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Academic title and name: M.Sc., Eleni Kanouta

Project title: Enabling safe delivery of proton FLASH therapy using an ultra-fast in vivo dosimetry system.

Background

FLASH Therapy

Recent pre-clinical studies have demonstrated remarkable normal tissue sparing with unchanged tumor growth delay during radiotherapy (RT) if the dose is delivered 1000 times faster than current standard of practice (1-4).This type of RT is called FLASH therapy. It is considered one of the most promising advances in radiotherapy, due to the clear therapeutic benefit, and the first patient was recently treated for a skin lymphoma with electron FLASH (5). Unlike electron FLASH, which can only treat superficial tumors, proton FLASH therapy has the potential to be scaled to broad clinical use since the proton dose can be shaped accurately to deep seated tumors.

The defining factor for FLASH therapy is the high dose rate. It is therefore essential to ensure that not only the correct total dose is delivered but also with the correct dose rate. However, current state-of-the-art dosimeters do not have the required temporal resolution to handle the high dose rates of FLASH. This poses severe constraints on any FLASH effect study.

Proton FLASH at DCPT

Current clinical proton delivery is too slow for FLASH (6), but FLASH dose rates can be achieved with beamline modifications (7), and the first normal tissue protection with proton FLASH was recently reported (8). In 2020, the experimental proton beamline at the Danish Centre for Particle Therapy (DCPT) will be upgraded to FLASH. FLASH dose rates are most easily obtained at high proton beam energies (~250MeV) which give large beam ranges (~35 cm). The first proton FLASH beams at DCPT will therefore be so-called transmission FLASH beams that pass through the entire irradiated subject, while the target is placed in the flat entrance dose plateau (Fig 1). Further beamline modifications will allow Bragg peak FLASH, where the spread-out Bragg peak with highest dose deposition coincides with the target and no dose is given beyond it (Fig 1).

With the proton FLASH beamline at DCPT, a series of radiobiological experiments will take place using a well-established mouse model setup for irradiation of mice legs submerged in a water bath (Fig 2)(9,10). Both transmission and Bragg peak FLASH experiments will be performed.

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Dosimetry for proton FLASH

While delivery of conventional proton therapy takes minutes, FLASH is given in a fraction of a second. The treatment is delivered with a narrow proton beam that scans over the target (Fig 3, left). To ensure correct FLASH delivery it is important to map out the dose delivered as function of time in each target point. The aim of this project is to develop an ultra-fast in vivo dosimetry system for exact dose and dose rate mapping during proton FLASH delivery.

A basic requirement for the dosimetry system is a high temporal resolution that allows several dose measurements within each proton spot, i.e. each of the tiny dose packets delivered by the scanning proton beam. The proton spot duration can be down to 1 ms, while commercial dosimetry systems only have time resolutions of up to around 10 Hz (every 100 ms). The time resolved dosimetry in this project will therefore be based on an in-house developed in vivo dosimetry system used clinically for brachytherapy (11). The system uses highly efficient inorganic ZnSe:O scintillator crystals to detect brachytherapy doses at 20 Hz. For proton FLASH dosimetry, this time resolution must be increased 1000-fold. It will be done by using faster photo multipliers and electronics. Studies have shown that dose detection with such a system allows a time resolution well above 1 kHz (12,13), which would give several dose measurements within each delivered proton spot (Fig 3, right). Similar to brachytherapy (11), we will combine the time resolved in vivo measurements in single points with treatment log files to reconstruct and map the time resolved dose and dose rate in each treated mice. In a preliminary study with relatively slow sample rates we have demonstrated such mapping for mouse treatments with conventional dose rates (Fig 4).

