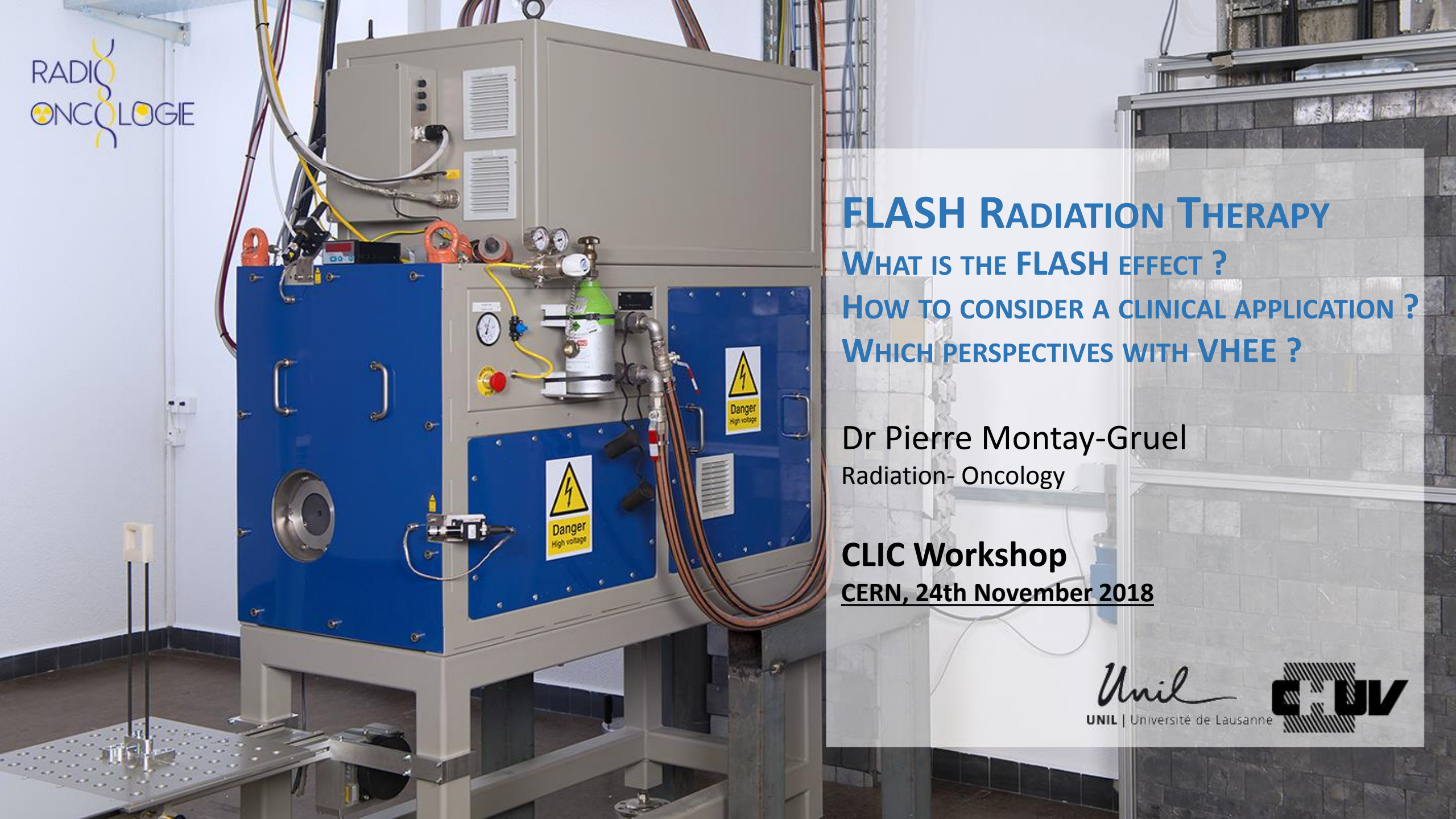


RADIO ONCOLOGIE

FLASH Radiation Therapy

What is the FLASH effect ?

How to consider a clinical application ?

Which perspectives with VHEE ?

Dr Pierre Montay-Gruel

Radiation- Oncology

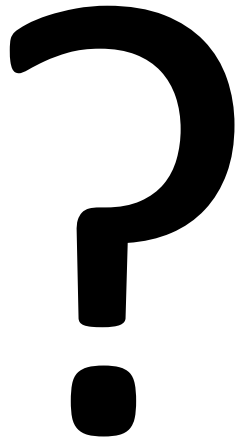
CLIC Workshop

CERN, 24th November 2018

UNIL | Université de Lausanne

CHUV

What is FLASH-RT

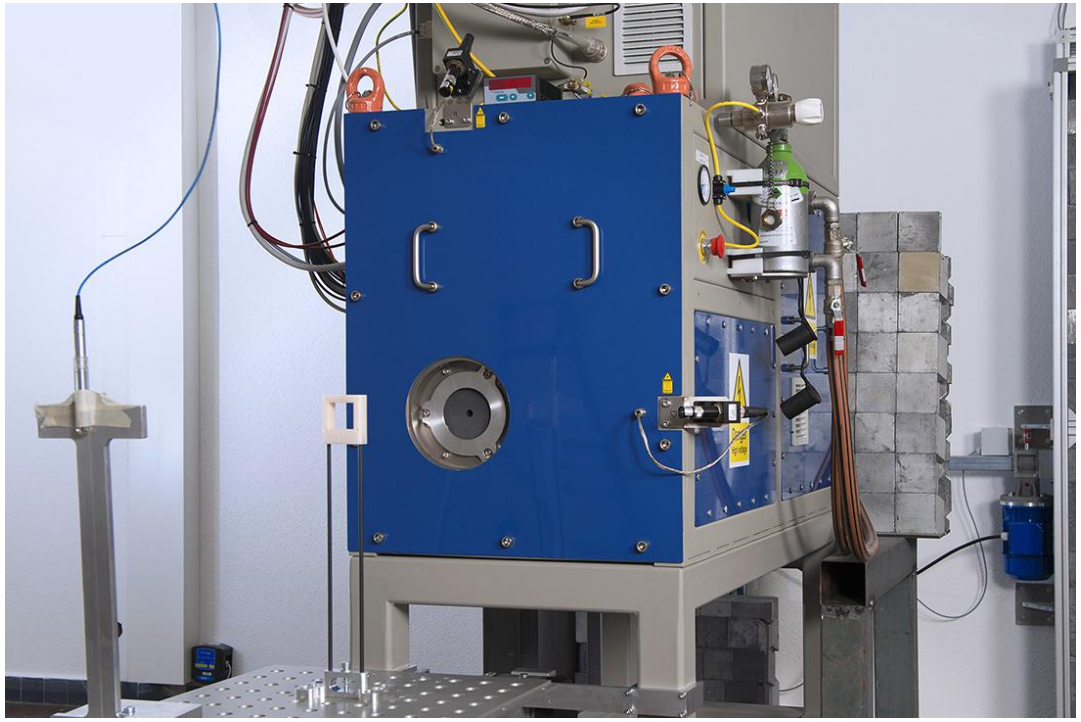


FLASH-RT technological basis

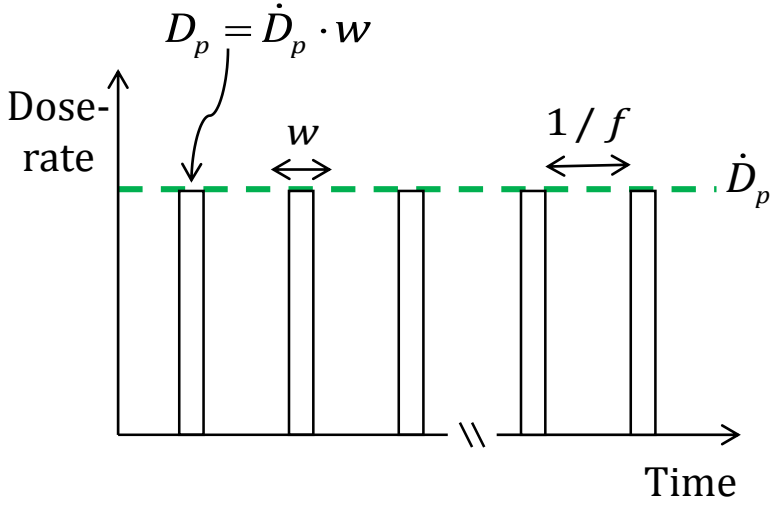
Electron beam
~ 5 MeV energy
Pulsed beam

