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Normal tissue and tumor response to FLASH-RT
Biological mechanisms

Disclosures

Collaborative Research project with PSI-Varian (CH)
Advisory Board IBA
Research project ROCHE pharma

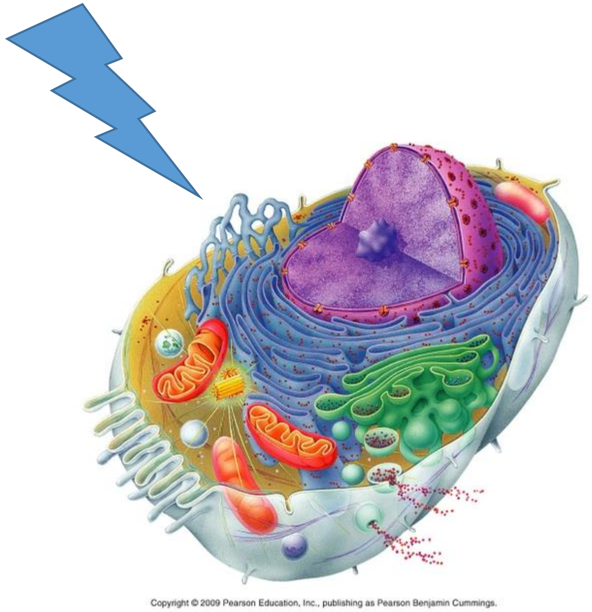
Learning objectives

- **Become familiar with the research strategies and the preclinical models**
- **Compare tumor response to CONV and FLASH-RT**
- **Identify the clinically relevant issues Identify the relevant biological mechanisms**
- **Identify the needs and limitations**

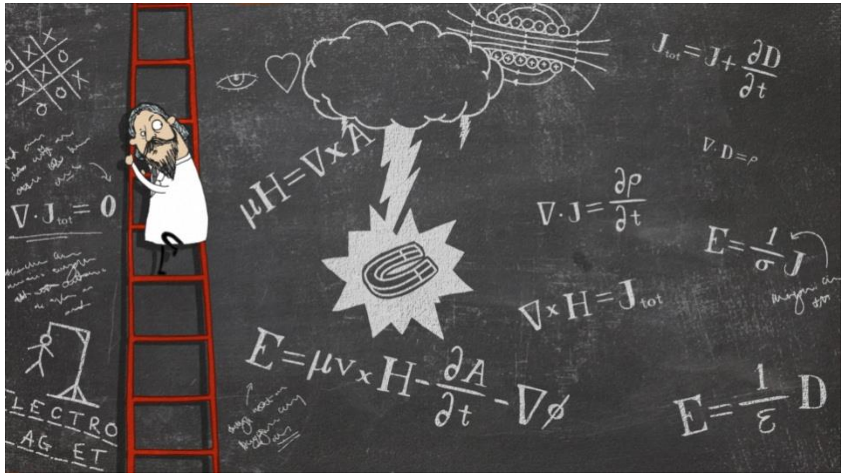
Enhancing the therapeutic ratio: a balance between tumour control and toxicity

What are the tools to improve the therapeutic ratio

Biology

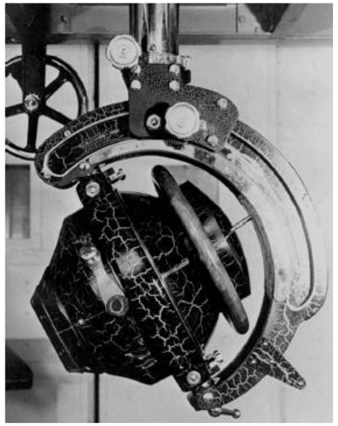


Technology

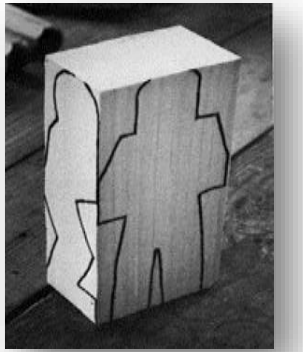


Fractionation and Enhanced precision

1930-1970

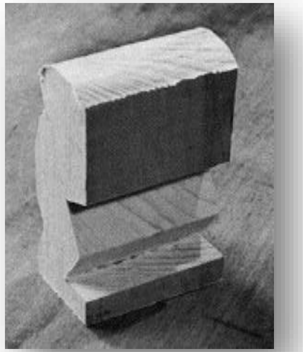


Target volume



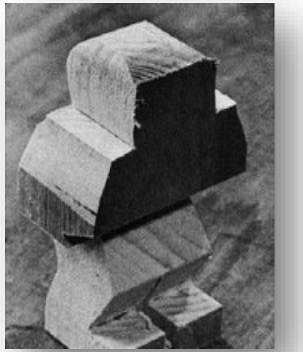
1970-1990

2D planning



1990-2000

3D Conformal



2016

Stereo-RT

High Precision

FLASH radiotherapy

Irradiation at ultra high dose rate

Very fast delivery of the dose

Shift from minute of exposure to milli- and even micro-second

eRT6 Oriatron PBM/Alcen
Electron beam, 5.5 MeV energy
Pulsed beam

THE FLASH EFFECT is a biological effect

Normal tissue sparing

FLASH-RT does not induce Normal tissue toxicity When CONV-RT does

Electron
Chabi et al. **IJROBP**2020
Montay-Gruel et al. **Rad Res**, 2020
Allen et al. **Rad Res**, 2020
Alaghban et al. **Cancers**, 2020
Bourhis J et al. **Radiother Oncol.** 2019.
Jorge PG et al. **Radiother Oncol.** 2019 Oct.
Montay-Gruel P et al. **Proc Natl Acad Sci U S A**. 2019.
Vozenin et al. **Clin Can Res**, 2019.
Montay-Gruel P et al. **Radiother&Oncol.**, 2017.
Jaccard M et al. **Med Phys**, 2018.
Favaudon V et al. **Sci Transl Med**. 2014.

X-ray-synchrotron
Montay-Gruel P et al. **Radiother Oncol.** 2018.

Electron
Ruan et al, **IJROBP**, 2021
Beyreuther et al., **Radiother Oncol**, 2021
Levy et al, **Sc Rep**, 2020
Soto et al. **Rad Res**, 2020.
Fouillade C et al. **CCR,** 2019.
Simmons et al. **Radiother Oncol.** 2019.
Loo B et al. **IJROBP**, 2017, abst.
Hendry et al. **Rad Res**, 1982.

Proton
Kim et al, **Cancers,** 2021 (BI)
Evans et al**, IJPT,** 2021
Cunningham et al., **Cancers**, 2021 (PBS)
Zhang et al. **Rad Res,** 2020.
Diffenderfer et al. **IJROBP**, 2020.
Girdhani et al. **Can Res**, 2019, abst.

And FLASH-RT is equally able to eradicate tumors compared to CONV-RT

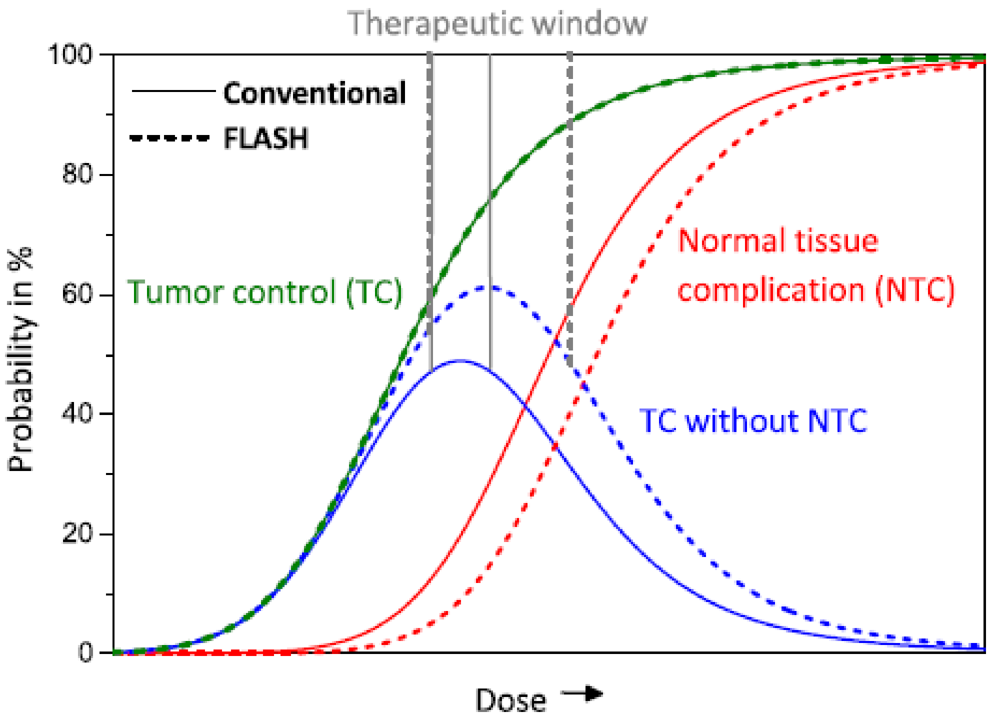
X -ray synchrotron
Smyth et al. **Sci Rep**, 2018.
Proton
Beyreuther et al. **Radiother Oncol.** 2019.
Electron
Venkatesulu at al. **Sc Rep**, 2019.

Electron
Chabi et al. **IJROBP**, 2020.
Montay-Gruel P et al. **CCR**, 2020.
Bourhis J et al. **Radiother Oncol.** 2019.
Jorge PG et al. **Radiother Oncol.** 2019.
Favaudon V et al. **Sci Transl Med**. 2014.

Electron
Kim et al. **IJROBP**, 2020
Levy et al, **Sc Rep,** 2020

Proton
Kim et al, **Cancers,** 2021 (BI)
Velalopoulou et al**, Can Res, 2021**
Cunningham et al., **Cancers, 2021**
Diffenderfer et al. **IJROBP**, 2020.
Girdhani et al. **Can Res**, 2019, abst.

FLASH-RT enhances the therapeutic window

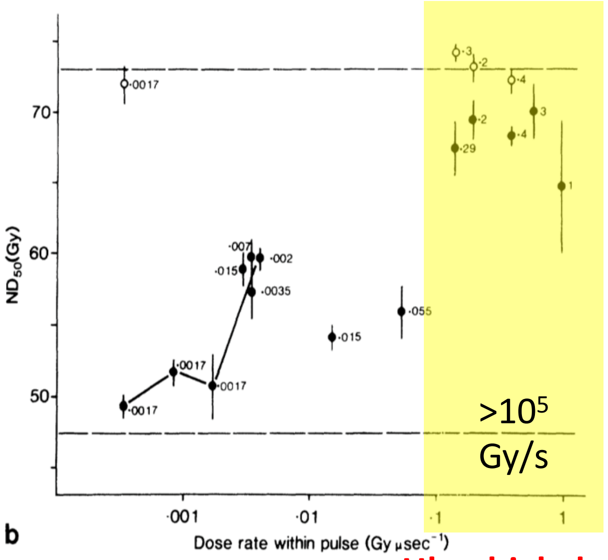


Physica Medica 80 (2020) 134–150
Contents lists available at ScienceDirect
Physica Medica
journal homepage: www.elsevier.com/locate/ejmp
Original paper

The European Joint Research Project UHDpulse – Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates

Andreas Schüller[a,*], Sophie Heinrich[b], Charles Fouillade[b], Anna Subiel[c], Ludovic De Marzi[b,d], Francesco Romano[e,c], Peter Peier[f], Maria Trachsel[f], Celeste Fleta[g], Rafael Kranzer[h,i], Marco Caresana[j], Samuel Salvador[k], Simon Busold[l], Andreas Schönfeld[m], Malcolm McEwen[n], Faustino Gomez[o], Jaroslav Solc[p], Claude Bailat[q], Vladimir Linhart[r], Jan Jakubek[r], Jörg Pawelke[s,t], Marco Borghesi[u], Ralf-Peter Kapsch[a], Adrian Knyziak[v], Alberto Boso[c], Veronika Olsovcova[w], Christian Kottler[f], Daniela Poppinga[h], Iva Ambrozova[x], Claus-Stefan Schmitzer[y], Severine Rossomme[z], Marie-Catherine Vozenin[q]

Explored 40 years ago… it was abandonned
Why?



Ultra high dose-rate per pulse

Hendry et al. 1982

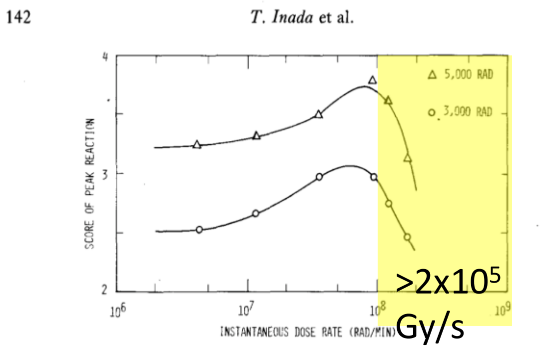


Figure 2. Peak skin reactions observed in various sets of average and instantaneous dose rates.

