Radio-Guided-Surgery: status and perspectives

R. Faccini

University "La Sapienza" and INFN Rome

Incontro Nazionale Fisica Nucleare 16/11/2016

Chirone→ Chir2

http://arpg-serv.ing2.uniroma1.it/arpg-site/index.php

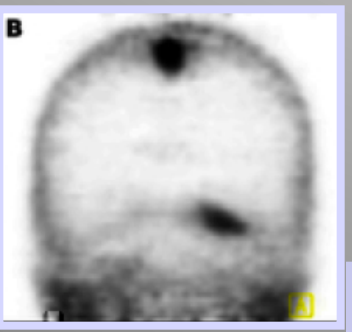
Overview

- Radio-Guided Surgery(RGS): basic concepts
- γ probes – briefly
- β^+ probes
- Novel development: β^- RGS

Radioguided surgery

Radio Guided Surgery

PET/SPECT scan to estimate receptivity and background



Each tumor requires its own tracer

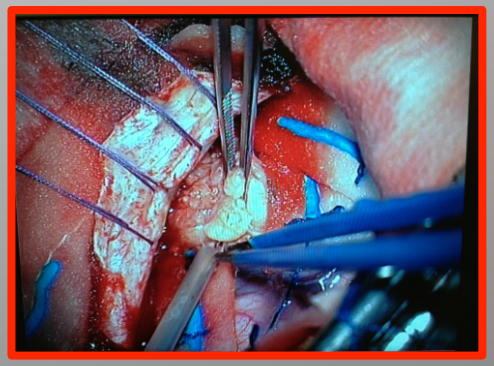
Administration of radio-tracer

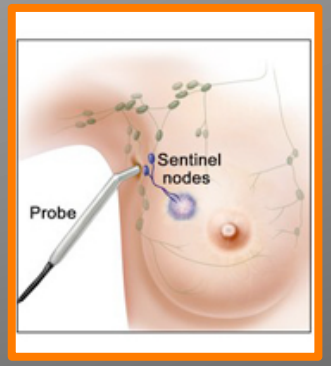
During surgery a probe is used to detect residuals/lymphnodes

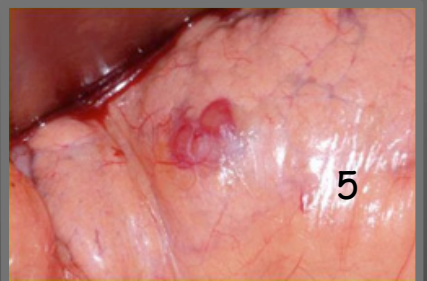
Probe adjustable to needs

Intra-operative probes

- Needed when
  - Complete Tumor resection is mandatory
    - example: brain, pediatric tumors
  - Identification of lymph-node is needed
    - Example: breast tumor, melanoma
  - Tumor identification can reduce invasiveness
    - Example: parathyroid adenoma, insulinoma,…







Critical Aspects

1. Identification of clinical applications
2. Choice of the radio-nuclide
3. Identification of tracer and its match with the radio-nuclide
4. Probe design
5. Tests

Possible radio-nuclides

- Already tested nuclides include

Radionuclide	Principali particelle emesse	$T_{1/2}$	Radiofarmaci
^{99m}Tc	γ	6.01 h	^{99m}Tc-MDP ^{99m}Tc-MIBI
^{18}F	β^+	110 min	^{18}F-FDG
^{111}In	γ	67.4 h	^{111}In-Octreotide
^{86}Y	β^+	14.7 h	^{86}Y-DOTATOC
^{68}Ga	β^+	68 min	^{68}Ga-DOTATOC
^{90}Y	β^-	64.1 h	^{90}Y-DOTATOC
^{177}Lu	β^-, γ	6.73 d	^{177}Lu-DOTATATE
^{131}I	β^-, γ	8.1 d	^{131}I-MIBG

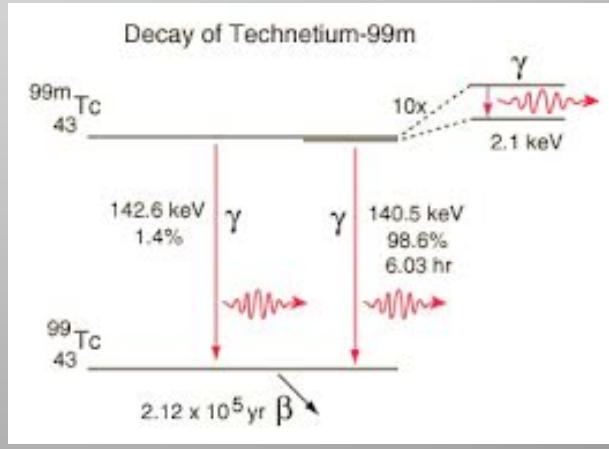
SPECT

PET

Molecular RT

Radioguided surgery: γ probes

Existing: gamma probes



1. Choice of radio-nuclide: gamma emitting, in particular ^{99m}Tc
   - well known detectors (camera or probes)
   - used for SPECT: large number of known radio-tracers

2. Applications of interest:
   - Search for tumor residuals (colon cancer, parathyroid adenoma, osteoid osteoma)
   - Complete sentinel-node mapping (malignant melanoma and breast cancer)

Gamma probes applications

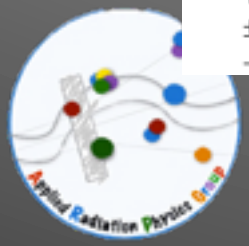
Local non-specific tracers

TARGET	TUMOR	UTILITY
Sentinel lymph node by intra- or peritumoral administration of ^{99m}Tc-colloids	Breast cancer	++
	Melanoma	+
	Skin cancer	++
	Penile/vulvar cancer	++
	Colon cancer	±
	Lung cancer	±
	Head and neck cancer	±
Tumor deposits by tumor-seeking agents (monoclonal antibodies, ^{99m}Tc-sestamibi)	Colon cancer	±
	Ovarian cancer	−
	Breast cancer	−
	Medullary thyroid cancer	+
	Melanoma	−
	Neuroblastoma	±
	Parathyroid adenoma	++
Bone abnormalities by ^{99m}Tc-diphosphonate	Osteoid osteoma	++
	Bone lesions suspected for bone metastasis	++
Occult tumors by intratumoral administration of an isotope tracer	Occult breast cancer	++

Legend:
++ = proven clinical value
+ = may be of clinical value
± = clinical relevance insufficiently evaluated
− = proven not to be of clinical value

Systemic administration

Mariani, Giuliano, Strauss 2004



LIMITS OF γ-RGS

140 keV photons

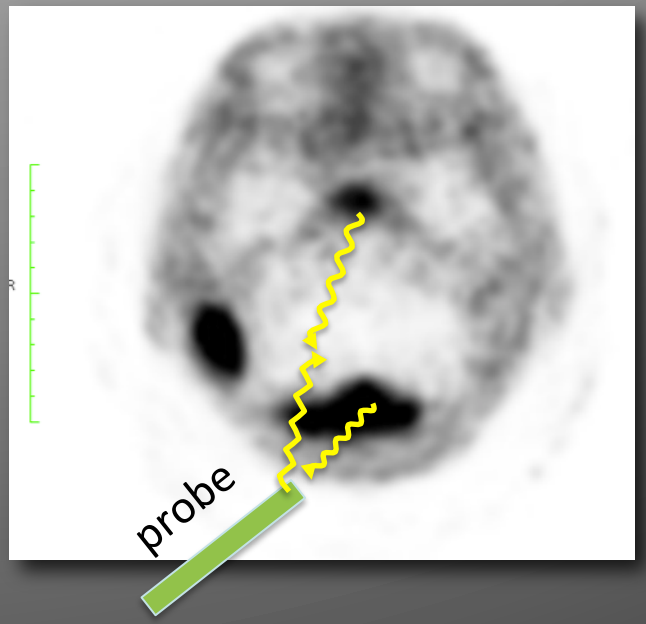
➔ attenuation in body ~8cm

Long range of gamma's involve:

- exposure of medical personnel
- Background from healthy organs

Difficult to apply in:

- Brain tumors
- Abdominal tumors
- Pediatric tumors

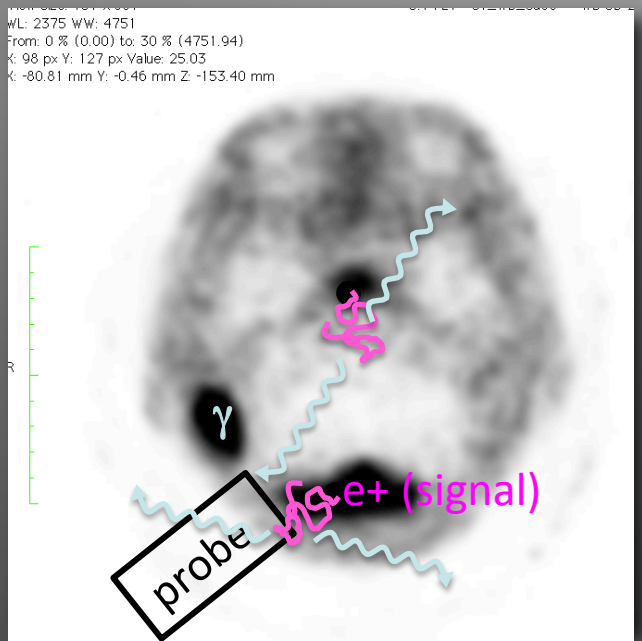


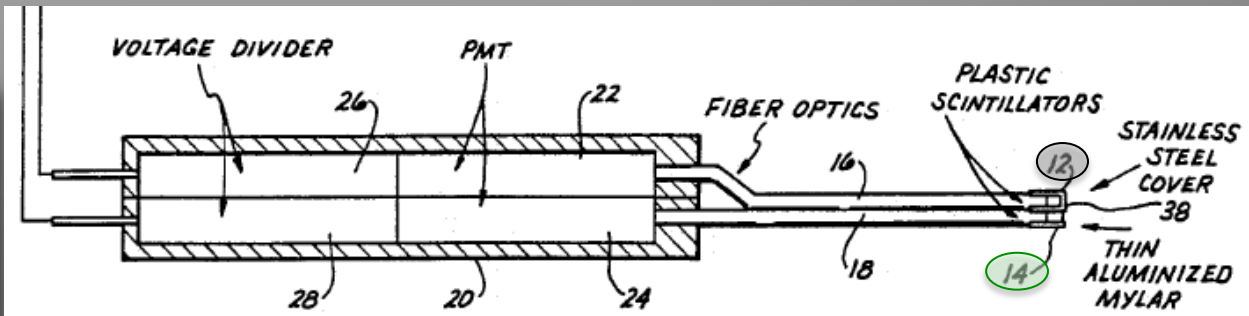
Radioguided surgery: β^+ probes

Daghighial et al 1994
Raylman et al 2001

β^+ RGS

- Use of β^+ decaying isotopes (same as PET) ➔ detect positron (little penetration)
- Dual detectors for gamma background subtraction





Two channels:

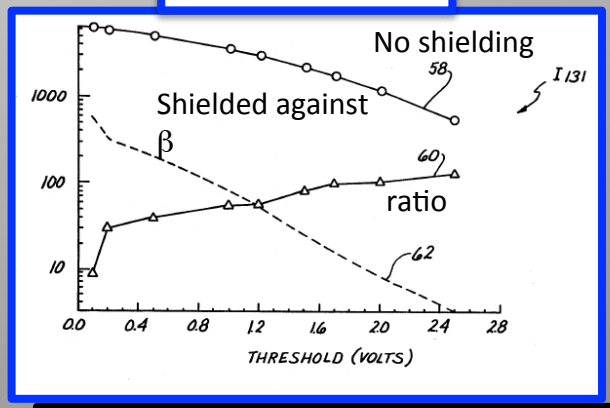
- one sensitive to both positrons and gamma (14) (N1=P+G)
- one sensitive only to gamma (12) (N2=G)

