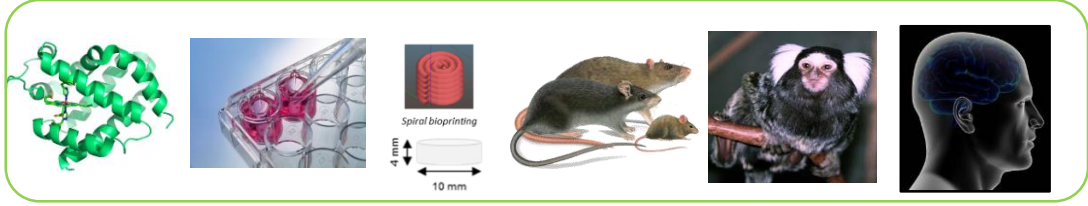
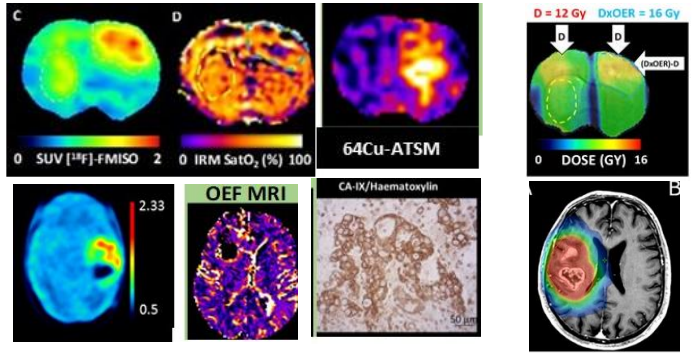
ISTCT UMR 6030
Caen/ GIP CYCERON



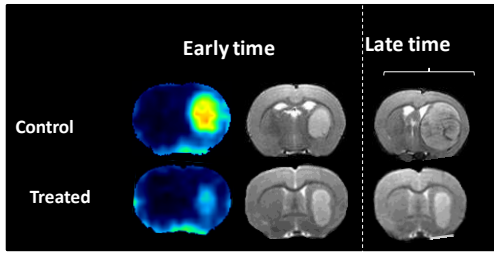
How to counteract hypoxia induced radioresistance

