Observation of immunological responses to different types of beam

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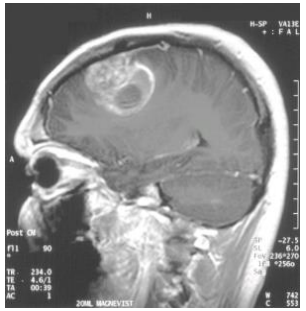
CERVOxy group, ISTCT Lab, Caen, France

Brain tumors : generalities

T1w-MRI



Glioblastoma (GBM)

➔ **GBM** (IDHwt or mutant) **are one of the worst type of tumor in term of survival**

Surgery
Radiotherapy
Chemotherapy

➔ **Median Survival = 15 Months**

➔ **Marked resistance to treatments**

Chinot *et al*., 2014

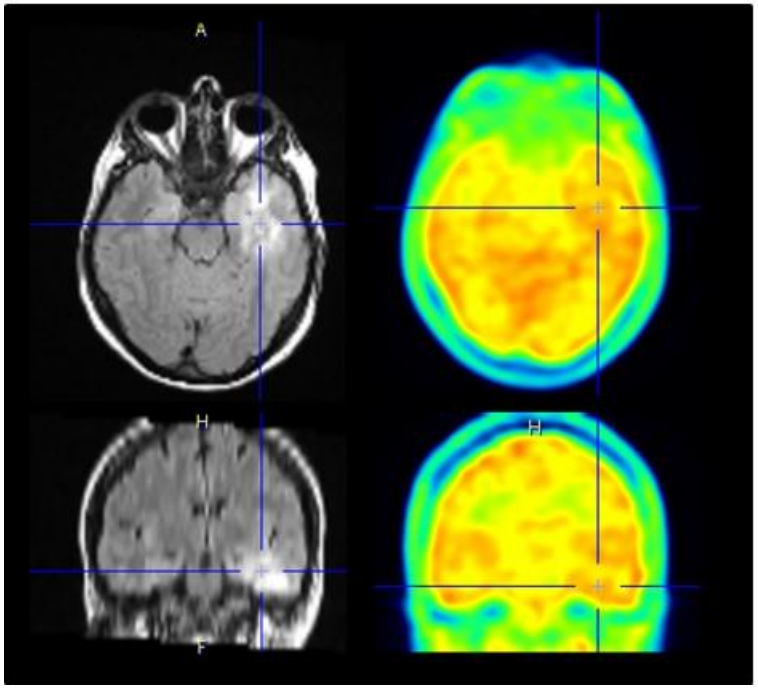
Non invasive detection of hypoxia with FMISO PET

