PRONTO: Protontherapy and nuclear techniques for oncology

Research and networking activities at GFN-UCM

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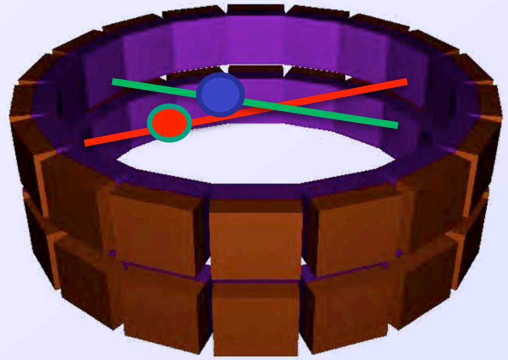
Outline

- ✓ Production of radioisotopes
  - → Multiple PET
  - → Cross-sections
  - → Application to proton-induced activity in PT
- ✓ PRONTO
  - → Motivation
  - → Description of the project
  - → Objectives
- ✓ Research and development on detectors
  - → Digital signal processing

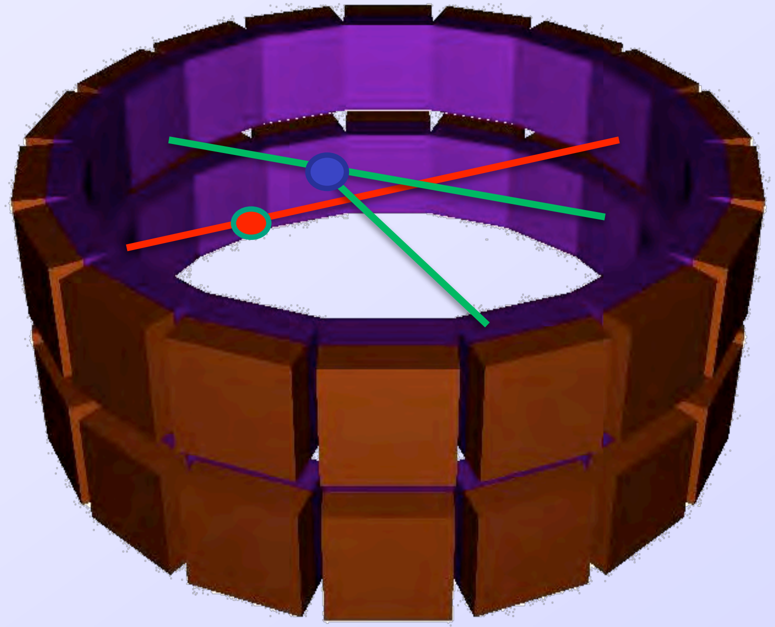
Simultaneous imaging of 2 PET tracers

PROBLEM: All annihilation gamma-rays have the same energy: 511 keV



PROPOSED SOLUTION: mPET

1) Use of (β^+) & ($\beta^+\gamma$) Emitters
2) Detect Triple Coincidences
3) Reconstruction & Separation



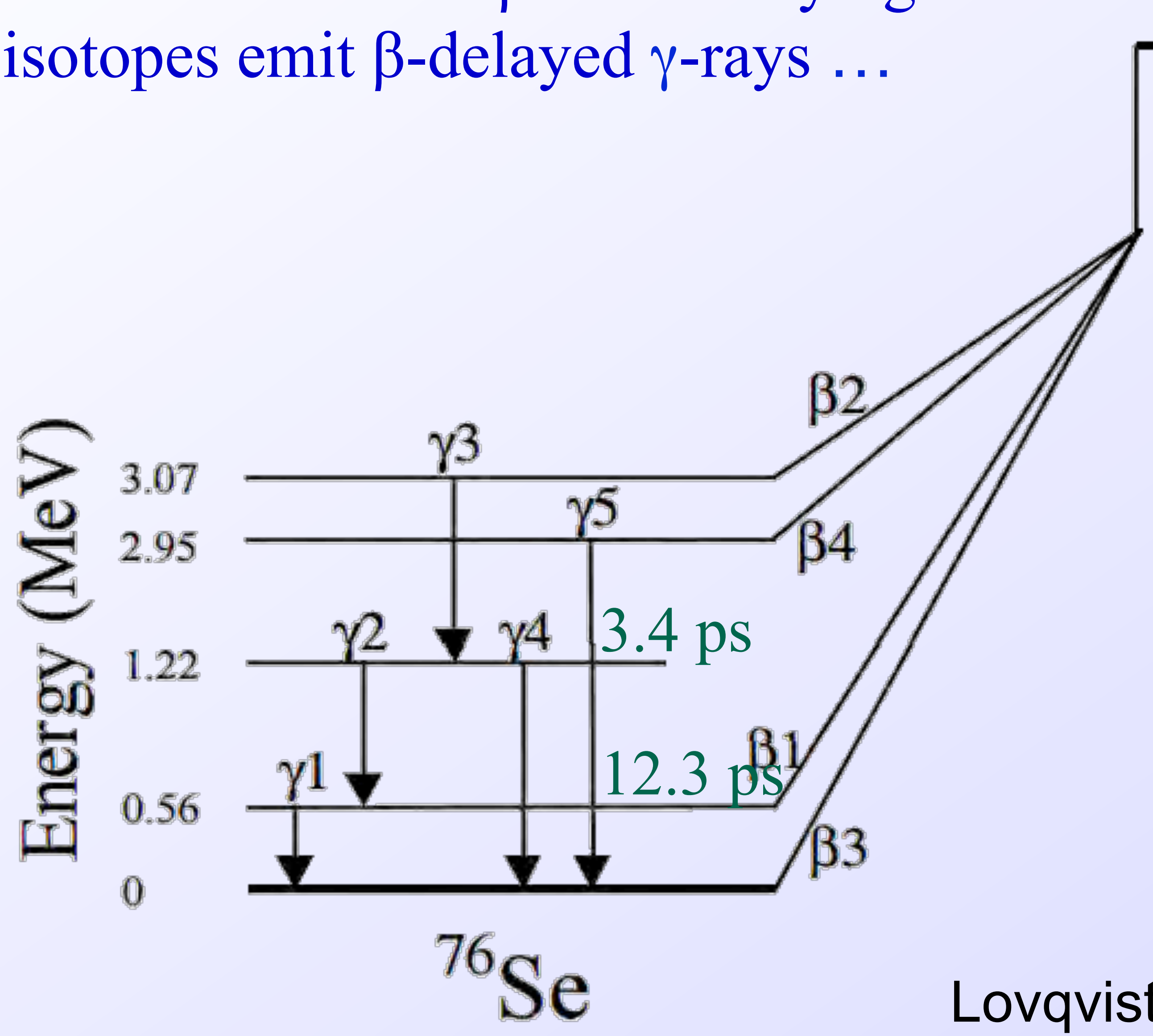
TRACER A : labeled β^+ emitter
Standard (e.g., ^{18}F, ^{13}**N**)
DOUBLES

TRACER B : labeled $\beta^+\gamma$ emitter
Non-standard (e.g., ^{124}I, ^{76}**Br**)
TRIPLES

A. Andreyev et al. PMB 2011
E. Lage et al Med. Phys, 2015
J. Cal-Gonzalez et al. PMB 2015

Several suitable $\beta^+\gamma$ emitters exist

Of course most of β^+/EC decaying isotopes emit β-delayed γ-rays …



	Energy (MeV)	Abundance (%)
β1	3.38	26
β2	0.87	6.3
β3	3.94	6.0
β4	0.99	5.2
γ1	0.56	74
γ2	0.66	16
γ3	1.85	15
γ4	1.22	8.8
γ5	2.95	7,4

