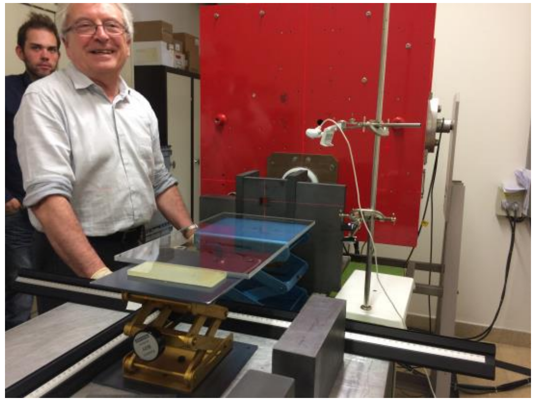
Irradiation at ultra high dose rate: from the FLASH effect to clinical translation

Prof. Marie-Catherine Vozenin

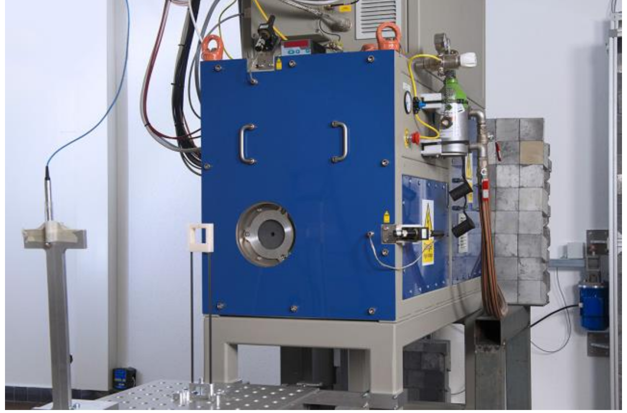
UNIL | Université de Lausanne

Disclosures

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



V Favaudon



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

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

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

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Conventional dose rate RT

FLASH-RT

THE FLASH EFFECT
is a biological effect

Normal tissue sparing

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

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

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

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

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

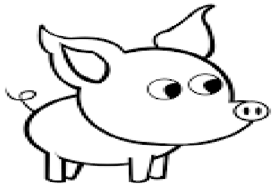
X -ray synchrotron
Smyth et al. **Sci Rep**, 2018.
Proton
Beyreuther et al. **Radiother Oncol.** 2019.
Electron
Venkatesulu at al. **Sc Rep**, 2019.

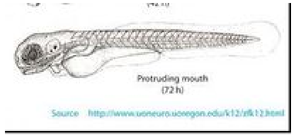
And FLASH-RT is equally able to eradicate tumors compared to CONV-RT

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.

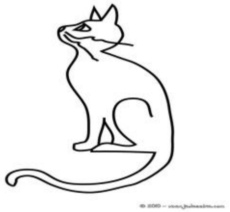
Electron
Kim et al. **IJROBP**, 2020
Levy et al, **Sc Rep,** 2020

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





Skin
Gut
Lung
HS
Brain



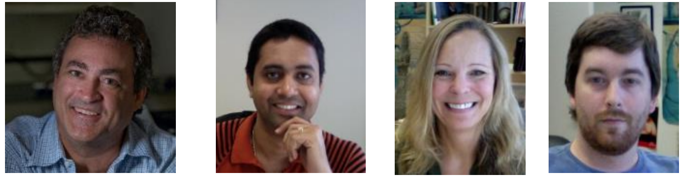
FLASH-RT spares normal tissue and is equally able to eradicate tumors compared to CONV-RT
Using TGD assay (no TCD50 assay has been published)

- Using electron and proton beam
- In preclinical mouse model
- Small volume
- Single dose and hypofractionated regimen

J Ollivier B Petit P Montay-Gruel

Normal Brain irradiation

10 Gy WBI with FLASH and CONV dose rate



C Limoli M Acharya J Baulch B Allen

Test	Endpoint	Neuronal pathways
Novel Object Recognition	Visual / Working memory	Hippocampus Pre-frontal cortex Perirhinal cortex
Temporal order	Visual / Working /Temporal memory	Hippocampus Pre-frontal cortex Perirhinal cortex
Fear Extinction	Conditioned learning Fear / Stress evaluation Fear suppression Dissociation learning	Hippocampus Pre-frontal cortex Amygdala
Object in Place	Visual / Working / Spatial memory	Hippocampus Pre-frontal cortex Perirhinal cortex

