A novel radio-guided surgery technique with β- radiation

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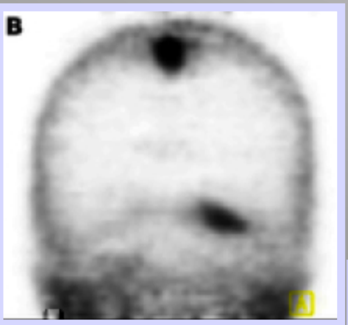
http://arpg-serv.ing2.uniroma1.it/arpg-site/index.php

Radio Guided Surgery



PET/SPECT scan to estimate receptivity and background

Administration of radio-tracer

Each tumor requires its own tracer

During surgery a probe is used to detect residuals/lymphnodes

Probe adjustable to needs

LIMITS OF γ-RGS

140 keV photons

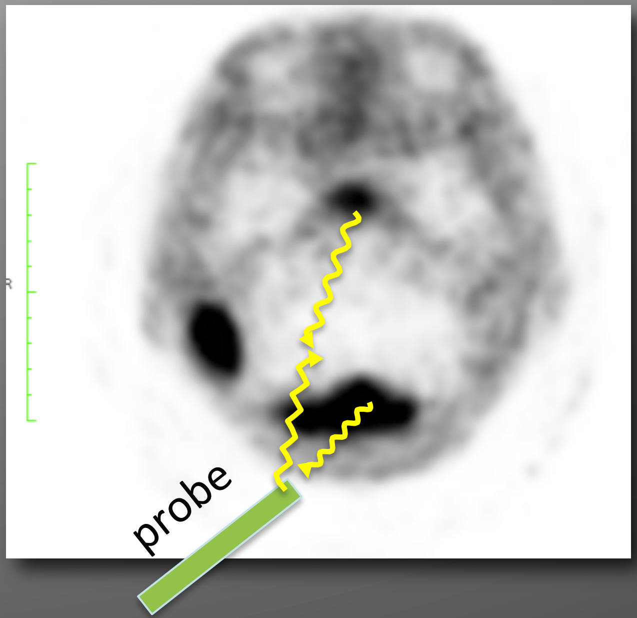
➔ attenuation in body ~8cm

Long range of gamma's involve:

- exposure of medical personnel
- Background from healthy organs

Difficult to apply in:

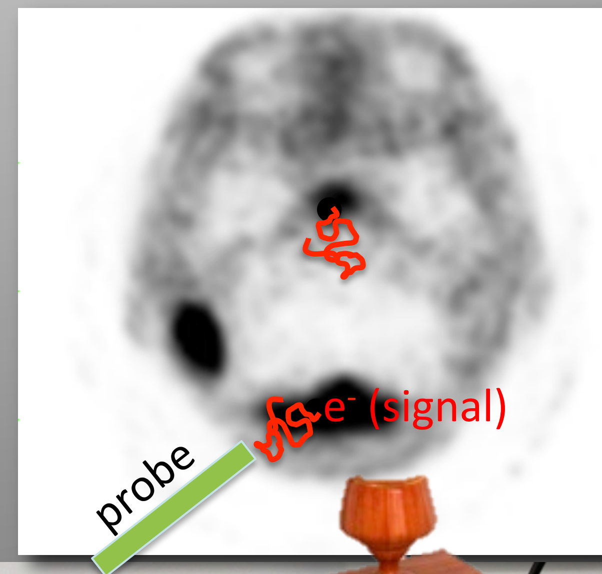
- Brain tumors
- Abdominal tumors
- Pediatric tumors



A CHANGE IN PARADIGM

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

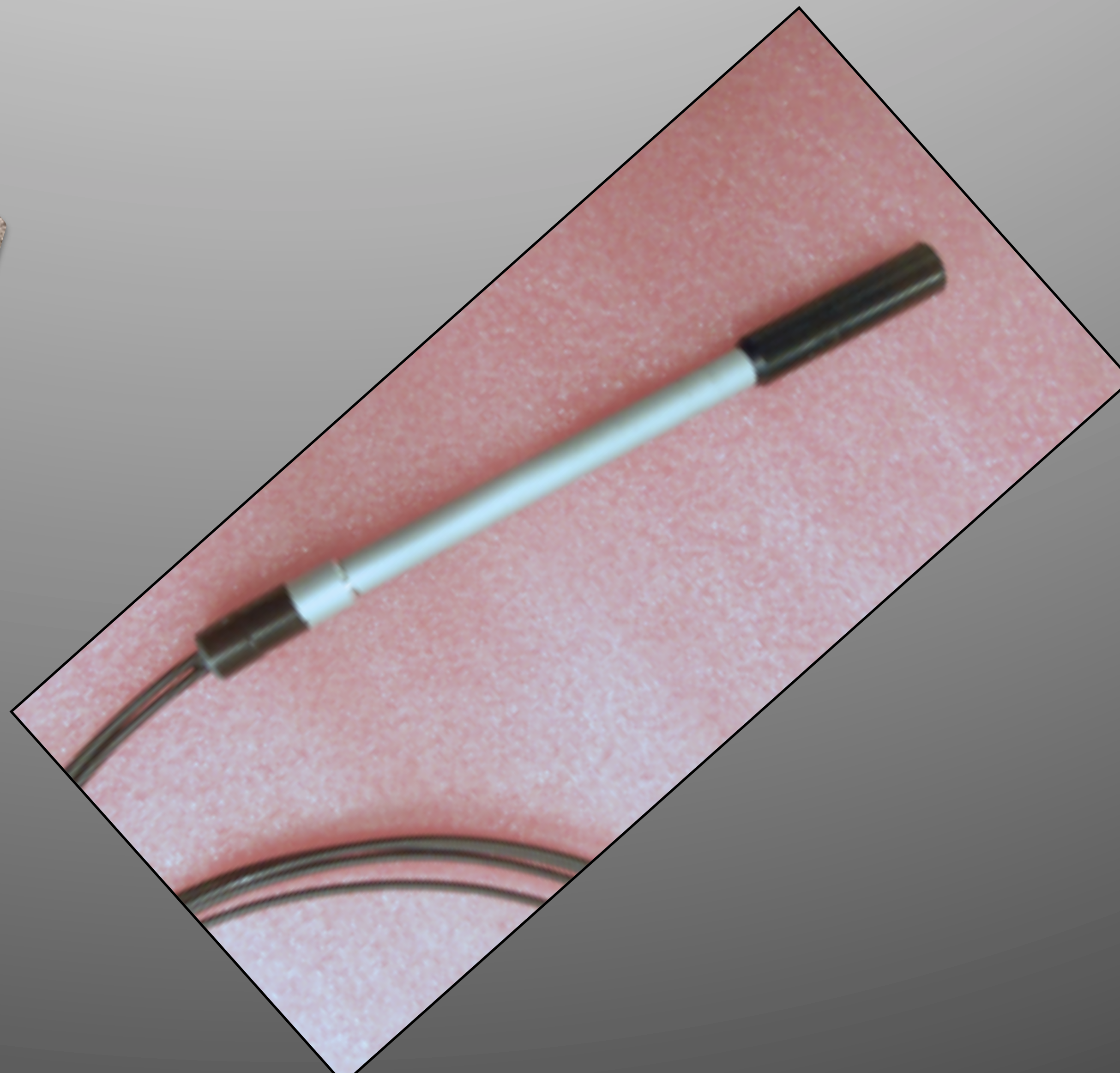
- Use of β^- tracers (electrons): pros
  - Detect electrons that travel ~100 times less than γ
  - Tracers with ^{90}Y can be used (already used for Molecular RT)
  - No background from gamma
    - Shorter time to have a response
      - » Smaller administered activity
    - Smaller and more versatile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



