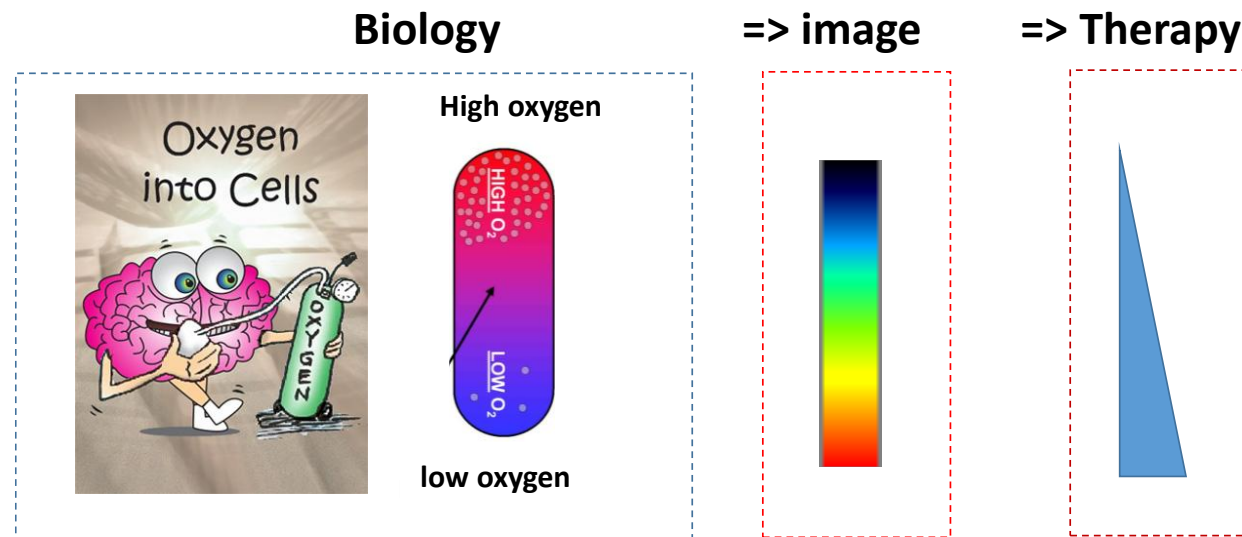


# Innovative strategies to overcome hypoxia-induced radioresistance in high grade brain tumors



« from gene to full body »  
Preclinical to clinical researches

**Microscopes** (visible/fluorescent, time lapse...)  
**Hypoxic chamber**

**MRI 7T, Micro-PET**  
**PET/MR 7T**  
**Angiography**  
**Histology lab**  
**Physiology lab**  
**Behaviour rooms**  
**X-Rays animal irradiator**  
**X-Rays cell irradiator**

**MRI 3T**  
**PET-CT**

**Biomedical Cyclotron**  
**Class D clean room**  
**HPLC/GC equipment**  
**Hot and cold lab**  
**Shielded cells**



## Promotes tumor growth

Metabolic changes

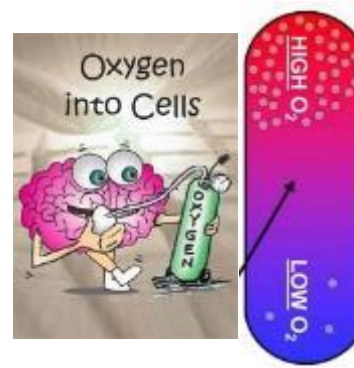
Angiogenesis

Invasion

Inflammation

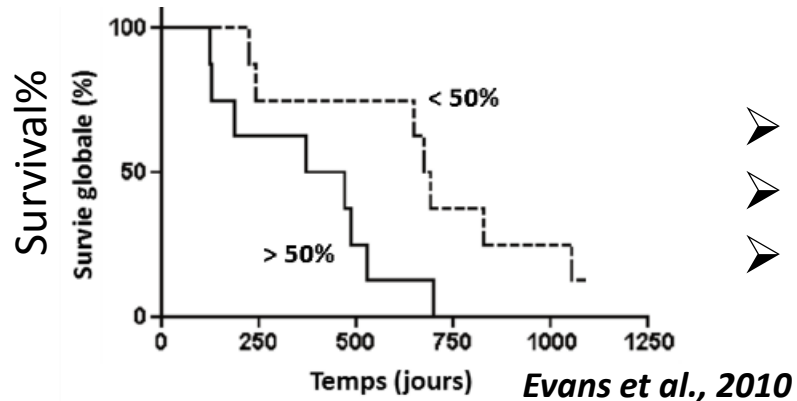
Leblond et al., Oncoimmunol 2015,  
Leblond et al., Oncotarget 2017  
Hélaine C et al., Cancers, 2020  
Fantin J et al., EJNMI , 2023  
Levallet J et al., Cell Death Dis, 2023

## HYPOXIA

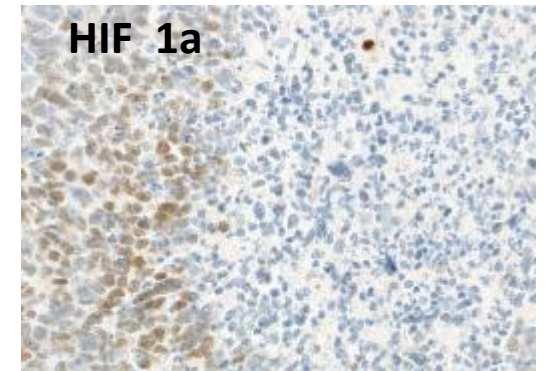


Resistance to  
Radiotherapy  
Chemotherapy

Torrise F et al., Cancers, 2020  
Valable S et al., Cancers, 2020  
Anfray C et al., Biomaterials, 2020  
Helaine C et al., Nanoscale 2024  
Amedlous A et al., ACS Ami, 2025



- Marked heterogeneity among patients
- Spatial heterogeneity
- Temporal heterogeneity