FLASH-RT preserves brain's function

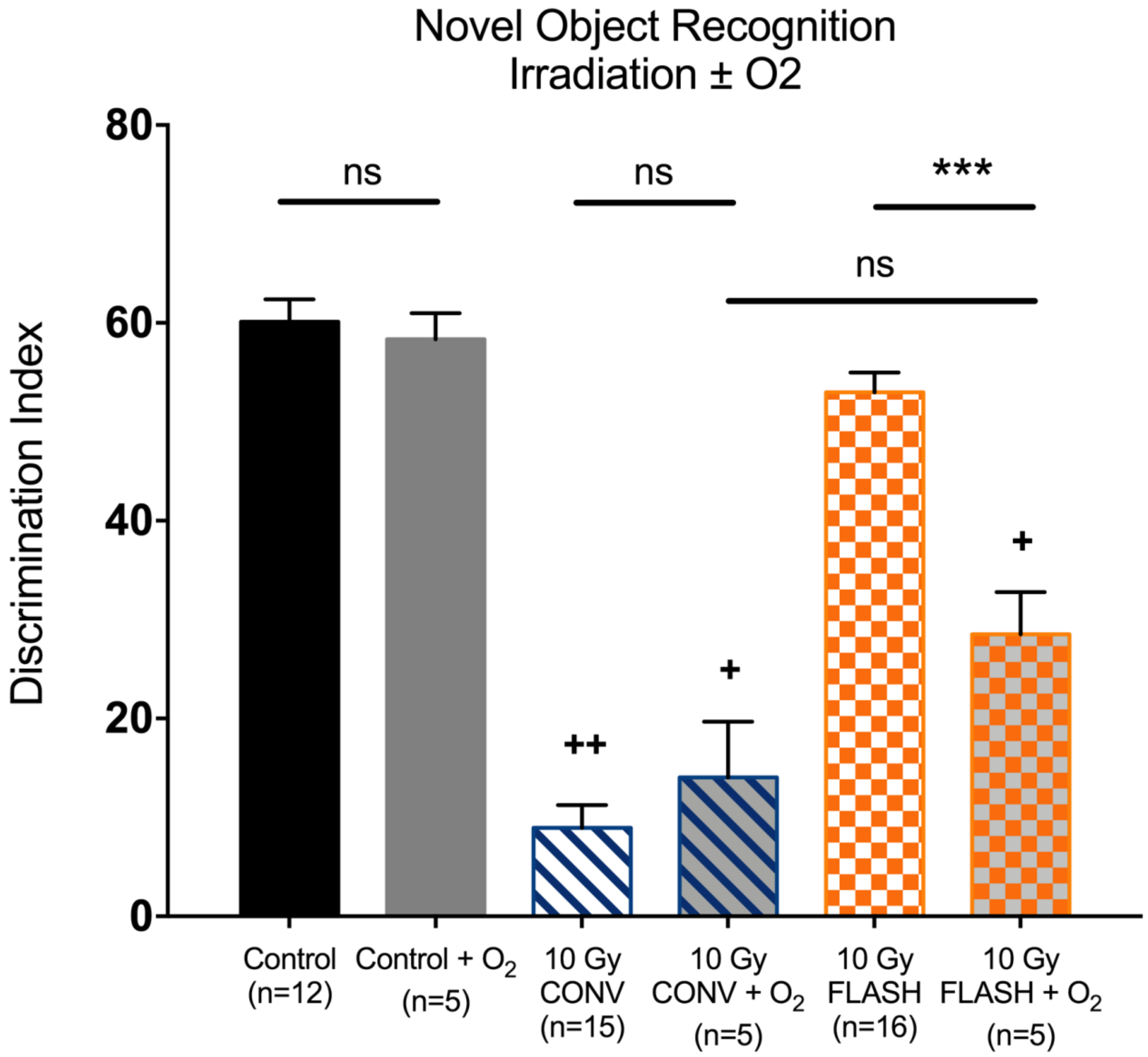
- Cognitive skills of FLASH-RT irradiated mice is equivalent to control mice

Montay-Gruel et al. 2019, PNAS
Montay-Gruel et al. 2018, Radiother&Oncol
Montay-Gruel et al. 2017, Radiother&Oncol

