Functional characterisation of tumours using patient-derived models - therapeutic implications

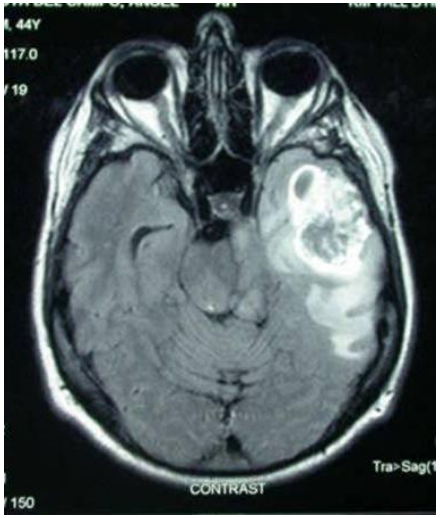
Joan Seoane
Vall d'Hebron Institute of Oncology (VHIO)
Vall d'Hebron University Hospital
Barcelona

VHIO
VALL D'HEBRON
Institut d'Oncologia

Vall d'Hebron
Hospital General

icrea
Institució Catalana de Recerca i Estudis Avançats

Grade IV glioma; Glioblastoma



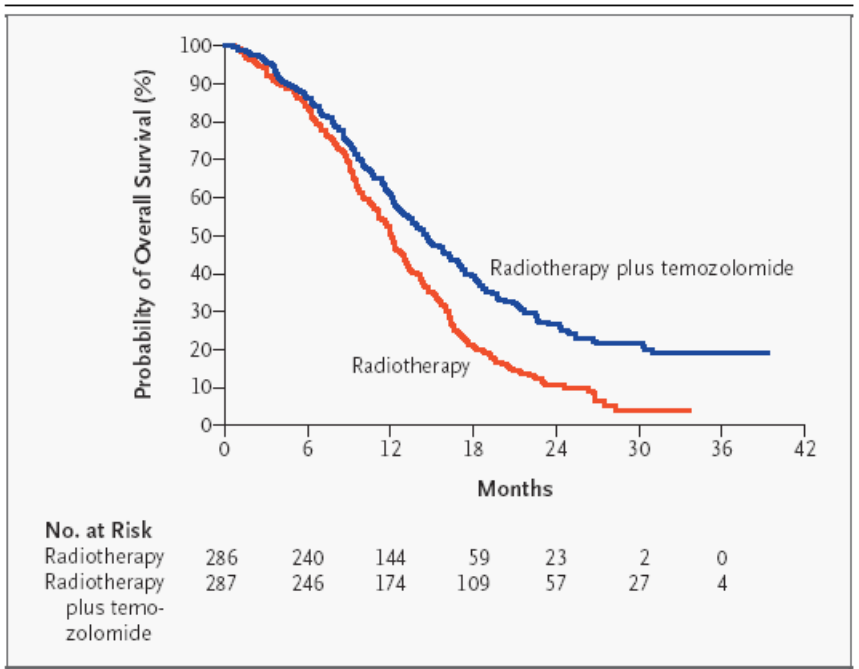


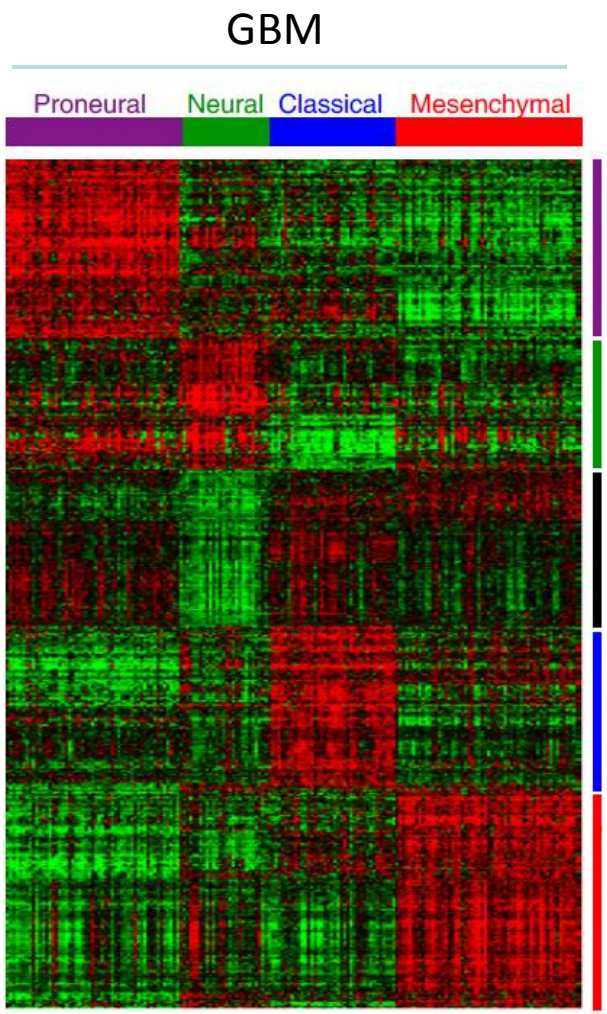
Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

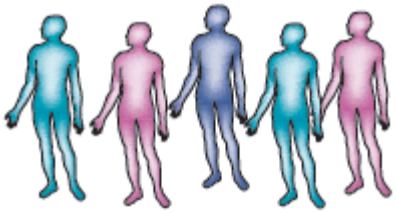
The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

