Open questions in FLASH therapy for a successful clinical translation

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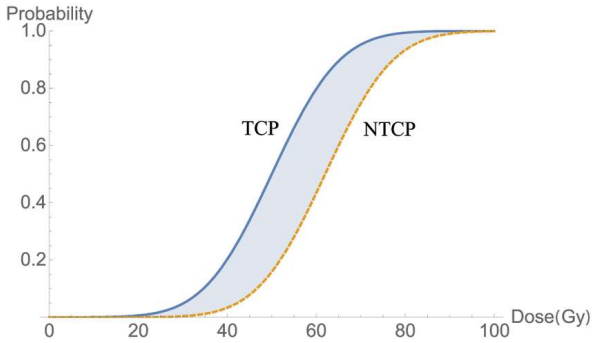
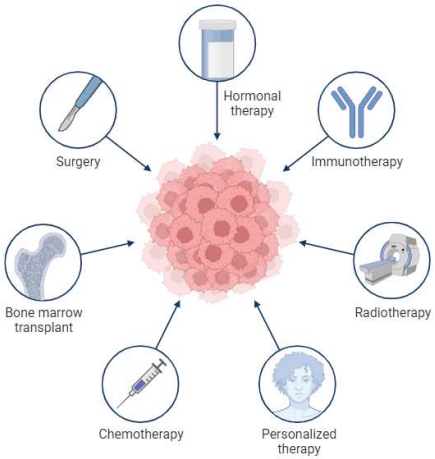
07/11/2024

Introduction to radiation therapy



Strategy 1: To increase tumor sensitivity to radiation without any additional effect on normal tissue

Strategy 2: To increase normal tissue resistance to radiation without any additional effect on tumor



Conventional RT

1 Gy/min

UHDR RT

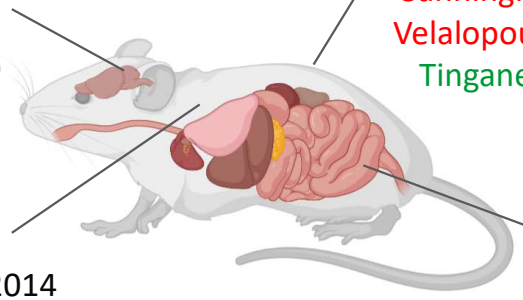
> 40 Gy/s

Flash effect

FLASH-RT limits radiation induced-toxicities while being isoeffective on tumors compared to conventional-RT

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

Skin :
Field et al. 1974
Inada et al. 1980
Soto et al. 2020
Cunningham et al. 2021
Velalopoulou et al. 2021
Tinganelli et al. 2022



Lung :
Favaudon et al. 2014
Girdhani et al. 2019
Fouillade et al. 2020

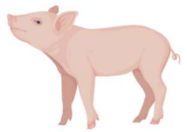
Gut :
Levy et al. 2020
Diffenderfer et al. 2020
Evans et al. 2021
Kim et al. 2021
Ruan et al. 2021