Dose Rate
x 10^6

	Conventional RT in clinics	FLASH-RT
Mean Dose Rate	0,1 Gy / sec	>50 Gy / sec
Time to deliver 10Gy	100 sec	1.8 x 10^{-6} s



Experimental LINAC eRT6
PMB Alcen, France



Complete and precise dosimetry

C Bailat's team at IRA

Petersson *et al.* 2017
Jaccard *et al.* 2017
Montay-Gruel *et al.* 2017
Jaccard *et al.* 2018

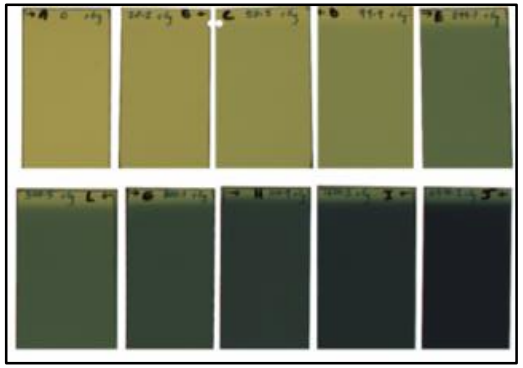
Dosimetry for ultra high dose-rate electron beam

Dose-rate Independent

Methyl Viologen

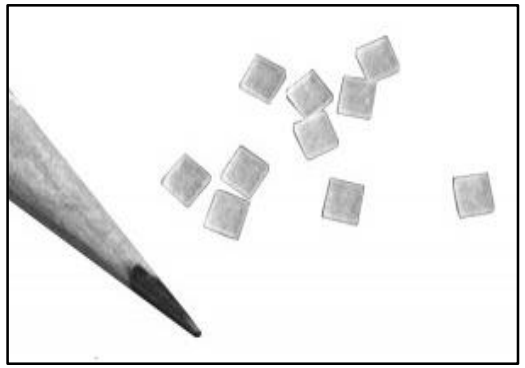
Historical
(Favaudon et al.)

Films



Used in clinics

Thermoluminescent Dosimeters



Alanine

Experimental

All calibrated on clinical electron irradiator
or
Co-60 source

Ionization chamber

Dose-rate dependent
→ **Use of a sorrection factor**

On-line

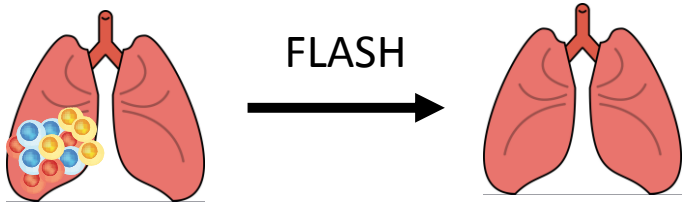
Petersson *et al.* 2017
Jaccard *et al.* 2017
Montay-Gruel *et al.* 2017
Jaccard *et al.* 2018

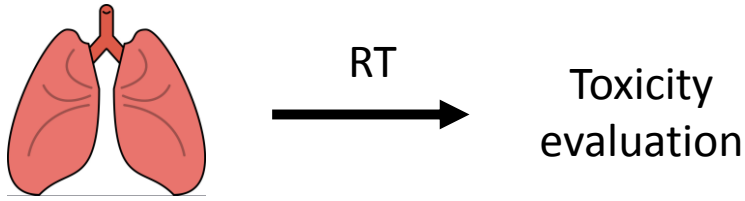
→ Evaluate the reliability of each dosimetry technique and their consistency to one another = **HAVE A PRECISE DOSIMETRY**

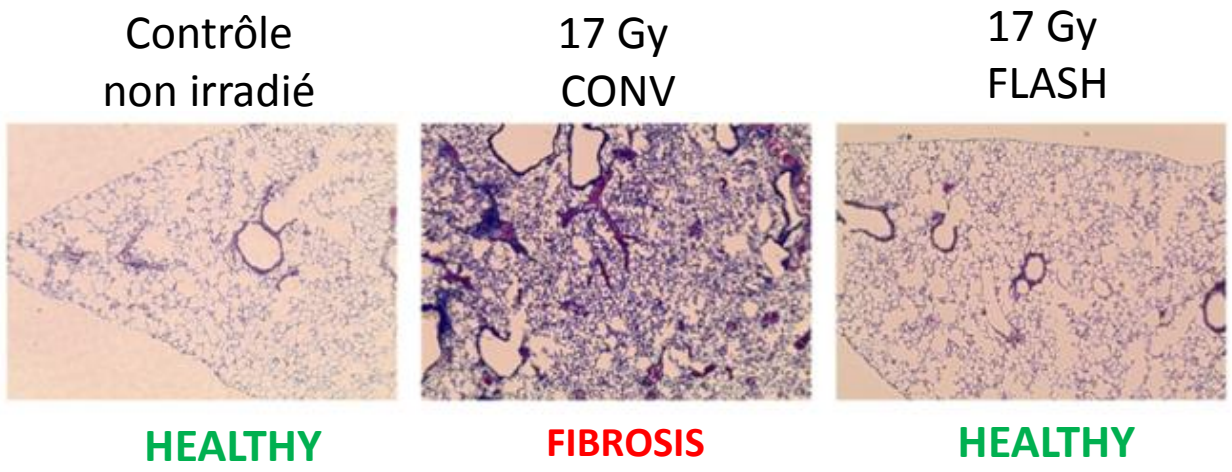
RADIATION TOXICITY

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

Vincent Favaudon,[1,2]* Laura Caplier,[3]† Virginie Monceau,[4,5]‡ Frédéric Pouzoulet,[1,2]§ Mano Sayarath,[1,2]¶ Charles Fouillade,[1,2] Marie-France Poupon,[1,2]‖ Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2] Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]





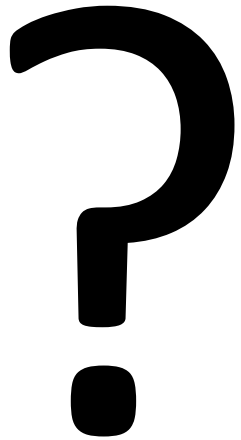


Anti-tumor efficacy

FLASH EFFECT

Absence of radiation-induced toxicity in the Normal lung

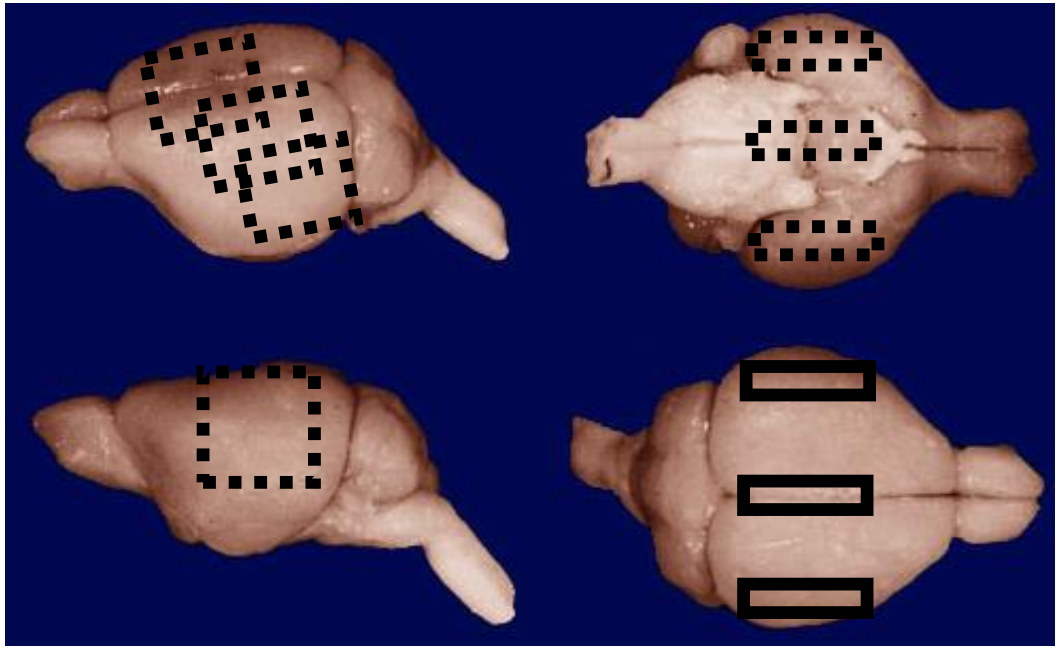
Does FLASH irradiation spare normal brain tissues from radiation-induced toxicities