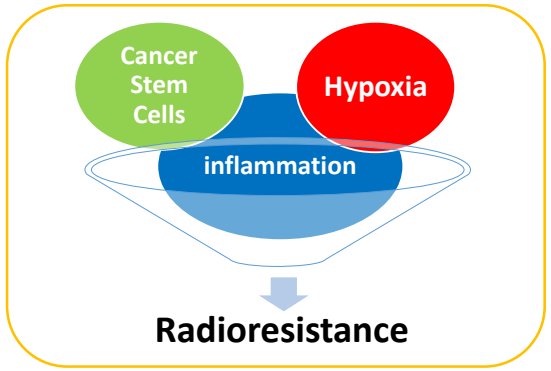
❖ Tumor microenvironment

Characterization of hypoxia
=> treatment orientation



Early imaging of treatment efficacy



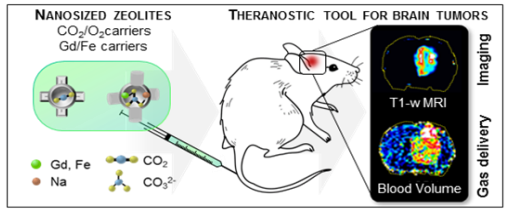


High LET RT

Hadron therapy

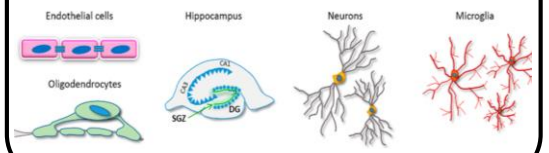
Targeted Alpha Therapy

Reoxygenating NP



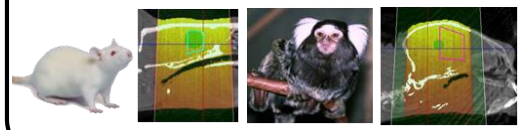
❖ Normal tissue

IN VITRO MODELS



Radiobiology

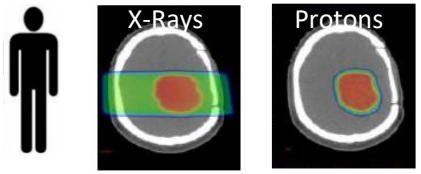
ANIMAL MODELS



Physiopathology

≠ Therapies

PATIENTS



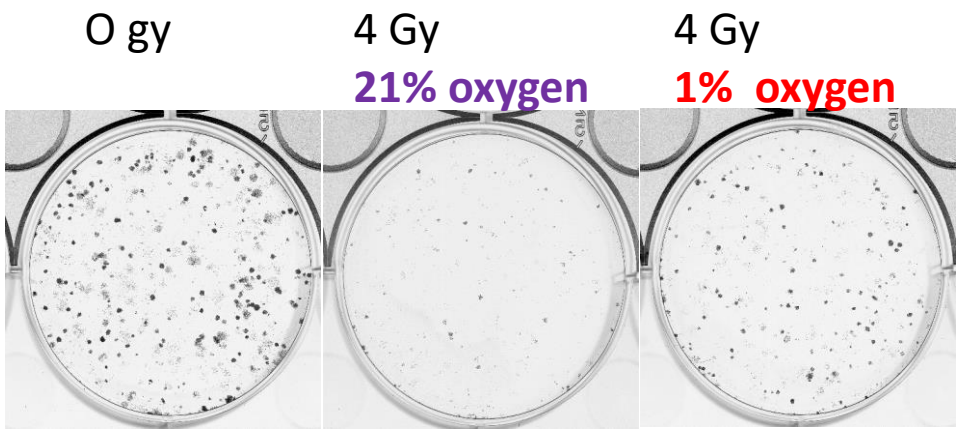
Biomarkers
Imaging, blood

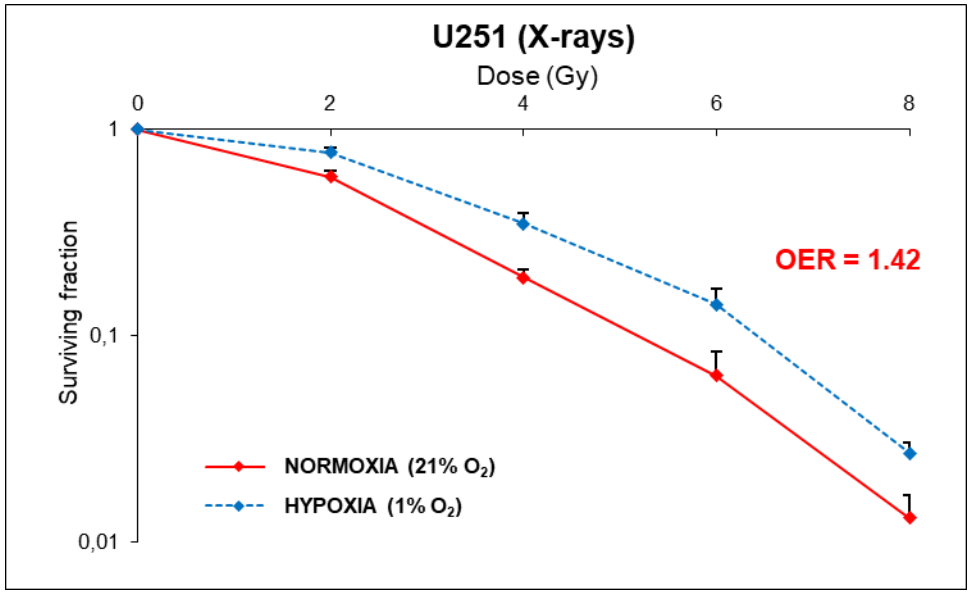
Glioblastoma radioresistance and hypoxia : interest of high LET particles

Oxygen effect → water radiolysis → ROS formation with oxygen increased radiotoxicity

Gray *et al.*, Br. J. Radiol., 1953; Rockwell *et al.*, Curr. Mol. Med., 2009

- Example with U251 GBM cells at 1% => OER 1% = dose hypoxia / dose normoxia = 1.42



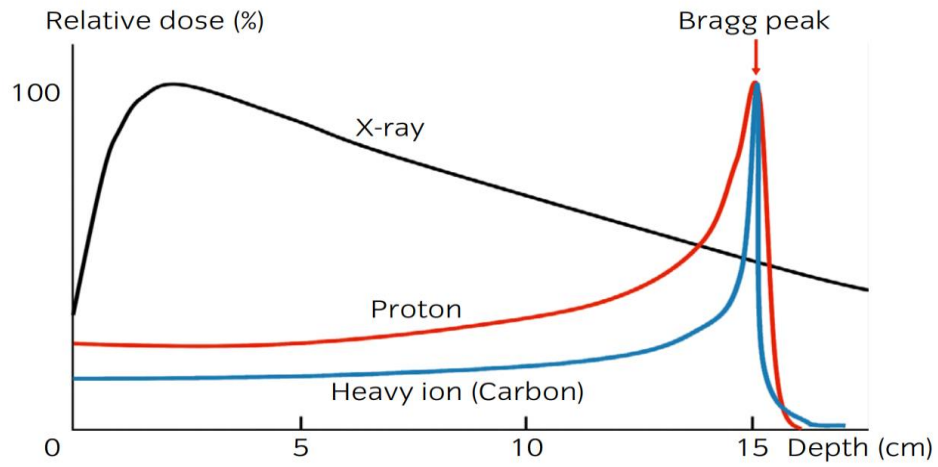


Pérès EA *et al.*, Oncotarget, 2014

What is the effect of high LET particles such as carbon ions to overcome hypoxia-induced radioresistance ?

