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AN INTRODUCTION LETTER

All Irradiations that are Ultra-High Dose Rate may not be FLASH: The Critical Importance of Beam Parameter Characterization and *In Vivo* Validation of the FLASH Effect

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The recent surge of interest in ultra-high-dose-rate ''FLASH'' radiotherapy (FLASH-RT) has opened a flood of investigations and a deluge of reviews trying to define, capitalize, validate and rationalize this intriguing phenomenon. While the field is primed for carefully conducted investigations ranging from physics to chemistry and biology implementing a number of model systems, care must be taken not to rush, and jeopardize the advancement of this promising yet burgeoning field of study. Moving forward requires a prudent approach, with an accumulated knowledge that certain prerequisite conditions must be established and defined such that data sets can be placed in the proper context as multidisciplinary research efforts converge and collaborate to critically evaluate the translation potential of FLASH-RT.

With this perspective, we highlight the critical features that investigators should try and incorporate as they initiate their research into ultra-high-dose-rate radiation science. By adopting and evaluating the important considerations detailed below, the development of further experimentation necessary to move the field of FLASH-RT forward in an unbiased, productive and efficient manner will only be hastened.

First, and critical to all FLASH studies, it is essential to provide specific information related to the physics parameters of the irradiation beam (*1, 2*). Unfortunately, these details have been frequently omitted for certain investigations, details that are fundamental to critically evaluate whether or not optimal beam delivery conditions were implemented to observe the FLASH effect. The physics parameters are of utmost importance and need to be properly documented when attempting to rigorously test whether the stated conditions are sufficient for normal tissue sparing at ultra-high dose rates. Details regarding the prescribed dose delivery as well as its dosimetry verification are also absolutely necessary. While FLASH-RT has been mainly characterized using the mean dose-rate ($\geq$ 40 Gy/s for FLASH-RT vs. $\geq$ 0.01 Gy/s for CONV-RT) (*3*), this definition has proven to be overly simplistic (*4, 5*). The full characterization of FLASH-RT is much more complex as it involves several inter-dependent physical parameters that need to be properly recorded for analysis and interpretation of the data [see Supplementary Data in (*4*)]. Our recent analyses show that the instantaneous dose-rate and the overall time of irradiation can be considered as two of the critical parameters (*6*). In addition, and with respect to pulsed electron beam structure, the pulse dose, number, interspacing (given by the repetition frequency) and width as well as the total duration of exposure although interdependent will impact the biological outcome (*1, 2*). Geometric parameters of the irradiation including volume specifications (i.e., amount of exposed tissue) are also important factors (*5, 6*).

Second, the FLASH effect is defined as a biological effect, best characterized in vivo, and any validation of a FLASH beam needs the combination of carefully selected physical parameters along with rigorous biological validation. Validation and/or refutation of the FLASH effect must be coupled with robust methodology supported at least by *dose rate escalation*. While we are cognizant that present technology limits the investigation of the FLASH effect, positive biological data have been generated with various devices including dedicated linacs *(1–3, 7*) and modified clinical linacs (*8, 9*). New results can be found in the present Focus Issue of *Radiation Research* that have included tables with specific beam parameters.

Third, *in vitro* experimentation does not substitute for in vivo validation, and in the former, attention must be paid in particular to the prevailing oxygen tension. While data and arguments for and against the oxygen hypothesis have stimulated lively scientific exchange, attention to detail is again critical, as there is a rich history of previously

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published studies describing the oxygen dependence of the FLASH effect (*10, 11*). Past and present work (*12*) showing that in vitro radioprotection cannot be observed under atmospheric conditions (21% oxygen) at doses below 20 Gy support the contention that carefully controlled studies should be replicated under physiological oxygen tension in efforts to provide meaningful mechanistic insight regarding the oxygen hypothesis.

In summary, FLASH radiotherapy and the FLASH effect are generating intense interest in the radio-oncology community, as these may significantly change oncology practice at reasonable cost. As with any innovation, it must be carefully investigated and evaluated by several independent investigators. Modeling approaches are also useful and accordingly, numerous theoretical frameworks including the role of redox biology and tissue oxygenation have been published recently *(13–17*). Ultimately, all such models will require data from carefully conducted experiments, and reporting of critical beam parameters over and above mean dose rates. Inclusion of such detail will help the field resolve the discrepancies in the literature where negative effects have been reported (*18–20*). In those instances, instantaneous dose rates may have been insufficient for the volumes irradiated, as similar (albeit not identical) experimental set-ups have found positive FLASH effects using synchrotron and proton beams (*21, 22*). Moving forward, we suggest that for future FLASH related publications, a table reporting the full physical parameters of the beam should be included. In the end however, it's important to remember that the FLASH effect is a *biology effect*, and this fact should drive our future efforts at defining the details of this innovative radiation modality more completely.

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