Lovqvist A et al., J. Nucl. Med. 1997

A sample of $\beta^+\gamma$ emitters

	$T_{1/2}$ Half-life	β^+ branching ratio (%)	Main Prompt γ [keV] & intensity [%]	Production
^{82}Rb	1.27 min	95	777 (13%)	Generator
^{52m}Mn	21.1 min	97	1434 (96%)	Generator
^{60}Cu	23.7 min	93	1333 (88%)	Cyclotron
^{94m}Tc	52.0 min	70	871 (96%)	Cyclotron
^{110m}In	1.15 h	62	658 (99%)	Generator
^{120}I	1.35 h	46	560 (72%)	Cyclotron
^{44}Sc	3.97 h	94	1157 (100%)	Generator
^{86}Y	14.7 h	33	1080 (85%)	Large $T_{1/2}$
^{76}Br	16.2 h	26	559 (58%)	Large $T_{1/2}$
^{72}As	1.08 d	88	834 (79%)	Generator
^{124}I	4.18 d	23	602 (51%)	Large $T_{1/2}$

Production of ^{60}Cu, ^{52m}Mn and ^{94m}Tc

✓ Studied at a linear accelerator (CMAM, Madrid)

→ They emit beta-delayed gamma-rays

→ They can label tracers of interest

→ Their half-life is suitable for PET studies

→ Can be produced by proton induced reactions at ~10 MeV

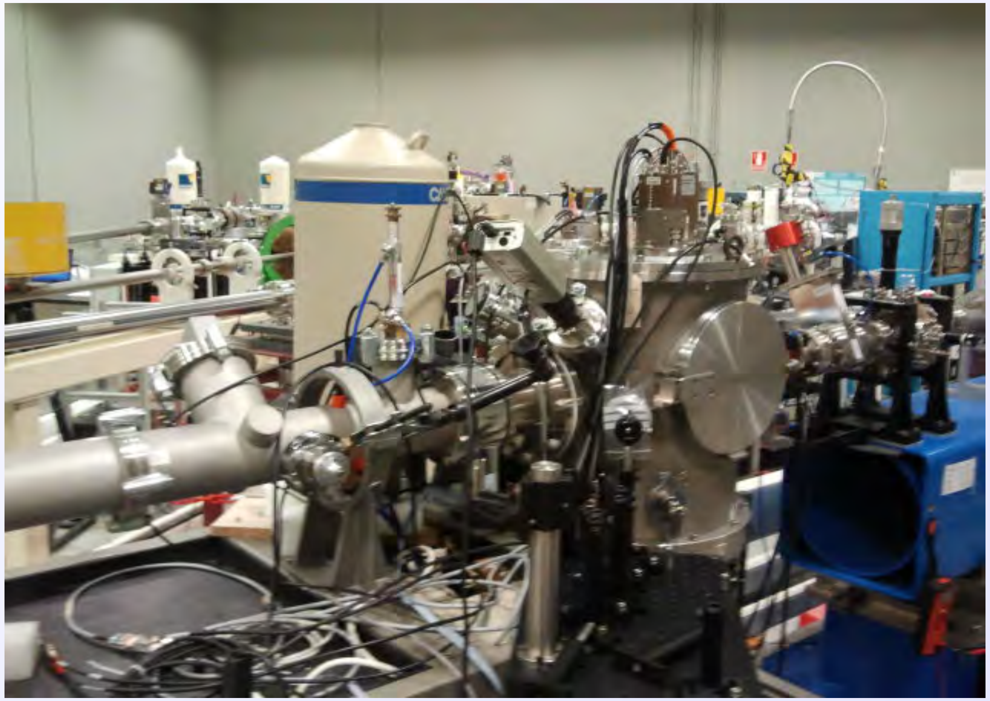
→ Cross-sections subject to uncertainties at low energy

Isotope	Half-life	β^+ branch (%)	Main Prompt γ (MeV) and Yield (%)	Target	Reaction	Energy threshold (MeV)	Cross – Section (barn) @ 10 MeV
^{60}Cu	23.4 min	93%	1.333 (80%) & 1.760 (52%)	^{Nat}Ni (26.16% ^{60}Ni)	$^{60}Ni(p,n)^{60}Cu$	6.91	0.25
^{52m}Mn	21.1 min	95%	1.434 (98%)	^{Nat}Cr (83.8% ^{52}Cr)	$^{52}Cr(p,n)^{52m}Mn$	5.49	0.35
^{94m}Tc	53 min	72%	0.871 (94%)	^{Nat}Mo (9.12% ^{94}Mo)	$^{94}Mo(p,n)^{94m}Tc$	5.04	0.55