HYPONCO

Investigator: Pr JS Guillamo, CHU of Caen

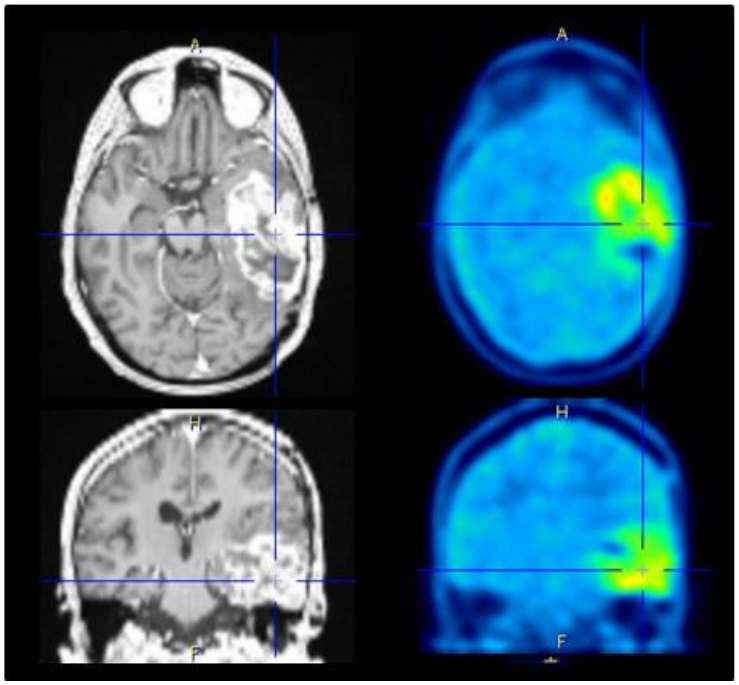
Low grade glioma

FLAIR [^{18}F]-FMISO PET



GBM

T1w-Gd [^{18}F]-FMISO PET

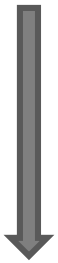


Ponte et al., 2017; Bekaert et al., 2017; Chakhoyan et al., 2017

Hypoxia and GBM

HYPOXIA

Promotes tumor growth
- Metabolic changes
- Angiogenesis
- Invasion

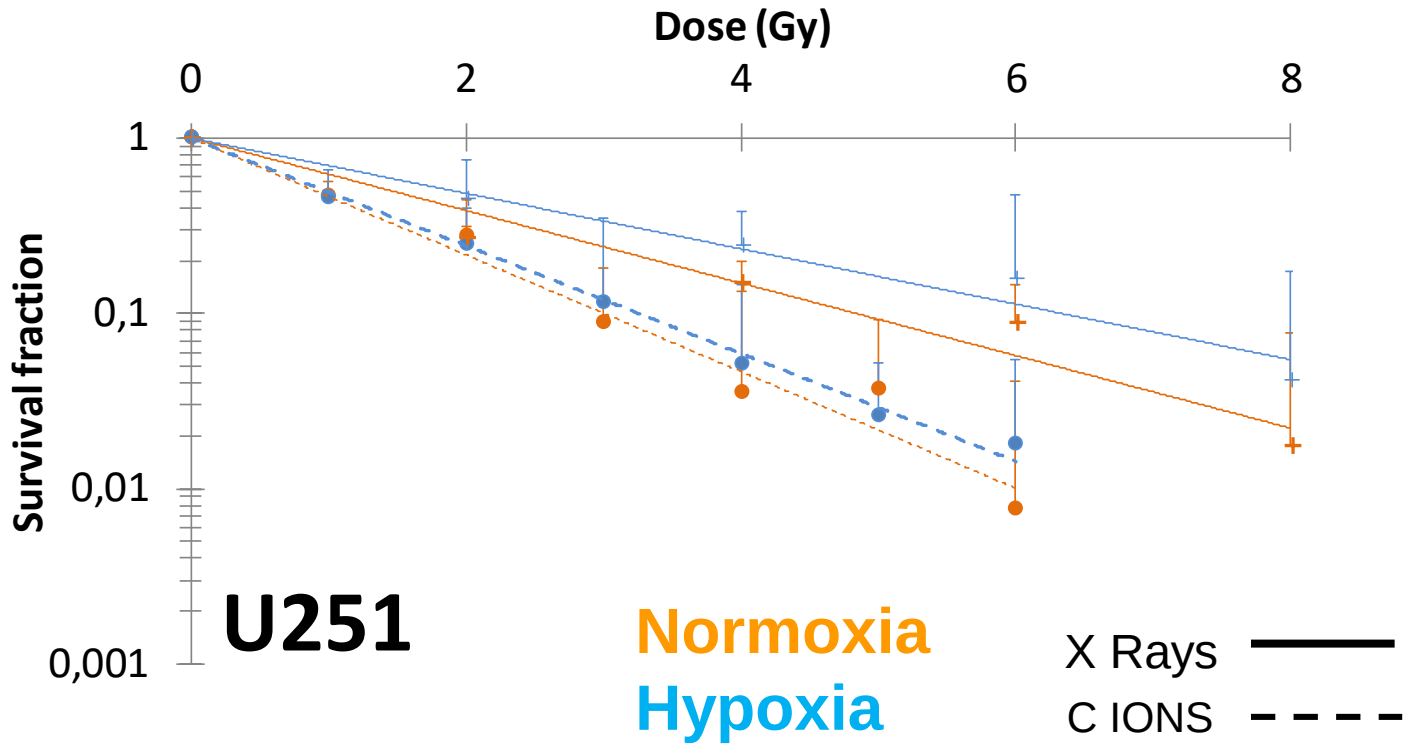


Resistance to Radiotherapy
Resistance to Chemotherapy

Poor prognosis

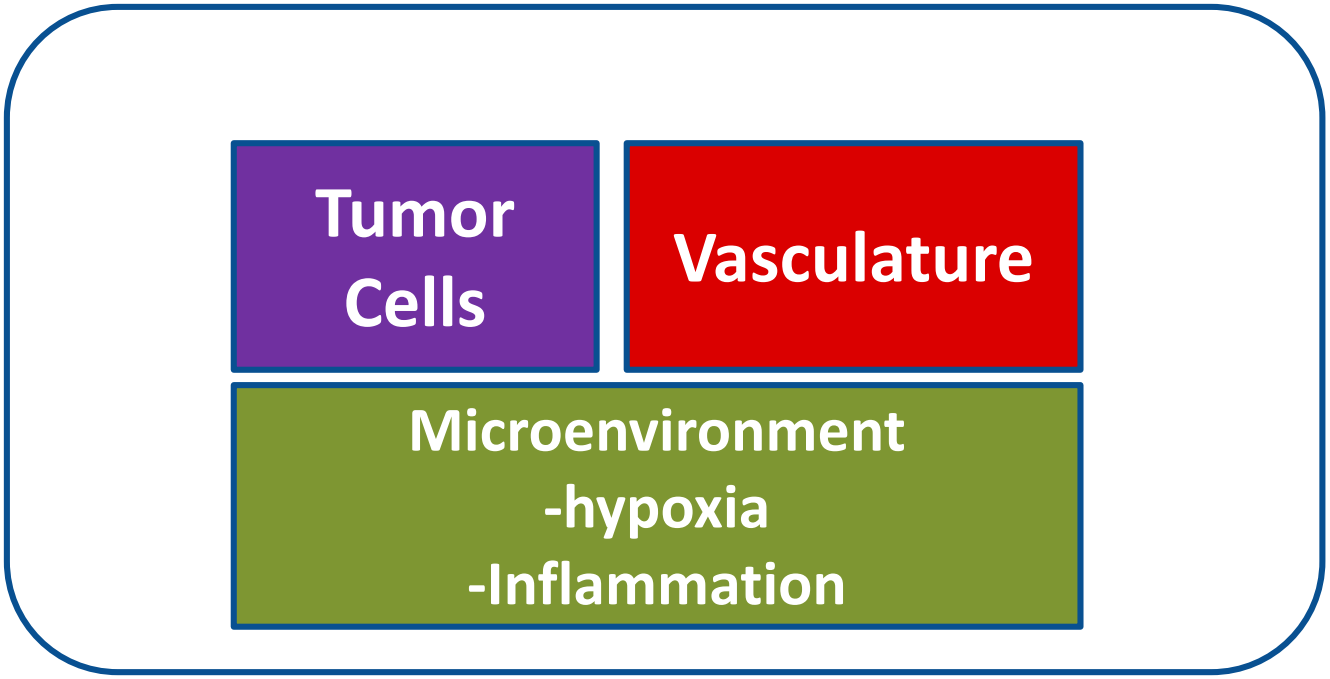
Advanced RT to overcome resistance to RT

Survival fraction following XRays ou C Ions in normoxia and hypoxia (1% O2)



OER (37%)	Photons	C IONS
U251	1.13 ± 0,03	0.96 ± 0,02

Glioblastoma = complexe environment



Leucocytes in glioblastoma

→ **Microglia/Macrophages (46%)** → **Macrophages :up to 30 % of the cells in the tumor mass**

→ **Lymphocytes (30%)**

→ **Myeloid-derived supressor cell (12%)**

→ **Dendritic cell (10%)**

Da Francesca & Badie, 2013

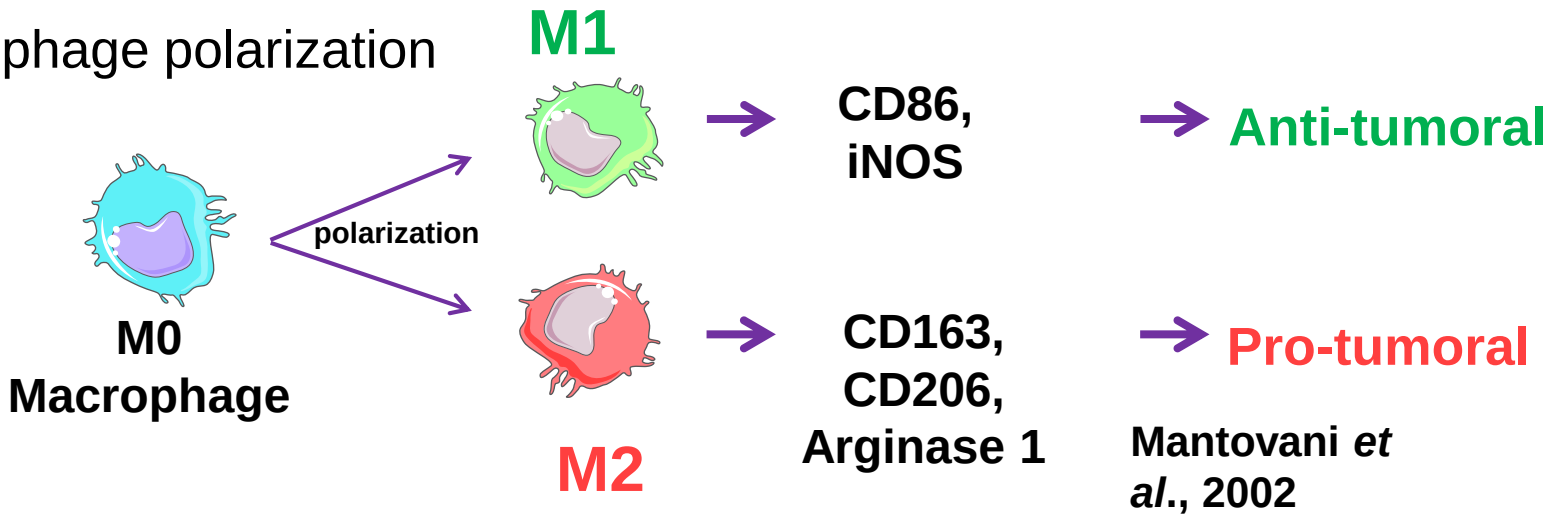
➢ Macrophages are associated with poor survival in glioblastoma

TAM Type/Location	Rho	*P* value
CD68+ bulk	−0.6382	.040
CD68+ infiltrative	−0.5379	.094
CD68+ normal	0.1309	NS

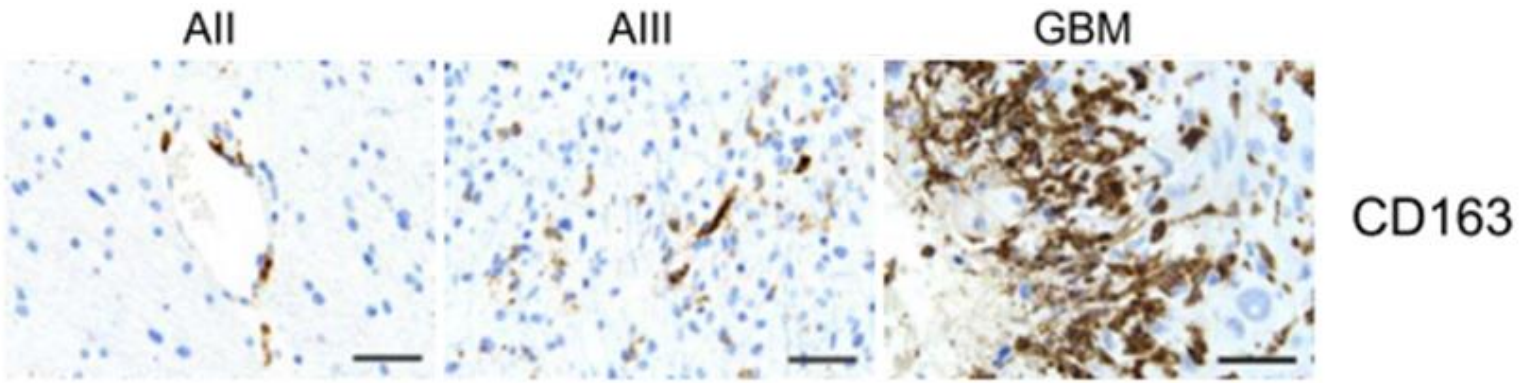
Lu-Emerson *et al*., 2013

GBM and inflammation

- Macrophage polarization

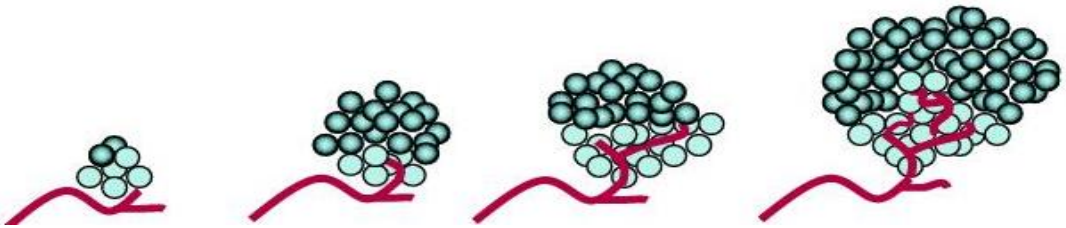


- M2 macrophages accumulation increases with grade



Prosniak *et al*., 2013

Tumor volume



M0 Macrophages

M1 Macrophages

M2 Macrophages

Anti-tumoral

Pro-tumoral

What are the factors influencing macrophages polarization ?

