A novel radio-guided surgery technique with β- radiation

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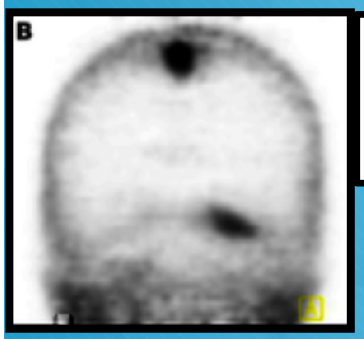
The Applied Radiation Physics Group

Collaborations with bio-engineers, medicinal chemists, nuclear medicine physicians, oncologists, surgeons:

Radio Guided Surgery

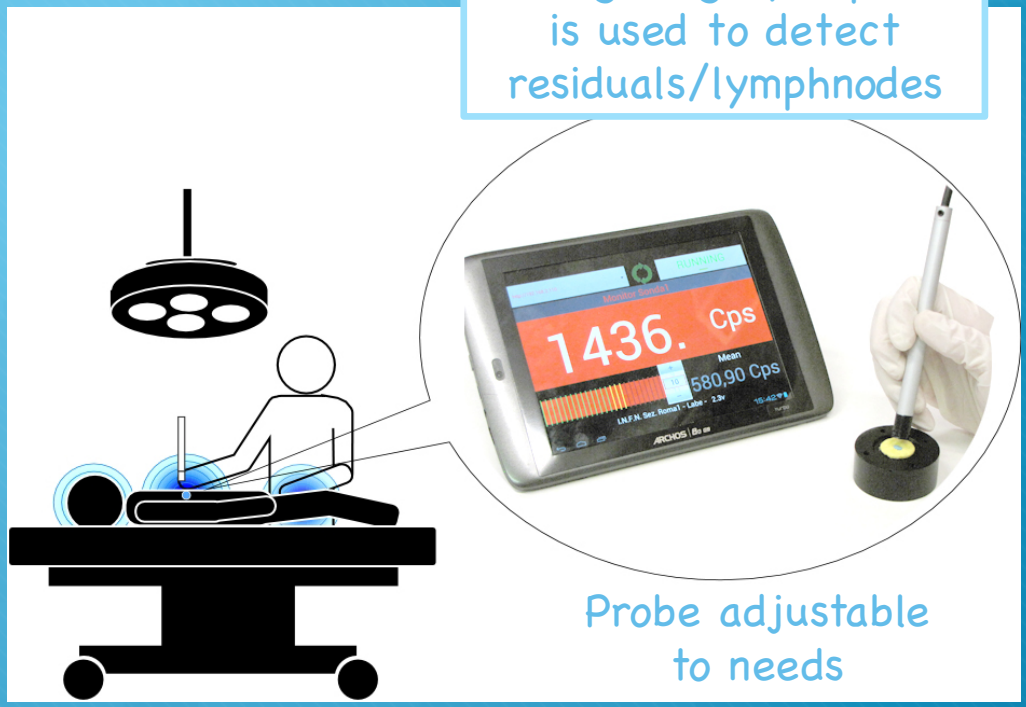


PET/SPECT scan to estimate receptivity and background

Administration of radio-tracer

each tumor requires its own tracer

During surgery a probe is used to detect residuals/lymphnodes



Probe adjustable to needs

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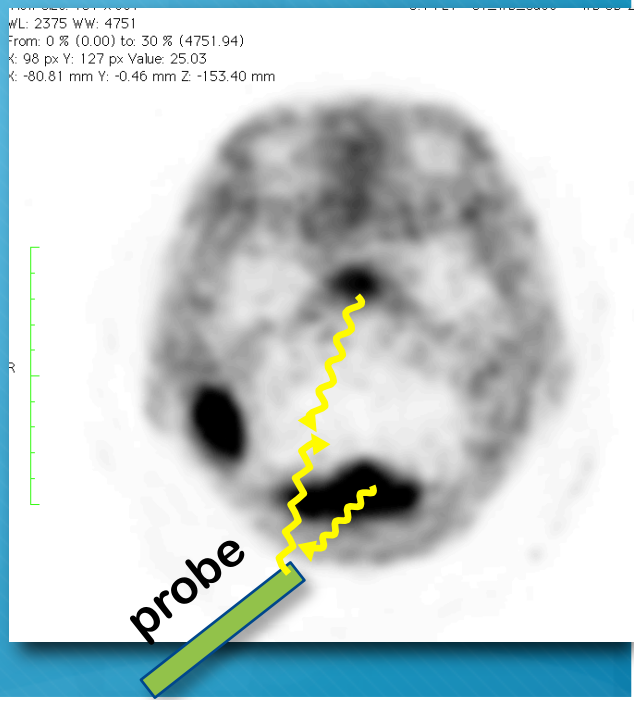
LIMITS OF γ-RGS

Long range of gamma's involve:

- **exposure of medical personnel**
- **Background from healthy organs**

Difficult to apply in:

- **Brain tumors**
- **Abdominal tumors**
- **Pediatric tumors**



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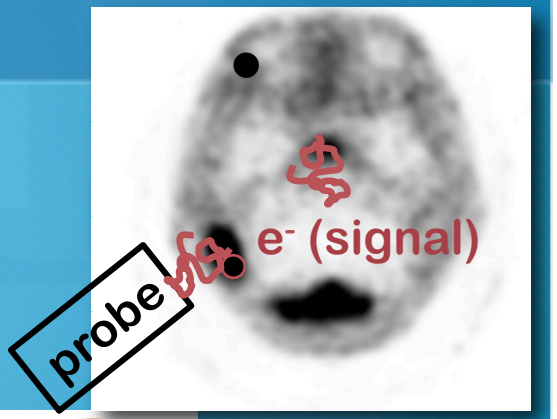
EXTEND RGS TO MORE CLINICAL CASES

