Towards a novel small animal proton irradiation platform for precision image-guided preclinical research

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Joint AAPM – COMP Virtual Annual Meeting

Conflict of Interest

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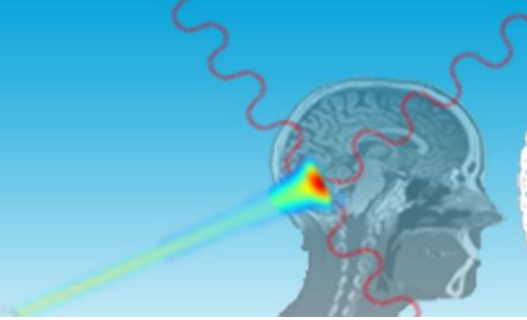


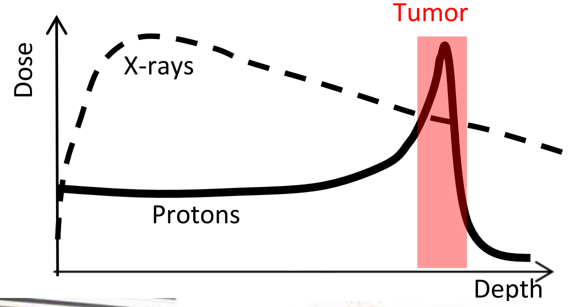
2 Research Collaboration & License Agreements with RaySearch Laboratories AB

LMU Department of Experimental – Medical Physics

RaySearch Laboratories

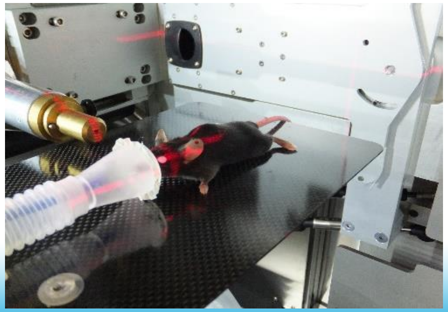
Motivation

- Proton therapy mainly exploits physical advantages of conformal delivery
- In addition to enhanced RBE, ions elicit different signaling pathways than X-rays: opportunity for breakthroughs & innovations



- Small animal irradiation offers unique tool for translational research
- Recent widespread adoption of commercial precision image-guided small animal X-ray irradiation platforms

Platforms for precision small animal research with protons?



Source: Verhaegen et al PMB 2011, Lauber LMU Munich

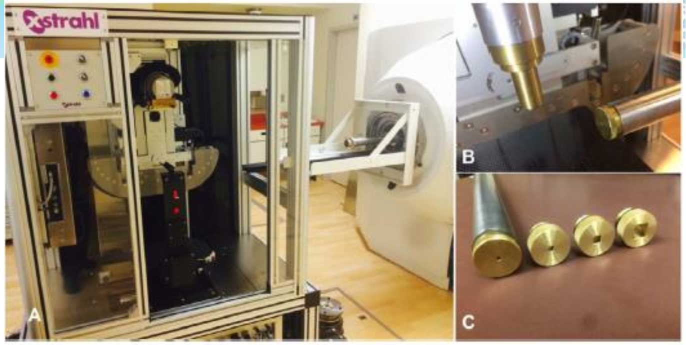
First projects in USA and Europe
(and new more starting…)

NEWSFEED

Apr 13, 2015

University of Washington buys SARRP system for pre-clinical proton therapy

6 April 2015 - University of Washington (UW) has purchased an Xstrahl Life Sciences SARRP platform and is integrating it with their Pre-Clinical Proton Therapy Facility.



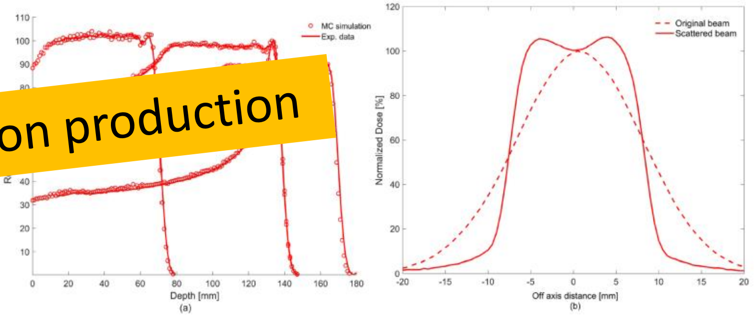
Beam source

Dedicated low-energy (≈ 50 MeV) proton accelerator
(e.g., *Washington University US*)

Experimental beamline of clinical facility (down to ≈ 70 MeV)
(e.g., *Orsay France & University of Pennsylvania US*)

Delivery

Passive energy degradation/modulation and
beam collimation *(all)*

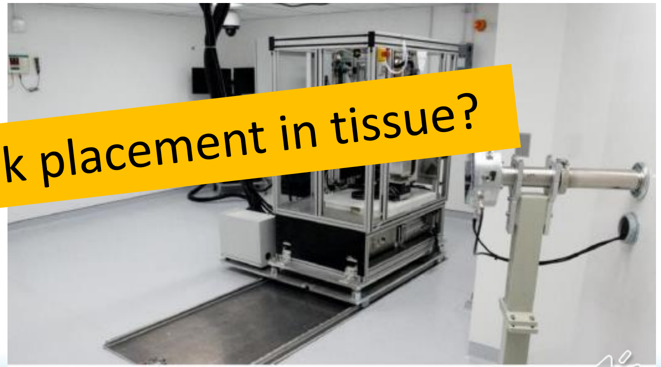


Fast field formation, but considerable neutron production

Imaging

X-ray CBCT imager of photon radiation platform (SARRP)
(e.g., Washington University US & University of Pennsylvania US)

Offline mouse positioning
(e.g., Orsay France)



Morphological alignment, but what about Bragg peak placement in tissue?

Ford et al, PMB 2018; Patriarca et al, IJROBP 2018; Kim et al, PMB 2019

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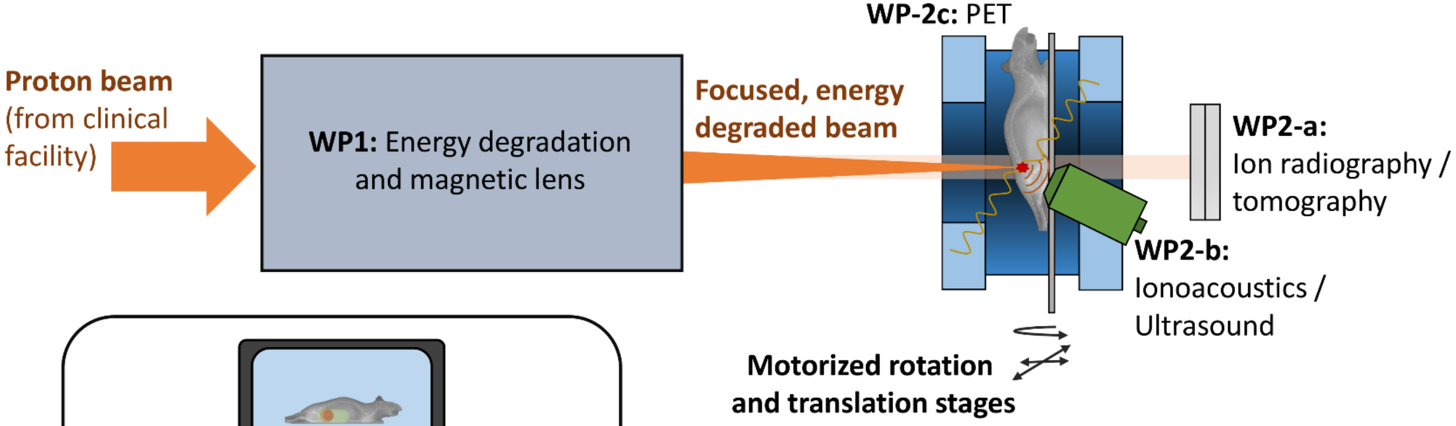
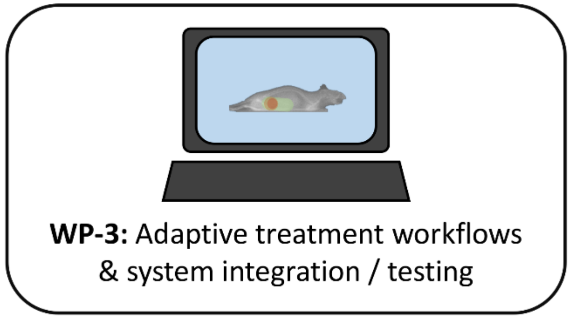
The SIRMIO project

