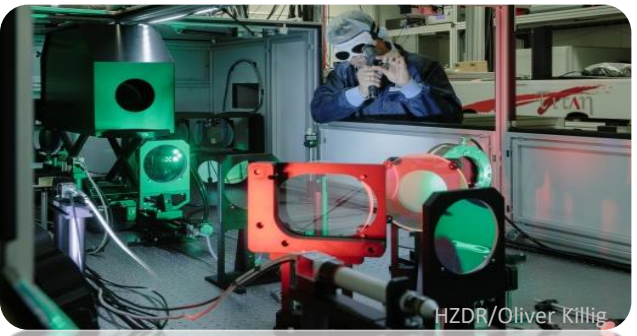
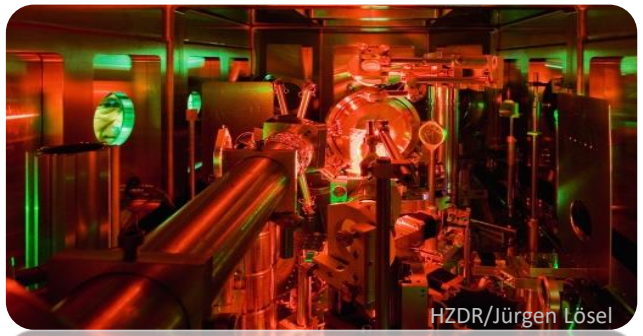
The status of research on the FLASH effect using laser-driven protons

LPAW 2025 – Laser Plasma Accelerator Workshop

Hotel Continental, Ischia Island (Naples, Italy)

13th - 19th April 2025





Josefine Metzkes-Ng

Application-oriented laser-plasma accelerators

Institute of Radiation Physics

Helmholtz-Zentrum Dresden – Rossendorf

Acknowledgements

Laser radiooncology

pre-clinical RT
radiobiological research

Laser particle acceleration

development & application of high power lasers for plasma-based particle acceleration

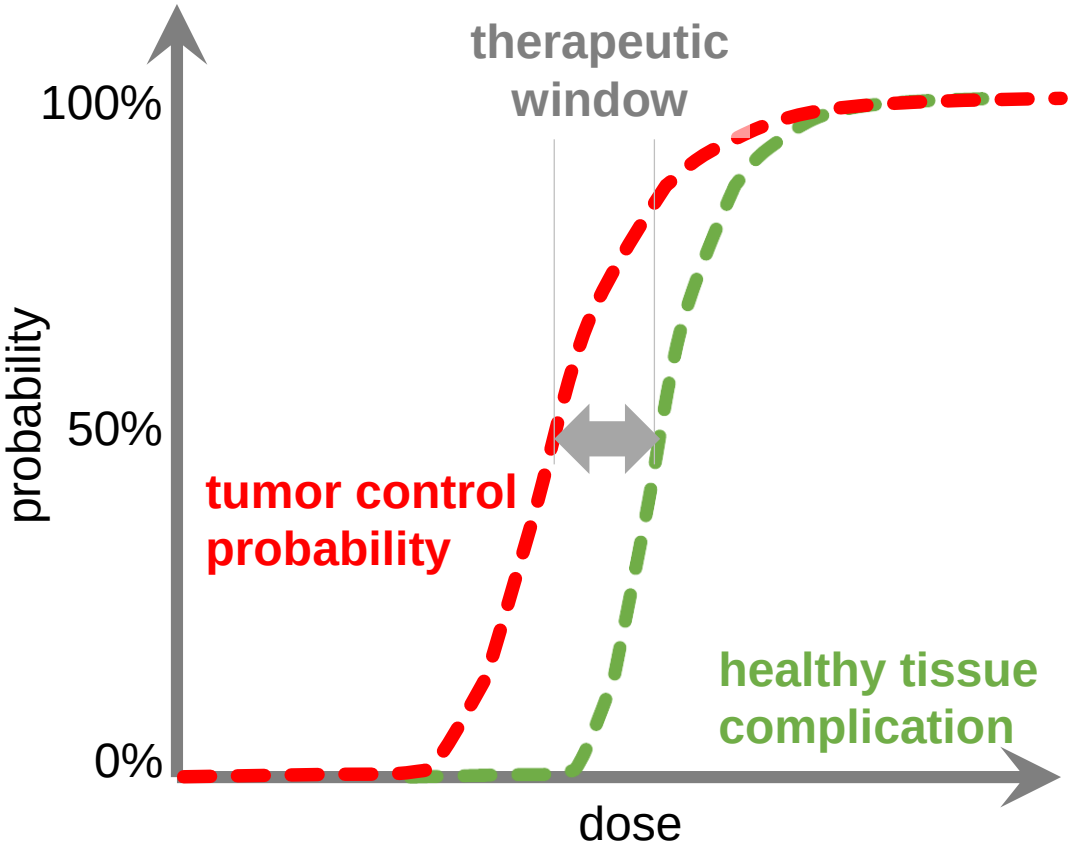
K. Zeil, J. Metzkes-Ng, F. Kroll, C. Bernert, E. Beyreuther, L. Gaus, S. Kraft, A. Nossula, M.E.P. Umlandt, M. Rehwald, M. Reimold, J. Schilz, H.-P. Schlenvoigt, M. Sobiella, T. Ziegler, S. Bock, R. Gebhardt, U. Helbig, T. Püschel, U. Schramm, T. Cowan, et al.

J. Pawelke, E. Beyreuther, K. Brüchner, E. Bodenstein, L. Karsch, E. Lessmann, M. Krause, E. Troost, N. Cordes, C. Richter, et al.

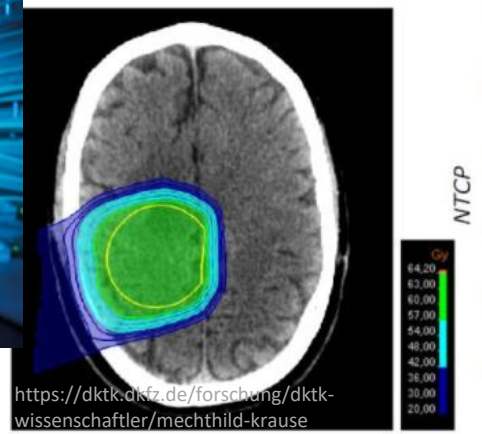
Josefine Metzkes-Ng I j.metzkes-ng@hzdr.de I www.hzdr.de

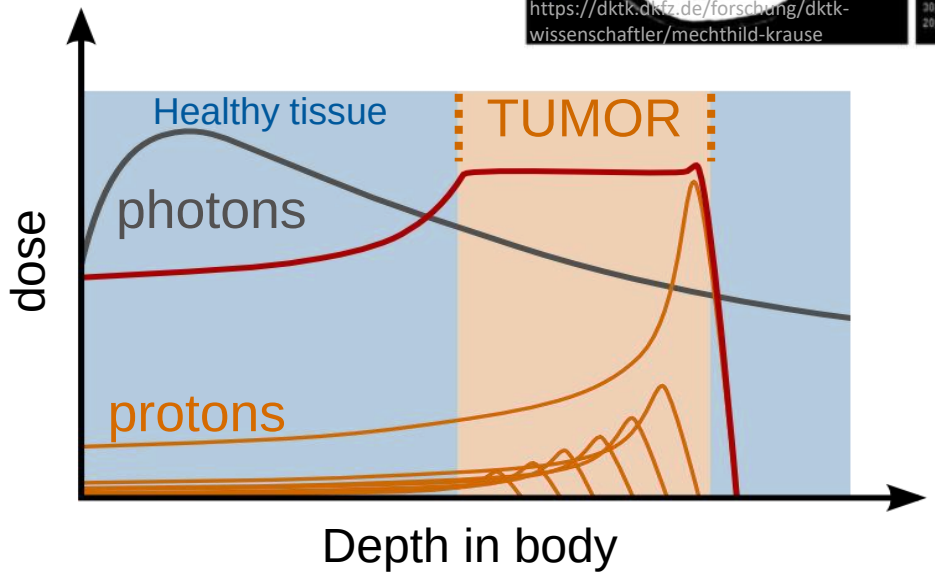
Radiation therapy

The therapeutic window



Protons

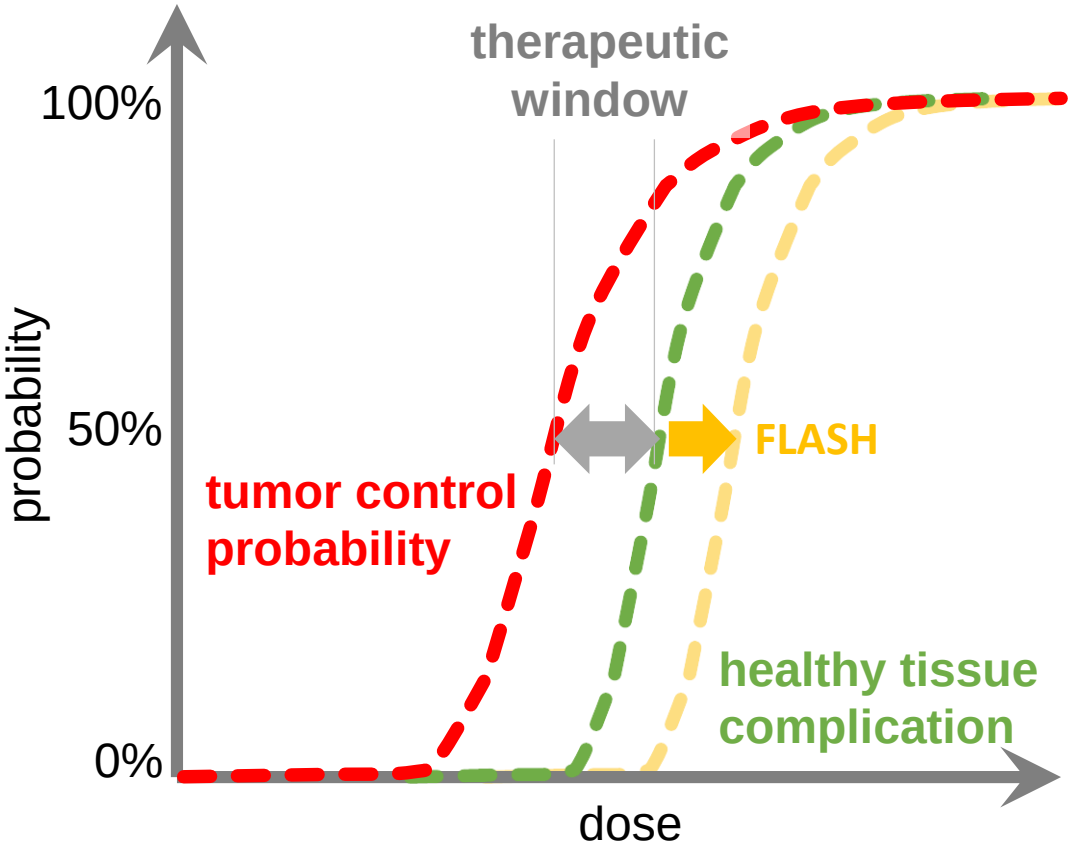




- pharmacological: radiosensitizers/radioprotectors …
- spatial: dose conformality (imaging, IMRT, prot. vs. phot.)
- temporal: fractionation, **FLASH**

