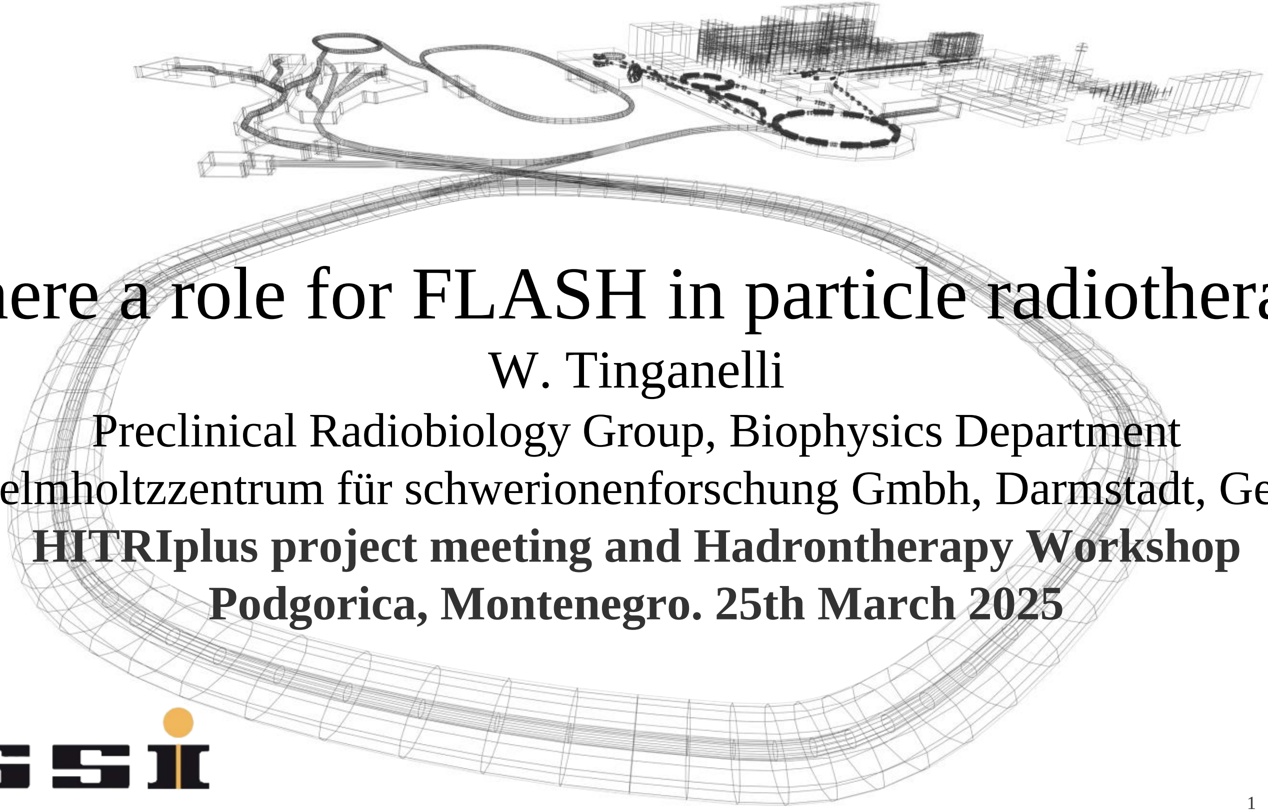


Is there a role for FLASH in particle radiotherapy?

W. Tinganelli
Preclinical Radiobiology Group, Biophysics Department
GSI Helmholtzzentrum für schwerionenforschung Gmbh, Darmstadt, Germany

HITRIplus project meeting and Hadrontherapy Workshop
Podgorica, Montenegro. 25th March 2025

FLASH RT: what's that?

Table 1. Comparison of characteristics of FLASH-RT and CONV-RT.

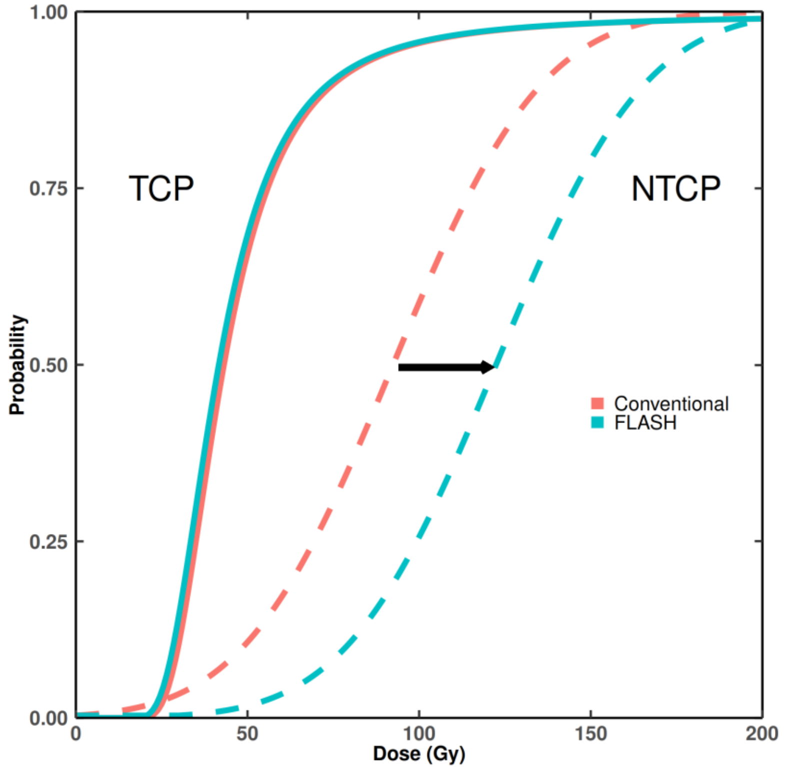
	FLASH-RT	CONV-RT
Mean dose rate	≥40 Gy/s	≤1 Gy/min
Delivery time	<200 ms	> 1 min
Dose delivery	High dose in a single fraction	Low dose in a single fraction
Tumor control	A similar antitumor effect as CONV-RT	Effective tumor killing
Normal tissue sparing	Reduce the damage to healthy tissues	Acute and late damage to healthy tissues
Defects	Few accessible irradiation facilities	Radiation injury and limited treatment window

FLASH-radiotherapy (FLASH-RT), Conventional dose rate radiotherapy (CONV-RT).

Mini-review

FLASH radiotherapy: A new milestone in the field of cancer radiotherapy

Rui Tang [a b 1], Jianqiong Yin [b 1], Yuanxin Liu [b 1], Jianxin Xue [b c d e]



Vozenin, Bourhis & Durante, *Nat. Rev. Clin. Oncol*. 2022

FLASH Effect hypothesis

The FLASH effect might stem from the **rapid generation of free radicals** and distinctions in redox and free radical chemistry between normal and tumor tissues;
R. Labarbe, et al. *Radiother. Oncol.* **153**, 303–310 (2020).

Irradiation at UHDR might partially **deplete oxygen** in the tissues;
R. Abolfath, et al. *Med. Phys.* **47**, 6551–6561 (2020).

Biological factors like changes in the **immune system response to radiation or altered signaling pathways** within cells exposed to UHDR;
J. Y. Jin, *et al.*, *Radiother. Oncol.* **149**, 55–62 (2020)
X. Shi, *et al.*, *Proc. Natl. Acad. Sci.* **119** (2022).

Blood (tumor) vessels (i.e., causing less damage), potentially preventing changes in tumor vasculature that could affect its response to treatment (e.g., through better immune cells infiltration);
C. W. Song, *et al.*, *Int. J. Radiat. Oncol. Biol. Phys.* **117**, 701–704 (2023).

