"Targeting Endoplasmic Reticulum proteostasis in cancer"

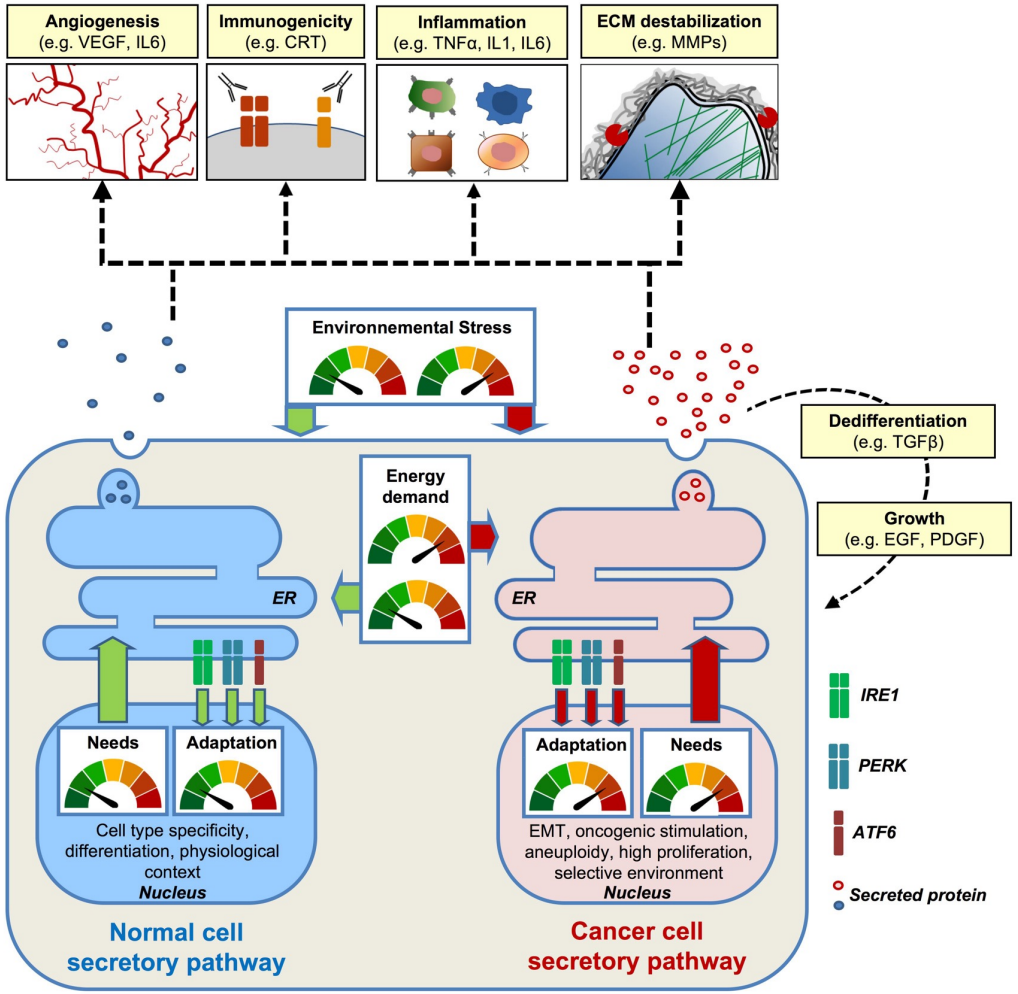
20 ans en 30 min.

Eric Chevet
INSERM U1242 Univ Rennes, CLCC Eugène Marquis, Rennes, France
eric.chevet@inserm.fr

Four parts

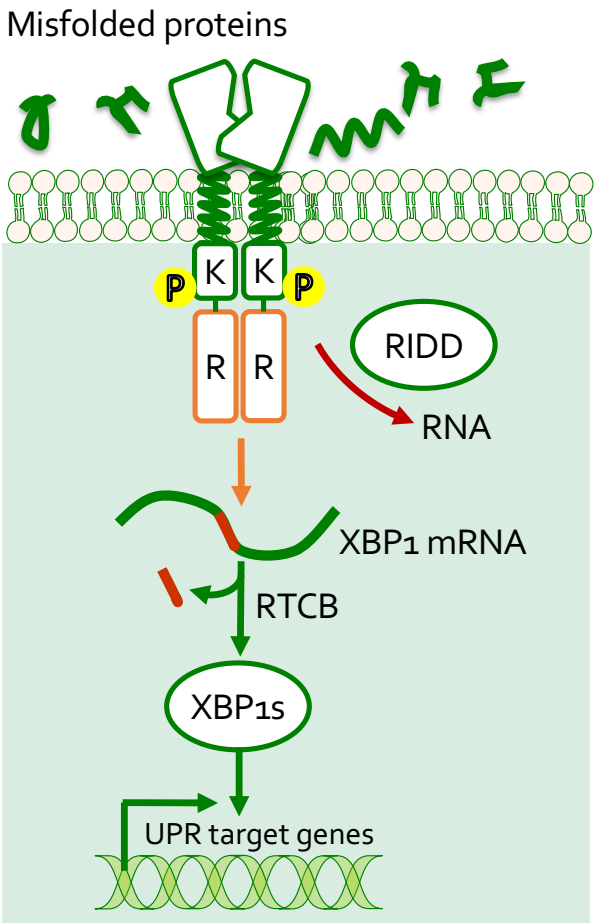
1) Qualification of the (*potential therapeutic*) target
2) Preclinical model and proof of concept
3) Screening and hit improvement
4) New information and mode of action

The secretory pathway in cancer



Dejeans 2015

IRE1 signaling & cancer



IRE1 RNase activity controls cellular reprogramming at both transcriptional and post-transcriptional levels

