EndoTOFPET-US: A multi-modal endoscope for Ultrasound and Time-of-Flight PET

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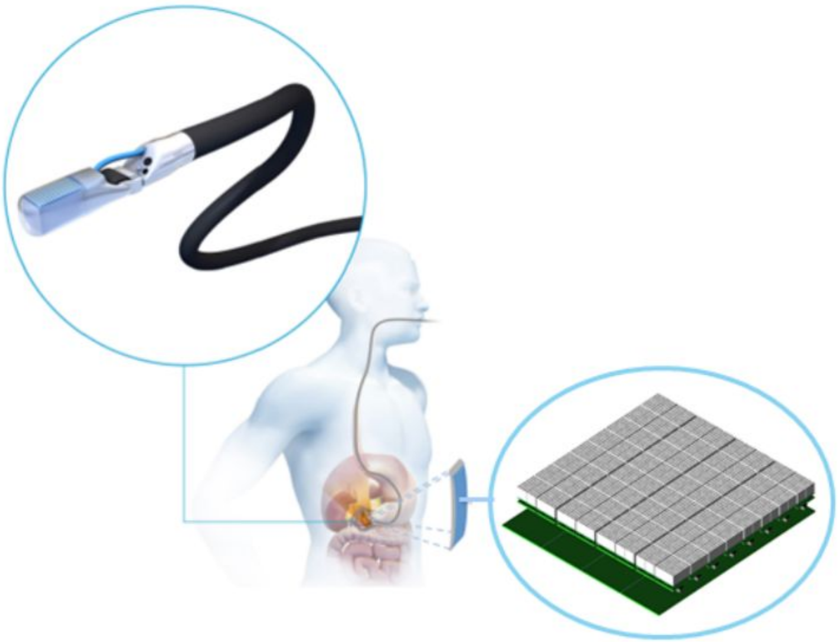
On behalf of the EndoTOFPET-US collaboration

IV Mediterranean Thematic Workshop in Advanced Imaging (MEDAMI)
Ajaccio, Corsica, May 1-5 2016

The EndoTOFPET-US project

Endoscopic Probe

- US detector
- PET head



External PET Plate

➔ An imaging tool for early diagnosis of **pancreas** and **prostate** cancer

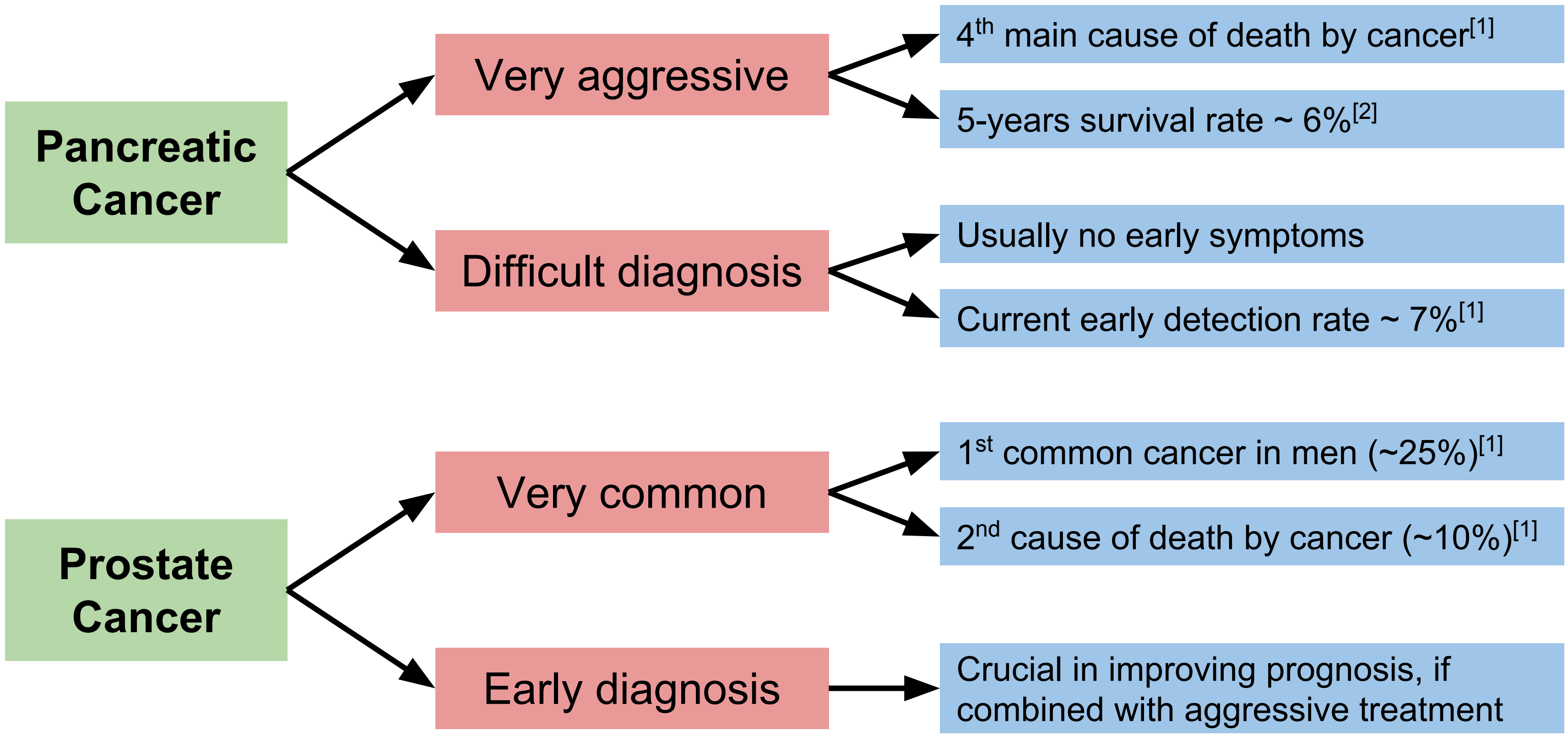
➔ Combine a **high resolution PET scanner** with an endoscopic US probe

- ➢ Early stage detection of cancer
- ➢ Development of new biomarkers for tumoral processes

➔ International collaboration in the frame of the **European FP7 program**

- ➢ 7 academic partners: CERN, DESY, LIP, TU-Delft, TUM, Heidelberg Uni, Milano-Bicocca Uni
- ➢ 3 industrial partners: KLOE, Fibercryst, Surgiceye
- ➢ 3 clinical partners: Aix-Marseille Uni, Klinikum Recht der Isar -TU Munich, Lausanne Uni

Pancreas and prostate cancers



- ➔ Standard imaging nowadays performed with **US**, **CT** and **MRI**
- ➔ Limited effectiveness of standard WB-PET/CT scanners (small organs, background)
- ➔ Need to develop an **early detection method**
  - ➢ High **spatial resolution** (in the order of 1mm)
  - ➢ High **Signal-to-Noise Ratio** (SNR)

[1] Jemal A, Siegel R, Ward E et al. (2008). "Cancer statistics, 2008". CA Cancer J Clin 58 (2): 71–96.
[2] American Cancer Society (2010). "Cancer Facts and Figures 2010"

Spatial resolution

➔ EndoTOFPET-US project goal: Δ**x$_{FWHM}$ = 1 mm**

$$\Delta x_{FWHM} \sim a\sqrt{\left(\frac{d}{2}\right)^2 + (0.0022D)^2 + r^2 + b^2}$$

W.W. Moses, S.E. Derenzo, J. Nucl. Med. 34 (1993) 101P

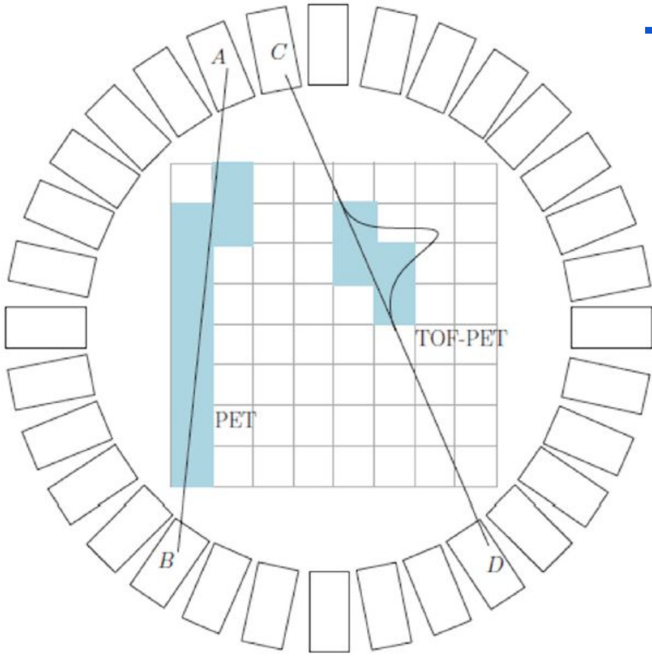
➢	**a**	= reconstruction degradation	**1.25**	
➢	**r**	= effective source size	**~0.5 mm**	
➢	**b**	= accuracy of positioning system	**0.5 mm**	➔ High precision tracking
➢	**d**	= crystal transversal size	**0.75 mm**	➔ High **granularity**
➢	**D**	= detector heads distance	**< 100 mm**	➔ **Endoscopic** approach

➔ High system **miniaturization**

➔ Challenging system **integration**

➔ Dedicated image **reconstruction**

Signal-to-Noise Ratio - Time of Flight (TOF)



S. Surti, J.S. Karp - Physica Medica 32 (2016) 12–22

➔ Compute the **difference in time of arrival** of gammas:

- ➢ Improve event localization along LORs, reject events from nearby organs (liver, heart, bladder)

$$\Delta x = c\frac{\Delta t}{2}$$

- ➢ Decrease noise correlation in overlapping LORs, improve Signal-to-Noise Ratio (SNR)

$$SNR_{TOF} \sim \sqrt{\frac{D}{\Delta x}} \cdot SNR_{CONV}$$

D = effective object diameter

Time resolution (ns)	Δx (cm)	TOF NEC gain	TOF SNR gain
0.1	1.5	26.7	5.2
0.3	4.5	8.9	3.0
0.6	9.0	4.4	2.1
1.2	18.0	2.2	1.5
2.7	40.0	1.0	1.0