Metabolic hibernation
CL Limoli and MC Vozenin *Annual review of Cancer Biology*. **7**:1-21 (2023).

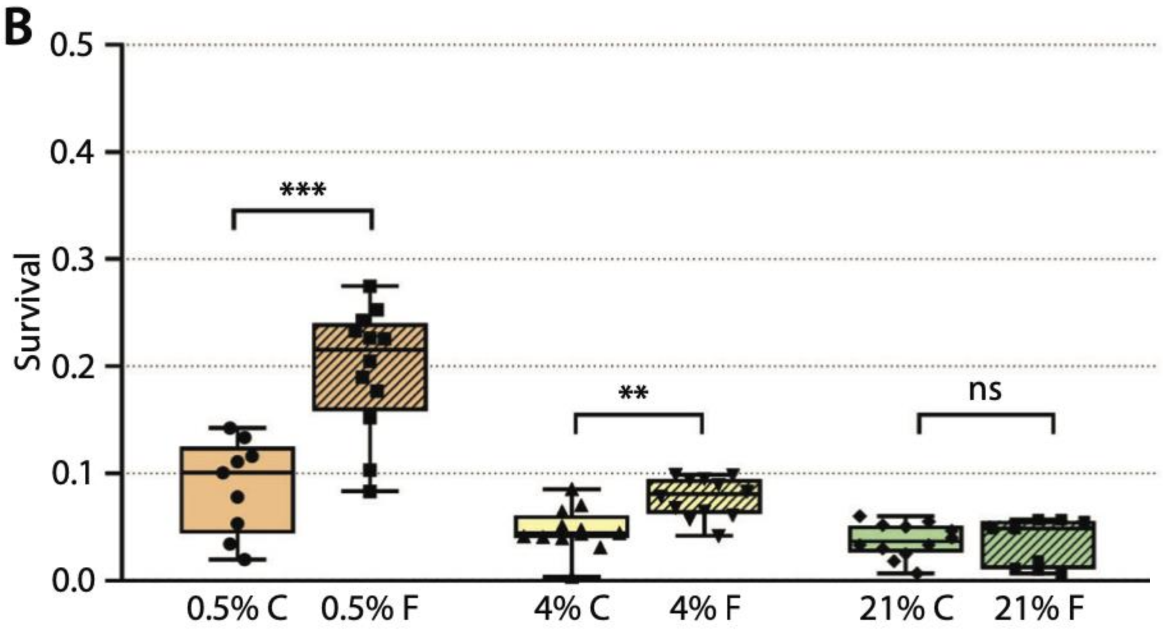
Three main reasons to test C-ions

1. Test of the current mechanistic models at high-LET;
U. A. Weber, E. Scifoni, M. Durante, FLASH radiotherapy with carbon ion beams. *Med. Phys.* **49**, 1974–1992 (2022).

2. Clinical implementation in C-ion therapy;
M. Durante, J. Debus, J. S. Loeffler, Physics and biomedical challenges of cancer therapy with accelerated heavy ions. *Nat. Rev. Phys.* **3**, 777–790 (2021).

3. If the sparing effect survives at high-LET, possibility of using very heavy ions (such as ^{20}Ne or ^{40}Ar) in therapy, and idea originally pursued by Cornelius Tobias at the Lawrence Berkeley Laboratory.
J. R. Castro, *et al.*, Treatment of cancer with heavy charged particles. *Int. J. Radiat. Oncol. Biol. Phys.* **8**, 2191–2198 (1982).
C. A. Tobias, Failla Memorial lecture. The future of heavy-ion science in biology and medicine. *Radiat. Res.* **103**, 1–33 (1985).

First test of C-ion FLASH at HIT in 2020



-**5x10^8 carbon ions**
per synchrotron cycle (SPILL)

-7.5 Gy at 1 cm depth in water (**entrance channel**).

-Extraction of the whole spill within **100 to 200 milliseconds** resulting in ulta-high dose rates of: **70 Gy/s**

The conventional irradiations took 12 seconds with a corresponding dose rate of
0.6 Gy/s.

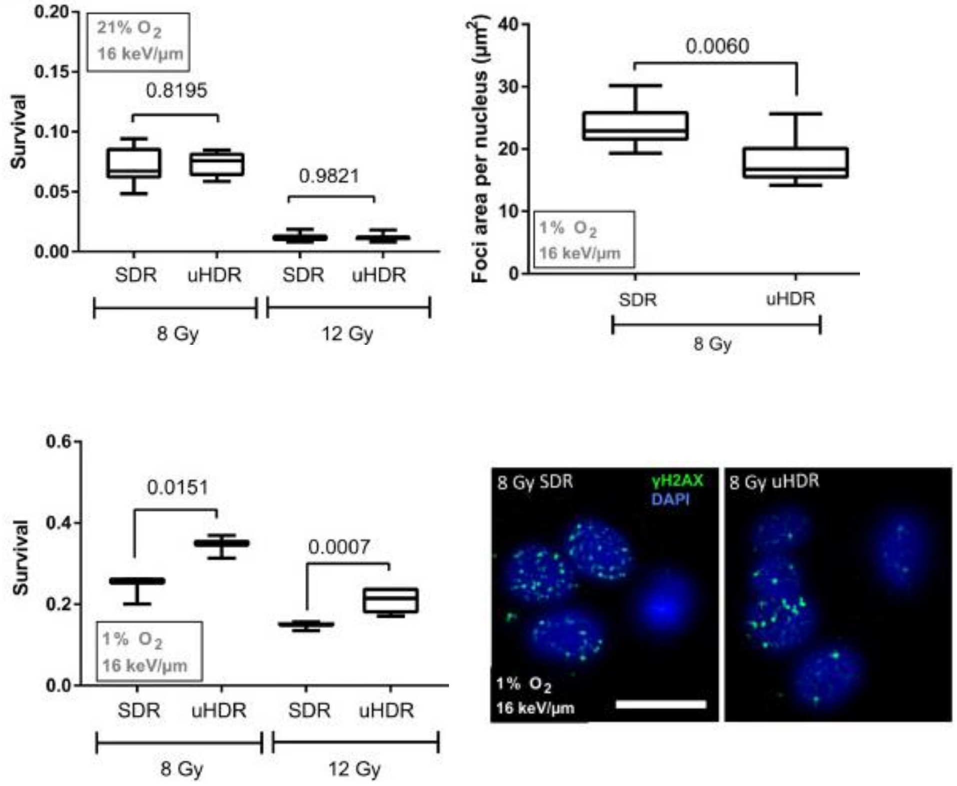
> Int J Radiat Oncol Biol Phys. 2022 Mar 15;112(4):1012-1022. doi: 10.1016/j.ijrobp.2021.11.020. Epub 2021 Nov 20.

