Proton acceleration and detection for clinical and preclinical research

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IGFAE Workshop on Technologies and Applied Research at the future Galician proton-therapy facility
Santiago de Compostela
May 9-10, 2023

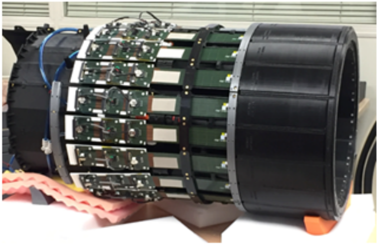
Instrumentation in Molecular Imaging

Institute i3M: located at Polytechnical University of Valencia (UPV/CSIC)

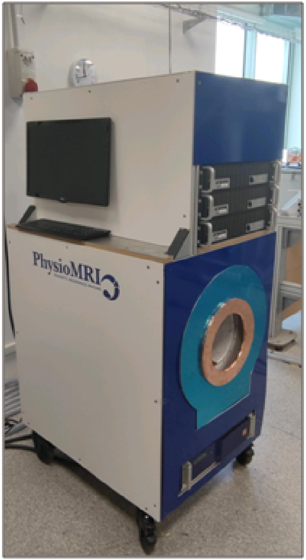
Research activities:

- Medical and preclinical imaging devices
- Grid y cloud computing
- Microelectronic engineering.

Focus on applied research.



MINDVIEW PET-MR insert



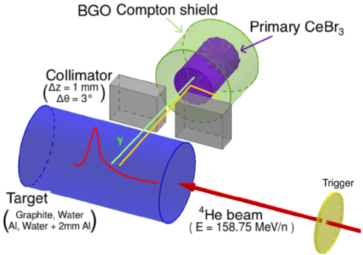
Physio-MRI portable NMR unit

Range measurement in hadron therapy

In treatment planning, depth of Bragg peak is calculated from density map of human body. Subject to daily changes, organ motion.

Detection of prompt-gamma emission in hadron therapy: J. Seco, German Cancer Research Center (DKFZ, Heidelberg)

- MeV-photons from fragmentation of beam/target nuclei
- Emission in 4π; detection at 90° to incoming beam
- Dense, fast scintillators with high energy resolution ($CeBr_3$)
- Needs beam trigger detector for background suppression.

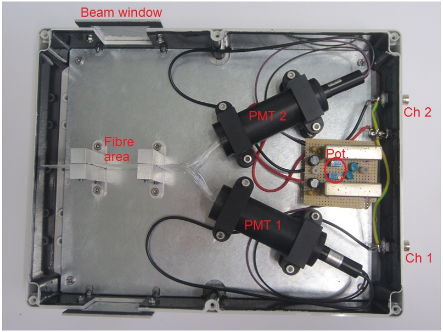


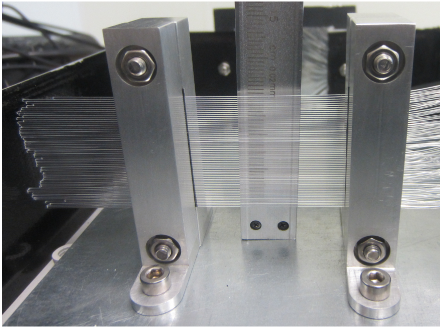
R. Dal Bello, PTCOG 57, Cincinatti (2018)

SciFi beam trigger

Lab model of hadron beam trigger detector based on scintillating fibres:

- Active area: 30×40 mm^2, 500 μm fibres, square cross section
- Two PMTs/output channels, digitization by FADC
- Used in coincidence with prompt-gamma detectors.





