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 tumour and tissue models in different microenvironments, to unravel the complex mechanisms of radiation damage in target and non-target tissues and assess the efficacy of novel therapeutic strategies. To this end, 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 a great 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 small animal proton irradiation, suitable for integration at existing clinical treatment facilities. The proposed design combines precise dose application with novel in-situ multi-modal anatomical image guidance and in-vivo verification of the actual treatment delivery for precision small animal irradiation.

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. The foreseen workflow includes pre-treatment proton transmission imaging for treatment planning and position verification, complemented by ultrasonic tumour localization, 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 in radiotherapy for future translation into innovative clinical strategies.

Keywords: small animal irradiation; proton therapy; image guidance

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Introduction

Over the last decade, several technological advances for millimetre-accurate delivery of intensity-modulated radiation along with in-room volumetric anatomical image guidance have enabled clinical introduction of more effective treatment schemes in modern external radiation therapy with photons and light ions [1]. However, biological understanding of the response of the microenvironment to radiation, both in terms of tumour and normal tissue, is still an unmet challenge, which is even more crucial for ion beams than for photons. In fact, compared to photons, ion beams induce another level of complexity due to their enhanced relative biological effectiveness (RBE). In addition to the remaining debated uncertainties in the clinically adopted constant (protons) and variable (carbon ions) RBE values, recent investigations have also highlighted that densely ionizing ion beams can elicit signalling pathways quite distinct from those involved in cell and tissue response to photons, thus opening innovative areas of research going beyond traditional RBE concepts [2]. Hence, new questions need to be answered to understand the complex response of tumour and normal tissue to light ions for possible future translation into clinical practice. To this end, experiments in animal tumour models are of paramount importance to test hypotheses, which would be difficult and often unethical to address at the clinical level, or inaccessible at the isolated cellular level. However, they require adequate platforms to accurately deliver therapeutic doses to a small tumour, while well sparing normal tissue.

Over the last years, for photon therapy, several dedicated small animal radiation research platforms have been realized and meanwhile commercialized to provide precision image-guided radiotherapy conditions similar to state-of-the-art human treatments. This was accomplished by downscaling the geometry and energy of the therapeutic photon beam and equipping the irradiator with at least volumetric X-ray computed tomography (CT) imaging [3]. In contrast, in ion beam therapy, pre-clinical experiments are still predominantly carried out in the experimental rooms of the few

available clinical facilities, without dedicated beamlines for accurate small animal irradiation. Here, common delivery solutions feature collimation of passively scattered broad beams or scanned pencil-like beams, moderated in range (i.e., penetration depth) by thick degraders just before entering the animal. Both methods exhibit limitations in terms of flexibility (for static collimation), beam intensity (due to attenuation especially in the collimation system), activation of the beam-shaping material (posing radiation protection issues) and production of secondary neutrons (which might affect biological outcome, due to their elevated biological effectiveness). In particular, even for state-of-the-art pencil-beam scanning, the smallest achievable beam sizes of low energy uncollimated beams is still in the range of few to few tens millimetres full-width half-maximum (FWHM), due to limitations of multiple Coulomb scattering in the upstream beam monitoring system and air gap between nozzle and isocentre, where irradiation typically takes place for optimal dosimetric conditions. For example, values around 30 mm FWHM were reported at 50 MeV in [4,5]. Besides limitations in achievable beam size and quality, the positioning accuracy of the animal is commonly challenged by the restriction to external reference lasers and special custom-made holders, since the experimental rooms hosting radiobiological research typically do not include X-ray morphological imagers. An additional source of uncertainty stems from the frequent treatment planning approximation that considers small animals just as homogeneous water for dose calculation purposes, without using animal-specific X-ray computed tomography (CT) images like for patient treatment. Limited accuracy in target positioning and insufficient knowledge of the traversed tissue properties, especially their stopping power, contribute to the ion-specific problem of range uncertainty, i.e., the uncertainty in the knowledge of the beam stopping position, where the maximum therapeutic dose deposition (Bragg peak) occurs. This problem can be even more critical for pre-clinical research in small animal irradiation, where sharper Bragg peaks are typically present due to the lower beam energies and the involved reduction of range straggling. Therefore, the clinical infrastructures currently used for small animal radiation research show substantial limitations that restrict the class of viable experiments and raise concerns on the reliability, relevance and scalability of results obtained in such suboptimal irradiation conditions. To overcome this, alternative proposed solutions aim to utilize dedicated low energy beam accelerators, independent from the clinical sites [6]. In contrast, the project SIRMIO (Small Animal Proton Irradiator for Research in Molecular Image-guided Radiation-Oncology) proposes a