Electrons ; Protons; Photons ; Carbon ions

Schoenauen al. 2024

Montay-Gruel et al. 2019
Beyreuther et al. 2019
Pawelke et al. 2021

Vozenin et al. 2019
Rohrer Bley et al. 2022

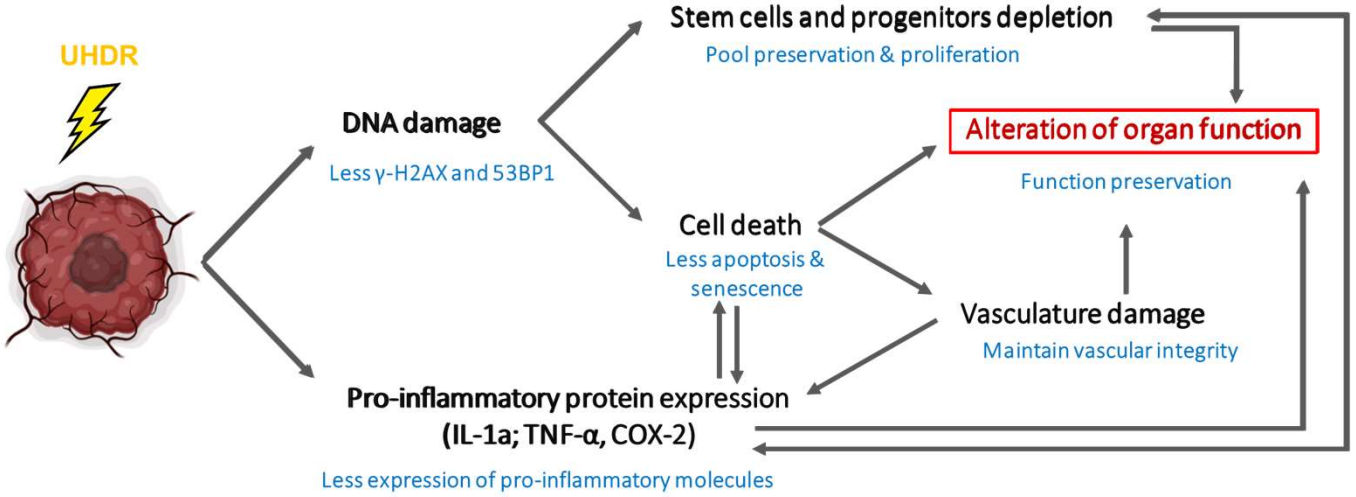


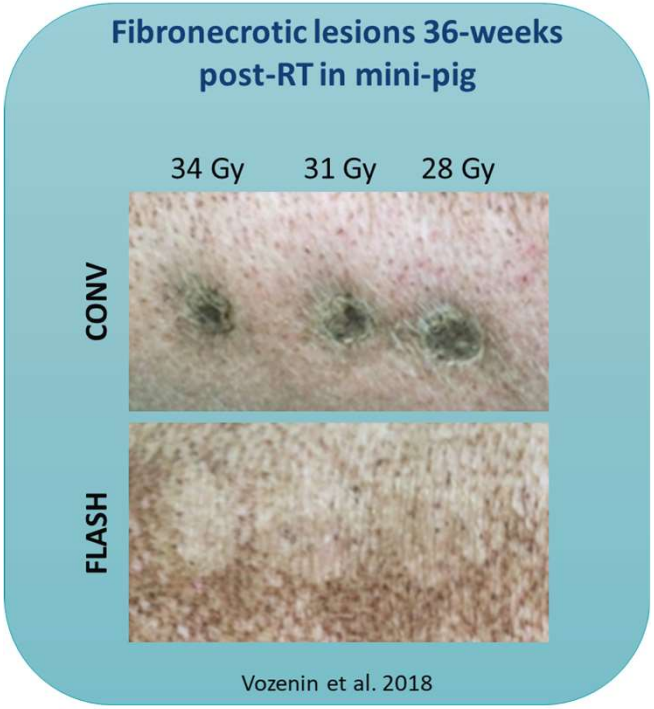
Vozenin et al. 2019
Rohrer Bley et al. 2022

Kondradsson et al. 2021
Velalopoulou et al. 2021

Biological features of FLASH irradiation

Pathogenic mechanisms induced by radiation is modulated by UHDR irradiation





FLASH facility at H.U.B

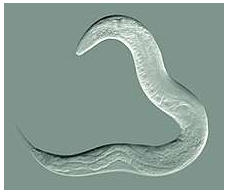
Mobetron by IntraOp

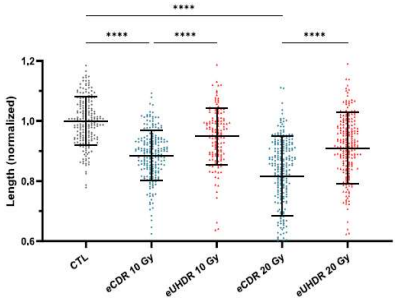
	CONV mode	UHDR mode
Energy [MeV]	6 / 9 / 12	6 or 9
Mean dose rate [Gy/s]	0,1	1 - 250
Pulse width [µs]	1.2	0.5 – 4.0
Pulse frequency [pps]	30	10 - 120
Instantaneous dose rate [Gy/s]	4.10^3	$\approx 10^5$
Dose delivery	Monitor Units	# of pulse and distance
Dose control	Dual Ion Chamber	FLASH-IQ™ Advanced Dosimetry

Cherenkov Effect

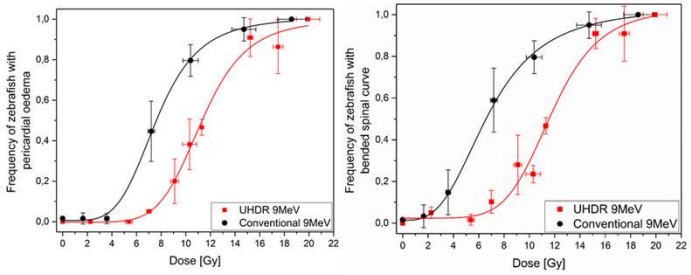
Mobetron Clinical Electron IORT System

FLASH results with Mobetron

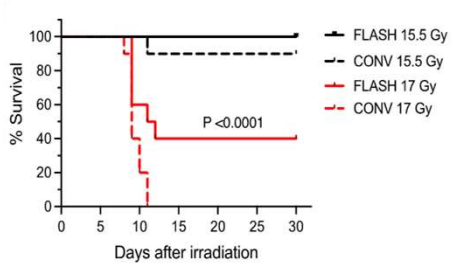


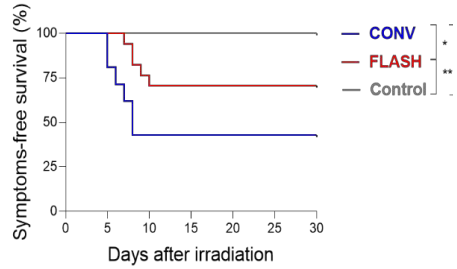


Schoenauen et al. CTRO (2024)