EXTEND RGS TO MORE CLINICAL CASES

RESEARCH PATH

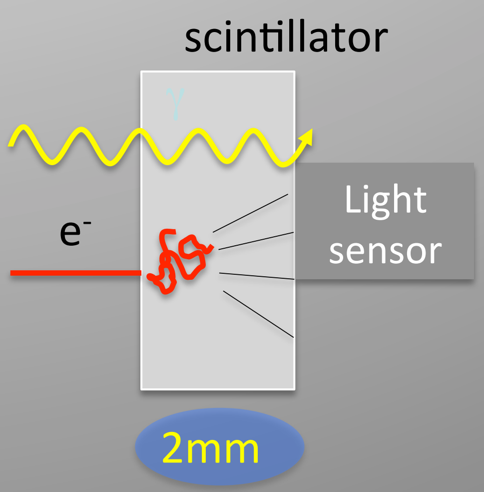
Probe Prototypes



Low energy e- detector

p-terphenyl as scintillator

- High signal:
  - LY(pterf)=3LY(Anthracene)
- Low Z
  - Low sensitivity to photons
- Small attenuation length
  - $\lambda=(4.73 \pm 0.06)$ mm



Usually unused because signal attenuates if detector too thick

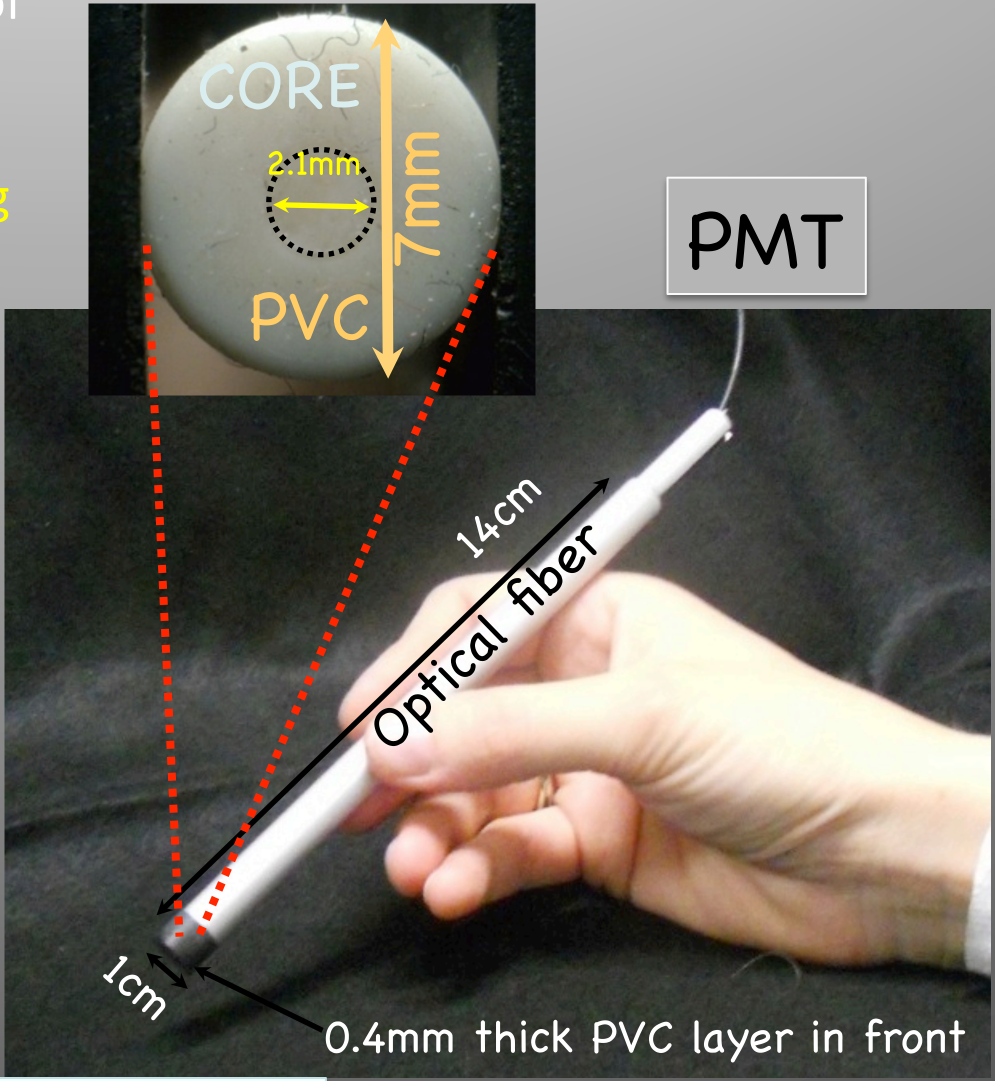
→ **Not for low energy electrons**

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)



