Requirements for clinical translation of FLASH radiotherapy

How can SPES-LNL contribute?

Prof MC Vozenin
marie-catherine.vozenin@hug.ch

Vincent Favaudon

Growing community
Of 1500 scientists

2024: 213 articles
2025: 82 articles

physicsworld
TOP 10
BREAKTHROUGH
2022

2018-2019

Published OnlineFirst June 6, 2018; DOI: 10.1158/1078-0432.CCR-17-3375

Clinical Trial Brief Report

Clinical Cancer Research

The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients

Marie-Catherine Vozenin[1], Pauline De Fornel[2], Kristoffer Petersson[1,3], Vincent Favaudon[4], Maud Jaccard[1,3], Jean-François Germond[3], Benoit Petit[1], Marco Burki[5], Gisèle Ferrand[6], David Patin[3], Hanan Bouchaab[1], Mahmut Ozsahin[1,6], François Bochud[3], Claude Bailat[3], Patrick Devauchelle[2], and Jean Bourhis[1,6]

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]

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2014

RESEARCH ARTICLE

RADIATION TOXICITY

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

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

RESEARCH HIGHLIGHTS

IN BRIEF

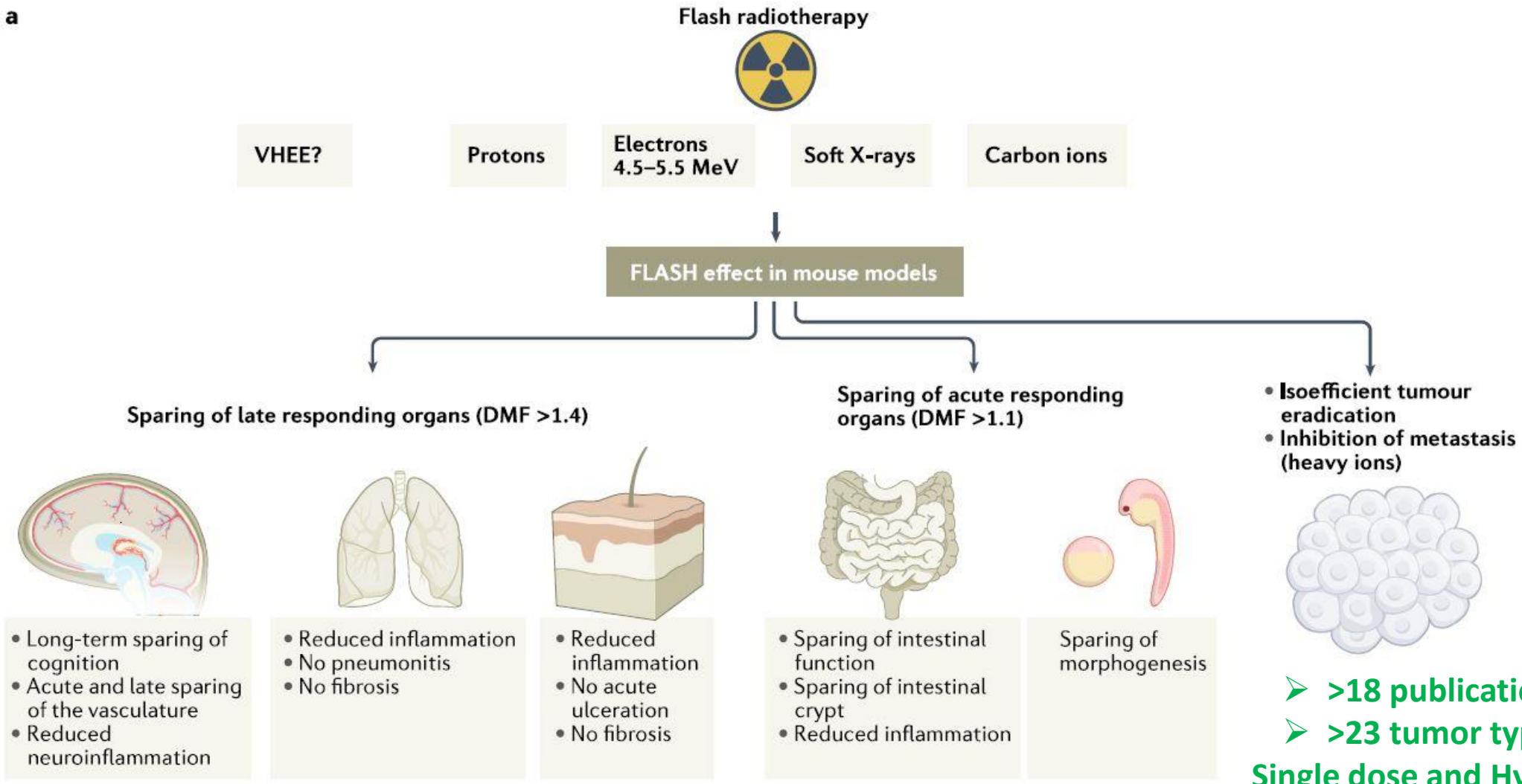
RADIOTHERAPY

FLASHing tumours

A new study in mice suggests that radiation delivered in short pulses at ultrahigh dose rates (FLASH) is as effective against lung tumours as conventional protracted single lower dose rates and has fewer side effects. Using both orthotopic lung tumours in immunocompetent mice and human lung tumour xenografts in nude mice, Favaudon *et al.* showed that FLASH irradiation caused less lung fibrogenesis and less apoptosis in normal tissue than conventional radiation. Although this technique was only tested in one tumour type, it suggests that delivery methods are crucial to minimizing radiation treatment side effects, and it has implications for therapeutic protocols.

ORIGINAL RESEARCH PAPER Favaudon, V. *et al.* Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. *Sci. Transl Med.* **6**, 245ra93 (2014)