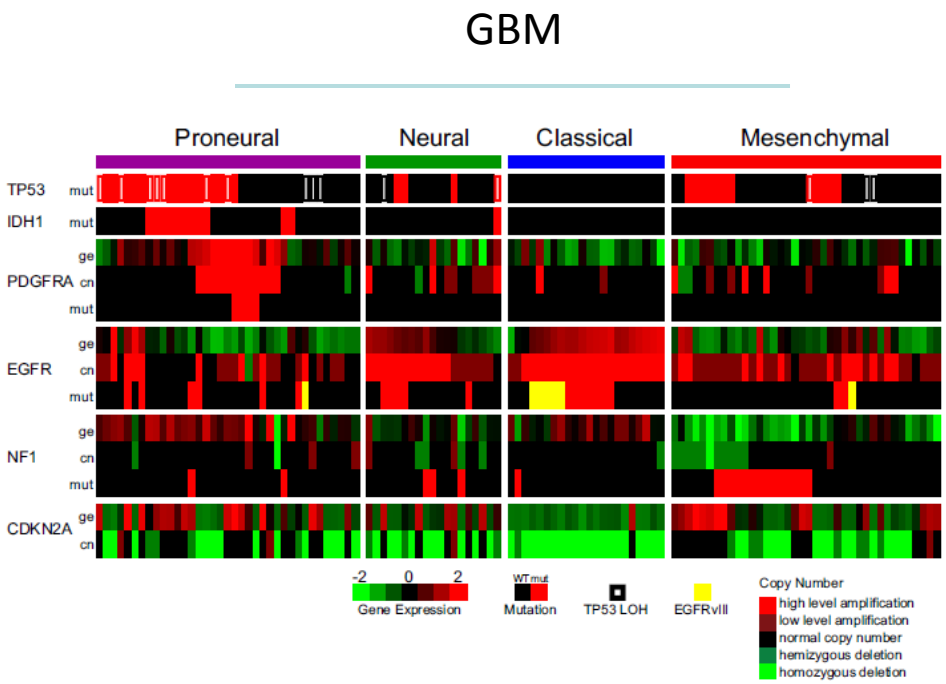
Stupp et al. New Engl. J. Med. 2005

Inter-tumor heterogeneity

Molecular diagnosis

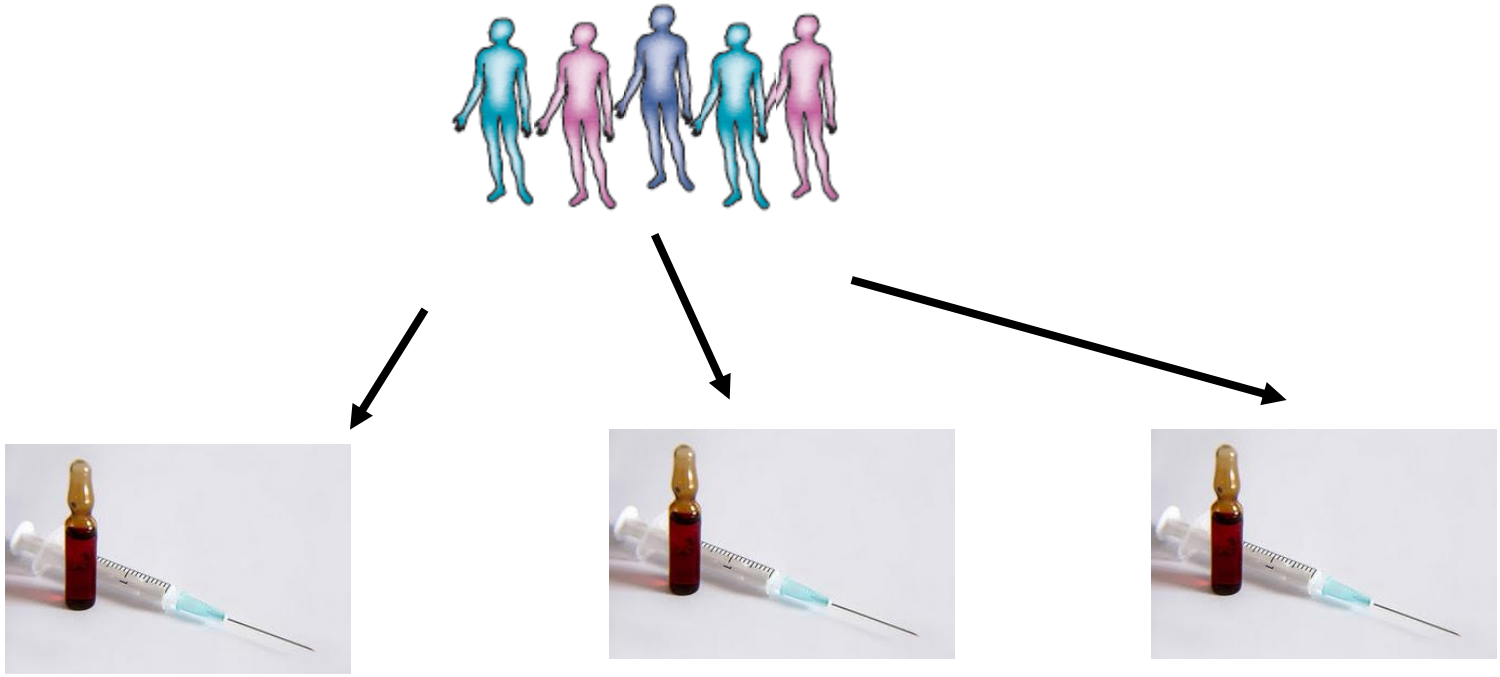




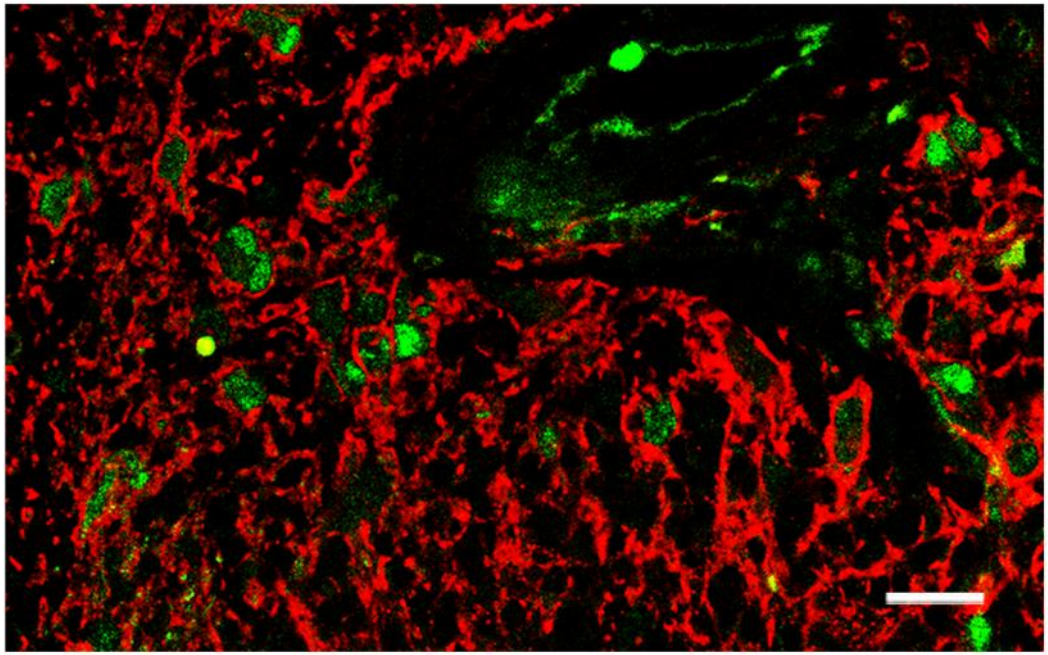


Verhaak et al. Cancer Cell 2010

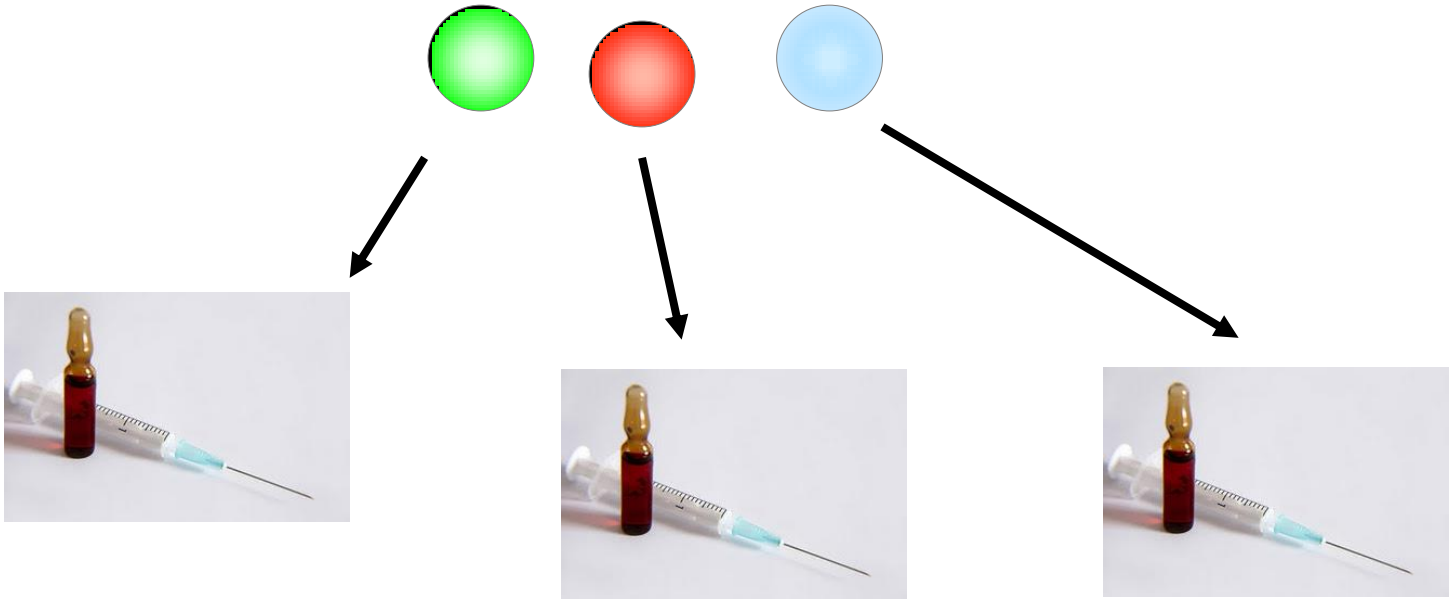
Patient specific treatment



Intra-tumor heterogeneity

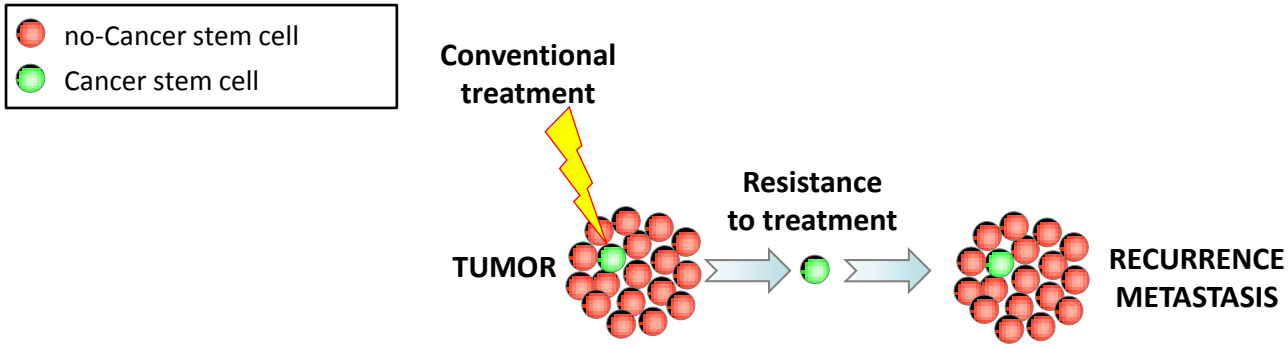


Cell specific treatment

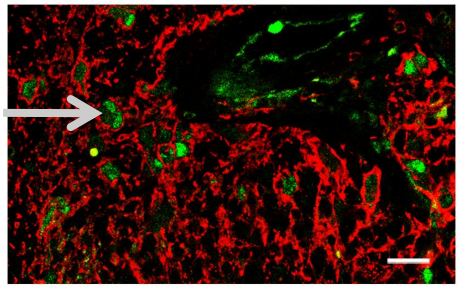


Cancer-initiating cells/ Cancer stem cells

Responsible for recurrence, metastasis and resistance to treatment



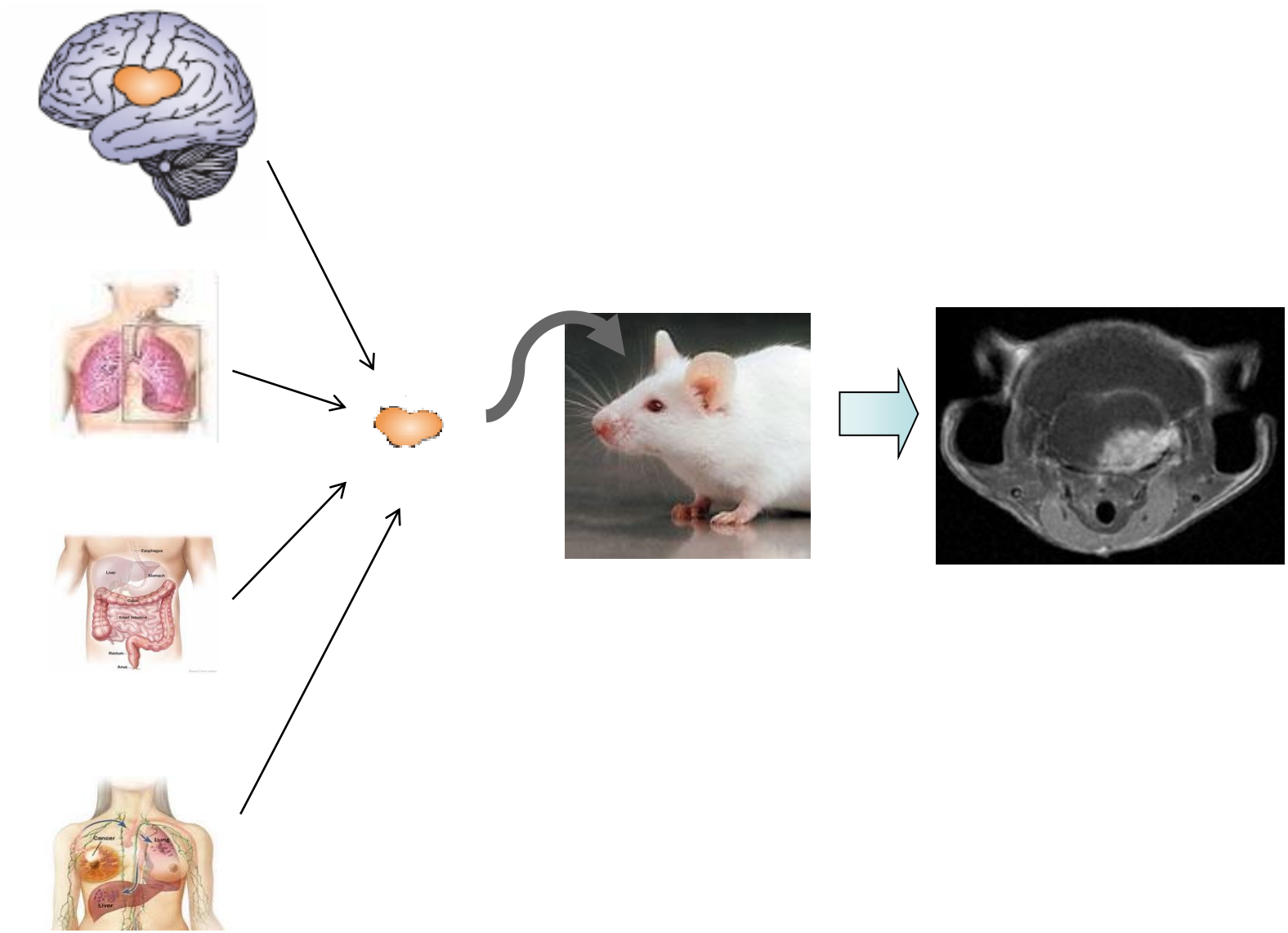
Cancer stem cell



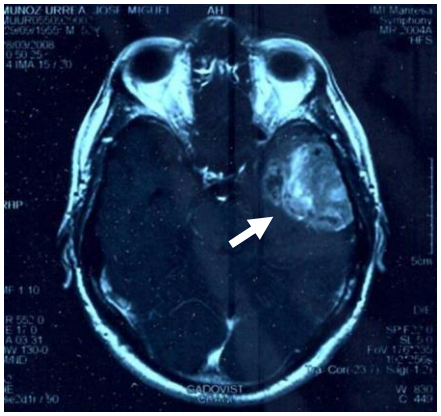
Pre-clinical models

- Established cell lines -> Xenograft
- Genetically engineered modified mouse models (GEMMS)
- Patient-derived xenografts