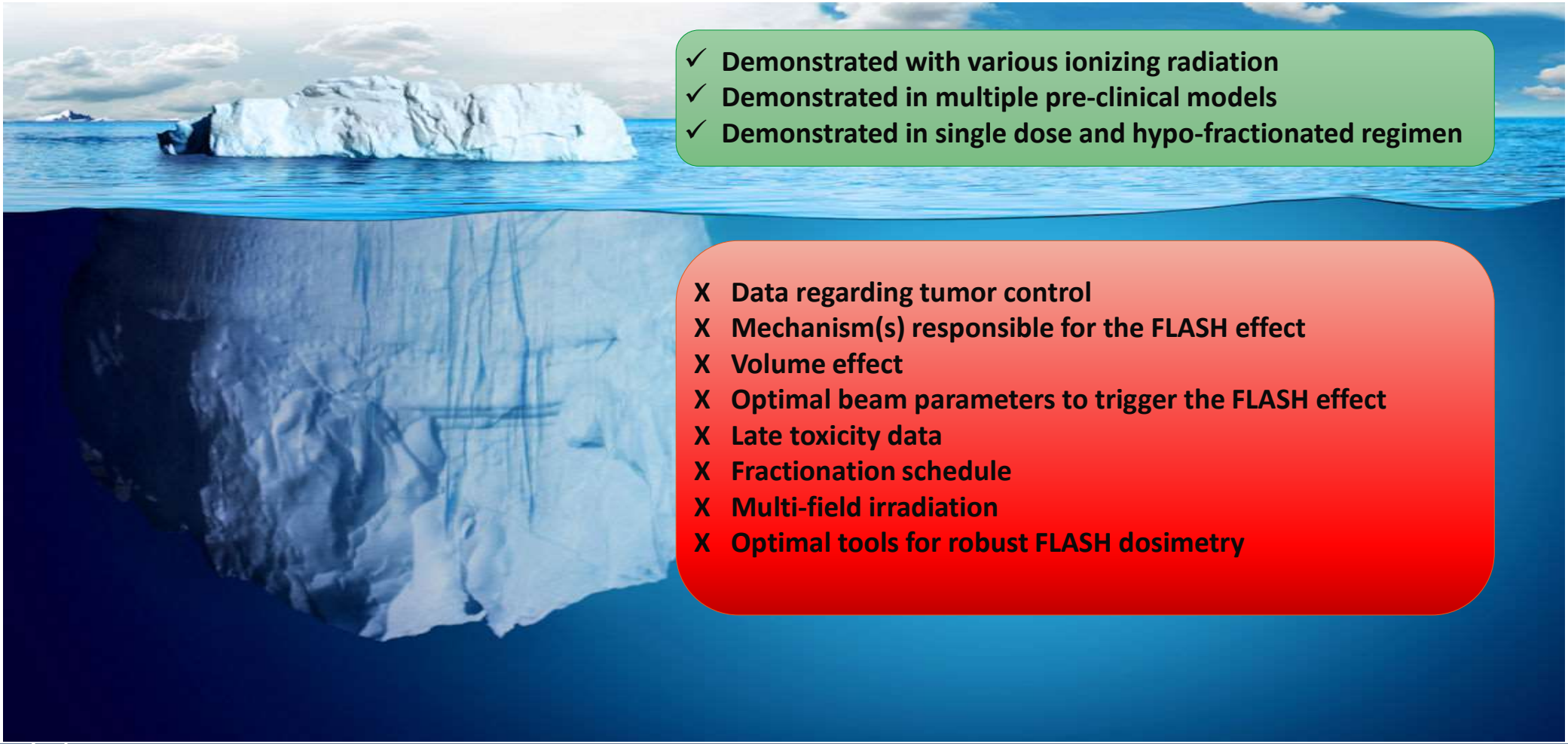
Data from Nina Blond (H.U.B)





Valdes Zayas et al. Cancers (2023)

What do we know, what do we don't know ?



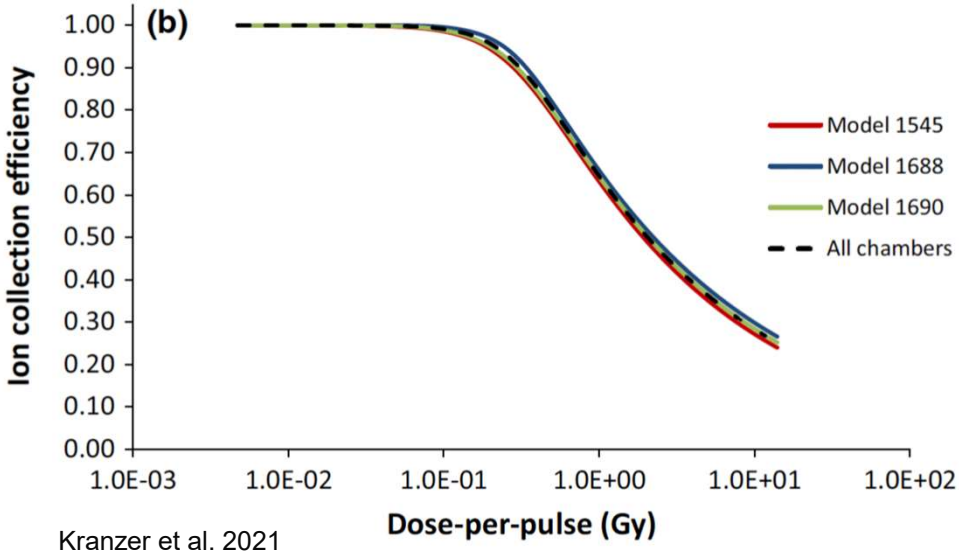
- ✓ Demonstrated with various ionizing radiation
- ✓ Demonstrated in multiple pre-clinical models
- ✓ Demonstrated in single dose and hypo-fractionated regimen

- X Data regarding tumor control
- X Mechanism(s) responsible for the FLASH effect
- X Volume effect
- X Optimal beam parameters to trigger the FLASH effect
- X Late toxicity data
- X Fractionation schedule
- X Multi-field irradiation
- X Optimal tools for robust FLASH dosimetry

Which tools do we have to use for dosimetry ?