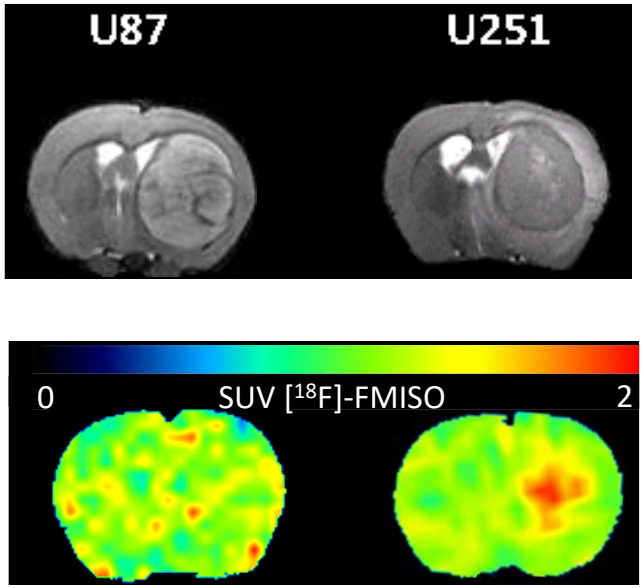
OncoImmunology

Oncoimmunology. 2016; 5(1): e1056442.
Published online 2015 Jun 5. doi: 10.1080/2162402X.2015.1056442

PMCID: PMC4760330
PMID: 26942063

Hypoxia induces macrophage polarization and re-education toward an M2 phenotype in U87 and U251 glioblastoma models

Marine M Leblond,[1,2,3,4] Aurélie N Gérault,[1,2,3,4] Aurélien Corroyer-Dulmont,[1,2,3,4] Eric T MacKenzie,[1,2,3,4] Edwige Petit,[1,2,3,4] Myriam Bernaudin,[1,2,3,4] and Samuel Valable[1,2,3,4,*]

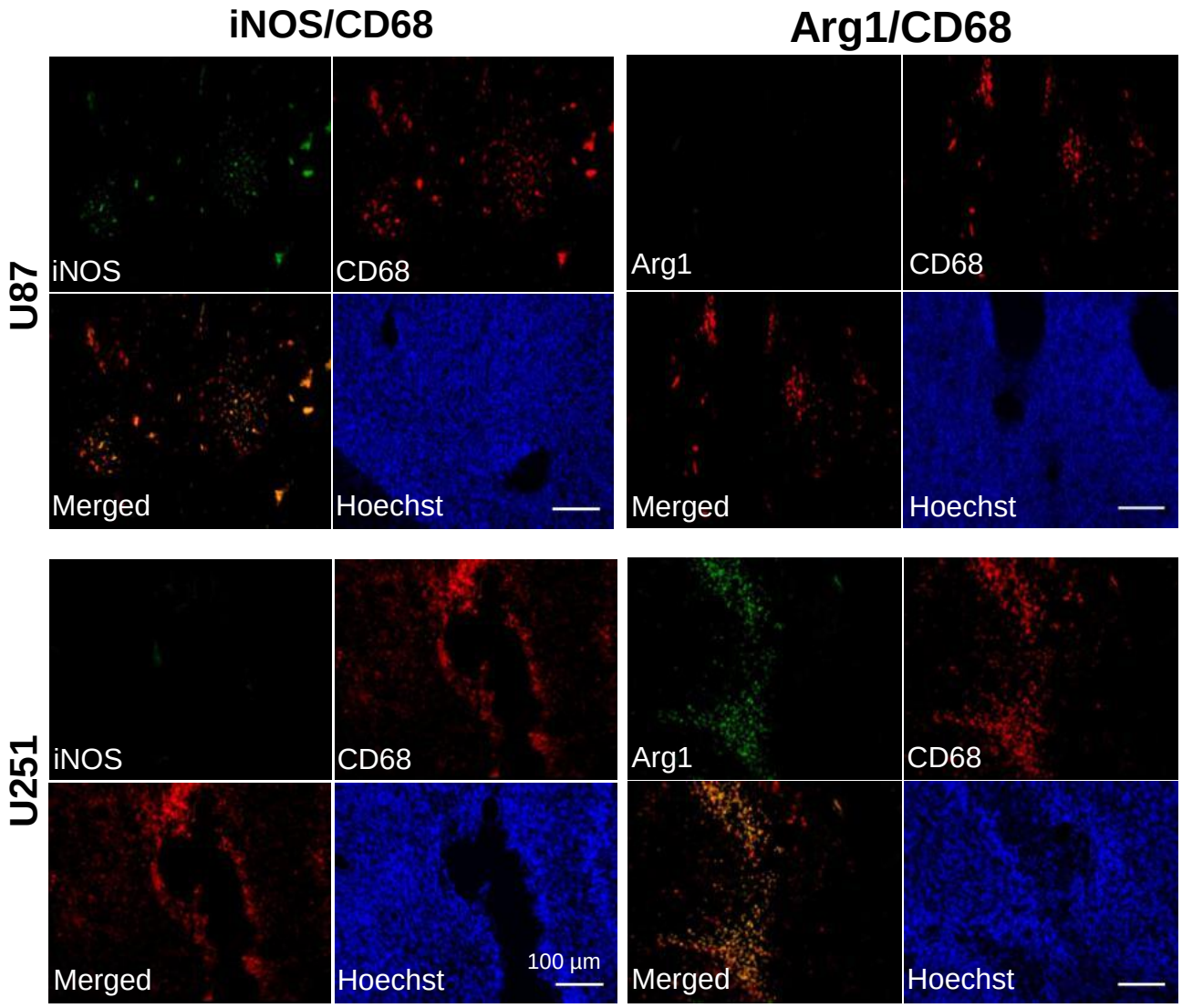


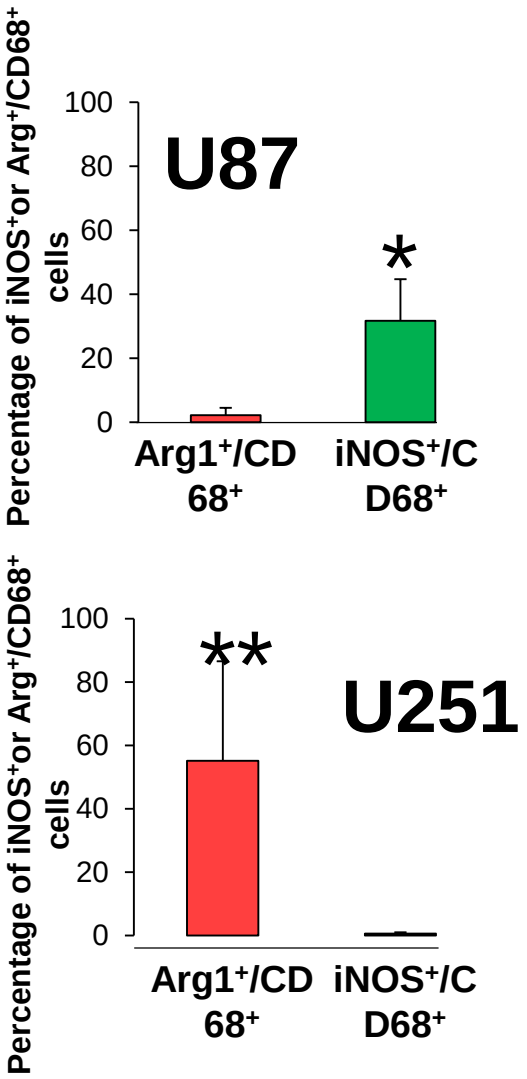
Biol Chem. 2013 Apr;394(4):529-39. doi: 10.1515/hsz-2012-0318.

Noninvasive assessment of hypoxia with 3-[18F]-fluoro-1-(2-nitro-1-imidazolyl)-2-propanol ([18F]-FMISO): a PET study in two experimental models of human glioma.

Corroyer-Dulmont A, Pérès EA, Petit E, Durand L, Marteau L, Toutain J, Divoux D, Roussel S, MacKenzie ET, Barré L, Bernaudin M, Valable S.

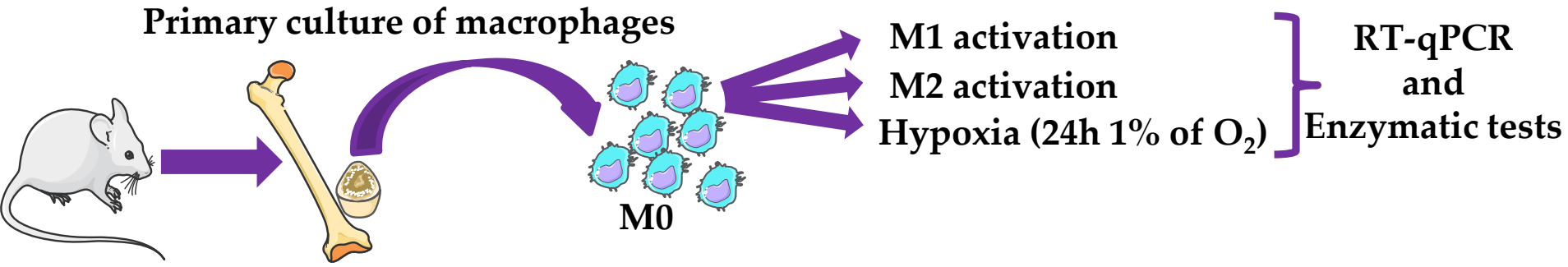
Macrophage polarization



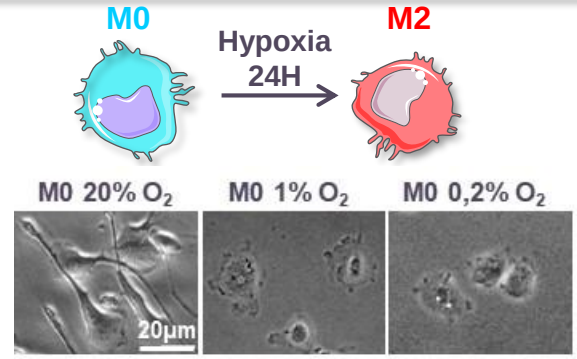


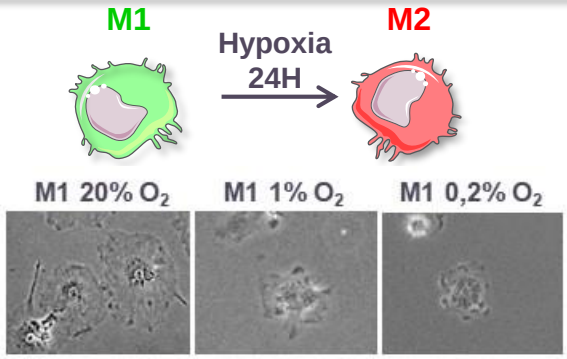
➔ **Link between hypoxia and M2 macrophages**