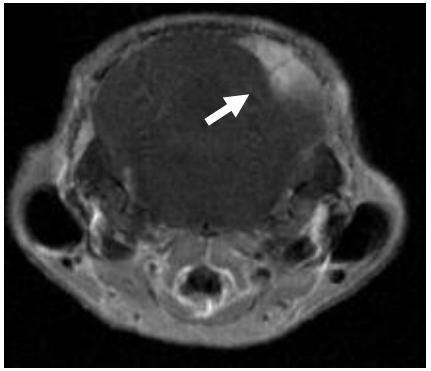
Patient-derived models



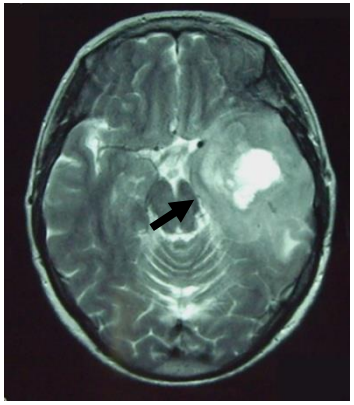
Patient GBM



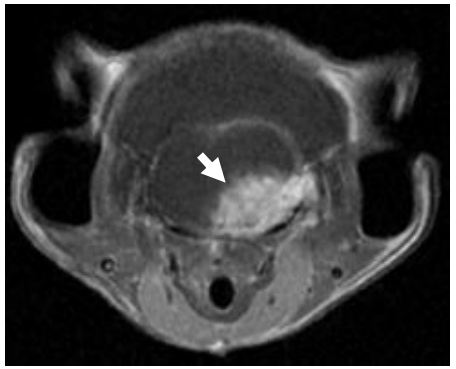
Mouse GBM

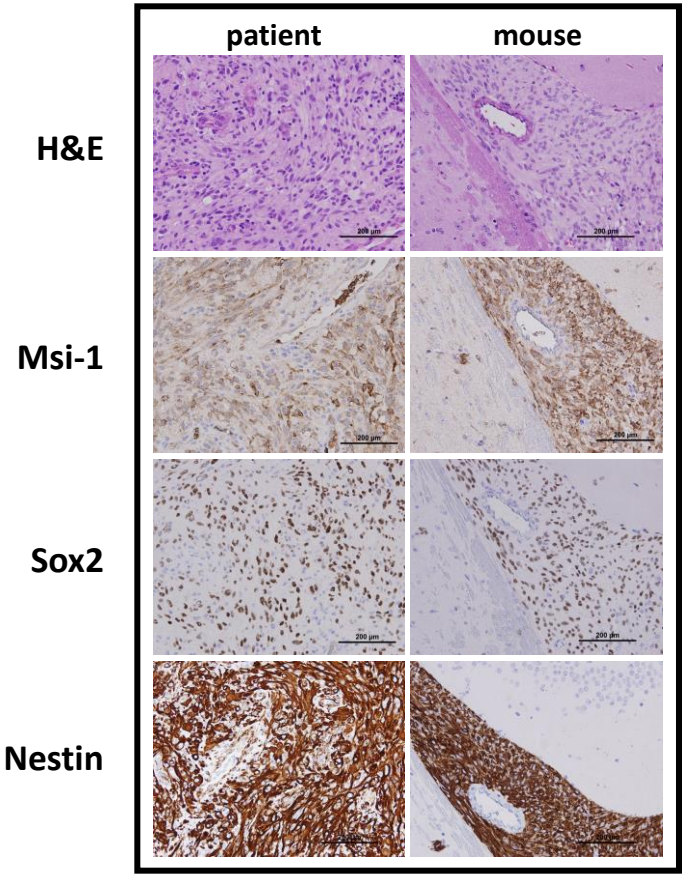


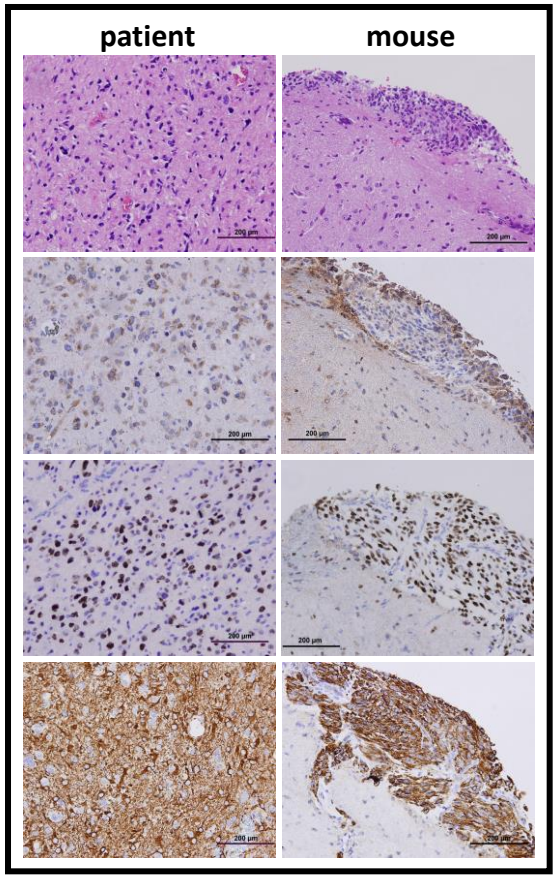
Patient GBM



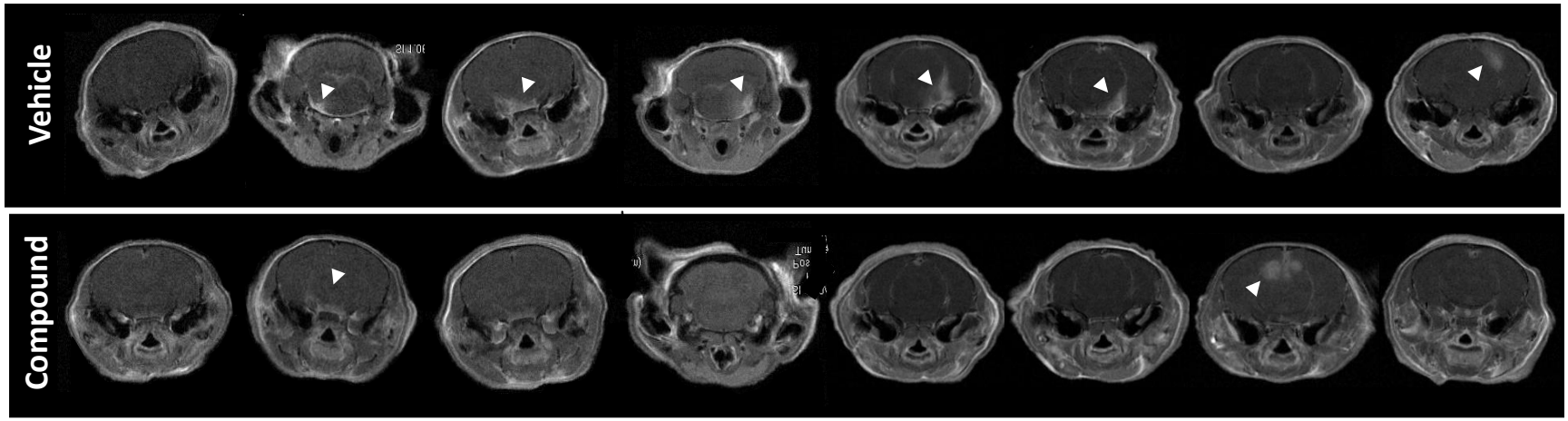
Mouse GBM

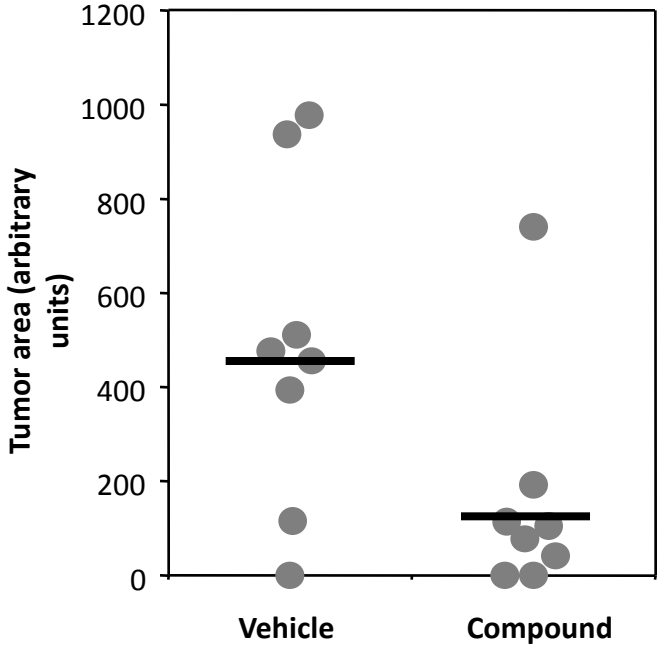


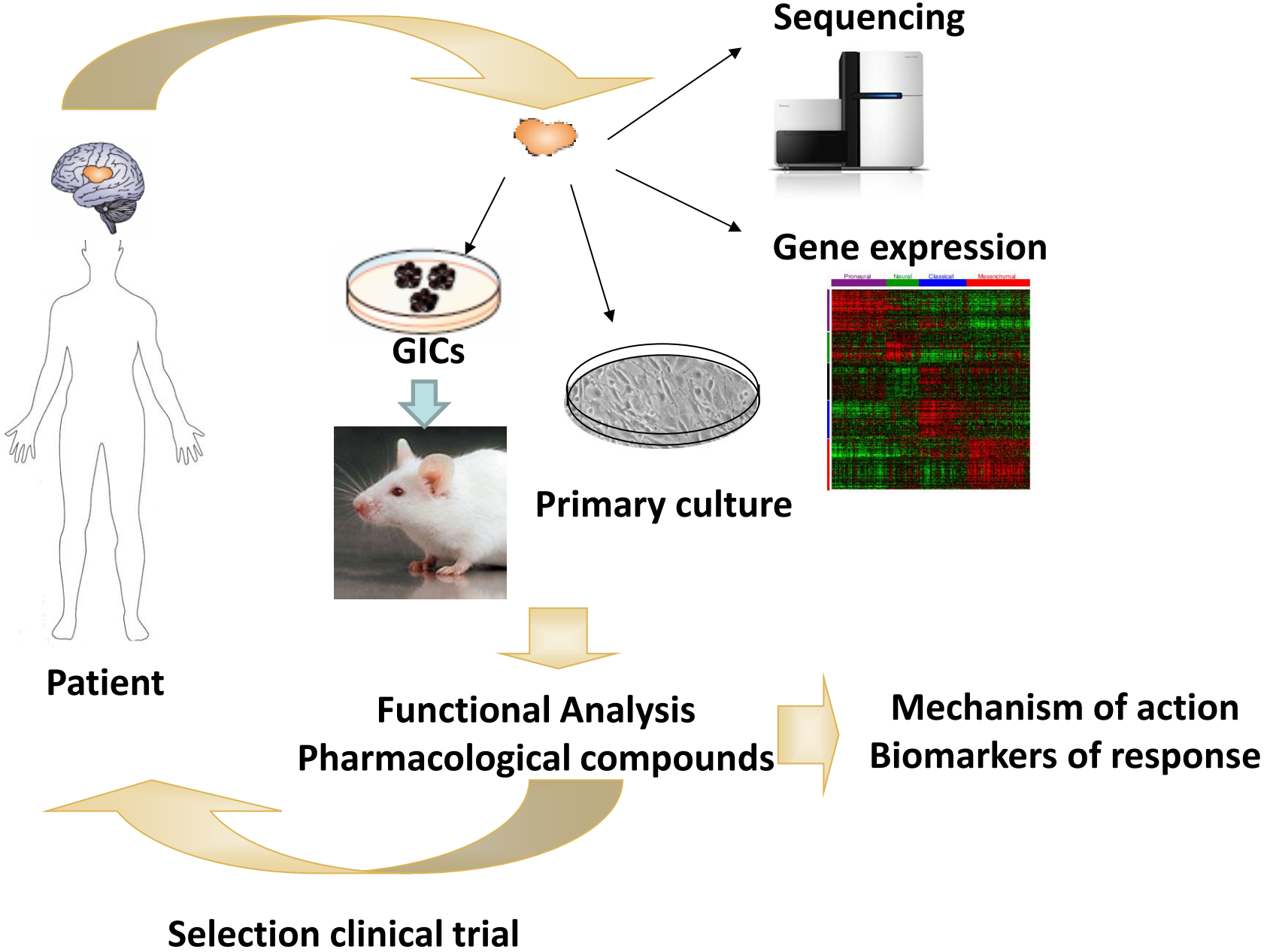