Preclinical results



Long-term sparing of vasculature
No fibrosis

> 40 publications

- **>18 publications**
- **>23 tumor types**

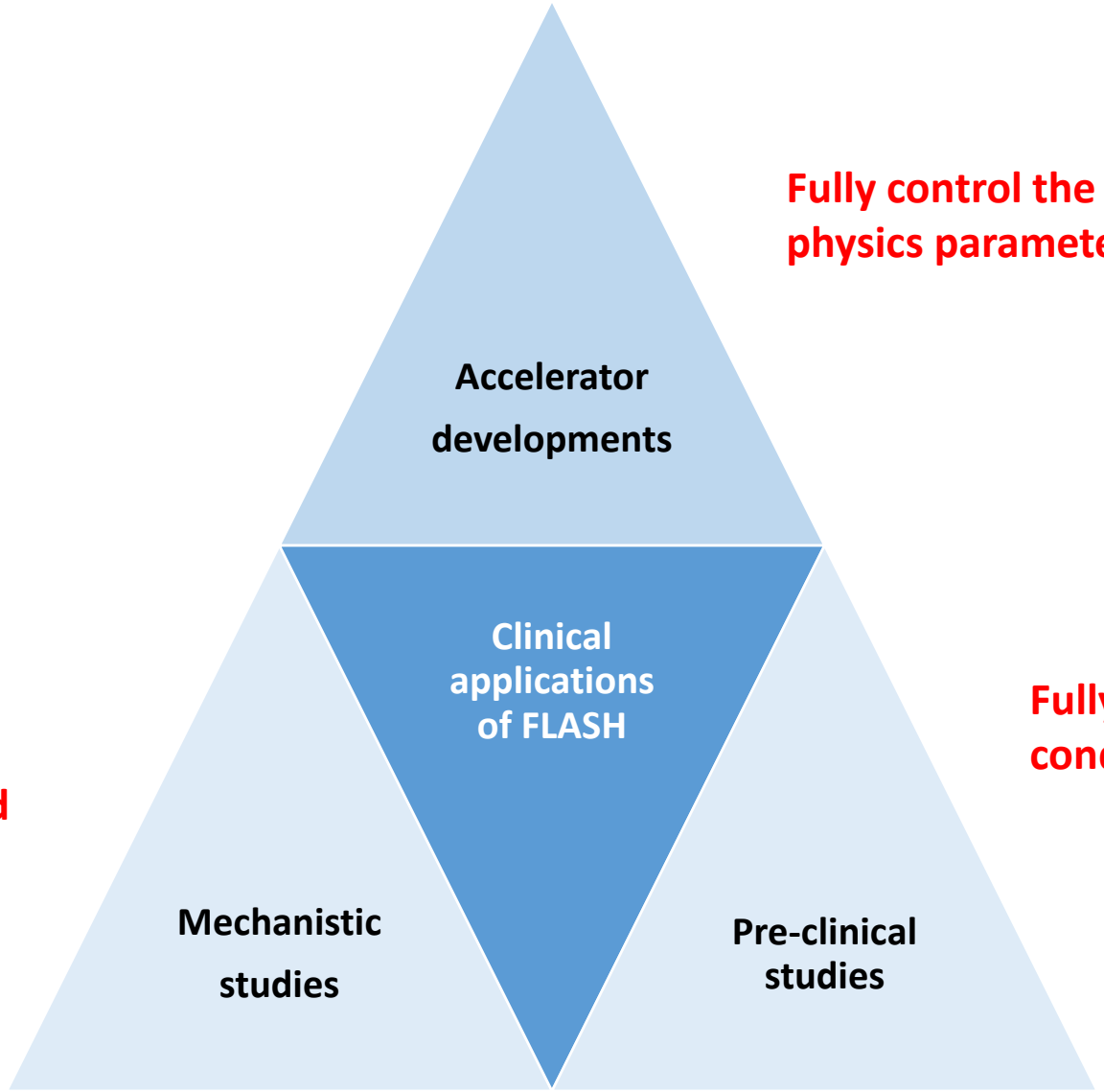
Single dose and HypoFx

TGD, TC and carcinogenesis

Chabi et al. study show Rr to FLASH

Not properly powered to show isoefficacy

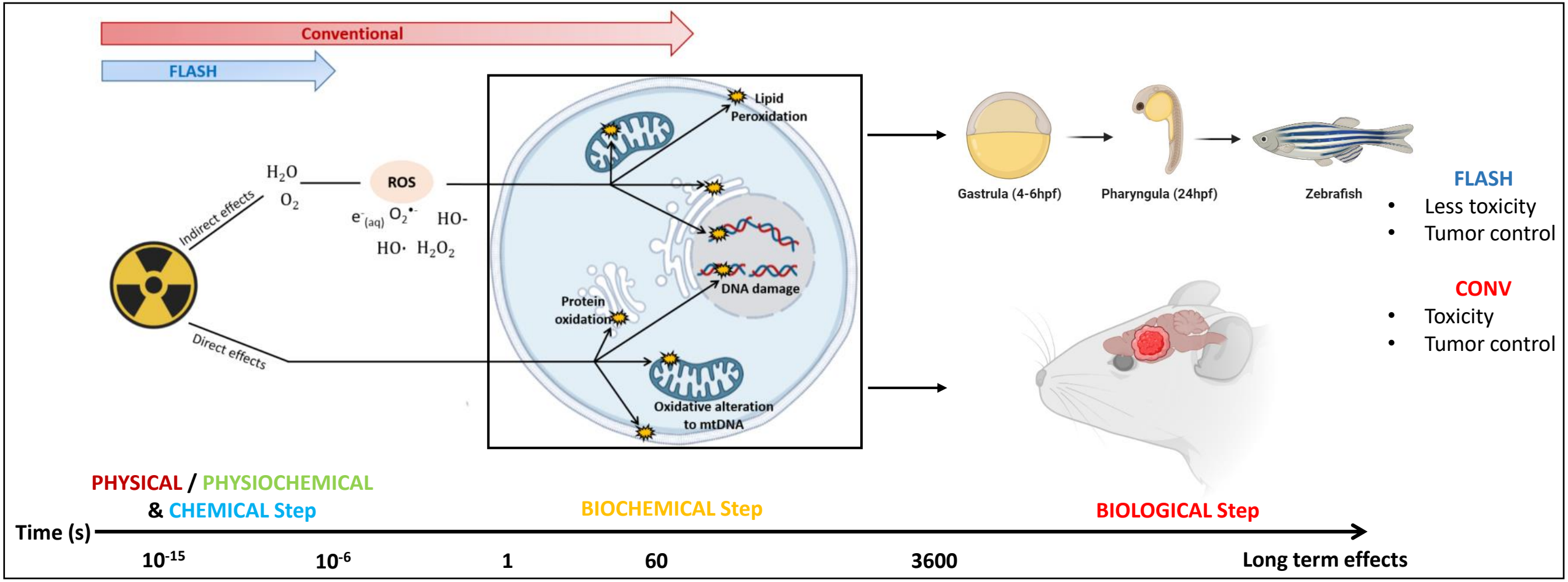
How can we use FLASH safely in the clinic?



Fully control the required physics parameters

Fully control the required conditions

Understand how Normal tissues are protected and Tumors destroyed?



Kacem et al., 2021, IJRB

Less ROS due to Radiolytic O2 depletion?

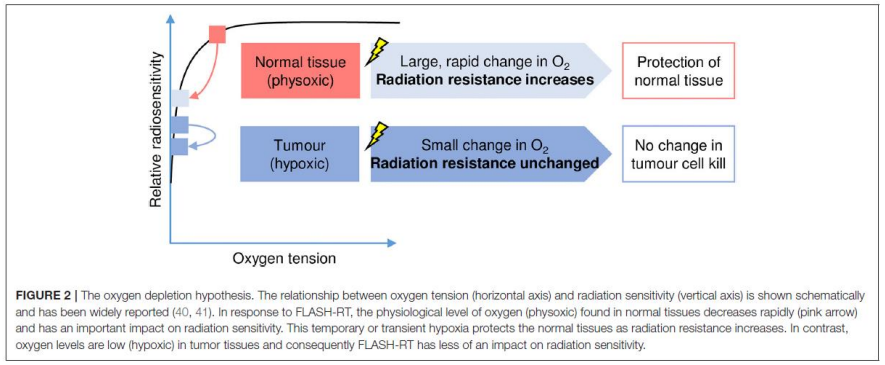


FIGURE 2 | The oxygen depletion hypothesis. The relationship between oxygen tension (horizontal axis) and radiation sensitivity (vertical axis) is shown schematically and has been widely reported (40, 41). In response to FLASH-RT, the physiological level of oxygen (physoxic) found in normal tissues decreases rapidly (pink arrow) and has an important impact on radiation sensitivity. This temporary or transient hypoxia protects the normal tissues as radiation resistance increases. In contrast, oxygen levels are low (hypoxic) in tumor tissues and consequently FLASH-RT has less of an impact on radiation sensitivity.

Wilson et al., Front in Oncol, 2020

Year	Lead author	Paper type	O_2 depletion per 100 Gy
1949	Day M.J.	experiment	3.3%
1969	Evans N.T.S.	experiment	2.6%
1974	Weiss H.	experiment	3.3%
1975	Ling C.	modelling	2.6%
1986	Michaels H.B.	experiment	3.3%
2019	Pratx	Modelling	5.5%
2020	Boscolo D.	Modelling	2.4%
2020	Petersson K.	Modelling	5% and 10%
2020	Zhou S.	Modelling	2.6%
2020	Hu A.	Modelling	3.7%
2020	Labarbe R. (IBA)	Modelling	2.2%

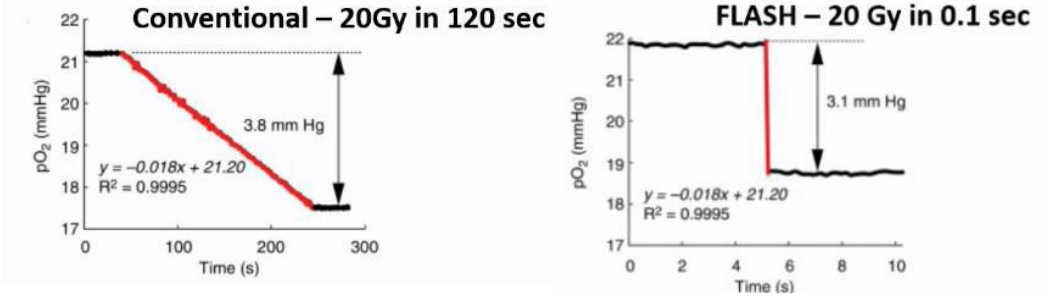
NO, Measurements do not support any radiolytic oxygen depletion at therapeutic doses (10 Gy) delivered FLASH