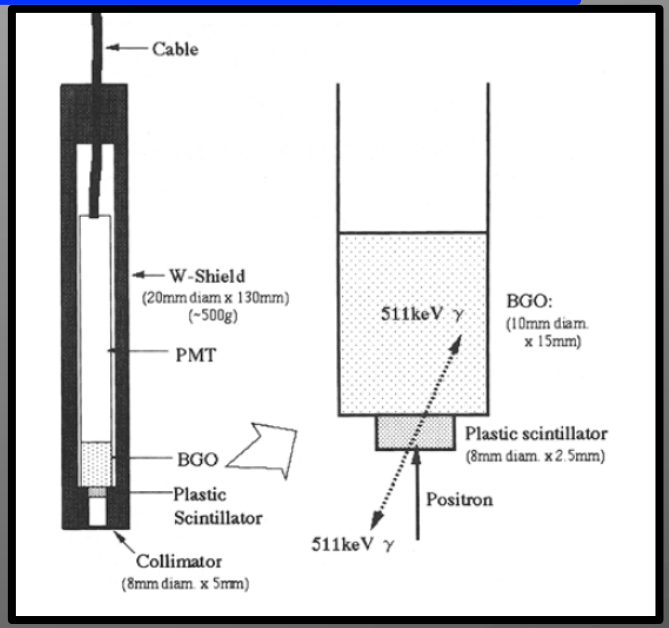
signal=N1-N2

β^+ RGS: developments

- 1994 Daghighian: two different detectors for beta and γ
- 2001 Raylman: integrated dual-detector with semi-conductor devices
- 2005 Yamamoto: plastic+BGO phoswitch

Tests with point-like source

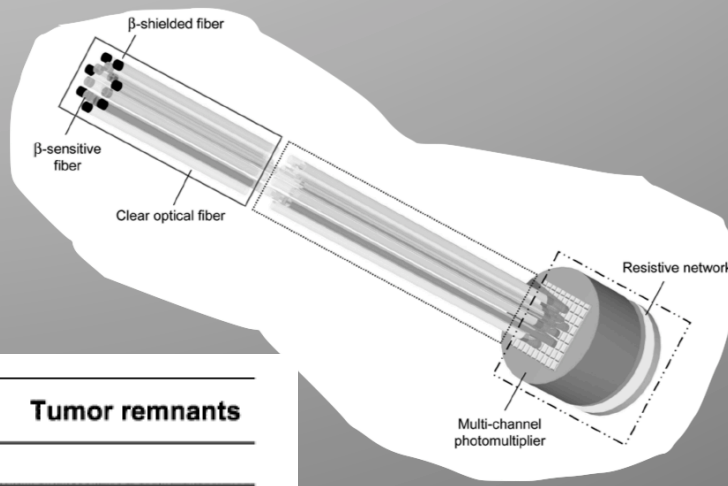




β^+ RGS: clinical applications

Brain tumors: difficult use of pre-operative information

- 2007Bonzom et al :
  - attach it to the surgical device
  - Different tracers considered to carry ^{18}F



Activity (μCi/ml)	Normal tissues		Tumor remnants
	White matter	Gray matter	
FDG	0.32	0.57	0.59
FET	0.075	0.104	0.29
Choline	0.019	0.017	0.170

- 2009 Bogalhas et al:
  - Test on phantom

Conclusions

This phantom also demonstrated the ability of the probe to detect tumour discs as small as 5 mm in diameter (20 mg) for tumour-to-background ratios higher than 3:1 and with an acquisition time around 4 s at each scanning step. These results indicate that our detector could be a useful complement to existing techniques for the accurate excision of brain tumour tissue and more generally to improve the efficiency of radio-guided cancer surgery.

β^+ RGS

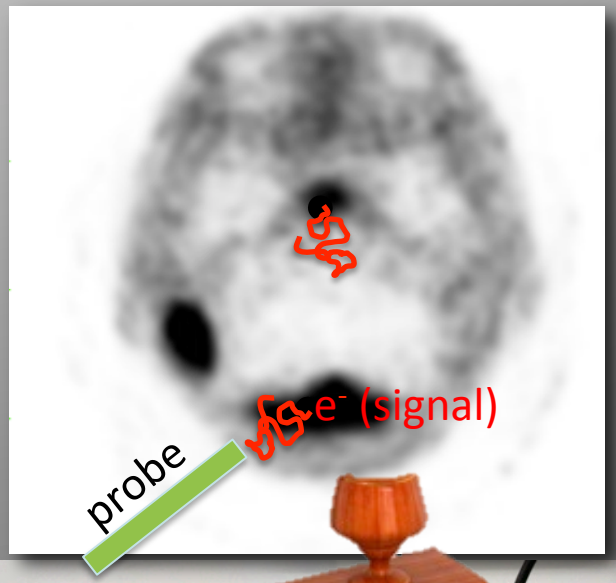
- Use of β+ tracers(positrons): pros
  - Detect positron that travels ~100 times less
  - PET tracers can be used
- Use of β+ tracers: cons
  - Large irradiation of medical personnel (~20 μSv/hr)
  - Positrons annihilate and produce photons → background → need to subtract background
    - » Longer time to have a response
    - » More encumbrant detector

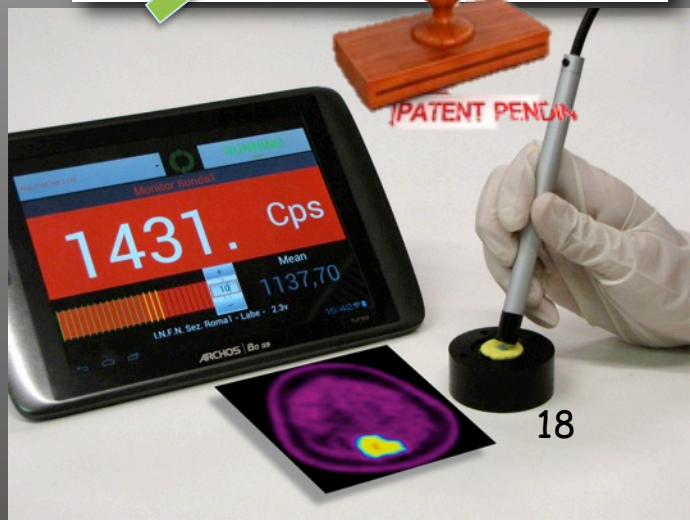
Radioguided surgery: β^- probes

A CHANGE IN PARADIGM

- Use of β^- tracers (electrons): pros
  - Detect electrons that travel ~100 times less than γ
  - Tracers with ^{90}Y can be used (already used for Molecular RT)
  - No background from gamma
    - Shorter time to have a response
      - » Smaller administered activity
    - Smaller and more versatile detector
    - Very reduced effect of nearby healthy tissues
    - Reduced dose to medical staff

E. Solfaroli Camillocci et al, Sci. Repts. 4,4401 (2014)

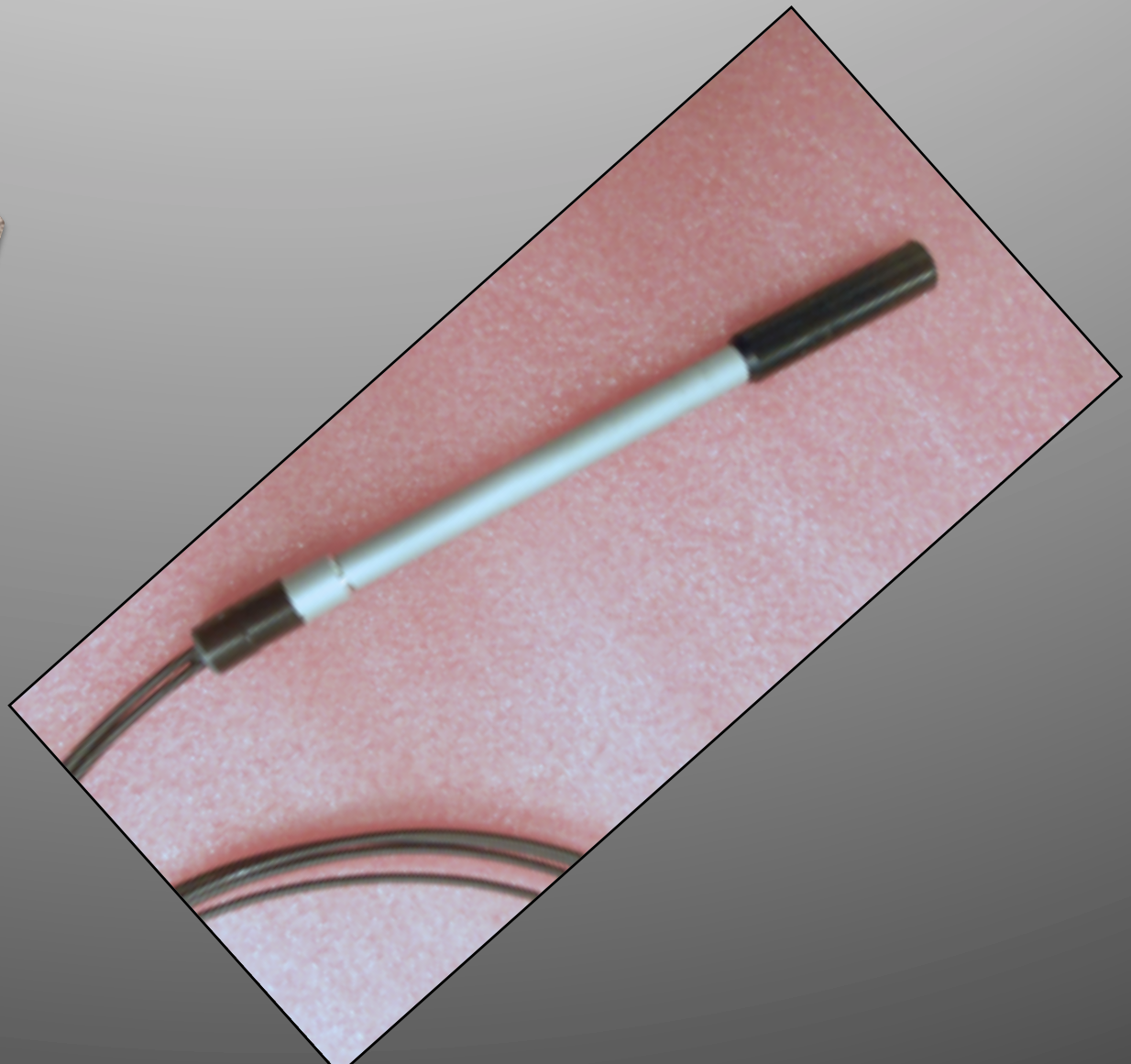




EXTEND RGS TO MORE CLINICAL CASES

RESEARCH PATH

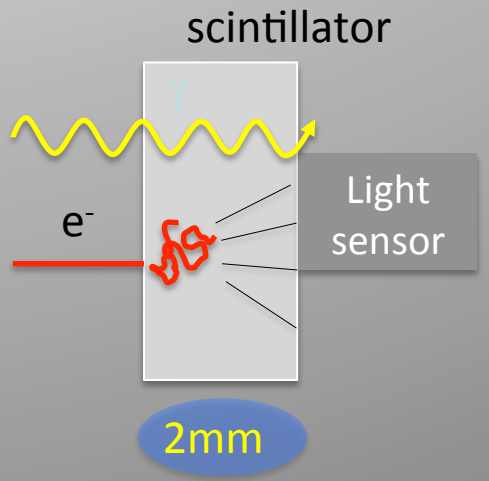
Probe Prototypes



Low energy e- detector

p-terphenyl as scintillator

- High signal:
  - LY(pterf)=3LY(Anthracene)
- Low Z
  - Low sensitivity to photons
- Small attenuation length
  - λ=(4.73 ± 0.06) mm



