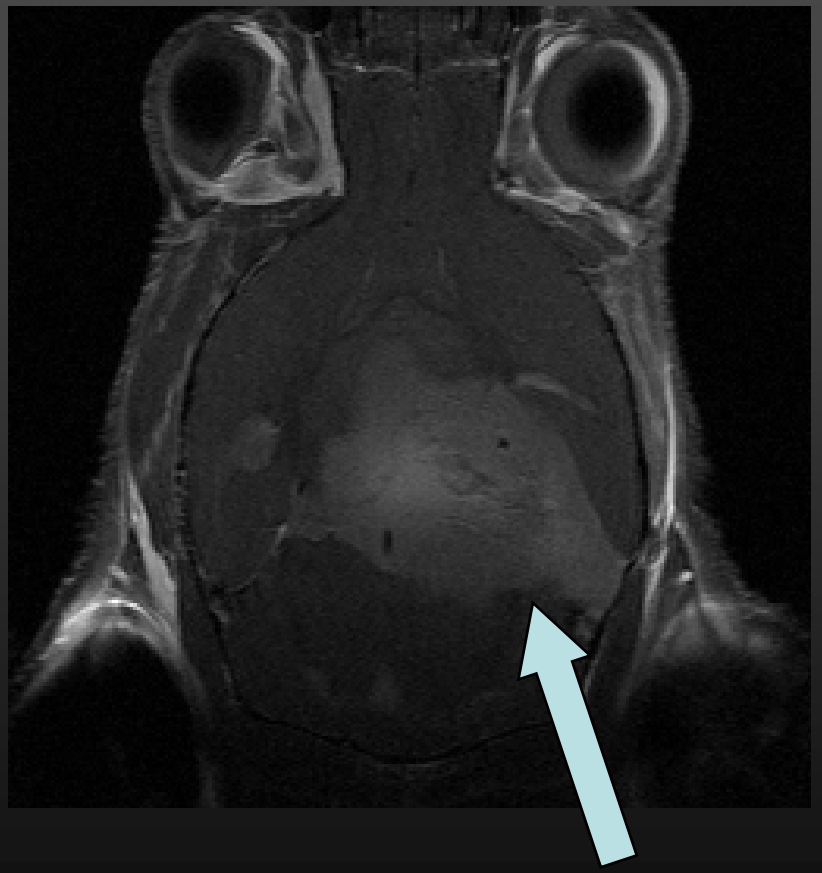


Contrast agents - MRI

Normal



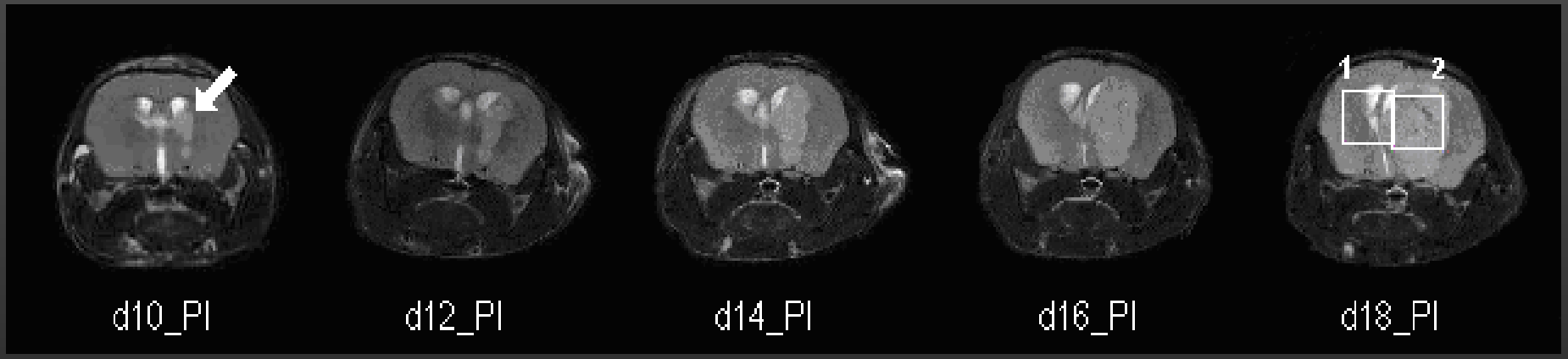
GEM (oligodendroglioma)