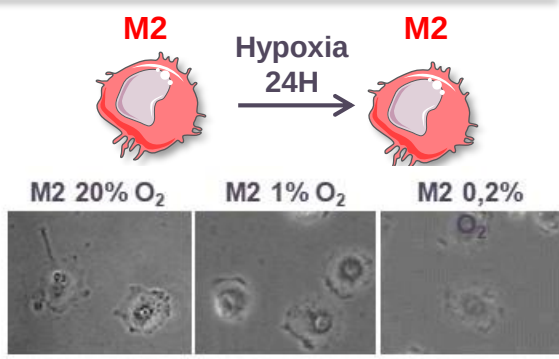
Effect of hypoxia on macrophage polarization

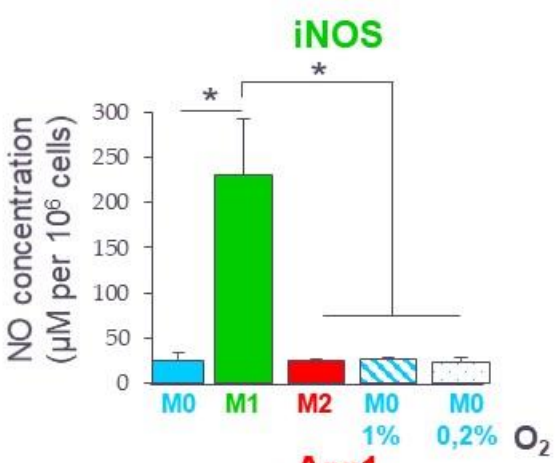


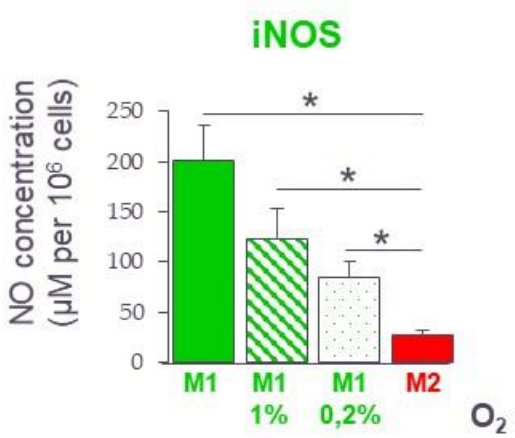
RESULTS : HYPOXIA AND MACROPHAGES PHENOTYPE

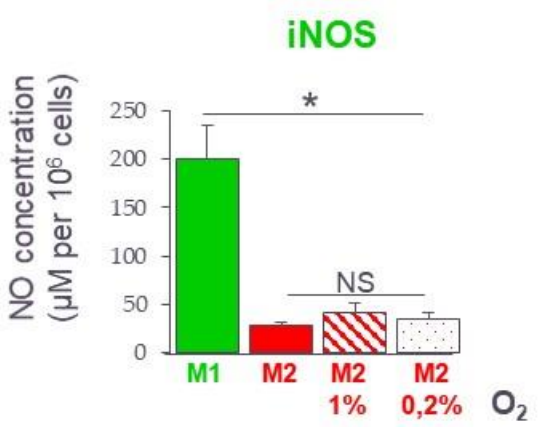


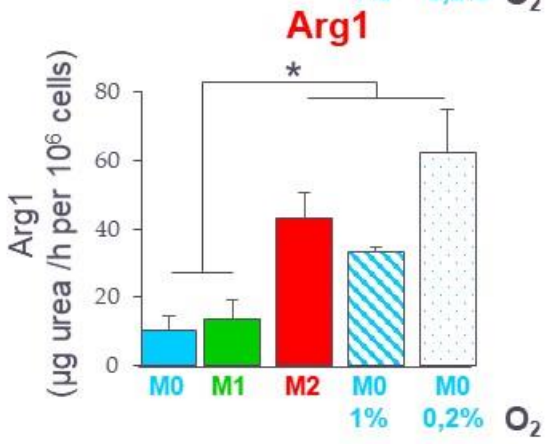


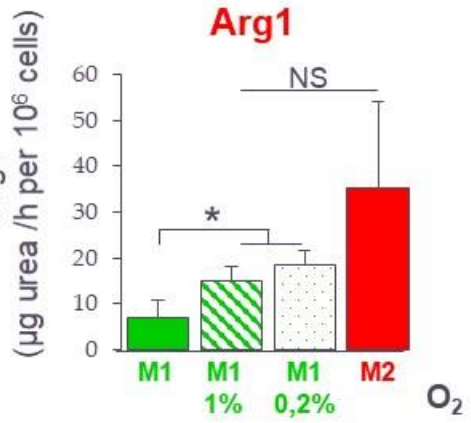


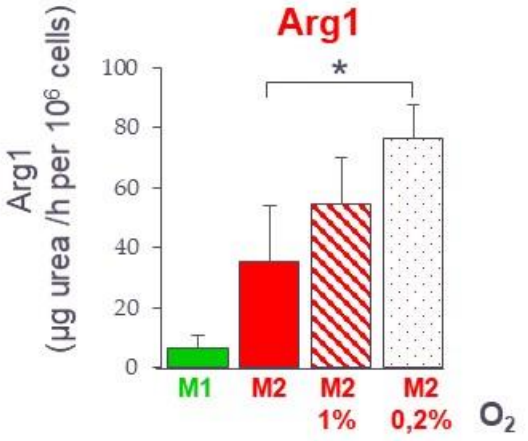




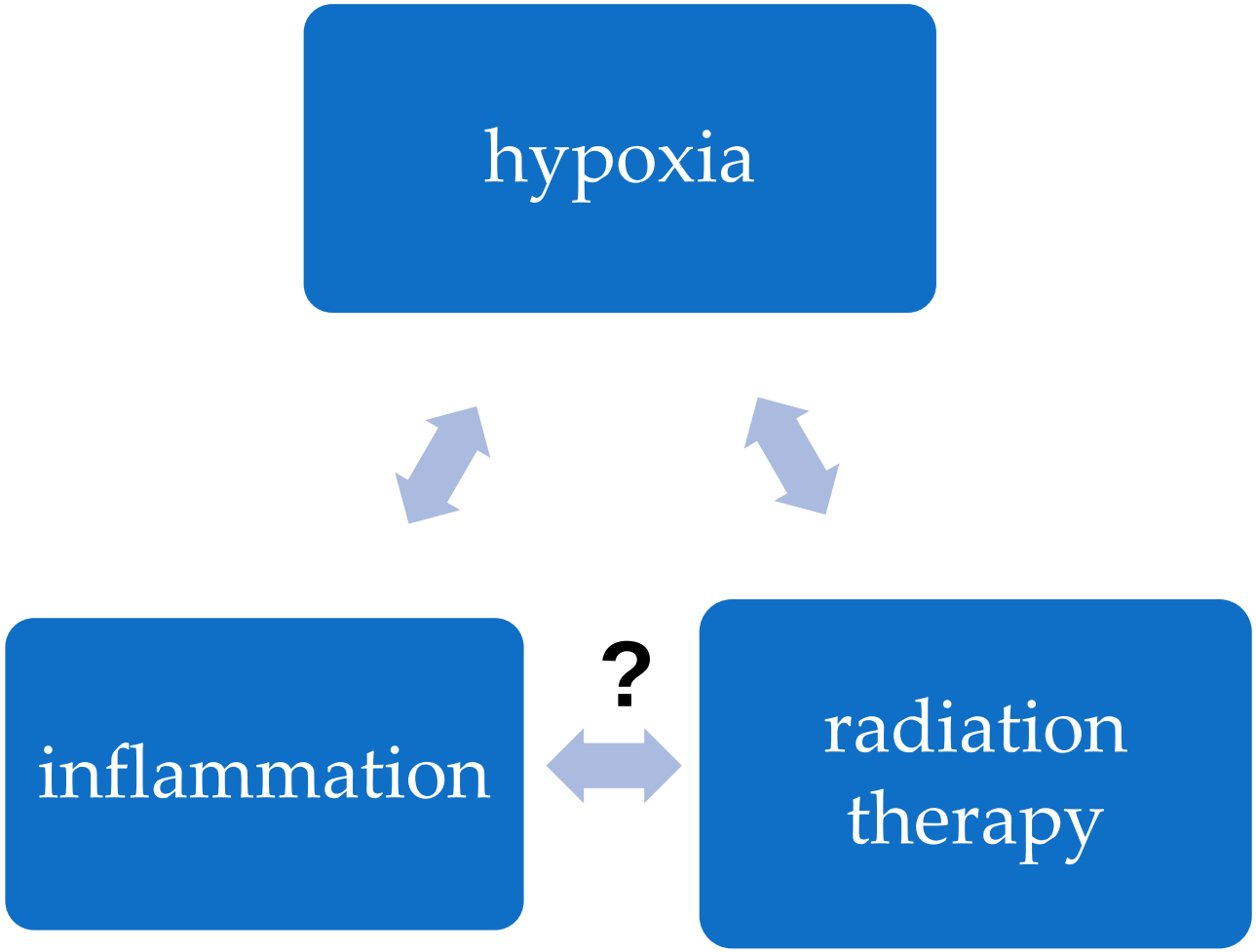