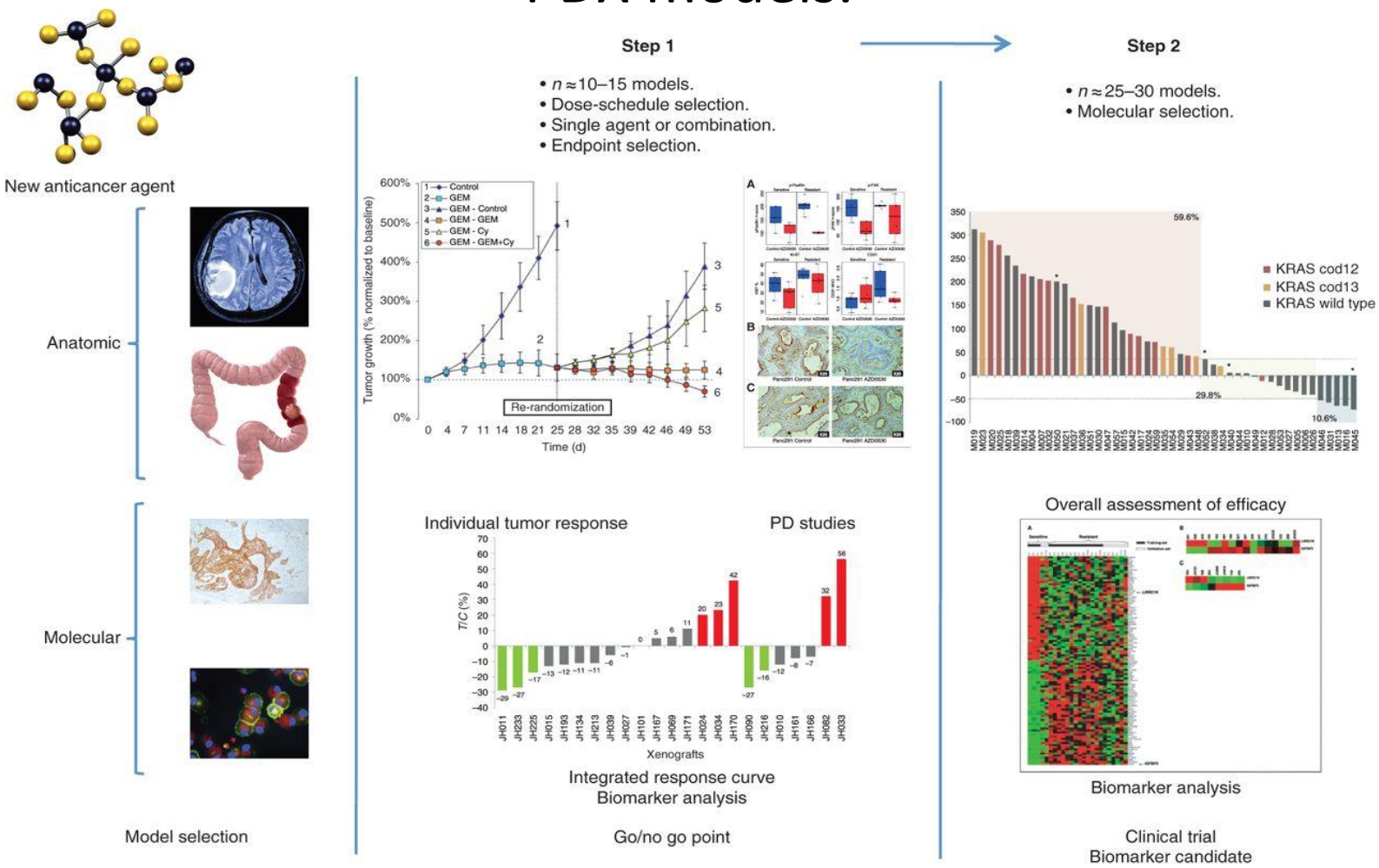
Preclinical model





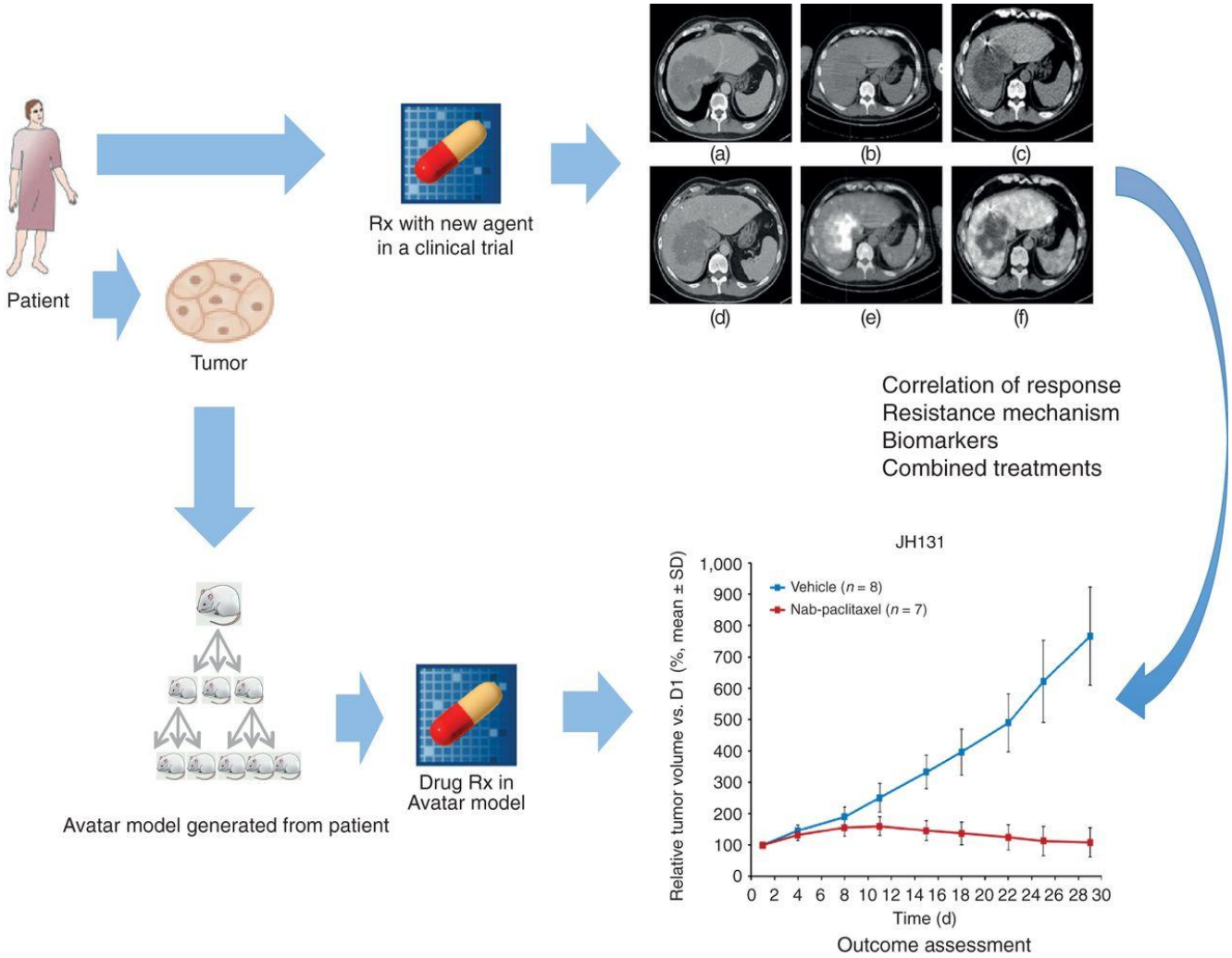

Sequencing
Gene expression
Proneural
Neural
Classical
Mesenchymal
GICs
Primary culture
Patient
Functional Analysis
Pharmacological compounds
Mechanism of action
Biomarkers of response
Selection clinical trial

Proposed preclinical screening and biomarker study in PDX models.



