the medical problem

importance of molecular imaging (multimodality, multidisciplinarity)

the project

- The challenges
- Layout
- TOF
- Multimodality
- SiPM/electronics
- preliminary results

Summary and outlook
- Etherogenous, multifocal, biologically not well understood

- The most common cancer in men, in western countries (97% of all cancers in men) (EJNM (2008), 35:1019-1025)

*The second leading cause of cancer death*

Global incidence of prostate cancer*

- Primary or recurrent cancer confined in the organ can be curatively treated

- Thus it is important, at primary diagnosis, follow up and recurrence, to obtain accurate assessment of the disease stage in order to decide the most effective treatment strategy (EJNM (2008), 35:1019-1025)

*Age-standardised incidence rates per 100,000 GLOBOCAN 2002*
PSA

**SENSITIVITY** 83%

**SPECIFICITY** 17%

CT

Selective indication:
- PSA > 10 ng/ml
- cT3
- Gleason score > 7

<table>
<thead>
<tr>
<th>PSA Level</th>
<th>Risk of Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA &lt;= 4.0 ng/ml</td>
<td>5%</td>
</tr>
<tr>
<td>PSA 4.1 ng/ml to 9.9 ng/ml</td>
<td>25%</td>
</tr>
<tr>
<td>PSA &gt;= 10 ng/ml</td>
<td>55%</td>
</tr>
</tbody>
</table>

Local staging (T)
- Very low accuracy in detecting lesions inside of the prostate and/or the extra-capsular extension

LYMPH NODE Staging
- Sensitivity 27-75%
- Specificity 66-100%

Need to consider fundamental changes in the approach to diagnosing prostate cancer

**In the future, multimodality imaging approach tailored to each patient**

PSA → DRE → TRUS → biopsy
Techniques (r.n.)

Radiotracer is as important as the detector!

Parallel hole  Pinhole  Multi-pinhole  Compton Camera

Basic physics of positron emission tomography

Positron emission and positron-electron annihilation

PET Scanner

Positron Emission Tomography
Medical Imaging: a pluridisciplinary approach

- Physics
  - $E=mc^2$
- Mathematics
  - $\int (x + \cos x + \tan x) \, dx = 0$
- Chemistry
- Medicine
- Biology
- Information Tech.
prostate: can we use a standard PET?

- detectors far away from prostate
- poor spatial resolution (6 – 12 mm)
- poor photon detection efficiency (<1%)
- activity outside the organ
  - poor contrast resolution
- relative high cost per study

drawback

Concept of a dedicated prostate imager

**Internal PET prostate probe in coincidence with one external PET detector.**

Transaxial View

**External high resolution detectors can augment imaging of superficial lymph nodes, especially from the bladder.**

**Limited angle coverage geometry**

**Good timing resolution can help in producing almost artifact free images (S. Surti and J. Karp, Dresden IEEE2008)**

Could we reduce the background?

**Yes we can**


drawback

- activity outside the organ
  - poor contrast resolution
- relative high cost per study
Radiotracer strategies for imaging prostate cancer are evolving. New radiotracers are coming soon, including radiotracers for SPECT and PET imaging.

**SPECT:** Prostascint, Bombesyn, 99mTechnetium nanocolloid (limphonodes), other coming soon...

**PET**
- C–11 Choline
- F-18-Choline
- Ga-68 Dotabomb (Hofmann (Rome workshop))
- Many others coming...

Collaboration with Johns Hopkins for testing in ISS (mice models for prostate available) and/or at JHU.

New radiotracers coming soon (M. Pomper, Johns Hopkins)

Radiotracers available for SPECT and PET
(from “New agents and Techniques for Imaging prostate cancer” A. Zahreer, S. Y. Cho, M. Pomper”, to be published on JNM)

**N-[(N-[(S)-1,3-Dicarboxypropyl] Carbamoyl]-4-[18F]Fluorobenzyl-L-Cysteine, [18F]DCFBC: A New Imaging Probe for Prostate Cancer**

Ronnie C. Mease,1 Crystal L. Dusich,1 Catherine A. Foss,1 Hayden T. Ravert,1 Robert F. Dannals,1 Jurgen Seidel,1 Andrew Prideaux,1 James J. Fox,1 George Sgouros,1 Alan P. Kozikowski,2 and Martin G. Pomper1

