New horizons and physics research opportunities in ion beam therapy

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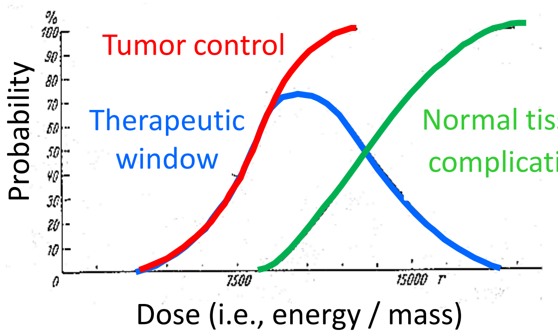
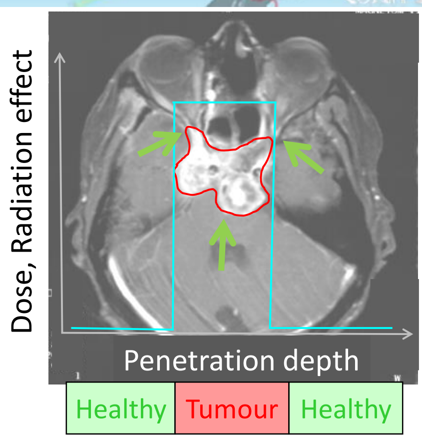
The goal of radiation therapy



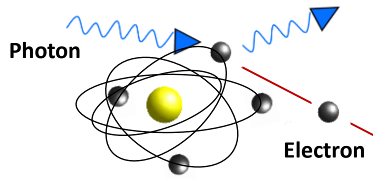


The quest for an external radiation able to
Kill tumour cells
Spare healthy tissue

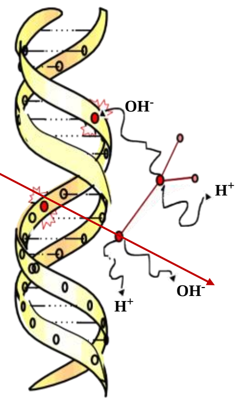
H. Holthusen, Strahlentherapie 57: 254-268, 1936

Basics of photon therapy

- Widely used photons (X-rays) transfer energy in few interactions with atomic electrons (mainly Compton scattering)

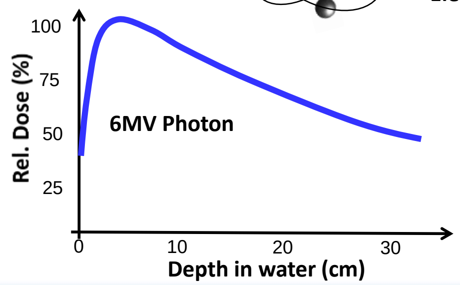


- Electrons can in turn damage DNA through
  - Direct ionization (≈1/3)
  - Creation of free radicals (≈ 2/3)



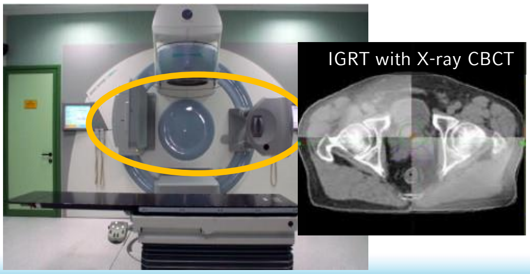
M. Hill, MRC, Harwell

- Depth dose limited by exponential attenuation, after initial build-up
  - Different beam directions and intensity modulation



Photon therapy in the 21th century

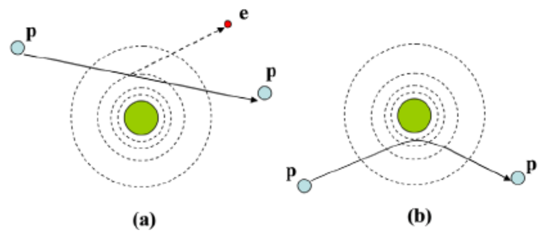
Advanced photon therapy (IMRT, VMAT, IGRT, ART…)

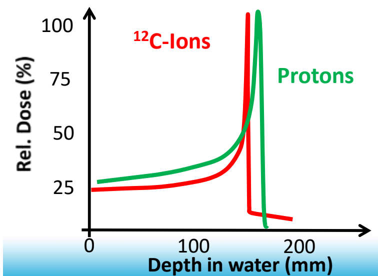


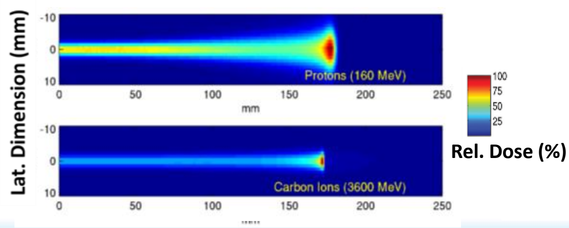
Source: Elekta, Accuray, ViewRay

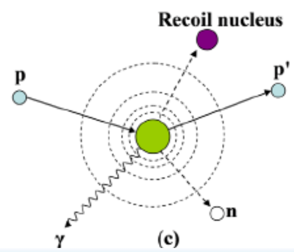
Basics of ion beam therapy

- Coulomb force interaction with tissue atoms
  - Energy loss with electrons ($\propto Z^2 / v^2$)
  - Lateral deflection on nucleus (↓ for ↑ E, m)
- Nuclear force interaction with nuclei
  - Attenuation of primary ions
  - Production of secondary particles and radiation









Newhauser and Zhang, Phys Med Biol 2015

Biological effectiveness

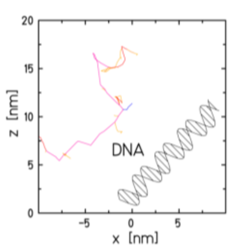
- Radiation effects are mainly due to complex DNA damage in cell nucleus
- Depend on ionization density of released electrons

Sparsely ionizing radiation

X-rays

Protons

(or high energy ^{12}C-ions in entrance channel)

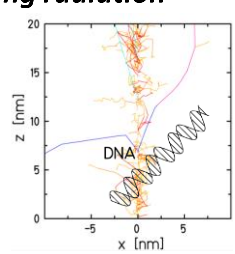


Simple DNA-damages (reparable)

Densely ionizing radiation

Low energy ^{12}C-ions

(in Bragg-Peak i.e. tumor)



Complex DNA-damages (limited reparable)

