RADIO
ONCOLOGIE

From irradiation at ultrahigh dose rate to FLASH Radiotherapy: Experimental, conceptual and clinical challenges

Prof. Marie-Catherine Vozenin

UNIL | Université de Lausanne
CHUV

Disclosures

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

V Favaudon

What is FLASH radiotherapy?

FLASH radiotherapy

Irradiation at ultra high dose rate

Very fast delivery of the dose

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

BUT

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*

What is the interest of FLASH radiotherapy?

THE FLASH EFFECT is a biological effect

Normal tissue sparing

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

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

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

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

Proton
Cunningham et al., **Cancers**, 2021 (PBS)
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

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

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

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

2019

March 2021

At Ohio State University,
President Biden Introduced to the Future Potential of FLASH with Electrons

Explored 40 years ago… it was abandonned Why?

1970 1980

2007/2008 2019

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

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

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

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

Tumor and Normal tissue response should be investigated in parallel

and

in vivo models should be used

How use FLASH-RT in the clinic?

Technology and medical physics' questions
Impact of fractionation/interval
Impact of the volume/conformality

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

TABLE 3 | Some relevant advantages and disadvantages of current and prospective FLASH radiotherapy sources (color coded by radiation modality).

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
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.
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

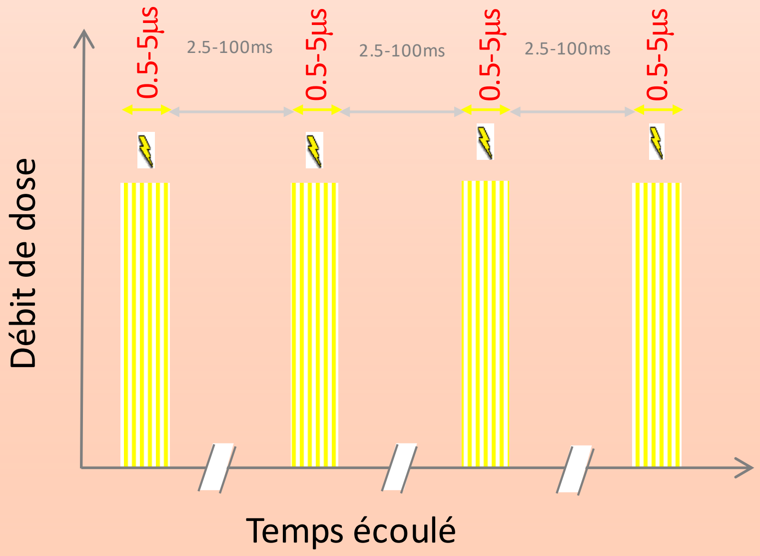
First demonstration of the FLASH effect with ultrahigh dose-rate high energy X-rays

Feng Gao[1,+], Yiwei Yang[2,+], Hongyu Zhu[3,+], JianXin Wang[4], Dexin Xiao[4], Zheng Zhou[4], Tangzhi Dai[1], Yu Zhang[1], Gang Feng[1], Jie Li[1], Binwei Lin[1], Gang Xie[5], Qi Ke[5], Kui Zhou[4], Peng Li[4], Xuming Sheng[4], Hanbin Wang[4], Longgang Yan[4], Chenglong Lao[4], Ming Li[4], Yanhua Lu[4], Menxue Chen[4], Jianheng Zhao[4], Song Feng[6], Xiaobo Du[1,*], and Dai Wu[4,*]

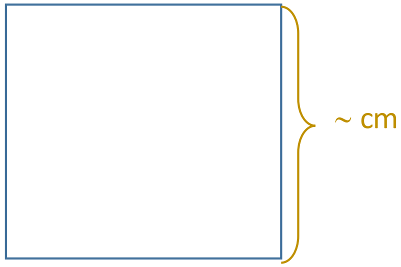
Gao et al., bioRxiv, 2020

Technology

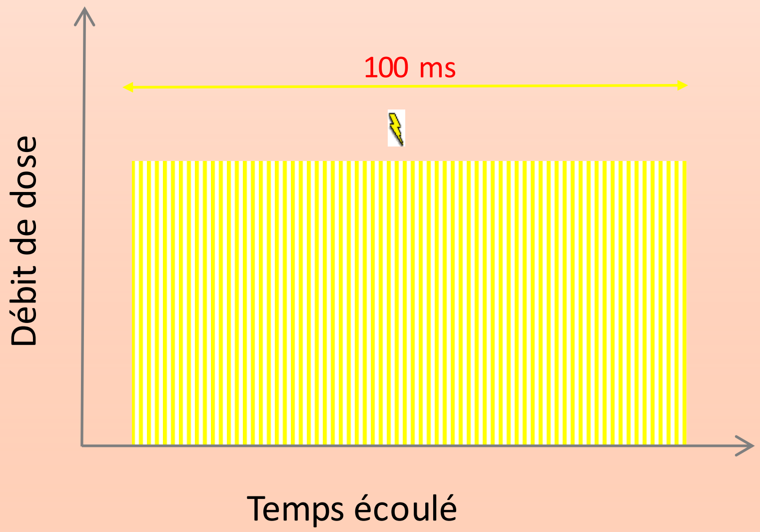
Structure pulsée d’un faisceau électron



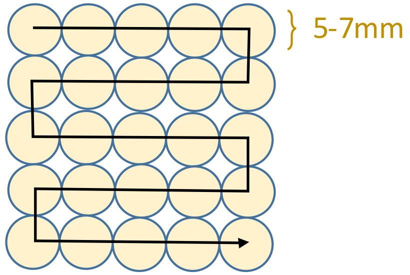
- 1 – 10 pulses
- Microstructure: 5000 bunches
- Pulse repetition frequency 10-250Hz



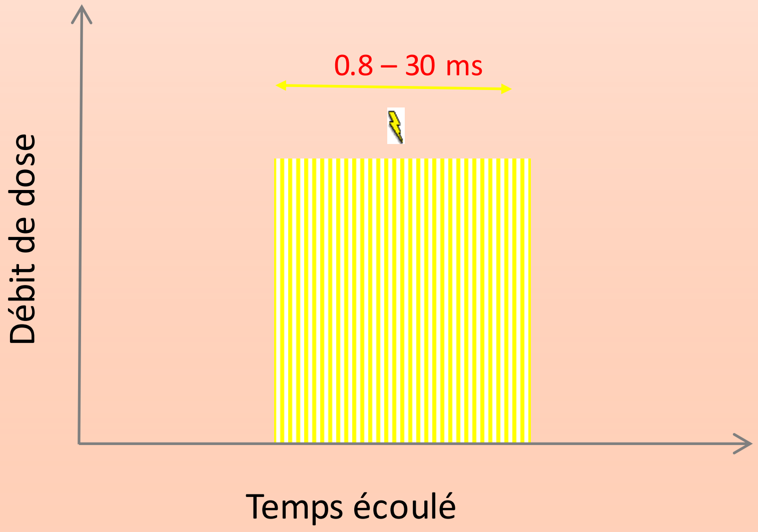
Structure d’un faisceau proton



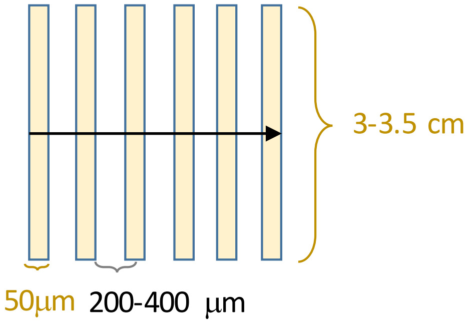
- 1 pulse
- Microstructure: 10^7 bunches
- Spot scanning (@1000Hz)



