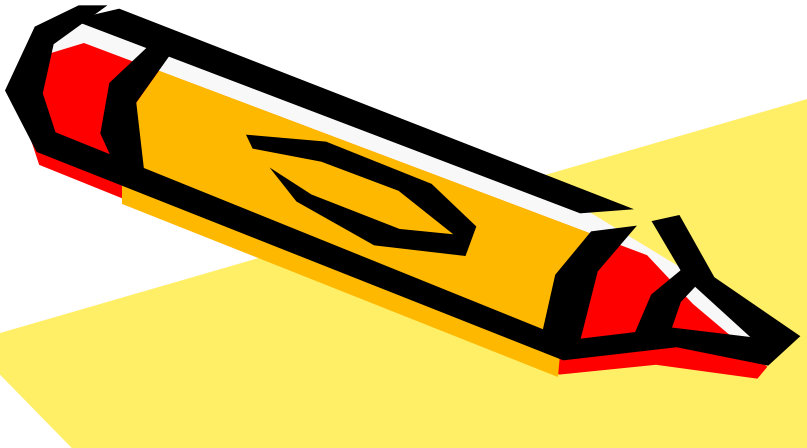


Medical Applications of radiation physics

Riccardo Faccini

Universita' di Roma "La Sapienza"

Outlook

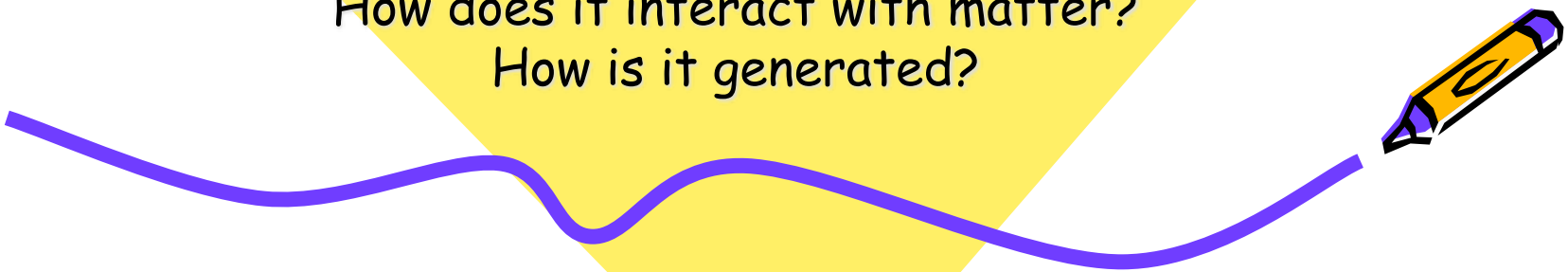
- Introduction to radiation
  - which one ?
  - how does it interact with matter?
  - how is it generated?
- Diagnostics and nuclear medicine:
  - Diagnostics (radiography, SPECT, PET,…)
  - Molecular radiotherapy
  - Radio-guided surgery
- Particle beams in medicine
  - Radiotherapy
  - hadrotherapy