Ultra-High Dose Rate (FLASH) Carbon Ion Irradiation: Dosimetry and First Cell Experiments

Walter Tinganelli [1], Olga Sokol [1], Martina Quartieri [1], Anggraeini Puspitasari [1], Ivana Dokic [2], Amir Abdollahi [2], Marco Durante [3], Thomas Haberer [4], Jürgen Debus [5], Daria Boscolo [1], Bernd Voss [1], Stephan Brons [4], Christoph Schuy [1], Felix Horst [1], Ulrich Weber [1]

Physics Contribution

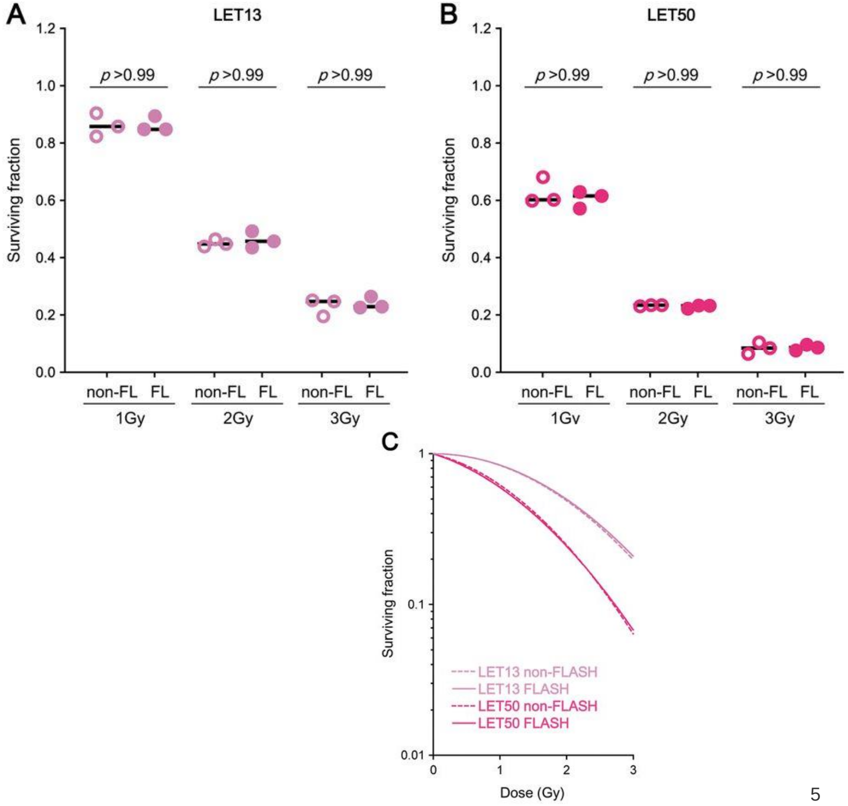
FLASH Dose Rate Helium Ion Beams: First In Vitro Investigations Tessonier et al. 2021



Anticancer Res. 2022 May;42(5):2469-2477. doi: 10.21873/anticanres.15725.

First Human Cell Experiments With FLASH Carbon Ions

Mutsumi Tashiro [1], Yukari Yoshida [2], Takahiro Oike [2 3], Masao Nakao [2], Ken Yusa [2], Yuka Hirota [3], Tatsuya Ohno [2 3]



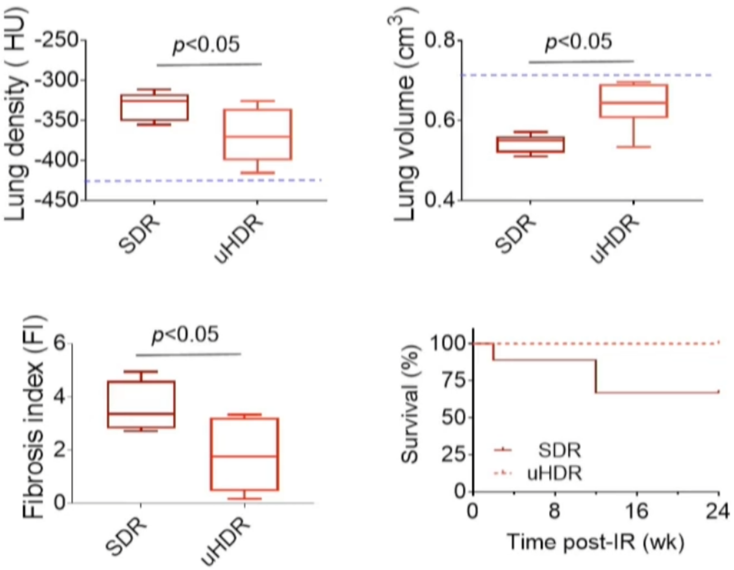
Test shot on radiochromic film before moving the mouse into the beam

Data NOT PUBLISHED

GSI SIS18
FAIR-phase-0:
12C-ions: 240 MeV/n
Plateau 10 Gy
FLASH local dose rate:
- **>100 Gy/s**
- ~ 5×10^9 ions per spill

Conventional dose rate:
~ 10 Gy/min
LET:
15 keV/micrometers

CT imaging



Courtesy of M. Moustafa, DKFZ

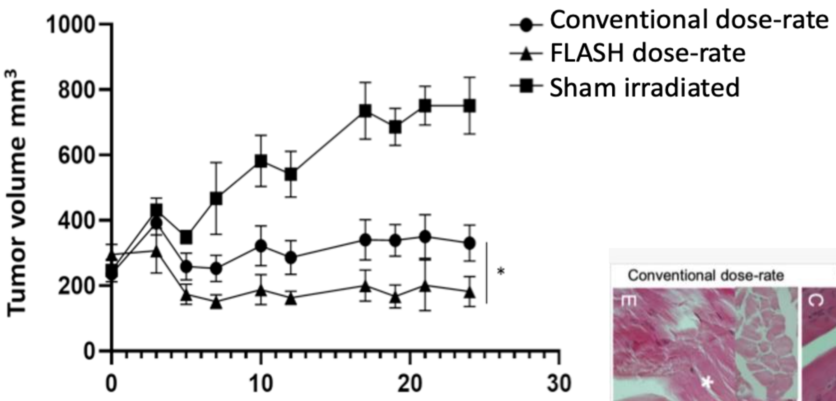
Radiotherapy &Oncology

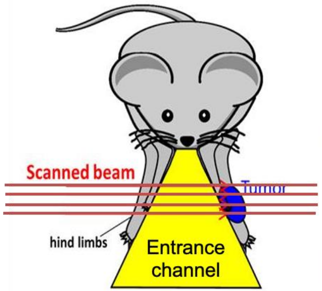
ORIGINAL ARTICLE · Volume 175, P185-190, October 2022 Download Full Issue

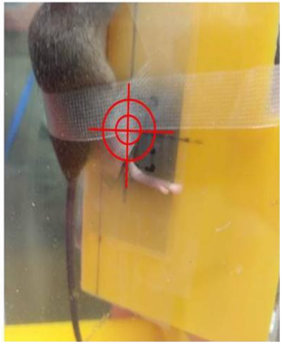
FLASH with carbon ions: Tumor control, normal tissue sparing, and distal metastasis in a mouse osteosarcoma model

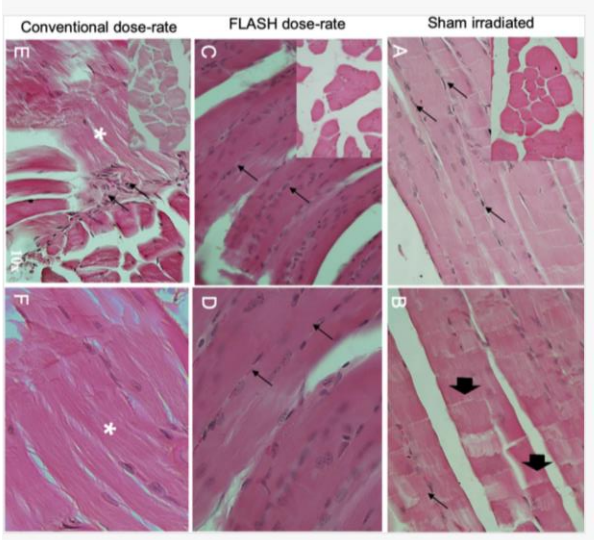
Walter Tinganelli [a] · Uli Weber [a] · Anggraeini Puspitasari [a] · Palma Simoniello [b] · Amir Abdollahi [c] · Julius Oppermann [a] · Christoph Schuy [a] · Felix Horst [a] · Alexander Helm [a] · Claudia Fournier [a] · Marco Durante [a,d] Show less

