Etat de l'art de la radiothérapie FLASH

A. Patriarca , Institut Curie, Hôpital, France

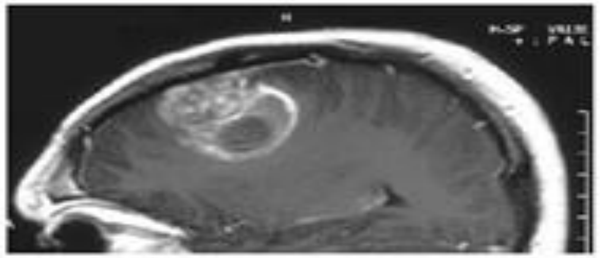
Cancer treatment : standard radiotherapy (RT)

- “Conventional” radiotherapy *(~95%)*

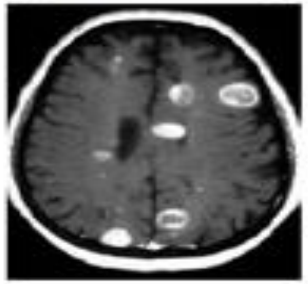
✓ **Particles**: X-rays 6-25 MV (every tumors), electrons 3-18 MeV (surface tumors)
✓ **Machines**: clinical electron accelerators, with multi leaf collimator and embedded imaging system
✓ **Time fractionation**: 2Gy/session, 5 session/week
✓ **Dose**: 40-70 Gy
✓ **Dose rate**: 30-70 mGy/s
✓ **Field sizes**: 2 -40 cm^2

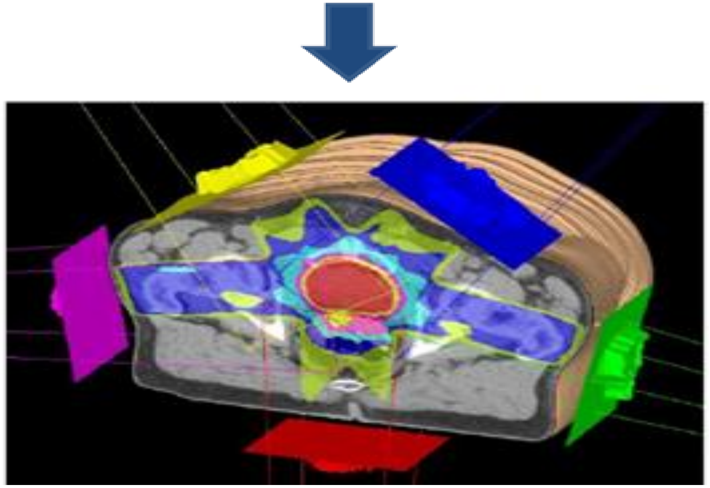
- Limitations of “conventional” radiotherapy

Radioresistant, bulky and diffuse cancers (glioblastomas)



Non-localized tumors (metastases)



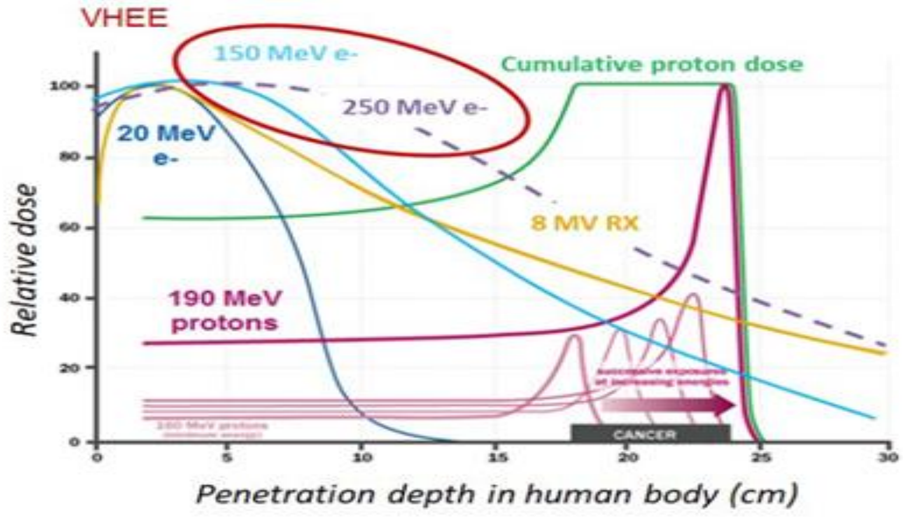


→ Toxicity of healthy tissues limits the dose

Limitations of radiotherapy

- How to improve the treatment

  - ➢ Induce a more efficient irradiation of the tumor
    - Particle/energy : hadrontherapy
    - Targeted radiotherapy : nanoparticles
    - Biological radiotherapy : immunotherapy
    - Imaging devices



  - ➢ Preserve the healthy tissues
    - Particle/energy : hadrontherapy
    - Dose delivery
      - **Spatial modulation of the dose** with small size beams (< mm)
      - **Temporal modulation of the dose** with high dose rates (> 40 Gy/s)

⟶ Play on physical parameters to induce a different biological effect

Bilateral thorax irradiation of C57BL/6J mice in single dose ≥ 15 Gy

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

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]

[1]Institut Curie, Centre de Recherche, 914[illegible] [illegible], France. [2]INSERM U612, 91405 Orsay, France. [3]Pathology Laboratory, Ecole Nati[illegible] Vétérinaire d[illegible], Université Paris-Est, 94704 Maisons Alfort, France. [4]Université [illegible] 9[illegible] Orsay, France. [5]INSERM U1030, Institut Gustave-Roussy, 94805 Villejuif, France. [6]Institut Curie, Centre de Recherche, 75248 Paris 05, France. [7]INSERM [illegible] 752[illegible] Paris [illegible], France. [8]Mines ParisTech, 77305 Fontainebleau, France. [9]CNRS UMR [illegible] 75248 Paris 05, France. [10]Radio-Oncologie/Radiothérapie, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland. [11]INSERM U967, Commissariat à l'Énergie Atomique (CEA), Division des Sciences du Vivant (DSV), Institut de Radiobiologie Cellulaire et Moléculaire (IRCM), 92265 Fontenay aux Roses, France.
*Corresponding author. E-mail: vincent.favaudon@curie.fr

A promise for radiation therapy?

institut Curie

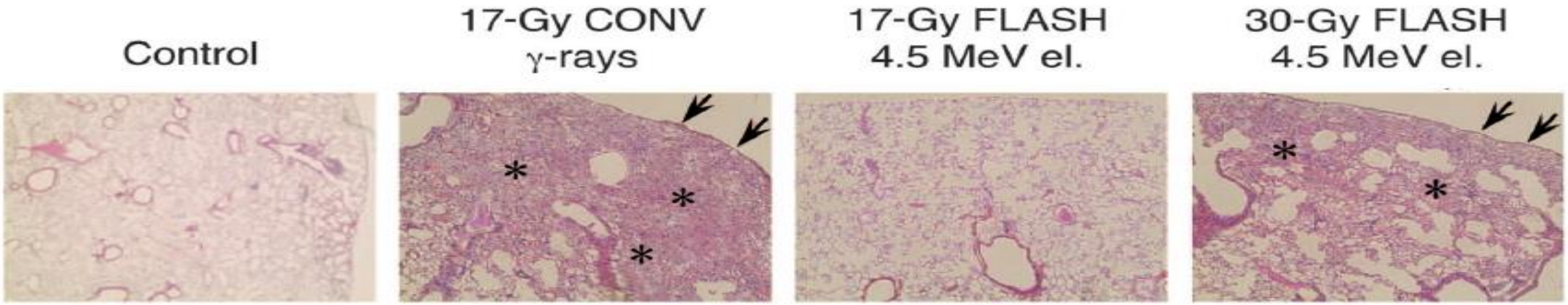
FLASH irradiation : dose delivery time ≤ 500 ms - dose rate ≥ 40 Gy/s

Tests on mice lung tumors with a 4.5 MeV electron linac have shown :

- ✓ **Same anti-tumoral** efficiency and **enhancement** of the differential responses between normal and tumor tissues wrt CONV (dose rate ≤ 0.03 Gy/s) radiotherapy

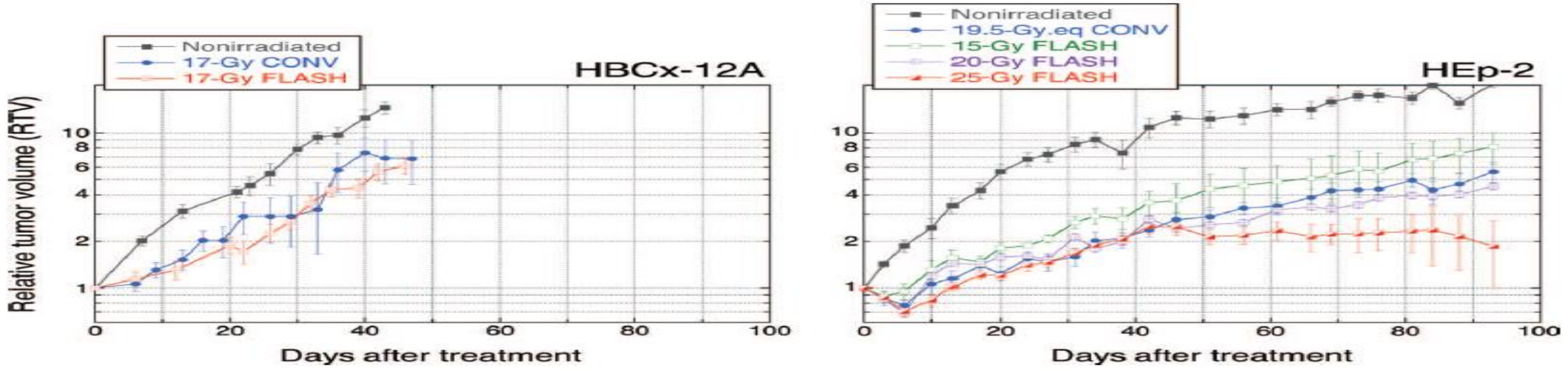
FLASH RT increases the therapeutic index

Sparing of healthy tissues



➢ FLASH spares lung at doses known to induce fibrosis in mice following conventional dose-rate irradiation (CONV).

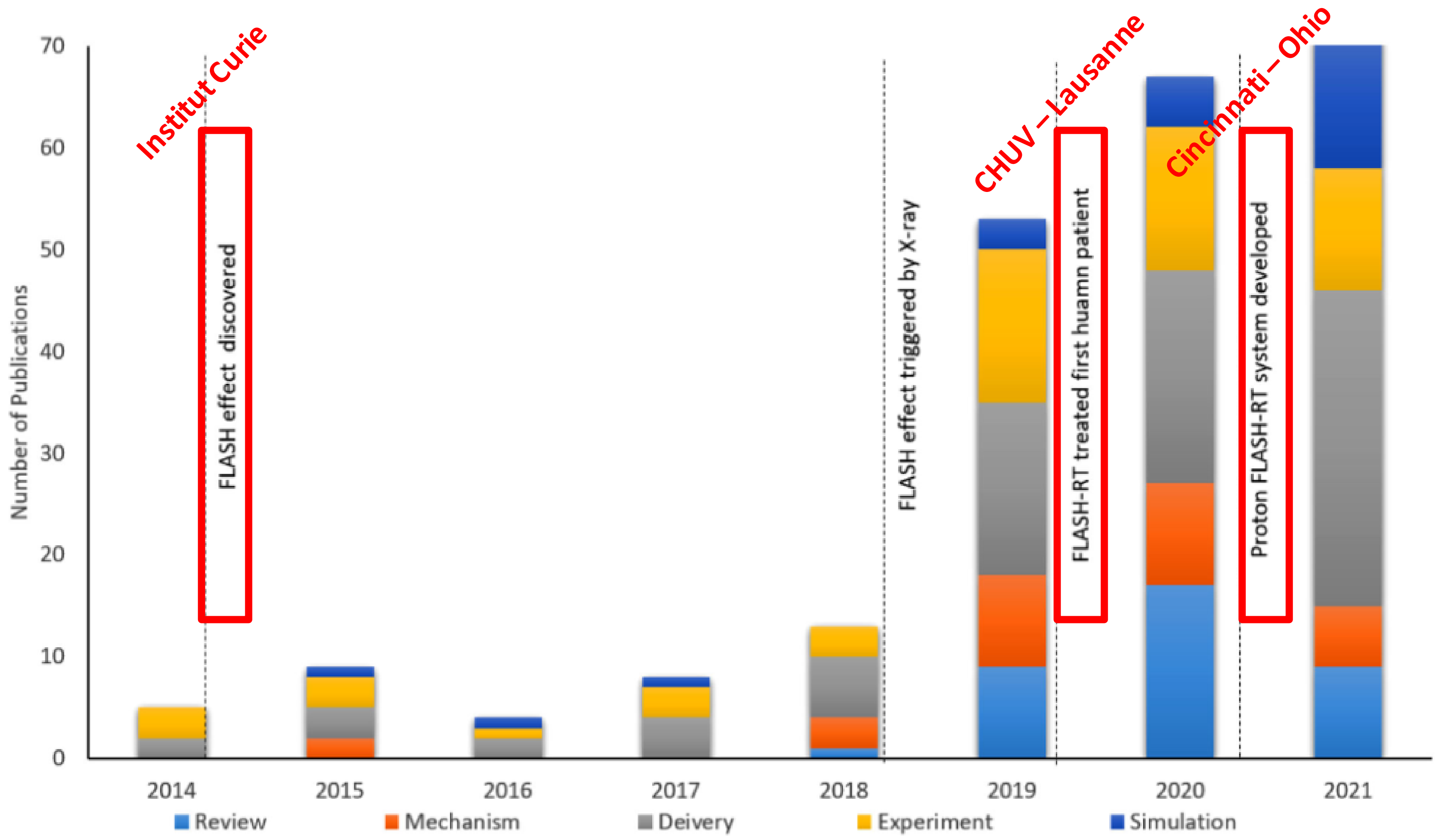
Iso-effect on tumors grafts



➢ FLASH proved to be as efficient as CONV irradiation to cure tumors (two human tumor xenografts and an orthotopically implanted syngeneic lung tumor).