M. Conti - Eur J Nucl Med Mol Imaging (2011) 38:1147–1157

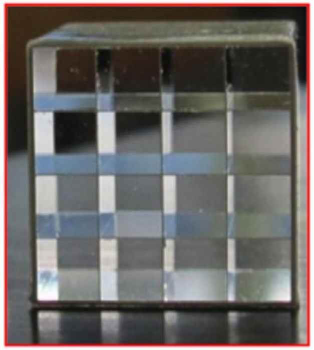
➔ Project goal **Δt_{FWHM} = 200 ps**

- ➢ Fast scintillating crystals
- ➢ High light yield
- ➢ Ultra fast photo-detection
- ➢ Digital approach for internal SiPM
- ➢ Low jitter readout electronics

PET detector design: external plate

➔ **Two plates** produced (one for prostate detector, one for pancreas detector)

PET detector design: external plate



- ➔ **Two plates** produced (one for prostate detector, one for pancreas detector)
- ➔ 256 arrays of 4x4 **LYSO:Ce** scintillators for each plate
  - ➢ Individual crystal size: **3.5x3.5x15 mm^2** for prostate, **3.1x3.1x15 mm^2** for pancreas
  - ➢ Crystal pitch: **3.6 mm** for prostate, **3.2 mm** for pancreas
  - ➢ Coating material: **ESR** by 3M

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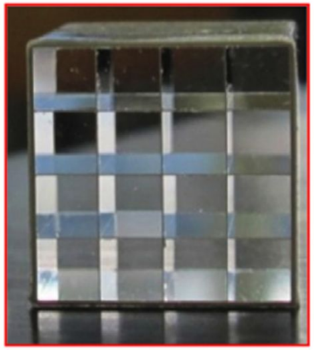

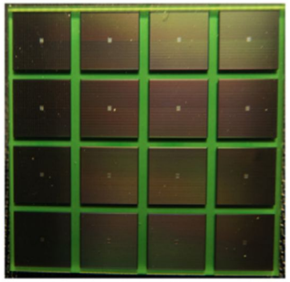

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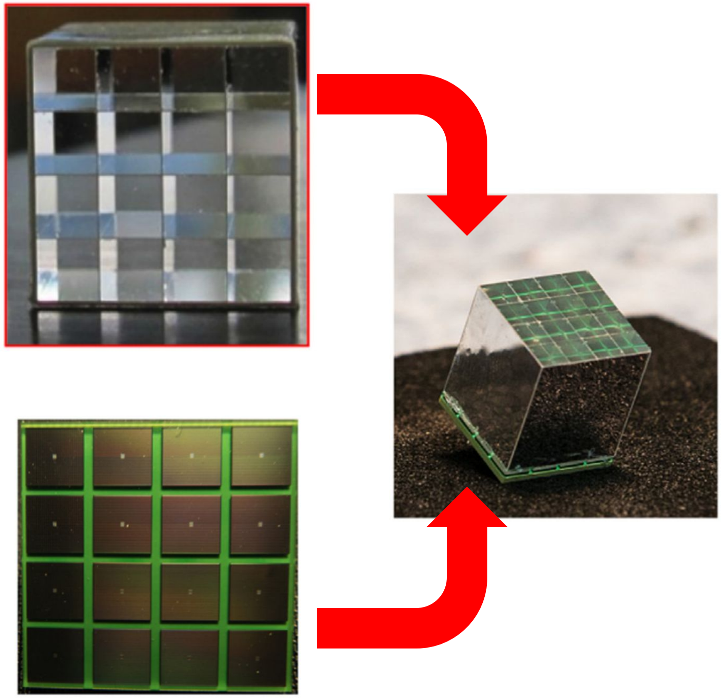

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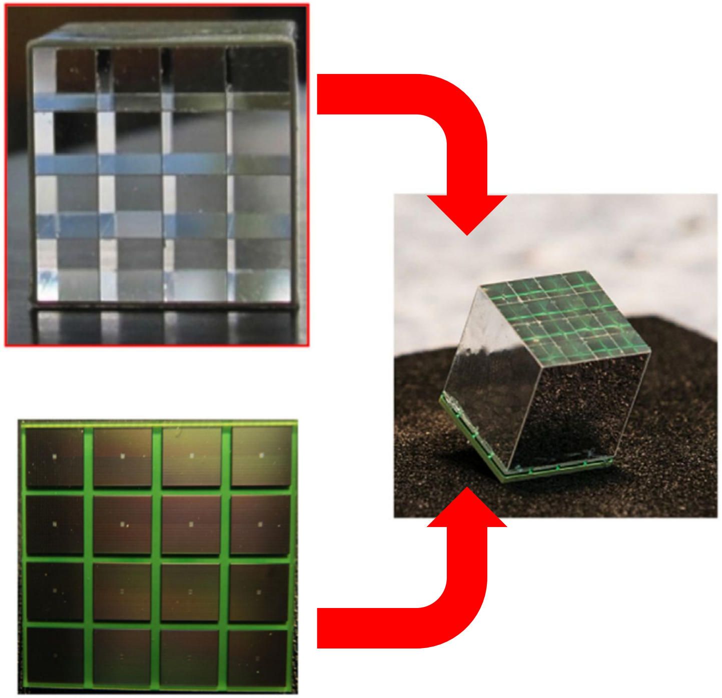

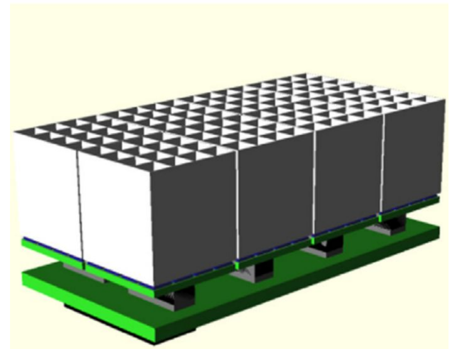

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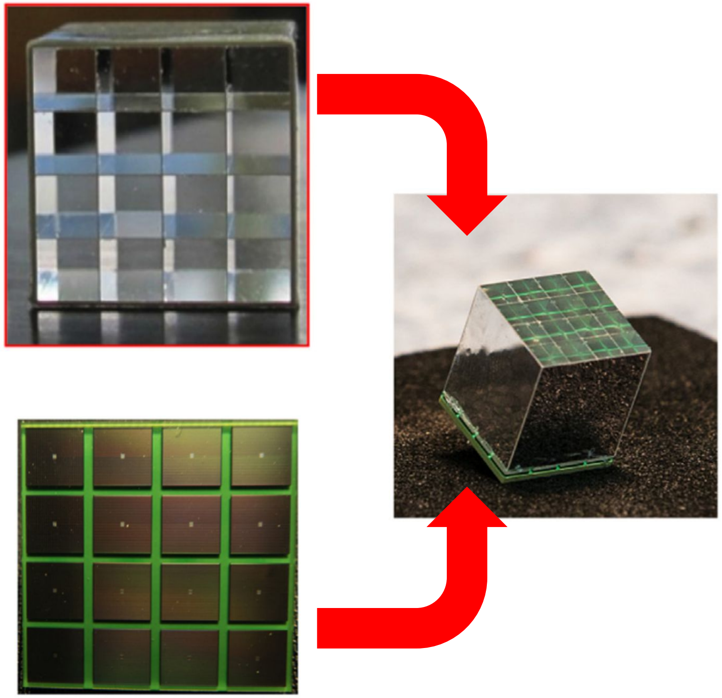

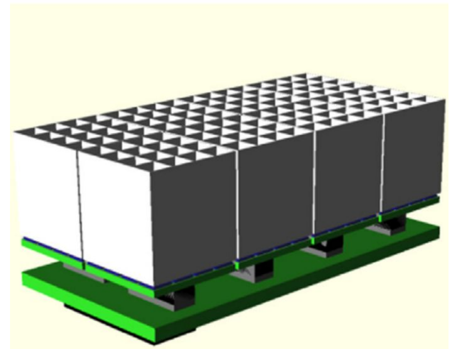

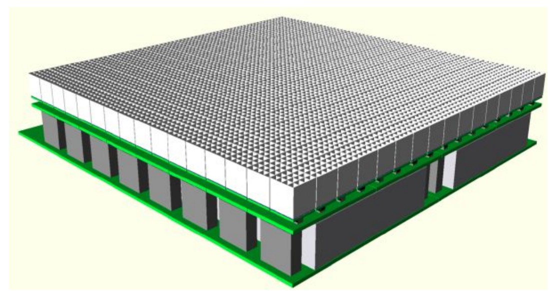

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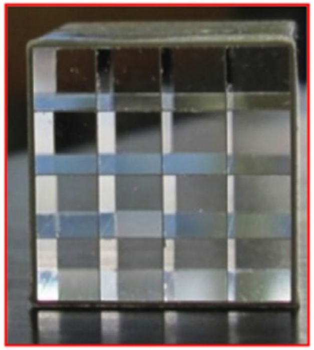