The system described above relies on beam profile assumptions and treatment log files for the dose and dose rate mapping. Furthermore, in a clinical setting it will only allow in vivo dosimetry with transmission FLASH beams because the crystals would perturb the target dose if placed before the target. Therefore, the crystals will be supplemented with fast two-dimensional (2D) plastic scintillator sheet dosimeters. Light emitted by the scintillator sheet when hit by the scanning proton beam can be imaged with a camera for direct 2D dose visualization with high spatial and temporal resolution (14-16). Dartmouth College is world leading in using fast camera based dosimetry, e.g. for detection of light emitted from patients' skin during radiotherapy (17). The Dartmouth group recently imaged 2D dose rate maps for a scanning proton beam with a detection rate of 100 Hz (Fig 5). In close collaboration with this group, we will develop fast scintillator sheet dosimetry for proton FLASH therapy and combine it with the crystal scintillators. Since the scintillator sheet perturbs the proton beam minimally, it can be placed on the entrance side of the proton beam providing ultra-fast in vivo dosimetry for all types of pre-clinical and clinical proton FLASH treatments.

The ultrafast in vivo dosimetry system developed in this project will be crucial to ensure correct conduction and interpretation of the preclinical proton FLASH experiments planned

at DCPT. It will also be crucial for securing safe clinical translation of proton FLASH in the future.

Part 1: Ultra-fast dosimetry in transmission proton FLASH therapy
The dosimetry system will be based on fiber coupled ZnSe:O scintillator crystals mounted behind the irradiated mouse legs in the pre-clinical studies (Fig 2). Preliminary results on conventional proton therapy show that the dosimetry system can be used for locating the detector position and mapping the delivered dose and dose rate (Fig 4). The dosimetry system is currently being scaled from one to four parallel detectors and the time resolution is increased to 50 kHz, which is sufficient for FLASH therapy.

Hypothesis
The dosimetry system allows mapping of the delivered dose and dose rate for proton FLASH therapy with 3% dose accuracy and 1mm spatial accuracy.

Research plan
The scintillator detector system will be optimized for both conventional and FLASH proton beams. The detector response and its dependence on dose, dose rate, proton energy, and 2D detector position will be thoroughly characterized to obtain a full detector calibration in the entrance plateau of conventional and FLASH transmission proton beams. Next, a computer algorithm will be developed to reconstruct dose and dose rate maps from the point detector measurements. The algorithm will first determine the exact position of each detector relative to the delivered proton spots (Fig 3). Then, it will reconstruct the entire 2D dose and dose rate maps relative to the detector positions in the measurement depth by combining measurements with treatment log files. The dosimetric and spatial accuracy of the system will be validated with film dosimetry.

Part 2: Ultra-fast dosimetry in Bragg peak proton FLASH therapy
The flat dose distribution along the beam axis of the transmission FLASH in Part 1 effectively reduces the dose mapping to a 2D problem. For Bragg peak FLASH, the dose will instead depend strongly on the depth, necessitating full 3D dose mapping.

Hypothesis
The dosimetry system can be extended to full 3D dose and dose rate mapping maintaining the 3 %/1mm accuracy.

Research plan
The in vivo dosimetry system of Part 1 will be extended to Bragg peak FLASH treatments (Fig 1). The detector calibration for transmission FLASH beams will be extended to 3D with response measurements as function of depth for determination of signal quenching effects in the Bragg peak (18). The mapping of dose and dose rate will be extended to 3D by exploiting

the steep dose gradient of the Bragg peak to determine the depth position of each dosimeter relative to the spread-out Bragg peak. The reconstructed doses will be compared with film dosimetry.