Favaudon et al. Science Translational Medicine (2014)

Building evidence for the FLASH effect



[Gao et al. J Appl Clin Med Phys.2022]

Building evidence for the FLASH effect

Evidence of sparing for a wide range of models (**mice, rat, cats, dogs, zebrafish, pig**), particle type (**electron, photon, proton, ions**), organs (**lung, brain, skin, gut**)

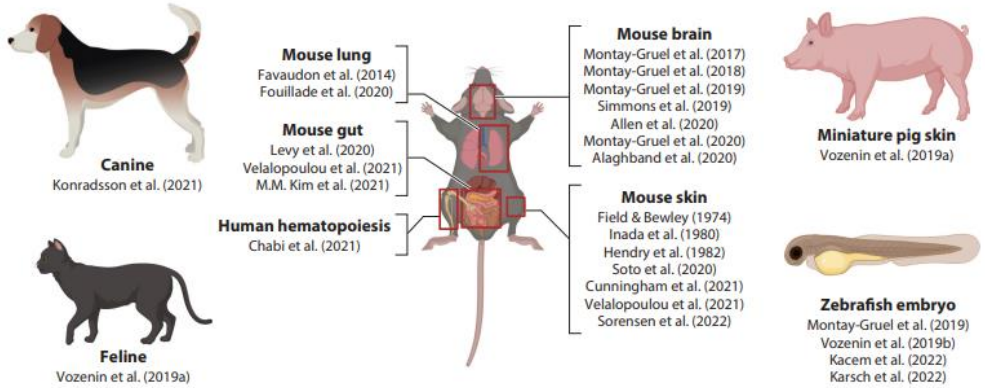


Table 2. Evidence of tumor control from FLASH irradiation.

Model	Assay/Endpoint	Dose (Gy)	Dose Rate (Gy/s)	Radiation Source	Reference
Mice, HBCx-12A, and Hep-2 human xenografts (local)	Tumor growth	17–25	60	Electron	[12]
Mice, orthotopic engrafted lung carcinoma luciferase+ TC-1 cells (thorax)	Tumor growth	15–28	60	Electron	[12]
Mice, ID8 syngeneic ovarian cancer (thorax)	Tumor number/weight	14	216	Electron	[18]
Mice, orthotopic engrafted Lewis lung carcinoma (thorax)	Tumor size	18	40	Proton	[29]
Mice, pancreatic MH641905 flank tumor	Tumor growth	12/15	78	Proton	[27]
Cat, nasal planum SCC (local)	Tumor growth	25–41	130–390	Electron	[14]
Human, CD30+ T-cell cutaneous lymphoma	Tumor response	15	167	Electron	[15]

Table 1. Evidence of normal tissue sparing from FLASH irradiation.

Model (Site of Irradiation)	Assay/Endpoint	Dose (Gy)	Dose Rate (Gy/s)	Radiation Source	Reference
Mice (WBI) [1]	Memory tests, neurogenesis	10	>100	Electron	[13]
Mice (WBI) [1]	Neurocognitive tests, mature/immature neurons, growth hormone levels	8	4.4×10^6	Electron	[22]
Mice (WBI) [1]	Neurocognitive tests, dendritic spine density, microglial activation, inflammation	30	200/300	Electron	[20]
Mice (WBI) [1]	Neurocognitive tests, neuroinflammation, neuronal morphology	10	>100	Electron	[23]
Mice (WBI) [1]	Neurocognitive tests, hippocampal cell division, astrogliosis	10	37	X-ray	[21]
Mice (thorax)	Survival, dermatitis, breathing function, lung pathology	15/17.5/20	40	Proton	[24]
Mice (thorax)	Lung fibrosis, skin dermatitis, survival	15/17.5/20	40	Proton	[25]
Mice (thorax)	Lung fibrosis, TGF-β signaling, apoptosis	17	40–60	Electron	[12]
Mice (thorax)	Cellular proliferation, pro-inflammatory gene expression, DNA damage (53BP1/γH2AX foci), senescence	17	40–60	Electron	[26]
Mice (abdomen)	Survival	10–22	70–210	Electron	[19]
Mice (abdomen)	Survival, stool production, crypt cell regeneration, apoptosis, DNA damage	12–16	216	Electron	[18]
Mice (abdomen)	Intestinal crypt cell proliferation	15 Gy	78	Proton	[27]
Mice (local intestinal)	Fibrosis	18 Gy	78	Proton	[27]
Mini-pig (skin)	Skin toxicity/injury	22–34	300	Electron	[14]
Zebrafish Embryo 	Morphology	8	>100	Electron	[23]

[1] WBI refers to whole brain irradiation.

From Hughes et al. 2020, Limoli and Vozenin 2023, Atkinson et al. 2023

First patient treated with eFLASH-radiotherapy

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*

CHUV – Lausanne

June 2019

1a : Day 0 1b : 3 weeks 1c : 5 months

15 Gy, in 90 ms, using a **5.6-MeV electron** linac, to a 75-years old patient with a multi-resistant cutaneous lymphoma :

On healthy tissues : no decrease of the thickness of the epidermis and no disruption at the basal membrane with limited increase of the vascularization.

On tumor : Tumor response was rapid, complete, and durable with a short follow-up of 5 months

First patients treated with pFLASH-radiotherapy

Oct 2022

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

Cincinnati – Ohio

FAST-01 is a prospective, single-center trial designed to assess the workflow feasibility, toxicity, and efficacy of FLASH therapy for the treatment of painful bone metastases in the extremities

10 subjects aged ≥18 years with up to 3 **painful bone metastases** in the extremities

8 Gy, in ~200 ms, using a 230 MeV **Varian Probeam proton cyclotron**

Dose rate of ≥40 Gy/s using the plateau (transmission) portion of the proton beam

Results : demonstration of the clinical feasibility of proton FLASH radiotherapy in terms of clinical workflow metrics, and safety. The treatment efficacy (pain relief) and the profile of adverse events were comparable with those of standard-of-care radiotherapy.

Recruiting ! FAST-02 FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases in the Thorax

Accelerators solutions for FLASH irradiations: pre-clinical studies with LINACS (low E electrons)

Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment
Volume 944, 11 November 2019, 162537

Time-resolved dosimetry of pulsed electron beams in very high dose-rate, FLASH irradiation for radiotherapy preclinical studies

Vincent Favaudon, Jean-Michel Lentz, Sop... Marzi, Charles Fouillade, Marie Dutreix

Institut Curie

applied sciences — MDPI

Article

Characterization of Ultra-High-Dose Rate Electron Beams with **Kinetron & ElectronFlash Linac**

Lucia Giuliano, Gaia Franciosini, Luigi Palumbo, Lilia Aggar, Marie Dutreix, Luigi Faillace, Vincent Favaudon, Giuseppe Felici, Federica Galante, Andrea Mostacci, Mauro Migliorati, Matteo Pacitti, Annalisa Patriarca and Sophie Heinrich

Experimental Platform for Ultra-high Dose Rate FLASH Irradiation of Small Animals Using a **Clinical Linear Accele...**

Emil Schüler, PhD,* Stefania Trov... Frederick Lartey, PhD,* Marjan Ra... A. Joe Praxel,* Billy W. Loo, Jr, M... and Peter G. Maxim, PhD*,†

*Department of Radiation Oncology and †Stanfo... of Medicine, Stanford, California

Stanford - USA

Modifying a **clinical linear accelerator** for delivery of ultra-high dose rate irradiation

Michael Lempart, Börje Blad, Gabriel Adrian, Sven Bäck, Tommy Knöös, Crister Ceberg, Kristoffer Petersson

Radiation Physics, Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital; Division of Oncology and Pathology, Clinical Sciences, Lund, Skåne University Hospital; and Department of Medical Radiation Physics, Clinical Sciences, Lund, Lund University, Sweden

Skane&Lund Uni - Sweden

MEDICAL PHYSICS
The International Journal of Medical Physics Research and Practice

Research Article

High dose-per-pulse electron beam dosimetry: Commissioning of the Oriatron eRT6 **prototype linear accelerator** for preclinical use

Maud Jaccard, Maria Teresa Durán, Kristoffer Pet... Marie-Catherine Vozenin, Jean Bourhis, François...

CHUV – Lausanne

cancers — MDPI

Article

Independent Reproduction of the FLASH Effect on the Gastrointestinal Tract: A Multi-Institutional Comparative Study

Anet Valdés Zayas, Neeraj Kumari, Kevin Liu, Denae Neill, Abagail Delahoussaye, Patrik Gonçalves Jorge, Reiner Geyer, Steven H. Lin, Claude Bailat, François Bochud, Raphael Moeckli, Albert C. Koong, Jean Bourhis, Cullen M. Taniguchi, Fernanda G. Herrera and Emil Schüler

MOBETRON -IORT

Lausanne + MD Anderson TX

Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Original Article

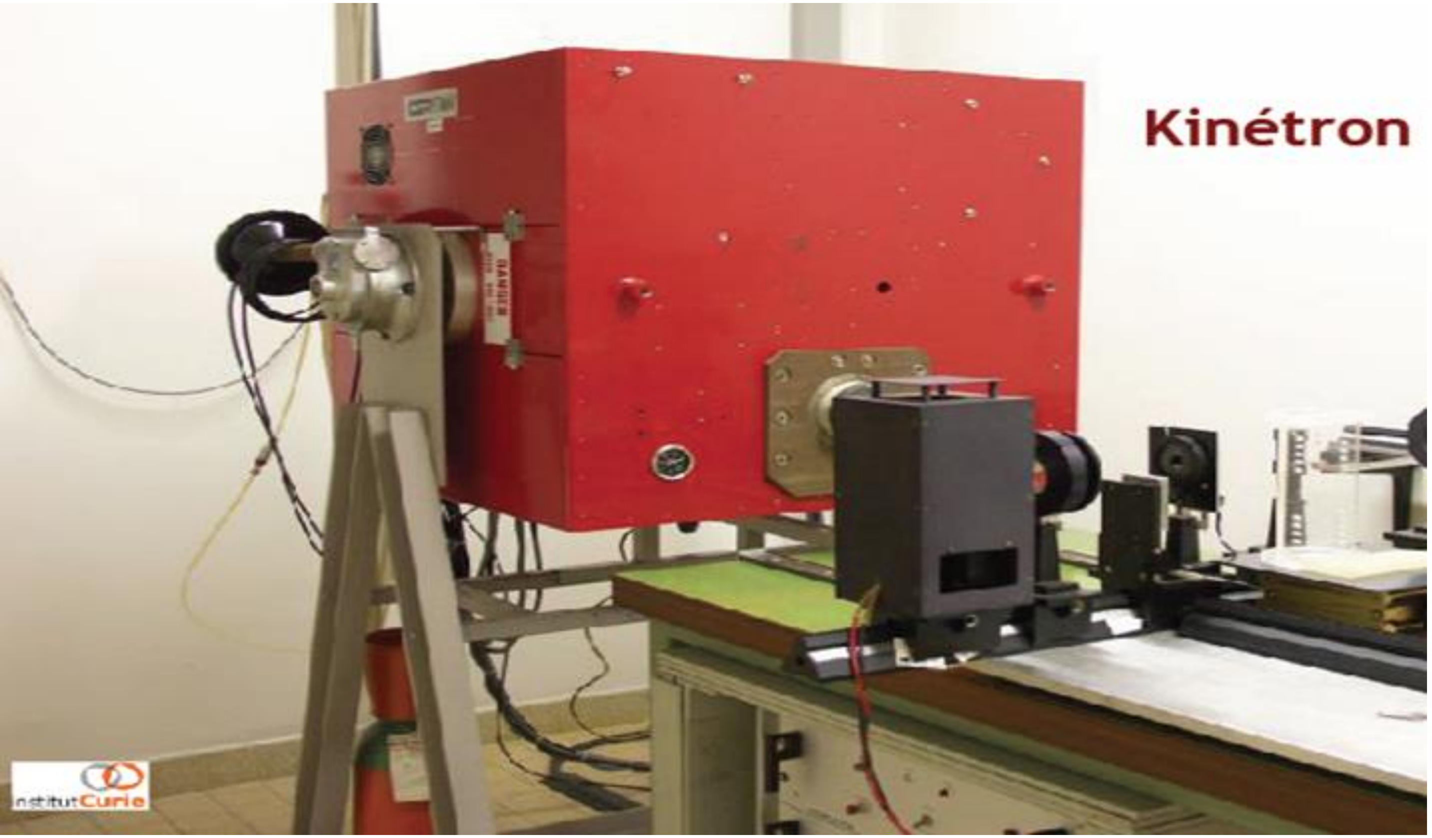
Enabling ultra-high dose rate electron beams at a clinical linear accelerator for isocentric treatments

Riccardo Dal Bello, Jens von der Grün, Silvia Fabiano, Thomas Rudolf, Natalia Saltybaeva, Luisa S. Stark, Md Ahmed, Manohar Bathula, Serpil Kucukker Dogan, Joshua McNeur, Matthias Guckenberger, Stephanie Tanadini-Lang

a Department of Radiation Oncology, University Hospital Zurich and University of Zurich, Zurich, Switzerland; b Varian Medical Systems a Siemens Healthineers Company, Palo Alto, CA, USA

Zurich Uni H + Varian

Accelerators for pre-clinical FLASH investigations: electrons (research machines)



LINAC “Kinétron” (1987)
4.0-5.0 MeV electrons
Triode electron gun

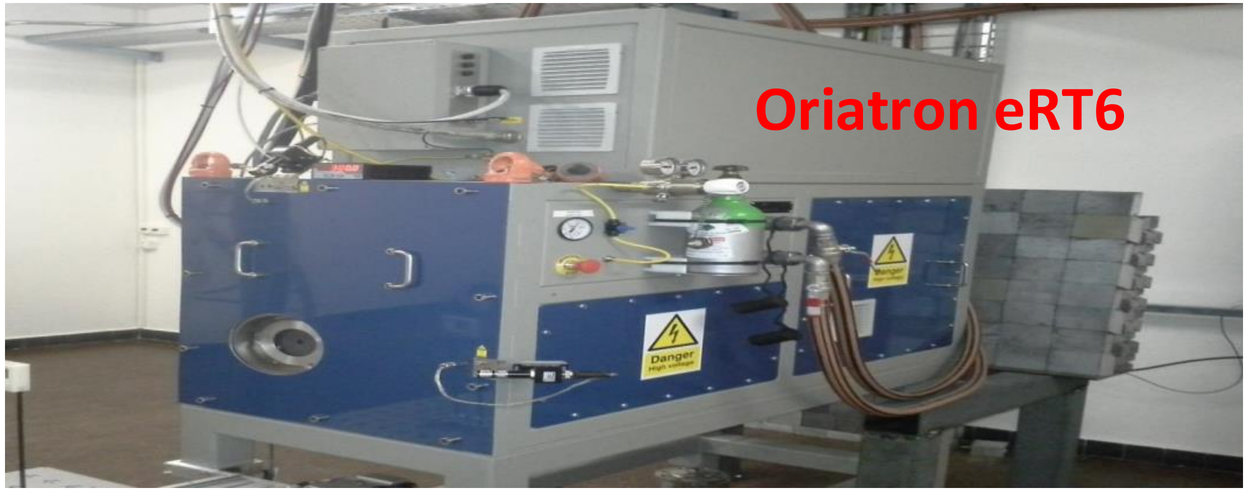
LET = 0.19 keV/µm
RBE = 1.00 relative to ^{60}Co
(Compton only)

Pulse width 0.05 - 2.2 µs
Repeat frequency 0.1 - 200 Hz
Peak current 0.01 - 220 mA
Dose per pulse 0.001 - 50 Gy