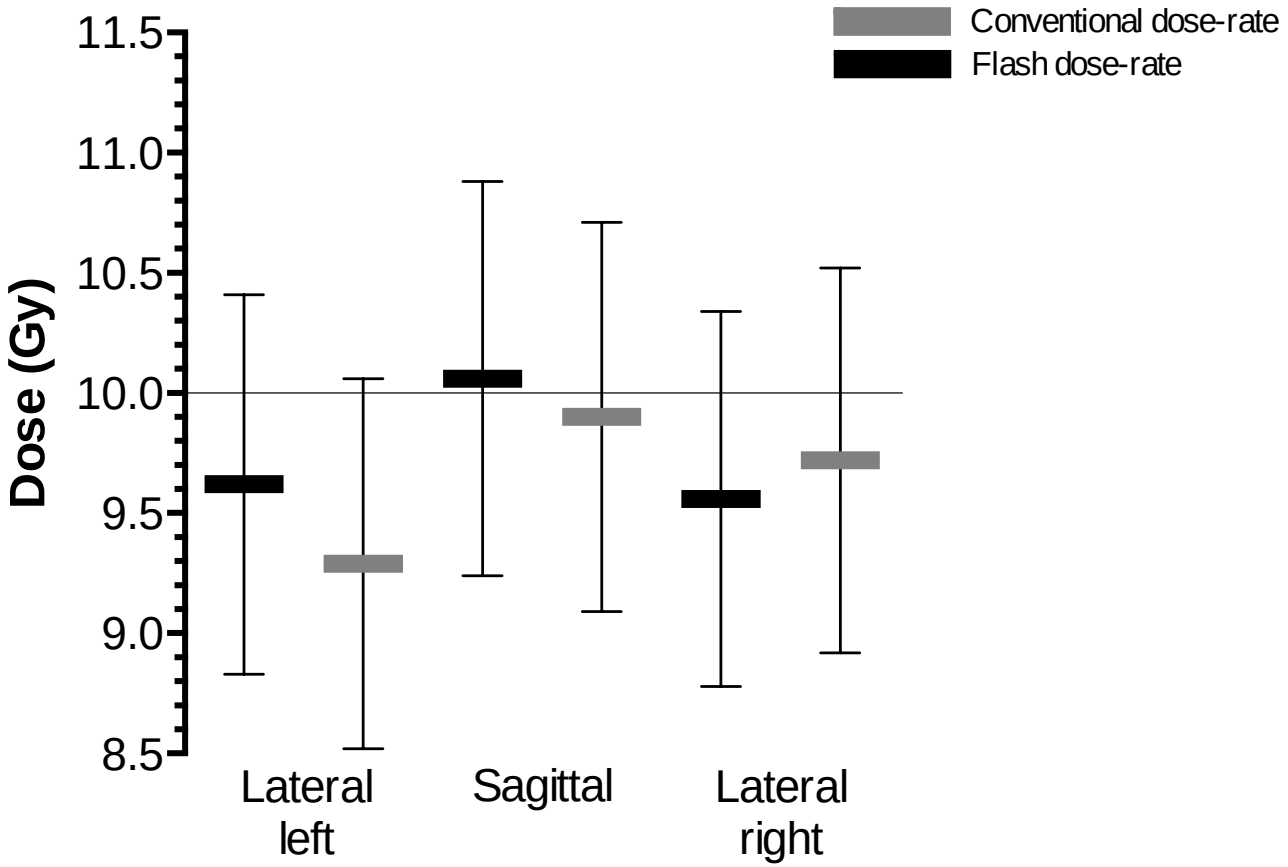


Delivery of a precise and homogenous dose to the brain

Montay-Gruel et al. 2017

TLDs implanted in the brain of a mouse cadaver





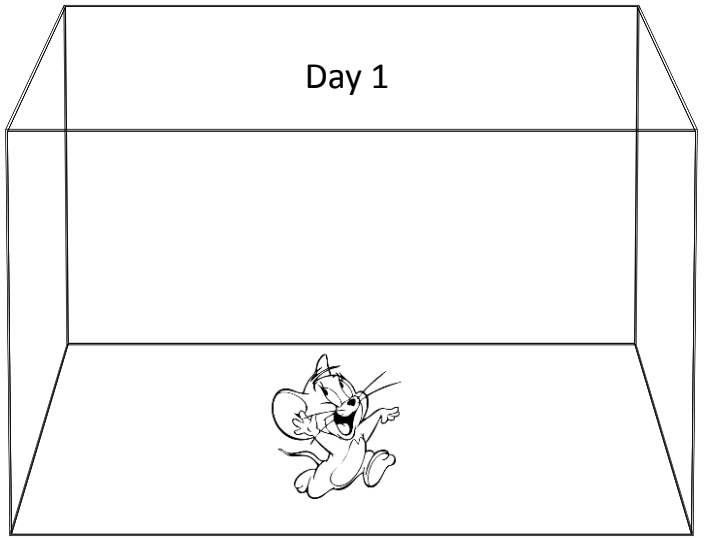
→ **Precise dose delivery + good homogeneity all over the brain**

Do irradiated mice develop cognitive alterations ?