Part 3: Camera-based scintillator sheet dosimetry in proton FLASH therapy
The point scintillators will disturb the target dose if placed in the entrance beam path. An additional dosimetry method is needed for dose validation on the entrance side.
Hypothesis
The full FLASH dose and dose rate distribution in patients can be obtained by combining the scintillator point measurements with a 2D scintillator sheet dosimeter.
Research plan
The ultra-fast point dose measurements of Parts 1-2 will be supplemented with scintillator sheet dosimeters for direct imaging of the 2D proton dose with a fast and ultra-sensitive camera system. This system will be carefully calibrated against the crystal dosimeters and tuned for optimal trade-off between temporal resolution and noise. For in vivo dosimetry, the scintillator sheet will be placed at the beam entrance while the scintillator crystals will be placed downstream in the target depth. The crystal scintillator signal will be combined with the 2D sheet signal to reconstruct the entire 3D dose and dose rate maps with ultra-high frequencies well above 1 kHz. The combined dosimetry system will work for pre-clinical and clinical proton FLASH therapy with both transmission and Bragg peak beams.

Time schedule
Part 1 takes place during the first PhD year. Parts 2 and 3 start in parallel in the second PhD year. The stay abroad takes place in the second PhD year.

Research group and collaborators
All work will be performed by the applicant, **Eleni Kanouta**, unless stated otherwise. The applicant will finish her MSc in June 2020. The applicant has relevant experience with the scintillator dosimeters from her MSc project, which forms a strong foundation for the proposed PhD project. The main supervisor, **Prof. Per Poulsen** has extensive experiences in experimental medical physics and co-supervisor **Post doc. Jacob Johansen** is leading the scintillator dosimetry research for brachytherapy at AUH. The project involves a research visit at Dartmouth College, USA to the world leading group on camera-based dosimetry. Co-supervisor **Ass. Prof. Petr Bruza**, Dartmouth, will provide expertise on the scintillator sheet dosimetry and support its installation at DCPT. Collaboration with DCPT research leader **Prof. Cai Grau** ensures alignment and close integration with other research and clinical activities at DCPT, facilitating clinical translation of proton FLASH therapy in the

future. Collaborator **Ass. Prof. Brita Sørensen,** Department of Experimental Clinical Oncology, will lead the pre-clinical mouse FLASH study.

Feasibility

All infrastructure needed for the project is available. The experimental proton beamline at DCPT will be upgraded for FLASH in 2020 and the setup for the in vivo dosimetry is already established. The scintillator crystal dosimeter was developed during the applicant's master's project and preliminary results of its use with conventional proton dose rates support the feasibility of the project. The project is highly technical and will be very useful for the clinical translation of FLASH. No clinical study is planned during the project and therefore no power analysis will be conducted.

Perspectives

Developing radiation techniques that spare normal tissue without compromising tumor control is central to modern RT. If proton FLASH therapy is demonstrated to preferentially spare normal tissue in general, it could revolutionize cancer management and enable treatment of new cancers that cannot be treated today due to unacceptable toxicity risks. The ultra-fast in vivo dosimetry system developed in this PhD project will enable the first proton FLASH therapy experiments in Denmark. Scaling of proton FLASH therapy to the clinic is an active research area (19) and this project will be very important for the clinical translation.