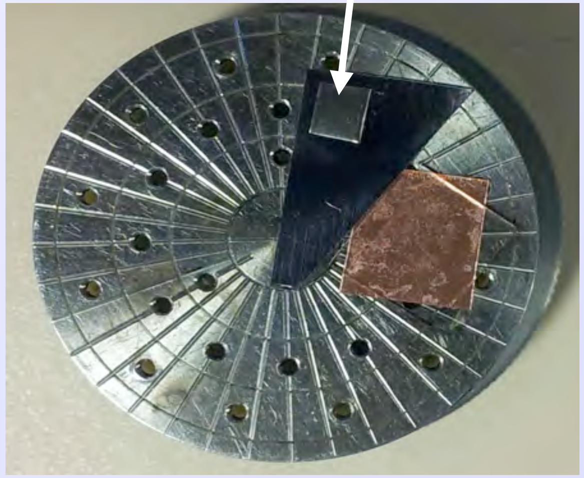
Experiment

✓ Cockcroft-Walton 5 MV tandetron accelerator at CMAM

→ 10 MeV proton beam with intensities up to ~1 μA



Natural Ni



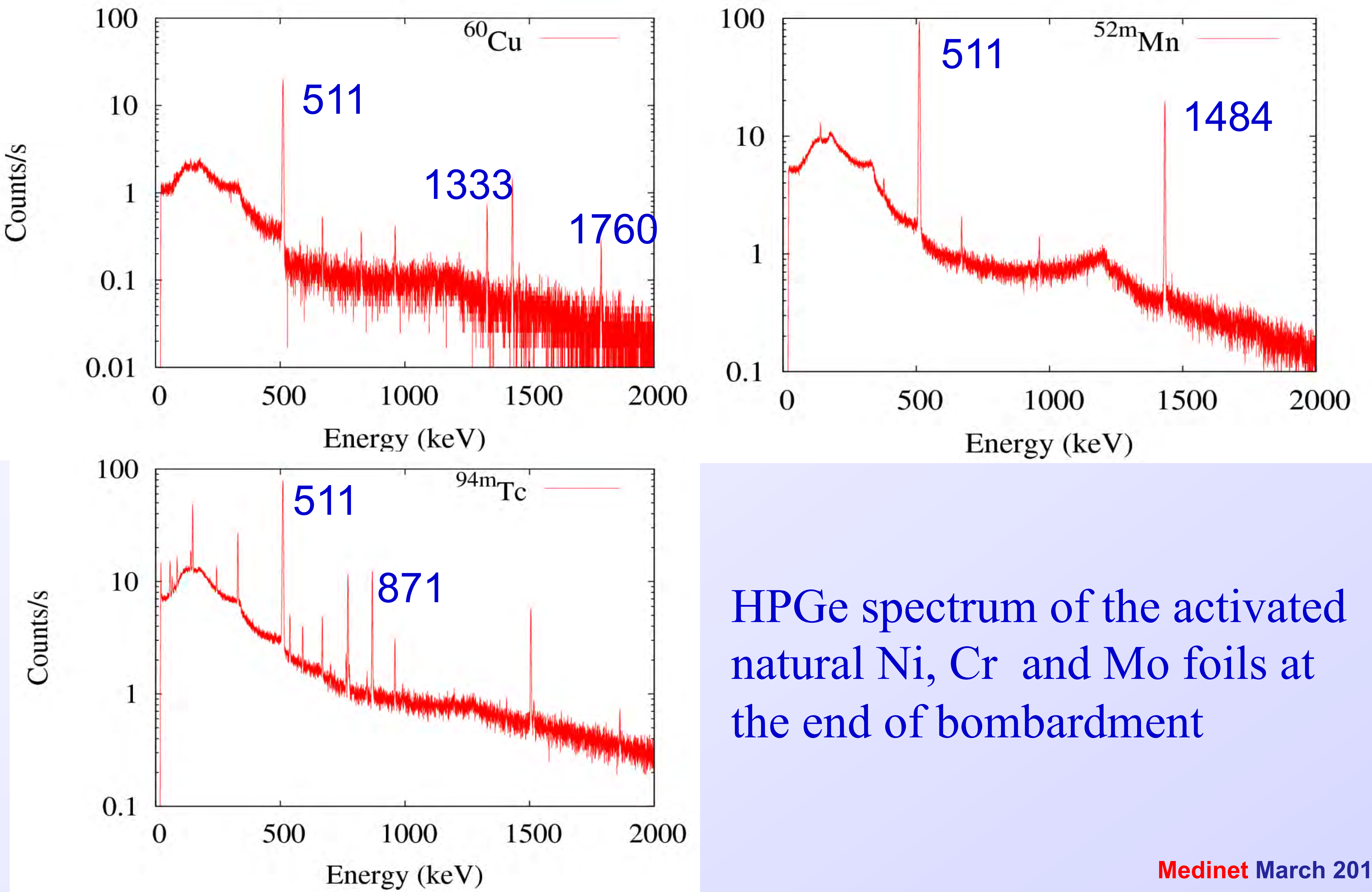
Low activation (<2 μCi) as proof of concept

Solid thin target foils, Ta backing

About 1 min activation

Monitoring by efficiency-calibrated HPGe detector

Activation results



HPGe spectrum of the activated natural Ni, Cr and Mo foils at the end of bombardment

Activation results

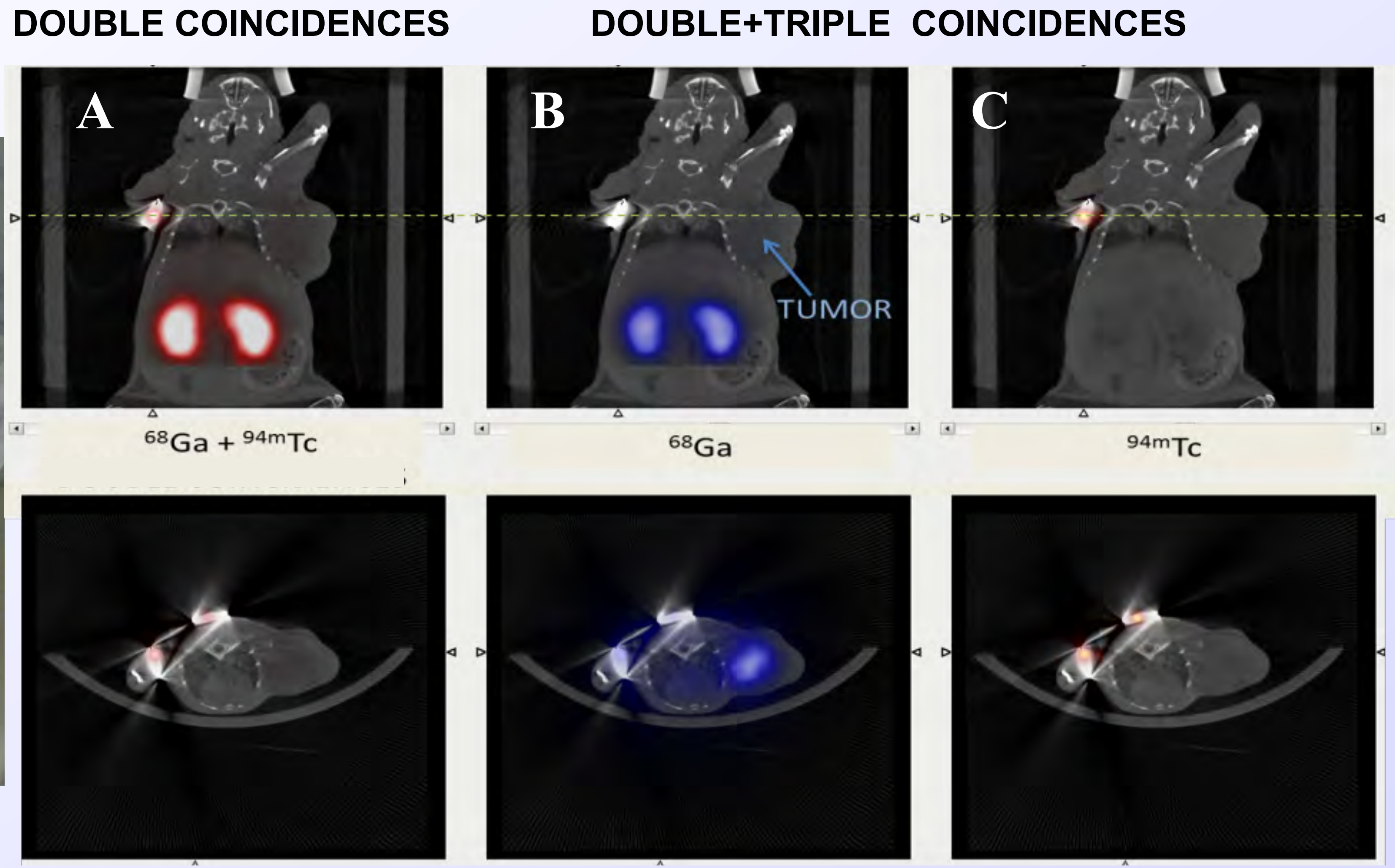
✓ Expected yields at the end of bombardment (EOB) vs. measured yields:

Target	Thickness (mm)	Total charge (nC)	Irradiation time (s)	Expected yield EOB (mCi/uAh)	Measured yield EOB (mCi/uAh)
^{Nat}Ni	0.200	100.3	10	11.91	**12.11**
^{Nat}Cr	3.175	506.7	10	100.27	**80.35**
^{Nat}Mo	0.100	3000	60	3.63	**5.34**

N. Soppera et al., JANIS Book of proton-induced cross-sections OECD NEA Data Bank
L.P. Szajek et al., Radiochim. Acta 91, 613–616 (2003)
F. Rösch, et al., Radiochim. Acta 62, 115 (1993) and J. Labelled Compd. Radiopharm. 35, 267 (1994)
S.M. Qaim, Nucl. Med. Biol. 27(4) 323 (2000)
D. W. McCarthy et al., Nuclear Medicine & Biology, Vol. 26, 351 (1999)
H. I. West et al., Phys. Rev. C35 (1987)

Imaging: iterative image separation

J.L. Herraiz



(Left) Mouse in the scanner bed with the foils located in the armpit and on the neck.

