Deutsches Elektronen-Synchrotron DESY
Ein Forschungszentrum der Helmholtz-Gemeinschaft

WHITE PAPER

Support the build-up of FLASH*lab*@PITZ and make it available for the FLASH RT and radiation biology communities

FLASH*lab*@PITZ - a multidisciplinary R&D platform under preparation at the Photo Injector Test facility at DESY in Zeuthen (PITZ) allowing R&D on FLASH radiation therapy and radiation biology in an uniquely wide parameter range

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Table of Contents

Executive Summary

The recent observation that radiation therapy treatments with ultra-high dose rate (UHDR) and sufficiently high total dose in short time intervals leads to considerably less toxicities at equal therapeutic response of the tumor, elicited enormous resonance in the radiation oncology community. Radiation oncologists around the globe strive for a rapid clinical exploitation of the differential response of tumor and normal tissue, which was termed FLASH effect.

Many of the ultra-high dose rates (UHDR) and FLASH radiation therapy (RT) community's recommendations on future research focus areas could be addressed in the coming years with the expansion of the FLASH*lab*@PITZ R&D. The extremely wide parameter range for studying electron UHDR and FLASH RT accessible at the PITZ facility at DESY together with its full flexibility and tight beam control capabilities gives worldwide unique opportunities to push forward the understanding, optimization and application of UHDR and FLASH RT[1].

The unique beam parameters of the PITZ accelerator could transform the facility into one of the leading radiation oncology research centers with a focus on FLASH and spatially fractionated radiation therapy exploring the translation of elementary radiation research questions into safe clinical trials.

I. Introduction

Cancer, responsible for 19.3 Mio new cases and 10 Mio deaths worldwide in 2020[2], is predicted to further expand up to 30.2 Mio new cases and 16.3 Mio deaths annually by the year 2040[3]. Radiation therapy (RT) is a common cost-effective standard of cancer care, primarily applied to cure localized tumors. Around half of all cancer patients receive radiation therapy as part of the disease management. Given the high number of affected patients, advances in the field of radiation oncology have substantial socio-economic implications.

Preclinical studies have shown that radiation delivery at ultra-high dose rates (UHDR) and sufficiently high total dose in short time intervals elicit the so-called FLASH effect that maintained anti-tumor efficacy and spared normal tissue as compared with standard dose rates, used in RT clinical practice[4–6]. However, the fundamentals of the effect are yet very poorly understood and research of many radiation oncology research groups is trying to explore the underlying radiobiological mechanisms[7–9]. Among others it remains unclear, which parameters are required to trigger the FLASH effect. It is of critical importance to probe the new UHDR parameter space which became accessible with recent cutting-edge technical advances in accelerator physics. Online tumor imaging can help targeting the radiation field with any moving tumor and realize conformal FLASH RT even for extremely short treatment times. Combinations with other innovative RT modes, such as spatial fractionation and adjuvant treatments such as chemo- and immunotherapy, have the potential to further improve RT outcome. Taken together, the listed measures could substantially widen the therapeutic window in radiation oncology and have the potential to keep tumor control while decreasing side effects, treat radioresistant cancer and reduce metastasizing, that allows new treatment options, shortens treatment time by several thousand times and ultimately offers not only comfort to the patient but also economic advantages.

The PITZ facility provides unique beam parameters and hence, can play an important future role to systematically explore the parameter range in FLASH radiation therapy. With the aim of a successful clinical translation, the extreme pulse structure and dose rates achievable at PITZ can help identifying necessary source parameters to evoke a FLASH response, probe the limits in radiochemical and radiobiological mechanisms and investigate the feasibility of new detector systems.

In order to become one of the leading centers for radiation oncology research of FLASH radiation therapy, the PITZ accelerator will undergo a careful dosimetry characterization of the treatment beam, the beam control units can be adapted for biological research, prerequisites for high-throughput preclinical work will be established and state-of-the art biological lab-facilities have to be set-up.

Prospectively, we aim for a clinical translation of research data. We will start with veterinary clinical trials to test safety and effectiveness of the developed RT modality. Ultimately, we envision clinical trials at PITZ, with a carefully identified patient cohort.

II. Key thesis

With this statement, we highlight the need to exploit a new territory of UHDR radiation with bunch lengths in the picosecond time range, single bunch doses and dose rates up to extremely high levels, and flexible choice of bunch timing structure and beam manipulation (e.g. beam size and beam scanning) available at FLASH*lab*@PITZ. The PITZ facility allows R&D on electron UHDR RT with radiation pulses that are up to 6 orders of magnitude shorter than what was usually used up to now in FLASH RT. Still the dose per bunch can be freely adjusted in the range from 0.02 to 1000 Gy in a 1 mm^3 volume by adjusting the electron bunch charge. This allows single bunch dose rates in the range from 10^9 Gy/s to 10^{14} Gy/s, which would allow testing of dose rates from those currently accessible to values up to 4 orders of magnitude higher than what is used for FLASH RT up to now (see Support Information, Fig.1 and Table 1). The electron beam energy currently available at PITZ is up to 22 MeV.
To summarize the unique capabilities of the electron bunches and their time structure, PITZ will allow a new approach to FLASH RT with:

- an individual bunch charge tunable over more than 5 orders of magnitude to the wanted local radiation dose and dose rate,
- a bunch length adjustable over about a factor 10 for fixed bunch charge to tune the wanted instantaneous dose rate for fixed dose per bunch,
- a beam size adjustable to match the tumor size or for scanning the tumor area with pencil beams allowing local dose variation,
- a bunch repetition rate and bunch train length tunable over 3 orders of magnitude to adjust the local dose and the average dose rate,
- a bunch train repetition rate adjustable between 1 and 10 Hz to tune the local dose

and the average dose rate by another factor 10.

In that way, the PITZ facility with a uniquely large range of available irradiation parameters would allow to do systematic studies to demonstrate under which conditions the FLASH effect is present and optimize the FLASH effect. A flexible tuning of irradiation parameters (like total dose, peak and average dose rate, irradiation time, spatial fractionation) and the treatment conditions (like oxygen concentration) will help to get insight into the FLASH mechanism. To perform key experiments, new detectors systems have to be developed and tested to reliably measure the delivered doses and dose rates in the full parameter range that is needed for the experimental studies. For the PITZ beam dosimetry an existing collaboration with the PTB in Braunschweig and the UHDpulse Consortium is already established and DESY has access to most modern dosimetry detectors that are developed in this consortium. In addition, with DESY's decades long experience in radiation hard high energy physics detectors, own approaches and those from other external partners can be tested. Further, a careful modelling of the experiments will be needed to verify or falsify different approaches of explaining the FLASH effect in conjunction with the experiments. Very good capabilities for in vivo experiments are mandatory since the leading conception defines the FLASH effect to have biological nature and to be proved to a higher extend at the organism level[10]. For the biological observation characterized in vivo, small animal model organisms are required to validate the FLASH effect. Currently, a first version of an animal lab container system is being prepared and installed to allow for a quick start up of in vivo experiments. Medium/long term infrastructure installations required for cutting edge research in FLASH RT include a well-equipped animal facility: small animal imaging CT/MRT/PET, histology, histochemistry, molecular biology (e.g. RT-PCR, flow cytometry), microscopy facilities. Possibly veterinarian trials may be good intermediate step to demonstrate feasibility and safety of the UHDR and FLASH RT at PITZ.

The core infrastructure and a multidisciplinary team of scientists are established at FLASH*lab*@PITZ that enable the first studies. The flexible and reliable machine PITZ offers reproducible, controlled and characterized beam parameters due to decades long experience in accelerator operation for leading FEL facilities like European XFEL and sufficient empty space for experimental area in shielded environment. Close collaboration with the neighboring Technical University, which is experienced in molecular biology and cancer treatment development as well as has required laboratory environment, enables on-site chemical and biological in vitro studies. Close collaboration with leading groups worldwide, which are eager to do experiments at PITZ, is established. Moreover, PITZ already works together with the Charité - Berlin University of Medicine on the investigation of UHDR radiation biological effects that enable to align research with the clinic requirements.

The extremely wide parameter range accessible at PITZ (from yet unexploited, extremely high dose rates via currently used FLASH RT dose rates down to dose rates comparable to conventional RT) together with the full flexibility of the facility, its tight beam control capabilities and strong infrastructure would give worldwide unique opportunities for systematic R&D on UHDR and FLASH RT. There is high potential that the studies done around FLASH*lab*@PITZ (experimental studies, simulations studies, test of theoretical hypotheses) can have a major contribution to the worldwide effort in defining the future directions of UHDR and FLASH RT and making the best options of this new treatment modality available for regular clinical use.

III. Question to you

If you like to support the activities around FLASH*lab*@PITZ by e.g. performing own experiments at FLASH*lab*@PITZ, providing simulations studies, proposing theoretical models that can be tested experimentally, providing person power or hardware for the operation or the experiments or any other support, please send a short document to frank.stephan@desy.de in which you clarify your support for FLASH*lab*@PITZ by e.g. answering the following questions:

- Which key capabilities of FLASH*lab*@PITZ would you like to exploit ?
- Which key experiments would you like to perform at FLASH*lab*@PITZ or which theoretical model would you like to test at FLASH*lab*@PITZ ?
- Which own resources (e.g. investments, person power, knowledge or own capabilities) do you plan to invest in preparing your sample/detector/simulation/theoretical model and preparing, performing and analyzing your experiment and publishing the results ?