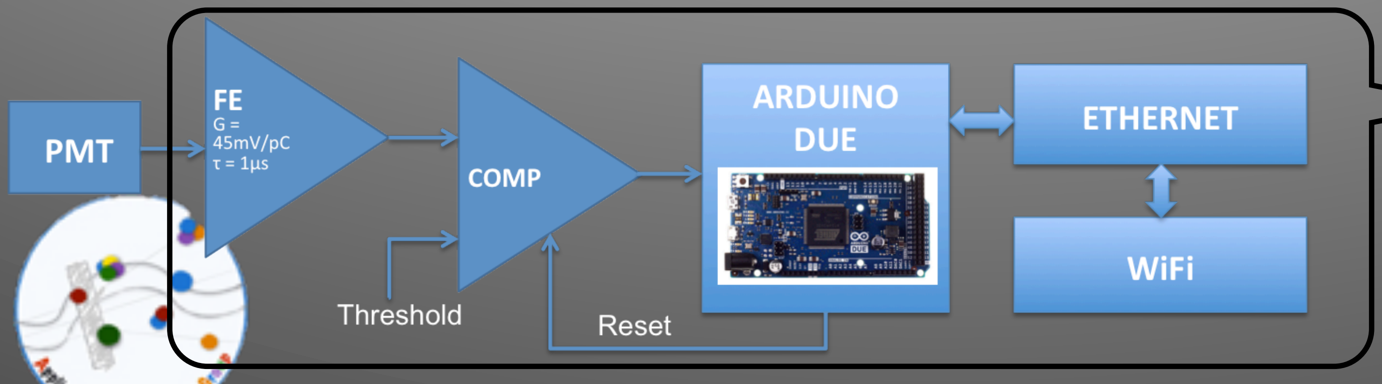
Constraints on medical devices apply

Electronics Read-out

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

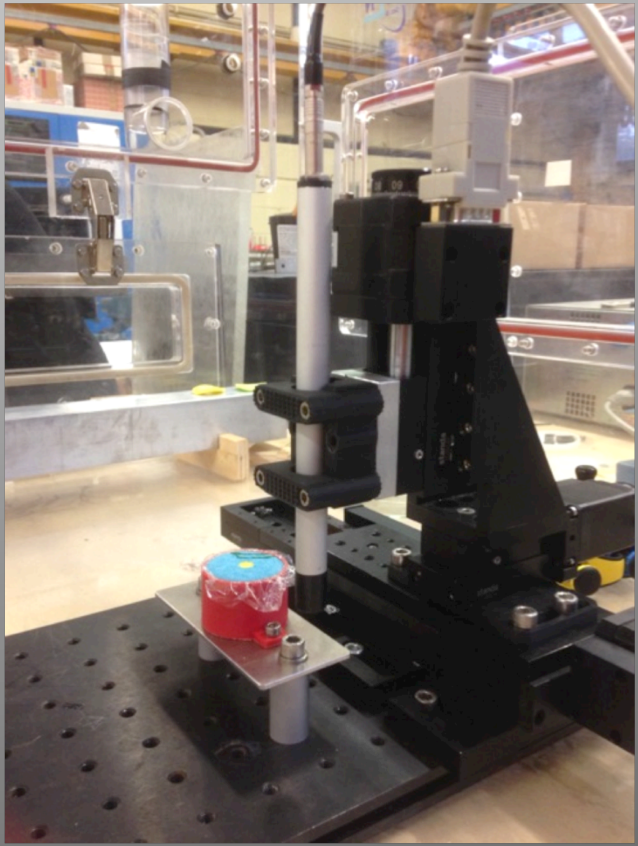


RESEARCH PATH

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



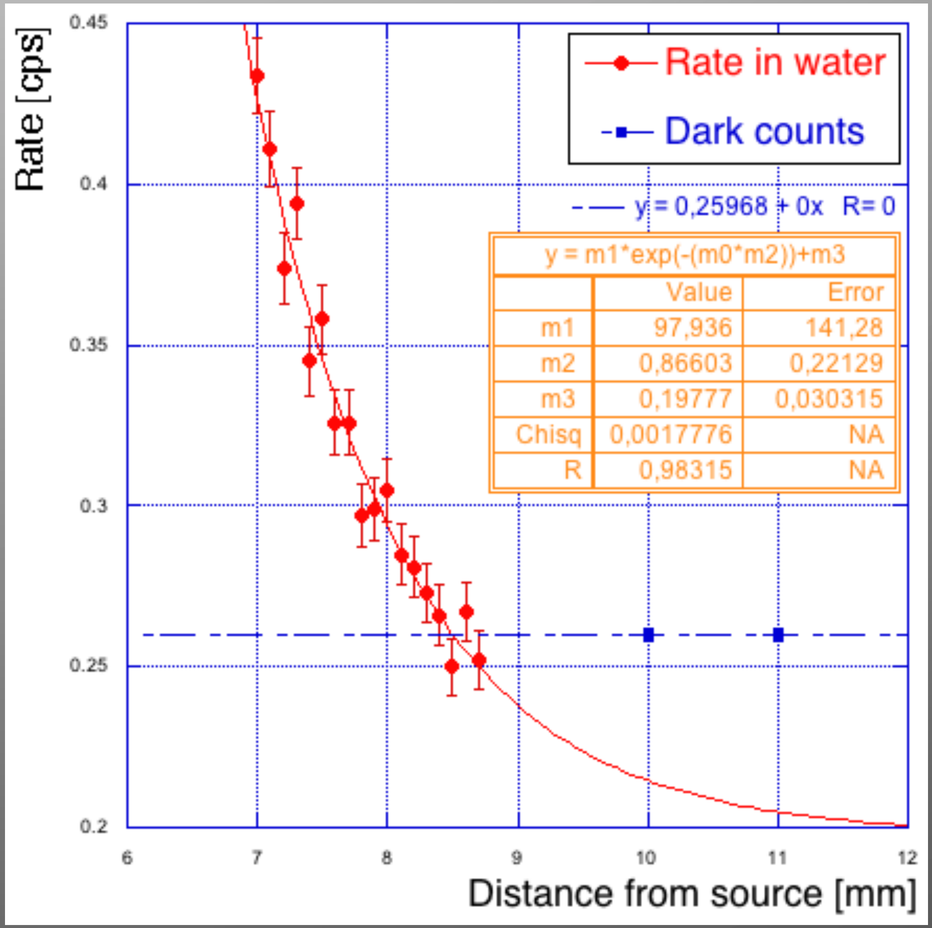
Estimated dose on surgeon administering 3MBq/kg:
1μSv/hr on surgeon's hands
0.13 μSv/hr on medical personnel

10

Sensitivity to Electrons

Scan with different thicknesses of water

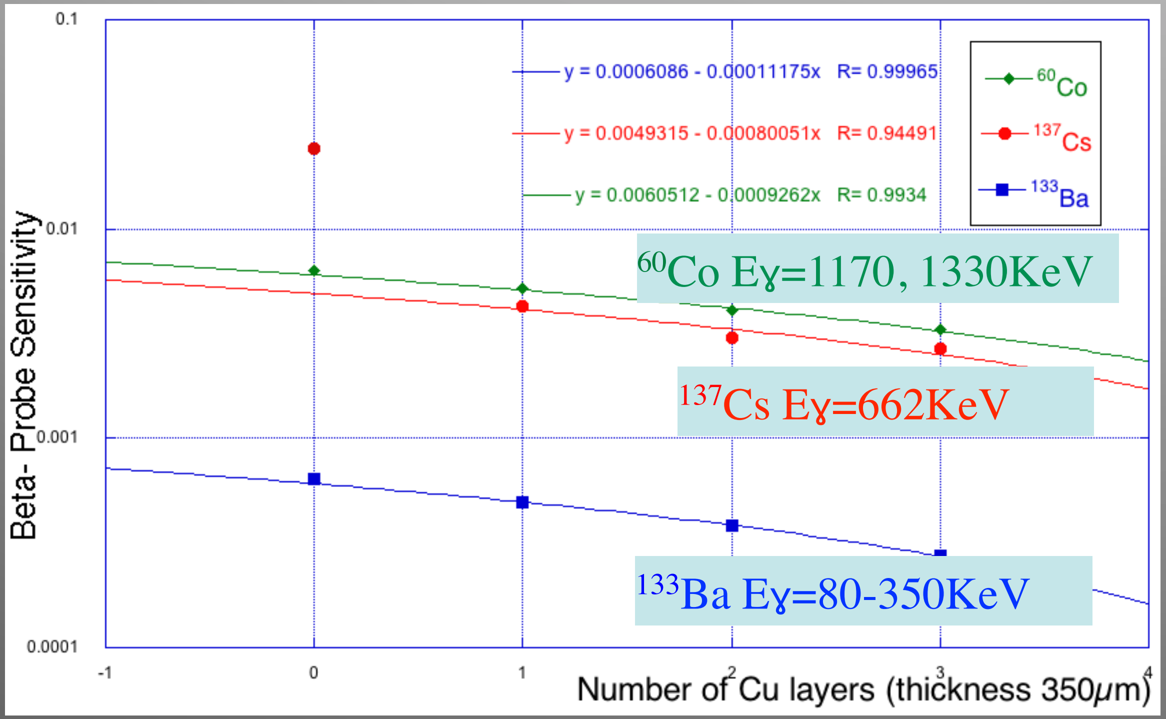
- Detection efficiency on ^{90}Sr point source
  - Rate $3.8 \cdot 10^5$ cps/MBq.
  - $\varepsilon_\beta = 40\%$
- Scan in water
  - $E_\beta > 500$ keV.
  - Detection efficiency $\varepsilon_\beta > 80\%$ in the β^- ^{90}Y energy range.



Background Rejection

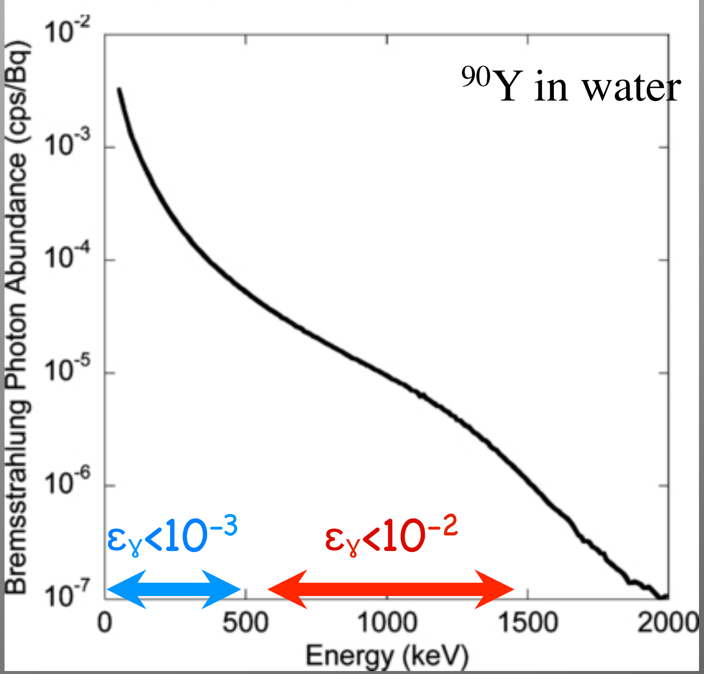
Background is mainly due to photons coming from Bremsstrahlung.