Usually unused because signal attenuates if detector too thick

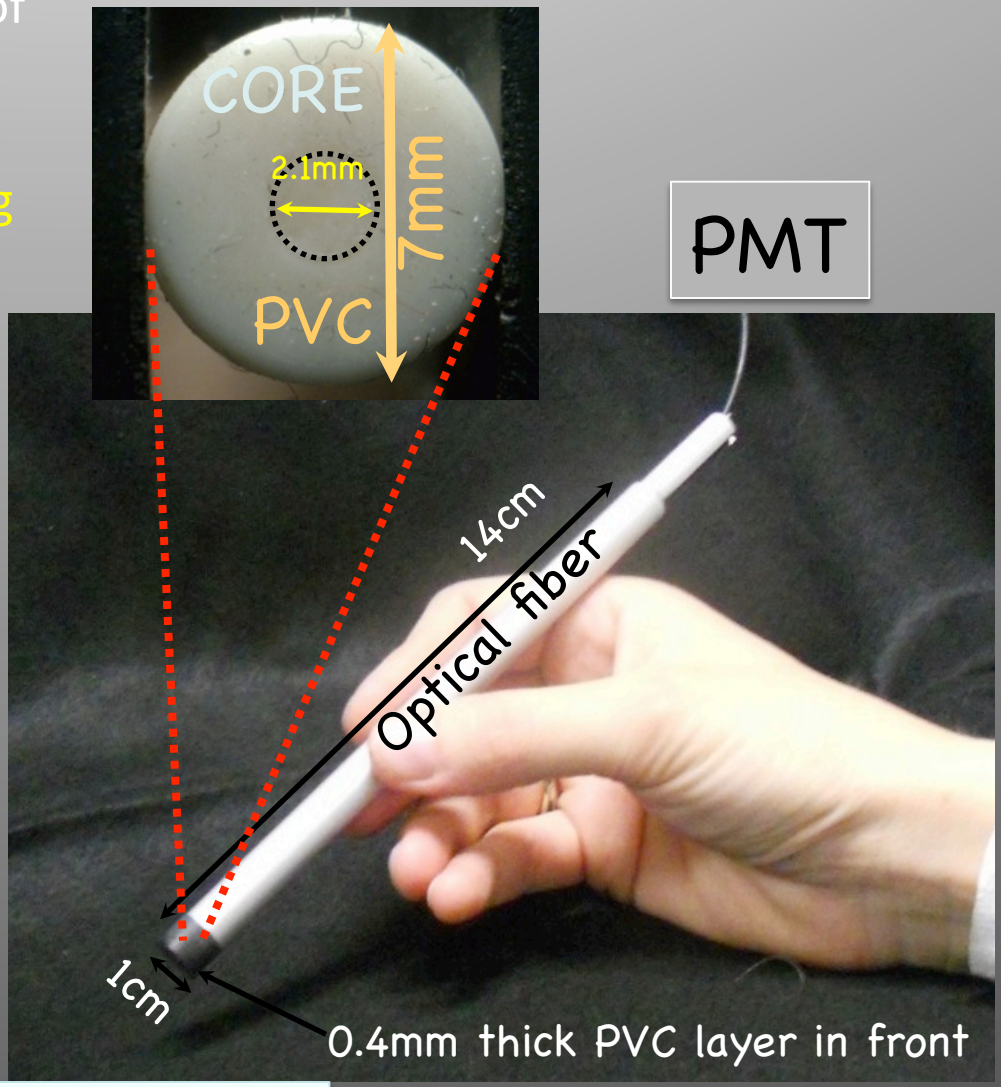
→ **Not for low energy electrons**

Note: also in case of pure β- emitters gamma rejection is important because of brehmsstrahlung

R. Faccini et al, **Properties of P-Terphenyl as detector for α, β, and γ radiation,** IEEE Trans. on Nucl. Sci. 2014; 61: 1483-7

Prototypes

- **Core**: cylindrical scintillator of p-terphenyl d=2.1mm, h=1.7mm
- encapsulated into a PVC ring to shield it against radiation coming from the sides;
- inserted as a tip inside an easy handling aluminum body.
- A thin black PVC cap makes the enclosure light tight.
- Two options for light collection:
  - Scintillating fiber and PMT
  - SiPM (SensL B/C-series)



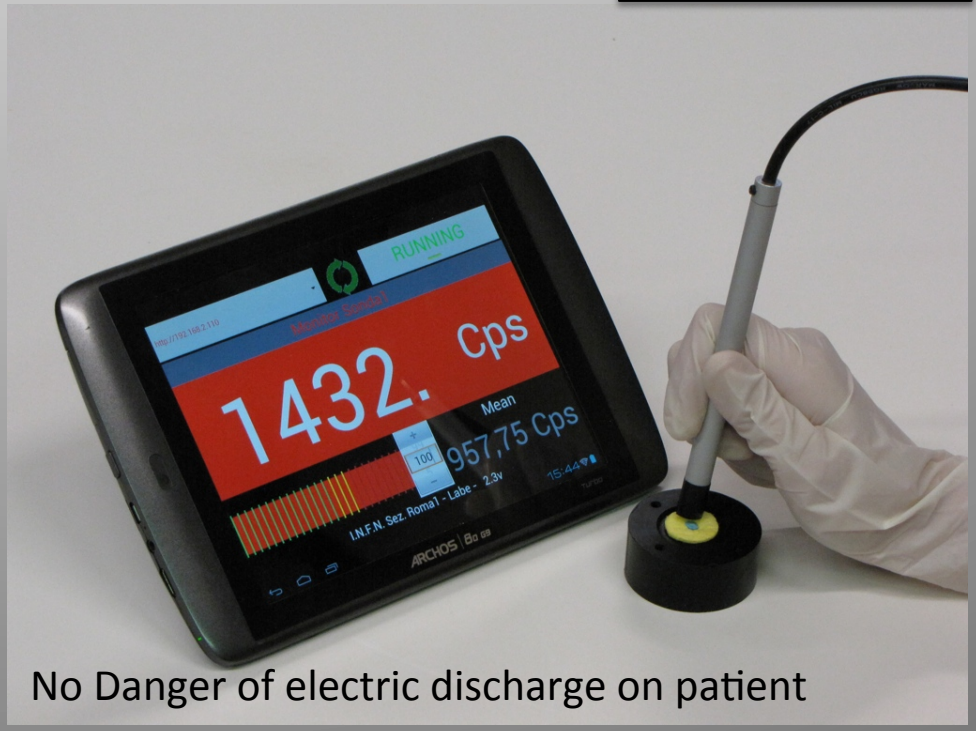
Constraints on medical devices apply

Electronics Read-out

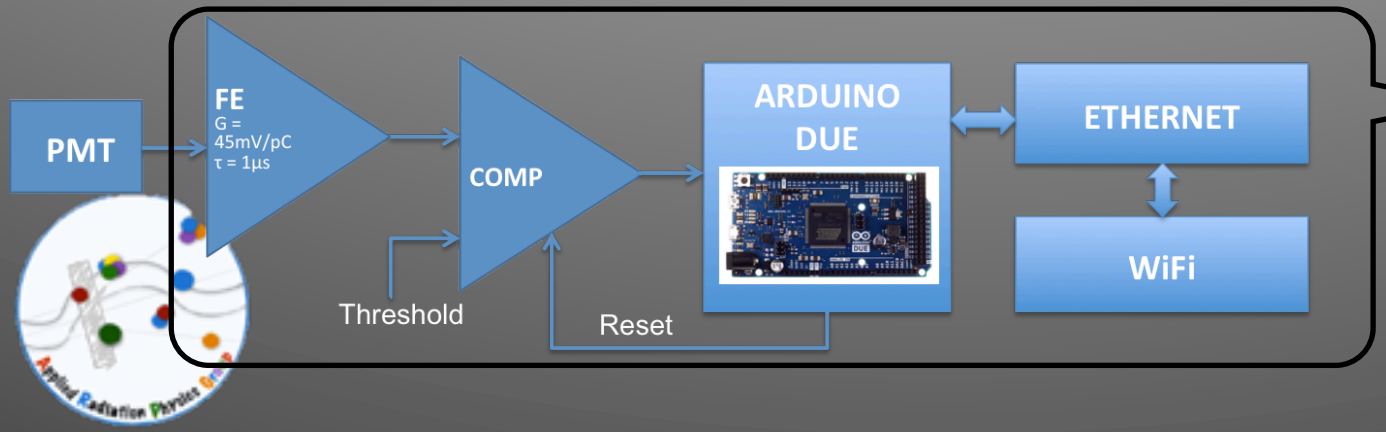
ARDUSiPM
LABE-INFN RM1

Electronics read-out is portable and customized to match the surgeon needs

- acoustic and visual alarm;
- wireless data transfer;
- no connection with electrical line (bacteries)
- user interface available both for PC or tablet.



No Danger of electric discharge on patient



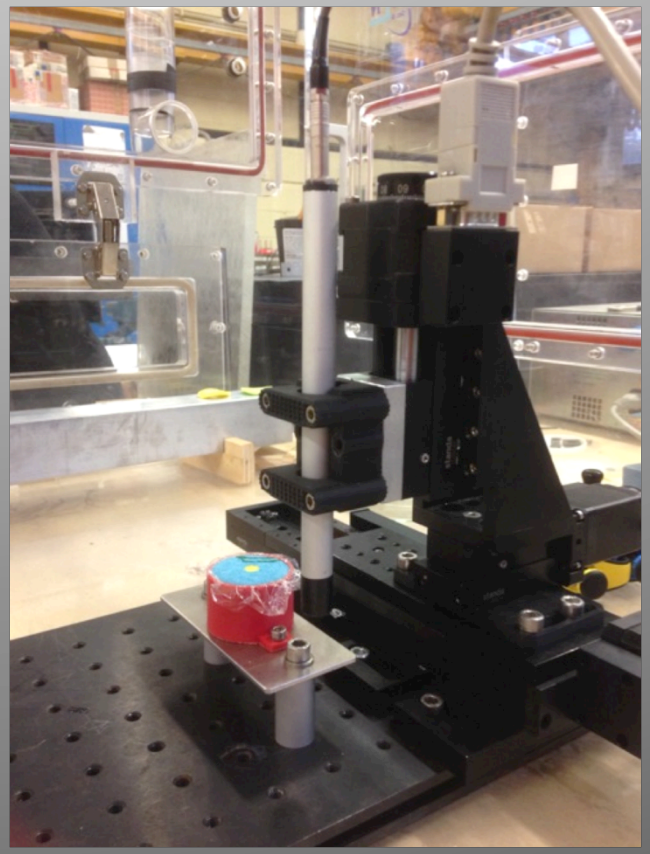
RESEARCH PATH

E. Solfaroli Camillocci et al, *J. Phys.: Conf. Ser.* **620** 012009(2015)

Probe Prototypes

Lab tests (phantom factory)

- Measure spatial sensitivity
- Gamma rejection
- Estimate performances on phantoms
- Estimate dose on surgeon



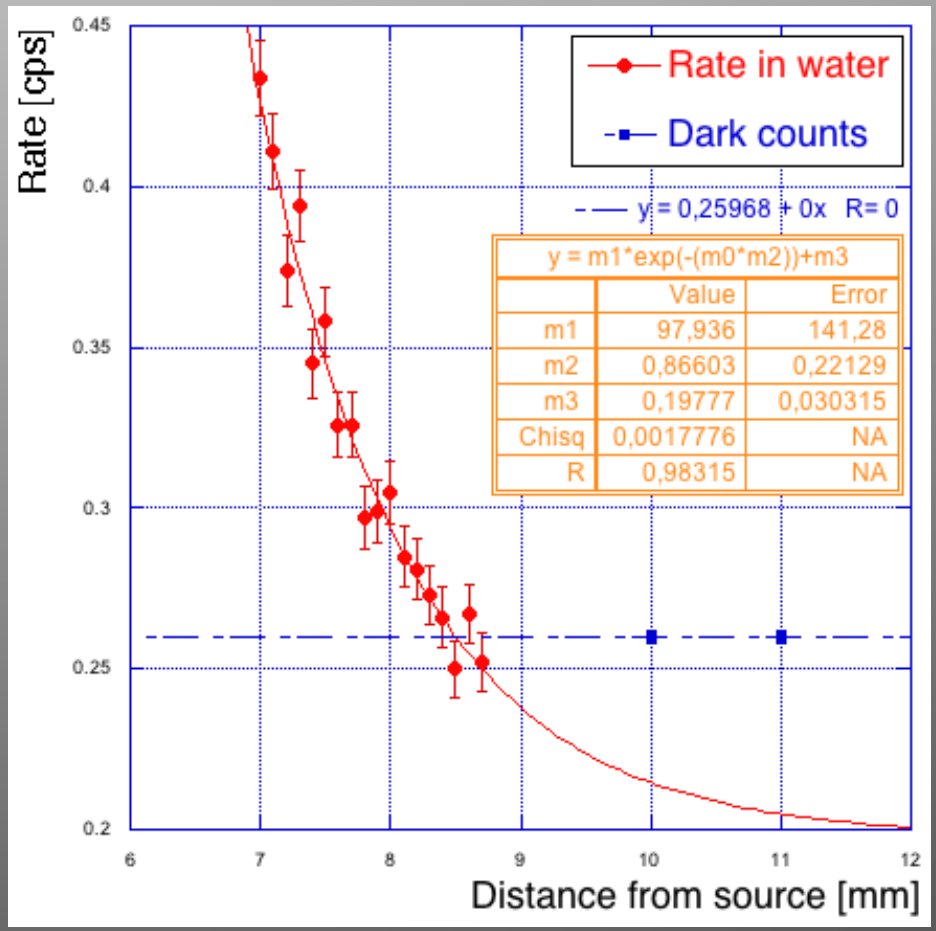
Estimated dose on surgeon administering 3MBq/kg:
1μSv/hr on surgeon's hands
0.13 μSv/hr on medical personnel

23

Sensitivity to Electrons

- Detection efficiency on ^{90}Sr point source
  - Rate $3.8 \cdot 10^5$ cps/MBq.
  - ε_β=40%
- Scan in water
  - E_β>500keV.
  - Detection efficiency ε_β>80% in the β^- ^{90}Y energy range.