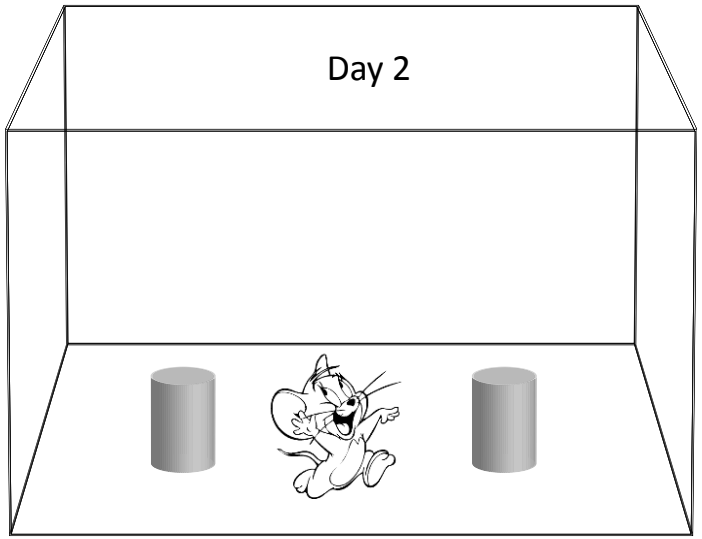
4 weeks post-RT

Memory test
Novel Object Recognition test

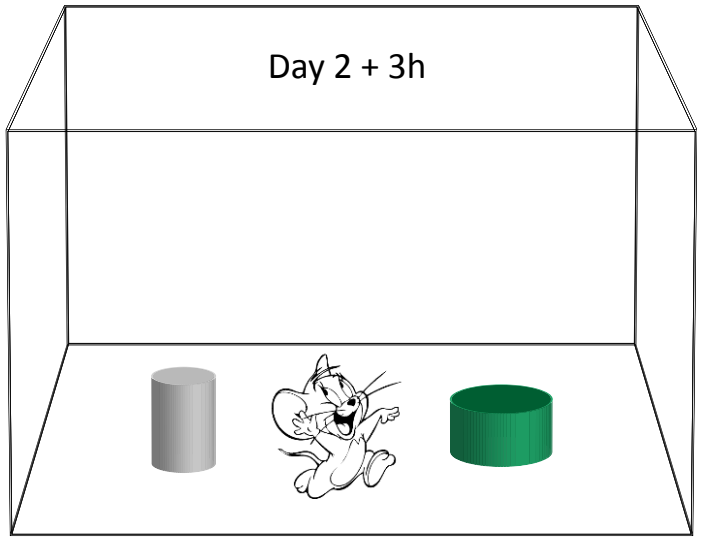
1.
Habituation to the environment



2.
Learn to know an object



3.
Check the knowledge

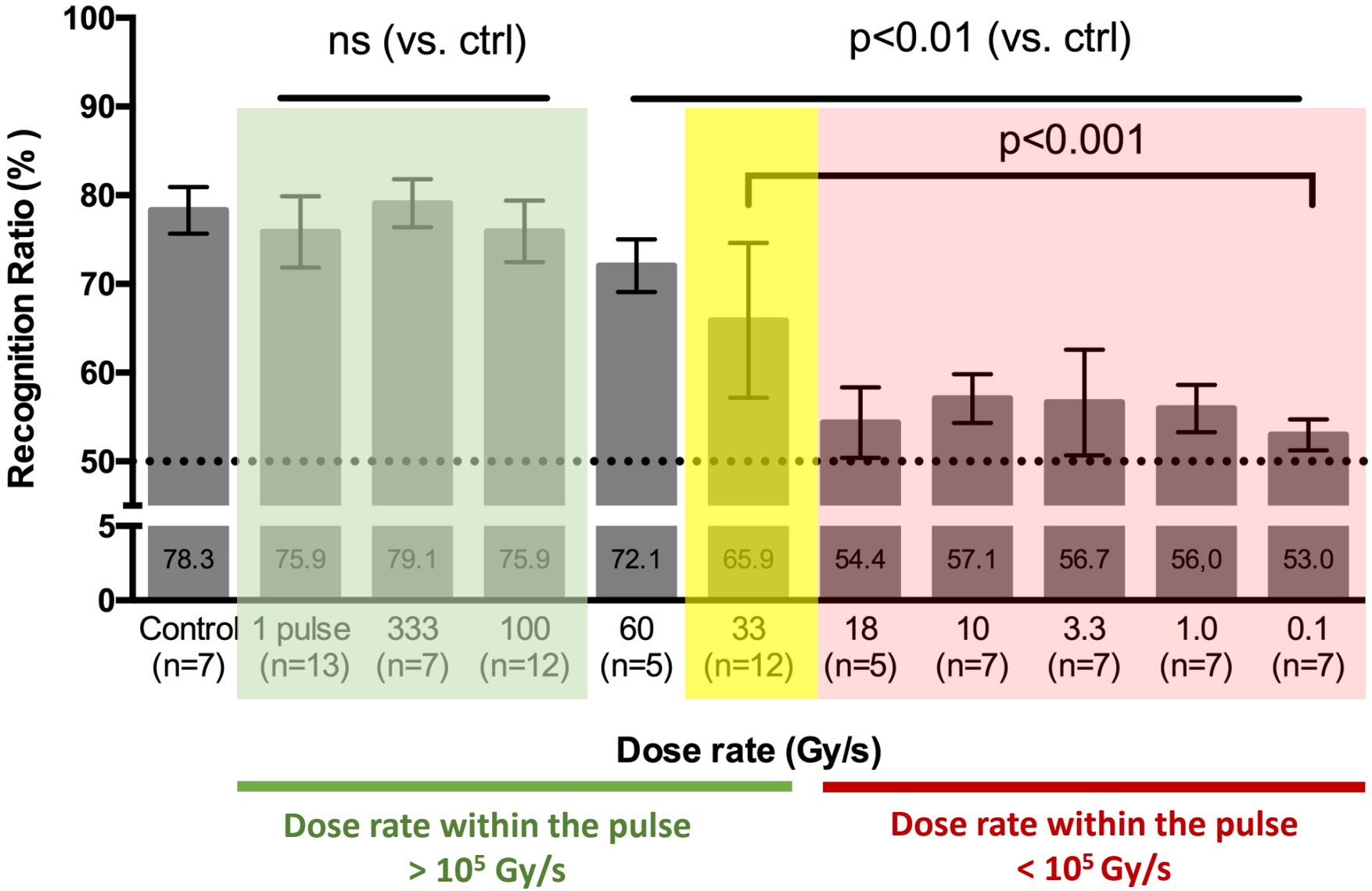


Natural animal curiostiy: Spend more time on the unknown object

UNLESS: the cognitive functions are altered

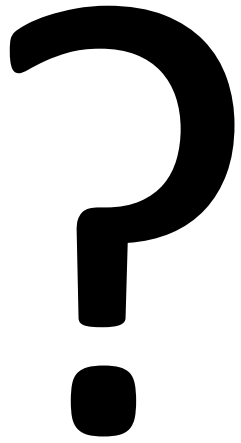
10Gy Flash-WBI preserves the spatial memory function above 100Gy/s

GOAL: Define the dose-rate limits of the functional preservation triggered by FLASH-RT

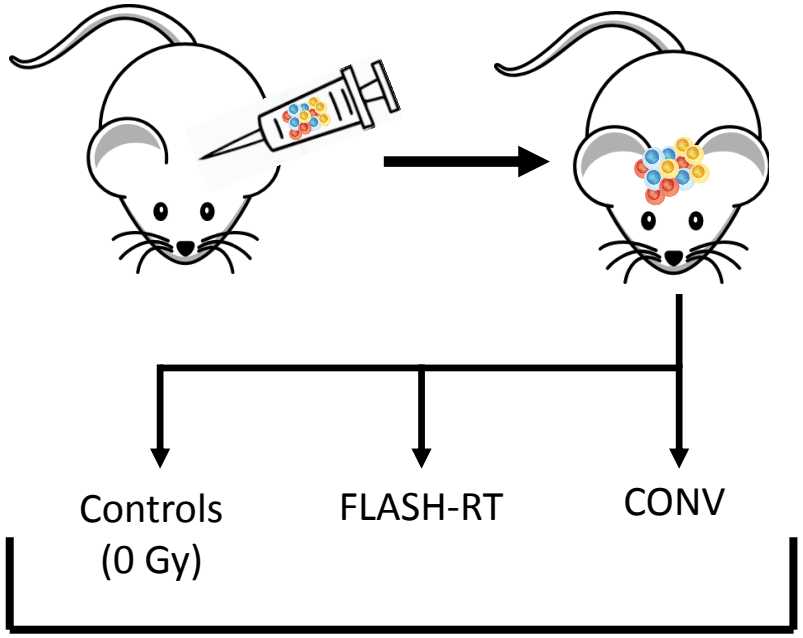


Montay-Gruel et al (2017)

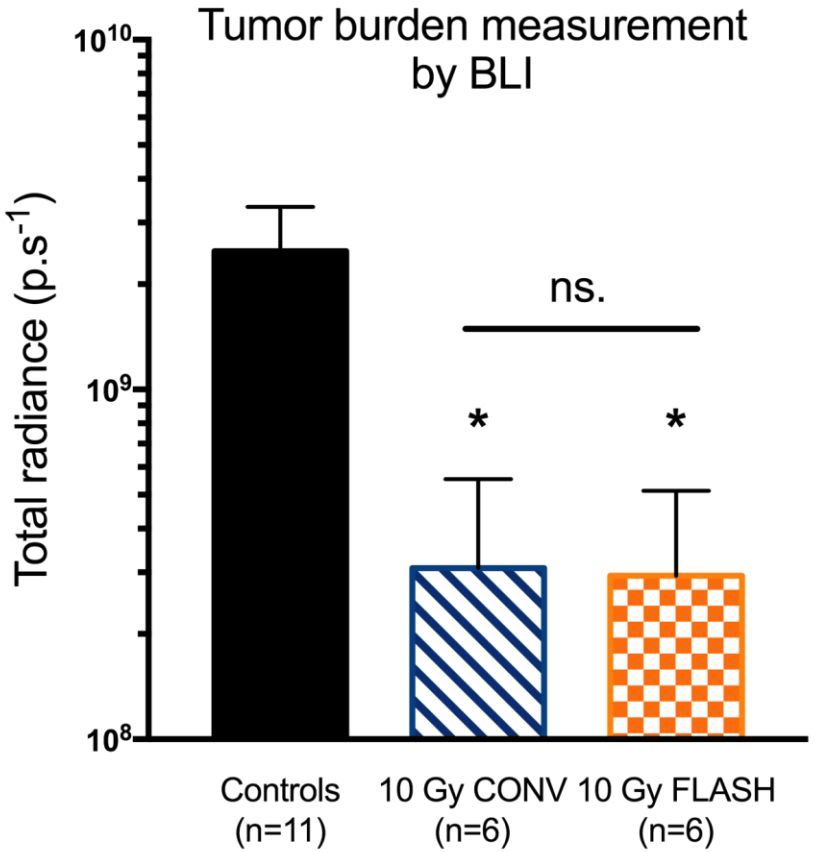
Is FLASH-RT efficient to treat brain tumors



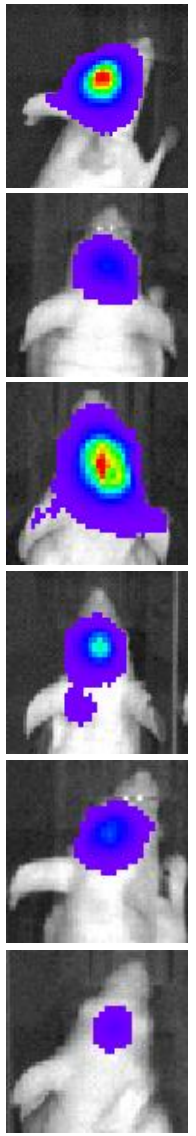
Does FLASH-RT trigger an antitumor effect on glioblastoma ?