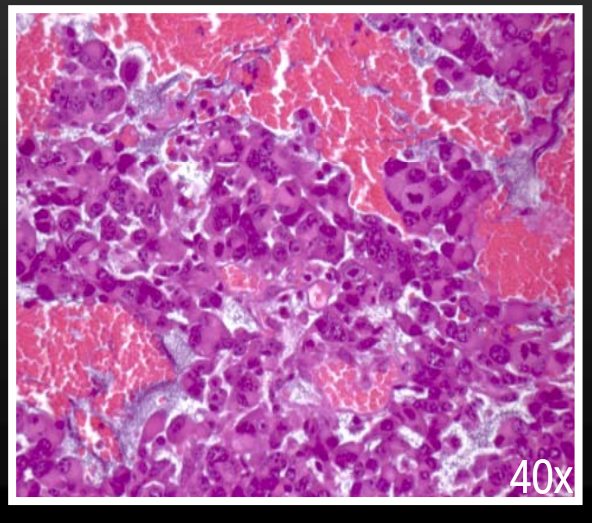
CE-T1

GL261 tumour size progression

MRI (T2-W)

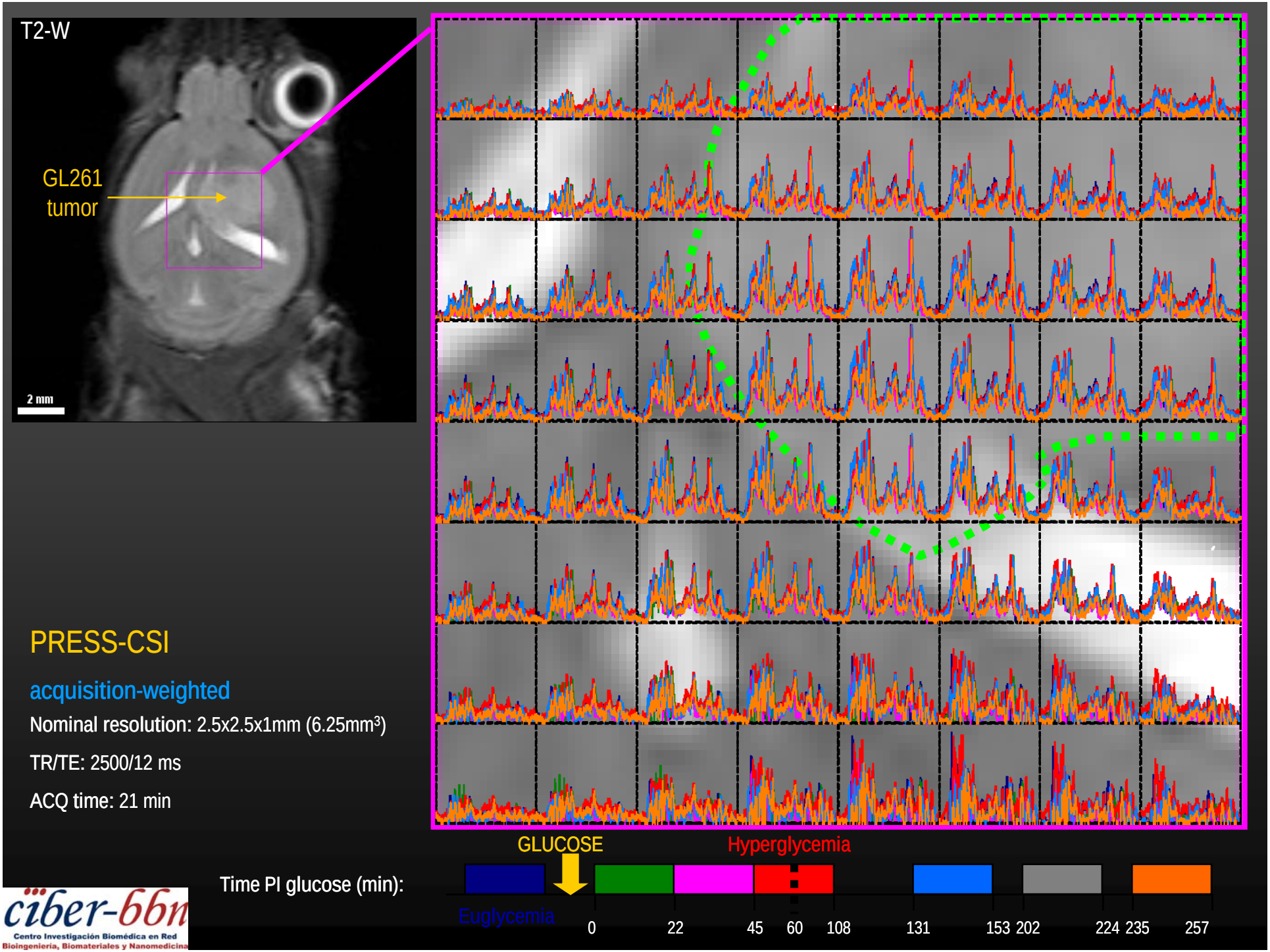


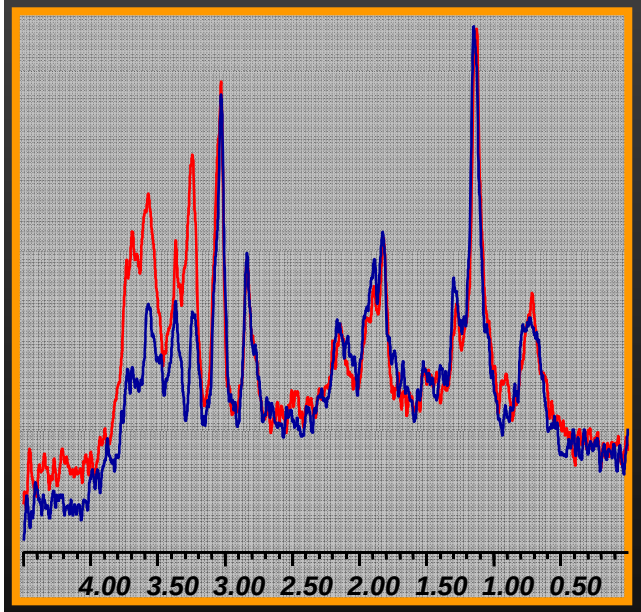
Histopathology (H&E):

