RADIATION PROTECTION ISSUES IN MODERN EXTERNAL BEAM RADIOTHERAPY
FLASH THERAPY

Prof Pelagia Tsoutsou MD, PhD
Head of Radiation Oncology Department,
Geneva University Hospital
Geneva University, Faculty of Medicine
Pelagia.Tsoutsou@hcuge.ch

Prof Marie-Catherine Vozenin, PhD
Head of Radiobiology Sector/Lab,
Geneva University Hospital
Geneva University, Faculty of Medicine
Marie.Catherine Vozenin@hcuge.ch

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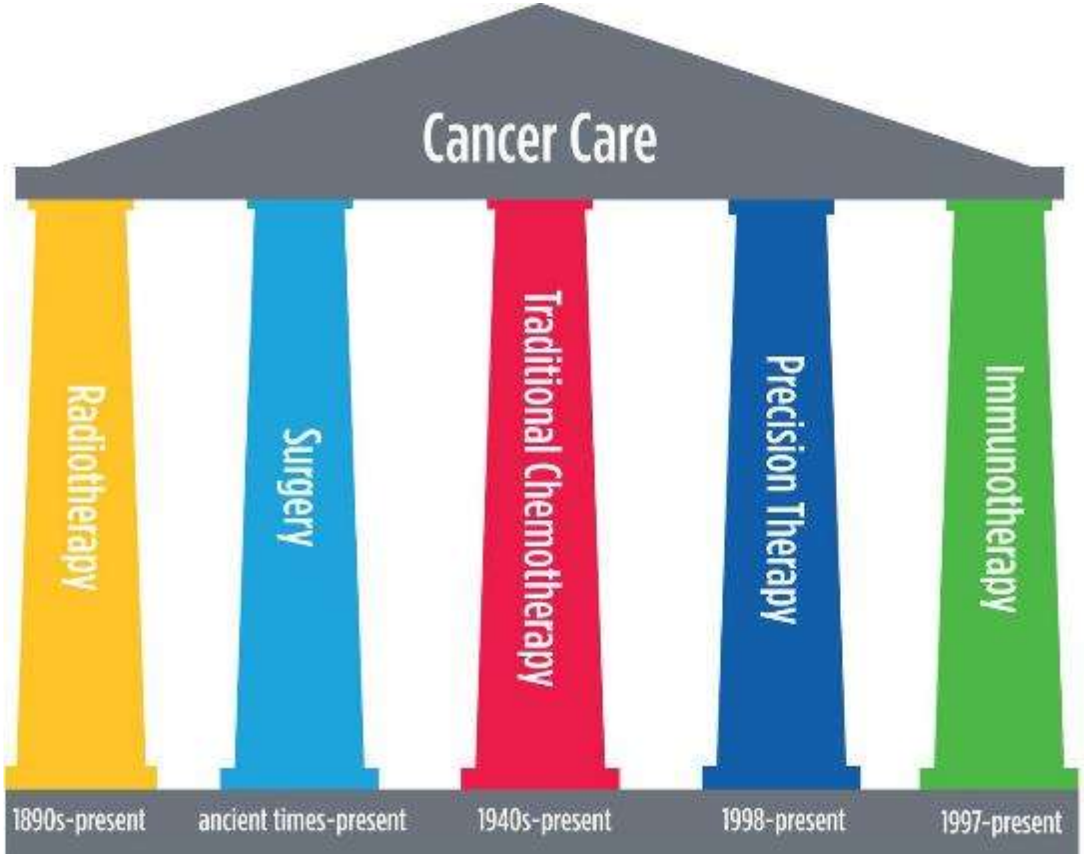
PILARS OF CANCER CARE



FLASH RADIOTHERAPY
IRRADIATION AT ULTRA HIGH DOSE RATE (UHDR)

Balistic advantage

Radiobiological advantage

Freeze motion

THE FLASH EFFECT

DIFFERENCES BETWEEN FLASH AND CONVENTIONAL RT

	Conv	Flash
Dose per pulse (Gy) d	mGy	Gy
Total dose (Gy) D=nd (n=number of pulses)	2-8Gx/fr 60-90 Gy	8 Gy in 1 fr
Delivery time T (n(	>1min	<200 msec
Mean dose rate D/T	1Gy/min	>40Gy/sec
Duty cycle DT	0.1-50%	

CONV:
1Gy/min
0.017Gy/sec

FLASH:
60Gy/sec

=X 3500 quicker

SOME CONTEXT

exponent	12	9	6	3	2	1	0	-1	-2	-3	-6	-9	-12
	10^{12}	10^{9}	10^{6}	10^{3}	10^{2}	10^{1}	$10^{0}=1$	10^{-1}	10^{-2}	10^{-3}	10^{-6}	10^{-9}	10^{-12}
prefix	tera	giga	mega	Kilo	hecto	deca	BASE	deci	centi	mili	micro	nano	pico
	T	G	M	k	h	da		d	c	m	μ	n	p

conv

protons

electrons

VHEE


P Montay-Gruel


C Limoli

"FLASH-RT deliveres radiation at **ultra-high dose rates** with **specific beam parameters** able to **effectively treat tumors without inducing adverse toxicity** within the surrounding normal tissues"

***in vivo* observation!**

1 – implements extremely **FAST** - Ultra-high dose rate (UHDR) irradiation

Defined beam parameters

2 – does not induce classical radiation induced toxicity in **normal tissue**

> 45 publications

3 – retains **antitumor efficacy** compared to standard RT

> 18 publications

"FLASH EFFECT"

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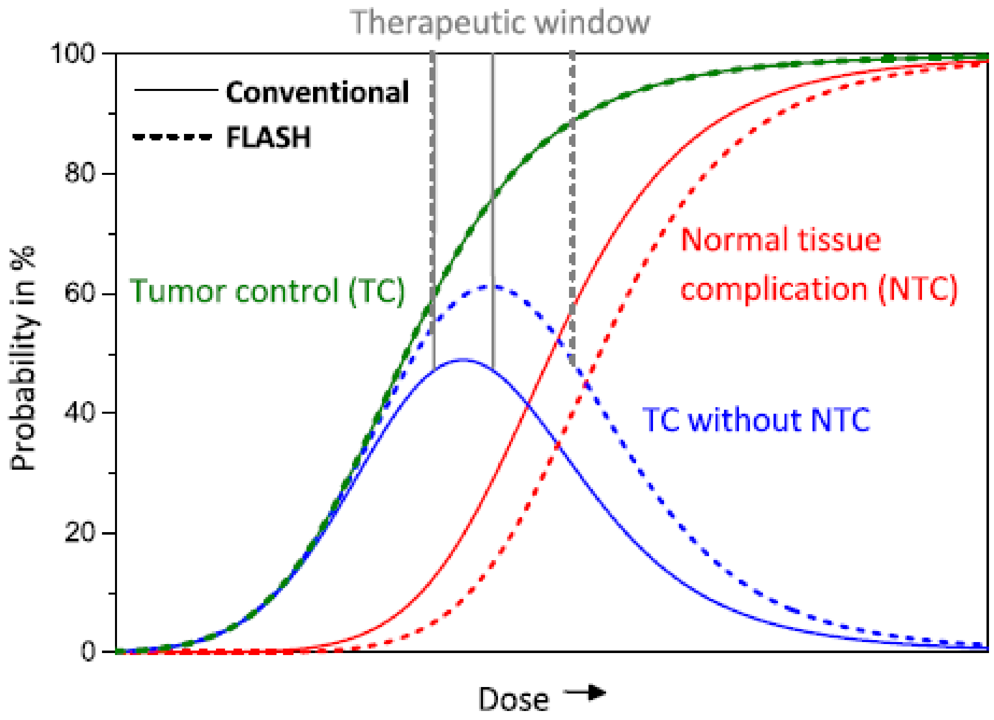
FLASH DOES ENHANCE THE THERAPEUTIC WINDOW




ELSEVIER

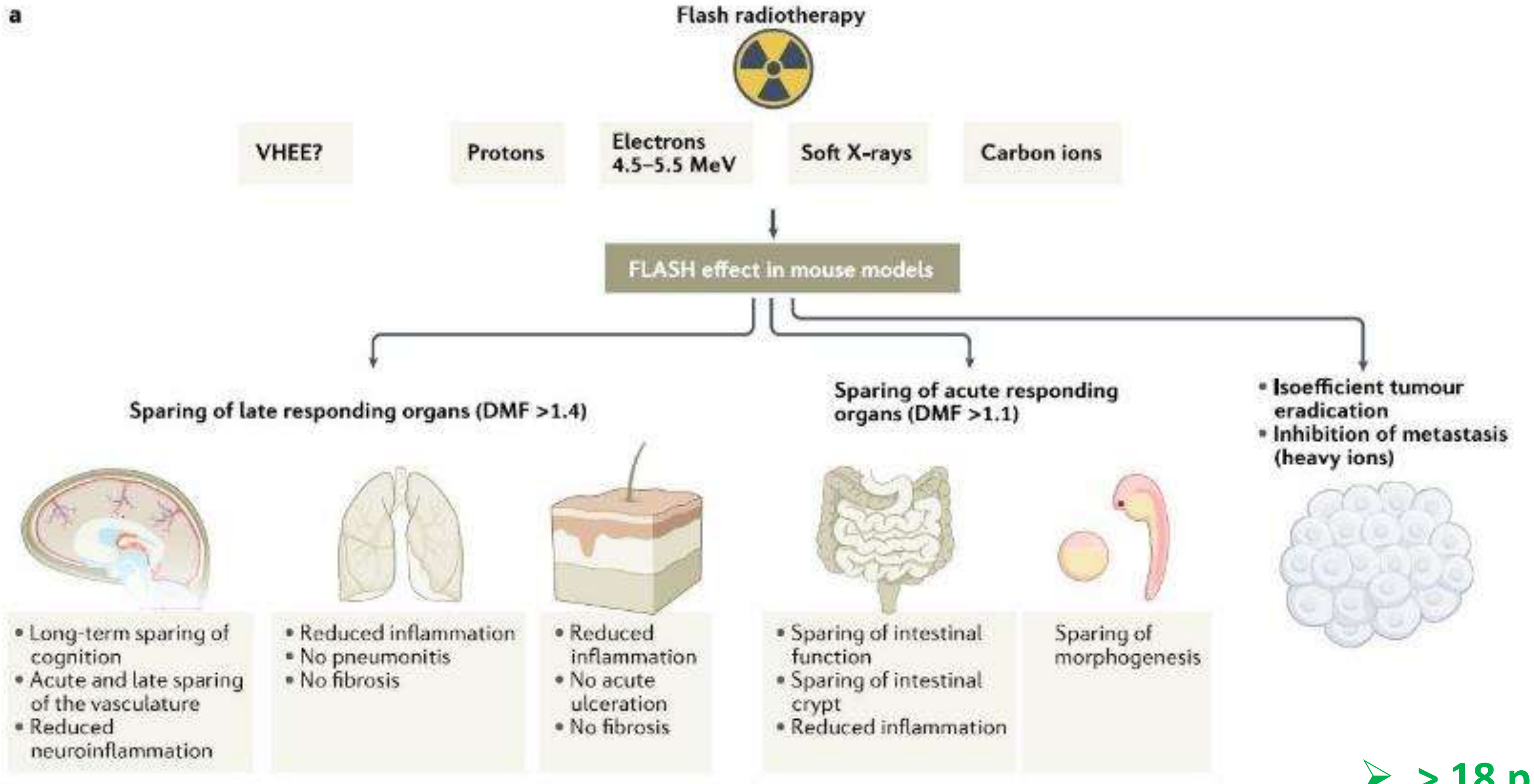
Physica Medica

Original paper

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

Andreas Schüller, Sophie Heinrich, Charles Fouillade, Anna Subiel, Ludovic De Marzi, Francesco Romano, Peter Peier, Maria Trachsel, Celeste Fleta, Rafael Kranzer, Marco Caresana, Samuel Salvador, Simon Busold, Andreas Schönfeld, Malcolm McEwen, Faustino Gomez, Jaroslav Solc, Claude Bailat, Vladimir Linhart, Jan Jakubek, Jörg Pawelke, Marco Borghesi, Ralf-Peter Kapsch, Adrian Knyziak, Alberto Boso, Veronika Olsovcova, Christian Kottler, Daniela Poppinga, Iva Ambrozova, Claus-Stefan Schmitzer, Severine Rossomme, Marie-Catherine Vozenin

VALIDATION OF FLASH BEAMS



- > 18 publications
- > 23 tumor types

Single dose and HypoFx
TGD, TC and carcinogenesis
Chabi et al. study show Rr to FLASH

> 45 publications
Single dose, HypoFx, Standard fx

THRESHOLD FOR FLASH EFFECT

Threshold for FLASH effect

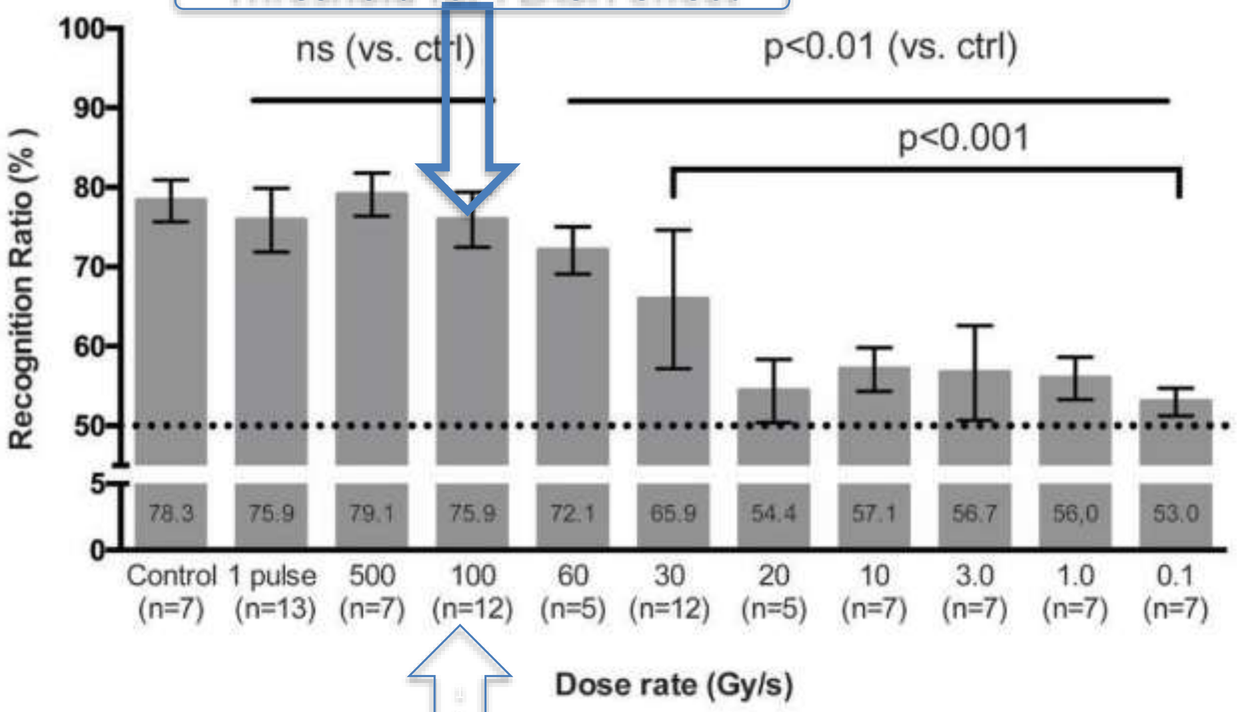
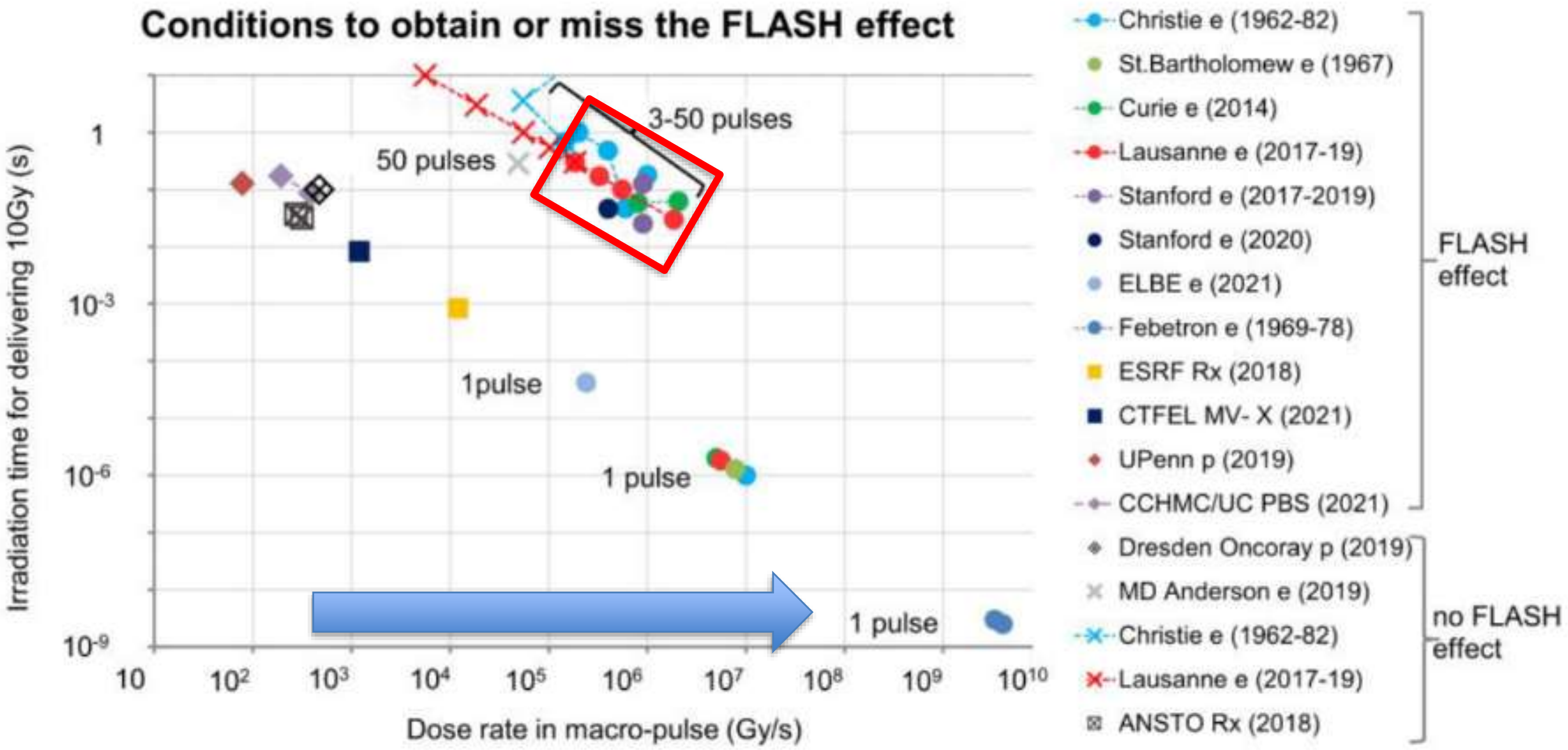


Figure 5: *From [39], neuroprotection demonstrated by the evaluation of the Recognition Ratio (RR) two months post irradiation for groups of mice (n=number of mice) that received 0 Gy (Control) and 10 Gy whole brain irradiation with an average dose rate of 0.1, 1.0, 3, 10, 20, 30, 60, 100, or 500 Gy/s, or with a single 1.8 μs electron pulse (1 pulse). Bars represent mean values and whiskers the standard deviations. Dose rates above 60 Gy/s or delivery times <167 ms were required for maximum neuroprotection at a dose of 10 Gy in this model.*

Maximum neuroprotection

CONDITIONS TO OBTAIN OR MISS THE FLASH EFFECT

JF Germond



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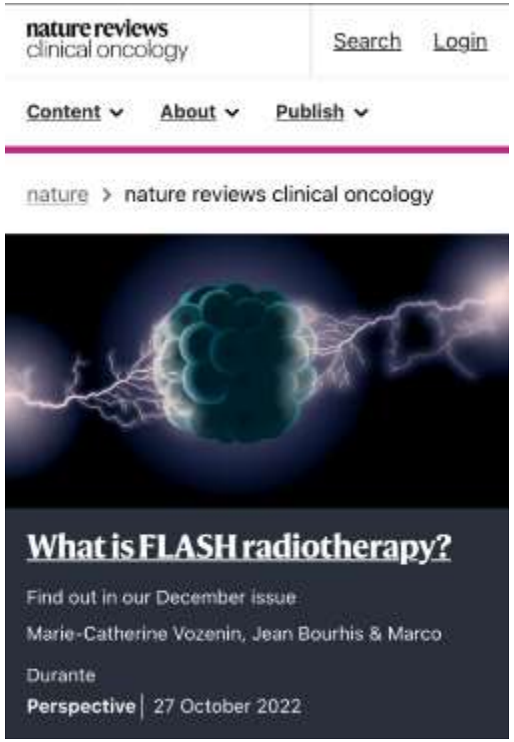
GREAT INTEREST FROM BOTH THE PHYSICS AND MEDICAL COMMUNITY

physicsworld
TOP 10
BREAKTHROUGH
2022



What is FLASH radiotherapy?

Find out in our December issue

Marie-Catherine Vozenin, Jean Bourhis & Marco Durante

Perspective | 27 October 2022

LEADING TO A FLASH- COMMUNITY

FRPT
FLASH RADIOTHERAPY & PARTICLE THERAPY 2022

650+
Participants

40+
Countries

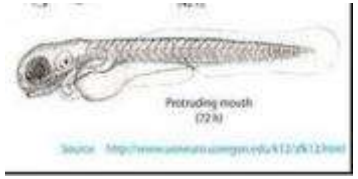
www.FRPT-Conference.org | #FRPT2022

PRECLINICAL EVIDENCE: FEASIBILITY AND MECHANISTIC EVIDENCE

NORMAL TISSUE SPARING: FLASH-RT DOES NOT INDUCE NORMAL TISSUE TOXICITY, WHEN CONV-RT DOES

Electron
Chabi et al. **IJROBP**, in press
Montay-Gruel et al. **Rad Res**, in press
Allen et al. **Rad Res**, in press
Alaghban et al. **Cancers**, in press
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.

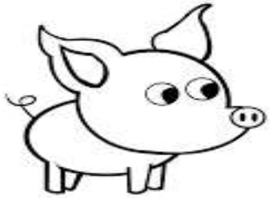
X-ray-synchrotron
Montay-Gruel P et al. **Radiother&Oncol.** 2018.

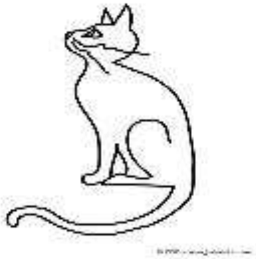


Skin
Gut
Lung
HS
Brain

Electron
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
Zhang et al. **Rad Res,** 2020.
Diffenderfer et al. **IJROBP**, 2020.
Girdhani et al. **Can Res**, 2019, abst.





X -ray synchrotron
Smyth et al. **Sci Rep**, 2018.

Proton
Beyreuther et al. **Radiother Oncol.** 2019.

Electron
Venkatesulu at al. **Sc Rep**, 2019.

AND FLASH-RT IS EQUALLY ABLE TO ERADICATE TUMORS COMPARED TO CONV-RT

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

Vincent Favaudon,[1,2*] Laura Caplier,[1†] 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]

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

Proton
Diffenderfer et al. **IJROBP**, 2020.
Girdhani et al. **Can Res**, 2019, abst.