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

A Change In Paradigm

- Use of β^- tracers (electrons): pros
  - Detect electrons that travels ~100 times less than γ
  - Tracers with ^{90}Y can be used (already in therapy)
  - 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



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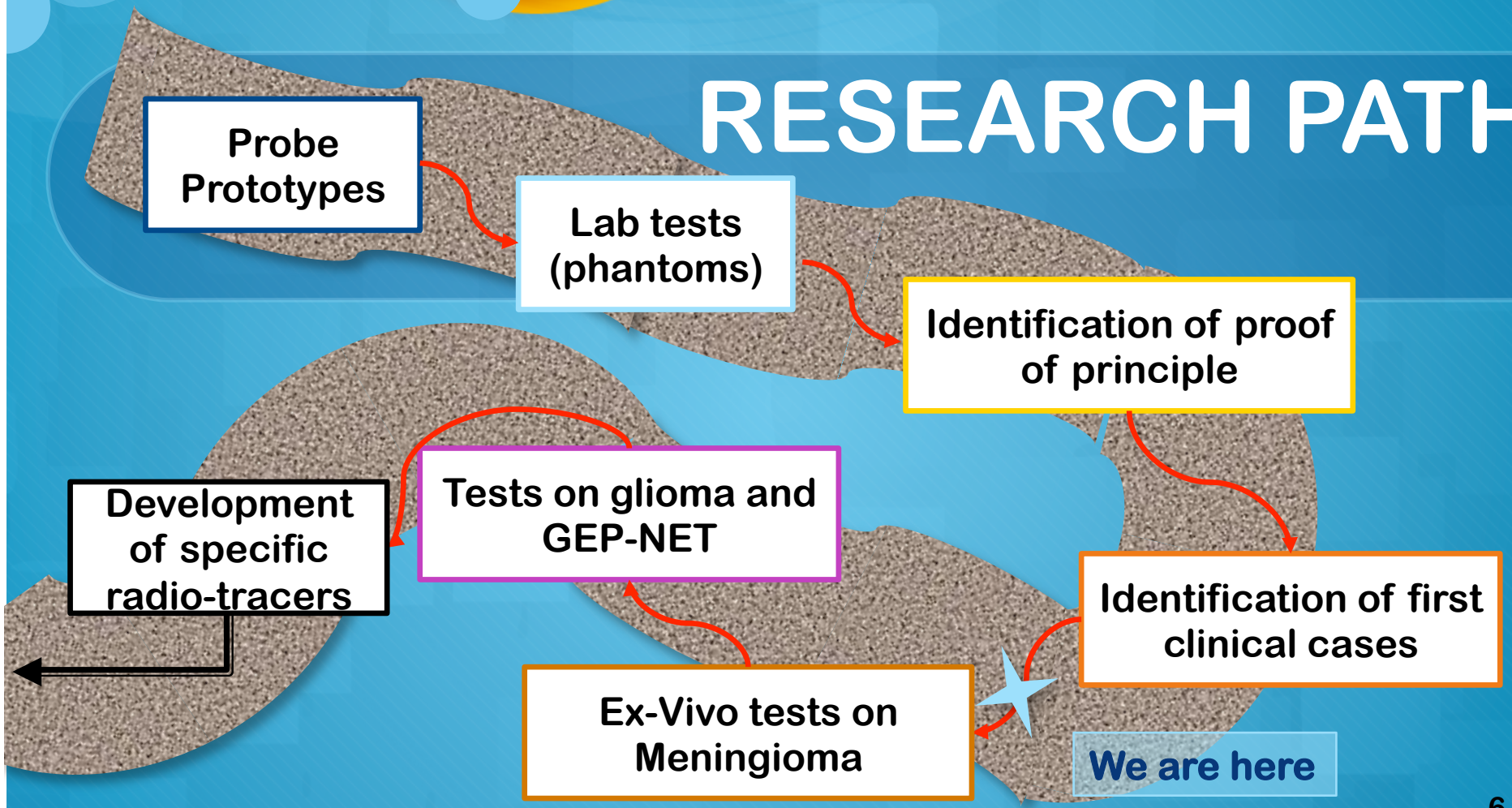
RESEARCH PATH



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A NOVEL RADIO-GUIDED SURGERY WITH β- DECAYS

Seeking collaboration

PATENT PCT/IT2014/000025

- To produce prototype certified for clinical tests. Current design:
  - P-terphenil crystal (avoid γ contamination)
  - SiPM read-out (interaoperatively safe?)
  - Thin Al shielding
- To perform (pre-)clinical tests of new radio-tracers
  - Attach beta- emitting isotopes to working tracers
  - Bio-kinetic tests
  - Pre-clinical tests
  - Clinical tests