Physics of UHDR beams differ from conventional ones ➔ Dedicated tools have to be used

Ionization chambers

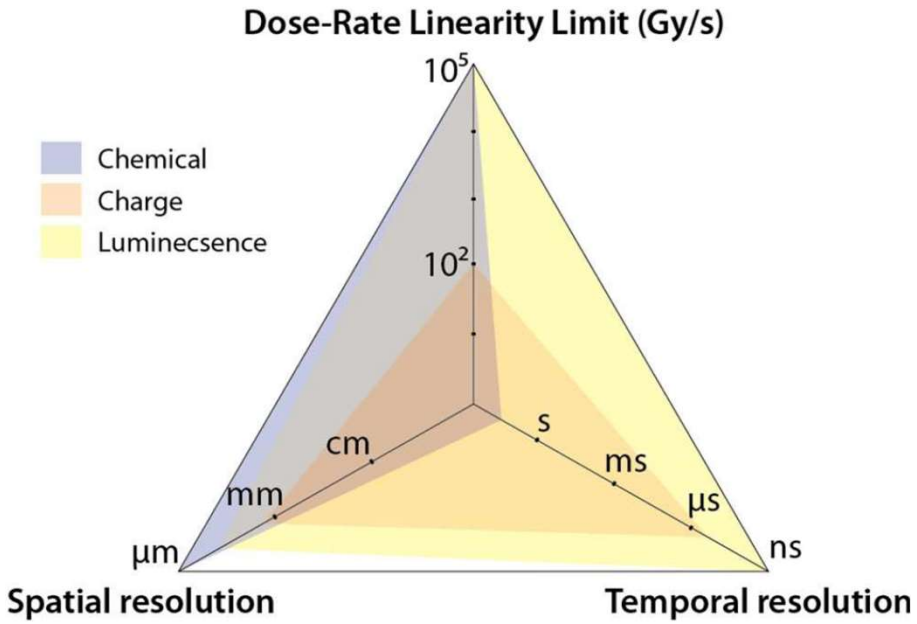


Kranzer et al. 2021

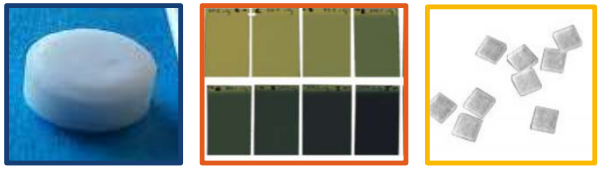
Wrong tools !

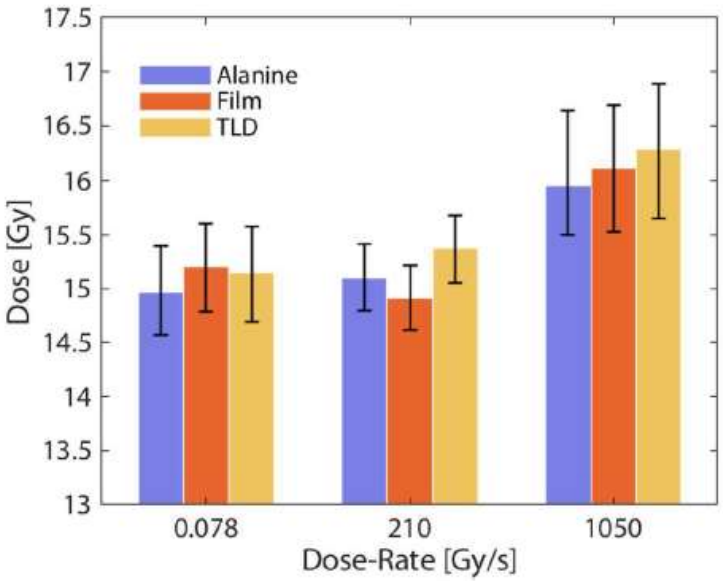
Usual tools need correction factors !

Which tools do we have to use for dosimetry ?



Ashraf et al. 2020

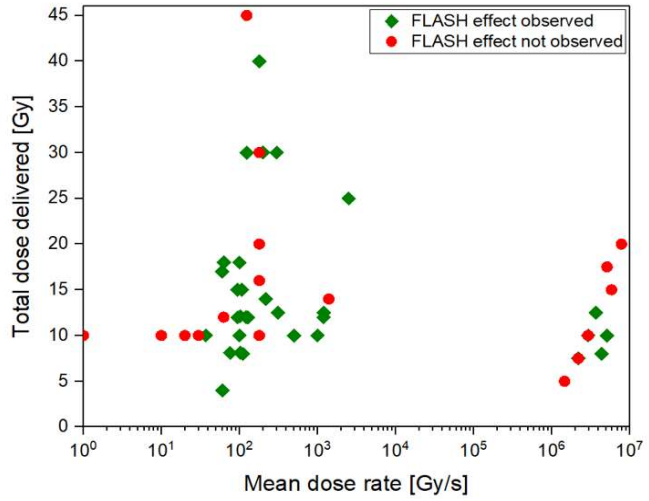


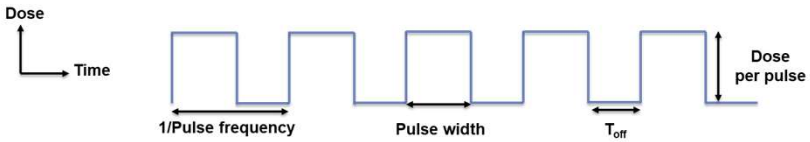


All detectors were found to agree within 3% at conventional and FLASH dose-rates, indicating excellent dose-rate independence

Jorge et al. 2019

Which tools do we have to use for dosimetry ?