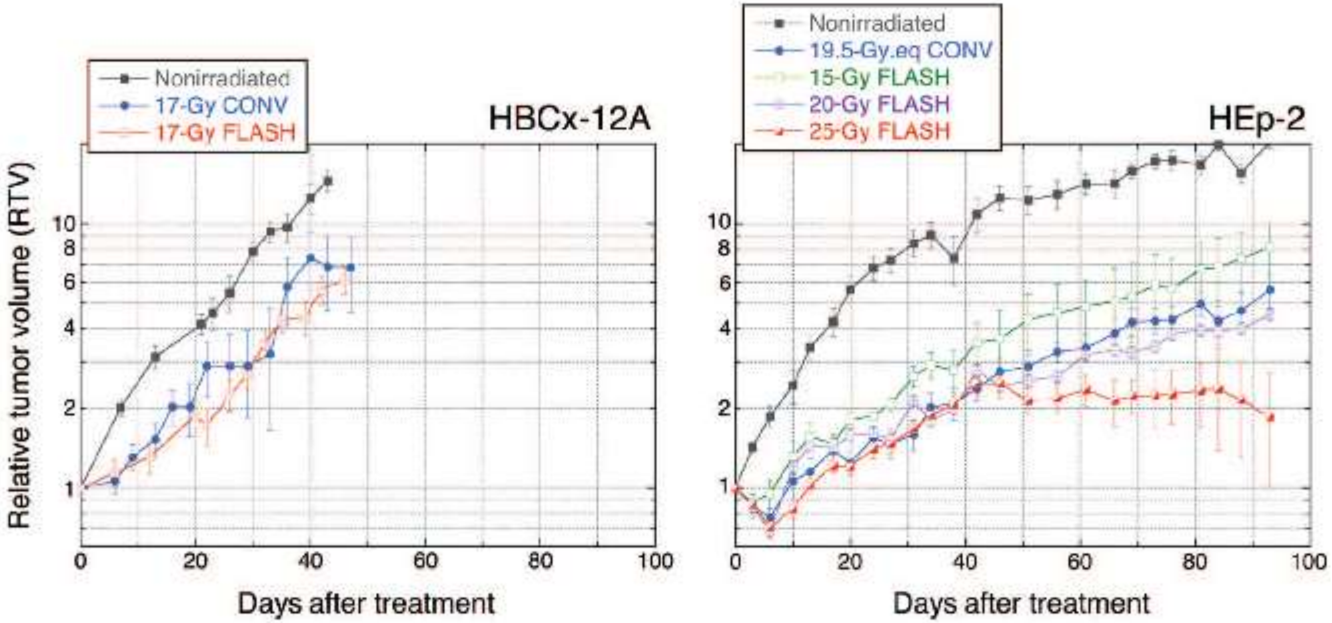
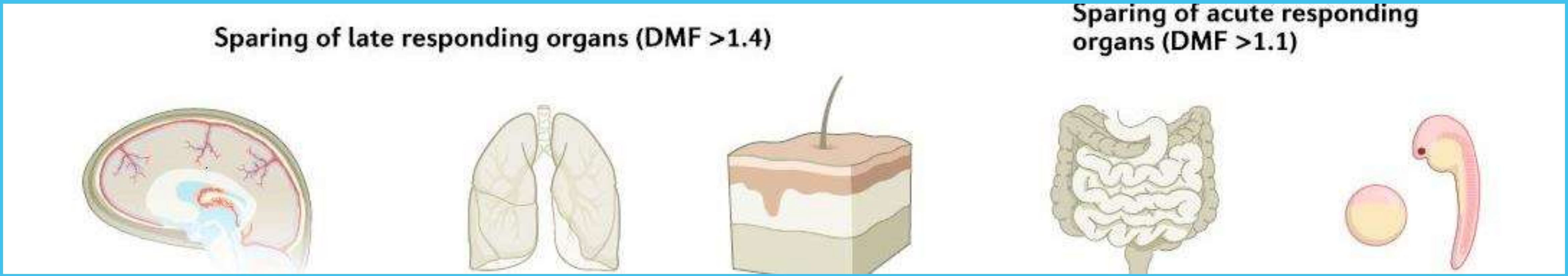


Fig. 3. Evolution of HBCx-12A and HEp-2 tumor xenografts after CONV versus FLASH irradiation.

www.ScienceTranslationalMedicine.org 16 July 2014 Vol 6 Issue 245 245ra93

FLASH PROTECTIVE EFFECT ON NORMAL TISSUES

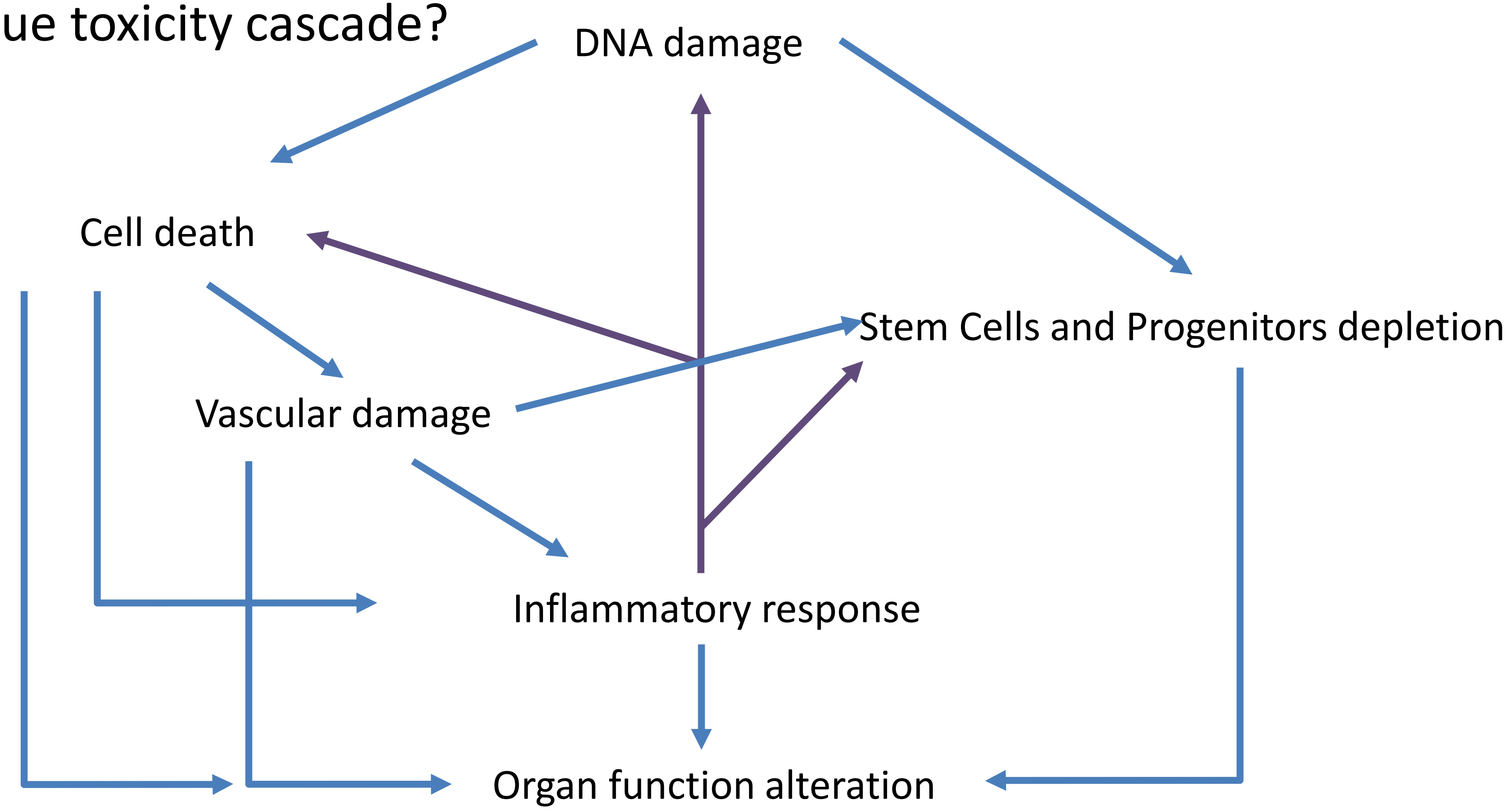


Sparing of late responding organs (DMF >1.4)

Sparing of acute responding organs (DMF >1.1)

Where does FLASH make a difference?

Normal tissue toxicity cascade?



DNA damage

Cell death

Stem Cells and Progenitors depletion

Vascular damage

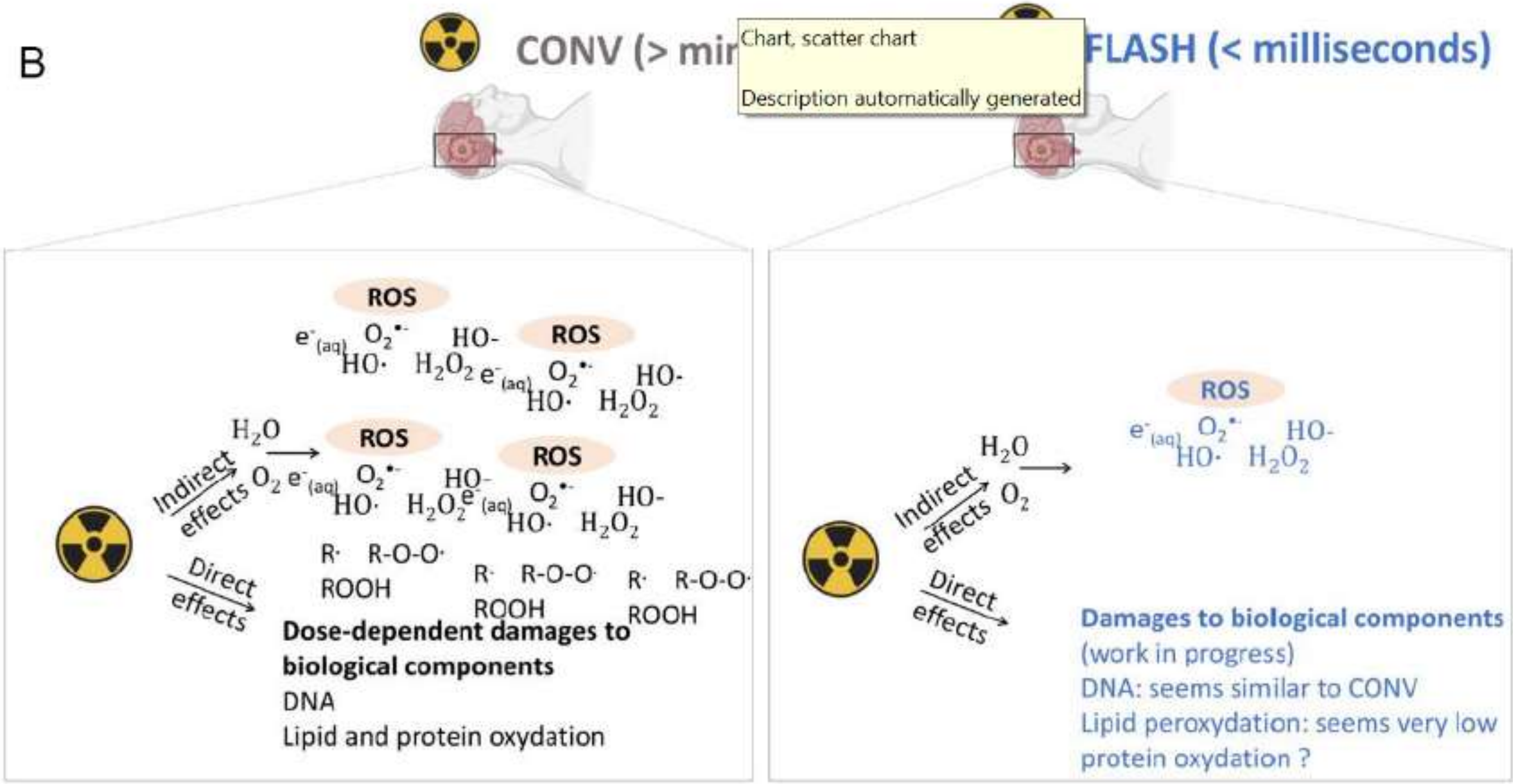
Inflammatory response

Organ function alteration

Pierre Montay-Gruel, PhD

UP TO THE MICROSECOND:
MOLECULAR RESPONSE

-6	-9	-12
10^{-6}	10^{-9}	10^{-12}
micro	nano	pico
μ	n	p



Chart, scatter chart

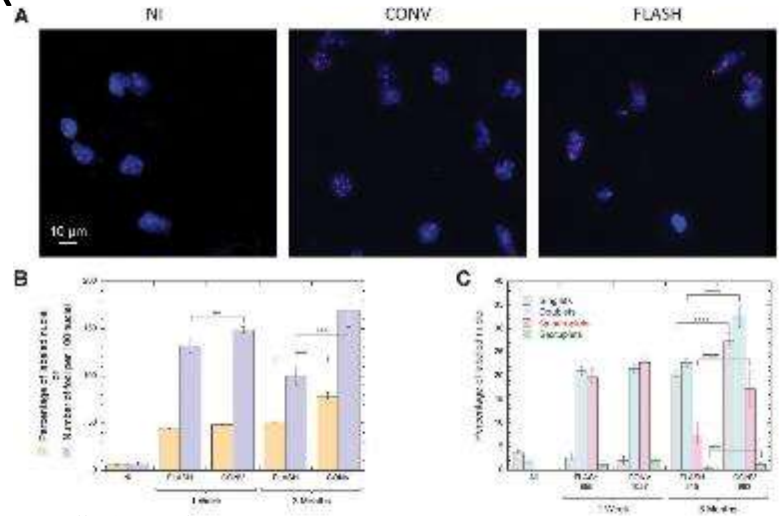
Description automatically generated

Dose-dependent damages to biological components
DNA
Lipid and protein oxydation

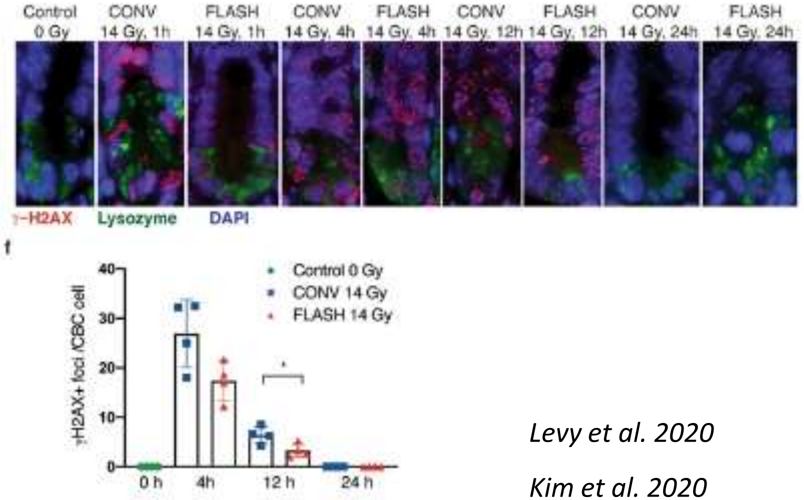
Damages to biological components
(work in progress)
DNA: seems similar to CONV
Lipid peroxydation: seems very low
protein oxydation ?

Less DNA damage *BUT NOT THE MOST SIGNIFICANT EVENT*

γH2AX



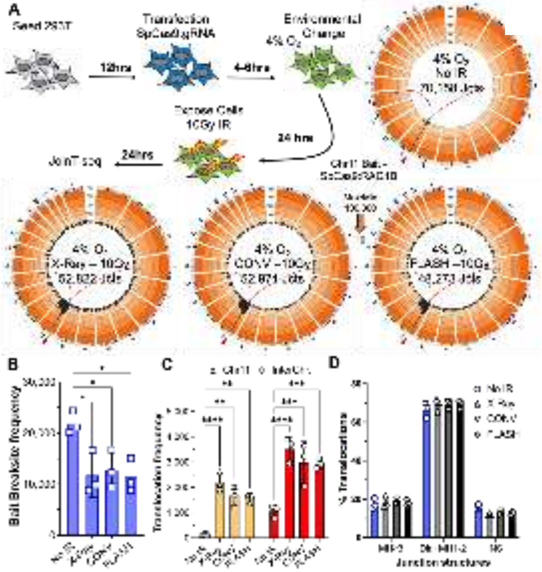
Fouillade et al. 2020



Levy et al. 2020

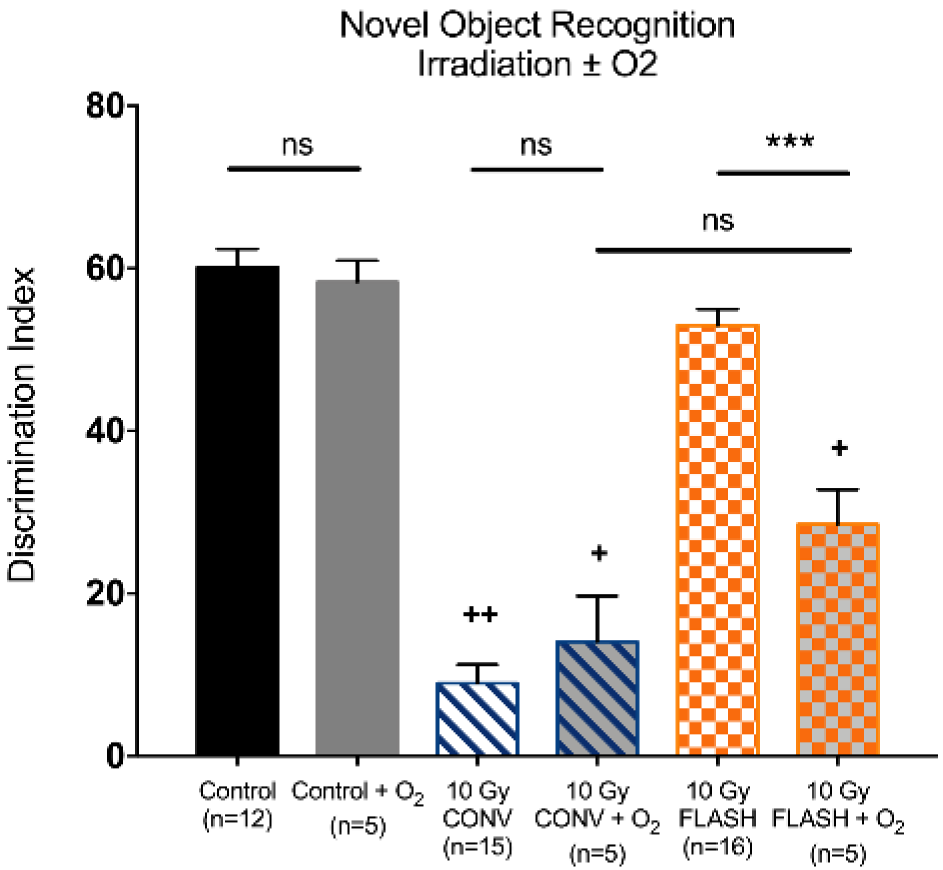
Kim et al. 2020

NO!



Barghouth et al., RO, 2023

DOUBLING BRAIN PO2 REVERSES FLASH EFFECT



J Ollivier **B Petit** **P Montay-Gruel**

Montay-Gruel et al. 2019

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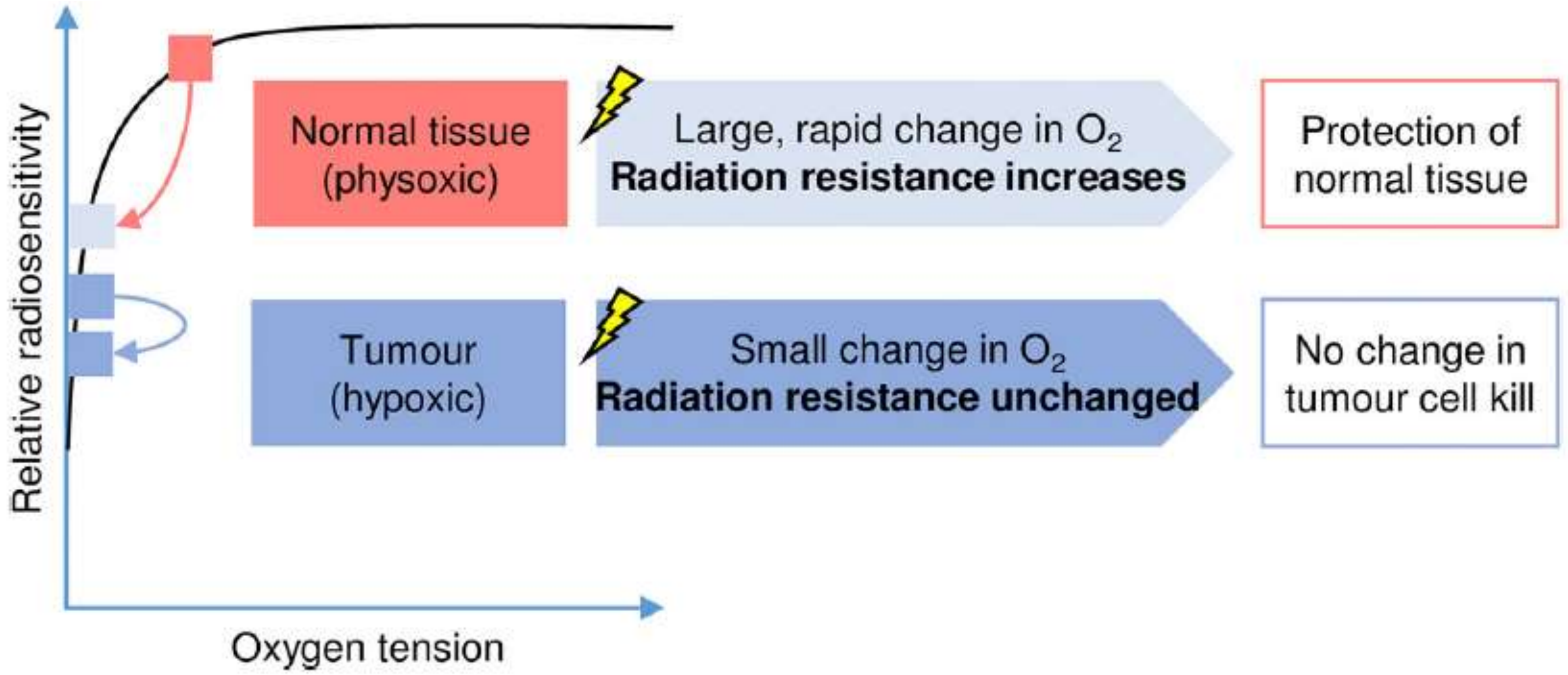
HYPOTHESIS THAT THE PRIMARY MECHANISM IS OXYGEN DEPLETION

Radiolytic oxygen depletion?



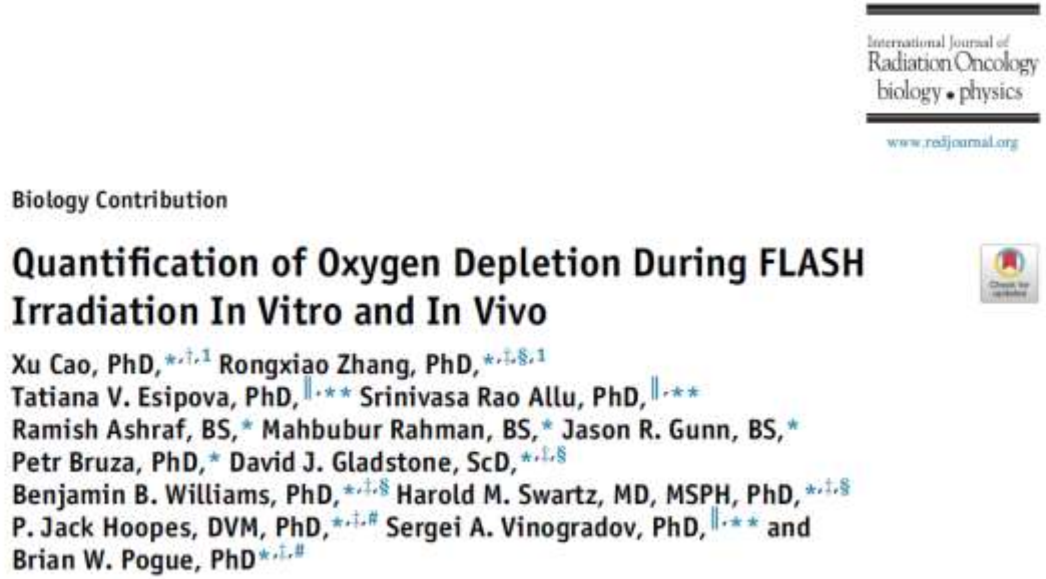
Normal tissue (physoxic) → Large, rapid change in O_2 **Radiation resistance increases** → Protection of normal tissue

Tumour (hypoxic) → Small change in O_2 **Radiation resistance unchanged** → No change in tumour cell kill

Normal tissue becomes hypoxic -> more radioresistant

Wilson et al., Front in Oncol, 2020

MEASUREMENTS DO NOT SUPPORT ANY RADIOLYTIC OXYGEN DEPLETION AT 10 GY FLASH



International Journal of
Radiation Oncology
biology • physics

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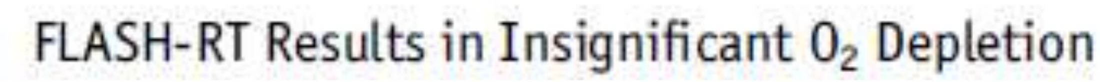
Biology Contribution

Quantification of Oxygen Depletion During FLASH Irradiation In Vitro and In Vivo

Xu Cao, PhD,[*,†,1] Rongxiao Zhang, PhD,[*,‡,§,1]
Tatiana V. Esipova, PhD,[‖,**] Srinivasa Rao Allu, PhD,[‖,**]
Ramish Ashraf, BS,[*] Mahbubur Rahman, BS,[*] Jason R. Gunn, BS,[*]
Petr Bruza, PhD,[*] David J. Gladstone, ScD,[*,‡,§]
Benjamin B. Williams, PhD,[*,‡,§] Harold M. Swartz, MD, MSPH, PhD,[*,‡,§]
P. Jack Hoopes, DVM, PhD,[*,‡,#] Sergei A. Vinogradov, PhD,[‖,**] and
Brian W. Pogue, PhD[*,‡,#]



FLASH-RT Results in Insignificant O_2 Depletion

Does FLASH deplete oxygen? Experimental evaluation for photons, protons, and carbon ions

Jeannette Jansen and Jan Knoll
Division of Biomedical Physics in Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany
Faculty of Physics and Astronomy, Ruprecht-Karls-University, Heidelberg, Germany

Elke Beyreuther
OncoRay–National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden–Rossendorf, Dresden, Germany
Helmholtz-Zentrum Dresden–Rossendorf (HZDR), Institute of Radiation Physics, Dresden, Germany

Jörg Pawelke
OncoRay–National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden–Rossendorf, Dresden, Germany
Helmholtz-Zentrum Dresden–Rossendorf (HZDR), Institute of Radiooncology-OncoRay, Dresden, Germany

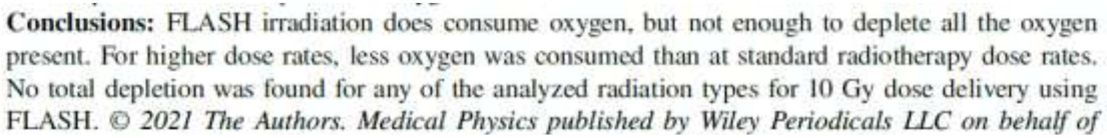
Raphael Skuza and Rachel Hanley
Division of Biomedical Physics in Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany
Faculty of Physics and Astronomy, Ruprecht-Karls-University, Heidelberg, Germany

Stephan Brons
Heidelberg Ion-Beam Therapy Center (HIT), Heidelberg, Germany

Francesca Pagliari
Division of Biomedical Physics in Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany

Joao Seco[a)]
Division of Biomedical Physics in Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany
Faculty of Physics and Astronomy, Ruprecht-Karls-University, Heidelberg, Germany

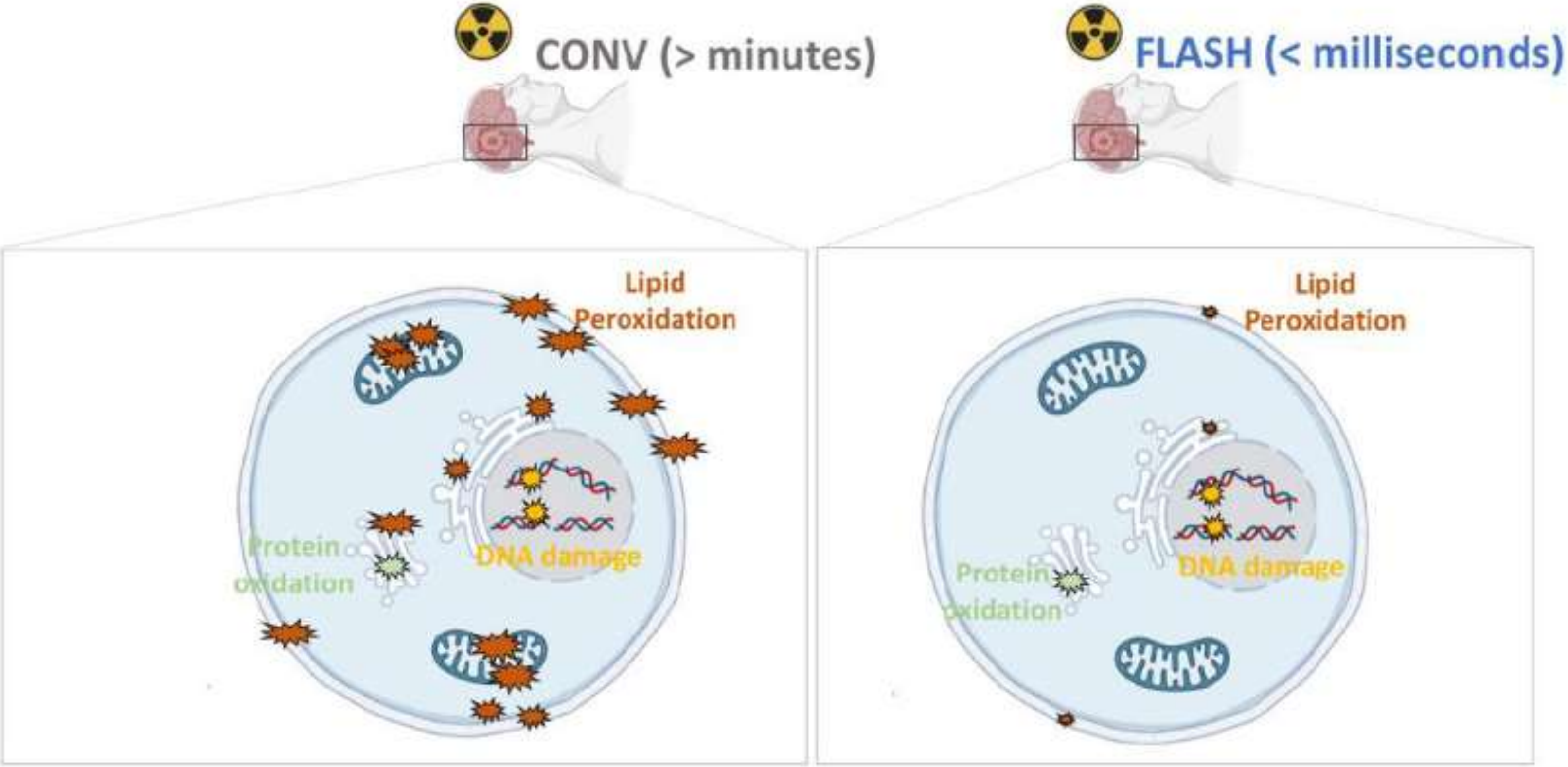
(Received 20 December 2020; revised 1 March 2021; accepted for publication 6 April 2021; published 27 May 2021)