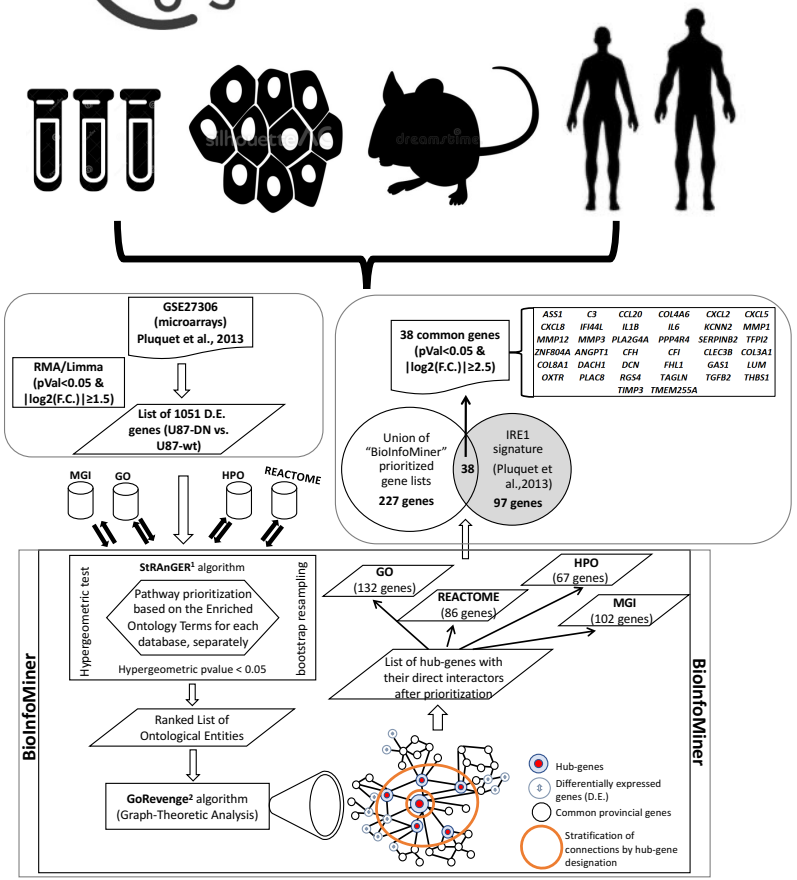
⇨ SIGNAL INTEGRATION

⇩

BIOLOGICAL OUTPUTS
-ER proteostasis maintenance
-Control of essential functions in TUMOR development (canonical and non canonical IRE1 signaling)

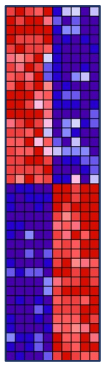
Drogat 2007.; Auf 2010; Dejeans 2012; Pluquet 2013; Higa 2014; Marza 2015