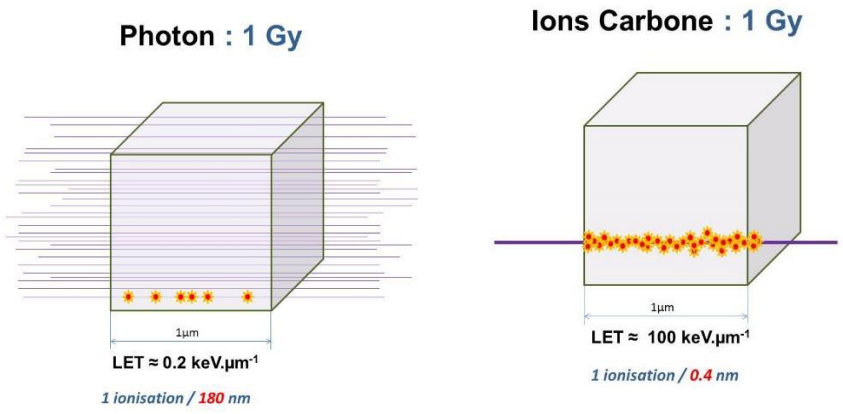
Glioblastoma radioresistance and hypoxia : interest of high LET particles

Better ballistic



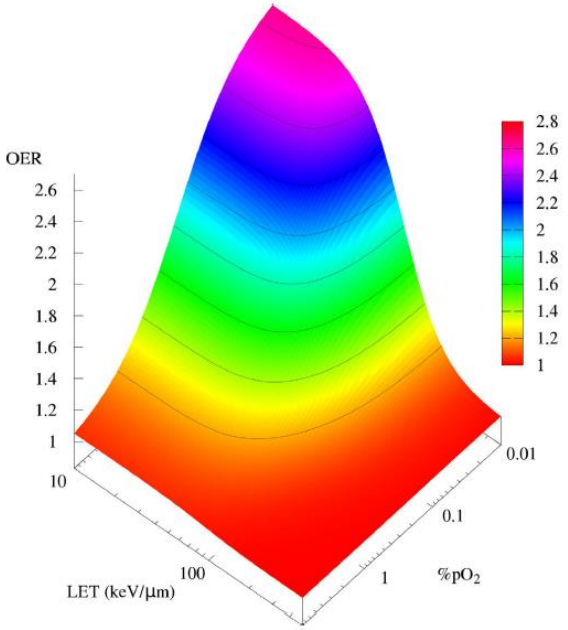
Kawamura *et al.*, Int J Urol, 2020

Greater biological efficacy



Kong *et al.*, Cancer Commun, 2019

Efficacy independent on oxygen effect ?