Synthesis and Evaluation of Technetium-99m- and Rhenium-Labeled Inhibitors of the Prostate-Specific Membrane Antigen (PSMA)

Sangeeta R. Banerjee,† Catherine A. Foss,† Mark Castanares,‡ Ronnie C. Mease,‡ Youngjoo Byun,‡ James J. Fox,‡ John Hilton,‡ Shawn Lupold,§ Alan P. Kozikowski,‡ and Martin G. Pomper*†,‡

Radiolabeled Small-Molecule Ligands for Prostate-Specific Membrane Antigen: *In vivo* Imaging in Experimental Models of Prostate Cancer

Catherine A. Foss,1 Ronnie C. Mease,1 Hong Fan,1 Yuchuan Wang,1 Hayden T. Ravert,1 Robert F. Dannals,1 Rafal T. Olszewski,2 Warren D. Heston,3 Alan P. Kozikowski,4 and Martin G. Pomper1
### PET: spatial resolution and efficiency

\[
\text{FWHM} = 1.2 \sqrt{\left(\frac{d}{2}\right)^2} + b^2 + (0.0022D)^2 + r^2 + p^2
\]

<table>
<thead>
<tr>
<th>(mm)</th>
<th>Crystal size</th>
<th>Coding</th>
<th>Non collinearity</th>
<th>Positron range</th>
<th>Parallax error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>Degradation due to reconstruction algorithm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- \(d\): Crystal pitch
- \(b\): Coding error
- \(D\): Detector separation
- \(r\): Effective source size (including positron range)
- \(p\): Parallax error

\[\eta = 100 \cdot \frac{\varepsilon^2 \cdot \varphi \cdot \Omega}{4\pi}\]

- \(\varepsilon\): Crystal detection efficiency
- \(\varphi\): Packing fraction
- \(\Omega\): Solid angle
Optimizing both DOI and TOF is very difficult ("orthogonal" needs (attenuation for DOI (loosing photons, rough scintillators surfaces) vs minimizing light path, maximizing n. photons for TOF (polished surfaces, "perfect" reflectors)).

Figure 6. The energy ratio as a function of depth for (a) 0.7 mm × 0.7 mm × 20 mm LSO array with the specular reflector, (b) 0.5 mm × 0.5 mm × 20 mm LSO array with the specular reflector, (c) 0.7 mm × 0.7 mm × 20 mm LSO array with the diffuse reflector and (d) 0.5 mm × 0.5 mm × 20 mm LSO array with the diffuse reflector.
Choice of the scintillator
LSO pixellated (dimension dictated by the spatial resolution) (1.5 x 1.5 x 10 mm³)

Choice of the photodetector
Silicon Photo Multipliers (SiPM) (dimension and timing properties)

1 to 1 coupling (minimizing light path, maximizing p.e.)

<table>
<thead>
<tr>
<th>Scintillator</th>
<th>BGO</th>
<th>GSO</th>
<th>BaF₂</th>
<th>LSO/LYSO</th>
<th>LaBr₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau$ (ns)</td>
<td>300</td>
<td>60</td>
<td>2</td>
<td>40</td>
<td>27</td>
</tr>
<tr>
<td>$\mu$ (cm⁻¹)</td>
<td>0.95</td>
<td>0.70</td>
<td>0.45</td>
<td>0.86</td>
<td>0.47</td>
</tr>
<tr>
<td>Photons/MeV</td>
<td>7000</td>
<td>10,000</td>
<td>2000</td>
<td>26,000</td>
<td>60,000</td>
</tr>
<tr>
<td>Initial rise of pulse photons / $\tau$</td>
<td>23</td>
<td>167</td>
<td>1000</td>
<td>650</td>
<td>2222</td>
</tr>
</tbody>
</table>
(a) non TOF: \( n_{\text{conv}} = \frac{D}{d} \)
- all \( n \) elements contribute to the noise in each image elements

(b) TOF: \( n_{\text{TOF}} = \frac{\Delta x}{d} \)
- events back-projected only in the position associated to such TOF information and into few elements adjacent to it \((Dx = cDt/2)\)