Small animal proton irradiator for research in molecular image-guided radiation-oncology

Realize and demonstrate **prototype system** for

- **precision, image-guided small animal proton irradiation**
- **integration in experimental beamlines of clinical facilities**





- WP1: High beam quality
- WP-2a…c: Innovative image guidance beyond morphology
- WP-3: Adaptive planning and delivery

Parodi et al, Acta Oncol 2019

WP1: Beamline

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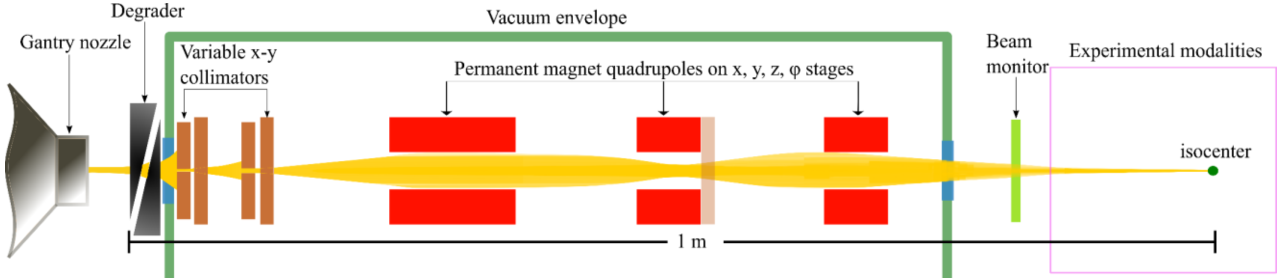
Energy degradation, transport and refocusing of lowest-energy (70 – 100 MeV) clinical beam

Requirements:

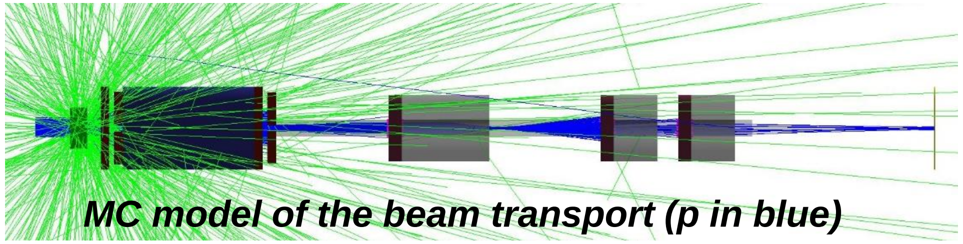
- Transport of energies between 20 and 50 MeV
- Sub-millimeter (sigma) spot sizes at isocenter
- Beam currents appropriate for treatment

Approach:

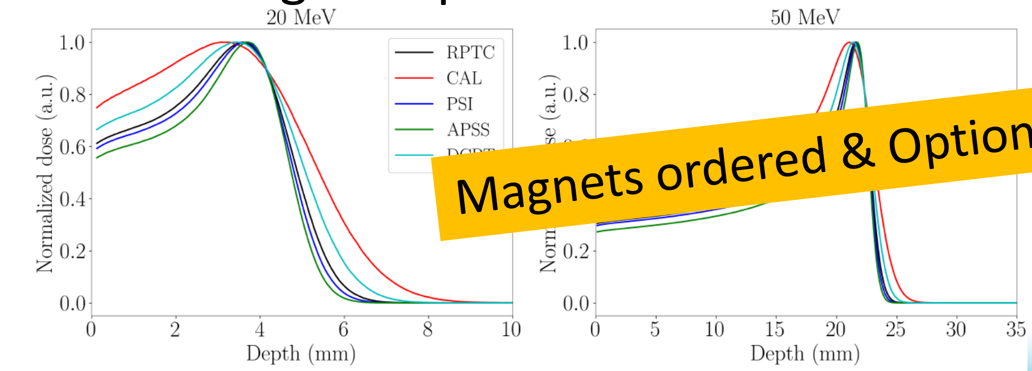
- Model lowest-energy clinical beam from exp. data (RPTC)
- Optimization of collimators & PMQ after variable degrader
- Monte Carlo (MC) validation of particle optics calculations
- MC testing of expected outcome for different facilities

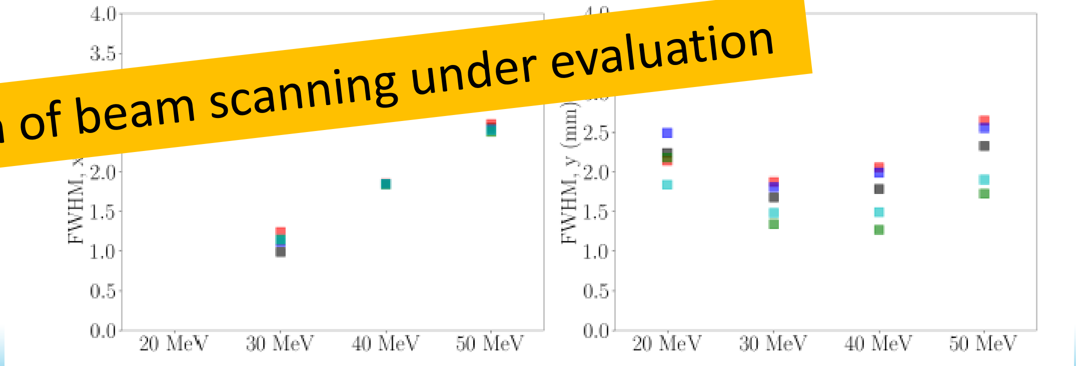


Schematic drawing of the SIRMIO beamline



MC model of the beam transport (p in blue)





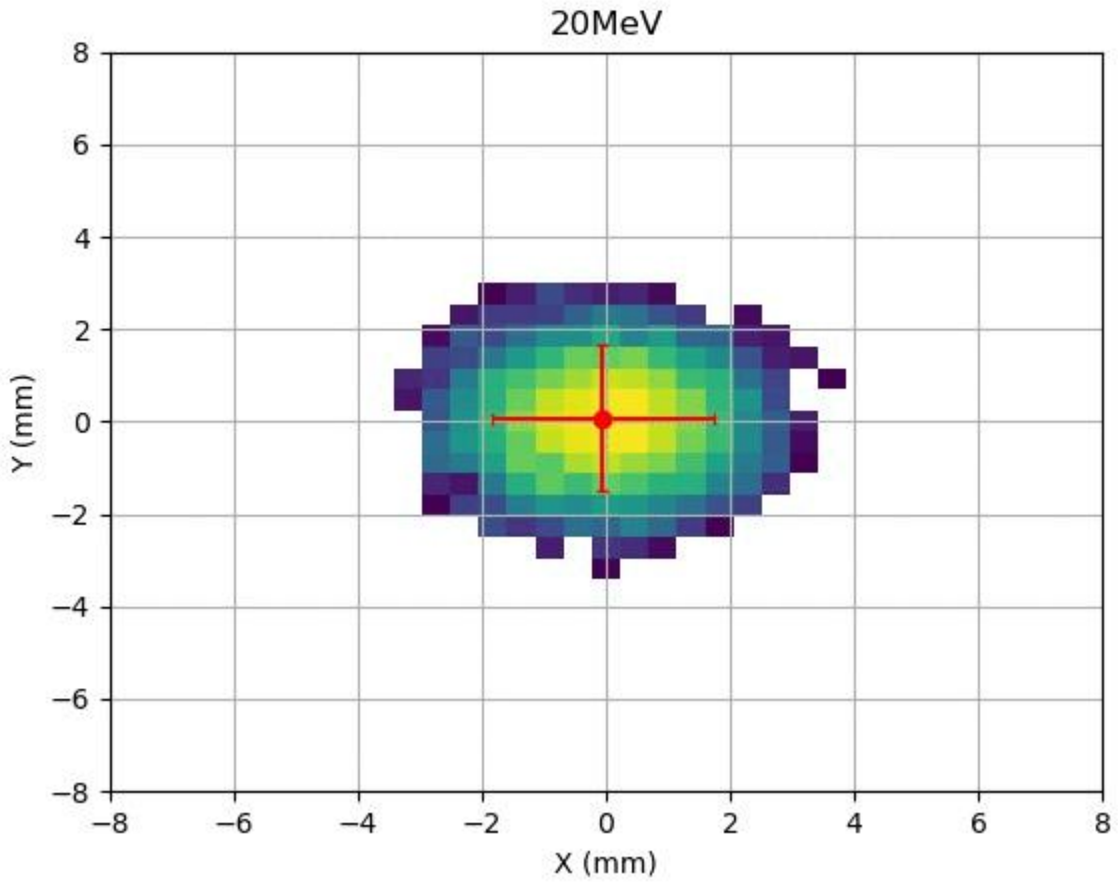
Magnets ordered & Option of beam scanning under evaluation