IRE1 activity molecular signature in GB models

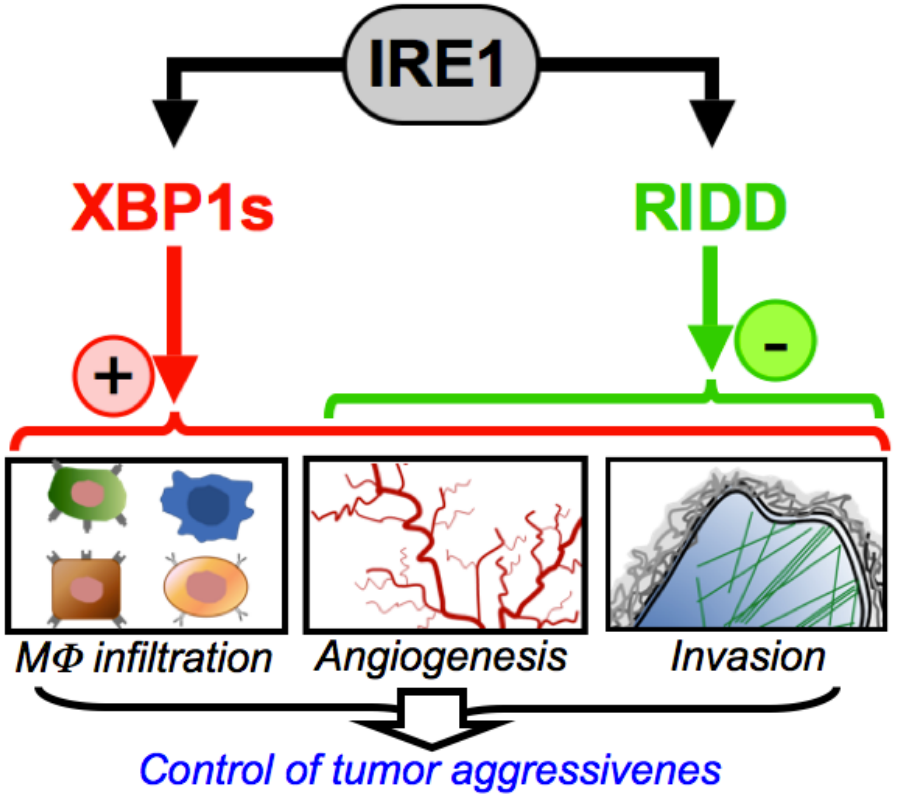


IRE1-38

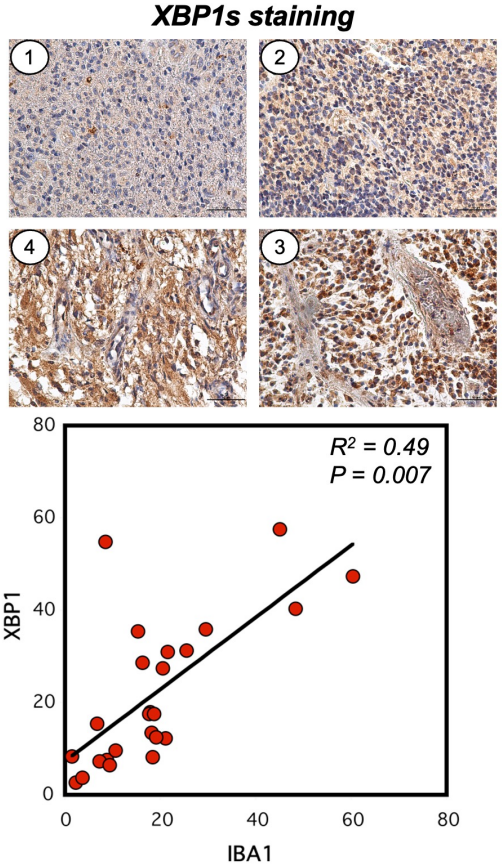
IRE1-activity signature

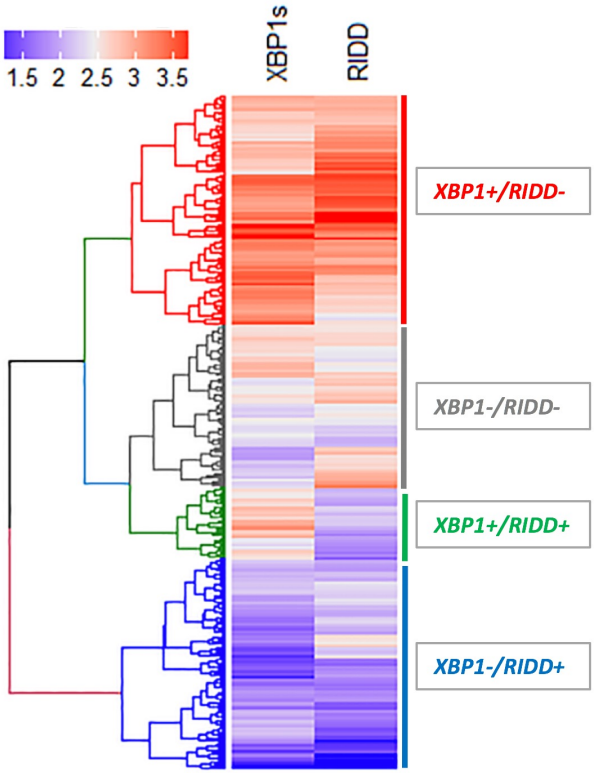


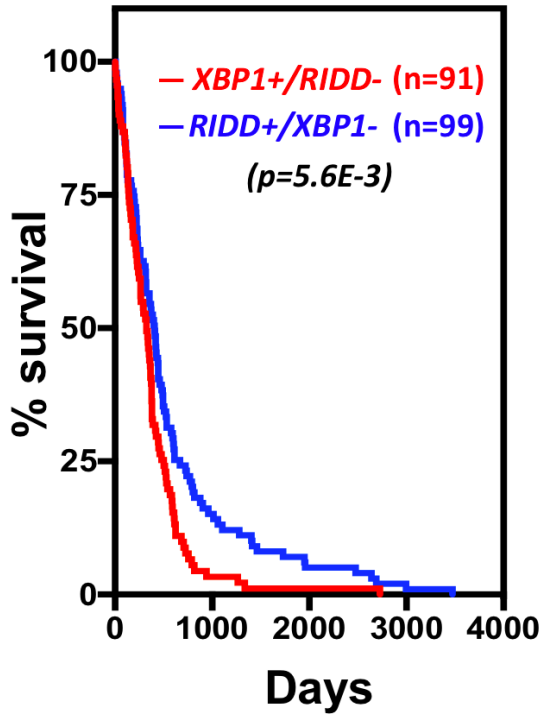
XBP1/RIDD



IRE1 activity molecular signature in human GB

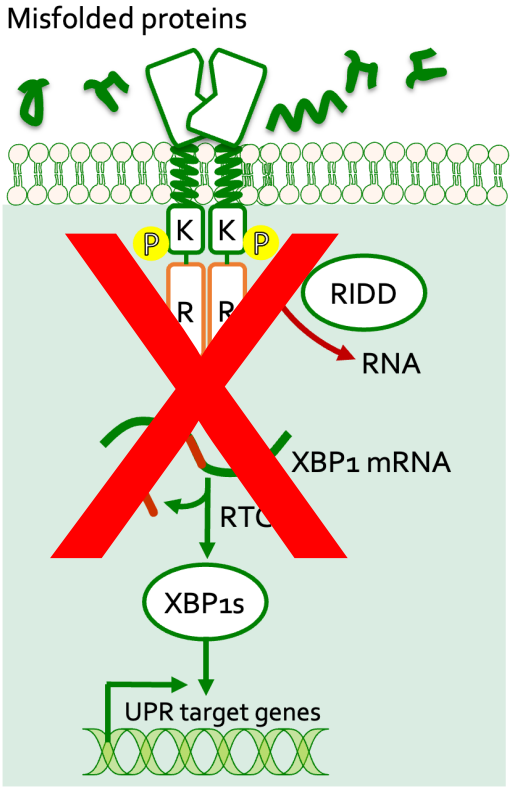


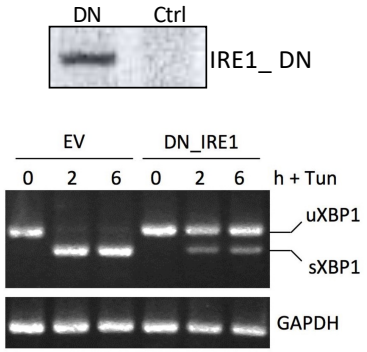


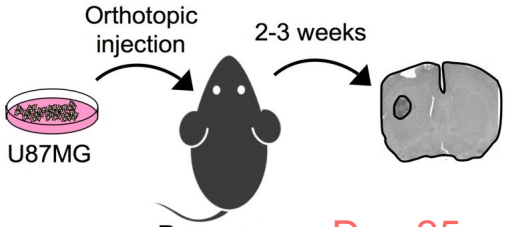


XBP1s is linked to tumor aggressiveness

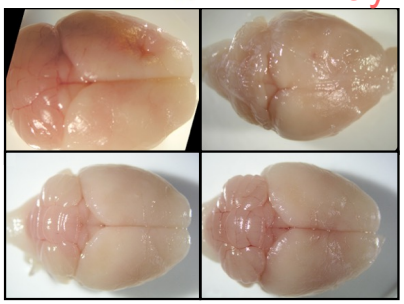
Genetic ablation of IRE1 signaling in GB