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Biology Contribution

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

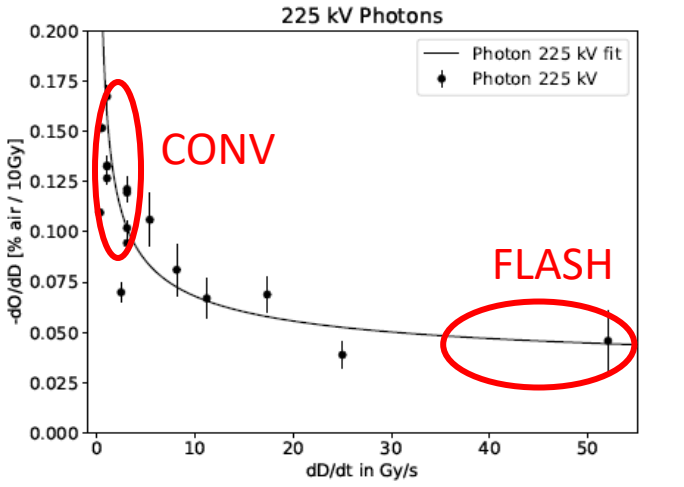
Xu Cao, PhD,*,†,1 Rongxiao Zhang, PhD,*,‡,§,1



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

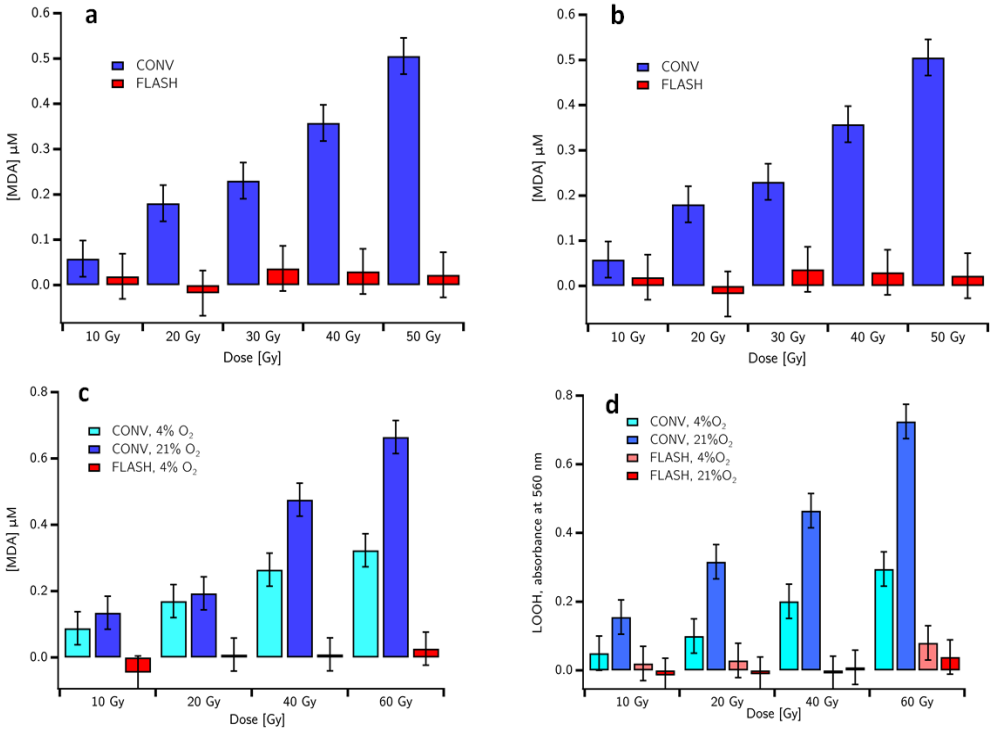


O2 depletion
NO

But oxygen status does matter

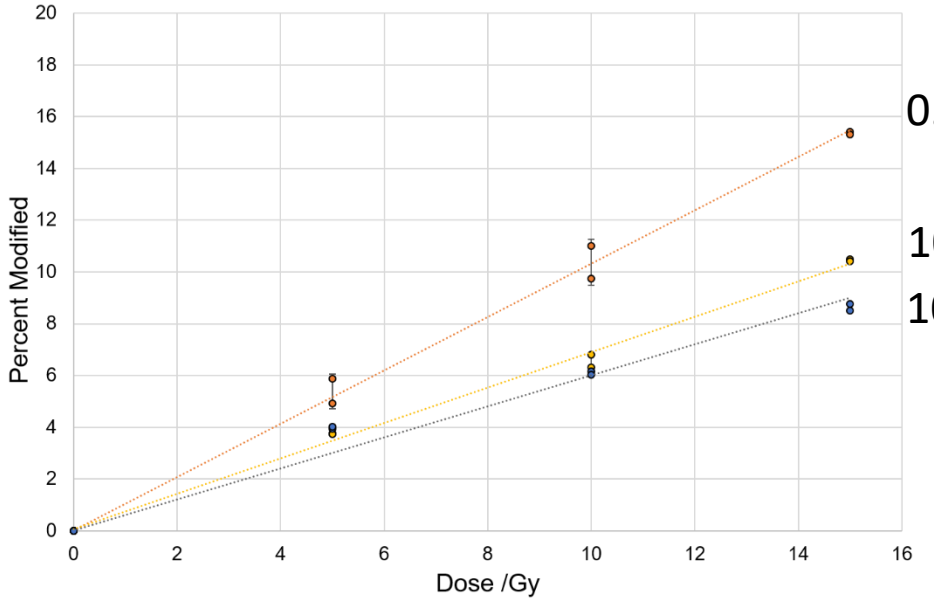
Froidevaux et al., Rad Phys Chem, 2023, doi: 10.1016/j.radphyschem.2022.110733