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Feedback is welcome!
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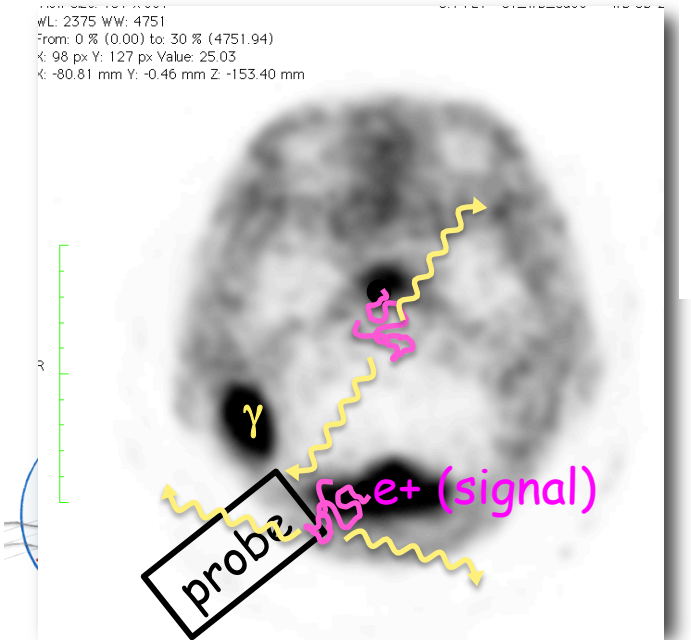
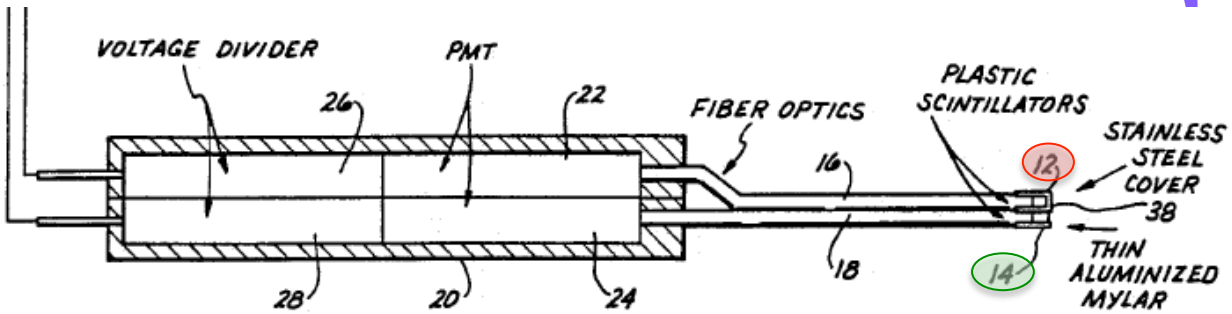
BACKUP

Daghighial et al 1994
Raylman et al 2001

Alternative: β^+ RGS

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





Two channels:

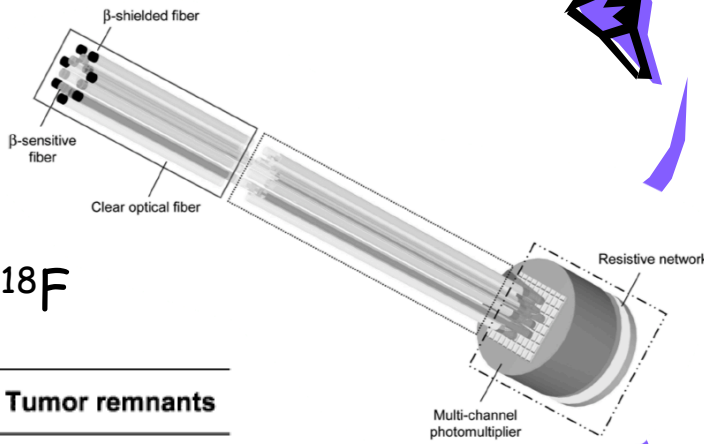
- one sensitive to both positrons and gamma (14) (N1=P+G)
- one sensitive only to gamma (12) (N2=G)

signal=N1-N2

β^+ RGS: 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

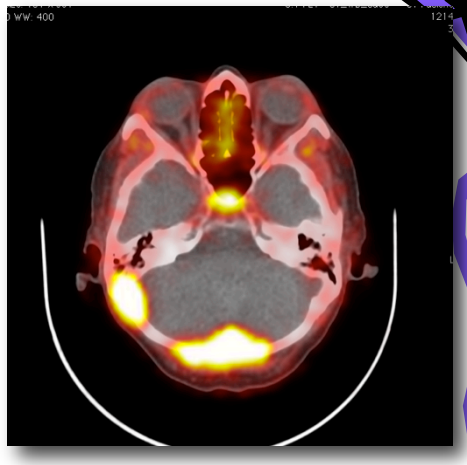
Conclusions

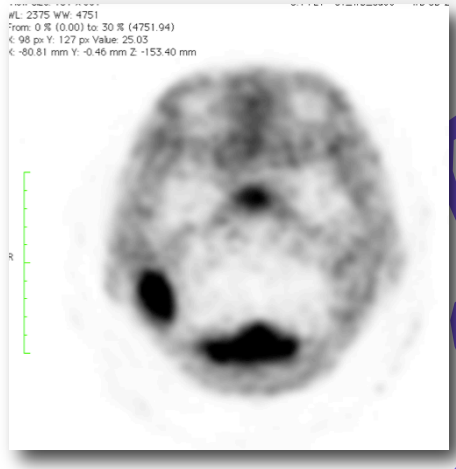
This phantom also demonstrated the ability of the probe to detect tumour discs as small as 5 mm in diameter (20 mg) for tumour-to-background ratios higher than 3:1 and with an acquisition time around 4 s at each scanning step. These results indicate that our detector could be a useful complement to existing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