Structure d’un faisceau RX synchrotron



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



FLASH-RT can be fractionated

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

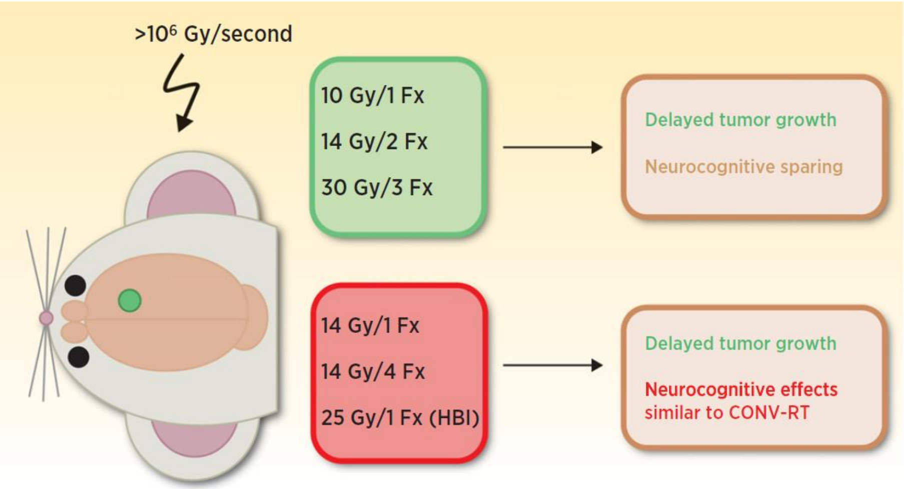
Hypofractionated FLASH-RT as an Effective Treatment against Glioblastoma that Reduces Neurocognitive Side Effects in Mice

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

CLINICAL CANCER RESEARCH | CCR TRANSLATIONS

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

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



Impact of dose and volume

2.6 cm
28, 31, 34 Gy
10p-100ms
>280 Gy/s

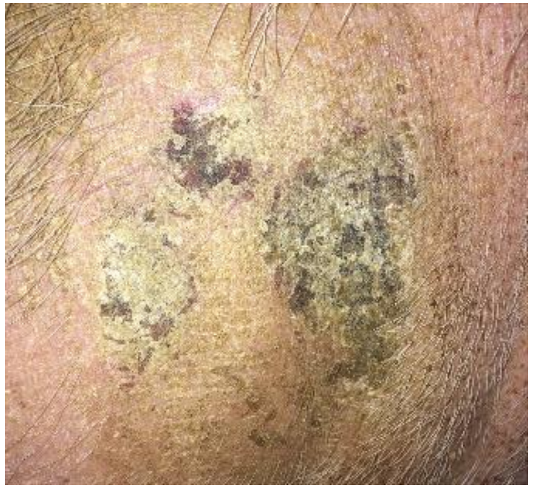
9 mo post-RT

3 years post-RT

8X8 cm
31 Gy 1 Fx
20 p-200 ms
150 Gy/s

4 mo post-RT

5 mo post-RT



6 mo post-RT

7 mo post-RT

12 mo post-RT

C Bailat R Moeckli P Jorge Goncalves

Development of a monitor chamber

Mandatory for clinical application

Real-time monitoring system of FLASH irradiation accelerators:

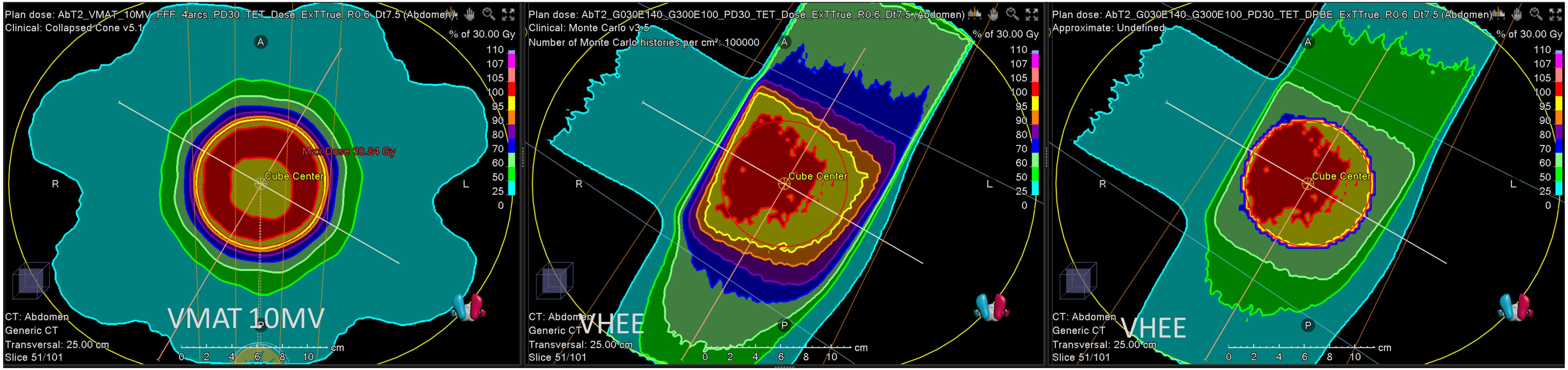
pilot, check and verify delivered doses.

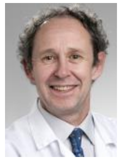
Jorge et al, Validation of an ultra-high dose-rate pulsed beam monitoring system using a current transformer for FLASH pre-clinical studies**, 2021, submitted.**

Implementing Conformality

R Moeckli

T Boehlen





J Bourhis

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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1a : Day 0

1b : 3 weeks

1c : 5 months

IntraOp

CHUV

Commissioning of an ultra-high dose rate pulsed electron beam medical LINAC for FLASH RT preclinical animal experiments and future clinical human protocols

Raphaël Moeckli[a)*] Patrik Gonçalves Jorge* Veljko Grilj, Roxane Oesterle and Nicolas Cherbuin
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(Received 17 December 2020; revised 11 February 2020; accepted for publication 31 March 2021; published 14 May 2021)

June 2021

Impulse Trial is the First to Evaluate the Curative Potential of the FLASH Effect

cancers

MDPI

Article

FLASH Proton Pencil Beam Scanning Irradiation Minimizes Radiation-Induced Leg Contracture and Skin Toxicity in Mice

Shannon Cunningham [1,†], Shelby McCauley [1,†], Kanimozhi Vairamani [1], Joseph Speth [2], Swati Girdhani [3], Eric Abel [3], Ricky A. Sharma [3], John P. Perentesis [1,4], Susanne I. Wells [1,4], Anthony Mascia [2] and Mathieu Sertorio [1,4,*]

Varian and the Cincinnati Children's/UC Health Proton Therapy Center Announce Initial Patient Treated in the FAST-01 First Human Clinical Trial of FLASH Therapy for Cancer

Oncology

November 19, 2020

PALO ALTO, Calif., and CINCINNATI, Ohio, Nov. 19, 2020 /PRNewswire/ -- Varian (NYSE: VAR) and the Cincinnati Children's/UC Health Proton Therapy Center today announce the start of the first clinical trial of FLASH therapy as part of the recently opened FAST-01 study (**F**e**A**sibility **S**tudy of FLASH Radiotherapy for the **T**reatment of Symptomatic Bone Metastases). The clinical trial involves the investigational use of Varian's ProBeam® particle accelerator modified to enable radiation therapy delivery at ultra-high dose rates (dose delivered in less than 1 second) and is being conducted at the Cincinnati Children's/UC Health Proton Therapy Center with John C. Breneman M.D., Medical Director of the center, serving as principal investigator.

The first clinical trial patient was treated this week. The FAST-01 study is expected to enroll up to 10 patients with bone metastases to evaluate clinical workflow feasibility, treatment-related side effects, and efficacy of treatment as assessed by measuring pain relief of trial participants. The clinical trial, informed by years of preclinical work, was designed by experts at Varian and multiple centers in the FlashForward™ Consortium, including Cincinnati's Children's/UC Health Proton Therapy Center and the New York Proton Center.

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

oncosuisse

FLASH-RT in superficial tumors
In the frame of a phase III clinical trial
In cats with SCC

C Rohrer

Arm 1
External radiotherapy
Accelerated 48 Gy (10X4.8 Gy)

Gasymova et al, BMC Vet Res, 2017

Arm 2
FLASH-RT
30 Gy single Fx
3p- 20 ms

Vozenin et al, CCR, 2019

after approval of our Ethical Committee, multicentric inclusion of cat-patients with biopsy proven squamous cell carcinoma T2/T3 of the nasal planum will be performed. Taking into account previous results of our phase I dose escalation trial, a dose of 34 Gy has been chosen for the phase III trial to offer an optimal ratio of tolerance vs anti-tumour efficacy. The **primary endpoint of the study** is tumour control rate at 1 year. Cat-cancer patients will be randomized between 34 Gy single dose (4.9 MeV) electron beam Flash and standard treatment with 48 Gy accelerated fractionated conventional RT (6MV) done with conventional photon irradiation (PFS=71%) (1). The **secondary endpoints** are overall survival, acute and late toxicity as described previously (2). The hypothesis that a 95% tumour control rate at 1 year will be achieved with Flash RT for doses above 30Gy. With an alpha value of 0.050 and a beta value of 0.2, 29 cats need to be included.