Tumor growth measurement by bioluminescence



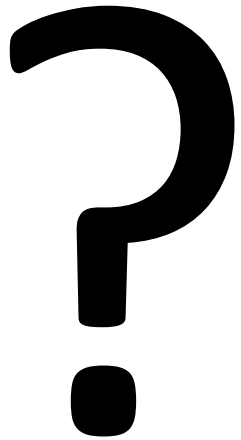
Control



→ **FLASH and CONV-RT trigger the same antitumor effect !**

Montay-Gruel et al (in revision)

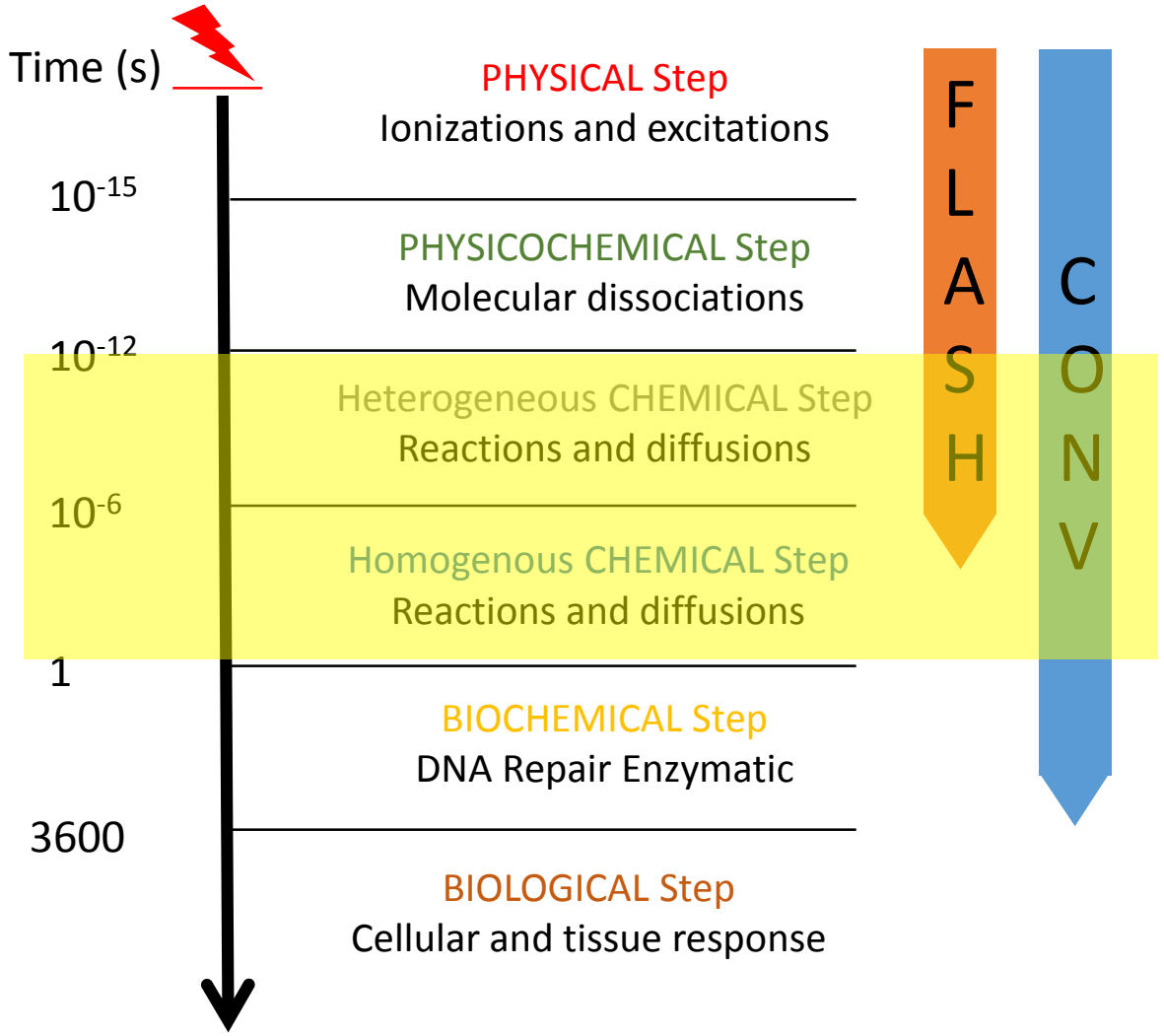
What are the underlying mechanisms to explain the FLASH effect

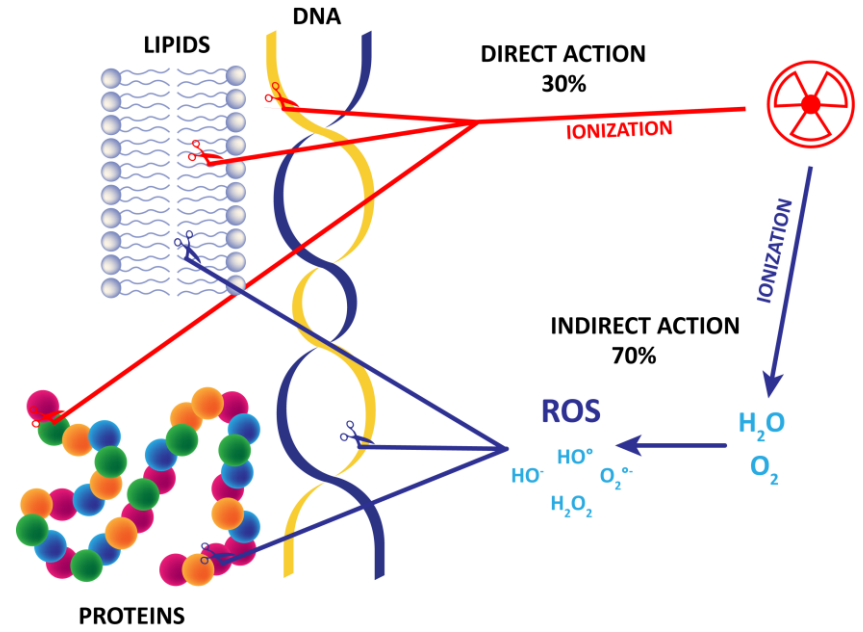


How to explain those striking differences ?

HYP: Back to radiobiology basics: early radio-induced events can explain those differences

Chronology of post-irradiation events and FLASH irradiation





Something different might happen during the chemical steps

→ O_2 consumption and ROS production ???

Prev. described
(Ling et al. Edward et al. Dewey et al.)
bacterian, mammalian cells, and *in-vivo*

Playing with the oxygen tension = modify ROS production

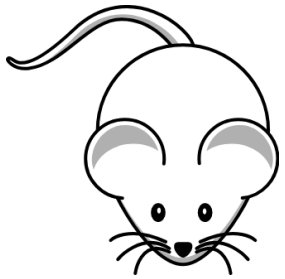
1 – Make mice breathe 95% of oxygen (before and during IR)

2 – Increase oxygen tension in the brain

3 – Deliver FLASH or conventional dose-rate irradiation

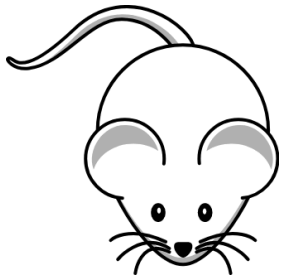
4 – Evaluate memory

CONV



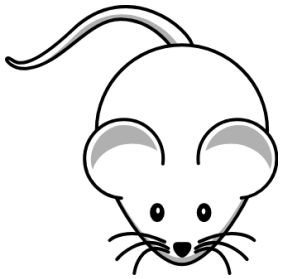
Memory Loss

CONV OXYGEN



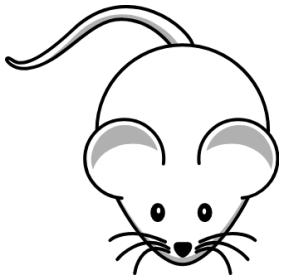
Memory Loss

FLASH



Memory OK

FLASH OXYGEN



Memory Loss

Increase in O2 tension reverses the FLASH effect

Less ROS produced by FLASH-RT ?