Enhanced relative biological effectiveness

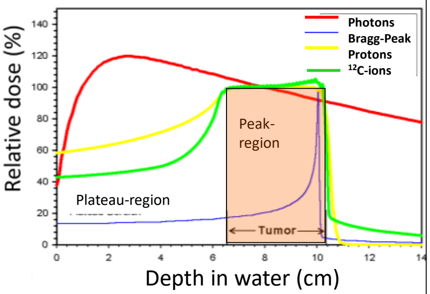
Krämer et al, Adv Space Res 1994

Kraft Prog Part Nucl Phys 2000

Physical and biological advantages of ion beam therapy

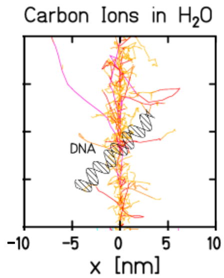
Physical selectivity

- Depth-dose profile (Bragg-Peak)
- ↓ lateral scattering *(Z>1)*



Biological effectiveness

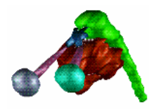
- Elevated local ionization density
- ↑ Biological effectiveness
- ↓ Influence of tumour oxygenation



Optimal differential effect Z ≈ 6 (^{12}C ions)

Clinical rationale

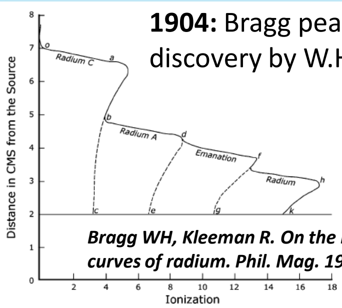
- Inoperable tumours close to organs at risk
- Pediatric tumours
- Radioresistant tumours (^{12}C ions)



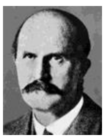
Karger and Jäkel, DKFZ Heidelberg

Krämer et al, Adv Space Res 1994

Paving the way to ion beam therapy



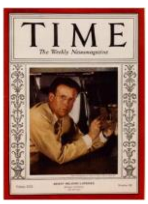
1904: Bragg peak discovery by W.H.Bragg

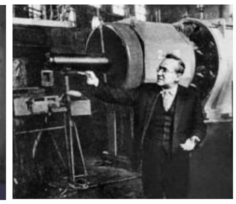


Bragg WH, Kleeman R. On the ionization curves of radium. Phil. Mag. 1904; S.6:726–38

1929: Cyclotron invention by E.O.Lawrence

1945: Synchrotron invention by E.M.McMillan and V.I.Veksler





1946: Proton therapy proposal by R.R. Wilson

Radiological Use of Fast Protons
ROBERT R WILSON
Radiol. 47 (1946) 487-91

- **Protons can be used clinically**
- Accelerators are available
- Maximum radiation dose can be deposited into the tumour sparing healthy tissues
- „**Heavier nuclei, such as very energetic carbon atoms**, may eventually become therapeutically practical“

Source: Wikipedia, Alamy stock photo, Lawrence Berkeley Lab/science photo library

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Ion beam therapy: An historical perspective

Fundamental Research | Clinical Research | Clinical Application

1946 *Ion therapy proposal for deep seeted tumors*

1954 Lawrence Berkeley National Laboratory starts proton therapy in USA

1957 Uppsala starts proton treatment in Europe (Sweden)

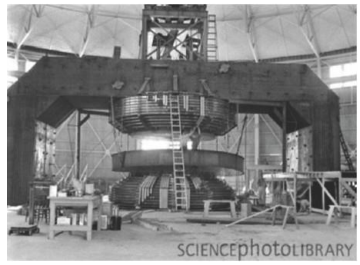
1975 Lawrence Berkeley National Laboratory starts using heavy charged particles

1990 Opening of the Proton Therapy Center in Loma Linda

1993 Start of Carbon Ion Therapy in Chiba (Japan)

1997 Carbon ion therapy with 2D active delivery starts in Darmstadt (Germany)

Since 2000: Various clinical centers



Source: Lawrence Berkeley Lab/science photo library, Loma Linda University Medical Center

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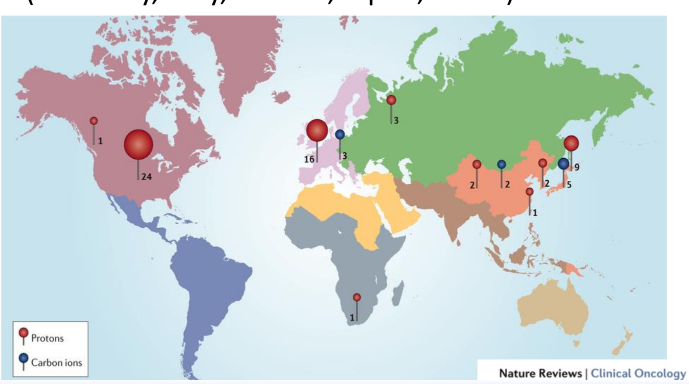
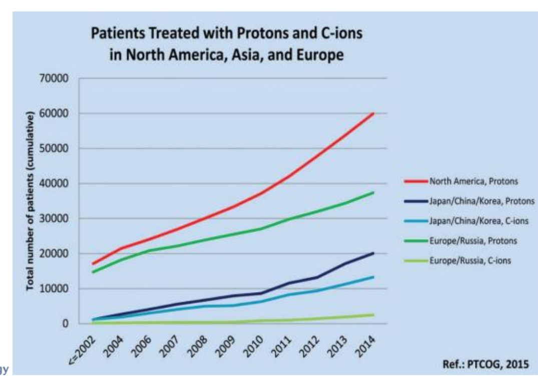
The worldwide spread of ion beam therapy

- > 90 proton therapy facilities (35 in USA)
- 13 carbon ion therapy facilities, 6 combined with protons (Germany, Italy, Austria, Japan, China)

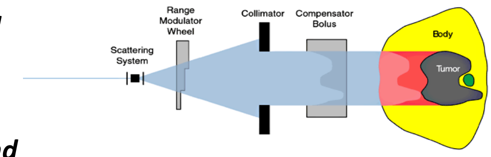
Worldwide >200,000 patients treated with ions



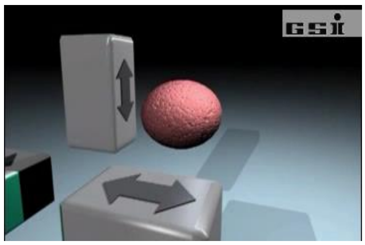


Technological evolution of ion beam therapy

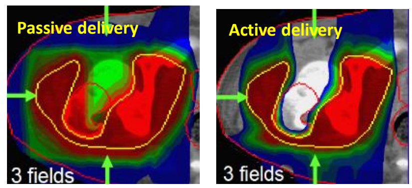
From fixed beamlines and passive beam delivery …