FLASH does not induce Lipid peroxydation

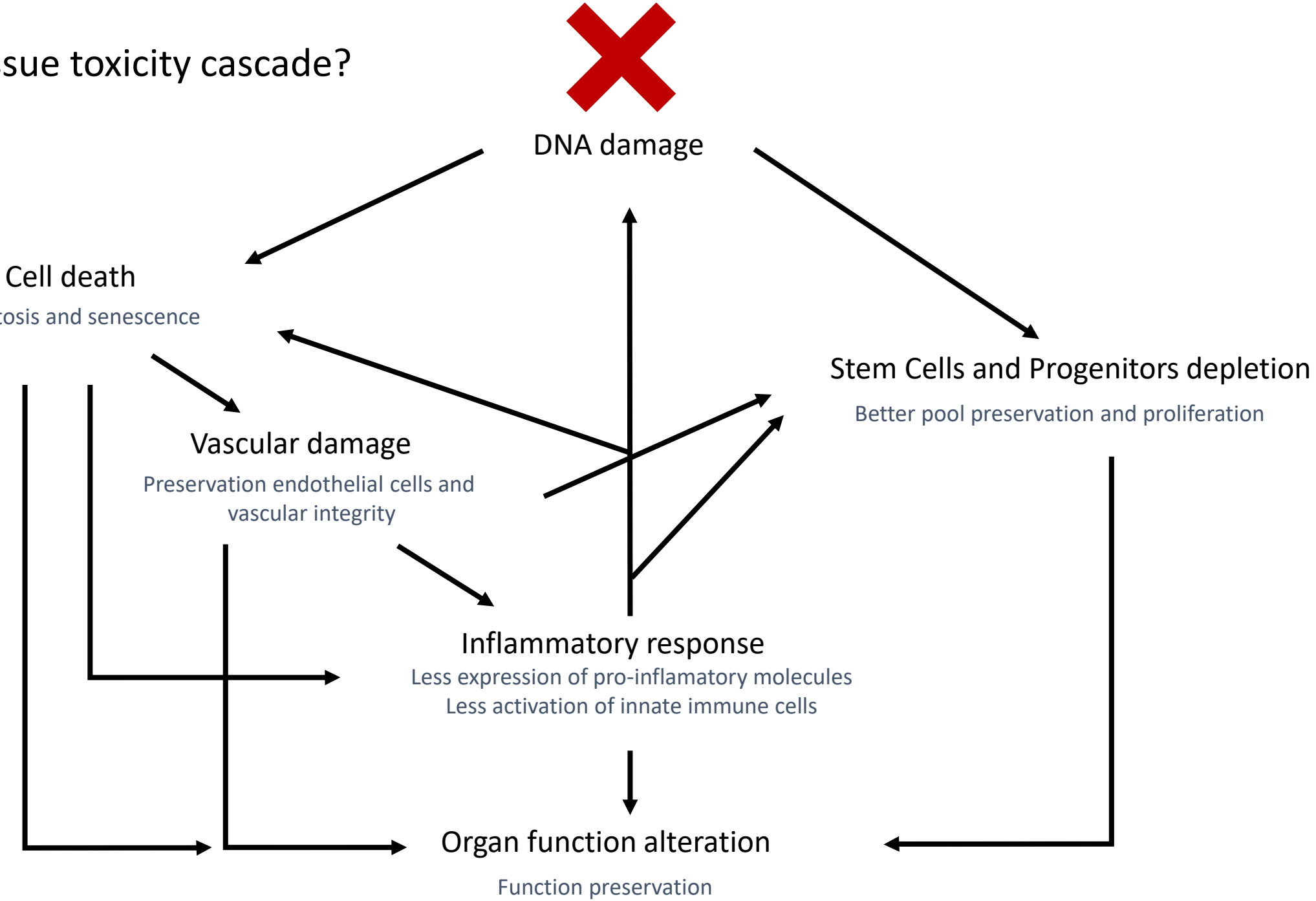


Gupta et al., Rad Res, 2024, doi: 10.1667/RADE-23-00131.1

Peptide oxidation is lower with FLASH

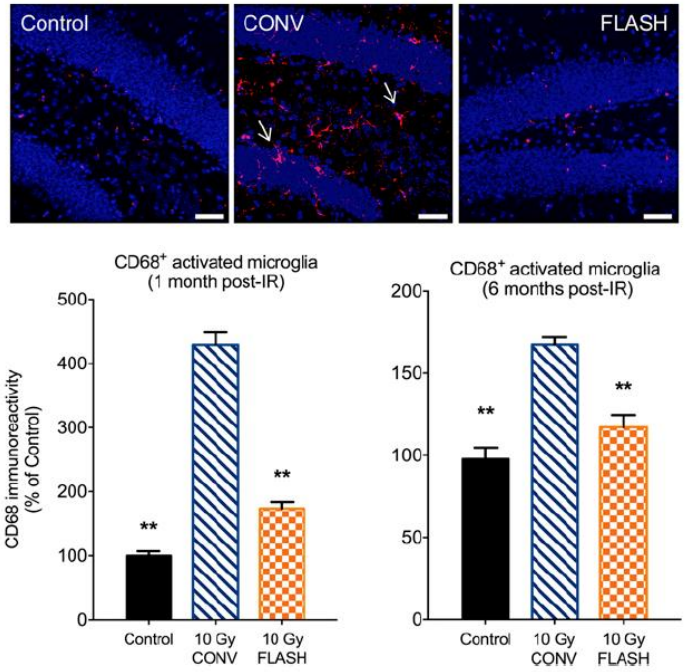


Normal tissue toxicity cascade?



Pierre Montay-Gruel, PhD

Less inflammation



in the brain

Montay-Gruel et al. 2019
Montay-Gruel et al. 2020
Simmons et al. 2019

in the lung

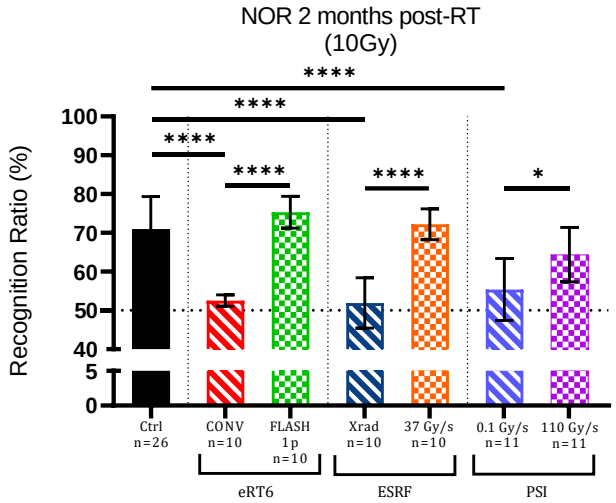
Favaudon et al. 2014

in the skin

Velalopoulou et al. 2021, pFLASH
Cunningham et al. 2021, pFLASH

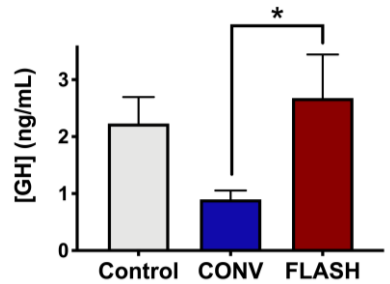
YES!

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



YES!

in the gut

Levy et al. 2017

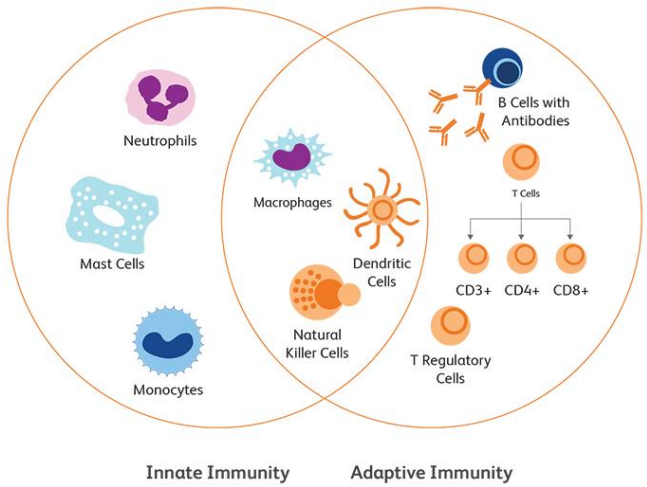
in the heart

Kim et al. 2024

in the salivary gland

Chowdhury et al. 2024

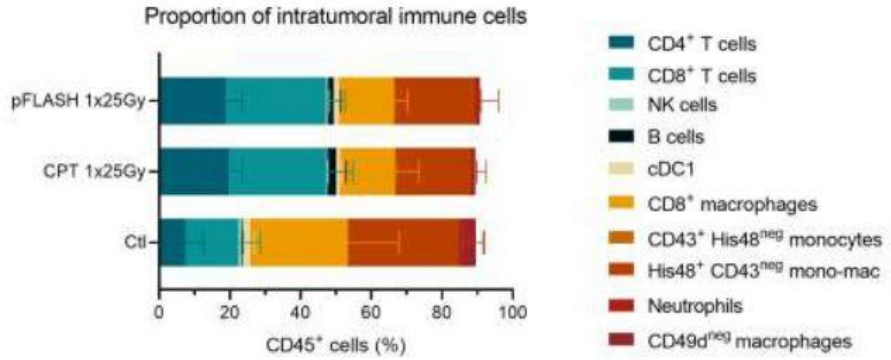
Better anti-tumor immunity?



Iturri et al., IJROBP, 2023, doi: 10.1016/j.ijrobp.2022.12.018.

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

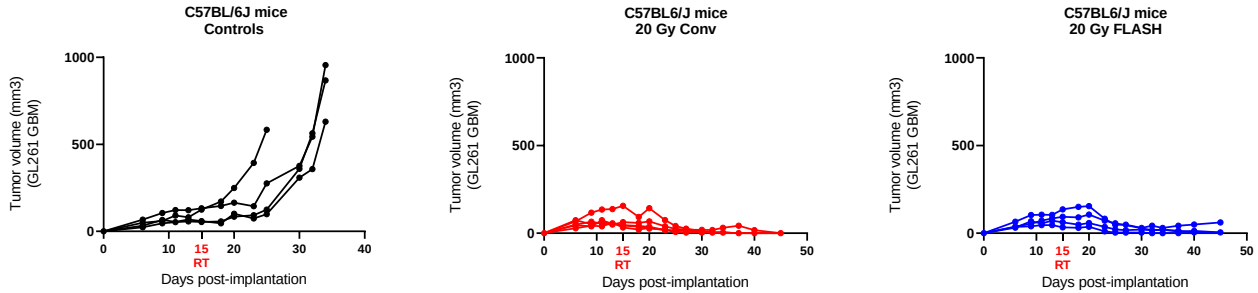
A



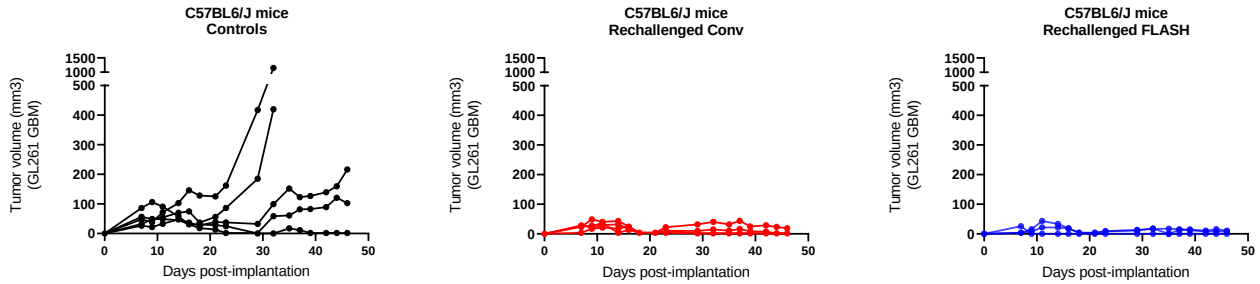
Almeida et al., R&O, 2023,
doi.org/10.1016/j.radonc.2023.109953