Mean dose-rate 0.01 - 7000 Gy.s^{-1}
Maximum dose-rate during the pulse ≈ 2 10^{7} Gy.s^{-1}

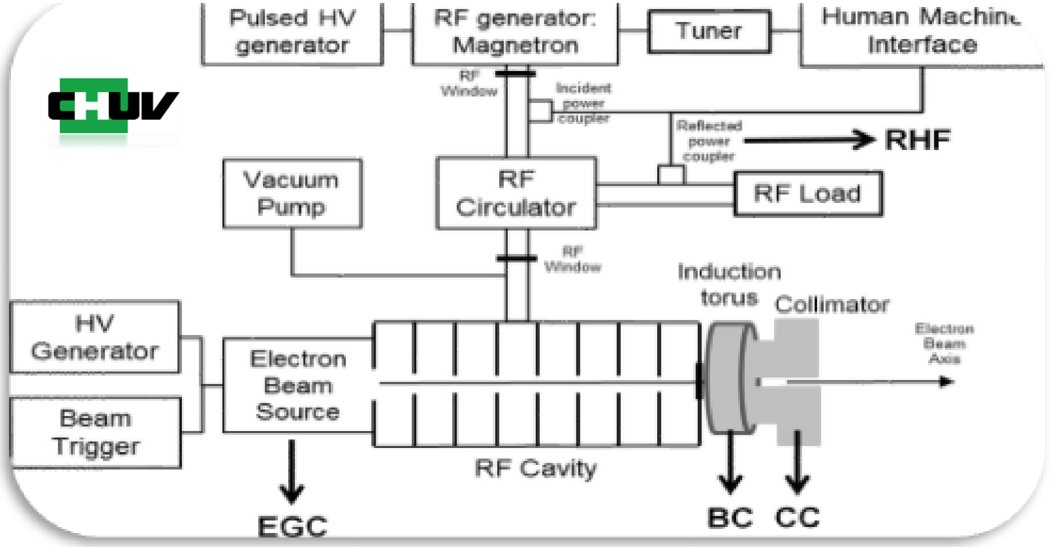
Favaudon et al. Science Translational Medicine (2014)

Accelerators for pre-clinical FLASH investigations: electrons (research machines)



LINAC eRT6	Parameters
Nominal energy (MeV)	5,5
Temporal structure	Pulsed
Pulse repetition frequency (Hz)	10 - 200
Dose per pulse (Gy)	10 - 30
Mean Dose rate (Gy/s)	up to 1000
Pulse width (µs)	1 - 2

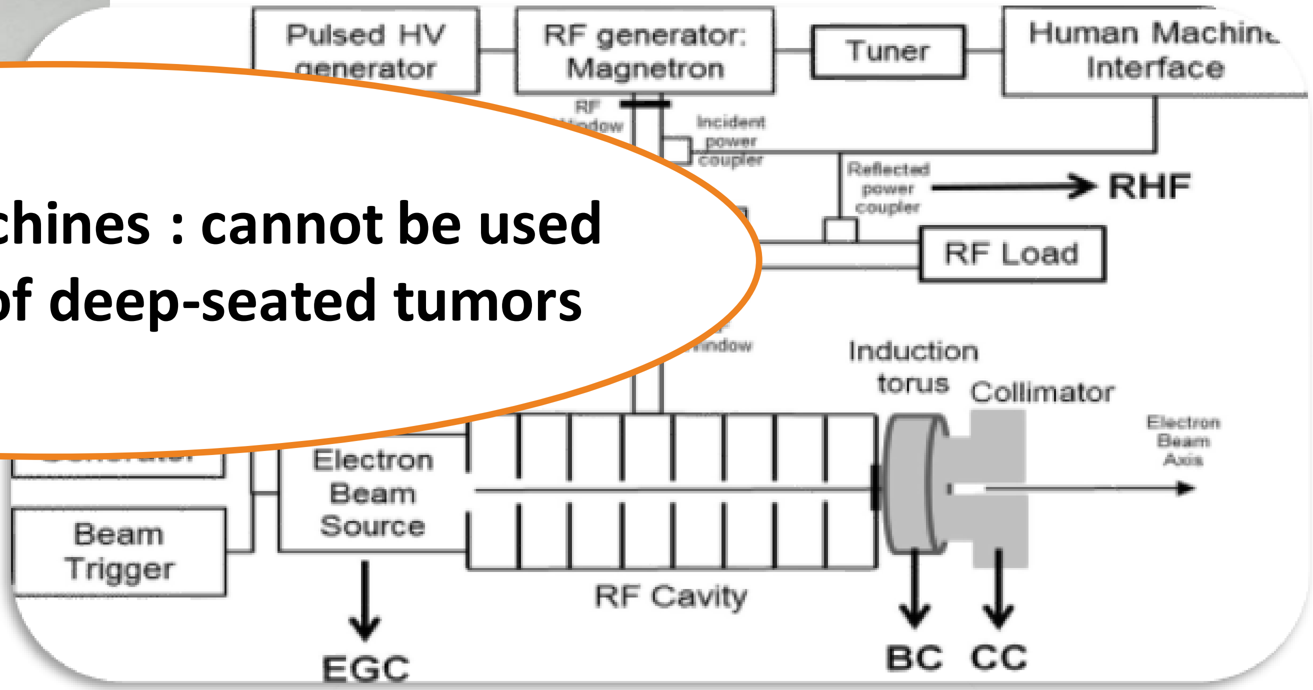
	Flash	Conv
GT (V):	300	100
w (µs):	2.2	1.0
f (Hz):	200	10
$\dot{D}_m$ (Gy/s)	200	0.05
$\dot{D}_p$ (Gy/s)	$4.5 \cdot 10^5$	$4.9 \cdot 10^3$
Peak current (mA)	300	1



Jaccard M et al.,Medical Physics,2018

Accelerators for pre-clinical FLASH investigations: electrons (research machines)

But low enery machines : cannot be used for the treatment of deep-seated tumors



LINAC eRT6	Parameters
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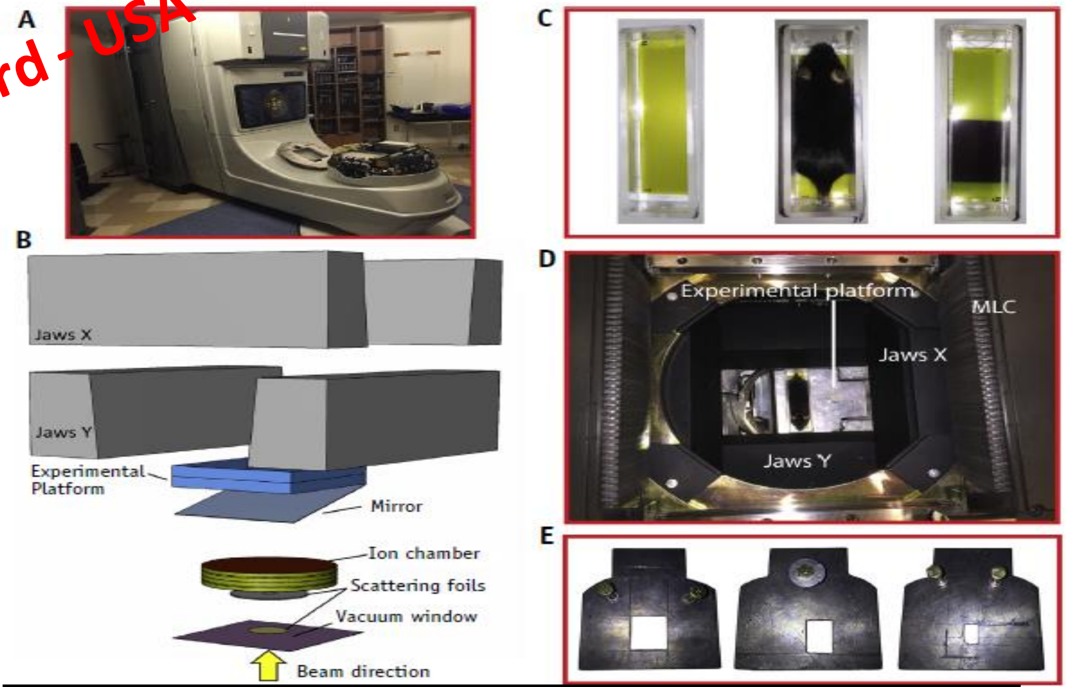
Mean Dose rate (Gy/s)	up to 1000
Pulse width (µs)	1 - 2

Jaccard M et al., «High dose-per-pulse electron beam dosimetry: Commissioning of the Oriatron eRT6 prototype linear accelerator for preclinical use.» Medical Physics,2018

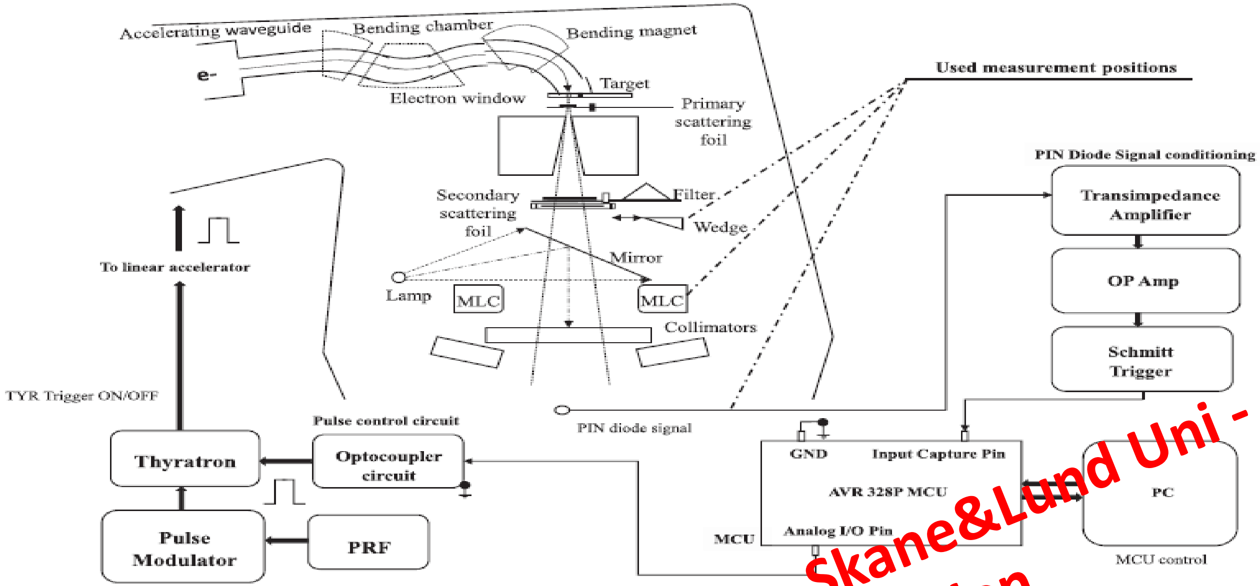
Accelerators for pre-clinical FLASH investigations: electrons (modified clinical LINACs)

Stanford - USA



Varian Clinac 21EX	Parameters
Nominal energy (MeV)	9, 20
Temporal structure	pulsed
Pulse repetition frequency (Hz)	180, 108
Dose (Gy)	1.9 Gy/pulse
Mean Dose rate (Gy/s)	200
Pulse width (µs)	5

Skane&Lund Uni - Sweden

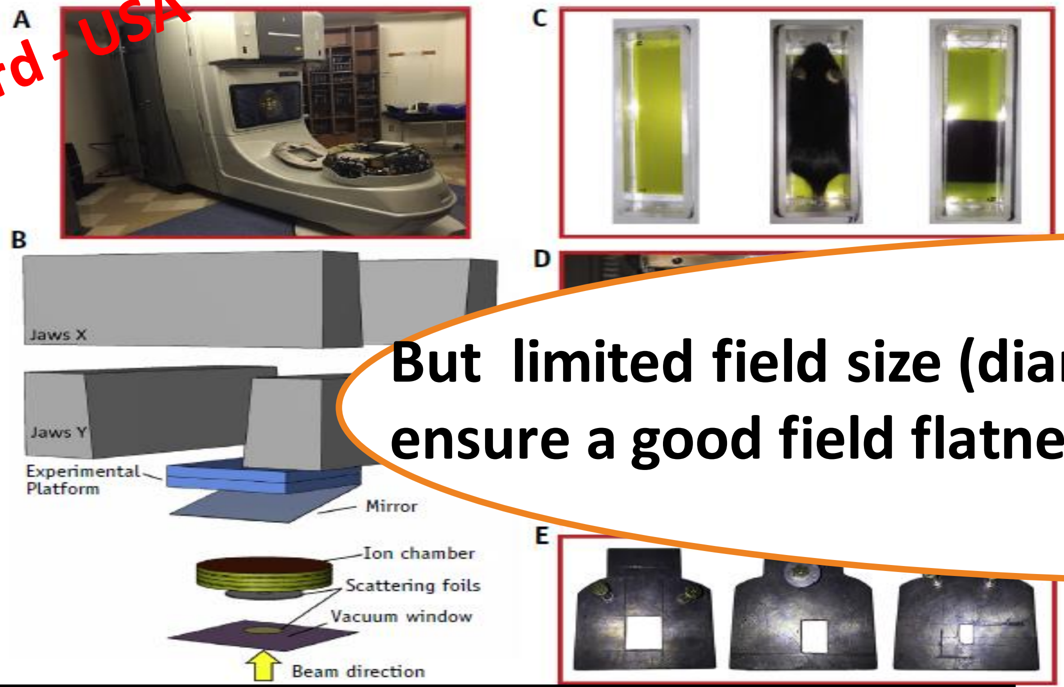


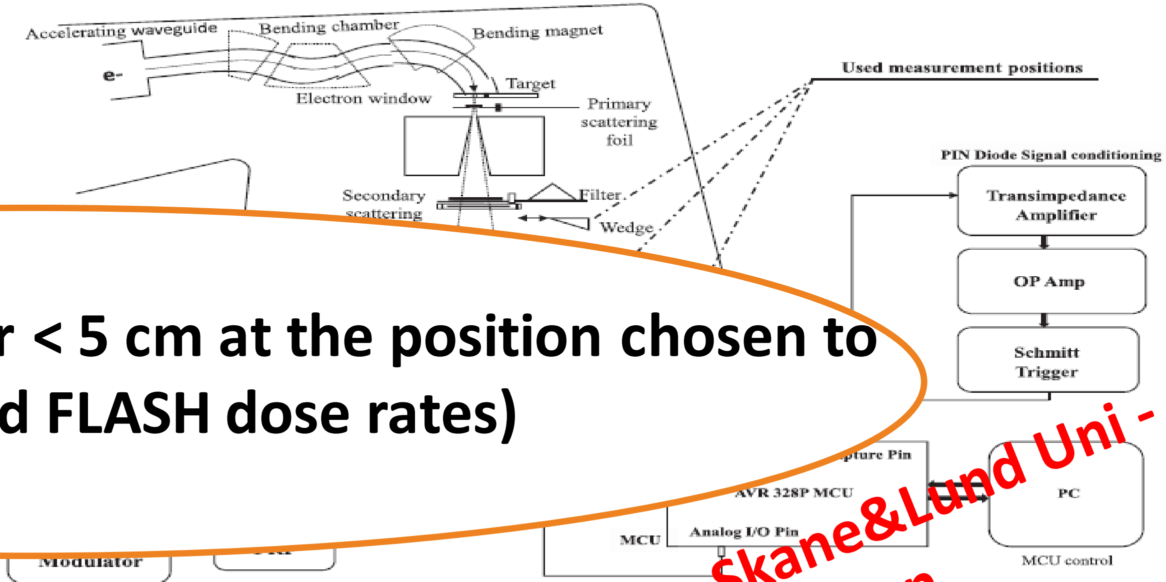
depending on measurement point within the treatment head