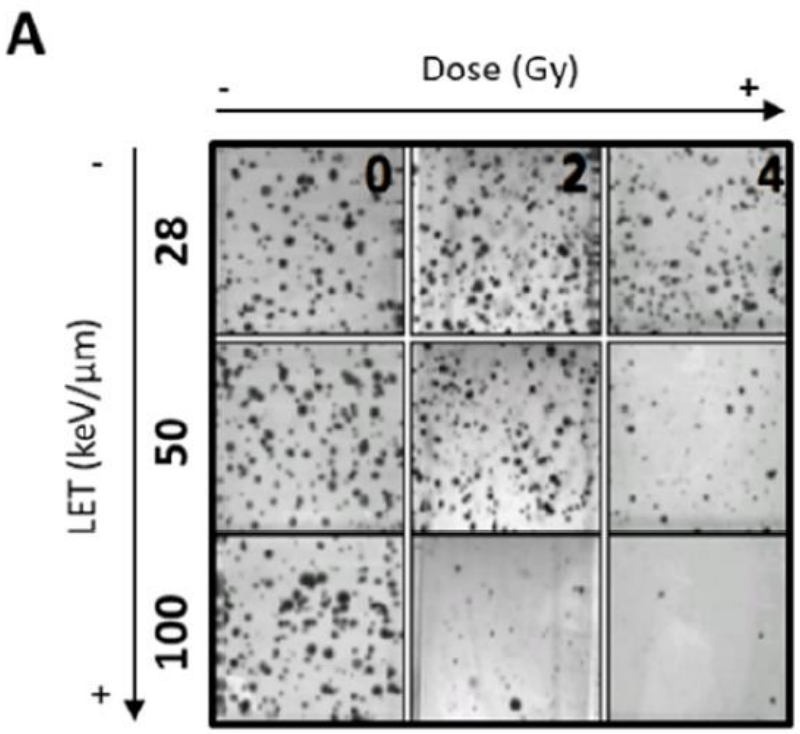


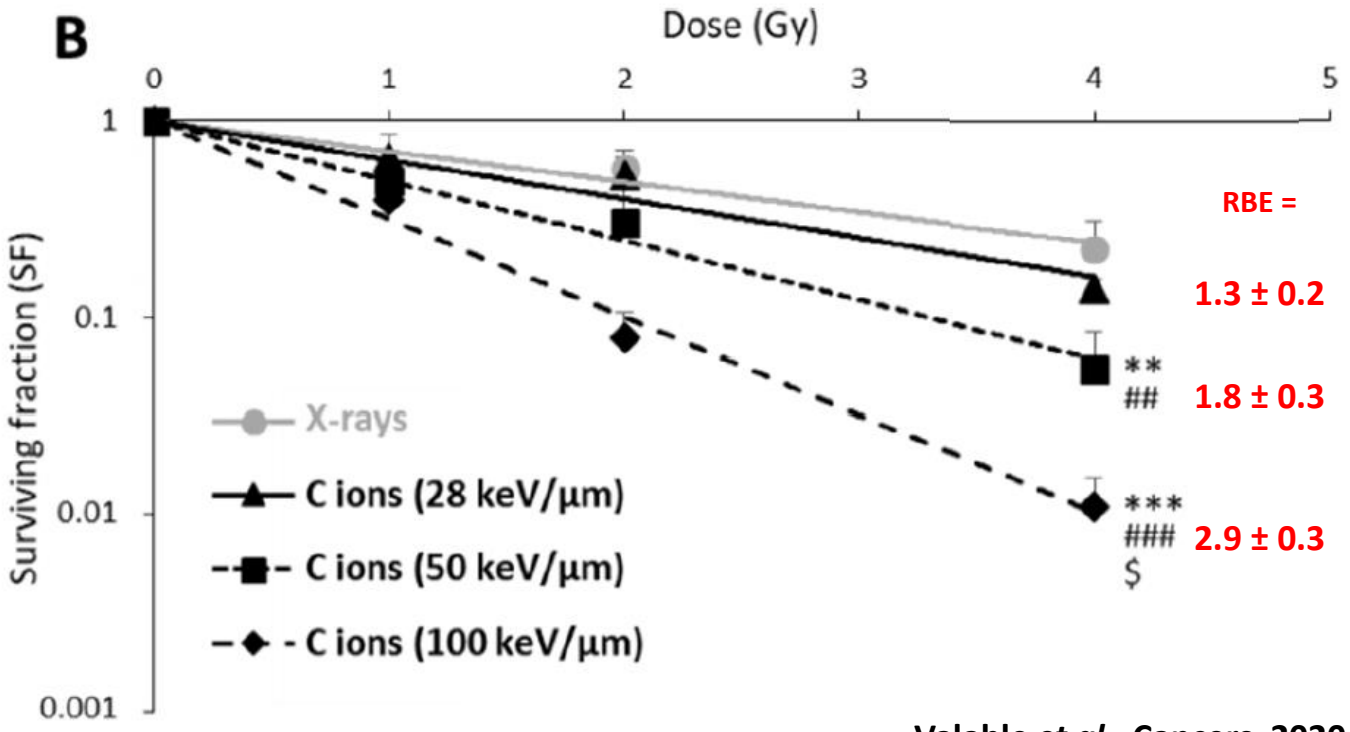
Tinganelli W et al., 2015

Gérard *et al.*, Front Med, 2019

Radiosensitivity of glioblastoma cells to carbon ions

- Relative biological effect (RBE) = dose X-rays / dose Carbon ions for the same effect on survival