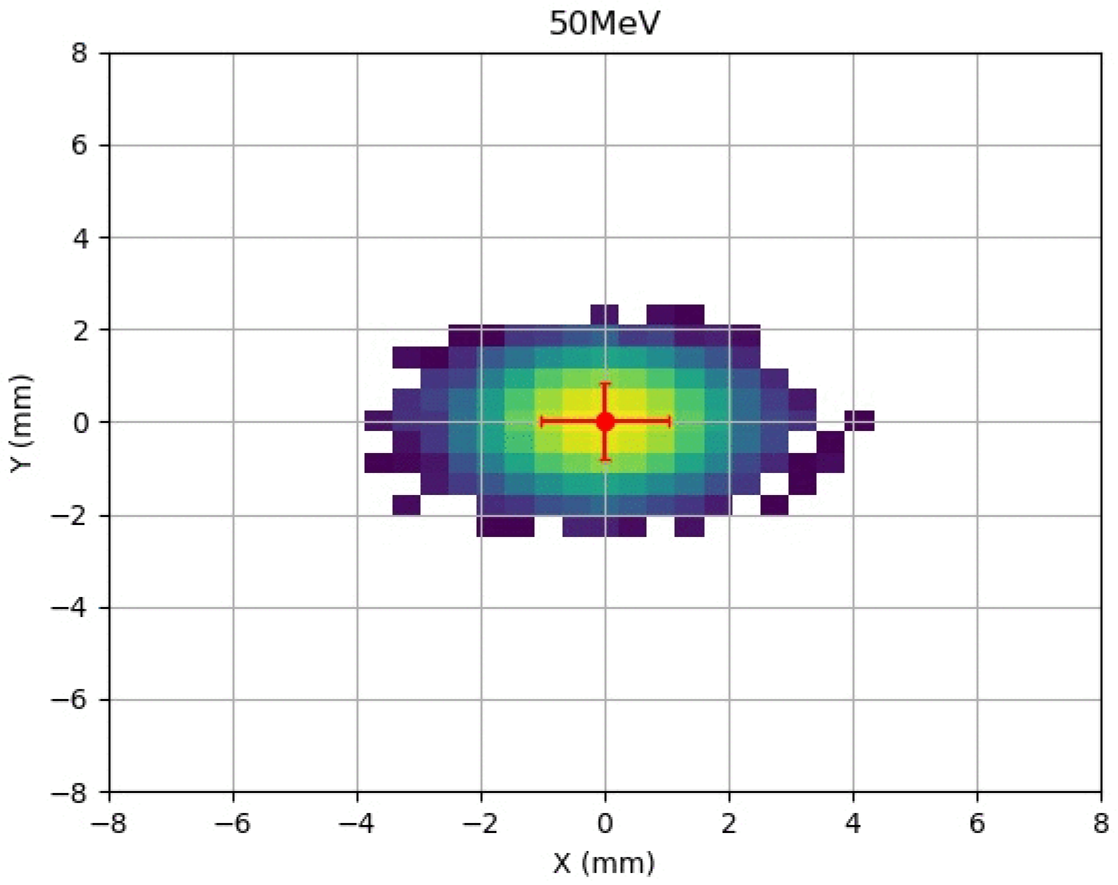
Gerlach, Pinto, Kurichiyanil…Parodi, submitted to PMB

RTPC: Munich; CAL: Nice; PSI: Villigen; APSS: Trento; DCPT: Aarhus

WP1: Beamline

Preliminary beam scanning studies





N. Kurichiyanil et al, to be published

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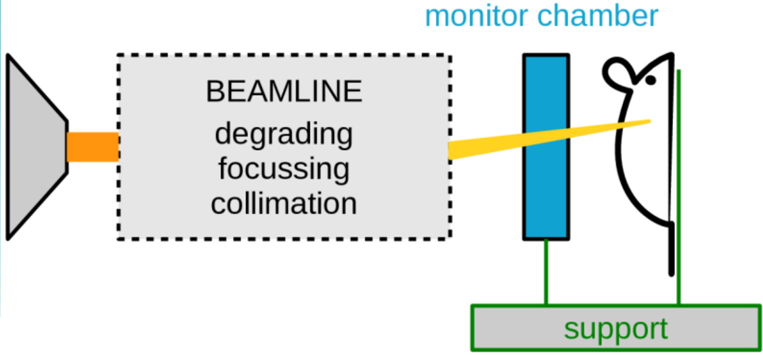
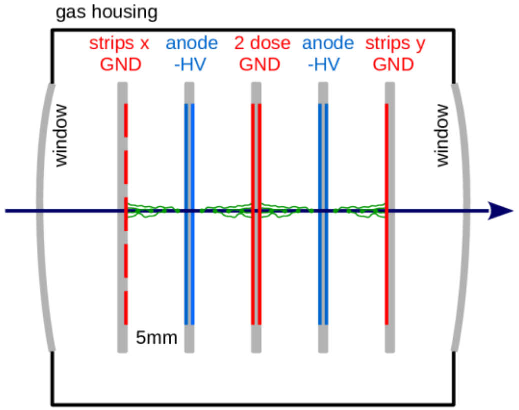
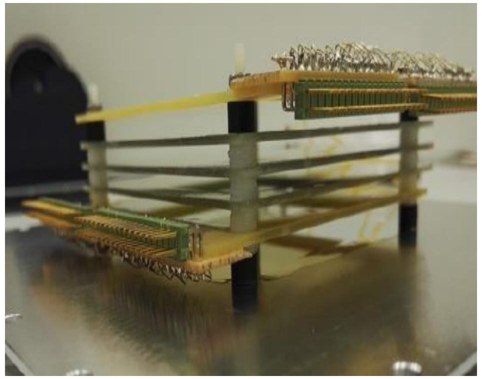
WP1: Beam monitor



Requirements

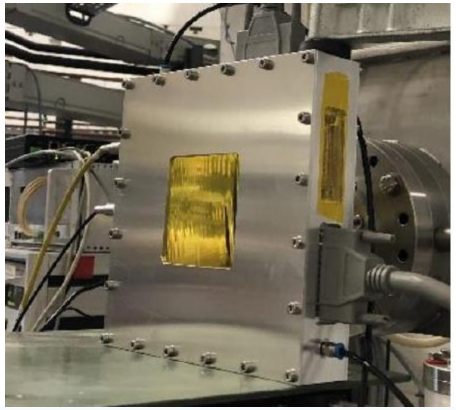
- 2D information of beam position
- Information on proton flux

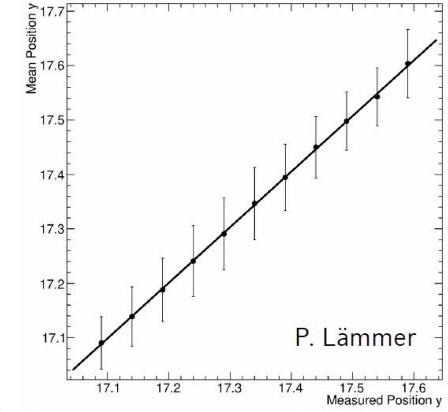




Ionization chamber (developed in-house)

- No single particle tracking
- Very low material budget (~ 0.1 mm WET)
- 64mm × 64mm, 5mm gaps
- x/y-electrodes: 64 strips @ 1mm pitch, 0.7 mm width (10µm Kapton + 40nm Aluminium)
- Dose electrode: 2µm Kapton + 40nm Aluminium