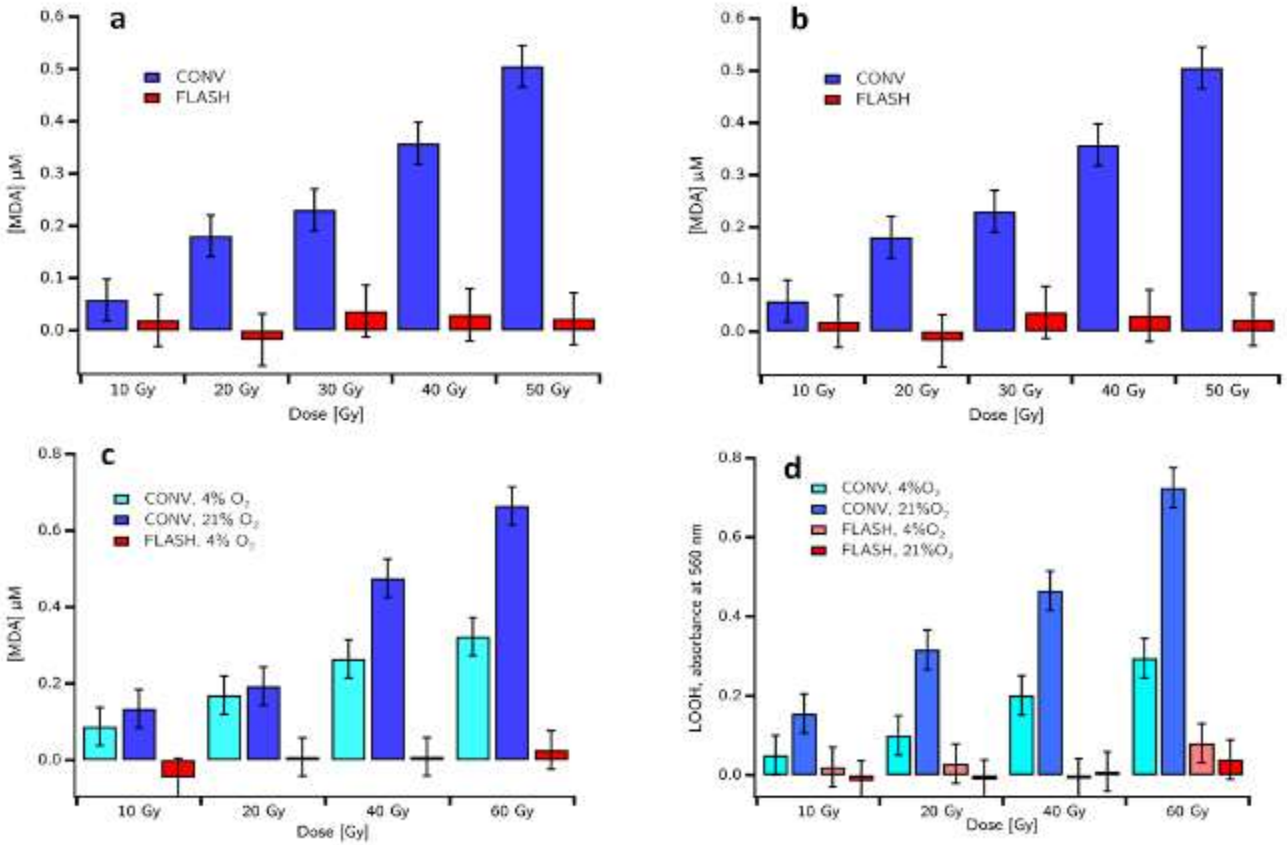
Conclusions: FLASH irradiation does consume oxygen, but not enough to deplete all the oxygen present. For higher dose rates, less oxygen was consumed than at standard radiotherapy dose rates. No total depletion was found for any of the analyzed radiation types for 10 Gy dose delivery using FLASH. © *2021 The Authors. Medical Physics published by Wiley Periodicals LLC on behalf of*

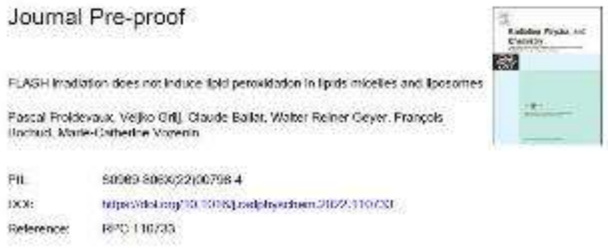
FROM MILLISECOND TO MINUTES:
CELLULAR RESPONSE

1	0	-1	-2	-3
10^1	$10^0=1$	10^{-1}	10^{-2}	10^{-3}
deca	BASE	deci	centi	mili
da		d	c	m



FLASH AND CONV-RT EFFECTS ON LIPID PEROXYDATION




Journal Pre-proof

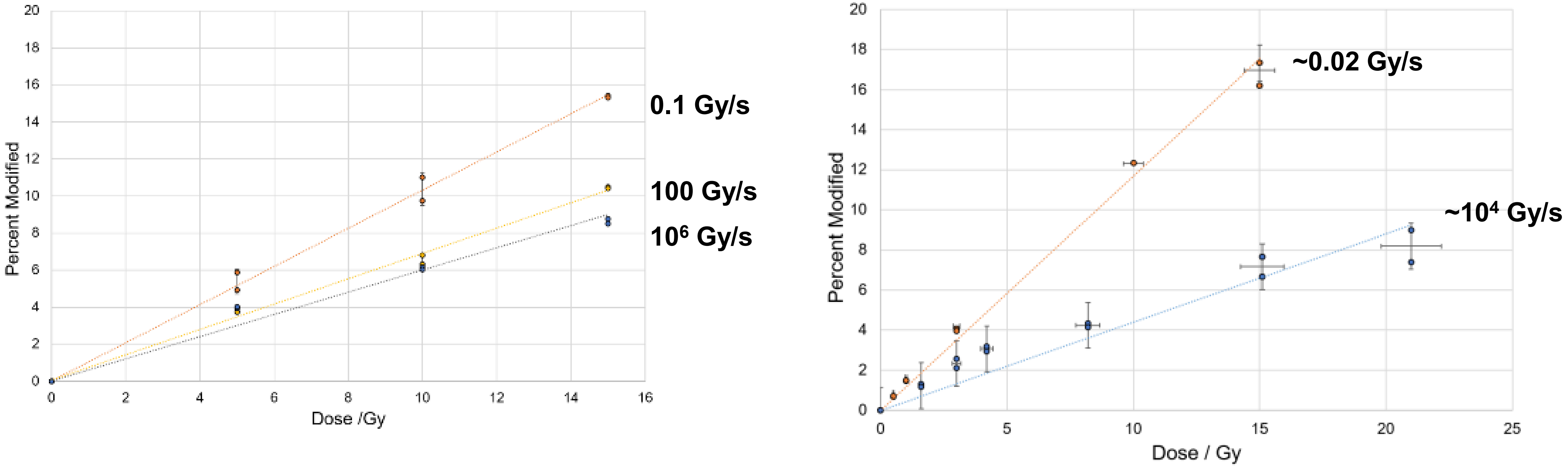
FLASH irradiation does not induce lipid peroxidation in lipids micelles and liposomes

Pascal Froidevaux, Veljko Grilj, Claude Bailat, Walter Reiner Geyer, François Bochud, Marie-Catherine Vozenin

PII: S0969-806X(22)00798-4
DOI: https://doi.org/10.1016/j.radphyschem.2022.110733
Reference: RPC 110733

FLASH AND CONV-RT EFFECTS ON PROTEIN PEROXYDATION

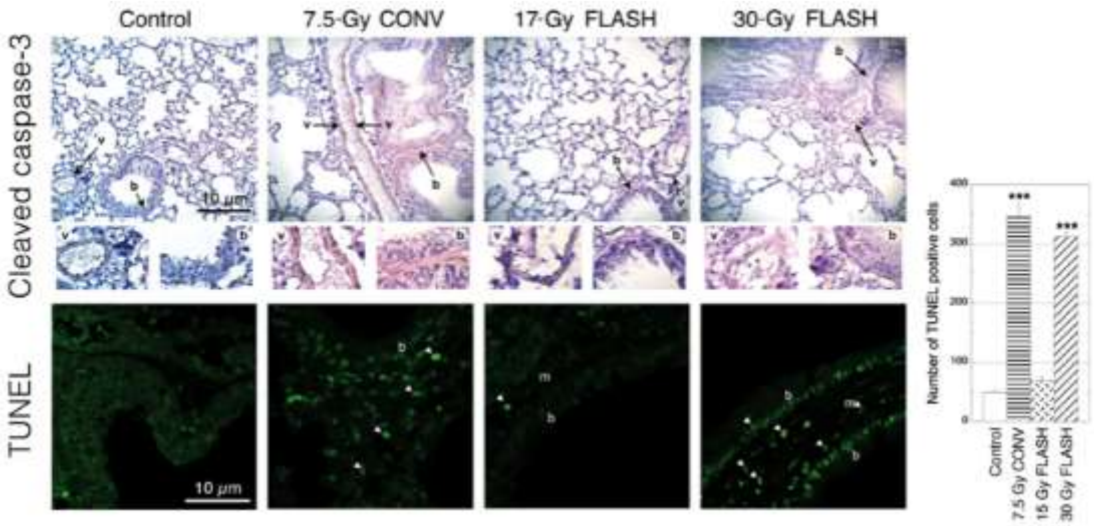
FKRIVQRIKDFLR peptide



Gupta et al, submitted

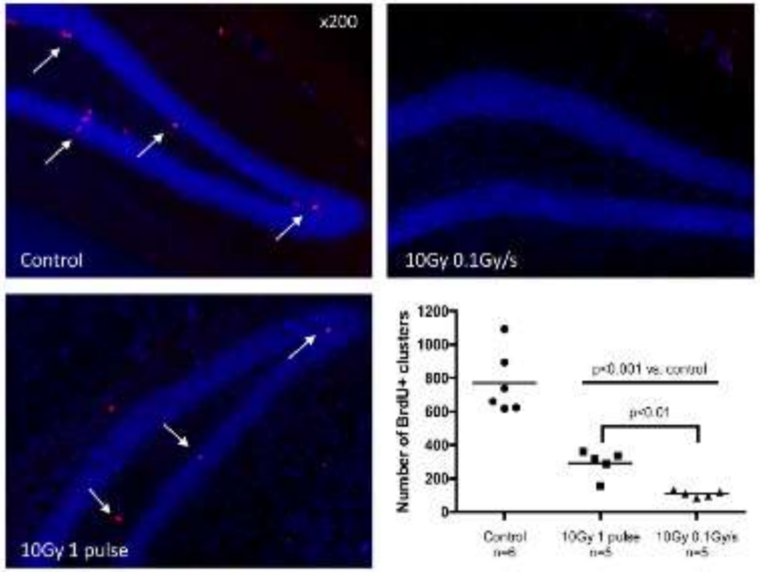
Less cell death

Less Apoptosis



in the lung	*Favaudon et al. 2014* *Fouillade et al. 2020*
in the gut	*Levy et al. 2020*
in microvessels of the brain	*Allen et al. 2020*

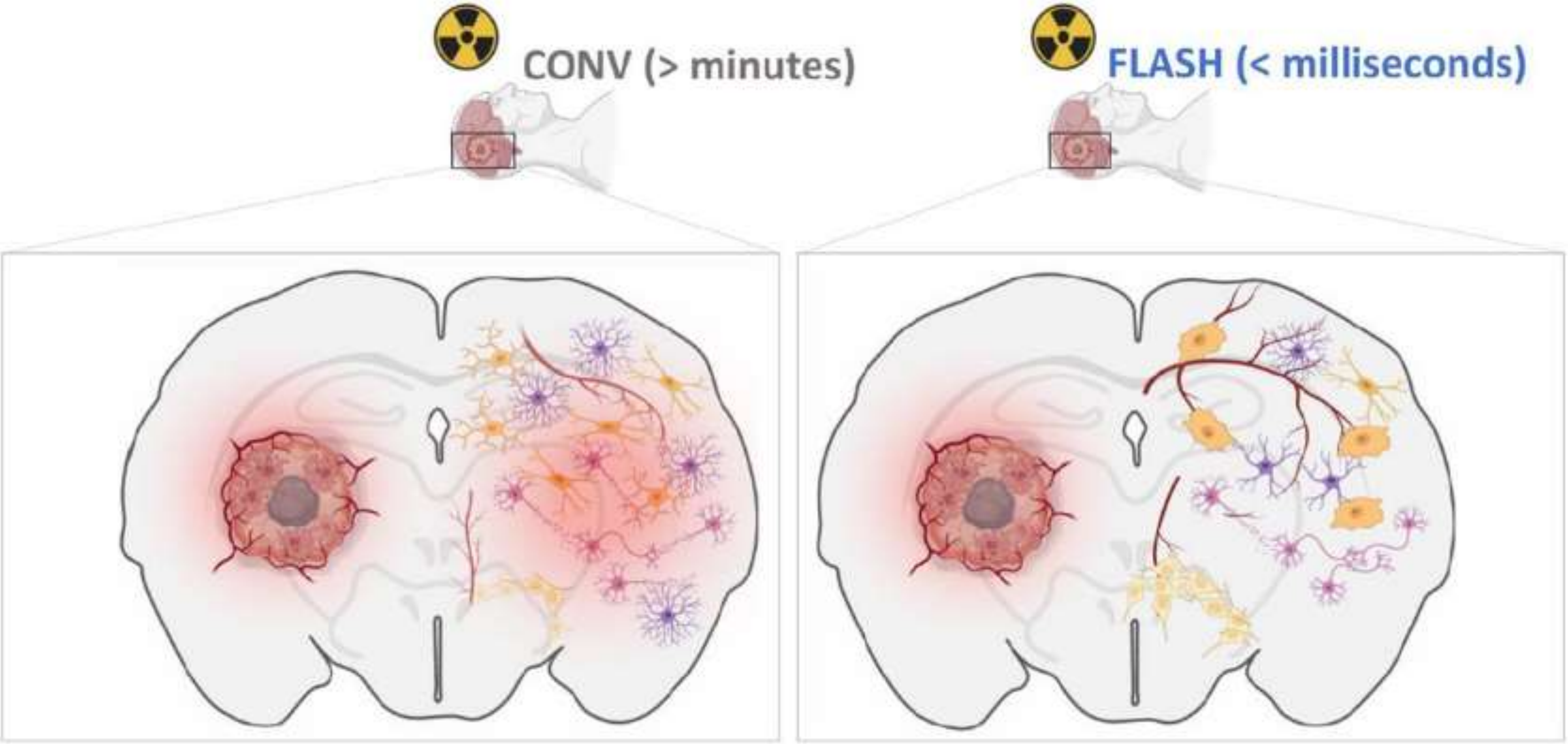
Preservation of progenitors and stem cells



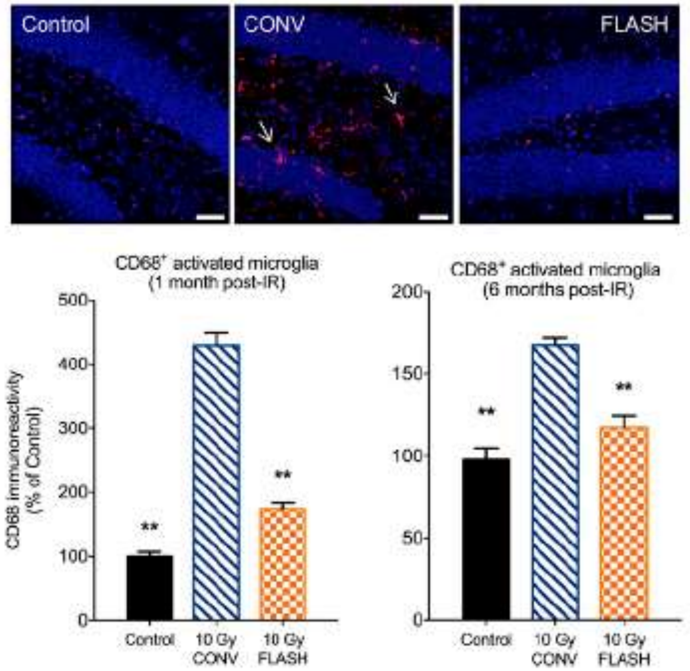
in the brain	*Montay-Gruel et al. 2017* *Montay-Gruel et al. 2018, xRay-FLASH*
in the gut	*Levy et al. 2017* *Diffenderfer et al. 2020. pFLASH:*
in the lung	*Fouillade et al. 2020*
in the hematopoietic system	*Chabi et al. 2020*

FROM MINUTES TO YEARS:
CELL AND TISSUE RESPONSE

12	9	6	3	2
10^{12}	10^{9}	10^{6}	10^{3}	10^{2}
tera	giga	mega	kilo	hecto
T	G	M	k	h

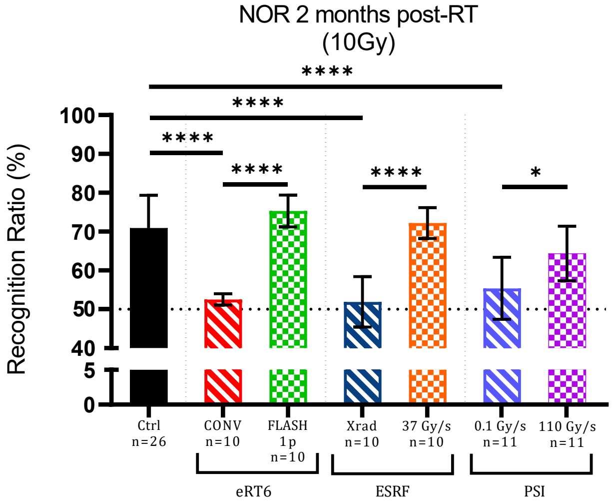


Less inflammation

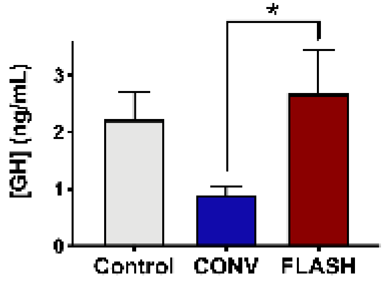


in the brain	*Montay-Gruel et al. 2019* *Montay-Gruel et al. 2020* *Simmons et al. 2019*
in the lung	*Favaudon et al. 2014*
in the skin	*Velalopoulou et al. 2021, pFLASH* *Cunningham et al. 2021, pFLASH*

Preservation of organ function



Montay-Gruel et al. 2017
Montay-Gruel et al. 2018
Montay-Gruel et al. 2019
Simmons et al. 2019
Alaghband et al. 2020
Allen et al, 2022
Alaghband et al., 2023
Limoli et al. 2023
Almeida et al., 2023



Pediatric
model

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LESS VASCULAR DAMAGE

FLASH-RT does not induce astrogliosis and reduces DAMPs production

FLASH-RT does not induce vessel damages in the brain

FLASH-RT does not induce neurocognitive damages in juvenile mice

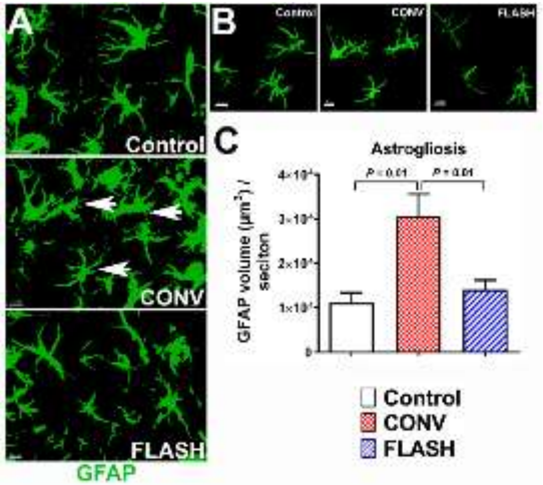

C Limoli


M Acharya

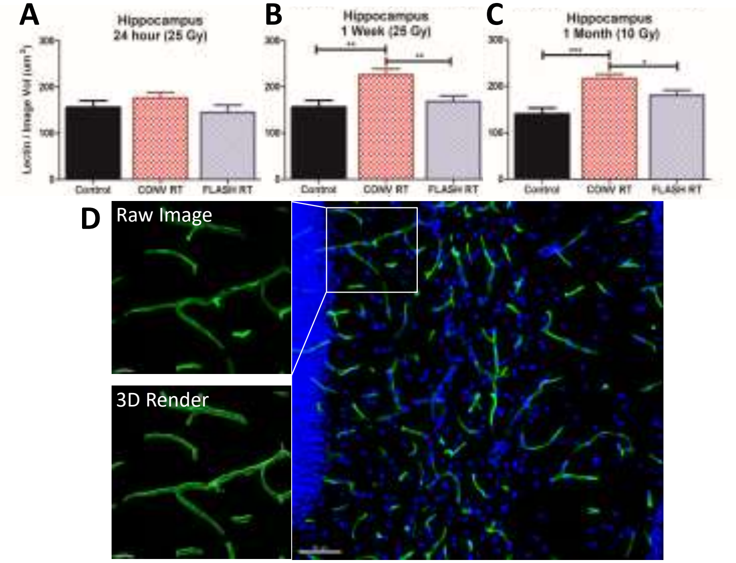

J Baulch


B Allen

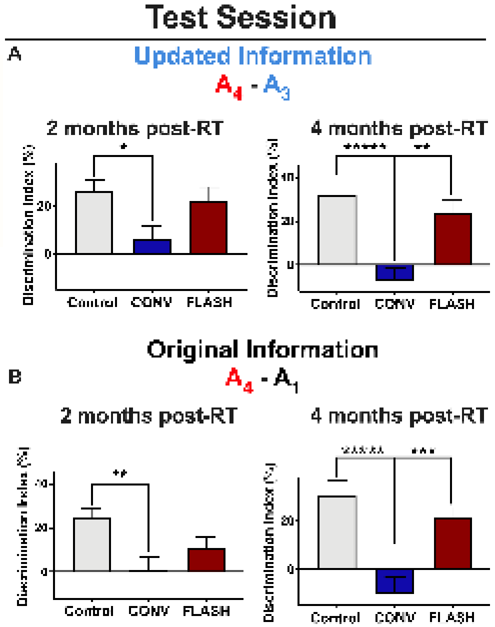

Y Alaghband

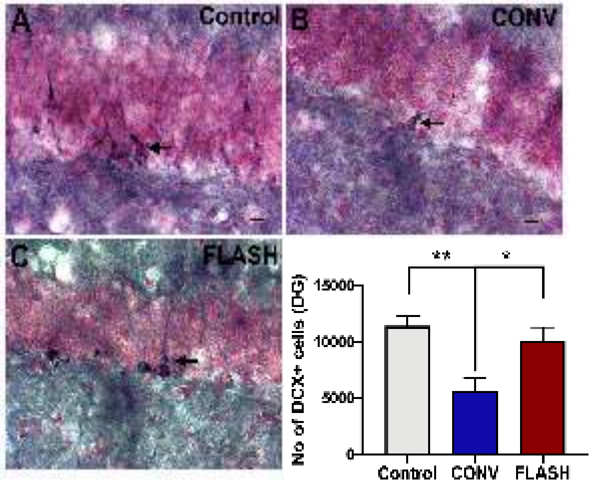


Montay-Gruel et al, Rad Res, 2020



Allen et al, Rad Res, 2020





Alaghband et al, Cancers, 2020

Table 1: Irradiation parameters

Single doses WBRT (Fig. 1, 3)		Beam parameters				
Mode	Prescribed Dose (Gy)	Frequency (Hz)	SSD (mm)	Pulse width (µs)	Number of pulses	Treatment time (s)
CONV	10	10	800	1.0	1170-1180	116.9-117.9
FLASH	10	100	369-370	1.8	1	$1.8 \cdot 10^{-6}$

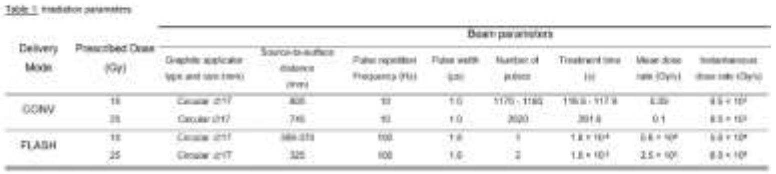
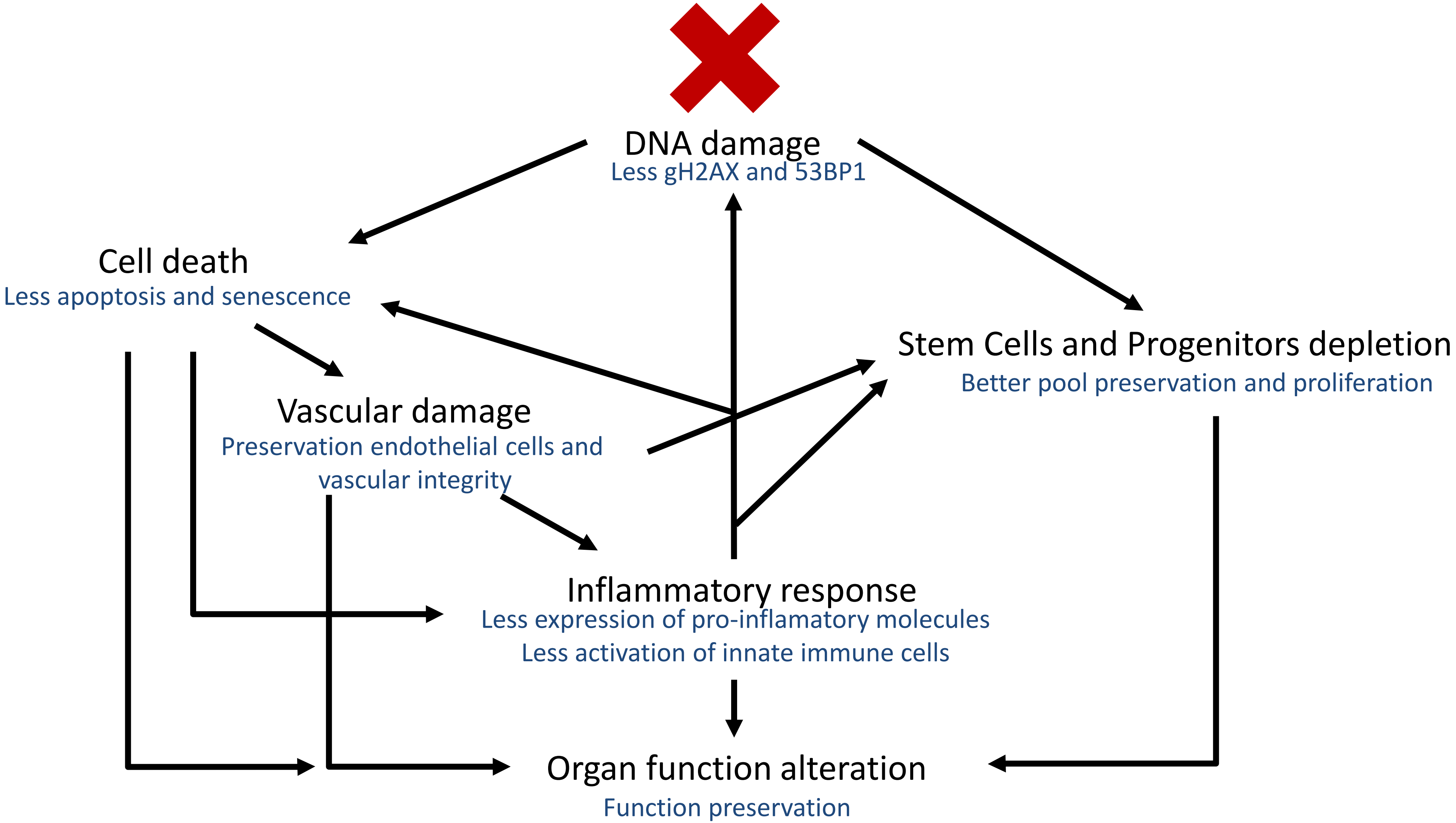


Table 1: Irradiation parameters

Delivery Mode	Prescribed Dose (Gy)	Beam parameters							
		Graphite applicator type and size (mm)	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	10	Circular ∅17	800	10	1.0	1170 - 1180	116.9 - 117.9	[illegible]	[illegible]
	25	Circular ∅17	746	10	1.0	2020	201.8	0.1	[illegible]
FLASH	10	Circular ∅17	369-370	100	1.8	1	[illegible]	[illegible]	[illegible]
	25	Circular ∅17	325	100	1.8	2	[illegible]	[illegible]	[illegible]

Table 1: Irradiation parameters.