PennVet
University of Pennsylvania

Lunds Universitet

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

Cancer Research
The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)
AACR American Association for Cancer Research

FLASH proton radiotherapy spares normal epithelial and mesenchymal tissues while preserving sarcoma response

Anastasia Velalopoulou, Ilias V. Karagounis, Gwendolyn M. Cramer, et al.

Cancer Res Published OnlineFirst July 28, 2021.

frontiers in Oncology
ORIGINAL RESEARCH
published: 13 May 2021
doi: 10.3389/fonc.2021.658004
Check for updates

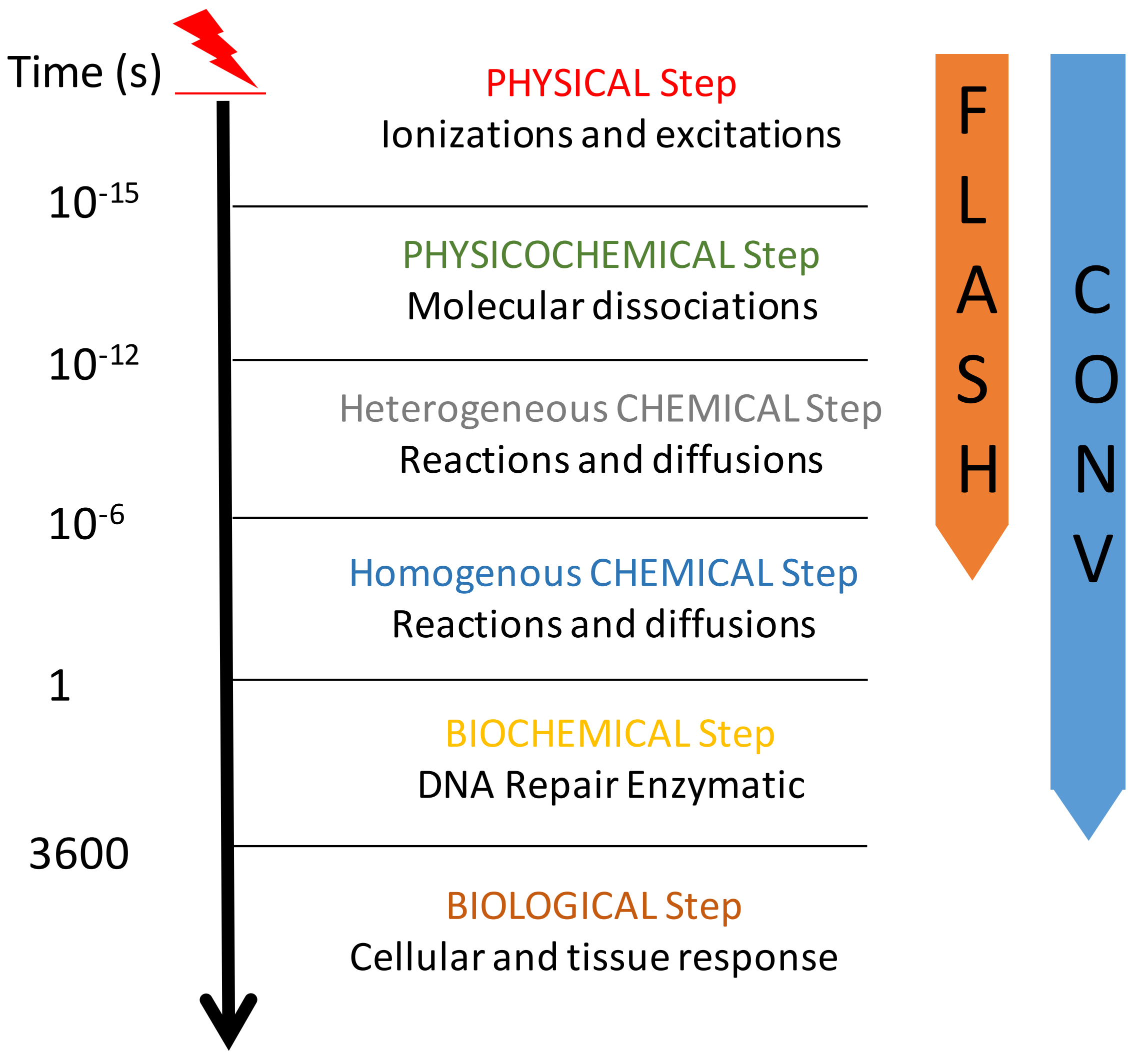
Establishment and Initial Experience of Clinical FLASH Radiotherapy in Canine Cancer Patients

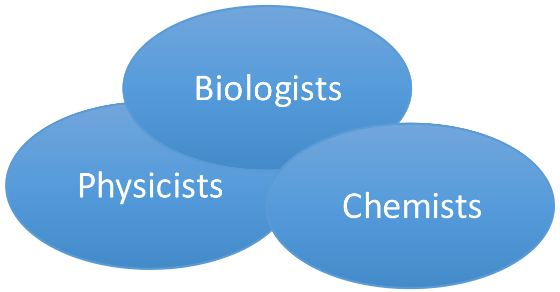
Elise Konradsson[1*†], Maja L. Arendt[2†], Kristine Bastholm Jensen[3], Betina Børresen[2], Anders E. Hansen[4], Sven Bäck[5], Annemarie T. Kristensen[2], Per Munck af Rosenschöld[5], Crister Ceberg[1‡] and Kristoffer Petersson[5,6‡]

10 Dogs (heterogeneous population, sarcoma, BCC, SCC, melanome, MastC)
Dose escalation from 15 to 35 Gy
Short term follow up (3 mo)

How it works…

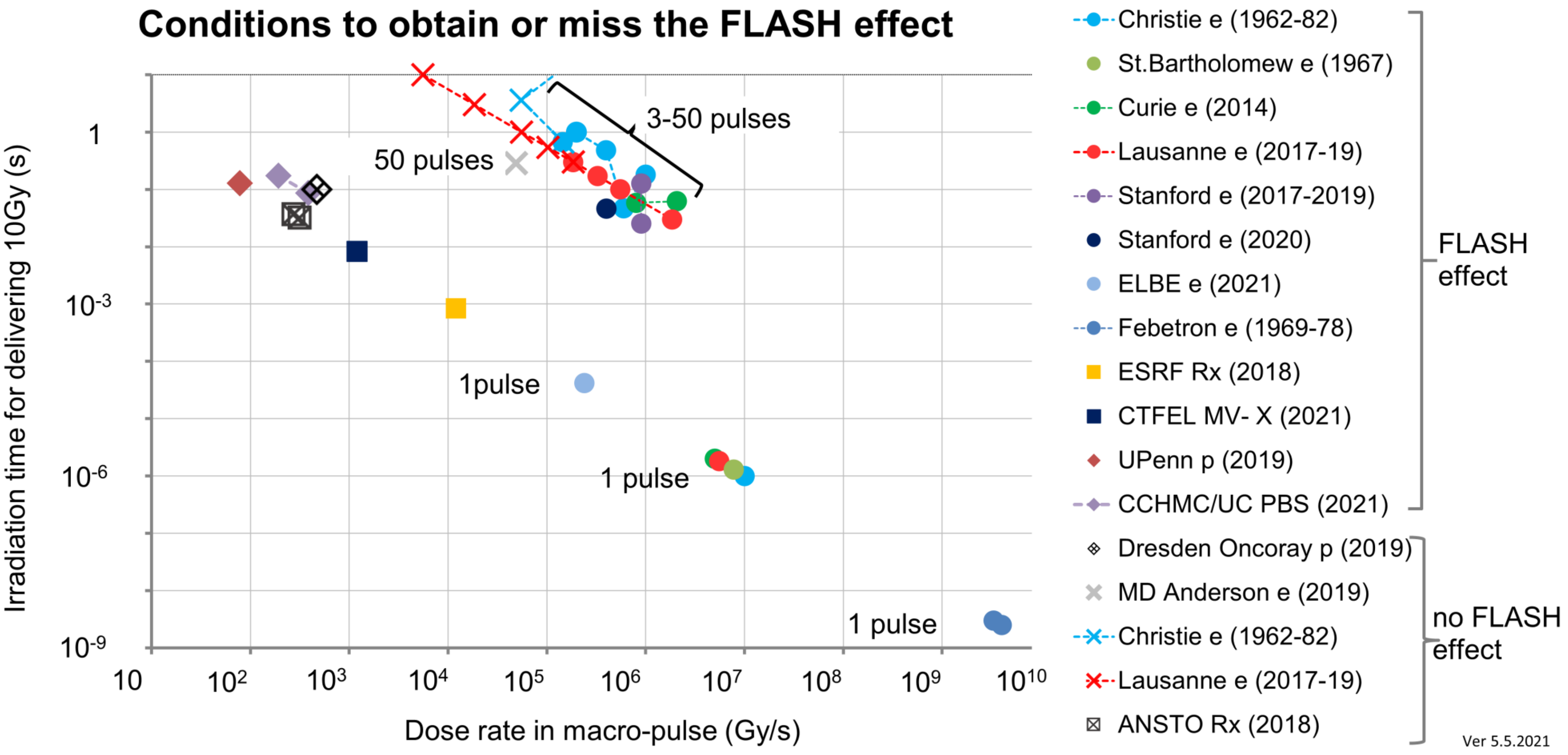
Chronology of post-irradiation events and FLASH irradiation