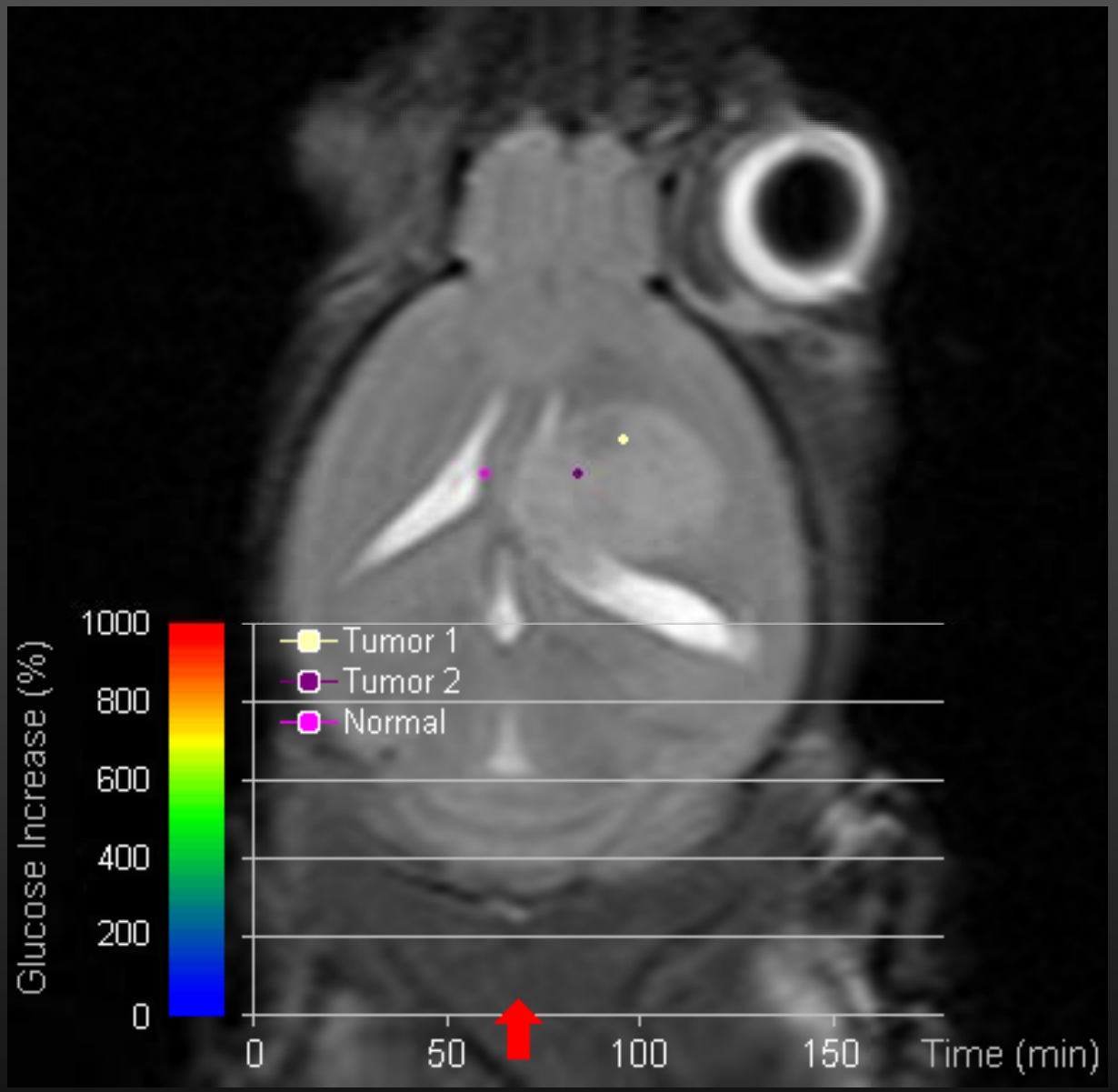


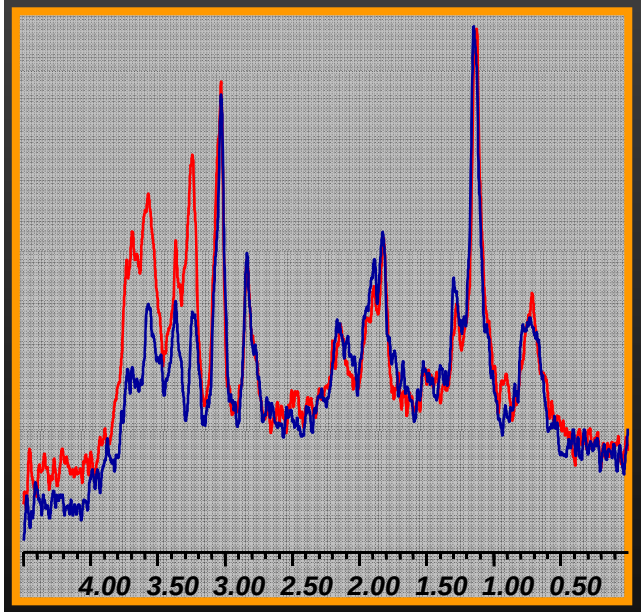
Effect of metabolome challenge in animal models of cerebral tumours:

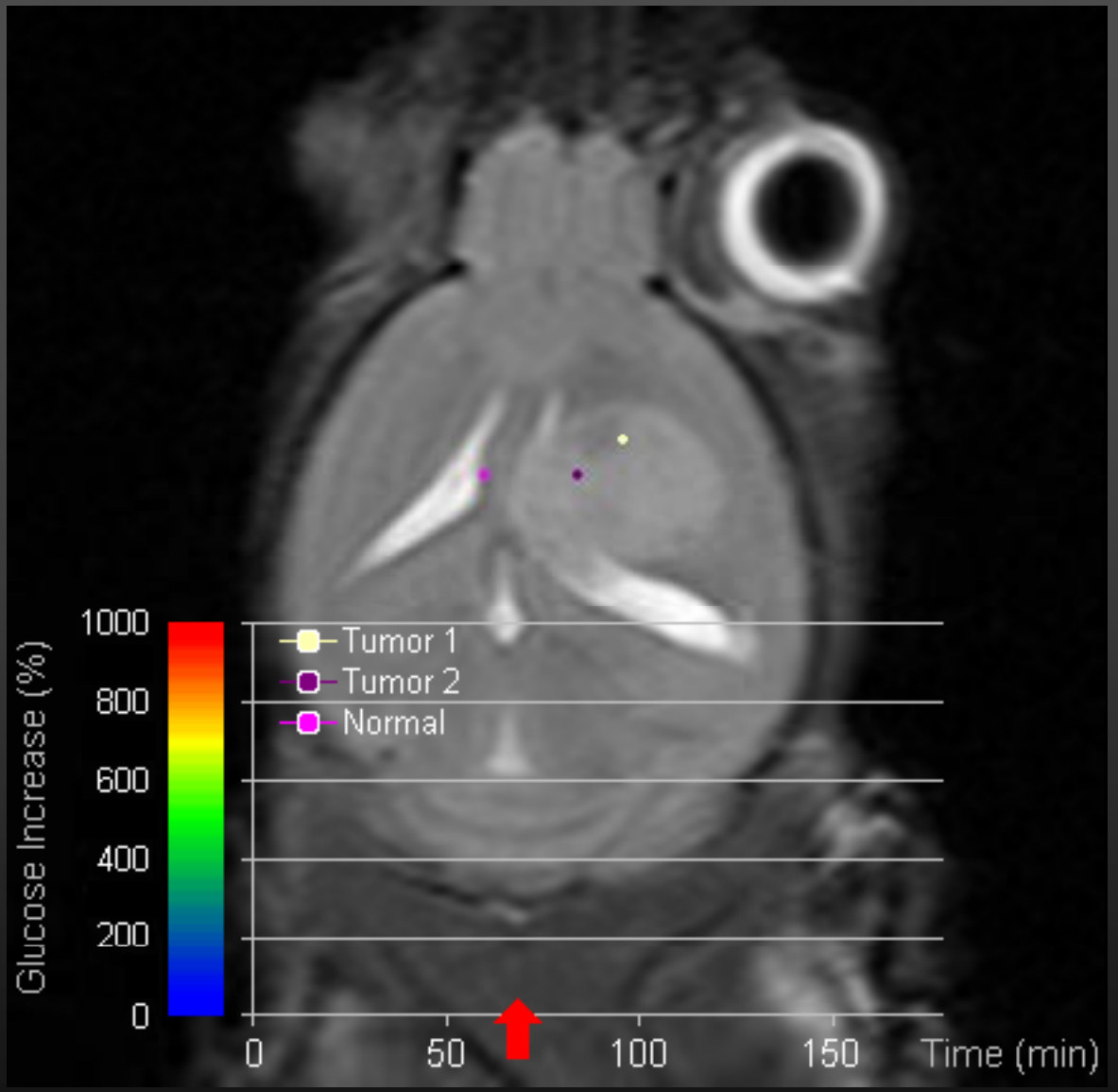
Hiperglycemia in GL261 tumours


T2-W
GL261
tumor
2 mm
PRESS-CSI
acquisition-weighted
Nominal resolution: 2.5x2.5x1mm (6.25mm³)
TR/TE: 2500/12 ms
ACQ time: 21 min
GLUCOSE
Hyperglycemia
Euglycemia
Time PI glucose (min):
0
22
45
60
108
131
153
202
224
235
257


4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50


Glucose Increase (%)
1000
800
600
400
200
0
Tumor 1
Tumor 2
Normal
0
50
100
150
Time (min)


4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50


Glucose Increase (%)
1000
800
600
400
200
0
Tumor 1
Tumor 2
Normal
0
50
100
150
Time (min)

Extended IMAFEN
4 new research groups

CB06-01-1039 GIB-UB	**IP:** Javier Pavía
CB06-01-1031 GOA-HSCSP	**IP:** Ramon Mangues
CB06-01-1035 CSIC-ICCC	**IP:** Jerónimo Blanco
CB06-01-1044 BIT-UPM	**IP:** Andrés Santos