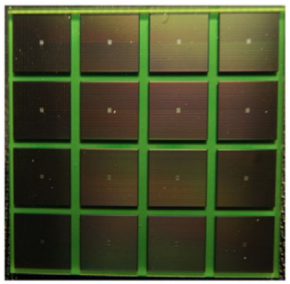

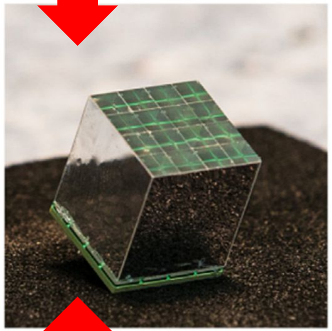

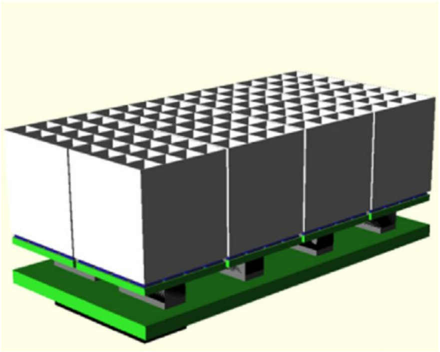

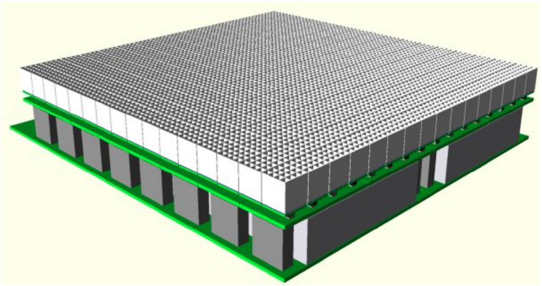

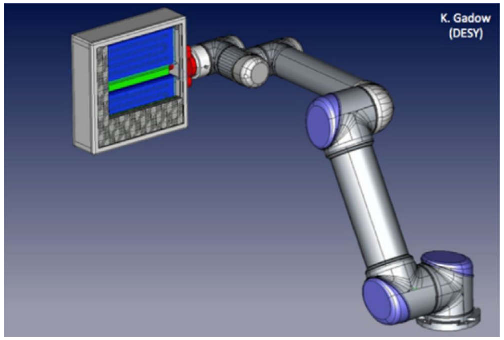

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- ➔ Cooling system, mechanical arm

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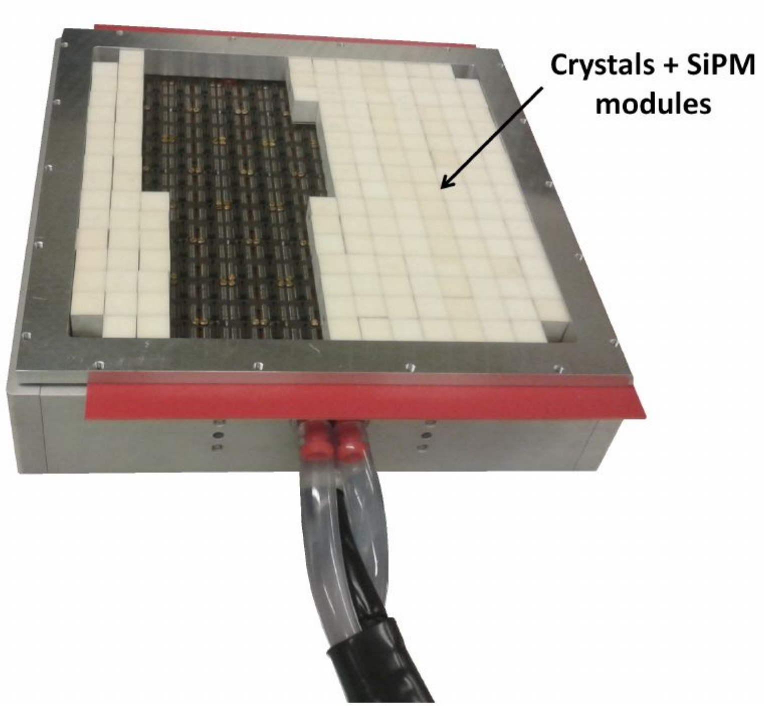

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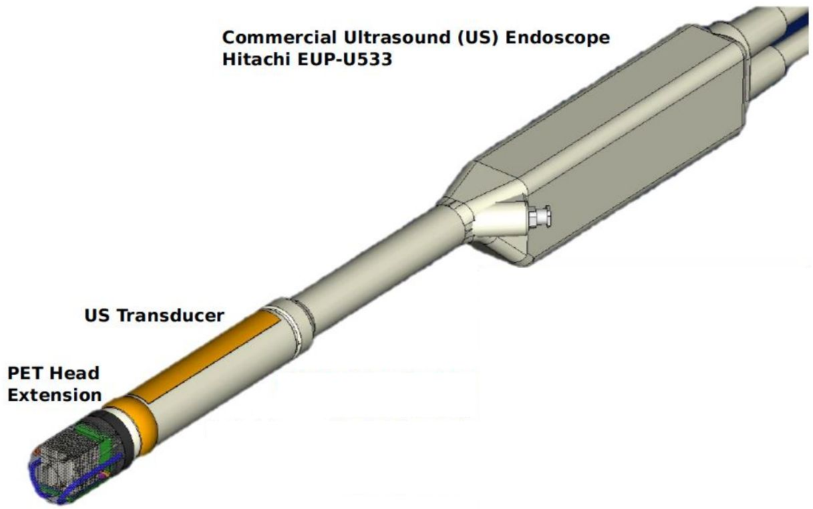
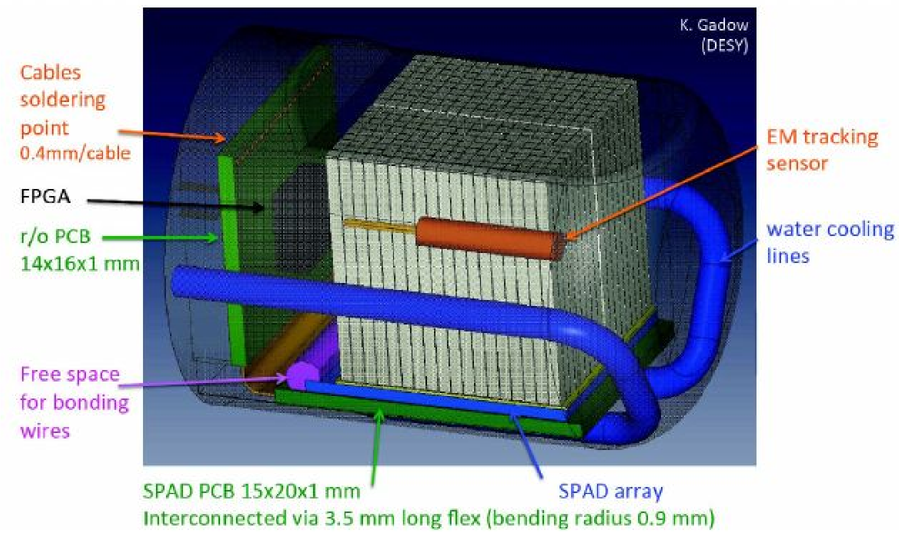
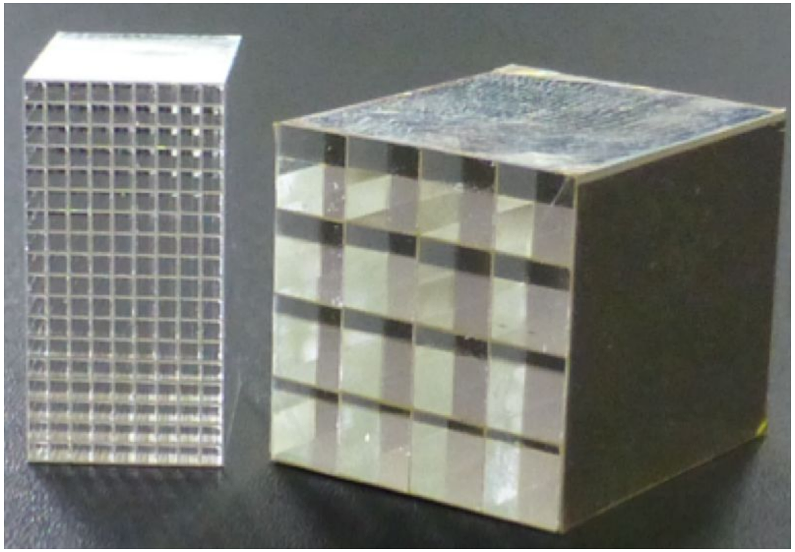
PET detector design: endoscopic probe





- ➔ **Two different versions** under development:
  - ➢ Pancreas probe, diameter **15 mm**
    - Clamped on Fujinon EG-530UR2
  - ➢ Prostate probe, diameter **23 mm**
    - Clamped on Hitachi EUP-U533
- ➔ **Scintillators**: 1 (pancreas) or 2 (prostate) arrays of **9x18 LYSO:Ce**
  - ➢ Individual crystal size **0.71x0.71x15**(or 10) **mm**^{3}
  - ➢ Crystal pitch **800 μm**
  - ➢ Coating material: ESR by 3M
- ➔ **Photo-detector**: custom **MD-SiPM** developed within the collaboration
- ➔ **Provisional probe** with analog MPPCs for testing
- ➔ EM, and optical **tracking**, water **cooling**

PET detector performance: scintillators



- ➔ **LYSO:Ce** polished scintillators, coating with ESR
- ➔ Required light output to reach 200ps = **20000-25000 Ph/MeV**
- ➔ 9x18 arrays of internal probes tested on standard PMTs (optical grease coupling)
  - ➢ Narrow sum photopeak ensure uniform light output within individual arrays
  - ➢ Average light output = **28000 +/- 1000 Ph/MeV**

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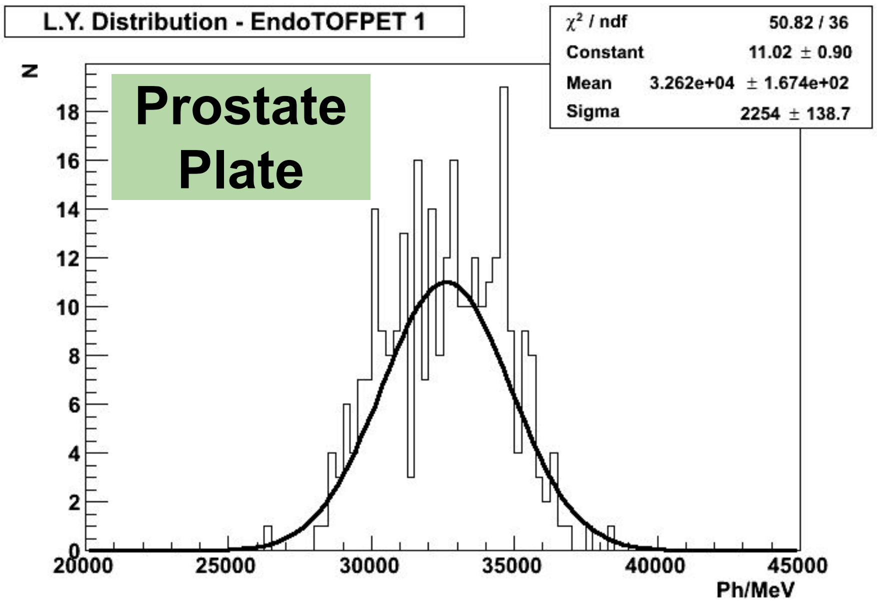