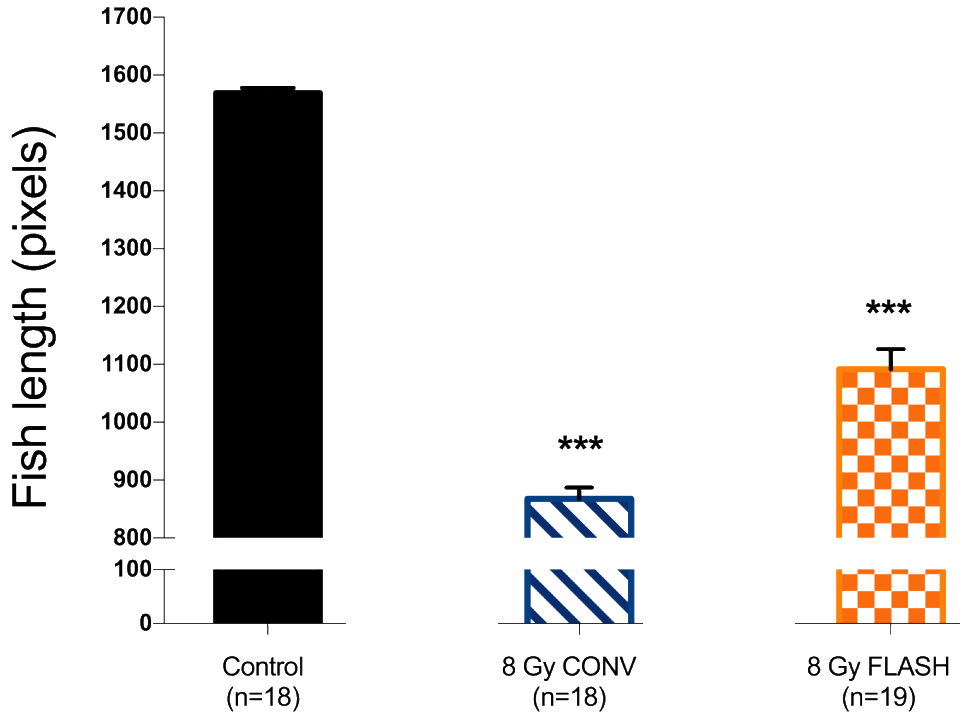
Montay-Gruel et al (in revision)

ROS Scavenging

RT of fish eggs
→ Development assessment

CONV

FLASH

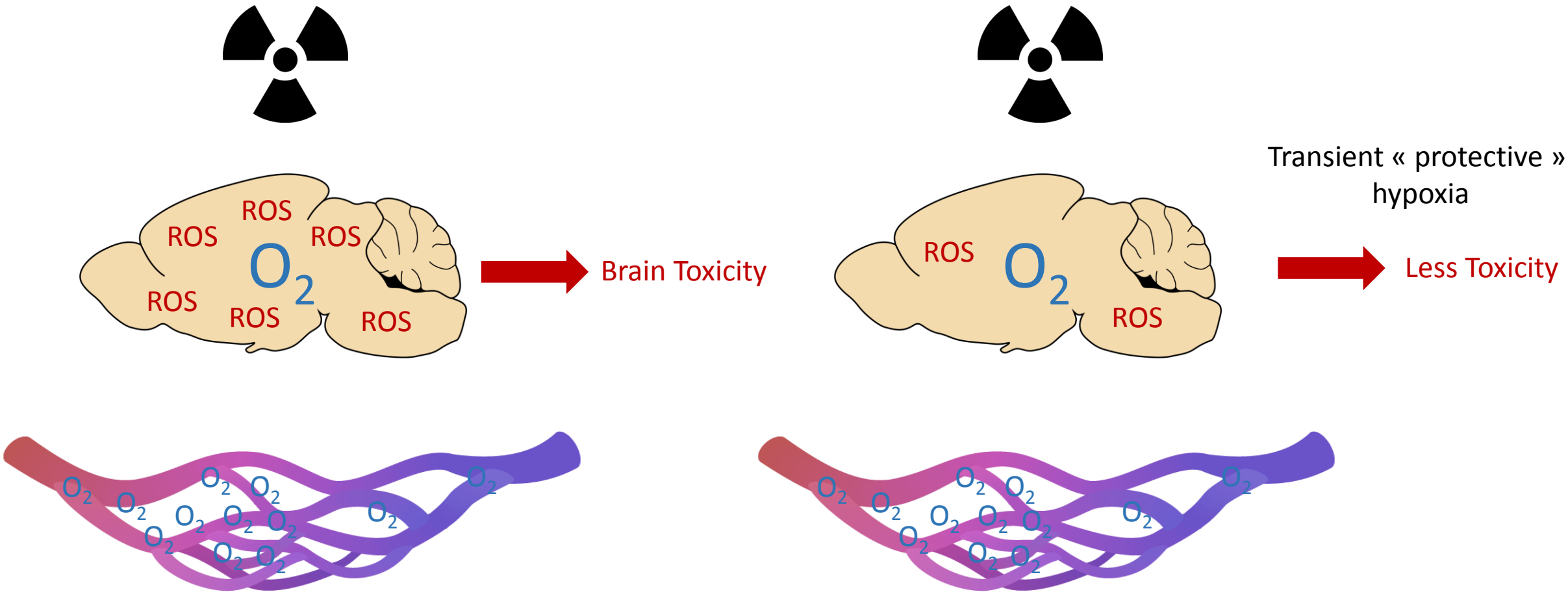


→ Antioxydant partially reverses the CONV effect
→ No effect of antioxydant on the FLASH-RT (still less armful)

Toxicity is not mediated by ROS production with FLASH-RT

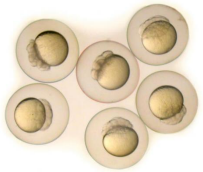
Montay-Gruel et al (in revision)

HYP: FLASH-RT induces a transient radiation-induced hypoxia that protects only the normoxic tissues

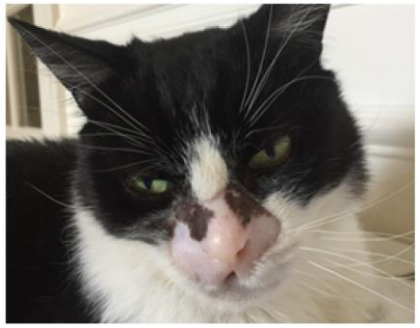


Montay-Gruel et al (in revision)

And then ?



Fish eggs
Few toxicity
Montay-Gruel et al. Sub (2)



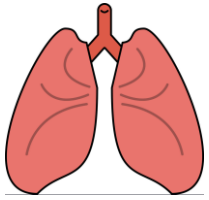
VET CLINICAL TRIAL
Cat patients with SCC
Few toxicity
Treats the tumor
Vozenin et al. 2018

MECANISMES BIOLOGIQUES

Mouse Brain
Few toxicity
Treats the tumor
Montay-Gruel et al. 2017
Montay-Gruel et al. Sub (1)
Montay-Gruel et al. Sub (2)

Keep investigating the mechanisms in translational research

Mini pipg
Few toxicity
Vozenin et al. 2018



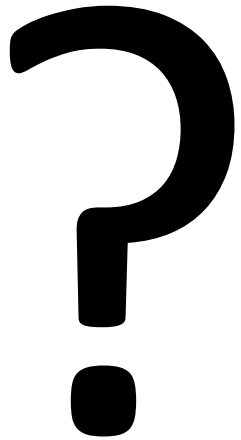
Mouse lung
Few toxicity
Treats the tumor
Favaudon et al. 2014

Clinical translation

- As soon as 2018
- 2020 for IORT

Induce less normal tissue toxicities
Increase the curative doses
Be more efficient to cure the tumors
Treat quickly
Increase the patient's QOL

How to extend the application of FLASH-RT in the clinical practice?



Dosimetry is a key stone !

Development of a monitor chamber
Mandatory for a clinical application

Real-time monitoring system of FLASH irradiation accelerators:

pilot, check and verify delivered doses.

FTI program in coll. with PMB-Alcen and Aix-Marseilles University

Courtesy of M.C. Vozenin

Which equipment?

Intra-Operative Radiation Therapy

Better in-depth access

Benefit from a rapid treatment

Under development

THERIC
ALCEN

CHUV

Courtesy of M.C. Vozenin

What are the devices able to operate at Ultra-high dose rate?