- non TOF case, voxels are coupled, statistical noise is increased, many iteration to converge

- TOF information reduces the coupling, so the statistical noise, if the distance between 2 voxels > \( \Delta x = c\Delta T/2 \) they are uncoupled \( \rightarrow \) Few iteration to converge

\[
\text{SNR}_{\text{TOF}} = \sqrt{\frac{D}{\Delta x}} \cdot \text{SNR}_{\text{conv}}
\]

\( n \) = number of volume elements influencing the noise in the image elements \( d \)

TOF-PET advantage vs timing resolution for different sizes
The photon is absorbed and generates an electron/hole pair. The electron/hole diffuses or drifts to the high-electric field multiplication region. The drifted charge undergoes impact ionization and causes an avalanche breakdown. Resistor in series to quench the avalanche (limited Geiger mode).
In conclusion, our results confirm that simultaneous PET and high-field-strength MR imaging with LSO-APD-based PET detectors is feasible without sacrificing the quality of images obtained with either system.

<table>
<thead>
<tr>
<th>Challenges</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>✔️ miniaturization</td>
<td>✔️ tradeoff</td>
</tr>
<tr>
<td>✔️</td>
<td>✔️ DOI/TOF</td>
</tr>
<tr>
<td>✔️</td>
<td>✔️ spatial resolution/efficiency (# ch, complication, cost)</td>
</tr>
<tr>
<td>✔️ electronics (ASIC vs non ASIC)</td>
<td>✔️ cooling</td>
</tr>
<tr>
<td>✔️ specific PET - MR problems</td>
<td>✔️ PET reconstruction (asymmetric system never done before?)</td>
</tr>
<tr>
<td>✔️ (one of the) detector(s) is into human body</td>
<td>✔️ standard proprietary software for the layout probe + standard PET</td>
</tr>
<tr>
<td>✔️ tracking</td>
<td>✔️ fusion</td>
</tr>
<tr>
<td>✔️ coil</td>
<td>✔️ difficulty for tests (big animals)</td>
</tr>
<tr>
<td>✔️ impact of possible movements of the probe</td>
<td>✔️</td>
</tr>
</tbody>
</table>
Layout (challenging)

Detector dimension: ~ 25 x 50 x (13(15) mm³

Pixellated LYSO (or LSO): 1.5 mm pixel size, coupled 1 to 1 to arrays of SiPM (maximize the light collection)

- Compatible with MR
- Transmitter receiver coil to be designed
- Specific problems (with respect to the standard PET - MR systems) (possible system movement, the detector is into the human body) etc

Cooling is needed to be able to reduce the noise and trigger on few p.e. (system under study)

Courtesy S. Majewski
Simulations (Geant4)

- Model 80cm x 15cm x 2cm BGO external ring
- Internal LSO probe, 2 layers of 1mm x 1mm x 3mm crystals in a 9 x 35 array
- Source in prostate 20mm from probe face
Spatial resolution and efficiency increase dominated by probe resolution and dimension. Adding one or two panel detectors close to the patient’s body would increase the efficiency helping also detecting the lymph nodes.
SiPM characterization for temperature dependence

Figure 2. The figure shows three typical spectra acquired using the same reverse bias voltage (32.0V), but the detector thermostated at different temperatures: a) 13.5°C, b) 24.3°C, c) 41.5°C. Gain reduction with temperature is due to the variation of breakdown voltage with temperature.

To optimize the timing resolution we will have to trigger on few p.e. decrease the temperature (37 deg → 22-25 deg), monitor it with feedback on power supply.