FIRST APPLICATION

Collaboration with Ist. Neurologico C. Besta and IEO

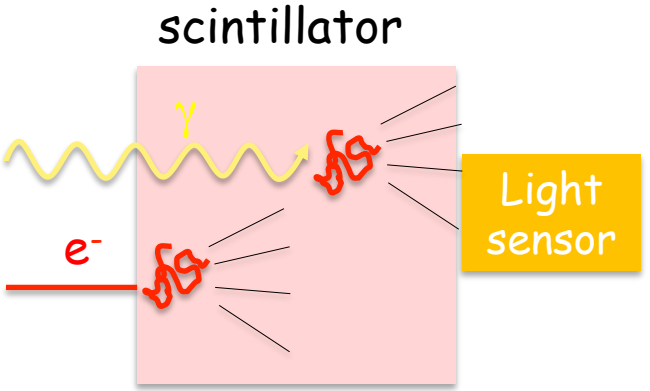
- ***Cerebral Glio Blastoma***
  - It's an aggressive cancer of brain cells, in which a **complete resection** of the neoplastic cells is crucial to raise the patient outcome
  - In this case *FDG* (the most common tracker) is useless, due to great glucosic avidity of normal brain tissue
    - the use of ^{90}Y bounded to *DOTATOC* can be much more specific to reveal residuals
      - Peptide Receptor Radio Therapy makes use of receptivity of brain tumors to somatostatin analogues
      - specificity already proved on *Meningioma*





Electron/positron detection

Sensitivity to gamma or e-/e+ dictated by scintillator



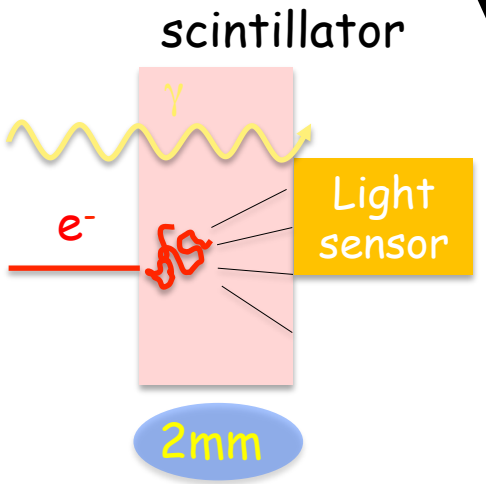
Two possible types of scintillators:

- organic: low signal/low sensitivity to photons
- inorganic(most used in nucl.med.): high signal/high sensitivity to photons

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 b- 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

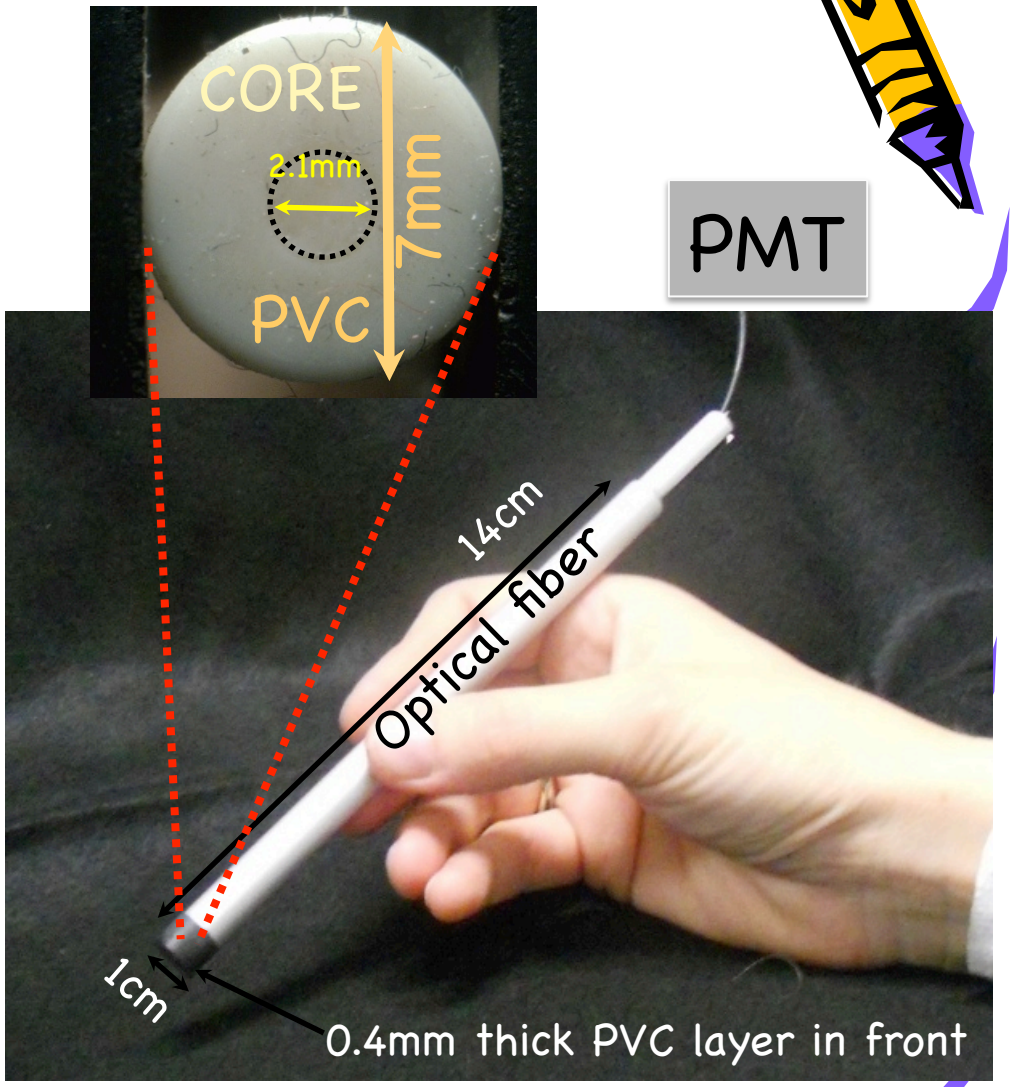
The First Prototype

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.