Sensitivity to photons



Bremsstrahlung Eγ spectrum

Figure 1 from Xing Rong et al 2012 Phys. Med. Biol. 57 3711



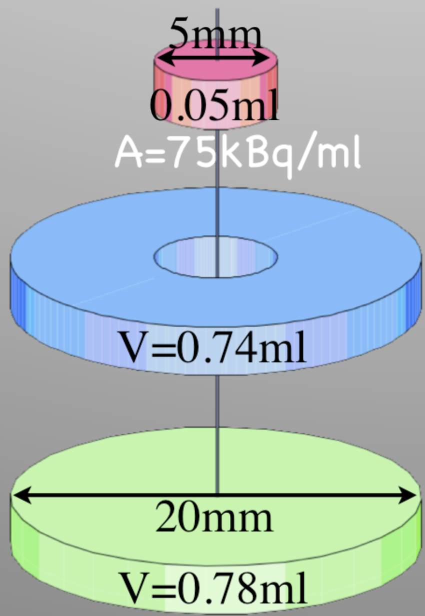
Almost transparent to Bremsstrahlung photons.

"Ad-hoc" Phantoms

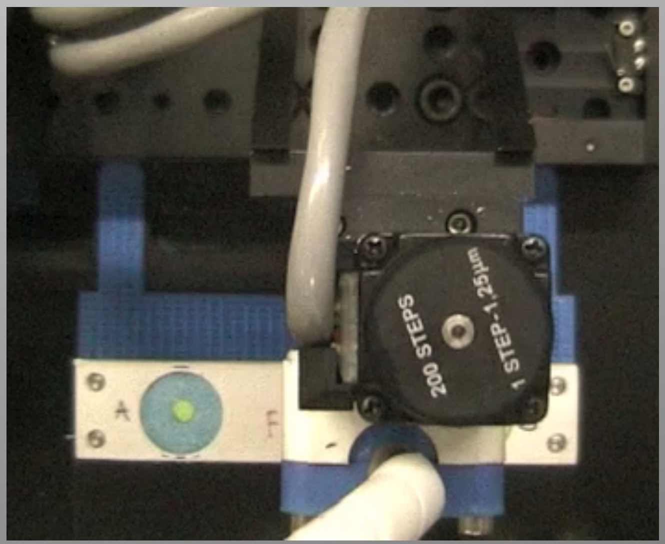
To simulate tumor remnant embedded in healthy tissue.

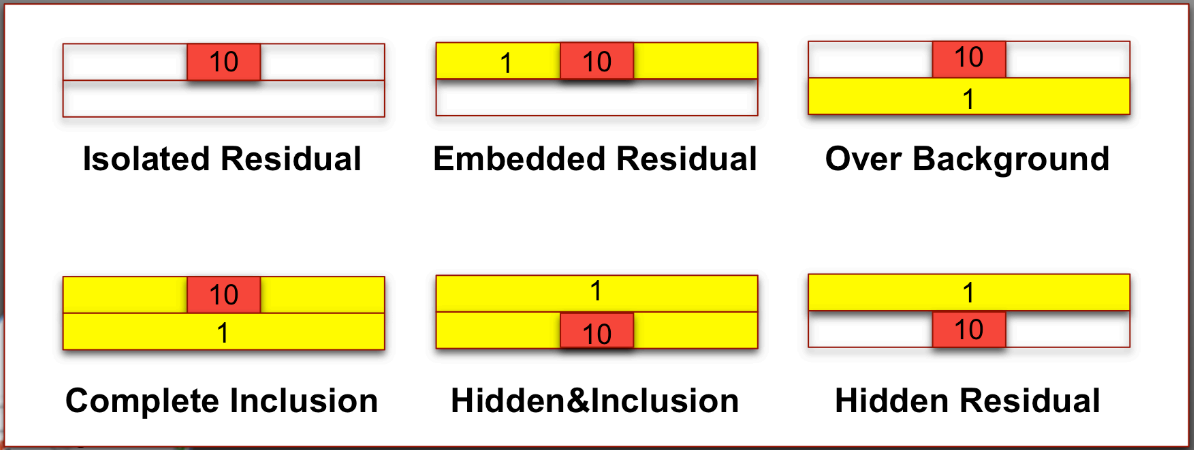
Tumor residual
V=0.05ml

embedded in
tissue with A/10



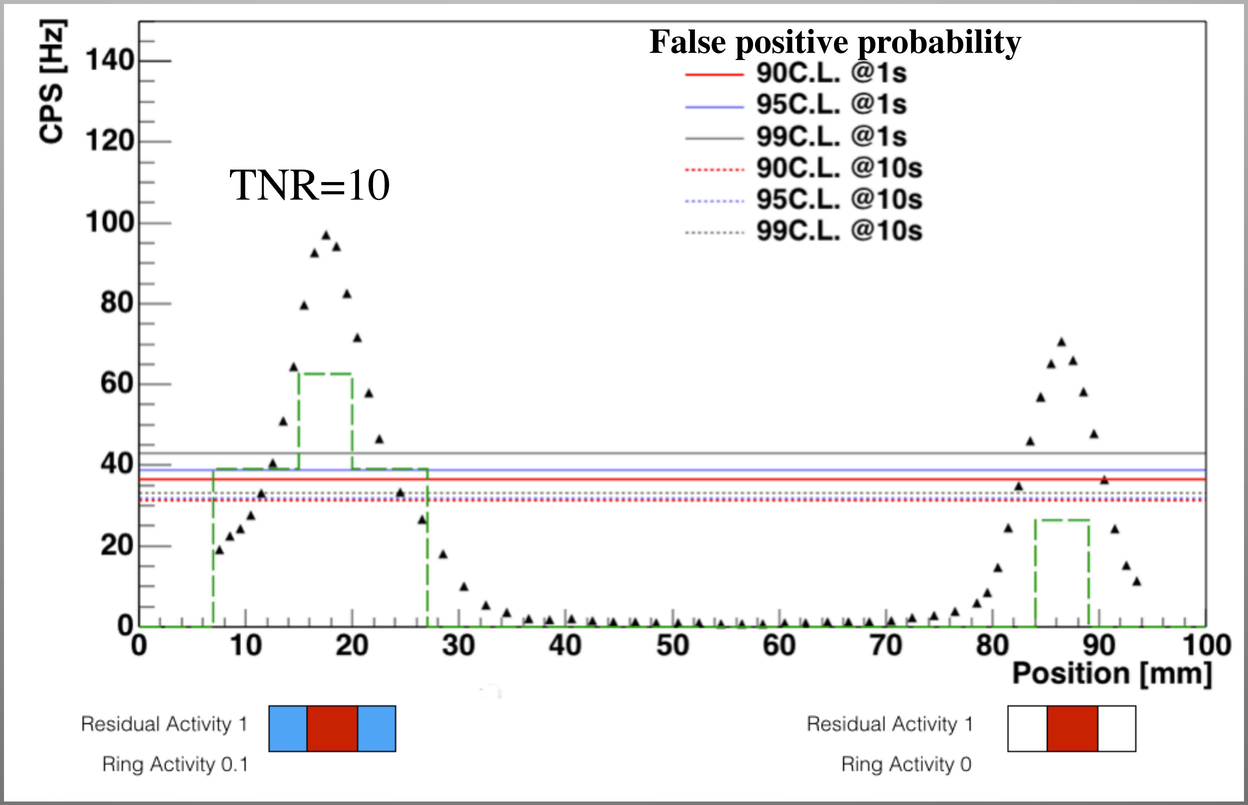
Motorized scans with S4-Probe





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

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

Probe Prototypes → Lab tests (phantoms) → Identification of proof of principle

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

RESEARCH PATH

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

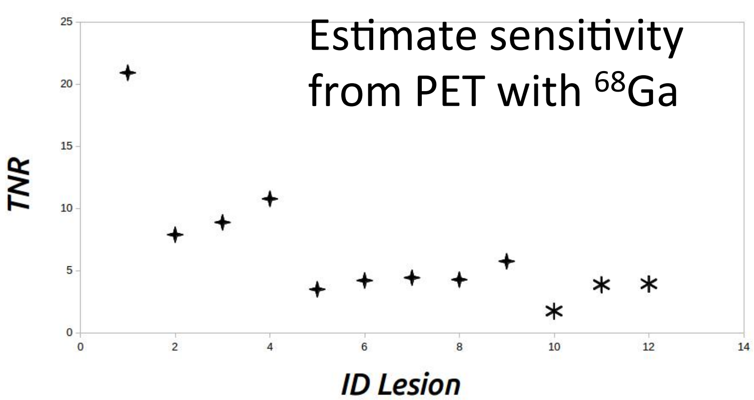
Probe Prototypes

Lab tests (phantoms)