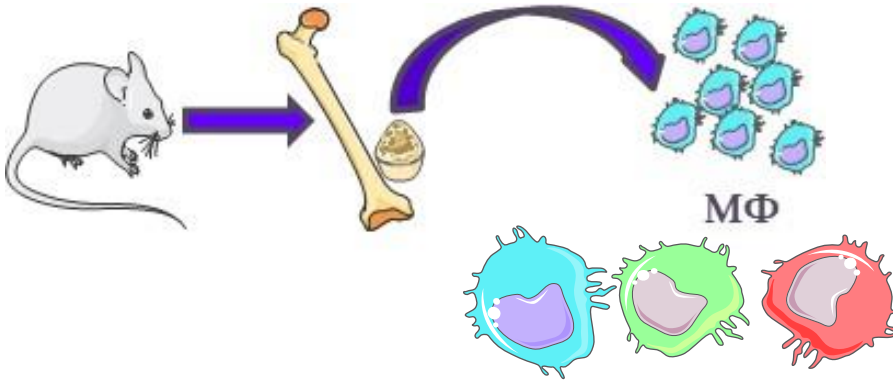
Hypoxia favors M2MΦ


hypoxia
inflammation
?
radiation therapy

RADIATION THERAPY AND TAM

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

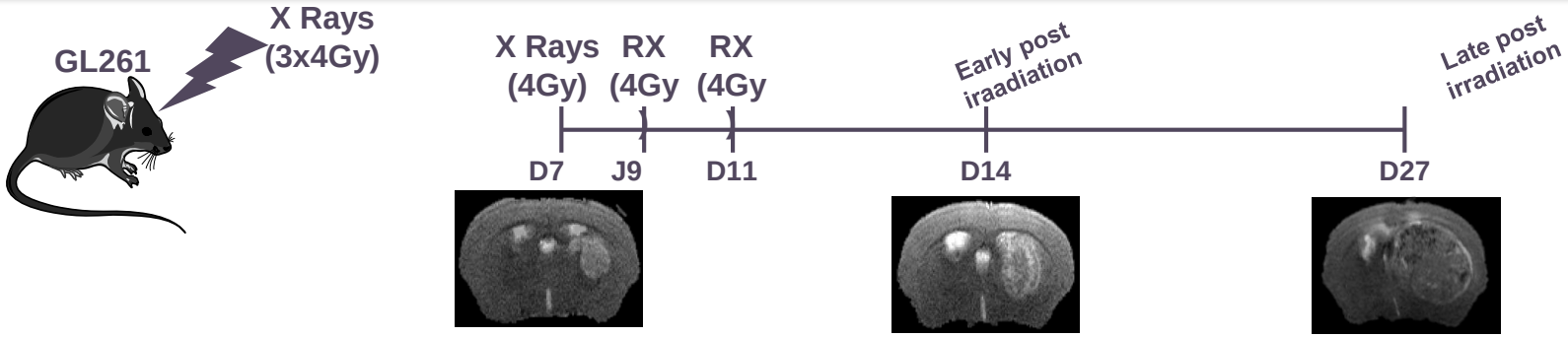
In vitro **: primary culture of BMDM**

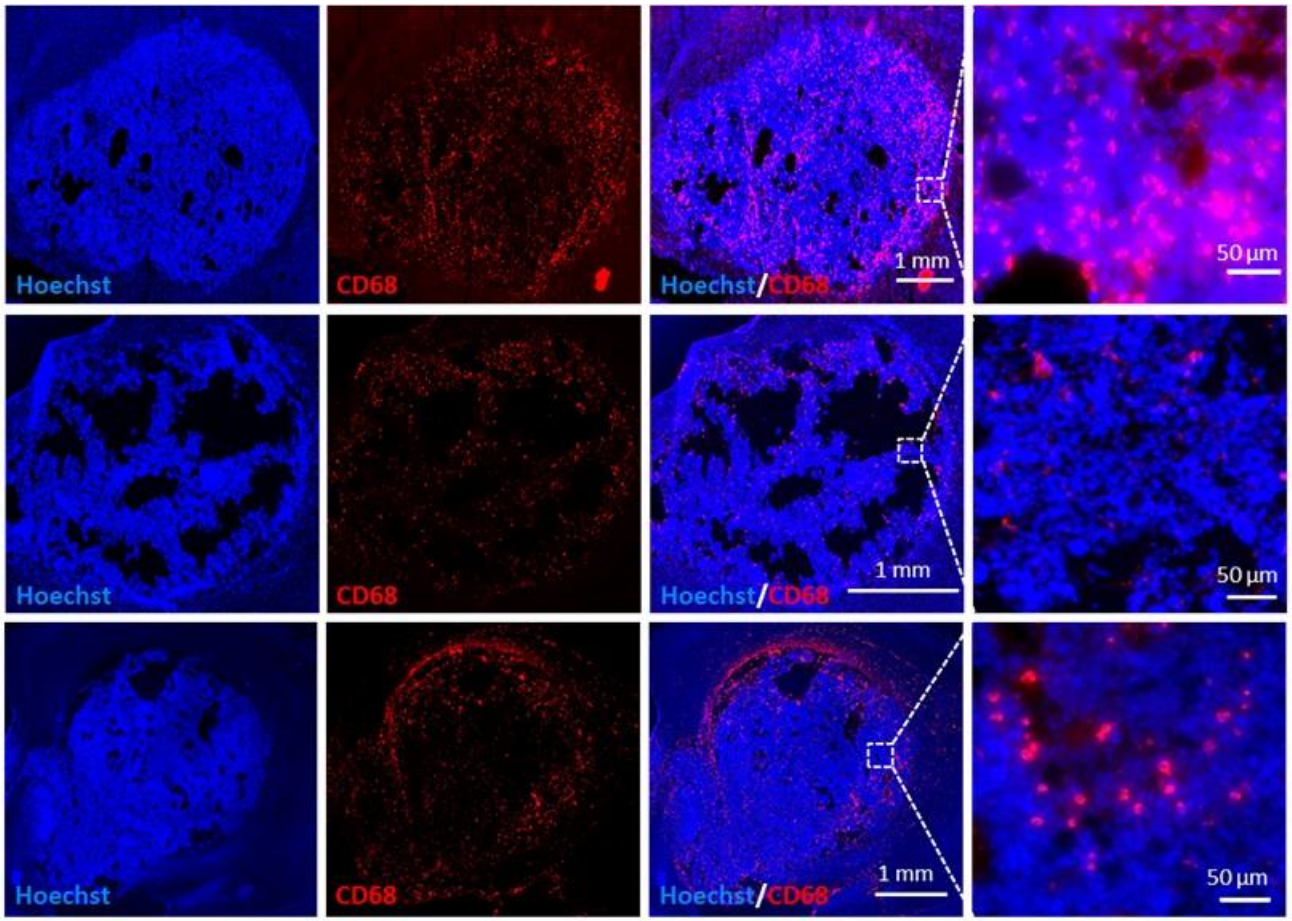


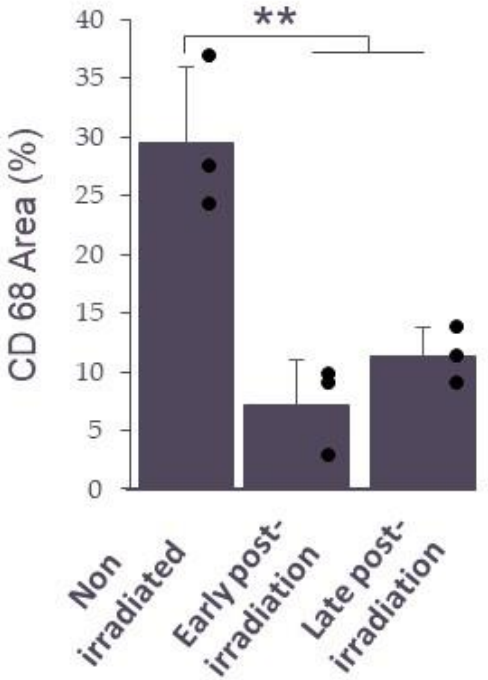
XRad225Cx irradiator

^{12}C ions, GANIL

MΦ DENSITY FOLLOWING RT