20 Gy
pFLASH: 100 Gy/s
pConventional: 0.1 Gy/s

Tumor experiment

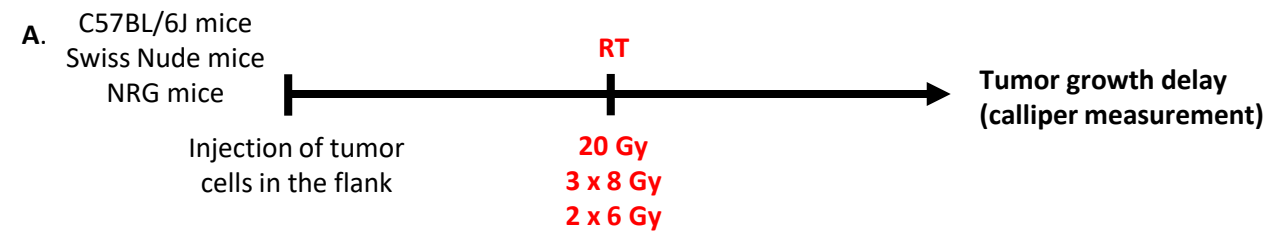


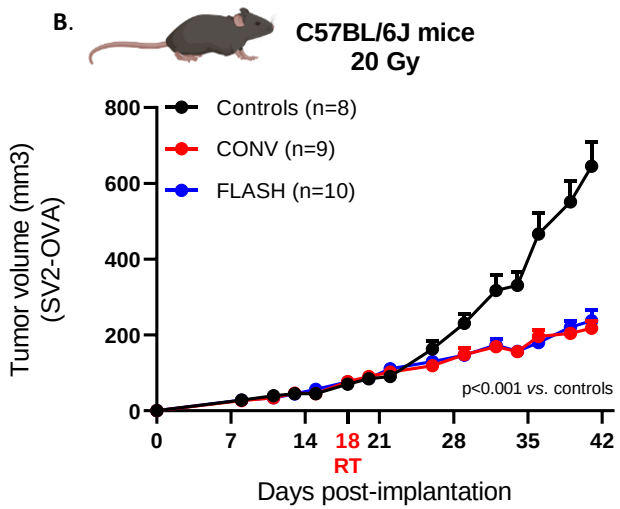
Rechallenge experiment

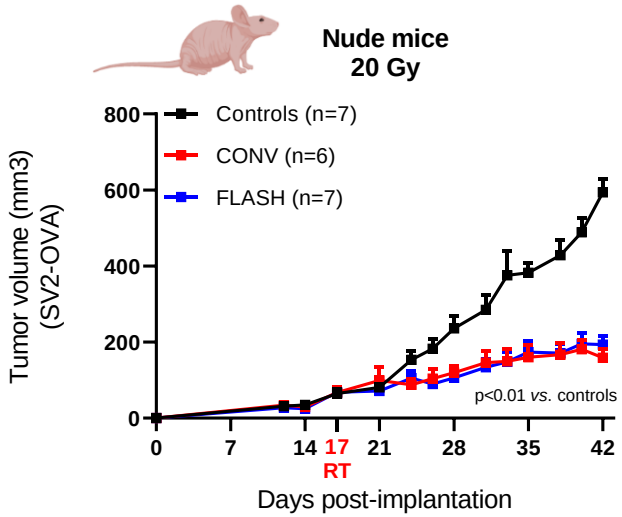


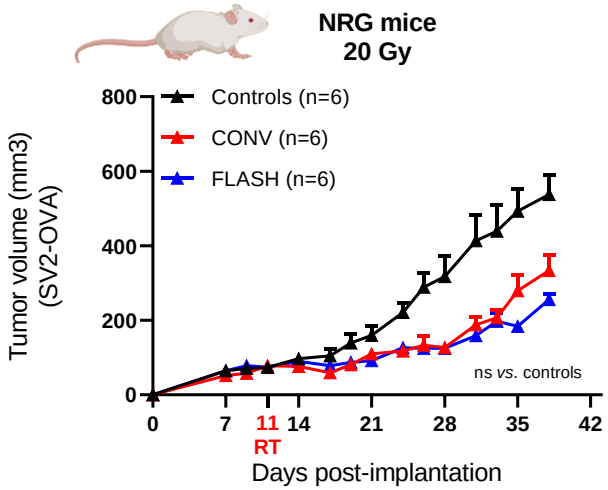
Almeida et al, IJROBP, 2024, doi: 10.1016/j.ijrobp.2023.10.031

20 Gy
eFLASH: 1000 Gy/s
eConventional: 0.1 Gy/s

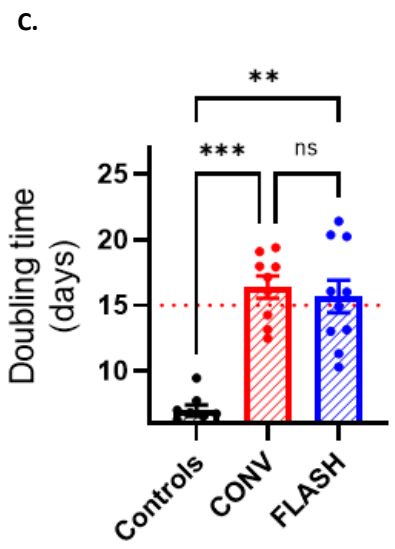


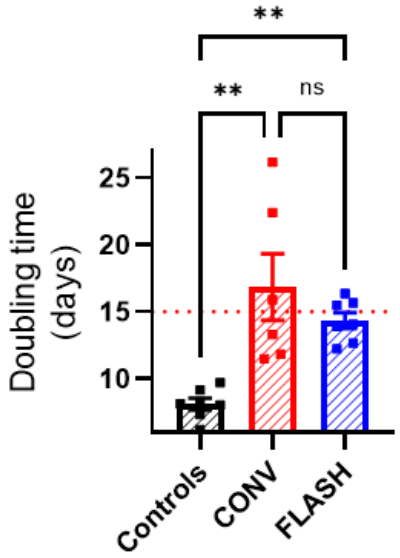


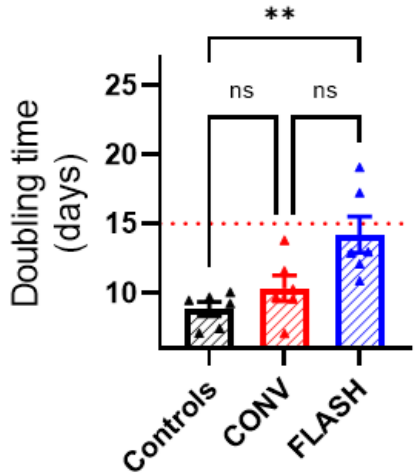




NO!