… to rotating gantries and active beam delivery…

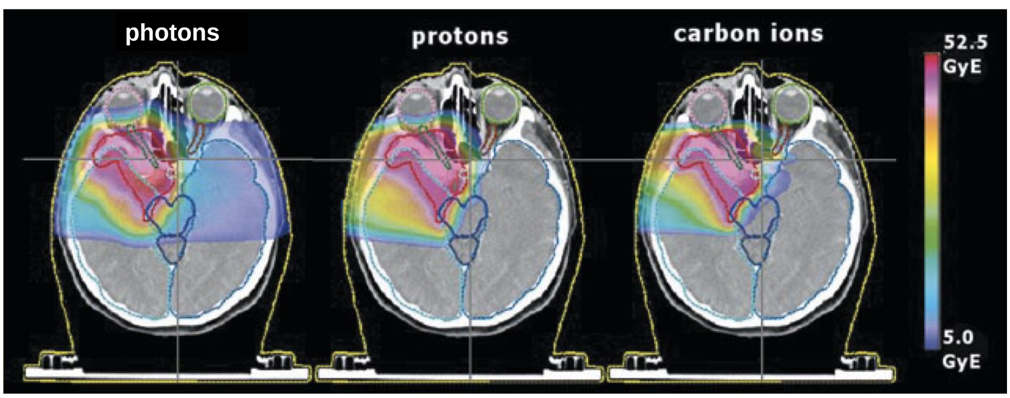


… to intensity modulated particle therapy (IMPT)



Sources: http://www.schaer-engineering.ch/en/rptc.html14, GSI Darmstadt, A. Lomax, PSI

Ion beam therapy in the 21th century



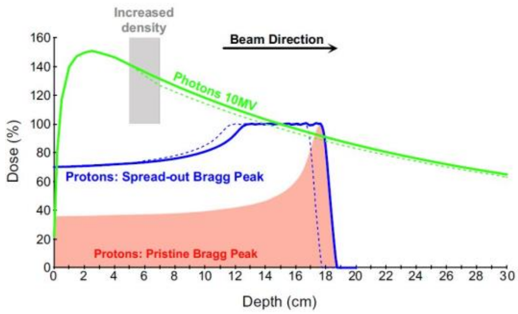
Is what we see what the patient receives?

Nuclear Physics for Medicine Report, NUPECC, 2014

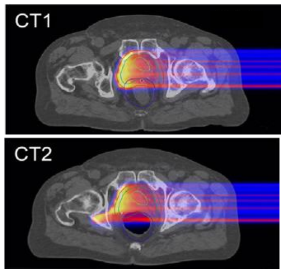
Challenges in clinical practice

Increased sensitivity to uncertainties in beam delivery

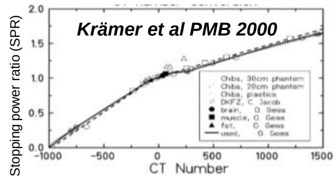
- Anatomical changes (inter- and intra-fractions)
- Tissue stopping power (relative to water, SPR)

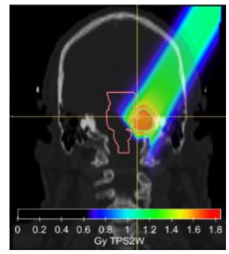


M. Engelsman et al, Seminars Rad. Onc. 2013



S. Schmid…K. Parodi, G. Dedes, PMB 2015



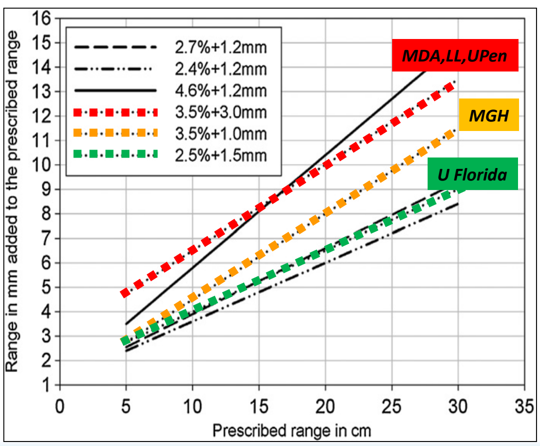


Bauer et al, HIT

How to reduce range uncertainties?

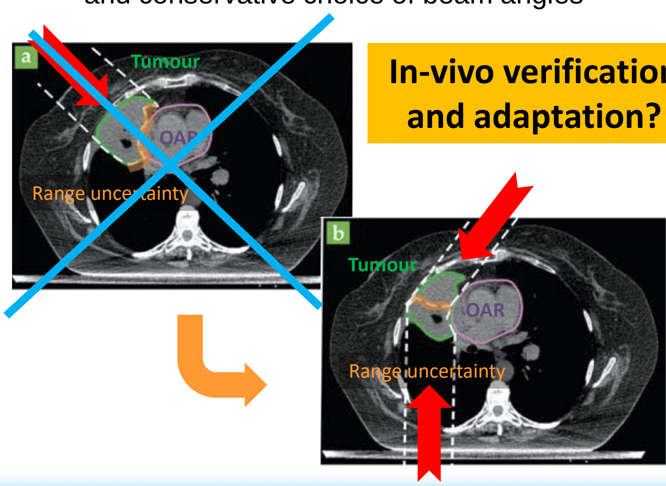
Mitigating range uncertainties in clinical practice

Usage of safety margins (non-isotropic) ≈ 2.5-3.5% + 1-3 mm



Paganetti, PMB 2012

and conservative choice of beam angles



In-vivo verification and adaptation?

Polf and Parodi, Phys Today 2015

In-room imaging for ion beam therapy

Anatomical imaging (as in modern photon therapy)

- Horizonzal/vertical CT
- On-board Cone Beam CT (CBCT)

- *Magnetic Resonance Imaging ?*

Source: TPC, Northwestern Medicine, Oncoray Dresden, MGH Boston, IBA, MedPhoton; Hoffmann …Parodi, RadOnc 2020

In-room imaging for ion beam therapy

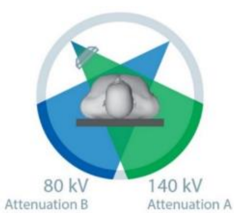
Imaging of tissue stopping power properties (SPR, specific to ion beam therapy)