Introduction to radiation

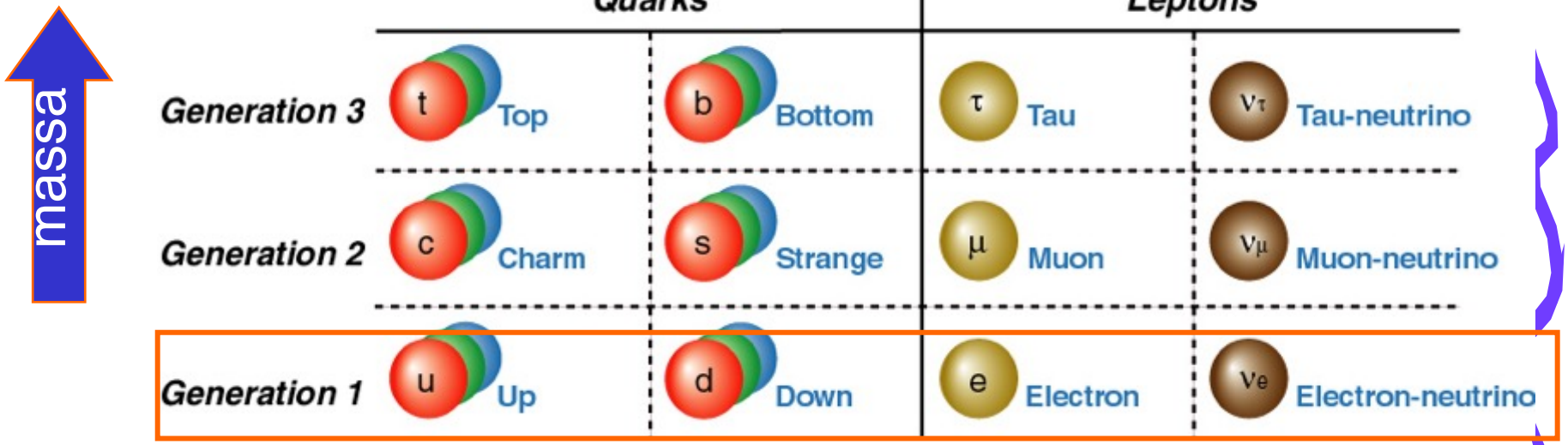
Which one ?

How does it interact with matter?

How is it generated?