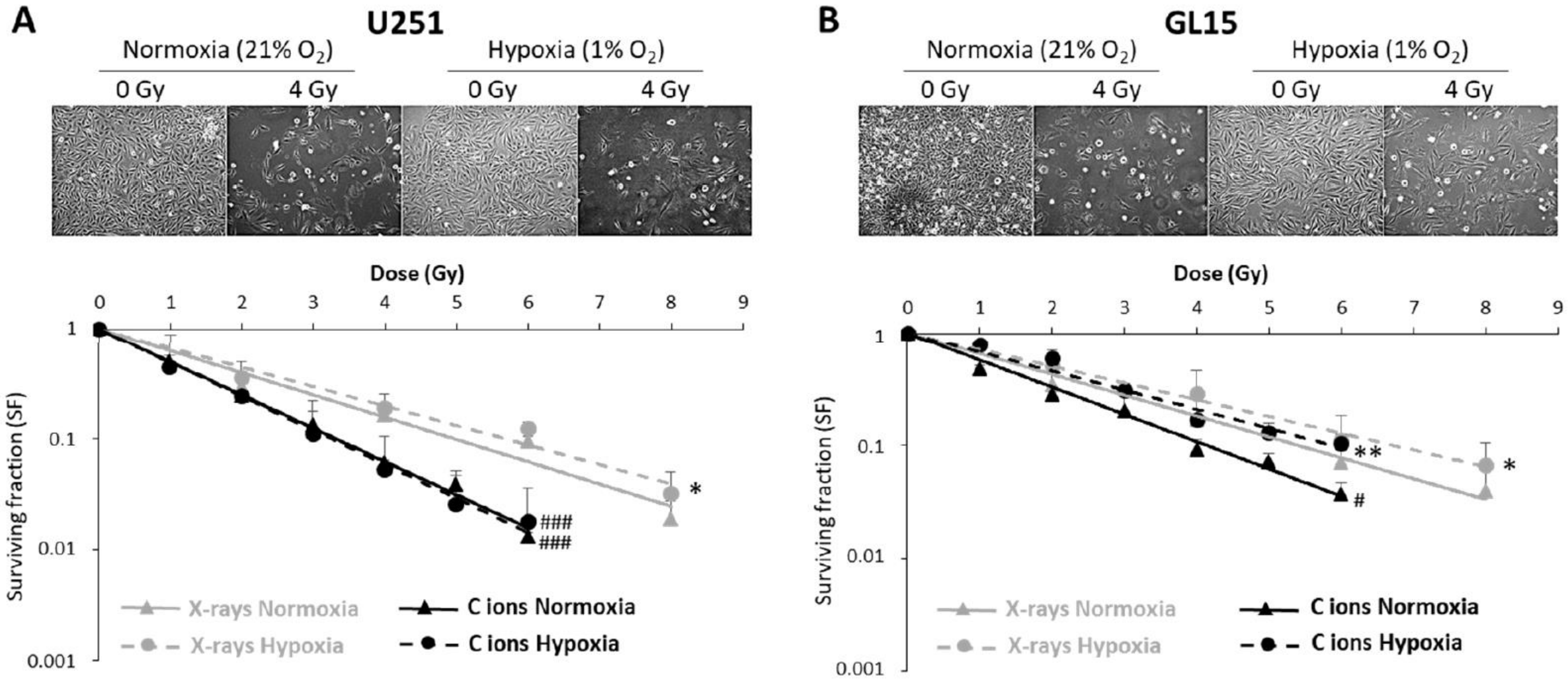




Valable *et al.*, Cancers, 2020

Cell sensitivity to carbon ions increases when increasing LET in normoxia
What about in hypoxia ?

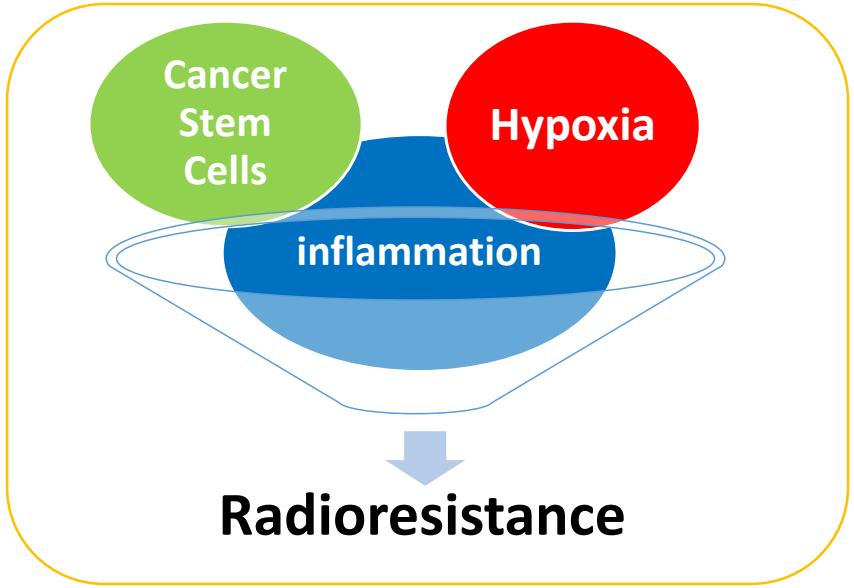
Comparison of survival after X-rays and carbon ions irradiation in normoxia and hypoxia



Hypoxia-dependent radioresistance with X-rays

But also with carbon ions in a cell-type manner

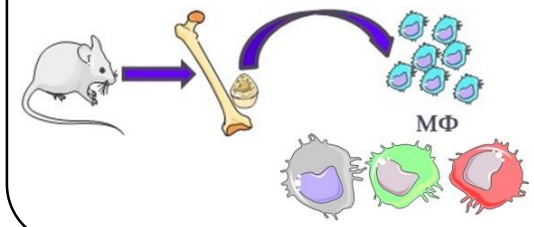
Valable *et al.*, Cancers, 2020



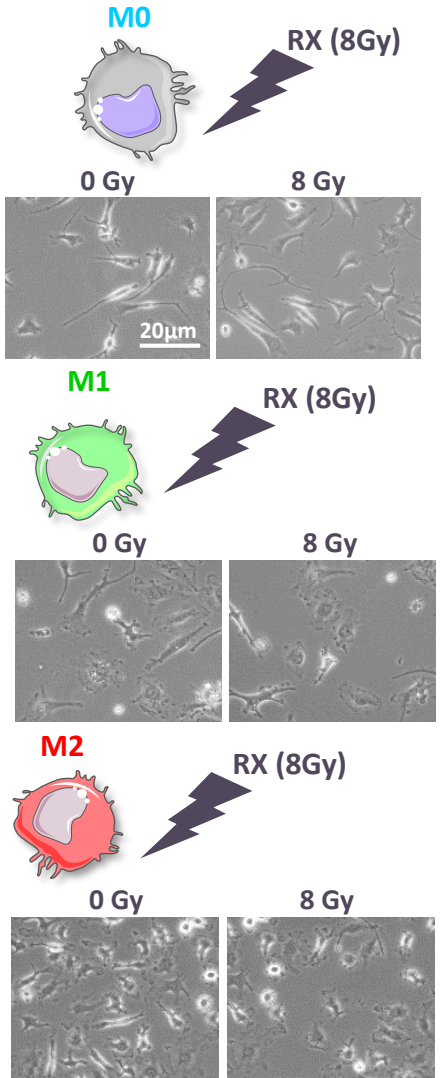
Archade
ADVANCED RESOURCE CENTRE
FOR HADRONTHERAPY IN EUROPE