The FLASH effect

Definition

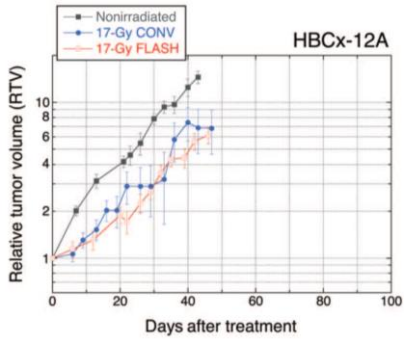


- pharmacological: radiosensitizers/radioprotectors …
- spatial: dose conformality (imaging, IMRT, prot. vs. phot.)
- temporal: fractionation, **FLASH**

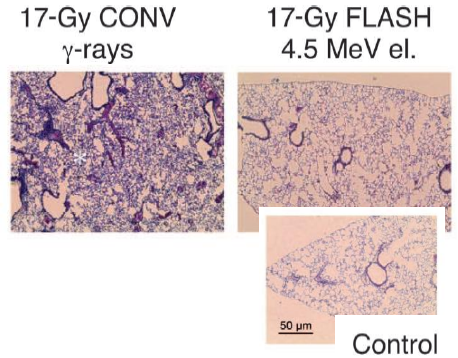
The FLASH effect is an ***in vivo* effect** where **normal tissue toxicities can be ameliorated** while maintaining **equal efficacy in tumor growth control**, achieved by delivering **radiation at ultra-high dose rates** above a prescribed threshold (mean dose rates = 100 Gy/s).

[Annu. Rev. Cancer Biol. 2023. 7:1–21]

Equal tumor growth efficacy



Normal tissue protection



Favaudon Sci. Transl. Med. 2014

Equal tumor growth efficacy

confirmed for almost all tumor types tested (> 23) in various *in vivo* models

Normal tissue protection

confirmed for almost all normal tissues examined in various preclinical *in vivo* models

Radiation quality

confirmed for all radiation qualities: electrons, photons, protons, heavier ions

Josefine Metzkes-Ng I j.metzkes-ng@hzdr.de I www.hzdr.de

The FLASH effect

From beam to tissues - relevant timescales

Annu. Rev. Cancer Biol. 2023. 7:1–21 & Rev. Mod. Phys. 2024. 96: 035002

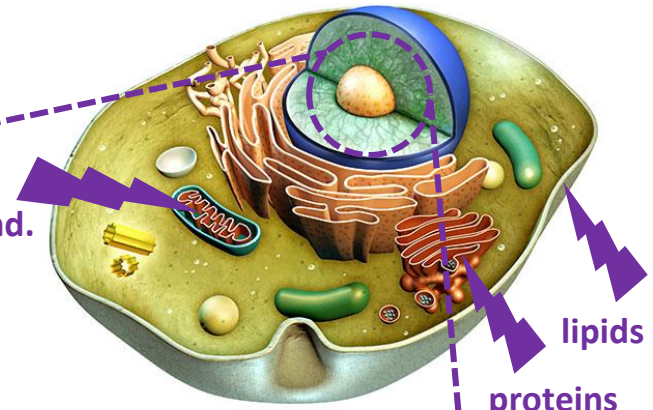
as - fs
- **PHYSICAL step**
- ionizations and excitations

fs - ps
- **PHYSIOCHEMICAL step**
- molecular dissociations

ps - s
- **CHEMICAL step**
- reactions and diffusions

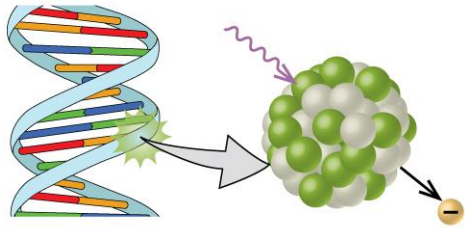
s - h
- **BIOCHEMICAL step**
- DNA repair and enzymatic reactions

> h
- **BIOLOGICAL step**
- cellular and tissue response

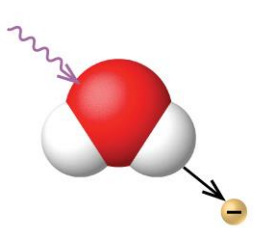


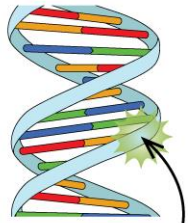
https://www.biotek.de/applications/cell-metabolism-new.html

direct effect



indirect effect





free radicals + oxygen → peroxyl radical

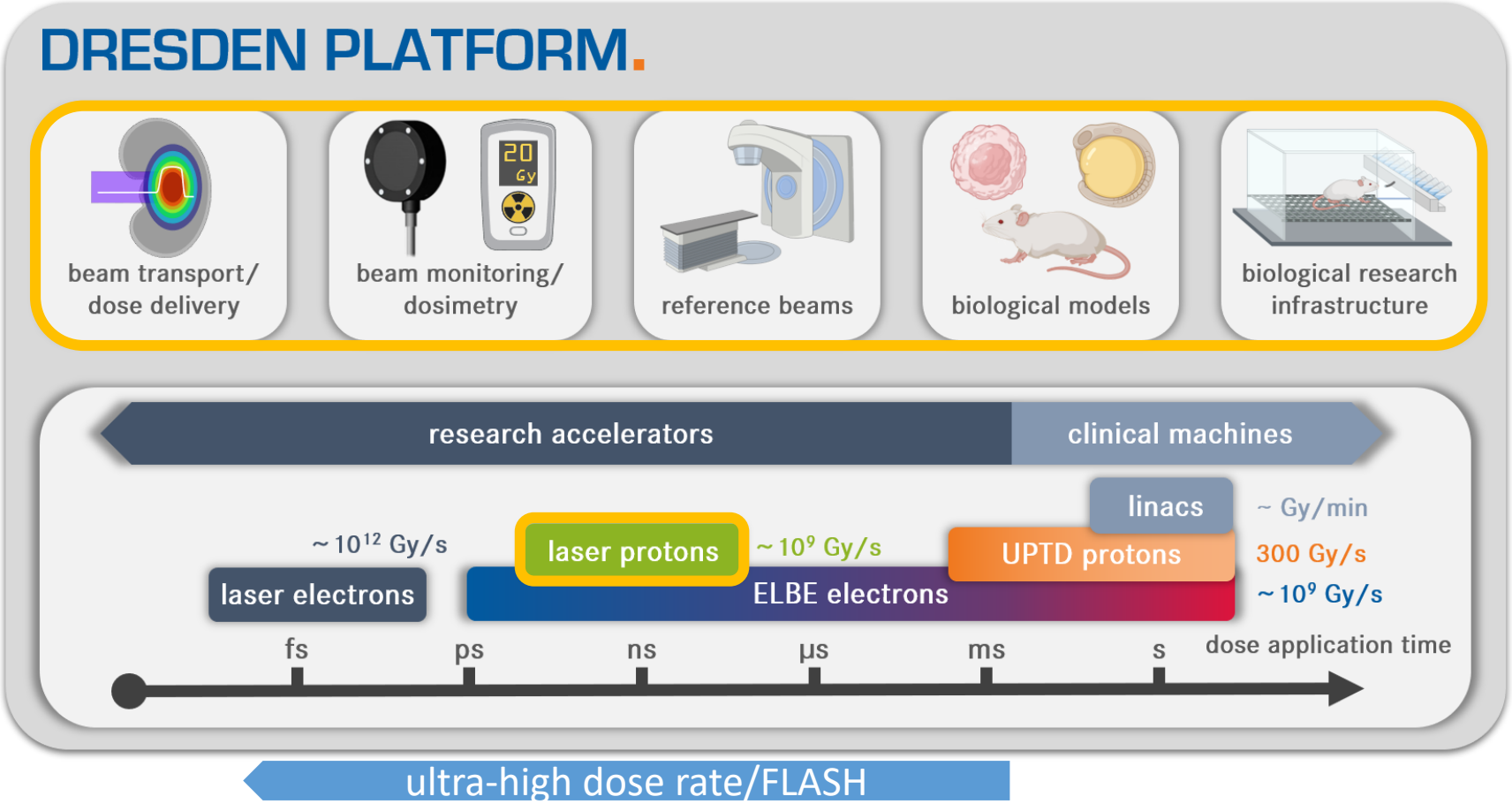
radical recombination

oxygen depletion

https://chem.libretexts.org/Bookshelves/Ancillary_Materials/Exemplars_and_Case_Studies/Case_Studies/Nuclear_Energy_for_Today%27s_World/14%3A_Effects_of_Radiation