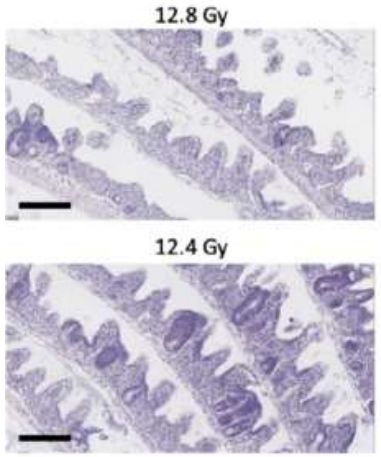


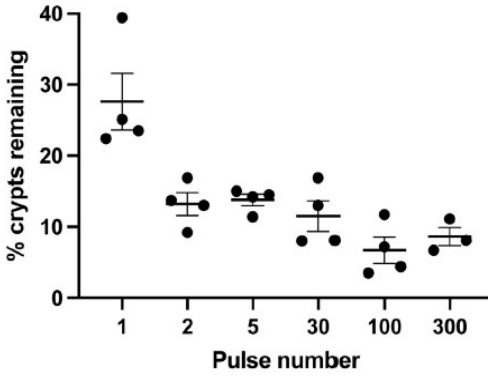


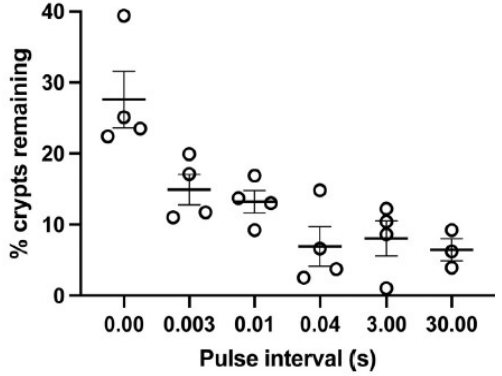
For a given mean dose rate and total dose, you can modulate 7 parameters :

- ✓ Pulse frequency
- ✓ Pulse width
- ✓ T off between pulse
- ✓ Number of pulses
- ✓ Total delivery time
- ✓ Dose per pulse
- ✓ Dose rate per pulse

C3H mice model



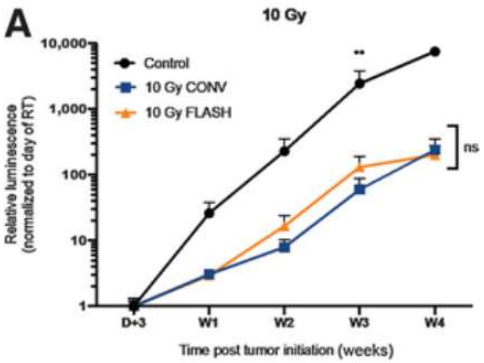


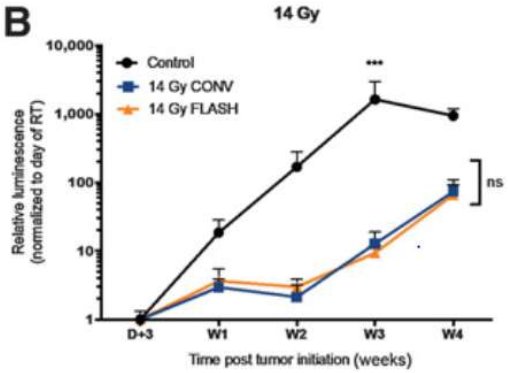


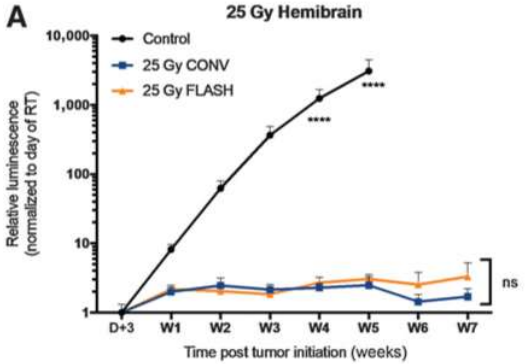
Ruan et al. Int. J. Radiat. Oncol. (2022)

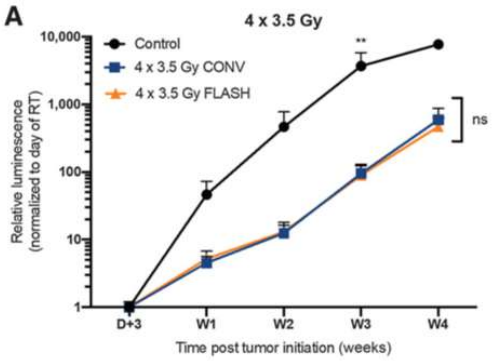
What is the impact of fractionation ?