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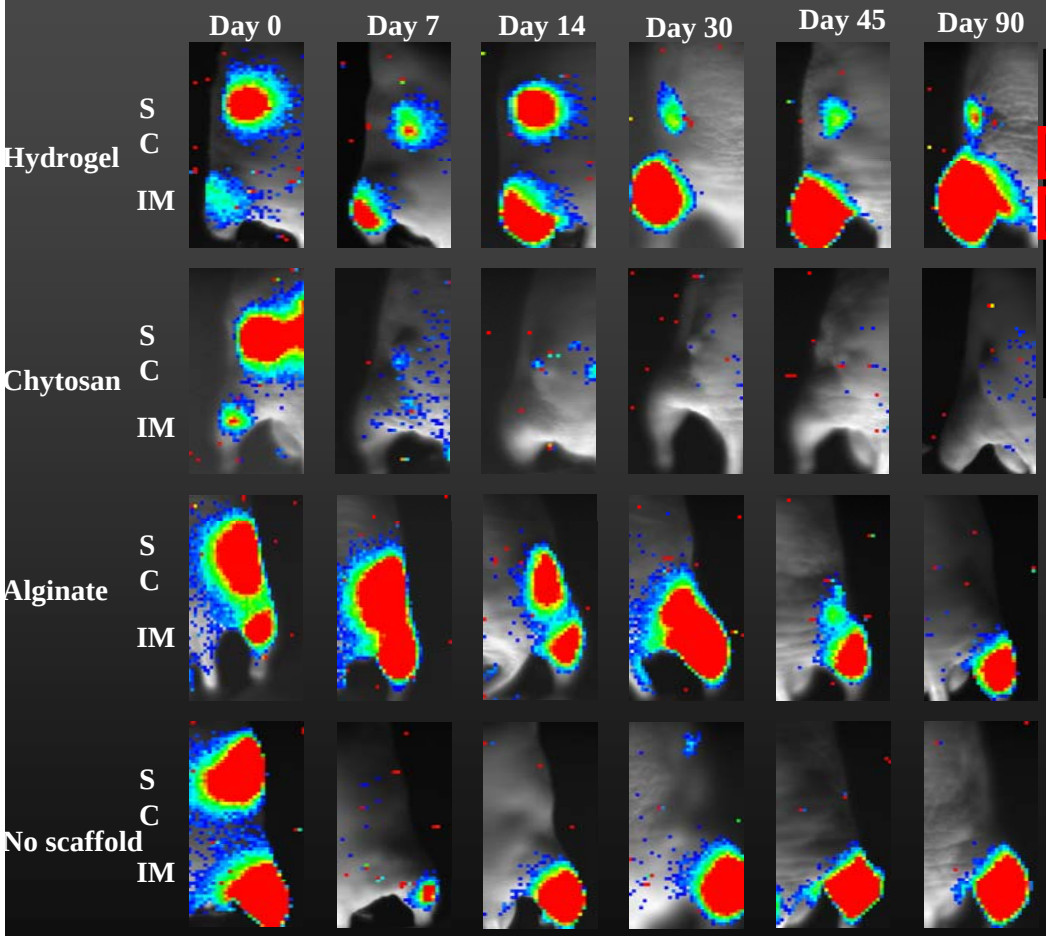
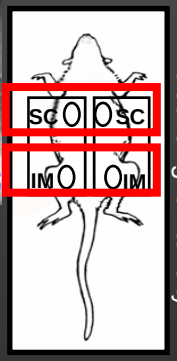
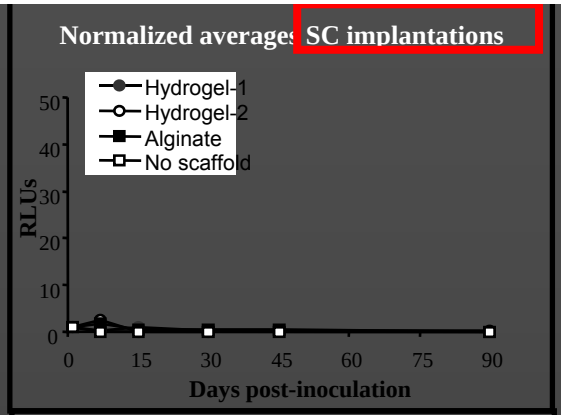
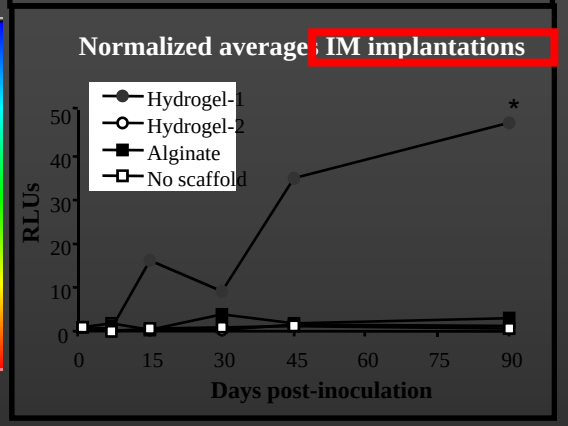
CB06-01-1035 CSIC-ICCC