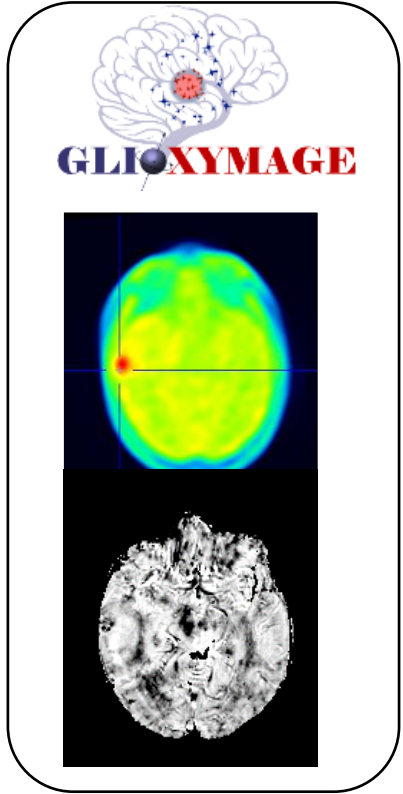
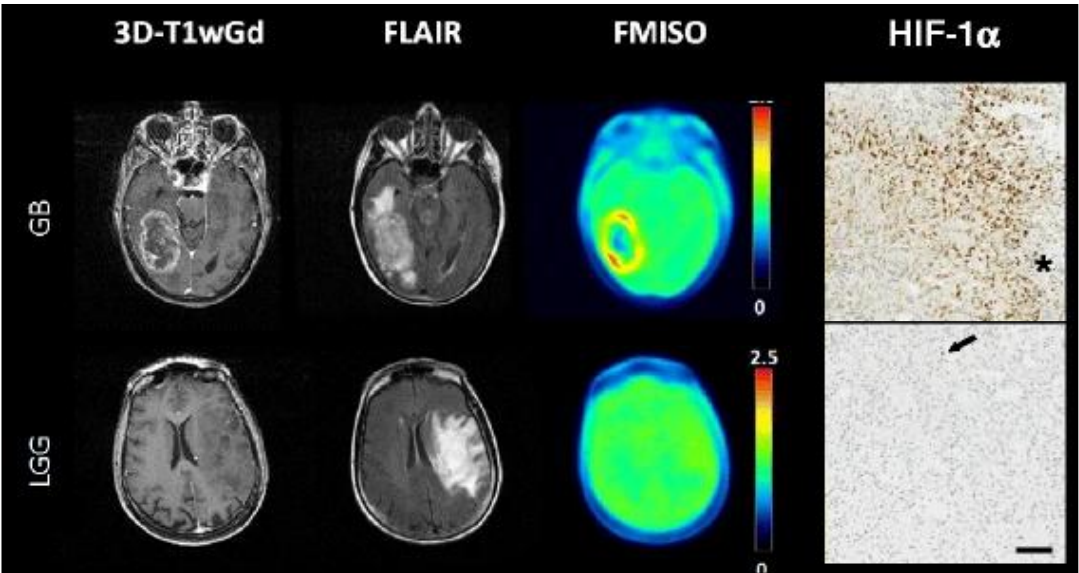
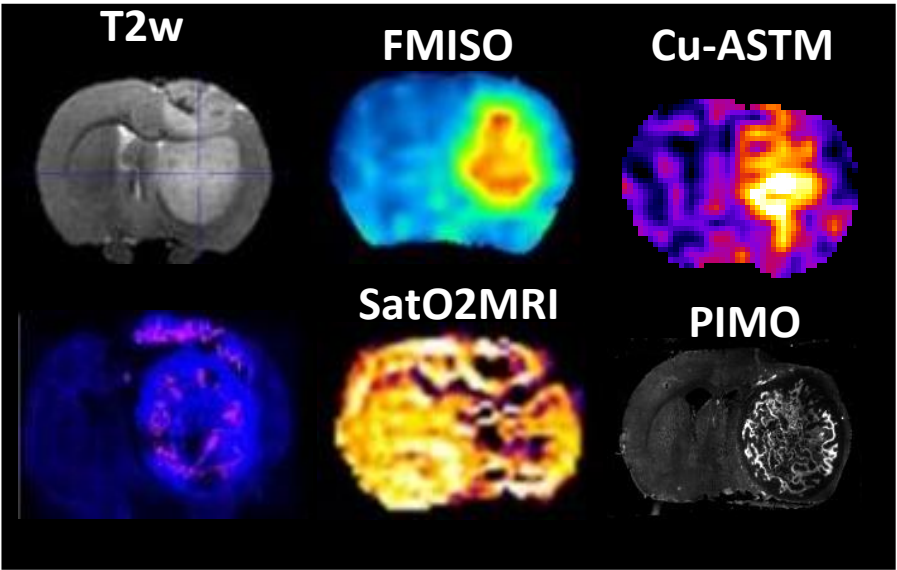


**Non invasive mapping of tumor hypoxia ?**



# Non invasive detection of hypoxia with imaging

Dr A. Corroyer-Dulmont   Dr J. Fantin   Dr M. Bernaudin



Valable S et al., 2017, JCBFM  
Pérès et al., 2019, EJNMMI Res  
Valable S et al., 2023, NMR In Biomed  
Fantin J et al., 2023, EJNMMI res



Ponte et al., 2017; JNM  
Bekaert et al., 2017; EJNMMI  
Chakhoyan et al., 2017, Sci Reports  
Collet S et al., 2021, JNM