Inada et al. 1980

Ultra high instantaneous dose-rate

1970

1980

2007/2008

2019

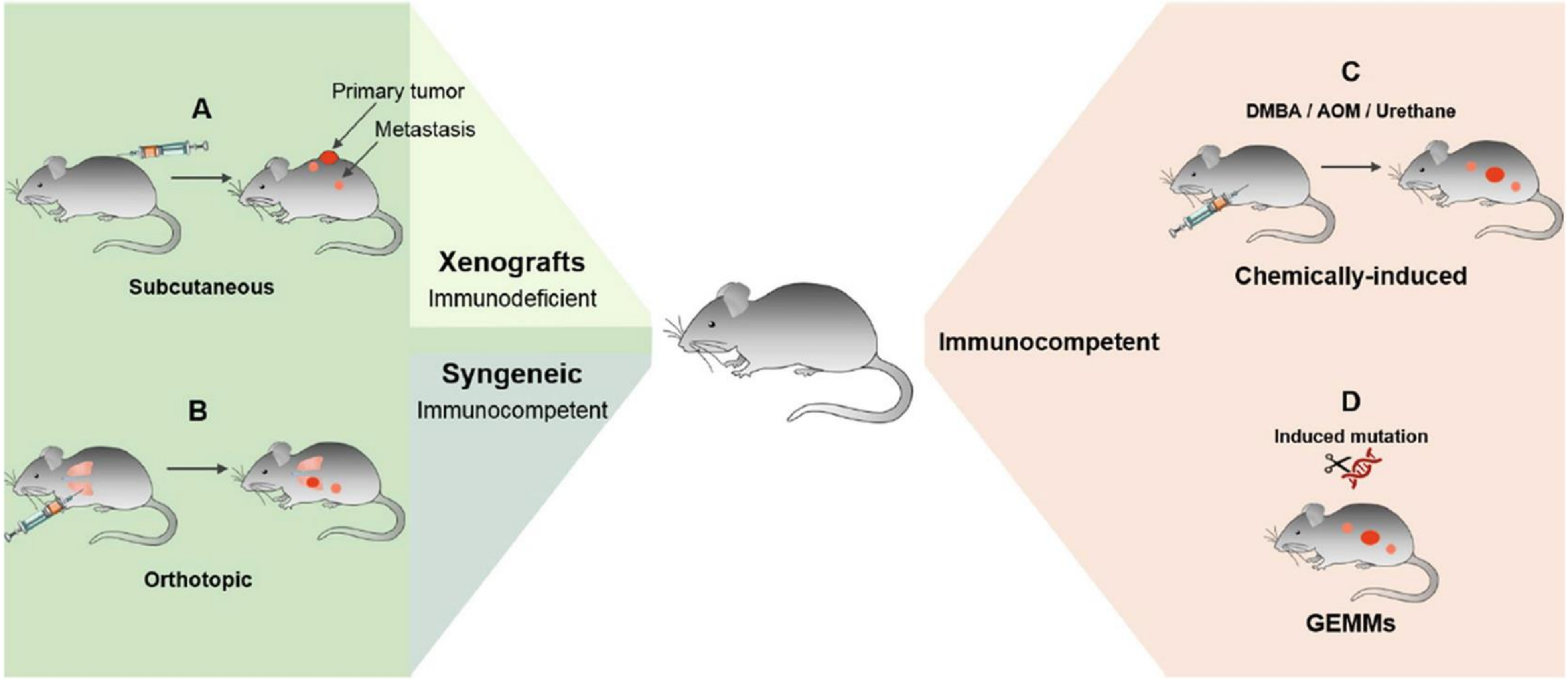
Field S, Bewley D. Effects of dose-rate on the radiation response of rat skin. *International Journal of Radiation Biology and Related Studies in Physics, Chemistry and Medicine.* 1974;26(3):259-267.

Inada T, Nishio H, Amino S, Abe K, Saito K. High dose-rate dependence of early skin reaction in mouse. *International Journal of Radiation Biology and Related Studies in Physics, Chemistry and Medicine.* 1980;38(2):139-145.

Hendry JH, Moore JV, Hodgson BW, Keene JP. The constant low oxygen concentration in all the target cells for mouse tail radionecrosis [published online ahead of print 1982/10/01]. *Radiat Res.* 1982;92(1):172-181.

Favaudon V, Caplier L, Monceau V, et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. *Science translational medicine*. 2014;6(245):245ra293-245ra293.

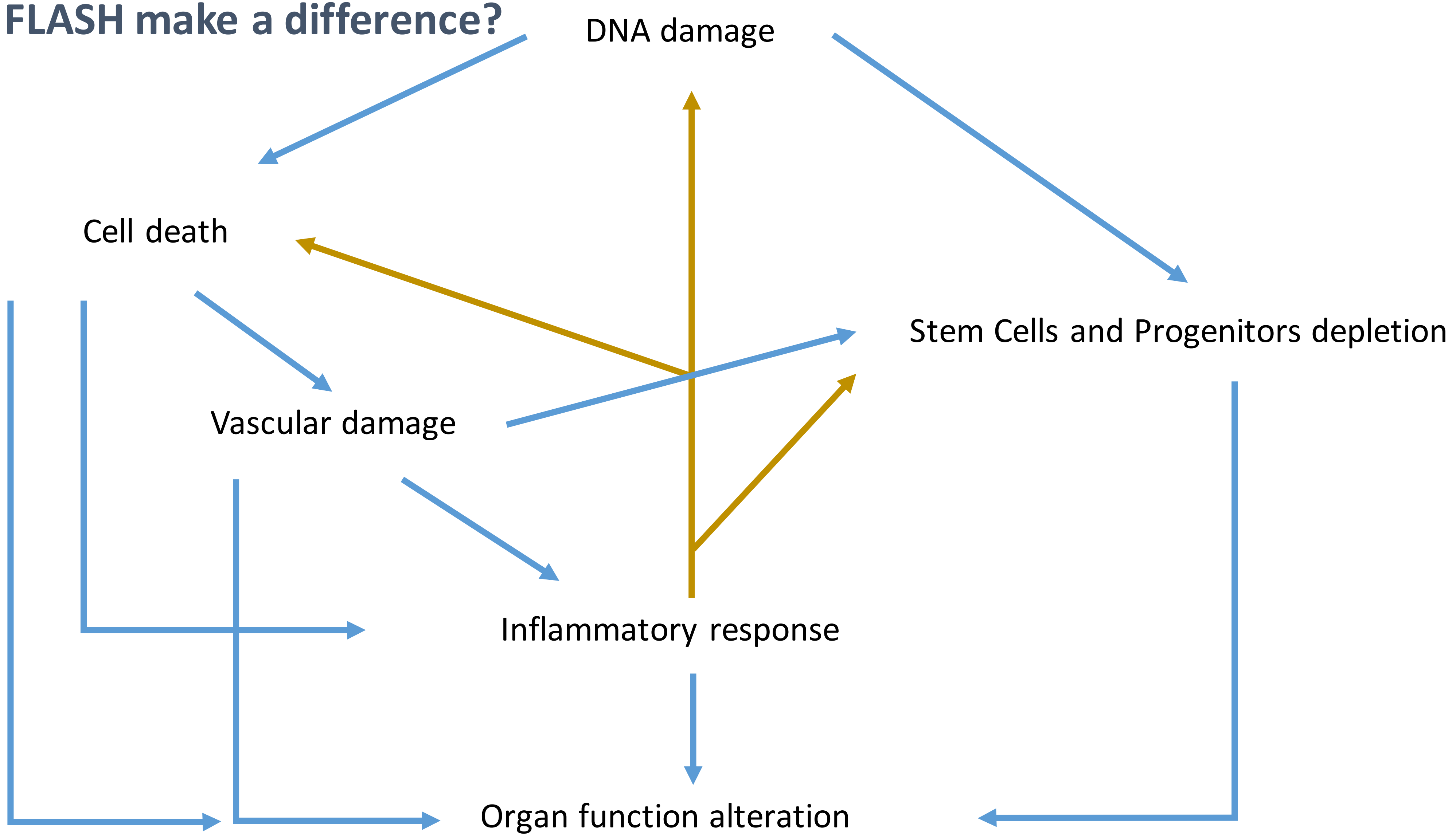
Tumor and Normal tissue response should be investigated in parallel
and
in vivo models should be used



Normal tissue response

Normal tissue toxicity cascade?

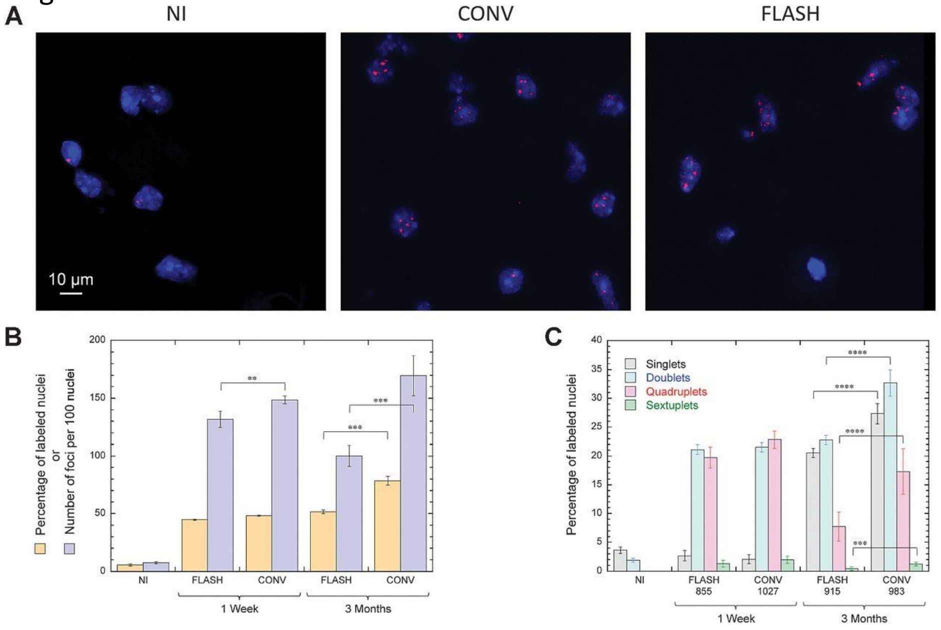
Where does FLASH make a difference?