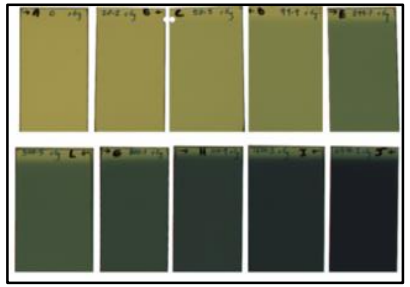
	Dose rate	Volume	Use
FLASH dedicated devices:			
Kinetron- Curie 4.4 MeV	0.1 to 300 Gy/s	10X10 cm	Pre-clinical studies Clinical studies for superficial tumors
Oriatron-CHUV 5.5 MeV	Instantaneous up to 10e7Gy/s (dose rate within pulse) Mean dose rate 0.1 to 1000 Gy/s	10X10 cm	Pre-clinical studies Clinical studies for superficial tumors
Modified linac-Stanford 20 MeV	0.1 to 250 Gy/s	10X10 cm	Pre-clinical studies
Modified linac-Lund 20 MeV	0.1 to 250 Gy/s	10X10 cm	Preclinical Studies
Proton-Therapy Centers with PBS	Instantaneous >200 Gy/s Mean dose rate 2-4 Gy/min	Few mm 20X20 cm	N.A. Used in clinical practice
Synchrotron light ESRF Brookhaven national Lab Australian synchroton	Instantaneous up to 18 000 Gy/s (dose rate within slice) Mean dose rate 40 Gy/s	mm 10X10 cm	Pre-clinical studies Clinical trial Via a technology called Microbeam/MRT
VHEE facilities 250 MeV	1 Gy delivered in 10e15 s	mm	In development

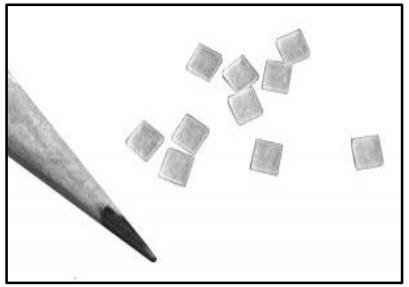
Courtesy of M.C. Vozenin

What is the strategy currently developed in collaboration with CLEAR

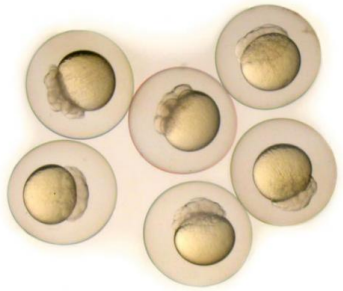
→ Use passive physical dosimeters to record the dose

- → Gafchromic films
- → TLDs
- → Alanine pellets





→ Use fish eggs as biological dosimeters



→ Answer the question:

Is CLEAR VHEE (> 200Mev) technology suitable to trigger a FLASH effect?

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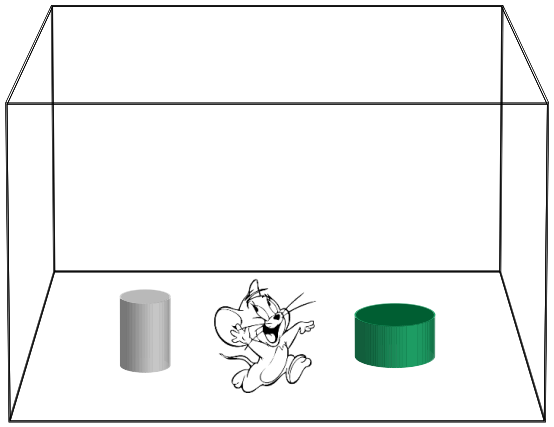
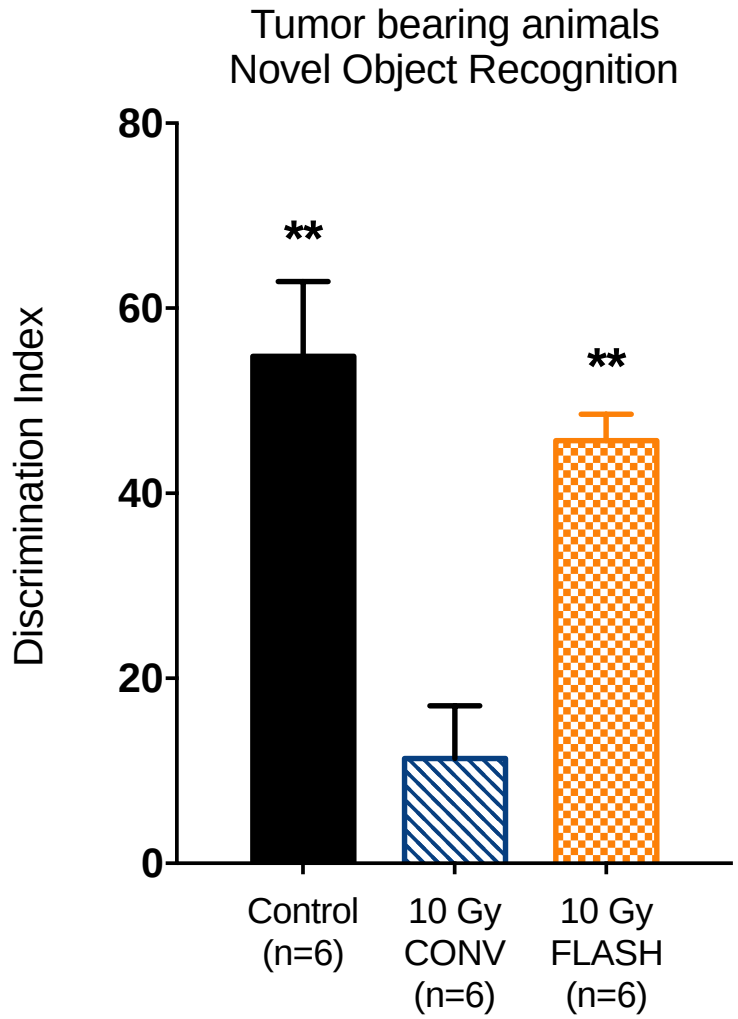
Do irradiated mice develop cognitive alterations ?



Montay-Gruel et al (in revision)

No toxic effect
of FLASH-RT
on the memory

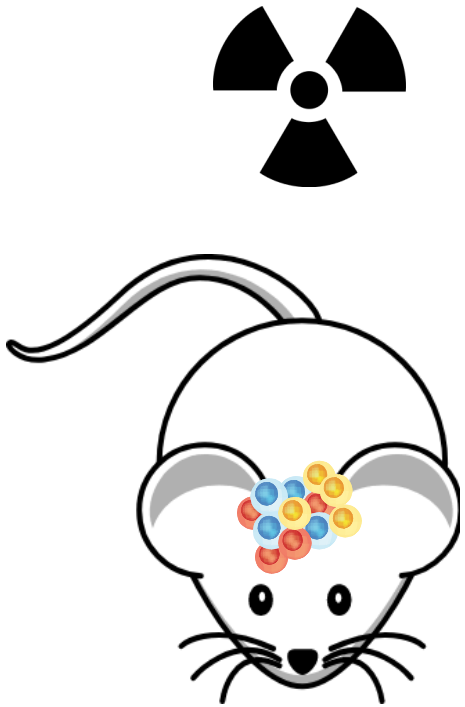
Time spent on the **unknown** ubject
Time spent on the **familiar** object
=
Memory evaluation parameter
Discrimination index



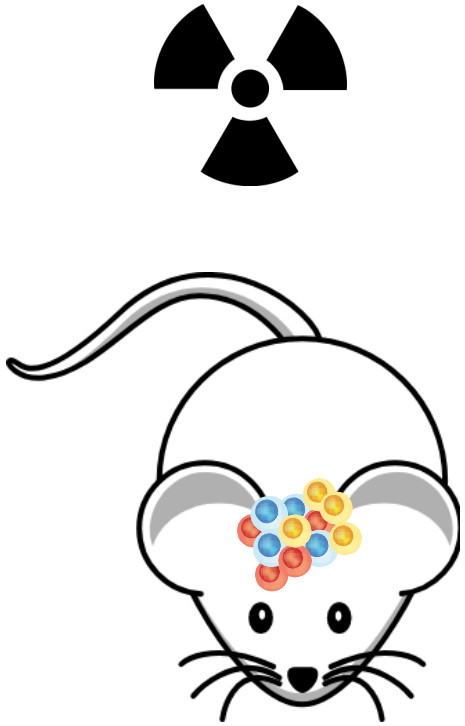
BUT: Why is FLASH-RT efficient to treat tumors ?