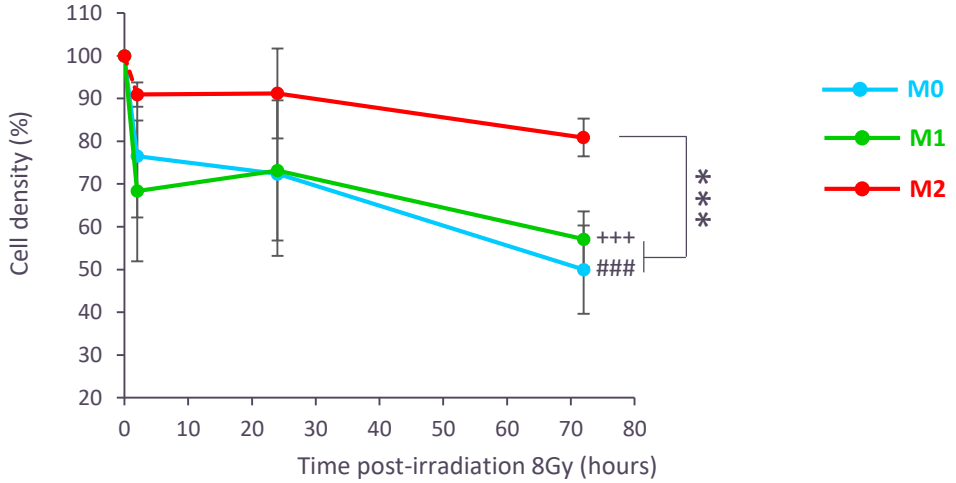
RÉGION
NORMANDIE

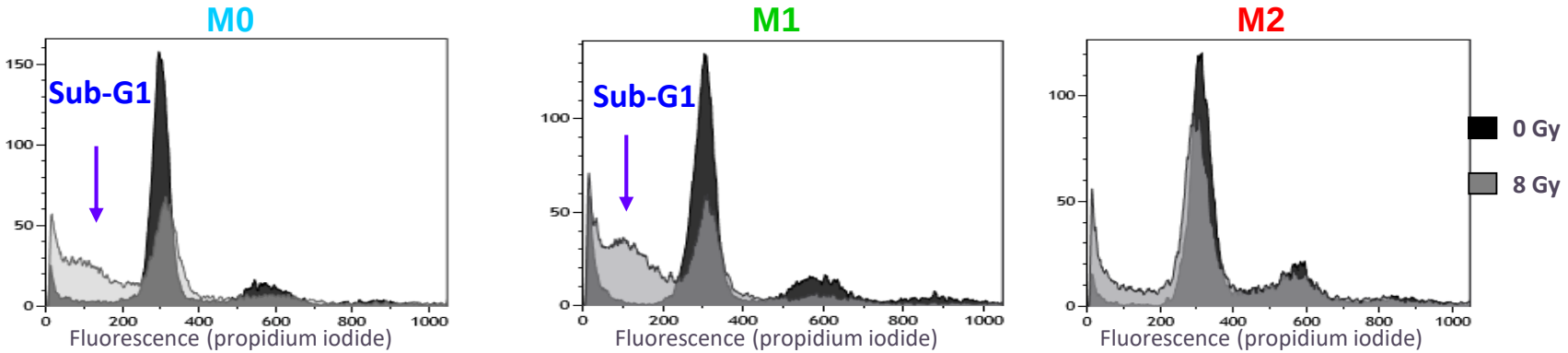
In vitro : primary culture of BMDM



XRad225Cx irradiator
(Equipex Rec-Hadron, GIP CYCERON)