Physics

JF Germond



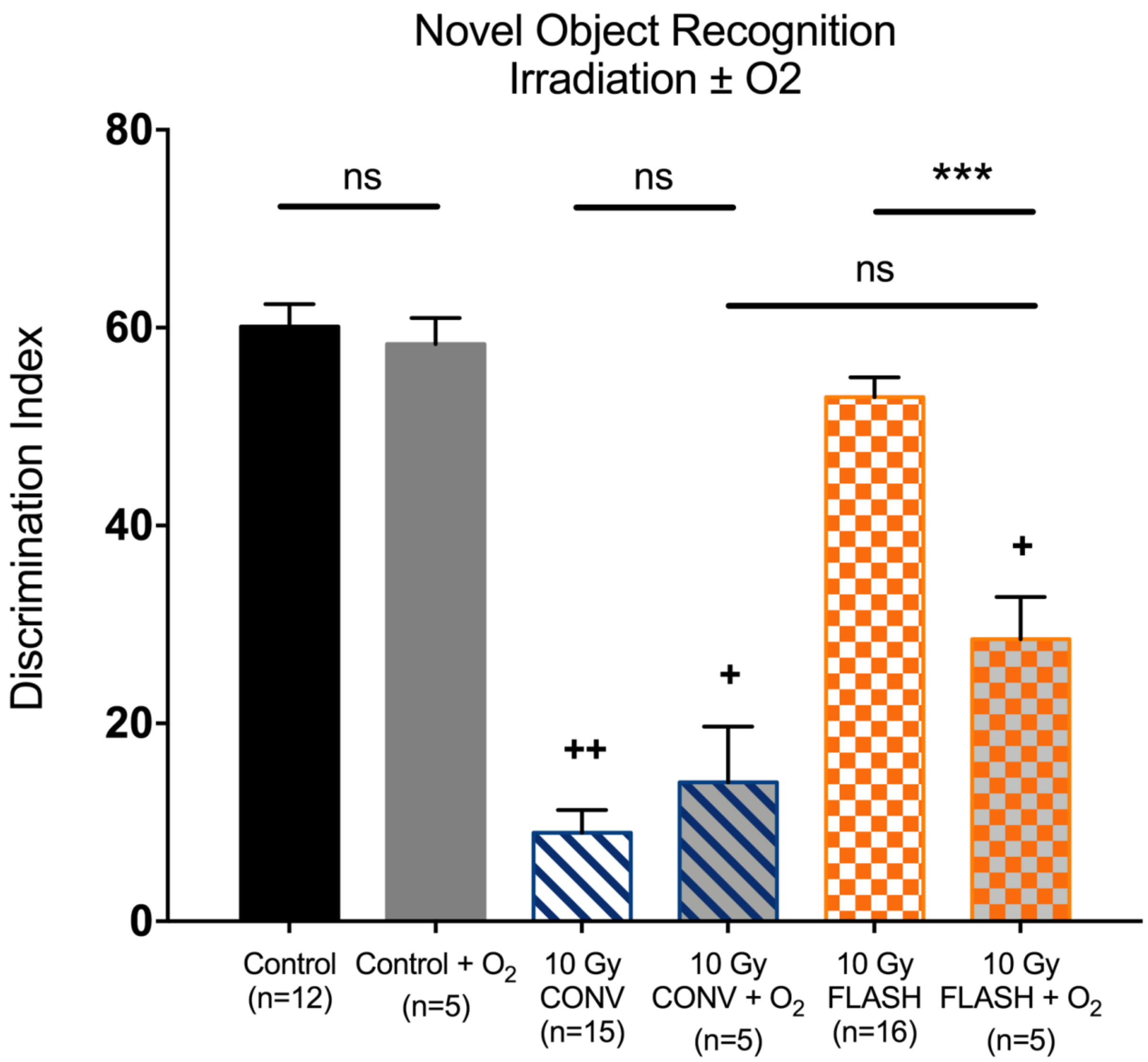
The shorter the better

The higher the better

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

Chemistry

Doubling brain pO2 reverses FLASH effect



Montay-Gruel P et al., PNAS, 2019

Testable hypothesis: O2 depletion

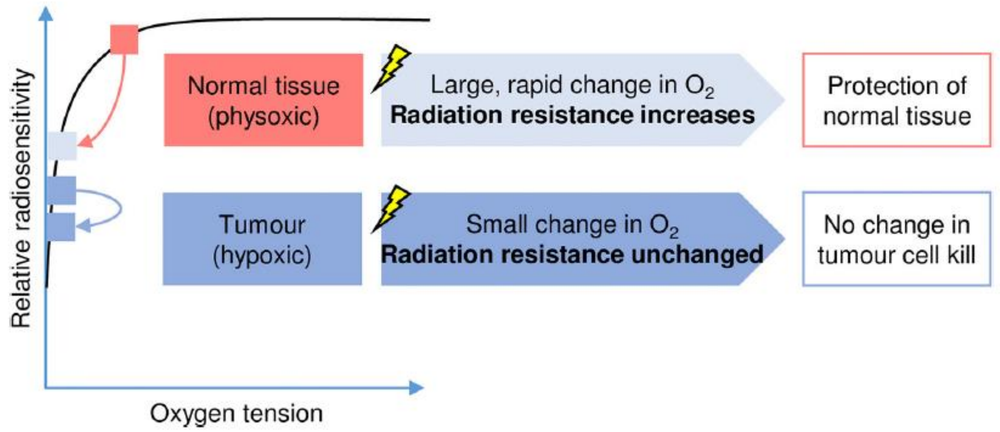


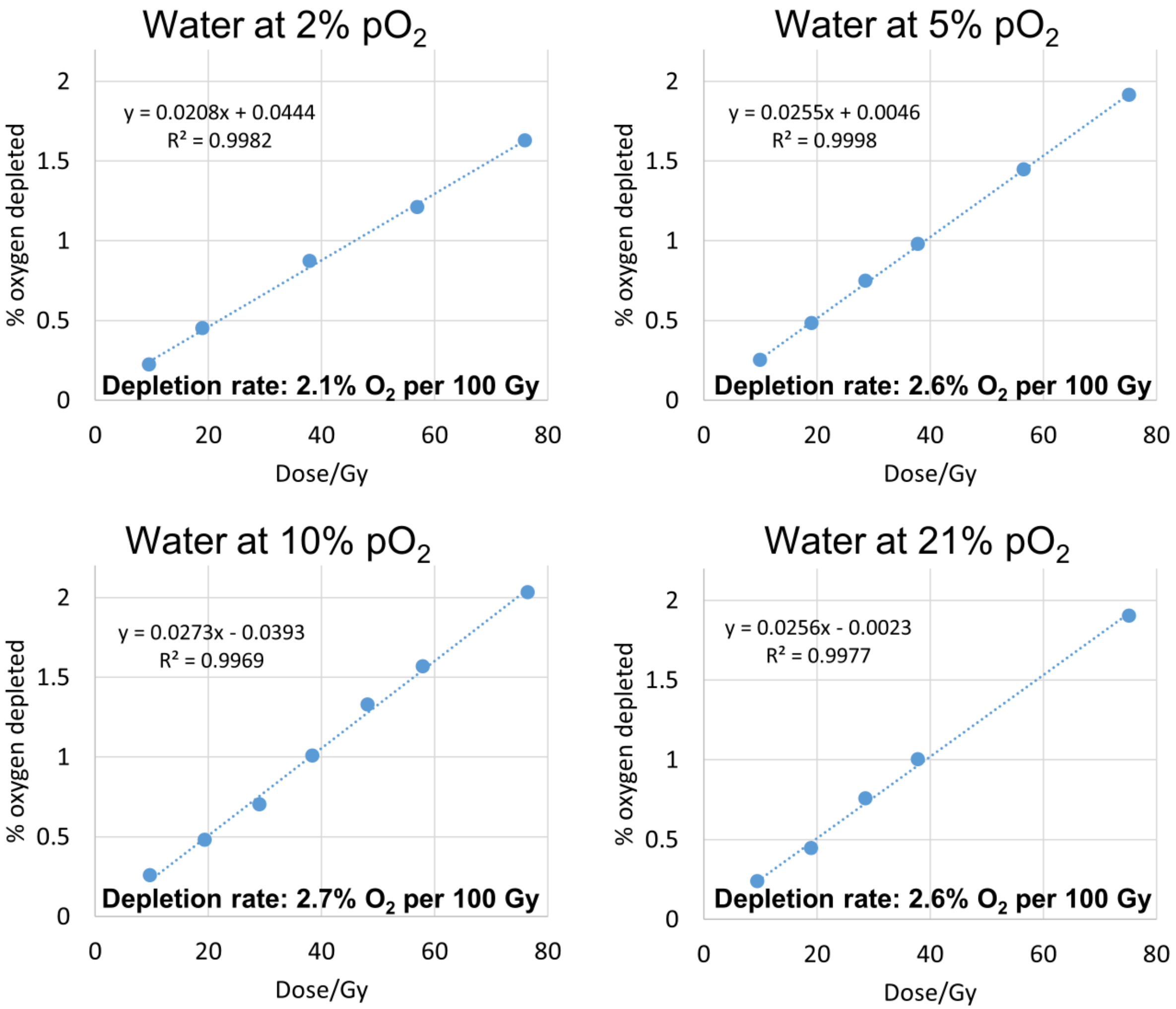
FIGURE 2 | The oxygen depletion hypothesis. The relationship between oxygen tension (horizontal axis) and radiation sensitivity (vertical axis) is shown schematically and has been widely reported (40, 41). In response to FLASH-RT, the physiological level of oxygen (physoxic) found in normal tissues decreases 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%

In situ Oxygen depletion after FLASH and CONV-RT- measured with oxylite irradiation

Veljko Grilj



Radiation	% O_2 depleted per 100 Gy
CONV, 7 Gy/min	2.1
CONV, 14 Gy/min	2.1
FLASH 1%	2.2
FLASH 2%	2.1
FLASH 5%	2.6
FLASH 10 %	2.7
FLASH 21%	2.6

FLASH depletes about 25% more O_2 than CONV, except at very low pO_2

Measurements do not support any radiolytic oxygen depletion at therapeutic doses (10 Gy) delivered 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