A research hub for ultra-high dose rate radiobiology

The DRESDEN PLATFORM

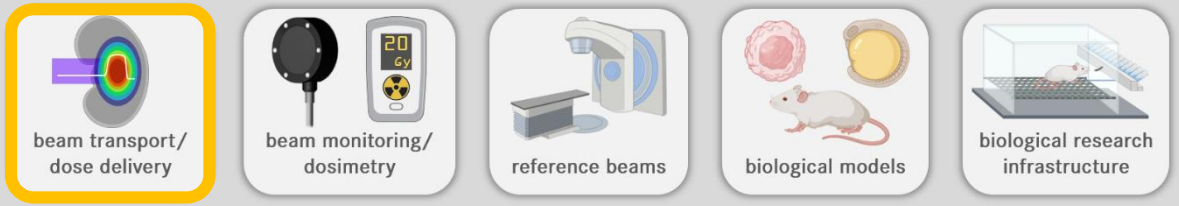


- F. Kroll, et al. “Tumour irradiation in mice with a laser-accelerated proton beam”, Nature Physics 18, 316 (2022)
- J. Jansen, et al. “Changes in Radical Levels as a Cause for the FLASH effect: Impact of beam structure para-meters at ultra-high dose rates on oxygen depletion in water”, Radiotherapy and Oncology 175, 193 (2022)
- L. Karsch, et al. “Beam pulse structure and dose rate as determinants for the flash effect observed in zebrafish embryo”, Radiotherapy and Oncology 173, 49 (2022)
- J. Jansen, et al. “Does FLASH deplete oxygen? Experimental evaluation for photons, protons, and carbon ions”, Medical Physics 48, 3982 (2021)
- J. Pawelke, et al. “Electron dose rate and oxygen depletion protect zebrafish embryos from radiation damage”, Radiotherapy and Oncology 158, 7 (2021)
- S. Brunner, et al. “Dose-dependent changes after proton and photon irradiation in a zebrafish model”, Anticancer Research 40, 6123 (2020)
- E. Beyreuther, et al. “Feasibility of proton FLASH effect tested by zebrafish embryo irradiation”, Radiotherapy and Oncology 139, 46 (2019)

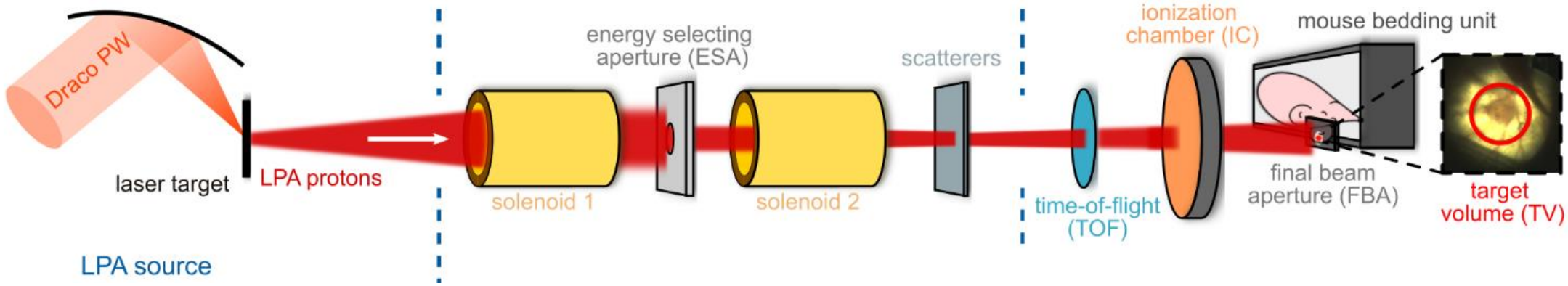
J. Metzkes-Ng et al. **The DRESDEN PLATFORM – A Research Hub for Ultra-high Dose Rate Radiobiology**
Scientific Reports 13 (2023), 20611

Realizing radiobiological *in vivo* studies at laser-driven sources

Worldwide-first tumor irradiations in mice

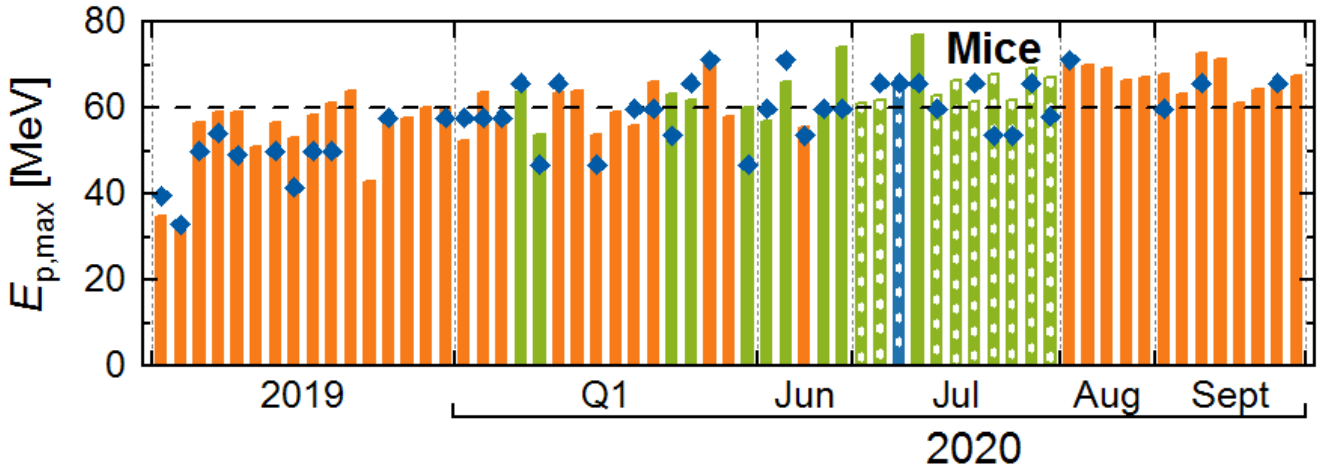


- **F. Kroll *et al.* 2022 *Nat Phys* 18 316**
- T. Ziegler *et al.* 2021 *Sci Rep* **11** 7338
- F.-E. Brack *et al.* 2020 *Sci Rep* **10** 9118
- M. Reimold *et al.* 2022 *Sci Rep* **12** 21488
- M. Reimold *et al. 2023 Phys Med Biol* **68** 185009



Draco – accelerator research (e^-/p^+) & application

- commercial Ti:Sapphire dual-beam laser system
  - 150 TW (4 J in 30 fs routinely on target) @ 10 Hz
  - **PW (30 J on target in 30 fs) @ 1 Hz**



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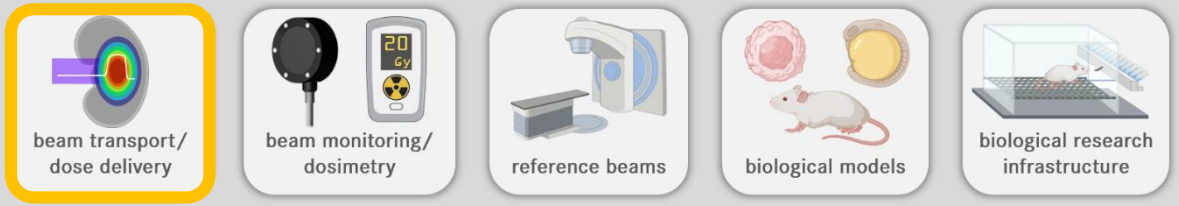

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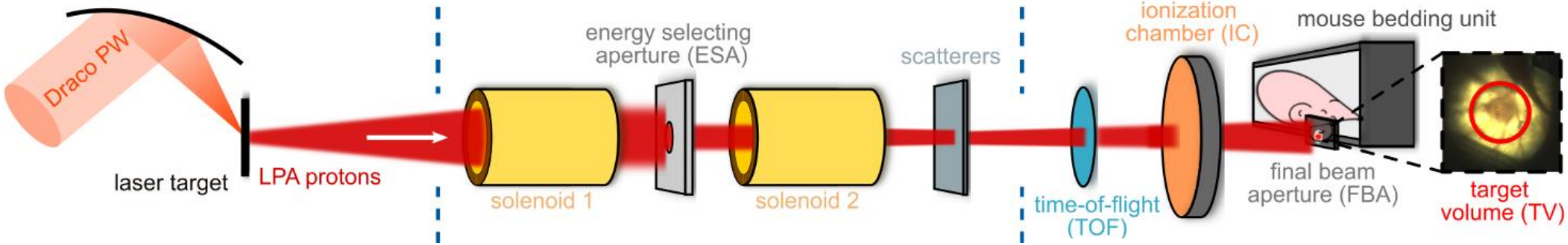
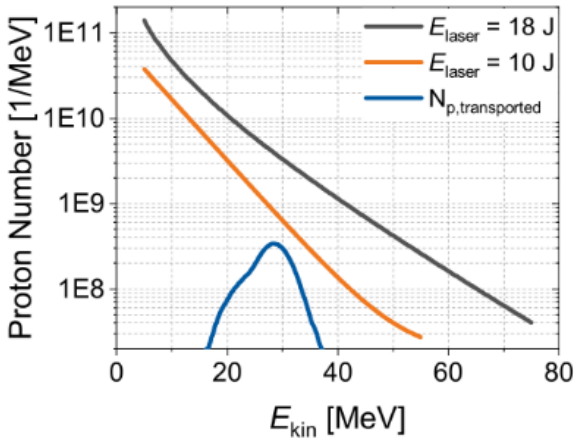
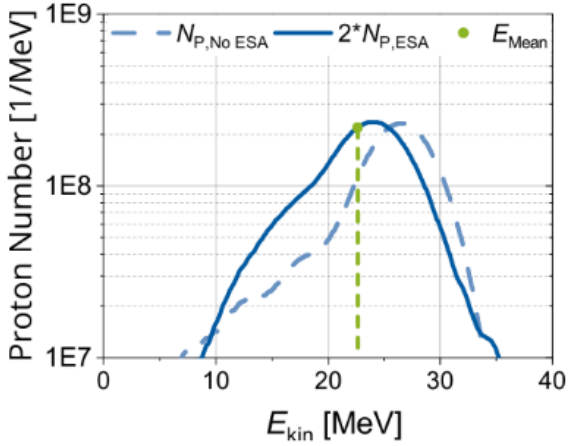


