

Zebrafish Embryo Model of the FLASH Effect - In Regard to Böhlen et al.

Horst, F. E.; Brand, M.; Hans, S.; Karsch, L.; Leßmann, E.; Löck, S.; Schürer, M.;
Pawelke, J.; Beyreuther, E.;

Originally published:

February 2023

International Journal of Radiation Oncology Biology Physics 115(2023)4, 1006-1007

DOI: <https://doi.org/10.1016/j.ijrobp.2022.11.015>

Perma-Link to Publication Repository of HZDR:

<https://www.hzdr.de/publications/Publ-35212>

Release of the secondary publication
on the basis of the German Copyright Law § 38 Section 4.

CC BY-NC-ND

In Regard to Böhlen et al. “Normal tissue sparing by FLASH as a function of single fraction dose: A quantitative analysis”

Zebrafish Embryo Model of the FLASH Effect

Felix Horst PhD^{1,2}, Michael Brand PhD³, Stefan Hans PhD³, Leonhard Karsch PhD^{1,2}, Elisabeth Lessmann⁴, Steffen Löck PhD^{2,5,6}, Michael Schürer PhD^{2,7}, Jörg Pawelke PhD^{1,2}, Elke Beyreuther PhD^{2,4*}

- 1 Helmholtz-Zentrum Dresden – Rossendorf, Institute of Radiooncology - OncoRay, Dresden, Germany
- 2 OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden – Rossendorf, Dresden, Germany
- 3 Center for Regenerative Therapies TU Dresden and Cluster of Excellence 'Physics of Life', Technische Universität Dresden, Dresden, Germany
- 4 Helmholtz-Zentrum Dresden – Rossendorf, Institute of Radiation Physics, Dresden, Germany
- 5 Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
- 6 German Cancer Consortium (DKTK), Partner Site Dresden, and German Cancer Research Center (DKFZ), Heidelberg, Germany
- 7 National Center for Tumor Diseases Dresden (NCT/UCC), Germany: German Cancer Research Center (DKFZ), Heidelberg, Germany; Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; Helmholtz-Zentrum Dresden – Rossendorf, Dresden, Germany

Corresponding author:

*Elke Beyreuther (E.Beyreuther@hzdr.de)

Helmholtz-Zentrum Dresden – Rossendorf, Institute of Radiation Physics,
Bautzener Landstraße 400, 01328 Dresden, Germany
Tel: +49 351 458 7436

Author responsible for statistical analysis: Felix Horst (Felix.Horst@oncoray.de)

Conflict of Interest: None

Funding: None

Data sharing agreement: Research data are stored in an institutional repository and will be shared upon reasonable request to the corresponding author.

Acknowledgement: We acknowledge Till Tobias Böhlen and Raphaël Moeckli, the corresponding authors from the original manuscript for sharing their data with us and for fruitful discussions. This research was carried out at ELBE at the Helmholtz-Zentrum Dresden – Rossendorf e. V., a member of the Helmholtz Association. We would like to thank Rico Schurig, Pavel Evtushenko, Ulf Lehnert, Christoph Schneider and Peter Michel from the ELBE crew for support and their ongoing interest in our high-dose rate electron experiments. We thank Sandra Spieß and Daniela

Zöller for help with zebrafish embryo transfer and Marika Fischer, Sylvio Kunadt and Daniela Mögel from the animal facility for dedicated zebrafish care.

Böhlen et al. [1] recently proposed a model that describes the magnitude of the normal tissue sparing Flash effect as a function of dose based on available *in vivo* data. The newly introduced flash modifying factor *FMF* translates doses applied at ultra-high dose rate to equivalent doses at conventional dose rate similar to the concept of relative biological effectiveness [1]. Primarily founded on rodent data, the model [1] includes only one study that demonstrated a dose-dependent Flash effect by length differences measured at 5 days-old zebrafish embryo (ZFE) after irradiation with electron doses of 5 – 12 Gy [2]. We studied this systematic overview about the available Flash data with great interest and acknowledged it as a very useful guidance for future Flash research. Coincidentally, we have just recently measured ZFE data in the high dose range (15 – 50 Gy) that appear to match very well with the existing rodent data.

Comparable to our previous studies at the ELBE accelerator [3, 4], one day-old ZFE were irradiated using electron beams of reference (mean dose rate 0.11 Gy/s) and ultra-high dose rate (UHDR; mean dose rate 0.9×10^5 Gy/s). Normal tissue toxicity was quantified by analyzing the length deficit of the 5 days-old embryos compared to unirradiated controls (Fig. 1a). Since the controls grew on average 30% from irradiation to analysis this is the maximum length deficit that can be caused by irradiation. The derived *FMF* values extend the available ZFE data [2] and cover in a single experiment almost the entire dose range applied in the rodent studies for different tissues. Comparable to the rodent data (Fig. 1b) the ZFE *FMF* increases with dose.