compact design of a dedicated portable beamline equipped with novel detector technologies, which can be integrated in the experimental rooms of operational clinical facilities for precision image-guided small animal proton irradiation. This is deemed necessary to provide a tight connection between radiation oncologists and biologists, without the need of building costly dedicated beamlines or additional proton sources tailored to deliver beams of (sub)millimetre size for pre-clinical research.

Material and methods

The SIRMIO project entails several dedicated technological developments aimed at enabling precision image- and dose-guided small animal proton radiation research at experimental beamlines of clinical proton therapy facilities. The relevant components, illustrated in the schematics of figure 1, and the related investigations, addressed in synergistic work packages, are detailed in the following.

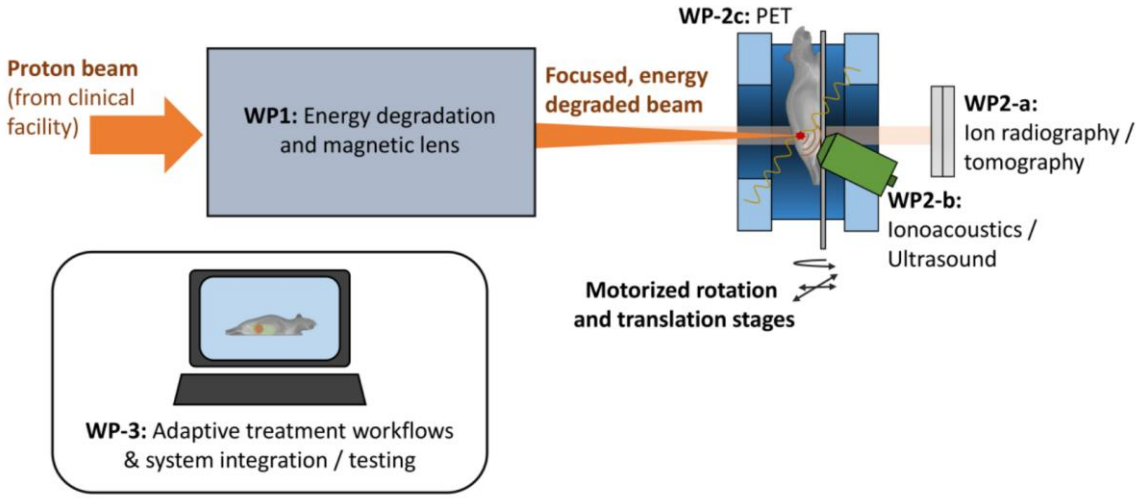

Figure 1: Schematic illustration of the SIRMIO project with related work packages (WPs), featuring manipulation of an incoming clinical proton beam into a focused and energy-degraded pre-clinical beam (WP1), pre-treatment ion transmission imaging (WP2-a), in-vivo range verification with US/ionoacoustics (WP2-b) and PET (WP2-c), system integration and deployment for adaptive treatment workflows (WP3).

Beam Degradation, Focusing and Monitoring

Monte Carlo 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 optimise 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 tumour is intended to be positioned. For the sake of simplicity and compatibility to generic experimental beamlines of proton therapy centres, which are often limited to fixed beams, the first version of the SIRMIO beamline is designed for the focusing of a fixed horizontal pencil beam, while moving the target for volumetric scanned beam irradiation. Since the beam characteristics need to be monitored after the dedicated SIRMIO beamline, close to the treatment isocentre, a segmented ionization chamber providing spatial profiling of the beam and total fluence measurement has also been developed in-house, and has been commissioned and characterized with 20 MeV protons in an experimental campaign at the Tandem accelerator of the Maier-Leibnitz laboratory Garching.