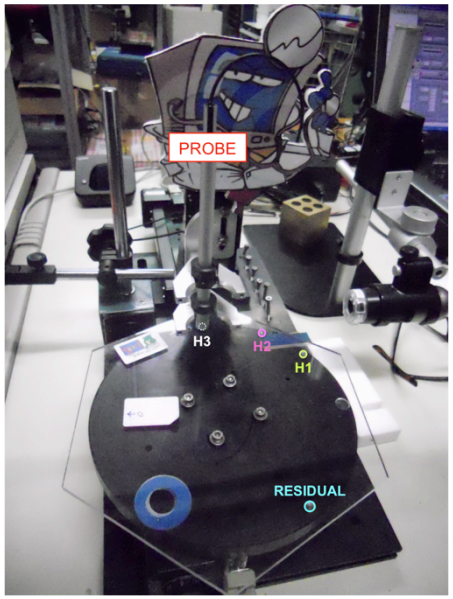


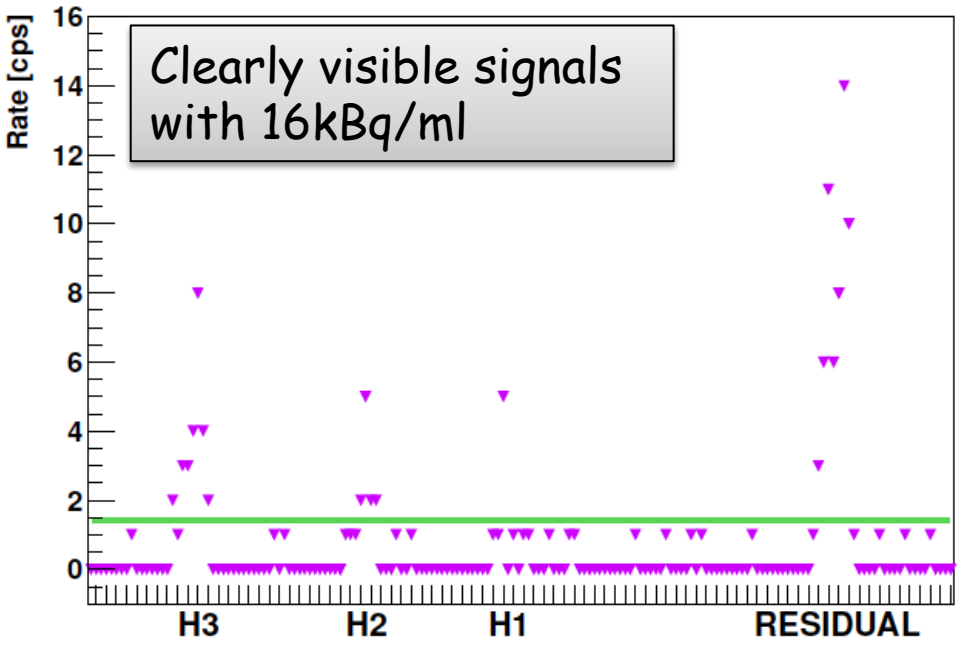
Test with Phantoms

Cylindrical volumes filled with ^{90}Y in saline solution simulating tumoral remnants with millimetric dimensions

"RESIDUAL" compatible with residual well identified by NMR imaging ➔ useful as reference during further clinical tests;

"H1, H2, H3" same areas, but different heights to check the effect of the depth on the probe response.





Extension to the Real Case

- FLUKA simulation + DICOM PET scans to extrapolate from source rates to clinical case
- Acceptable risk level is achieved by balancing the false-positive and false-negative probabilities: P(FalsePos)≈1%, P (FalseNeg)<5%

PHANTOMS	d(mm)	h(mm)	V(ml)	t(s)@22kBq/ml	t(s)@5kBq/ml
RESIDUAL	6	3.5	0.10	1	2
H1	4	1	0.01	2	>10
H2	4	2	0.02	1	4
H3	4	3	0.04	1	4