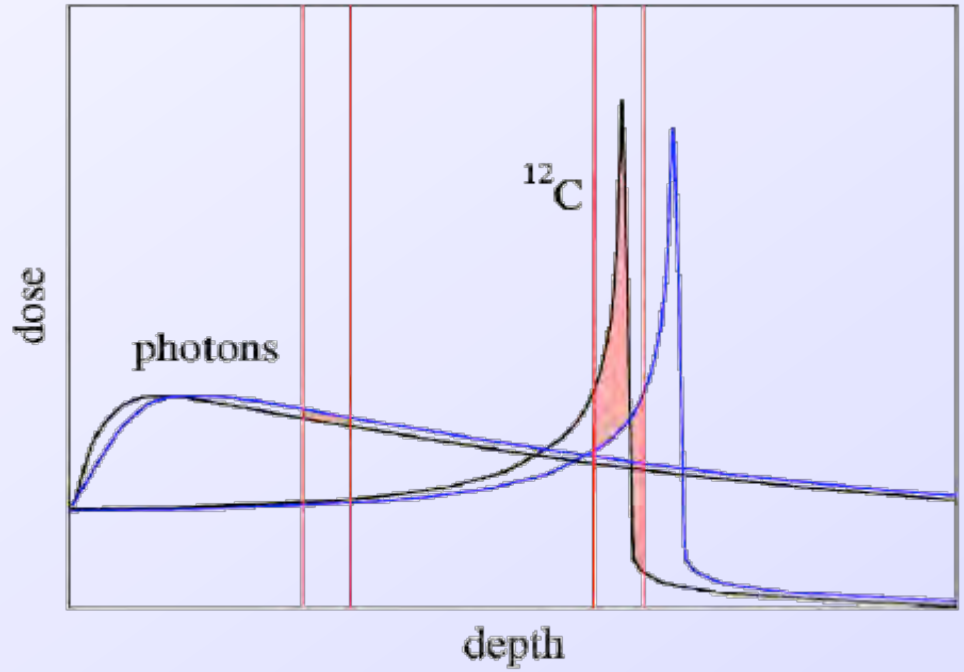
(Right) Reconstructed mPET images

(A) Image reconstructed using only double coincidences, standard

(B) (B,C) Reconstructed separated images of ^{68}Ga and ^{94m}Tc using double and triple coincidences, VLOR reconstruction

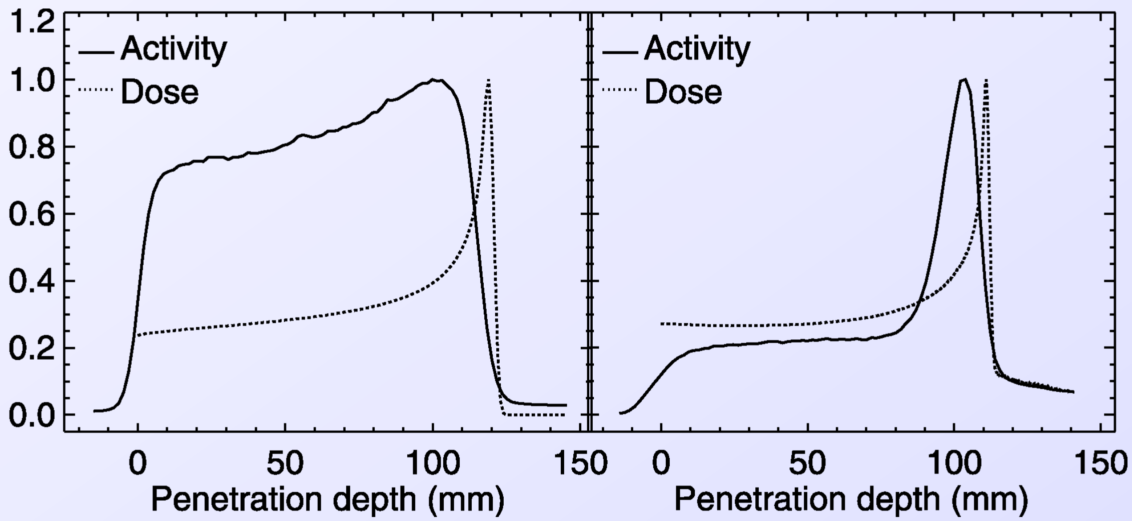
Proton activation for PT imaging?

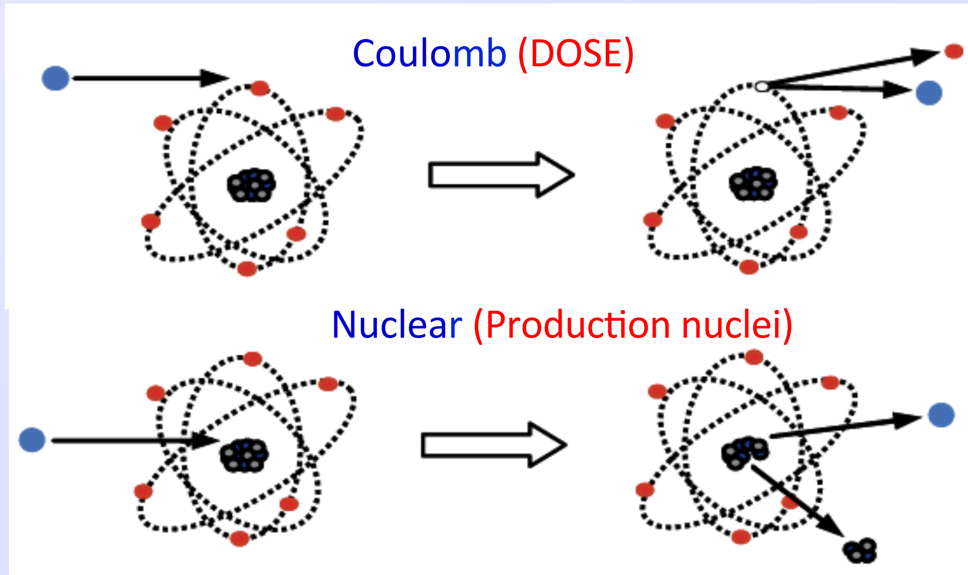
- ✓ Protontherapy
  - → Advantages
  - → Dose vs. nuclei production (PET, PG…)
  - → Range…



K. Parodi et al., IEEE Trans. Nucl. Science 52 (2005) 778

140 MeV protons **259.5 A MeV Carbon ions**





Cross sections, 9 MeV proton beam at CMAM

Nuclear Instruments and Methods in Physics Research A 814 (2016) 110–116

Contents lists available at ScienceDirect

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Experimental validation of gallium production and isotope-dependent positron range correction in PET