Cooling system (water or air) under design.
- Test measurements to be done very soon:
  - evaluation of DOI with double side readout for 5 mm, 10 mm thick arrays and 2 x 5 mm thick arrays with double side readout and comparison with continuous LYSO and LaBr3
  - first test PET-MRI compatibility (effect of MRI on PET and vice versa)
  - timing

**Scintillator comparison between LSO-Ca doped and LaBr3 planned**

**SiPM array comparison**
- Hamamatsu, SenSL and FBK planned
- Philips digital arrays?
Electronics

We will have a detector unit (with ASIC) and a control unit.
NINO chip + HTDC (multi-hit TDC)
(off line correction for the time walk)
ASIC: minimal implementation will have preamp-discriminators.
Very high density cabling will be necessary for off-detector signal processing.
Our goal is to design a final ASIC with all functionalities (ADC + TDC) with minimal wiring (serial communication)

~ 100 x 100 mm²

SiPM with power supply

Preamplifier-discriminator

TDC ADC board

Control and data transfer

Microcable technology
200 ch/20 mm

Successfully used in ALICE experiment
ASIC (front end)

Dimensions: 2.2 x 2.0 mm²

Next release
integrate TDC and serial readout
It will be available at the end of this year (64 channels)
$^{22}\text{Na}$ source: 2 gammas, 511keV - 50µm cell SiPM vertical crystal - small LYSO+PMT start

**DOI resolution < 1mm** (see talk by Cosentino)

$\Delta \text{ToF} (\text{LYSO} + \text{LYSO}) = 225\text{ps} \cdot \text{sqrt}(2) = 315\text{ps}$

$\Delta x = \Delta \text{TOF} \cdot c/2 = 4.7\text{cm}$

selection of all DOI positions on full-energy peak

FWHM = 400 ps
Summary and Conclusions

- prostate cancer detection, diagnosis and staging is very difficult

- standard imaging systems suffer from VERY low specificity

- better radiotracers + multimodality (dedicated probe TOF - PET & MRI (and MRS)) can be the solution

- Compact high resolution high sensititivity PET system is needed (prostate probe + external detector(s))
  - 3D positioning capability
  - ~1 mm - 1.5 mm spatial resolution, high coincidence detection efficiency
  - good energy resolution
  - to decrease the background → TOF capability 150-300 ps timing resolution highly desired (at least ~ 300 ps)

multimodality and multidisciplinarity

- Modern sensor technology allows to build a PET prostate probe ~insensitive to magnetic fields → PET MRI (and MRS) and PET TOF is possible
Outlook

- Assembling and testing (with phantoms) (also in a MR scan) the probe with small (~ 50 x 50 mm2) (LYSO + SiPM) detector in coincidence (by the end of 2013)

- looking for testing on animals?

- enginerization (involving small company)

- looking for other multimodality (optical, Very useful, especially in the surgical phase limphonodes and tumor margins

- looking for tests with non standard tracers (the ones used at present are PET FDG, PET Choline and others aren't so good for the task (diagnosis and follow up) on animals also small animals could be worth (M. Pomper promised to help on this)
Acknowledgements

**INFN**
- Roma1 and Univ. La Sapienza: F. Garibaldi, F. Meddi, S. Capuani, B. Maraviglia, F. Giove + technicians
- Bari: R. de Leo, A. Ranieri, F. Loddo
- Genova: P. Musico, ...
- LNS: L Cosentino, P. Finocchiaro, ...

**National collaboration**
Italian National Institute of Health (ISS): TESA, Farmaco, Oncologia
Ospedale Candiolo Torino: G. Muto, urologist
University Cattolica Rome: P. Bassi, urologist
Universita’ Tor Vergata: O. Schillaci (Nuclear Medicine), Manenti (MRI)

**International Collaboration**
- Soltan Institute for Nuclear Studies (Poland), M. Moszynski (TOF)
- West Virginia University: S. Majewski
- Michigan University: N. Clinthorne
- K. Ziemons (Ahaken): coil design
- Johns Hopkins: M. Pomper (tracers)
First Mediterranean Advanced Molecular Brain Imaging with compac high performance MRI compatible PET and SPECT Imagers -= Potential for a Paradigm Shift

and the adjunct satellite technical meeting:

The lastet enabling technological breacktroughs in compact radiation sensors, electronics and software for PET and SPECT

Giardini di Naxos August 30 - September 2 2012

Advanced Multimodality Endoscopic Instruments in the Detection, Diagnosis, Therapy and Follow-Up of Diseases. Marseille, France -13 - 14 January 2011

Next?: brain ?
Spectroscopy analysis of $^{12}$B $^\Lambda$: Aerogel vs. RICH K-selection