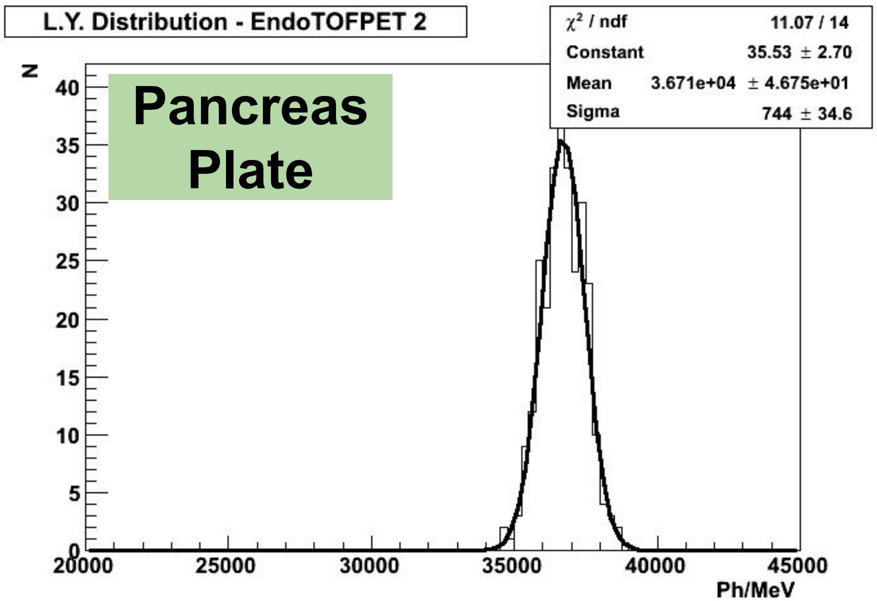

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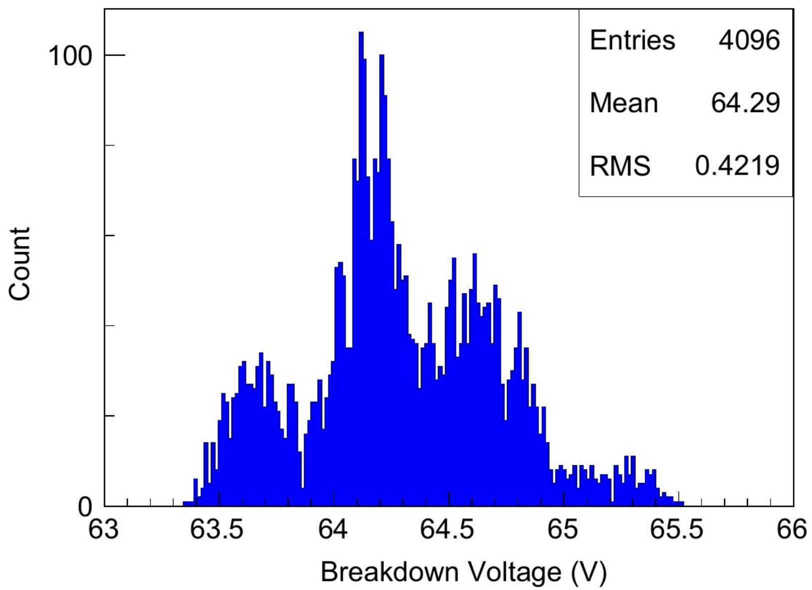
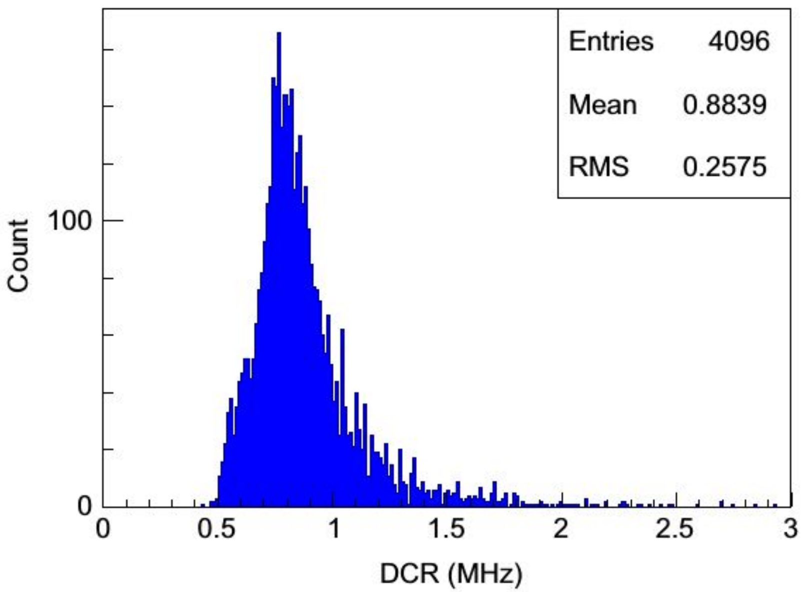
  - ➢ Narrow sum photopeak ensure uniform light output within individual arrays
  - ➢ Average light output = **28000 +/- 1000 Ph/MeV**
- ➔ Characterization of 276(x2) arrays produced for external plates with **MiniACCOS**
  - ➢ 25 arrays per teflon plate
  - ➢ Motorized X-Y movements
  - ➢ Average light output (Prostate) = **32000 +/- 2000 Ph/MeV**
  - ➢ Average light output (Pancreas) = **37000 +/- 3000 Ph/MeV**

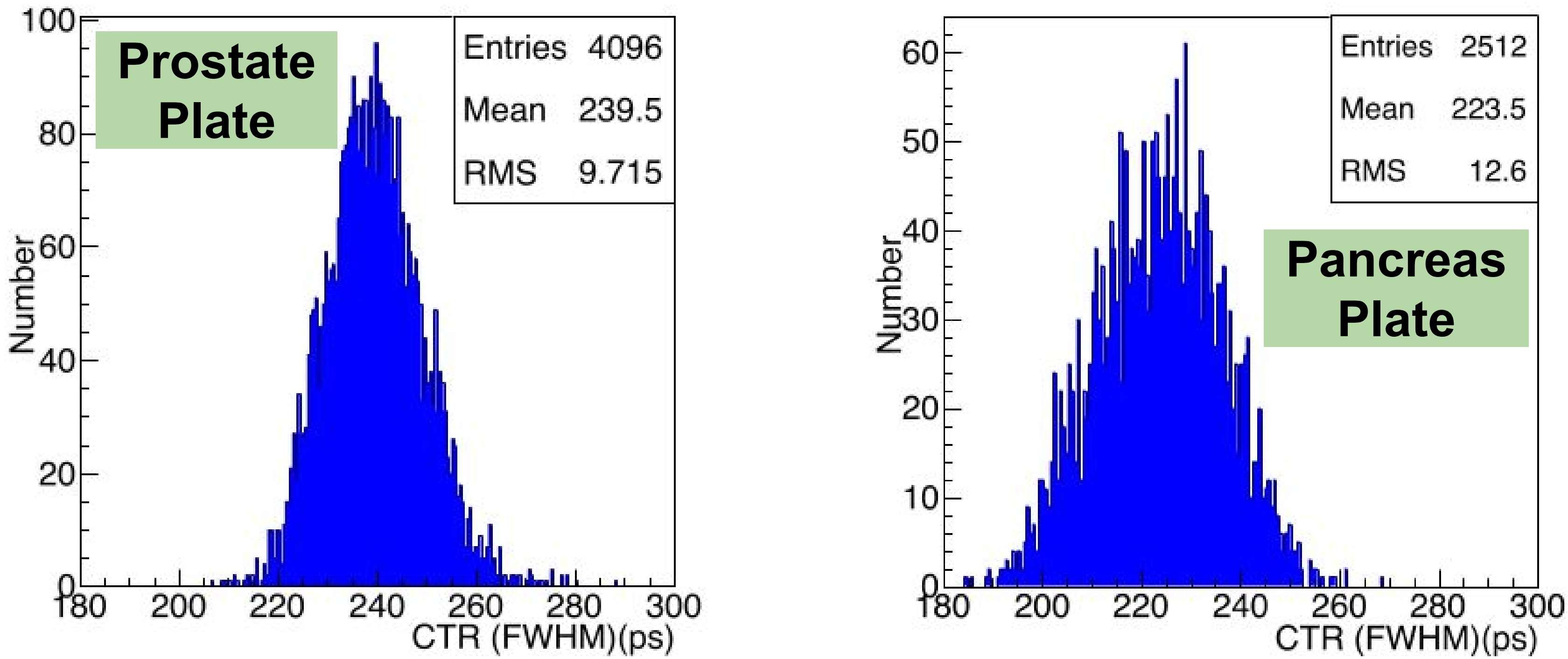
PET detector performance: MPPCs





- ➔ Characterization of breakdown voltage (V_{bd}) with I-V curves
  - ➢ Measured with Keithley 2410 for each channel of the 256 MPPCs, at 19 °C
  - ➢ **Excellent homogeneity** within 16 channels of each array
  - ➢ MPPCs sorted on the bases of V_{bd} distribution (common bias for 4 MPPCs)
  - ➢ Operational voltage set to $\mathbf{V_{bd}}$ **+ 2.5 V**
- ➔ Average Dark Count Rate (DCR) and Cross Talk
  - ➢ DCR measured as a function of the NINO amplifier/discriminator threshold
  - ➢ Average **DCR** at 19 °C = **0.88 MHz**
  - ➢ Cross Talk between SPADs measured as the ratio of DCR at 1.5 to 0.5 photoelectrons
  - ➢ Average **SPAD cross talk** at 19 °C = **41.4%**