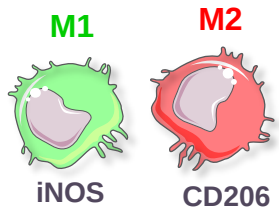


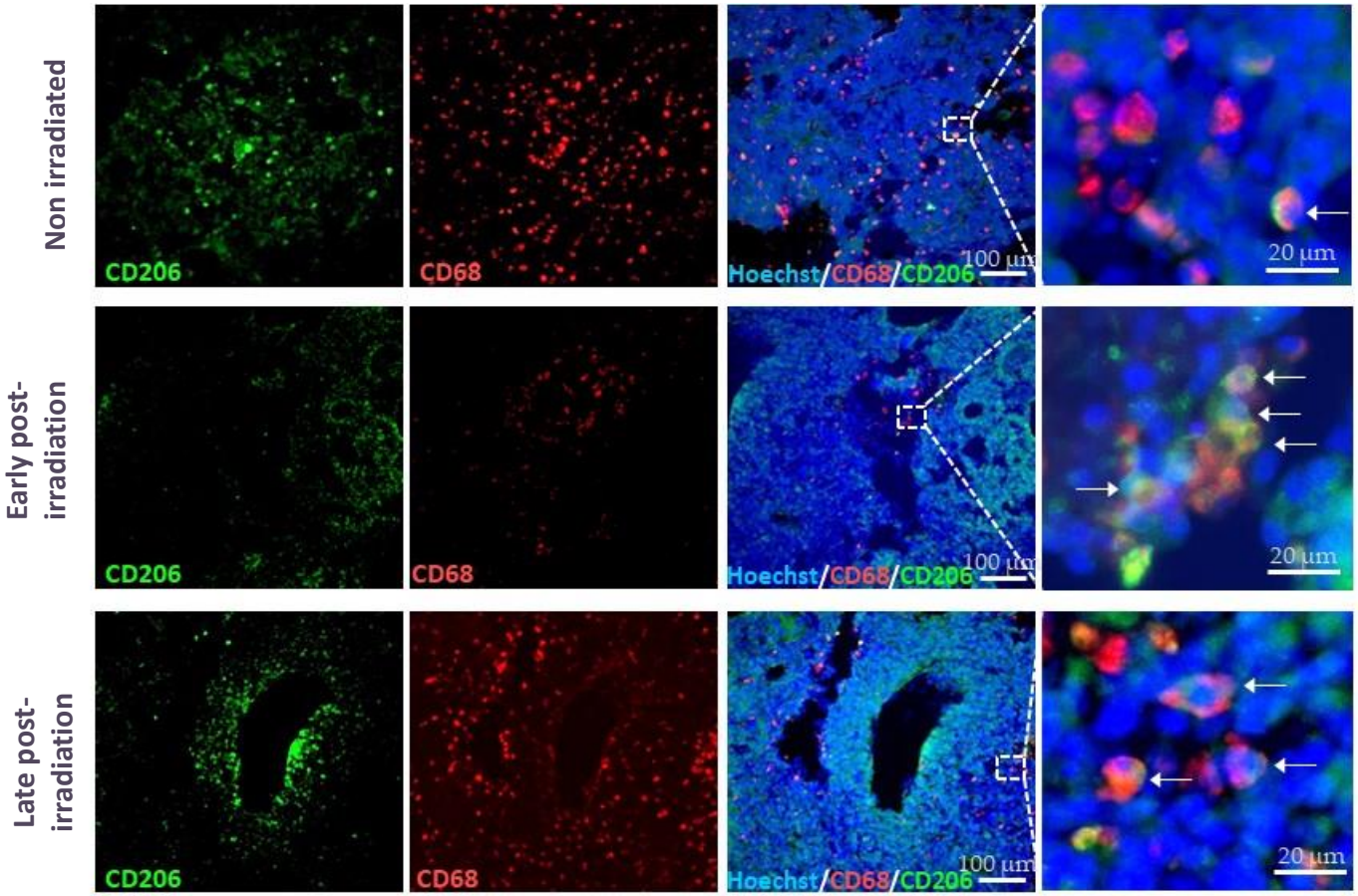


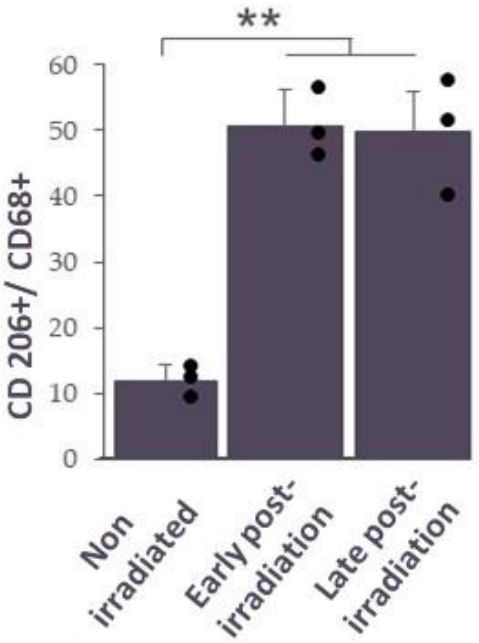


Decrease in MΦ density following RT

MΦ PHENOTYPE AFTER IRRADIATION

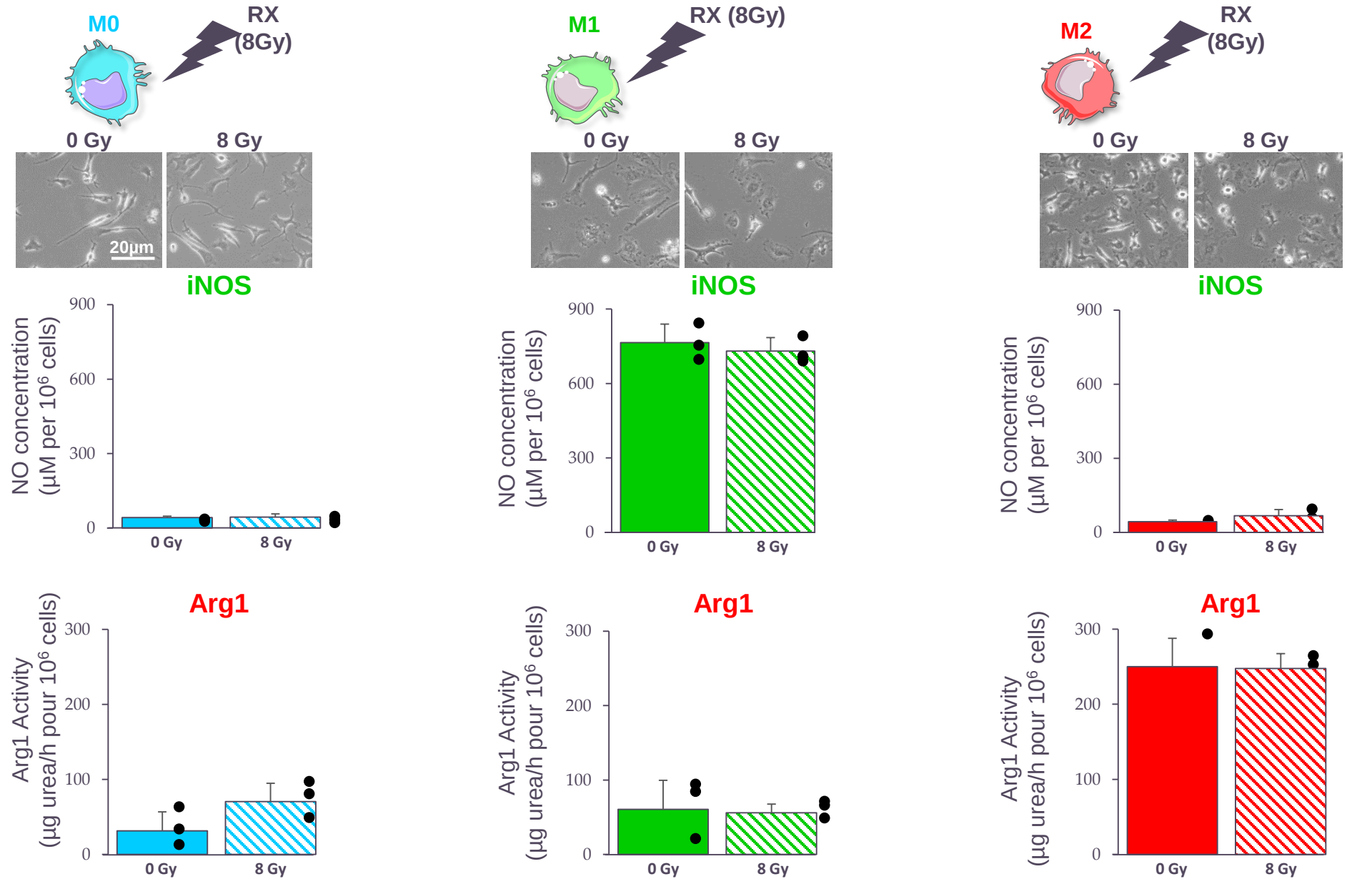






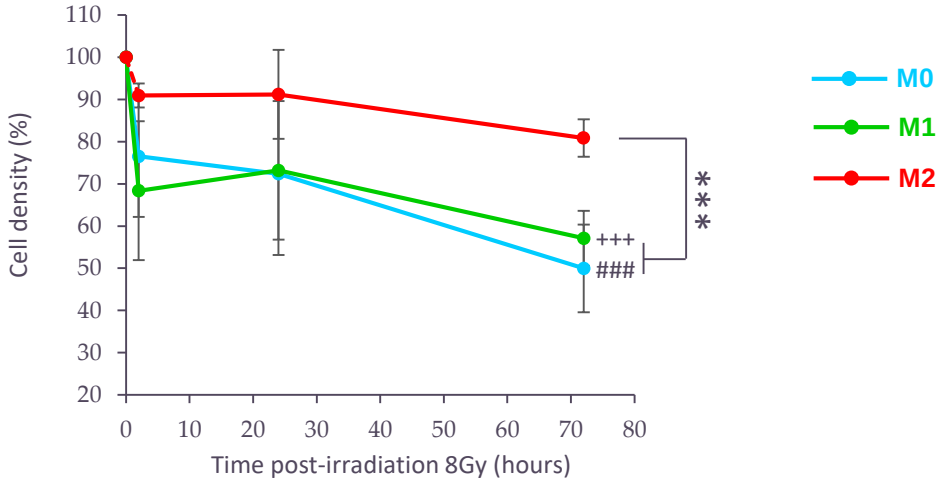
Increase in M2 proportion after RT

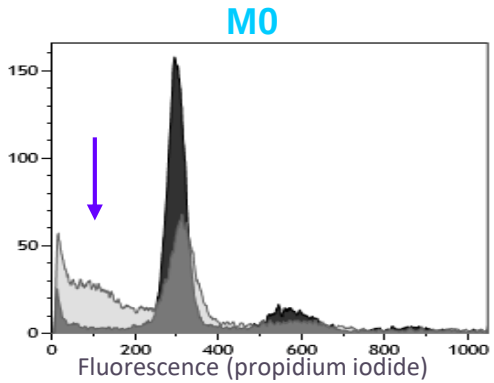
IRRADIATION AND MACROPHAGES PHENOTYPE (*IN VITRO*)