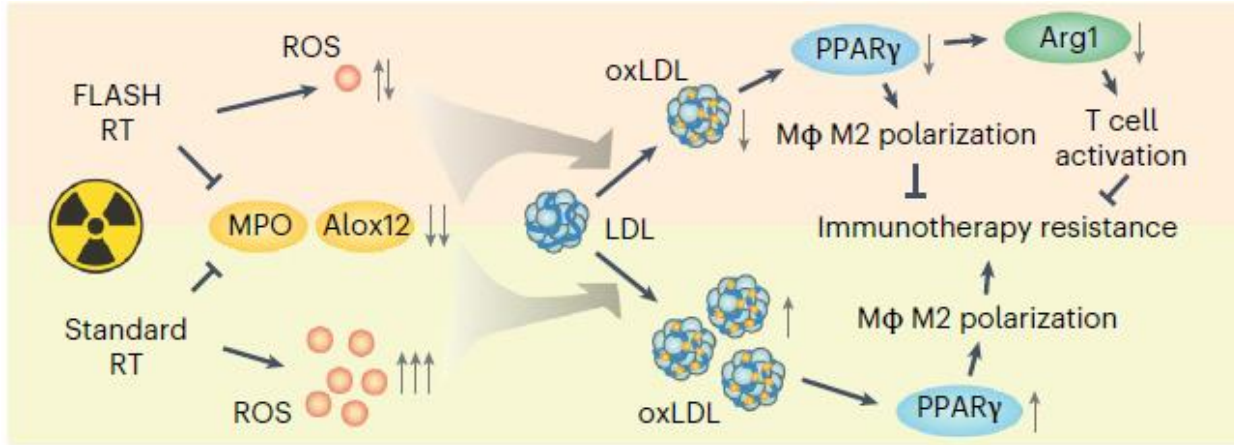


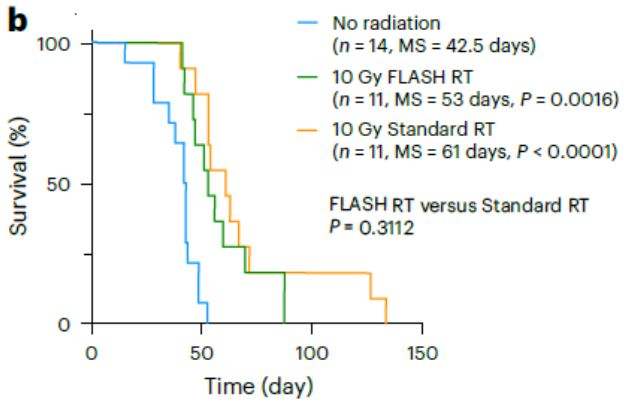
nature cancer

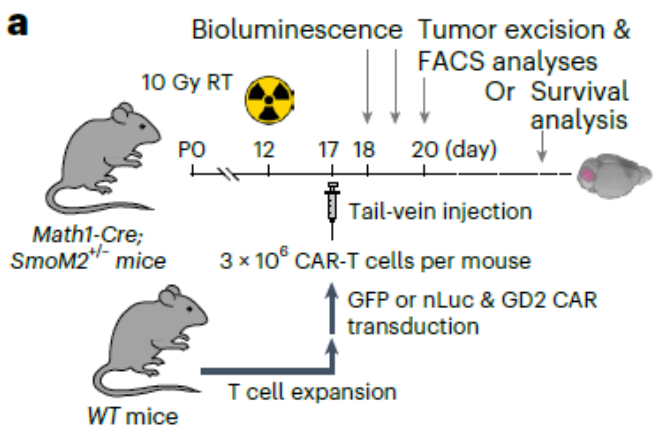
Article

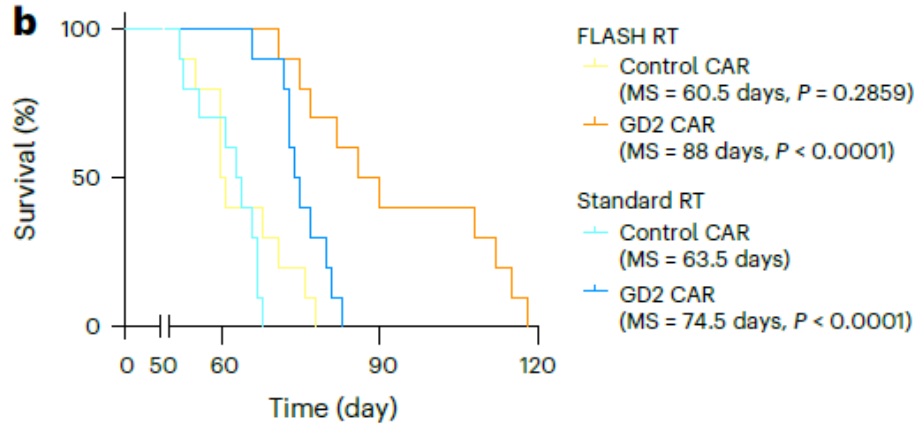
https://doi.org/10.1038/s43018-025-00905-6

FLASH radiation reprograms lipid metabolism and macrophage immunity and sensitizes medulloblastoma to CAR-T cell therapy









Take-home messages:

- **Normal tissue reponse is dose rate dependent but tumor killing is dose rate independent**
- **Radiolytic O2 depletion cannot explain the FLASH effect**

At least we can exclude some mechanisms

A common mechanism in normal tissue and tumors?

FLASH kill tumor the same way than CONV (DNA damage, cell death, immune response)

What needs to be explored

Differential effect betwen normal tissue and tumor => fundamental difference between normal and tumor tissue

- Metabolism
- Cell signaling

New hypothesis:

Contribution of proteostasis

Biophysical properties of Normal tissues vs tumors (stiffness)

FLASH-RT in the clinic
Current status

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]

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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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FLASH-RT
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.

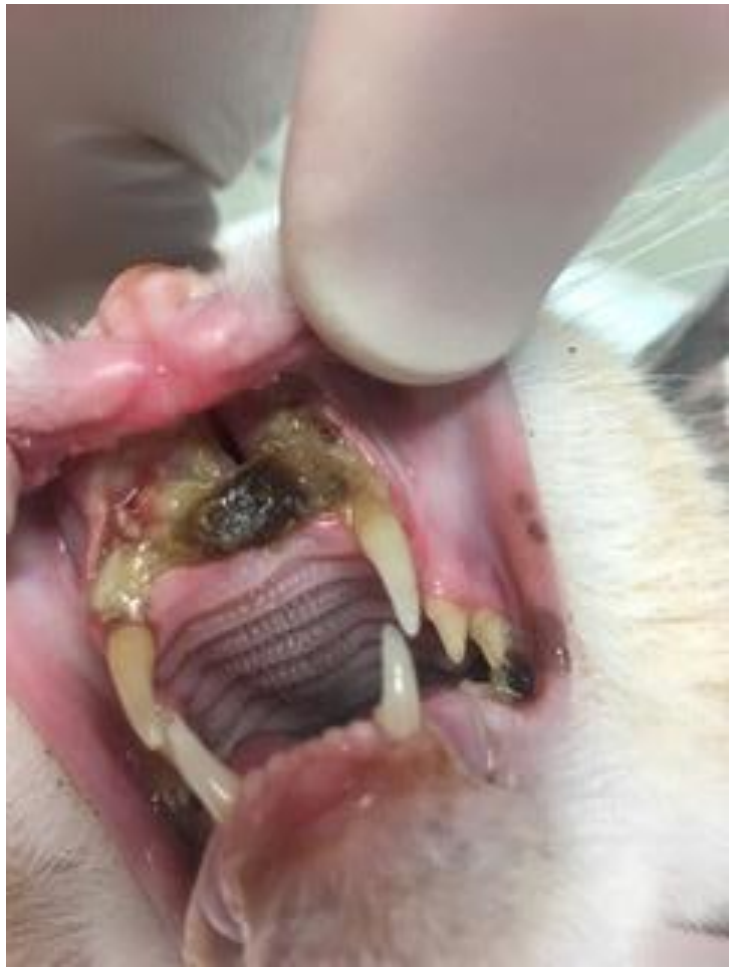
CONCLUSIONS AND RELEVANCE In this nonrandomized trial, clinical workflow metrics, treatment efficacy, and safety data demonstrated that ultra-high-dose-rate proton FLASH radiotherapy was clinically feasible. The treatment efficacy and the profile of adverse events were comparable with those of standard-of-care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

Single high dose

Rohrer-Bley et al., 2022 Clin Cancer Res
doi: 10.1158/1078-0432.CCR-22-0262

30 Gy
eFLASH: 1500 Gy/s
10x4.8 Gy
eConventional: 0.1 Gy/s

3/7 FLASH treated cats



Borresen et al., 2023 Front in Oncol
DOI 10.3389/fonc.2023.1256760

30-42 Gy
eFLASH: 115 Gy/s

4/7 FLASH treated dogs

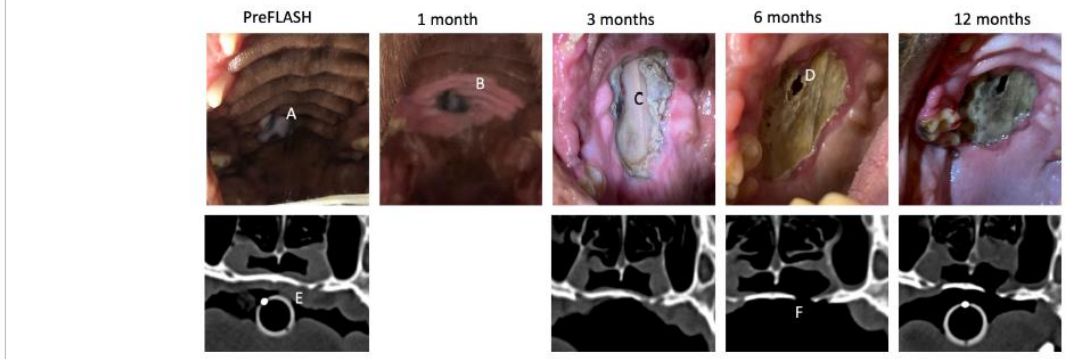


FIGURE 2
Dog no 5's treatment response and toxicity, pictures and CT. Pictures of dog no 5 from pre-FLASH radiotherapy treatment to 12 months post treatment, incl. CT before/after treatment. This dog experienced a complete response and ORN. **(A)** Malignant melanoma at pretreatment. **(B)** Delineation of the treatment field by mucosal depigmentation. **(C)** Grade 3 mucosal defect at 3 months post treatment which subsequently progressed. **(D)** ORN and oronasal fistula. **(E)** Decreased density of the palatine bone at pre-treatment at site of later oronasal fistula development. **(F)** Complete defect in palatine bone at 6 months post treatment.