PET detector performance: modules



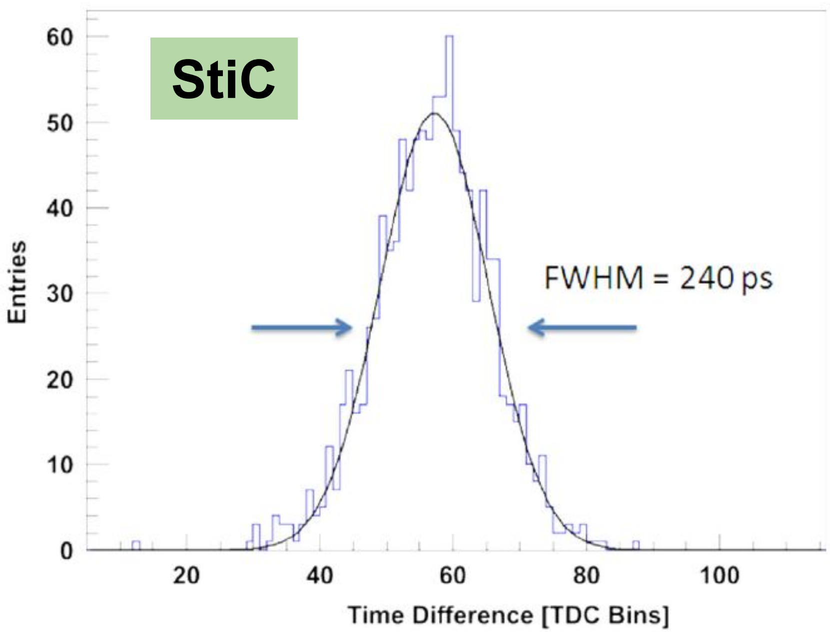
- Light Output of all modules determined as number of pixels fired
  - Module excited with ^{22}Na source
  - Current output integrated by QDC over 100 ns gate
  - Mean Light Output = 1876 +/- 100 pixels fired
  - Mean **Energy Resolution FWHM** = **12.8%**
- Coincidence Time Resolution (CTR)
  - Measured with NINO and HPTDC for each module against a reference module
  - Average prostate plate **CTR_{FWHM}** = **239.5 ps**
  - Average pancreas plate **CTR_{FWHM}** = **223.5 ps**

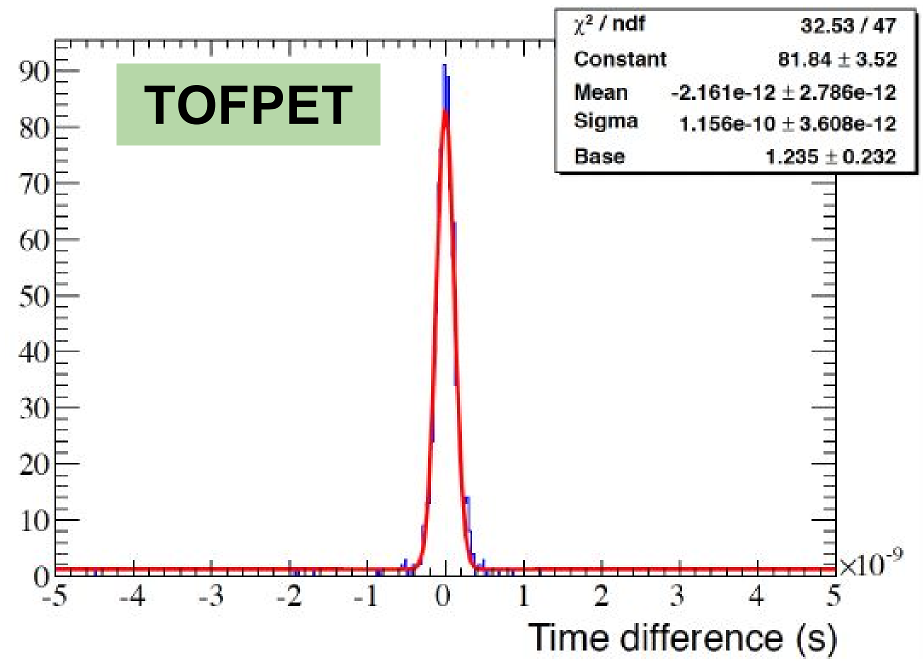
PET detector performance: ASICs

	STiC	TOFPET-ASIC
Jitter (at >5pC)	< 30 ps	< 25 ps
Input bias lin. range	0.7 V	0.5 V
TDC time bin width	50 ps	50 ps
Power consumption	19 mW/ch.	8 mW/ch
Output rate	160 MBit/s	160 MBit/s

➔ Two dedicated fast 64 channel ASICs developed: **StiC** and **TOFPET**
- ➢ Leading edge technique to get timing information
- ➢ Linearized Time-Over-Threshold method to provide energy information
- ➢ Low noise, low timing-jitter, low power consumption

PET detector performance: ASICs





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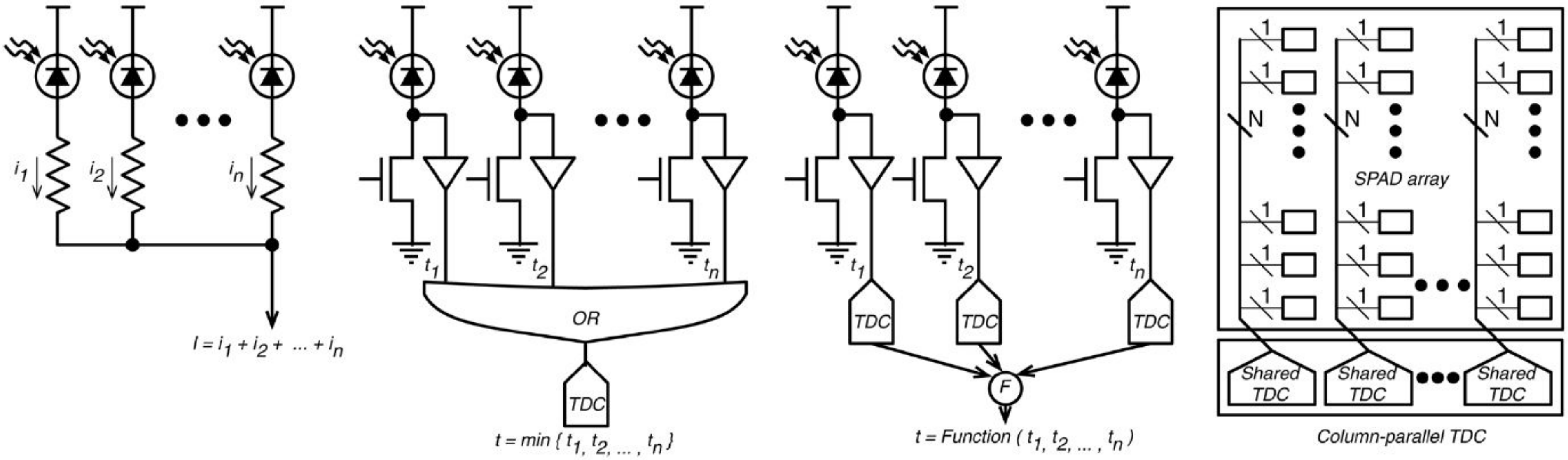
  - ➢ Leading edge technique to get timing information
  - ➢ Linearized Time-Over-Threshold method to provide energy information
  - ➢ Low noise, low timing-jitter, low power consumption
- ➔ **CTR** measured for both ASICs
  - ➢ Single 3.1x3.1x15 mm^3 crystals coupled to 2 Hamamatsu MPPCs
  - ➢ ^{22}Na source
  - ➢ StiC average $\mathbf{CTR_{FWHM}}$ = **240 ps**
  - ➢ TOFPET average $\mathbf{CTR_{FWHM}}$ = **270 ps**

