Towards a novel small animal proton irradiation platform – the SIRMIO project

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Towards a novel small animal proton irradiation platform – the SIRMIO project

Background: Precision small animal radiotherapy research is a young emerging field aiming to provide new experimental insights into tumor and normal tissue models in different microenvironments, to unravel complex mechanisms of radiation damage in target and non-target tissues and assess efficacy of novel therapeutic strategies. For photon therapy, modern small animal radiotherapy research platforms have been developed over the last years and are meanwhile commercially available. Conversely, for proton therapy, which holds potential for an even superior outcome than photon therapy, no commercial system exists yet.

Material and methods: The project SIRMIO (Small Animal Proton Irradiator for Research in Molecular Image-guided Radiation-Oncology) aims at realizing and demonstrating an innovative portable prototype system for precision image-guided small animal proton irradiation, suitable for installation at existing clinical treatment facilities. The proposed design combines precise dose application with in-situ multi-modal anatomical image guidance and in-vivo verification of the actual treatment delivery.

Results and conclusions: This manuscript describes the status of the different components under development, featuring a dedicated beamline for degradation and focusing of clinical proton beams, along with novel detector systems for in-situ imaging and range verification. The foreseen workflow includes pre-treatment proton transmission imaging, complemented by ultrasonic tumor localization, for treatment planning and position verification, followed by image-guided delivery with on-site range verification by means of ionoacoustics (for pulsed beams) and positron-emission-tomography (PET, for continuous beams). The proposed compact and cost-effective system promises to open a new era in small animal proton therapy research, contributing to the basic understanding of in-vivo radiation action to identify areas of potential breakthroughs for future translation into innovative clinical strategies.

Keywords: small animal irradiation; proton therapy; image guidance

Introduction

Biological understanding of the microenvironment response to radiation, both in terms of tumor and normal tissue, is still an unmet challenge of modern radiation therapy [1]. Especially for light ions, uncertainties remain in the clinically adopted values of relative biological effectiveness, and new intriguing questions emerge from recent findings of signalling pathways quite distinct from those of cell and tissue response to photons [2]. In-vivo pre-clinical studies in small animals can help elucidating these questions, but require accurate dose delivery to tiny structures. While this is possible for photons at precision image-guided radiation research platforms, meanwhile commercially available [3], pre-clinical experiments with ions are still predominantly carried out in experimental rooms of clinical facilities, without dedicated beamlines and image guidance for accurate irradiation. Common delivery solutions feature either collimation of passively scattered broad beams or scanned pencil-like beams, moderated in range by thick degraders before entering the animal. Both methods exhibit limitations in terms of flexibility (for static collimation), beam intensity (due to attenuation, especially in collimated systems), activation of beam-shaping materials (posing radiation protection issues) and secondary neutron production (potentially affecting biological outcome). For uncollimated low-energy scanned beams, upstream scattering limits their smallest lateral size to a few (tens of) millimeters full width at half maximum (FWHM) at isocenter [4,5], where irradiation is typically performed for optimal dosimetric conditions. In treatment planning, small animals are often approximated as homogeneous water, without using imaging data to infer the tissue stopping power properties for animal-specific range calculation. Moreover, positioning the animal for treatment typically relies on external reference lasers and custom-made holders, without internal morphological imaging. The resulting non-negligible range uncertainties affect correct placing of the maximum dose deposition (Bragg peak) in the tumor, thus restricting the class of viable experiments and raising concerns on their reliability, relevance and scalability. Therefore, alternative solutions were recently proposed to utilize dedicated low-energy ion accelerators, detached from clinical sites, along with X-ray image guidance solutions from small animal photon irradiators [6]. In contrast, the project SIRMIO (Small Animal Proton Irradiator for Research in Molecular Image-guided Radiation-Oncology) proposes a portable beamline

equipped with novel detector technologies for integration in clinical facilities, providing a tight connection between radiation oncologists and biologists for precision image- and dose-guided small animal proton radiation research.