Delivery Mode	Prescribed Dose (Gy)	Beam parameters							
		Graphite applicator type and size (mm)	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	8	Semicircular ∅17	798	10	1.0	1033	103.2	0.08	7.7×10^{3}
FLASH	8	Semicircular ∅17	383	100	1.8	1	1.8×10^{-6}	4.4×10^{6}	4.4×10^{6}



DNA damage
Less gH2AX and 53BP1

Cell death
Less apoptosis and senescence

Stem Cells and Progenitors depletion
Better pool preservation and proliferation

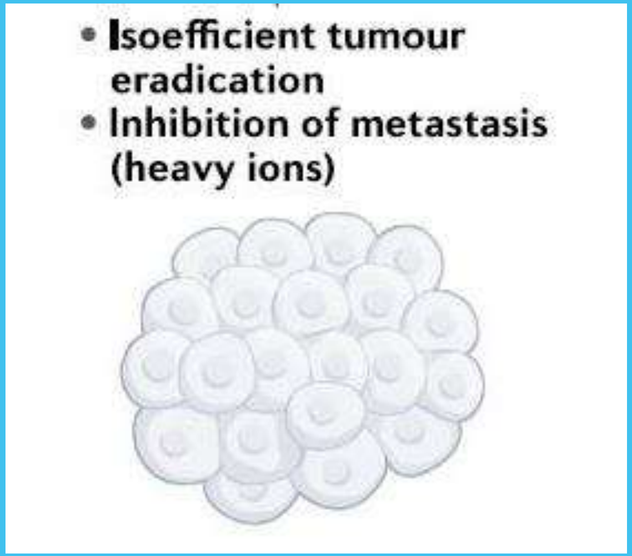
Vascular damage
Preservation endothelial cells and vascular integrity

Inflammatory response
Less expression of pro-inflamatory molecules
Less activation of innate immune cells

Organ function alteration
Function preservation

Pierre Montay-Gruel, PhD

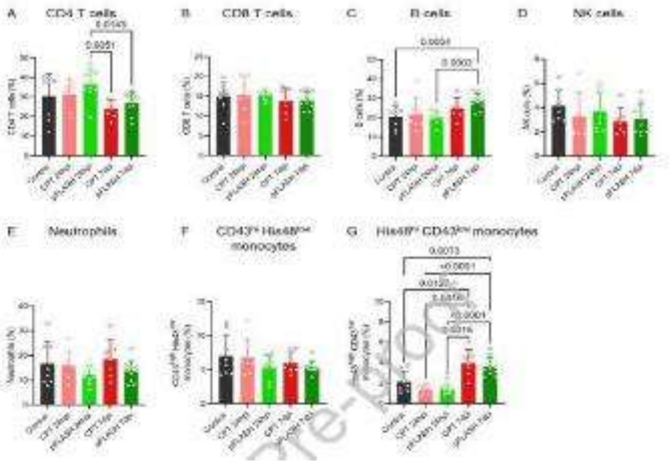
FLASH EFFECT ON KILLING TUMORS



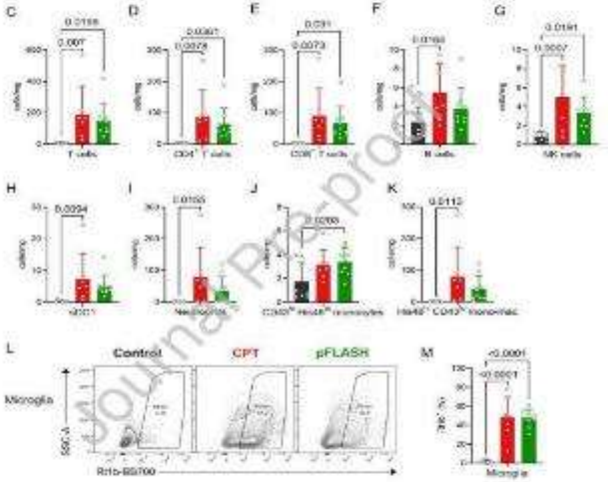
- Isoefficient tumour eradication
- Inhibition of metastasis (heavy ions)

HYPOTHESIS OF BETTER ANTI-TUMOR IMMUNITY

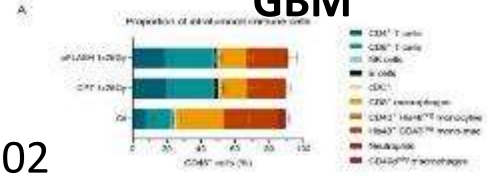
Circulating cells



Normal brain

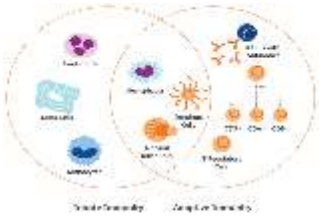


GBM

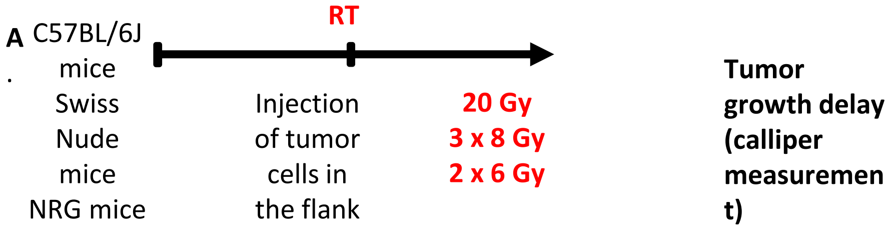


25 Gy
pFLASH: 257 ± 2 Gy/s
pConventional: 4 ± 0.02 Gy/s)

Itturi et al, IJROBP, 2022



HYPOTHESIS OF BETTER ANTI-TUMOR IMMUNITY: NOT VALIDATED



A. C57BL/6J mice
Swiss Nude mice
NRG mice

RT

Injection of tumor cells in the flank

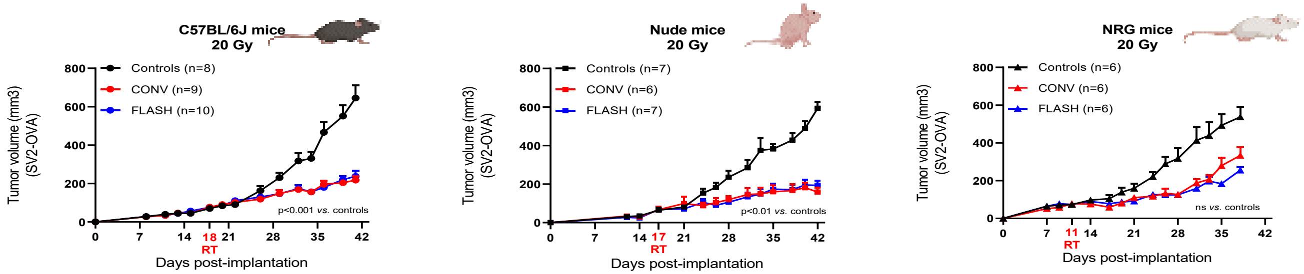
20 Gy
3 x 8 Gy
2 x 6 Gy

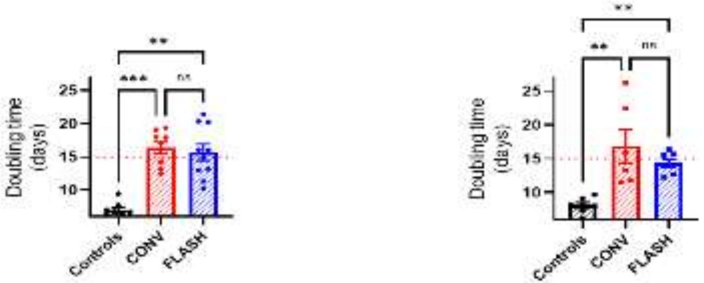
Tumor growth delay (calliper measurement)

20 Gy
eFLASH: 1 pulse
eConventional: 0.1 Gy/s

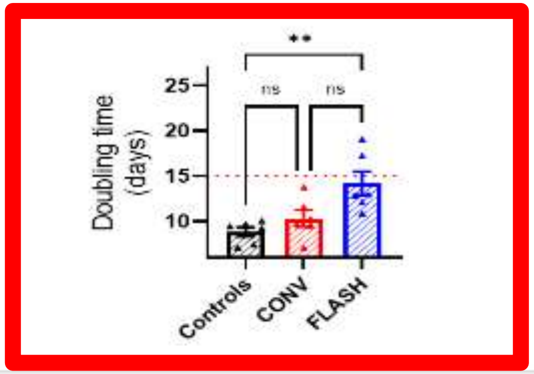
B.

C.





But works in highly immunocompromised mice



Almeida et al, IJROBP, 2023

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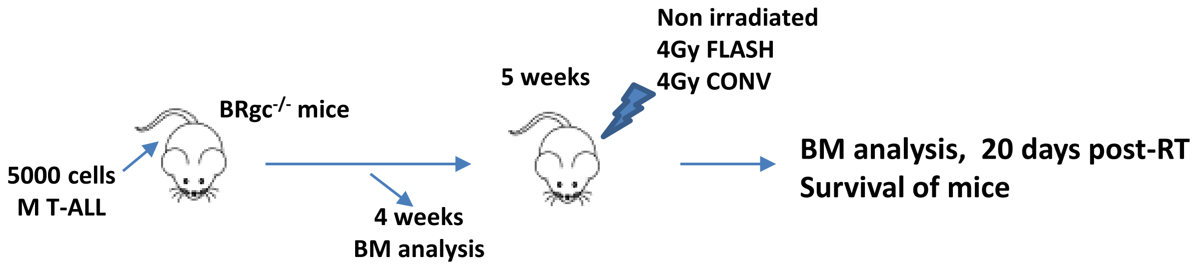
ALL TUMORS ARE NOT EQUALLY SENSITIVE TO FLASH-RT

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


F Pflumio


B Uzan


5000 cells
M T-ALL

BRgc$^{-/-}$ mice

4 weeks
BM analysis

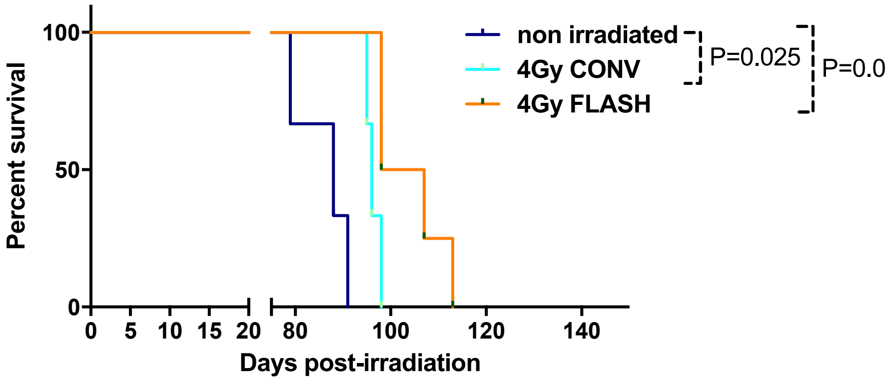
5 weeks

Non irradiated
4Gy FLASH
4Gy CONV

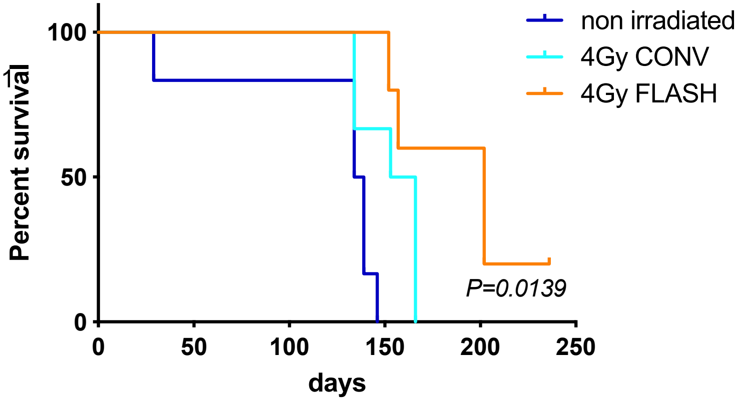
BM analysis, 20 days post-RT
Survival of mice

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

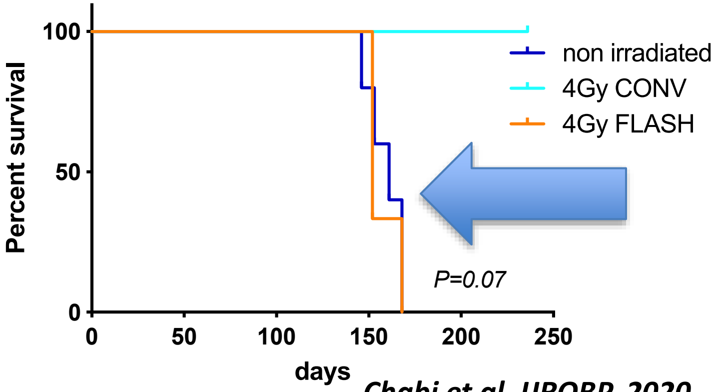
M106 PDX/T-ALL



M114 PDX/T-ALL



M108 PDX/T-ALL



Chabi et al, IJROBP, 2020

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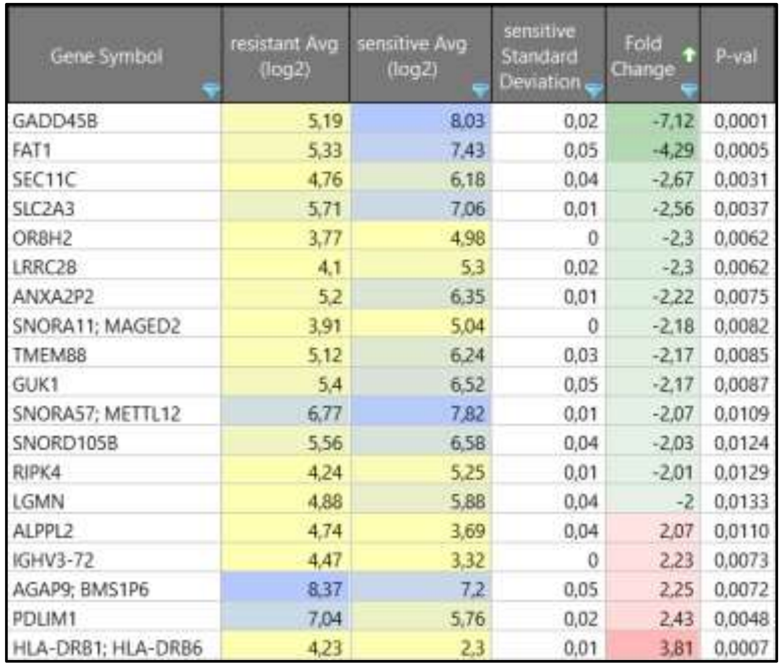
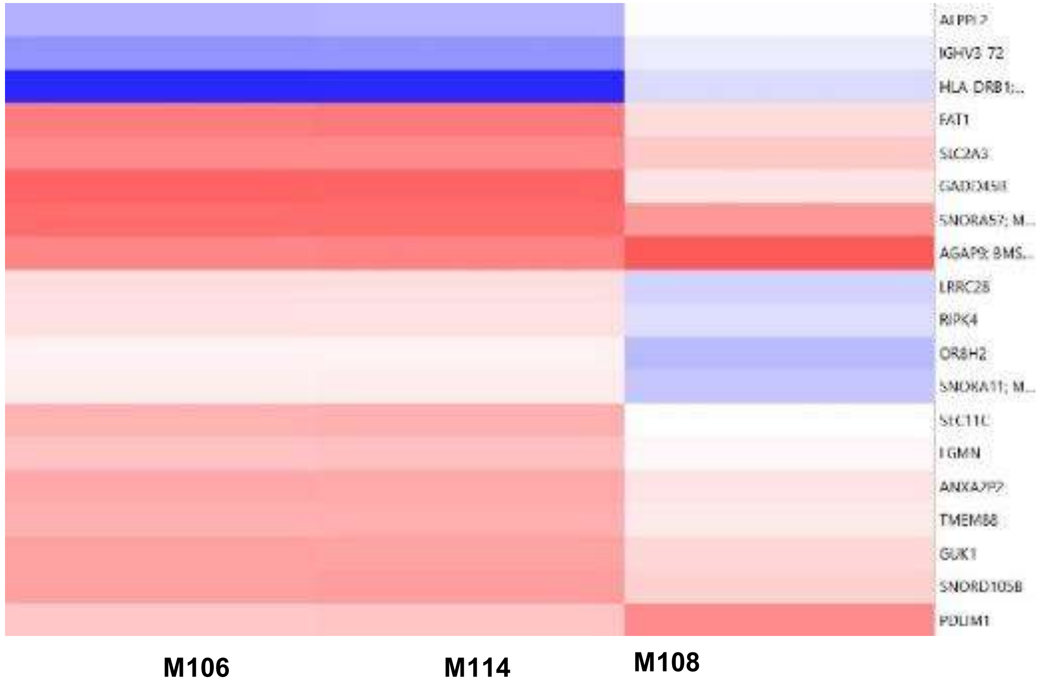
BIOMARKERS OF FLASH RADIOSENSITIVITY (TUMORS)

Inhibitor of cdc2/cyclinB1 kinase → GADD45B

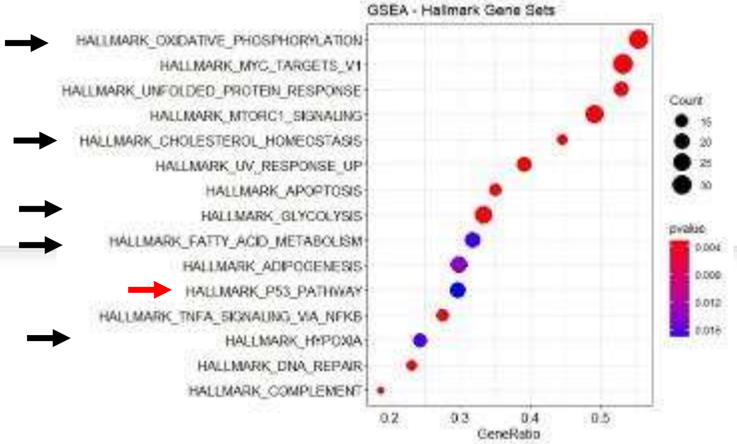
Wt pathway → FAT1, TMEM88



Gene Symbol	resistant Avg (log2)	sensitive Avg (log2)	sensitive Standard Deviation	Fold Change	P-val
GADD45B	5,19	8,03	0,02	-7,12	0,0001
FAT1	5,33	7,43	0,05	-4,29	0,0005
SEC11C	4,76	6,18	0,04	-2,67	0,0031
SLC2A3	5,71	7,06	0,01	-2,56	0,0037
OR8H2	3,77	4,98	0	-2,3	0,0062
LRRC28	4,1	5,3	0,02	-2,3	0,0062
ANXA2P2	5,2	6,35	0,01	-2,22	0,0075
SNORA11; MAGED2	3,91	5,04	0	-2,18	0,0082
TMEM88	5,12	6,24	0,03	-2,17	0,0085
GUK1	5,4	6,52	0,05	-2,17	0,0087
SNORA57; METTL12	6,77	7,82	0,01	-2,07	0,0109
SNORD105B	5,56	6,58	0,04	-2,03	0,0124
RIPK4	4,24	5,25	0,01	-2,01	0,0129
LGMN	4,88	5,88	0,04	-2	0,0133
ALPPL2	4,74	3,69	0,04	2,07	0,0110
IGHV3-72	4,47	3,32	0	2,23	0,0073
AGAP9; BMS1P6	8,37	7,2	0,05	2,25	0,0072
PDLIM1	7,04	5,76	0,02	2,43	0,0048
HLA-DRB1; HLA-DRB6	4,23	2,3	0,01	3,81	0,0007



Metabolic pathways



P53 pathway

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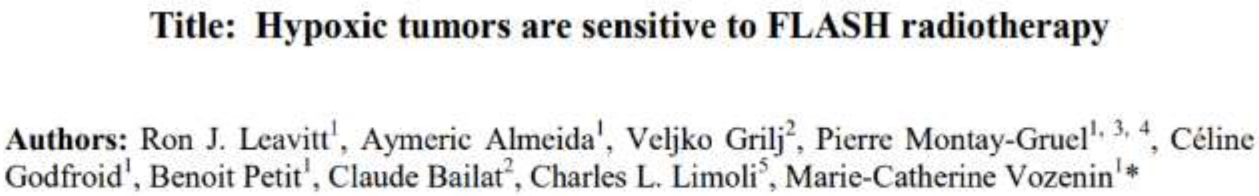
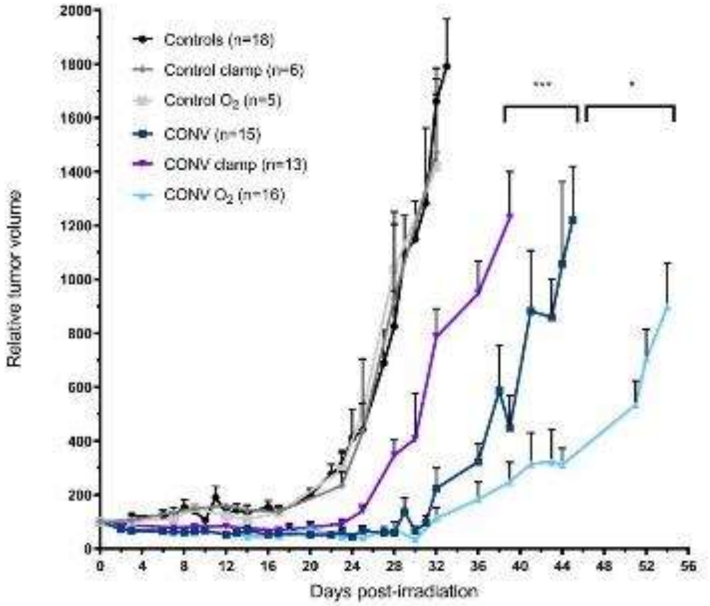
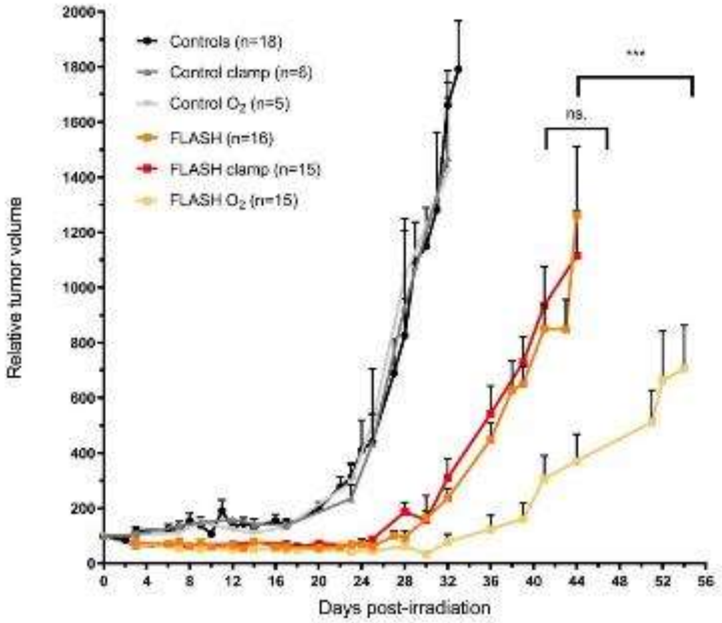
HYPOXIC TUMORS ARE SENSITIVE TO FLASH RT



Title: Hypoxic tumors are sensitive to FLASH radiotherapy

Authors: Ron J. Leavitt[1], Aymeric Almeida[1], Veljko Grilj[2], Pierre Montay-Gruel[1, 3, 4], Céline Godfroid[1], Benoit Petit[1], Claude Bailat[2], Charles L. Limoli[5], Marie-Catherine Vozenin[1]*