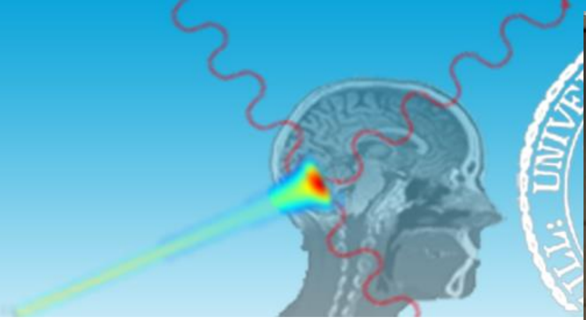


Commissioning at 20 MeV Tandem beam

- Spatial resolution within 10 µm
- Accurate (≤ 1%) fluence monitoring
  in wide dynamic range ($5 \cdot 10^5$ - $1 \cdot 10^{10}$ protons/s)

Bortfeldt et al, MPGD 2019, IEEE NSS-MIC 2019; Lämmer MSc thesis LMU

WP2a: Proton radiography/tomography



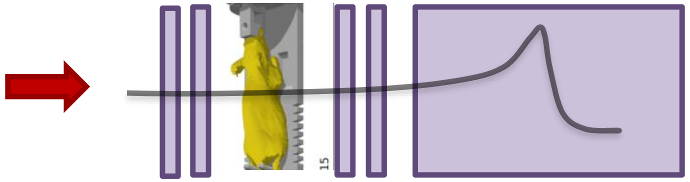
Pre-treatment radiographic & tomographic imaging

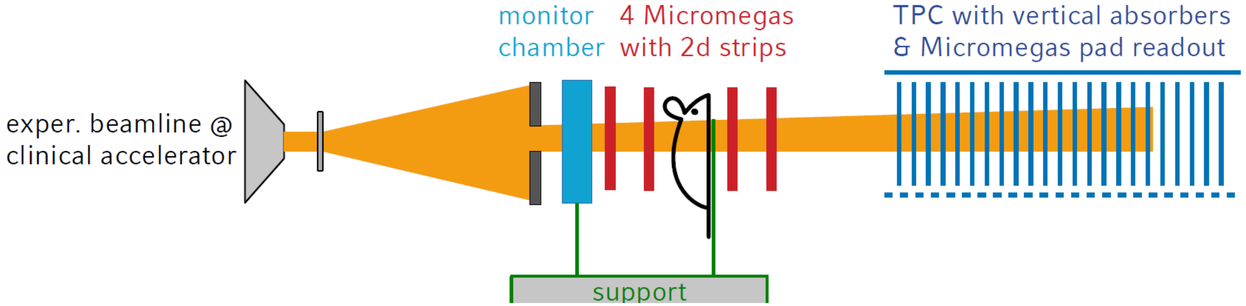
- Proton transmission imaging for recovery of tissue relative stopping power (to water, RSP)
- Vertical irradiation position for imaging & treatment
- In-house holder accommodating sterility, anaesthetization and temperature stabilization, with minimal material budget and possibility of acoustic coupling

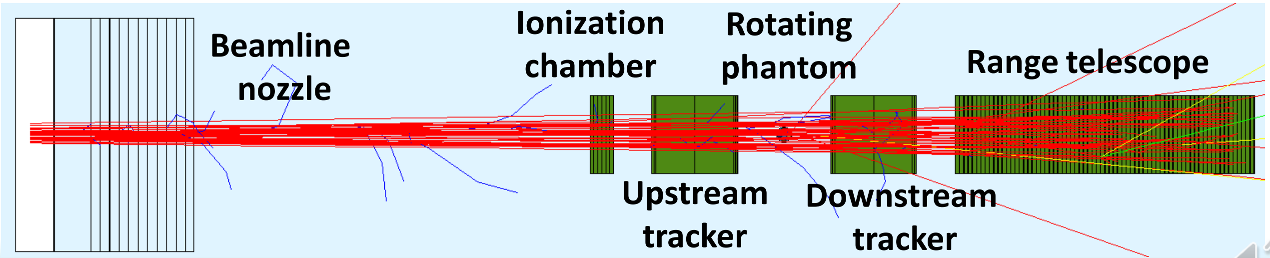
Two solutions being developed for conventional & synchrocyclotron-based facilities

1. Single particle tracking

- Low dose (< 1 mGy per radiography)
- Accounts for Coulomb scattering
- **Complex detectors**

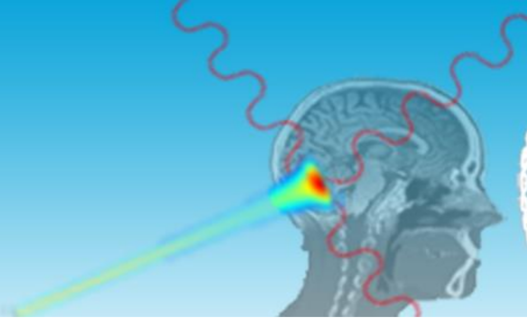






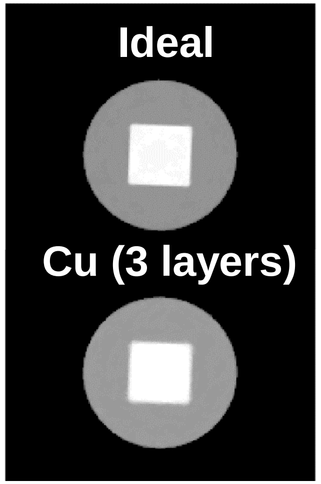
Detailed Monte Carlo modeling including all components and realistic beam

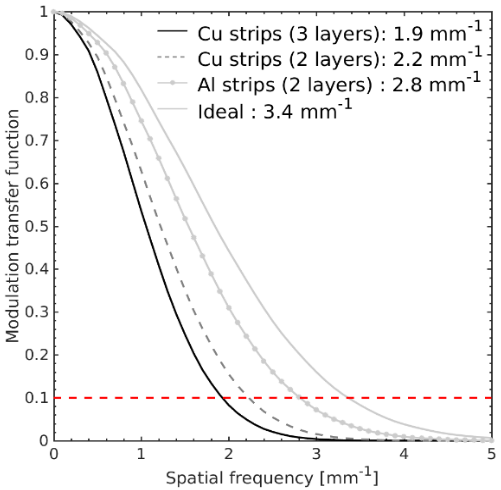
WP2a: Proton radiography/tomography

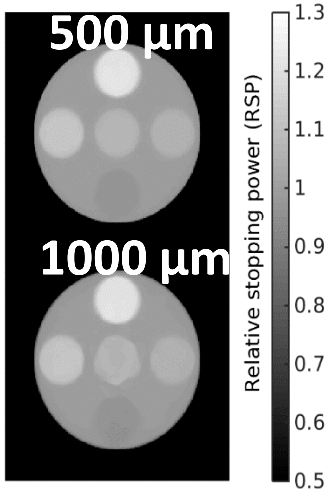


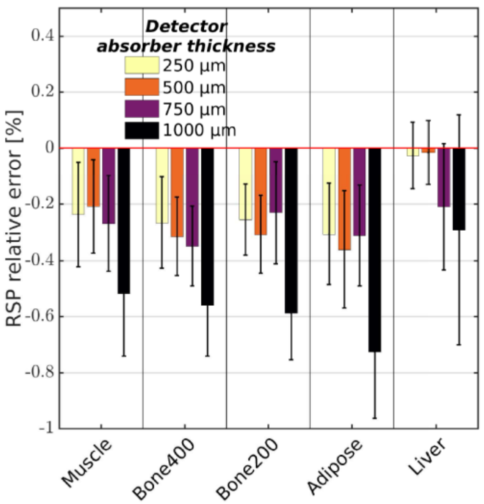
Optimization of tracker and range telescope design for best image quality