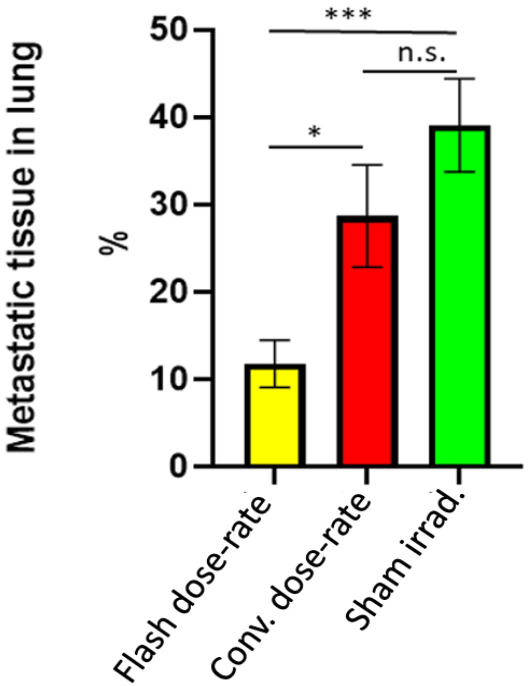
LM8 osteosarcoma in C3H mice





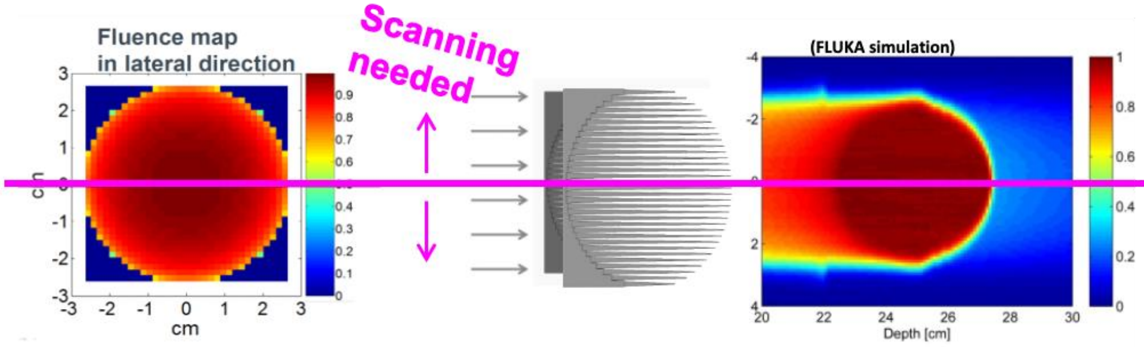






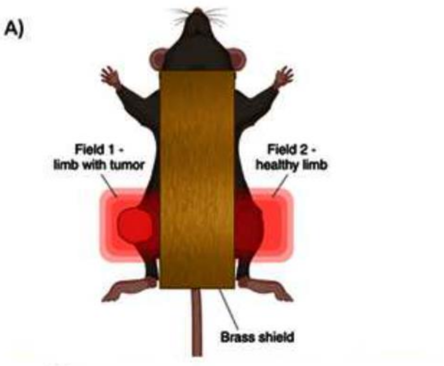
Irradiation plan

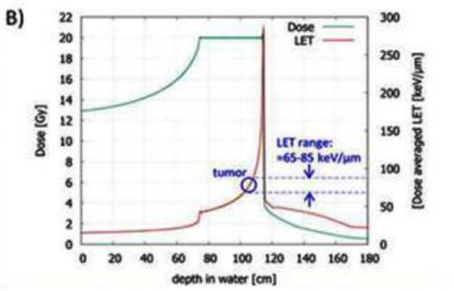
Beam application with 3D Range Modulators:Single-energy Irradiation

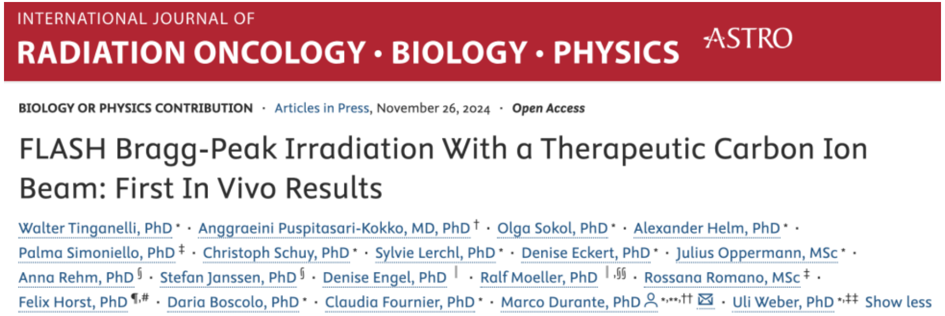


Example for a
spherical target volume,
5cm diameter,
^{12}C, E=400 MeV/u

Simenov et al. J.Med. Phys. 2020



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RADIATION ONCOLOGY • BIOLOGY • PHYSICS ASTRO

BIOLOGY OR PHYSICS CONTRIBUTION · Articles in Press, November 26, 2024 · Open Access

FLASH Bragg-Peak Irradiation With a Therapeutic Carbon Ion Beam: First In Vivo Results

Walter Tinganelli, PhD * · Anggraeini Puspitasari-Kokko, MD, PhD † · Olga Sokol, PhD * · Alexander Helm, PhD * · Palma Simoniello, PhD ‡ · Christoph Schuy, PhD * · Sylvie Lerchl, PhD * · Denise Eckert, PhD * · Julius Oppermann, MSc * · Anna Rehm, PhD § · Stefan Janssen, PhD § · Denise Engel, PhD ǀ · Ralf Moeller, PhD ǀ,§§ · Rossana Romano, MSc ‡ · Felix Horst, PhD ¶,# · Daria Boscolo, PhD * · Claudia Fournier, PhD * · Marco Durante, PhD *,**,†† · Uli Weber, PhD *,‡‡ Show less

Collagen deposition

Tinganelli et al. under revision

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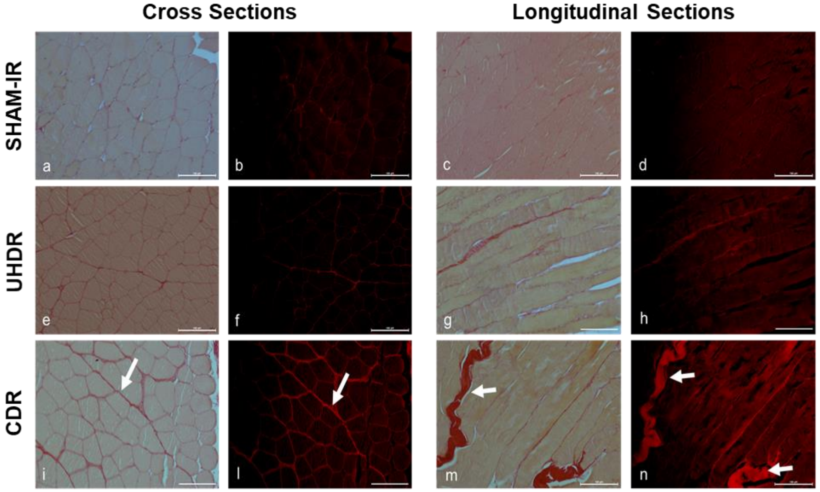