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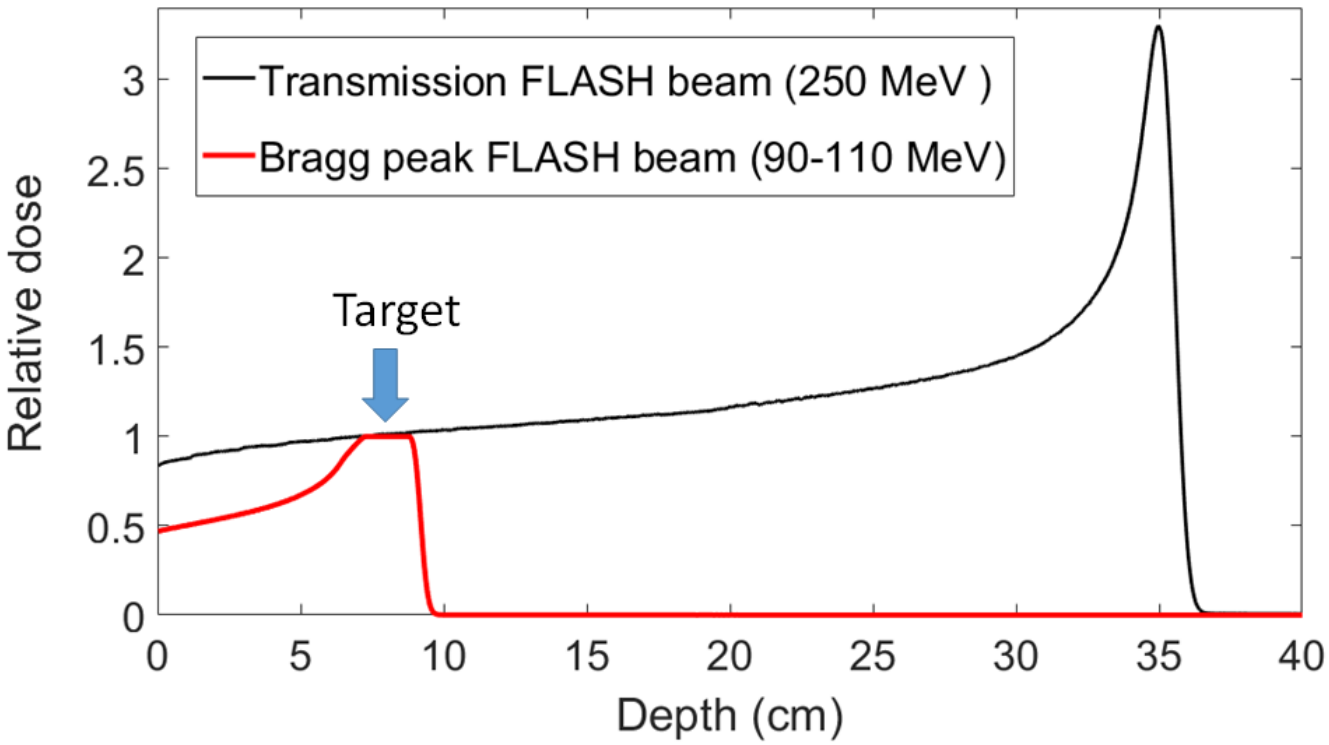

Figure 1. Relative proton dose as function of depth for a target in the depth marked with an arrow for a transmission FLASH beam (black) and a Bragg peak FLASH beam (red). The transmission beam gives dose throughout the irradiated subject while the Bragg peak beam gives a uniform dose across the target and no dose beyond the target [Poulsen, unpublished].

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Figure 2. Right: Mouse mounted in holder with a plastic bar supporting the right hind leg. Left: Zoomed view of the mouse holder with the mouse leg submerged in water for proton beam irradiation. A prototype fiber-coupled ZnSe:O scintillation crystal dosimeter is mounted behind the mouse leg target as seen from the proton beam [Poulsen et al., unpublished].