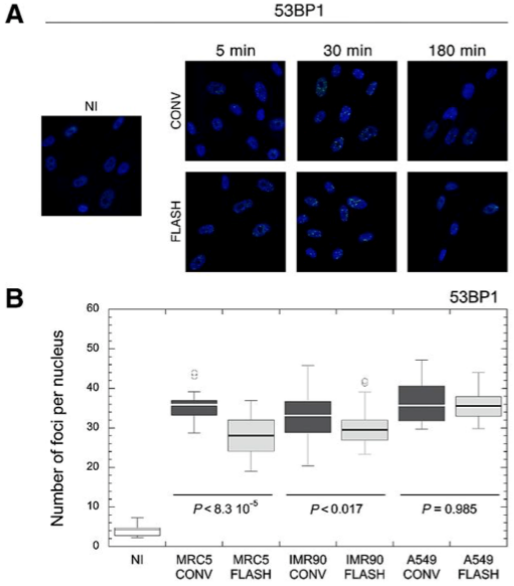


Pierre Montay-Gruel, PhD

Differential DNA damage *in vivo*

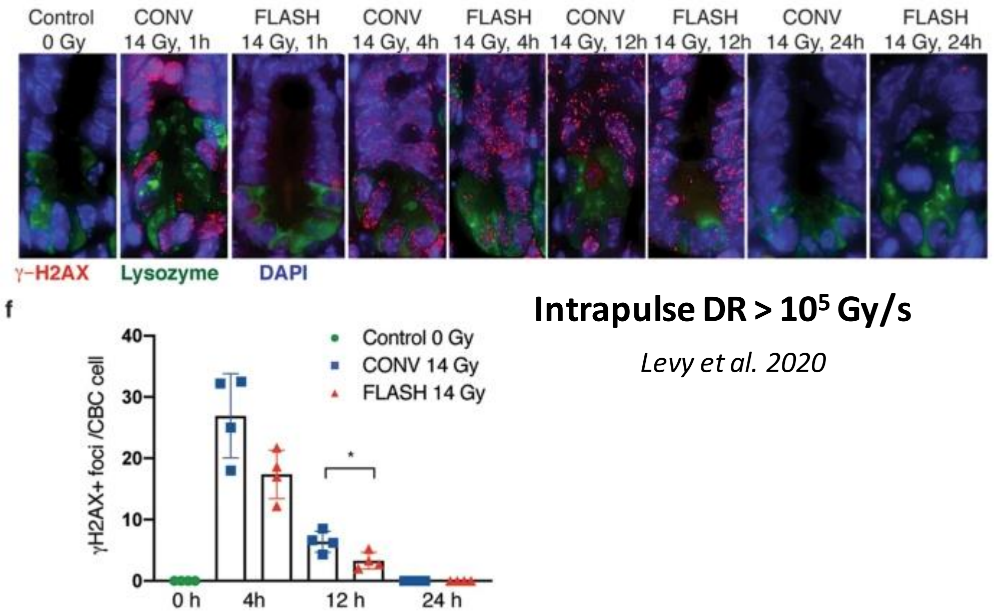
gH2AX





Intrapulse DR > 10^6 Gy/s

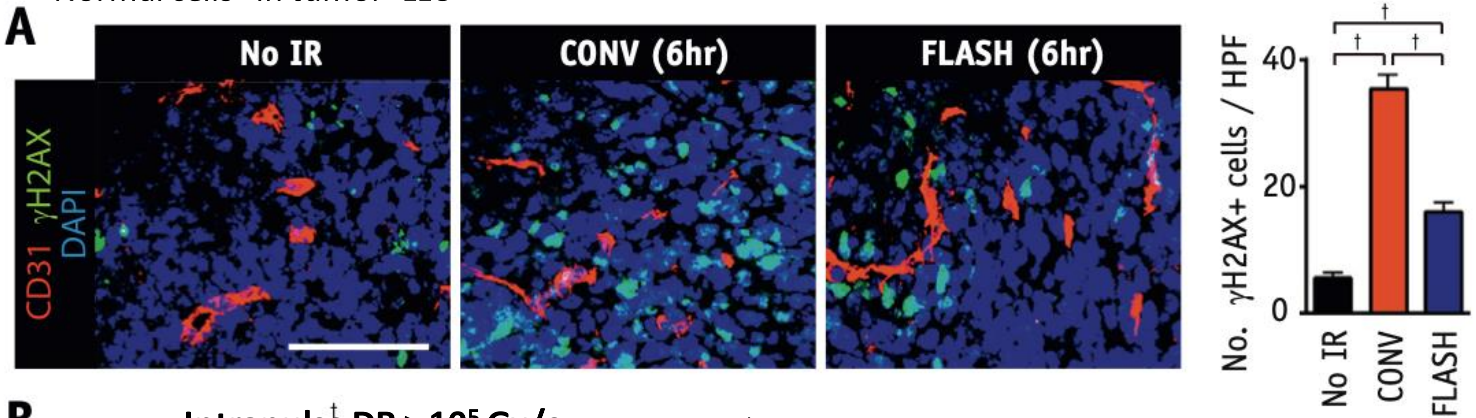
Fouillade et al. 2020



Intrapulse DR > 10^5 Gy/s

Levy et al. 2020

"Normal cells" in tumor- LLC

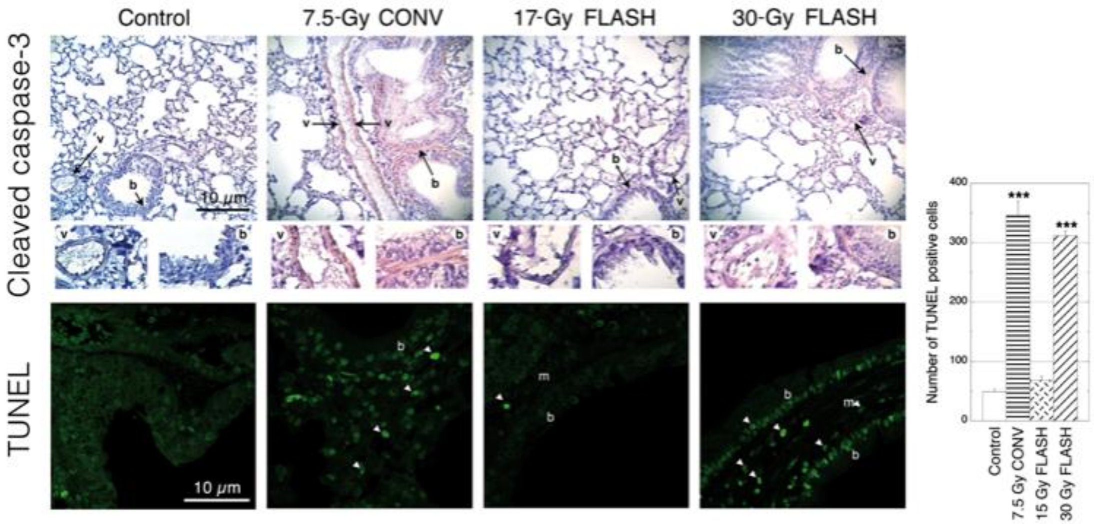


Intrapulse DR > 10^5 Gy/s

Kim et al. 2020

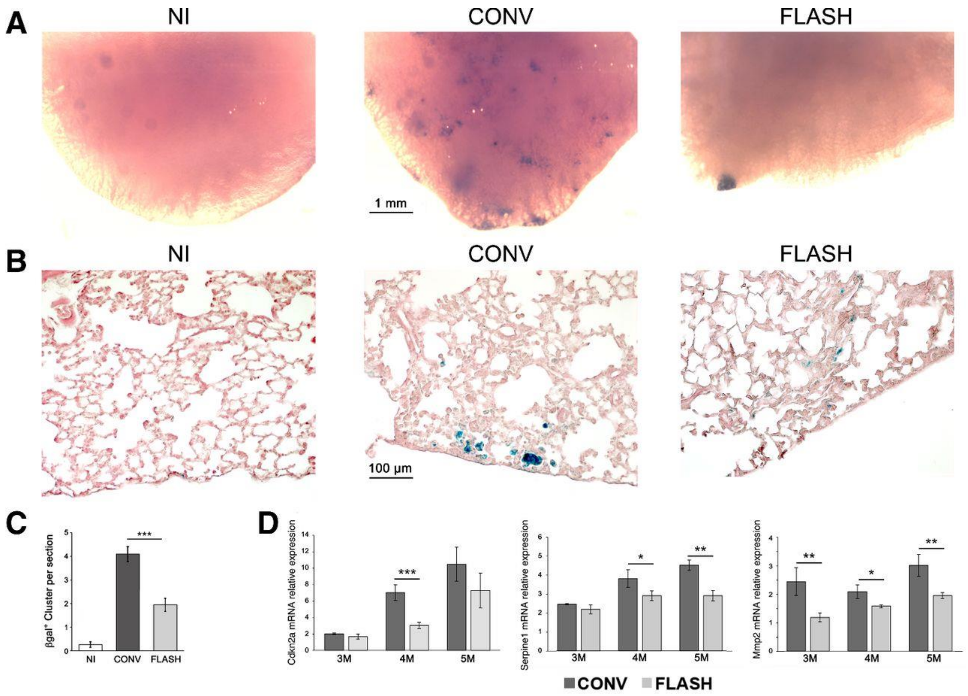
Differential cell death *in vivo*

Apoptosis

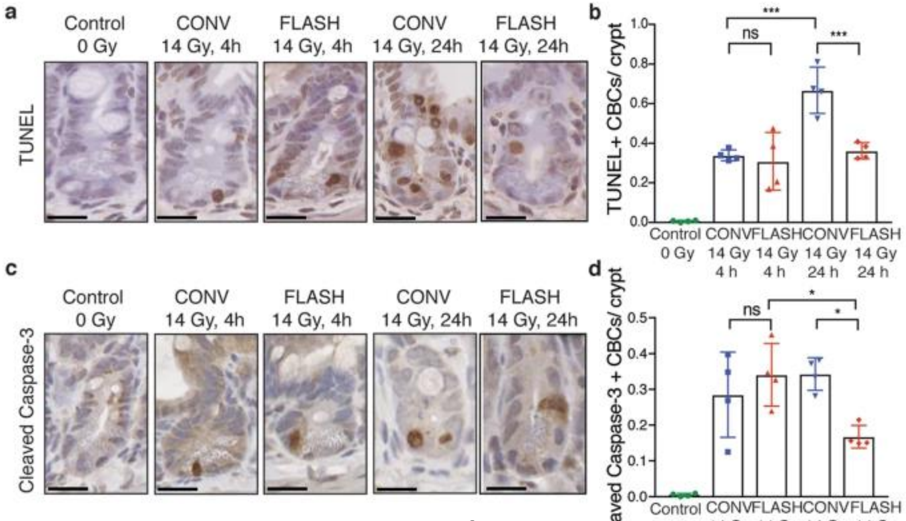


Intrapulse DR > 10^6 Gy/s *Favaudon et al. 2014*

Senescence



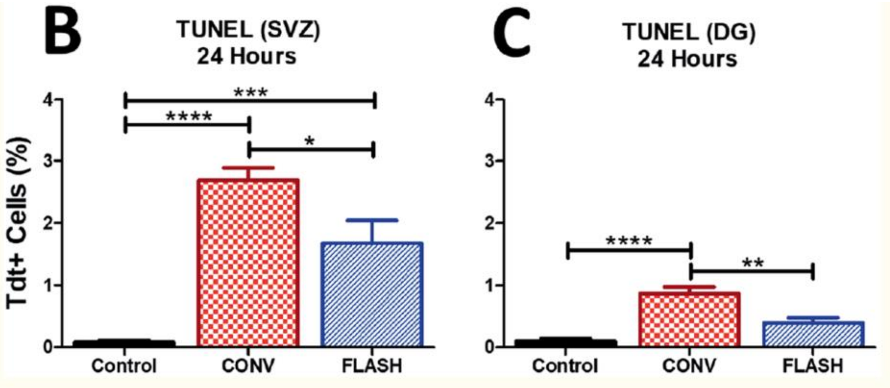
Intrapulse DR > 10^6 Gy/s *Fouillade et al. 2020*