- *Dual Energy X-ray CT (DECT)*

Commercially available

Enables patient-specific calibration

Improved SPR accuracy

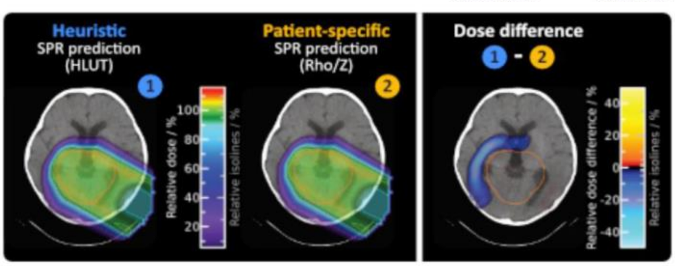


- *Ion transmission imaging?*

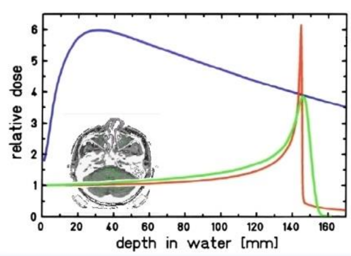
Under development

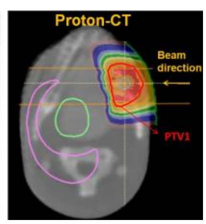
Enables direct SPR estimation

Low-dose imaging



Wolfahrt et al, IJROBP 2017





Oancea&Schulte, IEEE MIC 2018

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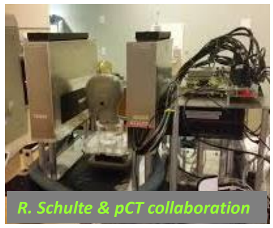
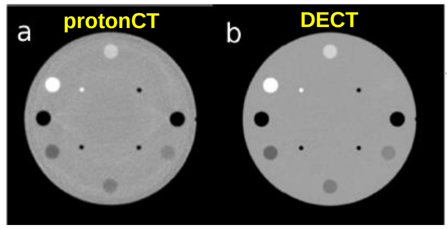
In-room imaging for ion beam therapy

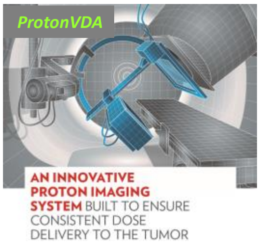
Imaging of tissue stopping power properties (SPR, specific to ion beam therapy)

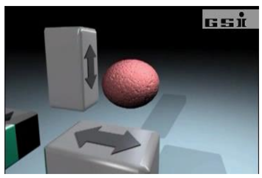
Competitive performance of proton CT prototype vs dual-source DECT at much lower imaging dose

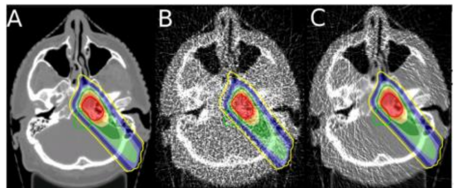




Ongoing efforts to translate this technology into clinical use







Further dose reduction possibilities in combination with fluence modulation

	A	B	C
noise in beam	Low	High	Low
dose outside beam	High	Low	Low

Dedes, ..., Parodi, PMB 2019 ; Dedes...Parodi, Landry MP 2018

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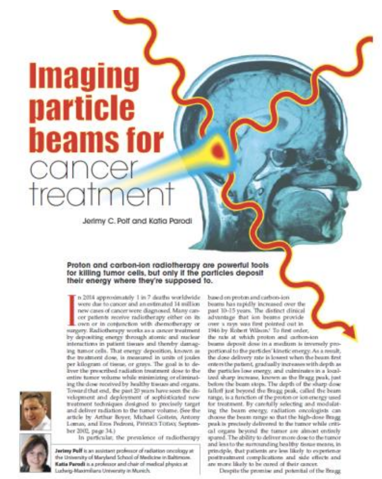
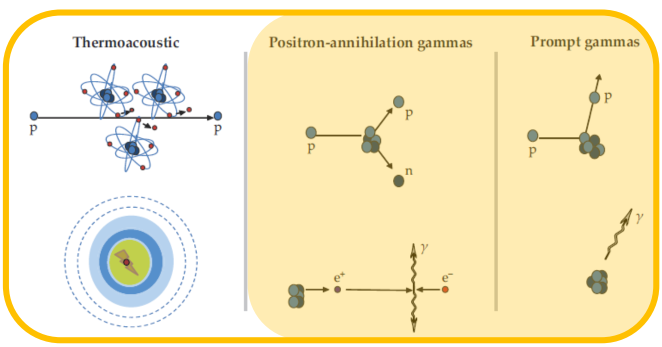
Make the invisible visible


Imaging particle beams for cancer treatment

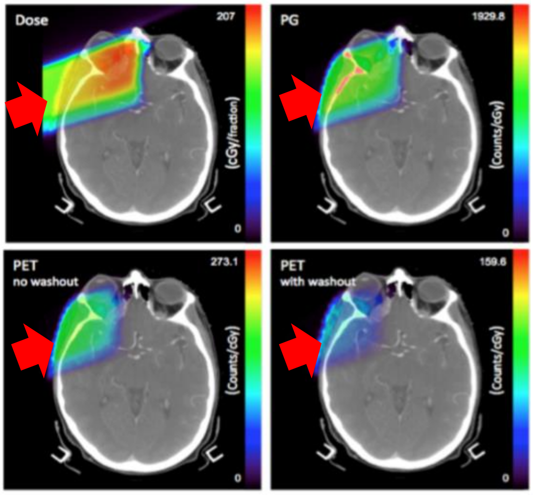
Jerimy C. Polf and Katia Parodi

Proton and carbon-ion radiotherapy are powerful tools for killing tumor cells, but only if the particles deposit their energy where they're supposed to.

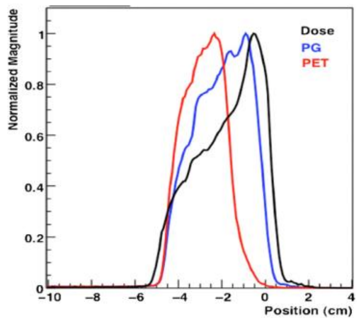
Different emission mechanisms

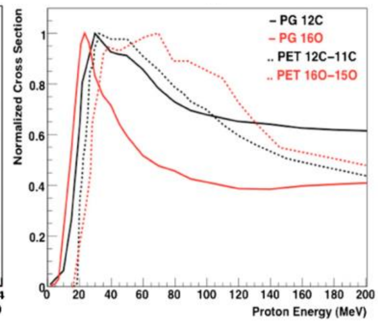


PET or PG imaging?