Mouse Holder

A prototype mouse holder system is being developed in-house to provide fixation of the animal in vertical position for optimal transmission imaging conditions (see next section). Major challenges taken into account include the biological requirements of sterility, anaesthetization and temperature stabilization of the mouse, along with minimal material budget to minimize 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 can provide on-site anatomical information for target positioning and treatment planning, with the great potential to reduce range uncertainties inherent to the semi-empirical conversion of X-ray Hounsfield units (HU) into relative (to water) stopping power (RSP). To this end, two proton imaging setups are being investigated, based on integration and single particle detection. The first concept, especially foreseen for deployment at accelerators with too large instantaneous beam current for single particle tracking (such as novel synchro-cyclotrons), relies on a large area CMOS sensor for spatially resolved energy loss measurements at multiple probing energies, similar to the work of [10]. The second concept, reported in more detail in this contribution, relies on the in-house development of low material budget Micromegas tracking detectors and a time projection chamber

with Micromegas readout structure containing multiple Kapton absorbers functioning as range telescope. Both systems are being investigated and optimised on the basis of extensive Monte Carlo simulations using the FLUKA code (version 2011.2x-5, [11,12]). Additional imaging modalities for tumour visualization are being evaluated for daily treatment planning, based on either gold nanoparticles-enhanced proton imaging or microbubbles-enhanced US imaging.

Treatment Planning

Two treatment planning system (TPS) solutions are being considered, both featuring Monte Carlo dose calculation engines. The first one relies on the prototype proton μ–RayStation of the RaySearch Laboratories AB company, for which a software license has been just purchased and a research collaboration agreement is being established. The alternative second option would be an extension of the in-house research TPS based on the coupling of a particle extension of the CERR (A Computational Environment for Radiotherapy Research) platform with a Geant4 dose calculation engine [13]. Both solutions should be able to import RSP maps from the proton transmission imaging, along with updated tumour contours from the daily image guidance for treatment planning shortly before start of irradiation.

Currently, treatment planning studies are in progress with a precursor of the proton μ–RayStation on the basis of X-ray cone beam computed tomography (CBCT) images acquired at a photon small animal radiation research platform (SARRP) at the LMU University Hospital for different orthotopic tumour entities, to identify more precisely the energy range requirements of the SIRMIO beamline.

In-Vivo Range Verification

Two solutions for in-vivo verification of the proton range in small animals are under development for application at different types of proton sources. For pulsed accelerators with high instantaneous beam current such as synchro-cyclotrons, sensing of the thermoacoustic emissions induced by the proton energy deposition (so called ionoacoustics [14]) is deemed an ideal solution for small animal proton range monitoring during irradiation. In fact, these ionoacoustic emissions, naturally enhanced at the Bragg peak location, are particularly favoured under the pre-clinical conditions of

small beam size and low beam energies (i.e., sharp Bragg peaks), besides lending themselves to almost real-time co-registration of the Bragg peak location with the ultrasound images of the small animal anatomy. The main challenge is the co-integration of ionoacoustic sensors and ultrasonic transducers, which operate in a different frequency range from few hundreds of kHz up to tens of MHz, respectively. To this end, different transducer technologies are being investigated in terms of their sensitivity and bandwidth, to enable optimal signal-to-noise ratio. For more generic application also at continuous wave cyclotrons and (slowly cycling) synchrotrons, a dedicated in-beam positron-emission-tomography (PET) scanner is being designed to measure the irradiation-induced pattern of β^+-activity, which is correlated to the primary proton beam range [15]. The partial ring PET system design is being optimised in terms of sensitivity and spatial resolution, based on detector technologies enabling depth-of-interaction, as developed at the collaborating National Institute of Radiological Sciences in Chiba, Japan (NIRS-QST, 16). In addition to range verification, the availability of an in-situ PET scanner could also open new opportunities for biological image guidance [15] in the foreseen pre-clinical experiments. Hence, integration of both ionoacoustics/US and PET imaging, along with the compatibility with the other SIRMIO components, is taken into account.