e

Intrapulse DR > 10^5 Gy/s

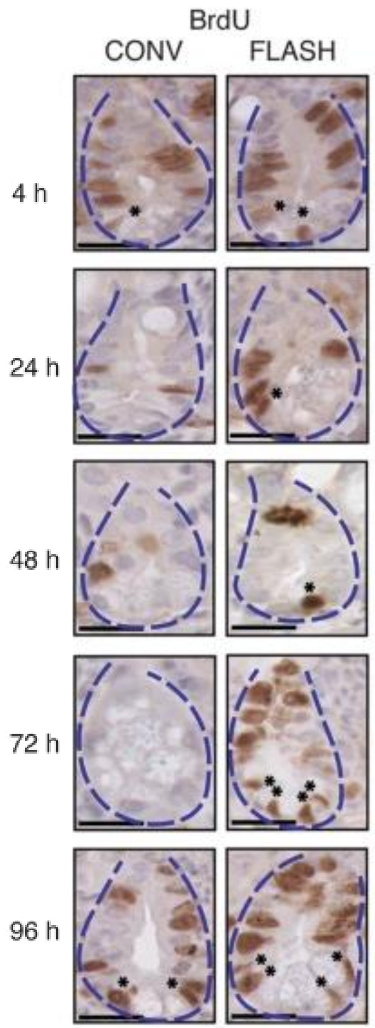
Levy et al. 2020



Intrapulse DR > 10^6 Gy/s

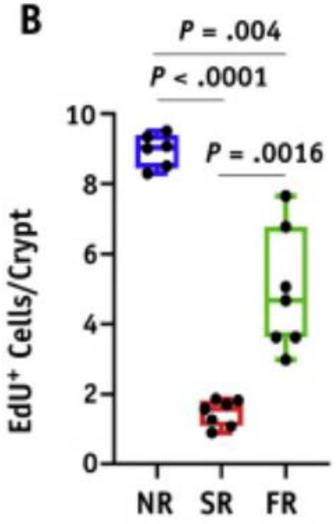
Allen et al. 2020

Differential effect on Stem cells and progenitors *in vivo*



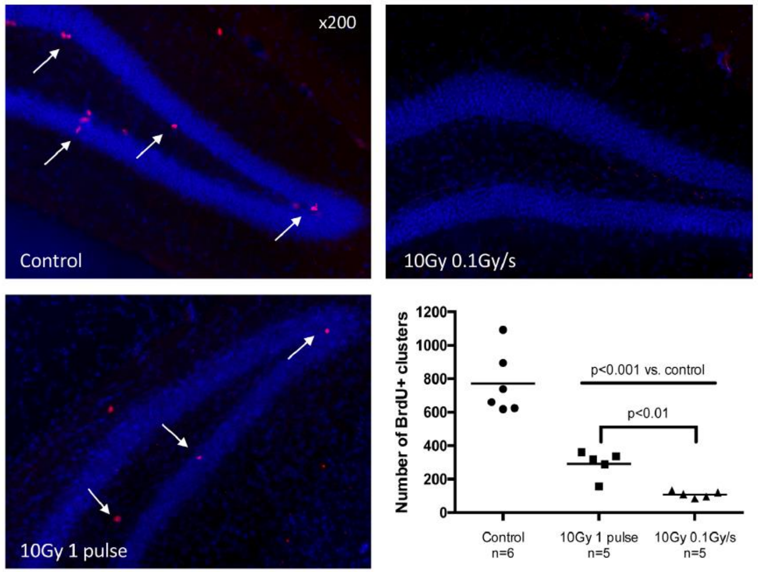
Intrapulse DR > 10^5 Gy/s

Levy et al. 2017

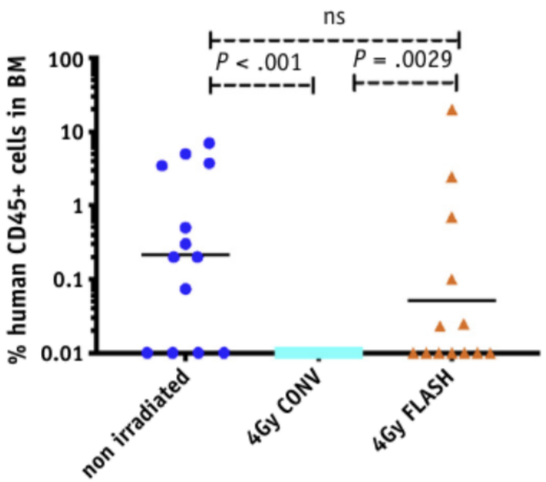


80 Gy/s

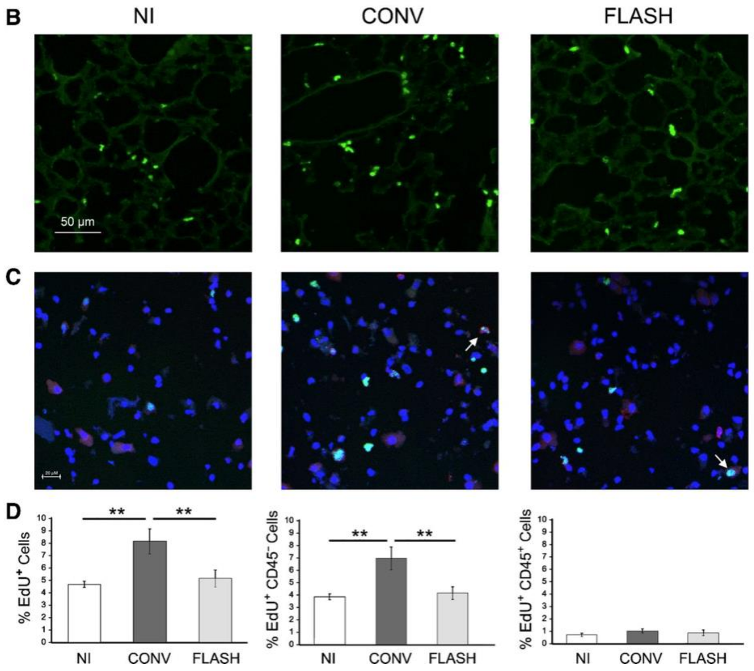
Diffenderfer et al. 2020



Intrapulse DR > 10^6 Gy/s *Montay-Gruel et al. 2017*

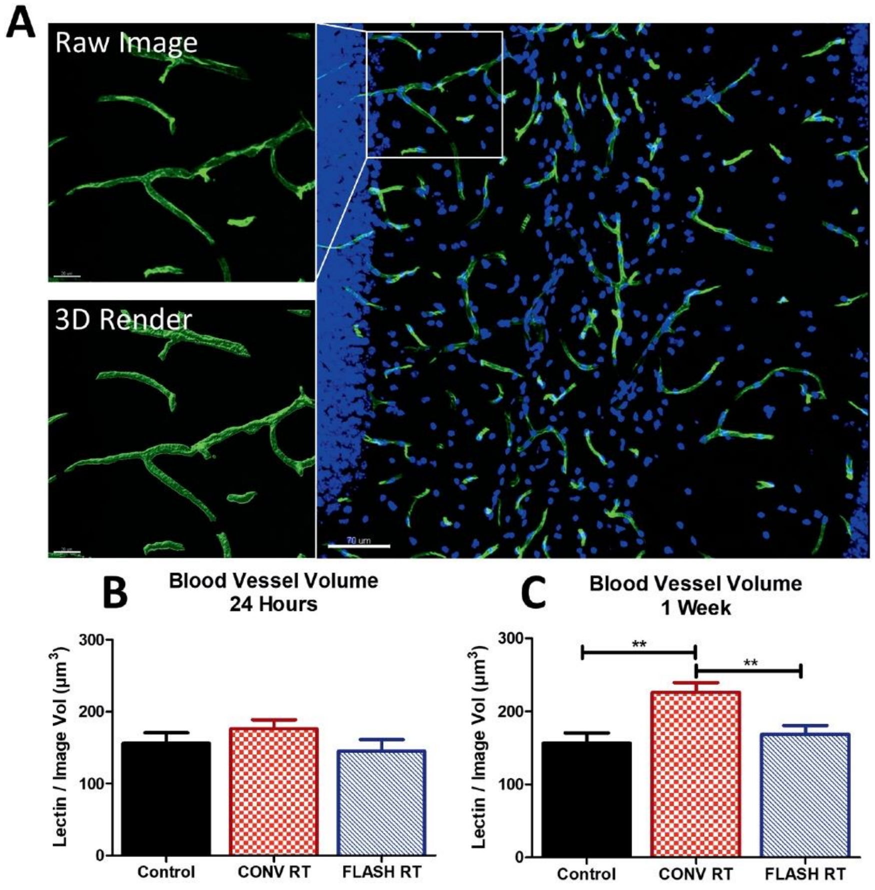


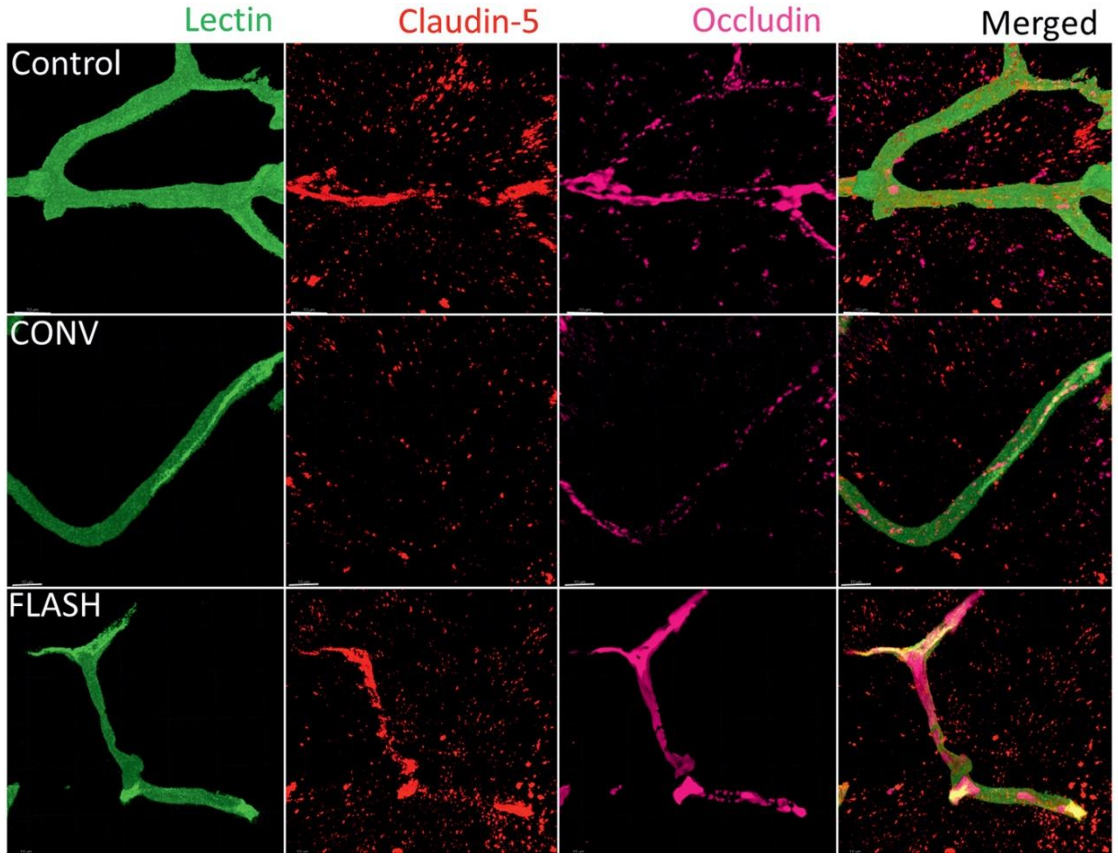
Intrapulse DR > 10^5 Gy/s *Chabi et al. 2020*



Intrapulse DR > 10^6 Gy/s *Fouillade et al. 2020*

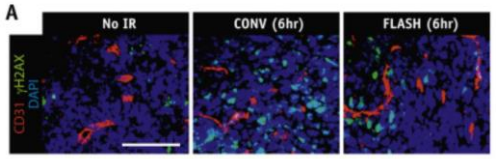
Differential effect on the vascular system





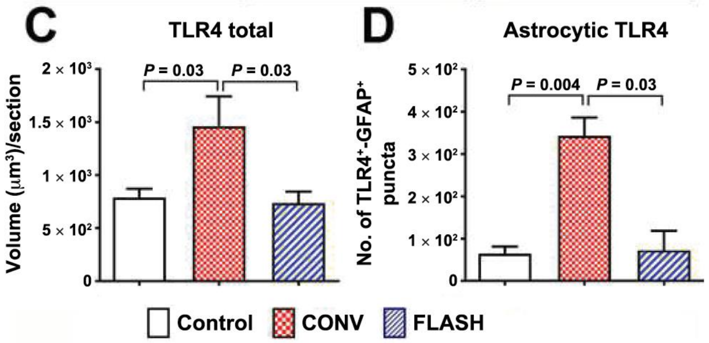
Intrapulse DR > 10^6 Gy/s

Allen et al. 2020



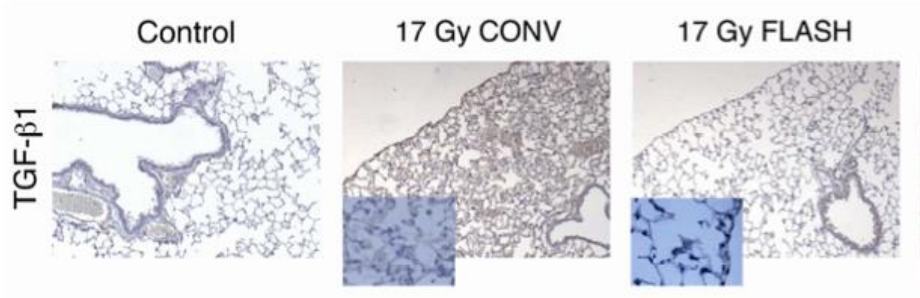
+ work on the **<u>tumor</u>** vasculature, Kim et al. 2021