Identification of proof of principle

Identification of first clinical cases

Estimate sensitivity from PET with ^{68}Ga



First clinical cases:

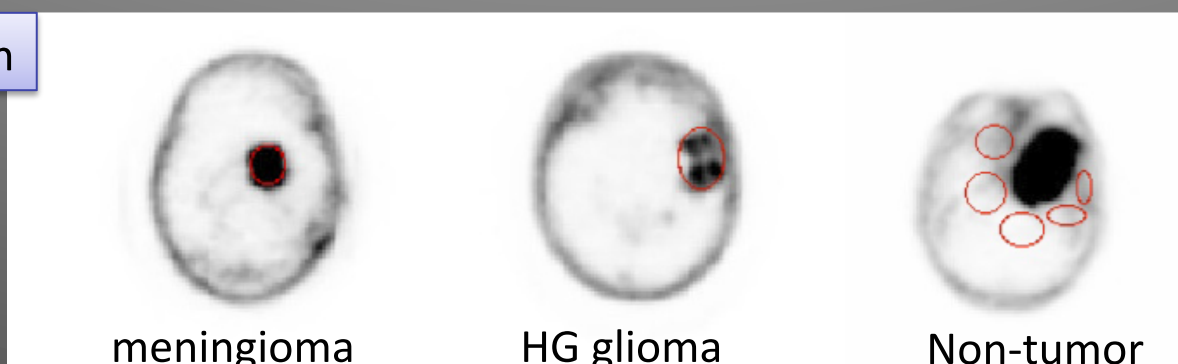
- Glioma (low and high grade)
- GEP-NET (start from small bowel)

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

DOTATOC uptake in glioma

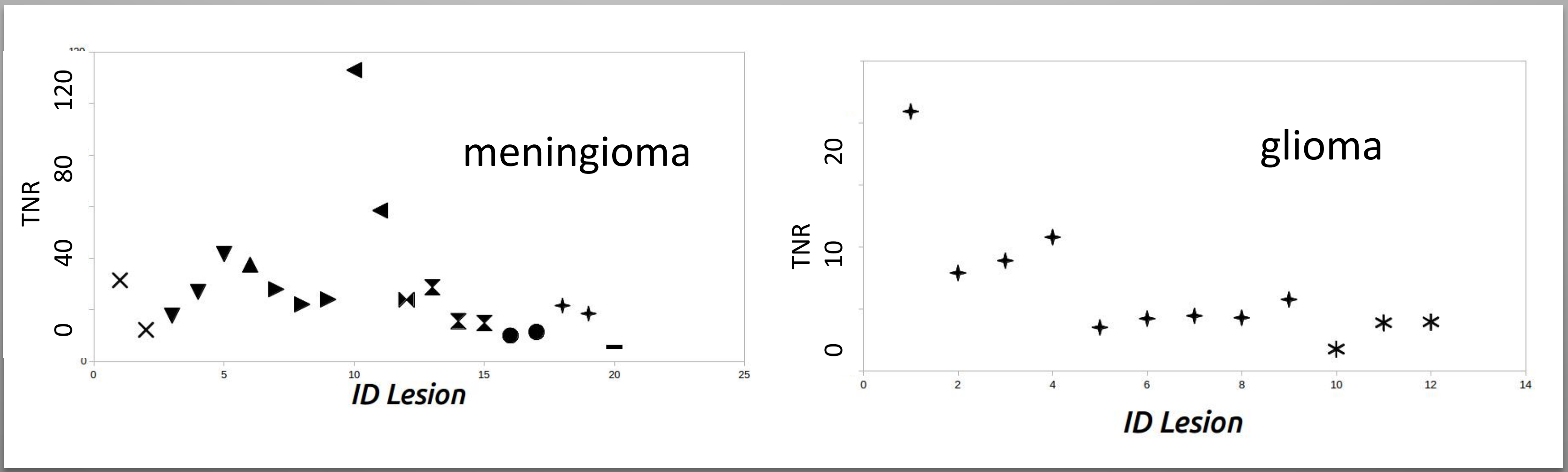
- DOTATOC is a somatostatin analog → known receptivity from NET .. but glioma?
- Even if TNR too low for therapy, can it be used for RGS?
- Use 68Ga-DOTATOC PET scans to estimate signal and background

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

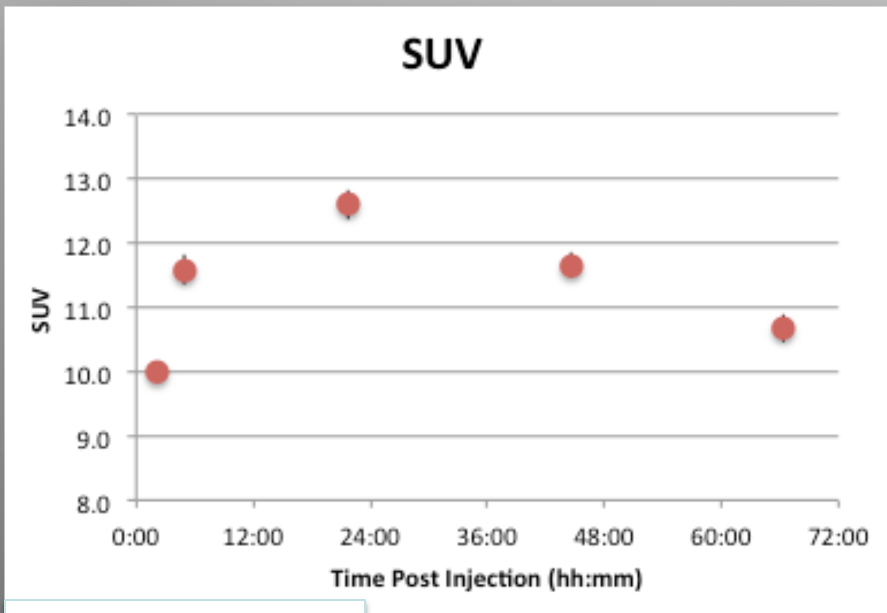
- Needs to wait for ~6s, but it works
- Margins to improve probe

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

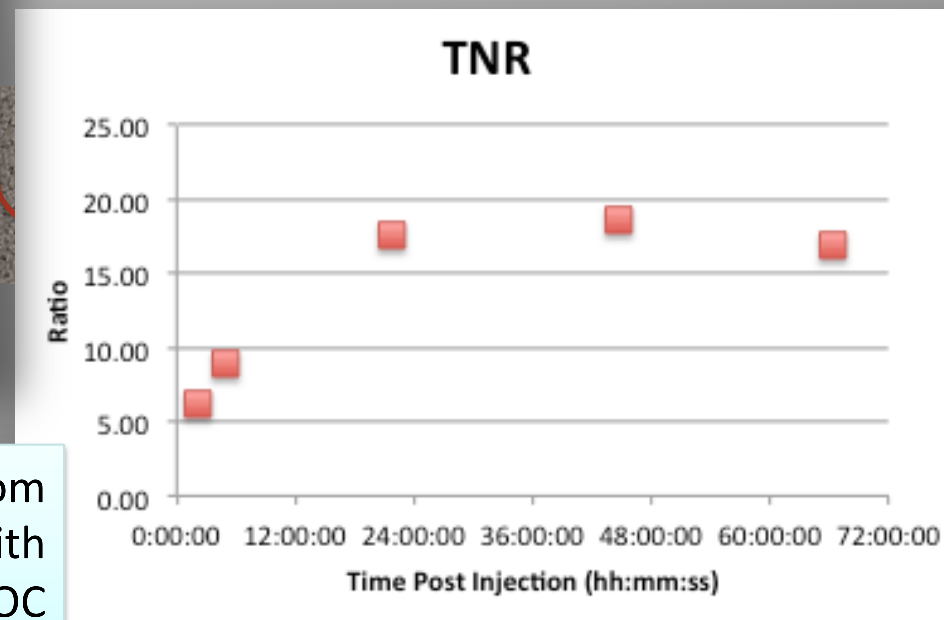
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliera di Reggio Emilia
Arcispedale S. Maria Nuova