Material and methods

The relevant components and dedicated developments of the SIRMIO platform are addressed in five synergistic work packages depicted in figure 1 and described in the following.

Beam Degradation, Focusing and Monitoring

Monte Carlo (MC) particle transport simulations using Geant4 (version 10.04.p02 [7]) were carried out in combination with beam-optics modelling based on the code *elegant* [8] to optimize the design of the SIRMIO beamline. The current layout foresees initial energy degradation and collimation of a 75 MeV proton beam from a clinical facility [9], followed by active magnetic focusing for achieving a sufficiently narrow beam at the focal point, where the mouse tumor will be positioned. For simplicity and compatibility to generic experimental beamlines of proton therapy centers, the first SIRMIO beamline is designed for focusing a fixed horizontal pencil-beam, while moving the animal for volumetric scanning irradiation. Beam characteristics downstream of the beamline close to the treatment isocenter are monitored using a segmented ionization chamber providing spatial beam profiling and total fluence measurement. This detector has been developed in-house and commissioned with 22 MeV protons in an experimental campaign at the Tandem accelerator of the Maier-Leibnitz-Laboratory (MLL), Garching.

Mouse Holder

A mouse holder is developed in-house to provide animal fixation in vertical position for optimal transmission imaging conditions. Major challenges accounted for include biological requirements of sterility, anaesthetization and temperature stabilization, along with minimal material budget to limit beam broadening and degradation of transmission ion imaging performances, as well as to ensure acoustic coupling for ultrasound (US)/thermoacoustic imaging.

Pre-Treatment Imaging

Proton radiographic and tomographic transmission imaging will provide pre-treatment anatomical image guidance for target positioning and 3D maps of tissue stopping power relative to water (RSP) for treatment planning with potentially better range calculation accuracy than using X-rays. To this end, two imaging setups based on integration and single particle detection are under development. The first system, especially tailored to facilities with accelerators of instantaneous beam currents impeding single particle tracking (e.g. synchro-cyclotrons), relies on a large-area CMOS sensor for spatially resolved energy loss measurements at multiple probing energies, similar to [10]. The second system is based on the in-house development of low material budget Micromegas tracking detectors and a time projection chamber with Micromegas readout structure containing multiple Mylar absorbers functioning as range telescope. Both system designs are investigated and optimized based on extensive MC simulations using FLUKA (version 2011.2x-5, [11,12]). For tumor visualization in daily treatment planning and adaptive workflows, gold nanoparticle-enhanced proton imaging and microbubble-