FEATHER: Phase 2/3 trial on feline oral squamous cell carcinoma

2 proton arms with comparable BED (for CONV)

- **Arm 1: 3x11Gy CONV**
- **Arm 2: 3x11Gy FLASH**

Transmission beams (RBE = 1)

- **Avoid energy-switching deadtime**
- **Avoid range and LET uncertainties**
- **Smaller beams = higher dose rate**

10x4.8 Gy = 48Gy		
	BED [Gy]	EQD2 [Gy]
α/β = 2	163.2	81.6
α/β = 3	124.8	74.9
α/β = 10	**71.0**	**59.2**

3x11 Gy = 33Gy		
	BED [Gy]	EQD2 [Gy]
α/β = 2	214.5	107.3
α/β = 3	154.0	92.4
α/β = 10	**69.3**	**57.8**

Primary endpoint: acute toxicity

Secondary endpoint: anti-tumor efficacy

KFS 5639-08-2022, PI: C. Rohrer Bley, UZH
S. Psoroulas, UZH / DC Weber, PSI / MCVozenin, HUG

How use FLASH-RT in the clinic?

ELSEVIER

Seminars in Radiation Oncology

Navigating the Critical Translational Questions for Implementing FLASH in the Clinic

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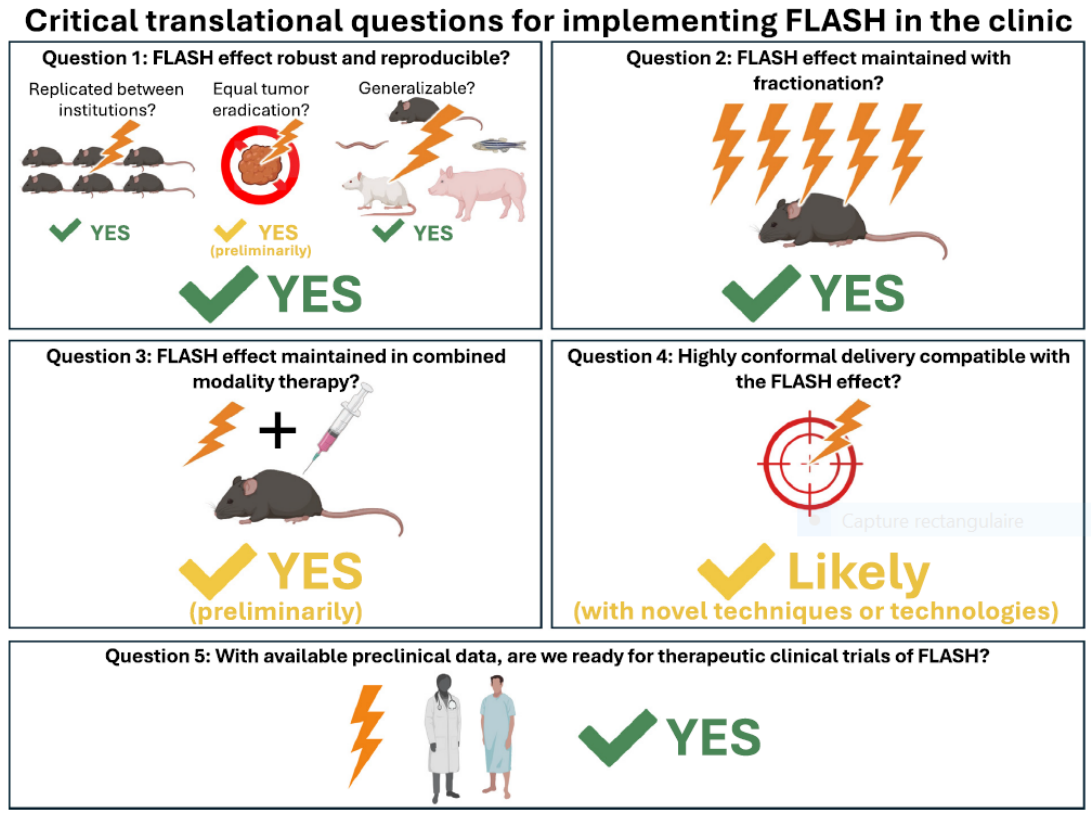


Pre-clinical research dedicated to answer clinical questions

How use FLASH-RT in the clinic?

Technology and parameters
Impact of the volume/conformality

Have we really defined the optimal beam parameters?