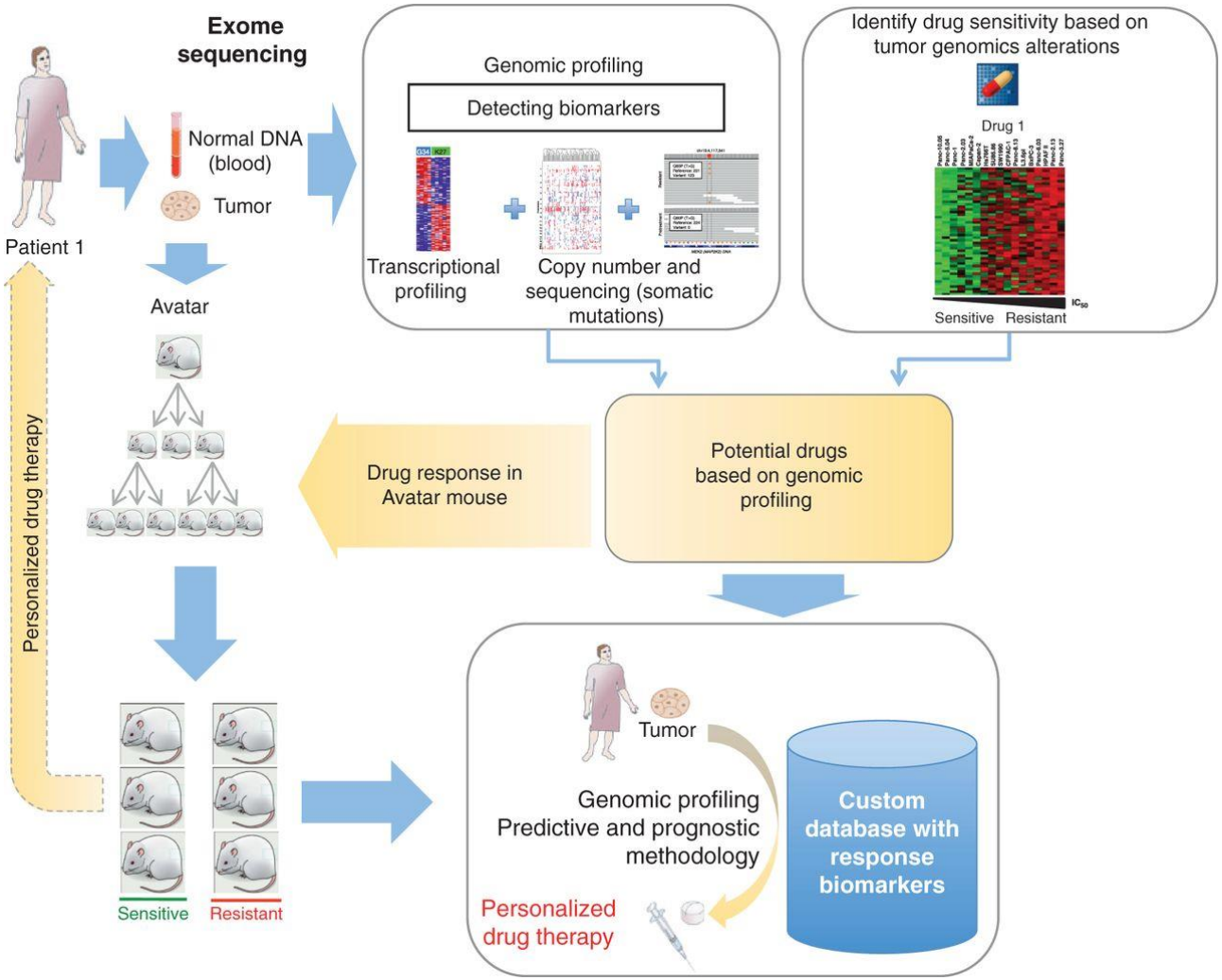
Hidalgo M et al. Cancer Discovery 2014;4:998-1013

Co-clinical trial approach with PDX models.



Hidalgo M et al. Cancer Discovery 2014;4:998-1013

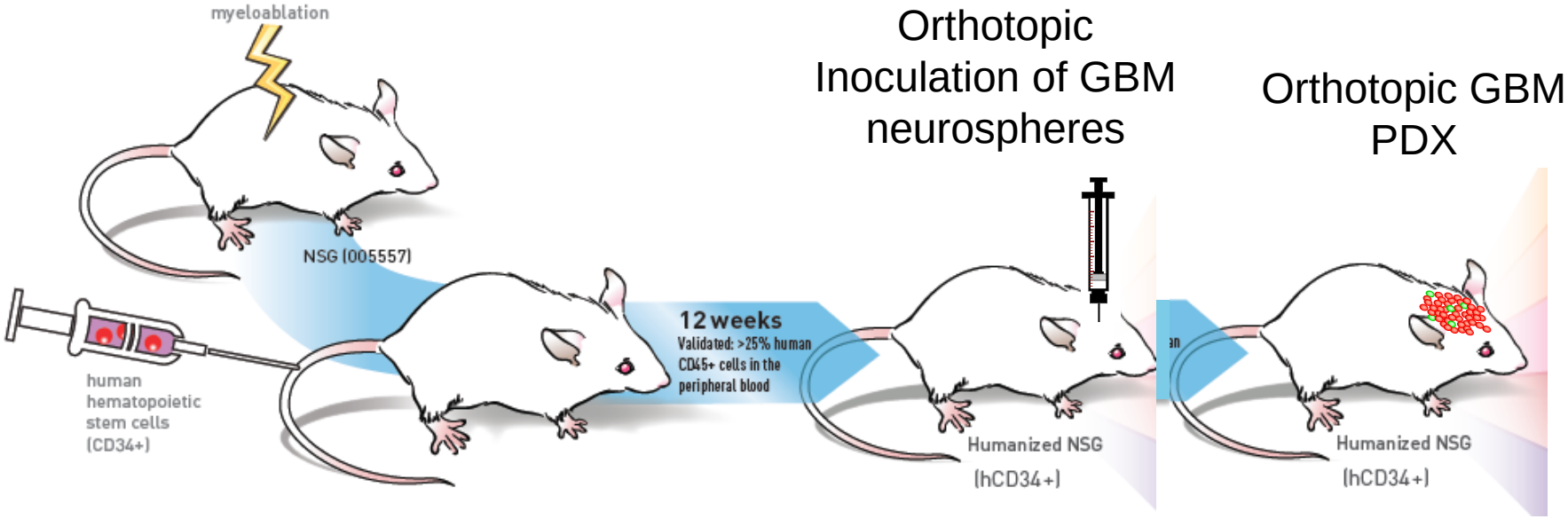
Precision medicine strategy.



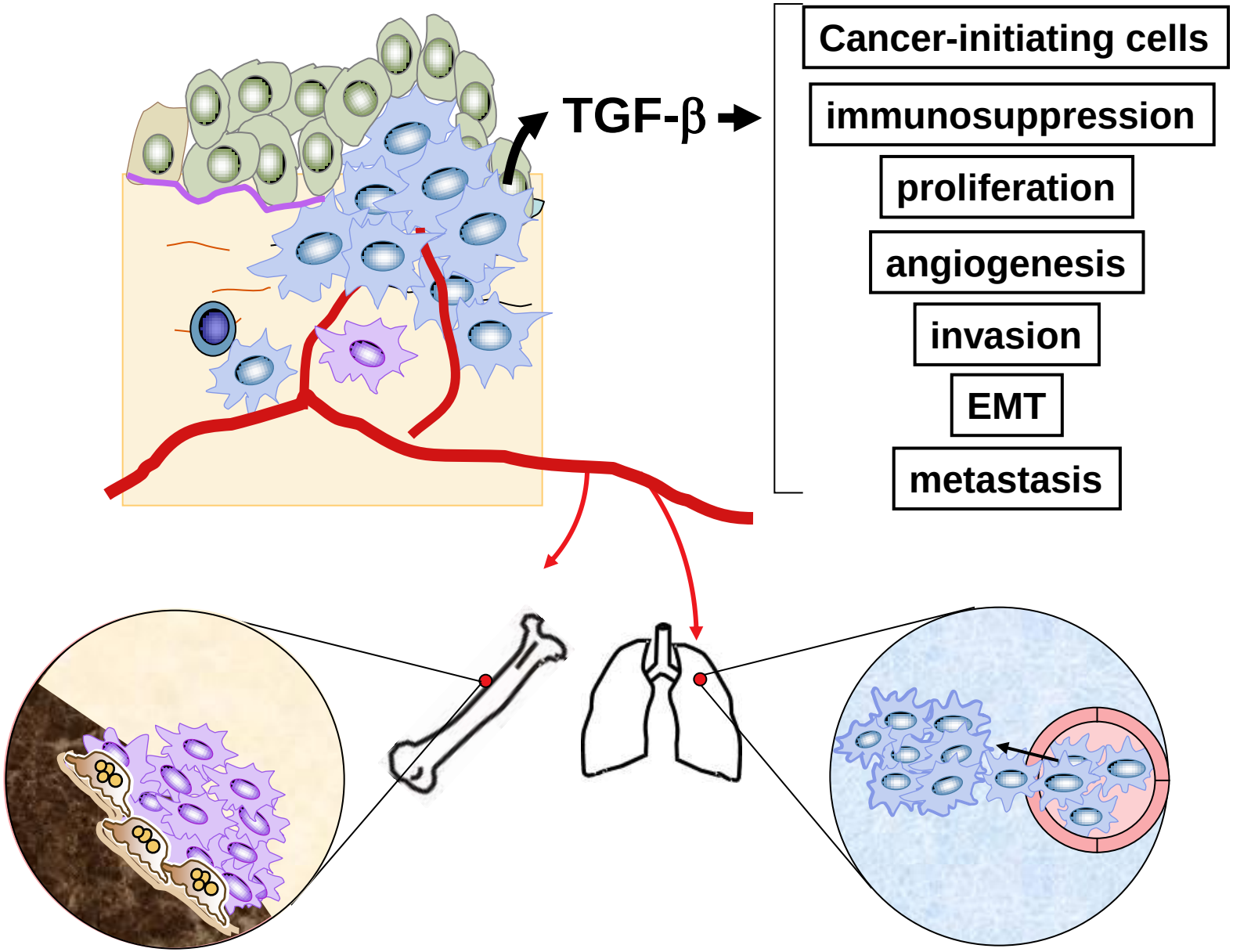
Hidalgo M et al. Cancer Discovery 2014;4:998-1013