Because most of them are hypoxic *per se*

CONV



FLASH



SAME EFFECT
ON THE TUMORS

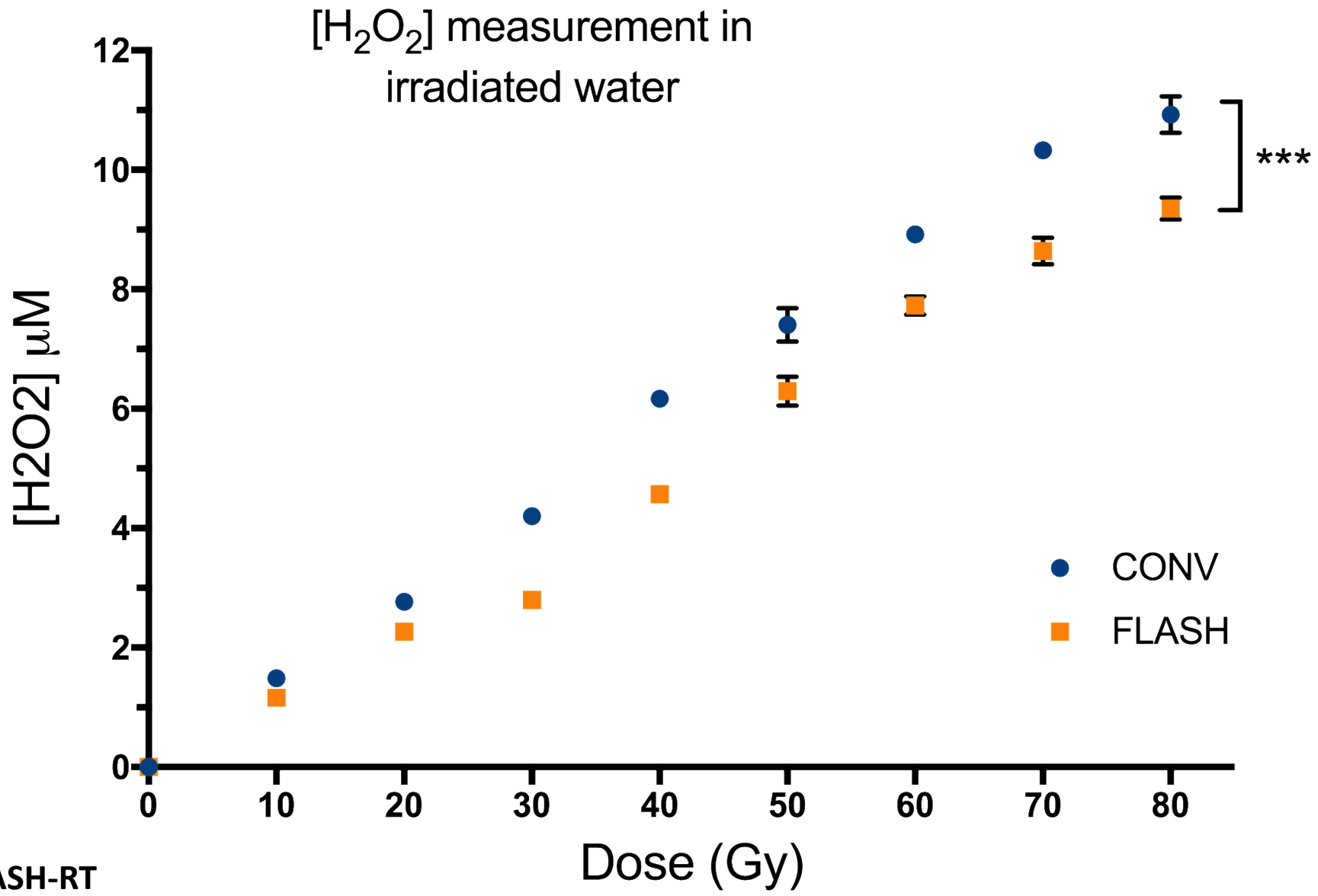
Direct effects +++ = TUMOR CONTROL
Few ROS production because of hypoxia

Same dose = Same direct effects
Few ROS production because of hypoxia and oxygen depletion

Production of ROS by water-radiolysis with FLASH-RT

4% O_2 water

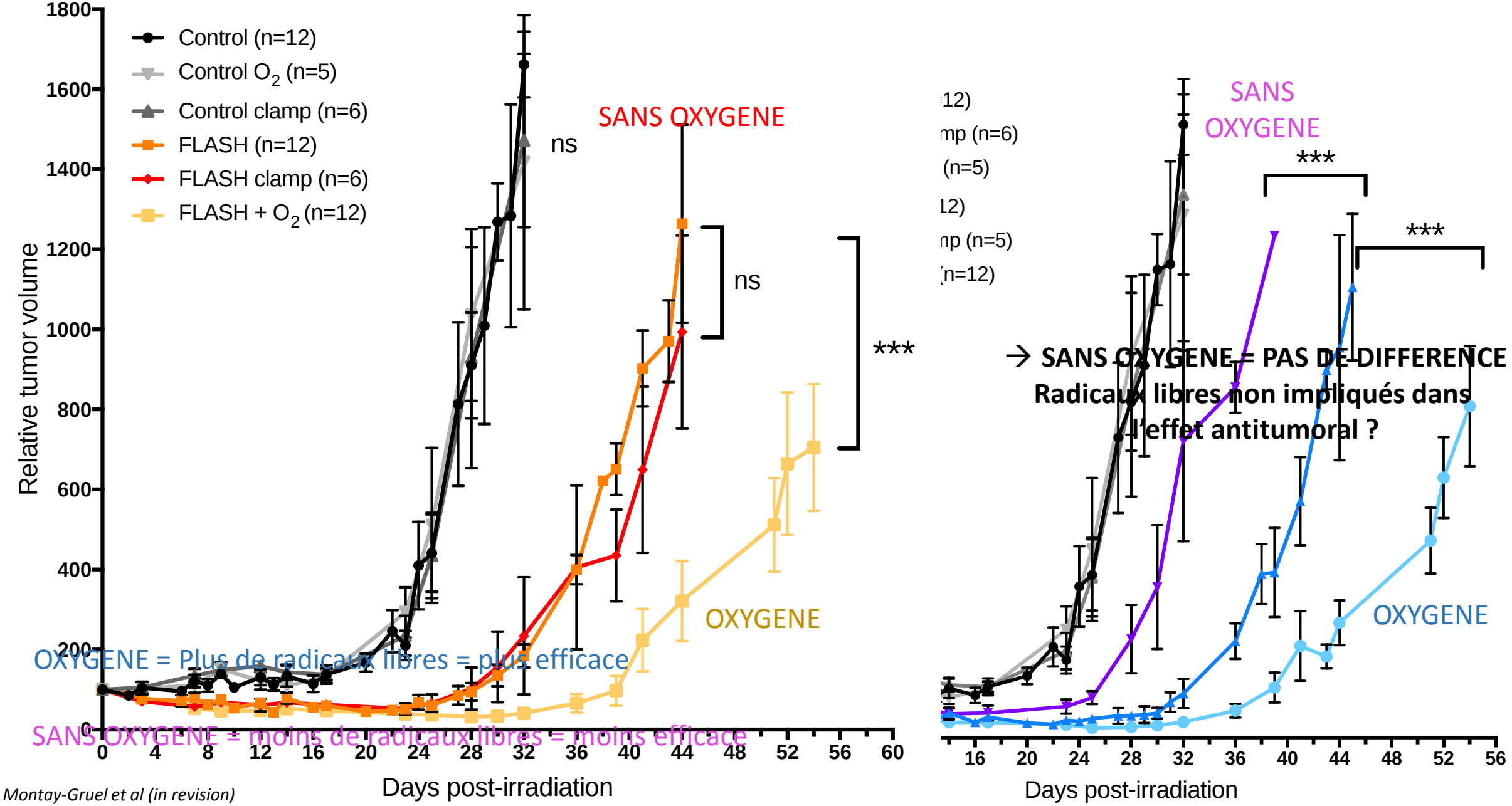
Water radiolysis
→ Non-biological model



→ Less production of H_2O_2 with FLASH-RT

Montay-Gruel et al (in revision)

Faire varier la quantité d'oxygène = faire varier la production de radicaux libres



Montay-Gruel et al (in revision)