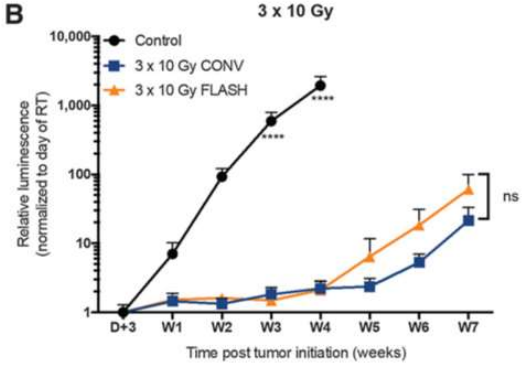
H454 orthotopic glioblastoma model

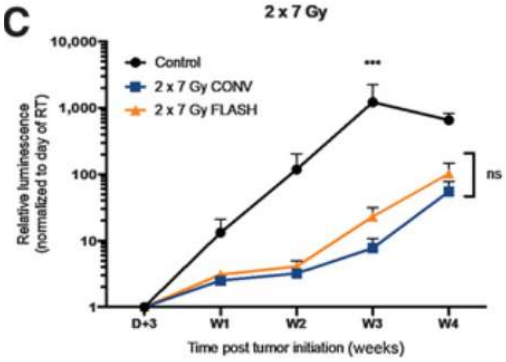












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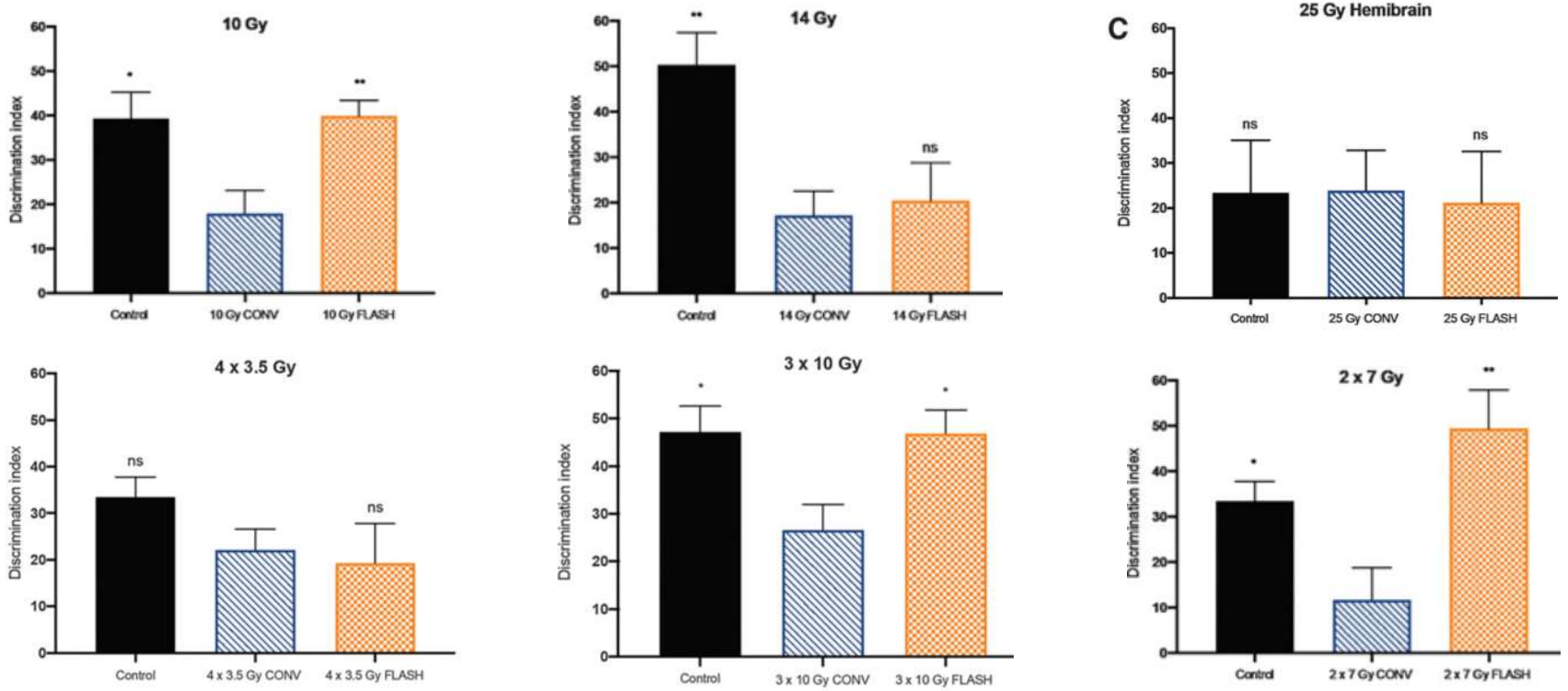
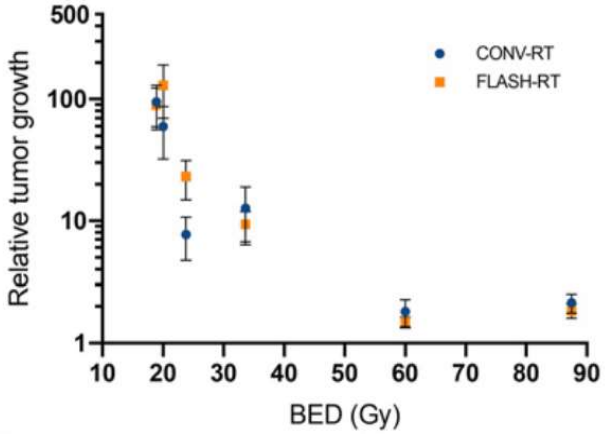
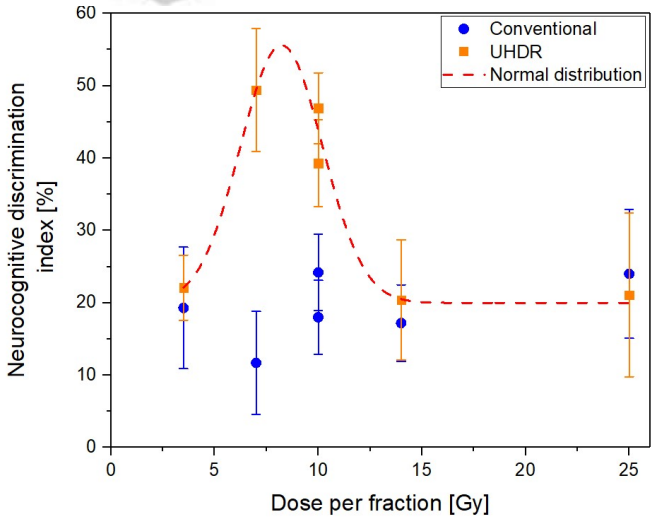
H454 orthotopic glioblastoma model