Immune system

humanized CD34+ PDX mouse model for GBM

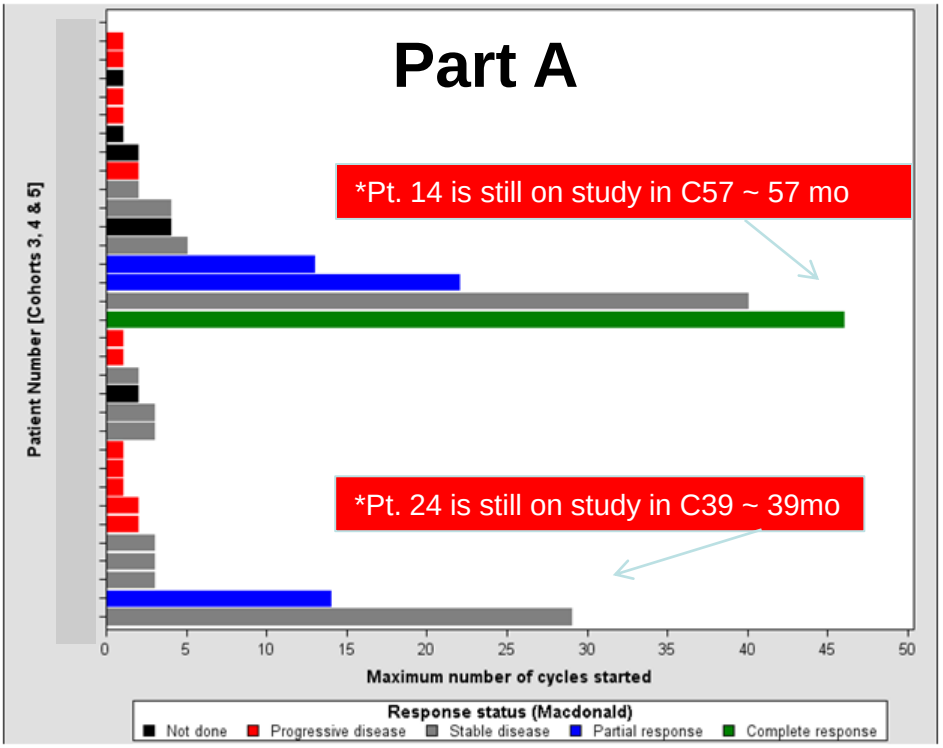


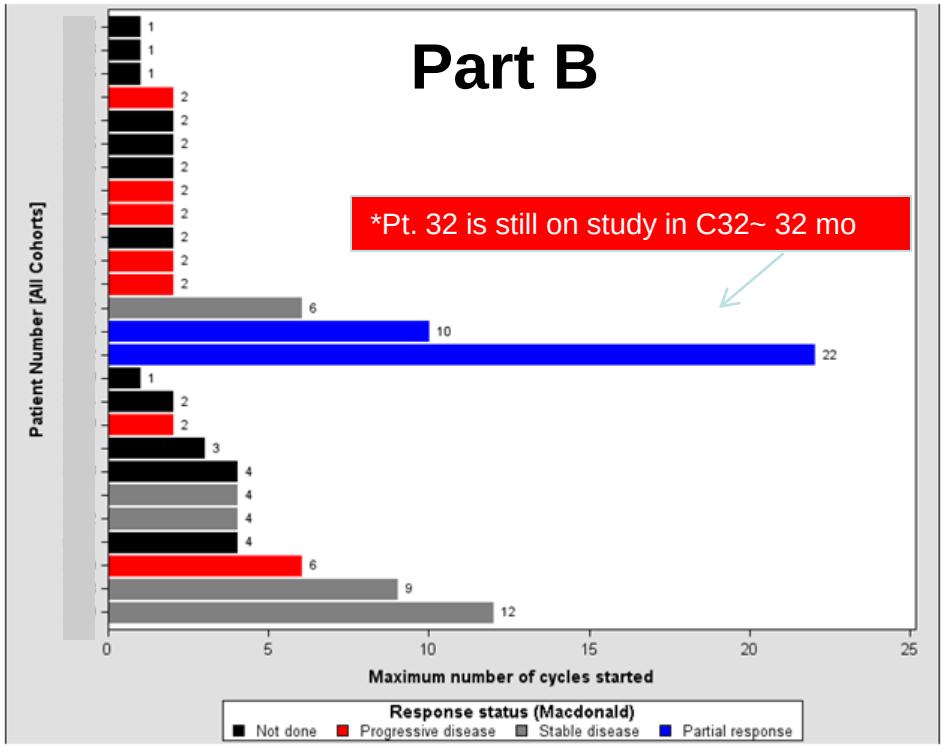
TGFβ oncogenic response



Seoane, Clin Trans Oncology 2008

First in human LY2157299 in patients with glioblastoma
Efficacy Outcomes

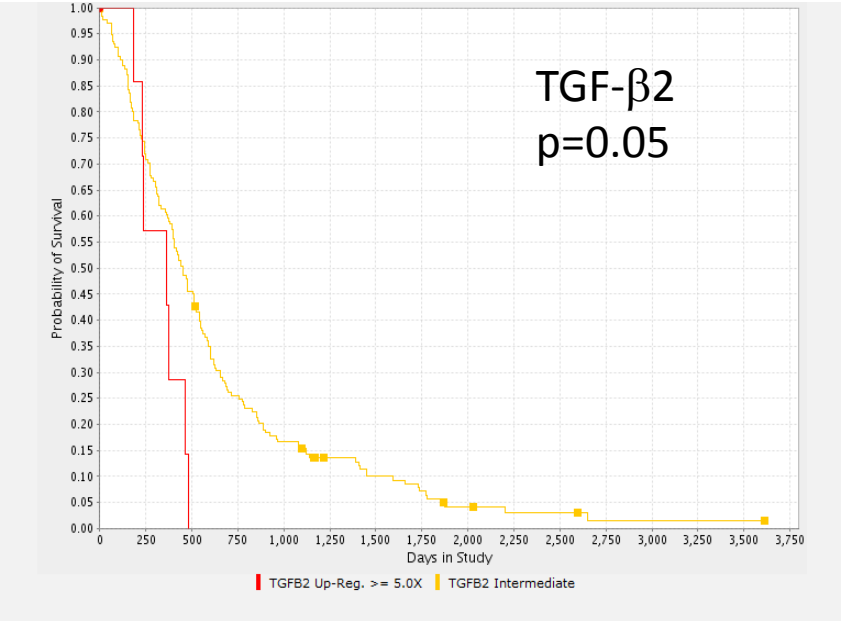


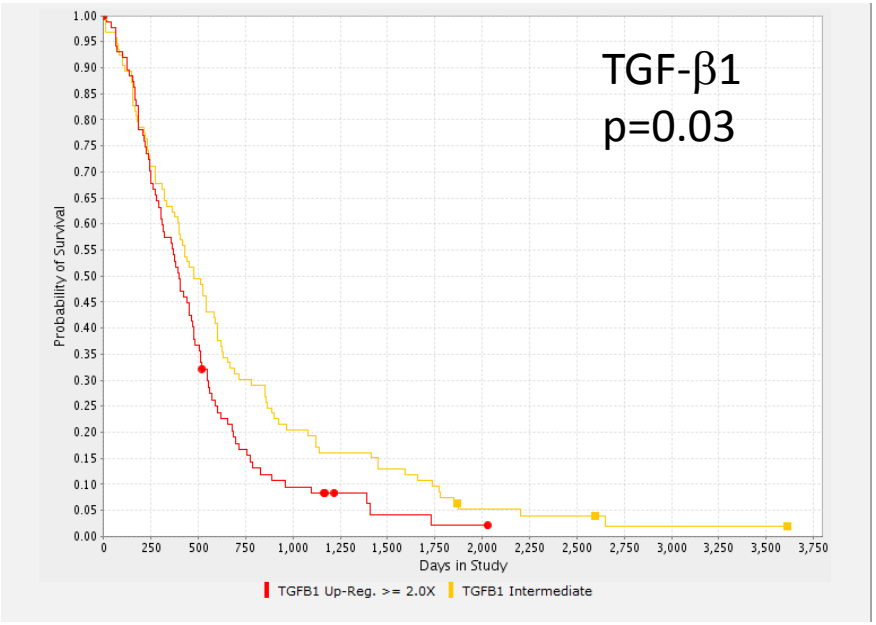


Rodón et al. ASCO, 2013

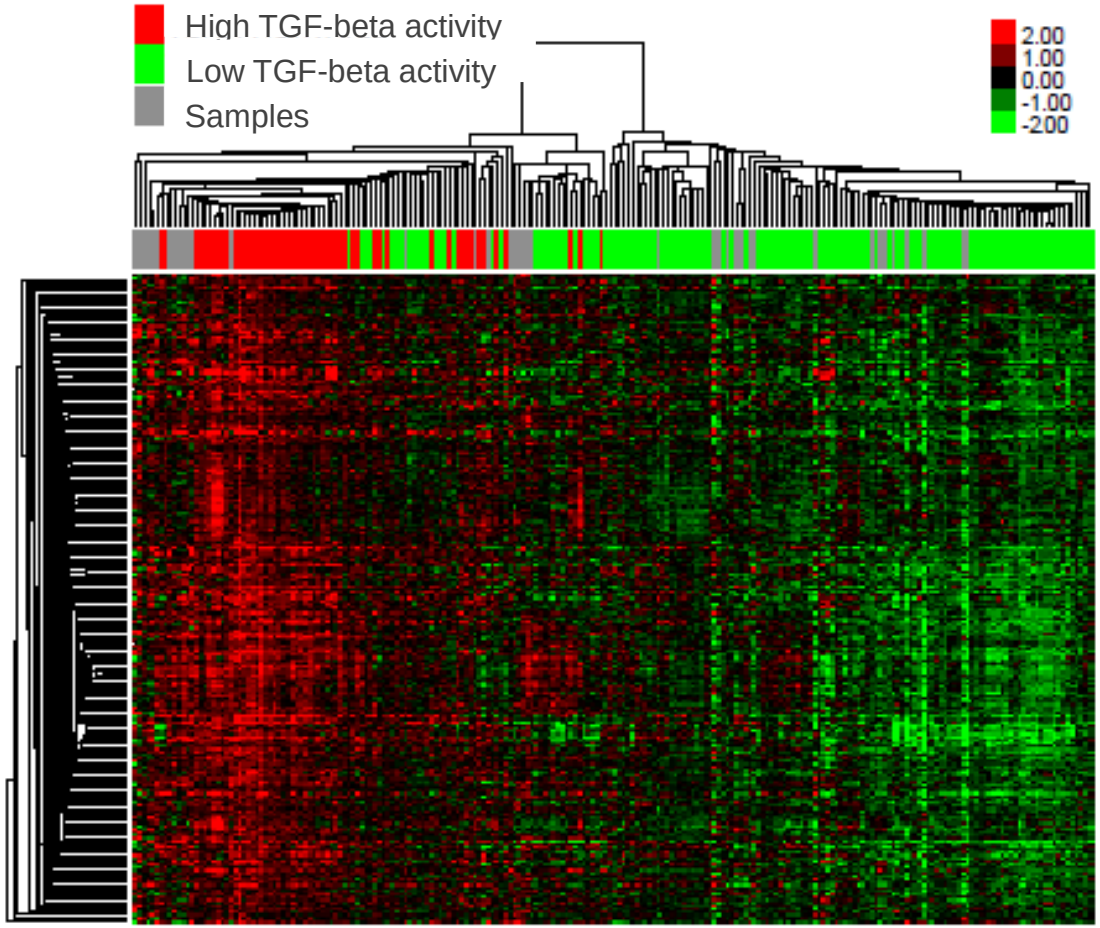
High TGF-beta is a poor prognostic factor in GBM

(Rembrandt, TCGA data base)