Image reconstruction using a **TVS OS-SART** algorithm

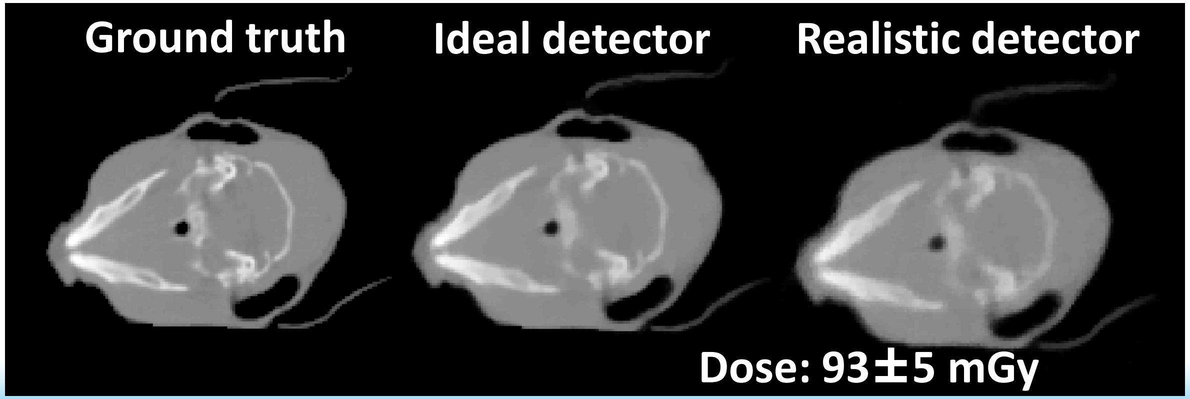


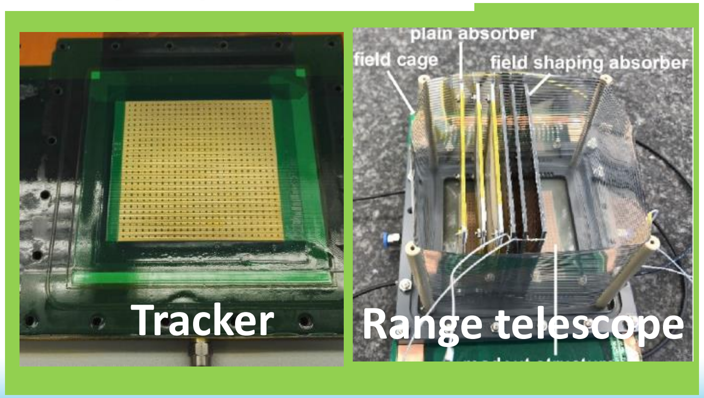






Final choice of tracker with Al strips and range telescope with 500 µm mylar plates





Currently finalizing detector production & assembly for first beam testing

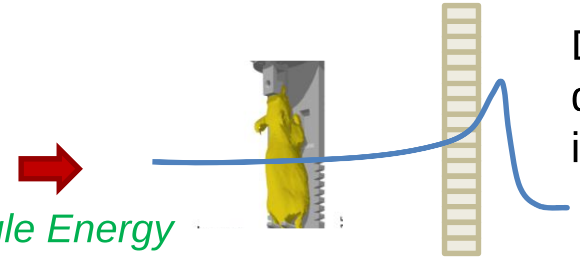
Bortfeldt et al, MPGD 2019; Meyer PhD thesis LMU; Meyer et al PMB 2020

WP2a: Proton radiography/tomography

Two solutions being developed for conventional & synchrocyclotron-based facilities

2. Commercial pixel-detectors

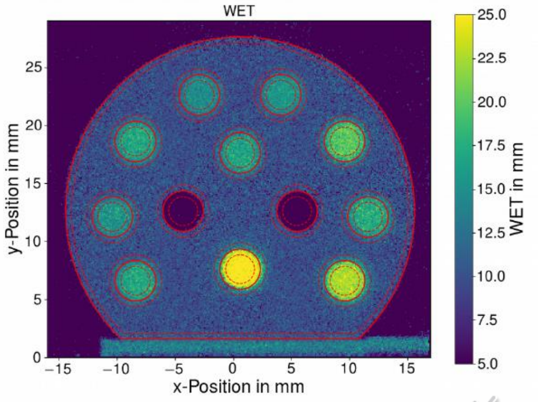
- High dose (> 1 mGy per radiography)
- Do not account for Coulomb scattering
- Relatively **simple detectors**
- Integrating / single particle detection



Comparing performance of

- Commercially available large area CMOS detector ($49.5 \times 49.5\ \mu m^2$ pixel size) with linear signal decomposition method to determine WET
- Minipix/Timepix, potentially able of single particle detection (in collaboration with Advacam Radiation imaging Solutions)

Preliminary Exp. results



Reconstructed WET distribution

Schnürle PhD project, Würl et al, submitted to IEEE MIC 2020

In-vivo range monitoring

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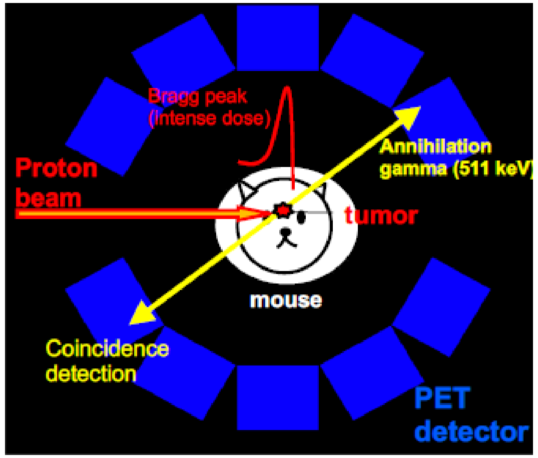
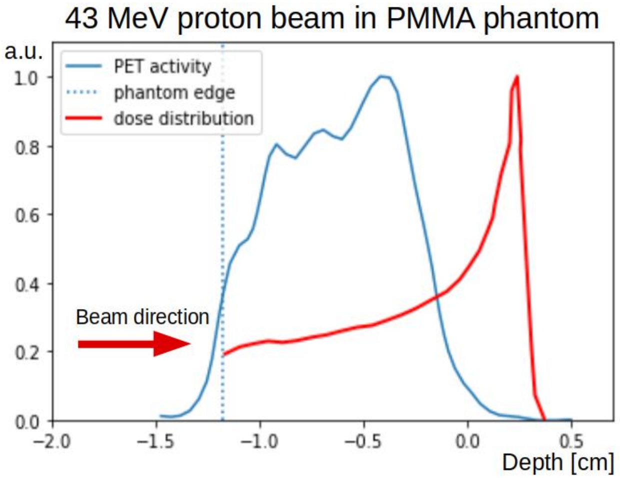
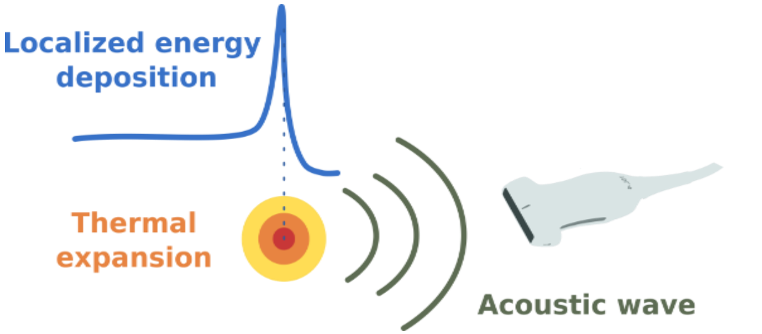
Two solutions being developed for conventional & synchrocyclotron-based facilities

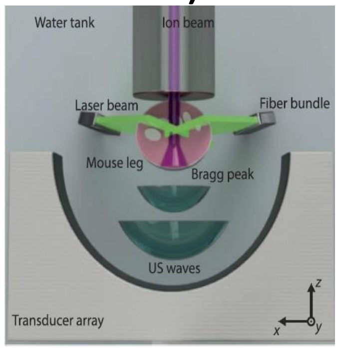
WP2.c Development of dedicated in-beam PET scanner to detect irradiation induced activity





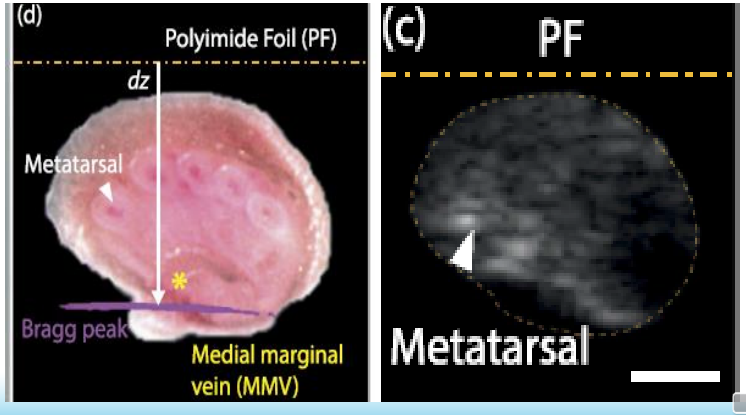
WP2.b Exploitation of thermoacoustic emissions from pulsed beam delivery (ionoacoustics)