Results

Beam Degradation, Focusing and Monitoring

The current beamline design features a triplet of permanent quadrupole magnets (PMQ) optimised for focusing 20-60 MeV proton beams at the treatment isocentre, at approximately 70 cm downstream of a variable energy degrader of graphite followed by two dynamic brass collimators to adjust the beam emittance prior to the magnets. Such a design is estimated to provide spot sizes smaller than 1 mm FWHM at the focal position at isocentre for an energy spread within 4%, with transmission up to 1% and neutron fluence below 10% [17]. In particular, the combination of passive and active beam shaping is observed to considerably improve the entrance-to-peak and plateau-to-peak ratios of the simulated laterally-integrated dose distributions in a water phantom, with respect to a collimator-only passive beam delivery (figure 2). However, further optimisation especially concerning the degrader material as well as the PMQ sensitivity to stray radiation, the beamline transmission efficiency and potentially more stringent

low energy requirements is the subject of ongoing simulation and treatment planning studies, prior to finalizing the magnetic lattice design. For the beam monitor, the first segmented ionization chamber prototype performs as required and expected. In particular, the preliminary data analysis suggests achievable spatial resolution of a few tens of microns along with accurate (within ~1%) fluence monitoring in a wide dynamic range ($5 \cdot 10^5$ - $1 \cdot 10^{10}$ protons/s), which might be improved even further by slightly modifying the detector design.

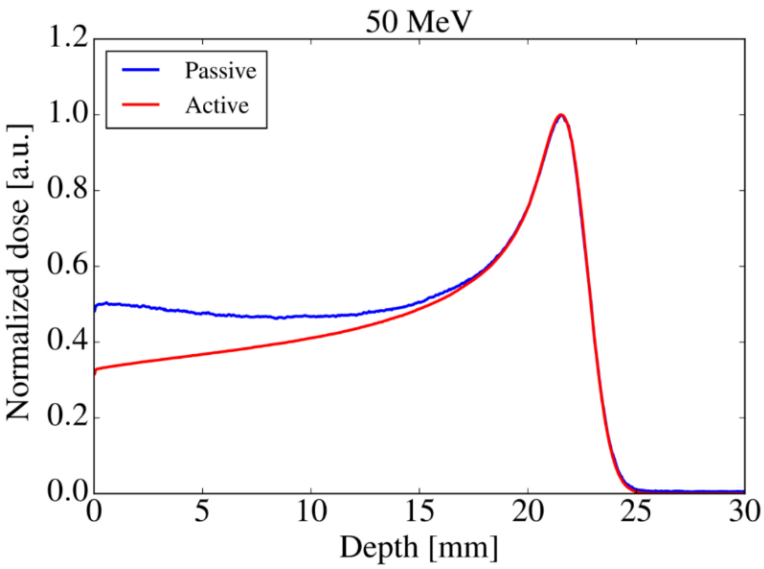

Figure 2: Normalized laterally-integrated dose distributions from passive (blue) and active (red) designs for a 50 MeV beam, degraded from a clinical 75 MeV proton beam [9]. The passive design uses a 1 mm diameter hole in a 6 mm brass collimator placed 10 cm upstream the isocentre. The active design is the proposed PMQ triplet beamline.

Mouse Holder

A first prototype system has been designed on the basis of the different specifications, accommodating the requirements for the foreseen biological studies, the need of minimal material budget as well as compatibility with the different SIRMIO components. The 3D model of the prototype and its first 3D printed realization for initial testing is presented in figure 3. Main features are the sterile separation from the outer environment through a thin foil along with the accommodation of anaesthesia equipment and integrated heating in the mouse support. The flexible and cost-effective design of the mouse support will be adapted in terms of material budget to the specific application, by either removing material in the beam path or adding specific material, which can act as additional range degrader or provide optimal acoustic coupling.

