PRONTO: Protontherapy and nuclear techniques for oncology
Research and networking activities at GFN-UCM

L.M. Fraile
Grupo de Física Nuclear, Dpto. Física Atómica, Molecular y Nuclear, Universidad Complutense, E-28040 Madrid, Spain
✓ 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
**PROBLEM:** All annihilation gamma-rays have the same energy: 511 keV

**PROPOSED SOLUTION:** mPET

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

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

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

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A. Andreyev et al. PMB 2011
J. Cal-Gonzalez et al. PMB 2015
Several suitable $\beta^+\gamma$ emitters exist

Of course most of $\beta^+/EC$ decaying isotopes emit $\beta$-delayed $\gamma$-rays …

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

<table>
<thead>
<tr>
<th></th>
<th>$T_{1/2}$</th>
<th>$\beta^+$ branching ratio (%)</th>
<th>Main Prompt $\gamma$ [keV] &amp; intensity [%]</th>
<th>Production</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{82}$Rb</td>
<td>1.27 min</td>
<td>95</td>
<td>777 (13%)</td>
<td>Generator</td>
</tr>
<tr>
<td>$^{52m}$Mn</td>
<td>21.1 min</td>
<td>97</td>
<td>1434 (96%)</td>
<td>Generator</td>
</tr>
<tr>
<td>$^{60}$Cu</td>
<td>23.7 min</td>
<td>93</td>
<td>1333 (88%)</td>
<td>Cyclotron</td>
</tr>
<tr>
<td>$^{94m}$Tc</td>
<td>52.0 min</td>
<td>70</td>
<td>871 (96%)</td>
<td>Cyclotron</td>
</tr>
<tr>
<td>$^{110m}$In</td>
<td>1.15 h</td>
<td>62</td>
<td>658 (99%)</td>
<td>Generator</td>
</tr>
<tr>
<td>$^{120}$I</td>
<td>1.35 h</td>
<td>46</td>
<td>560 (72%)</td>
<td>Cyclotron</td>
</tr>
<tr>
<td>$^{44}$Sc</td>
<td>3.97 h</td>
<td>94</td>
<td>1157 (100%)</td>
<td>Generator</td>
</tr>
<tr>
<td>$^{86}$Y</td>
<td>14.7 h</td>
<td>33</td>
<td>1080 (85%)</td>
<td>Large $T_{1/2}$</td>
</tr>
<tr>
<td>$^{76}$Br</td>
<td>16.2 h</td>
<td>26</td>
<td>559 (58%)</td>
<td>Large $T_{1/2}$</td>
</tr>
<tr>
<td>$^{72}$As</td>
<td>1.08 d</td>
<td>88</td>
<td>834 (79%)</td>
<td>Generator</td>
</tr>
<tr>
<td>$^{124}$I</td>
<td>4.18 d</td>
<td>23</td>
<td>602 (51%)</td>
<td>Large $T_{1/2}$</td>
</tr>
</tbody>
</table>
Production of $^{60}\text{Cu}$, $^{52}\text{mMn}$ and $^{94}\text{mTc}$

✅ 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 $\sim$10 MeV
  → Cross-sections subject to uncertainties at low energy

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life</th>
<th>$\beta^+$ branch (%)</th>
<th>Main Prompt $\gamma$ (MeV) and Yield (%)</th>
<th>Target</th>
<th>Reaction</th>
<th>Energy threshold (MeV)</th>
<th>Cross-section (barn) @ 10 MeV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{60}\text{Cu}$</td>
<td>23.4 min</td>
<td>93%</td>
<td>1.333 (80%) &amp; 1.760 (52%)</td>
<td>$^{\text{Nat}}\text{Ni}$ (26.16% $^{60}\text{Ni}$)</td>
<td>$^{60}\text{Ni}(p,n)^{60}\text{Cu}$</td>
<td>6.91</td>
<td>0.25</td>
</tr>
<tr>
<td>$^{52}\text{mMn}$</td>
<td>21.1 min</td>
<td>95%</td>
<td>1.434 (98%)</td>
<td>$^{\text{Nat}}\text{Cr}$ (83.8% $^{52}\text{Cr}$)</td>
<td>$^{52}\text{Cr}(p,n)^{52}\text{mMn}$</td>
<td>5.49</td>
<td>0.35</td>
</tr>
<tr>
<td>$^{94}\text{mTc}$</td>
<td>53 min</td>
<td>72%</td>
<td>0.871 (94%)</td>
<td>$^{\text{Nat}}\text{Mo}$ (9.12% $^{94}\text{Mo}$)</td>
<td>$^{94}\text{Mo}(p,n)^{94}\text{mTc}$</td>
<td>5.04</td>
<td>0.55</td>
</tr>
</tbody>
</table>
✓ Cockcroft-Walton 5 MV tandetron accelerator at CMAM
→ 10 MeV proton beam with intensities up to ~1 μA