Endoscopic probe: MD-SiPM



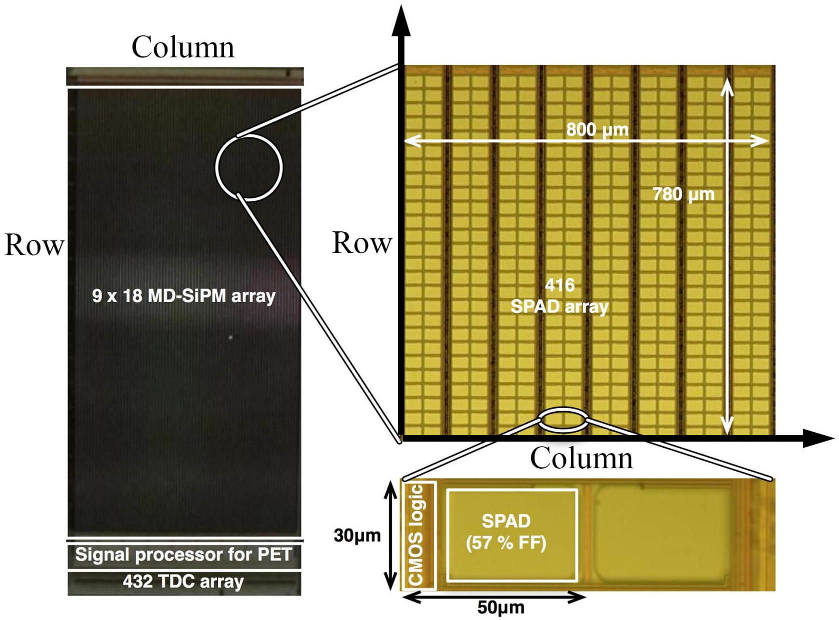
Analog SiPM

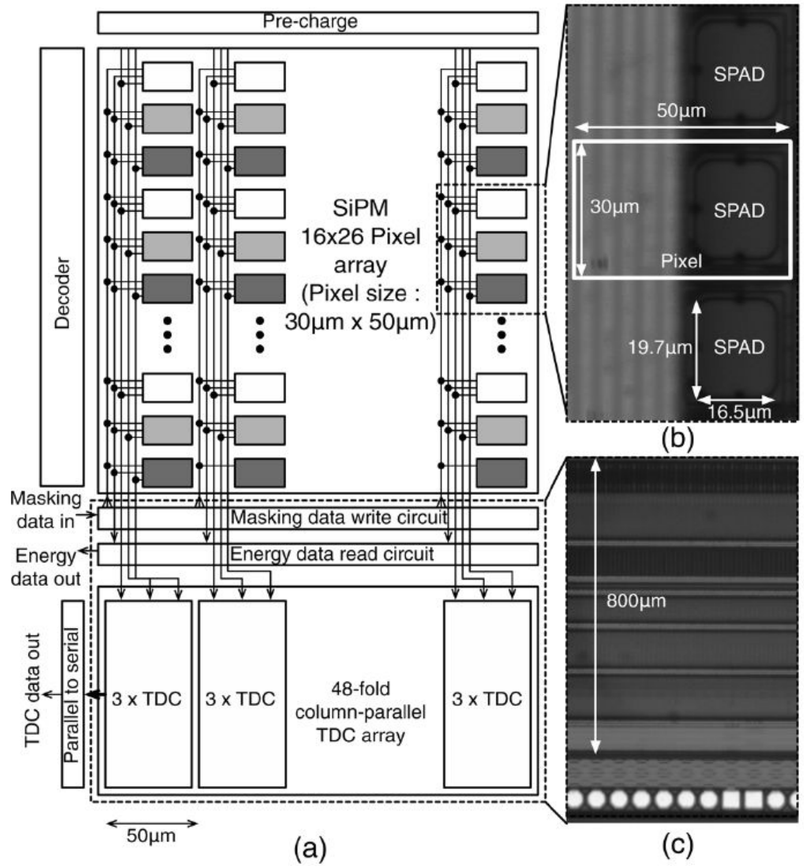
Conventional Digital SiPM

Fully digital SiPM

Multi Digital SiPM

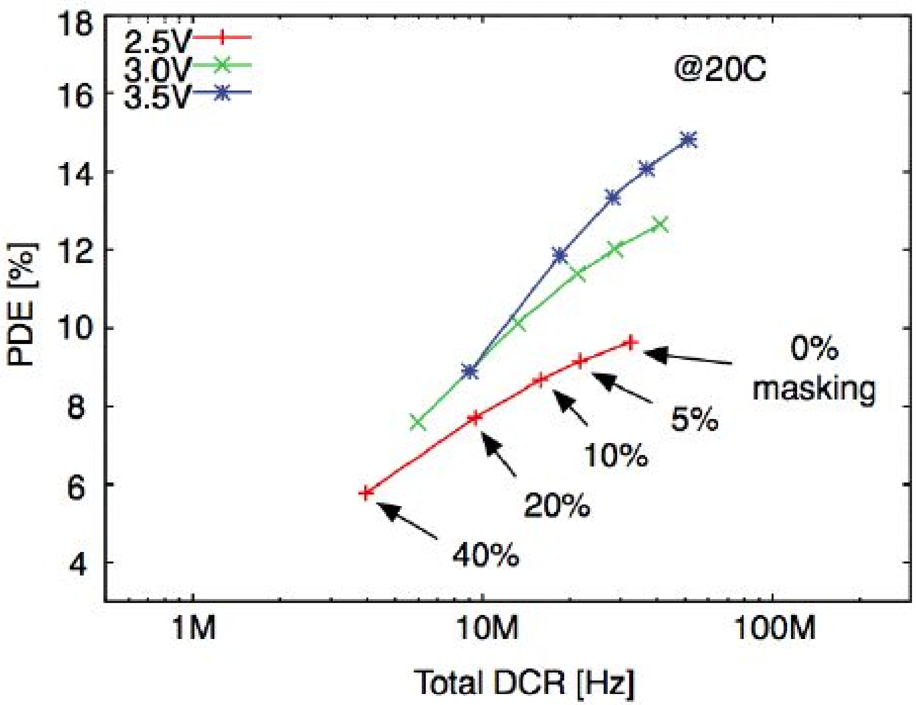
Endoscopic probe: MD-SiPM

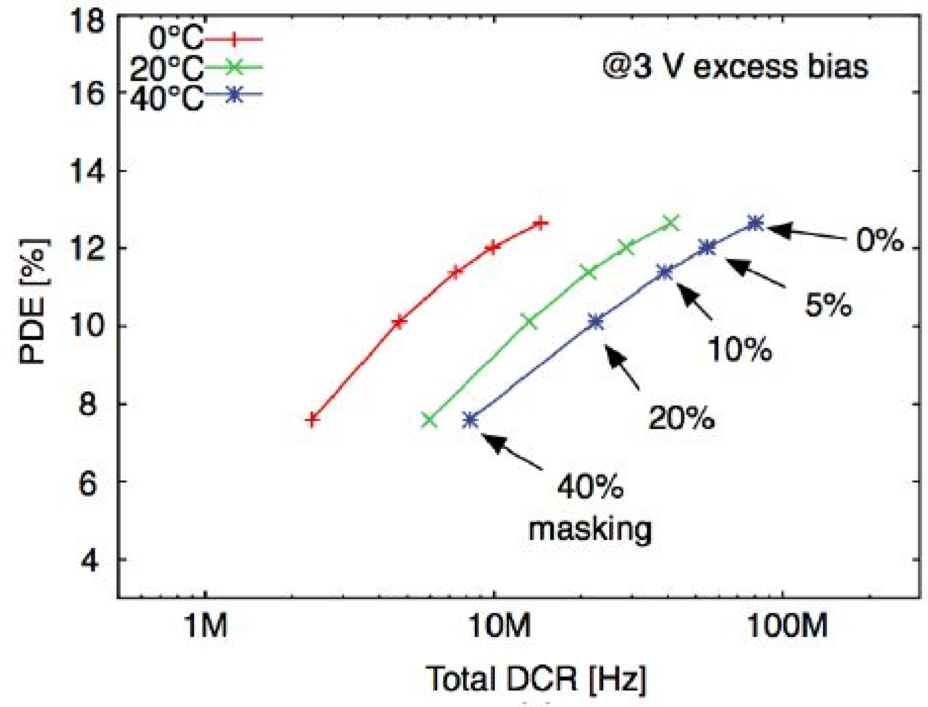




- ➔ Individual SPADs size **30x50 µm**, 57% fill factor
  - ➢ 1-bit counter per SPAD provides digital count of pixels fired
- ➔ 416 SPADs per MD-SiPM (16x26 array), size **780x800µm**
  - ➢ Pixel masking
- ➔ Array of **9x18 MD-SiPMs** matching the scintillator matrix
  - ➢ 432 column-parallel TDCs (48 per column)
  - ➢ Combining information of first 48 photons reaching **lower bound** of theoretically achievable CTR