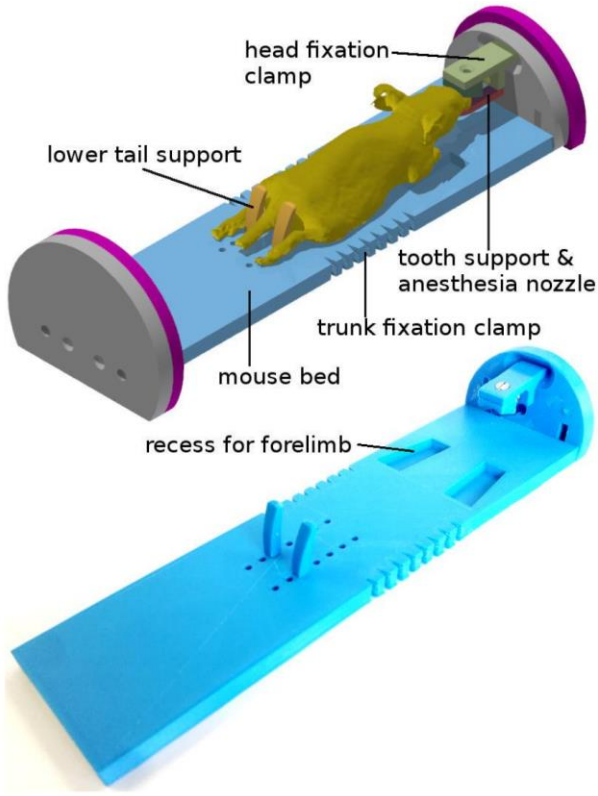

Figure 3: 3D model (top, including the mouse rendering from a real CBCT acquisition) and related 3D printed realization (bottom) of the mouse holder, with specific components highlighted (except the foreseen surrounding foil for sterile environment).

Pre-Treatment Imaging

For the integration detector solution featuring a CMOS-based system for energy loss measurement at different initial beam energies, preliminary results suggested the feasibility of the concept. In particular, when using multiple fan beams and small distances between imaged object and detector, sub-mm spatial resolution could be achieved [18]. Optimisation of the imaging performance is currently ongoing especially regarding a minimization of the imaging dose by special arrangement 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 optimised tracker configuration, resulting in a spatial resolution of around 0.2 mm [19]. The use of 500 µm thick Kapton absorbers in the range telescope is expected to provide a range accuracy close to the range straggling limit of the considered clinical-like proton beams of 75 MeV initial energy, resulting in sub-1% RSP accuracy for most investigated tissue-equivalent materials. An example of a simulated proton CT (pCT) image is shown in figure 4, based on the expected

performances of the proposed prototype. The feasibility of the detection concept was recently confirmed in first experiments with a small time projection chamber prototype using 22 MeV protons from the Tandem accelerator of the Maier-Leibnitz-Laboratory (MLL) [20], for which detailed data analysis is still ongoing. Further improvements of the detector performance in terms of reduced scattering and increased range resolution are also being evaluated, in combination with the possible usage of prior information from the SARRP X-ray CBCT scans, planned to be acquired to monitor tumour growth after implantation, prior to transfer of the animals to the proton facility for irradiation.

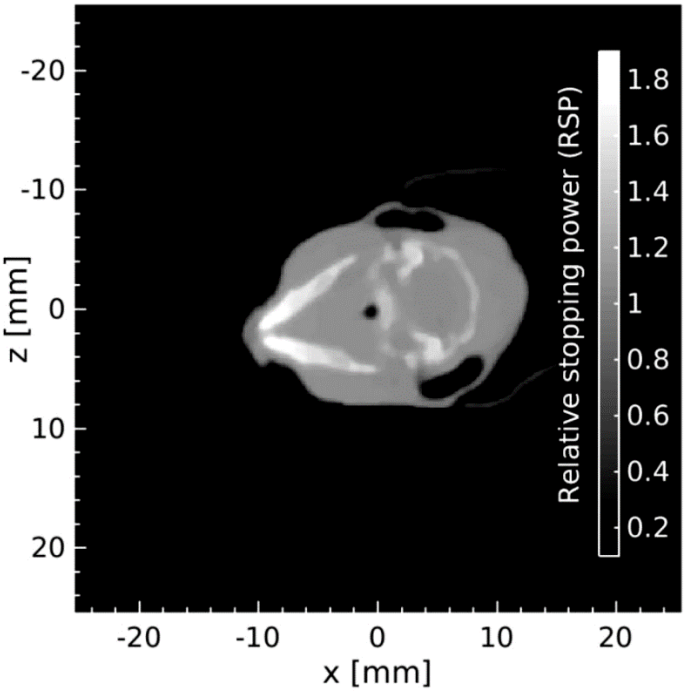

Figure 4: Example of MC simulated pCT image of a mouse, based on the expected realistic performance of the proposed single particle imaging system.