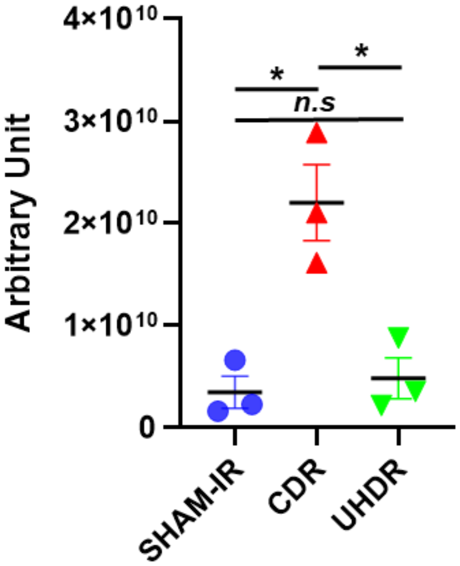

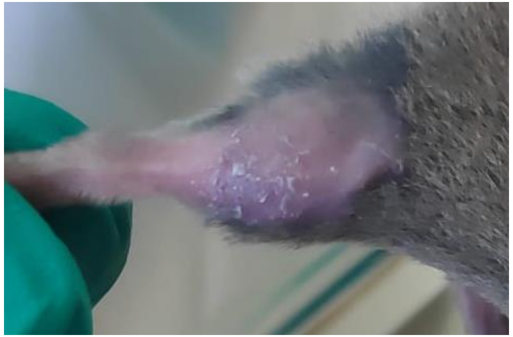

Grade	Description	Control	SHAM-IR	UHDR	CDR
0	No damage	5 (100%)	10 (100%)	3 (21%)	
1	Skin peeling and redness			11 (79%)	14 (93%)
2	Small wounds				1 (7%)

Table 1: Total and relative (in brackets) numbers of animals exhibiting skin damage in Control, Sham irradiated (SHAM-IR), Ultra high dose rate (UHDR), and Conventional dose rate (CDR) experimental groups.

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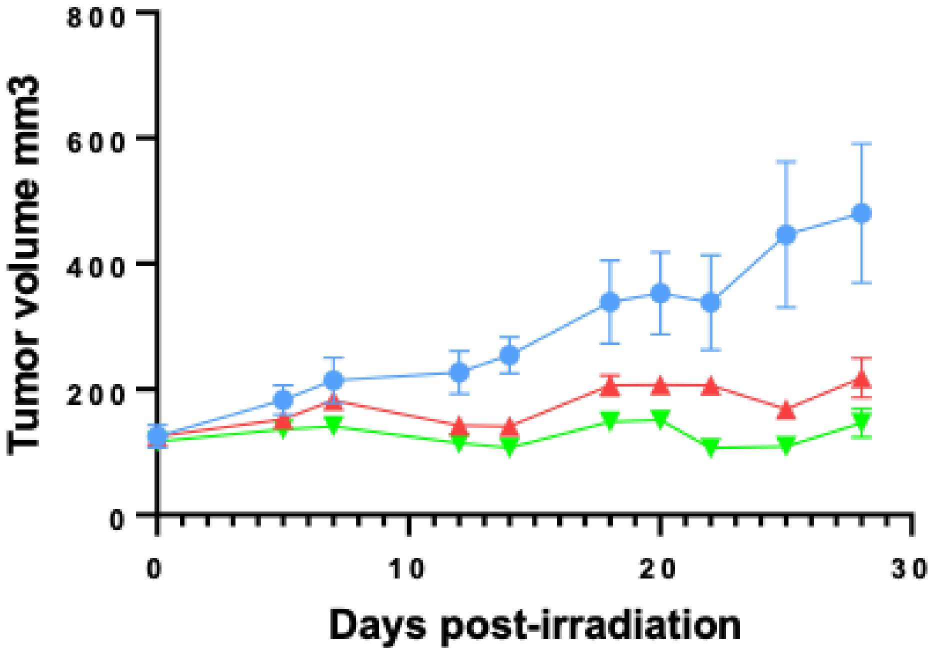
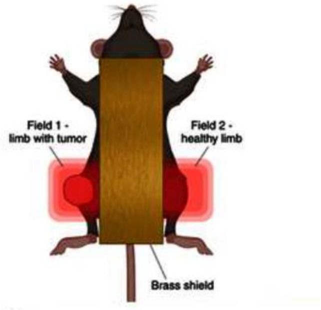
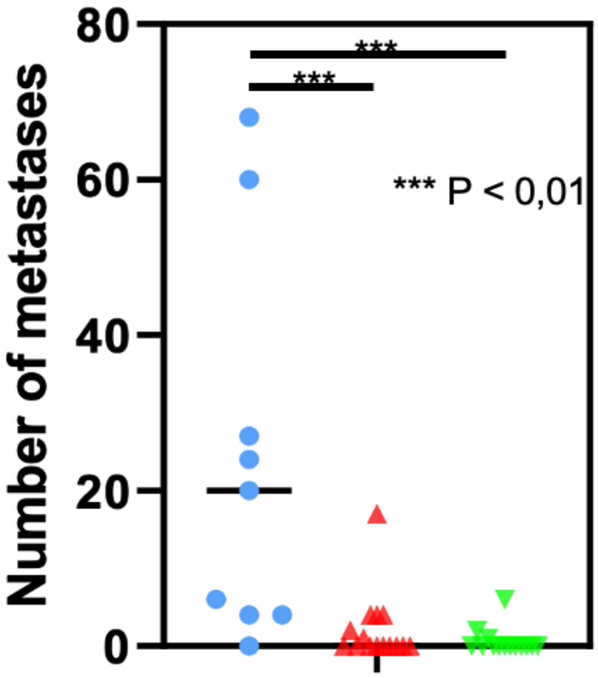
BIOLOGY OR PHYSICS CONTRIBUTION · Articles in Press, November 26, 2024 · *Open Access*

FLASH Bragg-Peak Irradiation With a Therapeutic Carbon Ion Beam: First In Vivo Results

Walter Tinganelli, PhD * · Anggraeini Puspitasari-Kokko, MD, PhD † · Olga Sokol, PhD * · Alexander Helm, PhD * · Palma Simoniello, PhD ‡ · Christoph Schuy, PhD * · Sylvie Lerchl, PhD * · Denise Eckert, PhD * · Julius Oppermann, MSc * · Anna Rehm, PhD § · Stefan Janssen, PhD § · Denise Engel, PhD ǀ · Ralf Moeller, PhD ǀ,§§ · Rossana Romano, MSc ‡ · Felix Horst, PhD ¶,# · Daria Boscolo, PhD * · Claudia Fournier, PhD * · Marco Durante, PhD *,**,†† · Uli Weber, PhD *,‡‡ Show less

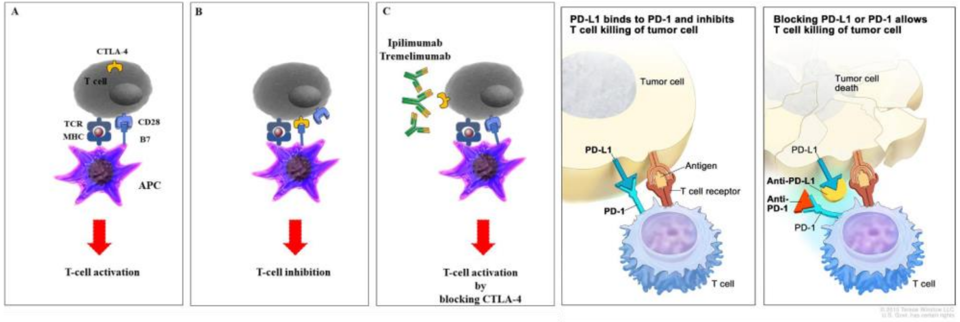






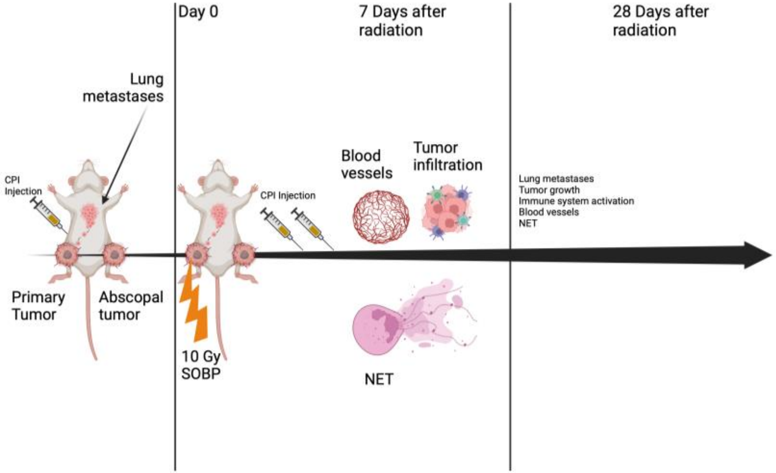
Combined treatments: Immune Checkpoint Inhibitors (ICI)