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

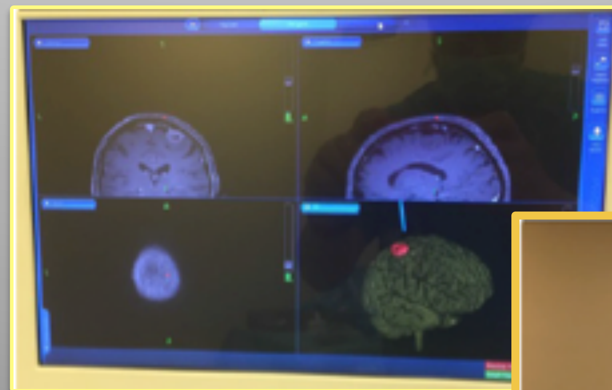
RESEARCH PATH

- Probe Prototypes
- Lab tests (phantoms)
- Identification of proof of principle
- Identification of first clinical cases
- Ex-Vivo tests on Meningioma

We are here

E. Solfaroli et al., submitted to JNM

Ex-vivo test on meningioma

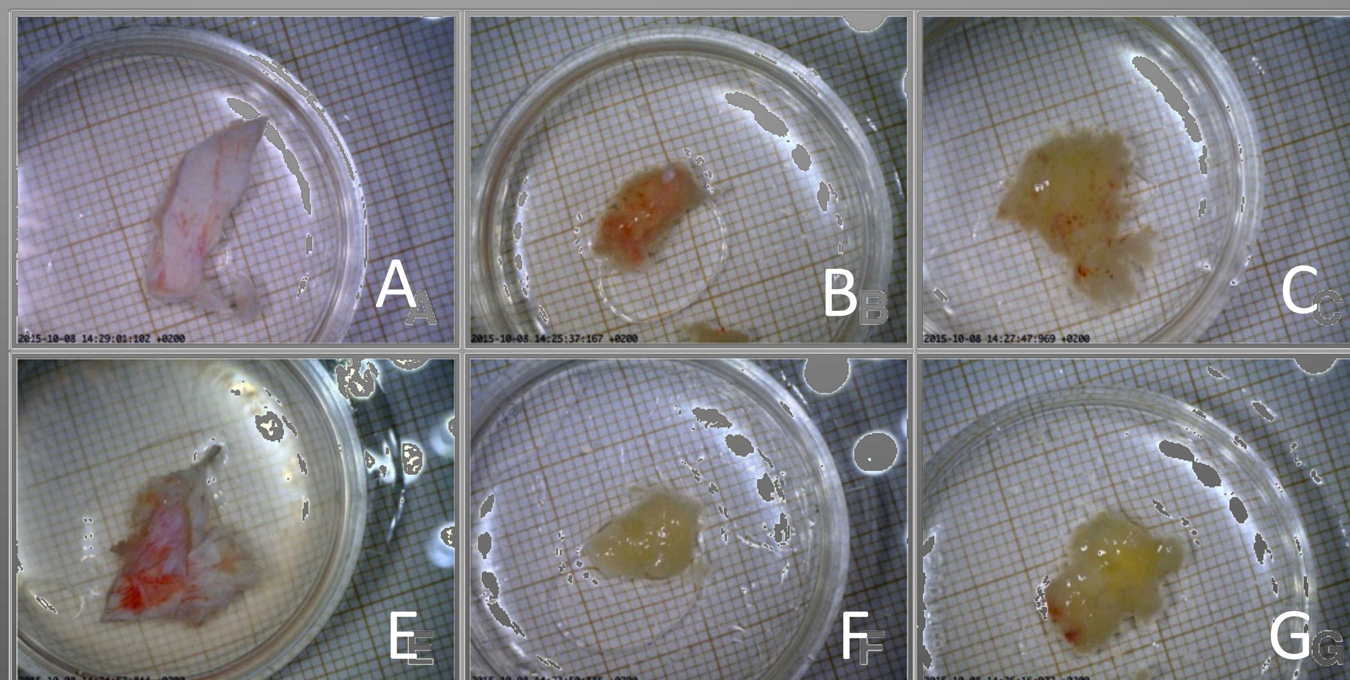


- PET with Ga68 on Sep 14th
  - Tumor SUV ~2g/ml (relatively low, but enough)
  - TNR ~ 14 (good)

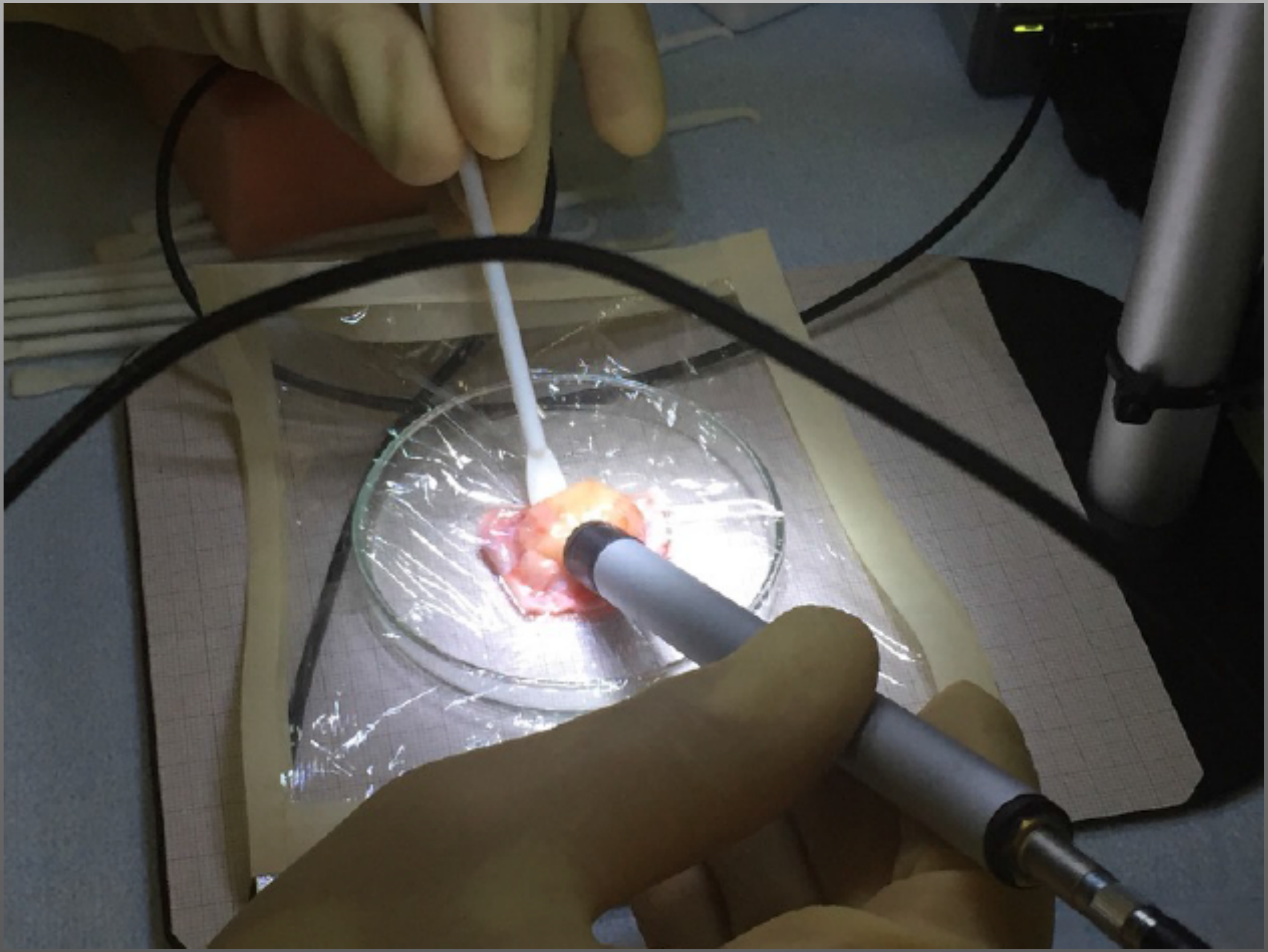
- 8mCi Y90—DOTATOC on Oct 9th
- Surgery on Oct 10th