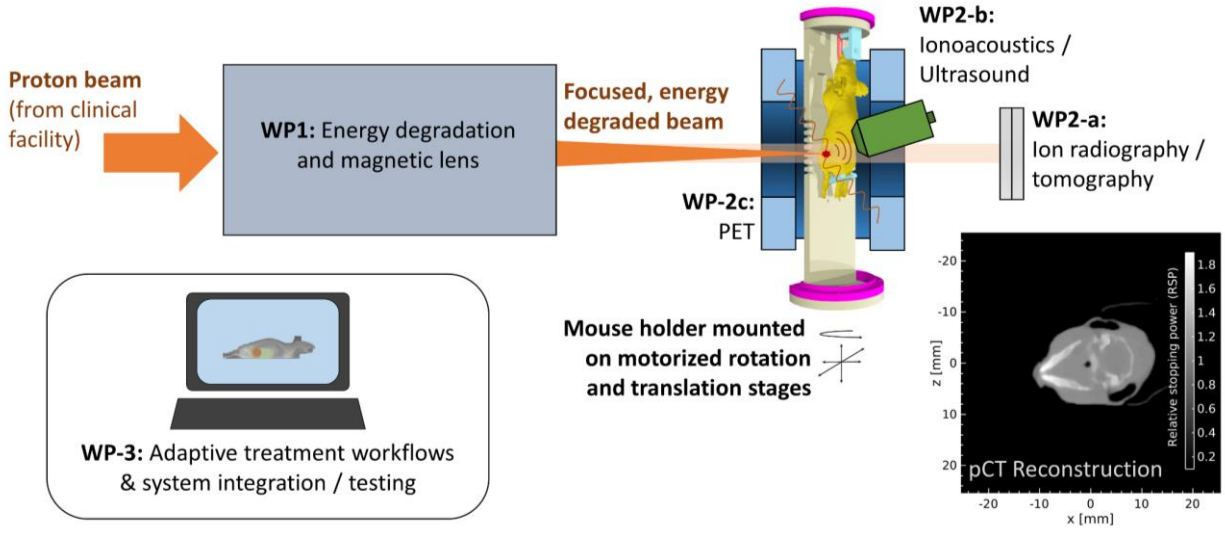

Figure 1: *Schematics of the SIRMIO project with related work packages (WPs), featuring: 1) manipulation of an incoming clinical proton beam into a focused and energy-degraded pre-clinical beam (WP1), 2) pre-treatment ion transmission imaging (WP2-a), with corresponding MC simulated "pCT reconstruction" slice based on the expected performance of the proposed single particle imaging system (see Pre-treatment imaging), 3) in-vivo range verification with ionoacoustics/US (WP2-b) and 4) PET (WP2-c), 5) system integration and deployment for adaptive treatment workflows (WP3). The 3D model of the customized mouse holder, including the mouse rendering from a real X-ray imaging acquisition, is shown.*

enhanced US imaging are also being evaluated, but results will be reported in a separate publication.

Treatment Planning

Treatment planning will rely on the prototype proton µ-RayStation (RaySearch Laboratories AB company), which will support direct import of RSP maps from proton imaging, along with updated tumor contours from the pre-treatment imaging modalities for daily treatment planning prior to irradiation. The first prototype system is currently being evaluated and commissioned to enable planning studies for different small animal tumor entities, to optimize the specifications of the SIRMIO beamline.

In-Vivo Range Verification

Two solutions for in-vivo range verification are under development for application at different types of proton sources. For pulsed accelerators with high instantaneous beam current such as synchro-cyclotrons, the favored solution is the sensing of thermoacoustic emissions induced by the proton energy deposition (so-called ionoacoustics [13]). Such emissions, mainly originating from the Bragg peak, are particularly enhanced under the pre-clinical conditions of small beam size and low beam energies (i.e., sharp Bragg peaks). Moreover, they can enable almost real-time co-registration of the retrieved Bragg peak location with ultrasound images of the small animal anatomy. Main challenge is the integration of ionoacoustic sensors and ultrasonic transducers operating in different frequency ranges from few hundreds of kHz up to tens of MHz, respectively. Hence, the sensitivity and bandwidth of different transducer technologies are under investigation to enable optimal signal-to-noise ratio. To this end, experimental campaigns were performed with pulsed low-energy proton beams of the MLL Tandem accelerator, properly modulated in energy to provide ionoacoustic emissions in a broad frequency range from 50 kHz to 5 MHz, as well as at a dedicated optoacoustic laboratory setup tailored to mimic the major features of the proton-induced ionoacoustic signal. For more generic application at continuous-wave cyclotrons and (slow-cycling) synchrotrons, a dedicated in-beam positron-emission-tomography (PET) scanner has been designed to measure the irradiation-induced pattern of β^+-activity, correlated to the primary proton beam range [14]. Different detector technologies and geometrical arrangements have been simulated and investigated in terms of sensitivity and spatial resolution. Besides range verification, in-situ PET imaging could also open new opportunities for biological image guidance [14] in the foreseen pre-clinical experiments. Hence, simultaneous integration of ionoacoustics/US and PET imaging is supported by the SIRMIO platform.