Treatment Planning

First treatment planning studies are being carried out with a prototype version precursor of the μ–RayStation, using an idealized beam model based on quasi-monoenergetic proton beams between 10 MeV and 80 MeV initial energy, with Gaussian energy spread. Preliminary results suggest that also energies below 20 MeV might be needed for optimal coverage of the orthotopic tumours often implanted at shallow depth, thus potentially posing more stringent requirements to the SIRMIO beamline under development. Ongoing work aims to provide more realistic treatment plans, enabling the direct modelling of the SIRMIO beamline in μ–RayStation, along with correct handling of the material assignment on the basis of the largely fluctuating grey values of

the SARRP CBCT images or direct import of RSP maps from the (so far only simulated) pCT images.

In-Vivo Range Verification

Integration of ionoacoustics/US imaging in SIRMIO entails the development of dedicated instrumentation able to handle the different frequency range of ionoacoustics (reception only) and US imaging (emission/reception). To this hand, different transducer technologies were investigated at the pulsed low energy proton beam 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 setup tailored to mimic the major features of the proton-induced ionoacoustic signal. In these experiments, a customized detection system 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 were identified as promising candidate for the development of bi-modality ultrasound systems, as required for co-registration of ionoacoustic and US imaging [21]. Additional data acquired with special phantoms featuring the presence of tissue heterogeneities and microbubble ultrasound contrast agent are being analysed to assess their influence on the ionoacoustic signal and to optimise the Bragg peak position reconstruction accuracy, along with first tests of ionoacoustics/US co-registration.

For the in-beam PET scanner, different detector solutions and geometrical configurations have been studied especially in terms of system detection efficiency and spatial resolution, seeking for an optimum compromise within the given space constraints for compatibility with the components of the SIRMIO beamline / beam monitor, the movable mouse holder and the integration of US/ionoacoustics. The current design features double-focused trapezoid-like detectors of LYSO with depth-of-interaction (according to technology developed at NIRS-QST, [16]) and optional TOF capability, promising point source resolution of 0.4 – 1.0 mm (FWHM) and detection efficiency from 10% to 5% in the relevant few centimetres around the centre of the scanner field of view, where the tumour will be located (figure 5).

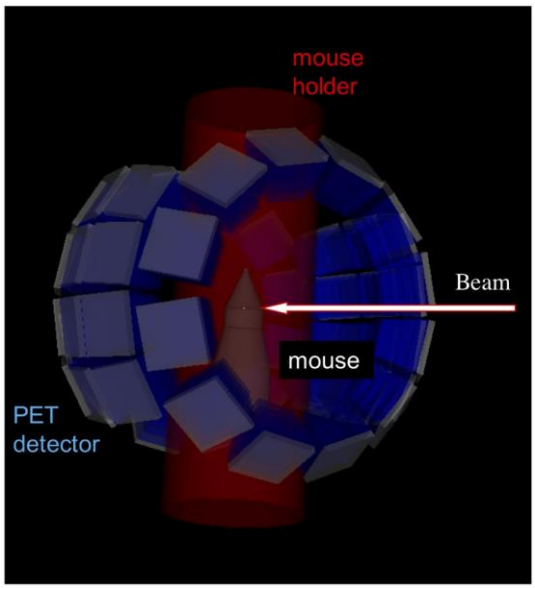

Figure 5: Schematic drawing of the dedicated in-beam PET scanner design for SIRMIO, with the mouse holder indicated by the red cylinder.

Discussion

The 4-years long SIRMIO project, started in November 2017, aims at realizing and demonstrating an innovative prototype system for precision 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 6 for the two relevant workflows, which foresee pre-treatment transmission ion imaging (up), potentially complemented by US tumour visualization and co-registration, followed by dose delivery (down). 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 optimisation studies, identifying the ideal trade-off 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 the course of 2020. This schedule aims at enabling first proof-of-principle phantom experiments within the

end of the project in fall 2021, prior to the deployment of the system for comparative in-vivo studies of different biological endpoints after image-guided proton and photon small animal irradiation at the SIRMIO and SARRP platforms, respectively. This way, SIRMIO will provide new experimental insights into animal-based proton therapy research, holding a great potential to foster relevant advances in bench-to-bedside translational research beyond state-of-the-art. Future versions of the system are already envisioned to enable also beam scanning, to minimize the small animal movement and potentially enhance the treatment throughput. Although the first prototype is especially optimised 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.