Differential inflammatory response



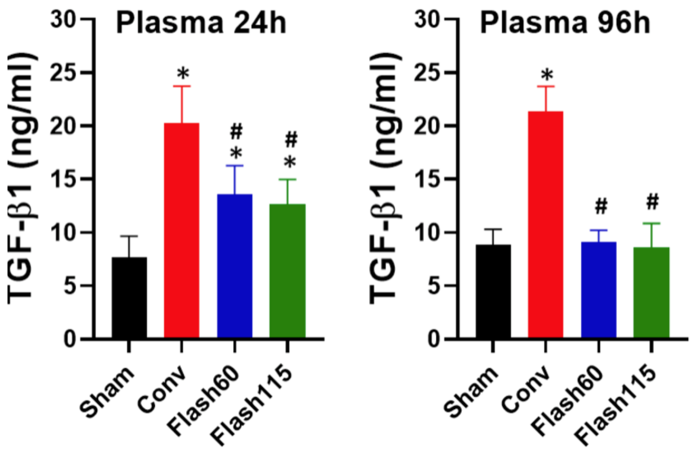
Intrapulse DR > 10^6 Gy/s

Montay-Gruel et al. 2020



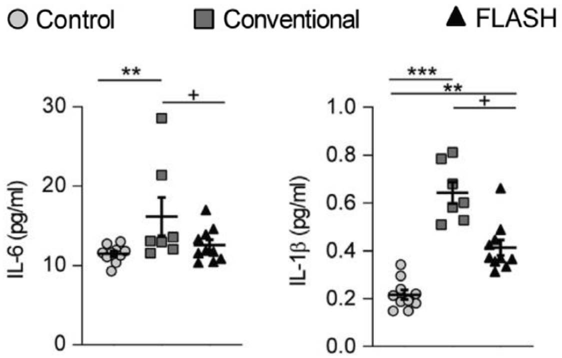
Intrapulse DR > 10^6 Gy/s

Favaudon et al. 2014



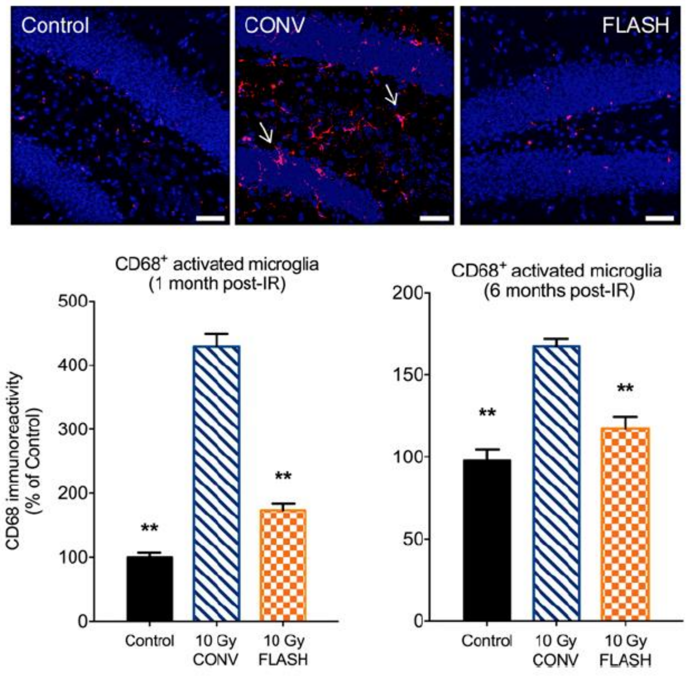
50 – 115 Gy/s

Cunningham et al. 2021



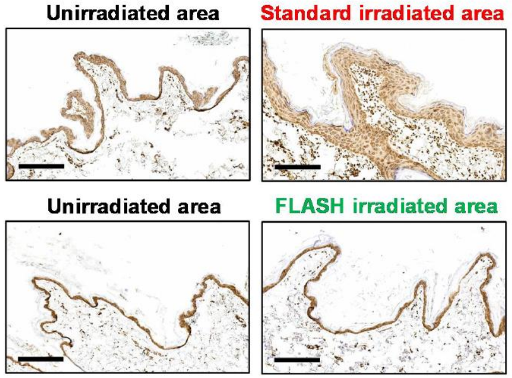
Intrapulse DR > 10^5 Gy/s

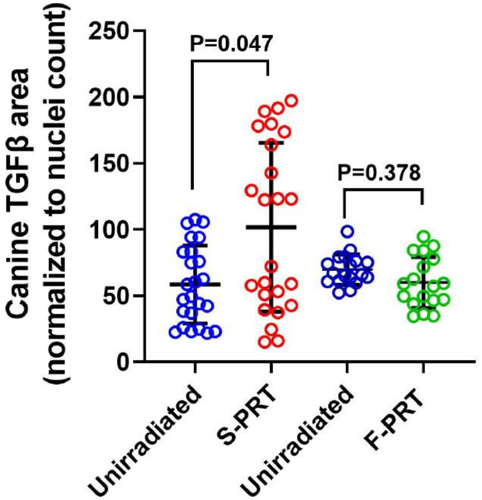
Simmons et al. 2019



Intrapulse DR > 10^6 Gy/s

Montay-Gruel et al. 2019

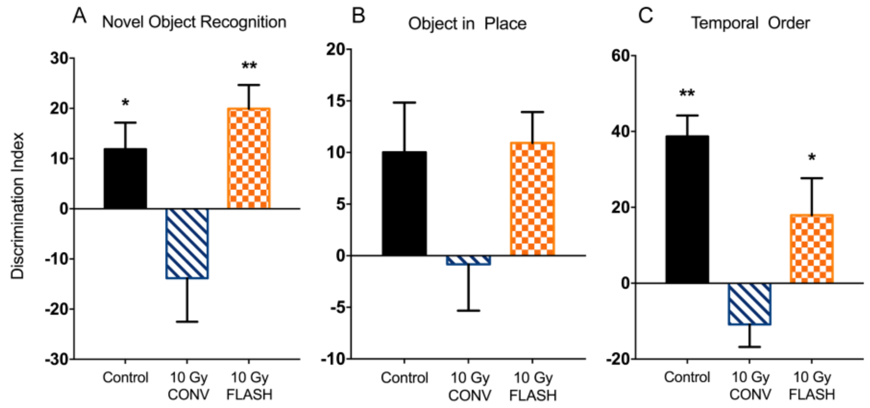




69 – 124 Gy/s

Velalopoulou et al. 2021

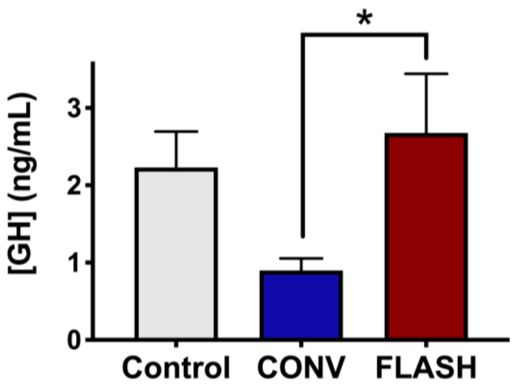
Organ outcome and function



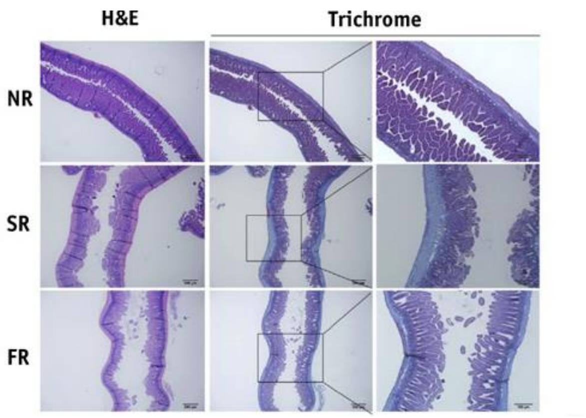
Brain function

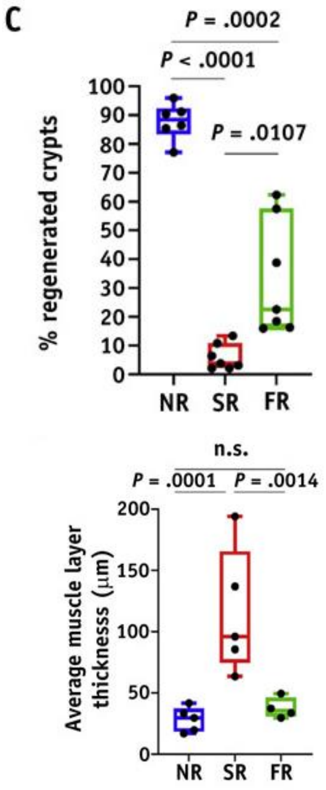
Cognition

Montay-Gruel et al. 2017
Montay-Gruel et al. 2018
Montay-Gruel et al. 2019
Simmons et al. 2019
Alaghband et al. 2020



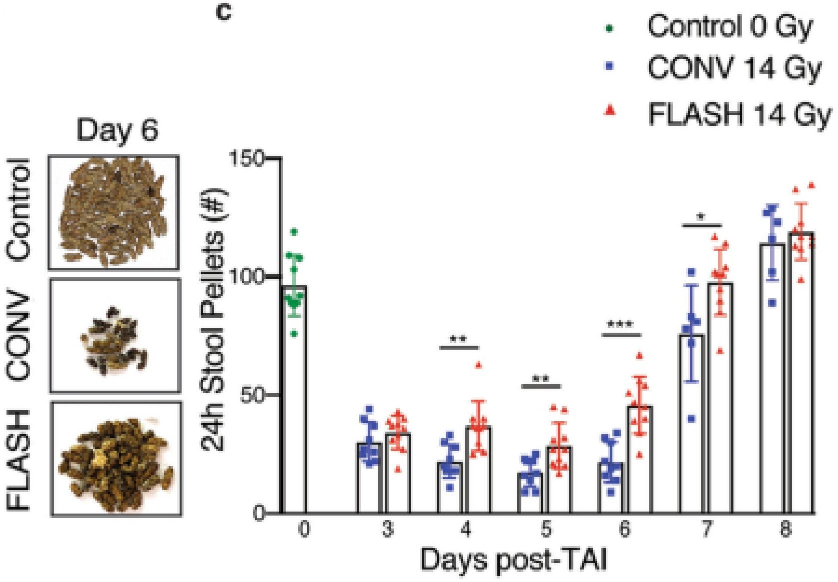
Intrapulse DR > 10^6 Gy/s *Alaghband et al. 2020*



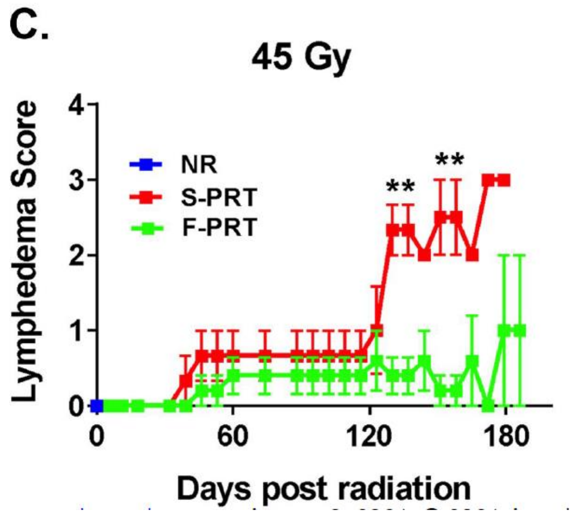


80 Gy/s

Diffenderfer et al. 2020



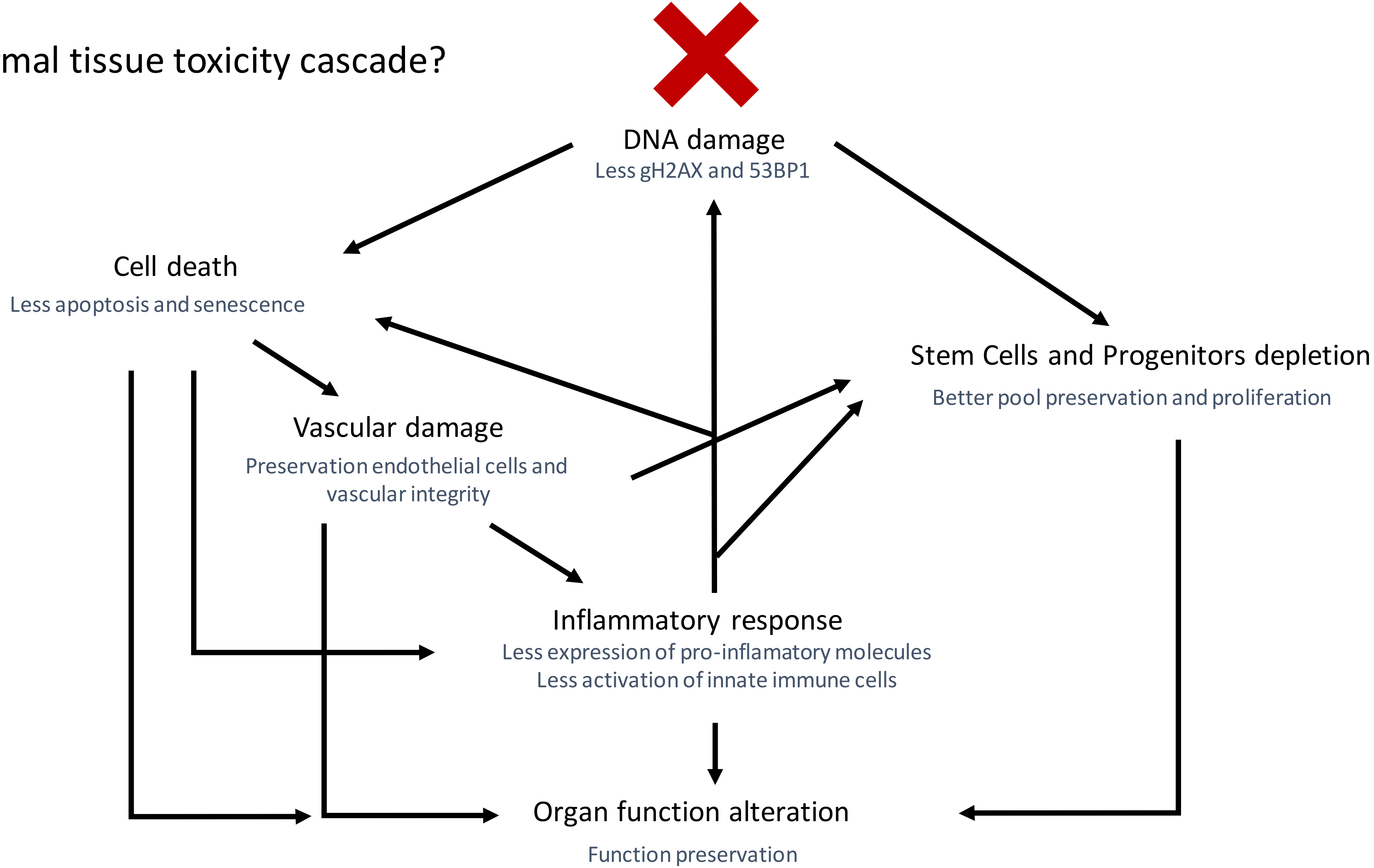
Intrapulse DR > 10^5 Gy/s *Levy et al. 2017*



69 – 124 Gy/s

Velalopoulou et al. 2021

Normal tissue toxicity cascade?