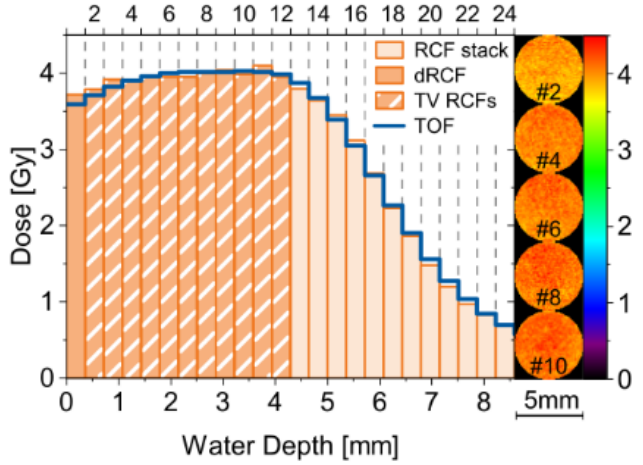
LPA source



beam transport system



beam monitoring and dosimetry



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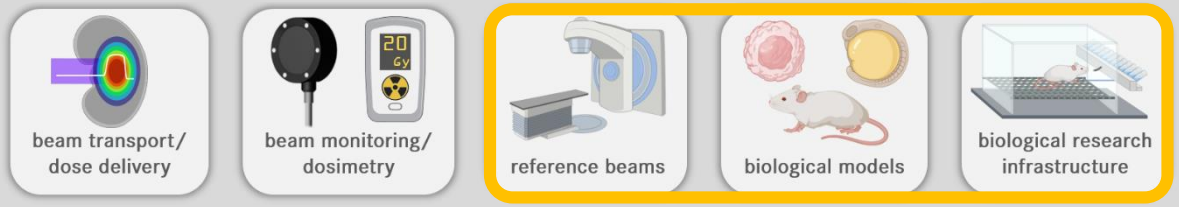

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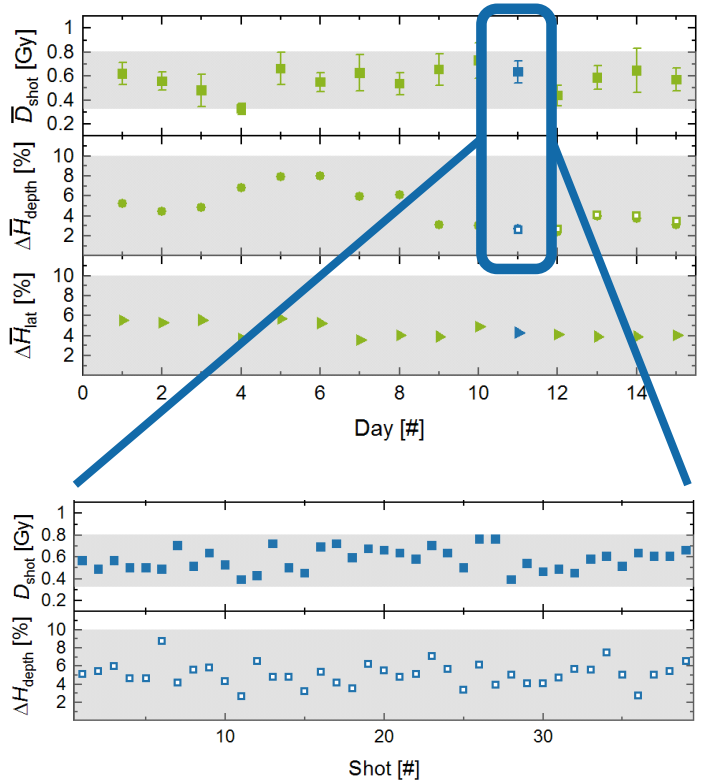
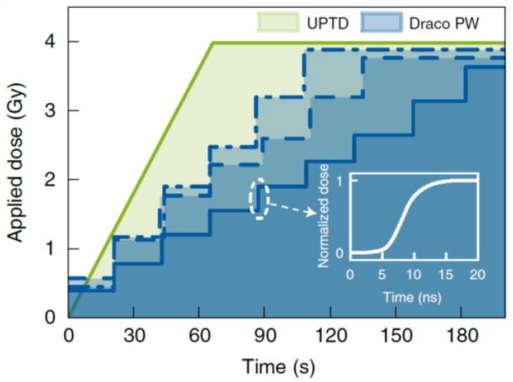
- K. Brüchner et al., Radiat. Onc., Vol. 9 (2014)
- M. Oppelt et al., Radiat Environ Biophys (2015)
- Animal study approval DD24-5131/338/35

- radiobiological endpoint: tumor-growth delay
- homogeneous (< 10% dev.) 3D dose distribution
- < 10% sample-to-sample variation
- mean dose rate > 1 Gy/min
- 2 cohorts (Draco PW & UPTD) w 5 treatment groups
- sample size: < 10 per setting



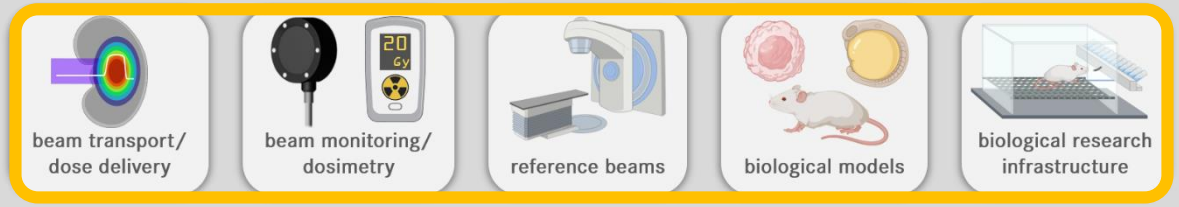
dose application scheme



- multi-pulse dose application
- 330 - 800 mGy/pulse
- lower limit: rep. rate & min. dose rate
- upper limit: specified dose accuracy

1st small animal pilot study with laser-driven proton pulses

Results



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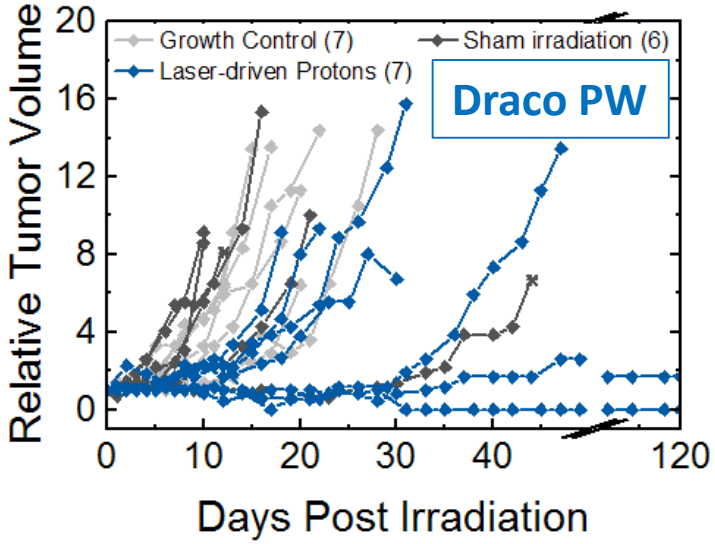
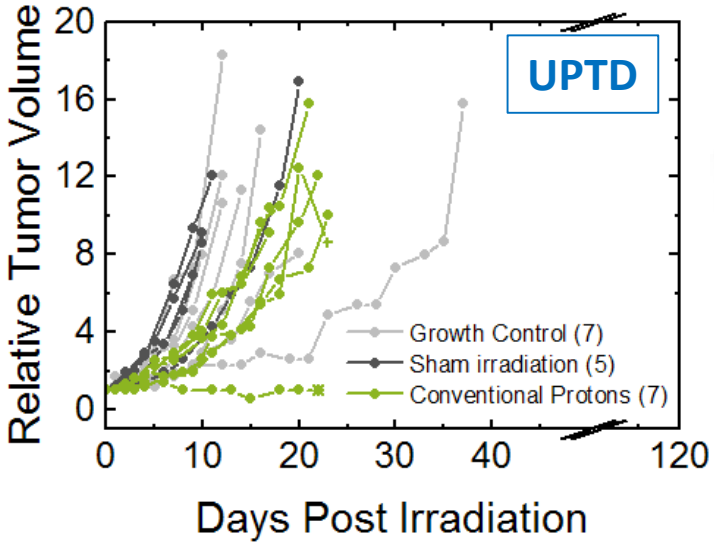
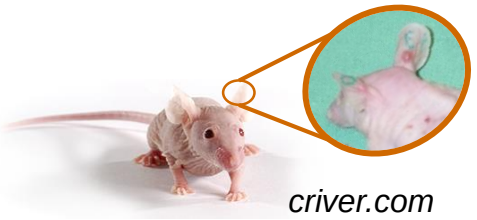






criver.com

	Draco PW	UPTD
mean dose [Gy]	3.9	3.9
mean dose rate [Gy/min]	1.2 – 2.2	3.6
peak dose rate [Gy/s]	10^8	-

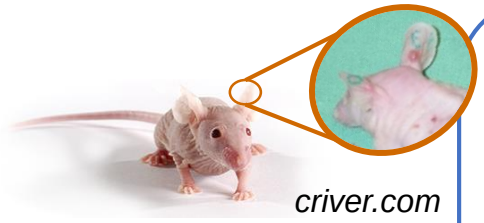
Excursion: peak vs. mean dose rate

Is this FLASH?

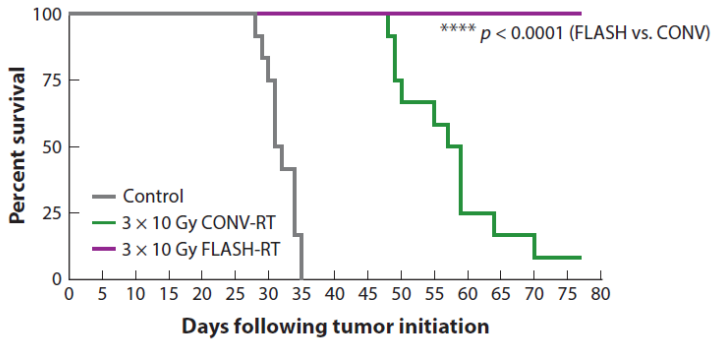
investigation of time structure effects (peak vs. mean dose rate) on tumor and healthy tissue

Is that FLASH?