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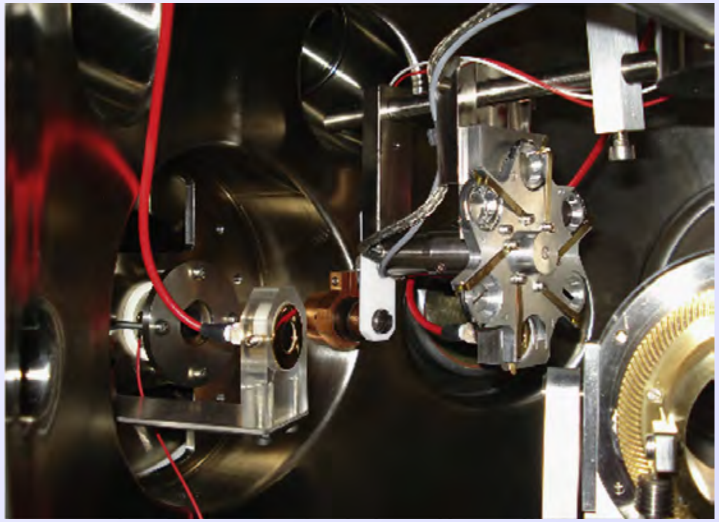
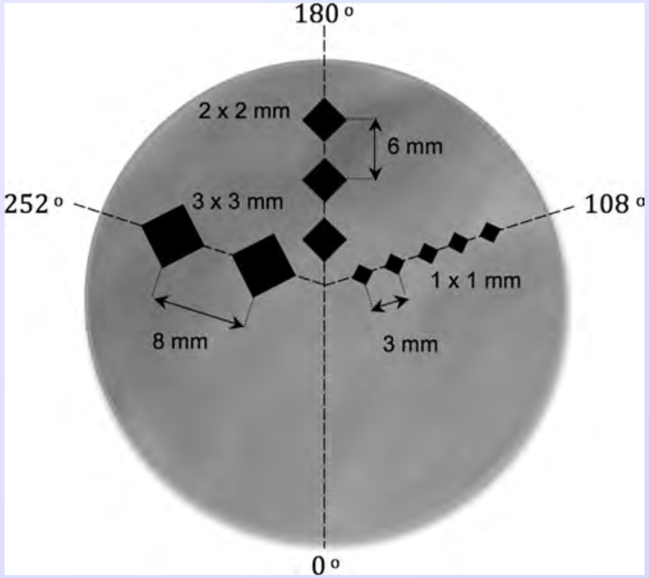
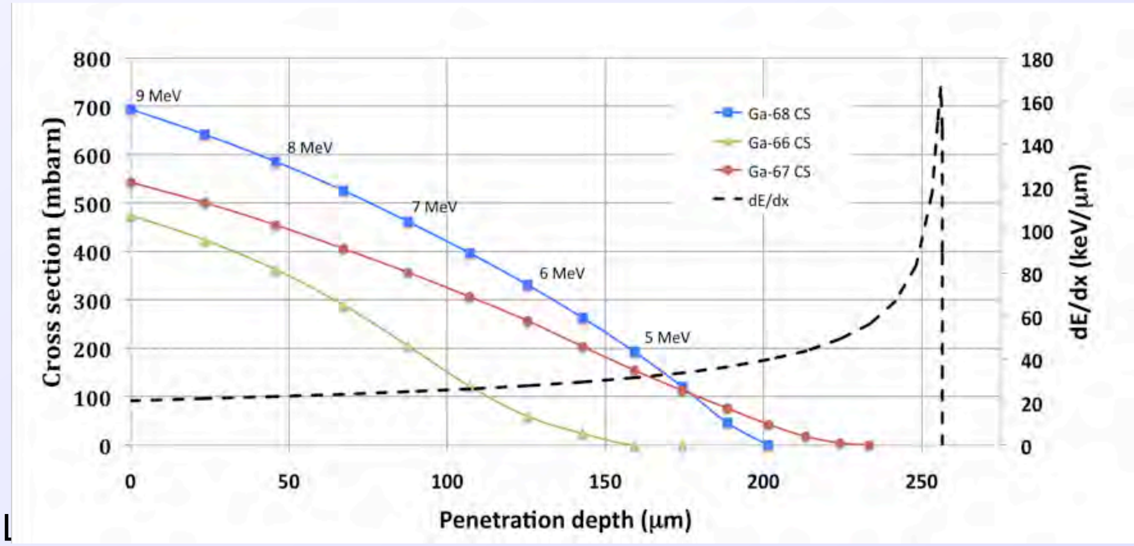
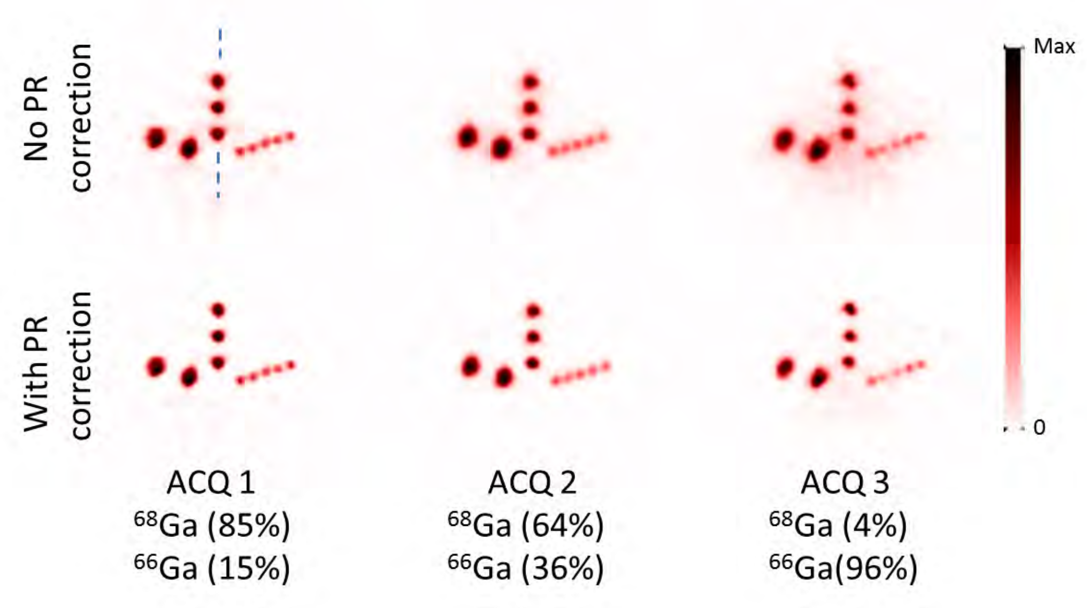






Isotope-dependent range correction



Reconstruction of the Derenzo-like pattern at different times after irradiation

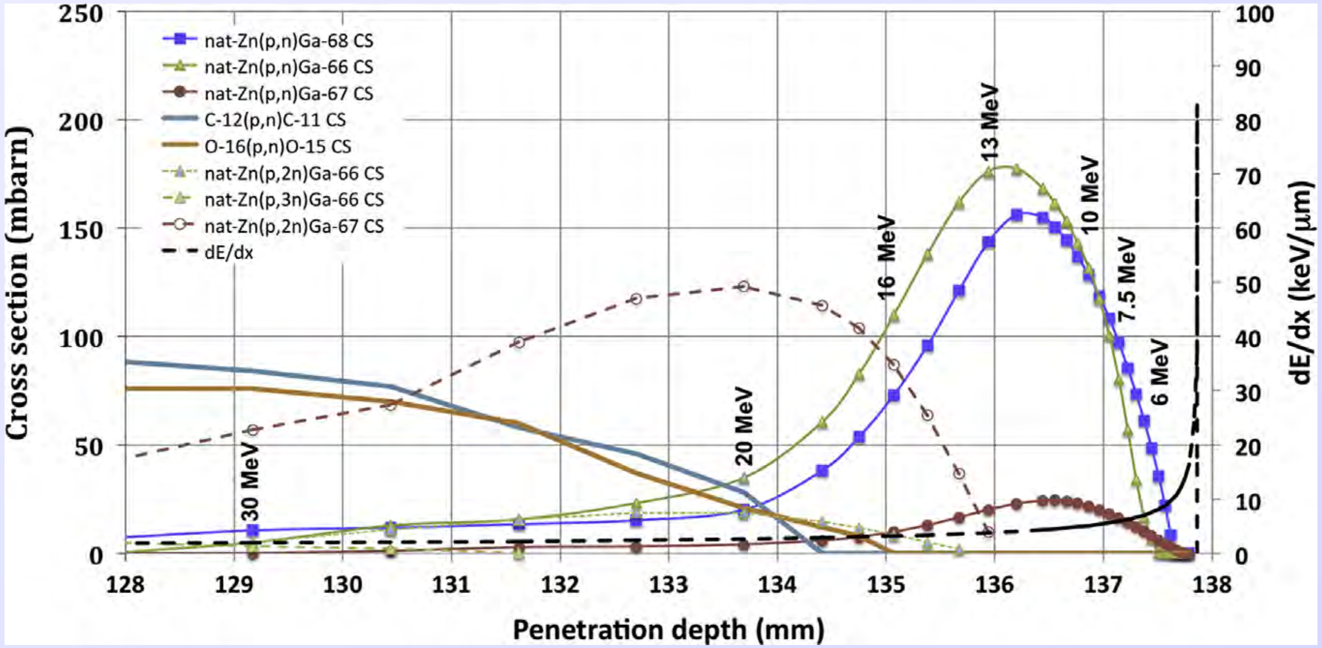
Range correction implemented (lower row)