The good agreement of our ZFE data with the rodent data [1] demonstrates the feasibility of the ZFE model for basic Flash effect studies, e.g., on the influence of physical beam parameters [3–6]. Hence, the ZFE model could be deployed as a high-throughput alternative to rodent studies at this translational level [5] promising the exploration of a large dose and dose rate range of clinically relevant beams.

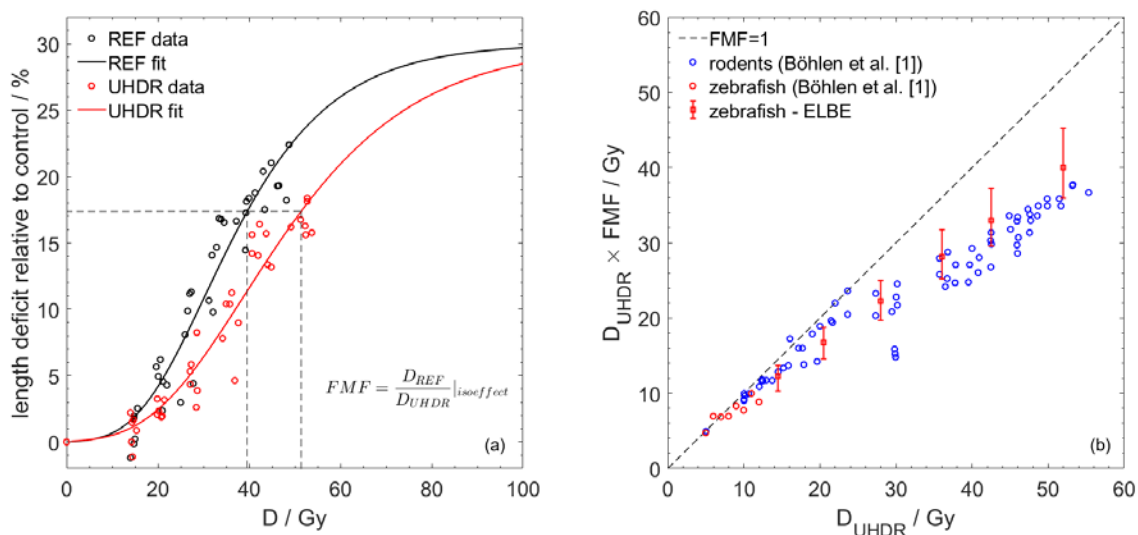


Figure 1: (a) Relative length deficits determined for 5 days-old ZFE following reference (black) and UHDR (red) irradiation. Dose dependent length deficits were fitted using a model based on Poisson statistics ([7], MATLAB R2021b). (b) *FMF* obtained for the recent experiment at ELBE (red triangles; *FMF* uncertainties derived from the fit; uncertainty of absolute dose was estimated $\leq 10\%$ [3]) overlaid with the original *FMF* data ([1], dots).

References

1. Böhlen TT, Germond J-F, Bourhis J, et al (2022) Normal Tissue Sparing by FLASH as a Function of Single-Fraction Dose: A Quantitative Analysis. *Int J Radiat Oncol*.
<https://doi.org/10.1016/j.ijrobp.2022.05.038>
2. Vozenin M-C, Hendry JH, Limoli CL (2019) Biological Benefits of Ultra-high Dose Rate FLASH Radiotherapy: Sleeping Beauty Awoken. *Clin Oncol* 31:407–415.
<https://doi.org/10.1016/j.clon.2019.04.001>
3. Pawelke J, Brand M, Hans S, et al (2021) Electron dose rate and oxygen depletion protect zebrafish embryos from radiation damage. *Radiother Oncol* 158:7–12.
<https://doi.org/10.1016/j.radonc.2021.02.003>

4. Karsch L, Pawelke J, Brand M, et al (2022) Beam pulse structure and dose rate as determinants for the flash effect observed in zebrafish embryo. *Radiother Oncol* 173:49–54. <https://doi.org/10.1016/j.radonc.2022.05.025>
5. Grilj V, Kacem H, Cherbuin N, et al (2022) FLASH Modalities Track (Oral Presentations) A PURSUIT FOR A HIGH-THROUGHPUT INDICATOR OF THE FLASH EFFECT. *Phys Medica Eur J Med Phys* 94:S7. [https://doi.org/10.1016/S1120-1797\(22\)01457-0](https://doi.org/10.1016/S1120-1797(22)01457-0)
6. Kacem H, Psoroulas S, Boivin G, et al (2022) Comparing radiolytic production of H₂O₂ and development of Zebrafish embryos after ultra high dose rate exposure with electron and transmission proton beams. *Radiother Oncol*. <https://doi.org/10.1016/j.radonc.2022.07.011>
7. Begosh-Mayne D, Kumar SS, Toffel S, et al (2020) The dose–response characteristics of four NTCP models: using a novel CT-based radiomic method to quantify radiation-induced lung density changes. *Sci Rep* 10:10559. <https://doi.org/10.1038/s41598-020-67499-0>