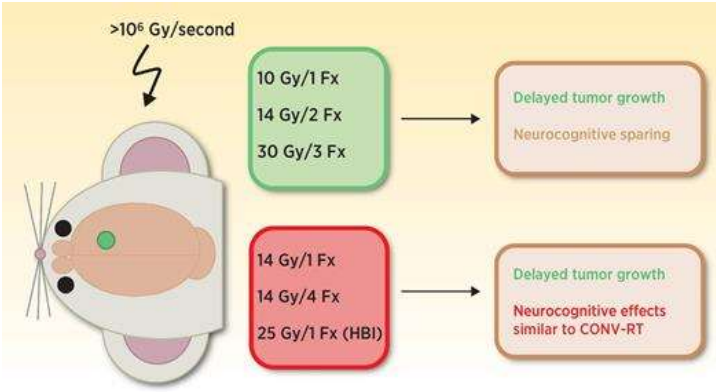


What is the impact of fractionation ?

H454 orthotopic glioblastoma model



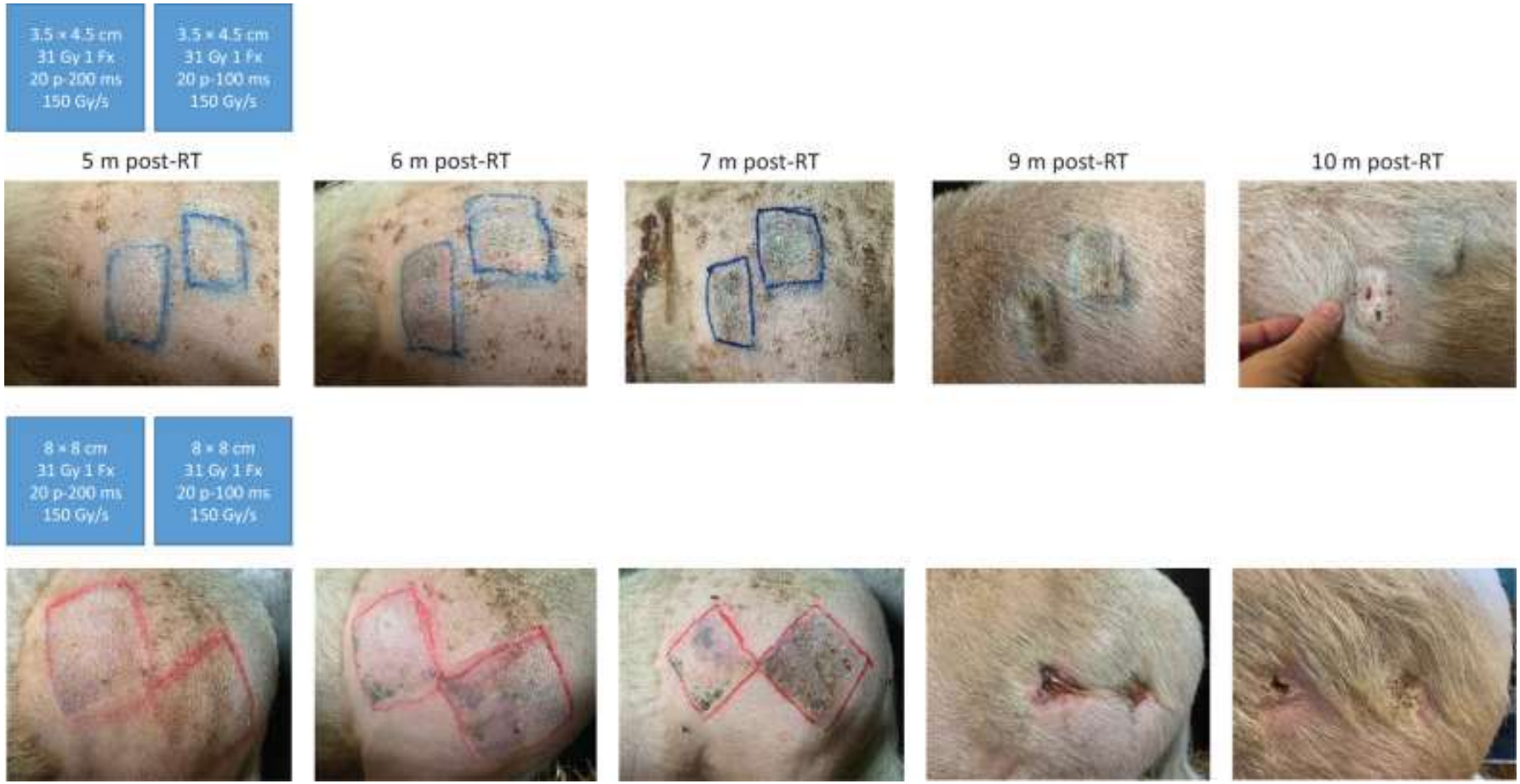




	4 x 3.5 Gy	1 x 10 Gy	2 x 7 Gy	1 X 14 Gy	3 x 10 Gy	1 X 25 Gy
BED tumor [Gy] (α/β = 10)	19	20	24	34	60	87
BED brain [Gy] (α/β = 3)	30	43	47	79	130	233

Data from Montay-Gruel et al. 2021

Volume effect



What are the mechanisms responsible for the FLASH effect ?

nature reviews clinical oncology

https://doi.org/10.1038/s41571-022-00697-z

Perspective

Towards clinical translation of FLASH radiotherapy

Marie-Catherine Vozenin[1], Jean Bourhis[1] & Marco Durante[2,3]

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Mechanisms of FLASH effect

Binwei Lin[1,2†], Dan Huang[3†], Feng Gao[1], Yiwei Yang[4], Dai Wu[4], Yu Zhang[1], Gang Feng[1], Tangzhi Dai[1] and Xiaobo Du[1*]

[1]National Health Commission (NHC) Key Laboratory of Nuclear Technology Medical Transformation, Mianyang Central Hospital, Department of Oncology, Mianyang Central Hospital, Mianyang, China, [2]State Key Laboratory of Ultrasound in Medicine and Engineering, College of Biomedical Engineering, Chongqing