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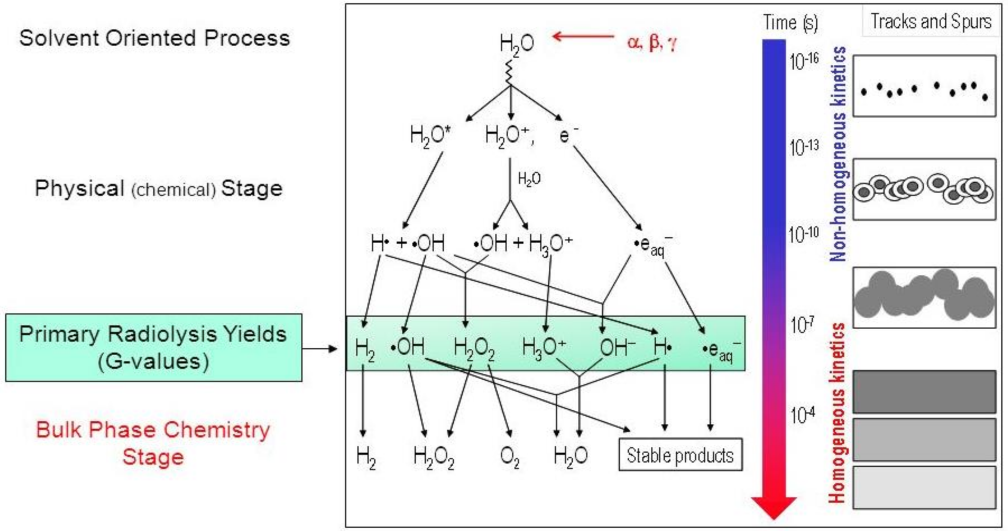
(Received 20 December 2020; revised 1 March 2021; accepted for publication 6 April 2021; published 27 May 2021)

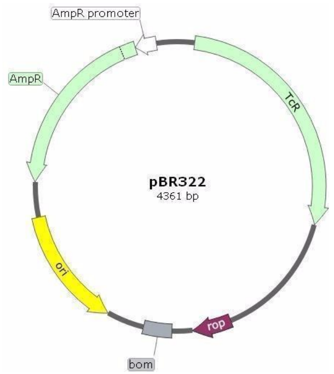
Conclusions: FLASH irradiation does consume oxygen, but not enough to deplete all the oxygen present. For higher dose rates, less oxygen was consumed than at standard radiotherapy dose rates. No total depletion was found for any of the analyzed radiation types for 10 Gy dose delivery using FLASH. [https://doi.org/10.1002/mp.14917]

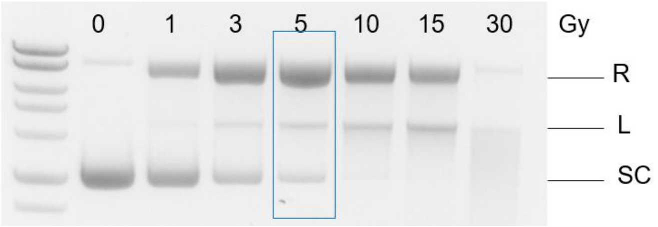
Water Radiolysis

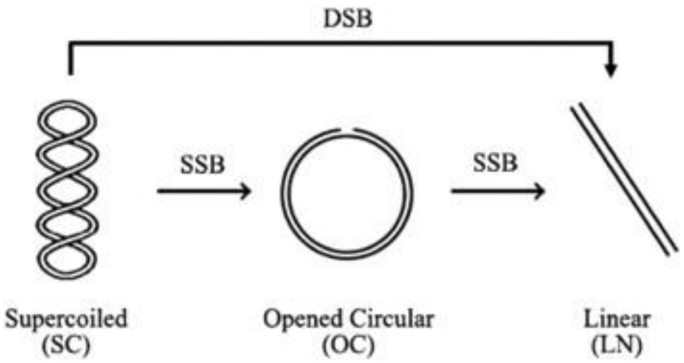
Houda Kacem

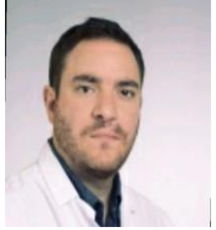


Particles	Chemical system	G°(H_2O_2) (molecules/100eV)	Reference
6 MeV Conv electrons	$[NO_2^-]$ /$[NO_3^-]$	0.81 ± 4.1×10^{-3}	Kacem et al. In prep
	CH_3OH/$[NO_3^-]$	0.73 ± 8.6×10^{-2}	
6 MeV FLASH electrons	$[NO_2^-]$ /$[NO_3^-]$	0.76 ± 7.06×10^{-2}	
	CH_3OH/$[NO_3^-]$	0.72 ± 1.35×10^{-2}	
^{137}Cs γ-rays	$[NO_2^-]$ /$[NO_3^-]$	0.72	Wasselin-Trupin 2001
^{60}Co γ-rays	CH_3OH/$[NO_3^-]$	0.69	Laverne 2002