LMF et al, NIM A814 (2016) 110

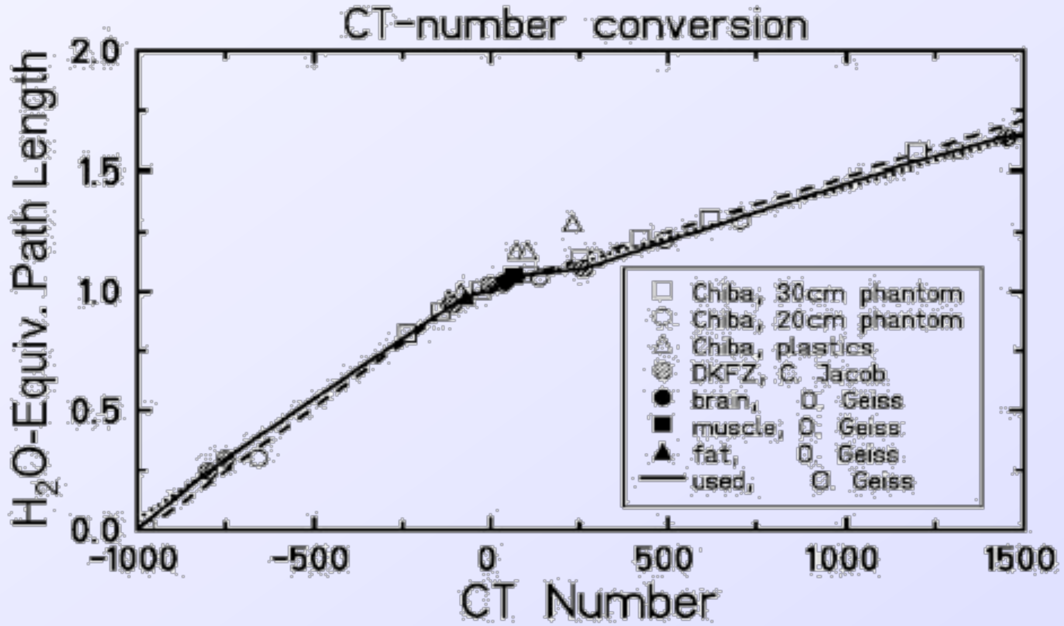
Cross-sections as a function of **depth in water**

- ^{68}Ga, ^{67}Ga and ^{66}Ga on Zn scaled to natural abundances
- ^{11}C and ^{15}O

Possibility for Zn contrast in PT?



- ✓ CT requires conversion to proton-equivalent stopping power



- ✓ Biological washout of produced isotopes: PET emitters

$$Washout(t) = M_f e^{-\lambda_f t} + M_m e^{-\lambda_m t} + M_s e^{-\lambda_s t}$$

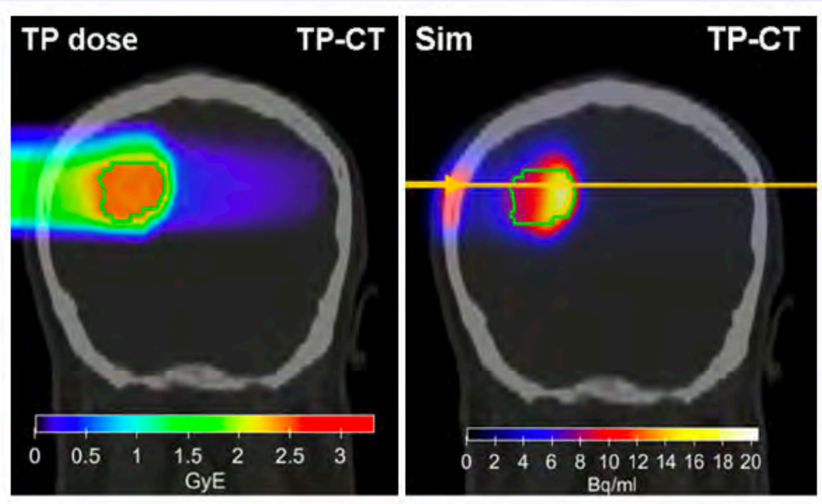
- ✓ Proton range needs to be known!

What is the effect of the proton range?

Source of range uncertainty in the patient	Range uncertainty without Monte Carlo
Independent of dose calculation	
Measurement uncertainty in water for commissioning	±0.3 mm
Compensator design	±0.2 mm
Beam reproducibility	±0.2 mm
Patient setup	±0.7 mm
Dose calculation	
Biology (always positive) ^	+~0.8%
CT imaging and calibration	±0.5%[a]
CT conversion to tissue (excluding I-values)	±0.5%[b]
CT grid size	±0.3%[c]
Mean excitation energy (I-values) in tissues	±1.5%[d]
Range degradation; complex inhomogeneities	−0.7%[e]
Range degradation; local lateral inhomogeneities *	±2.5%[f]
Total (excluding *, ^)	2.7% + 1.2 mm
Total (excluding ^)	4.6% + 1.2 mm

H. Paganetti,
Phys. Med. Biol. 57 (2012) R99

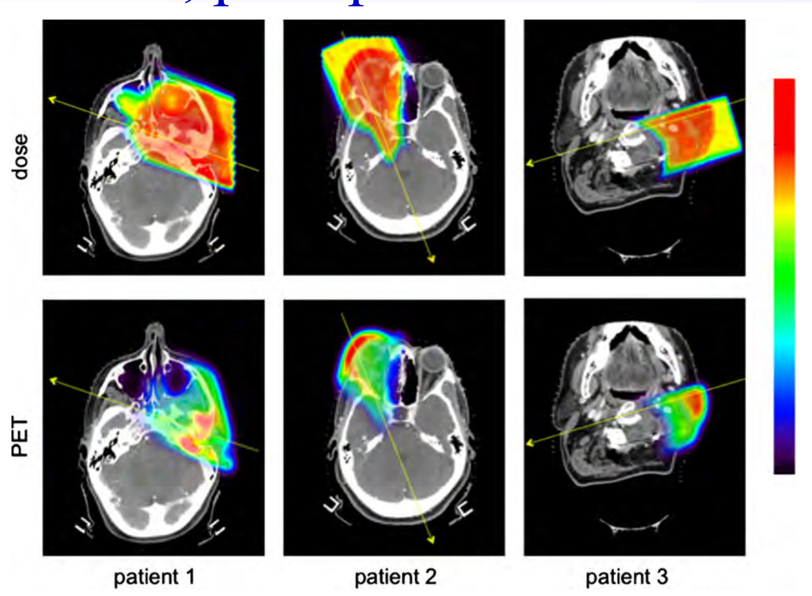
3.5%+3 mm implies 1 cm extra for a tumor at 20 cm depth