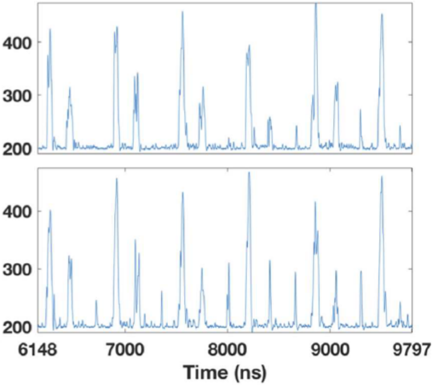
P. Magalhaes Martins, Front. Phys. 8, 169 (2020)

Performance with clinical beams

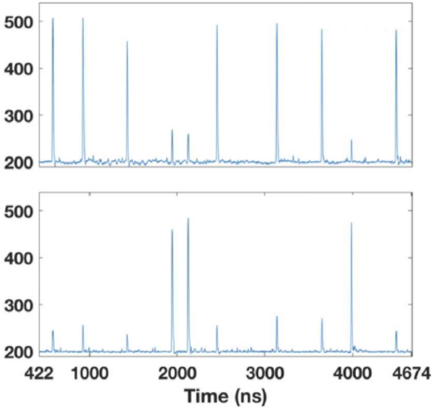
Tests at Heidelberg Ion Therapy Center (HIT):

- Single particle detection at clinical intensities
- Signals for even/odd fibres
- Protons: different ADC peak heights ⇒ multiple hits

p beam, $8 \cdot 10^7$ p/s



C ion beam, $2 \cdot 10^6$ p/s



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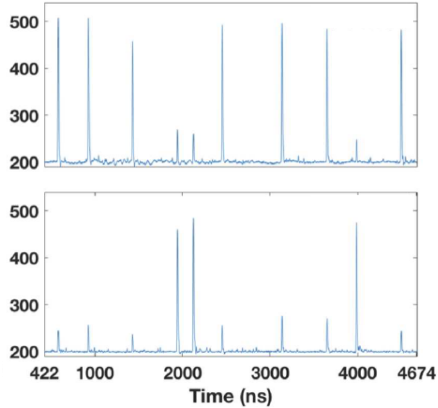


(12) **United States Patent**
Seco et al.

(10) **Patent No.:** **US 11,331,519 B2**
(45) **Date of Patent:** **May 17, 2022**

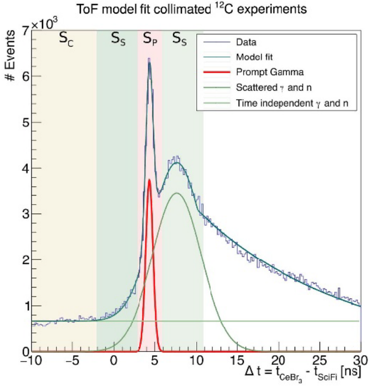
(54) **DETECTOR AND METHOD FOR TRACKING AN ARRIVAL TIME OF SINGLE PARTICLES IN AN ION BEAM**

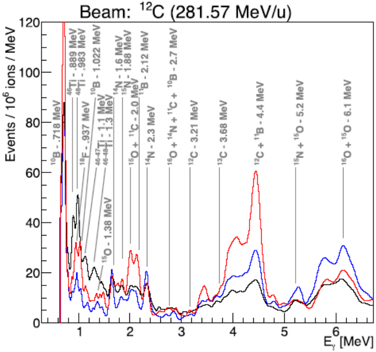
(56) **References Cited**

U.S. PATENT DOCUMENTS

Experiments with small beam monitor:

- Timing resolution wrt plastic scintillator: ~ 0.7 ns
- Clear separation of coincidence peak (~ 0.85 ns) from neutrons and fragment-induced γ
- Identification of spectral lines from nuclear reactions.





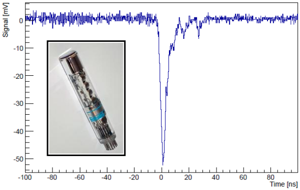
R. Dal Bello, Phys. Med. Biol. 65, 095010 (2020)

Multi-channel beam monitor

Next step: Multi-channel detector with digital output.

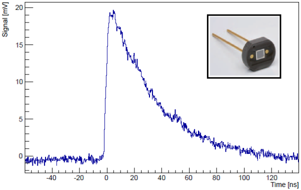
Model 1: PMT, Hamamatsu R647

- 13 mm ⌀, 10 mm cathode window
- HV supply (930 V)
- Gain $1.0 \cdot 10^6$
- Fast (ns) output pulse, good s/n ratio.