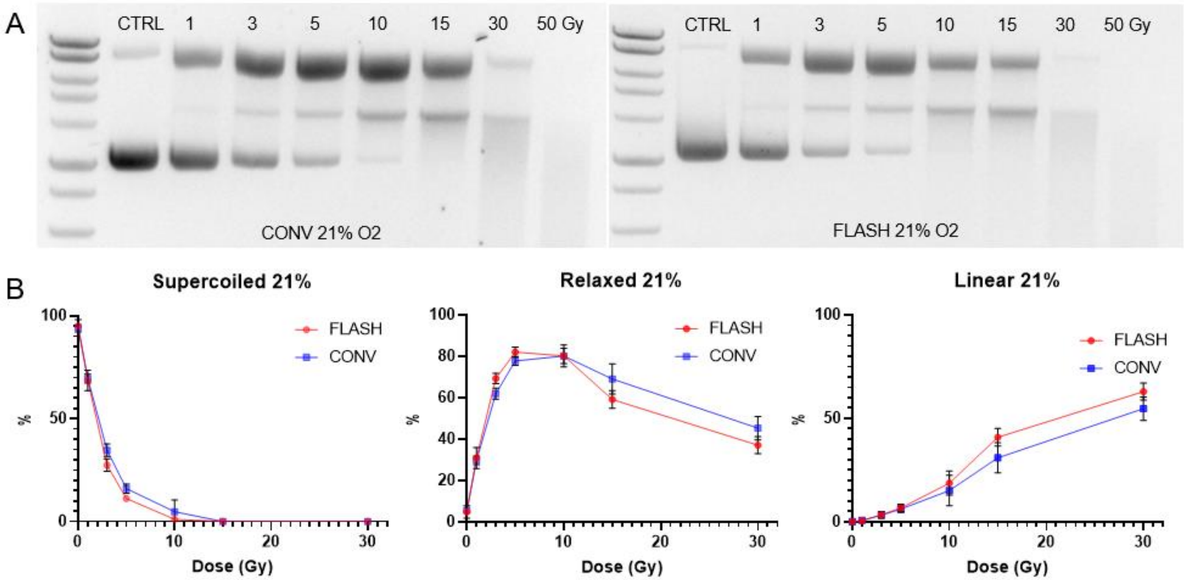


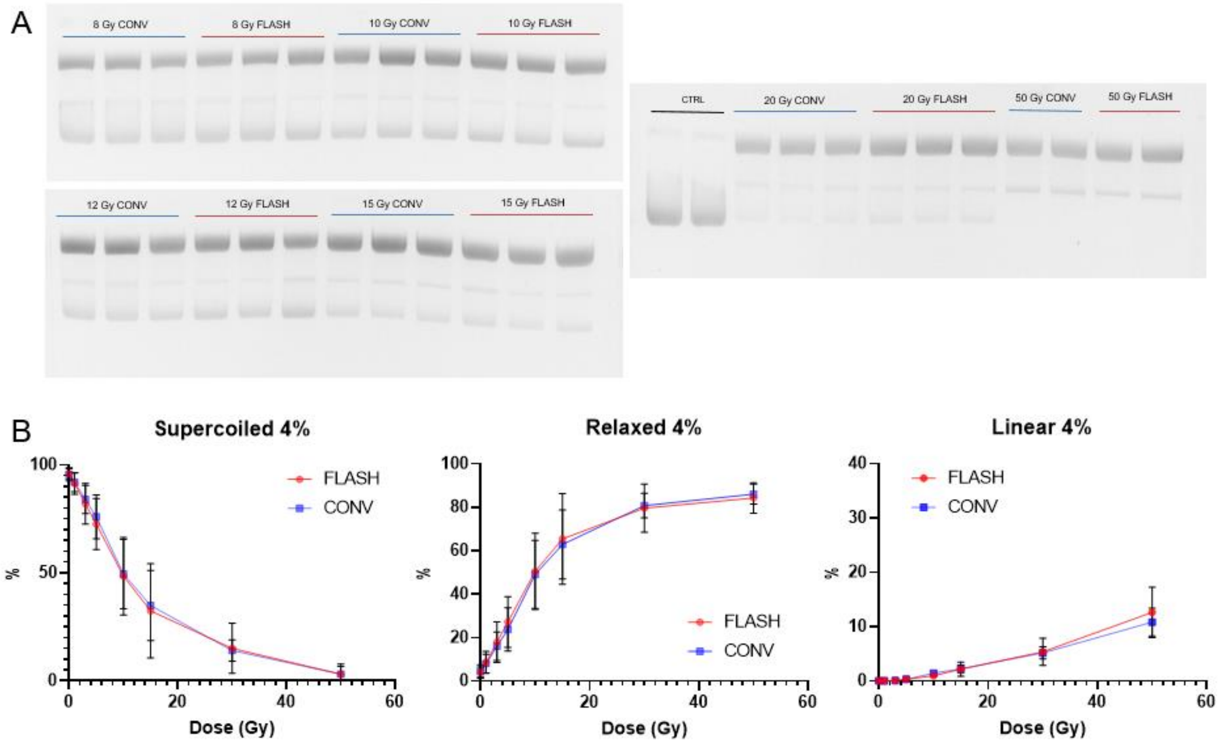




Nicolas Cherbuin

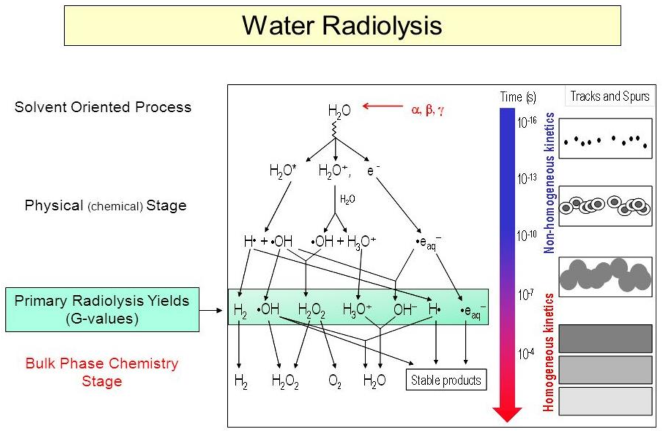
GEANT-4 DNA
S Incerti, L Desorgher





Consistently the impact on plasmid DNA is similar with CONV and FLASH-RT

Cherbuin et al, in prep

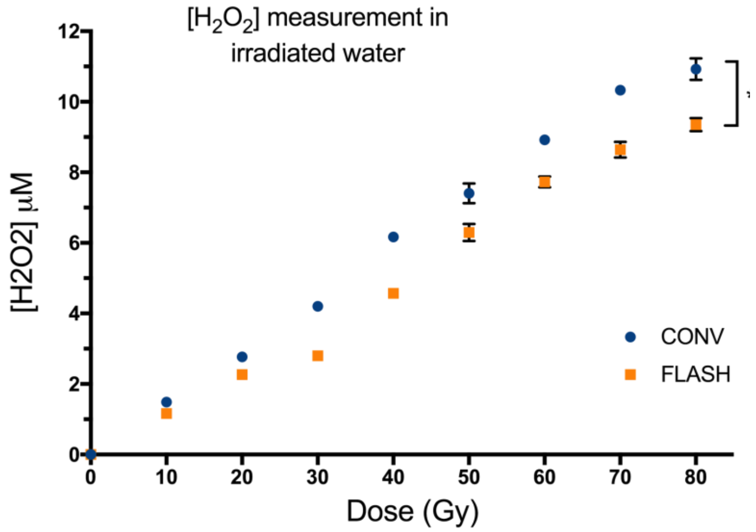


H2O2 Primary yield is similar FLASH and CONV

But at Isodose FLASH-RT produces less ROS (H2O2) than CONV-RT

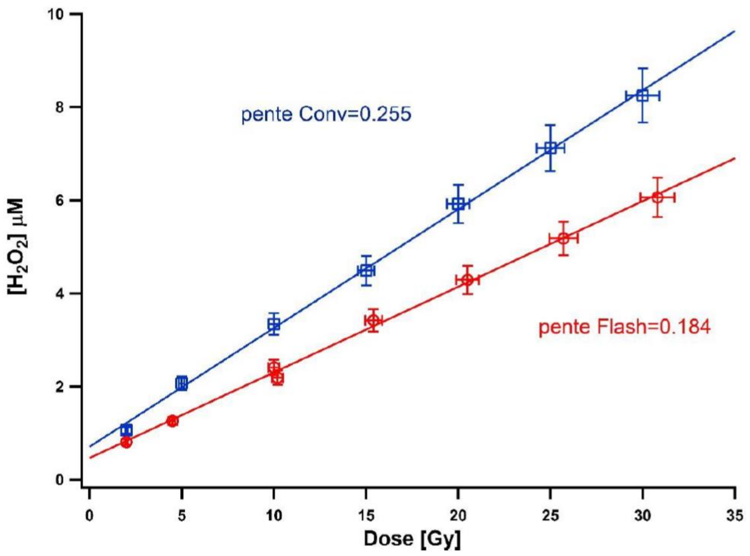
Minutes → $[H_2O_2]$ measurements from PNAS paper