The Samples

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



Evaluating the samples rate



Results

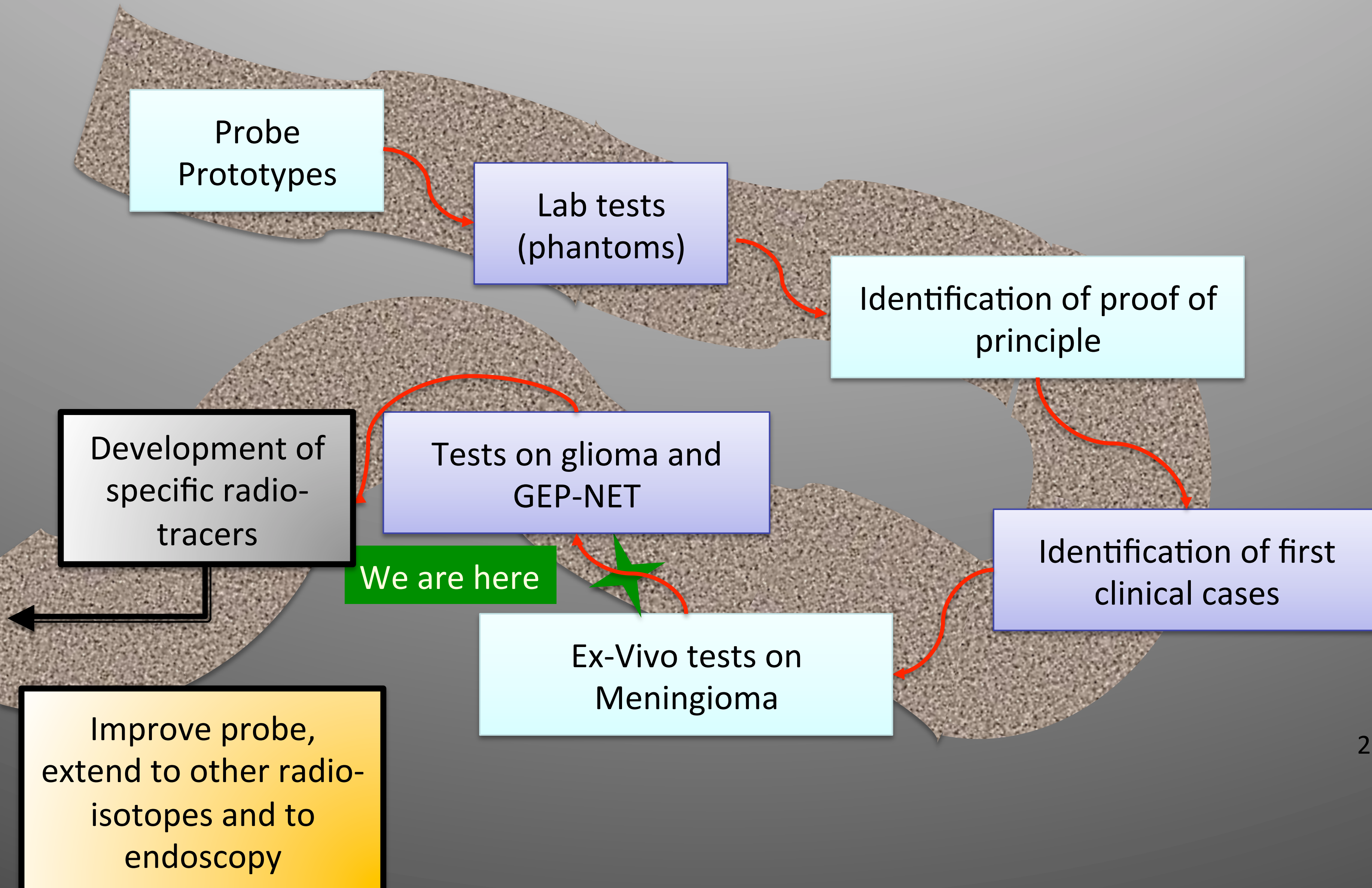
- Residuals as small as 0.2ml are visible
- Predictions with simulation are reliable (115 cps predicted, 105 observed)
- Healthy brain ~1cps (simulation) infiltrated dure can be identified

+ Confirmed very low exposure of medical personnell

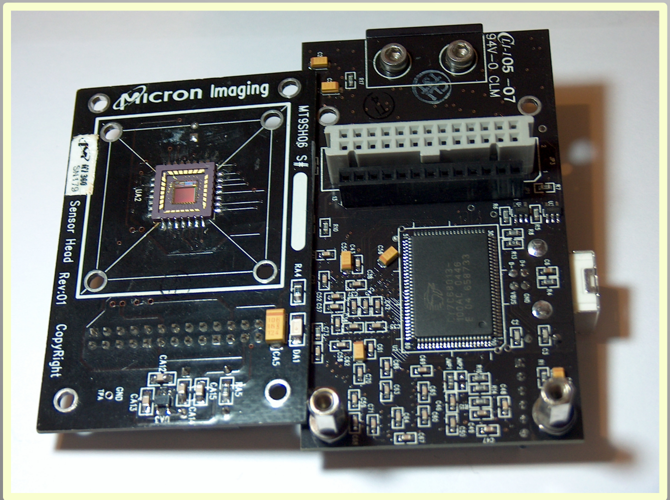
Sample	V (ml)	R(cps)	histology
A	0.38	5.0	Dural tissue infiltered by meningioma
B	0.23	51.5	Transitional meningioma
C	0.72	45.0	Transitional meningioma
D	4.84	105.0	Transitional meningioma
E	0.88	3.5	Dural tissue infiltered by meningioma
F	0.21	27.7	Transitional meningioma
G	0.39	39.3	Transitional meningioma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

IRRADIATION MEASUREMENTS

RESEARCH PATH

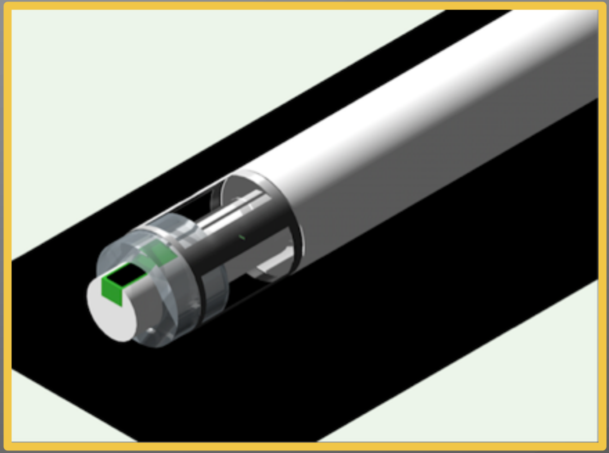


Probe developments



- Use CMOS technology to lower energy threshold (with L. Servoli, INFN PG)→ allow use of other isotopes
  - Matrix design for basic "imaging"