PG (ideal 100% detection efficiency, volumetric imaging, no background) vs post-treatment PET for proton therapy

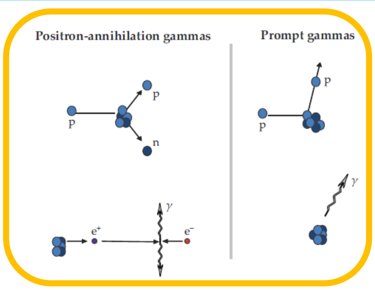


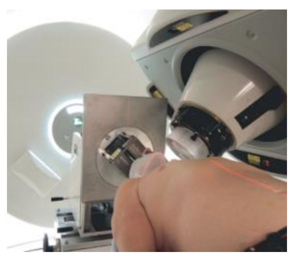


Ideal PG signal shows better correlation to range due to lower energy threshold of reaction cross sections

Moteabb, España, Paganetti, PMB 2011

PET or PG imaging?





PET

- Proven imaging technologies, with many ongoing developments for nuclear medicine applications (eg ultra-fast TOF)
- Intrisically 3D, possibility of combination with tracer imaging
- Issues of washout and „slow“ response

PG

- Requires dedicated instrumentation for detection of multi-MeV photons
- Not all implementations provide 3D imaging
- Online, real-time (no washout issue)
- Possibility to provide spectroscopic information

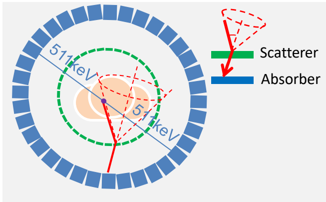
Ferraro et al, Sci Rep 2018

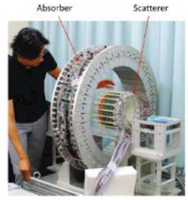
Richter et al, Radiother Oncol 2016

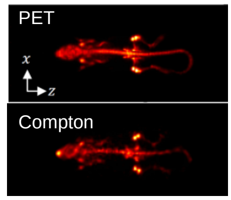
Further new trends combining PET&PG?

QST International Research Initiative (IRI)
Whole gamma imaging (WGI) research


Taiga Yamaya   Katia Parodi



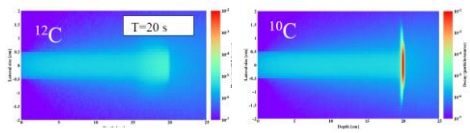




Tashima et al, PMB 2020

Hybrid γ-PET detector for future use with RIB beams at FAIR/GSI

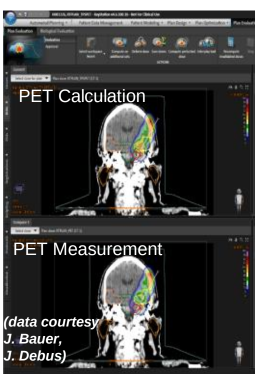

Marco Durante   Katia Parodi

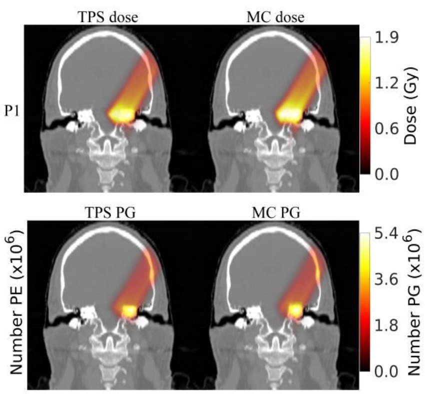


Safari …Yamaya, Thirolf, Parodi, to be presented at PTCOG 2021
Nitta, Binder, …Kang, Yamaya, Thirolf, Parodi, IEEE 2019, to be published

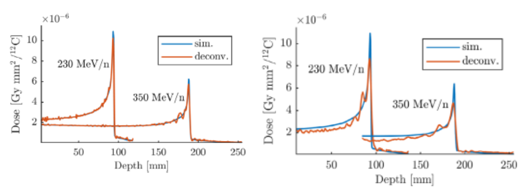
Integration in clinical workflow

Comparison meas. vs. prediction so far based on engines (mostly MC) external to treatment planning system (TPS)
Analytical PET & PG calculation in a research version of TPS "RayStation" for *p*, currently under extension for ^{12}C



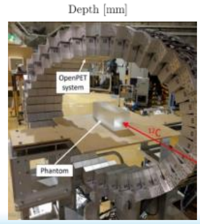


Pinto, …Parodi. PMB 2020



Opening the prospects of dose quantification

Hofmann, Pinto…Yamaya, Parodi, PMB 2019



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New horizons in small animal research

Bridging the gap: small animal radiotherapy research

Emerging irradiation platforms for protons and heavier ions

However mostly limited to morphological image guidance and passive beam shaping

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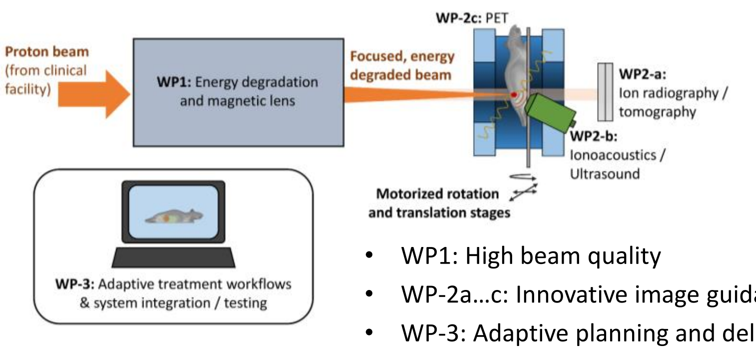
The SIRMIO project

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

SIRMIO

erc

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

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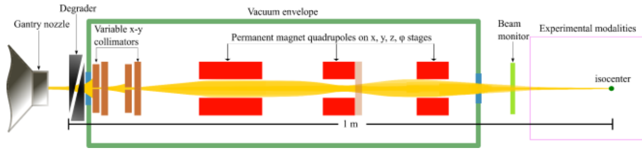
WP1: Beamline

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

Requirements:

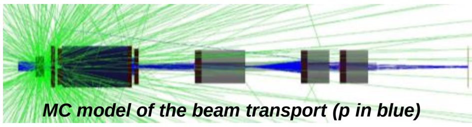
- Transport of energies between 20 and 50 MeV
- Sub-millimeter (sigma) spot sizes at isocenter
- Beam currents appropriate for treatment



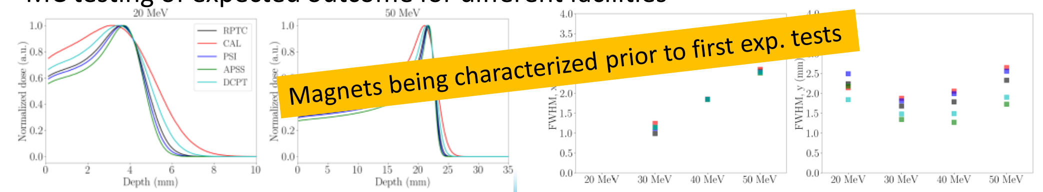
Schematic drawing of the SIRMIO beamline