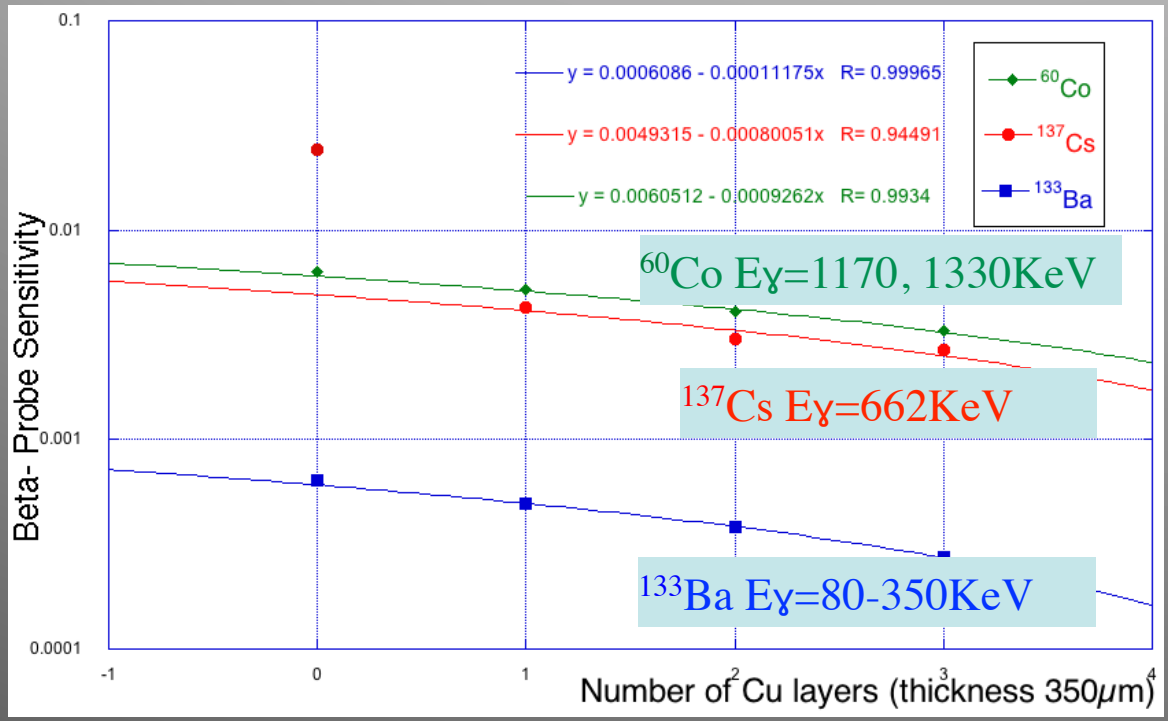
Scan with different thicknesses of water



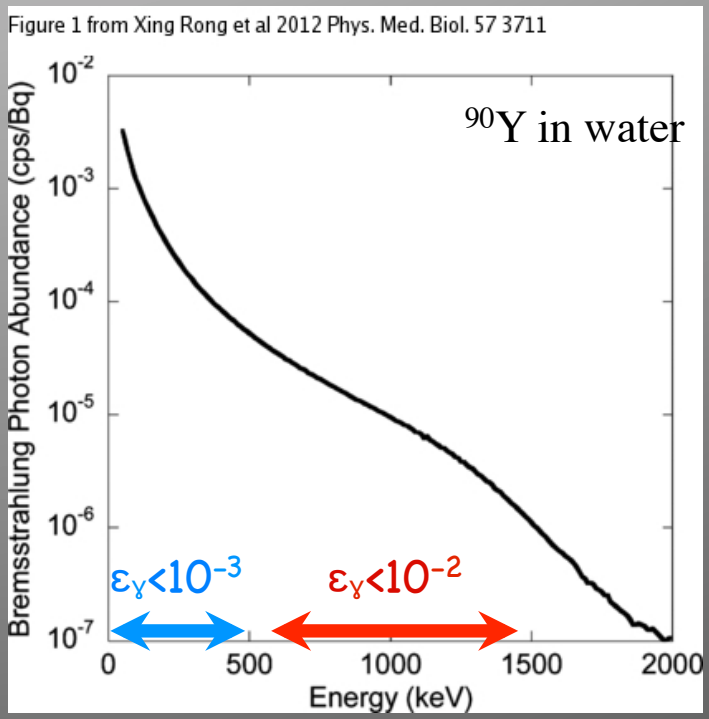
Background Rejection

Background is mainly due to photons coming from Bremsstrahlung.

Sensitivity to photons



Bremsstrahlung E_γ spectrum



Almost transparent to Bremsstrahlung photons.

“Ad-hoc” Phantoms

To simulate tumor remnant embedded in healthy tissue.

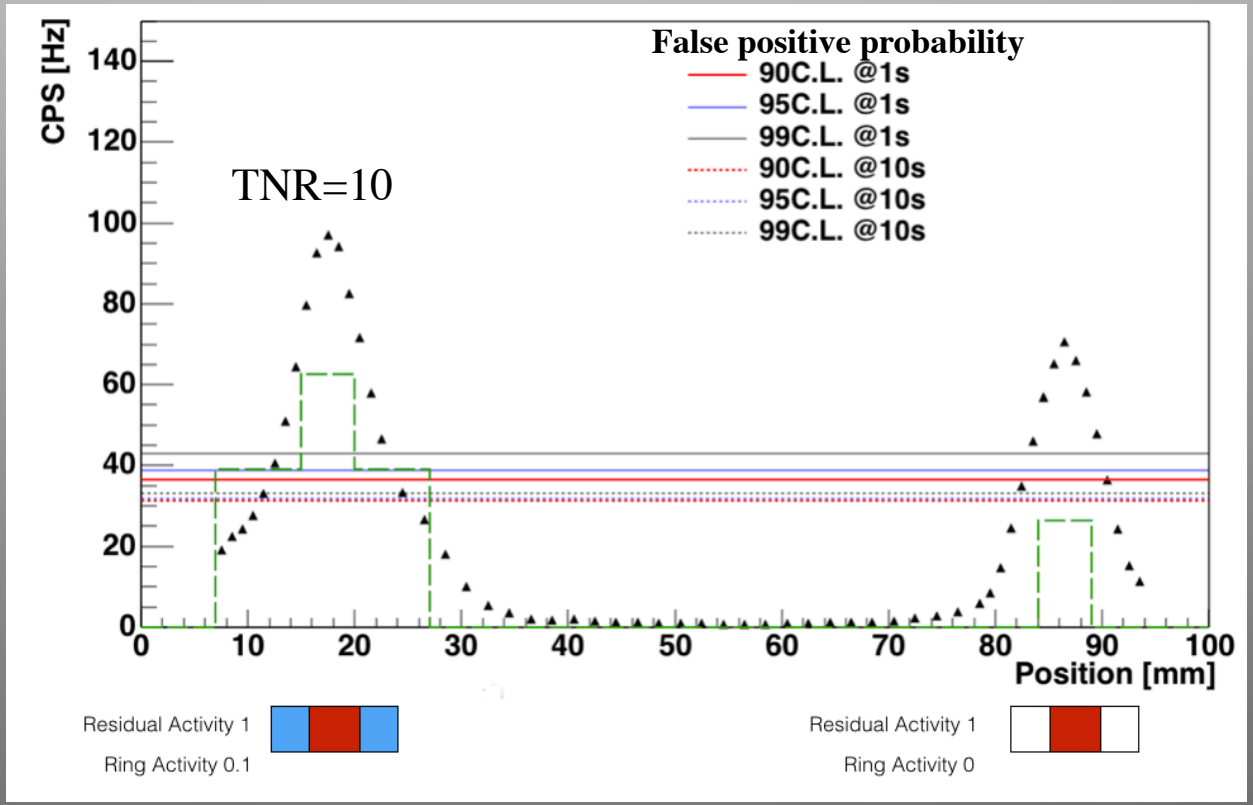
Tumor residual
V=0.05ml

embedded in
tissue with A/10

Motorized scans with S4-Probe

All the possible configurations of tumor residual embedded in healthy tissue.

Active Spot Identification



Human Factor

To include the human factor in the test colleagues were asked to simulate the surgeon:

Phantoms simulating tumor remnants embedded in healthy tissue with different TNRs

All “surgeons” required at least 4-5 seconds per position to take a decision.

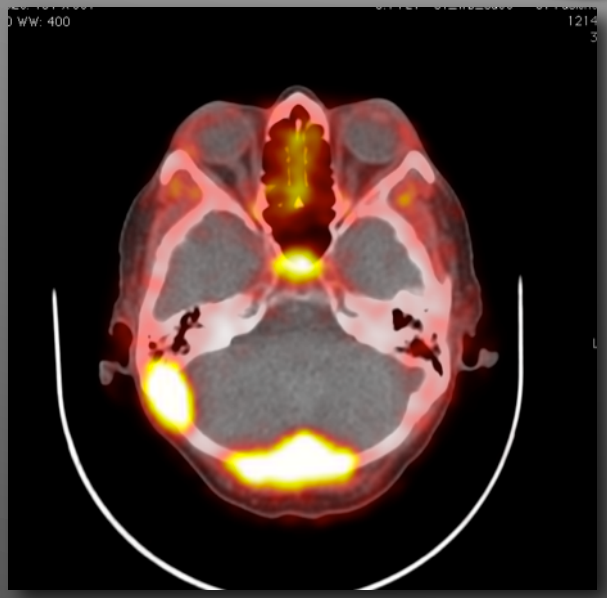
RESEARCH PATH

Probe Prototypes

Lab tests (phantoms)

Identification of proof of principle

Start with existing radiotracers: Somatostatine analogues marked ^{90}Y



Meningioma is avid of ^{90}Y-DOTATOC
➔ Able to detect 0.1 ml residuals administering only 1MBq/kg

RESEARCH PATH

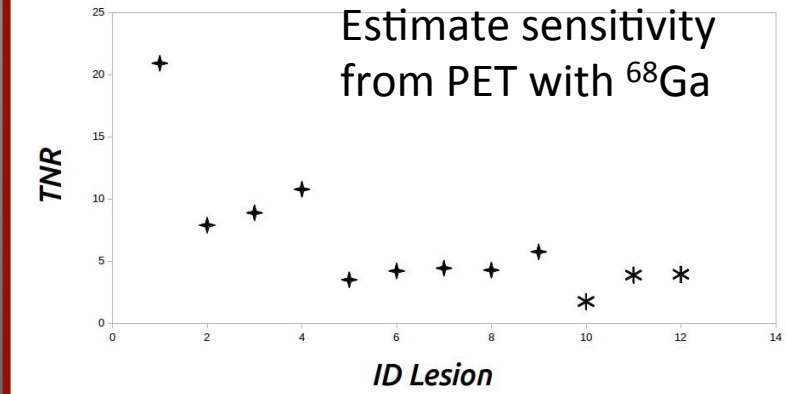
Probe Prototypes

Lab tests (phantoms)