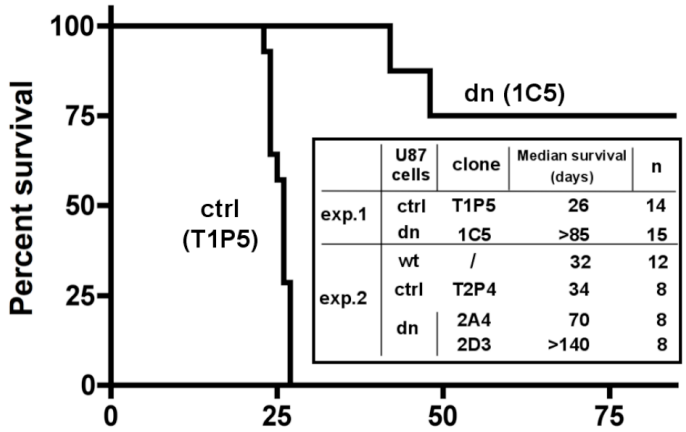






Day 25





	U87 cells	clone	Median survival (days)	n
exp.1	ctrl	T1P5	26	14
	dn	1C5	>85	15
exp.2	wt	/	32	12
	ctrl	T2P4	34	8
	dn	2A4	70	8
		2D3	>140	8

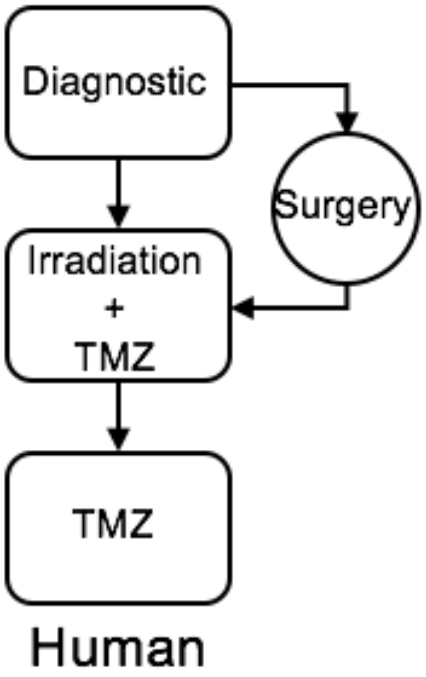
Nguyen 2004

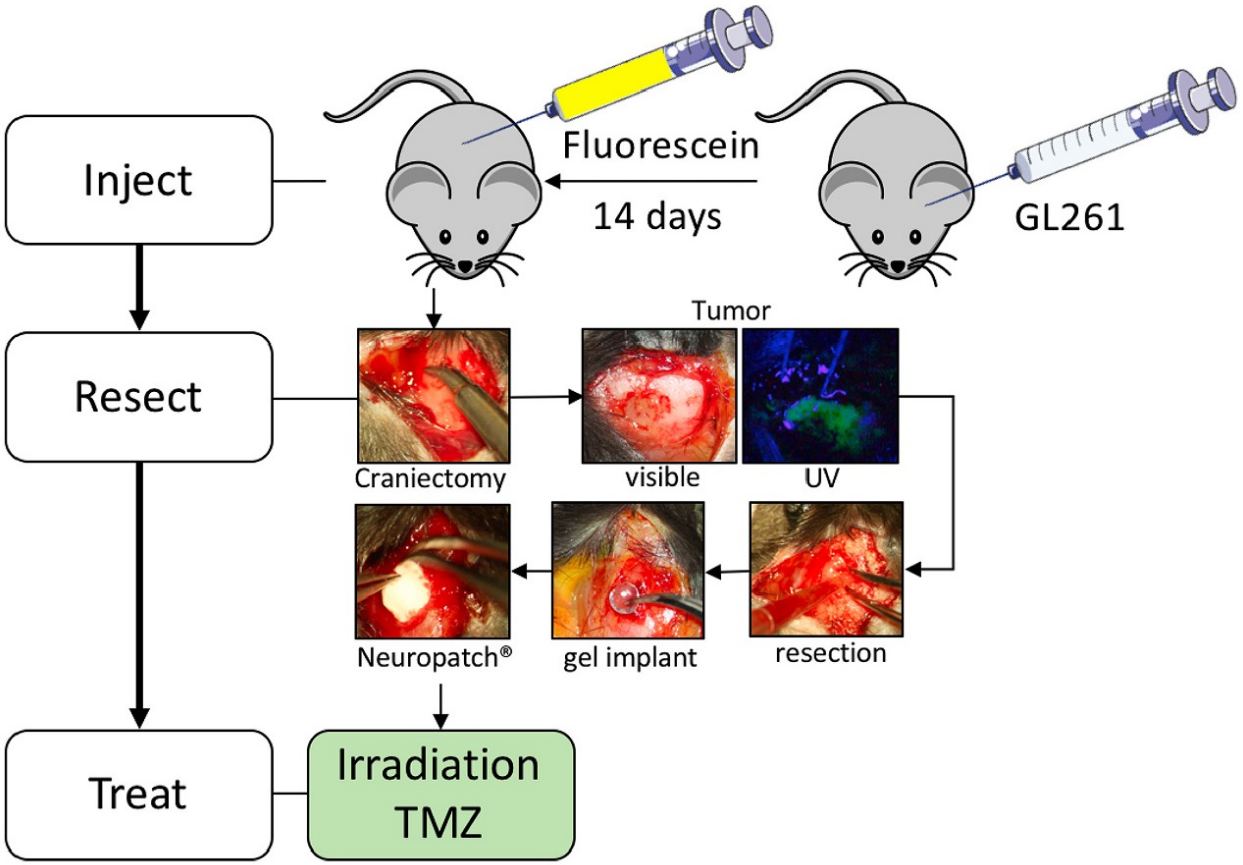
Drogat 2007

Relevant preclinical model of GB


PJ. Le Reste

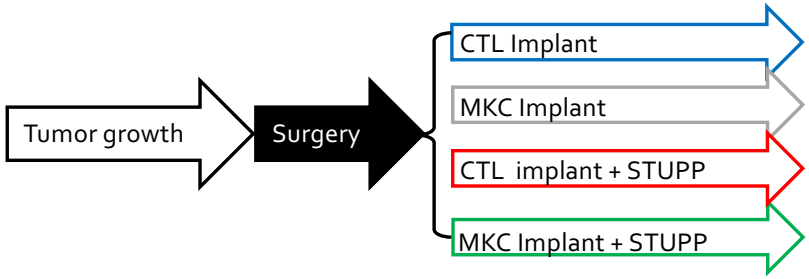

R. Pineau



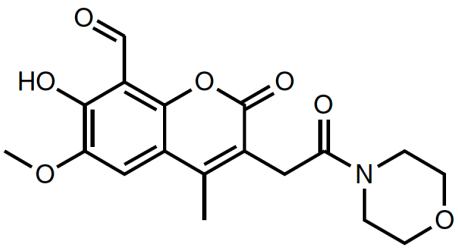


Le Reste 2020

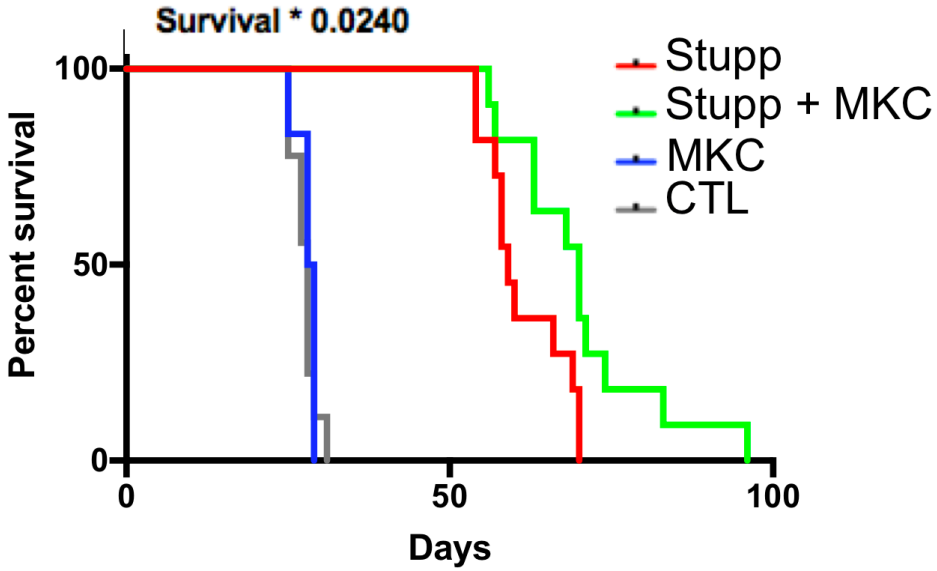