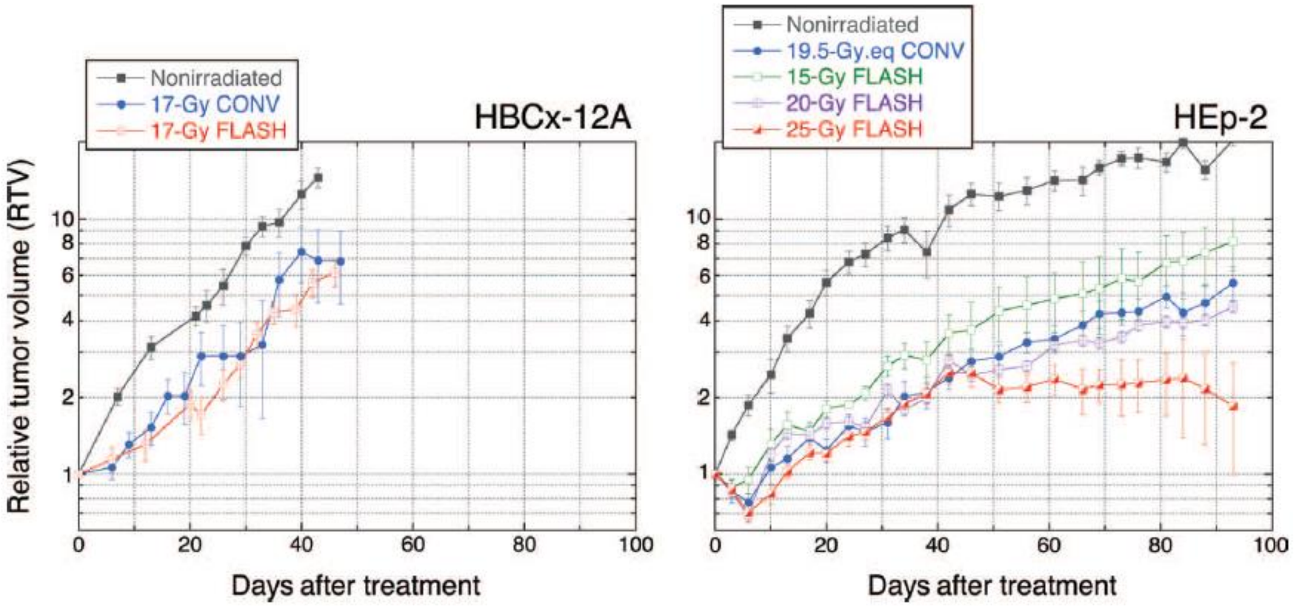
Pierre Montay-Gruel, PhD

Tumor response

With Electron beam- from simple SubQ model to orthotopic and GEMMs

SubQ breast and H&N cancer (immunocompromised mice)

60 Gy/s (2Fx HBCx and 1 Fx for HEp)



Favaudon et al, STM, 2014
In immunodeficient mice

SubQ GBM models (immunocompromised mice)

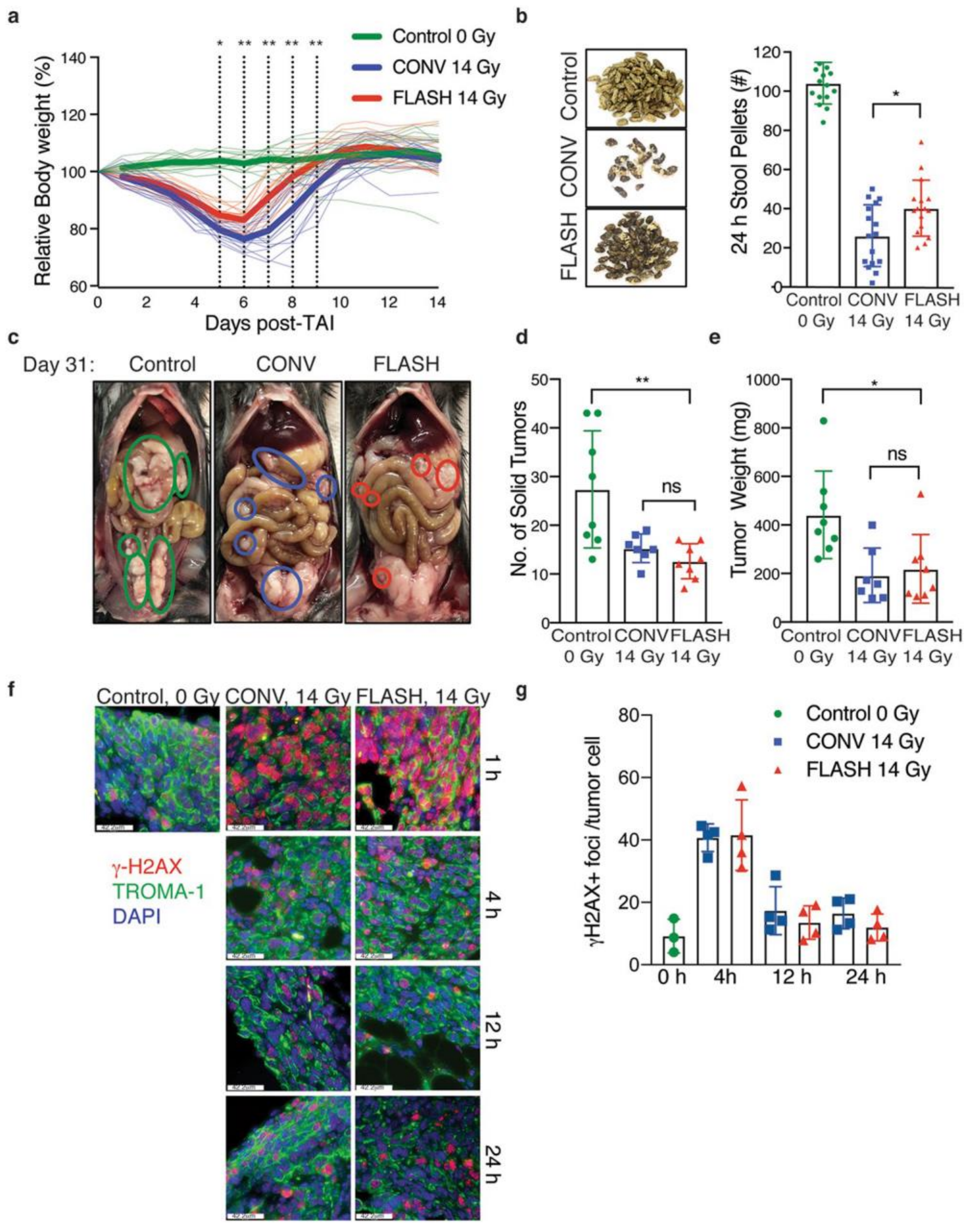
Bourhis J et al. Radiother Oncol. 2019.
Jorge PG et al. Radiother Oncol. 2019.

SubQ LLC model (immunocompotent mice)

Kim et al. IJROBP, 2021

Orthotopic ovarian cancer (ID8):

216 Gy/s, 2 Gy/pulse



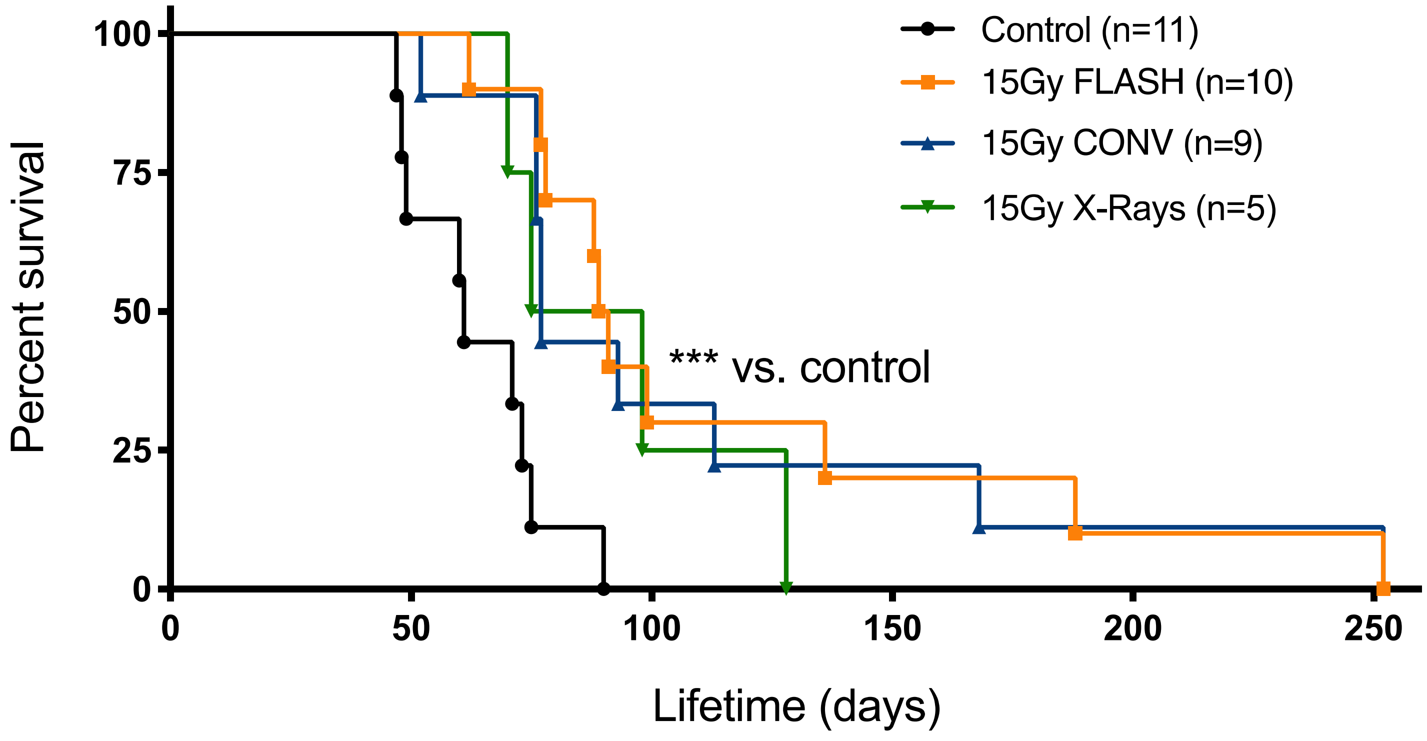
Orthotopic GBM

Montay-Gruel P et al. CCR, 2020.

Levy et al, Sc Rep, 2020
In immunocompetent mice

Transgenic GBM

GFAP-HRas^{V12}; GFAP-CRE; p53$^{flox/wt}$
8.3x10^{5} Gy/s



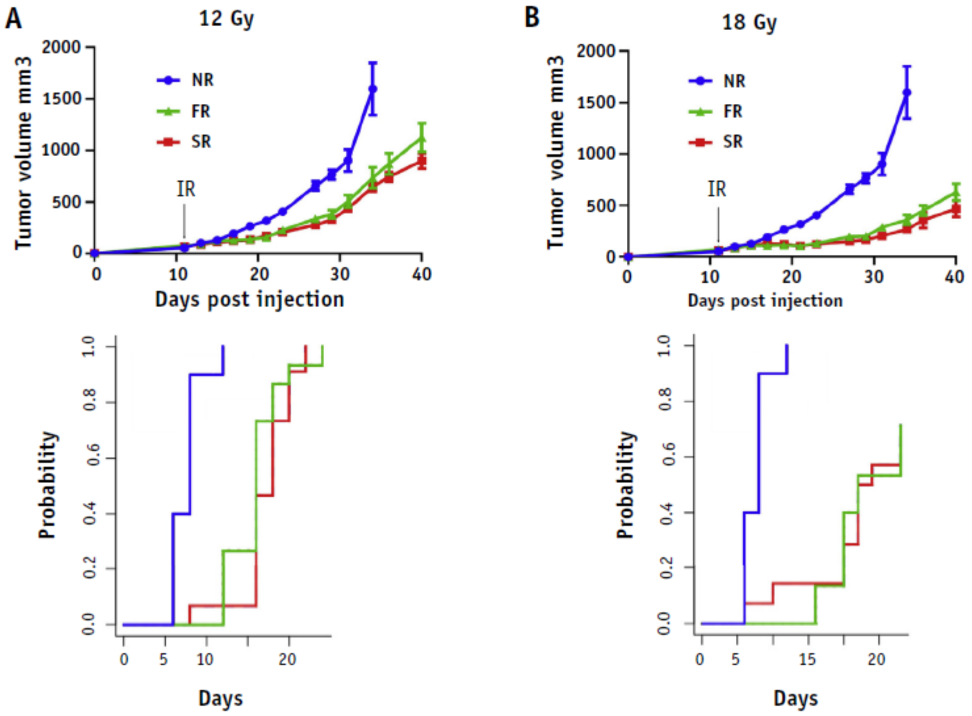
Limoli et al., Book review: *The Modern Technology of Radiation Oncology—a Compendium for Medical Physicists and Radiation Oncologists (Volume 4)* edited by Jacob Van Dyk