- … ultra-high dose rates above mean dose rates = 100 Gy/s …
  [Annu. Rev. Cancer Biol. 2023. 7:1–21]
- BUT: several indications for an UHDR effect on tumors

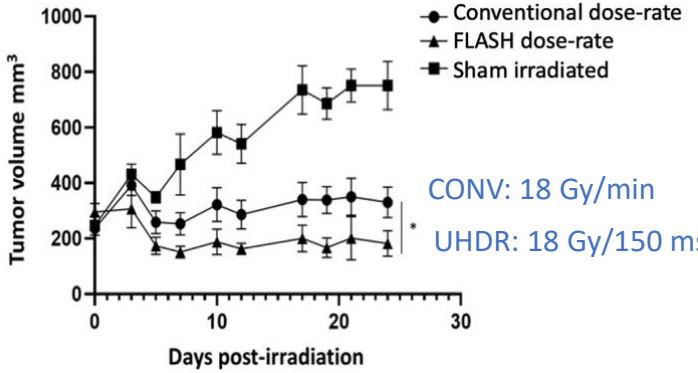


UHDR yields 100% survival after brain tumor irradiation in mice



[Annu. Rev. Cancer Biol. 2023. 7:1–21]

Carbon: UHDR yields significant reduction in tumor volume after irradiation

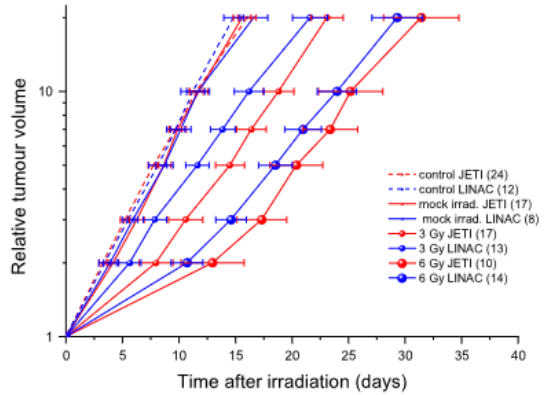


CONV: 18 Gy/min

UHDR: 18 Gy/150 ms

[Rad. Onc. 2022. 175:185]

LPA e^-: UHDR yields reduction in tumor volume after irradiation



- CONV: mean dose rate ~1 Gy/min
- UHDR:
  - peak dose rate: >10^{10} Gy/s
  - mean dose rate <2 Gy/min

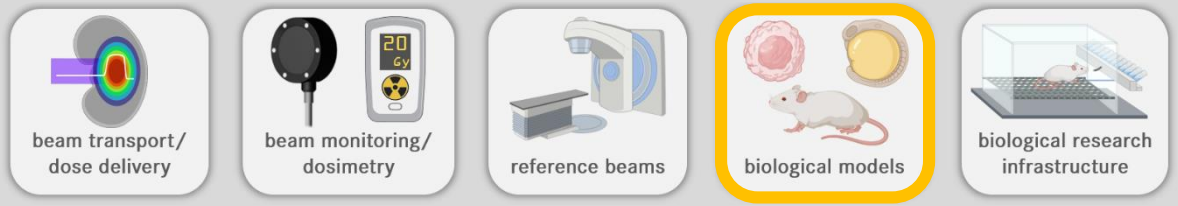
[Radiat. Environ. Biophys. 2015. 54:155–166]

+

Wei Lu group: [Nat. Comm. 2025. 16:1895]

FLASH research: normal tissue protection

The zebrafish embryo model



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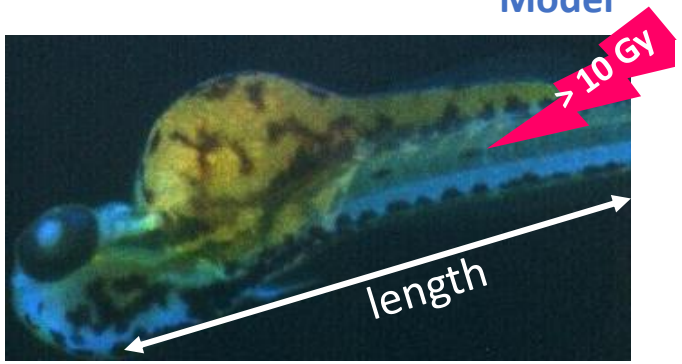
Model

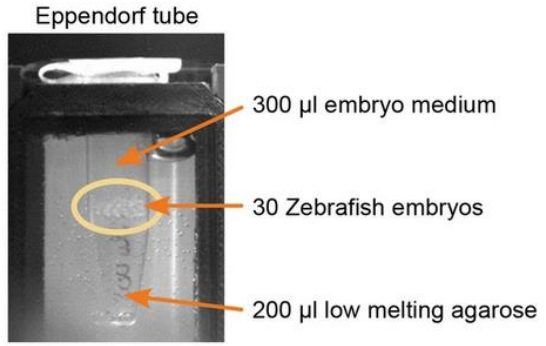


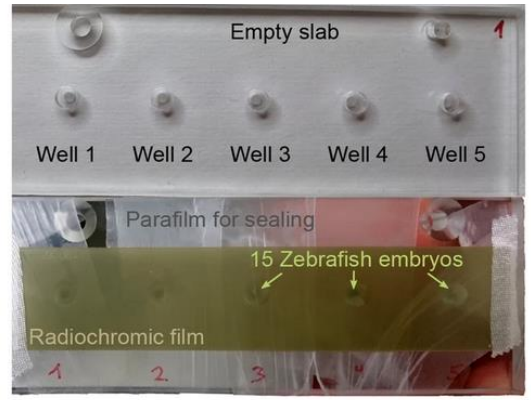
Zebrafish embryo
Montay-Gruel et al. (2019)
Vozenin et al. (2019b)
Kacem et al. (2022)
Karsch et al. (2022)

- model parameters
  - small in size: 1 mm diameter @ 24 hpf
  - simultaneous irradiation of several ZFE
- dose escalation > 10 Gy
- radiobiological endpoint: morphological changes

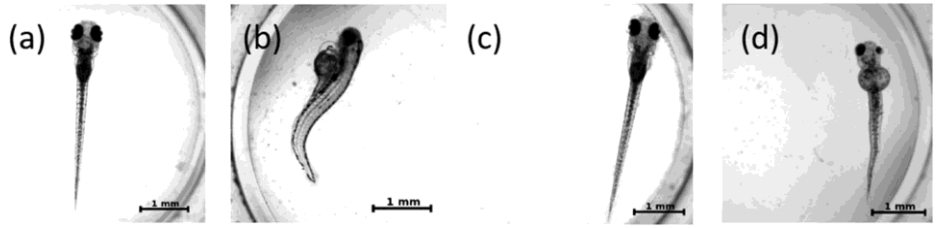
- J. Pawelke et al., Radiotherapy and Oncology 158 (2021), 7-12
- E. Beyreuther et al., Radiotherapy and Oncology 139 (2019), 46-50
- E. R. Szabo et al., PLOS ONE 13 (2018)11, e0206879

Irradiation setup & radiobiological endpoints





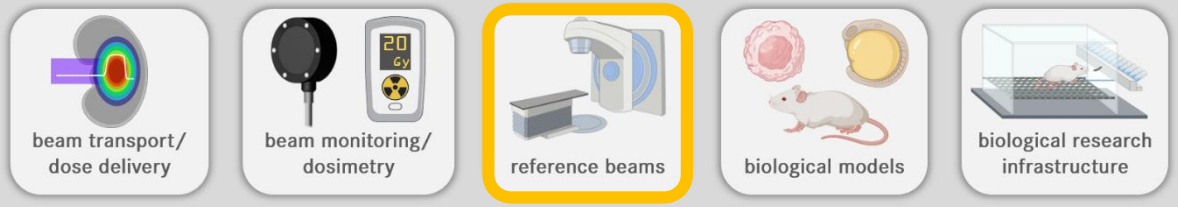
… first laser-proton irradiation study at LION (CALA, Munich) …