Pharmacologic ablation of IRE1 signaling in GB



1 single application of MKC8866



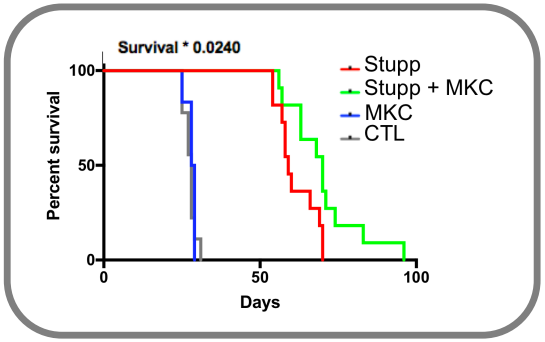
IRE1 RNase inhibitor MKC8866



Improvement of STUPP efficacy in GB by MKC8866 BUT limited efficacy due to delivery method.

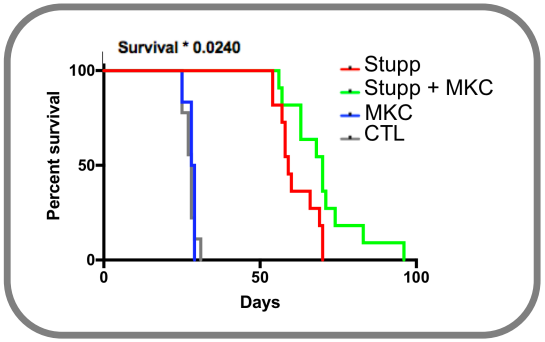
Le Reste 2020

Response improvement strategies



How to improve the effects of the IRE1 inhibitors?

Response improvement strategies



How to improve the effects of the IRE1 inhibitors?

Improve delivery (biogel)