Medical University, Chongqing, China, [3]Department of Radiology Mianyang Central Hospital, Mianyang, China, [4]Institute of Applied Electronics, China Academy of Engineering Physics, Mianyang, China

ANNUAL REVIEWS

Annual Review of Cancer Biology

Reinventing Radiobiology in the Light of FLASH Radiotherapy

Charles L. Limoli[1] and Marie-Catherine Vozenin[2]

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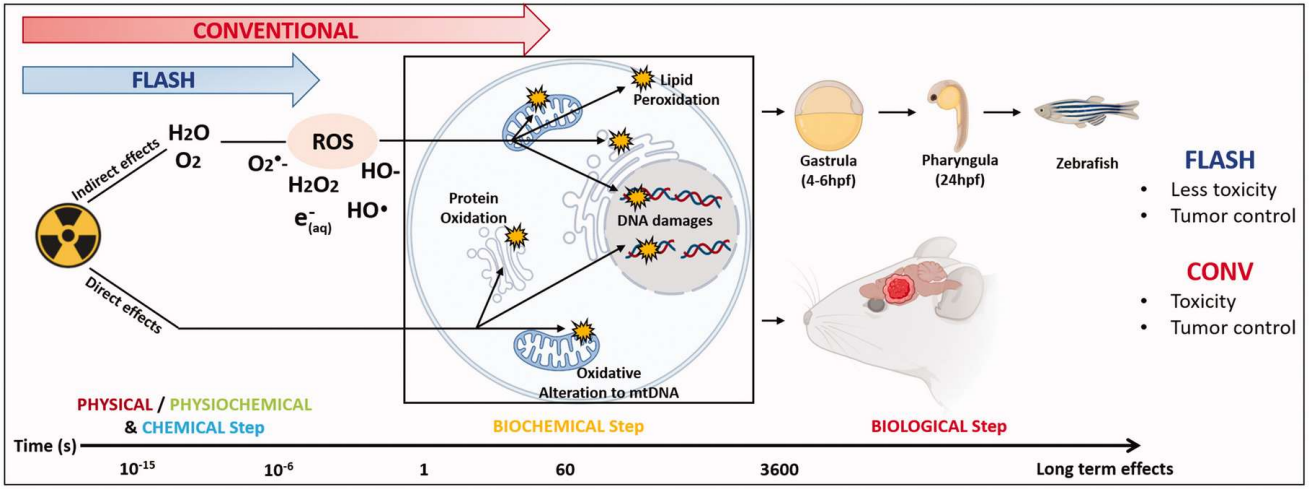
[2]Laboratory of Radiation Oncology, Radiation Oncology Service and Oncology Department, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

More than 20 hypotheses :

? Oxygen depletion / transient hypoxia
? Radiochemical alteration
? Immune response modulation
…



Take home message

- FLASH - RT spares normal tissue and is equally able to eradicate tumors compared to CONV-RT
- The effect was demonstrated in multiple pre-clinical models, in a broad range of tissues
- Preclinical radiobiology studies highlights several challenges to address in order to ensure a rapid and successful transition of the technology to the clinic

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