Elekta Precice	Parameters
Nominal energy (MeV)	8
Temporal structure	pulsed
Pulse repetition frequency (Hz)	200
Dose (Gy)	0.18-1.9 Gy/pulse
Mean Dose rate (Gy/s)	30 - 300

Accelerators for pre-clinical FLASH investigations: electrons (modified clinical LINACs)

Stanford - USA





But limited field size (diameter < 5 cm at the position chosen to ensure a good field flatness and FLASH dose rates)

Skane&Lund Uni - Sweden

depending on measurement point within the treatment head

Varian Clinac 21EX	Parameters
Nominal energy (MeV)	9, 20
Temporal structure	pulsed
Pulse repetition frequency (Hz)	180, 108
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Dose (Gy)	0.18-1.9 Gy/pulse
Mean Dose rate (Gy/s)	30 - 300

Accelerators solutions for FLASH irradiations: Towards clinical studies with LINACS

MOBETRON -IORT

[Valdés Zayas et al; 2023]

Values at CHUV
9 MeV
15.8–16.3 Gy
8
Single fraction
199 Gy/s
0.97×10^6 Gy/s
90 Hz
1.94 Gy
2 µs
78 ms
40 mm diameter

Clinical Trail : IMPulse

FLASH therapy in patients with metastases of melanoma

FLASHKNIFE

LIAC FLASH

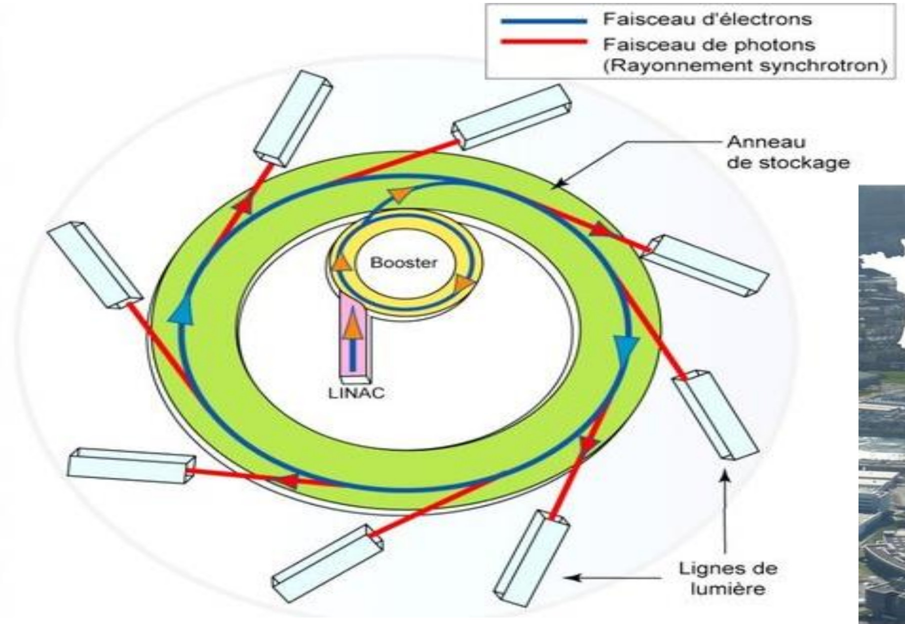
Varian TrueBeam (SN 1001)

[Dal Bello et al. 2023]

16 MeV UHDR (SSD = 100 cm)

- dose per pulse at isocenter : up to 1.28 Gy/pulse
- average and instantaneous dose rates up to 256 Gy/s
- instantaneous dose rates and $3{\cdot}10^5$ Gy/s
- field sizes up to 10x10cm^2 (potential treatments of tumours up to 5 cm in depth such as skin tumours, breast cancer, or certain head and neck cancers)
- beam reproducibility within ± 2.5% (via BGM firmware and ACF algorithm adaptations)
- Standard Imaging + positioning devices

Accelerators for pre-clinical FLASH investigations: photons (Synchrotrons)




Radiotherapy and Oncology 129 (2018) 582–588

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

FLASH irradiation

X-rays can trigger the FLASH effect: Ultra-high dose-rate synchrotron light source prevents normal brain injury after whole brain irradiation in mice

Pierre Montay-Gruel [a], Audrey Bouchet [b], Maud Jaccard [c], David Patin [c], Raphael Serduc [b,*], Warren Aim [b], Kristoffer Petersson [a,c], Benoit Petit [a], Claude Bailat [c], Jean Bourhis [a], Elke Bräuer-Krisch [d,1], Marie-Catherine Vozenin [a,1]

[a] Department of Radiation Oncology/DO/Radio-Oncology/CHUV, Lausanne University Hospital, Switzerland; [b] Rayonnement synchrotron et Recherche médicale, Université Grenoble Alpes, 38000 Grenoble, France; [c] Institute of Radiation Physics (IRA), Lausanne University Hospital, Switzerland; [d] ESRF, European Synchrotron Radiation Facility, Grenoble, France

cognitive sparing similar to the electron FLASH

ID17 Biomedical Beamline of the ESRF	Parameters
Nominal energy (KeV)	102
Temporal structure	Continuous
Accelerator current (mA)	178
Dose (Gy)	10
Mean Dose rate (Gy/s)	37
Dose rate in a slice (Gy/s)	12000

But kV x-rays are generally not used for the treatment of deep-seated tumors

Accelerators for pre-clinical FLASH investigations: photons (6-8 MeV e- superconducting linac)

Radiotherapy and Oncology 166 (2022) 44–50

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

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

Feng Gao [a], Yiwei Yang [b,1], Hongyu Zhu [c,1], Jianxin Wang [d], Dexin Xiao [d], Zheng Zhou [d], Tangzhi Dai [a], Yu Zhang [a], Gang Feng [a], Jie Li [a], Binwei Lin [a], Gang Xie [e], Qi Ke [e], Kui Zhou [d], Peng Li [d], Xuming Shen [d], Hanbin Wang [d], Longgang Yan [d], Chenglong Lao [d], Lijun Shan [d], Ming Li [d], Yanhua Lu [d], Menxue Chen [d], Song Feng [f], Jianheng Zhao [d], Dai Wu [d,*], Xiaobo Du [a,*]

[a] Department of Oncology, Nuclear Medicine Laboratory of Mianyang Central Hospital, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China; [b] Institute of Nuclear Physics and Chemistry, China Academy of Engineering Physics, Mianyang; [c] Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou; [d] Institute of Applied Electronics, China Academy of Engineering Physics; [e] Department of Pathology, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang; and [f] School of Nuclear Science and Technology, University of South China, Hengyang, China

Research accelerator, but observation of FLASH effect with high energy photons

PNAS RESEARCH ARTICLE | MEDICAL SCIENCES

FLASH X-ray spares intestinal crypts from pyroptosis initiated by cGAS-STING activation upon radioimmunotherapy

Xiaolin Shi[a,1], Yiwei Yang[b,1], Wei Zhang[c,1], Jianxin Wang[b,d,1], Dexin Xiao[b], Huangge Ren[a], Tingting Wang[e,f], Feng Gao[e,f], Zhen Liu[g], Kui Zhou[b], Peng Li[b], Zheng Zhou[b], Peng Zhang[b], Xuming Shen[b], Yu Liu[b], Jianheng Zhao[b], Zhongmin Wang[h], Fenju Liu[a], Chunlin Shao[i], Dai Wu[b,f,2], and Haowen Zhang[a,i,2]

Edited by James Cleaver, University of California San Francisco Medical Center at Parnassus, San Francisco, CA; received May 17, 2022; accepted September 11, 2022

A FLASH **photon beams (6–8 MV)** showed a significant FLASH effect in tumor-bearing mice irradiated to the **lungs and Intestine**.

PARTER platform at Chengdu, China	Parameters
Nominal energy (MV)	6-8
Temporal structure	Pulsed
Accelerator current (mA)	1-10
Dose (Gy)	12-30
Mean Dose rate (Gy/s)	700-1200

Building evidence for the FLASH effect : protons and ions

Evidence for several models (**mice, rat, dogs, zebrafish)**, organs (**lung, brain, skin, gut**)

Protons

Reference	Machine facility	Accelerator type	Energy (MeV)	Dose rate (Gy/s)	Delivery system	Assay
Auer, Hable[81]	SNAKE	Laser-driven proton beam	20	$\geq 10^9$ (pulse mode)	N/A	In vitro experiment
Buonanno, Grilj[41]	RARAF	Singletron	5.5	100 and 1000	Double scattering	In vitro experiment/dosimetry
Grilj, Buonanno[33]	RARAF	Singletron	5.5	100, 1000	Double scattering	In vitro experiment
Han, Mei[82]	CLAPA	Laser plasma accelerator	15	10^9	Not provided	In vitro experiment
Yang, Lu[46]	CLAPA	Laser plasma accelerator	15	10^9	Not provided	In vitro experiment
Zlobinskaya, Siebenwirth[83]	SNAKE	Laser-driven proton beam	23	$\geq 10^9$ (pulse mode)	N/A	In vivo experiment
Beyreuther, Brand[84]	UPTD proton beam	Not provided	224	100 (mean) 200 (0.5%)	PBS	In vivo experiment
Abel, Girdhani[85]	Not provided	Not provided	Not provided	40	PBS	In vivo experiment
Kourkafas, Bundesmann[86]	HZB	Cyclotron	68	75	Single scattering	In vivo experiment
Cunningham, McCauley[87]	Varian Probeam	Isochronous cyclotron	250	115.1	PBS	In vivo experiment/hardware
Patriarca, Fouillade[78]	IBA C230	Isochronous cyclotron	230	40 and 80	Double scattering	Hardware
Younkin, Bues[88]	Hitachi ProBeatV	Synchrotron	250	Not provided	PBS	Hardware
IBA[89]	IBA Proteus	Isochronous cyclotron	230	Up to 200	PBS	Hardware
Kolano[90]	AVO	LINAC	250	Not provided	PBS	Hardware
Darafsheh, Hao[91]	Mevion HYPERSCAN	Synchrocyclotron	230	100–200	Double scattering	Hardware/dosimetry
Nesteruk, Togno[80]	PSI Gantry 1	Cyclotron	250	1–9000	PBS	Hardware/dosimetry
Zou, Diffenderfer[92]	IBA	Cyclotron	226.2	160	Double scattering	Hardware/dosimetry
Diffenderfer, Verginadis[79]	IBA Proteus plus	Isochronous cyclotron	230	78	Double scattering	Dosimetry
Zhang, Cascio[32]	IBA C230	Isochronous cyclotron	227.5	120	Double scattering	Dosimetry
Kang et al.[93]	Varian Probeam	Isochronous cyclotron	250	115.1	PBS	Hardware/dosimetry

[Gao et al. J Appl Clin Med Phys.2022]

Building evidence for the FLASH effect : protons and ions

Evidence for several models (**mice, rat, dogs, zebrafish)**, organs (**lung, brain, skin, gut**)

Protons

Reference	Machine facility	Accelerator type	Energy (MeV)	Dose rate (Gy/s)	Delivery system	Assay
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[Gao et al. J Appl Clin Med Phys.2022]

Table 3. Summary of outcomes in in vivo studies comparing FLASH and conventional dose-rate PBT.

Hughes et al. 2020

Model	Dose (Gy)	FLASH Dose-Rate (Gy/s)	Outcome	Reference
Zebrafish embryo	0–43	100	No survival difference	[61]
Mice (thorax)	15/17.5/20	40	Normal tissue protection with FLASH	[24]
Mice (thorax)	15/17.5/20	40	Normal tissue protection with FLASH	[25]
Mice (abdomen)	15	78	Normal tissue protection with FLASH	[27]
Mice (local intestinal)	18	78	Normal tissue protection with FLASH	[27]
Mice, orthotopic engrafted Lewis lung carcinoma (thorax)	18	40	Improved tumor control with FLASH, increased T-lymphocyte tumor infiltration	[29]
Mice, pancreatic MH641905 flank tumor	12/15	78	No difference in tumor control	[27]
Mice, FaDu head, and neck squamous cell carcinoma transplantation	17.4	$>10^9$	No difference in tumor control	[62]

Building evidence for the FLASH effect : protons and ions

Evidence for several models (**mice, rat, dogs, zebrafish)**, organs (**lung, brain, skin, gut**)

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Carbon Ions

Ref	Year	Particle Type, Source, Delivery Mode	Model	Energy (MeV)	Dose (Gy)	Delivery Time (s)	Pulse/ Bunch Count	Pulse/ Bunch Rate (Hz)	FLASH Dose Rate Average (Gy/s)	FLASH Instantaneous Dose Rate (Gy/s)	Low or CONV (Gy/s)	Outcome
[76]	2022	Carbon, synchrotron: pulsed	Chinese hamster ovary cells (CHO-K1)	280 ****	7.5	0.13	1	1.45×10^{10}	70	70	0.6	A statistically significant increase in cell survival was displayed for CHO-K1 cells exposed to FLASH vs. CONV irradiation at 0.5% and 4% oxygenation. No significant difference was observed between dose rates for cells exposed to 21% oxygenation.
[55]	2022	Carbon, synchrotron: pulsed	Human lung fibroblasts (HFL1) and human salivary gland tumour line (HSGc-C5)	290 ****	1, 2, 3	0.005–0.031	1	NM*	96–195	96–195	8–13	FLASH and CONV irradiation of HFL1 cells exhibited no significant difference in post-irradiation impediment of cell growth and induction of senescence. This applied when using the entrance plateau region (13 keV/µm) and Bragg peak region (50 keV/µm) of the carbon beam. In HSGc-C5 cells, no significant difference was observed in clonogenic survival when comparing either FLASH or CONV dose rates, or when utilising the plateau or Bragg peak region of the beam.
[79]	2022	Carbon, synchrotron: pulsed	C3H/He mice, LM8 osteosarcoma model	240 *****	18	0.15 ± 0.02	1	NM*	100	100	0.3	Under either FLASH or CONV dose rates, tumour control was achieved with similar efficacy. However, under FLASH dose rates, the proportion of mice with lung metastases was significantly lower than those irradiated under CONV (FLASH: ~10%, CONV: ~30%, Control: ~40%). Irradiated muscle tissues exhibited disorganized morphology under CONV irradiation, which was greatly reduced in FLASH irradiated mice.