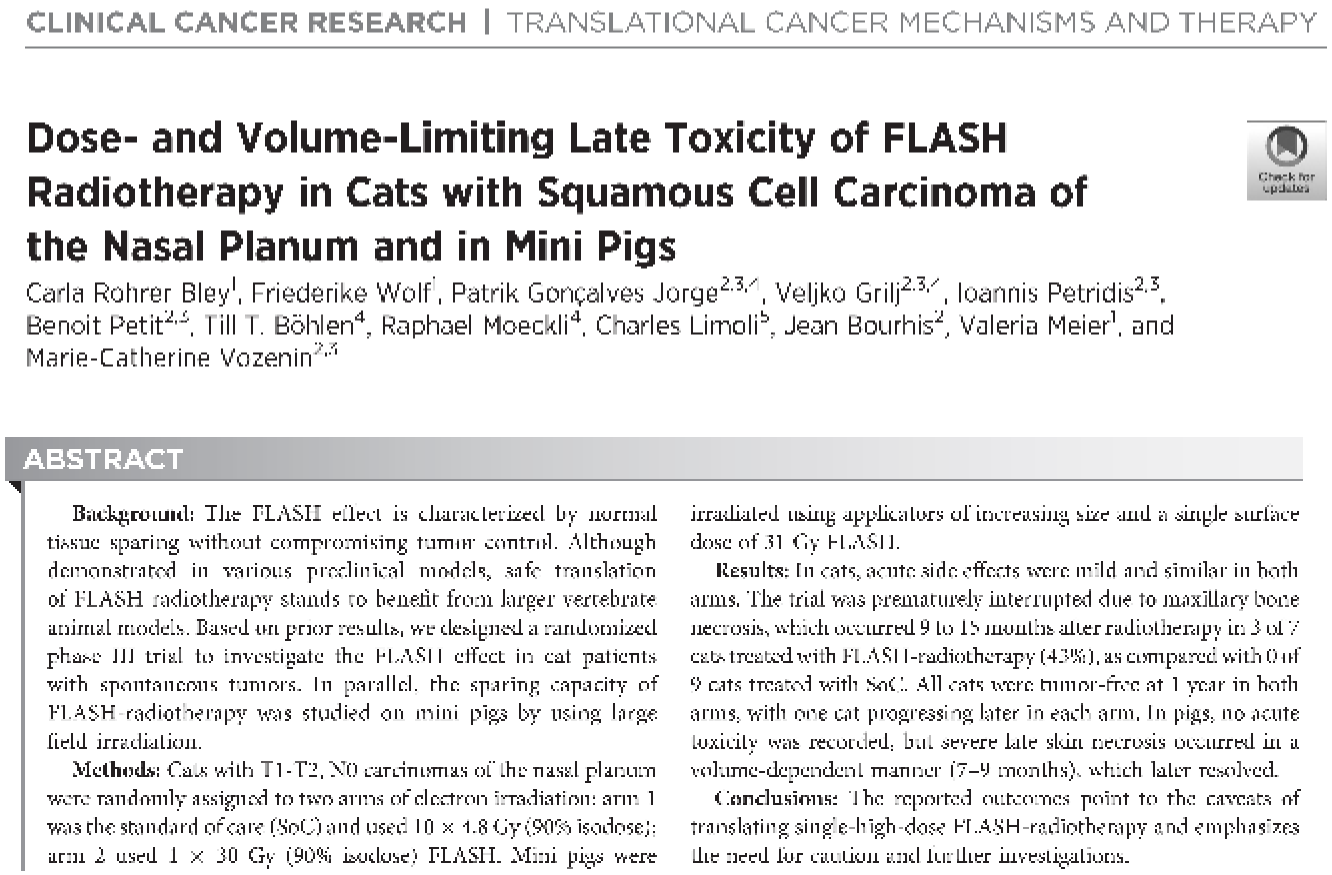


Leavitt et al., 2023, BioRxiv

CLINICAL EVIDENCE

FIRST PHASE III STUDY IN CAT PATIENTS


C Rohrer



CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

Dose- and Volume-Limiting Late Toxicity of FLASH Radiotherapy in Cats with Squamous Cell Carcinoma of the Nasal Planum and in Mini Pigs

Carla Rohrer Bley[1], Friederike Wolf[1], Patrik Gonçalves Jorge[2,3,4], Veljko Grilj[2,3,4], Ioannis Petridis[2,3], Benoit Petit[2,3], Till T. Böhlen[4], Raphael Moeckli[4], Charles Limoli[5], Jean Bourhis[2], Valeria Meier[1], and Marie-Catherine Vozenin[2,3]

ABSTRACT

Background: The FLASH effect is characterized by normal tissue sparing without compromising tumor control. Although demonstrated in various preclinical models, safe translation of FLASH radiotherapy stands to benefit from larger vertebrate animal models. Based on prior results, we designed a randomized phase III trial to investigate the FLASH effect in cat patients with spontaneous tumors. In parallel, the sparing capacity of FLASH-radiotherapy was studied on mini pigs by using large field irradiation.

Methods: Cats with T1-T2, N0 carcinomas of the nasal planum were randomly assigned to two arms of electron irradiation: arm 1 was the standard of care (SoC) and used 10 × 4.8 Gy (90% isodose); arm 2 used 1 × 30 Gy (90% isodose) FLASH. Mini pigs were irradiated using applicators of increasing size and a single surface dose of 31 Gy FLASH.

Results: In cats, acute side effects were mild and similar in both arms. The trial was prematurely interrupted due to maxillary bone necrosis, which occurred 9 to 15 months after radiotherapy in 3 of 7 cats treated with FLASH-radiotherapy (43%), as compared with 0 of 9 cats treated with SoC. All cats were tumor-free at 1 year in both arms, with one cat progressing later in each arm. In pigs, no acute toxicity was recorded, but severe late skin necrosis occurred in a volume-dependent manner (7–9 months), which later resolved.

Conclusions: The reported outcomes point to the caveats of translating single-high-dose FLASH-radiotherapy and emphasizes the need for caution and further investigations.

krebsliga schweiz
ligue suisse contre le cancer
lega svizzera contro il cancro

oncosuisse

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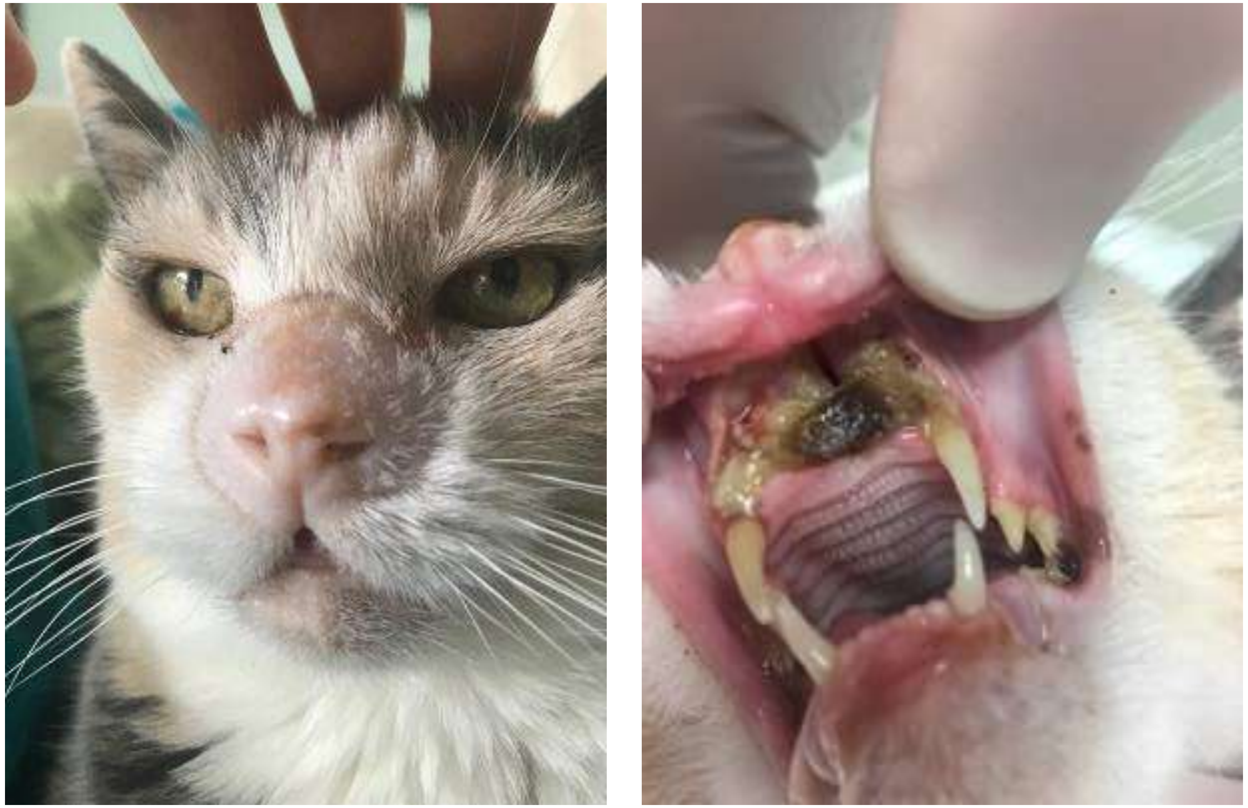
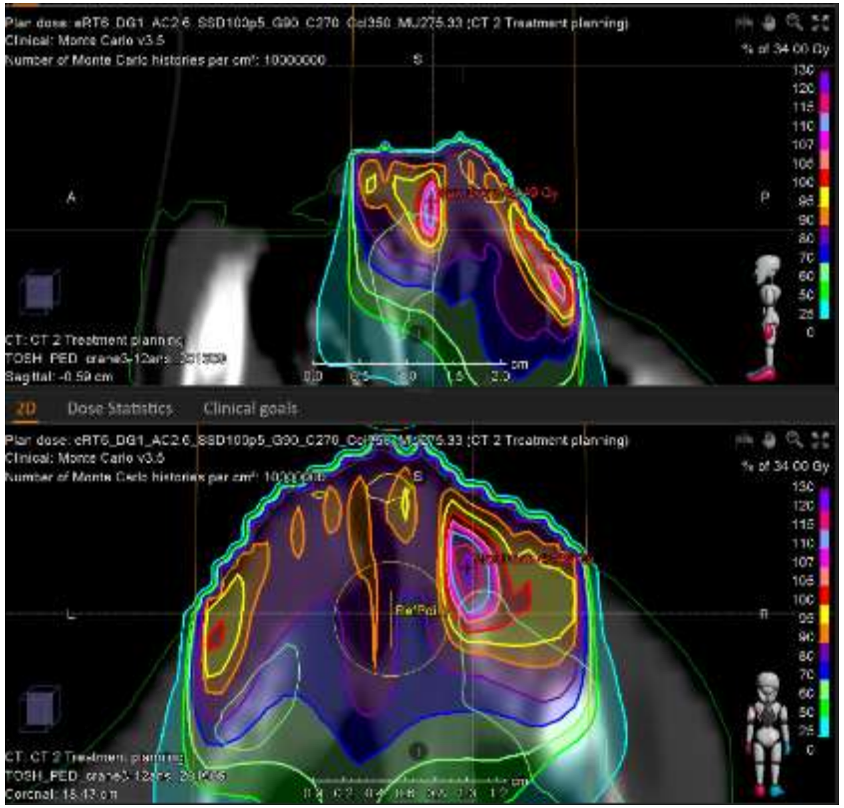
3 CATS OVER 7 DEVELOPPED OSTEORADIONECROSIS WITHIN 9-15 MONTHS



Musi, 13 months post FLASH



Plan dose: eRT6_DG1_AC2.6_SSD100p5_G90_C270_Col350_MU275.33 (CT 2 Treatment planning)
Clinical: Monte Carlo v3.5
Number of Monte Carlo histories per cm²: 10000000

CT: CT 2 Treatment planning
TOSH_PED_crane3-12ans
Sagittal: -0.59 cm

Plan dose: eRT6_DG1_AC2.6_SSD100p5_G90_C270_Col350_MU275.33 (CT 2 Treatment planning)
Clinical: Monte Carlo v3.5

CT: CT 2 Treatment planning
TOSH_PED_crane3-12ans
Coronal: 15.42 cm

Hot spots +125% of the dose

IMPACT OF DOSE AND VOLUME

2.6 cm
28, 31, 34 Gy

?

10p-90ms
>280 Gy/s

9 mo post-RT

3 years post-RT

Vozenin et al,
CCR, 2019

8X8 cm
31 Gy 1 Fx
20 p-190 ms
150 Gy/s

Technological
limitations

Rohrer-Bley et al
CCR, 2022

4 mo post-RT

5 mo post-RT

6 mo post-RT

7 mo post-RT

12 mo post-RT

Evaluation of Flash Proton RT in Dogs with Bone Cancer of the Leg

Aug 8, 2019Osteosarcoma (OSA) is an aggressive cancer that frequently arises in the long bones of large-breed dogs. Current treatment therapies involve amputation with or without chemotherapy, or radiation therapy (RT). However, in dogs receiving radiation therapy, survival time is typically only 2-4 months. Preliminary studies suggest that using a different kind of RT, “flash” proton radiation, may improve treatment by decreasing normal tissue damage while increasing toxicity to tumor cells and may also improve anti-tumor immune responses in the dog.

Inclusion Criteria:

- Dogs with newly diagnosed OSA who have received no prior treatment for cancer
- Dogs with OSA of the leg which is amenable to limb amputation
- Dogs with no evidence of metastasis at the time of enrollment
- Owners are willing to pursue amputation at Penn Vet

Benefits: Dogs will have a single treatment of flash proton radiation, followed by amputation 5 days later. Biopsies will be taken under anesthesia to evaluate tumor and healthy tissue response to radiation treatment.
The cost of radiation treatment and subsequent amputation surgery will be covered by the study. Clients are responsible for all other costs including initial consultation, pre-surgical diagnostics, and chemotherapy if elected.

First veterinary patient treated with electron FLASH radiotherapy at a clinical linear accelerator

Translational and clinical research

Elise Konradsson1, Maja L. Arendt2, Kristine Bastholm Jensen3, Betina Borresen2, Crister Ceberg1, Anders E.
Hansen4, Annemarie T. Kristensen2, Per Munck af Rosenschold5, Kristoffer Petersson5, 6

Introduction: There is a growing interest in advancing ultra-high dose rate radiotherapy (FLASH-RT) towards clinical studies. However, the availability of accelerators capable of delivering ultra-high dose rates in a clinical setting is still limited. We have initiated a veterinary clinical study of FLASH-RT for clinical canine cancer patients with superficial tumors using the electron beam of our modified clinical linear accelerator. Here we present the treatment of the first patient.

Methods: A clinical canine cancer patient diagnosed with a grade 1 soft tissue sarcoma at the right forelimb, with incomplete excision after surgery, was treated with 15 Gy FLASH-RT using a field size of 8x4 cm2 (Figure 1). The irradiation was delivered with a source-to-surface distance of 70 cm. Dosimetric equipment consisted of radiochromic film, an ionization chamber (for relative measurements) and phantom material mimicking the experimental setup for irradiation. *In vivo* dose measurements were performed with film to verify the delivered dose.

Results: For the canine patient, the prescribed dose was accurately delivered (14.8 — 0.5 Gy) using 7 pulses in 0.03 s, i.e. with an average dose rate of 500 Gy/s. Only grade 1 cutaneous side effects were observed at 7 and 30 days post treatment.

CLINICAL TRANSLATION OF FLASH-RT
CHUV'S PRAGMATIC APPROACH USING LINACS OF 5-12 MEV

Superficial tumors
Intra-operative FLASH-RT

1a : Day 0

1b : 3 weeks

1c : 5 months


Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]

[a] Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [b] Radiation Oncology Laboratory, Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [c] Institute of Radiation Physics, Lausanne University Hospital and University of Lausanne; and [d] Department of Dermatology, Lausanne University Hospital and University of Lausanne, Switzerland

J Bourhis

1 year post-RT

FLASH

Previous zones treated with conventional RT

Radiotherapy and Oncology 174 (2022) 87–91

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Short Communication

Comparison of ultra-high versus conventional dose rate radiotherapy in a patient with cutaneous lymphoma

Olivier Gaide[a,1], Fernanda Herrera[b,c,1], Wendy Jeanneret Sozzi[c], Patrik Gonçalves Jorge[b,d], Rémy Kinj[c], Claude Bailat[d], Fréderic Duclos[c], François Bochud[d], Jean-François Germond[b,d], Maud Gondré[d], Till Boelhen[b,d], Luis Schiappacasse[c], Mahmut Ozsahin[b], Raphaël Moeckli[d,1], Jean Bourhis[b,c,*,1]

[a] *Department of Dermatology, Lausanne University Hospital and University of Lausanne;* [b] *Radiation Oncology Laboratory, Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne;* [c] *Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; and* [d] *Institute of Radiation Physics, Lausanne University Hospital and University of Lausanne, Switzerland*

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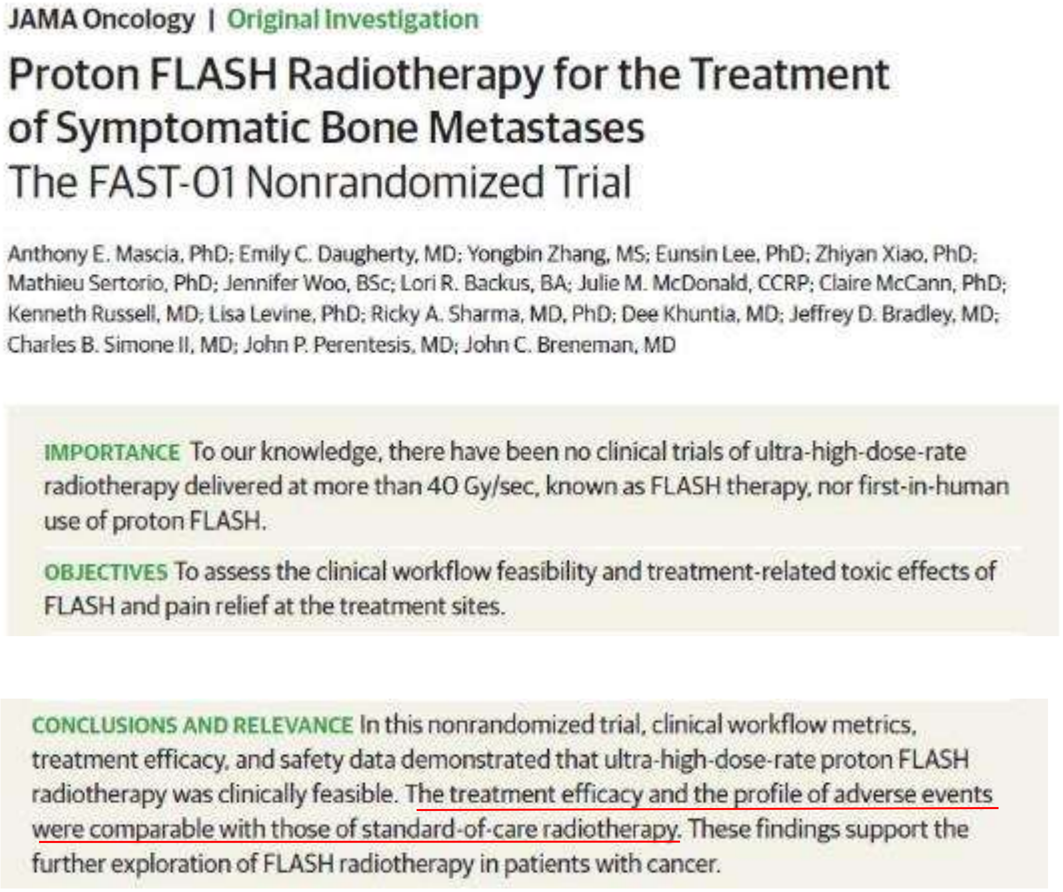
Normal skin protection
Differential effect
Clinical translation

ABSTRACT

A patient with a cutaneous lymphoma was treated on the same day for 2 distinct tumors using a 15 Gy single electron dose given in a dose rate of 0.08 Gy/second versus 166 Gy/second. Comparing the two treatments, there was no difference for acute reactions, late effects at 2 years and tumor control.



JAMA Oncology | **Original Investigation**

Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases

The FAST-01 Nonrandomized Trial

Anthony E. Mascia, PhD; Emily C. Daugherty, MD; Yongbin Zhang, MS; Eunsin Lee, PhD; Zhiyan Xiao, PhD; Mathieu Sertorio, PhD; Jennifer Woo, BSc; Lori R. Backus, BA; Julie M. McDonald, CCRP; Claire McCann, PhD; Kenneth Russell, MD; Lisa Levine, PhD; Ricky A. Sharma, MD, PhD; Dee Khuntia, MD; Jeffrey D. Bradley, MD; Charles B. Simone II, MD; John P. Perentesis, MD; John C. Breneman, MD

IMPORTANCE To our knowledge, there have been no clinical trials of ultra-high-dose-rate radiotherapy delivered at more than 40 Gy/sec, known as FLASH therapy, nor first-in-human use of proton FLASH.

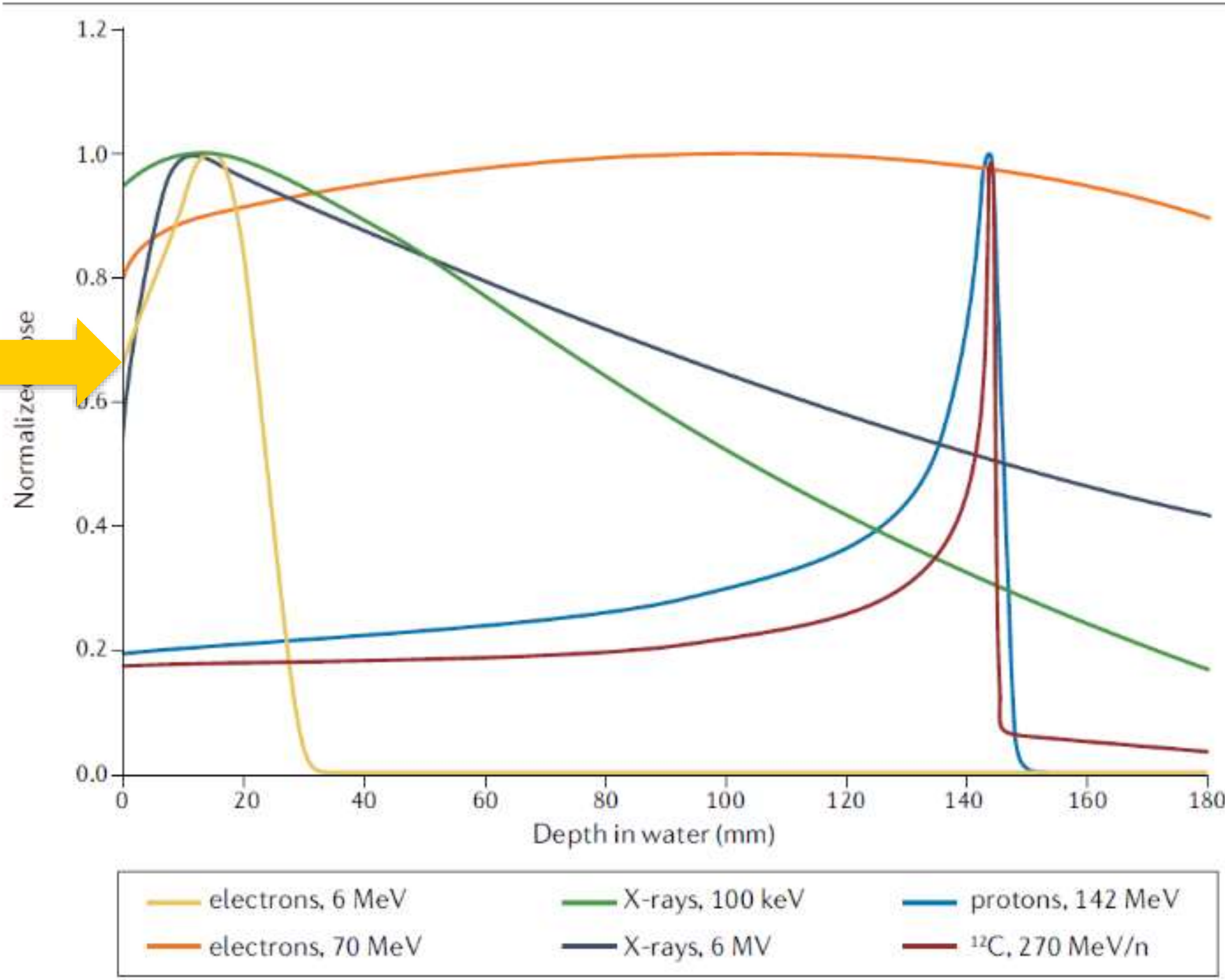
OBJECTIVES To assess the clinical workflow feasibility and treatment-related toxic effects of FLASH and pain relief at the treatment sites.

CONCLUSIONS AND RELEVANCE In this nonrandomized trial, clinical workflow metrics, treatment efficacy, and safety data demonstrated that ultra-high-dose-rate proton FLASH radiotherapy was clinically feasible. The treatment efficacy and the profile of adverse events were comparable with those of standard-of-care radiotherapy. These findings support the further exploration of FLASH radiotherapy in patients with cancer.