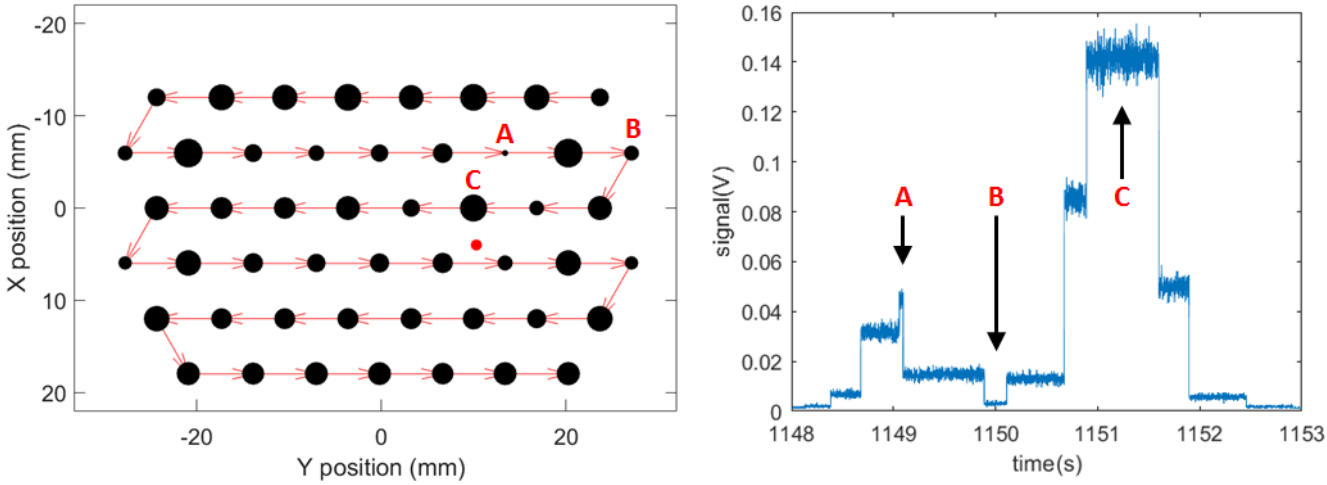

Figure 3. Left: Example of scan pattern for a scanning proton beam used for pre-clinical mouse irradiation at DCPT. The proton beam starts in the upper right corner and follows the red arrows, while it stops and delivers dose in the positions marked with black dots (so-called proton spots). The size of the black dots is proportional to the proton dose delivered in each spot. The red dot indicates the position of the dosimeter of Figure 2 as seen in beam's eye view. Right: Signal detected by the dosimeter as function of time. The detector signals marked with A, B, and C correspond to the spots marked in the same way in the left figure. The signal durations (in the right figure) are proportional to the spot dose (i.e. the dot size in the left figure). The signal height increases as the spots move closer to the detector, resulting in a high signal for spot C. Such information allows exact determination of the detector position within the scan spot pattern by triangulation, which again

allows reconstruction of the doses and dose rates as function of time in the vicinity of the detector [Poulsen et al., unpublished].