Doubling brain pO2 reverses FLASH effect



J Ollivier B Petit P Montay-Gruel



Montay-Gruel P et al., PNAS, 2019

Testable hypothesis: O2 depletion

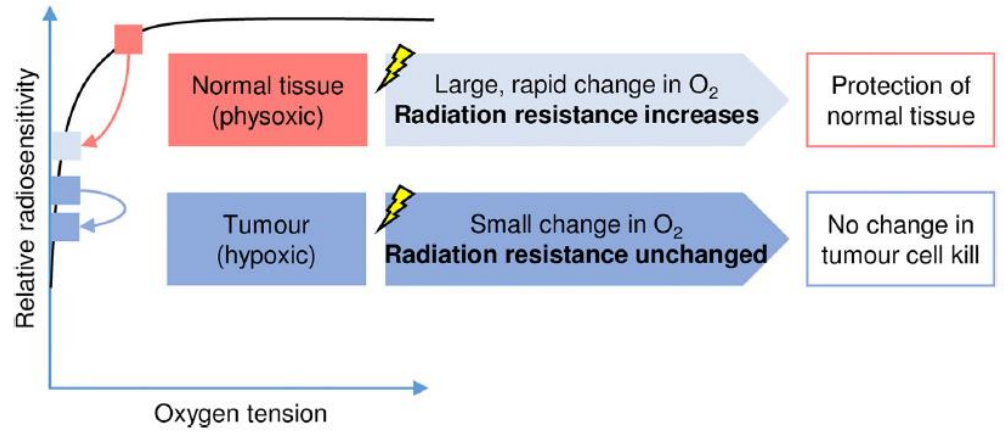


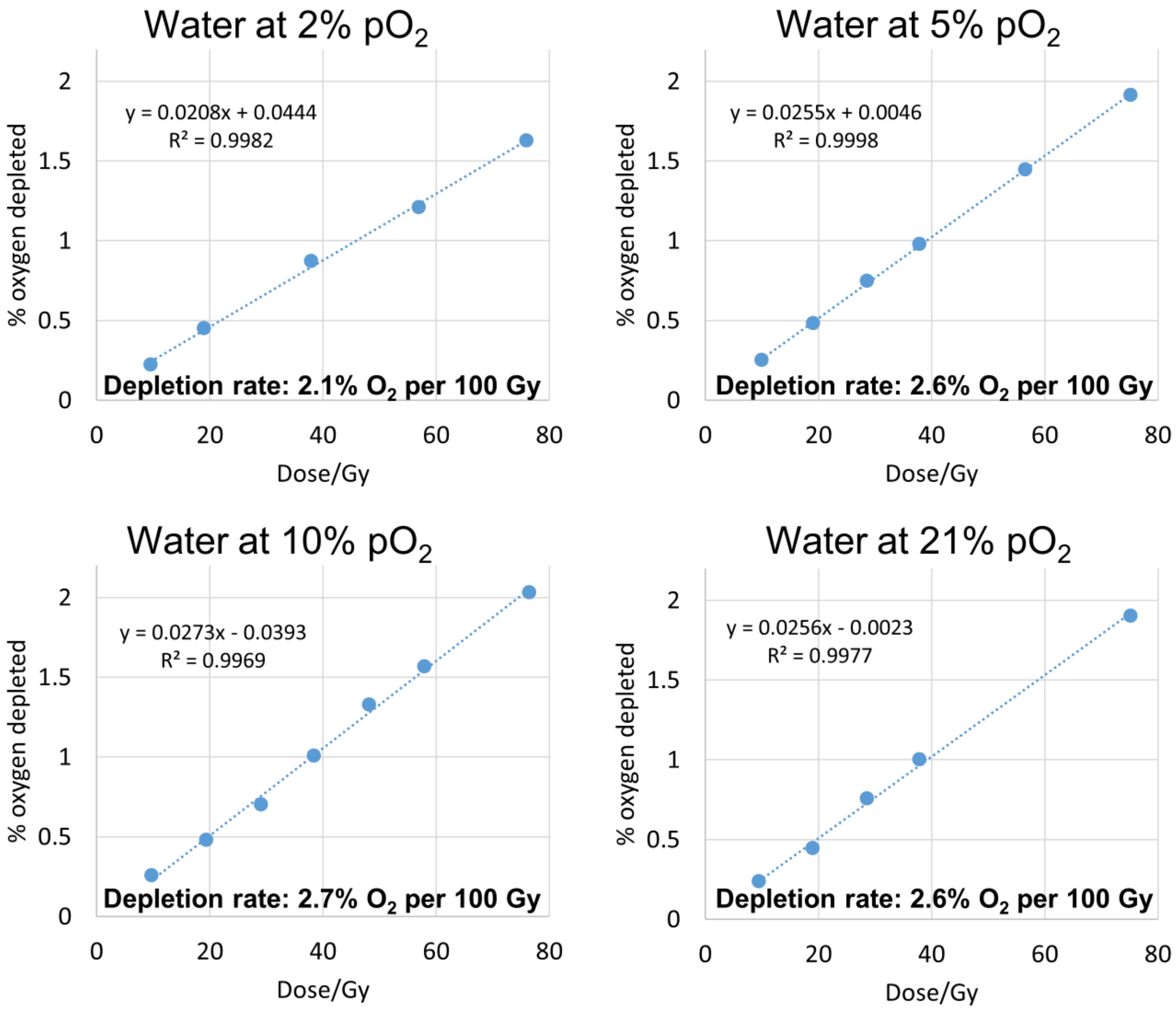
FIGURE 2 | The oxygen depletion hypothesis. The relationship between oxygen tension (horizontal axis) and radiation sensitivity (vertical axis) is shown schematically and has been widely reported (40, 41). In response to FLASH-RT, the physiological level of oxygen (physoxic) found in normal tissues decreases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

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FLASH-RT Results in Insignificant O_2 Depletion

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

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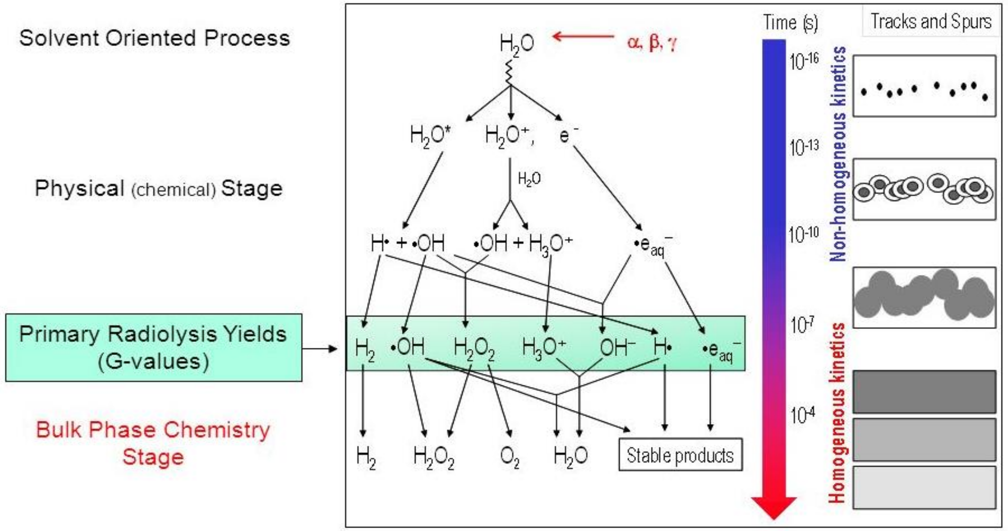
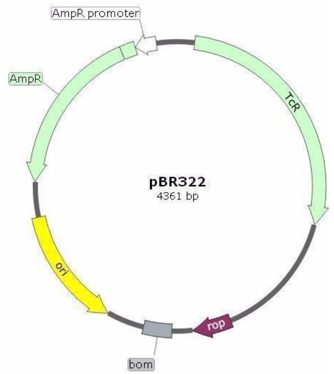
Conclusions: FLASH irradiation does consume oxygen, but not enough to deplete all the oxygen present. For higher dose rates, less oxygen was consumed than at standard radiotherapy dose rates. No total depletion was found for any of the analyzed radiation types for 10 Gy dose delivery using FLASH. [https://doi.org/10.1002/mp.14917]