Results

Beam Degradation, Focusing and Monitoring

The current beamline design features a triplet of permanent magnet quadrupoles (PMQ) optimized for focusing 20-60 MeV proton beams at the treatment isocenter, approximately 70 cm downstream of a variable energy degrader of graphite followed by two dynamic brass collimators to adjust the beam emittance in front of the magnets. Resulting laterally-integrated dose distributions simulated in water show considerably improved entrance-to-peak and plateau-to-peak ratios with respect to a collimator-only passive beam delivery (figure 1 supplementary material). The proposed design is estimated to provide spot sizes smaller than 1 mm FWHM at the focal position at isocenter for an energy spread within 4% and with transmission up to 1%, along with a neutron fluence below 10% relative to the considered passive-only configuration [15]. Additional simulations and treatment planning studies are currently ongoing to further optimize the beamline performance, especially concerning the choice of degrader material, PMQ sensitivity to stray radiation, transmission efficiency and potentially more stringent low-energy transport requirements, prior to finalizing the magnetic lattice design. For the beam monitor, the first segmented ionization chamber prototype performed as required. The first experimental data analysis suggests achievable spatial resolution of few tens of micrometers along with accurate (within ~1%) fluence monitoring in a wide dynamic range ($5 \cdot 10^5$ to $1 \cdot 10^{10}$ protons/s).

Mouse Holder

A first 3D printed prototype was realized, able to accommodate all requirements for the foreseen biological studies, the need of minimal material budget as well as compatibility with the different SIRMIO components (figure 1). Main features are the sterile separation from the outer environment through a thin foil, along with the accommodation of inhalation anaesthesia equipment and integrated heating in the mouse support bed. The flexible and cost-effective design of the latter support can be further adapted to the specific application, by either removing material in the beam path or adding specific material to act as range degrader or provide optimal acoustic coupling.

Pre-Treatment Imaging

First simulation studies in phantom geometries support the feasibility of sub-mm spatial resolution for the integration detector concept featuring a CMOS system close to the object, measuring spatially-resolved energy loss of multiple proton fan beams at different initial energies [16]. Ongoing investigations address possible improvements regarding a minimization of the imaging dose by further optimization of the beam shape, reduction of the probing beam energies and inclusion of supplemental information by an additional

detector, along with mitigation of the image quality degradation primarily due to scattering in the object. For the single particle tracking solution, MC simulations estimated a proton trajectory reconstruction accuracy better than 0.4 mm for a geometrically optimized tracker configuration, yielding a spatial resolution of around 0.2 mm [17]. The use of 500 µm thick Mylar absorbers in the range telescope is estimated to provide a range accuracy close to the range straggling limit of the considered clinical-like 75 MeV proton beams, resulting in sub-1% RSP accuracy for most investigated tissue-equivalent cylindrical inserts (8 mm diameter) in a cylindrical water phantom (3 cm diameter). An example of a simulated proton CT (pCT) slice of a mouse is shown in figure 1, based on the expected performances of the proposed prototype. The feasibility of the range telescope detection concept was recently confirmed in first experiments with a small time projection chamber prototype using 22 MeV protons from the MLL Tandem [18]. Further improvements of the overall system in terms of reduced scattering and increased range resolution are also under evaluation. For both imaging scenarios, we are also considering usage of prior information from X-ray cone beam computed tomography (CBCT) scans, planned to be acquired to monitor tumor growth after implantation, before transferring the animals to the proton irradiation site.

Treatment Planning

Treatment planning studies are ongoing based on X-ray CBCT images acquired at a photon small animal radiation research platform (SARRP) at the LMU University Hospital for different orthotopic tumour entities. First results using an idealized beam model of quasi-monoenergetic beams between 10-80 MeV suggested that also energies below 20 MeV might be needed for optimal coverage of shallow implanted tumors, thus potentially posing more stringent requirements on the SIRMIO beamline under development. For deeper investigations with more realistic plans, the beam properties of the current SIRMIO beamline design have been modelled in RayStation and related investigations are ongoing. Further activities aim at correctly handling the material assignment on the basis of the largely fluctuating grayscale values of the SARRP CBCT images, or directly importing RSP maps from pCT images.