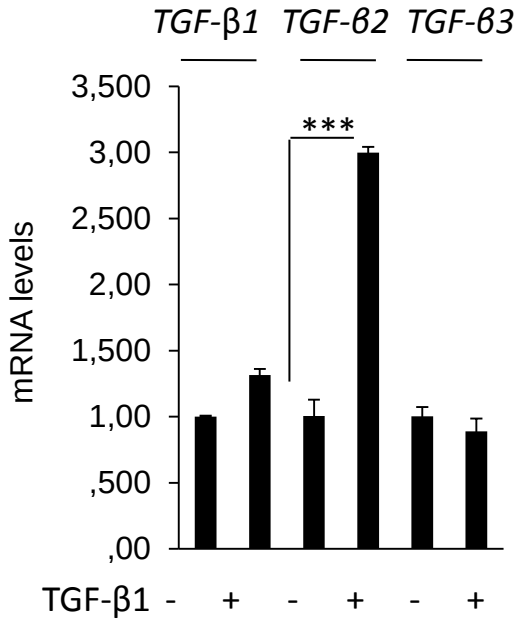


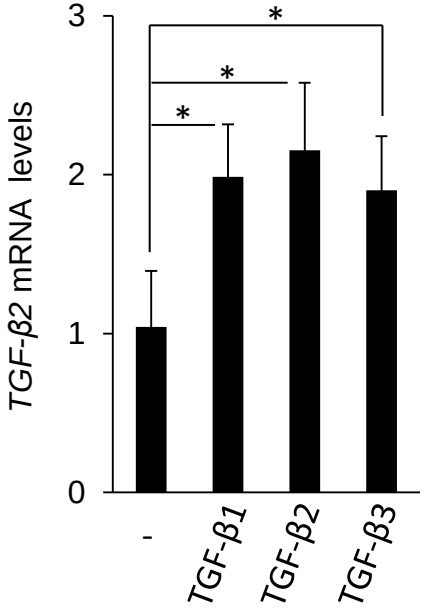


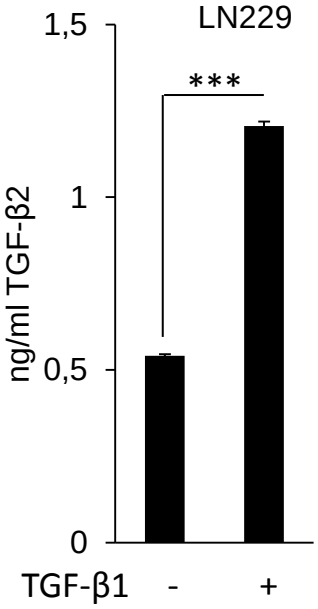
TGFβ activity in GBM

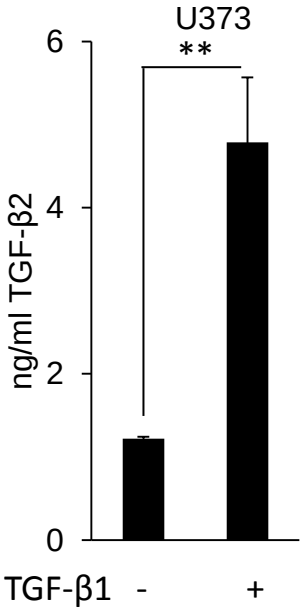


TGFβ can induce TGFβ2 in GBM

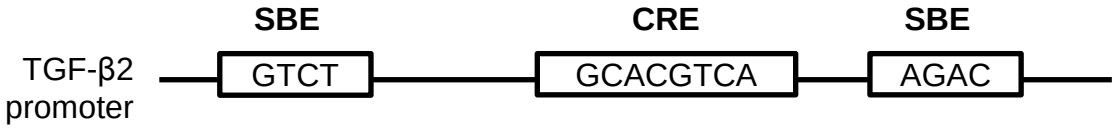


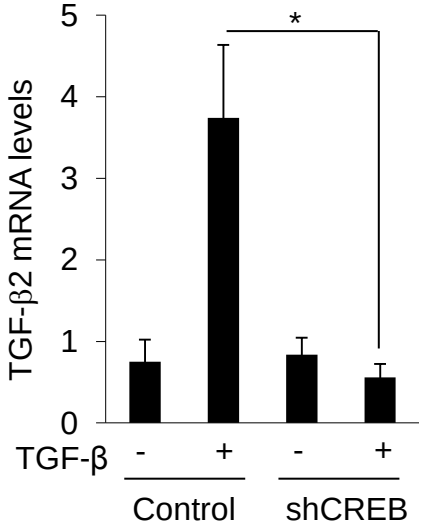


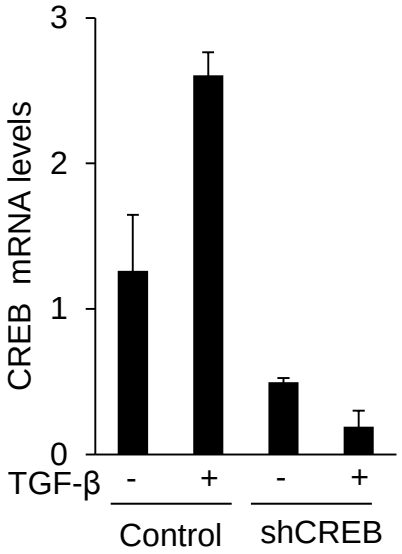




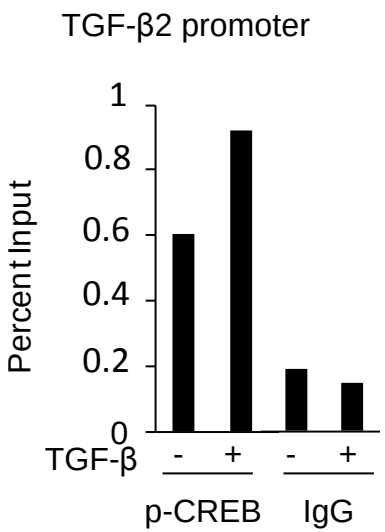
CREB regulates the induction of TGFβ2 by TGFβ

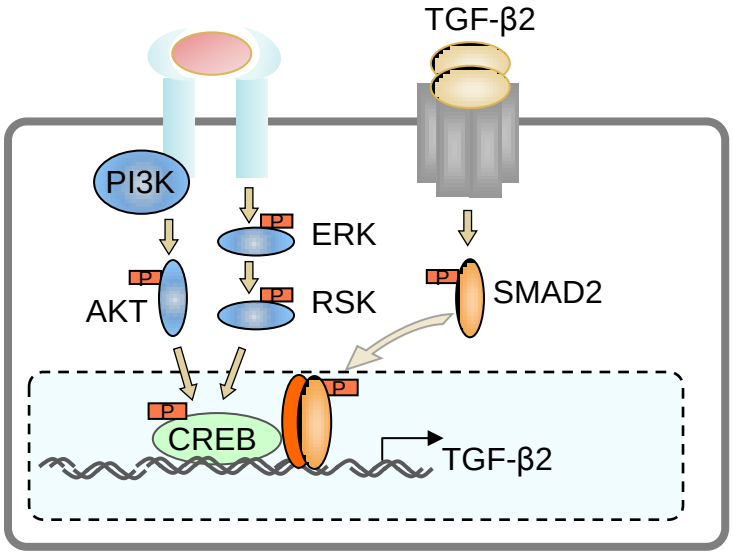




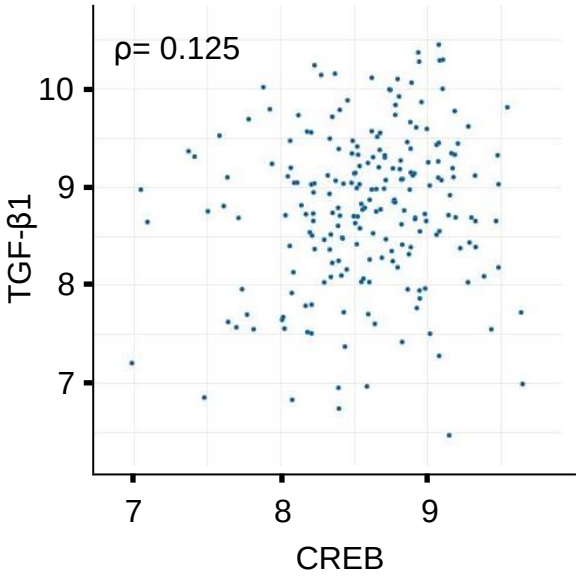


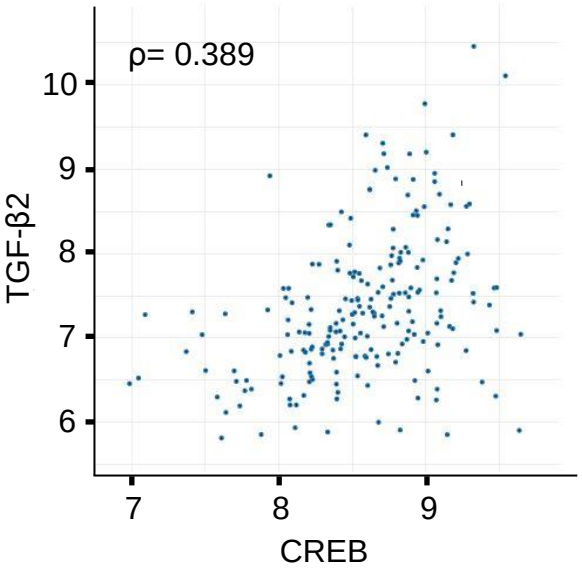
ChIP shows that CREB binds to the TGF-β2 promoter