RSI 91 (2020) doi:10.1063/5.0008512

FLASH research: normal tissue protection

The role of peak versus mean dose rate



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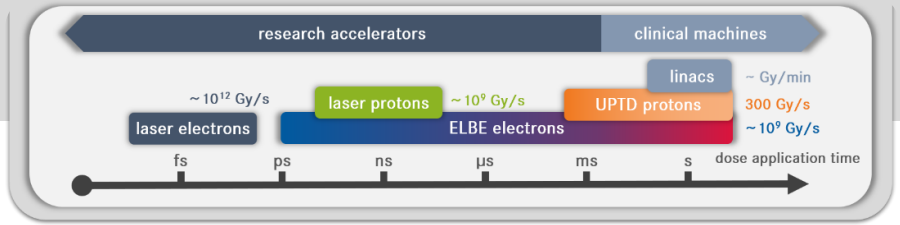
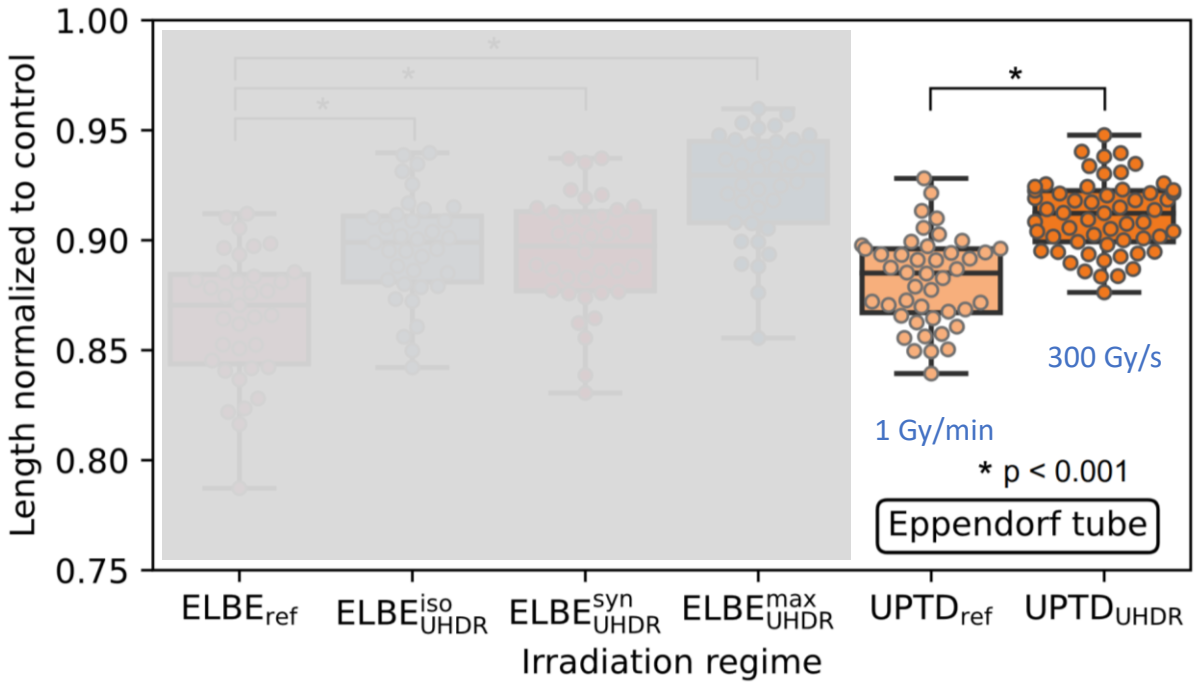
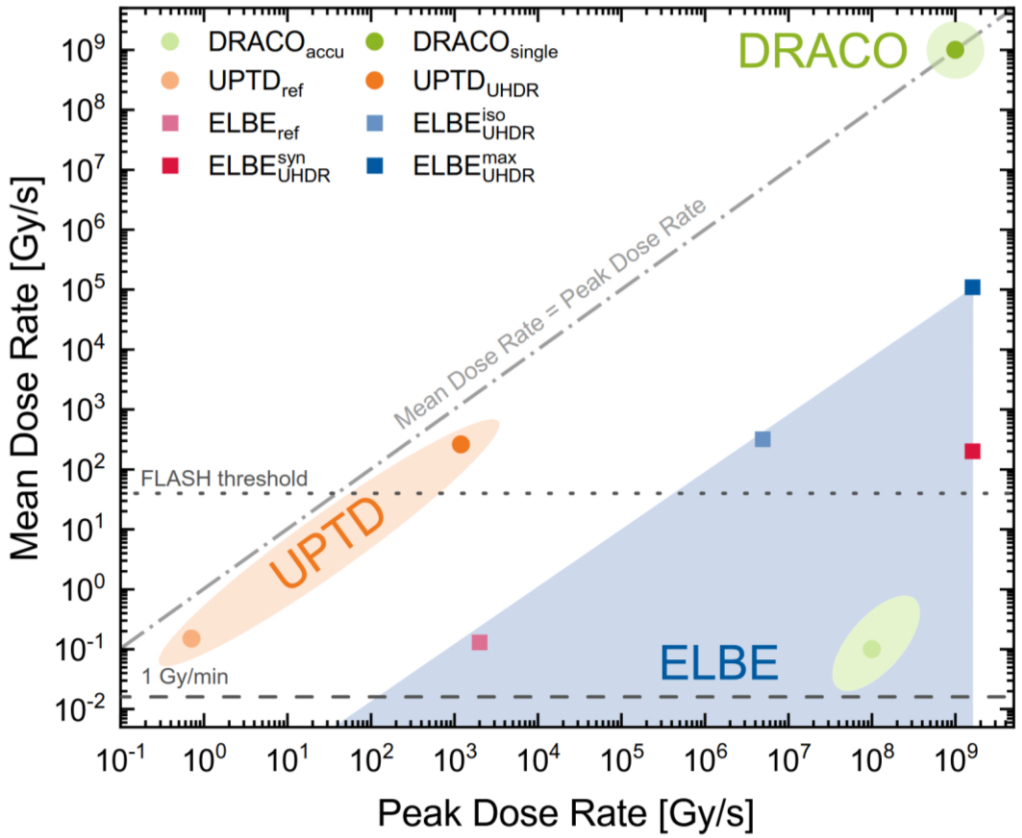




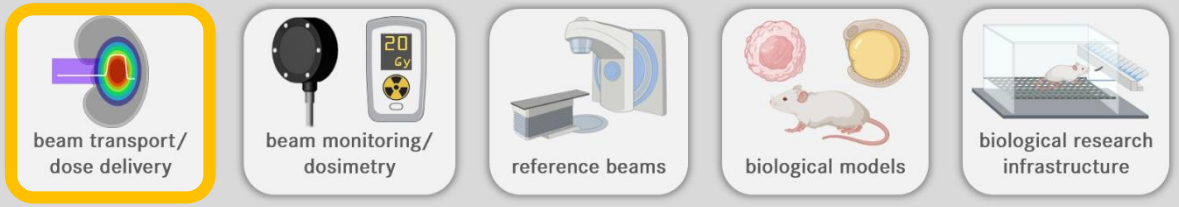


- laser-driven particle sources: single bunch ultra-high dose rates

Josefine Metzkes-Ng I j.metzkes-ng@hzdr.de I www.hzdr.de

Single-bunch dose escalated irradiation of ZFEs

Challenge 1: maximizing dose per bunch



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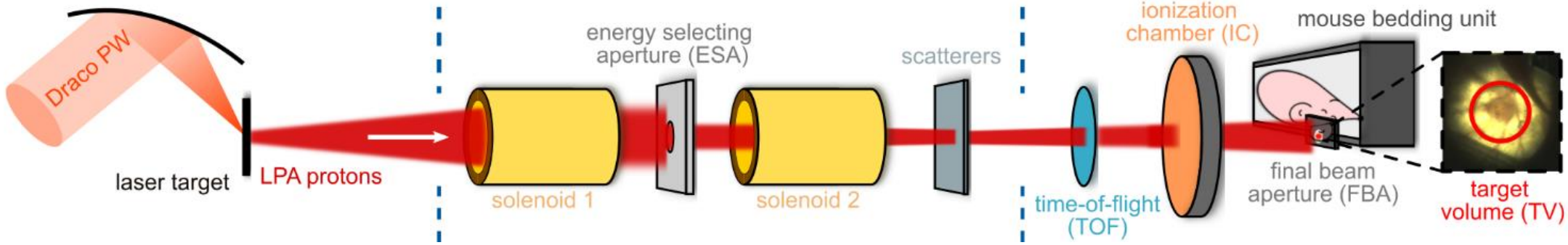
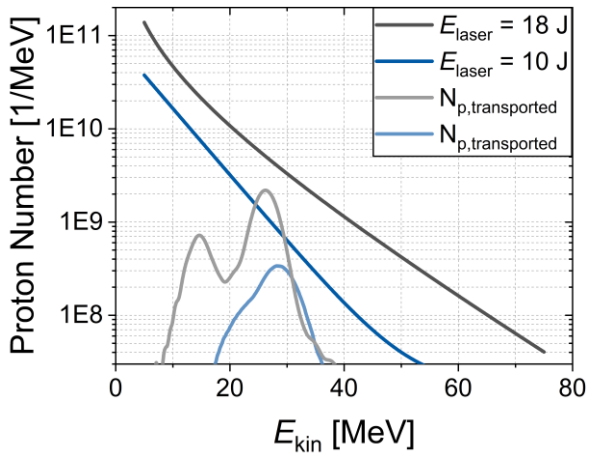
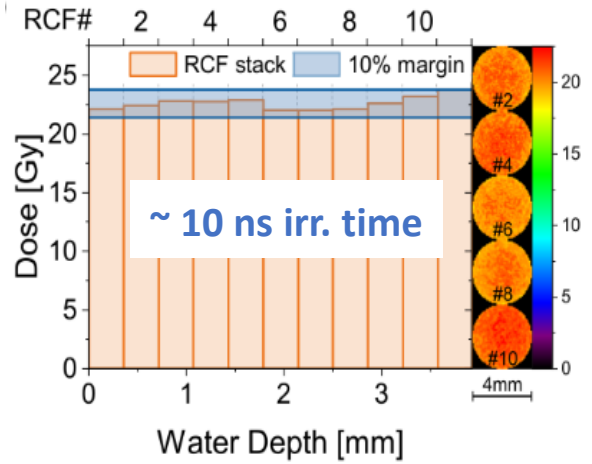
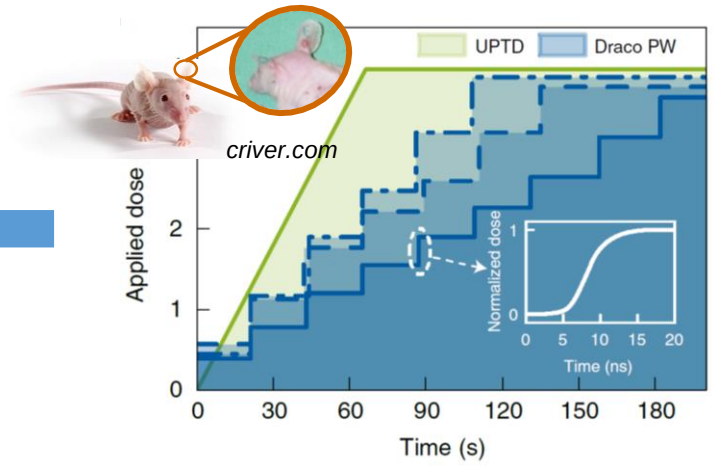