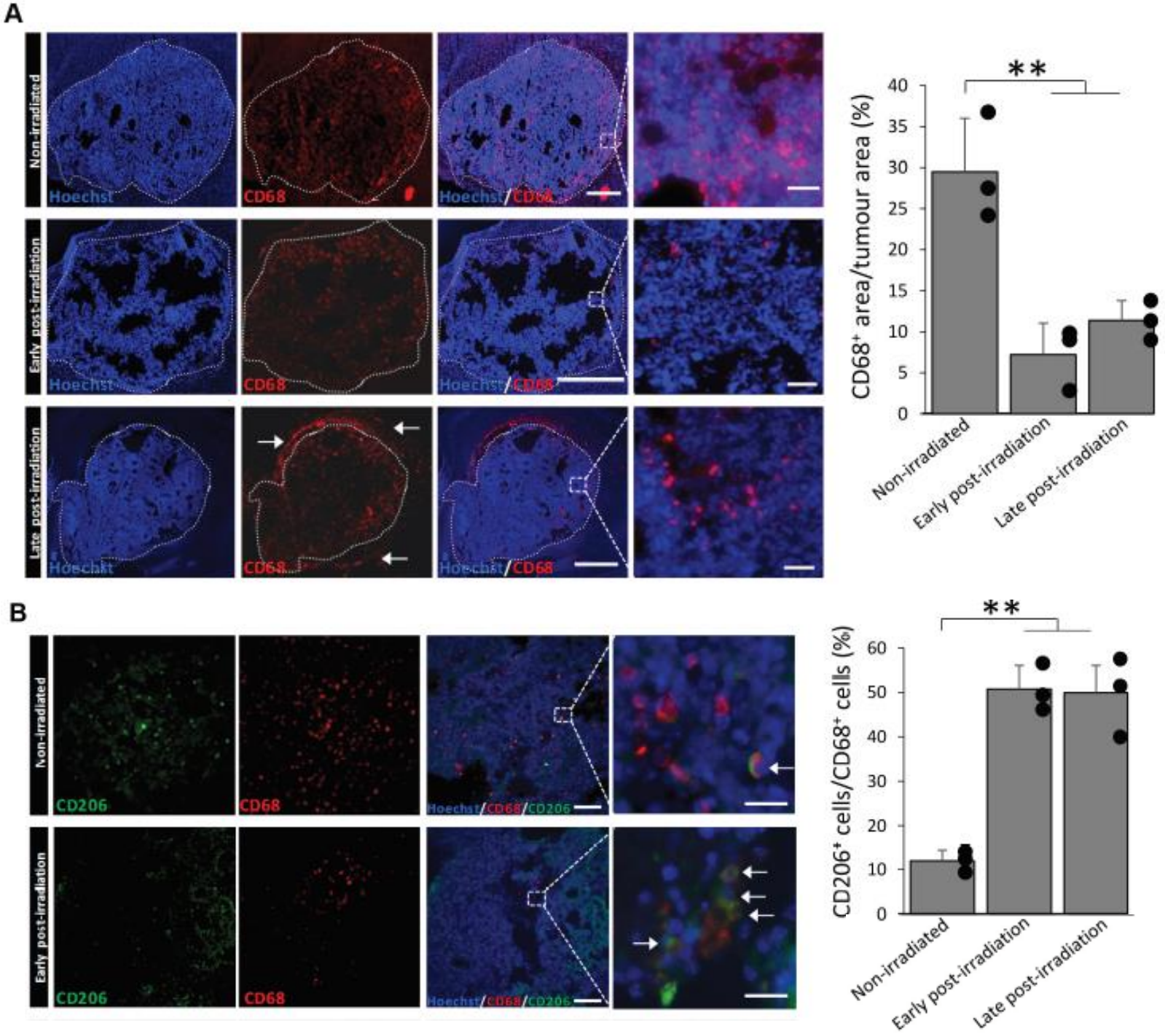




M0 and M1 MΦ are more sensitive to irradiation than M2 MΦ

In vivo **: GL261 Glioma model developped in immunocompetent mice**

XRad225Cx irradiator
(Equipex Rec-Hadron, GIP CYCERON)