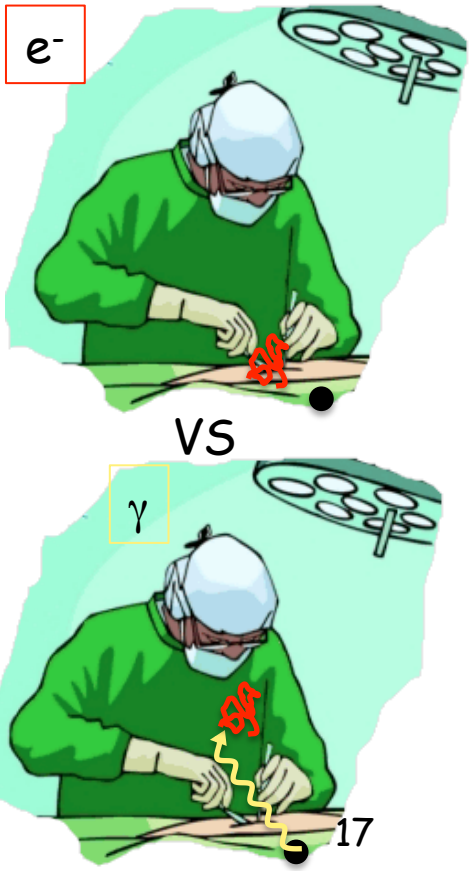
Administered activity: 3 0.7 MBq/kg

Expected exposure of medical personnel

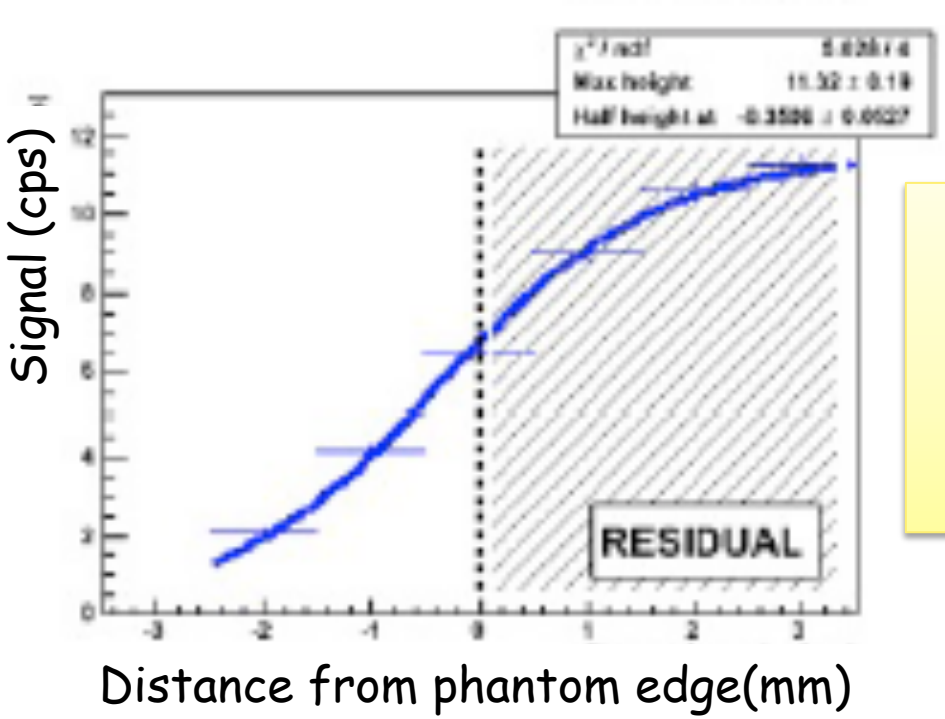
With FLUKA simulation we estimated that administering 3MBq/kg to the patient

- Surgeon's dose on hands: 1μSv/hr (24x less than γ)
- Medical personnel dose:

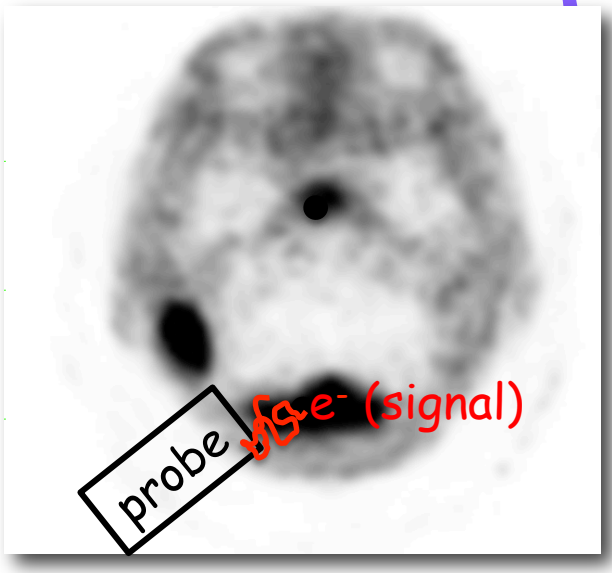
  0.13 μSv/hr (40x less than γ)



Spatial resolution



Scan at the edge of phantom (no signal after 2mm)



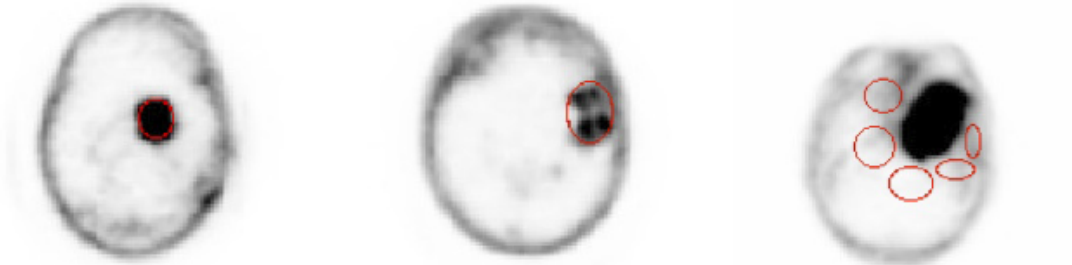
Short electron path length implies high locality:

- High spatial resolution
- Need for contact detection

DOTATOC uptake

- DOTATOC is a somatostatin analog ➔ known receptivity from NET
- Use 68Ga-DOTATOC PET scans to estimate signal and background