Amplex Red method (fluorometry)



Montay-Gruel et al , PNAS, 2019

DEDP $^{\cdot+}$ method (Spectroscopy)



Froidevaux P, unpublished data

Biology

Physico-chemical events

ROS signaling
(Montay-Gruel et al., 2019; Adrian et al., 2019)

Lower level of persistent DNA damages and senescent cells
(Fouillade et al., 2019)

Metabolism including redox
(Spitz et al., 2019; Labarbe et al., 2020)

Inflammation
(Favaudon et al., 2014; Montay-Gruel et al., 2019; Simmons et al., 2019; Diffenderfer et al., 2019)
FLASH-RT does not induce astrogliosis and reduces DAMPs production (Montay-Gruel et al., 2020)

Signaling pathways
(Montay-Gruel et al., 2017; Fouillade et al., 2019; , Kim et al., 2020, Cunningham et al., 2020)
FLASH-RT does not induce vessel damages in the brain (Allen et al., 2020)
FLASH-RT does not induce neurocognitive damages in juvenile mice (Alaghband et al., 2020)

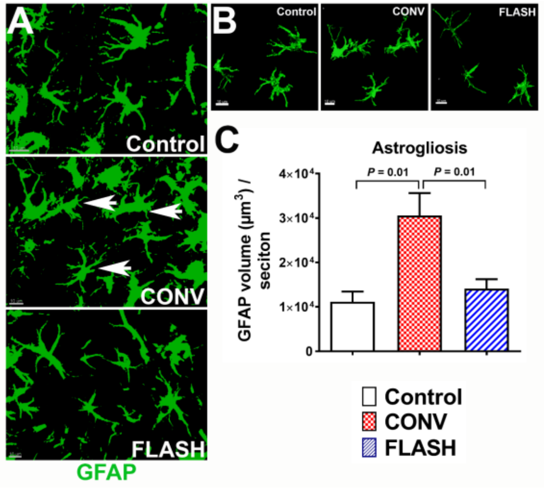
All tumor are not equally sensitive to FLASH-RT (Chabi et al., 2020)

Anti-tumor effect | **Normal tissue sparing**

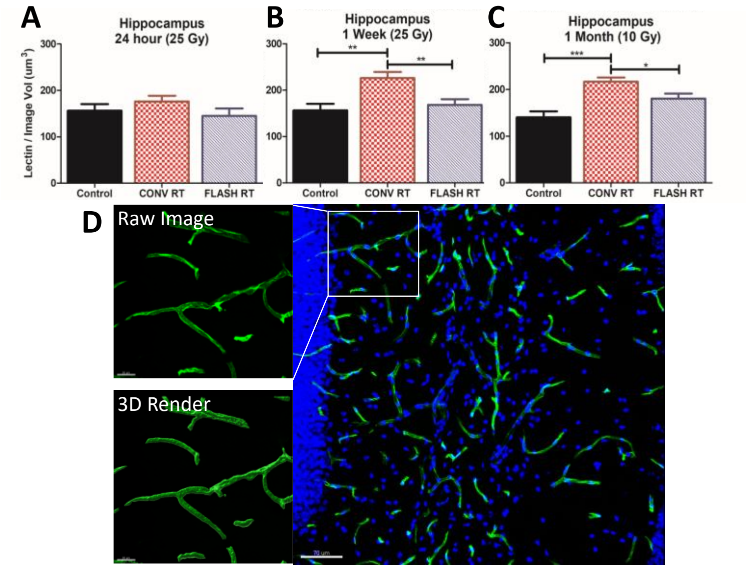
FLASH EFFECT

Normal brain

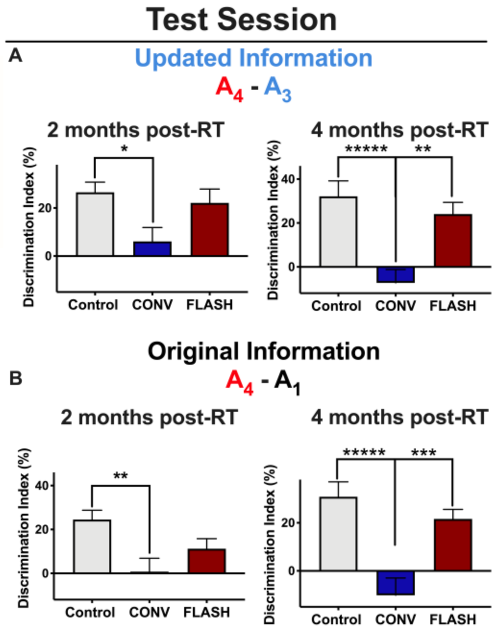
FLASH-RT does not induce astrogliosis and reduces DAMPs production
FLASH-RT does not induce vessel damages in the brain
FLASH-RT does not induce neurocognitive damages in juvenile mice

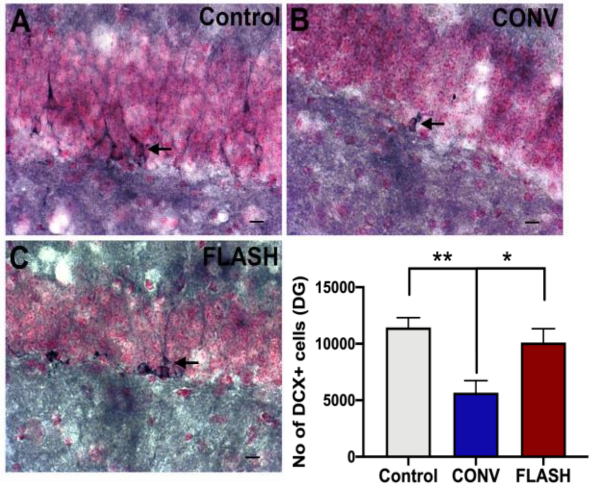


Montay-Gruel et al, Rad Res, 2020



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	0.09	8.5×10^3
	25	Circular ∅17	745	10	1.0	2620	261.9	0.1	9.5×10^3
FLASH	10	Circular ∅17	369-370	100	1.8	1	1.8×10^{-6}	5.6×10^6	5.6×10^6
	25	Circular ∅17	325	100	1.8	2	1.0×10^{-2}	2.5×10^3	6.9×10^6

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	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

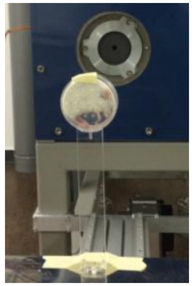
In Tumors

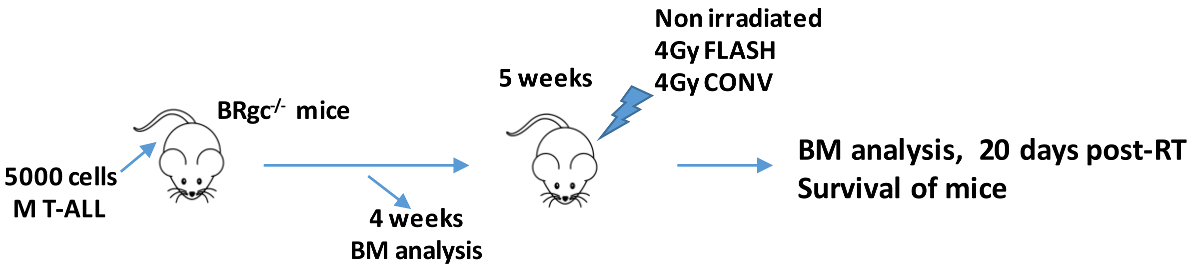
All tumors are not equally sensitive to FLASH-RT