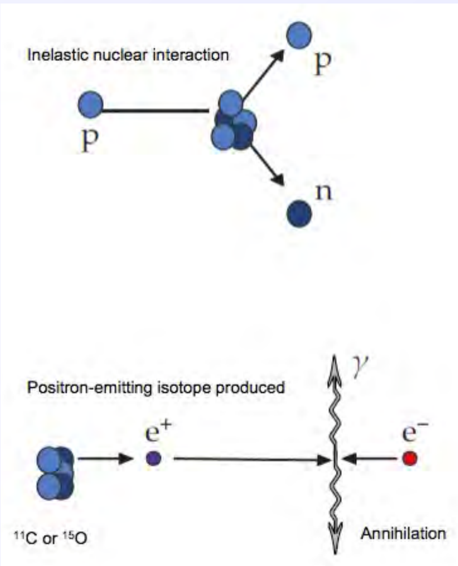
Monte Carlo simulations

Dose verification

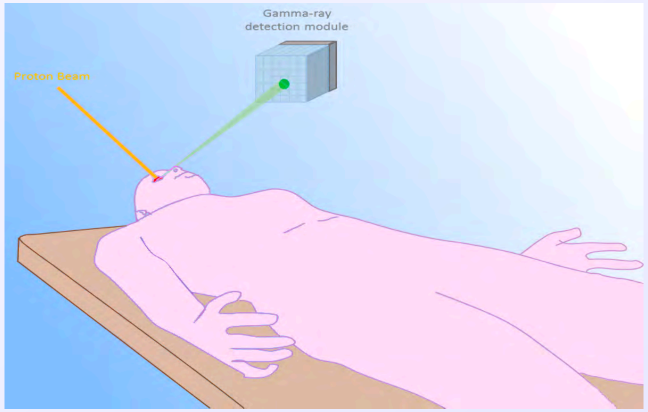
PET, prompt PET

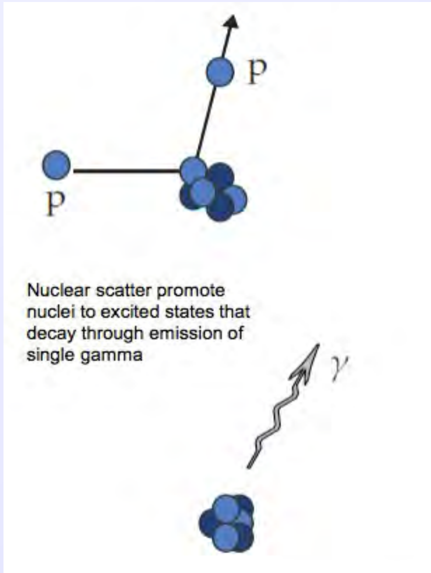


S. España and H. Paganetti
Phys. Med. Biol. **55** (2010) 7557

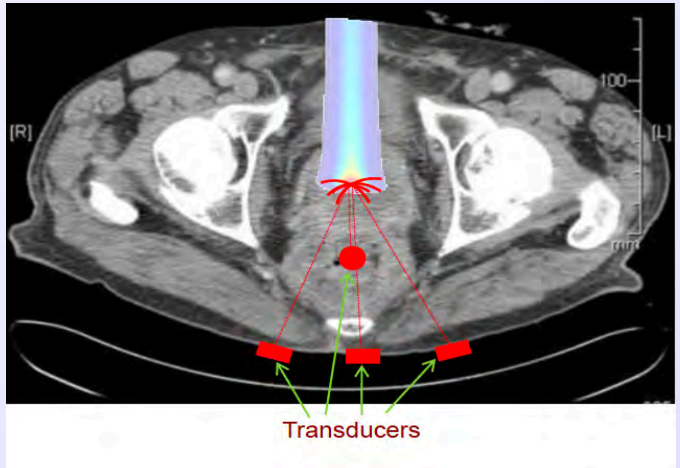


Prompt gamma-rays

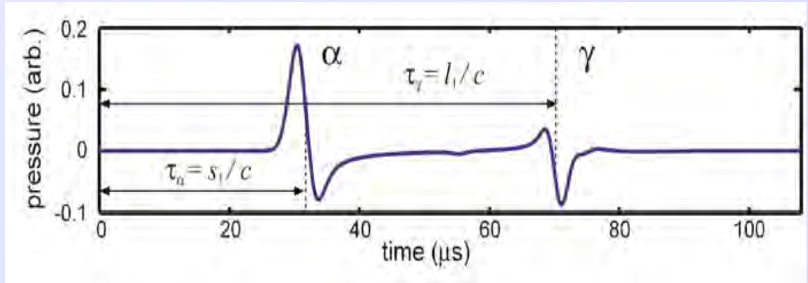


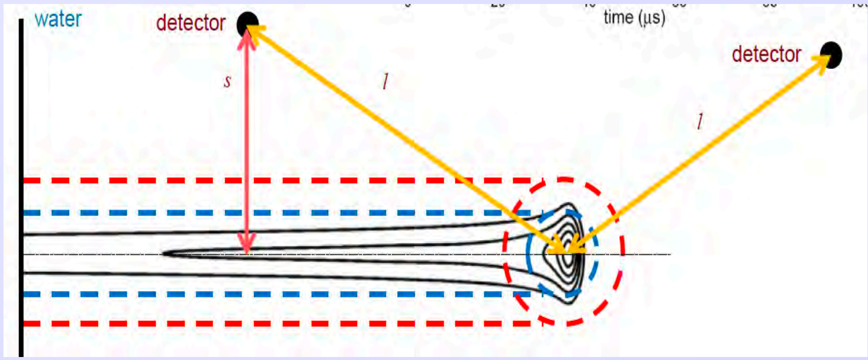


Protoacoustics



Talk by D. Sánchez-Parcerisa



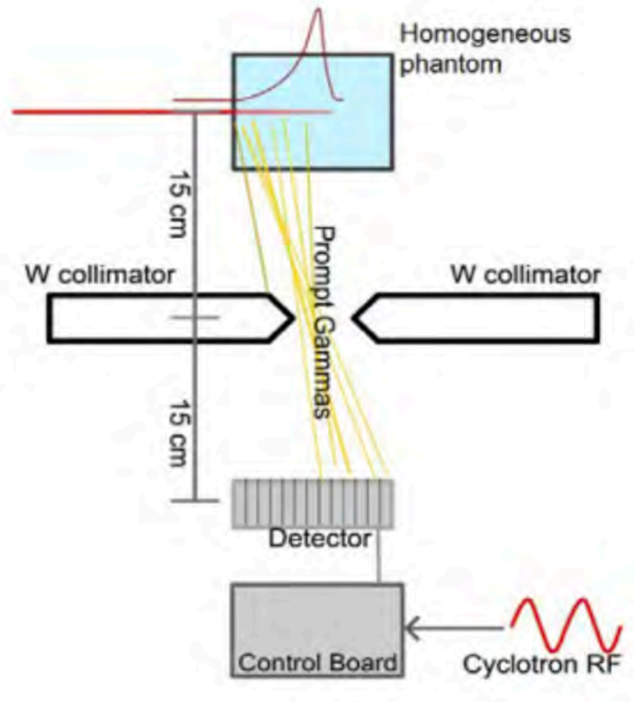


Clinical experience

- **PET clinical experience**
  - GSI (1997-2004) in-beam, off-spill measurements
  - HIT Germany (2013-2017): offline PET/CT after irradiation
    Pending results of clinical trial
  - MGH USA (2006-2011): offline PET/CT, in-room neuroPET
    Physical studies, Monte Carlo, cross sections
  - NCC Japan (2010): used to monitor changes in daily activity. Short in-room