Analysis of Progenitor Cell-Scaffold Combinations by In-Vivo Non-Invasive Photonic Imaging









I. Román et al. Biomaterials. 2007

Goals:

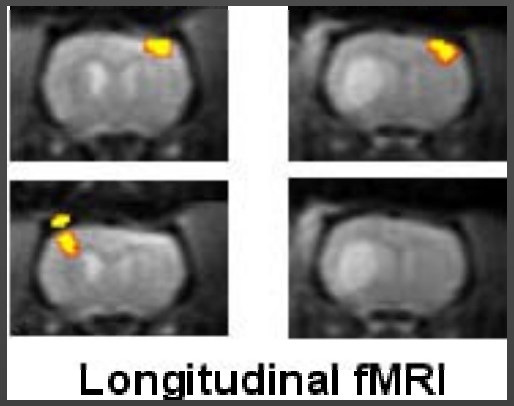
1-To generate a lentiviric vector expressing luciferasa, FE and TK.

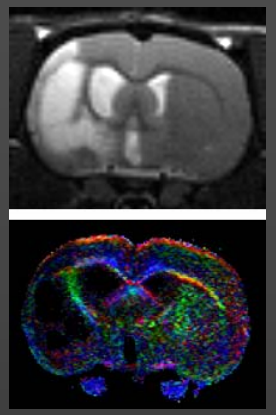
2- To generate a murine cerebral tumour model. Tumour progression will be monitorized by MR and or bioluminescence.

3- To generate MSCs tagged with LR, FE and TK.

4- To apply the antitumoural therapy by using Ganciclovir (TK substrate).

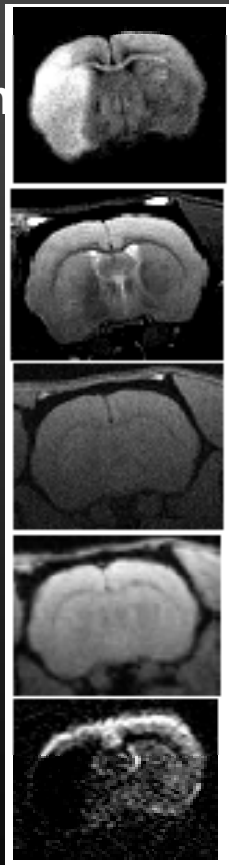
group **CB06/01/1039** (GIB-UB)





Diffusion tensor imaging

Multimodal Imaging



GOALS:

- To measure changes in multimodal MRI in an experimental model of cerebral ischaemia. To compare sequential images in the same animal in order to evaluate the damage and treatment effects. To improve postprocessing and co-registering.

- To acquire spectroscopic images and metabolite quantitation to better characterize the ischaemic penumbra.

- To quantify changes in cerebral perfusion by contrast injection, and to use new contrast agents to improve MRI enhancement. New contrast agents could be targeted against specific molecules to obtain molecular imaging in vivo.

- To visualize and track some specific cerebral cells, if the new contrast agents could target them.

Thank you!