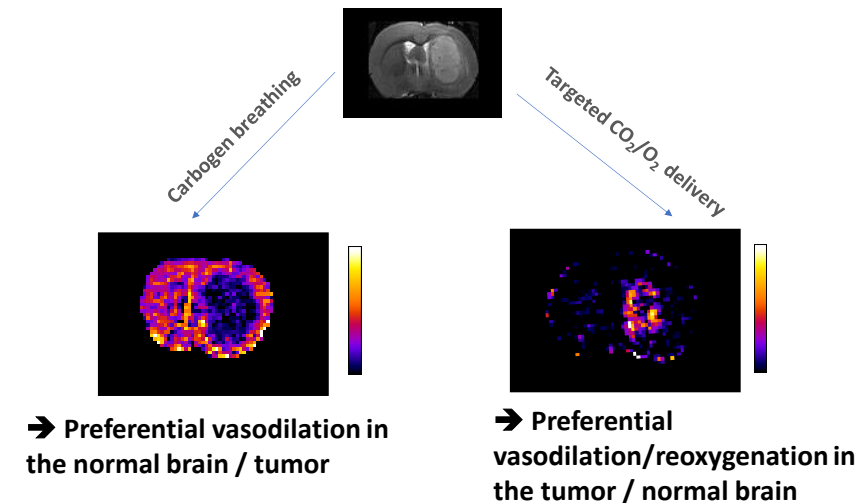
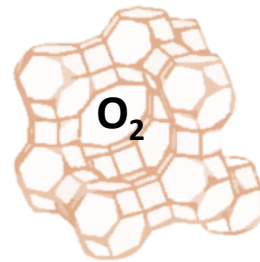
# Hypoxia and radioresistance

## More adapted treatments ?

Increasing dose prescription

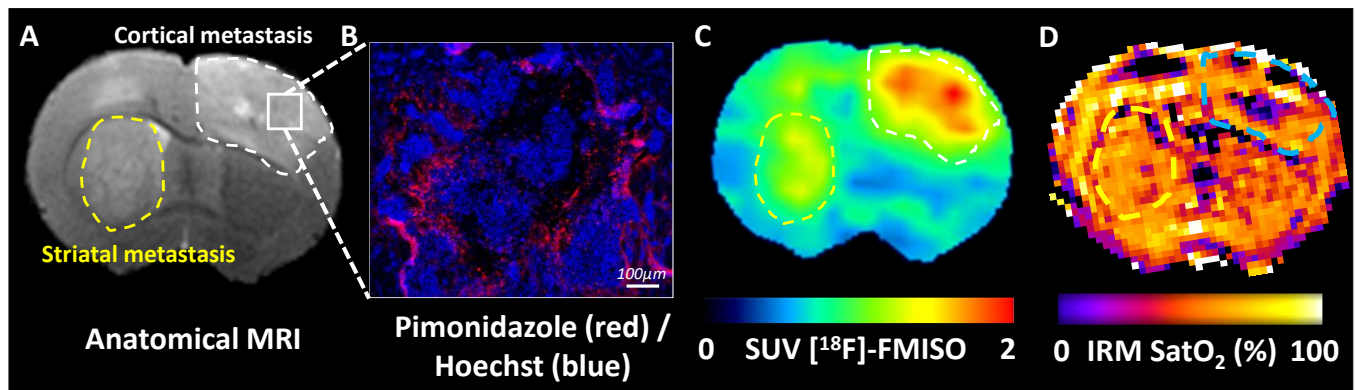
Changing the RT regimen

Increasing oxygen concentration?  
*Ex: zeolites*

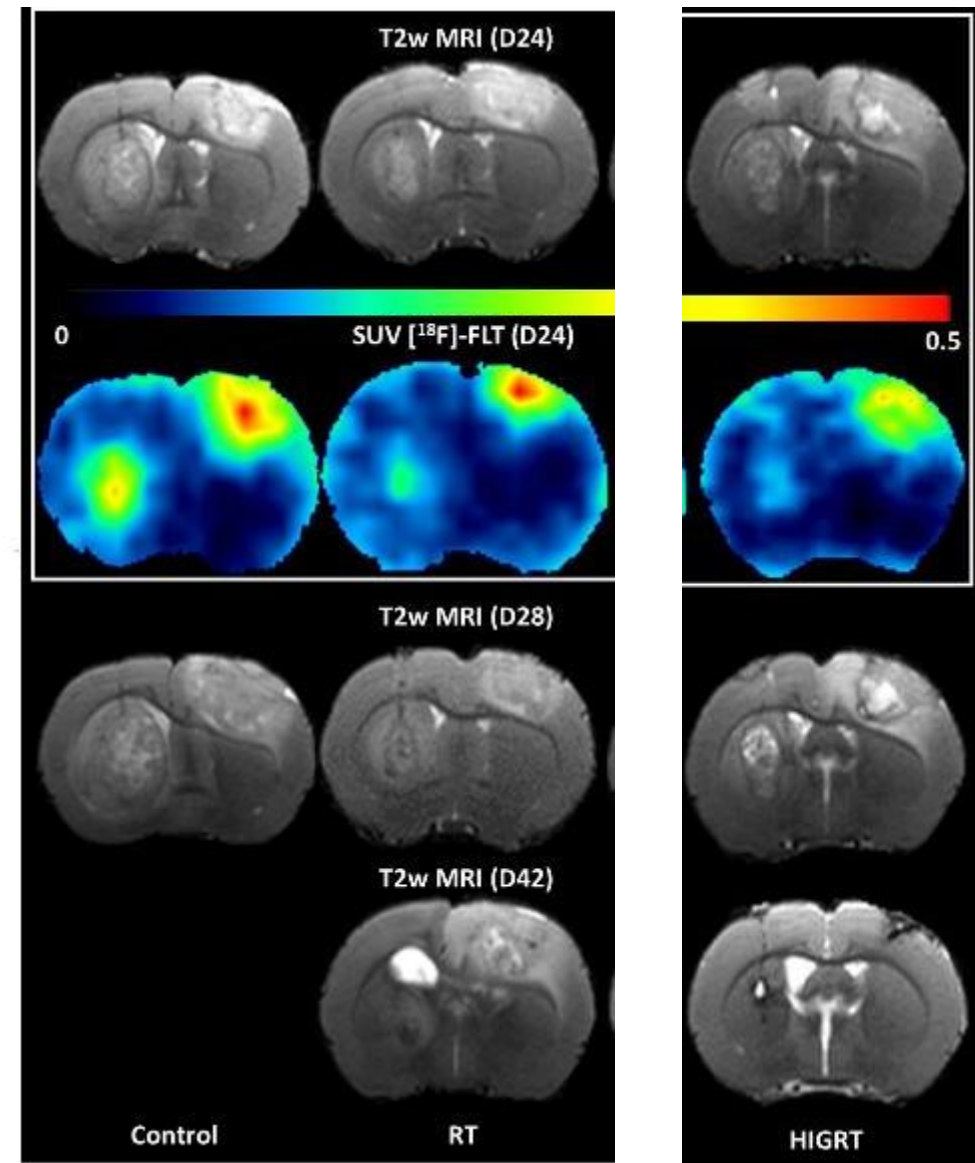
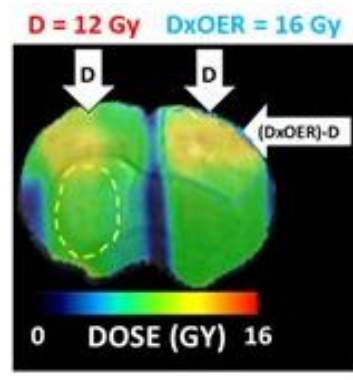