In immunocompetent mice

With Proton beam- double scattered beam

SubQ Pancreatic cancer MH641905

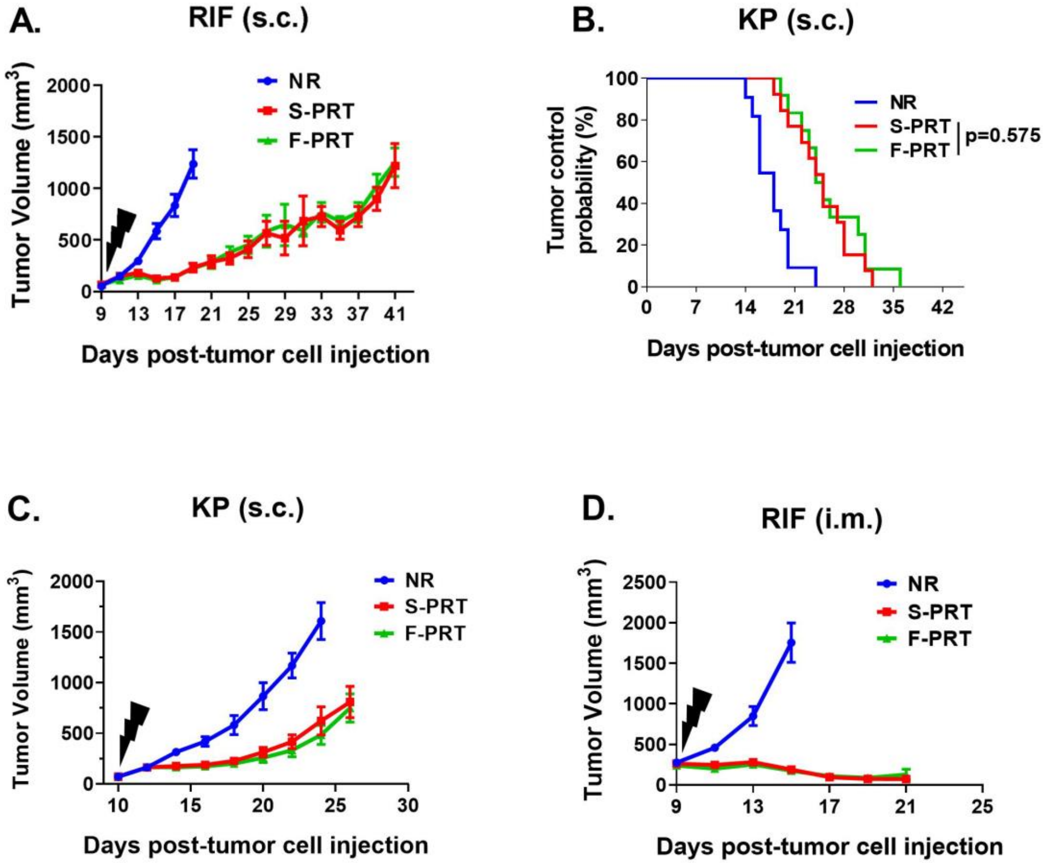
78 Gy/s +/-9



Diffenderfer et al. IJROBP, 2020

Sarcoma SubQ (30Gy) and GEMM (12 Gy) (immunoc

69-124 Gy/s

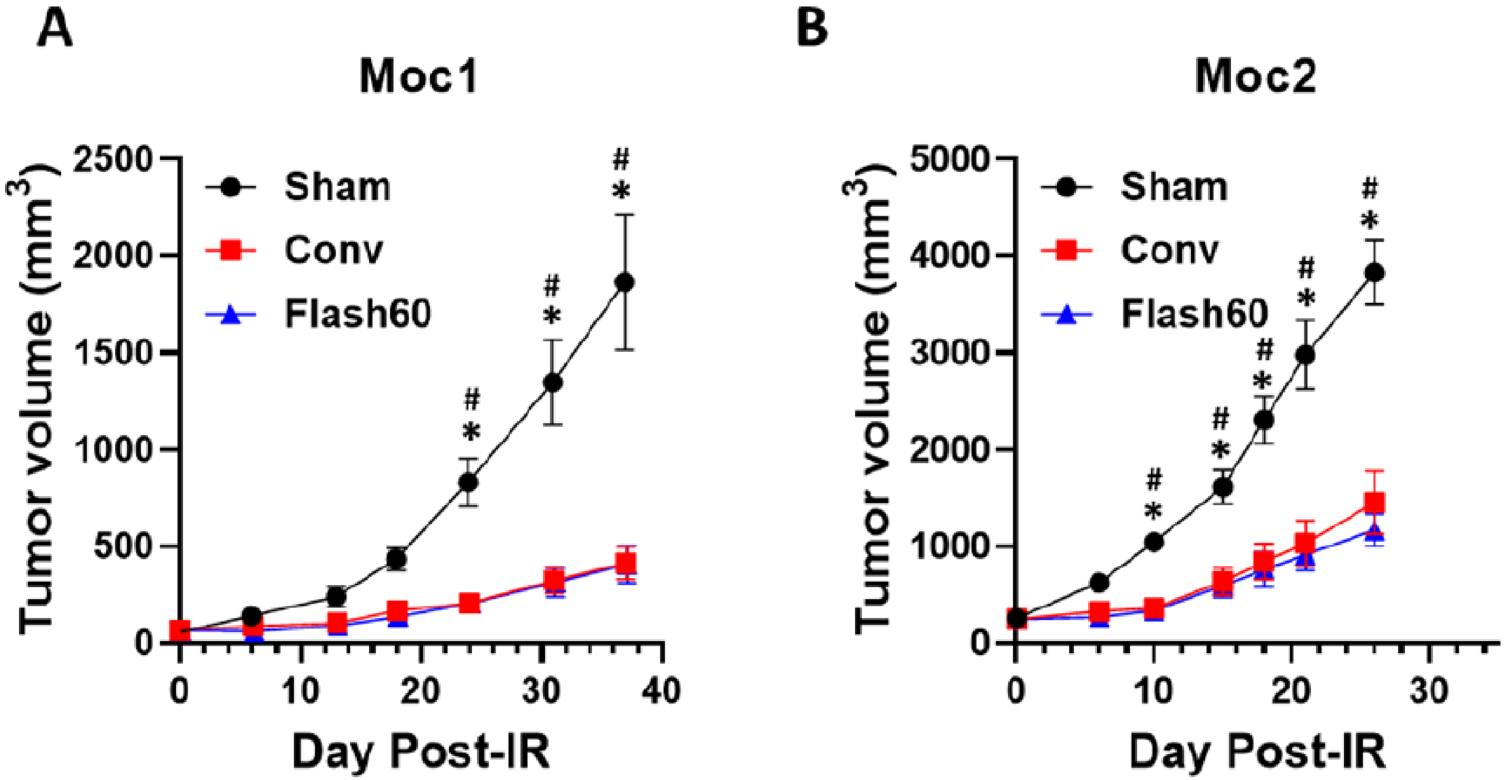


Velalopoulou et al. Cancer Res, 2021

With Proton beam- pencil beam scanning

SubQ MOC cells immunologically cold vs hot

62 Gy/s average and 207 Gy/s in the spot



Cunningham et al. Cancers, 2021

FLASH-RT can be fractionated

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

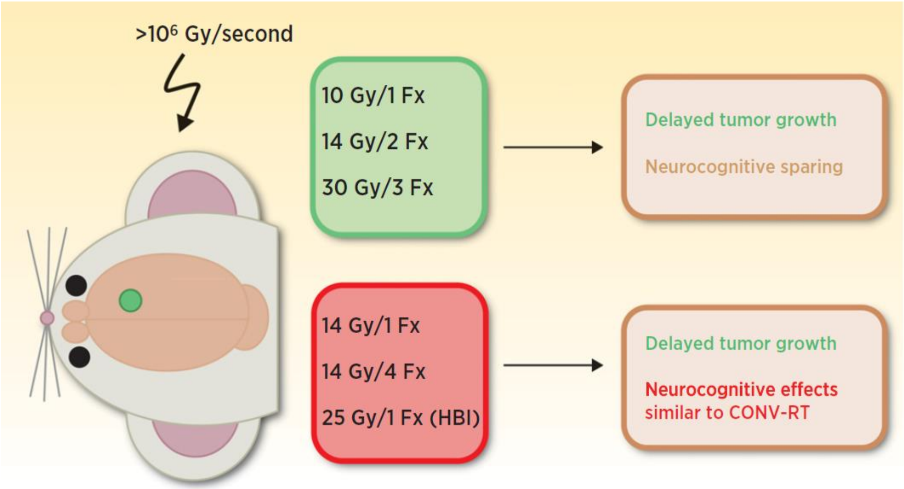
Hypofractionated FLASH-RT as an Effective Treatment against Glioblastoma that Reduces Neurocognitive Side Effects in Mice

Pierre Montay-Gruel[1], Munjal M. Acharya[2], Patrik Gonçalves Jorge[1,3], Benoit Petit[1], Ioannis G. Petridis[1], Philippe Fuchs[1], Ron Leavitt[1], Kristoffer Petersson[1,3], Maude Gondre[1,3], Jonathan Ollivier[1], Raphael Moeckli[3], François Bochud[3], Claude Bailat[3], Jean Bourhis[1], Jean-François Germond[3], Charles L. Limoli[2], and Marie-Catherine Vozenin[1]

CLINICAL CANCER RESEARCH | CCR TRANSLATIONS

News FLASH-RT: To Treat GBM and Spare Cognition, Fraction Size and Total Dose Matter

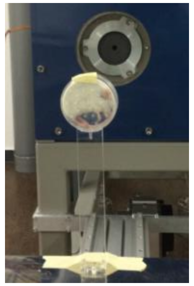
Christina C. Huang[1] and Marc S. Mendonca[1,2]

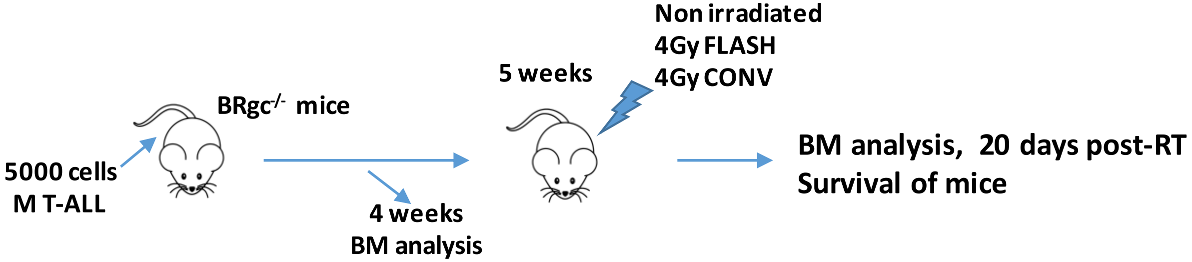


Human Tumors

All tumors are not equally sensitive to FLASH-RT

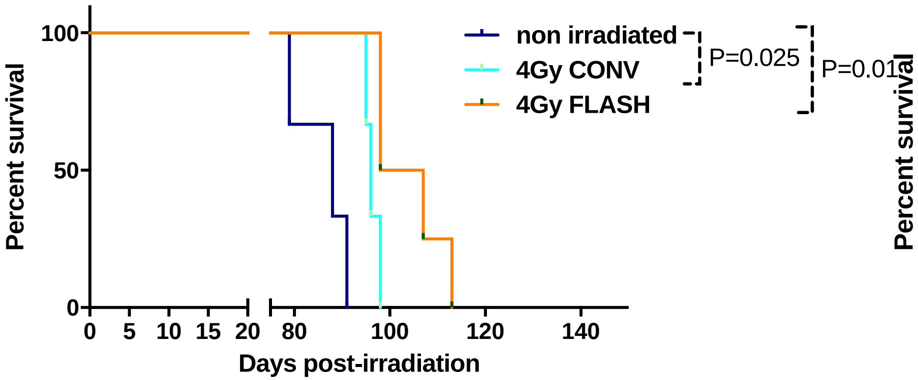
Human T-ALL with different susceptibility profile to FLASH-RT



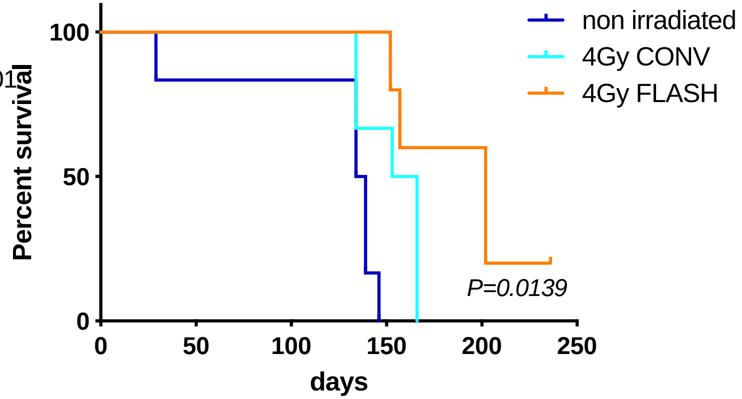


Delivery Mode	Prescribed Dose (Gy)	Beam parameters						
		Source-to-surface distance (mm)	Pulse repetition Frequency (Hz)	Pulse width (µs)	Number of pulses	Treatment time (s)	Mean dose rate (Gy/s)	Instantaneous dose rate (Gy/s)
CONV	4	880	10	1.0	>557	>55.6	<0.072	$<7.2 \times 10^3$
FLASH	4	800	100	1.8	3	0.02	200	7.4×10^5