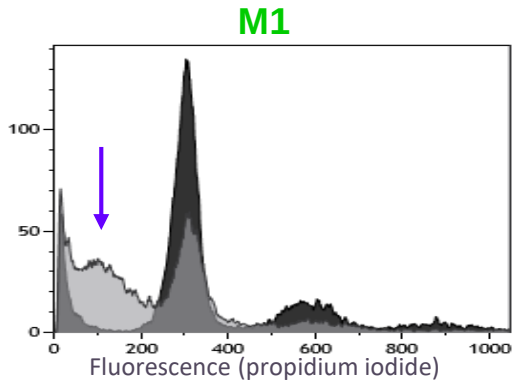


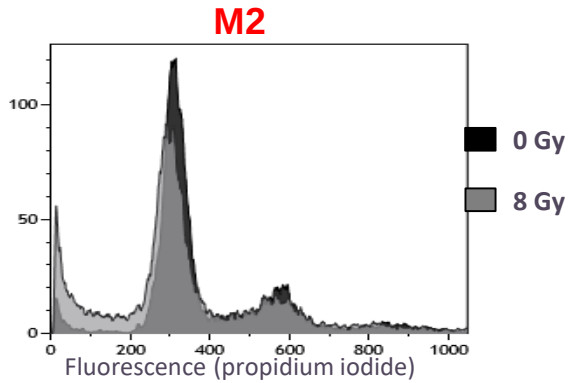
Irradiation does not modify MΦ phenotype

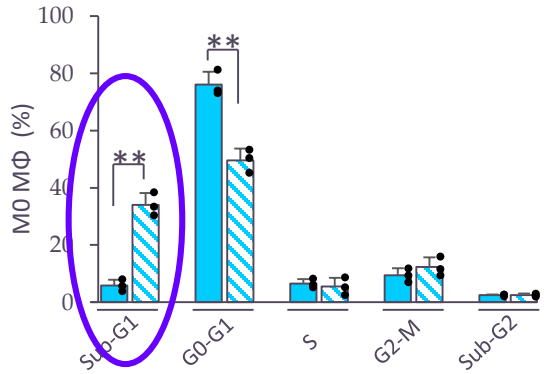
IRRADIATION AND MACROPHAGE VIABILITY (*IN VITRO*)

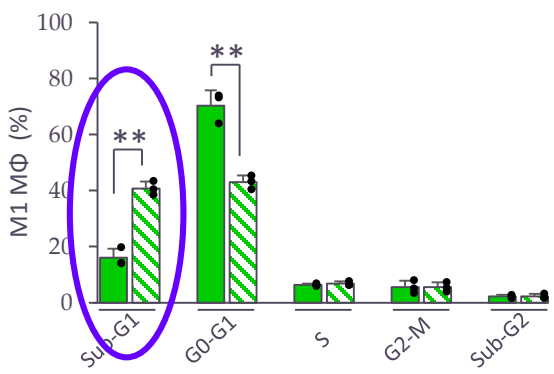


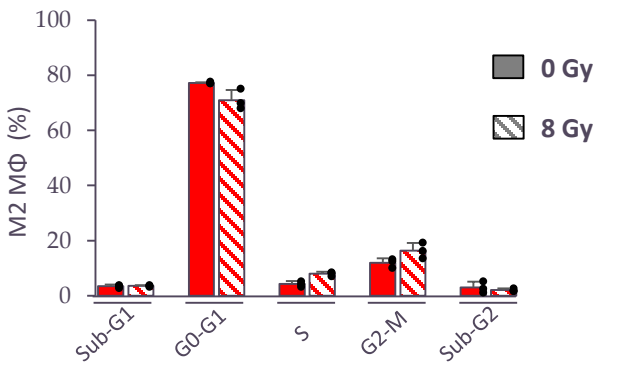






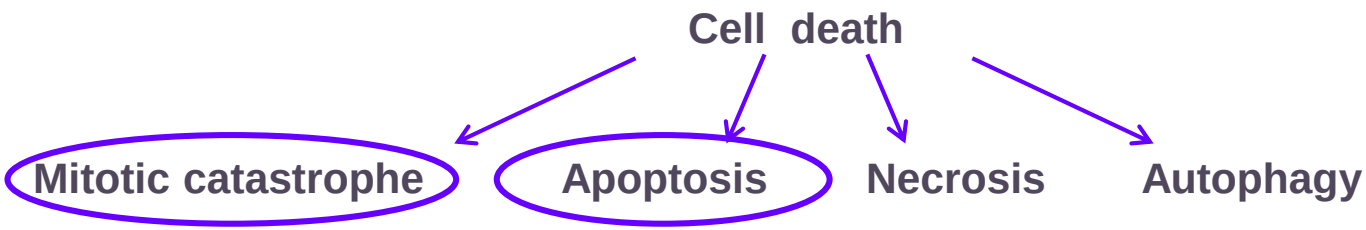






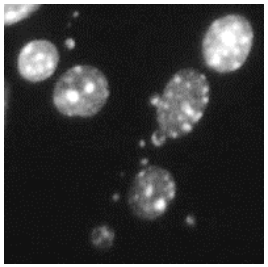
M0 and M1 MΦ are more sensitive to irradiation than M2 MΦ

MΦ CELL DEATH (*IN VITRO*)