In rodent, probably yes

Standard RT: Dose is delivered in several minutes

With FLASH, dose is delivered in milliseconds

In micro-seconds

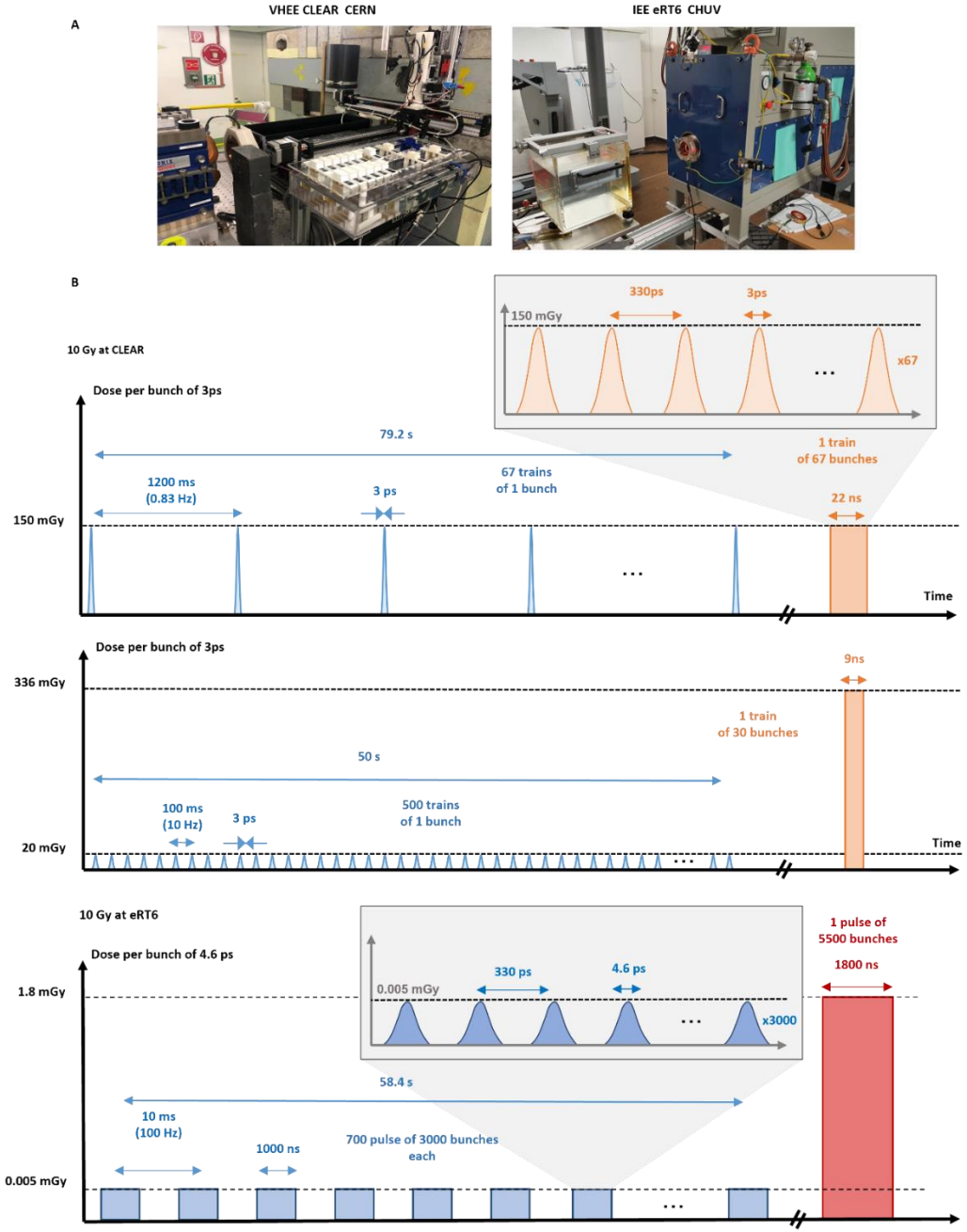
Even in nano-seconds

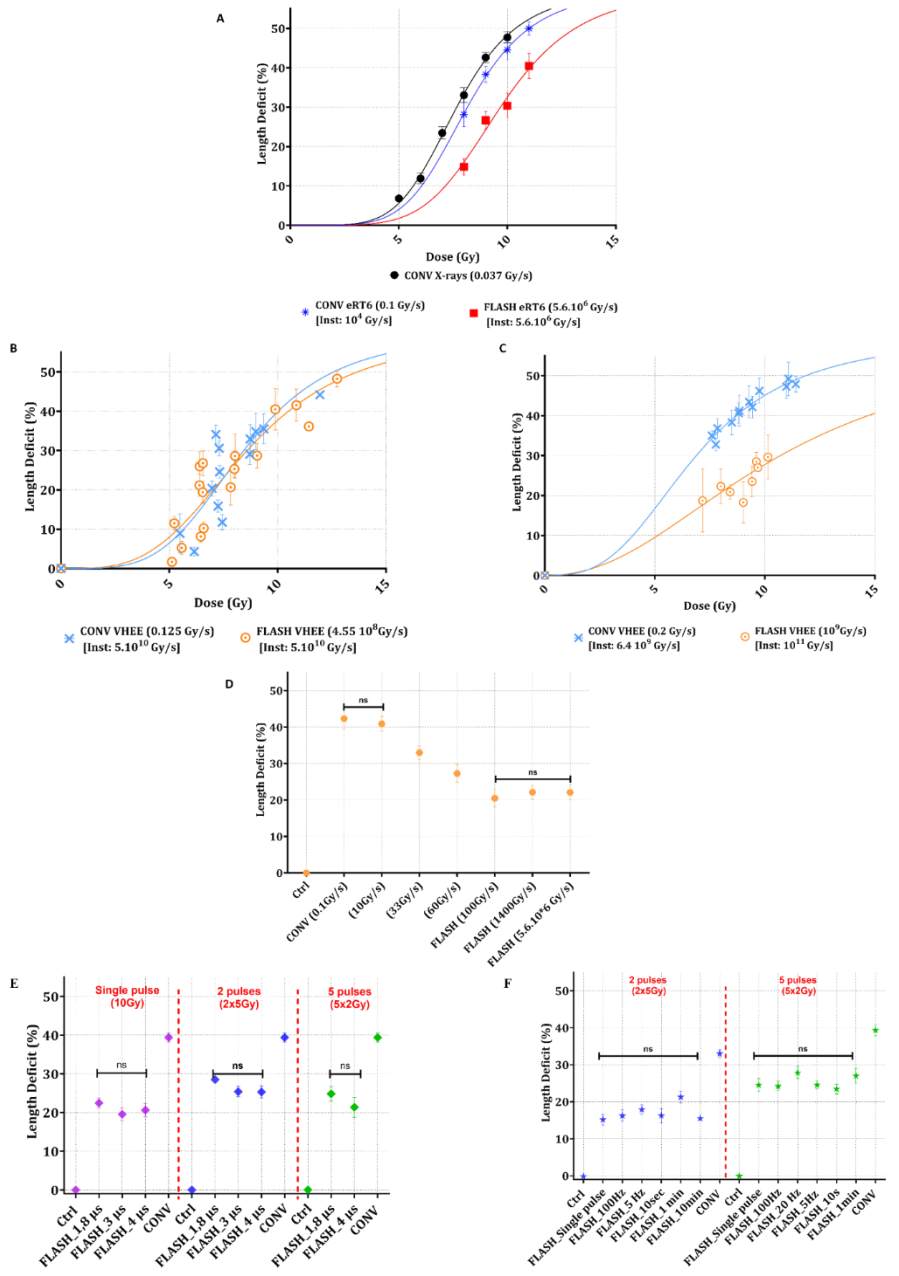
SPES cyclotron can contribute to define better the FLASH parameters

Intense 30 à 70 MeV proton beam: nanoAmps to 700 microAmps

The beam can be pulsed-
pulses width = microseconds- 100 Hz
Frequency = milliseseconds- 100 Hz

Beam size: 9 mm total
1 σ = 3mm


A
VHEE CLEAR CERN
IEE eRT6 CHUV
B
10 Gy at CLEAR
Dose per bunch of 3ps
150 mGy
330ps
3ps
x67
79.2 s
1 train
of 67 bunches
67 trains
of 1 bunch
1200 ms
(0.83 Hz)
3 ps
22 ns
Time
Dose per bunch of 3ps
336 mGy
9ns
1 train
of 30 bunches
50 s
100 ms
(10 Hz)
3 ps
500 trains
of 1 bunch
20 mGy
Time
10 Gy at eRT6
Dose per bunch of 4.6 ps
1 pulse of
5500 bunches
1800 ns
1.8 mGy
0.005 mGy
330 ps
4.6 ps
x3000
58.4 s
10 ms
(100 Hz)
1000 ns
700 pulse of 3000 bunches
each
0.005 mGy


A
Length Deficit (%)
Dose (Gy)
CONV X-rays (0.037 Gy/s)
CONV eRT6 (0.1 Gy/s)
[Inst: 10⁴ Gy/s]
FLASH eRT6 (5.6.10⁶ Gy/s)
[Inst: 5.6.10⁶ Gy/s]
B
C
CONV VHEE (0.125 Gy/s)
[Inst: 5.10¹⁰ Gy/s]
FLASH VHEE (4.55 10⁸Gy/s)
[Inst: 5.10¹⁰ Gy/s]
CONV VHEE (0.2 Gy/s)
[Inst: 6.4 10⁹ Gy/s]
FLASH VHEE (10⁹Gy/s)
[Inst: 10¹¹ Gy/s]
D
ns
Ctrl
CONV (0.1Gy/s)
(10Gy/s)
(33Gy/s)
(60Gy/s)
FLASH (100Gy/s)
FLASH (1400Gy/s)
FLASH (5.6.10⁶Gy/s)
E
Single pulse
(10Gy)
2 pulses
(2x5Gy)
5 pulses
(5x2Gy)
Ctrl
FLASH_1.8 µs
FLASH_3 µs
FLASH_4 µs
CONV
F
2 pulses
(2x5Gy)
5 pulses
(5x2Gy)
FLASH_Single pulse
FLASH_100Hz
FLASH_5 Hz
FLASH_10sec
FLASH_1 min
FLASH_10min
FLASH_20 Hz
FLASH_5Hz
FLASH_10s
FLASH_1min

SPES cyclotron can contribute to

- **Test of new detectors**
- **Understand better the mechanisms-**
  - **Radiation chemistry**
  - **Biology of normal tissue**
  - **Biology of tumors**

Swiss FLASH «dream» team

Biology team

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P Ballesteros-Zebadua
B Petit
J Ollivier
H Kacem
A Almeida
L Kunz
M Knol
A Job
A Martinotti
C Romero
C Godfroid
R Leavitt
J Jansen

Clinical team

P Tsoutsou
A Durham
N Koutsouvelis

Physics and clinical team PSI

D C Weber
S Psoroulas
T Lomax
M Togno
M David
S Sairos
R Schafer

Veterinary school Zurich

C Rohrer-Bley and team

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SCHWEIZERISCHER NATIONALFONDS
FONDO NAZIONALE SVIZZERO
SWISS NATIONAL SCIENCE FOUNDATION

SPIRIT

krebsforschung schweiz
recherche suisse contre le cancer
ricerca svizzera contro il cancro
swiss cancer research

oncosuisse

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

PHRT
Varian

NIH
NATIONAL CANCER INSTITUTE

P01/R01

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M Acharya
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Peter Maxim

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