F Pflumio


B Uzan

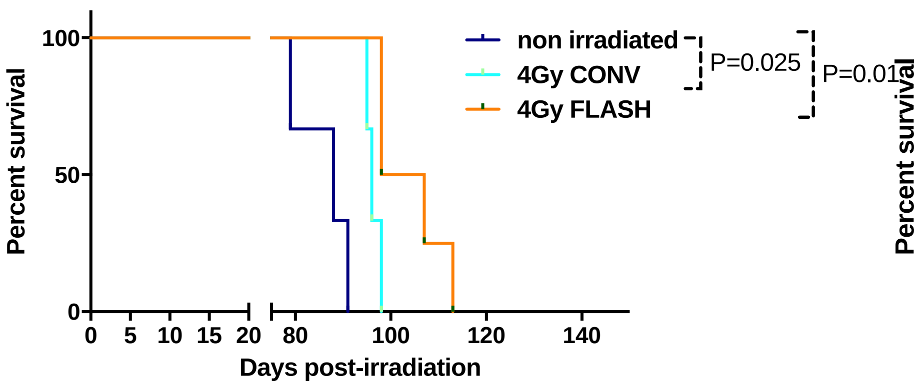
Human T-ALL with different susceptibility profile to FLASH-RT



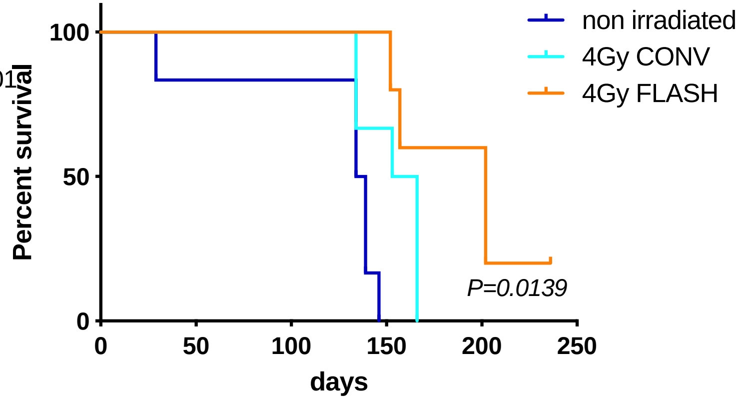


Delivery Mode	Prescribed Dose (Gy)	Beam parameters						
		Source-to-surface distance (mm)	Pulse repetition Frequency (Hz)	Pulse width (µs)	Number of pulses	Treatment time (s)	Mean dose rate (Gy/s)	Instantaneous dose rate (Gy/s)
CONV	4	880	10	1.0	>557	>55.6	<0.072	$<7.2 \times 10^3$
FLASH	4	800	100	1.8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

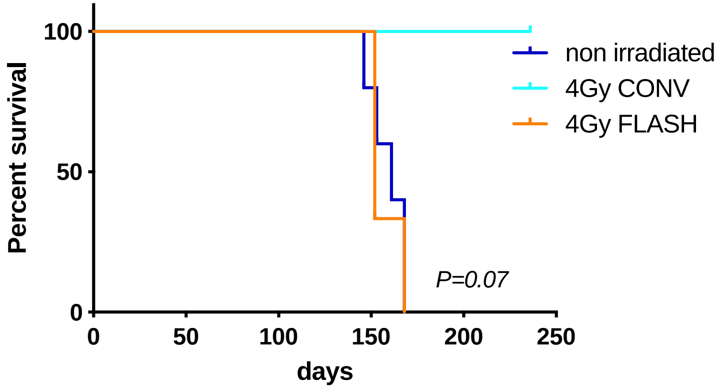
M106 PDX/T-ALL



M114 PDX/T-ALL



M108 PDX/T-ALL



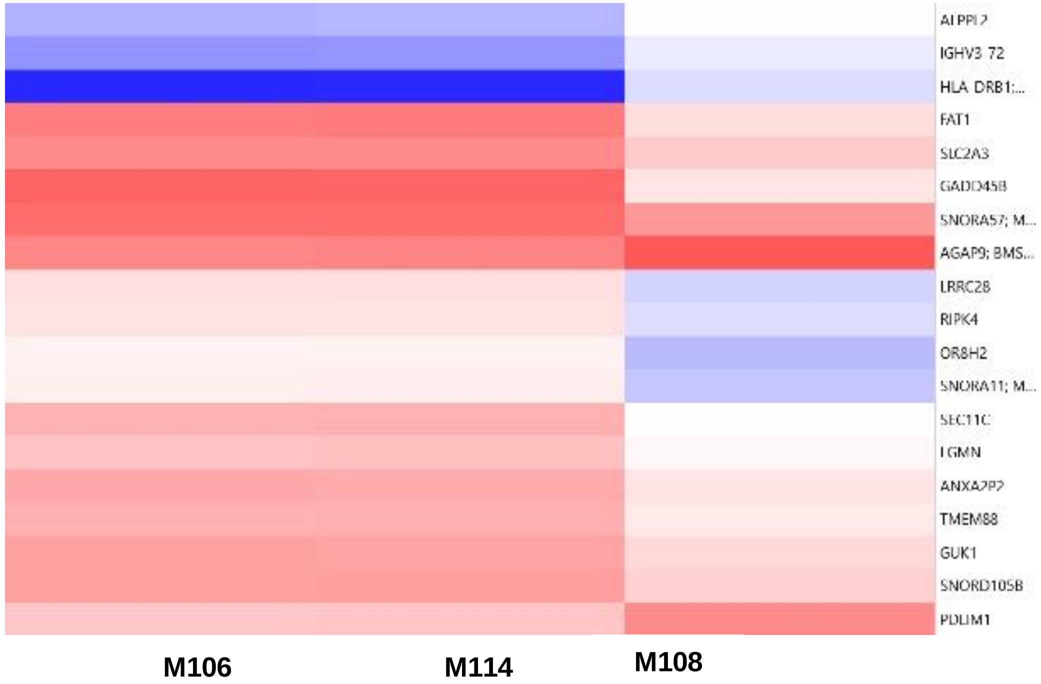
Chabi et al, IJROBP, 2020

Putative susceptibility profile found after FLASH-RT in T-ALL

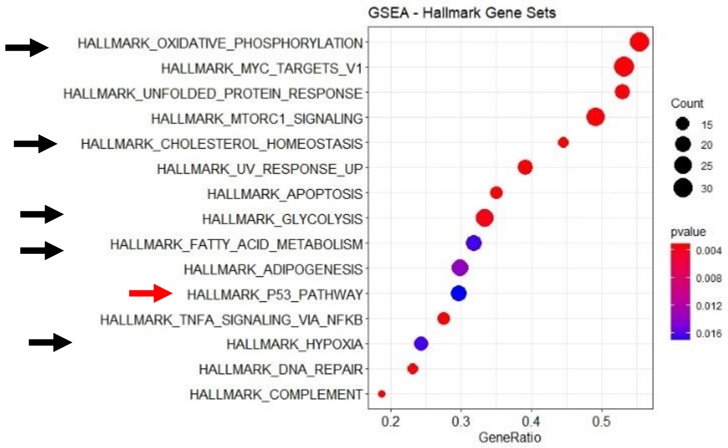
Inhibitor of cdc2/cyclinB1 kinase

Wt pathway

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

Summary

- The FLASH effect is a biological effect
- Physics parameters able to trigger the FLASH effect still need to be systematically investigated
- Radiolytic O2 depletion cannot explain the FLASH effect occuring
- Primary physico-chemical events are not different between CONV vs UHDR
- The mechanisms driving the FLASH effect start to be understood
- Clinical applications with validated parameters and biologically validated beams

  dose, time, volume


New horizon in therapy & treatment
FRPT
FLASH RADIOTHERAPY & PARTICLE THERAPY
2021
VIENNA, AUSTRIA
1-3 DECEMBER 2021
KENES GROUP
NHS
MANCHESTER 1824
The University of Manchester
Biophysics
CHUV
EMPIR
EURAMET
InspireProject
Horizon 2020
institutCurie
FRPT-Conference.org

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A Martinotti

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M Oszahin
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Richard Frock and team

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University of Zurich
Carla Rohrer and Team
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F Wolf

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