Anfray et al., 2020, Biomaterials  
Komaty et al., 2020 JCIS  
Anfray et al., 2017 ACS AMI  
Georgieva et al. 2016 MMM  
Łukarska et al. 2016 MMM

Amedlous et al., 2025, ACS AMI  
Helaine et al., 2024, NanoScale



XRad-225Cx  
REC-HADRON Equipex

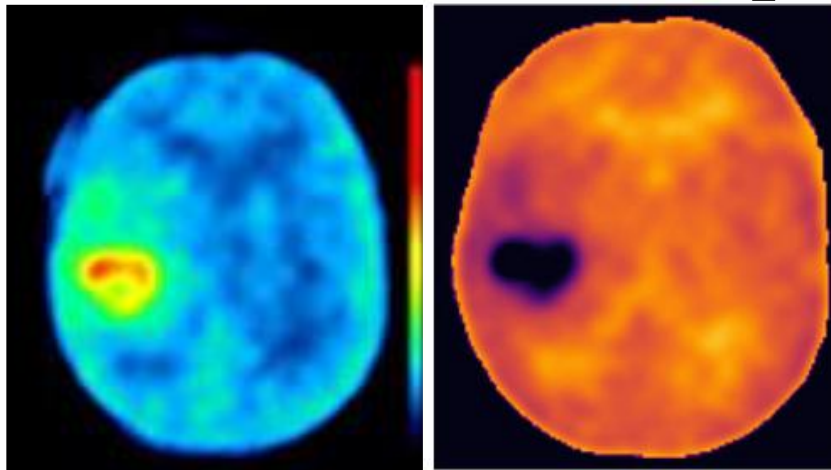




FMISO



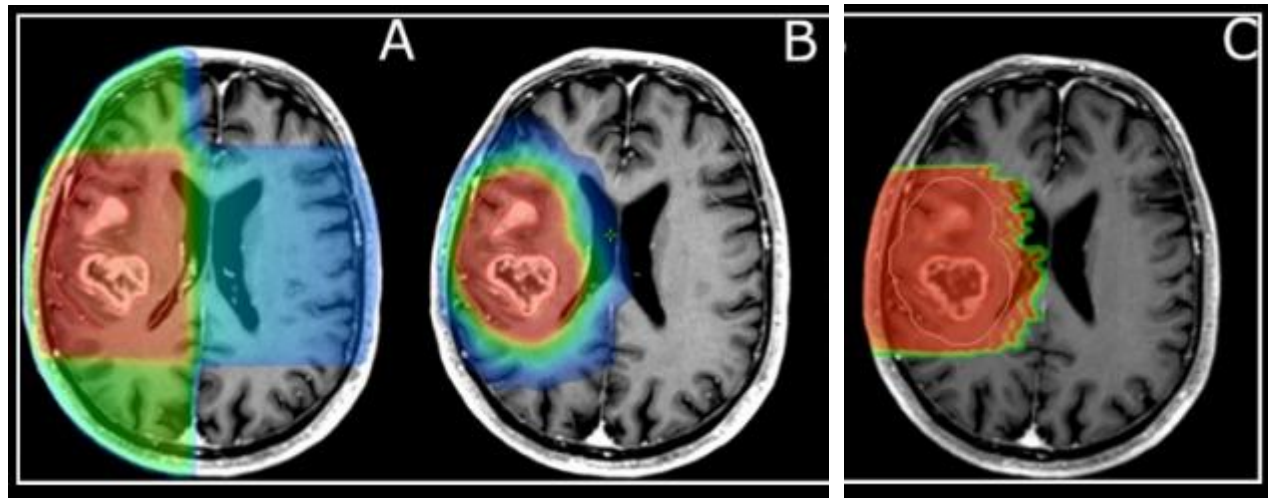
ptO<sub>2</sub>



Chakhoyan A et al., 2017 Sci Rep.

IMRT

ProtonT



Gérard M et al., 2019, Front. Med.