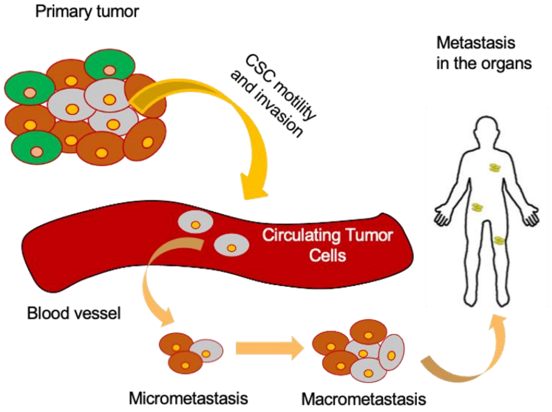
Monoclonal antibodies => **anti CTLA-4** and/or anti **PD-L1** or **PD-1**.

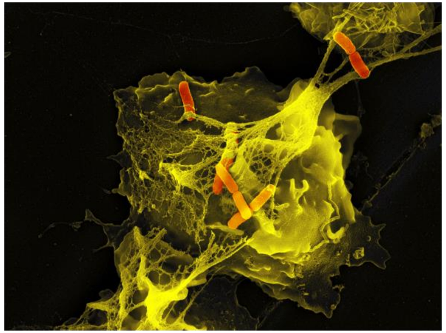


Kooshkaki et al. 2020

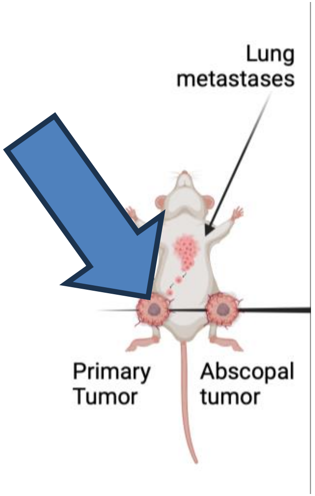
Circulating Tumor Cells
Neutrophile Extracellular Traps







Coloured scanning electron micrograph showing stimulated neutrophil with NETs and trapped Shigella bacteria. © Max Planck Institute for Infection Biology



Irradiated Tumor

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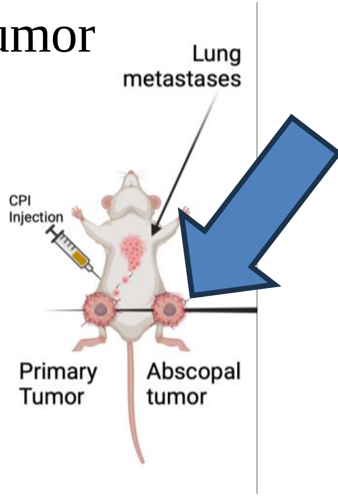
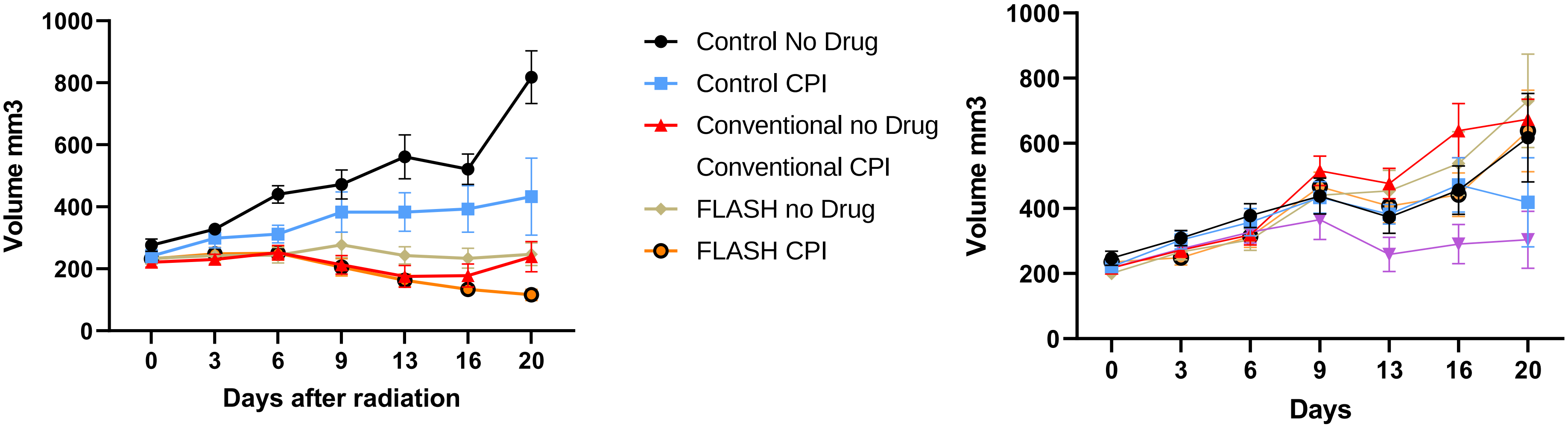
Abscopal Tumor