IV. References

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V. Support Information

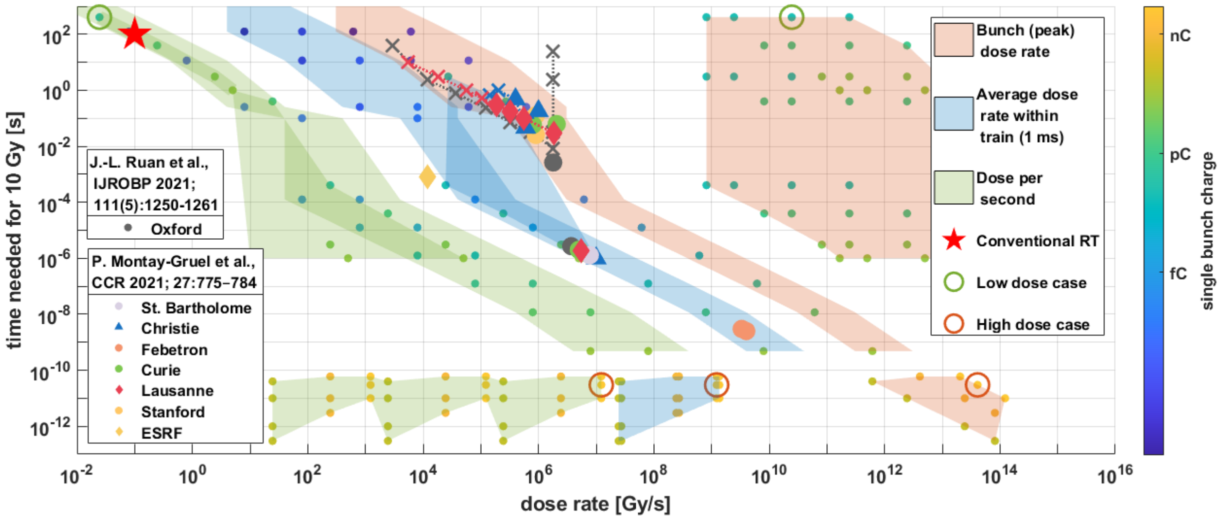

Fig. 1. The worldwide unique parameter space available at PITZ in comparison with state-of-the-art FLASH RT and conventional radiation therapy. *The vertical axis shows the time needed to deliver 10 Gy and the horizontal axis shows the dose rate for 3 different estimations: The red area shows the available bunch or peak dose rates; the blue area shows the available average dose rates within the bunch trains and the green area shows the available dose rate averaged over a full second. The color of individual dots represents the bunch charge that was assumed for the individual PITZ operation parameter set (see legend on the right). The two conditions listed in Table 1 are marked with circles. The conditions to obtain reproducible FLASH effects are included as fully filled data points in the center of the plot and cases which could not prove the FLASH effect are marked with crosses as summarized by the two mentioned publications. A star is added to represent conventional radiation therapy in the upper left corner. The PITZ parameter space available on the right side of and below the colored markers displayed in the center of the plot is yet unexplored and unexploited territory and gives potential for further improvement of FLASH RT in future. It must be noted that the colored areas show parameter combinations, which can be obtained quite easily, but none of the colored areas are sharp edged, since the parameter range can also be extended beyond the colored areas. For the dose and dose rate values the energy deposition of a 20 MeV electron beam over 1 mm depth in water and using a 1 mm² spot size was estimated.*

Table 1. List of some key operation parameters of PITZ for two (extreme) cases. *The bunch charge is the charge within a single electron bunch (i.e. within one RF cycle) and can be freely chosen. The user can also choose if a single bunch or a train of bunches is wanted. The RF pulses in which the single bunches or bunch trains are accelerated can have a length of up to 1 ms and can be repeated with a repetition rate between 1 and 10 Hz. The single bunch length is adjustable by laser shaping, RF phasing and the bunch compressor. The doses and dose rates are calculated per bunch (D_{bunch} and $\dot{D}_{bunch}$), per bunch train (i.e. within 1 ms, D_{train} and $\dot{D}_{train}$) and per second ($\langle\dot{D}\rangle$, average dose rate) depending on the parameters chosen in the upper lines of the table. For the dose and dose rate values the energy deposition of a 20 MeV electron beam over 1 mm depth in water and using a 1 mm² spot size was estimated.*

Options @PITZ	**Low dose case**	**High dose case**
Bunch charge [pC]	0.1	5 000
Individual bunches OR train	single bunch	1ms train, (i.e.1000 bunches)
RF pulse rep. rate	1 Hz	10 Hz
Bunch length [ps]	<1	~30
Dose (D_{bunch}) **per bunch** [Gy]	0.02	1000
Dose rate ($\dot{D}_{bunch}$) **per bunch** [Gy/s]	2x10^{10}	4x10^{13}
Dose (D_{train}) **per train** (ms) [Gy]	0.02	1x10^{6}
Dose rate ($\dot{D}_{train}$) **per train** (ms) [Gy/s]	20	1x10^{9}
Dose **per second** ($\langle\dot{D}\rangle$) [Gy/s]	0.02	1x10^{7}

VI. Responses from the scientific community

Here we will collect your support letters.

Impressum

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