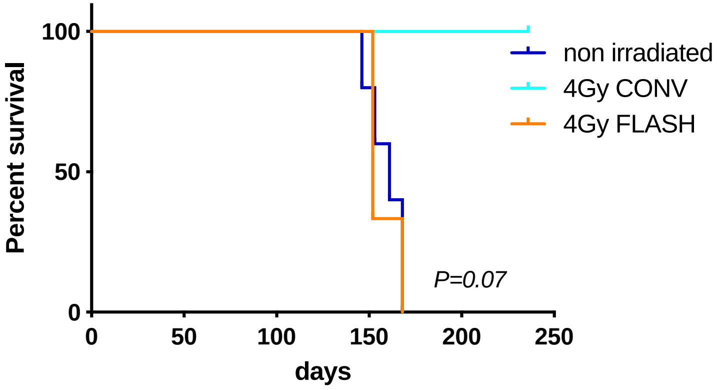
M106 PDX/T-ALL



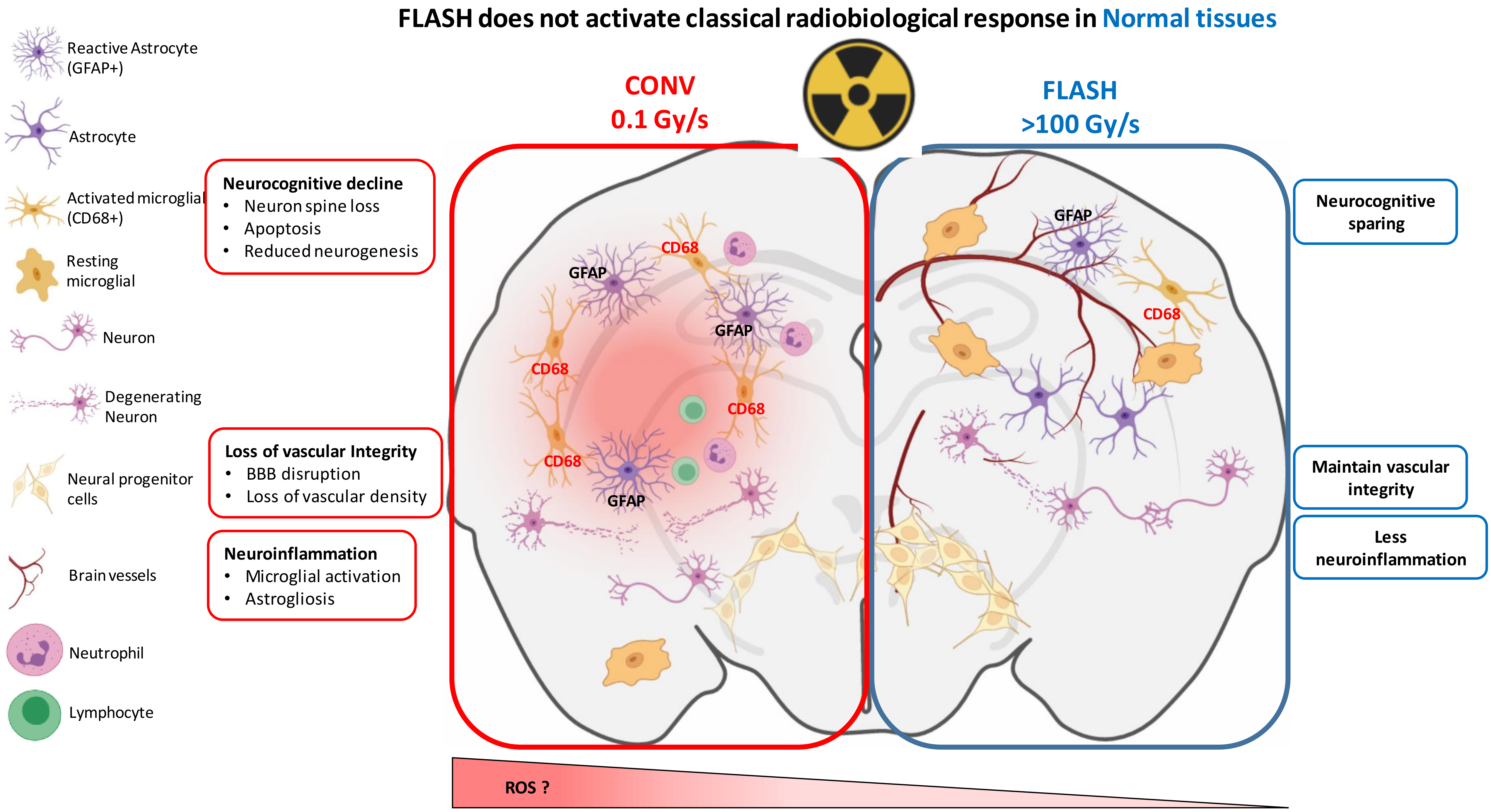
M114 PDX/T-ALL



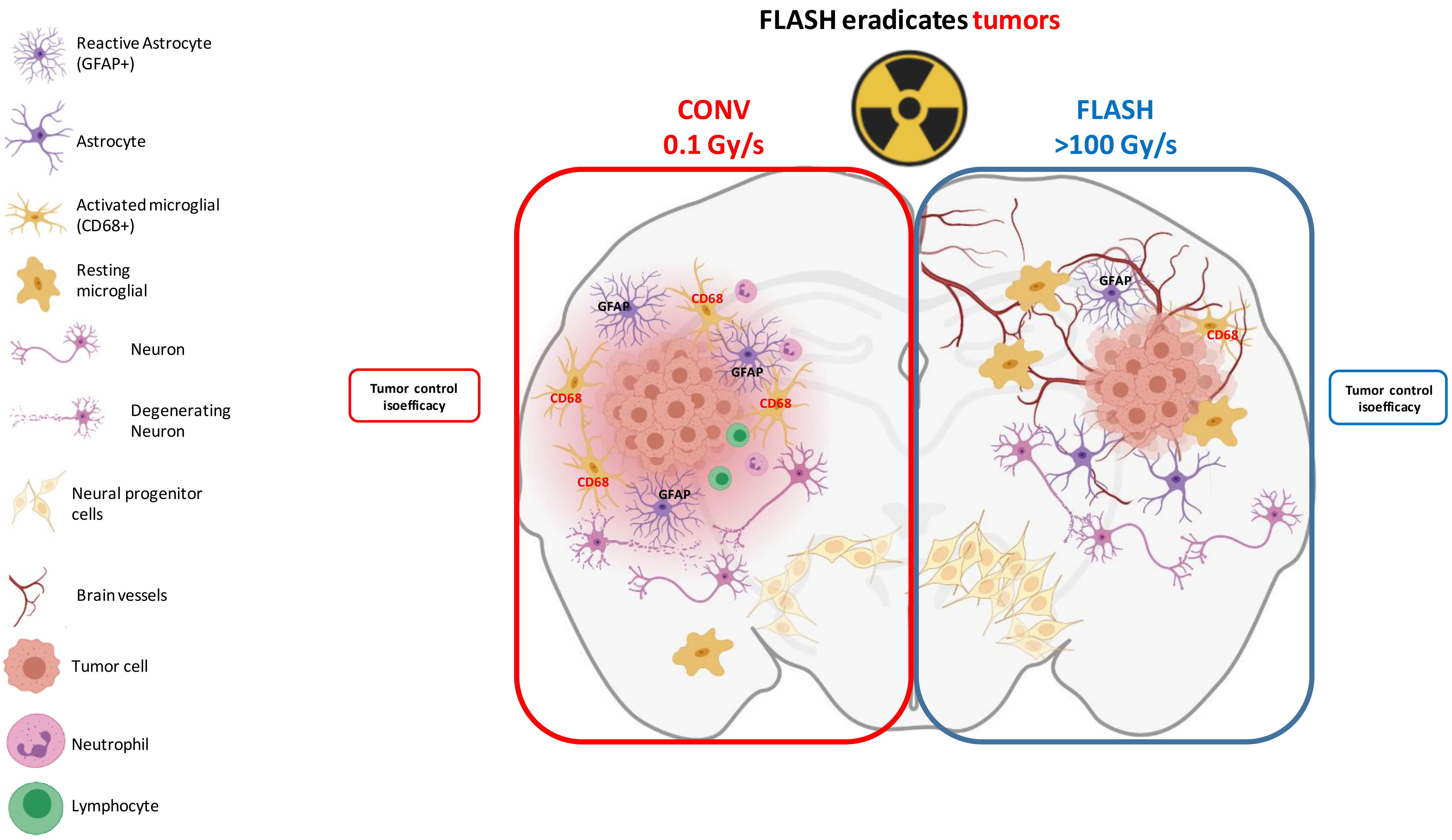
M108 PDX/T-ALL



Chabi et al, IJROBP, 2020



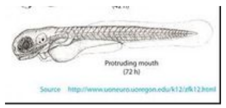
FLASH does not activate classical radiobiological response in Normal tissues
Reactive Astrocyte (GFAP+)
Astrocyte
Activated microglial (CD68+)
Resting microglial
Neuron
Degenerating Neuron
Neural progenitor cells
Brain vessels
Neutrophil
Lymphocyte
Neurocognitive decline
Neuron spine loss
Apoptosis
Reduced neurogenesis
Loss of vascular Integrity
BBB disruption
Loss of vascular density
Neuroinflammation
Microglial activation
Astrogliosis
CONV
0.1 Gy/s
FLASH
>100 Gy/s
GFAP
CD68
Neurocognitive sparing
Maintain vascular integrity
Less neuroinflammation
ROS ?



Rv in Kacem et al., IJRB, 2021

At the biology level

What is known about the FLASH effect



Skin
Gut
Lung
HS
Brain

FLASH-RT spares normal tissue and is equally able to eradicate tumors compared to CONV-RT
Using TGD assay (no TCD50 assay has been published)

- Using electron, photon and proton beams
- In pre-clinical mouse model
- Small volume
- Single dose and hypofractionated regimen

What is currently being explored

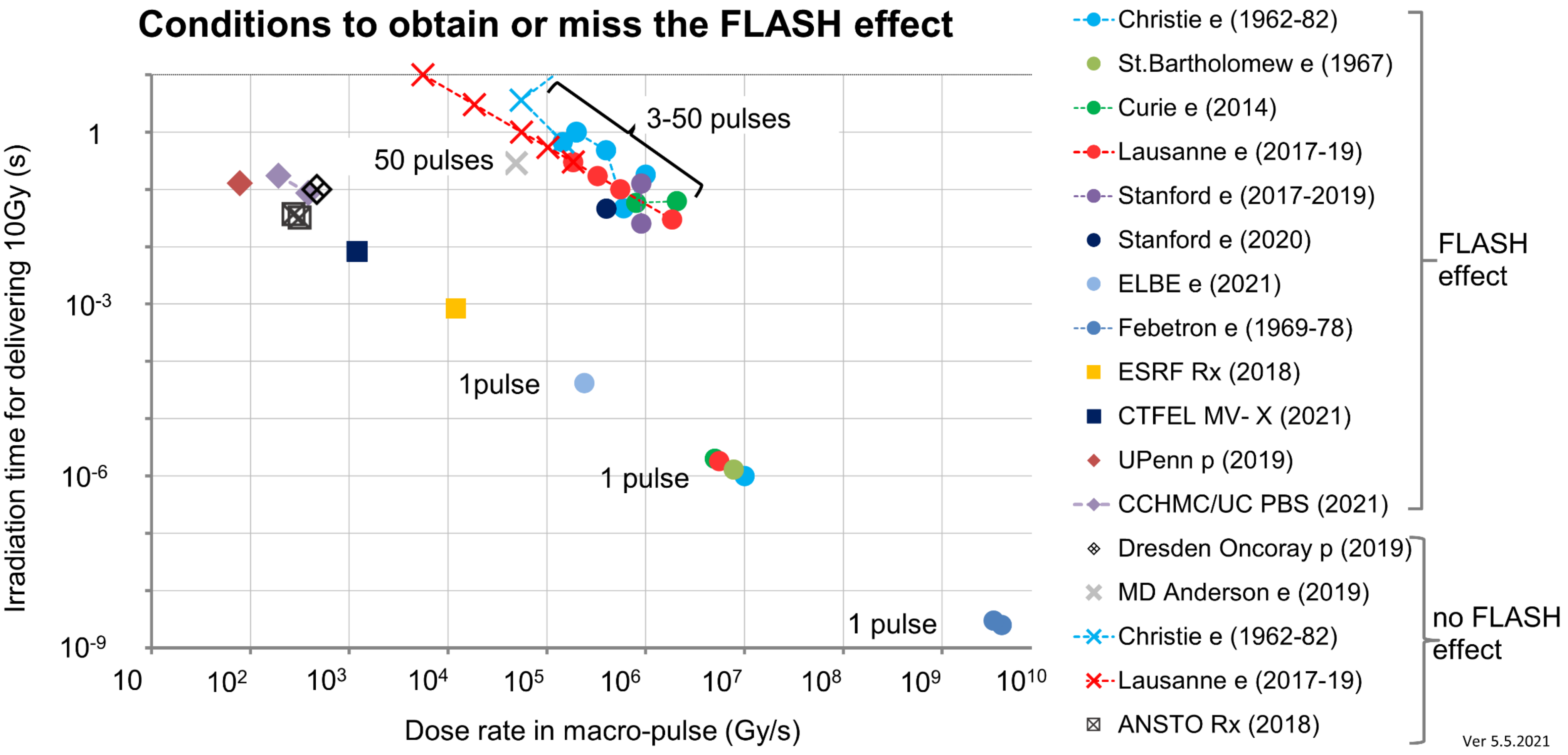
- Modality of cell death
- Immune component
- Metabolism
- DNA repair
- Cell signaling

What remains to be understood

Thinking outside the box
… New radiobiology

FLASH could be an unique tool to explore the fundamental difference between normal tissues and tumors

At the physics level



The shorter the better

The higher the better

Adapted from Montay-Gruel P et al., CCR, 2020.