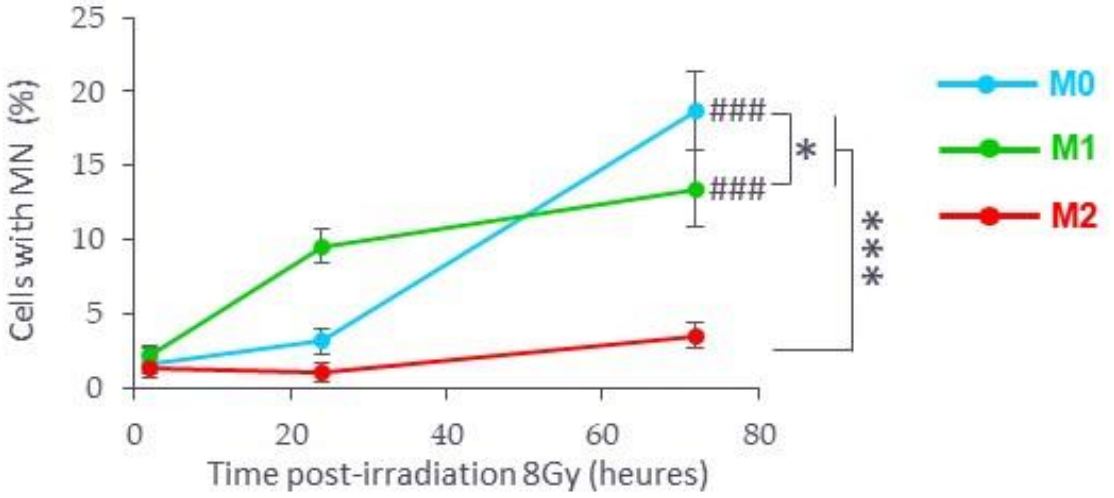


Surova et Zhivotovsky, 2013

MN



Micronuclei : mitotic catastrophe



M0 and M1 MΦ undergo cells death through mitotic catastrophe

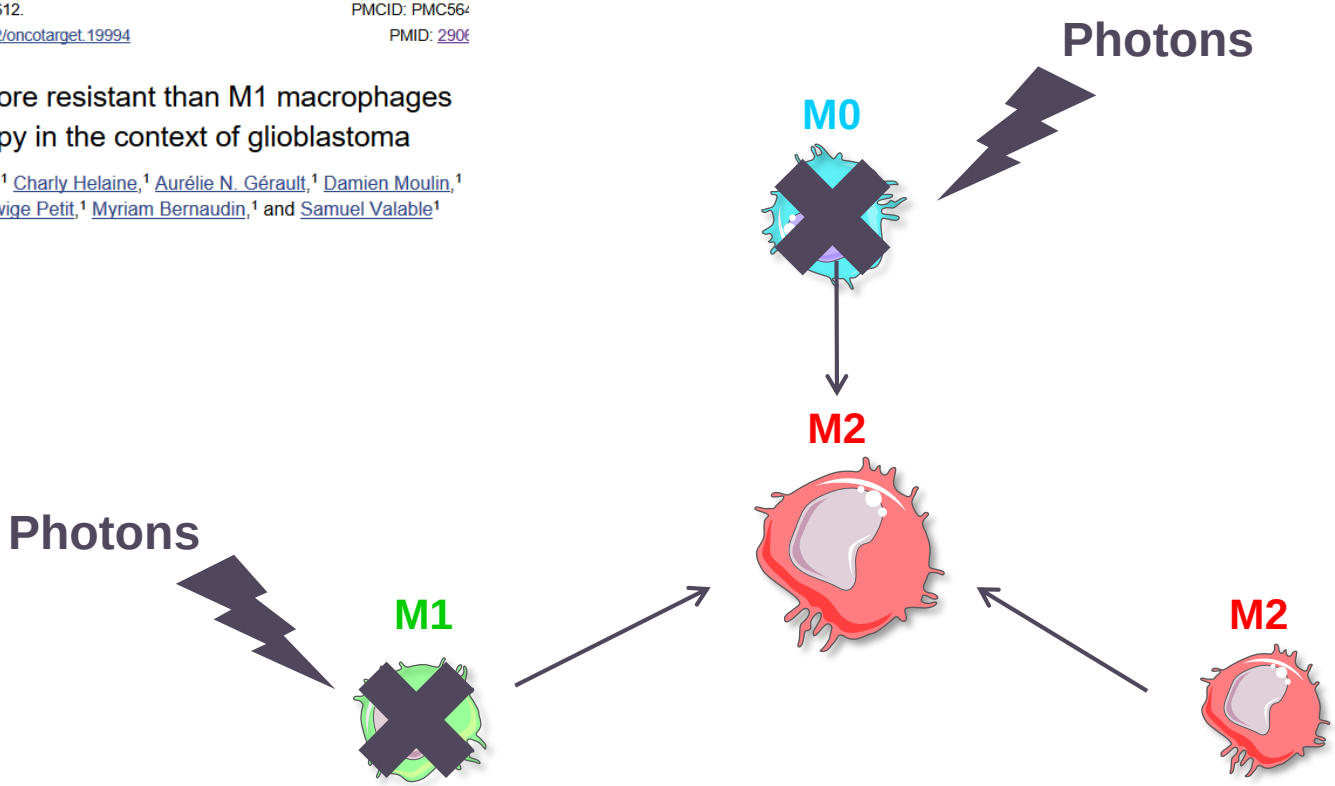
Similar results in Hypoxia

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: 290

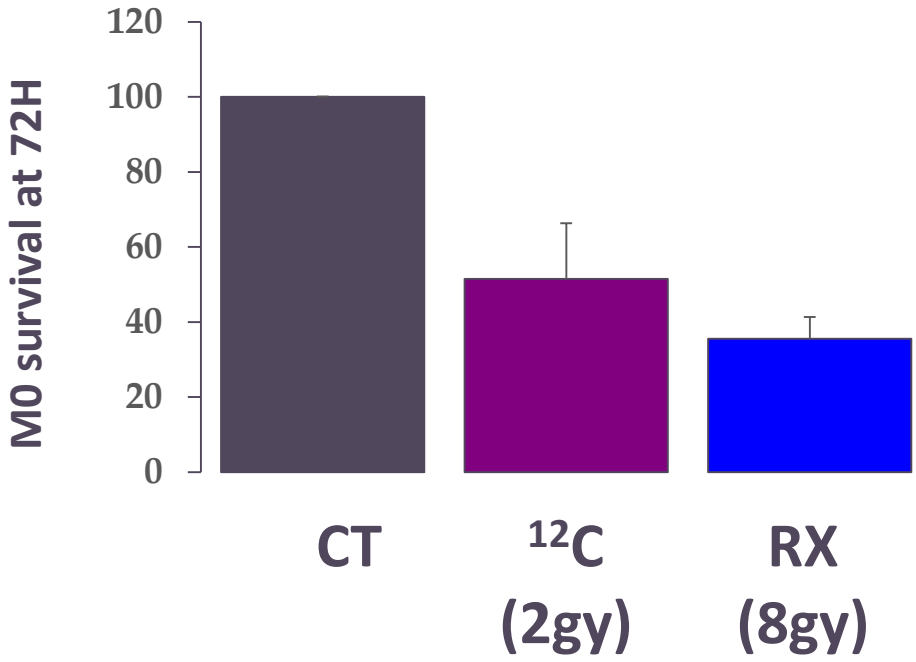
M2 macrophages are more resistant than M1 macrophages following radiation therapy in the context of glioblastoma

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]

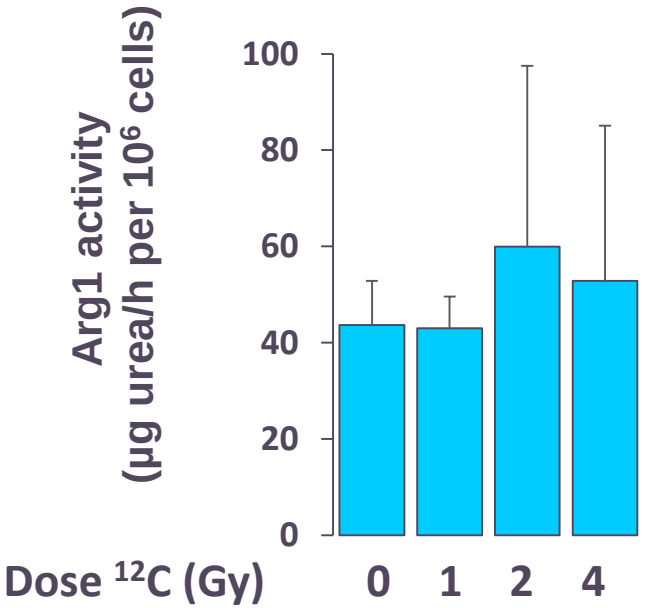


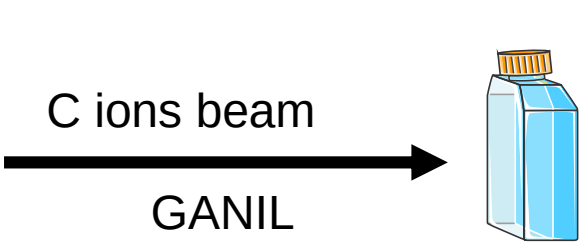
What about other type of RT ? ➔ questions with C Ions

Preliminary experiments with M0



^{12}C ions, GANIL

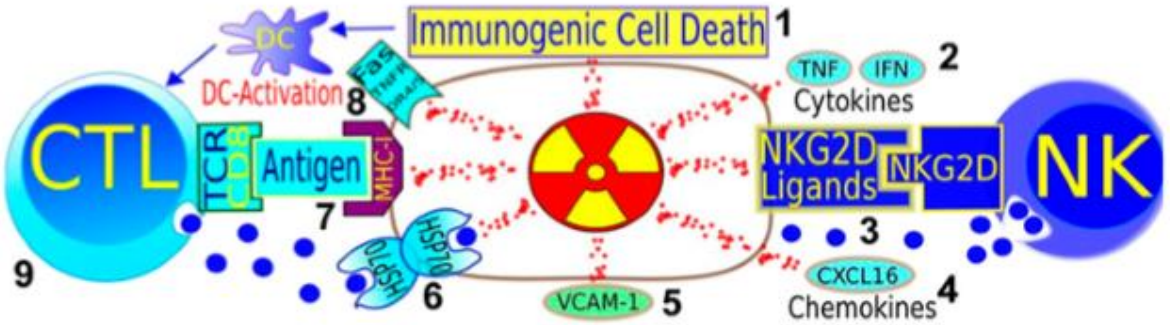




Not appropriate for primary cultures

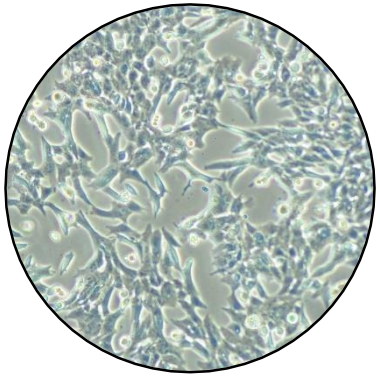
Tumor Cells

RT



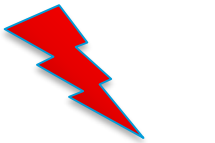
Durante M et al., BJR, 2014

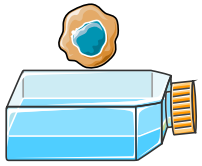
Microenvironment
-Inflammation



GL261 : GBM cell line

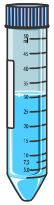
X Rays or ^{12}C





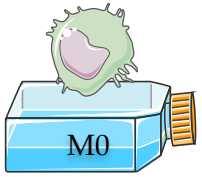
Irradiation of GL261 cells

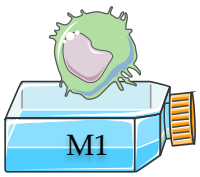
72h

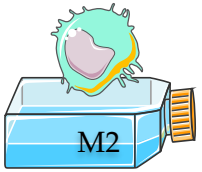


SN withdrawal/ filtration

+ cytokines







Conclusions

M2 macrophages seems to be more resistant than M0 and M1 to X Rays

Sensitivity to other type of beams needs to be further evaluated
➔ Direct effects of beam on macrophages ? On inflammation?
➔ Indirect effects through radio-induced products on cancer cells ?

In vivo experiments remain mandatory
➔ In vivo monitoring of inflammation with imaging (PET or MRI) ?

IMAGERIE & STRATÉGIES THÉRAPEUTIQUES DES PATHOLOGIES CÉRÉBRALES & TUMORALES

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