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



MC model of the beam transport (p in blue)



Magnets being characterized prior to first exp. tests

Gerlach, Pinto, Kurichiyanil…Parodi, PMB 2020

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

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WP2a: Proton radiography/tomography

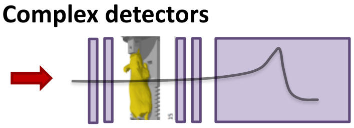
Pre-treatment radiographic & tomographic imaging

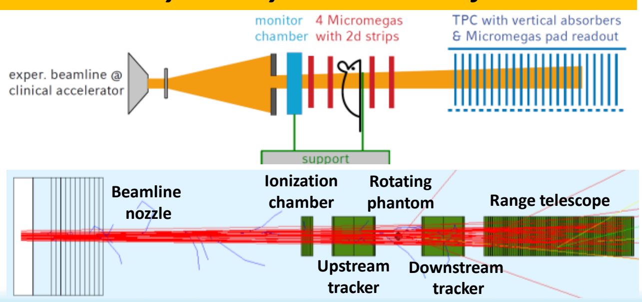
- Proton transmission imaging for recovery of tissue relative stopping power (to water, SPR)
- Vertical irradiation position for imaging & treatment
- In-house holder accommodating sterility, anaesthetization and temperature stabilization, with minimal material budget and possibility of acoustic coupling

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**



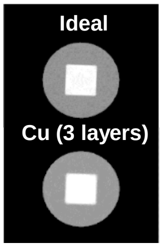


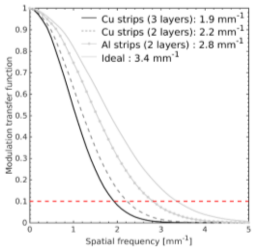
Detailed Monte Carlo modeling including all components and realistic beam

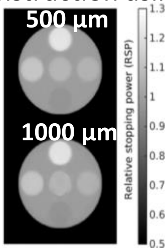
WP2a: Proton radiography/tomography

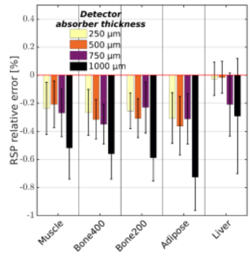
Optimization of tracker and range telescope design for best image quality

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

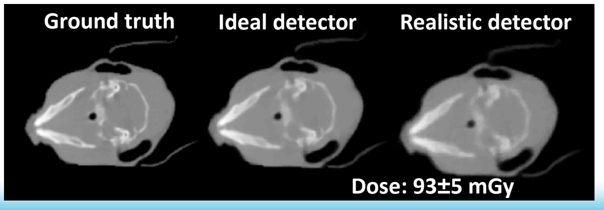


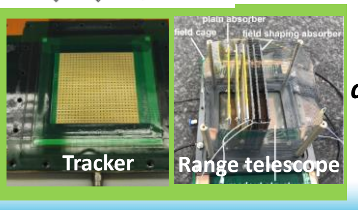






Final choice of tracker with Al strips and range telescope with 500 µm mylar plates





Currently finalizing detector production & assembly for first beam testing

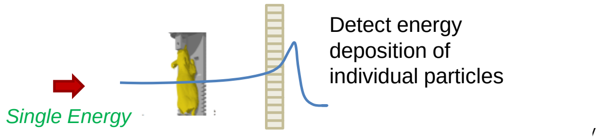
Bortfeldt et al, MPGD 2019; Meyer PhD thesis LMU; Meyer et al PMB 2020

WP2a: Proton radiography/tomography

Two solutions being developed for conventional & synchrocyclotron-based facilities

2. Commercial pixel-detectors

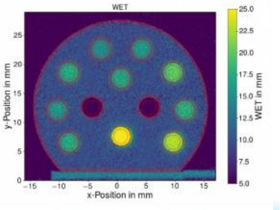
- High dose (> 1 mGy per radiography)
- Do not account for Coulomb scattering
- Relatively **simple detectors**
- Integrating / single particle detection



Comparing performance of

- Commercially available large area CMOS detector (49.5 × 49.5 µm^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



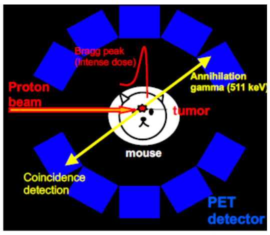
Reconstructed WET distribution

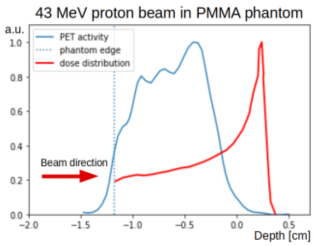
Schnürle PhD project, Würl et al, IEEE MIC 2020

In-vivo range monitoring

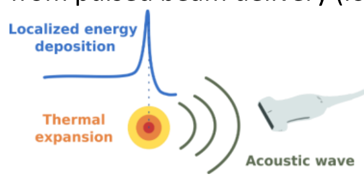
Two solutions being developed for conventional & synchrocyclotron-based facilities

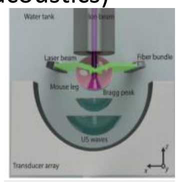
WP2.c Development of dedicated in-beam PET scanner to detect irradiation induced activity





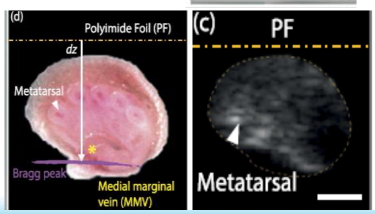
WP2.b Exploitation of thermoacoustic emissions from pulsed beam delivery (ionoacoustics)





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

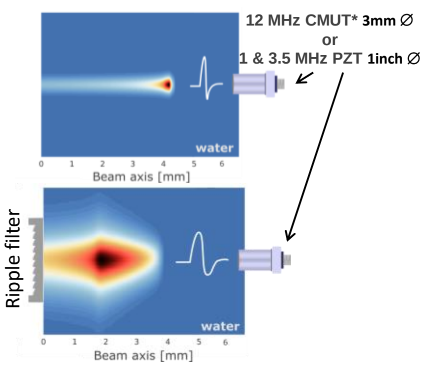
SCIENTIFIC REPORTS



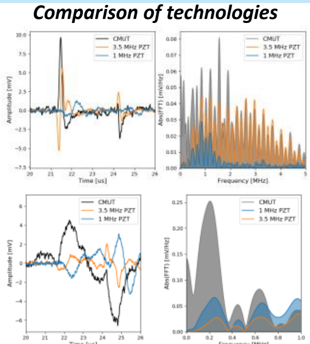
Nitta et al, IEEE MIC 2019, Lovatti PhD project