Find new molecules BBB permeable

New BBB permeable IRE1 inhibitors - discovery


D. Pelizzari

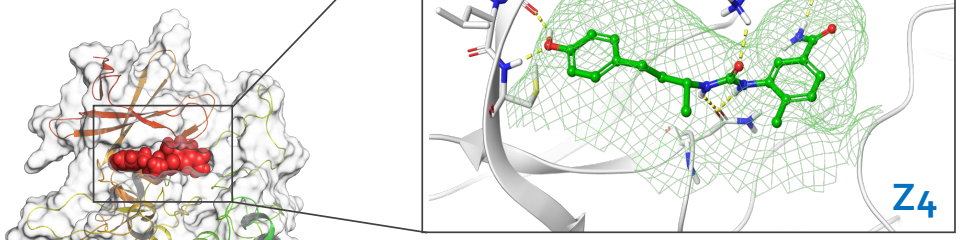

D. Doultsinos

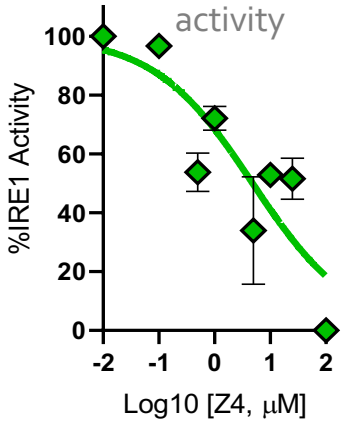

X. Guillory

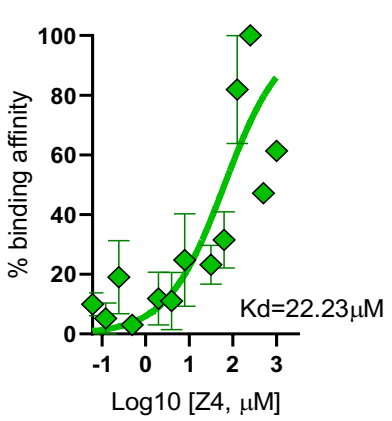

L.A. Eriksson

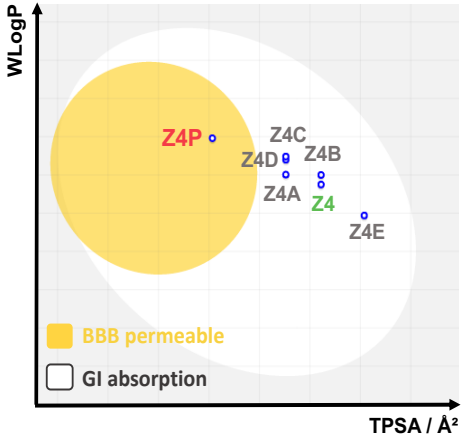
UNIVERSITY OF GOTHENBURG

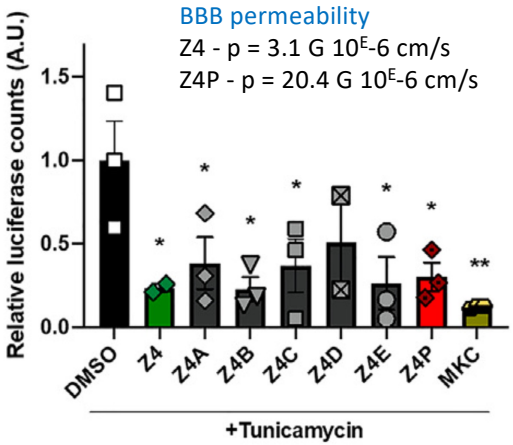
- Design of the IRE1 kinase pocket pharmacophore
- 13 x 10^6 compounds screened *in silico (ZINC15)*
- 75 compounds selected (docking score > ATP)
- 30 best compounds tested *in vitro*
- 2 compounds (Z4, Z6) selected for further analyses





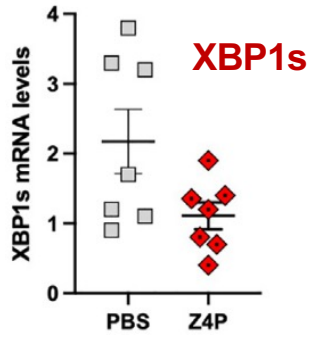


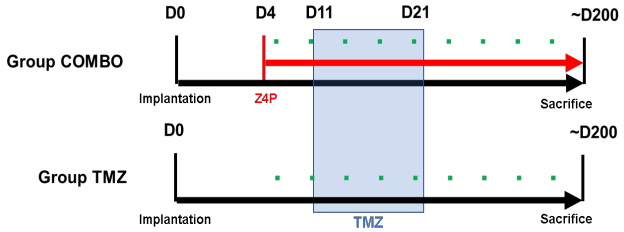


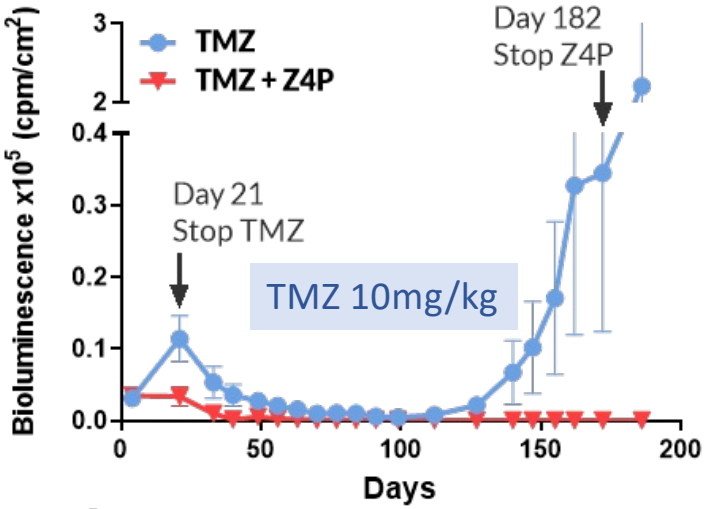


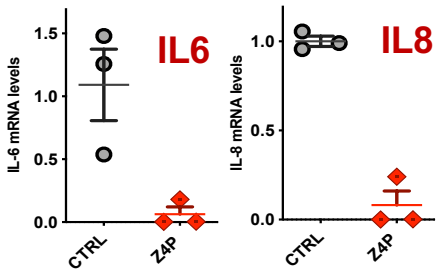
Pelizzari-Raymundo, Doultsinos 2023

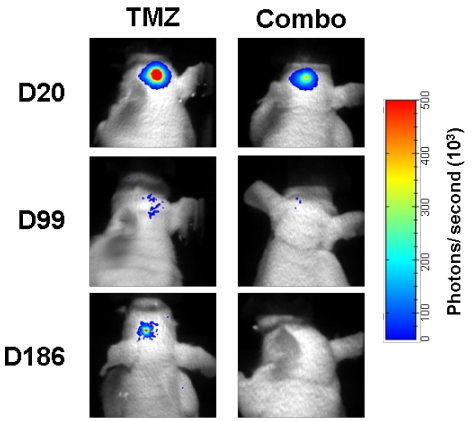
New BBB permeable IRE1 inhibitors - preclinical