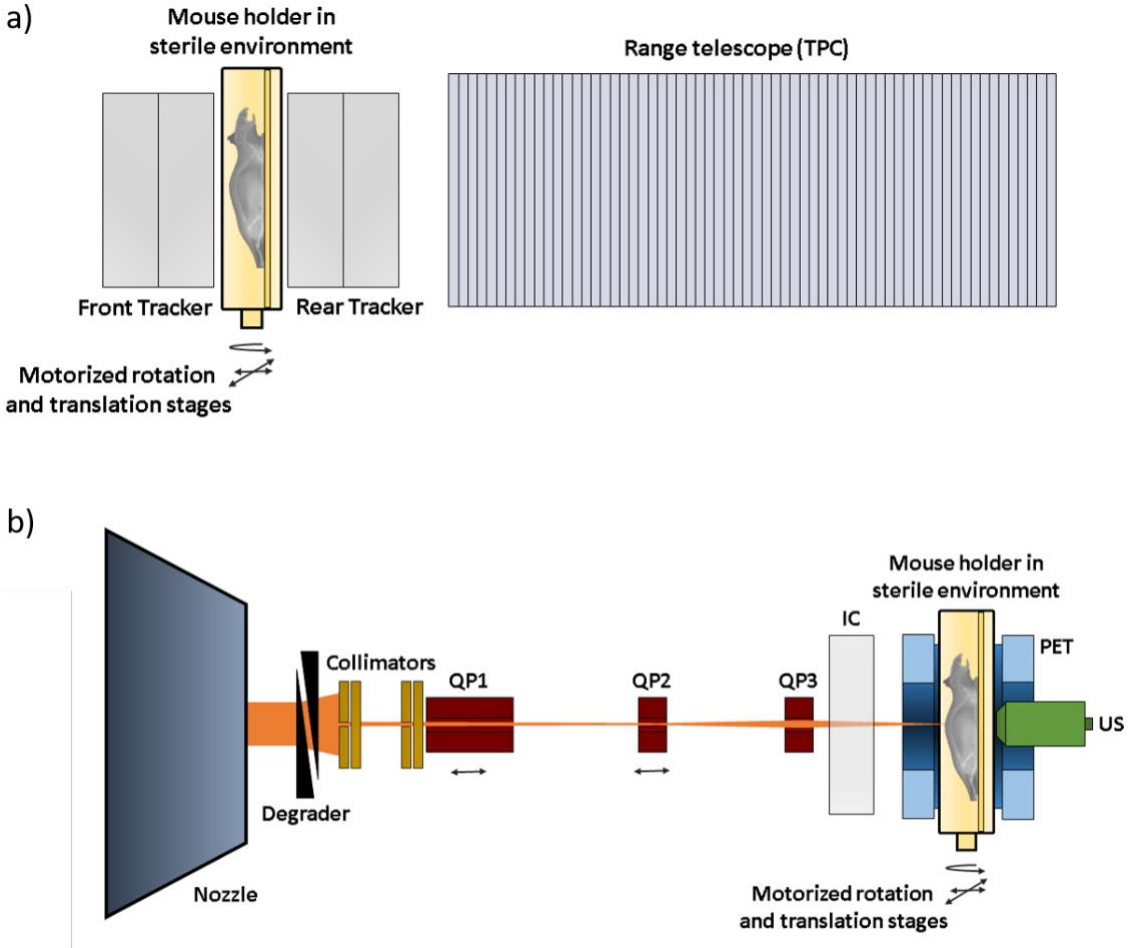

Figure 6: Illustration of the SIRMIO configurations for pre-treatment imaging (a, top), using the clinically available (scanned) beam with the proposed single particle tracking

imaging system, followed by image-guided dose delivery (b, bottom), with the dedicated beamline and detector instrumentation in place.

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Disclosure statement

The LMU Medical Physics Department has a license and (planned) research collaboration agreement with the company RaySearch Laboratories AB for the μ-RaySearch small animal treatment planning system, as well as a collaborative research agreement with the Department of Engineering of Roma Tre University.

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