Leblond M *al.*, Oncotarget, 2017

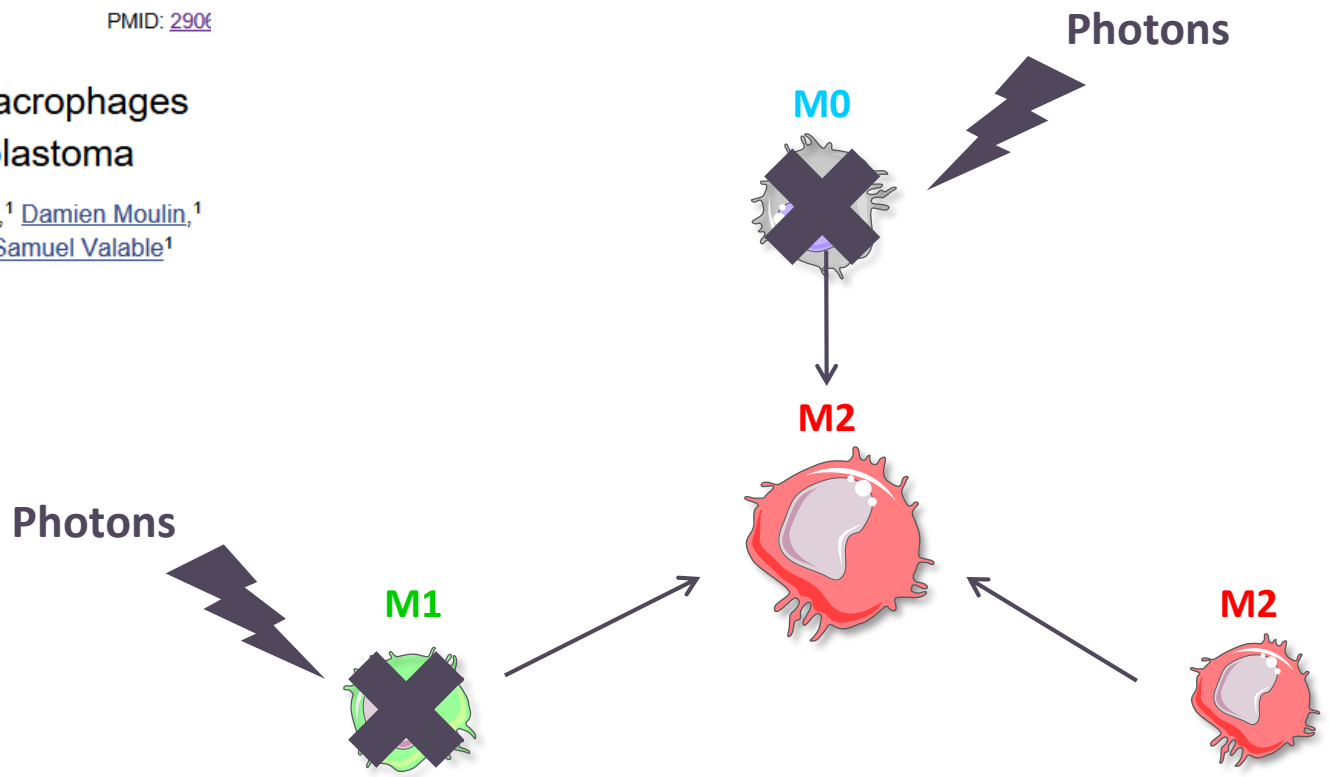
Oncotarget
Open Access Impact Journal

Oncotarget. 2017 Sep 22; 8(42): 72597–72612.
Published online 2017 Aug 7. doi: 10.18632/oncotarget.19994

PMCID: PMC564
PMID: 2906

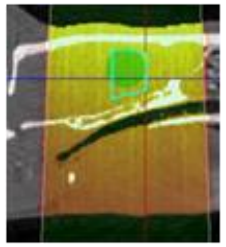
M2 macrophages are more resistant than M1 macrophages following radiation therapy in the context of glioblastoma

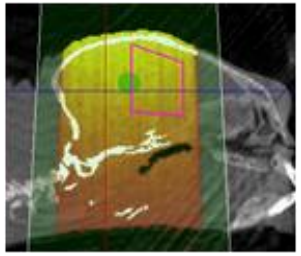
Marine M. Leblond,[1] Elodie A. Pérès,[1] Charly Helaine,[1] Aurélie N. Gérault,[1] Damien Moulin,[1] Clément Anfray,[1] Didier Divoux,[1] Edwige Petit,[1] Myriam Bernaudin,[1] and Samuel Valable[1]



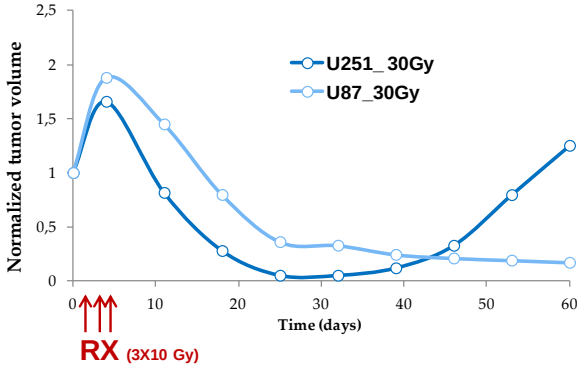
Other types of RT ? ➔ what about with C Ions ?

IN VIVO APPROACHES

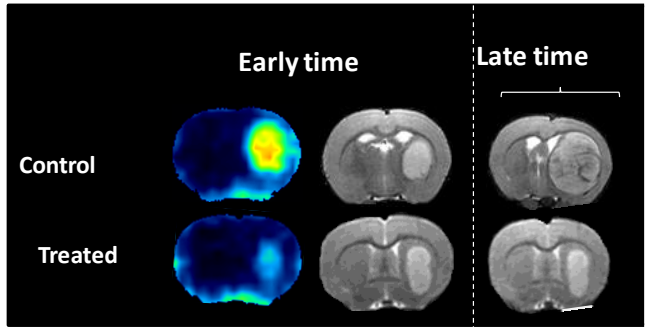




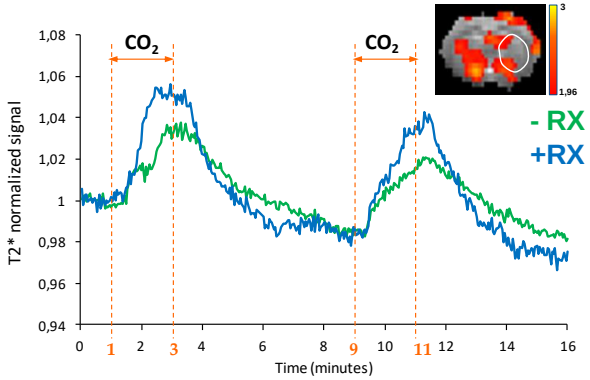
Tumor Volume



Multimodal Imaging to assess treatment efficacy and effects onf the healthy brain tissue



Brain healthy tissue



Other related parameters

- -immunology
- -biochemistry
- -behavioral tests
- -physiology

Hypoxia
Angiogenesis
ROS formation
Inflammation

	In vitro	In vivo
X-Rays	 **Cyceron@Caen**	 **Cyceron@Caen**
Protons	Cyclhad Cyclotrons pour l'Hadronthérapie **+ ?**	 **Precy@Strasbourg**
C-ions	 **GANIL@Caen** **+ ?**	**?**