Endoscopic probe: MD-SiPM

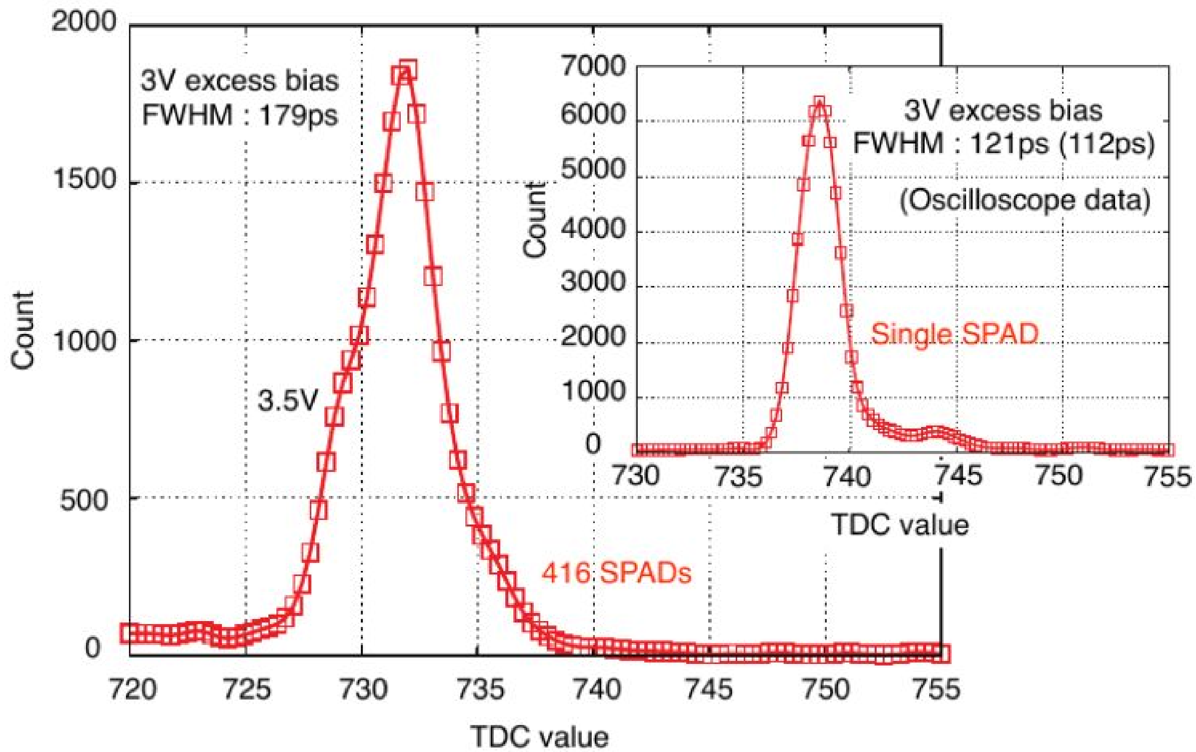




➔ DCR measured for different temperatures and bias voltages

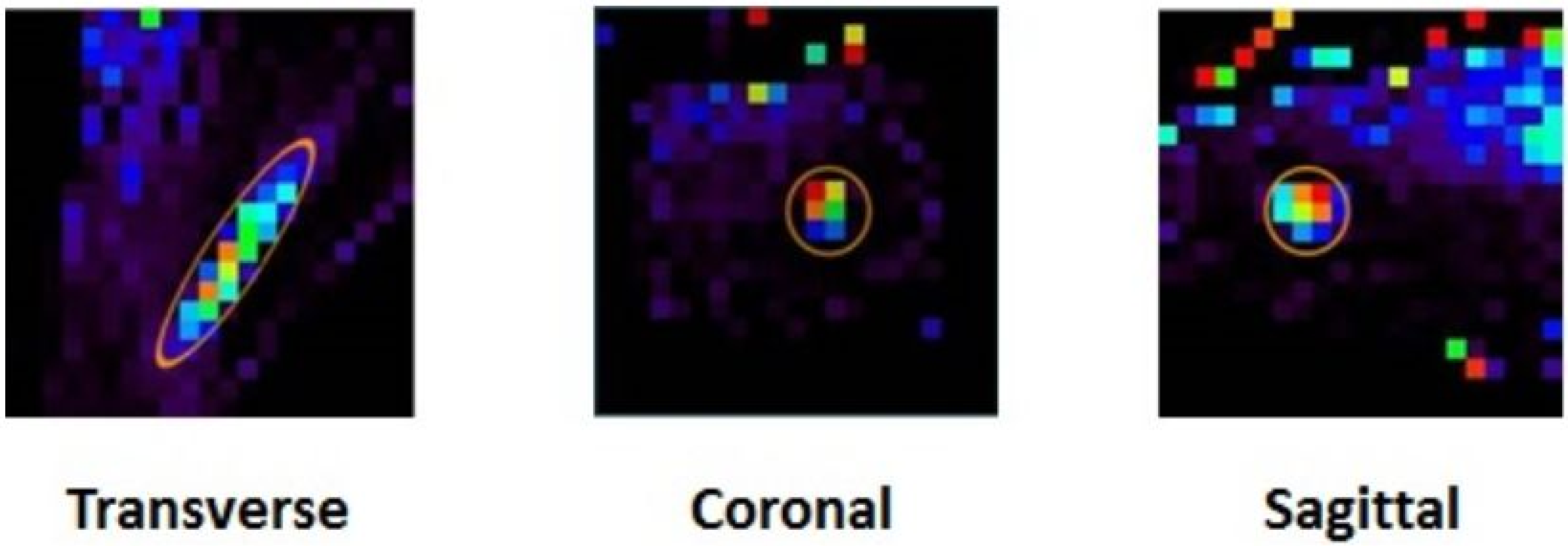
- DCR 41 MHz at 20 °C and 3 V excess bias
- Can be reduced to 23 MHz with 10% masking
- PDE after masking about 12%

Endoscopic probe: MD-SiPM



- ➔ DCR measured for different temperatures and bias voltages
  - DCR 41 MHz at 20 °C and 3 V excess bias
  - Can be reduced to 23 MHz with 10% masking
  - PDE after masking about 12%
- ➔ Single Photon Timing Resolution (SPTR) evaluated
  - Pulsed laser (250 mW, 405 nm, 40ps pulse width)
  - Internal TDCs (45 ps LSB)
  - $SPTR_{FWHM}$ measured in **121 ps** for single SPAD and **179 ps** for entire 16x26 array

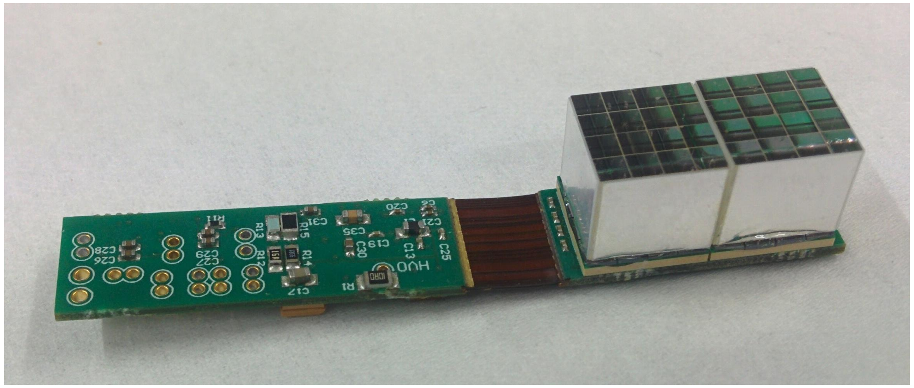
Reconstruction Algorithm - Simulations



➔ Dedicated reconstruction algorithm developed within the collaboration
- Iterative **histogram based ML-EM** reconstruction
- Incorporates TOF information
- Copes with detector asymmetry
- Takes into account the limited rotation capabilities
- Massive parallelization by GPU programming

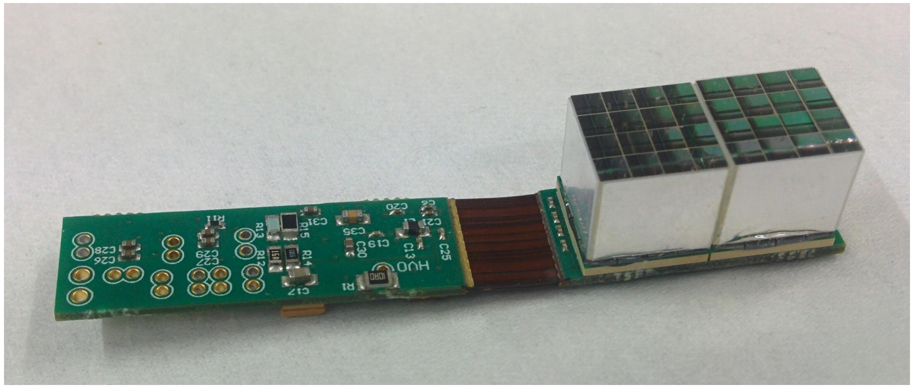
➔ Expected performance tested on **simulated datasets**
- Based on GAMOS toolkit
- **1 mm resolution** within reach with **10 minutes** scan time

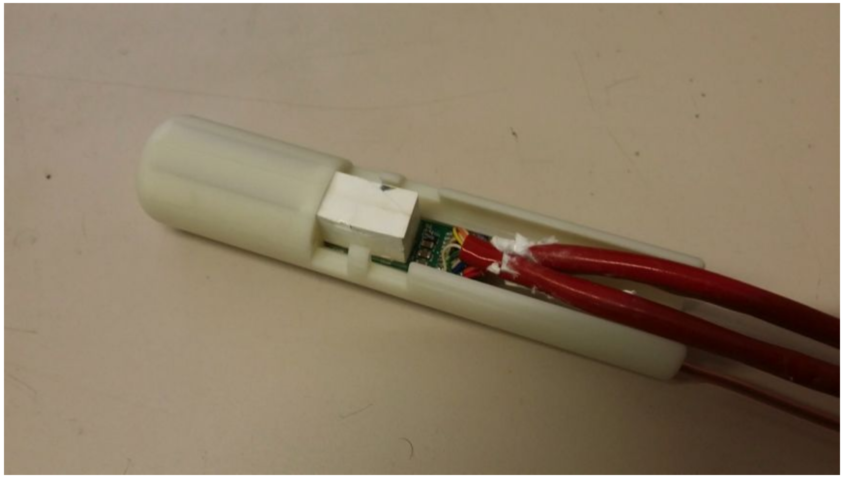
Commissioning and testing of first prototype

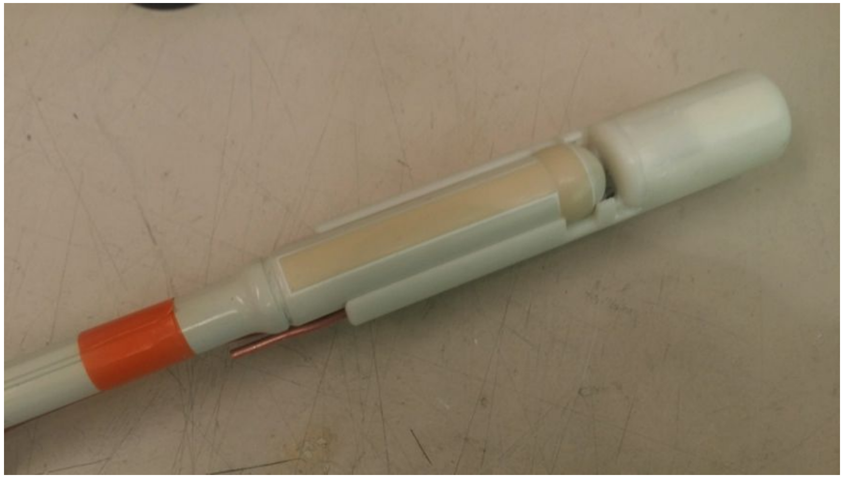


➔ **Provisional probe** with 2 MPPCs and 2 4x4 LYSO:Ce arrays (3.1x3.1x15 mm^3)

Commissioning and testing of first prototype







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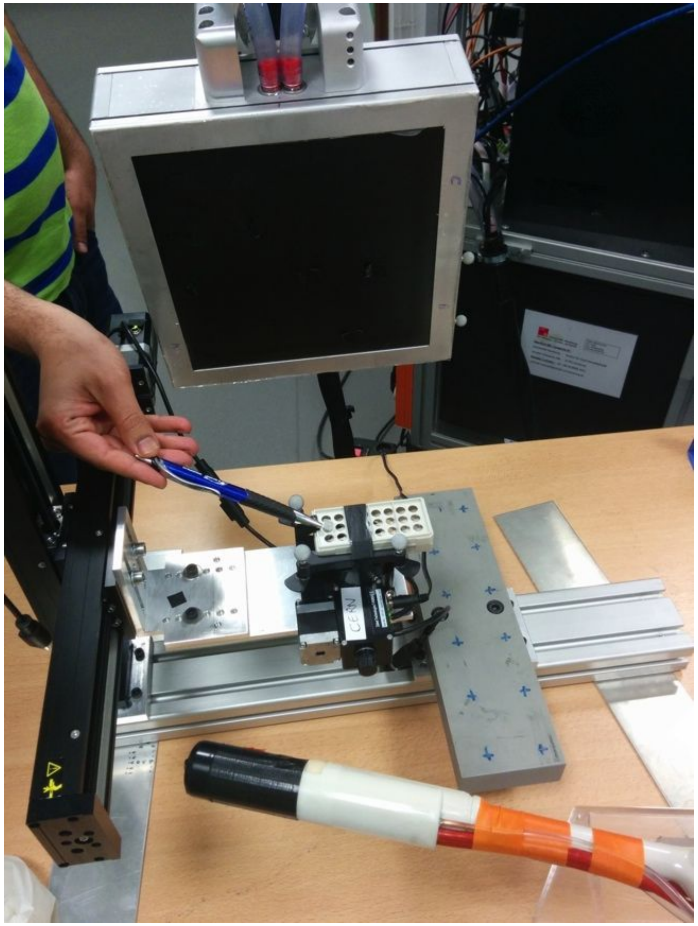