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Original Article

FLASH with carbon ions: Tumor control, normal tissue sparing, and distal metastasis in a mouse osteosarcoma model

Walter Tinganelli[a], Uli Weber[a], Anggraeini Puspitasari[a], Palma Simoniello[b], Amir Abdollahi[c], Julius Oppermann[a], Christoph Schuy[a], Felix Horst[a], Alexander Helm[a], Claudia Fournier[a], Marco Durante[a,d,*]

morphology sparing, improved survival, **less metastasis**.

Accelerators for FLASH investigations: protons

Isochronous cyclotrons

Institut Curie

International Journal of Radiation Oncology biology • physics

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Biology Contribution

Experimental Set-up for FLASH Proton Irradiation of Small Animals Using a Clinical System

Annalisa Patriarca, PhD,* Charles Fouillade, P... Michel Auger, MSc,* Frédéric Martin, MSc,* Fré... ...uzoulet, PhD,‡ Catherine Nauraye, PhD,* Sophie Heinrich, PhD, Vincent Favaudon, PhD,† Samuel Meyroneinc, MSc,* Rémi Dendale, MD,* Alejandro Mazal, PhD,* Philip Poortmans, MD, PhD,* Pierre Verrelle, MD, PhD,*,§ and Ludovic De Marzi, PhD*

UPENN - USA

International Journal of Radiation Oncology biology • physics

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Physics Contribution

Design, Implementation, and in Vivo Validation of a Novel Proton FLASH Radiation Therapy System

Eric S. Diffenderfer, PhD, Ioannis I. Verginadis, PhD, Michele M. Kim, PhD, Khayrullo Shoniyozov, PhD, Anastasia Velalopoulou, PhD, Denisa Goia, MS, Mary Putt, PhD, Sarah Hagan, MS, Stephen Avery, PhD, Kevin Teo, PhD, Wei Zou, PhD, Alexander Lin, MD, Samuel Swisher-McClure, MD, Cameron Koch, PhD, Ann R. Kennedy, PhD, Andy Minn, MD, PhD, Amit Maity, MD, PhD, Theresa M. Busch, PhD, Lei Dong, PhD, Costas Koumenis, PhD, James Metz, MD, and Keith A. Cengel, MD, PhD

Dresden - Germany

ARTICLE IN PRESS

Radiotherapy and Oncology xxx (xxxx) xxx

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Original Article

Feasibility of proton FLASH effect tested by zebrafish embryo irradiation

Elke Beyreuther[a,b,*], Michael Brand[c], Stefan Hans[c], Katalin Hideghéty[d], Leonhard Karsch[a,e], Elisabeth Leßmann[a], Michael Schürer[f], Emília Rita Szabó[d], Jörg Pawelke[a,e]

JAMA Oncology | Original Investigation

CINCINNATI - USA

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

PSI - Switzerland

› bioRxiv. 2023 Apr 21;2023.04.20.537497. doi: 10.1101/2023.04.20.537497. Preprint

Dosimetric and biologic intercomparison between electron and proton FLASH beams

A Almeida, M Togno, P Ballesteros-Zebadua, J Franco-Perez, R Geyer, R Schaefer, B Petit, V Grilj, D Meer, S Safai, T Lomax, D C Weber, C Bailat, S Psoroulas, M C Vozenin

PMID: 37131769 PMCID: PMC10153243 DOI: 10.1101/2023.04.20.537497

Aarhus - Denmark

Radiotherapy and Oncology

Volume 175, October 2022, Pages 178–184

ELSEVIER

Original Article

Pencil beam scanning proton FLASH maintains tumor control while normal tissue damage is reduced in a mouse model

Brita Singers Sørensen[a b], Mateusz Krzysztof Sitarz[a], Christina Ankjærgaard[c], Jacob G. Johansen[a], Claus E. Andersen[c], Eleni Kanouta[a], Cai Grau[a], Per Poulsen[a d]

RARAF – New York - USA

Radiotherapy and Oncology xxx (xxxx) xxx

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

Original Article

Biological effects in normal cells exposed to FLASH dose rate protons

Manuela Buonanno*, Veljko Grilj, David J. Brenner

Radiological Research Accelerator Facility (RARAF), New York, United States

4.5 MeV at 1000 Gy/s

8 June 2023

Laser-FLASH: high dose, ultrahigh dose rate, single-pulse radiobiology with a laser-driven proton source

A new platform for ultra-high dose rate radiobiological research using the BELLA PW laser proton beamline

Jianhui Bin, Lieselotte Obst-Huebl, Jian-Hua Mao, Kei Nakamura, Laura D. Geulig, Hang Chang, Qing Ji, Li He, Jared De Chant, Zachary Kober, Anthony J. Gonsalves, Stepan Bulanov, Susan E. Celniker, Carl B. Schroeder, Cameron G. R. Geddes, Eric Esarey, Blake A. Simmons, Thomas Schenkel, Eleanor A. Blakely, Sven Steinke & Antoine M. Snijders

Laser

MD Anderson - USA

Physics in Medicine & Biology

IPEM Institute of Physics and Engineering in Medicine

PAPER

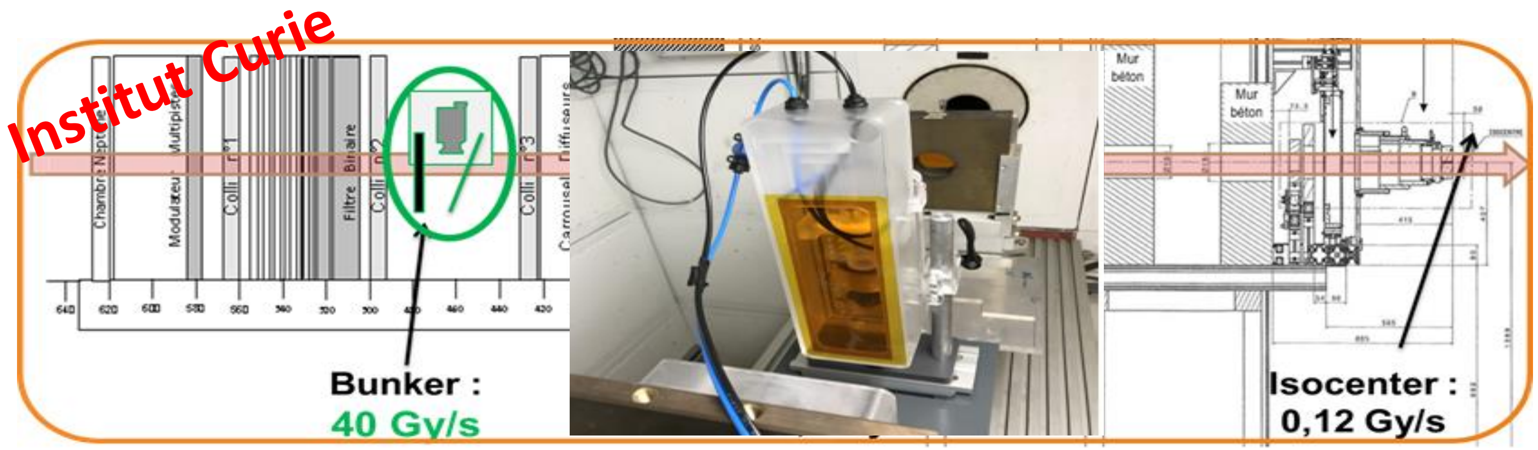
Adaptation and dosimetric commissioning of a synchrotron-based proton beamline for FLASH experiments

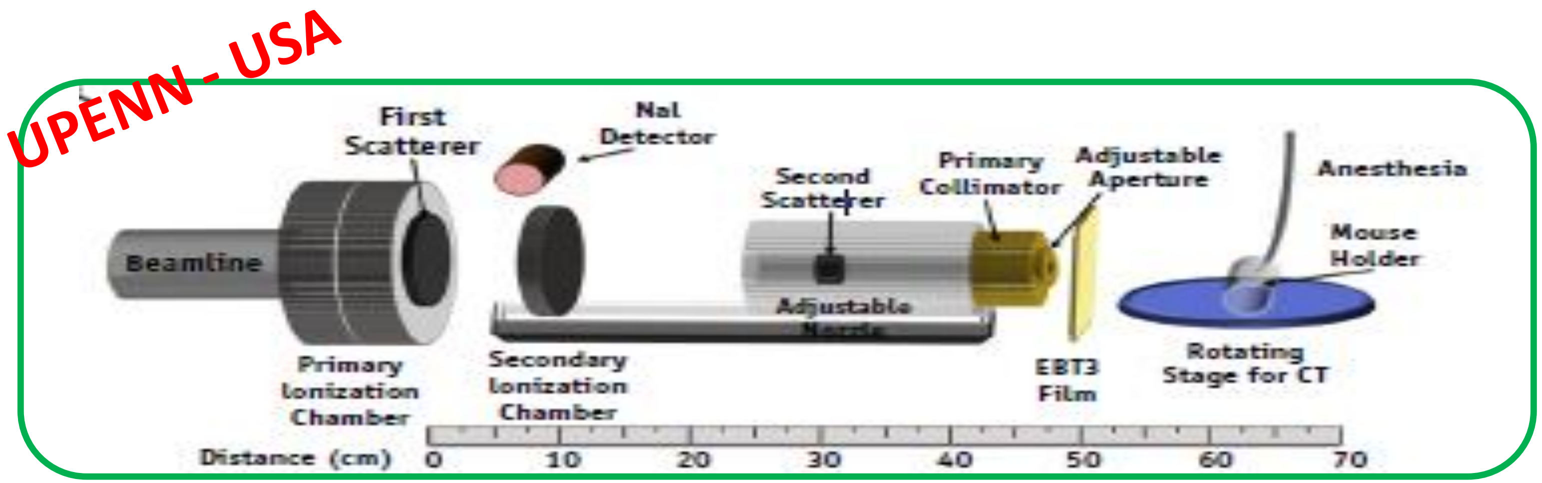
Ming Yang[1,6], Xiaochun Wang[1,6], Fada Guan[2,6], Uwe Titt[1], Kiminori Iga[3], Dadi Jiang[4], Takeshi Takaoka[3], Satoshi Tootake[5], Tadashi Katayose[5], Masumi Umezawa[5], Emil Schüler[1], Steven Frank[4], Steven H Lin[4], Narayan Sahoo[1], Albert C Koong[4], Radhe Mohan[1] and X Ronald Zhu[1,*]

[1] Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston...

Synchrotron

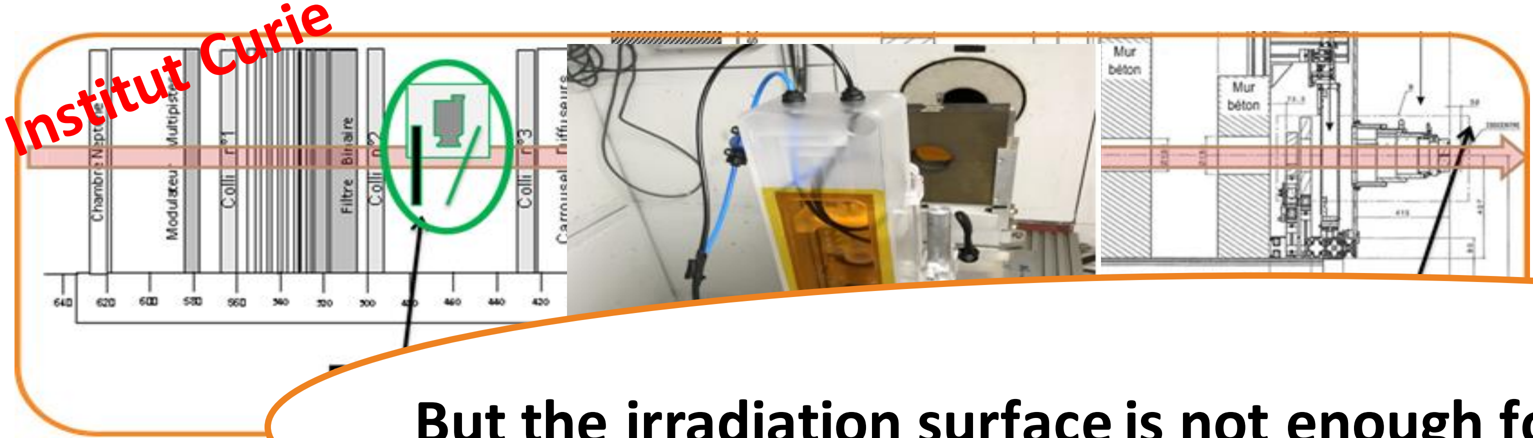
Pre-clinical pFLASH investigations: double scattering



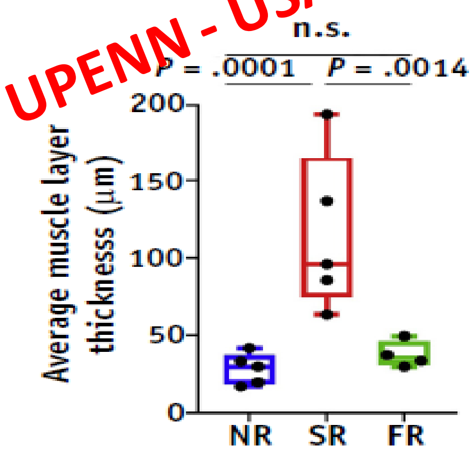


- Isochronous cyclotrons and passive beams
- Energy : 200 and 230 MeV
- Frequency : 106 MHz
- Beam current at cyclotron : 200 - 300 nA
- Dose rate at the sample level : 40 – 100 Gy/s
- Irradiation surface : 12 × 12 mm^2

Pre-clinical pFLASH investigations: double scattering



But the irradiation surface is not enough for clinical applications



A clear proton FLASH sparing effect on early and delayed toxicities (irradiation of intestinal crypts)

- Isochronous cyclotrons and passive beams
- Energy : 200 and 230 MeV
- ...cyclotron : 200 - 300 nA
- Dose rate at the sample level : 40 – 100 Gy/s
- Irradiation surface : 12 × 12 mm^2

Pre-clinical pFLASH investigations: scanning

Proton FLASH-RT in a rat glioblastoma model @ Curie proton therapy center

BIOLOGY CONTRIBUTION

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Proton FLASH Radiation Therapy and Immune Infiltration: Evaluation in an Orthotopic Glioma Rat Model

Lorea Iturri, PhD,* Annaïg Bertho, PhD,* Charlotte Lamirault, PhD,† Marjorie Juchaux, PhD,* Cristèle Gilbert, MSc,* Julie Espenon, MSc,* Catherine Sebrie, PhD,‡ Laurène Jourdain, MSc,‡ Frédéric Pouzoulet, PhD,† Pierre Verrelle, MD, PhD,§,‖ Ludovic De Marzi, PhD,§,‖ and Yolanda Prezado, PhD*