In-Vivo Range Verification

Integration of ionoacoustics/US imaging entails the development of dedicated instrumentation able to handle the different frequency ranges of ionoacoustics (reception only) and US imaging (emission/reception). From the experiments performed so far, customized sensors based on Capacitive Micromachined Ultrasonic Transducers (CMUT) developed at the Department of Engineering Roma Tre University (Rome, Italy), along with dedicated low-noise amplifier electronics, have been identified as promising candidate for the development of bi-modality ultrasound systems for ionoacoustic/US co-registration [19]. Additional data acquired with special phantoms including tissue heterogeneities and microbubble ultrasound contrast agents are being analyzed to assess their influence on the ionoacoustic signal and to optimize the range verification accuracy, along with first tests of ionoacoustics/US co-registration.

For the in-beam PET scanner, an optimum compromise has been sought within the given space constraints for compatibility with the SIRMIO beamline, the movable mouse holder and integration of US/ionoacoustics. The current design features a spherical-like assembly of pyramid-like LYSO scintillators with depth-of-interaction [20], according to detector technologies developed at the collaborating National Institute of Radiological Sciences, NIRS-QST, Japan [21]. Iterative reconstruction of simulated positron point sources showed a promising resolution of 0.4 – 1.0 mm (FWHM) and detection efficiency from 12% to 7% [20] in the relevant few centimeters around the center of the scanner field of view, where the tumor will be located (figure 2 supplementary material).

Discussion

The SIRMIO project, started in November 2017, aims at realizing and demonstrating an innovative prototype system for precision image-guided small animal proton irradiation, suitable for integration at existing clinical treatment facilities. Although the platform is still under development, the design of its main components has been largely completed and first devices are either in the process of being manufactured/tested or close to being ordered/constructed. The envisioned overall assembly is depicted in figure 2 for the two relevant workflows of pre-treatment transmission ion imaging (top), potentially complemented by US tumor visualization and co-registration, followed by dose delivery (bottom). The in-house developed holder is designed to guarantee sterile conditions between a portable laminar-flow biological safety cabinet, where the animals will be prepared after transportation from the animal facility, and the treatment site. Moreover, it has to guarantee stable positioning of the mouse, which will be moved with a precision rotational and translational stage during both the imaging and dose delivery process. Fine-tuning of the beamline design and related ordering of the components will follow the outcome of the ongoing treatment planning and beamline optimization studies, identifying the ideal compromise between the conflicting requirements of increased transmission (for faster irradiation and sufficient energy deposition rate for ionoacoustics) and small spot size. According to the current timeline, construction and first testing of the SIRMIO beamline is expected by the end of 2019, while integration of the different detector components is planned in 2020. This schedule aims at enabling first proof-of-principle phantom experiments before the project end in fall 2021, prior to the deployment in comparative in-vivo studies of different

