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

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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

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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.

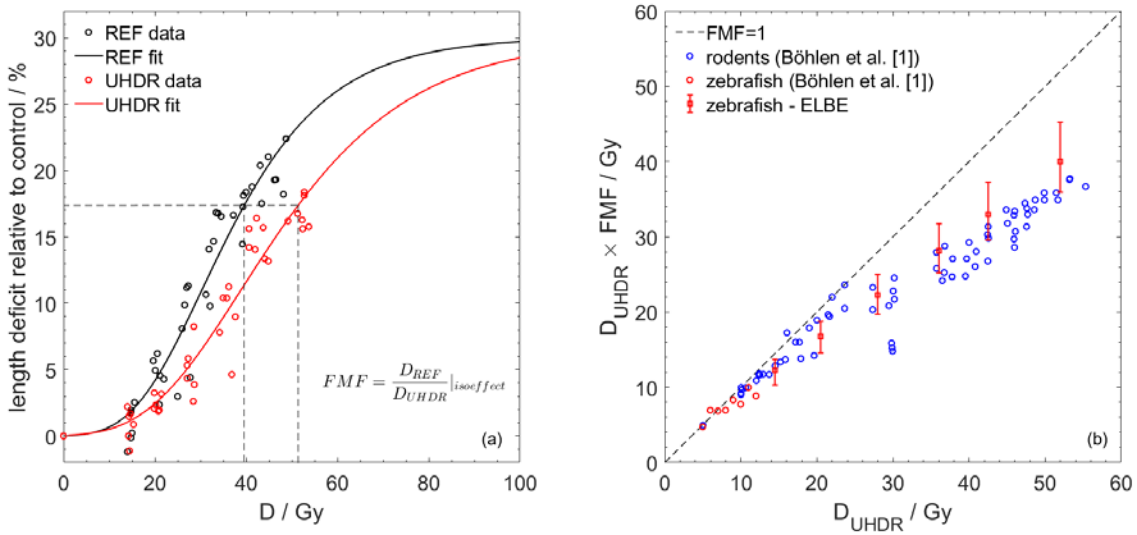

Figure 1: (a) Relative length deficits determined for 5 days-old ZFE following reference (black) and UHDR (red) irradiation. Dose dependent length deficits were fitted using a model based on Poisson statistics ([7], MATLAB R2021b). (b) *FMF* obtained for the recent experiment at ELBE (red triangles;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

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