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



Extension to other tumors: existing tracers

isotope	half Life	E gamma [keV]	% gamma	Endpoint beta- [keV]	% beta-
P32	343.2 h	0	0	1710	100
Ra223	273.4 h	400	2	0	0
Pb211	36.1 min			535 6	6.28
Tl207	4.7 min			1418 5	99.729
Sr89	1217 h	909	<1	1492	100
Re188	17 h	63	2	1962	25
Re188		155	15	2118	72
Re186	90.72 h	59	3	939	22
Re186		137	9	1077	72
Bi213	46 min	440	26	983	31
Bi213		0	0	1423	66
Dy165	2 h	0	0	1192	15.0
Dy165		0	0	1287	83.0
K42	12 h	1525	18	2001	18
K42		0	0	3525	82
Na24	15 h	472	99.95	1393	99.8
I131	192 h	365	82	334	7
I131		637	7	606	90
Sm153	46.8 h	41	49	634	35
Sm153		47	12	703	44
Sm153		103	28	807	21
Kr85	4.48 h	151	75	840	79
Kr85		305	14	687	99

Either:

- Find other applications with Y90 (and somatostatine analogues)
- Use a tracer marked with one of the isotopes in the table, already known in nucl med

Extension to other tumors: new tracers

- Collaboration with Gemelli and Chemists@Sapienza to develop new tracers ongoing
- Radio-nuclides of interest:

F18 also being explored

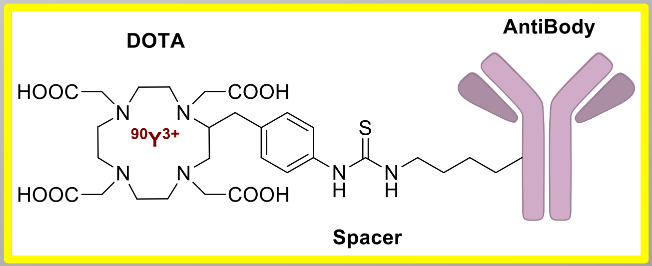
Previous slide +

isotope	half Life	E gamma [keV]	% gamma	Endpoint beta- [keV]	% beta-
Si31	2.62 h	1266	<1	1491	100
I133	20.80 h	539	87	1227	83
Br83	2.4 h	529	1	935	99
In117	43 min	553	100	744	99

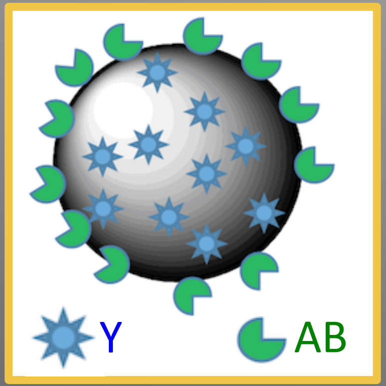
Isotopes of the same family as those already used in NM

Current Efforts

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

Nucl . Medicine and Chemistry

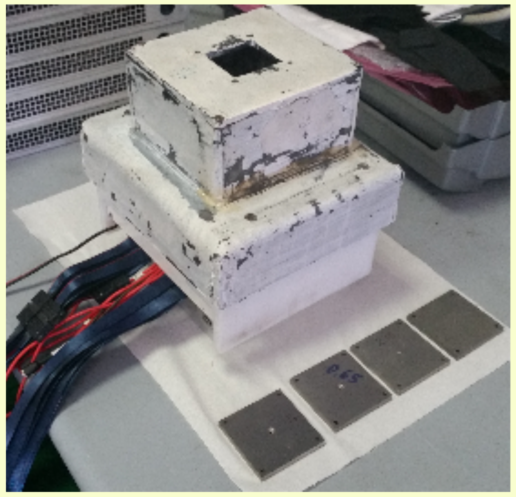
Chemistry and CTF

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

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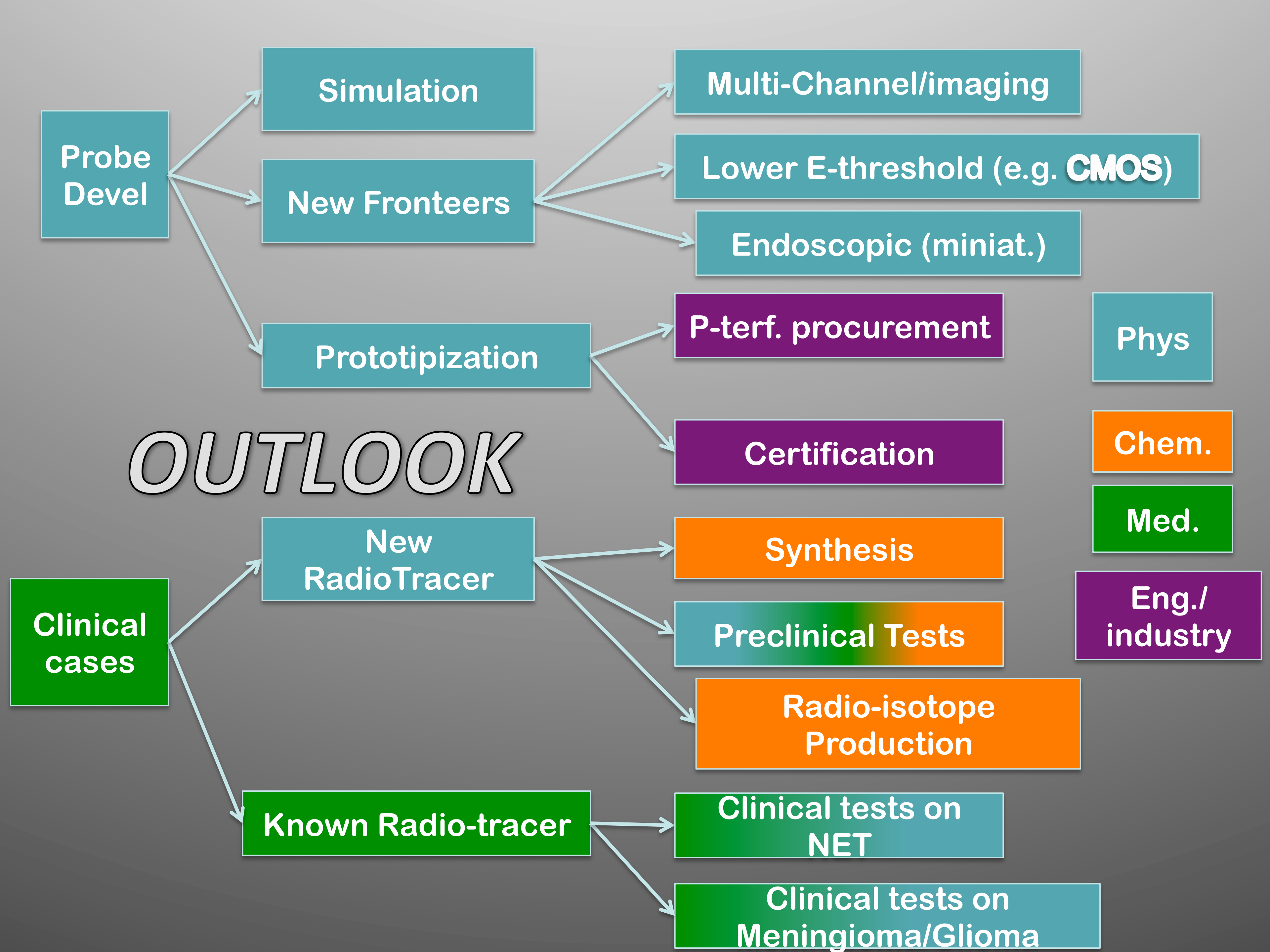
Nucl . Medicine and Chemistry

Chemistry and CTF



OUTLOOK
Probe Devel
Simulation
New Fronteers
Prototipization
Multi-Channel/imaging
Lower E-threshold (e.g. CMOS)
Endoscopic (miniat.)
P-terf. procurement
Certification
Phys
Chem.
Med.
Eng./ industry
Clinical cases
New RadioTracer
Known Radio-tracer
Synthesis
Preclinical Tests
Radio-isotope Production
Clinical tests on NET
Clinical tests on Meningioma/Glioma

Summary

A NOVEL RADIO-GUIDED SURGERY WITH β- DECAYS

Basic idea:

no background from gamma allows for

- Shorter time to have a response
- A smaller and more versatile detector
- Much reduced noise from nearby healthy organs
- Reduced dose to medical staff

A translational research involving physics, chemistry, nuclear medicine, oncology and engineering …

.. we still have a long way to go

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