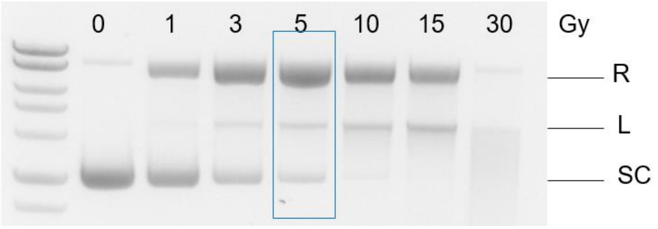

Houda Kacem

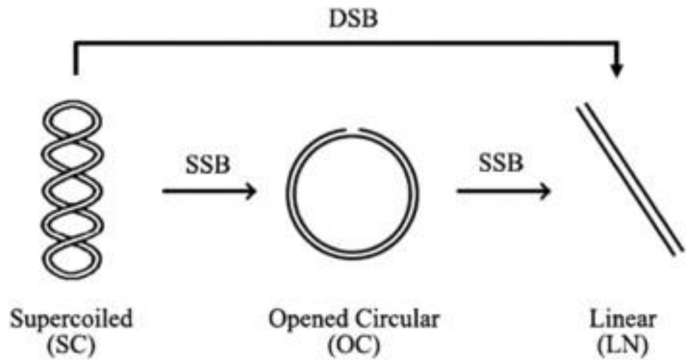
Water Radiolysis

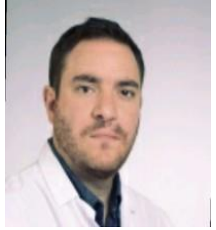


Particles	Chemical system	G°(H_2O_2) (molecules/100eV)	Reference
6 MeV CONV electrons	$[NO_2^-]/[NO_3^-]$	0.77 ± 6.07x10^{-3}	Kacem, in prep
6 MeV FLASH electrons		0.71 ± 5.2x10^{-3}	
^{137}Cs γ-rays		0.726	Wasselin-Trupin 2001
^{60}Co γ-rays	$CH_3OH/[NO_3^-]$	0.69	Laverne 2002