Start with existing radiotracers: Somatostatine analogues marked ^{90}Y

Identification of proof of principle

Identification of first clinical cases



First clinical cases:

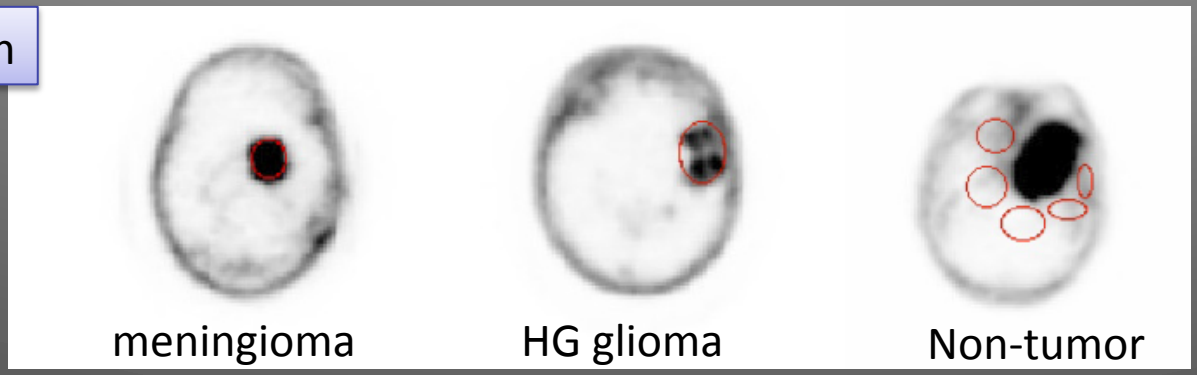
- Glioma (low and high grade)
- GEP-NET (start from small bowel)

F. Collamati et al,. J Nucl Med 56 (2015) 3-8

DOTATOC uptake in glioma

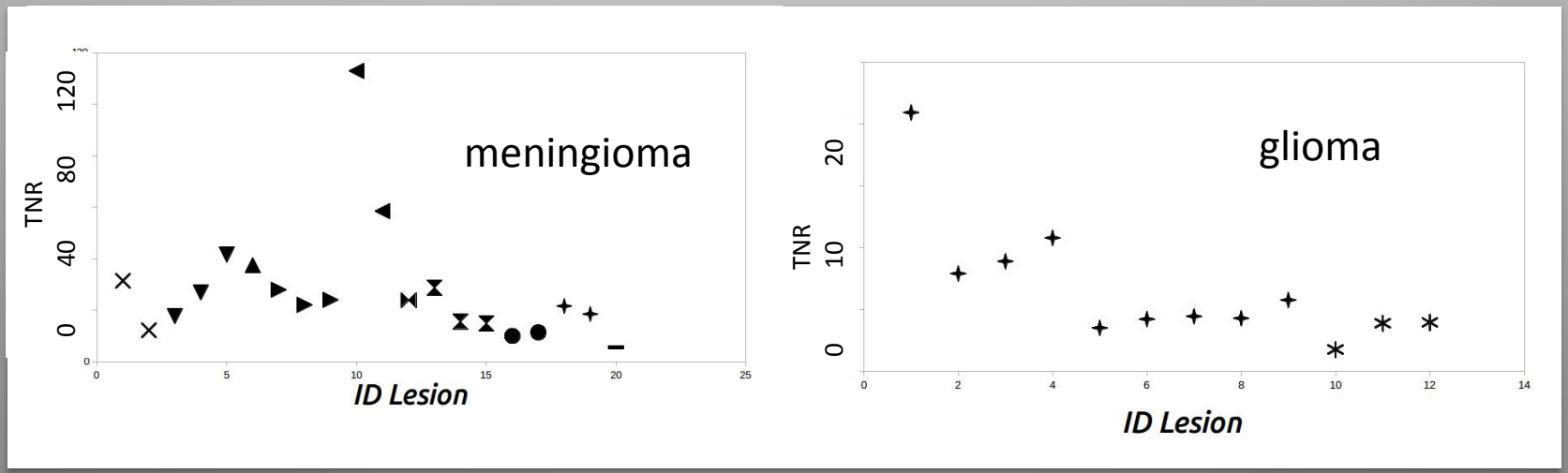
- DOTATOC is a somatostatin analog → known receptivity from NET .. but glioma?
- Even if TNR too low for therapy, can it be used for RGS?
- Use 68Ga-DOTATOC PET scans to estimate signal and background

ROI definition



F. Collamati et al,. J Nucl Med 56 (2015) 3-8

Glioma vs Meningioma



Meningioma has a definitely larger uptake, but is the glioma one acceptable?

Use FLUKA simulation to translate from activities to false positive (FP) and false negative (FN) rates

Consider a residual identified if FP<1% and FN<5%

TNR of glioma is acceptable if probe can take >~6s to give answer

RGS for meningioma

Patient ID	$N_{les.}$	W (kg)	A_{adm} (MBq)	ν (Hz)	ν_{NT} (Hz)	t^{min}_{probe}* (s)	A^{min}_{1s} ** (MBq/kg)	Diagnosis	Previous Treatment
M01	1	63	220	32.2	1.9	0.2	0.7	atypical	S
M02	1	80	160	17.6	2.6	0.6	1.9	atypical	S/RT/PRRT
M03	3	95	305	33.7	3.5	0.3	0.9	likely atypical	S/RT
				50.3	3.5	0.3	0.5		
				76.8	3.5	0.1	0.3		
M04	1	48	200	89.4	4.5	0.1	0.2	atypical	S/RT/CT
M05	3	57	130	66.7	4.4	0.2	0.3	relapse	S/RT/CT/PRRT
				53.2	4.4	0.2	0.5		
				57.6	4.4	0.2	0.4		
M06	2	90	145	107.6	1.8	0.1	0.1	unknown	PRRT
				56.1	1.8	0.2	0.4		
M07	1	74	237	50.2	3.9	0.2	0.5	anaplastic	S/RT
M08	3	105	223	55.7	3.6	0.2	0.5	atypical	S/RT
				31.2	3.6	0.2	0.9		
				29.6	3.6	0.4	0.9		
M09	2	48	145	13.4	2.4	0.9	2.7	atypical	S/RT
				15.1	2.4	0.7	2.5		
M10	1	70	240	14.6	1.2	0.6	1.8	atypical	S/RT
				12.6	1.2	0.8	1.9		
M11	1	75	220	12.7	3.8	1.6	5.0	atypical	unknown

- Very large uptake
- Can inject as low as 0.5 MBq/kg

* Time needed to detect 0.1 ml residual if 3MBq/kg are administered

** Activity that needs to be administered to achieve 1s response time

RGS for glioma

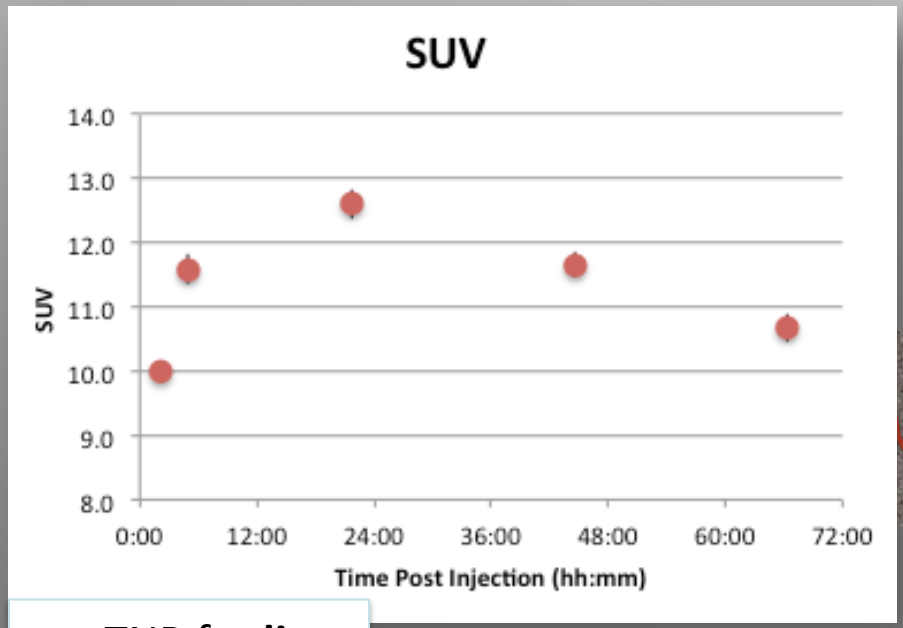
Patient ID	W (kg)	A_{adm} (MBq)	ν (Hz)	ν_{NT} (Hz)	t^{min}_{probe} * (s)	A^{min}_{1s} ** (MBq/kg)	Diagnosis	Previous Treatment
G01	97	246	16.5	1.4	0.5	1.5	HGG	S/RT/CT/PRRT
G02	68	223	5.2	1.1	2.6	8.5	HGG	RT/CT/B
G03	80	152	9.6	1.9	1.4	4.3	HGG	S/RT/CT
G04	93	198	22.4	3.7	0.6	1.8	HGG	S/RT/CT/PRRT
G05	90	192	4.6	2.0	7.4	23.6	HGG	S/RT/CT/PRRT
G06	60	185	4.4	1.6	5.8	20.0	HGG	S/RT/CT
G07	63	194	4.8	1.7	5.1	17.6	HGG	S/RT/CT
G08	70	266	2.1	0.8	-	40.0	HGG	RT/CT
G09	85	255	3.7	1.1	5.3	17.6	HGG	S/RT/CT
G10	80	224	2.2	1.6	-	-	oligodendroglioma	S/RT/CT/I
G11	70	234	5.1	2.0	5.5	18.8	HGG	RT/CT
G12	15	38	5.0	2.0	5.9	18.8	pontine glioma	RT/CT/PRRT

- Needs to wait for ~6s, but it works
- Margins to improve probe

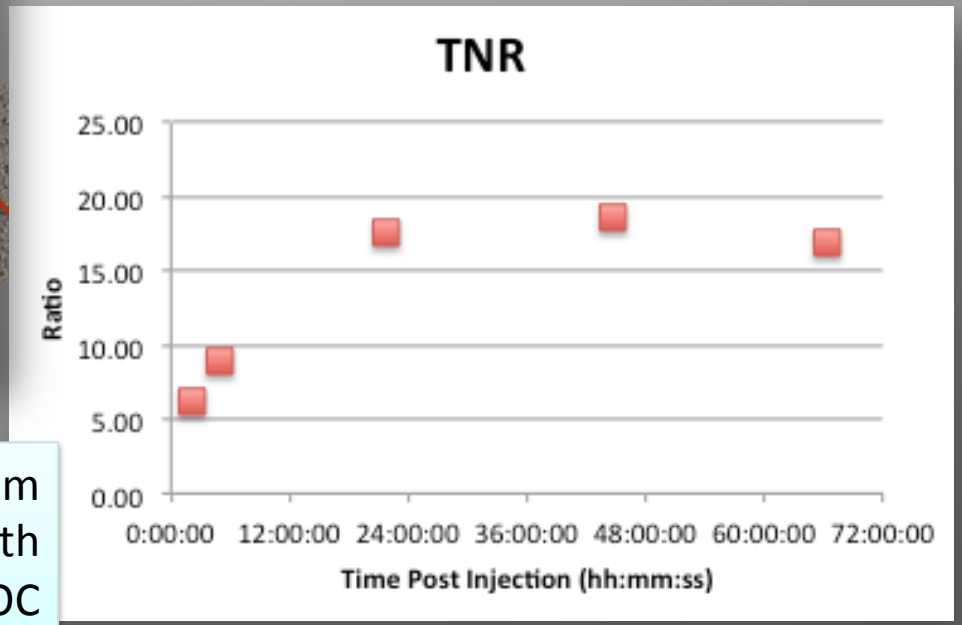
* Time needed to detect 0.1 ml residual if 3MBq/kg are administered
** Activity that needs to be administered to achieve 1s response time