*Institut Curie, Université PSL, CNRS UMR3347, Inserm U1021, Signalisation Radiobiologie et Cancer, 91400 Orsay, France; †Institut Curie, Université PSL, Département de Recherche Translationnelle, CurieCoreTech-Experimental Radiotherapy (RadeXp), Paris, France; ‡CEA, CNRS, Inserm, Service Hospitalier Frédéric Joliot, BIOMAPS Université Paris-Saclay, Orsay, France; §Institut Curie, Campus Universitaire, PSL Research University, University Paris Saclay, INSERM LITO (U1288), Orsay, 91898 France; and ‖Centre de Protonthérapie d'Orsay, Radiation Oncology Department, Campus Universitaire, Institut Curie, PSL Research University, Orsay, 91898 France

Received Jun 15, 2022; Accepted for publication Dec 10, 2022

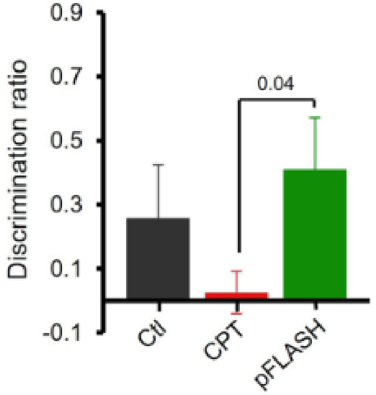
CONV PT: 4 Gy/s ***vs*** **pFLASH: 257 Gy/s**

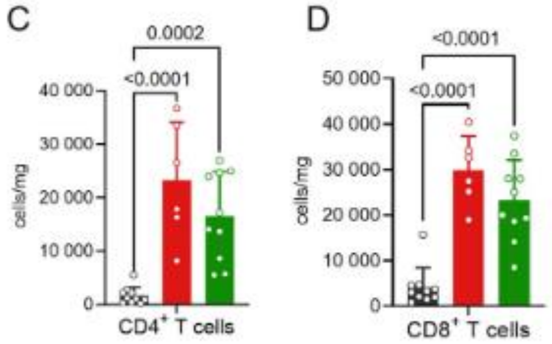
Healthy rats → Behavioural tests

Rats bearing glioblastoma → Analysis of immune populations

- **Proton FLASH-RT spares memory** after cranial irradiations.
- Loss of microglia and a neuroinflammation in both therapies.
- Significant immune cell recruitment observed after proton-RT.
- **pFLASH elicits more important lymphoid than myeloid cells.**

E ORT, memory assessment





Technology issues (protons)

How to produce/control a beam current capable to deliver tens of Gy in less than 500(100) ms?

- Common clinical specification for minimum dose rate for conventional proton therapy :

deliver a dose of **2 Gray** for a **single field** to a **1 liter volume in 1 minute**

- For a FLASH irradiations (assuming the same fractionation scheme)

An **average dose rate of 40 Gy/s** is assumed for a **single field plan**, requiring **an average current of 600 nA** for the **1 liter volume**

Technology issues (protons)

How to produce/control a beam current capable to deliver tens of Gy in less than 500(100) ms?

- Common clinical spe[…]tional proton therapy :
  deliver a […] **minute**
  - For a FL[…]scheme)

Possible with existing accelerator technology
But limited to specific working hypothesis

An **average dose rate of 40 Gy/s** is assumed for a sing[…] **average current of 600 nA** for the **1 liter volume**

Technology issues (protons)

How to produce/control a beam current capable to deliver tens of Gy in less than 500(100) ms?

- Common clinical spe… …ional proton therapy :
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  - For a FL… …scheme)

An **average dose rate of 40 Gy/s** is assumed for a sing… …average current of 600 nA for the **1 liter volume**

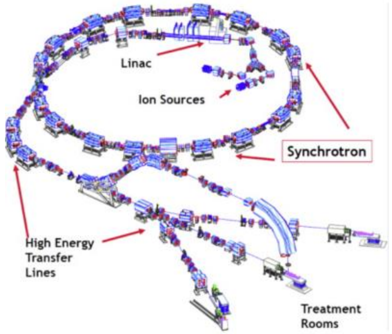
Possible with existing accelerator technology
But limited to specific working hypothesis

Which accelerator would be more adapted?

Isochronous cyclotrons

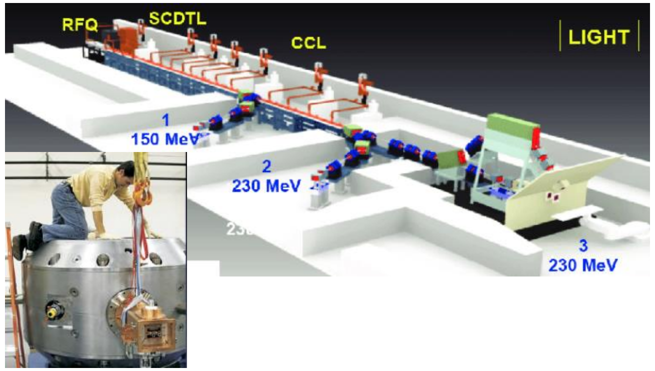
Continuous beam, high beam currents, but beam energy changes remains challenging

Synchrotrons



The whole dose has to be delivered in a single synchrotron spill - 100 ms

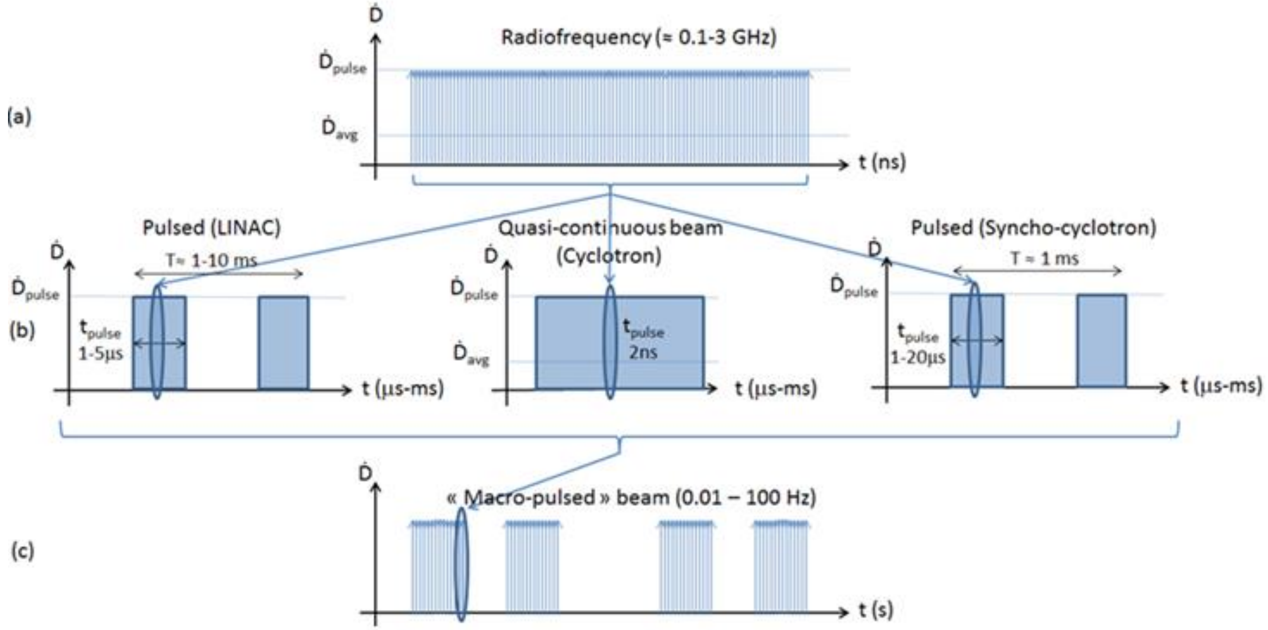
Synchro-cyclotrons and linacs



Low repetition rate (1kHz and 200 Hz), but high peak current, limited to small volume

Technology issues

Dependence of the time structure of the accelerator



[De Marzi et al. 2020]

Pulse :
F = 50 -100 Hz (LINAC)
F = 1 kHz (synchro-cyclotron)

Macropulse :
F = 0.1 - 100 Hz (IMRT/IMPT)

Typical time structure of accelerators (except laser plasma):

Micropulse : quasi-continuous beam
F = 60 MHz – 3 GHz (usually)

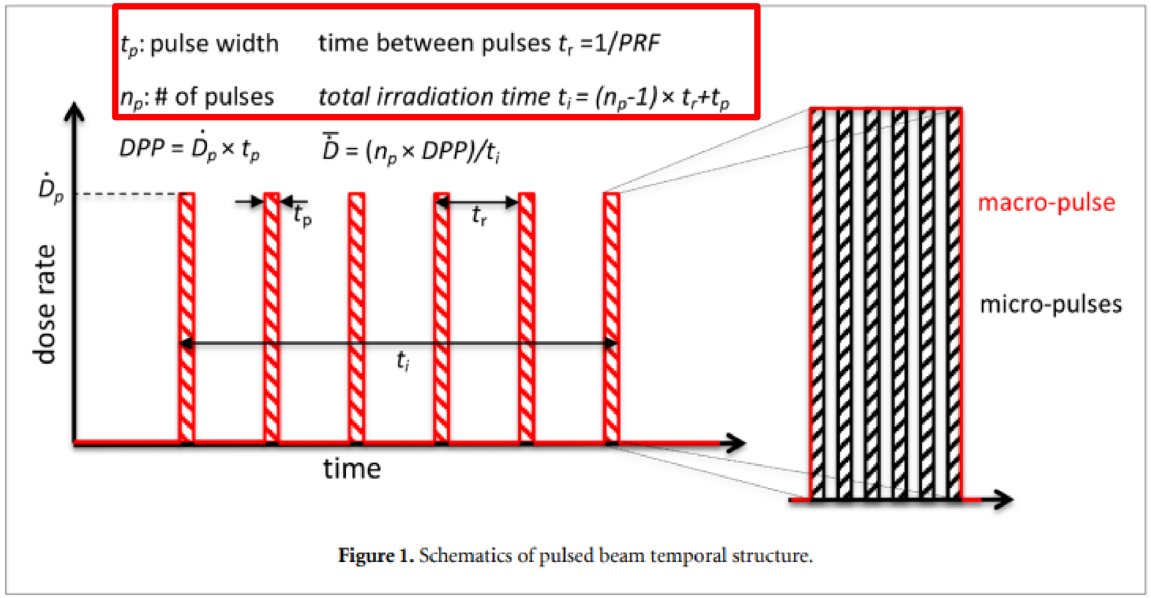


Figure 1. Schematics of pulsed beam temporal structure.

[Esplen et al. 2020]

Technology issues

Dependence of the time structure of the accelerator

> bioRxiv. 2023 Apr 21;2023.04.20.537497. doi: 10.1101/2023.04.20.537497. Preprint

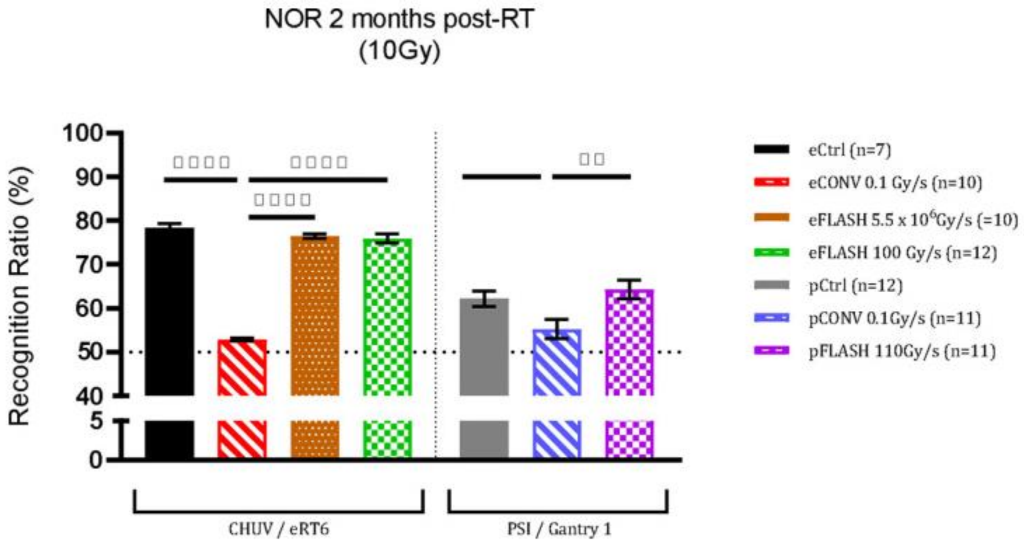
Dosimetric and biologic intercomparison between electron and proton FLASH beams

A Almeida, M Togno, P Ballesteros-Zebadua, J Franco-Perez, R Geyer, R Schaefer, B Petit, V Grilj, D Meer, S Safai, T Lomax, D C Weber, C Bailat, S Psoroulas, M C Vozenin

PMID: 37131769 PMCID: PMC10153243 DOI: 10.1101/2023.04.20.537497

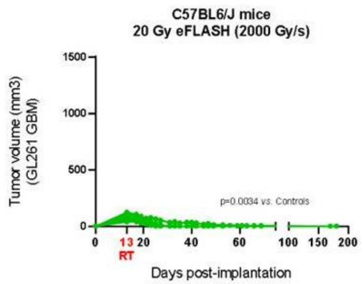
PSI/CHUV-Switzerland

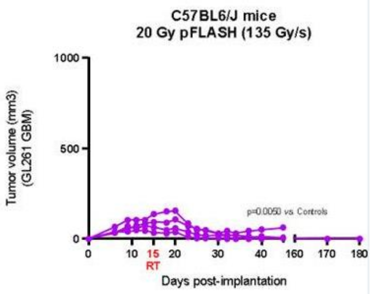
Neurocognitive capacity of e and pFLASH irradiated mice at 10 Gy is indistinguishable from the control



Complete anti-tumor response is beam-type and dose-rate independent (20Gy irradiation and follow up@4months)

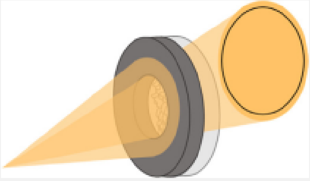
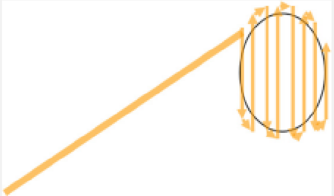
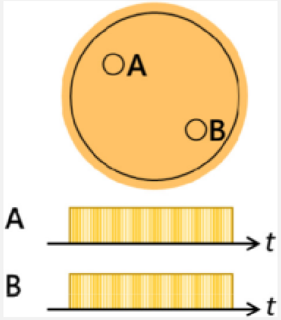
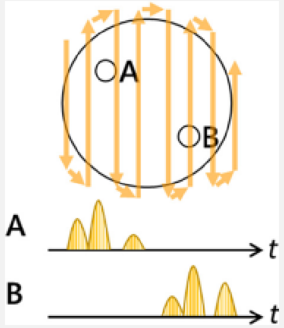
eFLASH @2000 Gy/s vs pFLASH @135 Gy/s