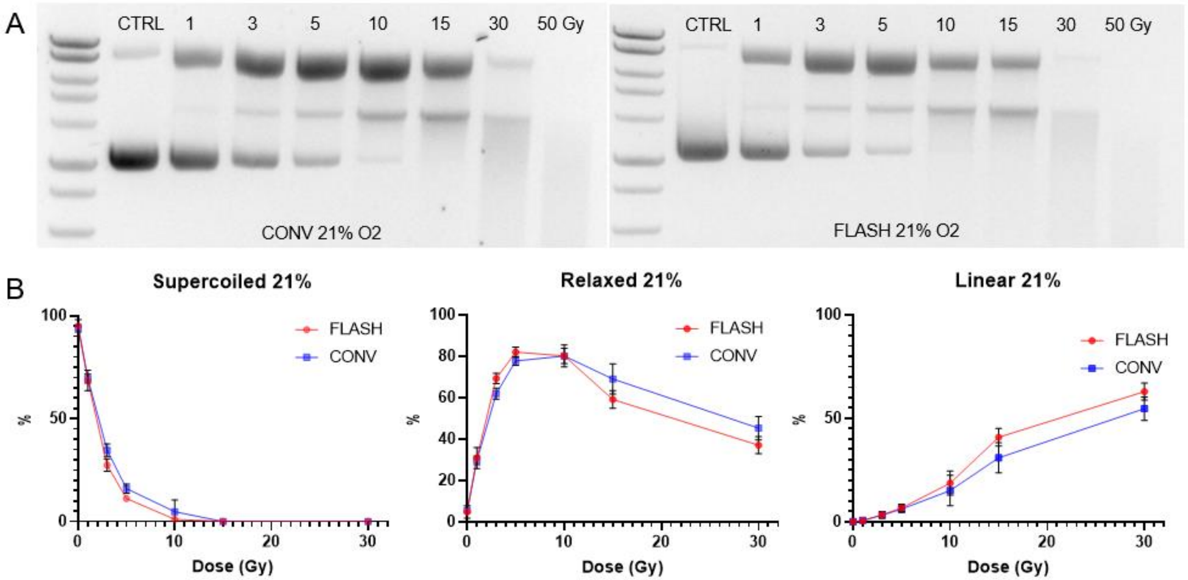


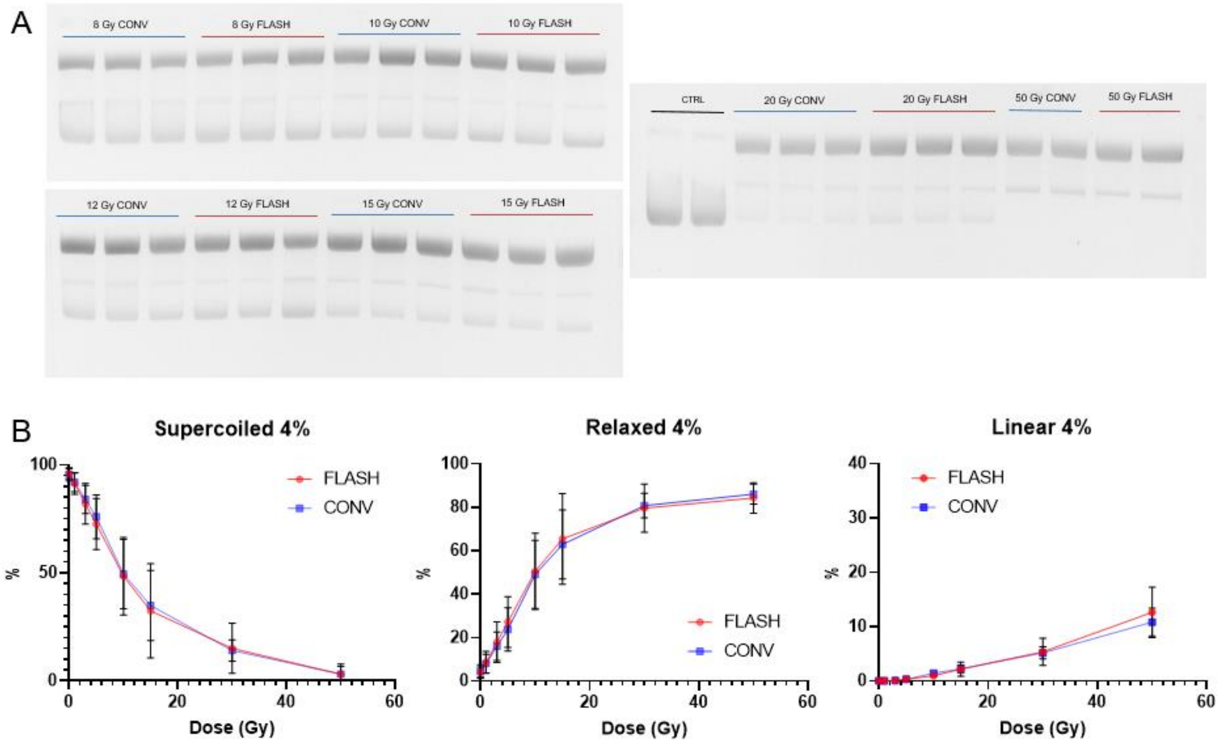




Nicolas Cherbuin

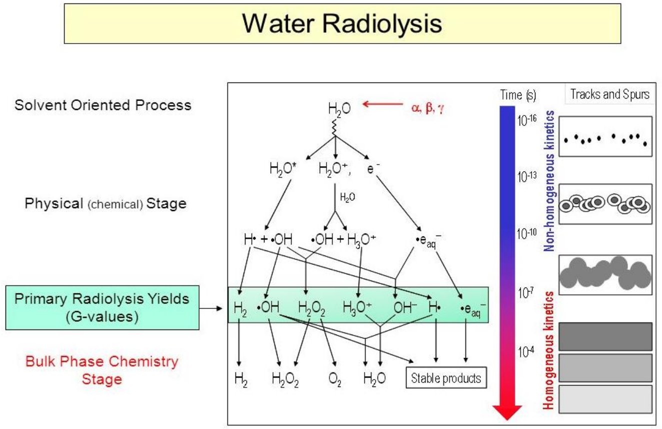
GEANT-4 DNA
S Incerti, L Desorgher





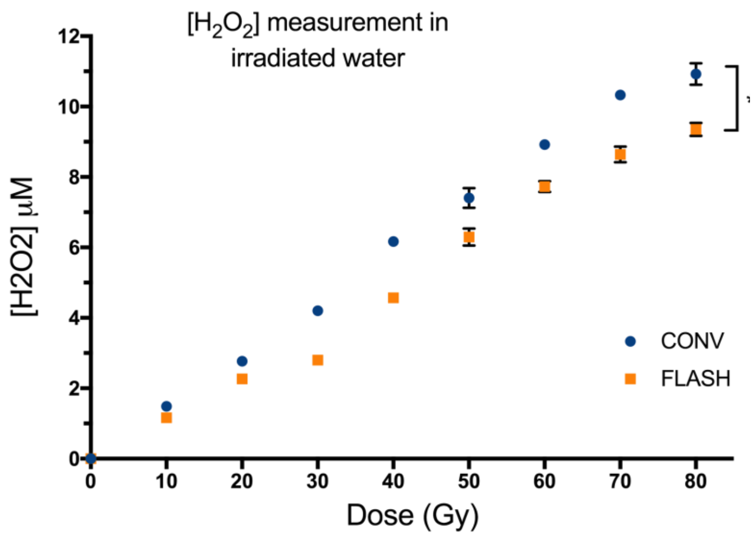
Consistently the impact on plasmid DNA is similar with CONV and FLASH-RT