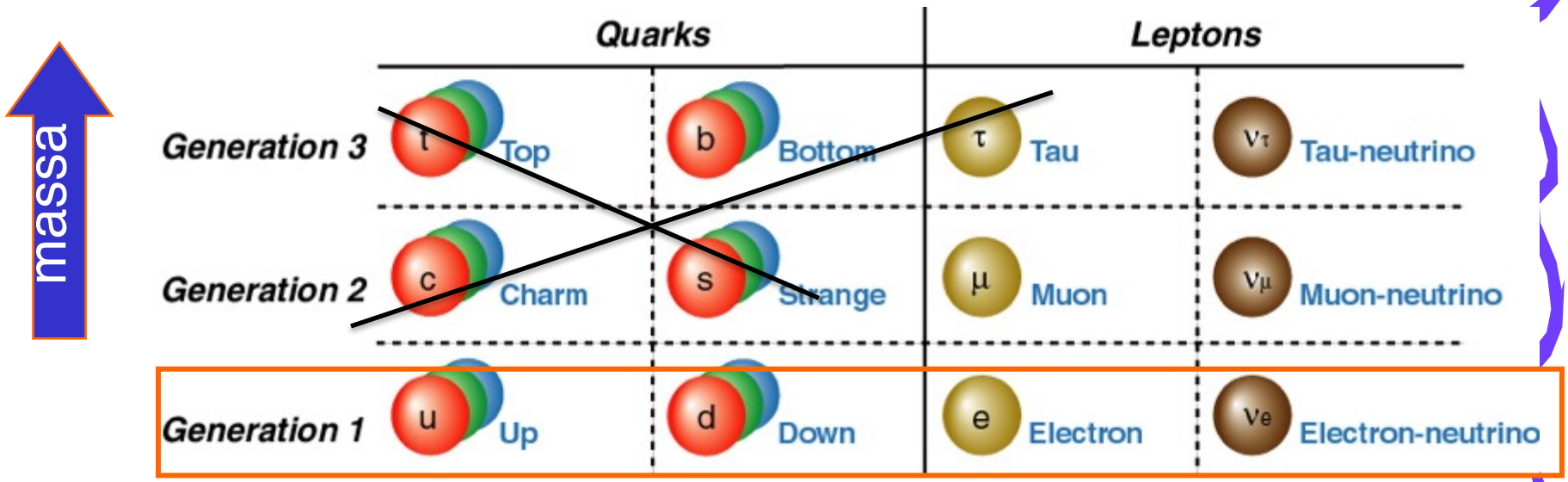
Possible particles



Materia ordinaria

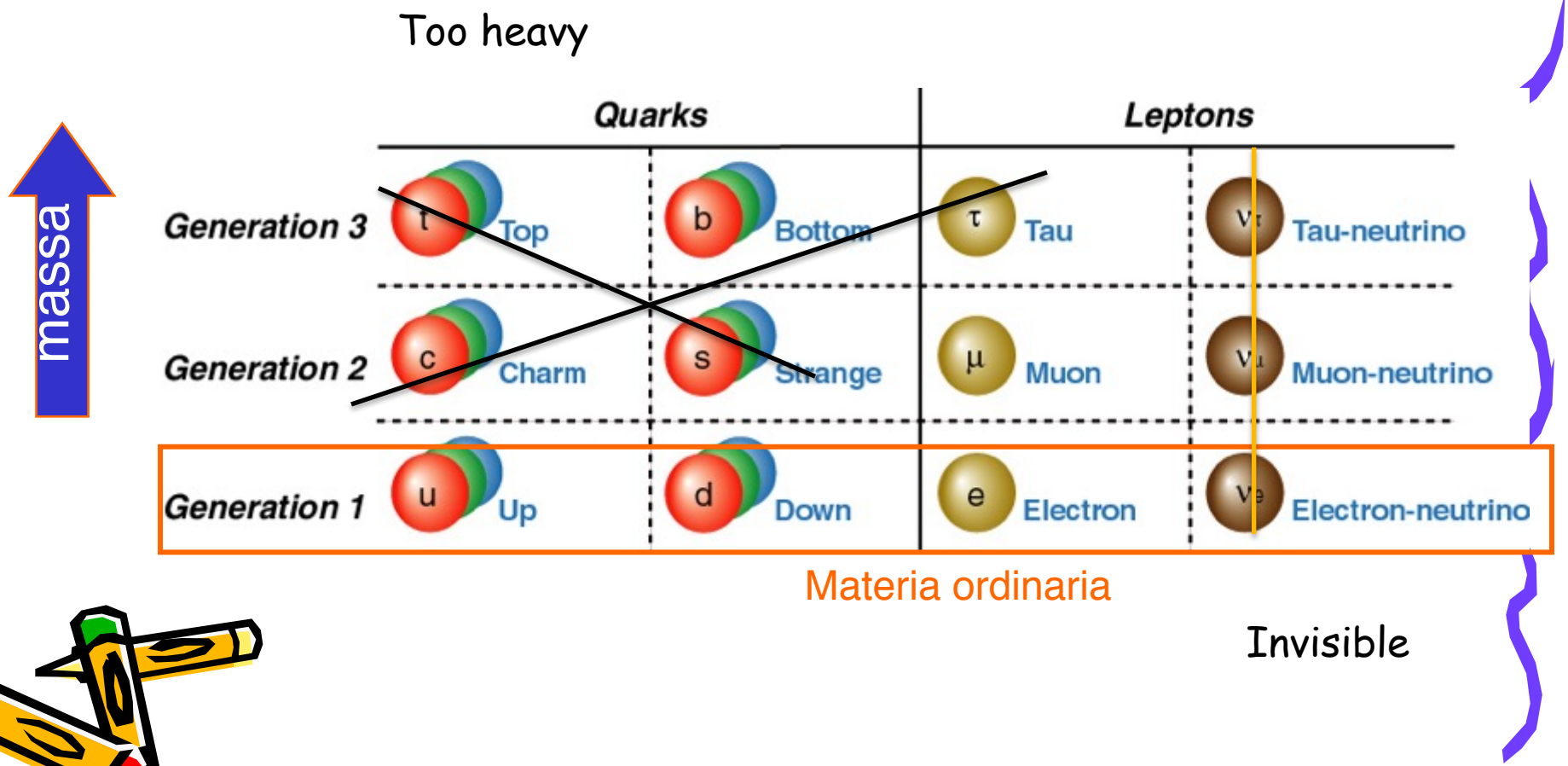
Possible particles

Too heavy and unstable



Materia ordinaria

Possible particles



Introduction to radiation

Which one ?