Technology issues

Which beam delivery method would be more adapted? scattering vs scanning

	Passive scattering	Pencil beam scanning
		
Conformality	Reduction in proximal conformality with fixed width SOBP. Lateral conformality may be improved due to the use of collimators.	Improved conformality. Enables multi-field optimisation techniques which can further improve conformality.
Patient-specific hardware requirements	Requires beam-specific collimators (to shape the beam) and compensators (to achieve distal conformality to the target volume).	No patient specific devices required (or potentially used with a collimator which can improve conformality).
Treatment limitations	Maximum field sizes typically up to 25 cm diameter at the isocentre plane.	Maximum field sizes typically up to 40 cm × 30 cm at the isocentre plane.
Time structure of dose delivery	 There may be a fine time structure to dose delivery arising from the pulse repetition rate of the particle accelerator, the use of range modulating wheels or other passive techniques (e.g. wobbling or uniform scanning). For energy modulated fields the use of a rotating range modulator wheel (with a rotation time of ~0.1 s) may not be appropriate for FLASH delivery. Alternatively, static energy modulation devices may be used which deliver all energies simultaneously. Dose is delivered to the entire volume at the same time i.e. each voxel sees the same energy deposition time structure.	 The pencil beam is scanned across the volume resulting in spatially varying time characteristics on a longer time frame than the pulse repetition frequency of the cyclotron. Dose is delivered to different parts of the volume at different times with contributions from spots in close proximity as well as from the low dose penumbra from other neighbouring spots. With multiple energy layers the dose to a given point may have contributions from the entrance region of multiple different energy layers. Energy layer switching may be of the order of 1 s.
Delivery system requirements	Static beam line.	Active beam line – needs steering.
Existing evidence with FLASH	Preclinical: [9,41]	Preclinical: Clinical study: FAST-01 trial [42]

[Rothwell et al, 2022]

Differences:

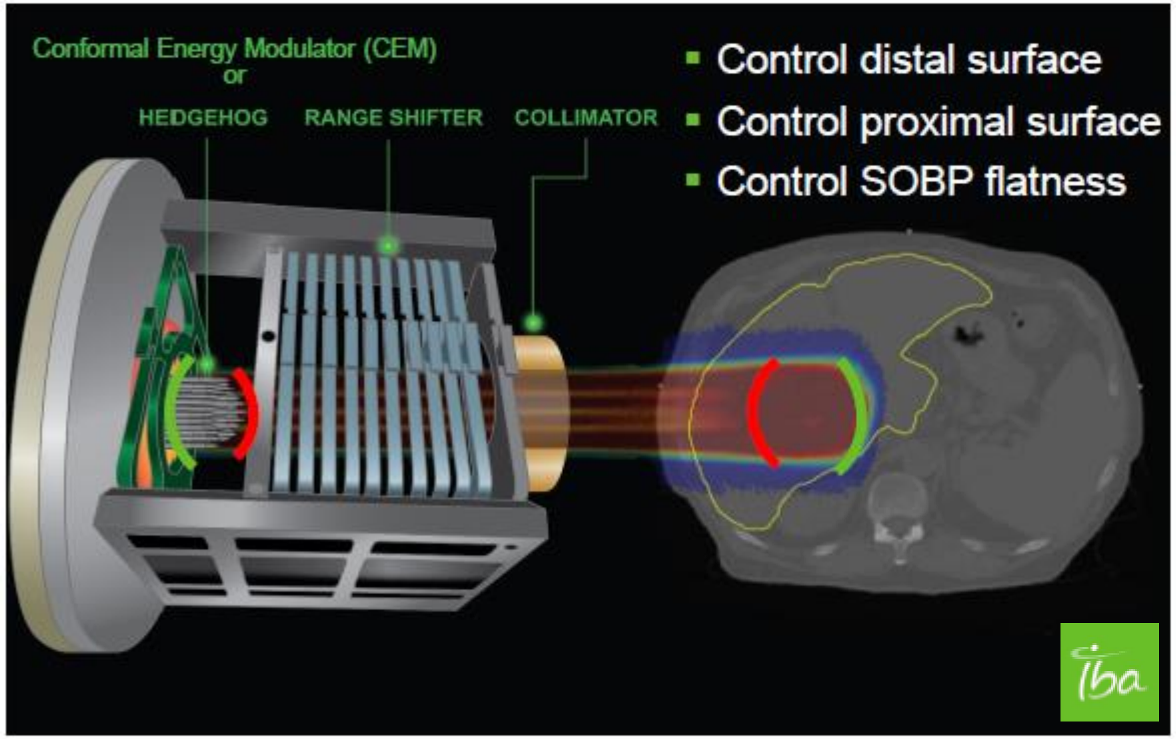
- Scattering requires **patient-specific devices.**
- Dose is delivered to various volumes at the same time or not.
- **Conformality levels** depends on the target location.
- Scanning across the volume (~mins): **spatially varying time characteristics** → motion management and daily fractionation issues.
- **High dose rate** (plan robustness/ reproductibility/dosimetry/QA) issues.

For tumor irradiation, the 3D volumetric scanning is too slow (each energy change takes ∼1 s).
The most mature approach for clinical applications of particle is **hybrid active–passive systems** using patient-specific, 3D-range modulators

Exploiting the potential of protons:Conformal-FLASH

ConformalFLASH® :
An IBA solution for SOBP proton FLASH

Combines the **biological** tissue **sparing** effects of **FLASH** with **physics sparing** effects of the Proton Bragg Peak



Possible drawbacks: penumbras degradation (lateral and distal),
More secondary particles (neutrons) use of static collimators and ridge filters,
how will it compare with dynamic PMAT or very conformal IMPT plans?

How translate these studies into clinical operation?

From the accelerator point of view :

how to produce a beam current capable to deliver tens of Gy in less than 500 ms?

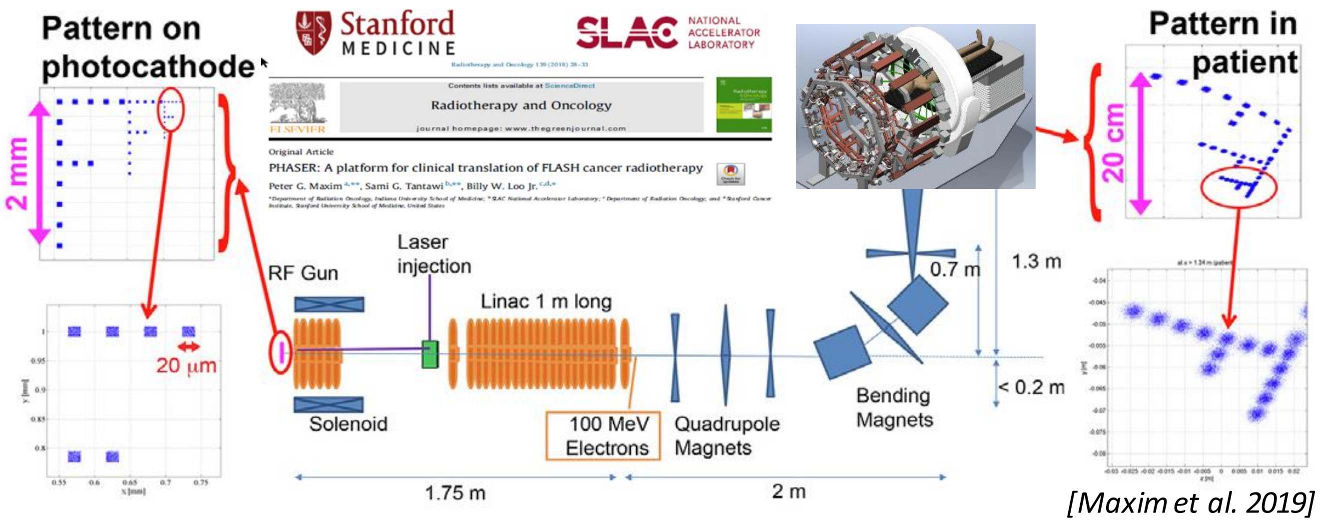
- **Increase** hundreds-fold the **beam output**
- **Eliminate mechanical motion** (gantry and/or collimators)
- **Integrate** fast, high-quality volumetric **imaging**

The accelerator solution should be:

- **Compact**, to ideally fits in existing vaults
- **Power efficient**
- **Economical** to manufacture and operate

Proposed solutions for clinical FLASH irradiations: PHASER for photons and VHEE

Pluridirectional High-energy Agile Scanning Electronic Radiotherapy



[Maxim et al. 2019]

Photon concept

- Distributed RF-coupling Architecture with Genetically Optimized cell desigN (DRAGON), achieved at high frequencies (X-band), provides 100MeV/m acceleration.
- At 10MeV, large FLASH intensities can be obtained.
- Scanning Pencil-beam High-speed Intensity-modulated X-ray source (SPHINX) as a replacement for MLC-based intensity modulation.

Electron (VHEE) concept

- A spatially patterned electron source is produced by projecting an optical image onto a photocathode.
- The electron ‘‘pattern” is accelerated into a high-gradient linac then steered and magnified to the treatment volume, producing an intensity-modulated field (eg 16x linacs).

Proposed solutions for clinical FLASH irradiations: the interest on VHEE

VHEE in RT were originally proposed by DesRosiers et al. at Indiana University in 2000

VHEE beams: advantages

Depth dose profile: deep-seated tumors with flatter profile than photons

Lateral scattering: reduced, low penumbrae

Magnetic collimation: pencil beam scanning

Heterogeneities: no electronic disequilibrium at interfaces

cancers 2021 MDPI

Review

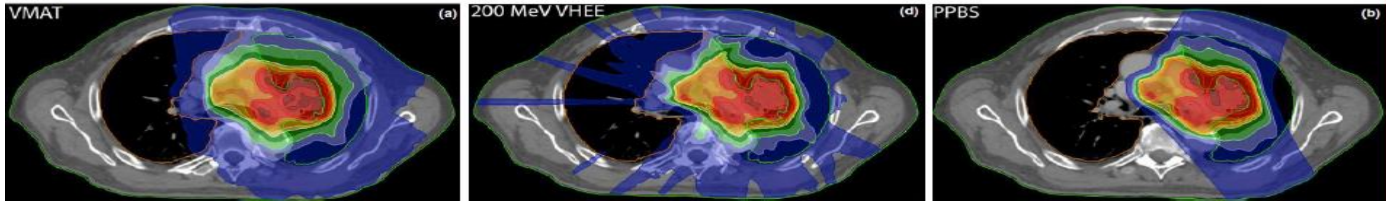
Back to the Future: Very High-Energy Electrons (VHEEs) and Their Potential Application in Radiation Therapy

Maria Grazia Ronga [1,2], Marco Cavallone [1], Annalisa Patriarca [1], Amelia Maia Leite [1,3], Pierre Loap [1], Vincent Favaudon [4], Gilles Créhange [1] and Ludovic De Marzi [1,3,*]

1 Centre de Protonthérapie d'Orsay, Department of Radiation Oncology, Campus Universitaire, Institut Curie, PSL Research University, 91898 Orsay, France; mariacrazia.ronga@curie.fr (M.G.R.); marco.cavallone@curie.fr (M.C.); annalisa.patriarca@curie.fr (A.P.); amelia.maialeite@curie.fr (A.M.L.); pierre.loap@curie.fr (P.L.); gilles.crehange@curie.fr (G.C.)

2 Thales AVS Microwave & Imaging Sub-Systems, 78141 Vélizy-Villacoublay, France

Lung tumor : comparison X-ray, VHEE, & protons *Schuler, 2017 (Stanford)*



- Thanks to recent **High-Gradient linac technology developments**, VHEE (100–250 MeV) could be a cost-effective option in RT and open up innovative treatment modalities , i.e. FLASH, and/or spatial fractionation of the dose (grid minibeams)
- Compactness, low breakdown rate, micron-tolerance alignment and a high RF-to-beam efficiency (around 30%) could make possible a compact VHEE radiation therapy accelerator

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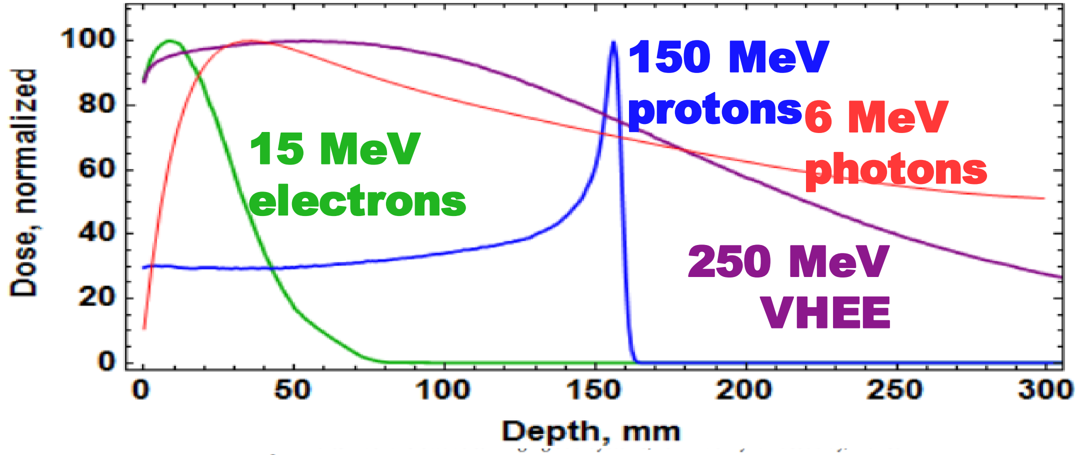

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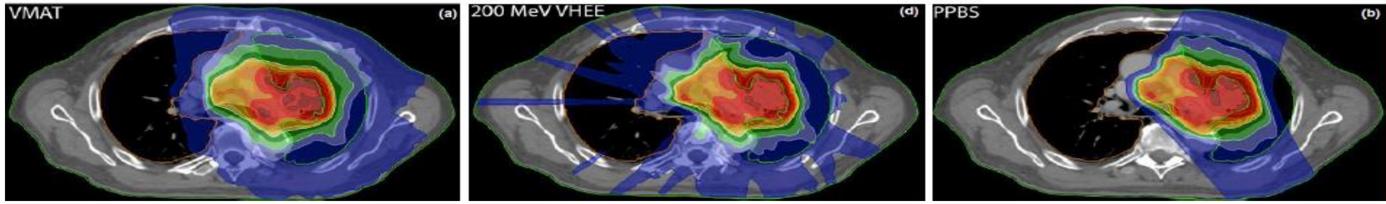