Cherbuin et al, in prep



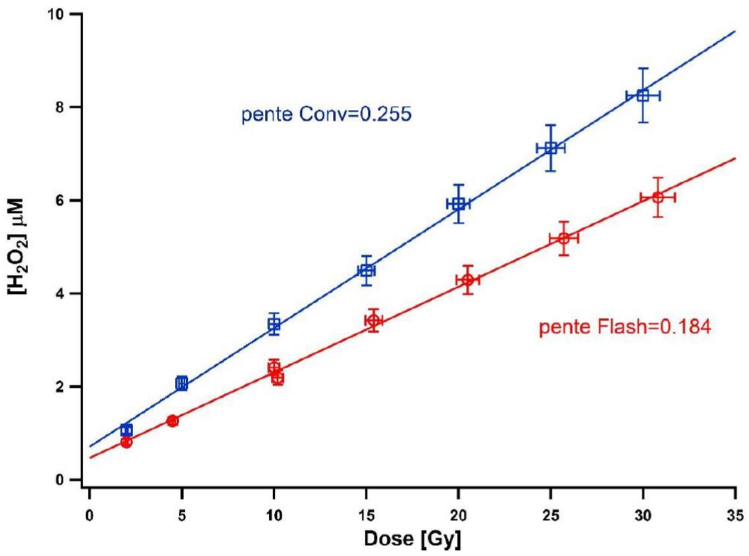
Minutes → $[H_2O_2]$ measurements from PNAS paper

Amplex Red method (fluorometry)



Montay-Gruel et al , PNAS, 2019

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



Froidevaux P, unpublished data

FLASH-RT spares normal tissue and is equally able to eradicate tumors compared to CONV-RT

- No radiolytic oxygen depletion at therapeutic doses (10 Gy) delivered FLASH

- H_2O_2 Primary yield is similar FLASH and CONV

- But at Isodose FLASH-RT produces less ROS (H_2O_2) than CONV-RT

Recombinaison process?

Alteration of the biological cascade?

2019

IntraOp March 2021

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

SIT PMB ALCEN radiabeam TECHNOLOGIES

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

FLASH-RT can be fractionated

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

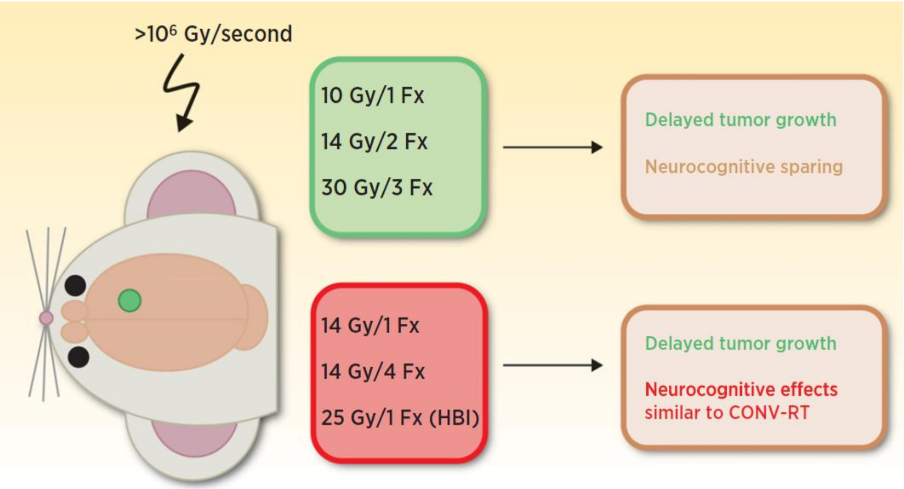
Hypofractionated FLASH-RT as an Effective Treatment against Glioblastoma that Reduces Neurocognitive Side Effects in Mice

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]