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

<table>
<thead>
<tr>
<th>Target</th>
<th>Thickness (mm)</th>
<th>Total charge (nC)</th>
<th>Irradiation time (s)</th>
<th>Expected yield EOB (mCi/uAh)</th>
<th>Measured yield EOB (mCi/uAh)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NatNi</td>
<td>0.200</td>
<td>100.3</td>
<td>10</td>
<td>11.91</td>
<td>12.11</td>
</tr>
<tr>
<td>NatCr</td>
<td>3.175</td>
<td>506.7</td>
<td>10</td>
<td>100.27</td>
<td>80.35</td>
</tr>
<tr>
<td>NatMo</td>
<td>0.100</td>
<td>3000</td>
<td>60</td>
<td>3.63</td>
<td>5.34</td>
</tr>
</tbody>
</table>

N. Soppera et al., JANIS Book of proton-induced cross-sections OECD NEA Data Bank
(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 $^{68}\text{Ga}$ and $^{94}\text{mTc}$ using double and triple coincidences, VLOIR reconstruction
Proton activation for PT imaging?

✓ Proton therapy
  → Advantages
  → Dose vs. nuclei production (PET, PG…)
  → Range…

Cross sections, 9 MeV proton beam at CMAM

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

L.M. Fraile a,⁎, J.L. Herráiz a, J.M. Udías a, J. Cal-González a,1, P.M.G. Corzo a,2, S. España a,3, E. Herranz a,4, M. Pérez-Liva a, E. Picado a, E. Vicente a,b, A. Muñoz-Martín a, J.J. Vaquero c

a Grupo de Física Nuclear, Dpto. Física Atómica, Molecular y Nuclear, Universidad Complutense de Madrid, Spain
b Centro de Microanálisis de Materiales, Universidad Autónoma de Madrid, E-28049 Madrid, Spain
c Departamento de Bioingeniería e Ingeniería Aeroespacial, Universidad Carlos III de Madrid, Spain

⁎ Corresponding author.

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Fig. 1. Experimental chamber at the standard beam line at CMAM.

Fig. 2. The beam line at CMAM with the Derenzo-like Ga Derenzo-like implantation pattern was submerged in water and measured in the ARGUS small animal PET/CT scanner. The Ga activity was concentrated on a 175 μm thick Zn foil, and its intrinsic activity, arising from the 67Zn(p,n)67Ga reaction, which was almost completely disappearing after the irradiation, was used as activity monitor, has been calculated in the same manner.

Table 1: Natural abundances of zinc isotopes, (p,n) reaction products and their decay mode, branching ratio and half-life. The energy of the main gamma decay transitions is also shown.

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Natural abundance (%)</th>
<th>(p,n) Reaction Product</th>
<th>Branching Ratio</th>
<th>Half-life (days)</th>
<th>Energy (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>64Zn</td>
<td>13.92</td>
<td>65Ga</td>
<td>100.0</td>
<td>93.3</td>
<td>991.5, 807.5, 3365.9</td>
</tr>
<tr>
<td>66Zn</td>
<td>0.37</td>
<td>67Ga</td>
<td>100.0</td>
<td>184.6</td>
<td>1039.2, 2751.8</td>
</tr>
<tr>
<td>67Zn</td>
<td>8.97</td>
<td>67Ga</td>
<td>97.5</td>
<td>300.2</td>
<td>176.2, 511.0, 1077.3</td>
</tr>
</tbody>
</table>

The penetration in the Zn foil was obtained from the stopping power calculation, using the SRIM code. The results of the cross-section measurement in 9 MeV et al. showed consistency with the estimate of 0.25 kBq discussed in Section 3.

Fig. 3. Cross section, 9 MeV proton beam at CMAM.
Cross-sections as a function of depth in water
- $^{68}\text{Ga}$, $^{67}\text{Ga}$ and $^{66}\text{Ga}$ on Zn scaled to natural abundances
- $^{11}\text{C}$ and $^{15}\text{O}$

Possibility for Zn contrast in PT?
Dose verification in protontherapy

- CT requires conversion to proton-equivalent stopping power
- Biological washout of produced isotopes: PET emitters

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

- Proton range needs to be known!
What is the effect of the proton range?

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

H. Paganetti,  

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

Monte Carlo simulations
Dose verification

PET, prompt PET

Prompt gamma-rays

Protoacoustics

Figure 3. Conversion curves from HU into weight fraction for hydrogen, carbon, oxygen and calcium using different numbers of bins. Default weight fractions used in the BEAMnrc code are also shown.

Figure 4. Dose distributions (top) and PET images (bottom) obtained from the Monte Carlo simulation for one field for the three patients included in this study. Arrows represent the profiles included in figure 5.

S. España and H. Paganetti

Talk by D. Sánchez-Parcerisa

Nuclear scatter promotes nuclei to excited states that decay through emission of single gamma.
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)

‘None of the present implementations can be classified as satisfactory’
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
✓ 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
✓ Prospects in Madrid

→ Quirón Salud
→ Clinica Universitaria de Navarra: HITACHI
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 $\beta^+$ 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
✓ 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 objectives and utility for future practice
    • Contact with facility and oncologists
Acknowledgements

Thank you!

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"Una manera de hacer Europa"

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