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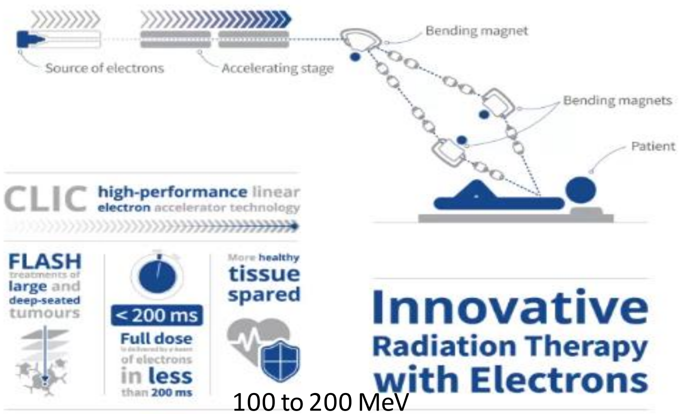
Proposed solutions for FLASH irradiations: the interest on VHEE

FLASHDEEP
CHUV, CERN, THERYQ



100 to 200 MeV

SAFEST
INFN SAPIENZA

ELSEVIER

Physica Medica
Volume 104, December 2022, Pages 149-159

Original Paper

Perspectives in linear accelerator for FLASH VHEE: Study of a compact C-band system

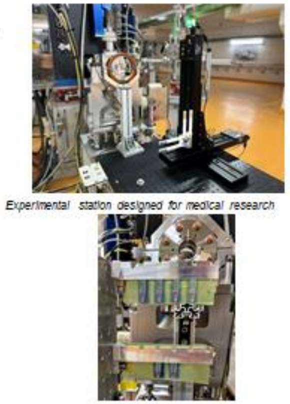
L. Faillace [a], D. Alesini [a], G. Bisogni [d j], F. Bosco [b c], M. Carillo [b c], P. Cirrone [e], G. Cuttone [e], D. De Arcangelis [b c], A. De Gregorio [c i], F. Di Martino [f], V. Favaudon [g], L. Ficcadenti [b c], D. Francescone [b c], G. Franciosini [c i], A. Gallo [a], S. Heinrich [g], M. Migliorati [b c], A. Mostacci [b c], L. Palumbo [b c], V. Patera [b c]...L. Giuliano [b c]

ARES

INNOVATION & TECHNOLOGIE TRANSFER

- Up to 160 MeV high precision electron beams for **research & development**.
  - **Cutting-edge stability** of the electron pulse energy
  - **In-vivo experiments possible**
- Ideally suited for VHEE and medical experiments

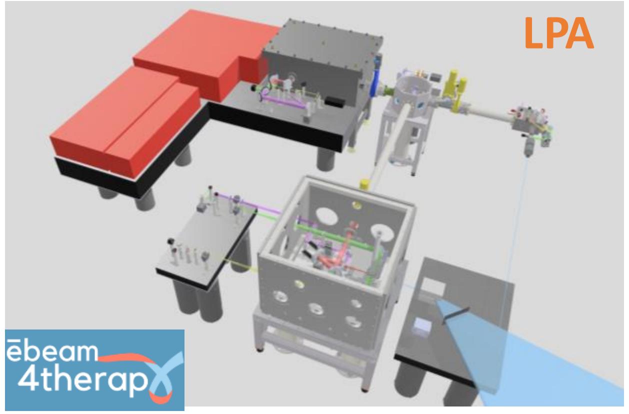
From F. Burkart [VHEE23 conference]



Experimental station designed for medical research

First in-vivo experiment [Manchester UNI]

Weizmann Institute



TWAC

Funded by the European Union

A novel dielectric acceleration project for ultra-high dose rate applications

Dielectric THz acceleration@300 GHz/gradient >100 MV/m

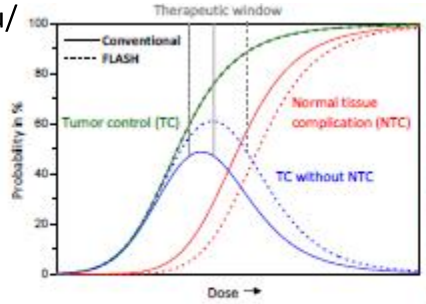
Proposed solutions for FLASH dosimetry

UHDpulse

http://uhdpulse-empir.eu/

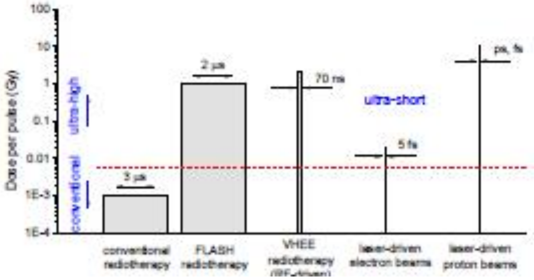
SRT-h21 UHDpulse

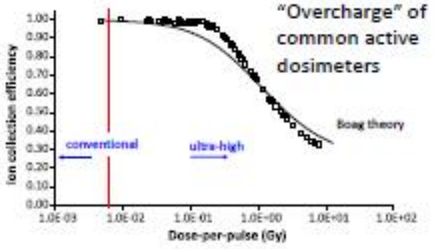
Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates



Cat cancer patient (nasal carcinoma not eligible for surgery)

New techniques in radiation therapy requires that its performance, safety and effectiveness can be reliably measured and optimized.





WP1: Primary standards

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

WP2: Secondary standards, relative dosimetry

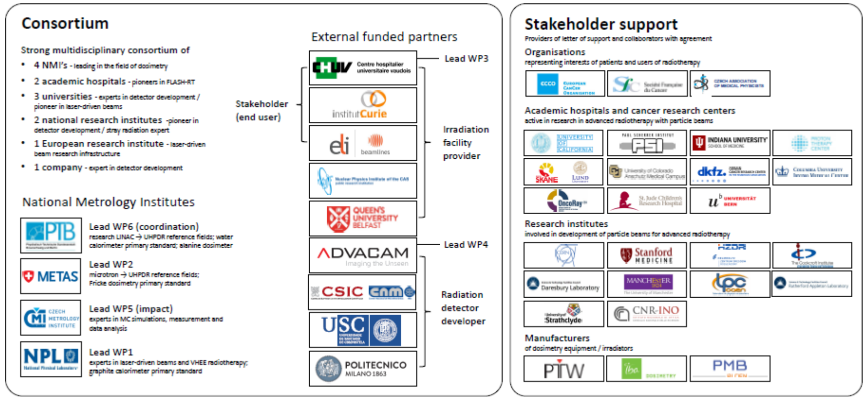
- Transfer from primary standards
- Characterizing established detector systems
- Formalism for reference dosimetry for future Code of Practice

WP4: Detectors and methods outside primary beam

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

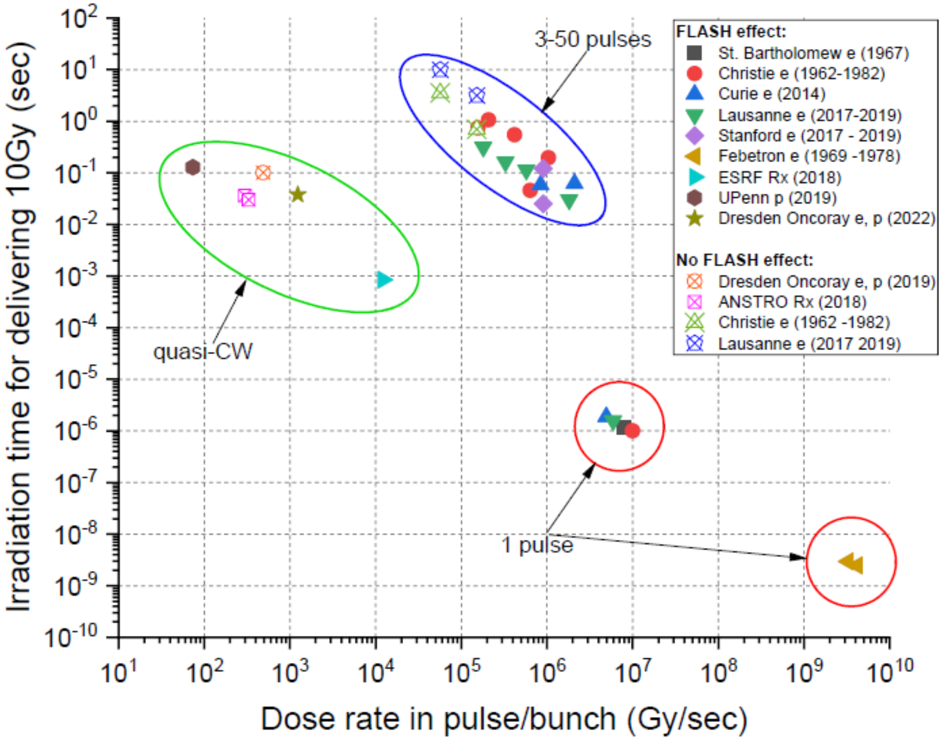
WP3: Detectors for primary beam

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



Global perspective

Summary of preclinical studies at different accelerator facilities with different radiation types as a function of the instantaneous dose rate.



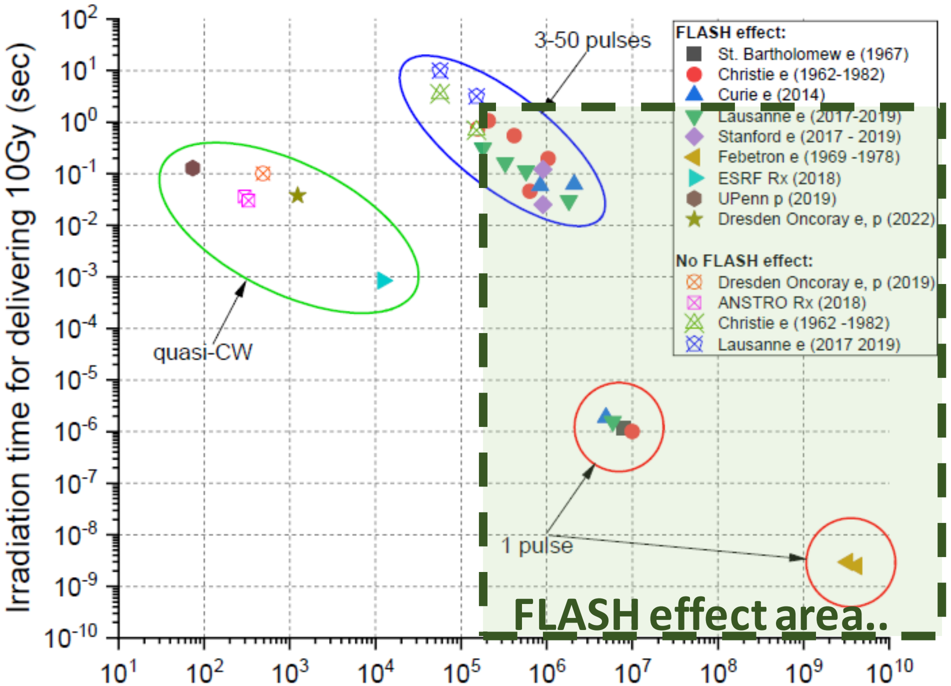
2021: pooled data as a function of the dose rate

[Montey Gruel et al. 2021]

Still numerous unknowns to elicit the FLASH effect:
dose rate, total dose delivered, pulse rate/duration/width/number, total delivery time and type of particle.

Global perspective

Summary of preclinical studies at different accelerator facilities with different radiation types as a function of the instantaneous dose rate.



2021: pooled data as a function of the dose rate

[Montey Gruel et al. 2021]

Still numerous unknowns to elicit the FLASH effect: dose rate, total dose delivered, pulse rate/duration/width/number, total delivery time and type of particle.

Table 1. Preclinical electron FLASH properties relevant to a clinical application of FLASH.

Electron Beam	Min. for Observed FLASH	Optimal for FLASH
Average dose rate	30 Gy/s	100 Gy/s
Intrapulse dose rate	~10^5 Gy/s	≥10^6 Gy/s
Total dose	<10 Gy	≥10 Gy—tissue dependent
Delivery time for 10 Gy	<1 s	1 μs–10 ms

Dose Delivery Mode	Protons	Carbon
Conventional: 2.6 Gy/fraction	2×10^9 p/s	1.7×10^8 C/s
Delivery time: 100 s	0.4 nA	0.2 nA
FLASH: ≥10 Gy/fraction	1×10^{13} p/s	0.8×10^{12} C/s
Delivery Time: 100 ms	1.6 μA	0.8 μA

Conclusions

FLASH-RT studies has proved an increased therapeutic index enabling higher doses to be tolerated by normal tissues

- Multidisciplinary teams are working to provide further studies to fully define the impact of **total dose**, temporal **patterning**, **total exposure rate, radiation quality** on response, the fundamental **biological mechanisms**
- The **accelerator community** could play an important role in the development of alternative solutions to provide FLASH irradiators and beam monitoring devices

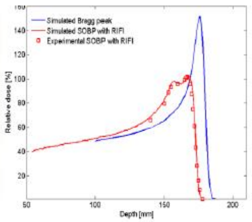
For future clinical applications, it has to be defined

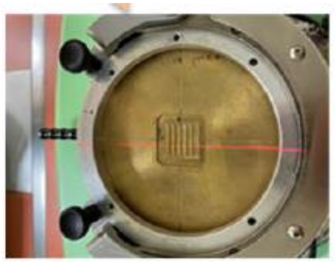
- how to irradiate **large volumes** in less than 500/100 ms with a consistent dose
- protocols for **beam calibration and absolute dosimetry**
- **MV/X-rays imaging** (positioning, pre-irradiation) solutions

Travailler ensemble @ Institut Curie

- Un exemple de **succès ou de fierté**

Faire partie d'une communauté de personnes/métiers multidisciplinaires travaillant ensemble pour l'amélioration continue de la prise en charge du patient. À l'hôpital nous (techniciens, ingénieurs, physiciens) travaillons avec les chercheurs en radiobiologie/médecine pour rendre possible les études précliniques avec comme objectif le transfert vers la clinique en réalisant les setup expérimentaux nécessaires aux irradiations (notamment pour le FLASH et pMBRT).





- Un exemple **difficile**

Faire **coexister soins et activités expérimentales ou de recherche**.

Il faut toujours rendre le système en condition nominales pour la reprise des traitements le lendemain. Il peut y avoir une panne bloquante pendant l'expérimentation qui oblige à annuler les irradiations avec réorganisation des plannings, impact sur les chercheurs, etc.

~ 50 patients/day from 6h30 to 19h30
2-3 evenings/week for patient/machine QA
1-2 evening/week for experimental activity + week-ends

Merci pour votre attention

Multidisciplinarity

Institut Curie

- Hospital
- Research Centre
- Département de radiothérapie
  - Team New Approaches in Radiotherapy
- Centre de protonthérapie