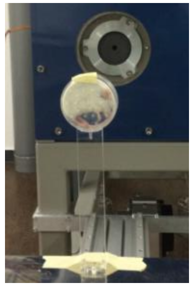


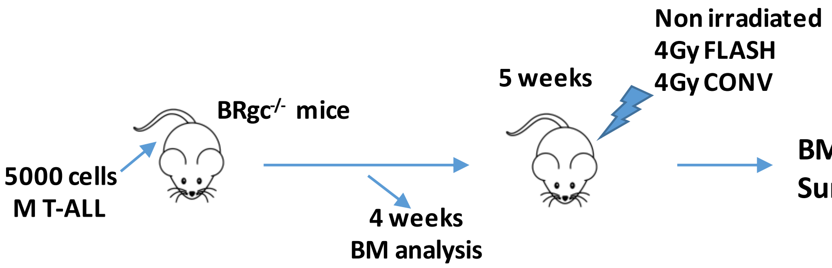
In Tumors

All tumors are not equally sensitive to FLASH-RT


F Pflumio B Uzan

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

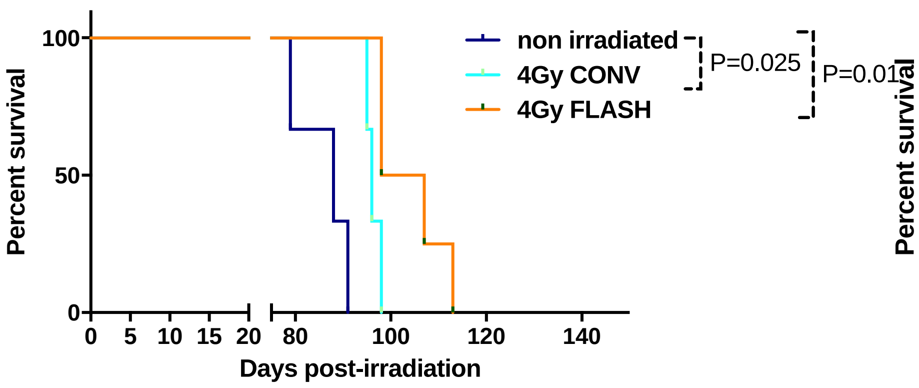




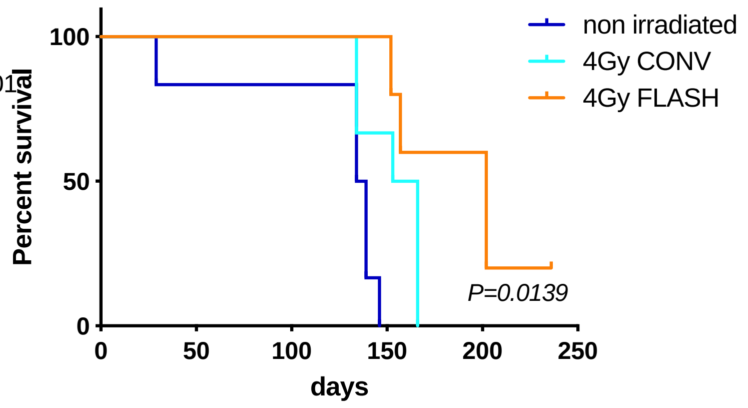
BM analysis, 20 days post-RT
Survival of mice

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

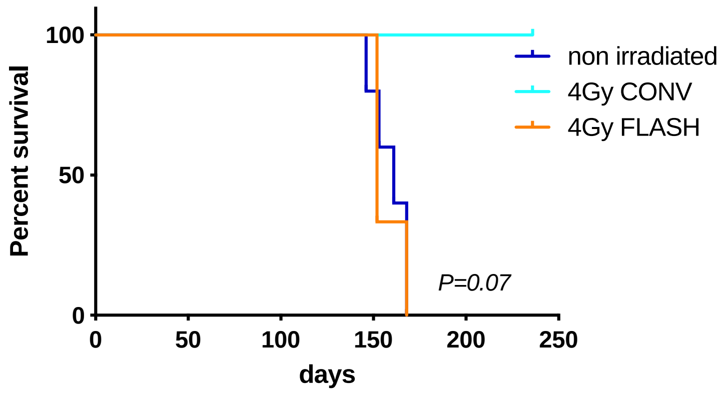
M106 PDX/T-ALL



M114 PDX/T-ALL



M108 PDX/T-ALL



Chabi et al, IJROBP, 2020

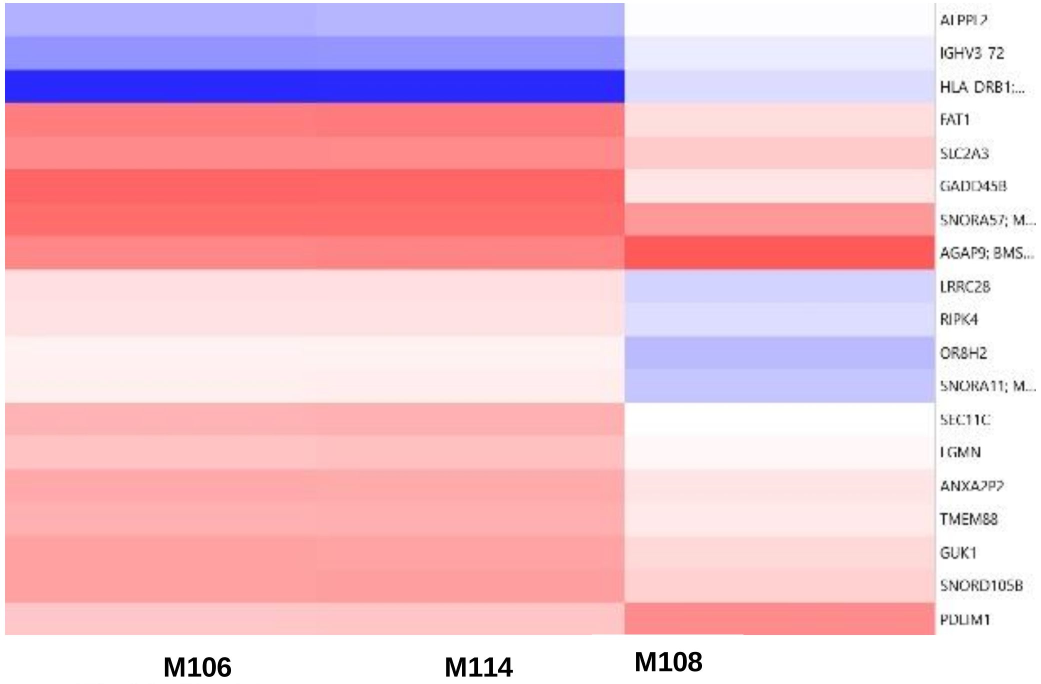
Putative susceptibility profile found after FLASH-RT in T-ALL