Model 2: SiPM array, Hamamatsu S13361 SPL

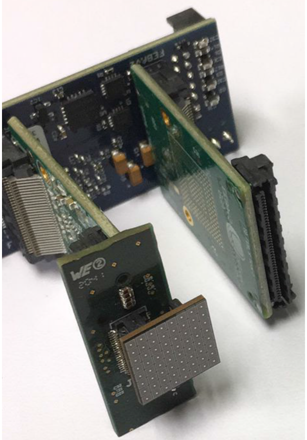
- 8×8 channels
- 1.3×1.3 mm^2 sensitive area
- 50 μm pixel pitch, 660 pixels/ch
- 53 V nominal
- Gain $1.7 \cdot 10^6$.

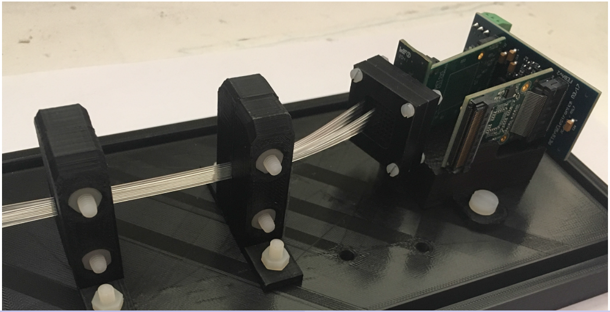


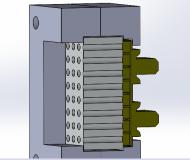
Signal digitization

Digital readout: TOFPET2 ASIC (PETsys)

- TOFPET e-kit connected to PC
- 64 ch per ASIC
- Up to 600k evts/s per channel
- Precise timing
- QDC dynamic range: 1500 pC, adjusted to gain $\sim 10^6$.



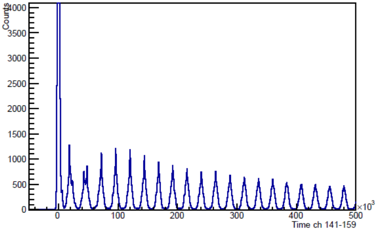


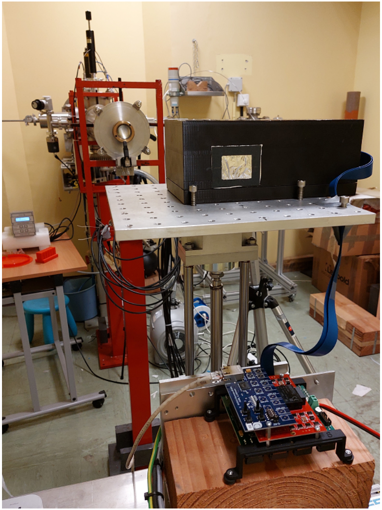


Tests with proton beam

Proton detection at CNA:

- 18 MeV cyclotron, external beamline
- 10 fibres irradiated; 100 pA
- QDC peaks of protons in all channels; rate-dependent drift
- Indications of optical cross-talk in close-by fibres
- Timing: resolve cyclotron bunch structure (2.4 ns each 24 ns).





Beam monitor: Conclusions and outlook

Lab models of SciFi detector:

- ✓ Precise coincidence timing in prompt-gamma detection
- ✓ Basic tests performed with multi-channel version
- ✓ Scalable readout via TOFPET2 ASIC.

Observations requiring further attention:

- X Optical cross-talk ⇒ use fibres with opaque cladding
- X Count rates limited to 560k evts/s per channel. For clinical intensities up to $10^{10} p/\mathrm{s}$, pencil beam, sampling at some M evts/s
- X Not tested so far: response to ultra-intense particle bunches ⇒ important for laser-ion acceleration, FLASH RT.