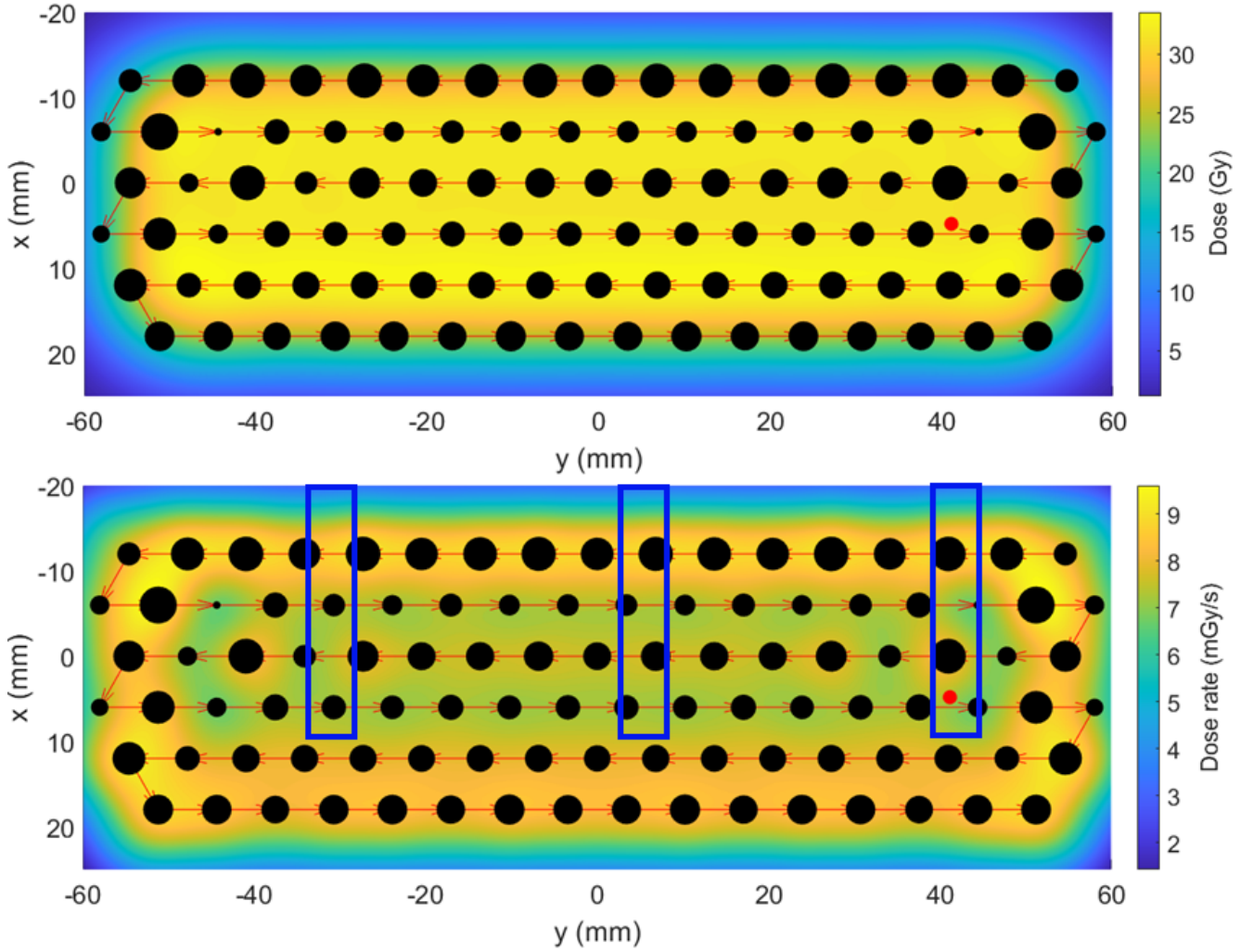

Figure 4. Maps of total dose (top) and dose-weighted mean dose-rate (bottom) in the depth of the detector determined from the time resolved dose measured with a single detector (red dot) during proton irradiation of mice at conventional dose rates. The black dots show the spot pattern. The blue rectangles indicate the leg positions of the three mice irradiated in this experiment. Note that FLASH requires dose rates about 1000 times higher than in this experiment [Poulsen et al., unpublished].

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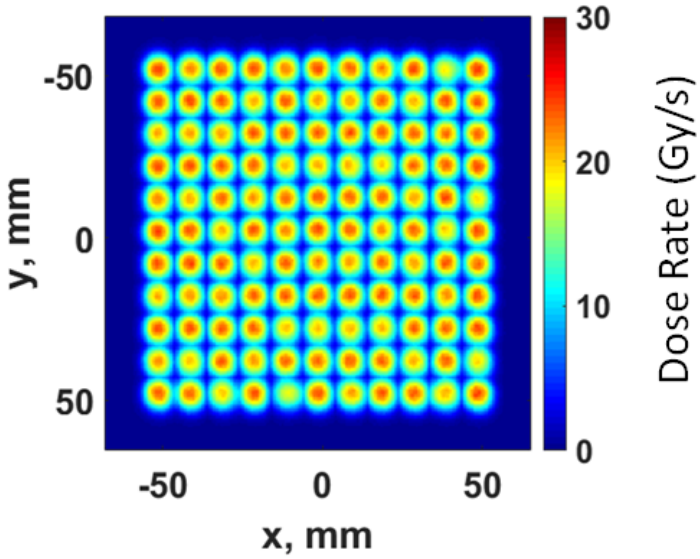

Figure 5. The spatial dose rate distribution of a standard proton beam measured with a fast camera using a scintillator sheet. [Bruza, unpublished].