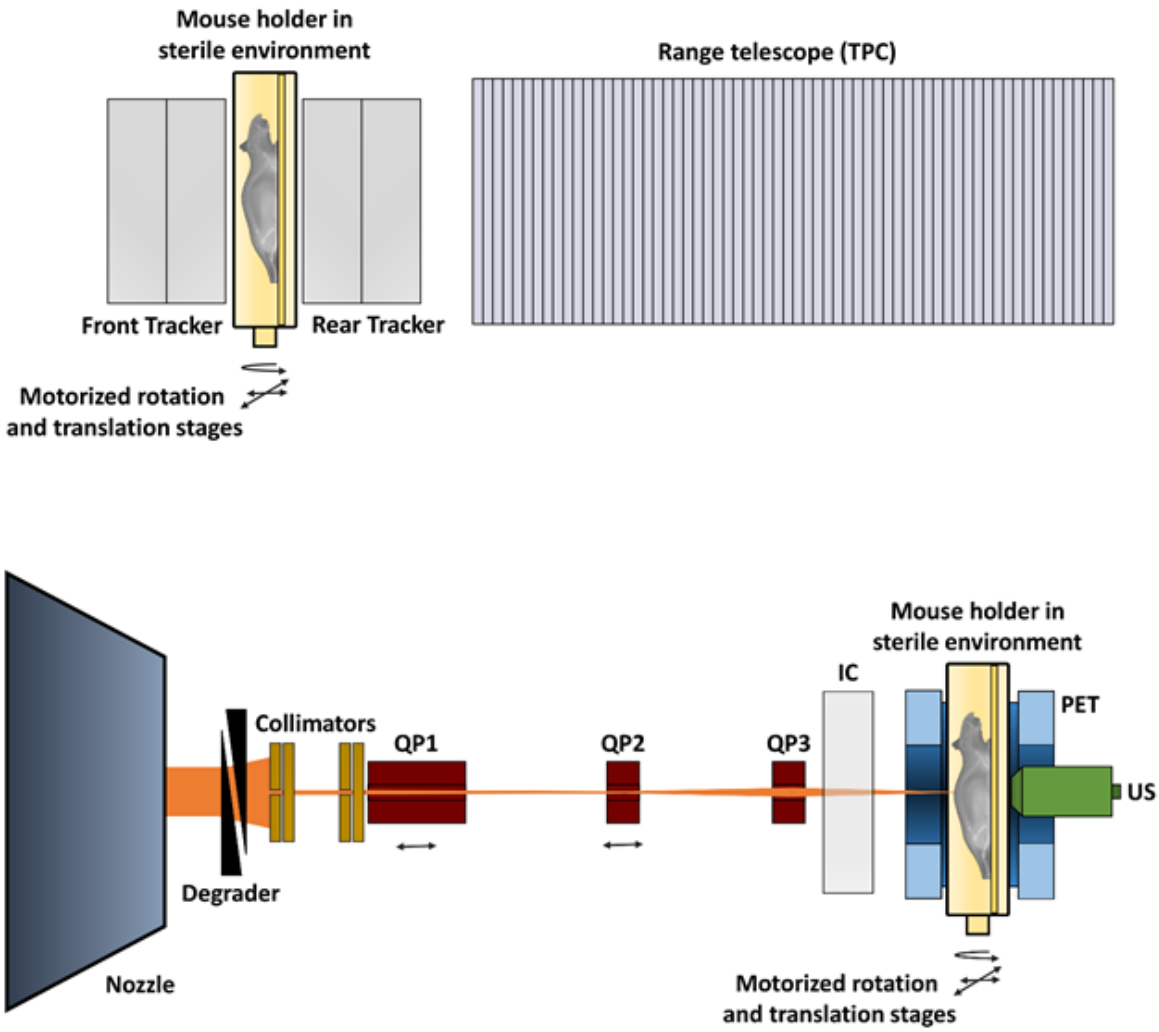

Figure 2: *Illustration of the SIRMIO configurations for pre-treatment imaging (a, top), using the clinically available (scanned) beam with the proposed single particle tracking imaging system, followed by image-guided dose delivery (b, bottom), with the dedicated beamline and detector instrumentation in place.*

biological endpoints after proton and photon small animal irradiation. Future versions of the system are envisioned to enable beam scanning in order to minimize the small animal movement and potentially enhance the treatment throughput. Although the first prototype is especially optimized on the basis of experimentally-benchmarked MC phase-space information from a ProBeam facility [9], the design is flexible enough to accommodate (possibly with minor modifications) the low-energy beam characteristics of different proton therapy facilities from different vendors. Hence, the proposed new platform is deemed suitable for wide deployment in the proton therapy community to enable innovative radiobiological research not possible with current infrastructures, thus holding a great potential to foster relevant advances in bench-to-bedside translational research beyond state-of-the-art.

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Disclosure statement

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Supplementary figure captions

Supplementary figure 1: Comparison of normalized distributions of laterally-integrated dose simulated in water for a 50 MeV beam degraded from a clinical 75 MeV proton beam [9] using the current beamline design (red, see *Beam Degradation, Focusing and Monitoring*) and a purely passive design (blue, using a 1 mm diameter hole in a 6 mm thick brass collimator placed 10 cm upstream of the isocentre).

Supplementary figure 2: Schematic drawing of the dedicated in-beam PET scanner design for SIRMIO, with the mouse holder indicated by the red cylinder.