Proton range measurement with PET

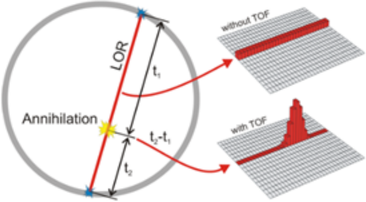
β^+ emitters generated in hadron therapy, can be detected by Positron Emission Tomography:

- Offline PET, outside the treatment room
- In-room PET, standard PET scanner inside the treatment room
- In-beam PET, during irradiation.

Challenges of in-beam PET with open geometry:

- Artifacts, limited image quality
- Low sensitivity
- Limited FOV.

Improve with time-of-flight (TOF) measurement.

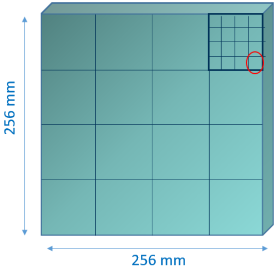


the10ps-challenge.org

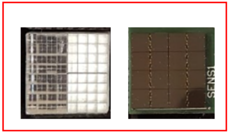
Proton range measurement with PET

Open Imaging PET (ERC-2022-POC1),
J.M. Benlloch, L. Moliner:

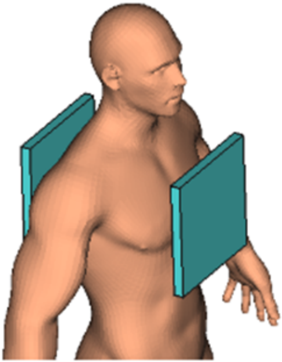
- Two-paddle PET system, 256 mm width
- Close to patient
- LYSO crystals coupled to SiPM arrays
- Row/column readout to reduce channels
- On-module digitization with TOFPET2 ASIC.



4 x 4 MODULES



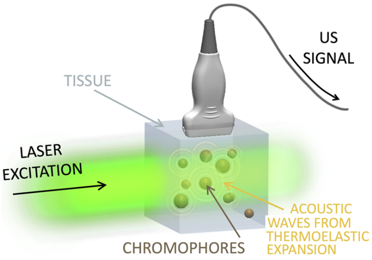
8x8 LYSO crystals 2x2x12 mm^3
coupled to a 4x4 array of SiPM of 4x4 mm^2

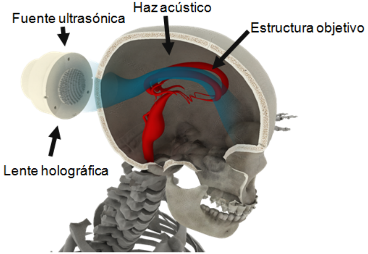


i3M Ultrasound group (F. Camarena, N. Jiménez):

- Localization of subcutaneous lesions by US waves generated in pulsed IR laser absorption
- Application of focused US to precisely localized volumes inside the brain
- Correction of wavefront distortion caused by the skull using 3D-printed holographic lenses.

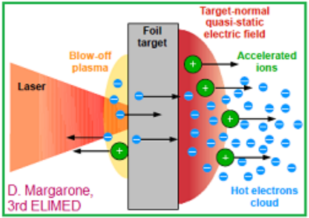
These techniques can be combined to localize the Bragg peak in proton therapy of deep seated lesions using US transducers.



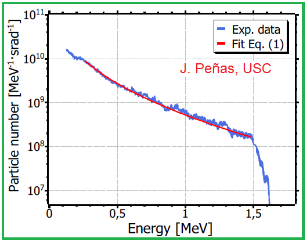


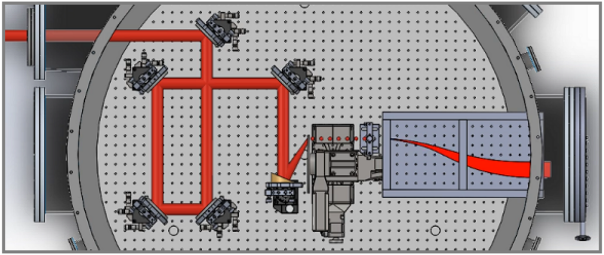
Target normal sheath acceleration (TNSA):

- Ultra-short (femtosecond) laser focused on thin foil, $I > 10^{18}$ W/cm^2
- Laser energy (J) $\Rightarrow e^- \Rightarrow \vec{E}$ field (TV/m) $\Rightarrow p$/ions (MeV/u)
- Particles spread over wide energy interval
- 10^9 protons in bunch of a few ns.