NEEDS FOR THE CLINICAL TRANSFER

EXISTING TECHNOLOGY AND ITS LIMITATIONS

PHYSICAL QUALITIES OF ELECTRONS

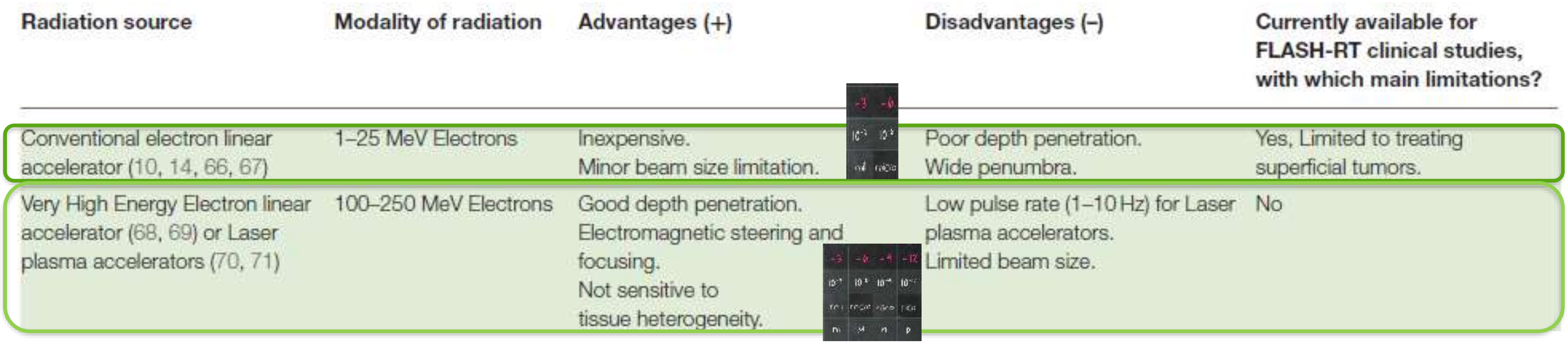


Short target distance

e

VHEE

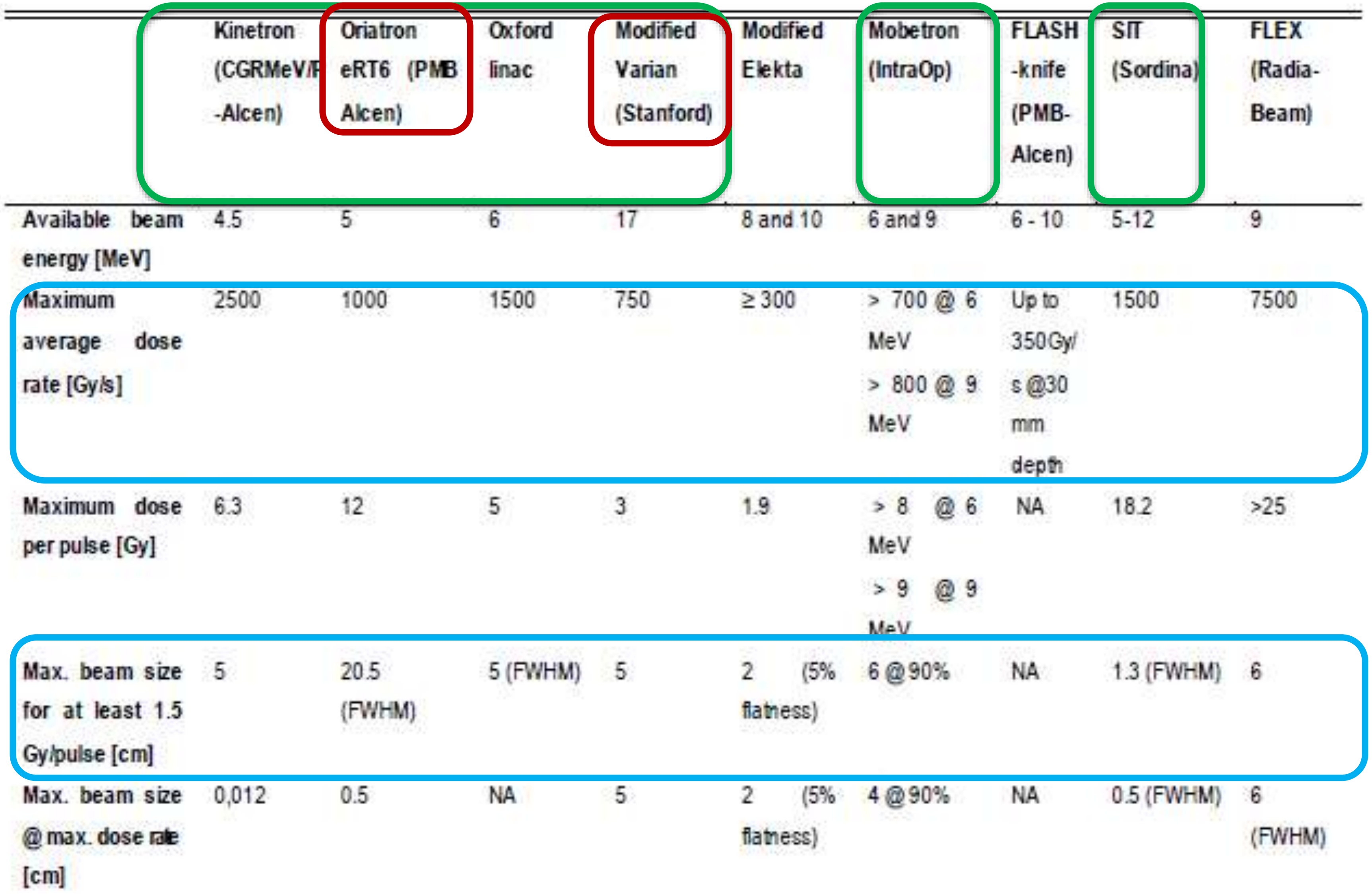
DEVICES ABLE TO OPERATE AT ULTRA-HIGH DOSE RATE ELECTRONS



Radiation source	Modality of radiation	Advantages (+)	Disadvantages (–)	Currently available for FLASH-RT clinical studies, with which main limitations?
Conventional electron linear accelerator (10, 14, 66, 67)	1–25 MeV Electrons	Inexpensive. Minor beam size limitation.	Poor depth penetration. Wide penumbra.	Yes, Limited to treating superficial tumors.
Very High Energy Electron linear accelerator (68, 69) or Laser plasma accelerators (70, 71)	100–250 MeV Electrons	Good depth penetration. Electromagnetic steering and focusing. Not sensitive to tissue heterogeneity.	Low pulse rate (1–10 Hz) for Laser plasma accelerators. Limited beam size.	No

Wilson et al., Front in Oncol, 2020

EXISTING LINACS FOR FLASH RT
ELECTRONS OF INTERMEDIATE ENERGY



	Kinetron (CGRMeV/P -Alcen)	Oriatron eRT6 (PMB Alcen)	Oxford linac	Modified Varian (Stanford)	Modified Elekta	Mobetron (IntraOp)	FLASH -knife (PMB-Alcen)	SIT (Sordina)	FLEX (Radia-Beam)
Available beam energy [MeV]	4.5	5	6	17	8 and 10	6 and 9	6 - 10	5-12	9
Maximum average dose rate [Gy/s]	2500	1000	1500	750	≥ 300	> 700 @ 6 MeV > 800 @ 9 MeV	Up to 350Gy/s @30 mm depth	1500	7500
Maximum dose per pulse [Gy]	6.3	12	5	3	1.9	> 8 @ 6 MeV > 9 @ 9 MeV	NA	18.2	>25
Max. beam size for at least 1.5 Gy/pulse [cm]	5	20.5 (FWHM)	5 (FWHM)	5	2 (5% flatness)	6 @90%	NA	1.3 (FWHM)	6
Max. beam size @ max. dose rate [cm]	0,012	0.5	NA	5	2 (5% flatness)	4 @90%	NA	0.5 (FWHM)	6 (FWHM)

Flash effect validated

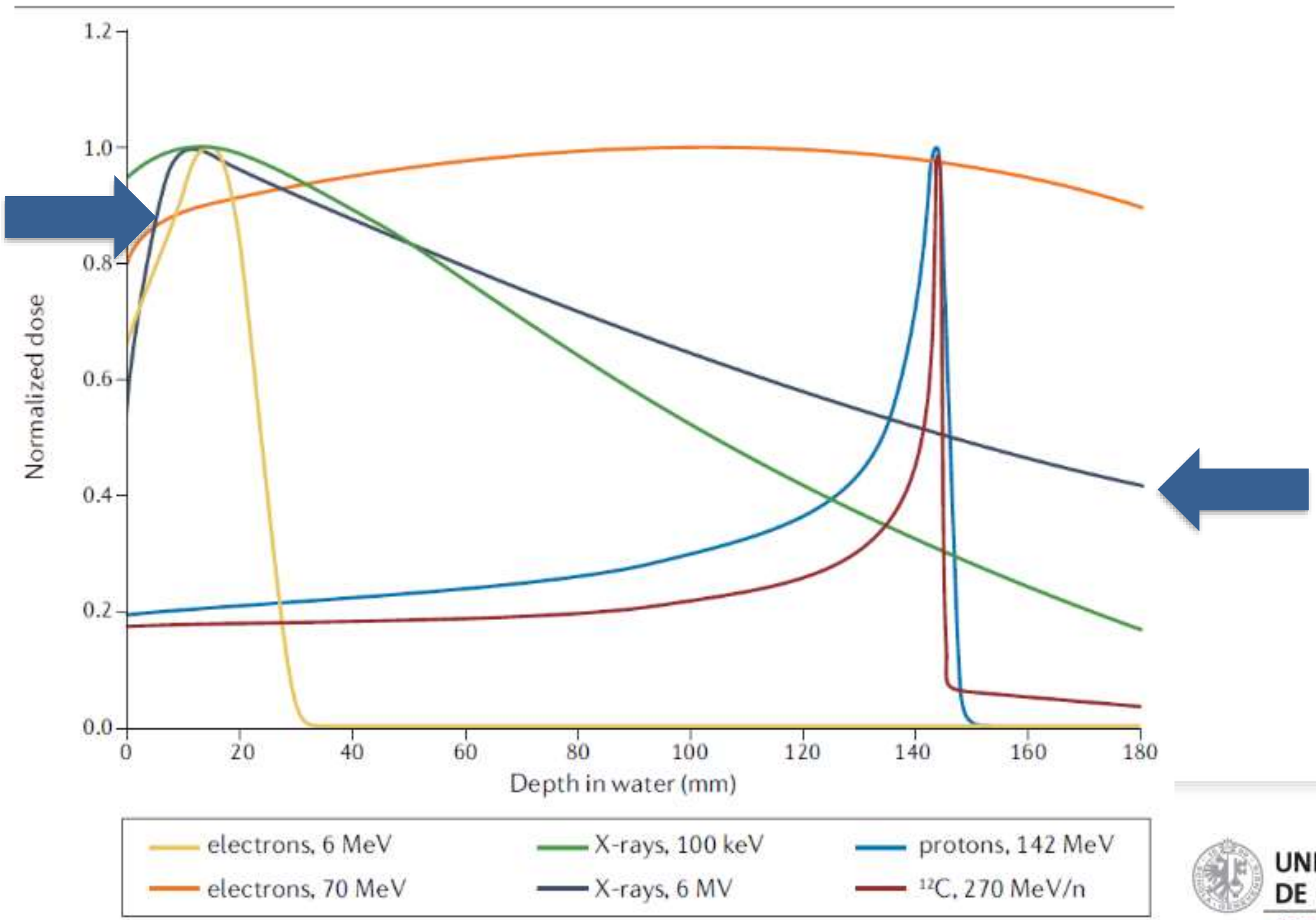
Biologically and dosimetrically intercompared

Vozenin et al., Reviews in Modern Physics, 2023

PHOTONS

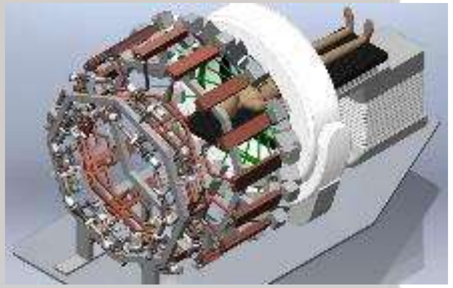
90% of clinical applications today

photons



DEVICES ABLE TO OPERATE AT ULTRA-HIGH DOSE RATE PHOTONS

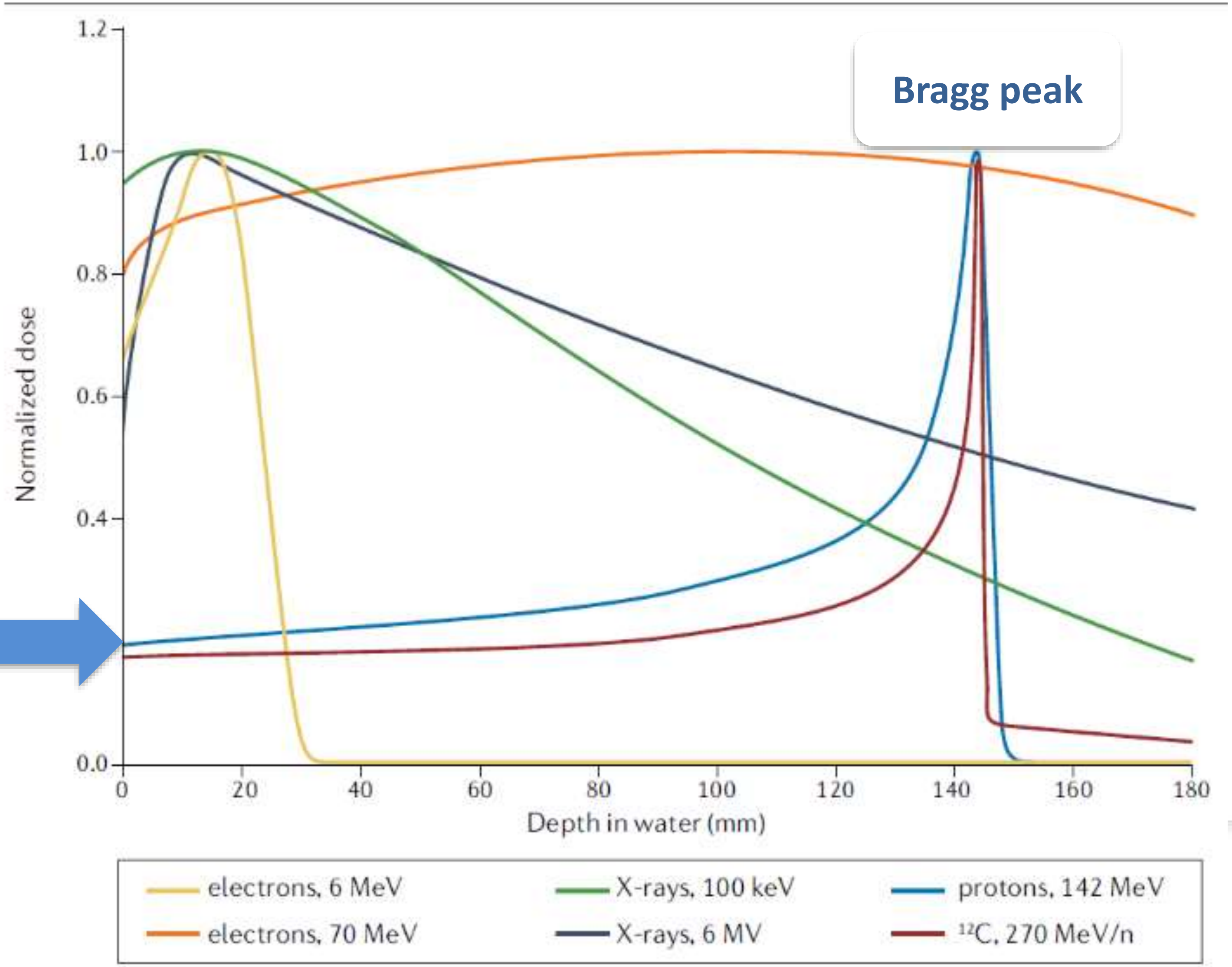
Radiation source	Modality of radiation	Advantages (+)	Disadvantages (–)	Currently available for FLASH-RT clinical studies, with which main limitations?
X-ray tube (72)	50–250 keV X-rays	Inexpensive. Compact design.	Very limited depth penetration. Limited beam size. High entrance dose.	Yes, Limited to treating small and very superficial tumors.
Synchrotron (24, 32)	50–600 keV X-rays	Microbeam Radiation Therapy possible.	Very large. Very expensive. Limited depth penetration. Very limited availability. Limited beam size requires scanning of sample/target.	Yes, Very limited availability.
Electron linear accelerator with high density target (20)	6–10 MV X-rays	Good depth penetration. Narrow penumbra. Minor beam size limitation.	Multiple beam angles required.	No



Wilson et al., Front in Oncol, 2020

PROTONS

100 facilities worldwide



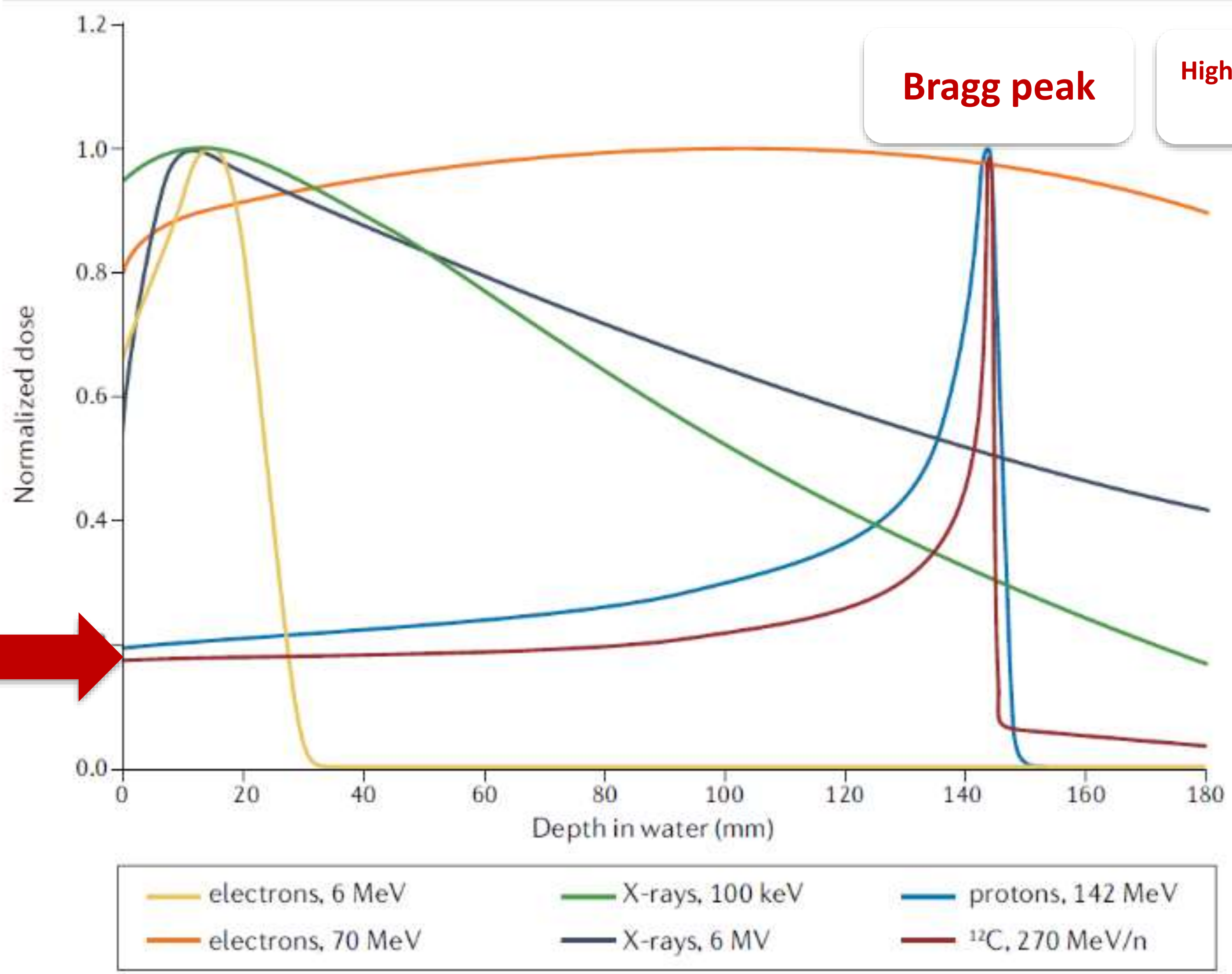
Bragg peak

protons

HEAVY IONS

12 facilities worldwide

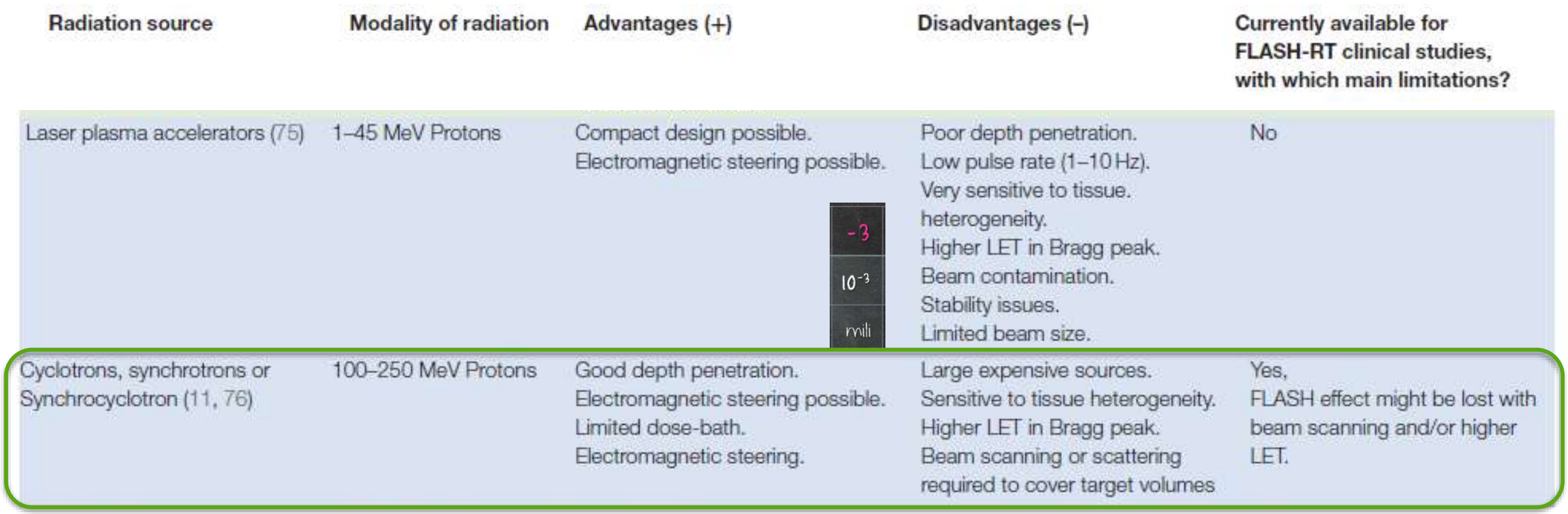
Heavy ions



Bragg peak

Higher relative biologic efficacy

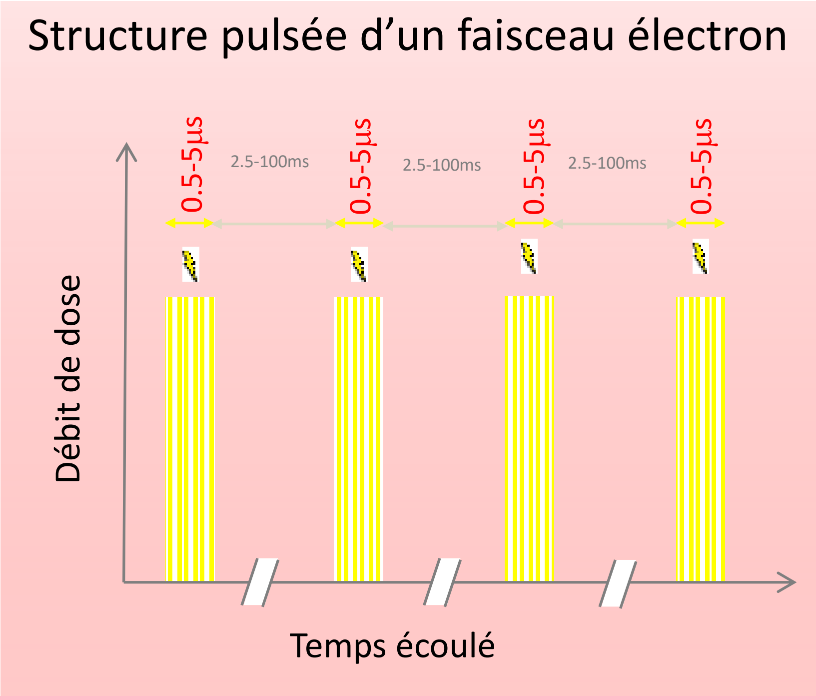
DEVICES ABLE TO OPERATE AT ULTRA-HIGH DOSE RATE PROTONS



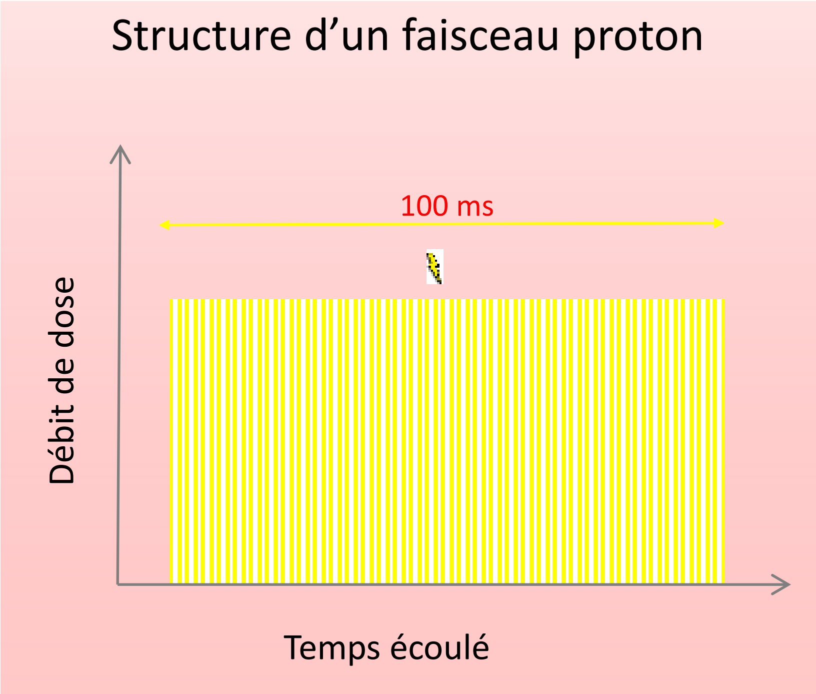
Radiation source	Modality of radiation	Advantages (+)	Disadvantages (–)	Currently available for FLASH-RT clinical studies, with which main limitations?
Laser plasma accelerators (75)	1–45 MeV Protons	Compact design possible. Electromagnetic steering possible.	Poor depth penetration. Low pulse rate (1–10 Hz). Very sensitive to tissue. heterogeneity. Higher LET in Bragg peak. Beam contamination. Stability issues. Limited beam size.	No
Cyclotrons, synchrotrons or Synchrocyclotron (11, 76)	100–250 MeV Protons	Good depth penetration. Electromagnetic steering possible. Limited dose-bath. Electromagnetic steering.	Large expensive sources. Sensitive to tissue heterogeneity. Higher LET in Bragg peak. Beam scanning or scattering required to cover target volumes	Yes, FLASH effect might be lost with beam scanning and/or higher LET.