- **maximizing proton number**



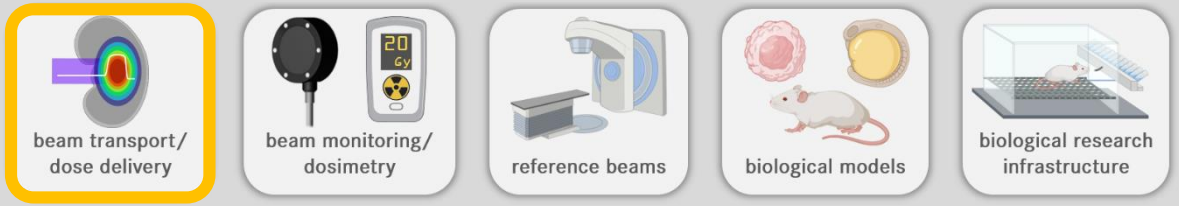
- **from multi-bunch accumulation to single-bunch multi-10 Gy irradiation**





Single-bunch dose escalated irradiation of ZFEs

Challenge 1: maximizing dose per bunch



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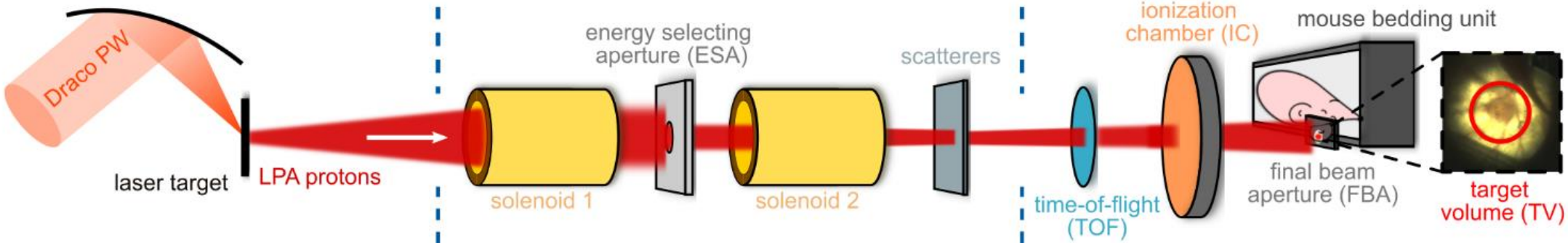
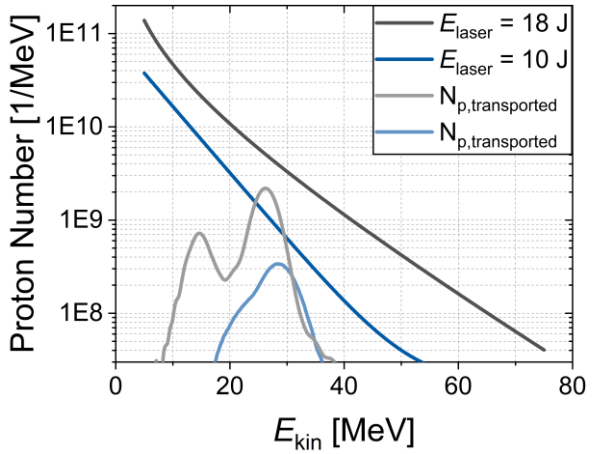


- **maximizing proton number**



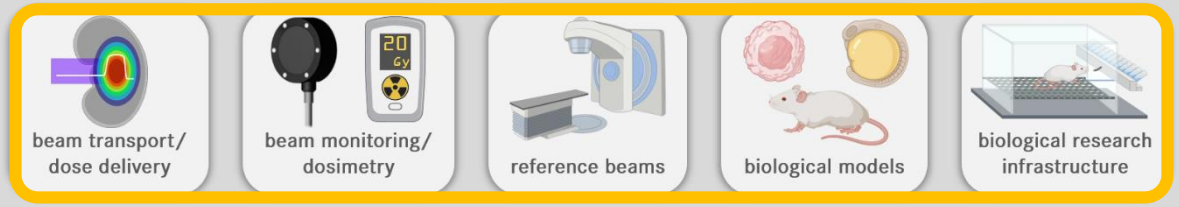
- **from multi-bunch accumulation to single-bunch multi-10 Gy irradiation**

- **Challenges 1**
- goal: D > 20 Gy

→ only achievable for best laser performance

Single-bunch dose escalated irradiation of ZFEs

First results



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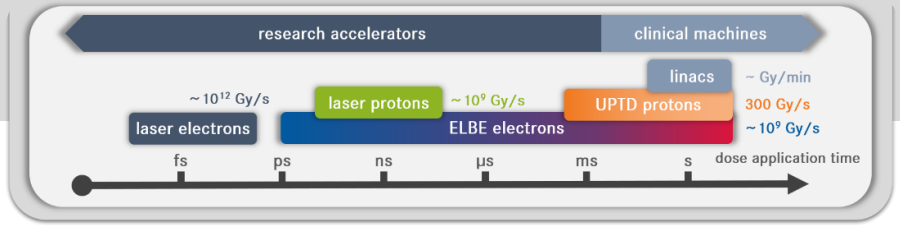
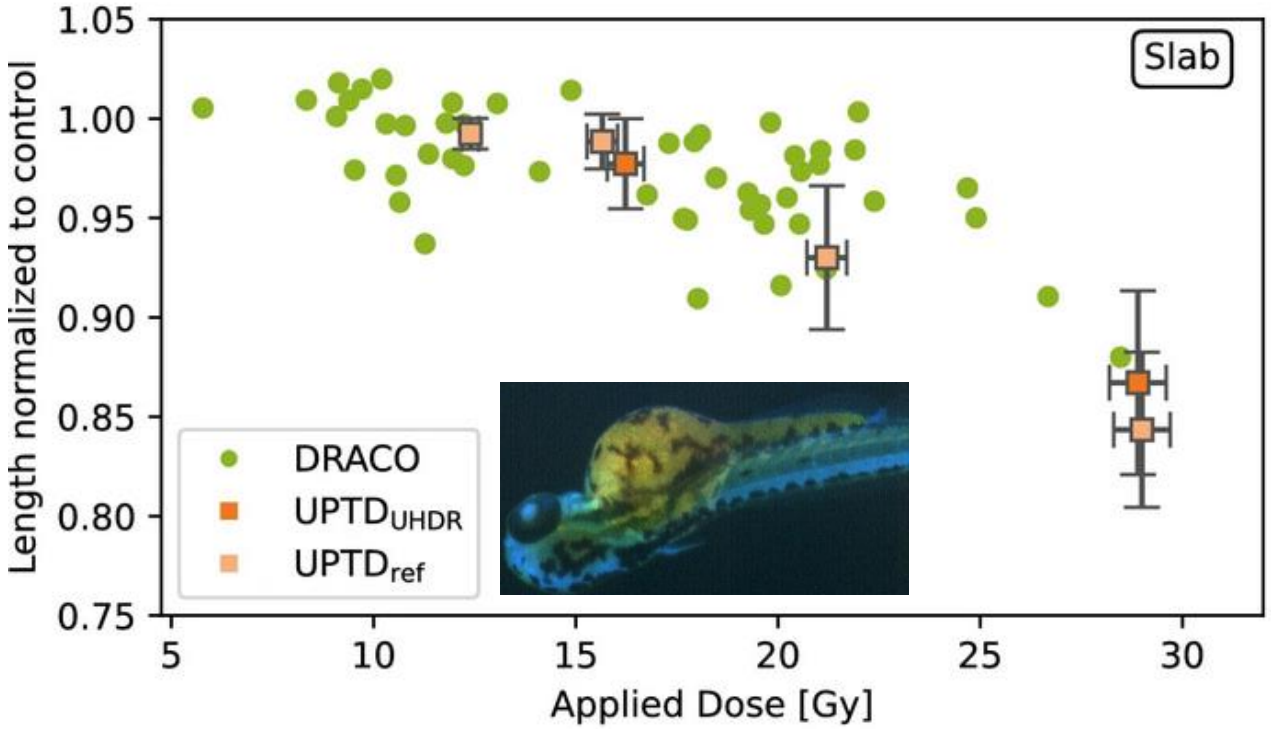
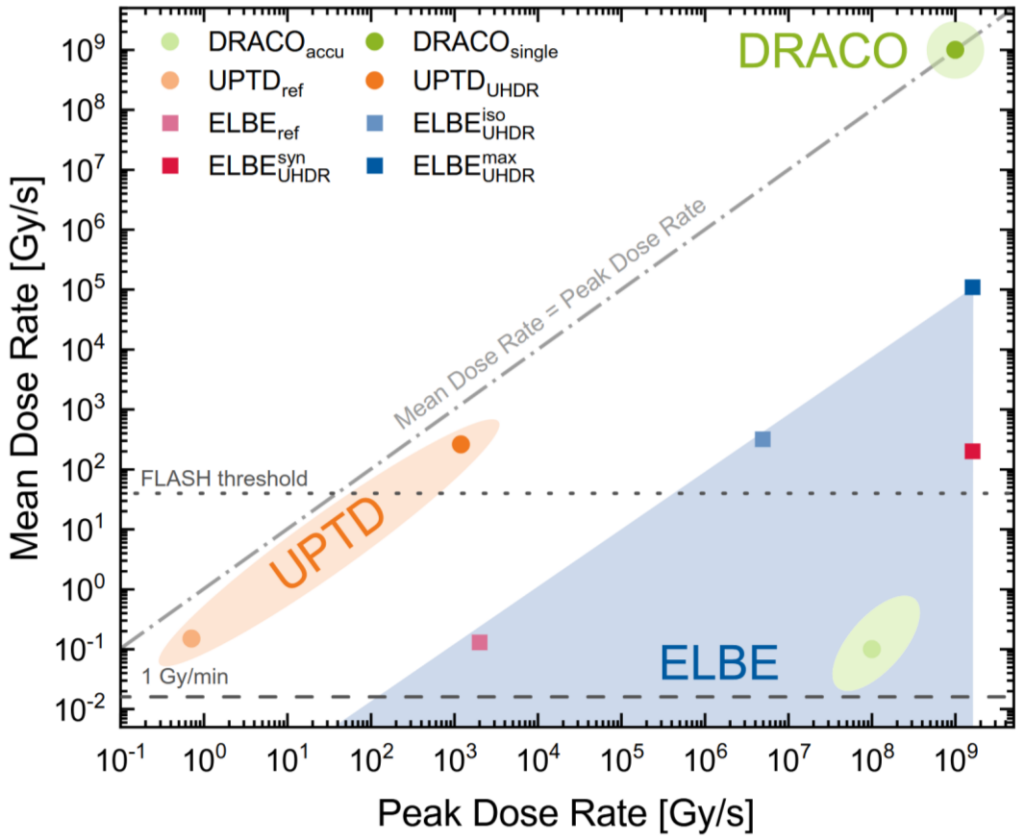
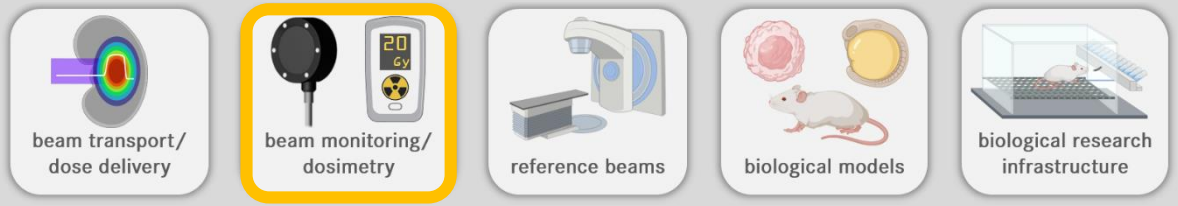