F. Collamati et al,. J Nucl Med 56 (2015) 1501-6

Time Evolution of uptake



TNR for **liver NET** vs time

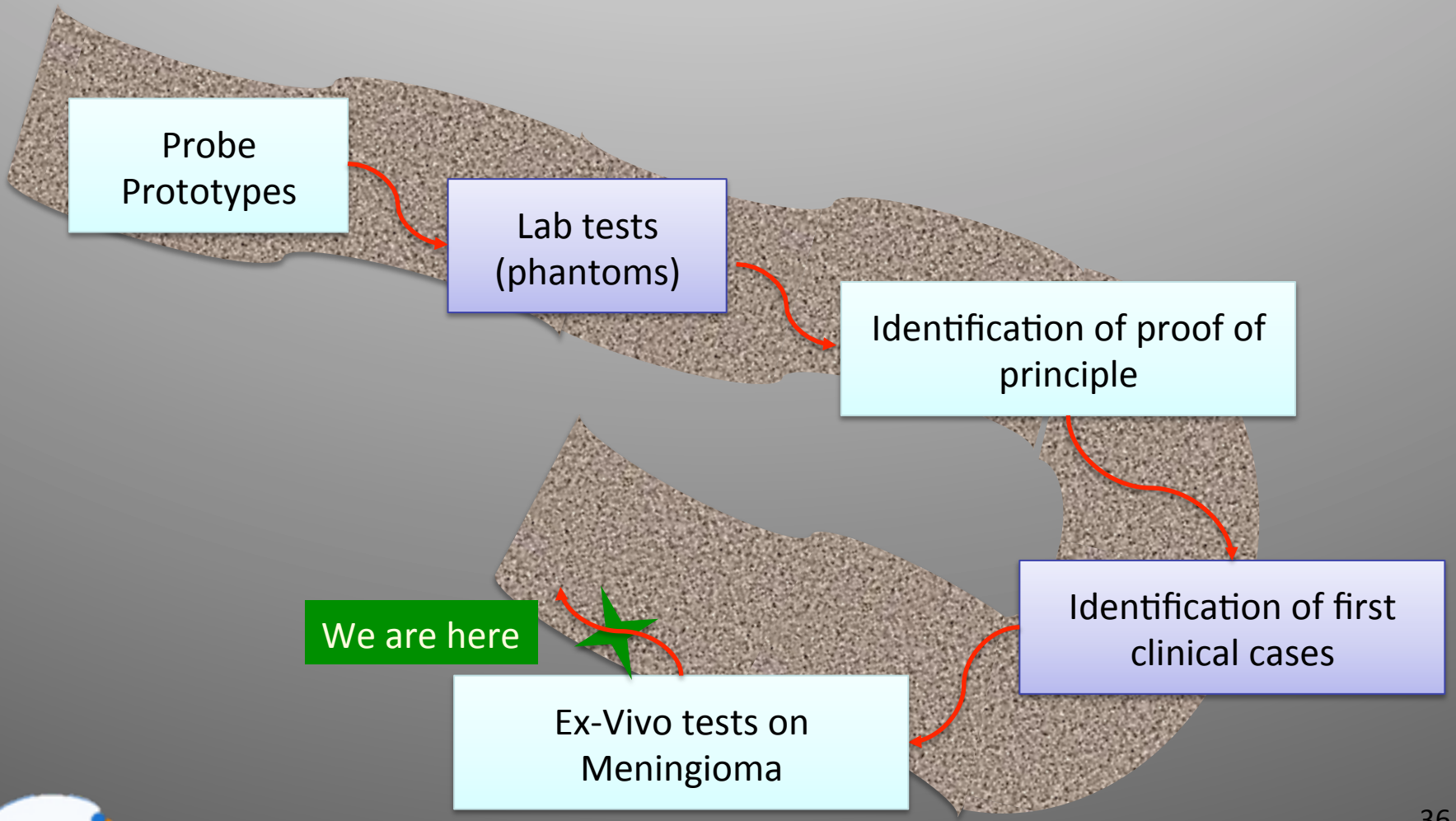


Values estimated from dosimetric SPECTs with ^{177}Lu-DOTATOC

CONCLUSIONS:

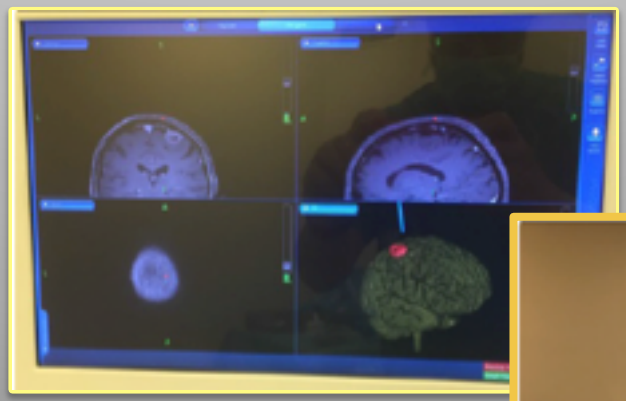
- GEP-NETs (small bowel, insulinoma, …) are a good candidate and similar among each-other
- the best SUV and TNR are achieved if surgery is 24hrs after injection

RESEARCH PATH



E. Solfaroli et al., submitted to JNM

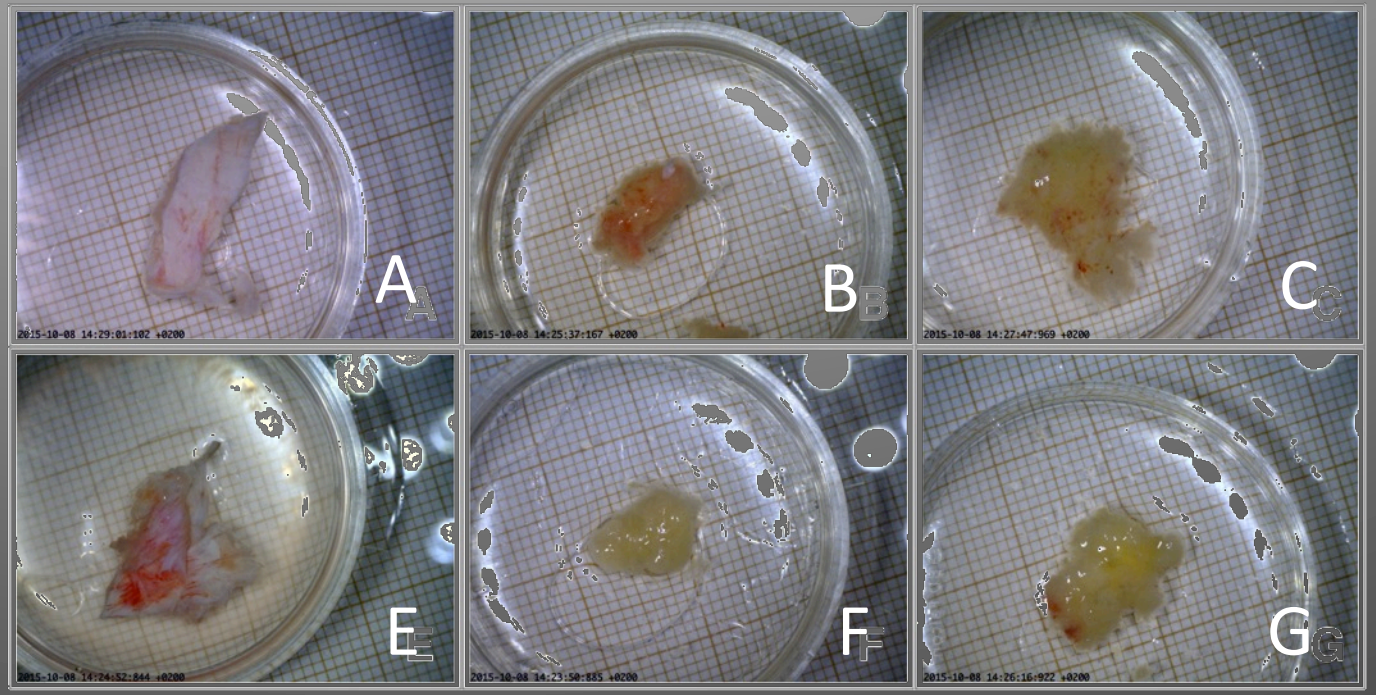
Ex-vivo test on meningioma



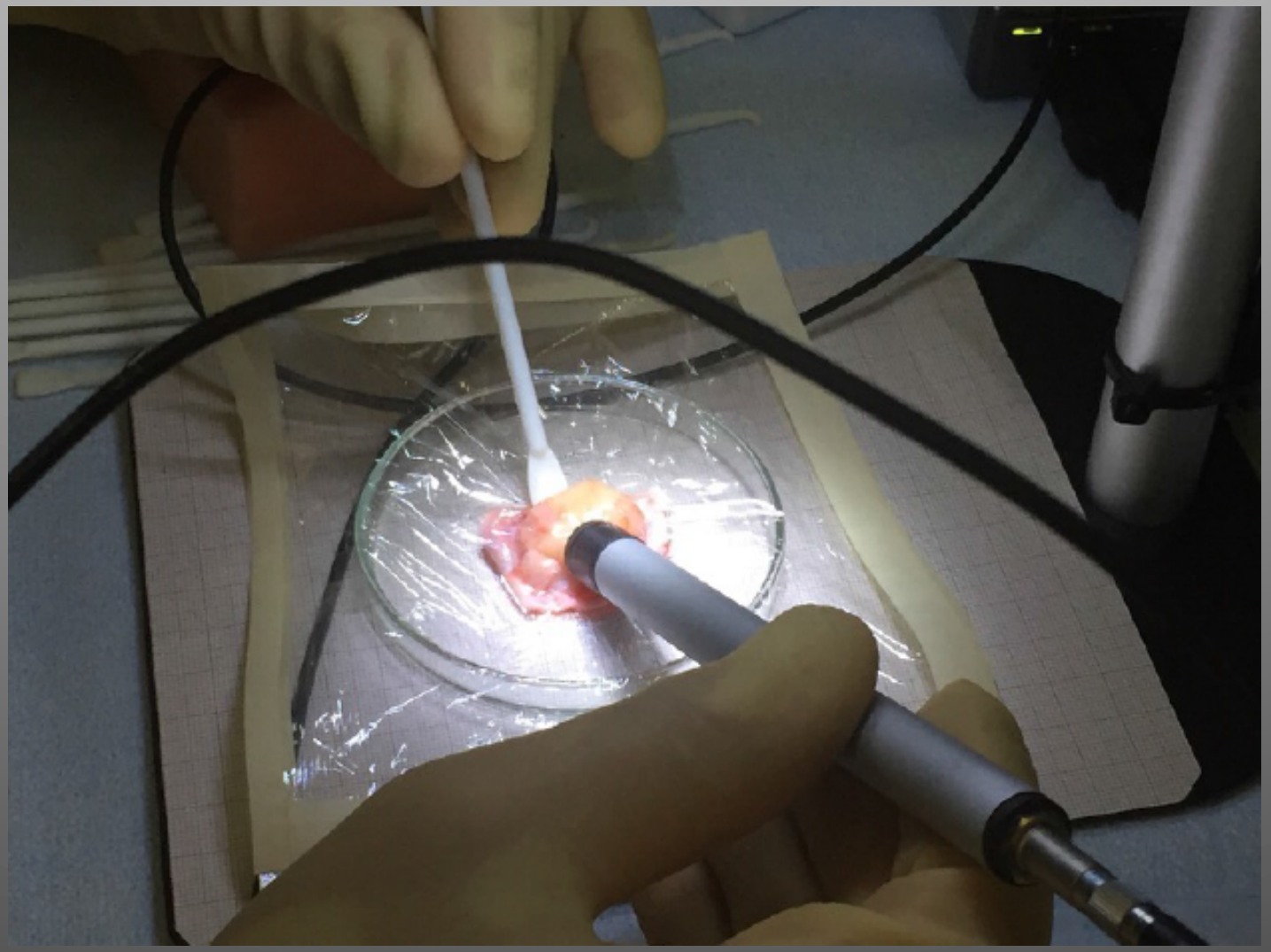
- PET with Ga68 on Sep 14th
  - Tumor SUV ~2g/ml (relatively low, but enough)
  - TNR ~ 14 (good)
- 8mCi Y90—DOTATOC on Oct 9th
- Surgery on Oct 10th