Wilson et al., Front in Oncol, 2020

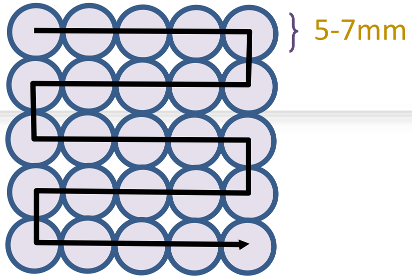
TECHNOLOGY

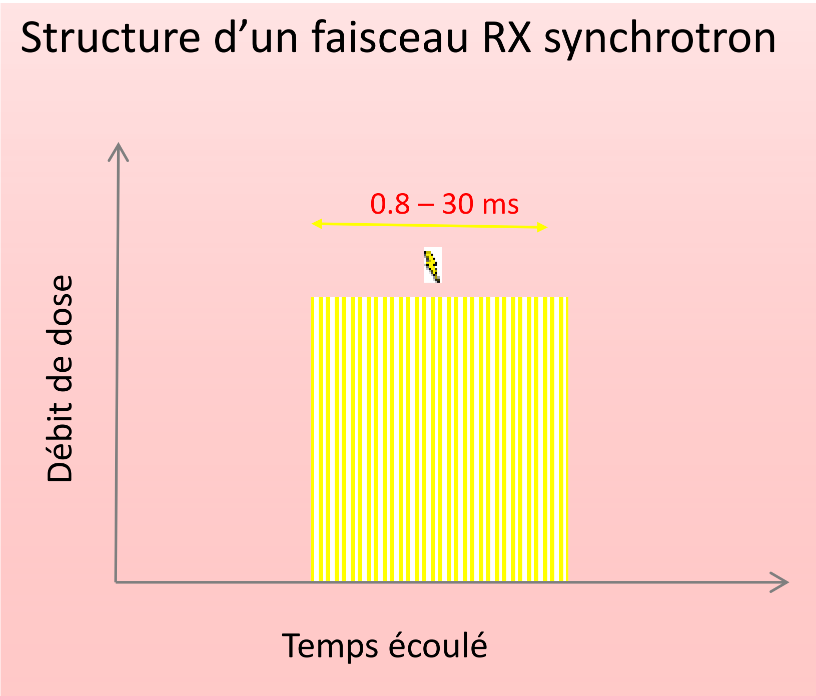

Structure pulsée d'un faisceau électron

- 1 – 10 pulses
- Microstructure: 5000 bunches
- Pulse repetition frequency 10-250Hz

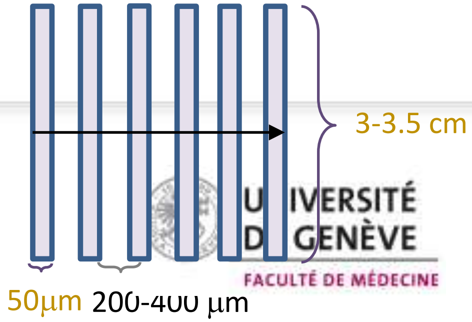

Structure d'un faisceau proton

- 1 pulse
- Microstructure: 10^7 bunches
- Spot scanning (@1000Hz)




Structure d'un faisceau RX synchrotron

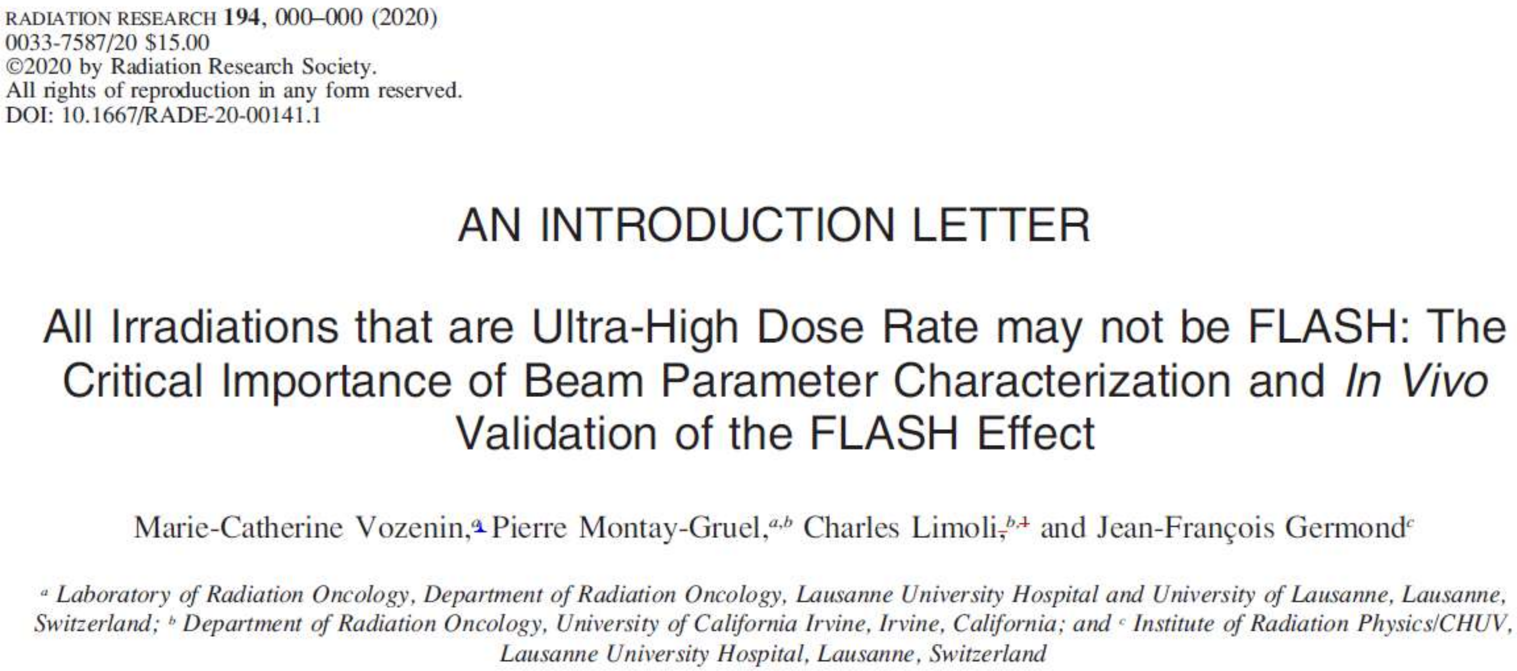
- 1 pulse = 1 stripe
- Microstructure: 10^7 bunches
- Stripe scanning (60mm/s)



ALL IRRADIATION THAT IS ULTRA-HIGH DOSE RATE IS NOT NECESSARILY FLASH

The FLASH effect is a biological effect

Importance of the parametric characterization of the FLASH effect



RADIATION RESEARCH **194**, 000–000 (2020)
0033-7587/20 $15.00

DOI: 10.1667/RADE-20-00141.1

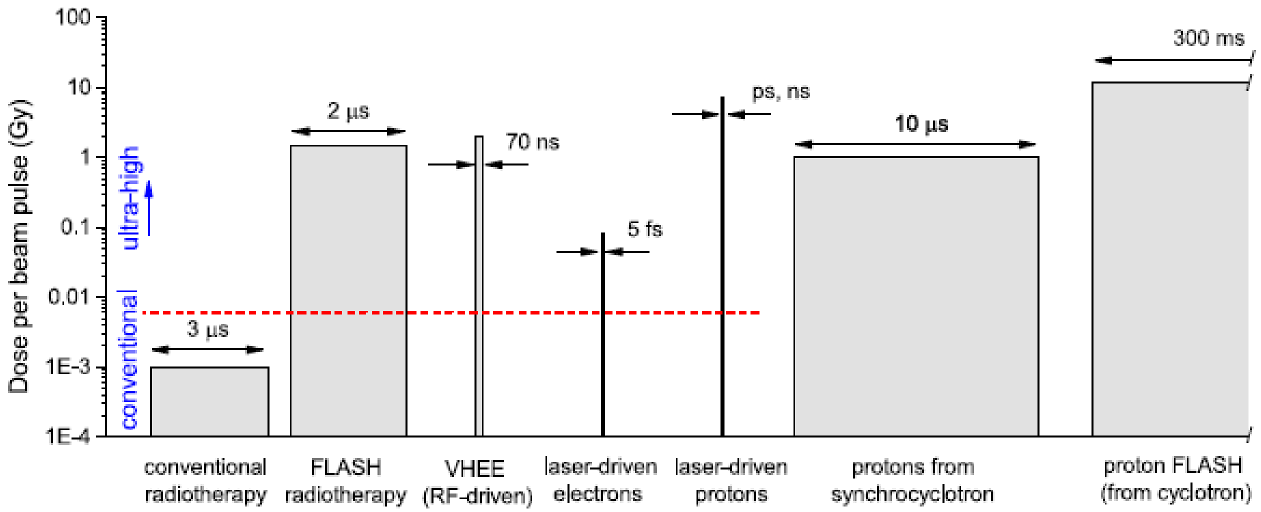
AN INTRODUCTION LETTER

All Irradiations that are Ultra-High Dose Rate may not be FLASH: The Critical Importance of Beam Parameter Characterization and *In Vivo* Validation of the FLASH Effect

Marie-Catherine Vozenin,[a,1] Pierre Montay-Gruel,[a,b] Charles Limoli,[b,1] and Jean-François Germond[c]

[a] *Laboratory of Radiation Oncology, Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland;* [b] *Department of Radiation Oncology, University of California Irvine, Irvine, California; and* [c] *Institute of Radiation Physics/CHUV, Lausanne University Hospital, Lausanne, Switzerland*

PHYSICAL PARAMETERS REQUIRED TO PRODUCE THE FLASH EFFECT



- **FLASH effect with proton, electron, photon beams**
- **FLASH effect in milliseconds to microseconds range**
- **FLASH effect at 100 to 10^7 Gy/s**

=> Suggest that the relevant metric is the average dose rate


Physica Medica

Original paper

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

METROLOGY: DOSIMETRY-TPS-RADIOPROTECTION

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FLASH DOSIMETRY IS CHALLENGING REGARDLESS OF IRRADIATION SOURCE

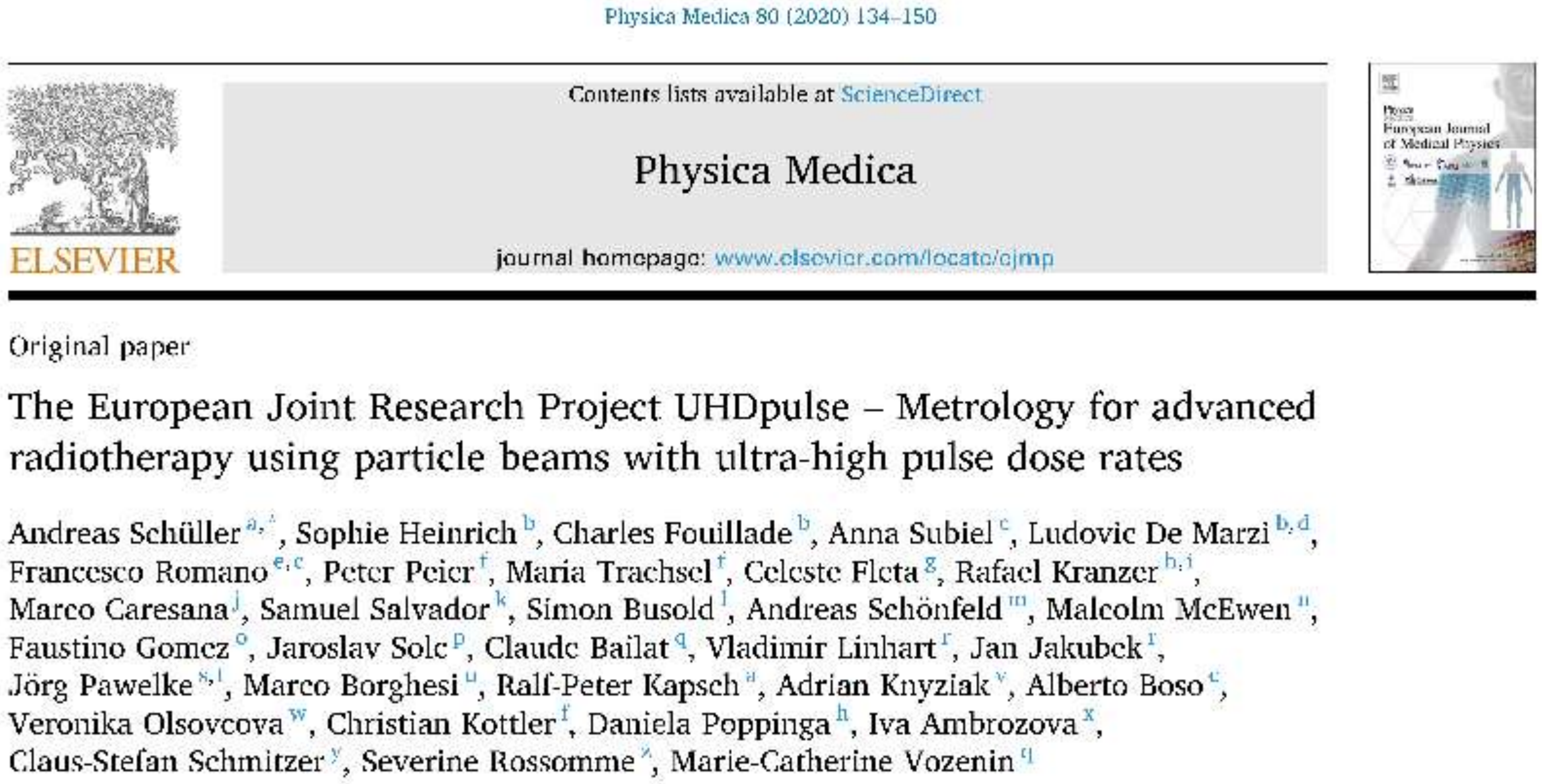
Radiochromic films: most commonly used
Independent to dose rate + high spatial resolution but measure the dose after exposition

Real-time, online dose monitoring essential for clinical RT: ionization chambers but: saturation and reduced ion collection efficiency at high dose rates

Ideal FLASH dosimetry**: high time resolution + wide dynamic range** to monitor doses and dose rates

Vozenin MC et al, Nature 2022

A NEED TO GET ACCESS TO METROLOGY FOR UHDR RT



Physica Medica 80 (2020) 134–150

Contents lists available at ScienceDirect

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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]

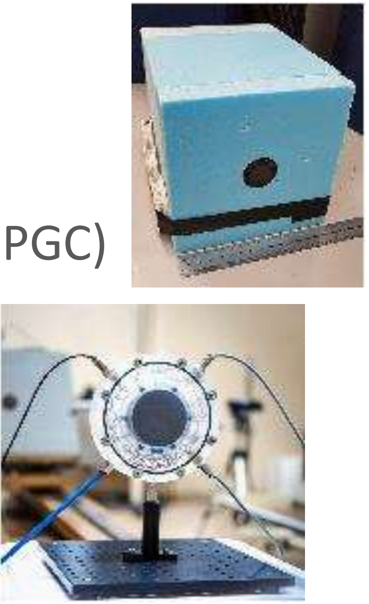
DOSIMETRIC OPTIONS: PRIMARY STANDARDS

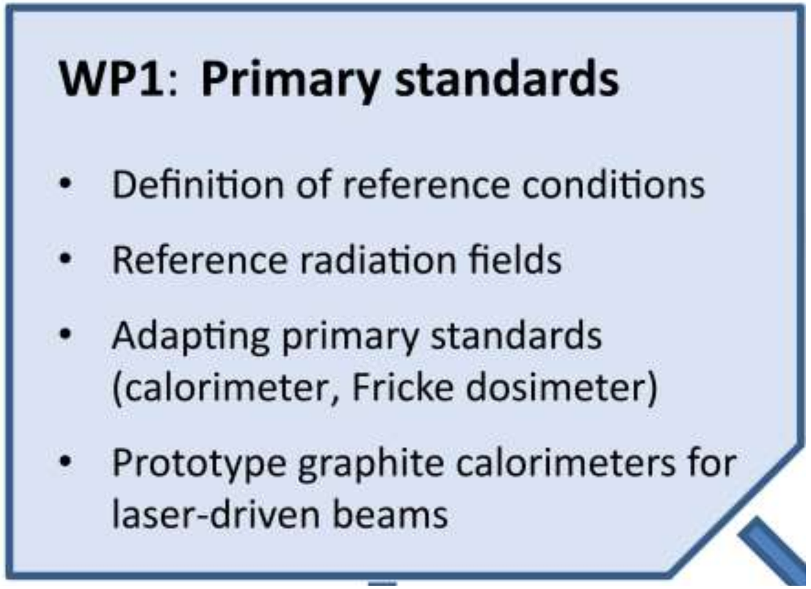
- **Frickle dosimetry**

used in conventional electron beams
independent of dose rate
evaluation for UHDR ongoing

- **Graphite calorimeter**

proton UHDR
NPL commissioning first portable calorimeter (SPGC)
GUM portable to be tested for UHDR electron
aluminium calorimeter for UHDR electron





WP1: Primary standards

- Definition of reference conditions
- Reference radiation fields
- Adapting primary standards (calorimeter, Fricke dosimeter)
- Prototype graphite calorimeters for laser-driven beams

Schuller A et al, Physica Medica 2020

DOSIMETRIC OPTIONS: SECONDARY STANDARDS AND RELATIVE DOSIMETRY

- **Ionization chambers STANDARD FOR CONVENTIONAL**

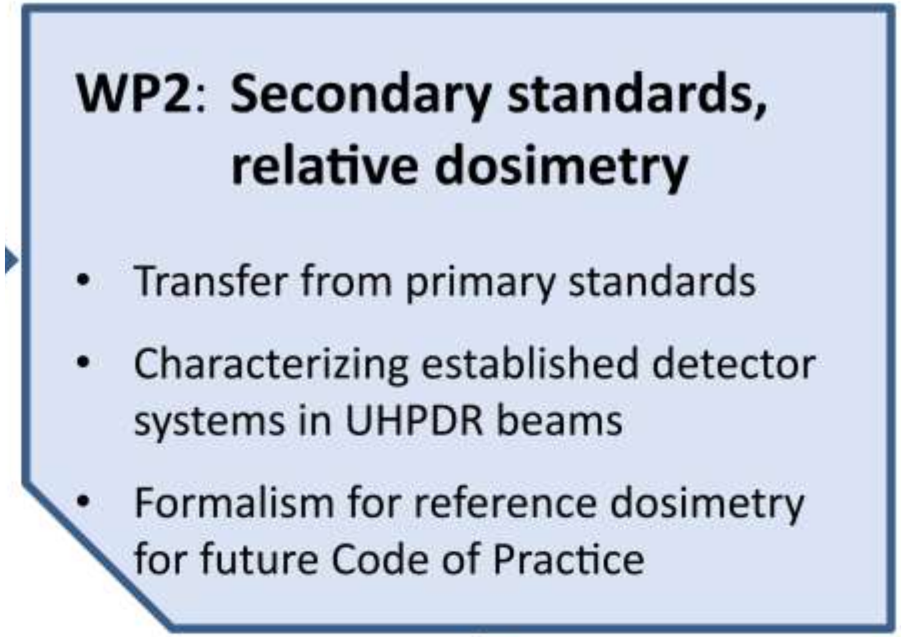
international code of practice: plain parallel ionization chambers for measurement of absorbed dose -> challenging with UHDR

- **Absolute dosimetry for FLASH électrons**

with **chemical and passive dosimeters**
radiochromic films, alanine and thermo-luminescent dosimeters
not dependent on dose rate
but uncertainties 3%
impossible direct reading
REMAINS THE REFERENCE BUT IS RETROSPECTIVE
NEED TO WORK ON MONITOR CHAMBERS FOR REAL-TIME DOSIMETRY

- **Semiconductive detectors**

silicon and diamond
standard for ptotons: higher sensitivity, good spatial resolution, compact



WP2: Secondary standards, relative dosimetry

- Transfer from primary standards
- Characterizing established detector systems in UHPDR beams
- Formalism for reference dosimetry for future Code of Practice

Schuller A et al, Physica Medica 2020

BEAM MONITORING

- **UHDR électrons**

Ionization chambers saturate at UHDR

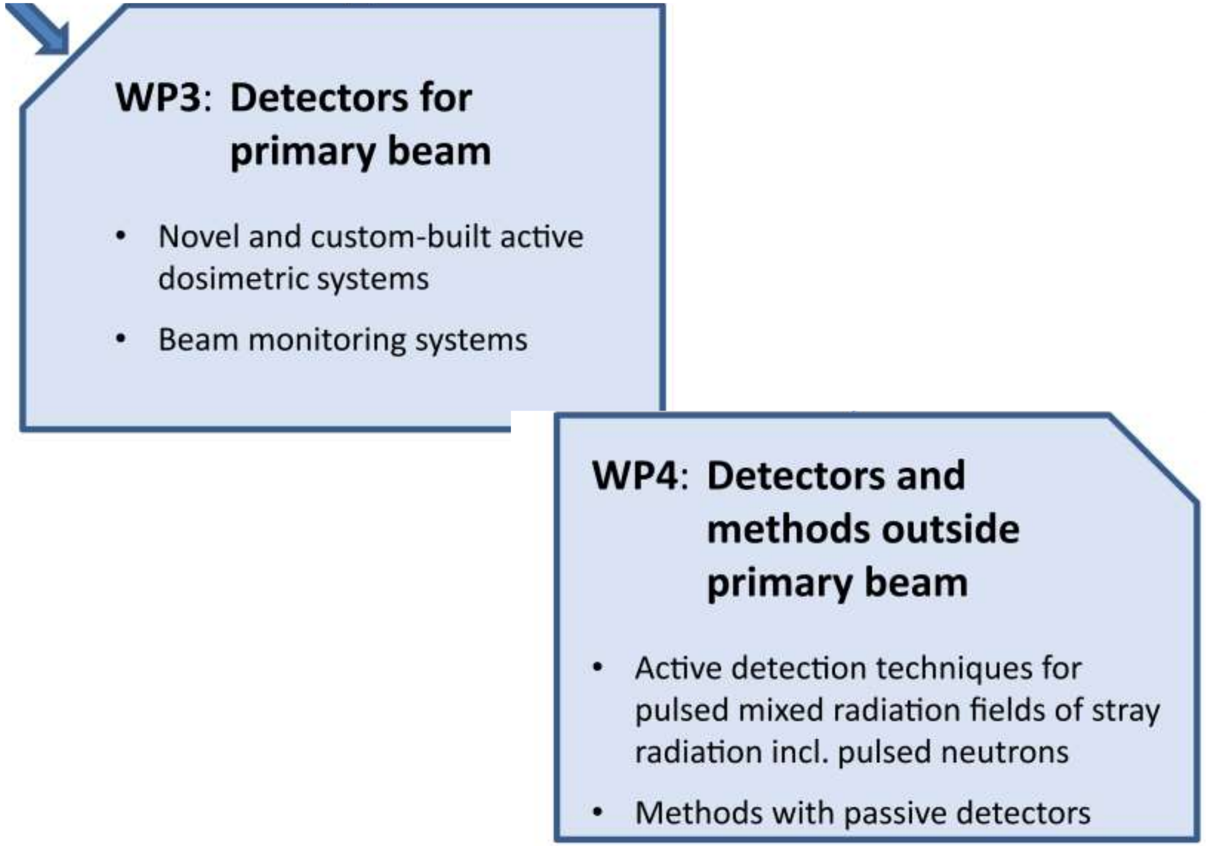
FOR UHDR: **beam current transformers (BCT): AC Current Transformer (ACCT) or Integrating Current Transformer (ICT)**
Not classically used in the clinic

- **UHDR protons**

Air-filled transmission ionization chambers= standard
With FLASH RT, recombination losses

- **Stray radiation**

Even more challenging: need for proper identification of field components
Key requirement: possibility to distinguish between particle types -> TimePix3 detector



WP3: Detectors for primary beam

- Novel and custom-built active dosimetric systems
- Beam monitoring systems

WP4: Detectors and methods outside primary beam

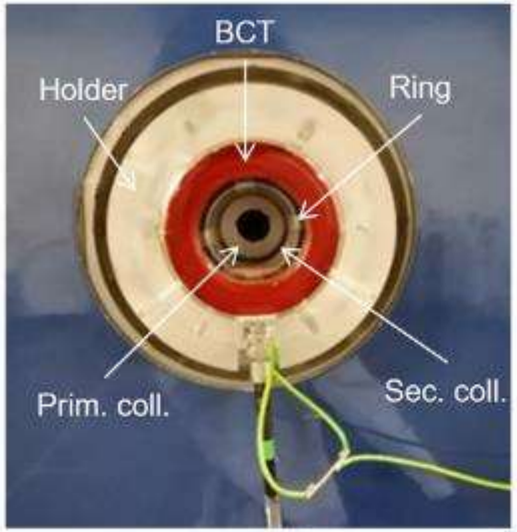
- Active detection techniques for pulsed mixed radiation fields of stray radiation incl. pulsed neutrons
- Methods with passive detectors

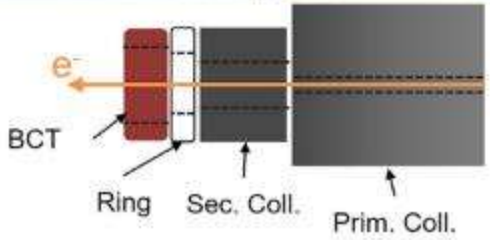
Schuller A et al, Physica Medica 2020

TOWARDS THE DEVELOPMENT OF A MONITOR CHAMBER USING BEAM CURRENT TRANSFORMERS (BCT) OR ACCT

Mandatory for clinical application

Real-time monitoring system of FLASH irradiation accelerators: pilot, check and verify delivered doses

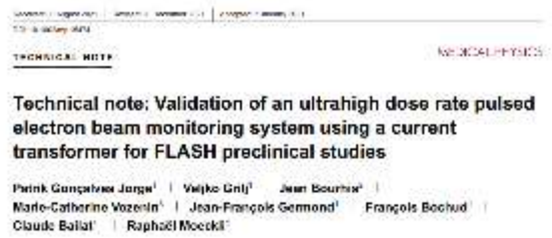





C Bailat


R Moeckli


P Jorge Goncalves

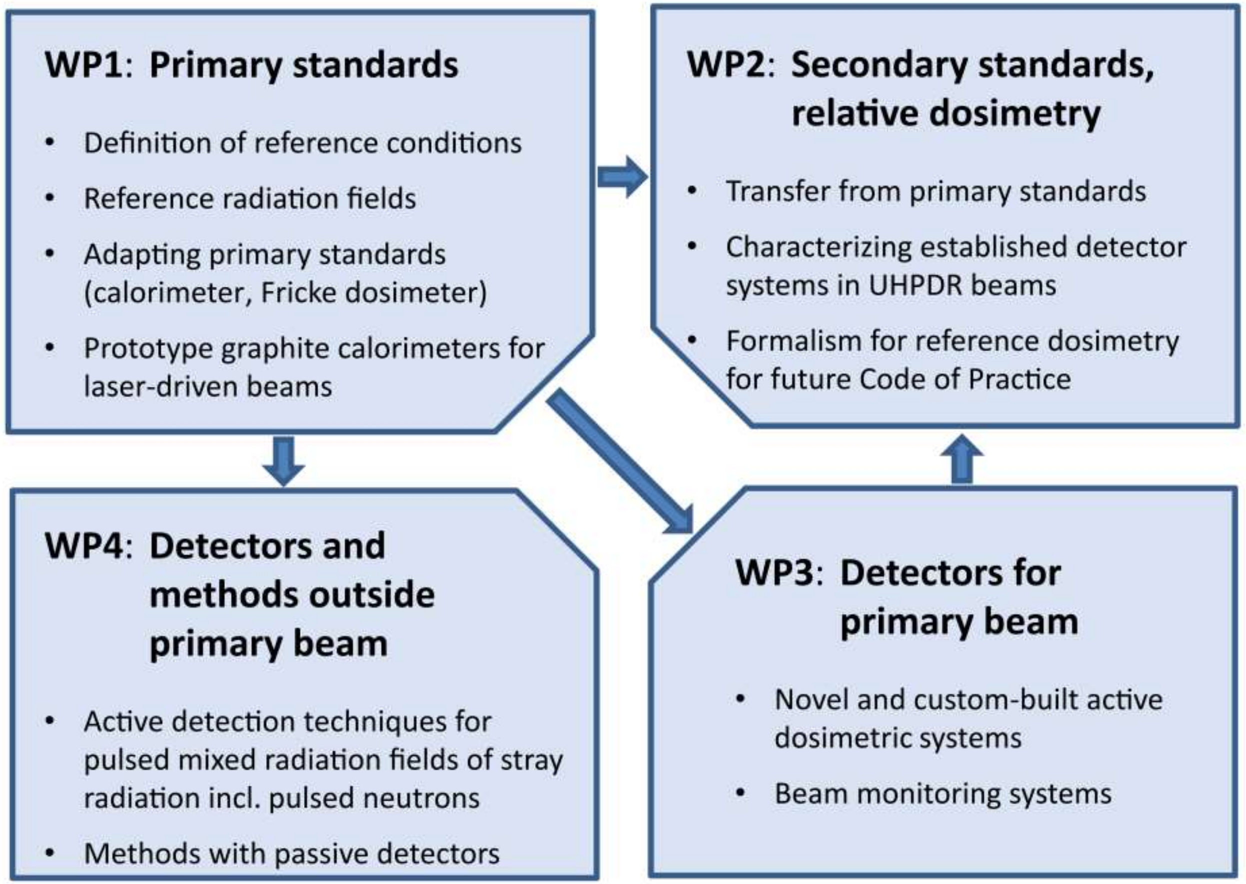

TECHNICAL NOTE

MEDICAL PHYSICS

Technical note: Validation of an ultrahigh dose rate pulsed electron beam monitoring system using a current transformer for FLASH preclinical studies

Patrik Gonçalves Jorge[1] | Veljko Grilj[1] | Jean Bourhis[2] | Marie-Catherine Vozenin[2] | Jean-François Germond[1] | François Bochud[1] | Claude Bailat[1] | Raphaël Moeckli[1]

THE UHD PULSE PROJECT -> COMPLETED



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- Methods with passive detectors

- **UHD** (Andreas Schüller)
Induction and diamond chambers

- **NPL** UK: Anna Subiel
Minicalorimeters: absolute dose measurements

- **CHUV**: Claude Baillat/ Maud Jaccard
passive dosimetry

Pour protons: Faraday-cup

Schuller A et al, Physica Medica 2020

RADIATION PROTECTION AT UHDR

- **Current regulatory framework**

annual doses received by personnel= restricted- established at international and national level

- **For UHDR**

Standard radiation protection instruments not designed to measure pulsed beams
designed in nuclear power plants
they accumulate the signal during seconds but operate well in the microsec frame ? Sensitive enough ?