Single-bunch dose escalated irradiation of ZFEs

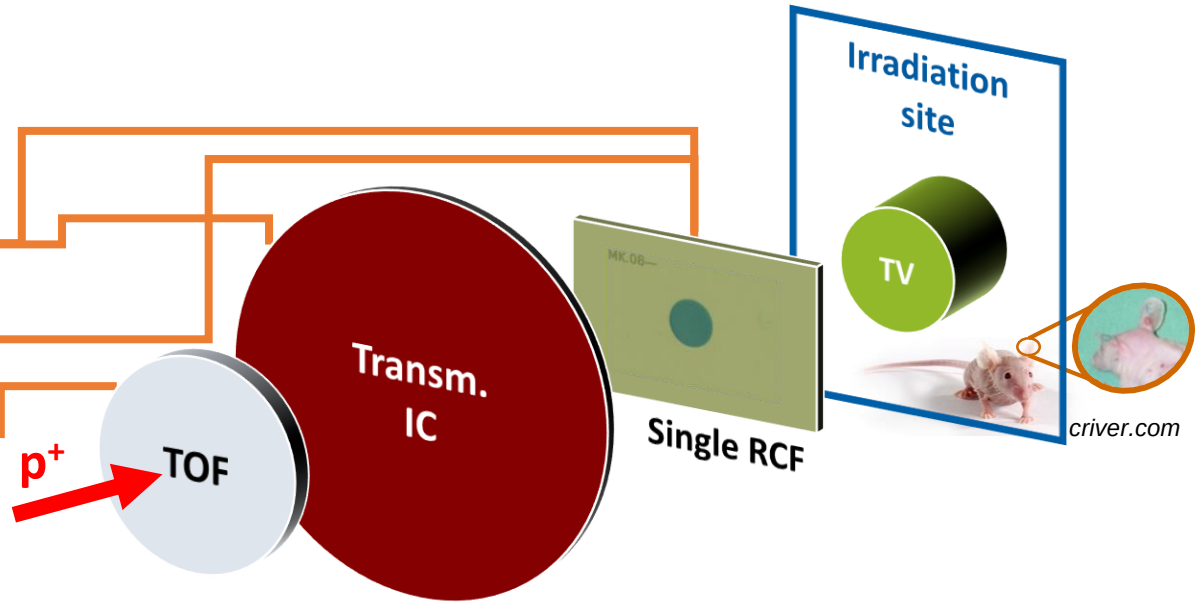
Challenge 2: Dosimetry at ultra-high dose rates

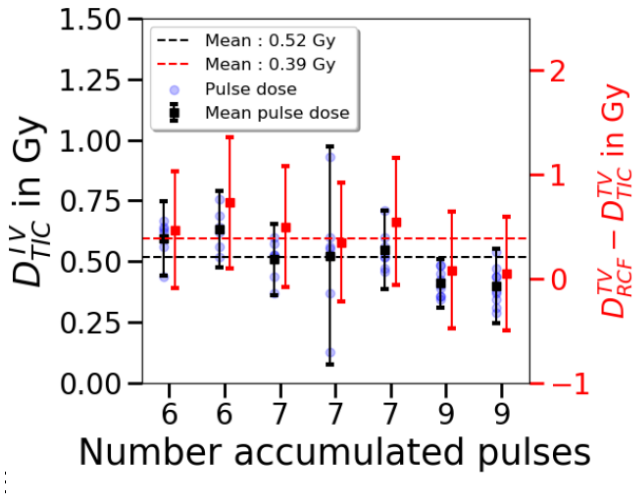


- F. Kroll *et al.* 2022 *Nat Phys* 18 316
- T. Ziegler *et al.* 2021 *Sci Rep* **11** 7338
- F.-E. Brack *et al.* 2020 *Sci Rep* **10** 9118
- M. Reimold *et al.* 2022 *Sci Rep* **12** 21488
- M. Reimold *et al. 2023 Phys Med Biol* **68** 185009

3D dose distribution in target volume (TV)

- volume dose
- lateral homogeneity
- depth homogeneity





charge recombination in ionization chambers for UHDR
→ saturation → Corrections reliable?

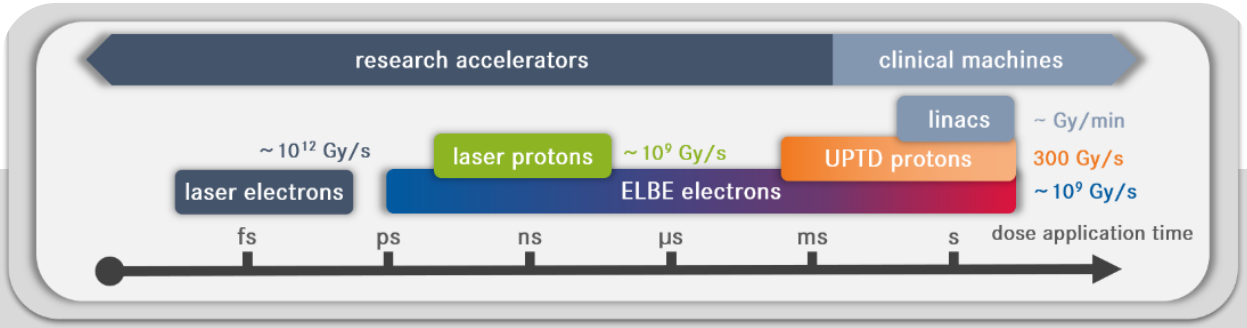
[Phys. Med. Biol. 2017. 62:8634]

indication of dose rate dependence in EBT3 films above 20 Gy
→ dose overestimation

[Med. Phys. 2022. 49:2732]

UHDR effects in scintillating material
→ change in decay time & LET dependence of signal
[DOI:10.48550/arXiv.2502.05477]
[HPLSE 2024. 12:e17]

Summary and outlook



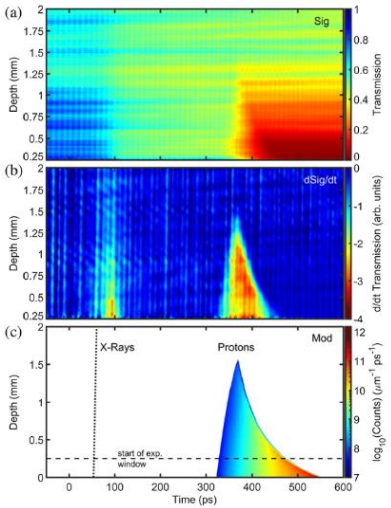
At this juncture it remains a challenge to account for how subsecond irradiation can discriminate between tumors and normal tissue. [Annu. Rev. Cancer Biol. 2023. 7:1–21]

Challenges … apart from reproducibility …

- maximizing dose per bunch via advanced targetry
- source-adapted dose prediction via spectroscopic methods

Opportunities

- exploit the time-resolution capabilities due to ultra-short pulses
- investigation of sub-systems instead of full *in vivo* models



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A Novel Platform for Evaluating Dose Rate Effects on Oxidative Damage to Peptides: Toward a High-Throughput Method to Characterize the Mechanisms Underlying the FLASH Effect

Sayan Gupta [a,1], Jamie L Inman [b,1], Jared De Chant [c], Lieselotte Obst-Huebl [c], Kei Nakamura [c], Shawn M Costello [d], Susan Marqusee [e], Jian-Hua Mao [b], Louis Kunz [f], Ryan Paisley [f], Marie-Catherine Vozenin [f], Antoine M Snijders [b,2], Corie Y Ralston [a,2]

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PHYSICAL REVIEW LETTERS **127,** 186001 (2021)

Real-Time Electron Solvation Induced by Bursts of Laser-Accelerated Protons in Liquid Water

A. Prasselsperger,[1,2] M. Coughlan,[2] N. Breslin,[2] M. Yeung,[2] C. Arthur,[2] H. Donnelly,[2] S. White,[2] M. Afshari,[2] M. Speicher,[1] R. Yang,[1] B. Villagomez-Bernabe,[3] F. J. Currell,[3] J. Schreiber,[1] and B. Dromey[2,*]

[1]*Fakultät für Physik, Ludwig-Maximilians-Universität München, 85748 Garching, Germany*

[2]*Centre for Plasma Physics, School of Mathematics and Physics, Queens University Belfast, Belfast BT7 1NN, United Kingdom*

[3]*The Dalton Cumbria Facility and the School of Chemistry, The University of Manchester, Oxford Rd, Manchester M13 9PL, United Kingdom*

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Thank you for your attention!