ROI definition

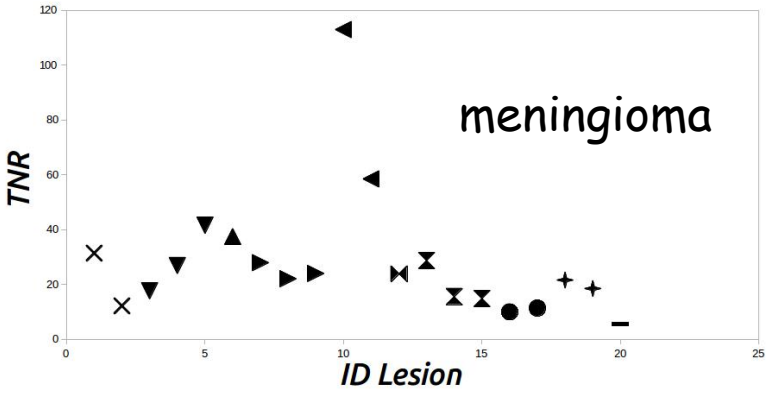


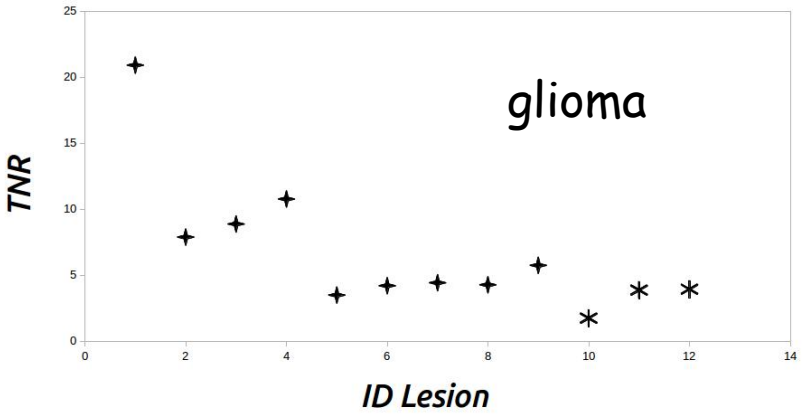
meningioma HG glioma Non-tumor

Statistical average of several ROIs

Results

11 meningioma and 12 HG glioma patients





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%

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

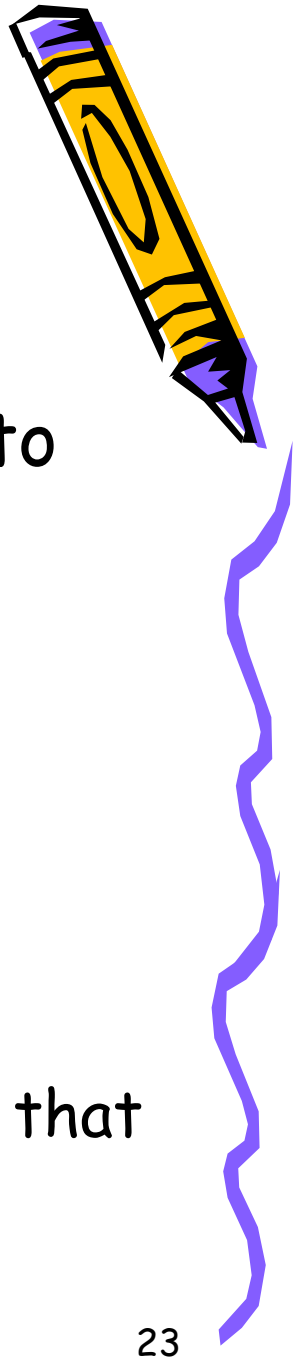
RGS for glioma

Patient ID	W (kg)	A_{adm} (MBq)	ν (Hz)	ν_{NT} (Hz)	t_{probe}^{min} * (s)	A_{1s}^{min} ** (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

What next?



- Clinical tests on meningioma close to start (last bit of bureaucracy…)
- Further developments on probe:
  - Higher light collection efficiency
  - Matrix design for basic "imaging"
- Identify other clinical cases. Two classes:
  1. There exists already a radio-tracer that carries ^{90}Y (for radiomethabolic therapy) or ^{68}Ga (PET)
  2. No known radio-tracer

Case 1 (existing tracer)

- Examples of known tracers

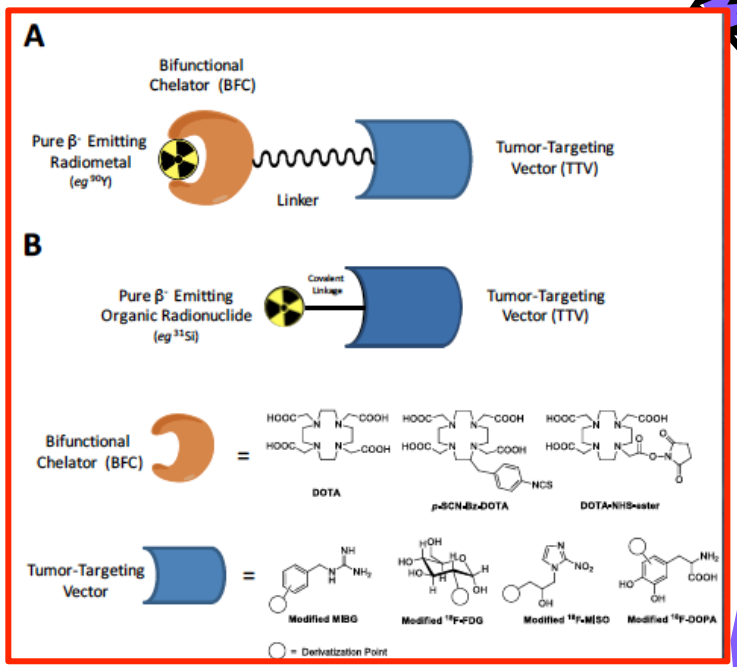
Radiopharmaceutical	Targeting mechanism	Indications
I-131 as iodide	Thyroid hormone synthesis	Differentiated thyroid carcinomas
I-131 Tositumomab	CD20 Antigen binding	Non-Hodgkin's lymphoma
Y-90 Ibritumomab tiuxetan	CD20 Antigen binding	Non-Hodgkin's lymphoma
Y-90 microspheres	Intravascular trapping	Liver metastasis Hepatocellular carcinoma
Sr-89 chloride	Calcium analogue	Bone pain palliation
Sm-153 EDTMP	Chemoadsorption	Bone pain palliation
Y-90 Octreotide	Somatostatin receptor binding	Neuroendocrine tumors
I-131 MIBG	Active transport into neuroendocrine cells and intracellular storage	Neuroblastoma Pheochromacytoma Carcinoid Paraganglioma Medullary thyroid carcinoma