**CYCLHAD**

International Multi-Ion  
Hadrontherapy Center

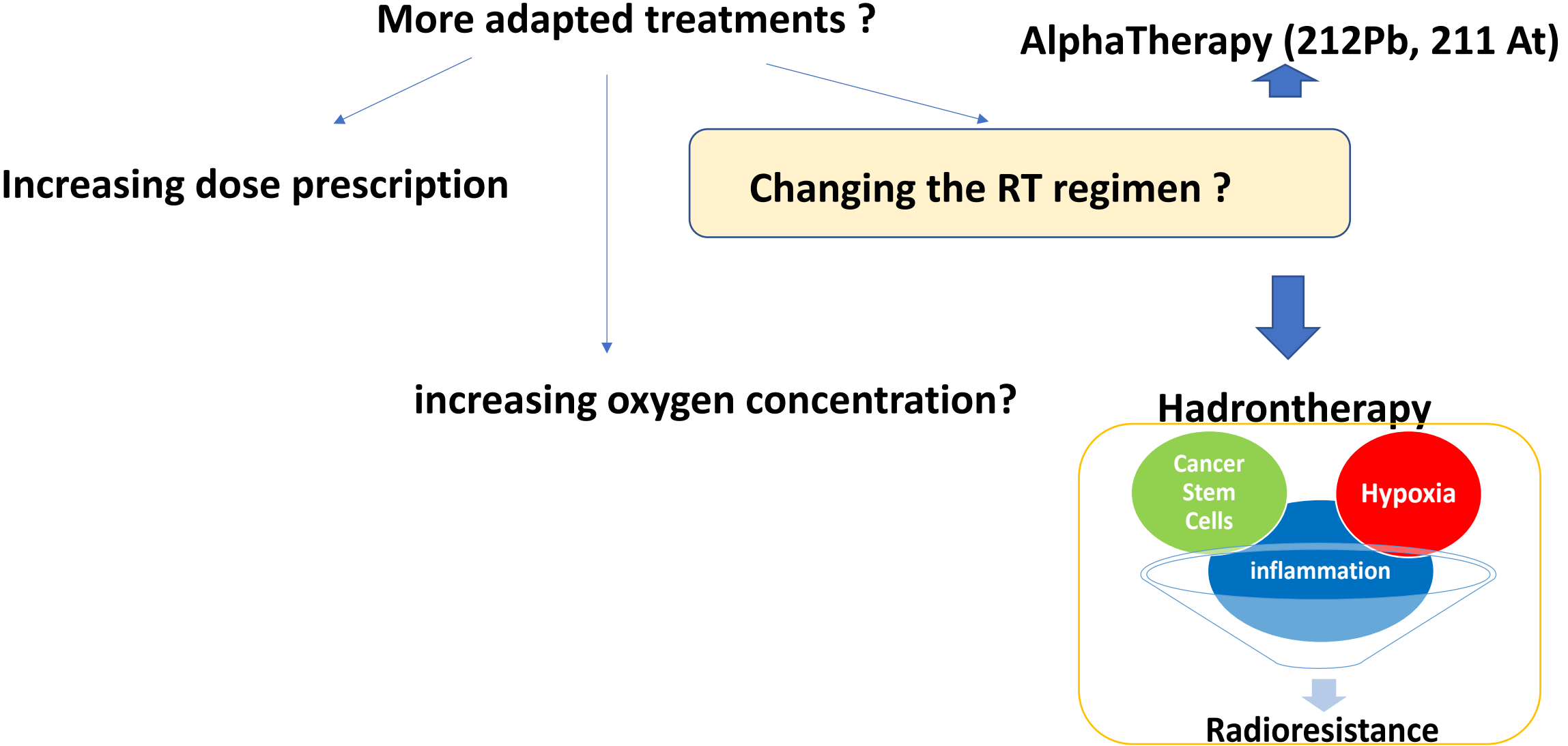


*ProteusONE*

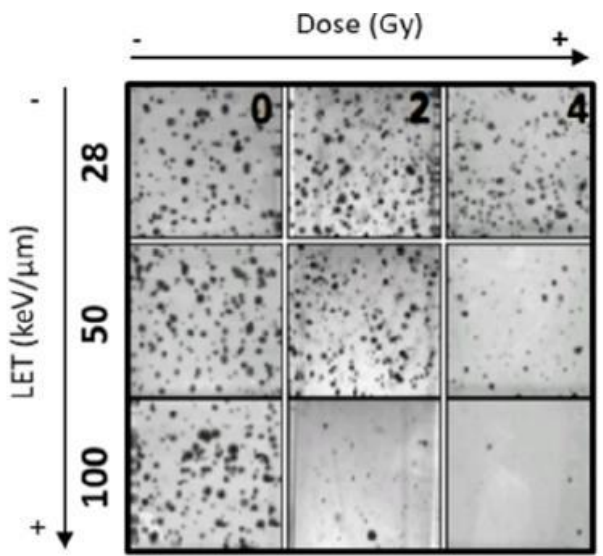


*C400 IONS*

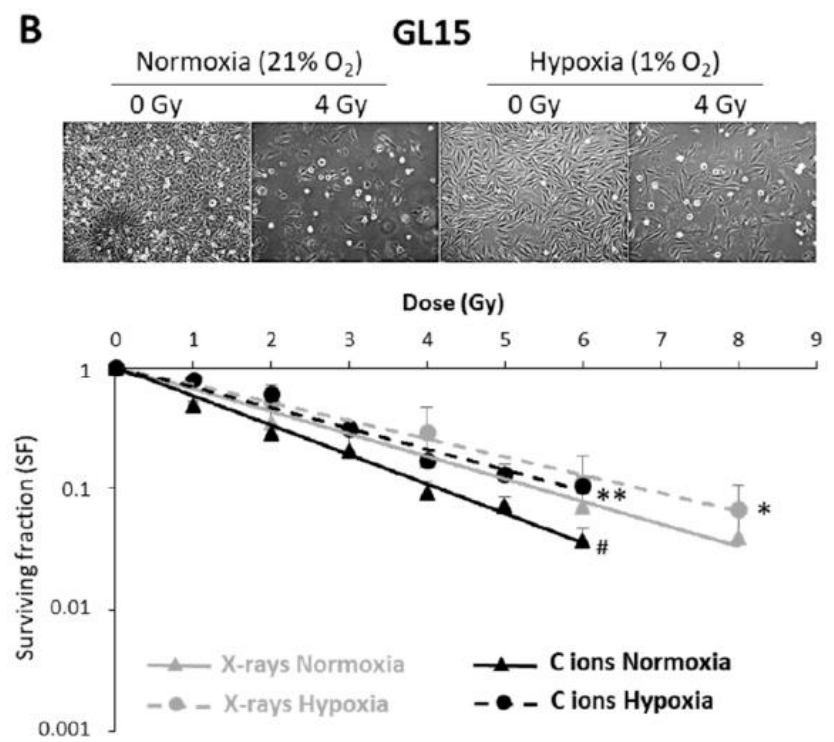
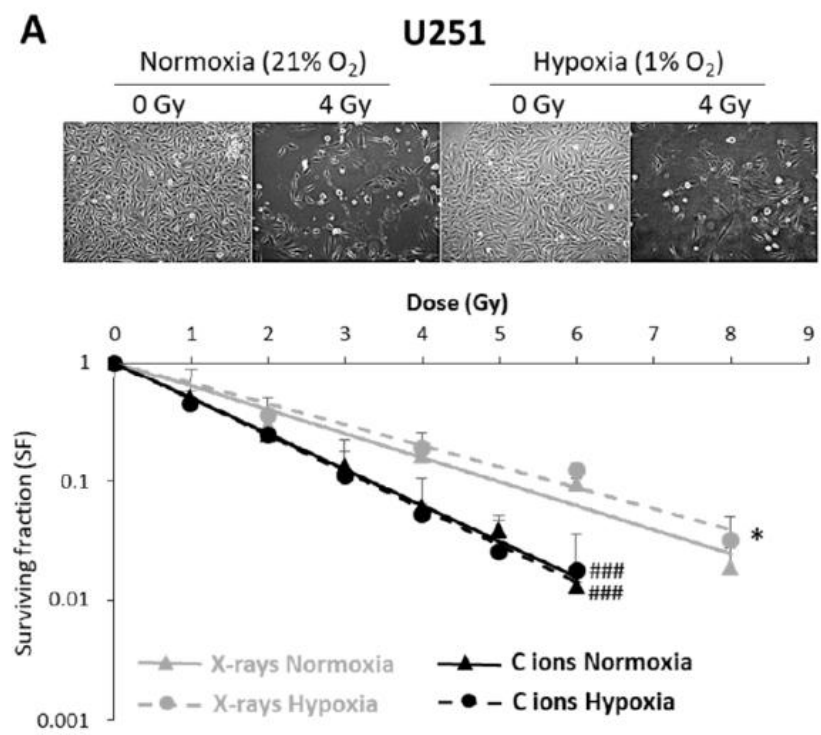
H, He, B ....and C