- **Prompt Gamma experience**
  - OncoRay (Dresden, Alemania) with Slit Camera by IBA (2016)
  - UPenn (Philadelphia, USA) with Slit Camera de IBA (2017)

Slit Camera



'None of the present implementations can be classified as satisfactory'
K. Parodi, Med. Phys. 42:12 (2015) 7153

PRONTO project

1. Biophysics simulation package including PET and prompt-gamma activation

2. Exploration of contrast agents for PET and PG

3. Development of new detectors for these imaging modalities

4. Collaboration with clinical partners to eventually include results in clinical protocols

PRONTO

- ✓ Partners
  - → GFN-UCM (coordinator): LMF, S. España, D Sánchez-Parcerisa, JM Udías, J.L. Herraiz
  - → BIOMED-CIEMAT: M.A. Morcillo, E. Romero, N. Magro
  - → FNEXP-IEM-CSIC: E. Nácher, M.J.G. Borge, O. Tengblad
- ✓ Associates
  - → Sedecal Molecular Imaging
  - → CUN: clinical beam (+patients)
  - → Justesa Imagen: radiopharmaceuticals
  - → CMAM: low energy beams
- ✓ Funded for 4 years (2018-2021) by Comunidad de Madrid

Clinical beam in Spain?

✓ Prospects in Madrid

→ Quirón Salud

→ Clinica Universitaria de Navarra: HITACHI

HITACHI
Inspire the Next

News Release

FOR IMMEDIATE RELEASE

Hitachi to Install New Proton Beam Therapy System in Spain

Tokyo, December 15, 2017--- Hitachi, Ltd. (TSE:6501) today announced that it has entered into an agreement to provide Clínica Universidad de Navarra (CUN) with its proton beam therapy (PBT) system. The agreement includes PBT system maintenance following completion of the systems' installation.

The PBT System will be installed at CUN's facility in Madrid, Spain and is equipped with state of the art technology including spot scanning capability* for treating certain forms of cancer. The System includes a compact synchrotron accelerator, full rotating gantry with cone beam CT and the option to add an additional gantry treatment room in the future. PBT patient treatment using the new system is expected to start at the hospital in the spring of 2020.

PBT is an advanced type of cancer radiotherapy. Protons, the atomic nucleus of hydrogen, are accelerated at high speed and its energy is concentrated on the tumours. PBT improves the quality of life for cancer patients since patients experience no pain during treatment and the procedure has fewer impacts on bodily functions. In most cases, patients can continue with their normal daily activities while undergoing treatment.

Objectives

- ✓ Biophysics simulation package
  - → Study of existing MC packages: PeneloPET, GATE, TOPAS…
  - → Cross sections
  - → Inclusion of PET/PG isotope activation in FoCa / matRad
  - → Washout models
  - → Experimental validation, phantoms, tissues: CMAM + …
- ✓ Development of contrasts
  - → ex. Zn for several Ga β^+ emitters (channel open at low E)
  - → What concentration can we provide? In which form?
  - → Apart from radiation, what other biological effects can appear?
  - → Other isotopes for PET?
  - → PG isotopes

Objectives (2)

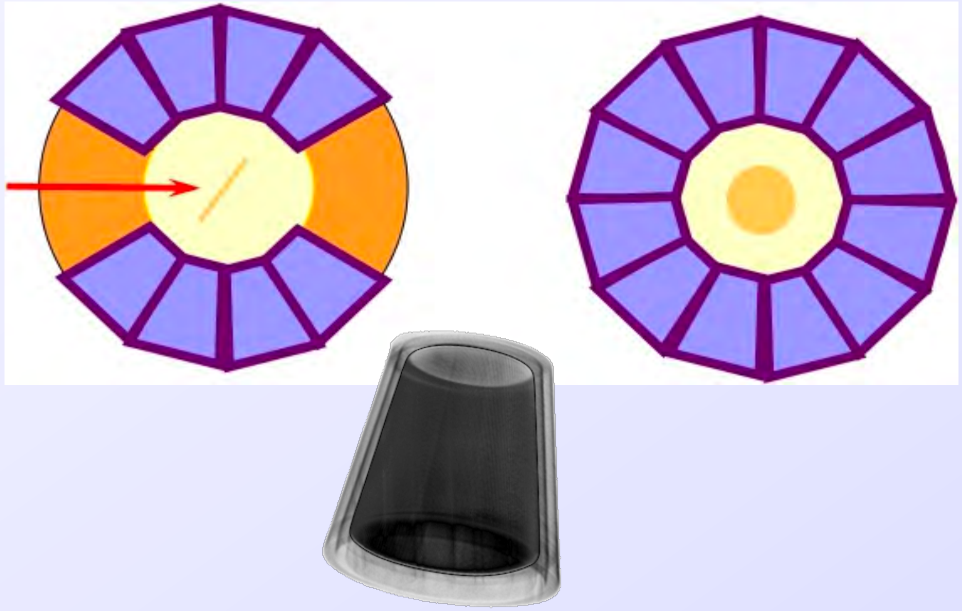
✓ Detector developments

→ PG detector based on FATIMA technology

- comparison with SEDECAL design
- Fast and efficient detectors

→ Adapt CEPA detector for proton range verification

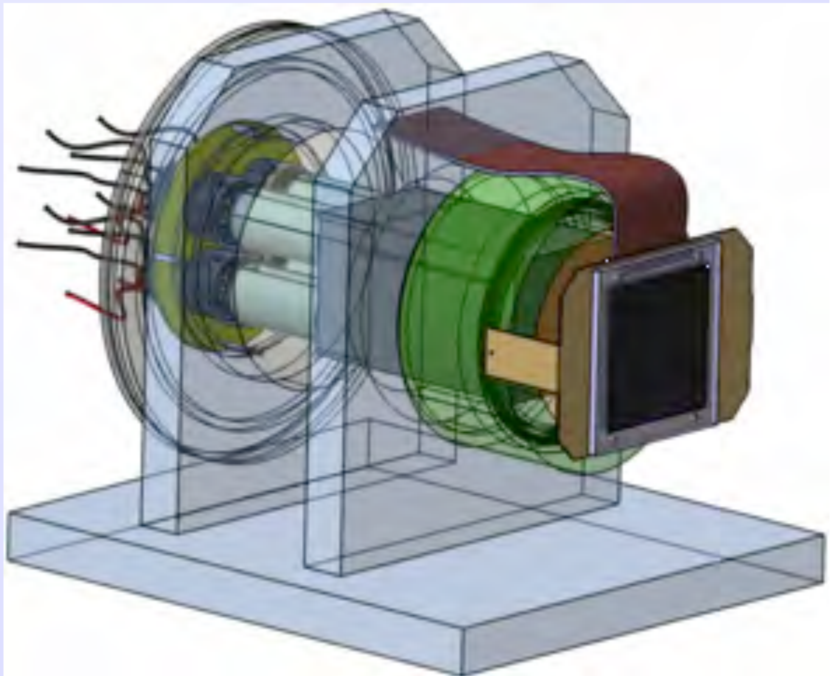
- Protons and gamma-rays
- Good energy range



✓ Clinical application

→ Guide research by realistic ojectives and utility for future practice

- Contact with facility and oncologists



Acknowledgements

Comunidad de Madrid

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FONDO EUROPEO DE DESARROLLO REGIONAL
"Una manera de hacer Europa"

Grupo de Física Nuclear

Thank you!

B2017/BMD-3888
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