Circulating Tumor Cells and Neutrophile Extracellular traps

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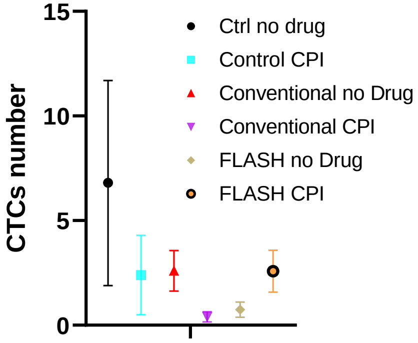
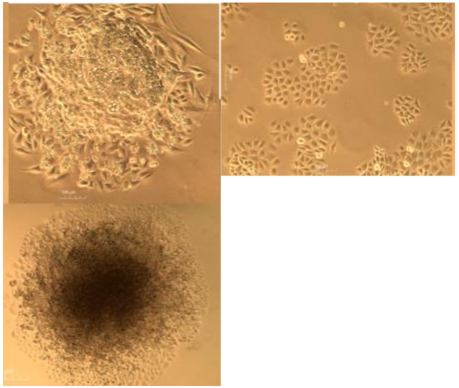
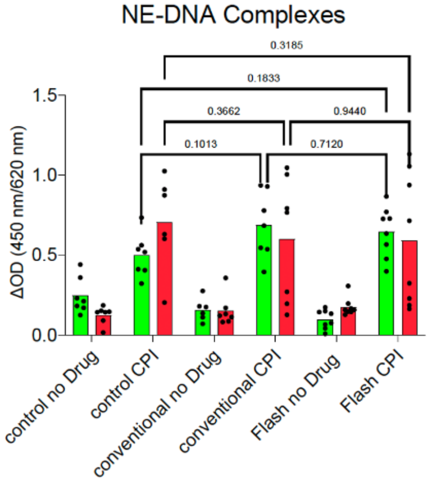
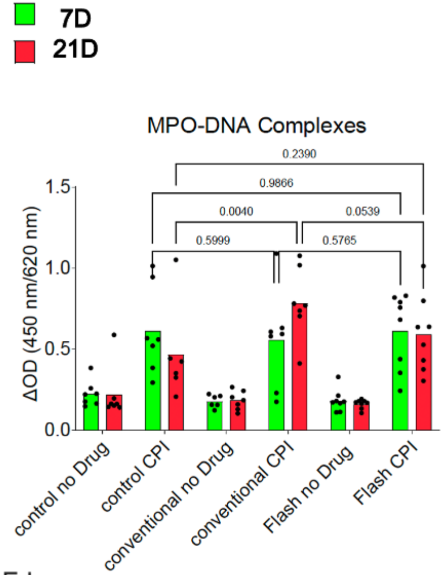
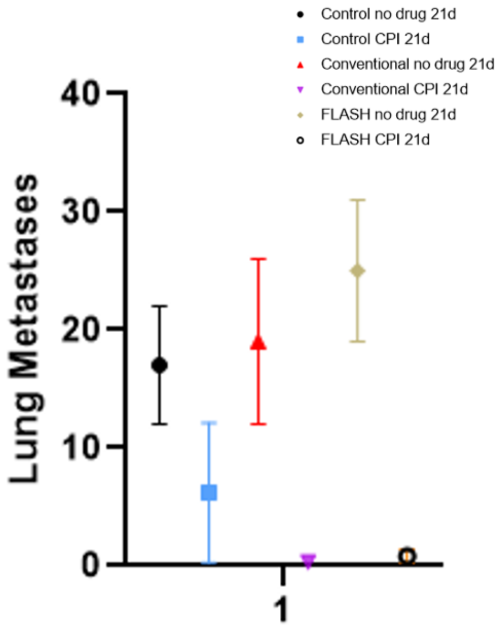




Universitätsklinikum Erlangen



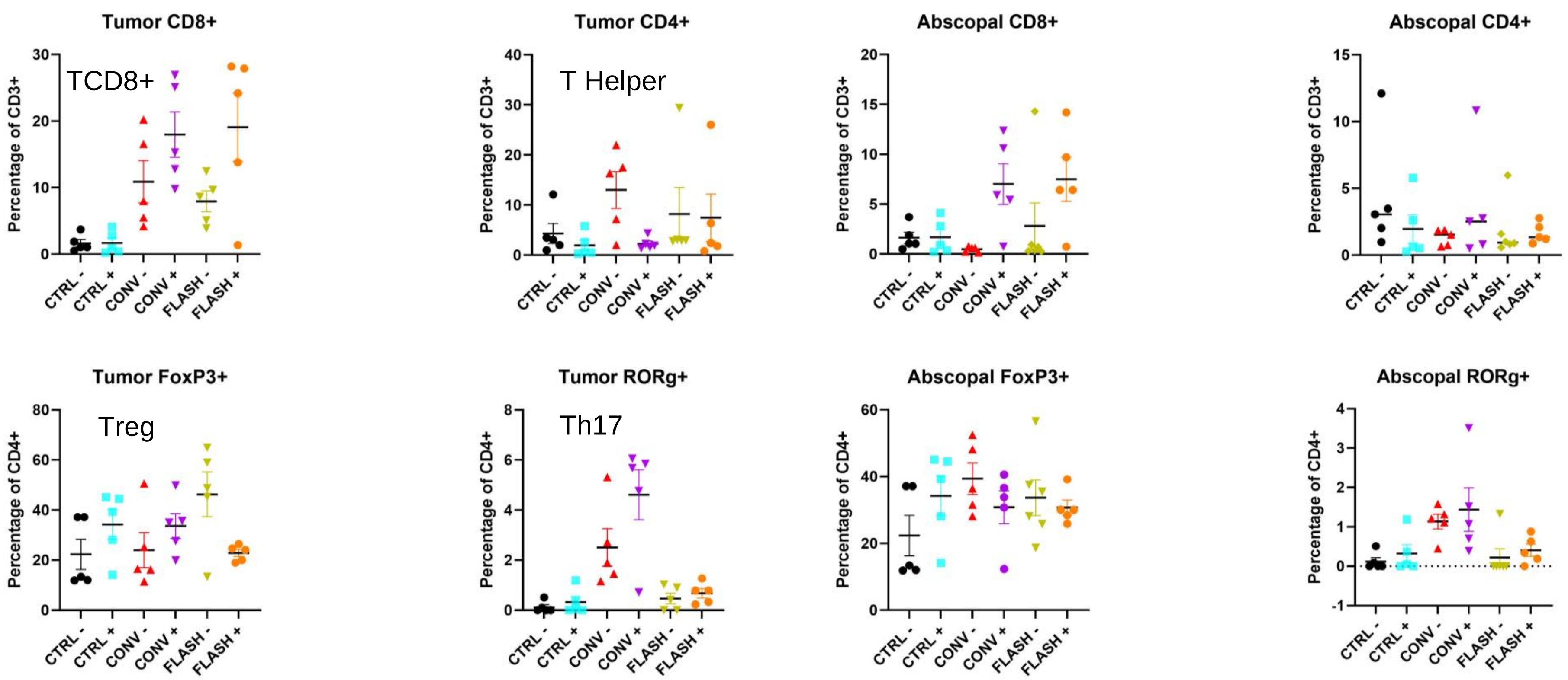




Courtesy of L. Munoz, Universitätsklinikum Erlangen

Immune cell infiltration (7 days after radiation)

Data NOT PUBLISHED



Conclusions

- HIGH-LET correlates with a predicted substantial lowering of several conditions connected with the onset of the FLASH effect, accor
- **Oxygen dep**
- **Intertrack r** anning pathway) returns a neg ns;
- **FLASH effe** ons in vitro and in vivo.
- **FLASH is p** ments at high LET are nec
- In addition t ering distal metastasis. T e investigated more in detail.
- Preliminary studies suggest no difference between conventional and FLASH dose rate in activating the immune system.

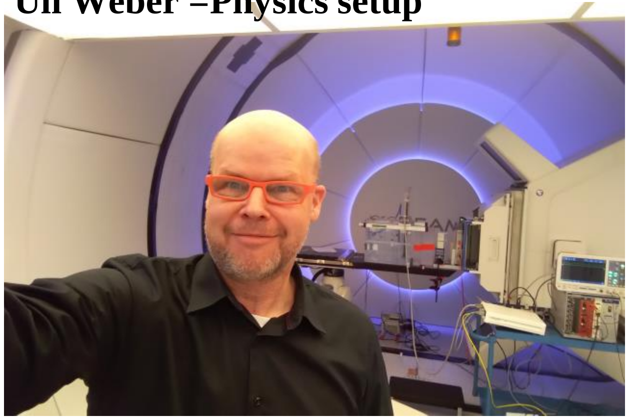
Is there a role for FLASH in particle radiotherapy?

Yes, FLASH has a role in particle therapy!