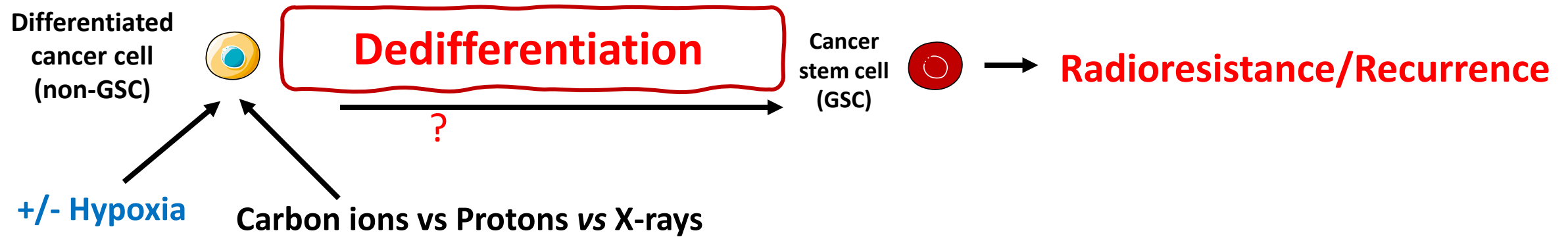


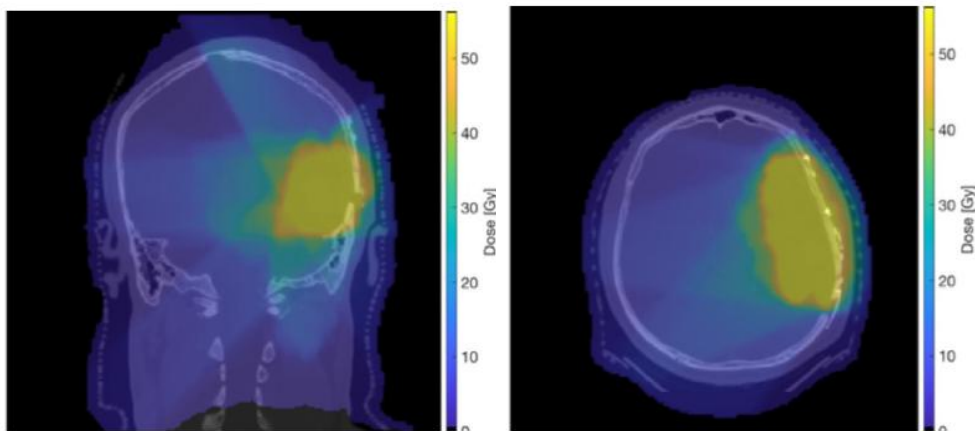
Cell sensitivity to carbon ions increases when increasing LET



Valable *et al.*, Cancers, 2020

Hypoxia-dependent radioresistance with X-rays  
But also with carbon ions in a cell-type dependant manner