Sample	"Diagnosis"
A	non-infiletered dura
B	Tumor upper margin
C	Tumor lower margin
D	Tumor Bulk
E	Medial dural border
F	Tumor center
G	Tumor center

The Samples



Evaluating the samples rate



E. Solfaroli et al, Physica Medica 32 (2016), pp. 1139-1144

Results

- Residuals as small as 0.2ml are visible
- Predictions with simulation are reliable (115 cps predicted, 105 observed)
- Healthy brain ~1cps (simulation) infiltrated dure can be identified

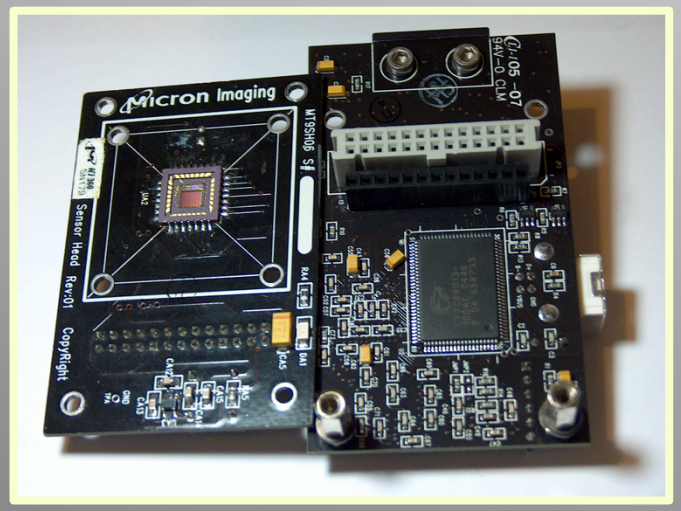
+ Confirmed very low exposure of medical personnell

Sample	V(ml)	R(cps)	histology
A	0.38	5.0	Dural tissue infiltered by meningioma
B	0.23	51.5	Transitional meningioma
C	0.72	45.0	Transitional meningioma
D	4.84	105.0	Transitional meningioma
E	0.88	3.5	Dural tissue infiltered by meningioma
F	0.21	27.7	Transitional meningioma
G	0.39	39.3	Transitional meningioma with micronecrosis and occasional mitosis

IRRADIATION MEASUREMENTS

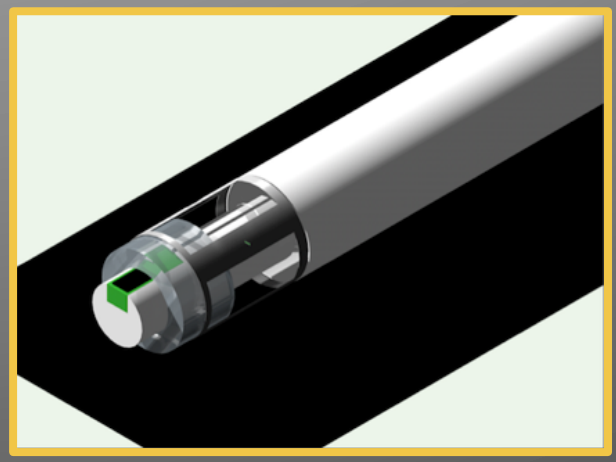
Probe developments

CHIR2



- Use CMOS technology to lower energy threshold (with INFN& Uni PG) → allow use of other isotopes
  - Matrix design for basic “imaging”

- Develop prototype for endoscopic (laparoscopy/Da Vinci …) use
  - Multichannel design with p-terphenil



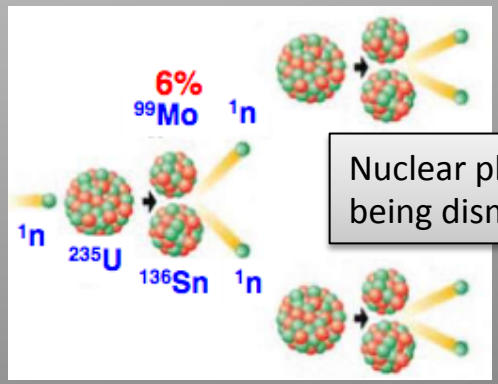
Radiotracers for Radioguided surgery

γ-RGS: the Tc crysis

- ^{99m}Tc is produced from ^{99}Mo decays
- Current production method
  - Canada 50%, Netherland 40%

    + …
- Need alternative methods
  - ^{100}Mo(p,2n)^{99m}Tc [direct ^{99m}Tc production] → Canada
  - ^{100}Mo(γ,n)^{99}Mo, ^{238}U(γ,f)^{99}Mo →USA, Canada
  - ^{98}Mo(n,γ)^{99}Mo → testing
  - ^{100}Mo(n,2n)^{99}Mo → testing

  } parent ^{99}Mo production (easier to implement)



Developments in accelerator physics required

β^+ RGS: different isotopes

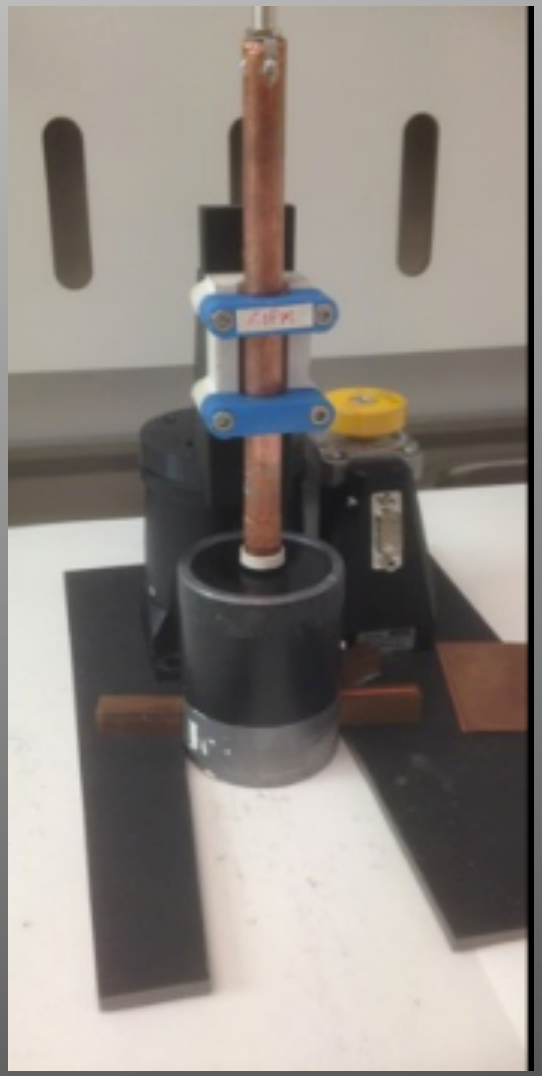
- ^{18}F not the only tracer
- Mean β^+ energy critical parameter
- Each tracer has different clinical applications

Isotope	*Half-life*	β^+ *Energy (MeV)*
C-11	20.4 m	0.385 (99.8%)
N-13	9.97 m	0.492 (99.8%)
O-15	122 s	0.735 (99.9%)
F-18	110 m	0.250 (100%)
K-38	7.64 m	1.216 (99.3%)
Cu-62	9.74 m	1.315 (97.6%)
Cu-64	12.7 h	0.278 (17.9%)
Ga-68	68.1 h	0.836 (87.9%) 0.352 (1.12%)
Rb-82	75 s	1.523 (83.3%), 1.157 (10.2%)
I-124	4.18 d	0.686 (11.3%), 0.974 (11.3%)

β^- probe on β^+ isotopes

- Positron/γ separation with copper layers
- Results scaled to 10kBq/ml

10 kBq/ml	^{18}F	^{68}Ga
Counts no shield (e+γ)	11.9±0.3	51.2±0.8
Counts with Cu shield (γ)	3.0±0.1	1.7±0.1
Difference (e)	8.9±0.3	49.5±0.8



β- RGS: Other isotopes (I)

C. Mancini-Terracciano et al., arXiv:1610.09246

- used in Nucl. Med.
- Isotopes of those used in Nucl. Med.
- Same chem family of those used in Nucl. Med.

Isotope	$T_{1/2}$(h)	E_g(keV)	I_g(%)	EP_b(keV)	I_b(%)	Use
^{18}F	1.8	511	200	633.5	97	FDG, most tumors
^{21}Si	2.6			1491	100	Same family as C (used in PET)
^{32}P	343			1710	100	Brain tumors [1]
^{67}Cu	62	93/184	16/48	377/468/561	22/20/99	Cu-64 in immuno-PET[3]
^{83}Br	2.4			935	99	Same family as F
^{90}Y	64			2280	100	NET & Brain tumors[1]
^{97}Zr	17	743	93	759	88	^{89}Zr used in immuno-PET [2]
^{131}I	192	365/637	82/7	334/696	7/90	Thyroid[1]
^{133}I	20.8	530	87	1227	83.4	Thyroid
^{153}Sm	46	103	29	635/704/808	31/49/18	Bone Cancer[1]
^{177}Lu	160	112/208	6/10	500	79	NET & Brain tumors[1]
^{188}Re	17	155	15	1962/ 2118	25/72	Bone & Liver [2] Cancer

[1] Review in Yeaong C.H. et al. J. Zhejiang Univ. SCIENCE B Vol.15 No.10 P.845-863 (2014)
[2] van de Watering F.C. et al. Biomed Res Int. 2014;2014:203601.
[3] Asabella A.N. et al. BioMed Res. Intl. 786463 (2014)

β- RGS: Other isotopes (I)

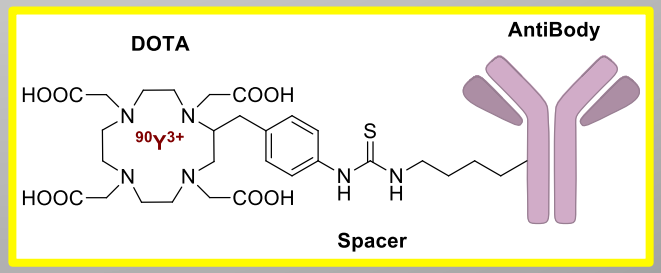
* Time needed to detect a 0.1 ml residual with FN<5% FP<1% if 3MBq/kg are administered and SUV=4, TNR=8

Isotope	E_g(keV)	I_g(%)	EP_b(keV)	I_b(%)	T^*_{min} (s)
^{18}F	511	200	633.5	97	>25
^{21}Si			1491	100	0.4
^{32}P			1710	100	0.3
^{67}Cu	93/184	16/48	377/468/561	22/20/99	>25
^{83}Br			935	99	0.9
^{90}Y			2280	100	0.5
^{97}Zr	743	93	759	88	0.8
^{131}I	365/637	82/7	334/696	7/90	>25
^{133}I	530	87	1227	83.4	2.8
^{153}Sm	103	29	635/704/808	31/49/18	3.1
^{177}Lu	112/208	6/10	500	79	>25
^{188}Re	155	15	1962/ 2118	25/72	0.4

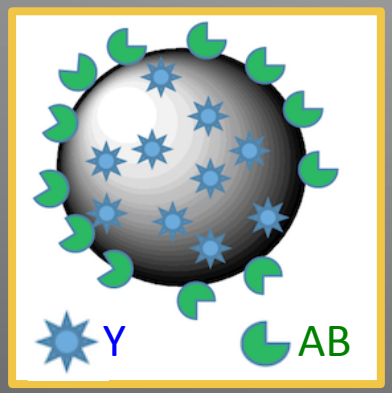
- OK with current probe
- High SUV and TNR required: improvements in γ rejection and energy threhold useful
- Significant improvements in γ rejection and energy threhold required