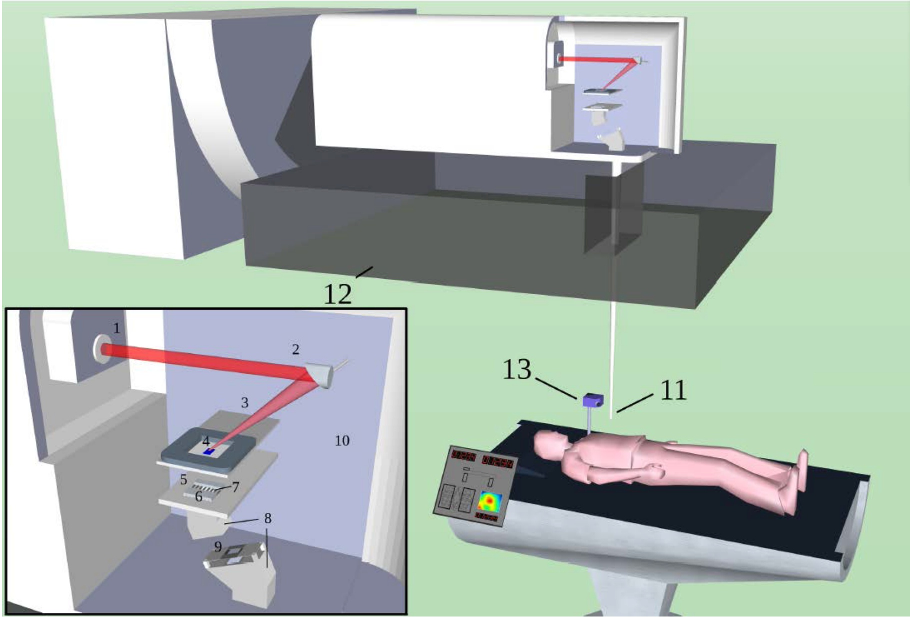


Collaboration USC-i3M at L2A2 since 2018.

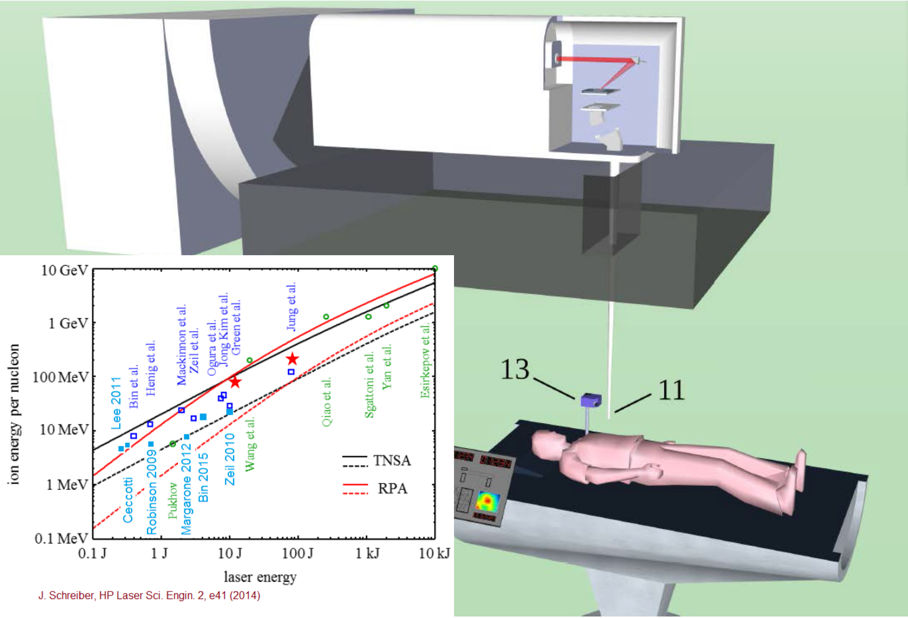




Laser-ion acceleration for medicine



Laser-ion acceleration for medicine



J. Schreiber, HP Laser Sci. Engin. 2, e41 (2014)

Radiobiological effects of laser-accelerated ions:

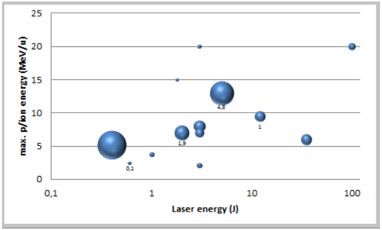
- Ultra-short (ns), ultra-intense pulses; peak dose $\sim 10^9$ Gy/s
- Single-shot dose $\sim 0.1 - 2$ Gy
- At 1-10 Hz rep rate: FLASH regime.

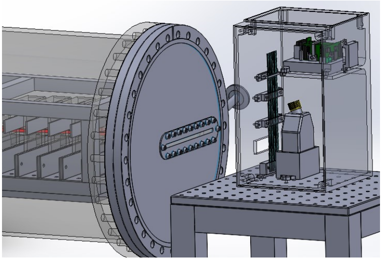
Requirements (for monolayer cell cultures):

- Stable particle source, 5-10 MeV/u
- $\Phi_p \Leftrightarrow D \Rightarrow$ narrow energy interval
- Shot-to-shot dose control
- Manipulation of biological samples in laser lab.

Experiment at L2A2 under preparation

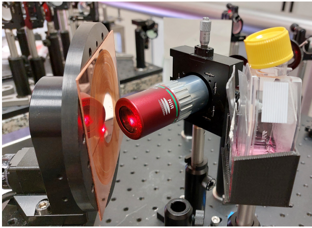
A. Torralba, QuBS 6, 10 (2022).

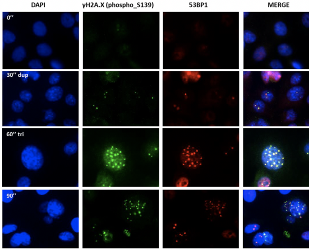




Preparation and analysis of cell cultures at Health Research Institute of Santiago de Compostela (IDIS) (Ana Vega, Miguel Aguado):

- Sterile Cell culture flasks (25 cm^2) with 70 μm peel-off foil
- Cells adhere to foil for minimum energy loss of protons
- Upright position during irradiation
- Tested with laser-X-ray source, 1 mJ on Cu target in air, 1 kHz; 0-120 keV, 70 mGy/s
- First cell line: human lung adenocarcinoma (A549)
- Visualization of γ-H2AX/53BP1 foci by immunostaining and microscopy.





A. Reija, EuNPC 2022

Collaboration with clinical facility

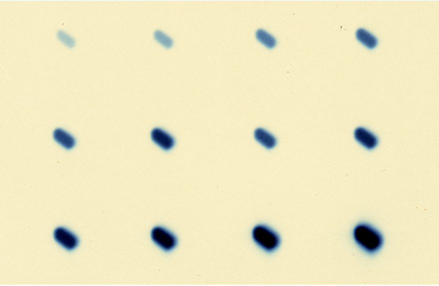
Interest in collaborating with proton therapy facility:

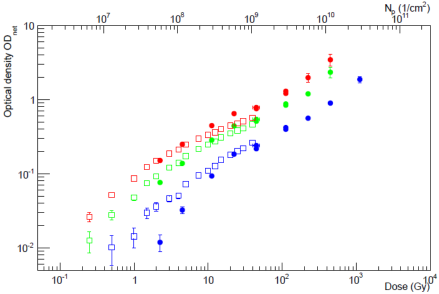
1. Tests of techniques and devices
   - Detectors to measure energies, fluence etc. of different (mixed) particle species
   - Shot-to-shot fluctuations of laser-plasma interactions
   - Strong electromagnetic pulse

$\Rightarrow$ Previous performance tests with mono-energetic particle beams at known intensities.