Instruments for radiodiagnostics might be better suited

Passive dosimeters require the delivery of large, absorbed dose in a large water tank

For clinical operations
total dose delivery not expected to differ between conventional and FLASH RT

More deeply penetrating electrons will require **neutron dosimetry**

Vozenin MC et al, RMP 2023

TPS FOR FLASH ?

A need to create a FLASH dedicated TPS

Currently, Monte Carlo is used, but this does not integrate time of RT delivery

IMPLICATIONS OF RADIOBIOLOGICAL MECHANISMS ON CLINICAL TRANSFER

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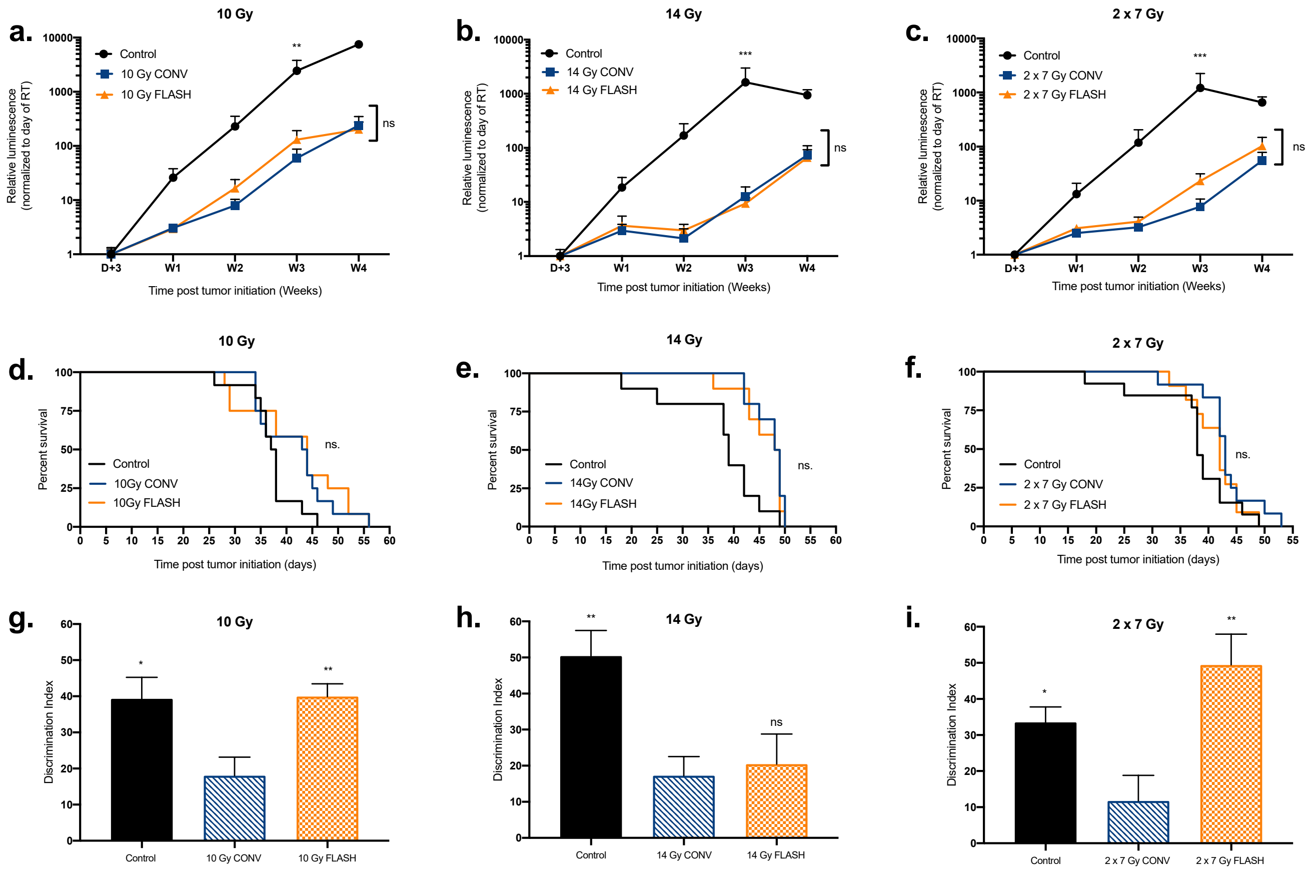
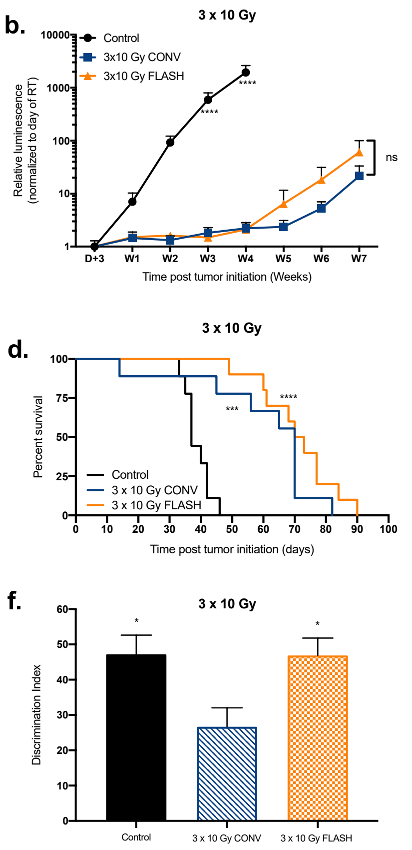
FRACTIONATION

IMPACT OF DOSE, FRACTIONATION AND INTERVAL

B Petit

P Montay-Gruel





FLASH dose delivered in 1 pulse (1.8 micros)

Montay-Gruel et al, CCR, 2020

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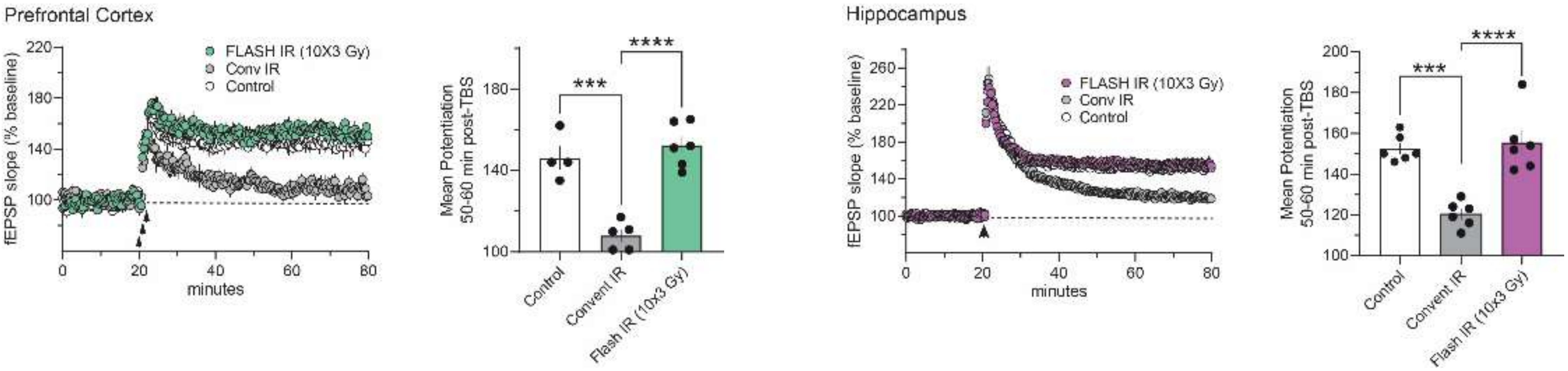
STANDARD FRACTIONATION REGIMEN 10X3GY SPARES NORMAL BRAIN FUNCTION



=> Suggest that standard fractionation is feasible

Limoli et al, RO, 2023

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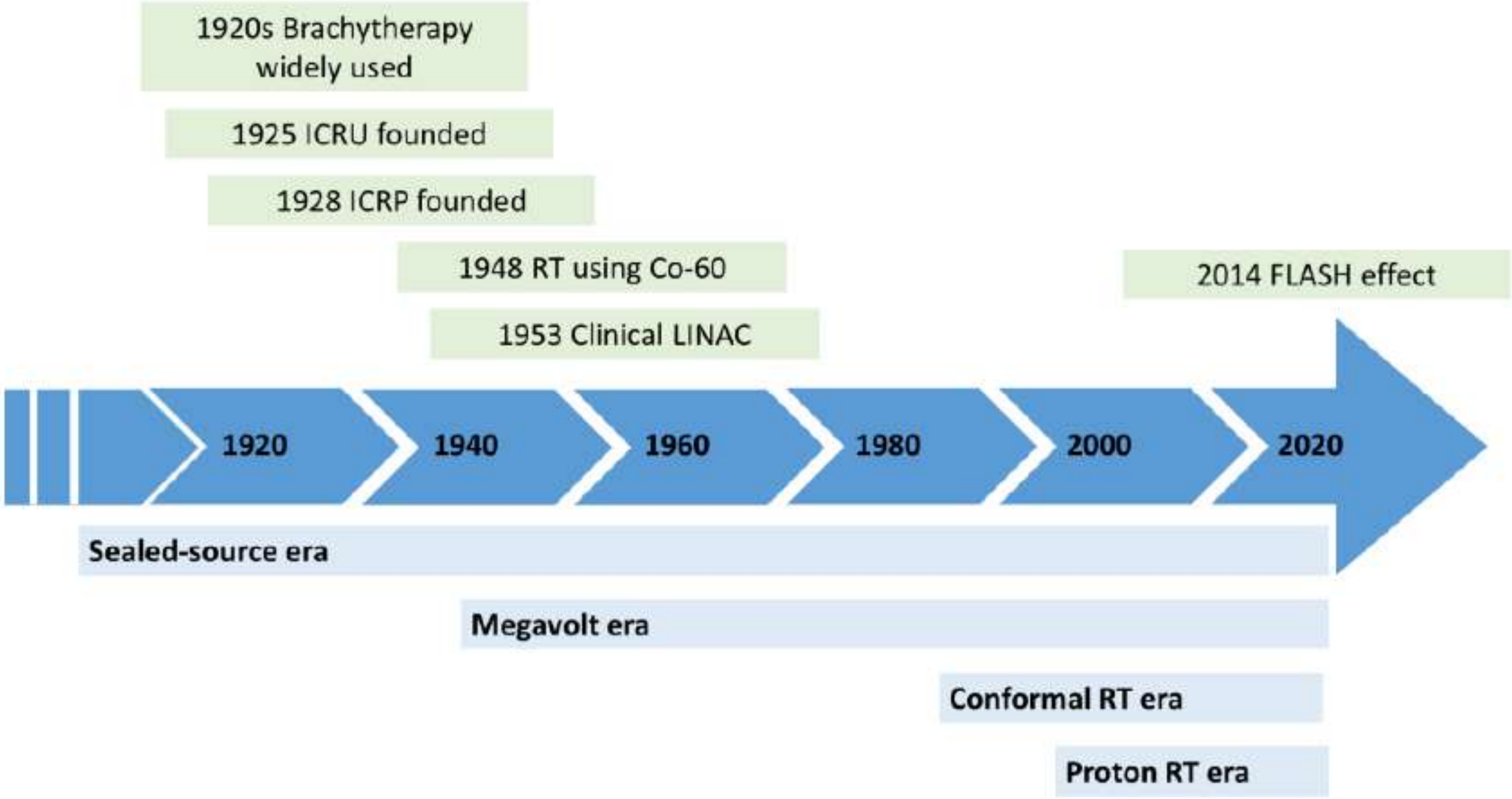
IMPACT OF DOSE AND VOLUME

CONFORMALITY

A NEED TO BRING FLASH RT TO THE SAME LEVEL OF TECHNOLOGICAL INNOVATION AS CONVENTIONAL



1920s Brachytherapy widely used

1925 ICRU founded

1928 ICRP founded

1948 RT using Co-60

1953 Clinical LINAC

2014 FLASH effect

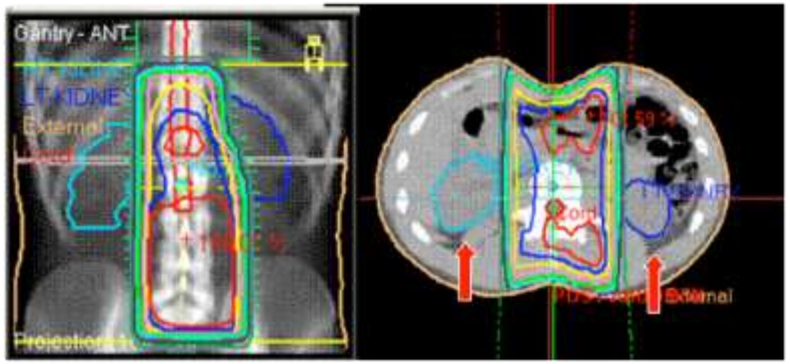
Sealed-source era

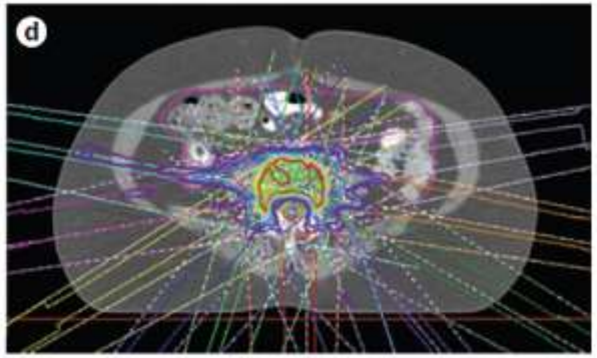
Megavolt era

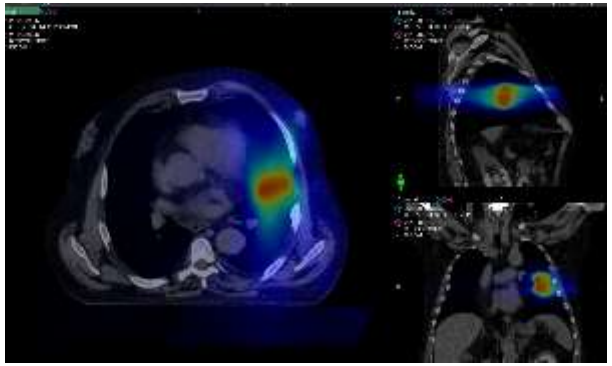
Conformal RT era

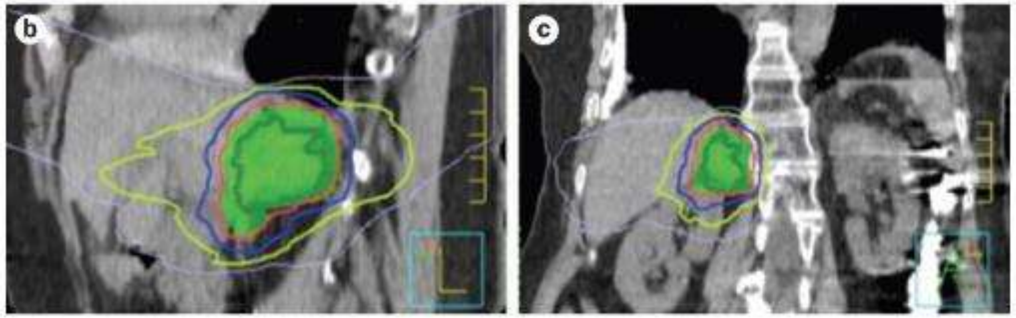
Proton RT era

WITH FLASH RT, FROM A CONFORMALITY POINT OF VIEW, WE ARE NOT EVEN IN THE 3D ERA



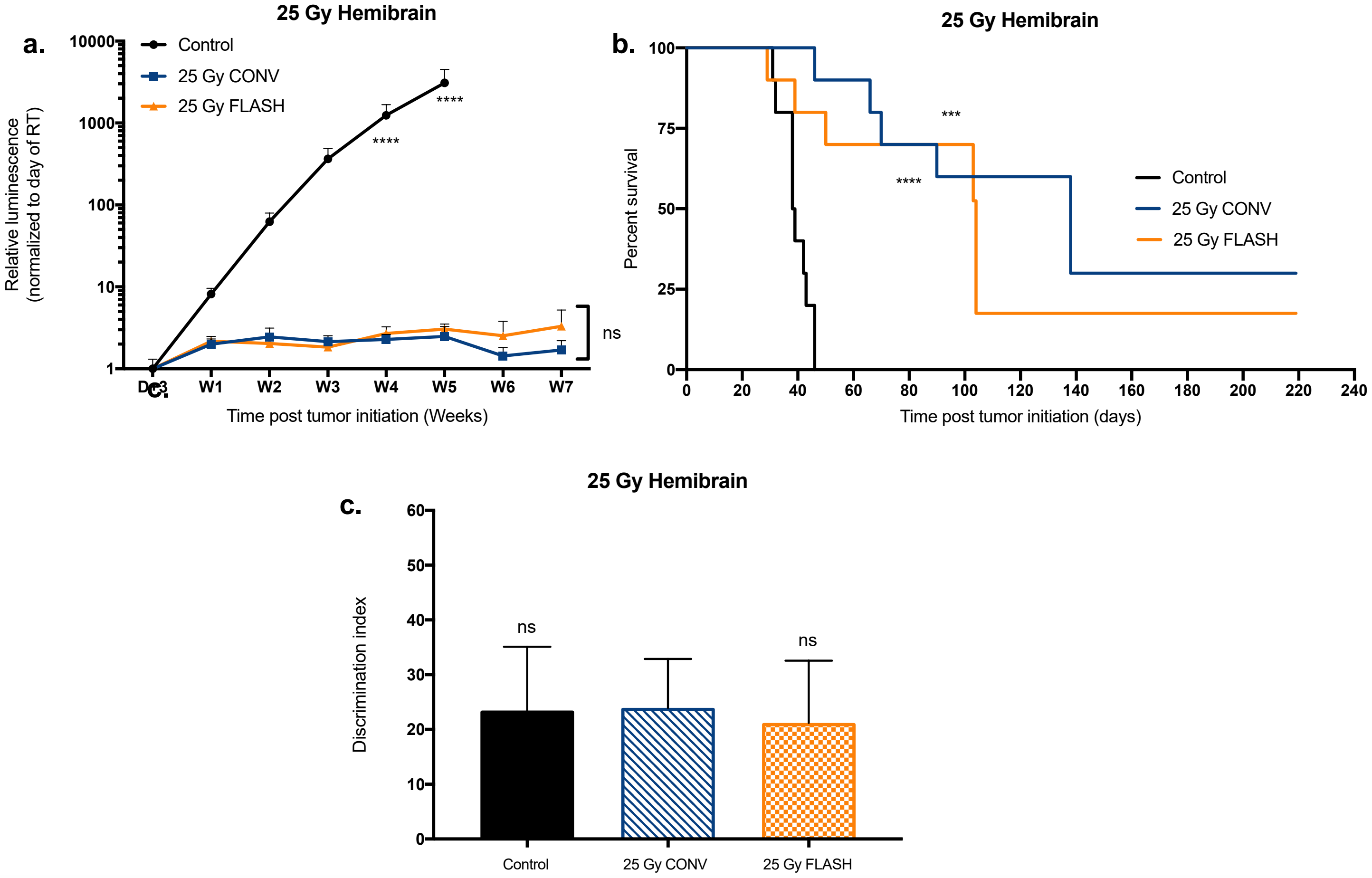






Salama, J. K. et al. *Nat. Rev. Clin. Oncol.* 9, 654–665 (2012)

CONFORMALITY



UNMET NEEDS IN MODERN RT

Oncological outcome: Local control/overall survival/organ preservation	Access to care	Quality of life: Normal tissue tolerance/ RT burden RT as less invasive ablation
Radioresistant tumors -> dose escalation	Availability of compact equipment	Quality of life: normal tissue tolerance-> after dose escalation
Tumor burden and tolerance of big Rt volumes	Workload of equipment	Quality of life: normal tissue tolerance-> at actual standard doses
Organ preservation -> dose escalation	Access to innovation	Quality of life: long-term toxicity of young survivors

RESOLVED QUESTIONS IN FLASH RT

Flash effect

- Protects normal tissues by 30-40%
- Kills tumors at least as well as conventional RT
- Observed with any fractionation
- Observed in many species and all tissues

Flash technology

- Flash can be produced with all RT modalities
- Observed at dose rates >40/100 Gy/s
- Total irradiation time <500 msec

Flash clinical transfer

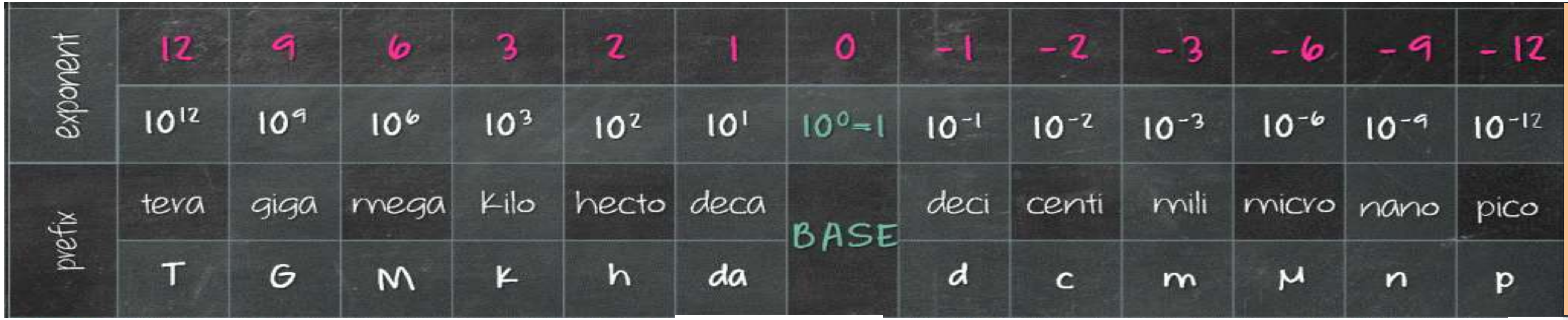
- Clinical studies in animal patients
- First-in-human
- First feasibility study in 10 patients

OPEN QUESTIONS AND UNMET NEEDS IN FLASH RT

Flash effect	**Flash technology**	**Flash clinical transfer**
🔋 Fully understanding underlying mechanism	🔋 Metrological needs for safe application : dosimetry, TPS, radioprotection	🪫 Defiining safe dose and volume starting points
🔋 Understand essential physical parameters to produce it	🪫 Conformality	🔋 Feasibility and safety studies in common indications
🪫 Understand relationship with volume	🪫 Compact and available equipment for deep-seated tumors and large volumes	🪫 Studies adressing unmet clinical needs

WHICH OF THE UNMET NEEDS IN MODERN RT COULD THEORITICALLY BE ADRESSED WITH FLASH RT

Oncological outcome: Local control/overall survival/organ preservation	Access to care	Quality of life: Normal tissue tolerance/ RT burden RT as less invasive ablation
✓ Radioresistant tumors -> dose escalation	? Availability of compact equipment	✓ Quality of life: normal tissue tolerance-> after dose escalation
? Tumor burden and tolerance of big RT volumes	✓ Workload of equipment	✓ Quality of life: normal tissue tolerance-> at actual standard doses
✓ Organ preservation -> dose escalation	? Access to innovation	✓ Quality of life: long-term toxicity of young survivors



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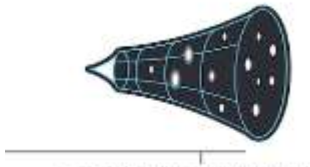
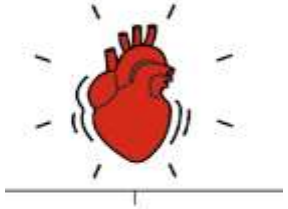
prefix	tera	giga	mega	Kilo	hecto	deca	BASE	deci	centi	mili	micro	nano	pico	Atto
	T	G	M	K	h	da		d	c	m	μ	n	p	



AGE OF THE UNIVERSE
1,000,000,000,000,000,000 SECONDS

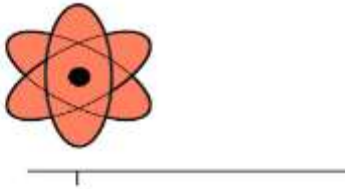


HEARTBEAT
1 SECOND

pFlash

eFlash

VHEE



ATTOSECOND
1/1,000,000,000,000,000,000 SECOND

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Pierre Agostini, Ferenc Krausz, Anne L'Huillier.
Electron in pulses of lights in the attoseconds' time scale

Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

FLASH «dream» team moved @ HUG

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DE GENÈVE

Biology team

R Leavitt
A Almeida
B Petit
J Ollivier
C Romero
C Godfroid
A Martinotti
J Franco-Perez
P Ballesteros-Zebadua
J Jansen

Clinical team

P Tsoutsou
A Durham
N Koutsouvelis

Charles Limoli and Team
M Acharya
P Montay-Gruel
J Baulch
B Allen
Y Alaghband
Peter Maxim

Billy Loo and Team
Richard Frock and team

Doug Spitz and team

Pedro Romero team (Immunology)

Genrich Tolstonog team (H&Neck)

FNSNF
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SCHWEIZERISCHER NATIONALFONDS
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recherche suisse contre le cancer
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swiss cancer research

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