Inhibitor of cdc2/cyclinB1 kinase → GADD45B

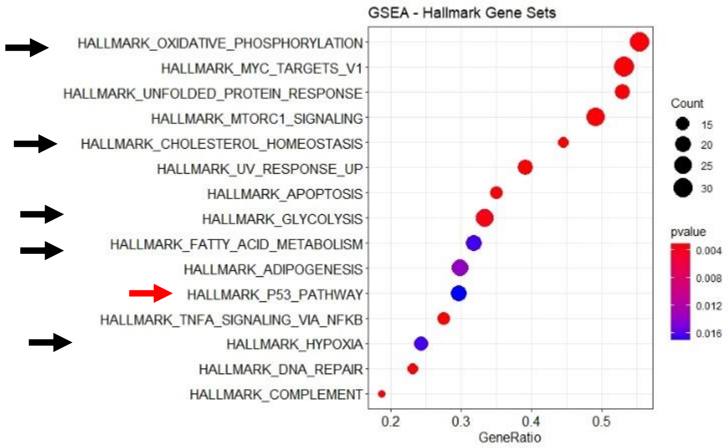
Wt pathway → FAT1

→ 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

Impact of dose and volume

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

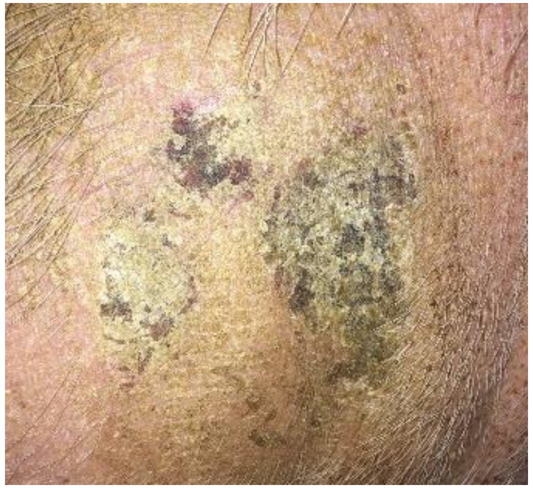
9 mo post-RT

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

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]

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


C Rohrer

Arm 1	**Arm 2**
External radiotherapy	FLASH-RT
Accelerated 48 Gy (10X4.8 Gy)	30 Gy single Fx
	3p- 20 ms
Gasymova et al, BMC Vet Res, 2017	*Vozenin et al, CCR, 2019*

PennVet
University of Pennsylvania

Lunds Universitet

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

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

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

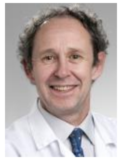
Anastasia Velalopoulou, Ilias V. Karagounis, Gwendolyn M. Cramer, et al.

Cancer Res Published OnlineFirst July 28, 2021.

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)



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]

[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

1a : Day 0

1b : 3 weeks

1c : 5 months

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)

IntraOp

CHUV

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.

What is needed

Technological development
FLASH specific TPS?

Implementation of conformality
Conventional fractionation

Impact of beam structure
Impact of beam parameters

What remains to be explored

Does one dose rate fit all purposes?

Impact dose rate vs volume
Impact of dose rate vs Organ
FLASH effect in human

What about combined therapie?

EDITORIAL

FLASH Radiation Therapy: New Technology Plus Biology Required

Jeffrey C. Buchsbaum, MD, PhD, AM, FASTRO, C. Norman Coleman, MD, FASTRO, Michael G. Espey, PhD, MT, Pataje G.S. Prasanna, PhD, Jacek Capala, PhD, Mansoor M. Ahmed, PhD, Julie A. Hong, MS, and Ceferino Obcemea, PhD

Radiation Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

New horizon in
therapy & treatment

FRPT

FLASH RADIOTHERAPY & PARTICLE THERAPY 2021

VIENNA, AUSTRIA

1-3 DECEMBER 2021

FRPT-Conference.org

FLASH «dream» team

Biology team

P Montay-Gruel
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J Ollivier
I Petridis
R Leavitt
P Barrera
C Romero
G Boivin
H Kacem
N Cherbuin
V To
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C Godfroid
A Martinotti

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C Bailat
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P Froidevaux
L Desorgher
P Jorge Goncalves
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F Chappuis

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T Boehlen
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M Jaccard

Clinical team

Radiation-Oncology
J Bourhis
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D Clerc
C Simon
K Lambercy

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S Chabi
B Uzan

Charles Limoli and Team
M Acharya
P Montay-Gruel
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Billy Loo and Team
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F Wolf

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FONDO NAZIONALE SVIZZERO
SWISS NATIONAL SCIENCE FOUNDATION

NATIONAL CANCER INSTITUTE

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ISREC Foundation thank to Biltema donation

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