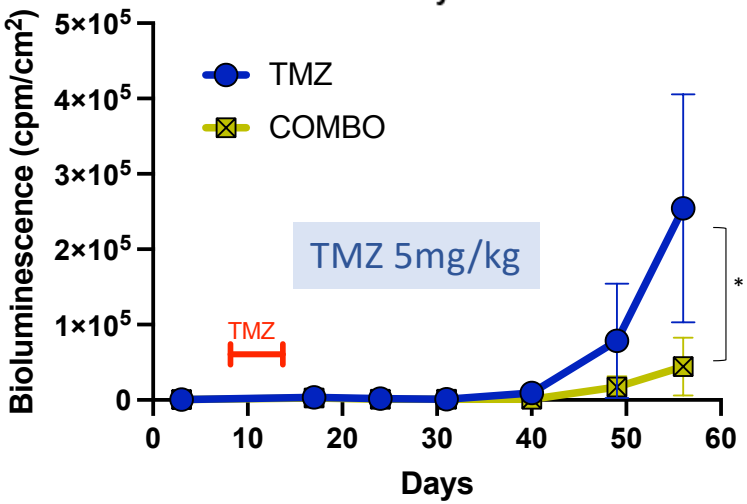








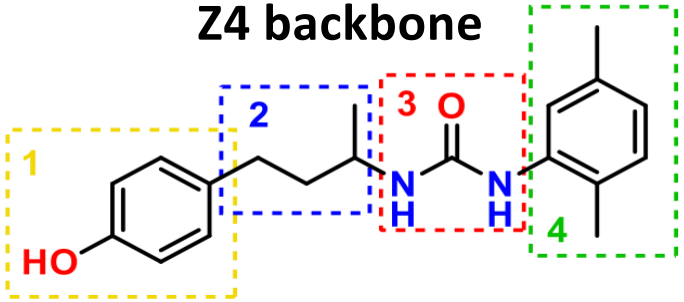




Pelizzari-Raymundo, Doultsinos 2023

New BBB permeable IRE1 inhibitors - preclinical

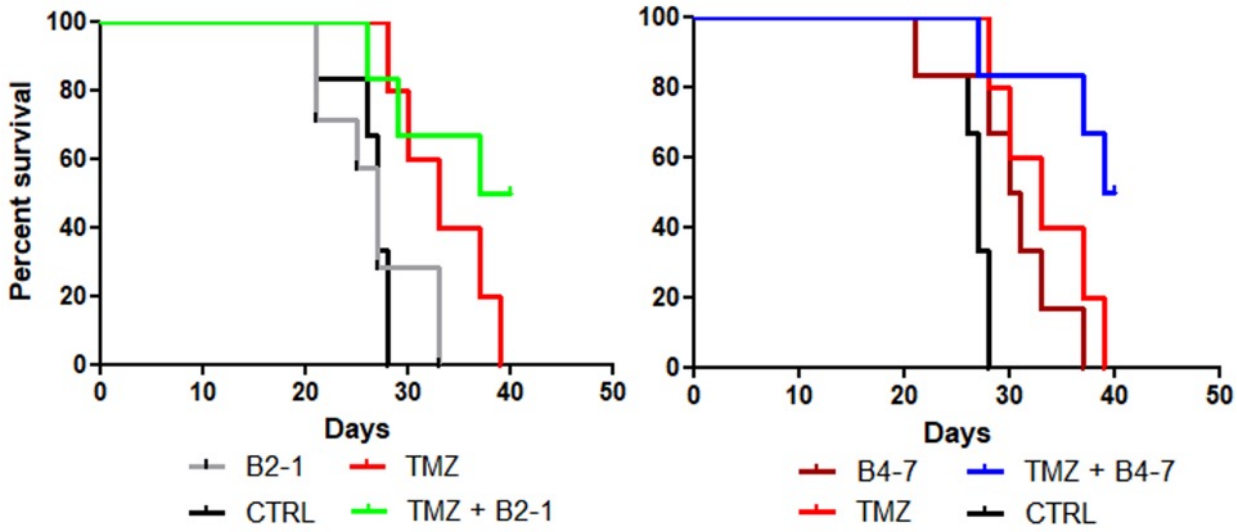
Z4 backbone



SAR STUDY

Better compounds (B2.1, B4.7) with nM range IC50

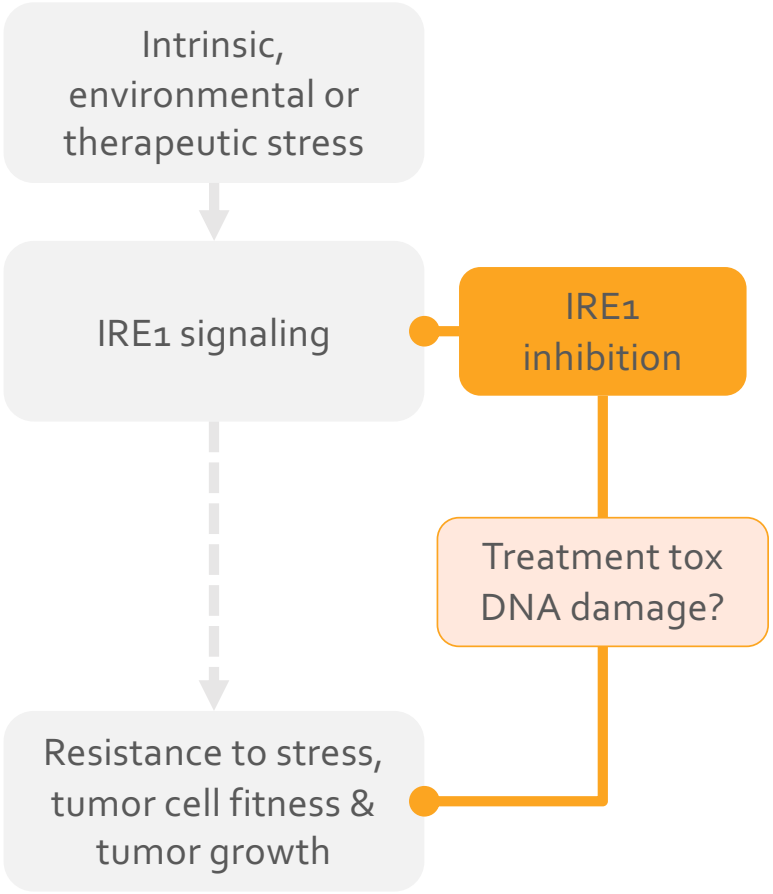
Mouse CT2A
Syngeneic model



Mouse survival

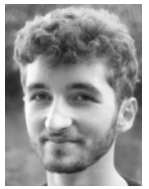
Sébastien Suéron - unpublished

MOA – working hypothesis




J. Mosser

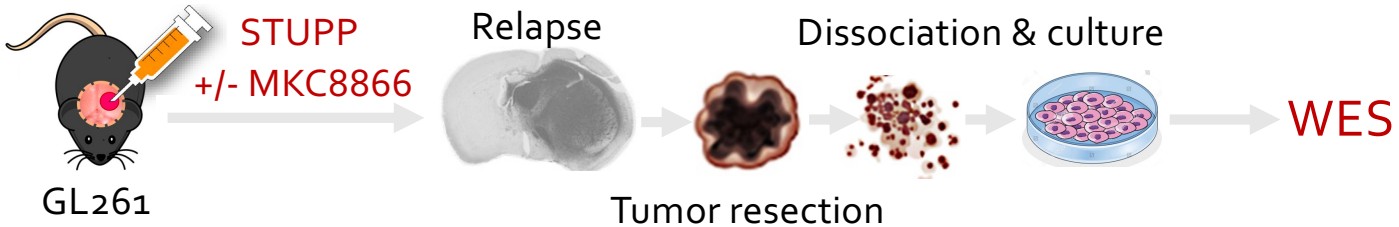

M. Aubry

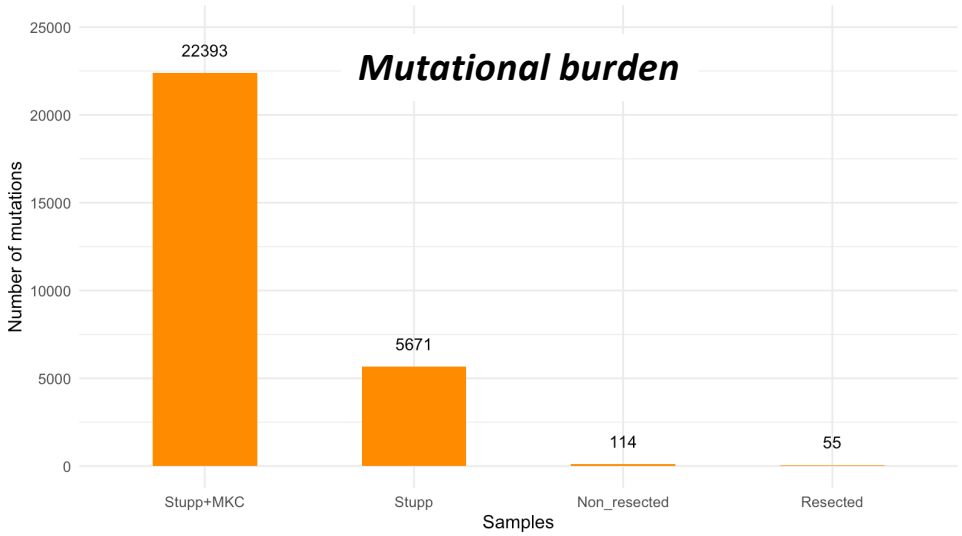

M. Lodé

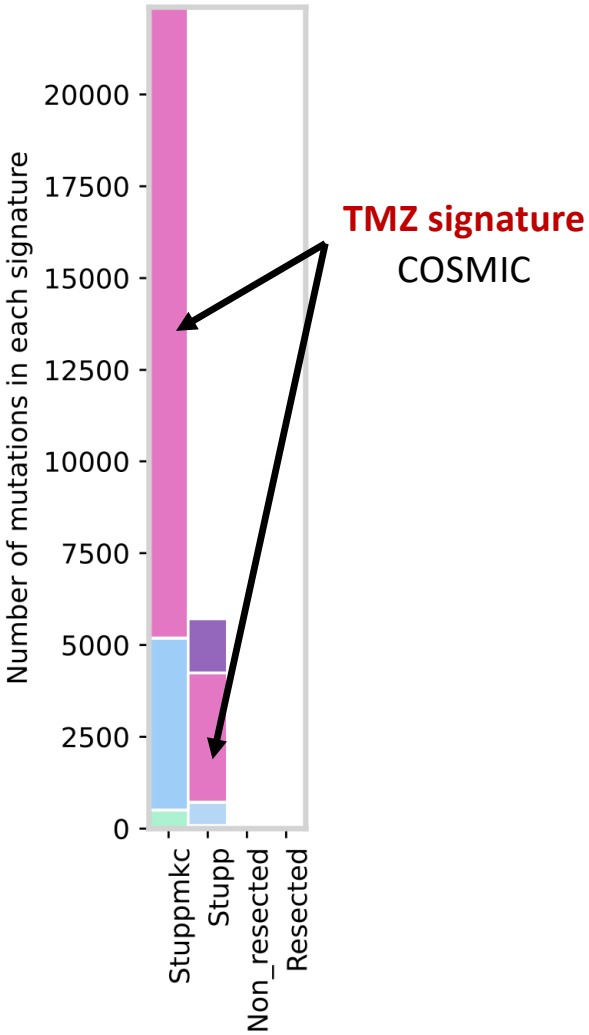

A. Chatziioannou

ACADEMY OF ATHENS
BRFAA

IRE1 inhibition and GB cells sensitivity to standard of care – MoA2







IRE1 signaling might contribute to DNA repair through catalytic mechanisms

Mathéo Lodé - unpublished

CONCLUSION & PERSPECTIVES

- The **IRE1/XBP1s** axis is critical for tumor aggressiveness (in GB and other cancers);
- **IRE1 inhibition** (pharmacological) or silencing sensitizes tumor cells to DNA damage;
- The sensitization mechanisms imply unexpectedly **DNA repair** mechanisms which remain to be fully elucidated.

Collaborations & funding

PROteostasiS And Cancer team

Marc Aubry
Tony Avril
Ketsia Bakambamba
Rachel Boniface
Flavie Caradec
Xavier Guillory
Elodie Lafont
Pierre-Jean Le Reste
Mathéo Lodé
Victoria Maltret
Sophie Martin
Manon Nivet
Annabelle Monnier
Jean Mosser
Diana Pelizzari
Raphael Pineau
Sébastien Suéron
Elodie Vauléon

Collaborators

Aristotelis Chatziioannou, BRFAA, Greece
Leif Eriksson, UGOT, Sweden
Pierre Close, U Liège, Belgium
Arnaud Blomme, U Liège, Belgium
Claudio Hetz, U Chile, Chile
Aeid Igbaria, BGU, Israel
Rémy Pedeux, OSS, France
François-Hugues Porée, ISCR, France

Accepting submissions