Sub-mm Bragg peak characterization & co-registration with US at pulsed 20 MeV

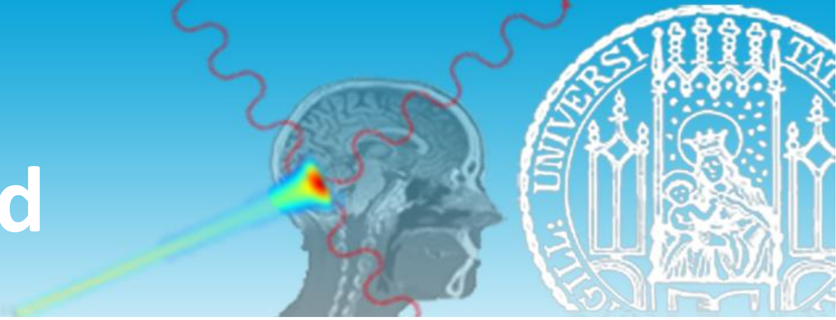
SCIENTIFIC REPORTS



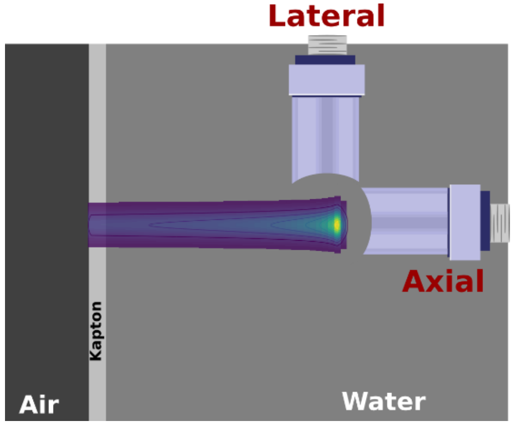
Nitta et al, IEEE MIC 2019, Lovatti PhD project

Kellnberger, … Parodi, Ntziachristos, Sci Rep 2016

WP2b: Ionoacoustics/Ultrasound

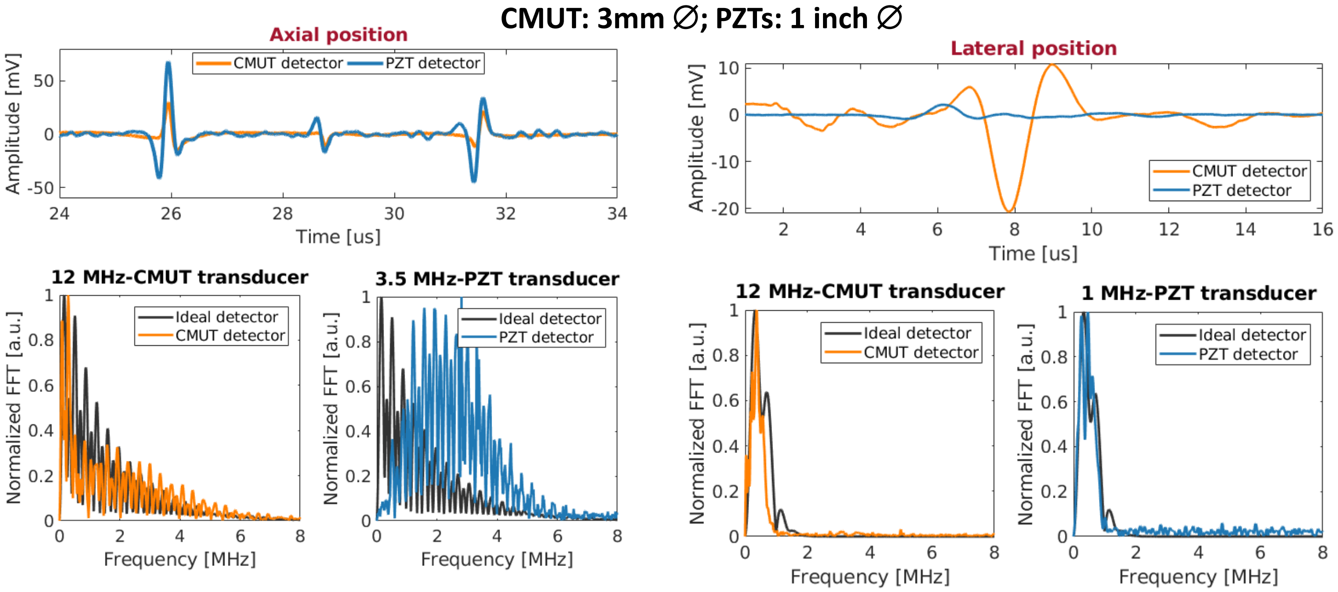


Impact of transducer technology and positioning: comparison of **CMUT*** detectors to commercially available transducers (**PZT**-based) in axial and lateral position



CMUT: Capacitive Micromachined Ultrasonic Transducers, developed by Dr. A.S. Savoia in Università Tre Rome, Italy

Ongoing development of alternative sensor technologies (e.g., PVDF)



Larger bandwidth and better sensitivity of CMUT vs PZT:

- Improved range verification accuracy
- SNR enhancement
- Independent of beam energy and probe position
- Bi-modality imaging (US / Ionoacoustics)

J. Lascaud …H. Wieser…Parodi, IEEE IUS 2019; R. Kalunga PhD project

WP2b: Ionoacoustics/Ultrasound

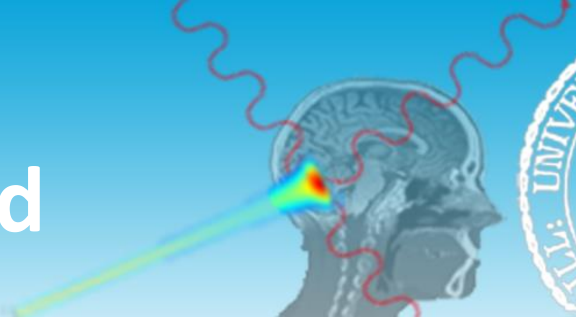
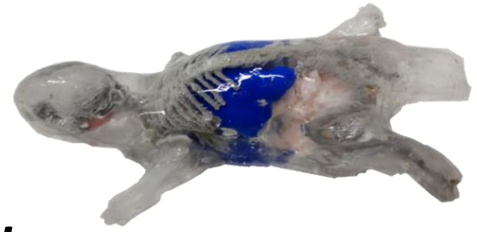
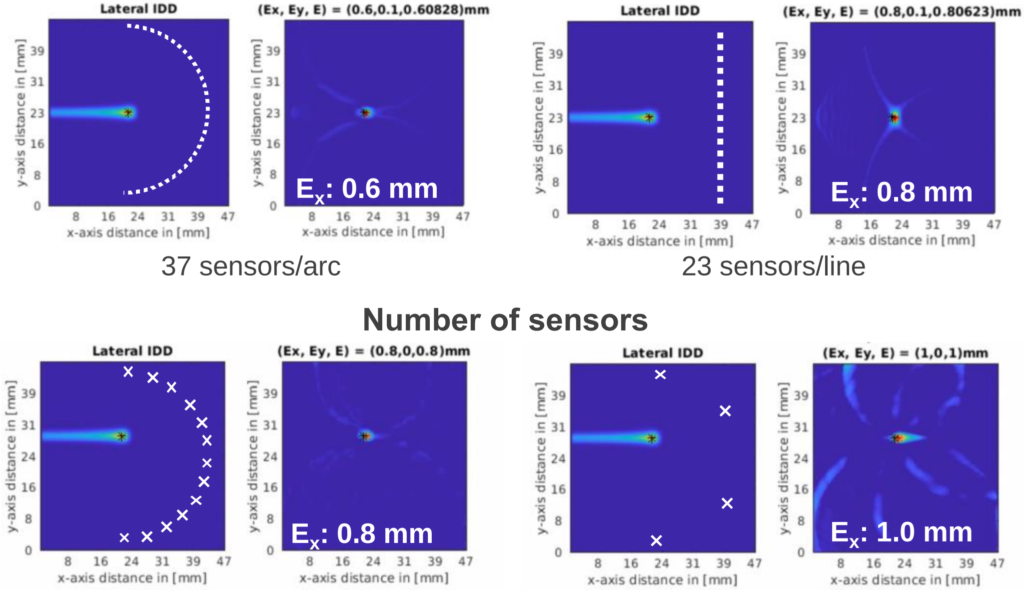