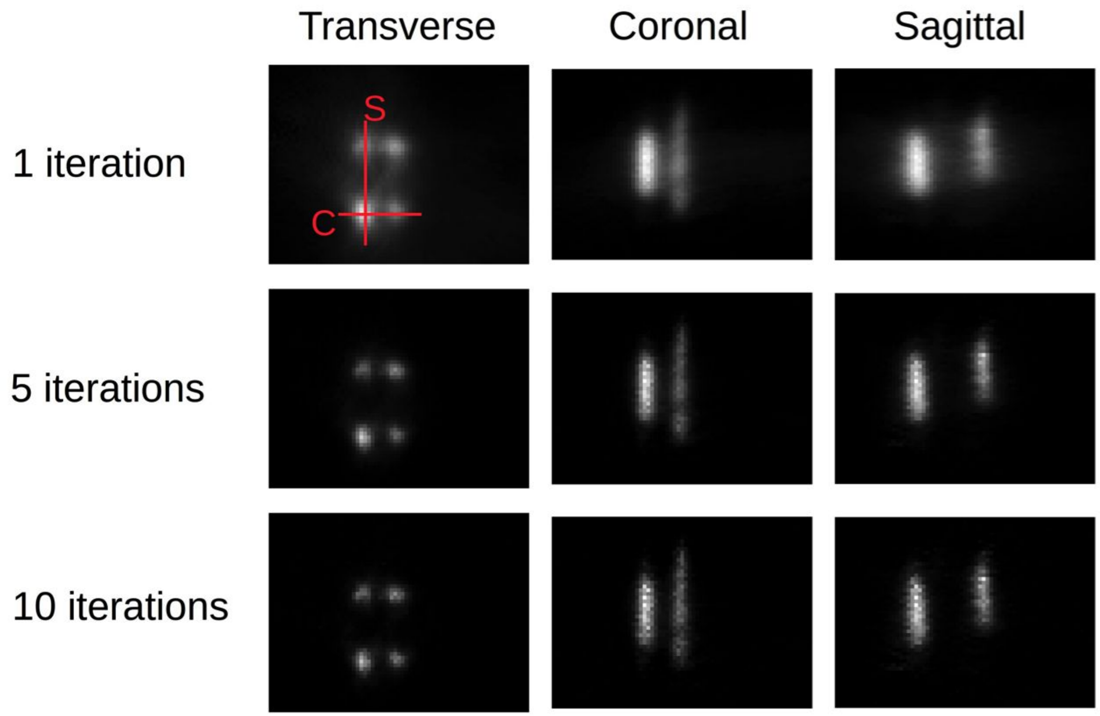

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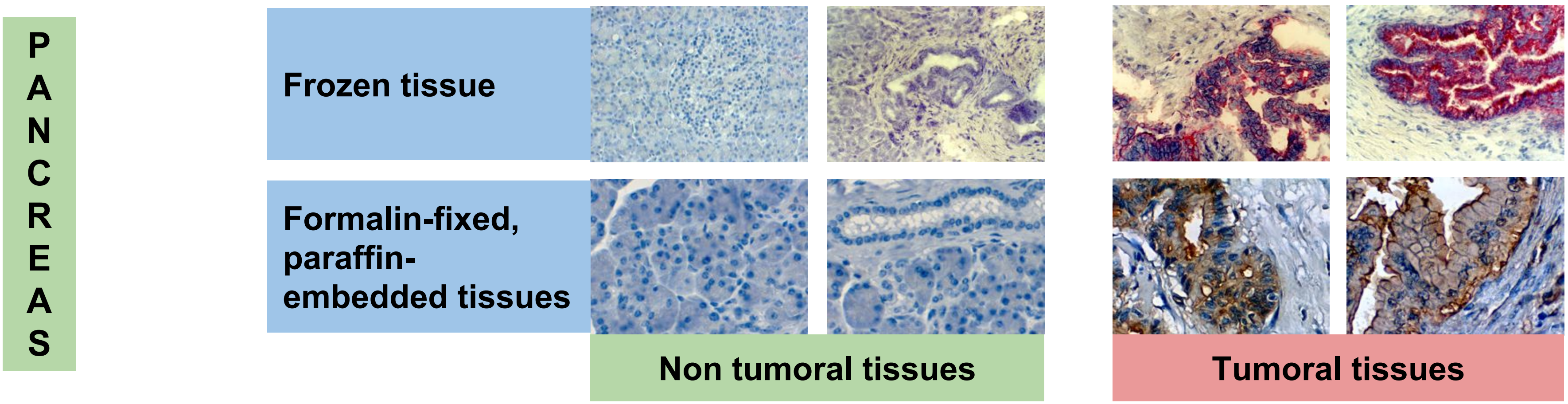
- ➔ Clamping on prostate US endoscope
- ➔ Preliminary images obtained at **CERIMED-Marseille** on cylinders filled with **FDG**

Development of new biomarkers

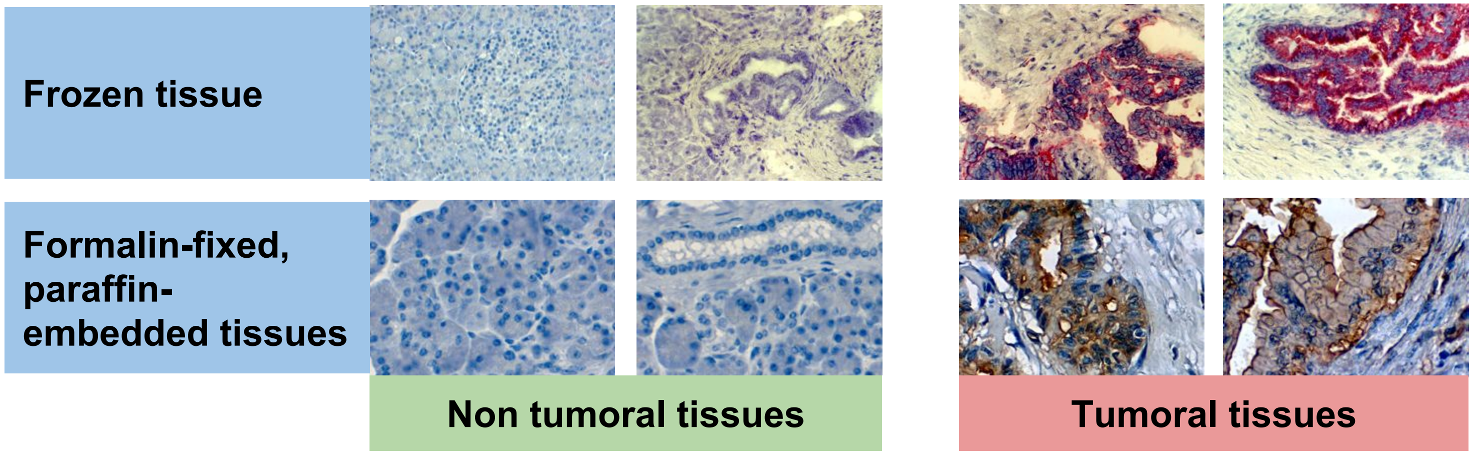


➔ Pancreas cancer: **mAb16D10**

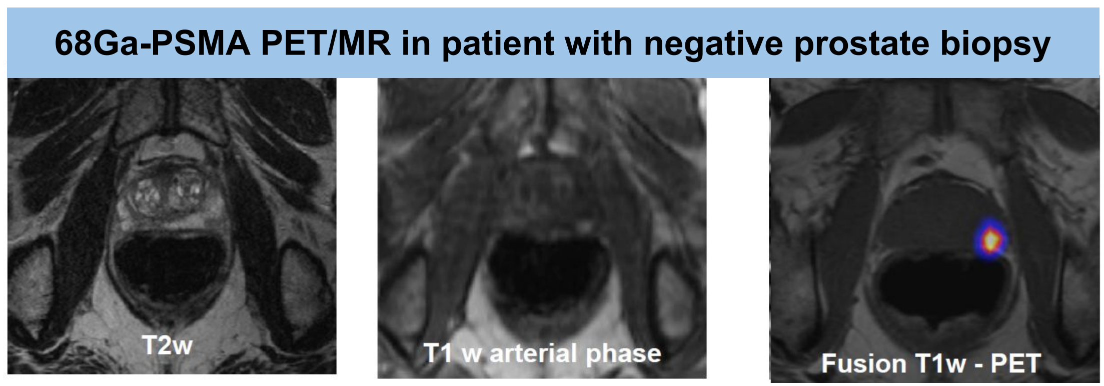
- ➢ **Recognizes** human pancreatic tumor cells
- ➢ **Does not recognize** non-tumoral pancreatic tissue, other cancers or normal tissue
- ➢ **Therapeutic** properties: decreases tumor growth and mobility

Development of new biomarkers

PANCREAS



PROSTATE



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  - ➢ **Therapeutic** properties: decreases tumor growth and mobility
- ➔ Prostate cancer: **^{68}Ga-PSMA**
  - ➢ **Enzyme** expressed by prostate epithelial cells
  - ➢ **More specific** as compared to standard ^{18}F and ^{11}C tracers

Conclusions

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- **Early diagnosis**, via spatial resolution and SNR and NEC improvement from TOF
- Tool for development of new **biomarkers**
- Research to develop this scanner will be instrumental in the **effort towards the "10 ps PET"** (e.g. MD-SiPM, fast ASICs, scintillators, etc.)

Conclusions

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  - ➢ **Early diagnosis**, via spatial resolution and SNR and NEC improvement from TOF
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- ➔ Performance of single components evaluated, design targets **within reach**
- ➔ Two external detectors assembled, **first tests** with provisional internal probe
- ➔ Assembly of final version for the endoscopic PET probe ongoing

Thank you for your attention!

Thanks to all the collaborators of
EndoTOFPET-US and PicoSEC-MCNet

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