Kellnberger, … Parodi, Ntziachristos, Sci Rep 2016

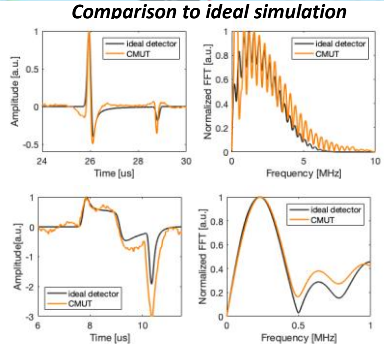
WP2b: Ionoacoustics/Ultrasound



Comparison of technologies



Comparison to ideal simulation



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

Larger bandwidth and better sensitivity of CMUT* vs PZT:

- Increased SNR
- Independent of beam energy and probe position
- Bi-modality imaging (US / Ionoacoustics)

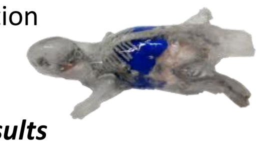
18 ***CMUT developed by Dr Savoia in Università degli Studi Roma Tre, Italy**

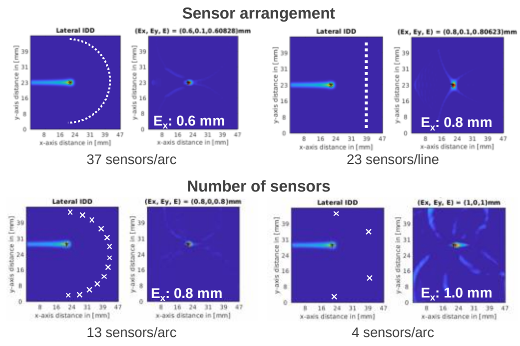
J. Lascaud …Parodi, IEEE IUS 2019

WP2b: Ionoacoustics/Ultrasound

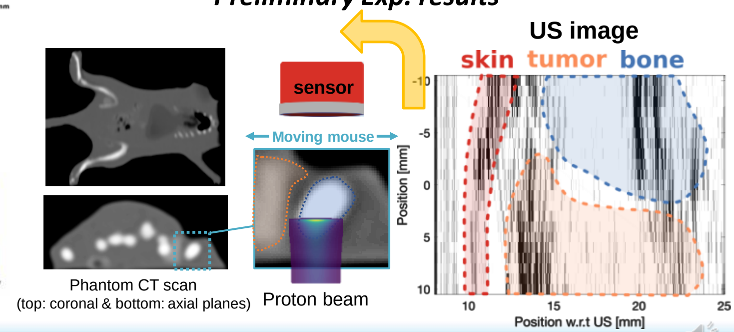
Image reconstruction and co-registration

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





Preliminary Exp. results



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

WP2c: In-beam PET

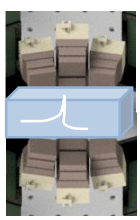
Requirements of high-sensitivity, (sub)-millimeter spatial resolution, in-beam integration

Proposed novel spherical design

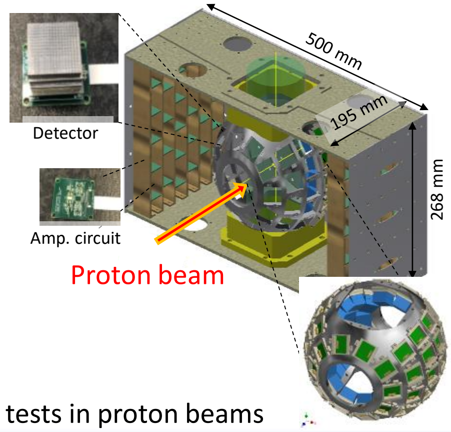
- 56 LYSO DOI detectors and spherical design (7-12% efficiency)
- Spatial resolution ≤ 1.0 mm FWHM
- Wide opening for beam, mouse holder & ultrasound transducers

First in-beam operation

- 8 LYSO DOI successfully tested in $^{10,11}C$ beams @ GSI



3-layer DOI block with 0.9 pixel width



Ongoing work & Next steps

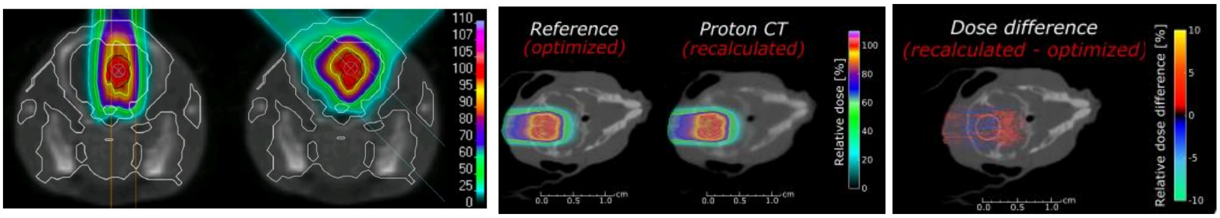
- Characterization and assembly of all 56 LYSO DOI detectors
- Finalization of simulation and image reconstruction framework
- Final evaluation of scanner imaging performance and first in-beam tests in proton beams

Nitta, Lovatti…Yamaya, Thirolf, Parodi, IEEE NSS-MIC 2019, 2021; Lovatti PhD project; Haghani MSc thesis

WP3: Adaptive treatment workflows

Beamline optimization and future SIRMIO operation requires TPS planning system

- License agreement and research collaboration agreement 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)

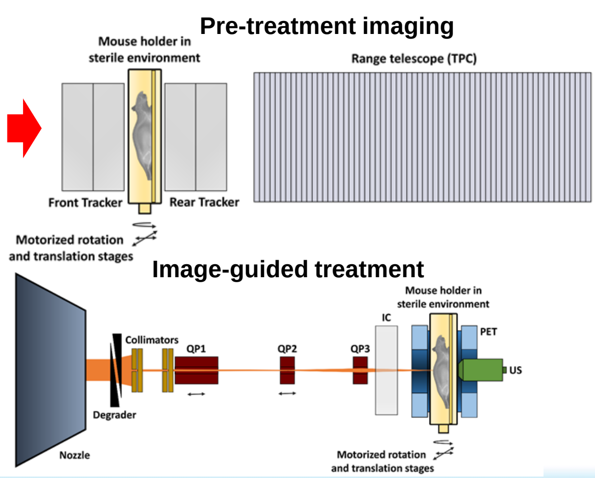
Meyer et al, PMB 2020; Pinto (LMU), Nilsson, Traneus (RaySearch), PhD thesis S. Meyer, MSc thesis S. Kundel & L. Zott

SIRMIO status & outook

Several WPs ongoing to realize prototype SIRMIO platform

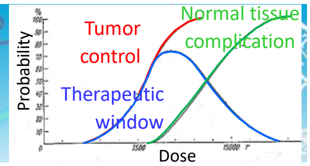
Several beamtimes scheduled in summer/fall 2021 to test performance of different components, prior to final demonstration early 2022

Final system will be adaptable to different proton centers and could thus offer a versatile platform for precision small animal radiation research

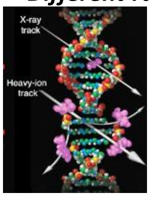


Parodi … Würl, Acta Oncologica 2019; Meyer…Parodi PMB 2020

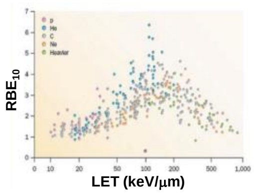
New frontiers to widen therapeutic window?