Image reconstruction and co-registration

- Evaluation of optimal sensor position for triangulation or image reconstruction
- Development of 3D printed multimodal mouse
- Ionoacoustics/US co-registration with single sensor in heterogenous media



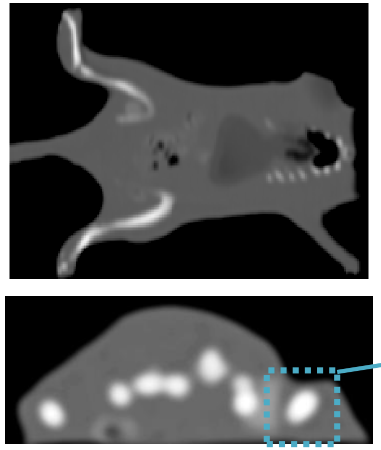
Sensor arrangement



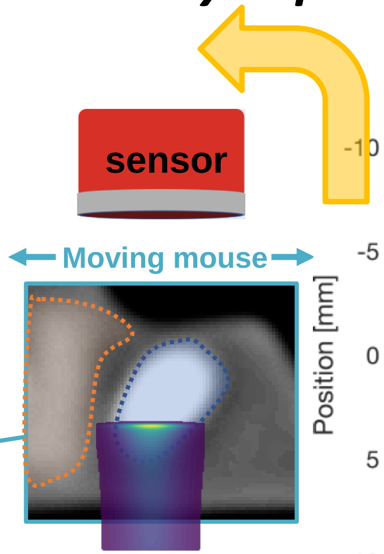
13 sensors/arc

4 sensors/arc

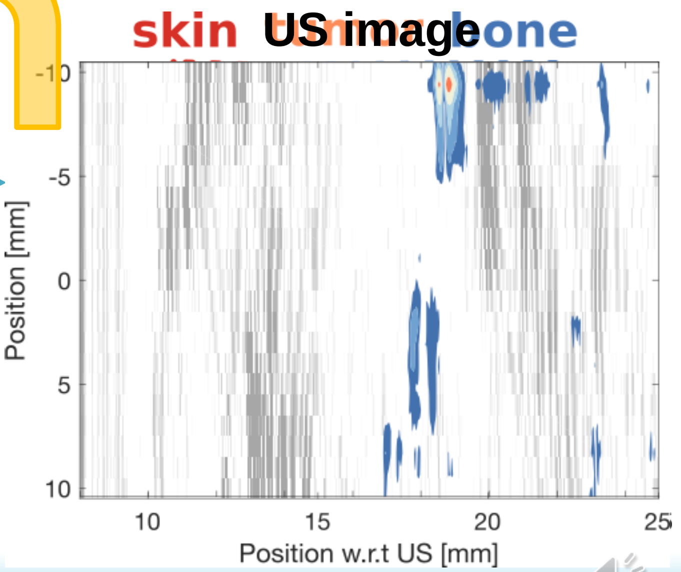
Preliminary Exp. results



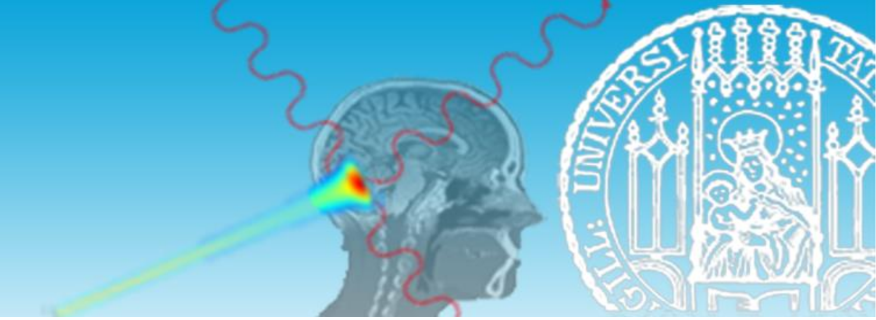
Phantom CT scan
(top: coronal & bottom: axial planes)



Proton beam



Lascaud … Parodi, talk at Small Animal Precision IGRT conference; Lascaud … Parodi, submitted to IEEE MIC 2020; Dash MSc thesis



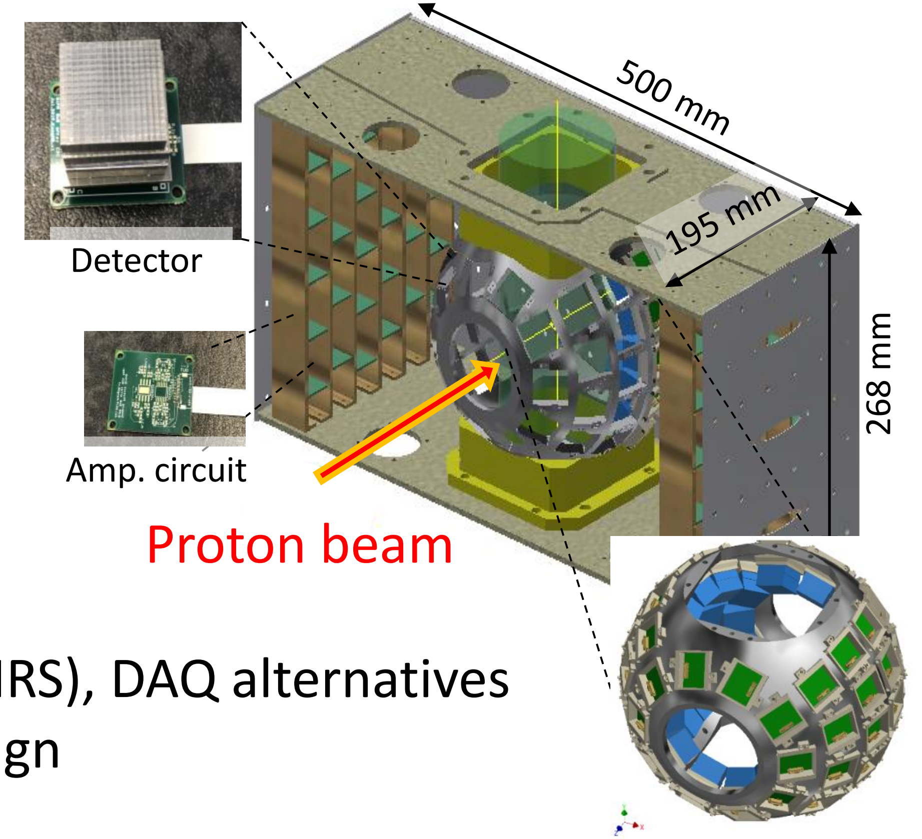
WP2c: In-beam PET

Requirements of high-sensitivity, (sub)-millimeter spatial resolution, in-beam integration

Investigations

- Detector materials (L(Y)SO, GAGG, GSO)
- Layout (pixelated vs monolithic, block vs pyramid)
- Geometrical arrangements with Geant4 simulations (incl. optical photons) and MEGAlib imaging framework

3-layer DOI block with 0.9 pixel width



Solution

- 56 LYSO DOI detectors and spherical design (7-12% efficiency)
- Spatial resolution <1.0 mm FWHM
- Wide opening for beam, mouse holder & ultrasound transducers