From PET or SPECT images we can estimate (with simulation) the tumor-noise-ratio

- Clinical tests "easy" to setup
- Possible candidates: glio-blastomas, NET (liver methastases, insulinoma,…)

Case 2

- Collaboration with chemists to develop new tracers ongoing
  - Still looking for molecular biologists
- Two classes of possible solutions
  - Radio-nuclides of interest



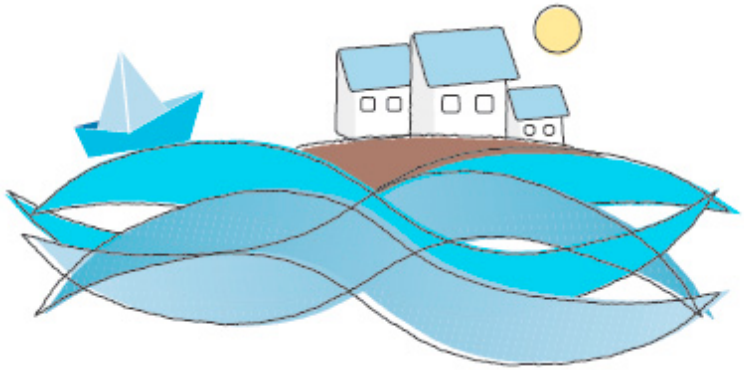
Isotope	½-life	Pure?
^{90}Y	64h	Y
^{89}Sr	50d	Y
^{49}Sc	1hr	Y
^{31}Si	2hr	Y
^{69}Zn	1hr	Y
^{42}K	12h	N
^{153}Sm	46h	N
^{131}I	8d	N

Conclusions (I)

- Radio-Guided surgery established with gamma probes:
  - Few types of tumor addressed
  - Developments towards:
    - Improved detection
    - New applications
- Extension to beta radio-tracers:
  - Little activity in the field:
    - Beta+ techniques suffer from background
    - Beta- techniques seem promising (low background, high locality):
      - 0.5 MBq/kg enough to detect 0.1ml residuals of meningioma
      - Surgeon dose <1μSv/hr
    - → extend field of application
- Collaborations are needed to extend application of our radio-guided-surgery technique: oncologists, medical physicists and nuclear physicians, molecular biologist and chemists

Conclusions (II)

- There is still room for improvement in Radio-Guided-Surgery
- Medical-oriented, devoted workshops with all the interested professional figures (like MEDAMI) are needed.



Mediterranean
Thematic Workshops
in Advanced Molecular Imaging

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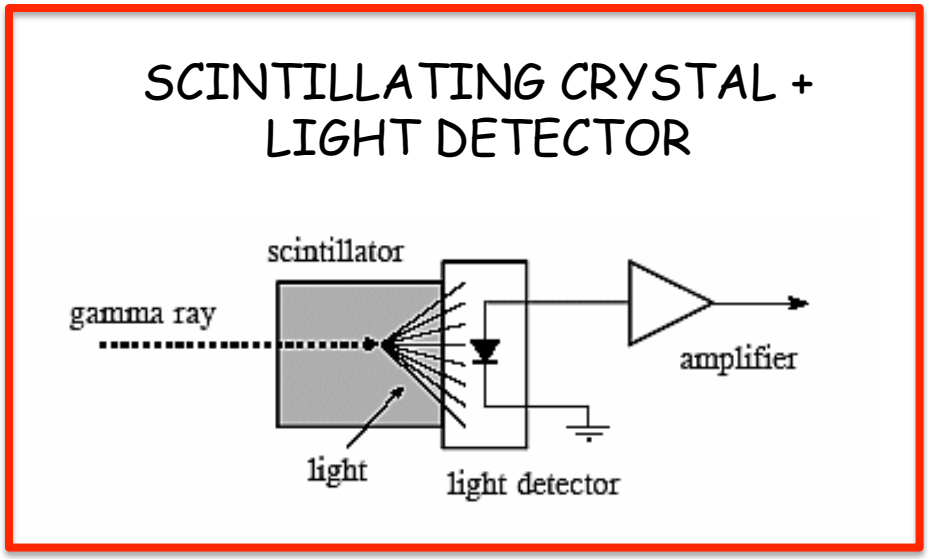
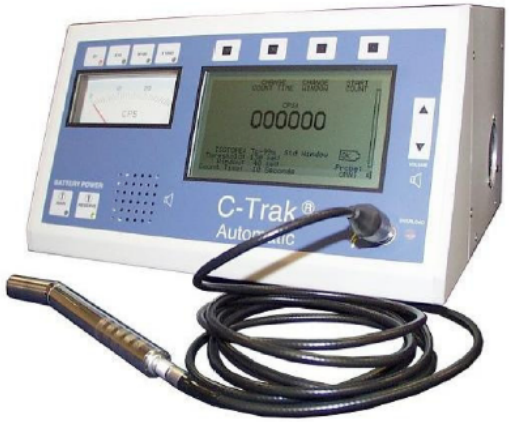
Detectors





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