β- RGS:
alternative tracers with ^{90}Y

Synthesis of new radio-tradiotracers (with ^{90}Y)



- Monoclonal antibodies (NIMOTUZUMAB) for EGFR receptors
- MIBG



Development of nano-scale carriers composed of polymers, antibody and ittrium

Nuclear Physics

Oncology

Radio-Chemistry

Nuclear Medicine

Radio-Guided-Surgery

Radiation detection

Particle accelerators

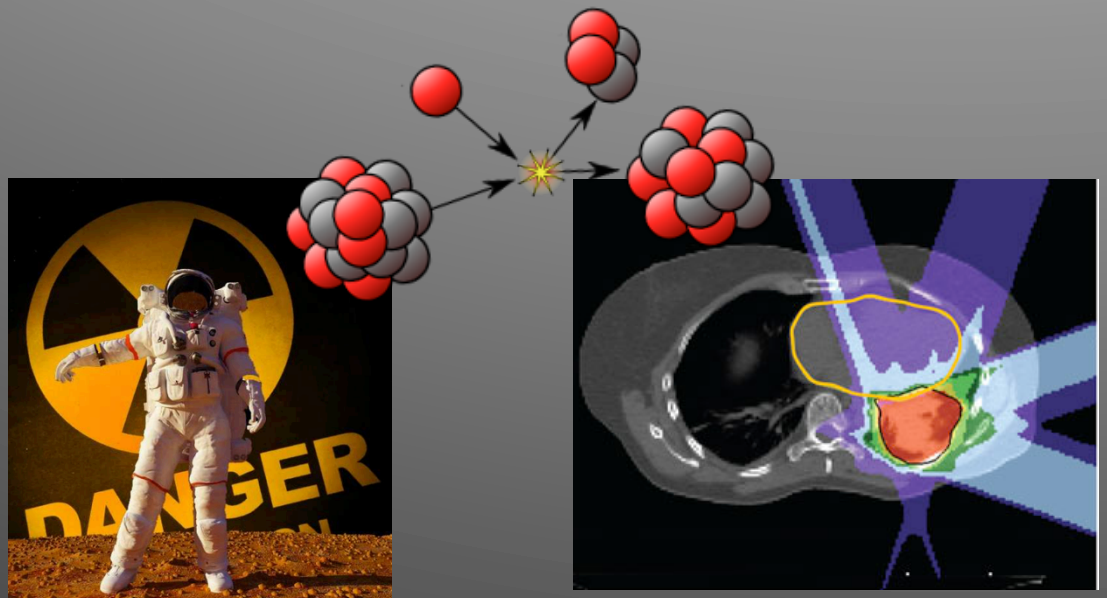
BACKUP

FOOT in pills

Sections/Labs: Bologna, Frascati, Milano, Napoli, Perugia, (Pavia), Pisa, Roma1, Roma2, Torino, Trento

People: ~50 researcher, ~24 FTE

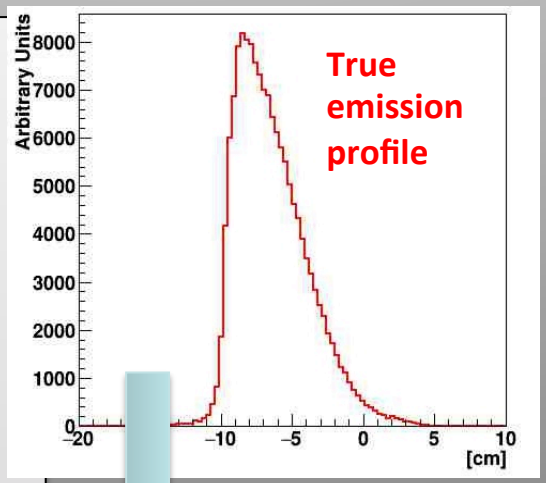
DATA taking foreseen @ CNAO, TIFPA, LNS, BTF

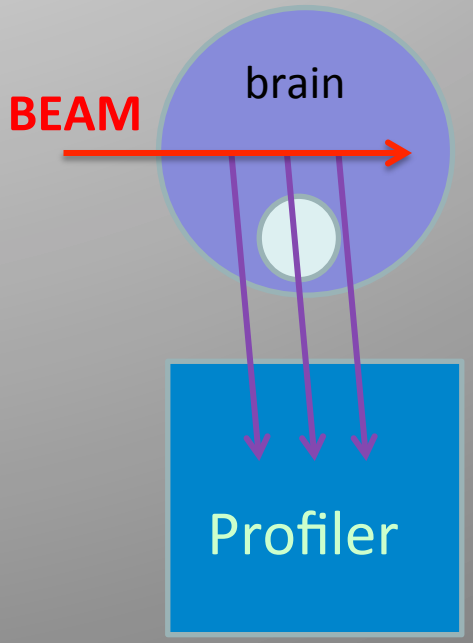


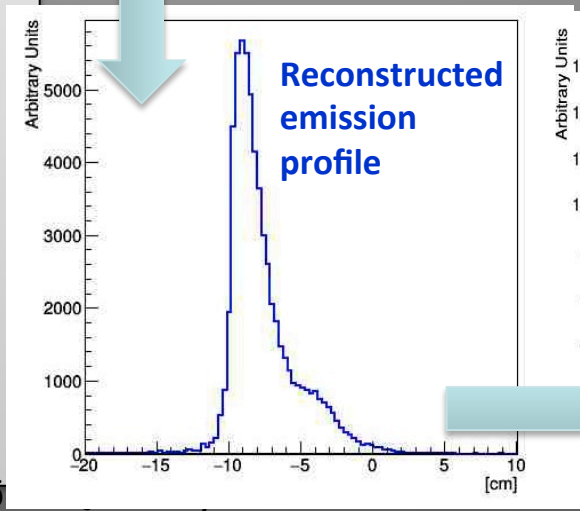
Experiment with translational approach: focus on nuclear physics, physics applied to medicine and radioprotection in space

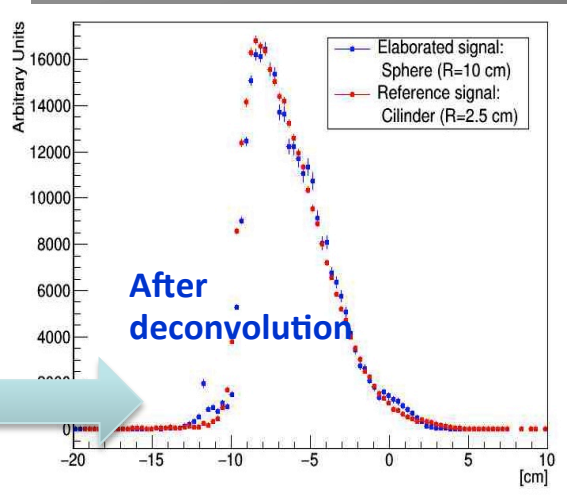
Dosimetric imaging

- Generation of calibration database for deconvolution of material absorption using FLUKA MC trained with experimental data.
- Development of lookup table to connect the emission point distribution of the secondary charged particle with the BP, in different, non homogeneous material



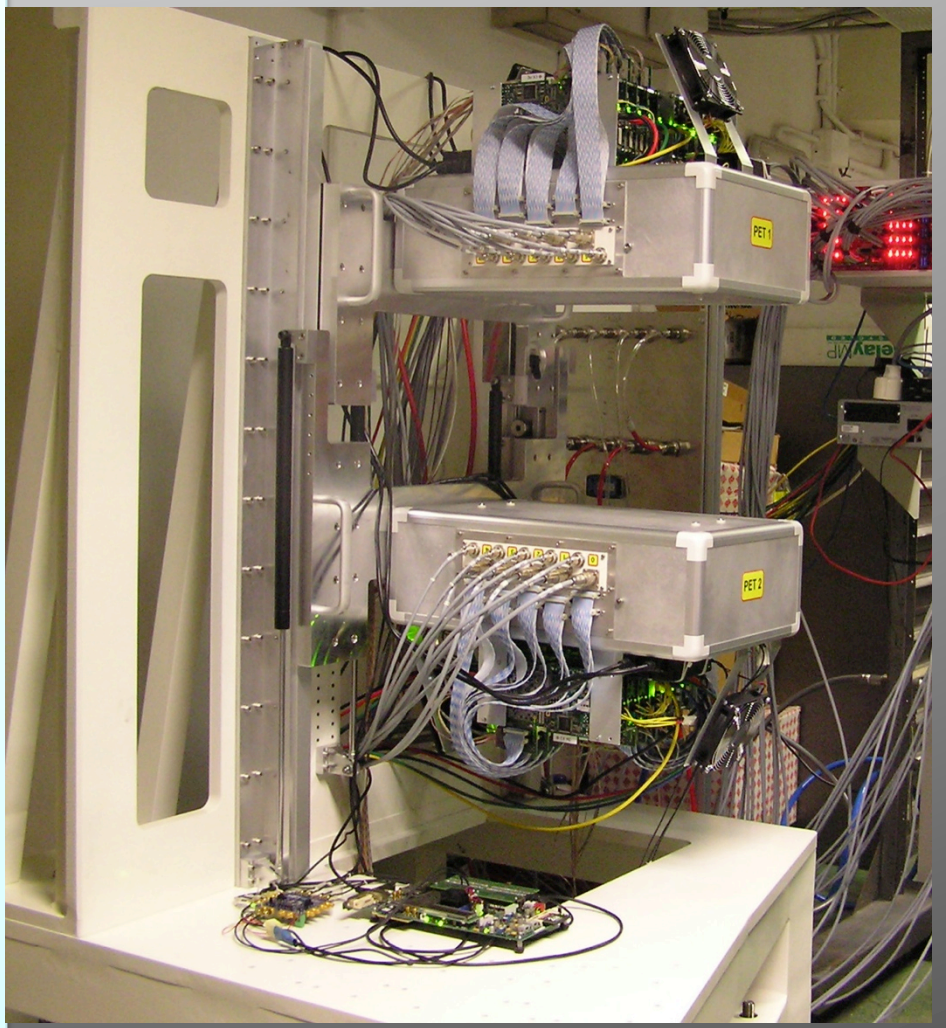






The INSIDE PET system

- DAQ sustains annihilation and prompt photon rates during the beam irradiation
- Two planar panels each 10 cm x 20 cm wide. Each panel will be made by 2 x 4 detection modules
- Each module is composed of a pixelated LYSO scintillator matrix 16 x 16 pixels, 3x3 mm^2 crystals, 3.1 mm pitch, for a total sensitive area of 5x5 cm^2
- One SiPM array (16x16 pixels) is coupled to each LYSO matrix. 200 ps FWHM TOF capability

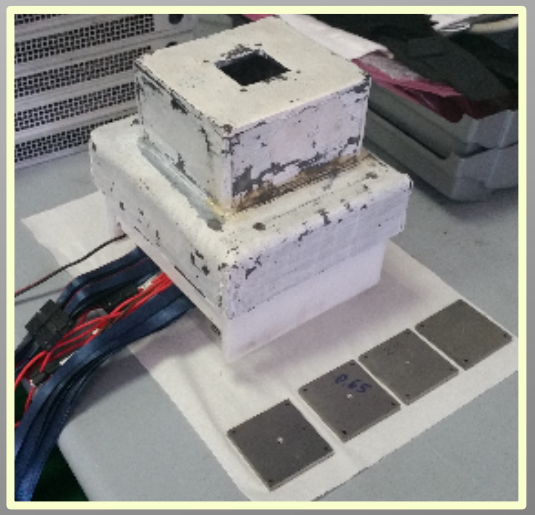


Current Efforts (II)

Setup the **whole chain** for radio-tracer development:

- cold synthesis
- hot synthesis
- in vitro tests
- animal tests

→ equip a facility for animal tests with radioactivity



→ Need imaging capable to measure biodistribution of β-emitting tracers → SPECT with Brehmsstrahlung