Different radiation qualities

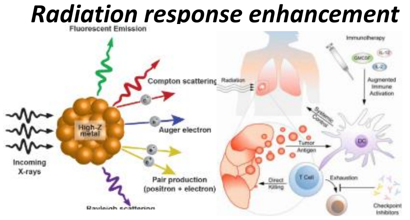


Source: NASA

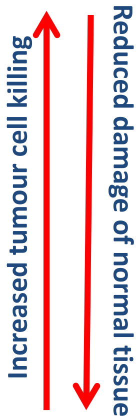


Source: GSI

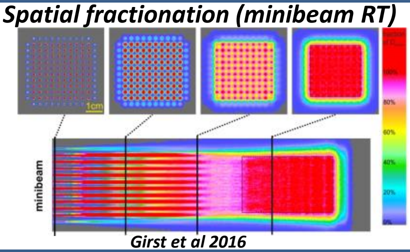
Radiation response enhancement



Kwatra et al 2013 Campbell, Decker 2017

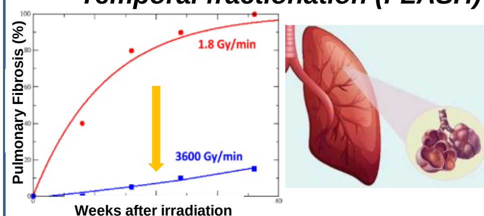


Spatial fractionation (minibeam RT)



Girst et al 2016

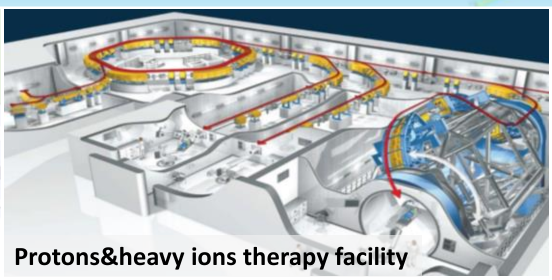
Temporal fractionation (FLASH)



Favaudon et al 2014, Durante et al 2017

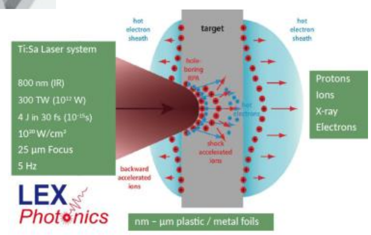
Laser-driven ion acceleration

Proton therapy facility



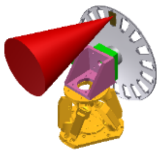
Protons&heavy ions therapy facility

From RF-accelerators (~ kV/mm)
to optical systems (~ MV/μm)?

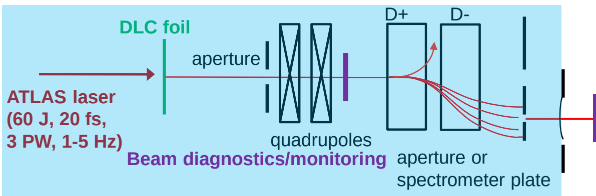


Sources: West German Proton Therapy Center & HIT Heidelberg

LION @ Center for Advanced Laser Application



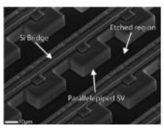
Laser-driven proton source with new targets and beamline *(AG Prof. Schreiber)*



γ– PET

Can provide instantaneous ultra-high dose rate (~1Gy/ns) for FLASH investigations

Proton radiography



L. Tran (2015), IEEE Trans Nuc Sci, 62, 6

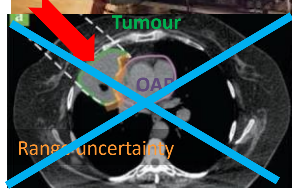
New detector prototypes *(collaboration with Wollongong University, Australia)*

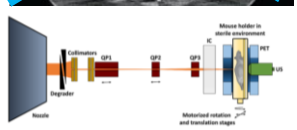
Ionoacoustics

PhD thesis S. Lehrack, S. Aldawood, S. Liprandi, M . Würl; project F. Englbrecht (ongoing)

Conclusion & Outlook

- Promising techniques for full exploitation of ion therapy advantages in clinical practice close to or just starting clinical translation & evaluation
- Reduction of uncertainties at planning & delivery stage will enable more accurate dose delivery and likely impact clinical outcome
- New technologies for precision pre-clinical research will support ongoing studies on new frontiers effects to widen therapeutic window





Research at the LMU Department of Experimental Medical Physics

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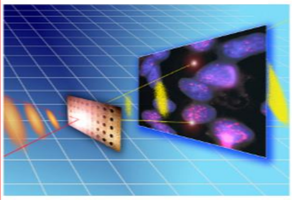
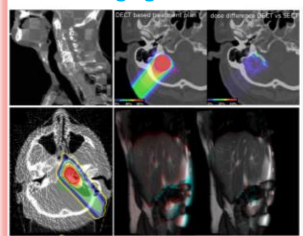
Laser Ion Acceleration

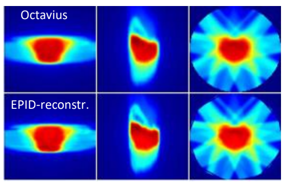


Range verification in PT

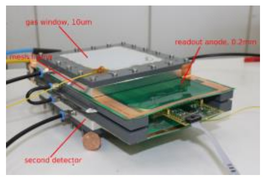
Image guidance



Dosimetry



Detector development



Acknowledgement

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LMU Department of Experimental –Medical Physics

Collaborations

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- R. Schulte et al, Loma Linda University
- T. Yamaya, NIRS
- E. Traneus, R. Nilsson RaySearch
- M. Vidal, J. Herault, CAL
- A. Savoia, University Roma Tre
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- …

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