**Aerogel Kaon selection**

**RICH Kaon selection**

\[
12 \text{C}(e,e'K)12B^\Lambda \text{Signal} = 2.5 \text{Signal Background} > 7
\]

**Hermes aerogel RICH similar is not always the same!**
Molecular Imaging Modalities

CT
- Tissue Density, Z: 20-50 µm

Ultrasound
- Structure: 0.1 mm
- Doppler

MRI
- H Concentration: 0.1 mm
- BOLD, DCE
- β-galactosidase: 0.1 µmole H / µmole ³¹P

PET/SPECT
- Radiotracer: <10⁻¹² mole
- Observations: ~1-2 mm

Optical
- (Bioluminescence, fluorescence)
- Topography: µm to mm
- Unique!!

~10^3 cells

Quantitative
Molecular Imaging
• probe the molecular abnormalities that are the basis of disease rather than to image the end effects of these molecular alterations.

- imaging of specific molecular targets enables:
   earlier detection and characterization of disease;
   earlier and direct molecular assessment of treatment effects;
   more fundamental understanding of disease processes.

MedscapeWire
MRI and CT Ranked the Top Medical Innovations by Physicians
October 11, 2001

New York - Physicians surveyed about the most important innovations of the last 25 years ranked interventions for cardiovascular disease and high-tech scanning devices such as magnetic resonance imaging (MRI) and computed tomography (CT) among the most important. They ranked bone marrow transplantation and the erectile dysfunction drug sildenafil among the least important innovations.

The ranking of the 30 medical innovations in the study are as follows:

1. MRI and CT
2. ACE inhibitors
3. Balloon angioplasty
4. Statins
5. Mammography
6. Coronary artery bypass graft
7. Proton pump inhibitors and H2 blockers
8. Selective serotonin reuptake inhibitors (SSRIs) and new non-SSRI antidepressants
9. Cataract extraction and lens implant
10. Hip and knee replacement
11. Ultrasoundography and echocardiography
12. Gastrointestinal endoscopy
13. Inhaled steroids for asthma
14. Laparoscopic surgery
15. Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors
16. Cardiac enzymes
17. Fluoroquinolones
18. New hypoglycemic agents
19. HIV testing and treatment
20. Tamoxifen
21. Prostate-specific antigen testing
22. Long-acting and local opioid anesthetics
23. Helicobacter pylori testing and treatment
24. Bone densitometry
25. Third-generation cephalosporins
26. Calcium channel blockers
27. Intravenous conscious sedation
28. Sildenafil (Viagra)
29. Non-sedating antihistamines
30. Bone marrow transplant

Fuchs and Sox, Health Affairs 2001 20(5):30-43
Statistical Noise in PET

If there are $N$ counts in the image,

$$\text{SNR} = \frac{N}{\sqrt{N}}$$

Signals from Different Voxels are Coupled

⇒ Statistical Noise Does Not Obey Counting Statistics
Adding Time-of-Flight to Reconstruction \[\Rightarrow\] Faster Convergence

Conventional:
- Detected event projected to *all* voxels between detector pairs
- Lots of coupling between voxels
  \[\Rightarrow\] Many Iterations to Converge

Time-of-Flight:
- Detected event projected *only* to voxels consistent w/ measured time
- Little coupling between voxels
  \[\Rightarrow\] Few Iterations to Converge
Spatial Resolution Away From Center

Point Source Images in 60 cm Ring Diameter Camera

Near Tomograph Center 14 cm from Tomograph Center

Resolution Degrades Significantly...
• **Dominant Factor is Crystal Width**
• **Limit for 80 cm Ring w/ Block Detectors is 3.6**
Accurate Quantitation ⇒ Large Regions

Hot Spot Fraction = Activity Measured / True Activity

Cold Spot Fraction = Activity Measured / Background Activity

Object Must Be 2x–4x Larger Than Scanner FWHM
20% prostate cancer

**PERIPHERAL ZONE**
Region postero-lateral
70% prostatic parenchyma

≥ 70% prostate cancer

**TRANSITION ZONE**
Around to prostatic urethra
25% prostatic parenchyma

**CENTRAL ZONE**
Encircles the
eyaculatory ducts
10% prostatic parenchyma

1-5%
Prostate cancer

**CANCER LOCALIZATION**