Acknowledgments

A. Puspitasari, A. Helm, P. Simoniello, C. Schuy, D. Boscolo, S. Lerchl, D. Eckert, A. Rehm, S. Janssen, D. Engel, R. Moeller, R. Romano, L. Munoz, U.Gaipl, C. Reichardt, S. Hui, C. Fournier, M. Durante

Special Thanks
Uli Weber =Physics setup



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Senior Scientist

Julius Oppermann

Dennis Fritsche

Reema Chowdhury

Tamara Vitacchio

Malte Benje

TECHNISCHE UNIVERSITÄT DARMSTADT

ANNEX SLIDES

…but there is also a dose dependence as well

Authors correlate the magnitude of the FLASH effect (normal tissue sparing) as a function of the delivered dose.
FLASH modyfing factor: FMF= $D_{CONV}/D_{UHDR}|_{isoeffect}$

Up to 10 Gy => no FLASH effect or little effect for (single shot) irradiations (all data)

From 10 Gy to 20 Gy => up to 20% of the effect (mouse gut data)

Around 30 Gy => circa 30% sparing effect (mammalian skin-reaction data)

Conclusion: «The magnitude of normal tissue sparing by FLASH increases with dose and is dependent on the irradiated tissue»

Böhlen T.T., Germond J.-F., Bourhis J., Vozenin M.-C., Ozsahin E.M., Bochud F., et al. Normal Tissue Sparing by FLASH as a Function of Single-Fraction Dose: A Quantitative Analysis. *Int J Radiat Oncol.* 2022 doi: 10.1016/j.ijrobp.2022.05.038.

Low Toxicity on Normal tissues

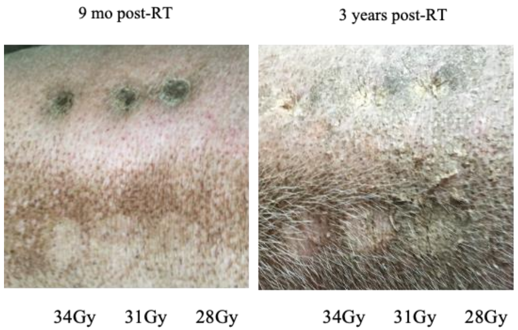
Annual Review of Cancer Biology

Reinventing Radiobiology in the Light of FLASH Radiotherapy

Charles L. Limoli[1] and Marie-Catherine Vozenin[2]

[1]Department of Radiation Oncology, University of California, Irvine, California, USA; email: climoli@uci.edu

[2]Laboratory of Radiation Oncology, Radiation Oncology Service and Oncology Department, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland



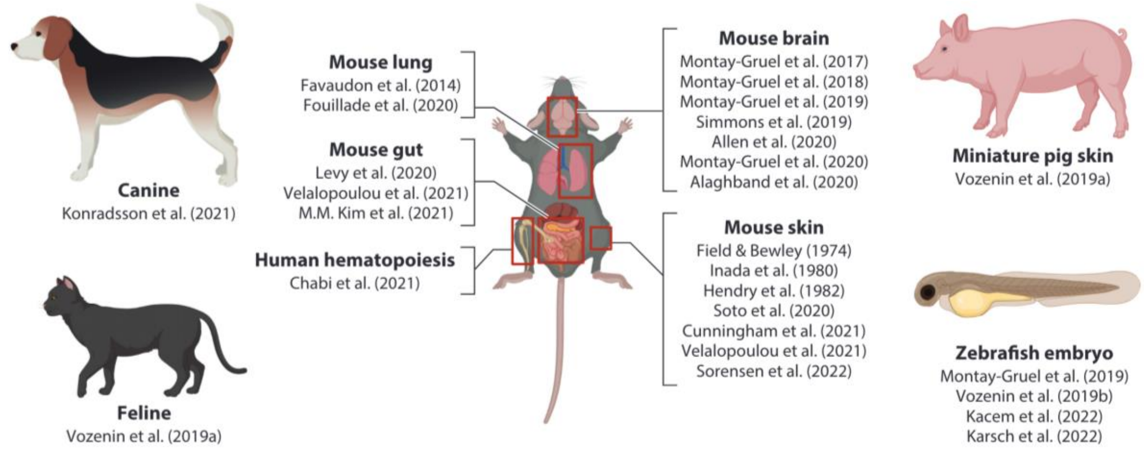


Figure 1

Normal tissue sparing by FLASH radiotherapy. FLASH radiotherapy provides a unique opportunity to dose escalate while minimizing normal tissue toxicities throughout a variety of normal tissue beds. Reduced normal tissue complications have been found in nearly all normal tissues examined to date, using a variety of preclinical models. Figure adapted from images created with Biorender.com.

…and in Human with Proton FLASH:

FAST-01: The first-in-human study investigates the use of ultrahigh dose rate proton FLASH therapy

Single-fraction treatment of painful bone metastases (12 metastatic sites) in the extremities in a routine clinical setting. Sample size 10 patients (27-81 years)

Dose rate of ≥40 Gy per second; Enrollment on November 3, 2020;

Results:

Complete-partial pain relief following FLASH was seen in 8 of 12 sites (7 of the 10 subjects) for an **overall response rate of 66.7%.**

E.C.Daugherty et al. FAST-01: Results of the First-in-Human Study of Proton FLASH Radiotherapy. 114(3)S4, 2022

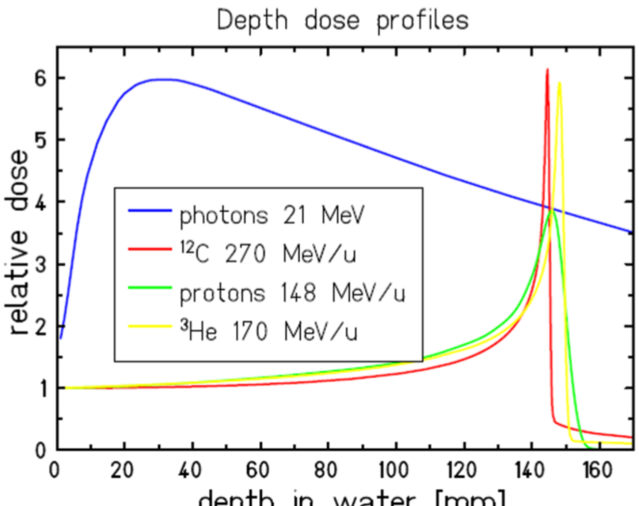
From photon to particle therapy: The beginning.

- Patients in Berkley were treated in the period 1975-1992 with several ions:
  He, N, O, C, Ne, Si, and Ar.

- Carbon is a good compromise for the more radioresistant tumors with an LET in the entrance channel between 11 and 13 keV/μm and a farily high LET in the SOBP between 40-80 keV/μm.

Carbon Ion Radiobiology

Walter Tinganelli [1], Marco Durante [1 2]



Ultra High Dose Rate Radiation

- Dewey and Boag in 1959:
  Ultra-high dose-rate 1.5-MV X-rays were used to irradiate a **bacterium**, *Serratia marcescens*.
  The profile of radioresistance to ultra-high dose rates was similar to that observed under hypoxic conditions, in which bacteria have the greatest resistance to radiation. *Dewey, D. L. & Boag, J. W. Nature 183, 1450–1451 (1959).*

- Berry et al. showed similar results in **hamster cells and HeLa cells** using ultra-high dose-rate (1,000 rads for the 15-ns pulse) irradiation. A series of experiments showed that the flash effect is related to oxygen consumption.

- In the 2010s, a paradigm-shifting set of experiments was performed in the frame of a collaboration between Institut Curie, Institut Gustave Roussy (Paris) and Centre Hospitalier Universitaire Vaudois (CHUV, Lausanne): **Ultra-high dose rate irradiation can widen the therapeutic window killing tumours while sparing non-malignant tissues.**
  The study was performed using the Kinetron LINAC, a linear accelerator (linac) delivering 4.5 MeV electrons originally built to investigate pulsed radiolysis and, thus, able to reach extremely high dose intensities.