**Undesired side effects ?**

# Interest of proton therapy to spare circulating leucocytes ?

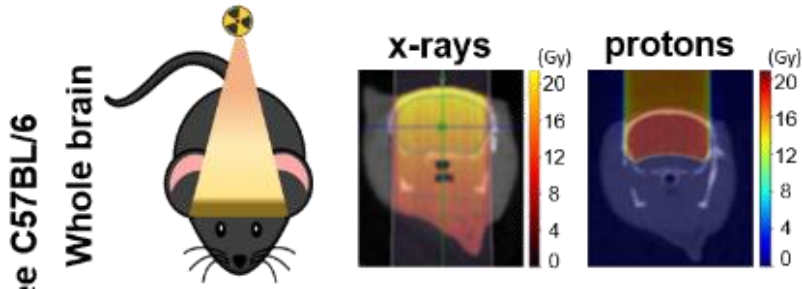
Dr J. Coupey



Dr T. Pham



Pr J. Thariat



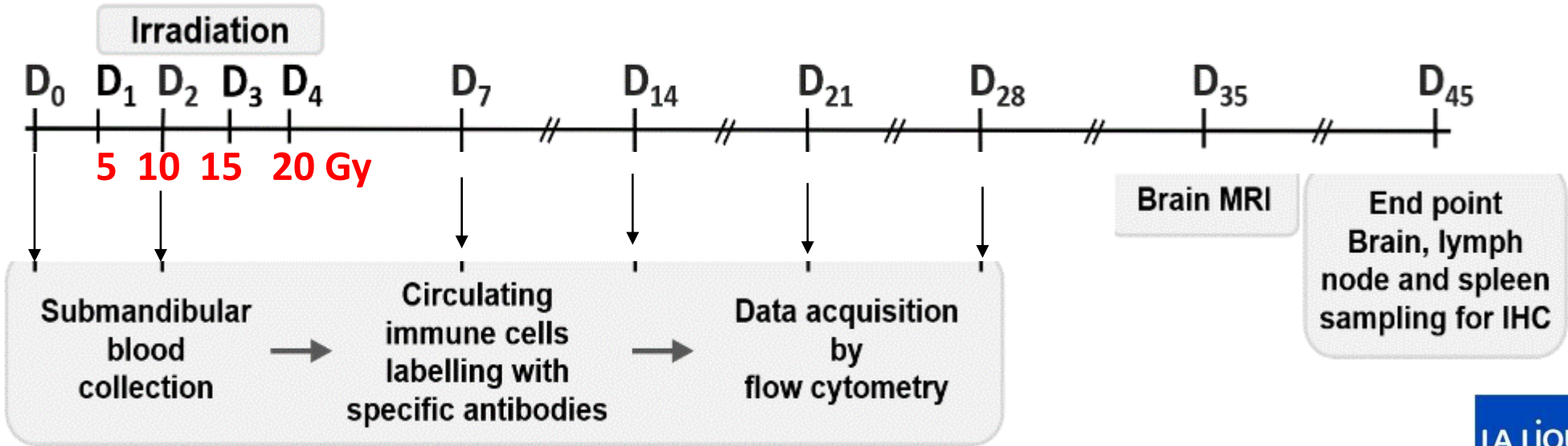
Cyceron, Caen   
Irradiateur XRad-225Cx



PRECy platform, Strasbourg  
CYRCé cyclotron, 24 MeV



Pr Marc Rousseau



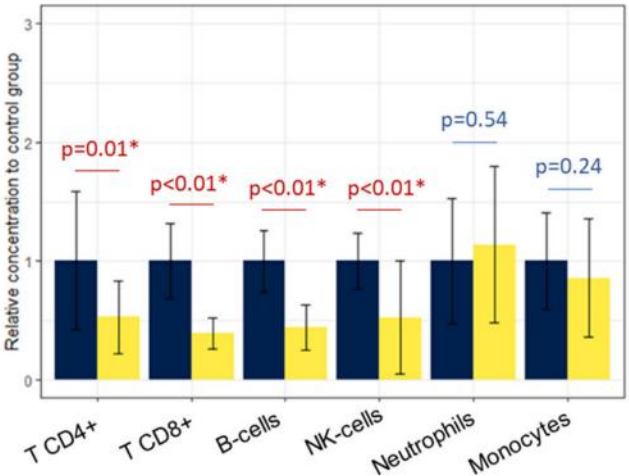
Coupey J et al., 2024, Methods In Cell Biology



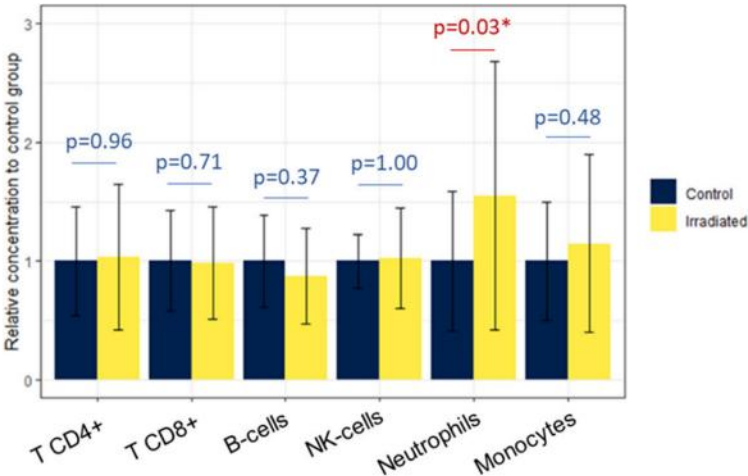
# Effects of X-Rays and Protons on circulating lymphoid cells

Day 2

## X-Rays



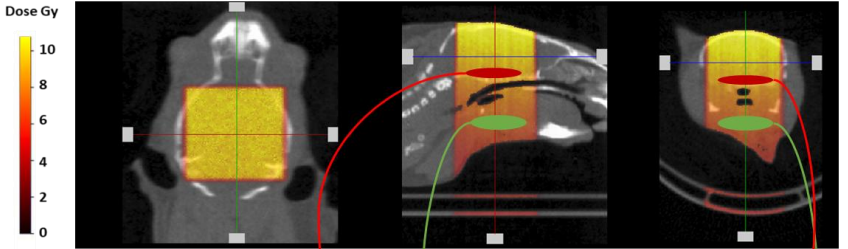
## Protons



Pham TN, 2024Cancer Radiother.  
Pham TN, 2024 Comput Methods Programs Biomed.  
Pham TN, 2024 J Leukoc Biol.  
Pham TN, 2024 Radiother Oncol.  
Pham TN, 2024, Int J Radiat Biol.