2. Absolute dose calibration at low-high intensities
   - Radiochromic film (EBT3-U): Optical density ⇔ dose; ideally independent of particle type, dE/dx
   - Ionization chambers: quenching at high multiplicities
   - Scintillators: saturation effects

⇒ Calibration against therapy devices.

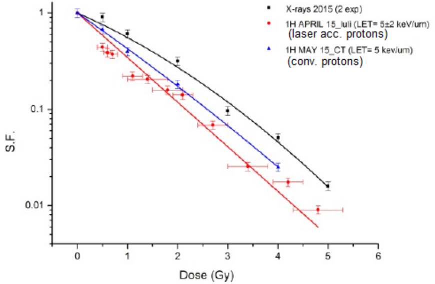




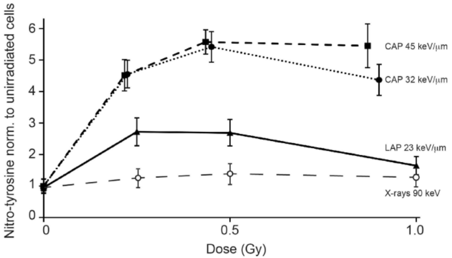
Collaboration with clinical facility

3. Interpretation of *in-vitro* data
   - Cell survival as function of total dose
   - Relative biological effectiveness (RBE)
   - Dose rate effects (clinical vs. laser-acc. protons)

⇒ Meaningful experiments require comparison of cellular effects among different radiation fields



L. Manti, J. Instrum. 12 (2017) C03084

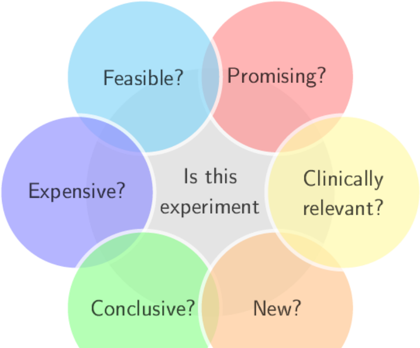


S. Raschke, Sci. Rep. 6 (2016) 32441

Collaboration with clinical facility

4. Search for interesting biological samples and endpoints
   - Cell lines, radioresistant subspecies, ...
   - DNA double strand breaks, clonogenic survival, proliferation, ...
   - Culture conditions: oxygen concentration, ...
   - Reactive oxygen species (ROS): direct/indirect markers
   - Tissue cultures; small organisms (zebra fish embryos), ...

⇒ Need to identify clinically relevant parameters.



Conclusions

Collaboration i3M-CHUS proton facility? Yes, please!

- Proton beam monitor for prompt-gamma detection and spectroscopy
- Proton range detection by TOF-PET and ultrasound
- Radiobiology program at L2A2
- Others?

Acknowledgements

Collaborators:

- i3M: F. Barranco, J. Juan
- DKFZ: J. Seco, P. Magalhaes Martins, R. Dal Bello
- USC: J. Benlliure, A. Alejo, A. Bembibre, A. Coathup, J. Peñas, A. Reija
- IDIS/FPGMX: A. Vega, M.E. Aguado
- CNA: M.C. Jiménez, J. García
- USal: C. Ruiz

Thank you for your attention!

Acknowledgements

Project LINKA20351 financed by CSIC through the i-LINK+2020 program.

Co-financed by the European Union through Programa Operativo del Fondo Europeo de Desarrollo Regional (FEDER) of the Comunitat Valenciana 2014-2020, IDIFEDER/2021/004.

Ayuda EDGJID/2021/204 financiada por Generalitat Valenciana.

Proyecto RTI-2018-101578-B financiado por MCIN/AEI /10.13039/501100011033 y por FEDER Una manera de hacer Europa.

Proyecto AICO/2020/207 financiado por Generalitat Valenciana en el programa Grupos de Investigación Consolidables.