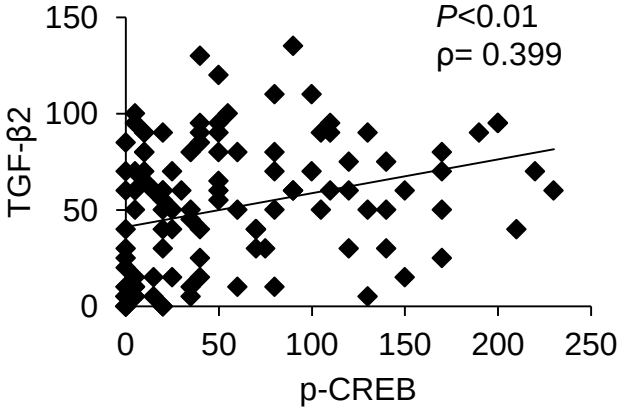


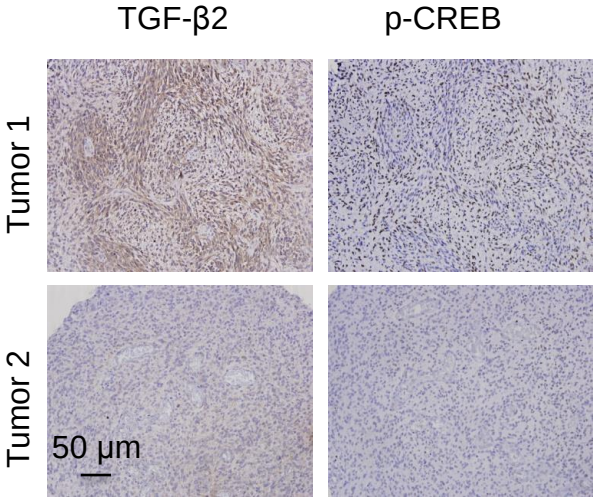

TGF-β2
PI3K
ERK
AKT
RSK
SMAD2
CREB
TGF-β2

p-CREB levels correlate with TGF-β2

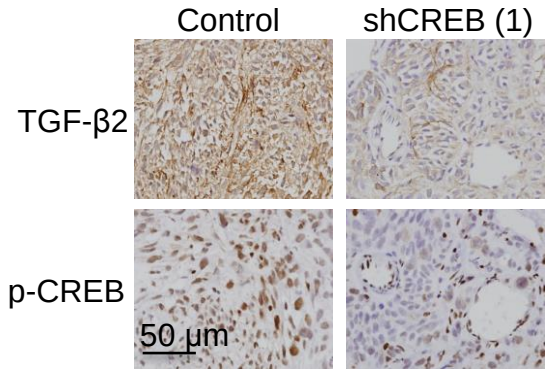


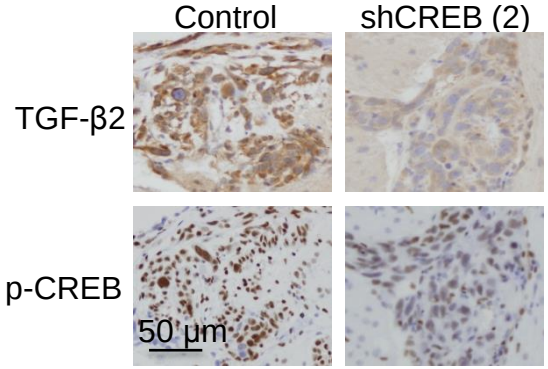


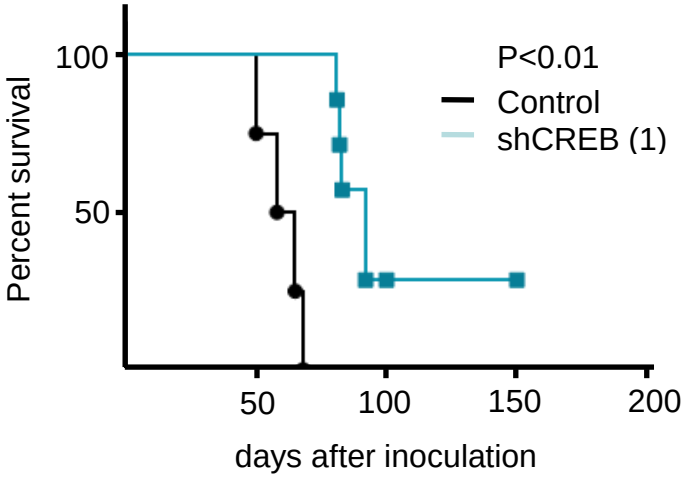


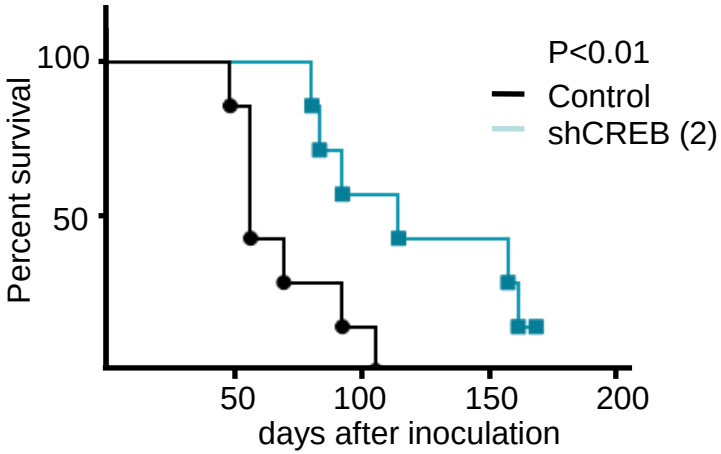


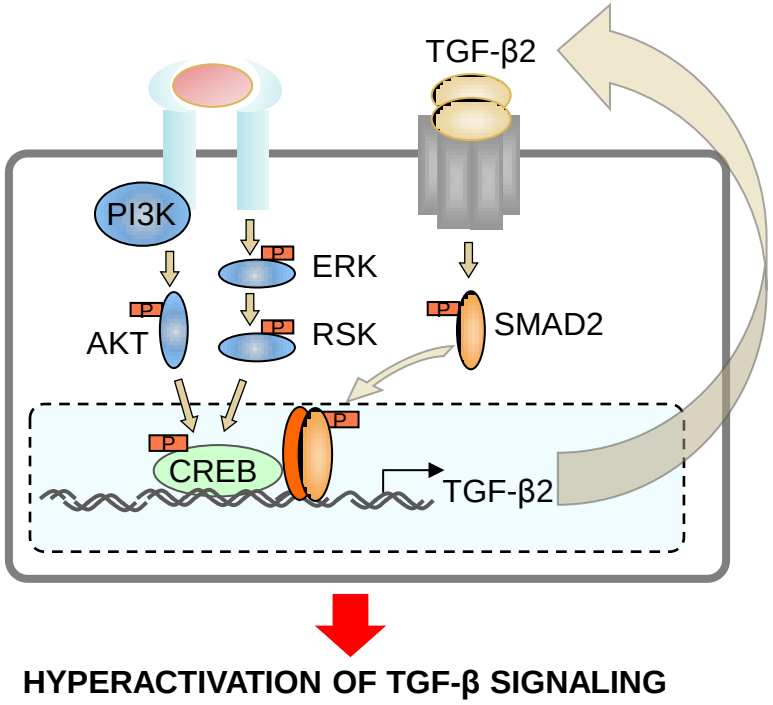
CREB regulates TGF-β2 and oncogenesis in patient-derived models





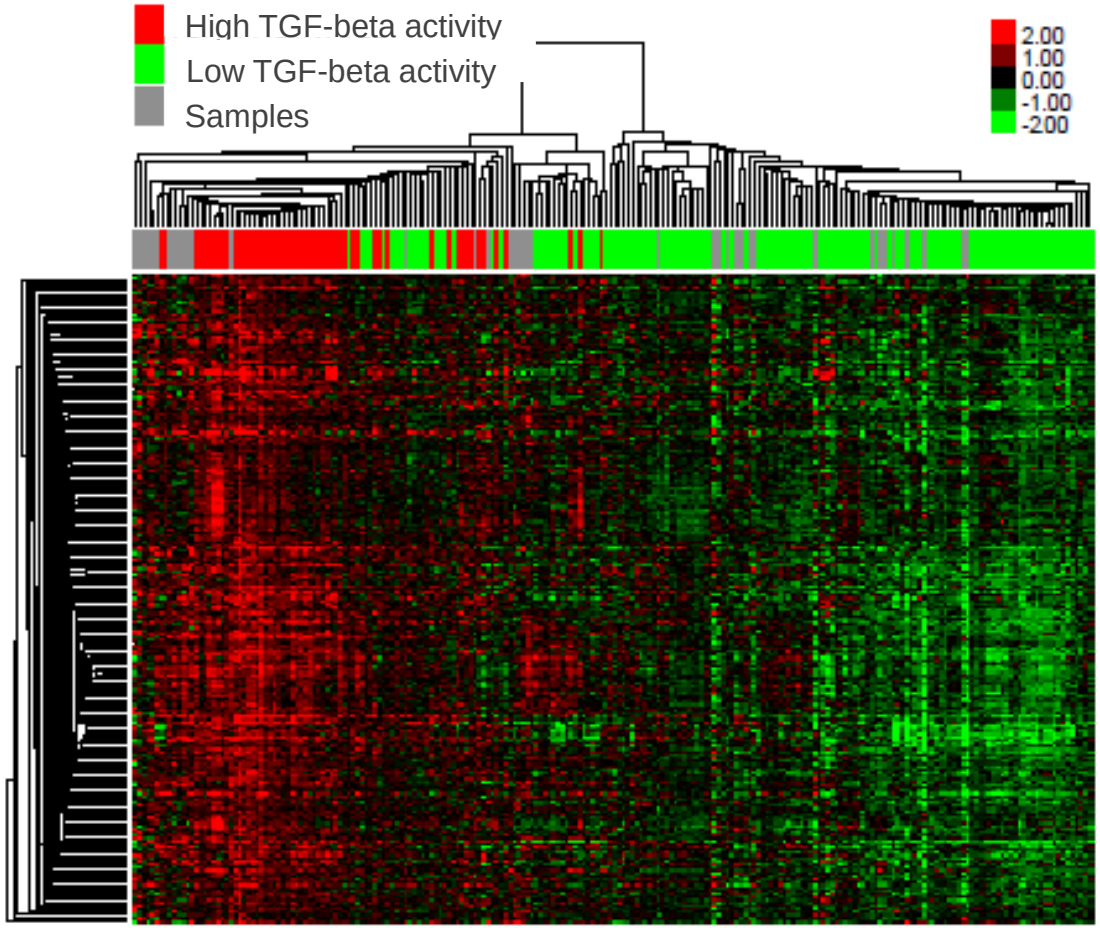






Rodon L., Cancer Discovery 2014

TGFβ activity in GBM



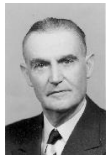
Maria del Mar Inda
Pieter Eichhorn
Isabel Huber
Rudy Bonavia
Judit Anido
Leticia De Mattos-Arruda

Gerard Folch
Laura Rodón
Alba Gonzàlez-Juncà
Ada Sala

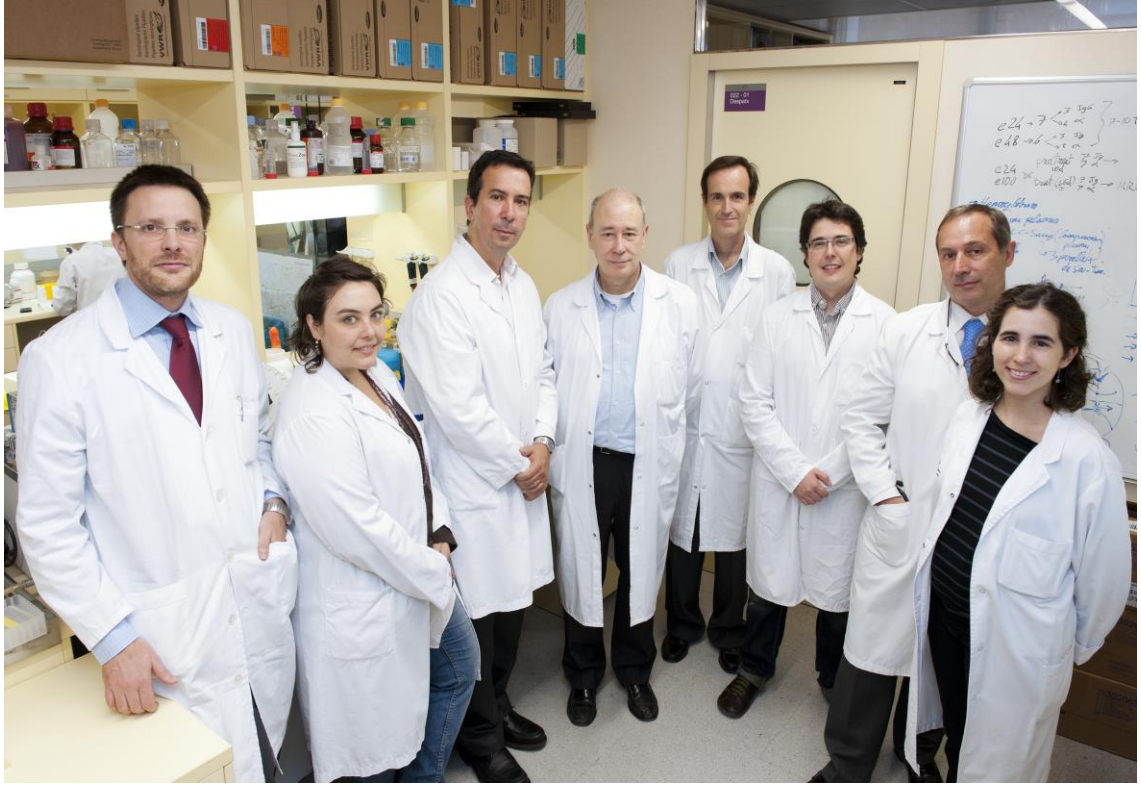
Alexandra Arias
Isabel Cuartas
Carolina Raventós

European Research Council

Instituto de Salud Carlos III



Steiner Foundation



Medical Oncology
Josep Tabernero
Jordi Rodón
Joan Carles

Neurosurgery
Juan Sahuquillo
Fran Martínez
Maria Antonia Poca

Radiotherapy
Xavier Maldonado

Pathology
Elena Martínez
Claudia Aura
Paolo Nuciforo

Genomics Unit
Ana Vivancos

Proteomic Unit
Francesc Canals
Nuria Colomé

Vall d'Hebron Institute of Oncology (VHIO)
Vall d'Hebron University Hospital
Barcelona