Ongoing work & Next steps

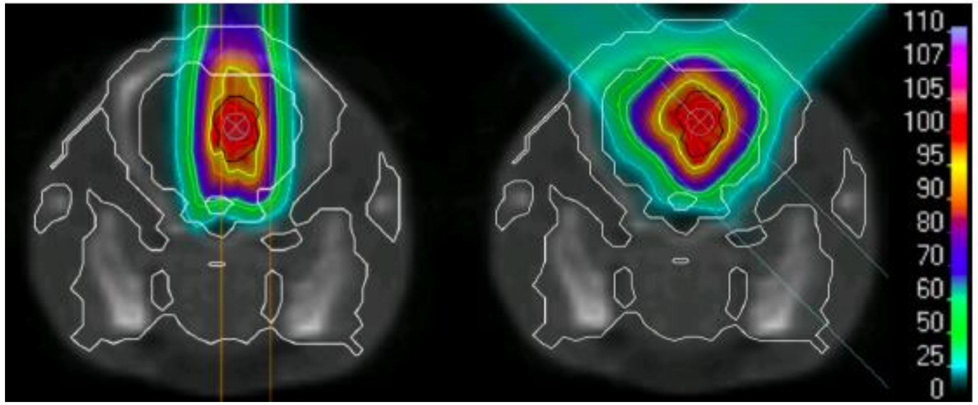
- Exp. characterization of new detector technology (developed at NIRS), DAQ alternatives
- Finalization of image reconstruction framework & mechanical design
- Start of realization

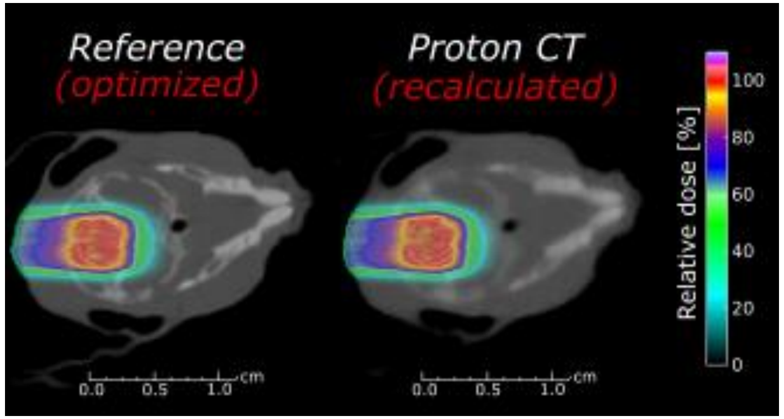
Nitta, …Yamaya, Thirolf, Parodi, IEEE NSS-MIC 2019; Lovatti PhD project; Haghani MSc project

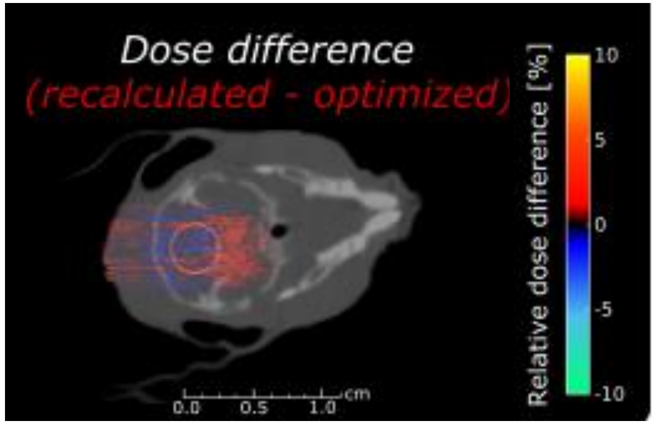
WP3: Adaptive treatment workflows

Beamline optimization and future SIRMIO operation requires TPS planning system

- License agreement and RCA with RaySearch Laboratories







Average range error (0.87±0.98)%

Ongoing work & Next steps

- Validation of μ-RayStation against full Monte Carlo transport code
- Systematic planning studies for final optimization of setup and assessment of pCT image quality
- Import/handling of all SIRMIO imaging data to develop adaptive treatment workflow
- μ-RayStation upgrade to explicitly handle SIRMIO beamline (with RaySearch)

Conclusion & Outlook

Several WPs ongoing to realize prototype SIRMIO platform

Constant dialogue with end-users regarding positioning system, hygienic restrictions & workflow

Pre-treatment imaging

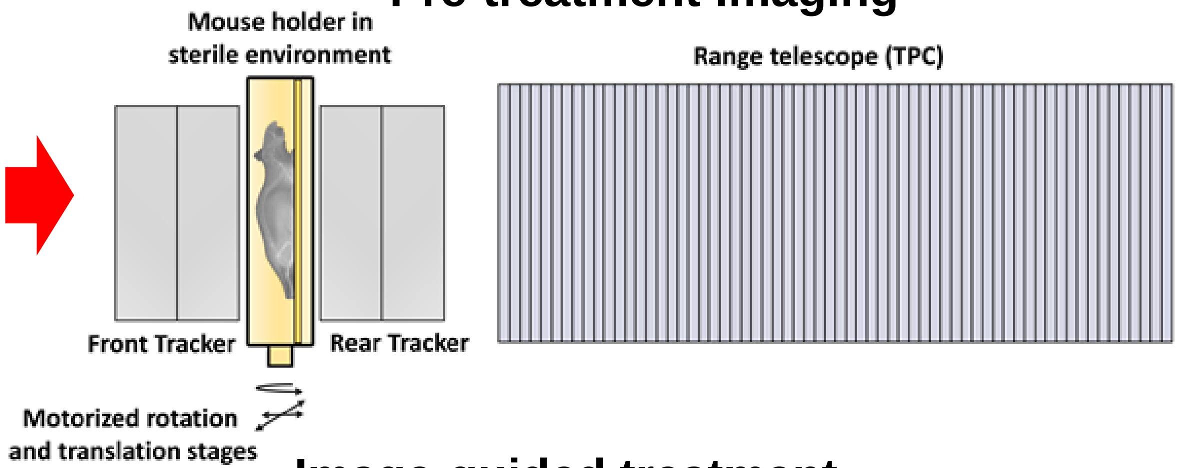
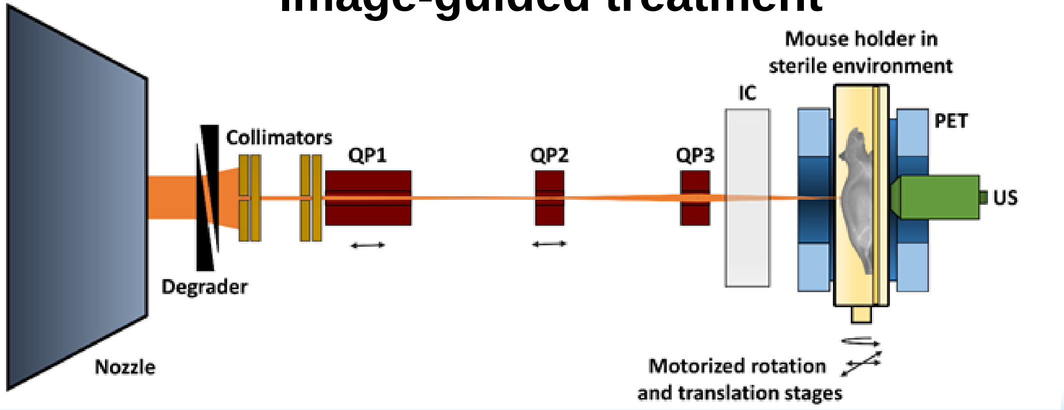


Image-guided treatment



Final system, to be realized in ~1.5 years, should be adaptable to different proton centers and could thus offer a versatile platform for precision small animal radiation research

Parodi … Würl, Acta Oncologica 2019; Meyer…Parodi PMB 2020

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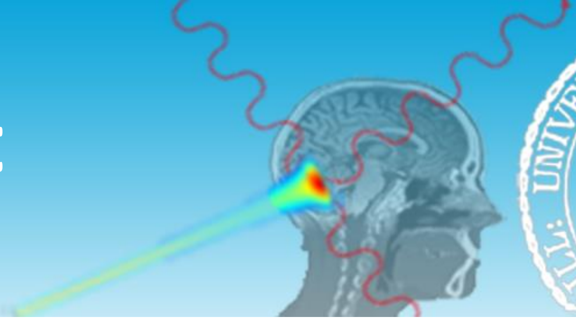
SIRMIO

Acknowledgement



WP1/WP3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M. Pinto


S. Gerlach


F. Neri


L. Zott


P. Lämmer


J. Bortfeldt

WP2.a


S. Meyer


M. Würl


K. Schnürle

WP2.b


J. Lascaud


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WP2.a

WP2.b

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Thank you for your attention!

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