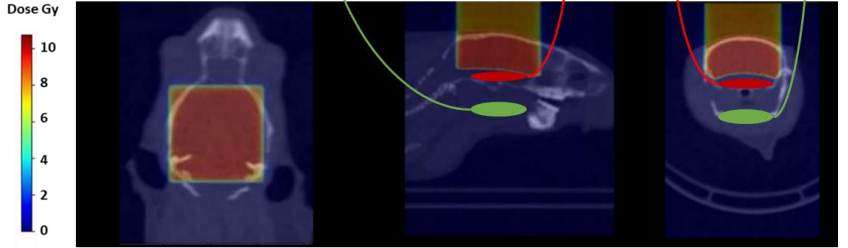
Coupey J., 2026 IJROBP  
Pham TN, 2025 Radiother Oncol.  
Pham TN, 2025Comput Biol Med.  
Coupey J., 2024, BioRxiv,

### X-ray irradiation



Region of mandibular/submandibular lymph nodes  
Region of supplying arteries to the brain

### Proton irradiation



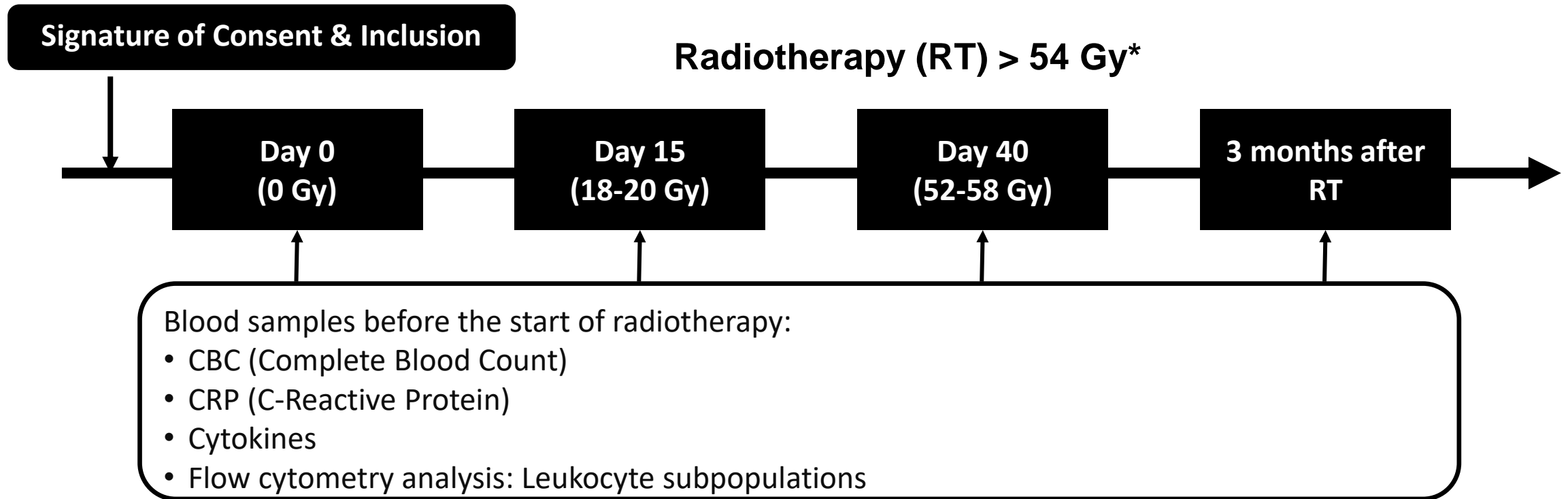
Blood and lymph nodes are source of lymphocytes

- More blood exposure to radiation dose in X-ray than in proton irradiation
- 4 lymph nodes exposed to radiation dose in X-ray irradiation, which were spared in proton irradiation



Explanation for difference in circulating lymphocyte count following Xray/Proton irradiation?

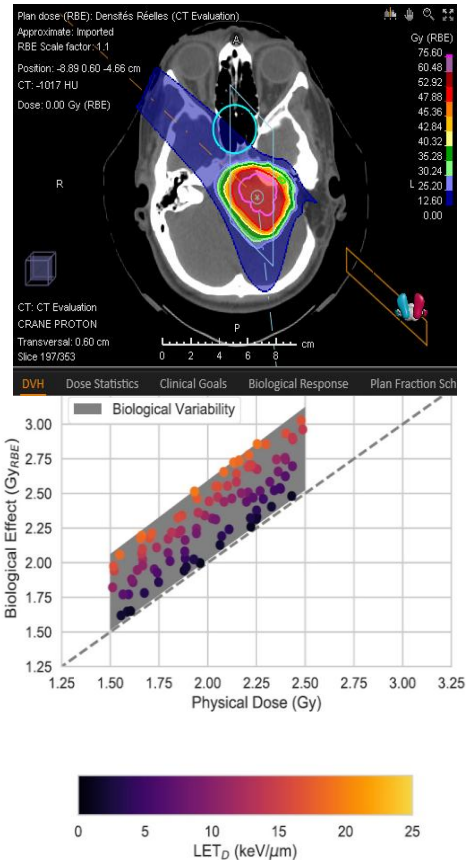
## CYRAD study (NCT05082961)





# Evaluation of Brain MRI Changes and Neurocognitive Toxicities Following Proton Therapy: Impact of Linear Energy Transfer and Effective Biological Dose

BrainTEL study (NCT04584086) and Cog Proton study (NCT05895344)



Lesueur P, Radiat Oncol. 2025  
Lesueur P, BMC Cancer. 2024



Contact: [bernaudin@cyceron.fr](mailto:bernaudin@cyceron.fr) / [samuel.valable@cnrs.fr](mailto:samuel.valable@cnrs.fr)