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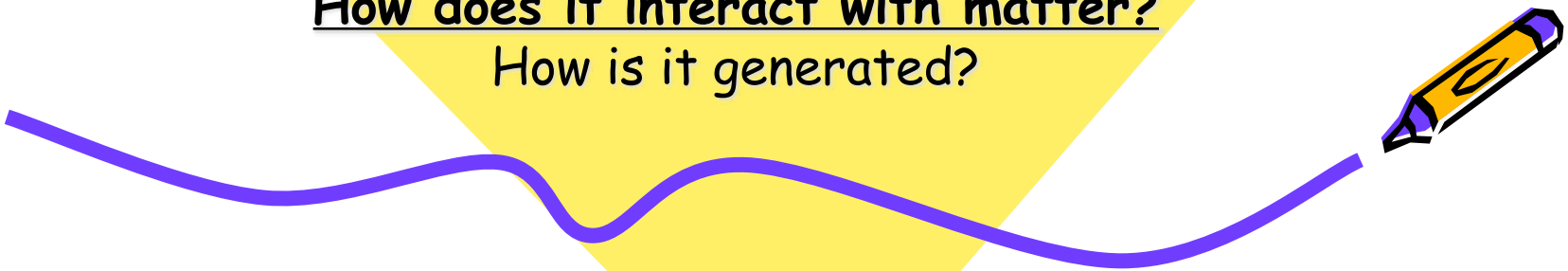


Radiation of interest

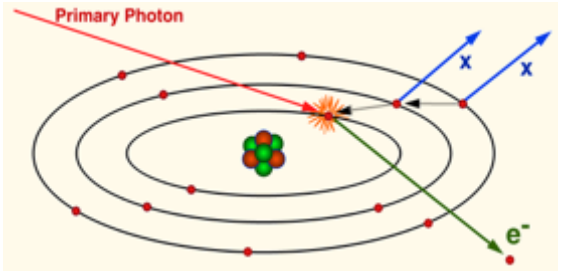
Neutral particles:
High penetration before interacting
Gamma rays: produce electrons
Neutrons: produce low energy protons → more "aggressive"

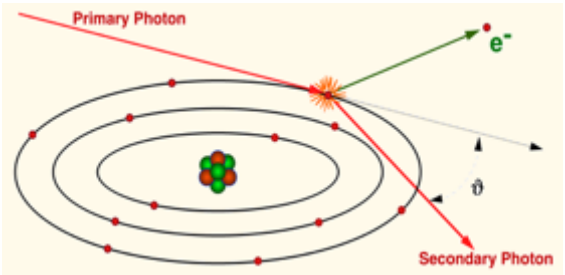
positrons: positrons annihilate with e- and produce 2 photons that escape patient and interact outside

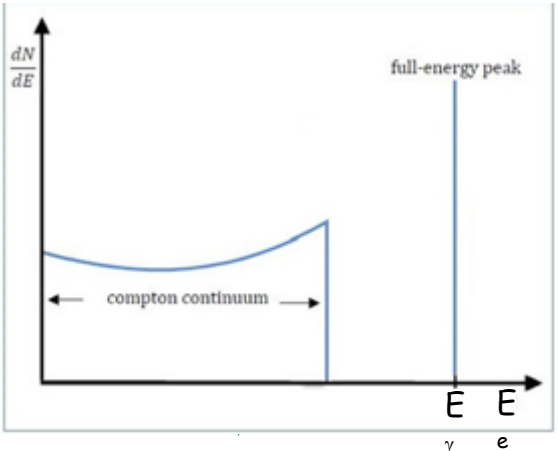
Other charged particles (electrons, protons, ions):
low penetration, short path, depending on energy

gamma- matter interactions

Gamma rays







- Photoelectric effect

  Emission of electron with same energy as impinging photon

- Compton scattering

  Only part of the energy is transferred to an electron

  → photon "remnant" with lower energy and different direction

- Pair production

$\gamma\gamma \rightarrow e^- e^+$ (only if $E_\gamma > 2m_e$)

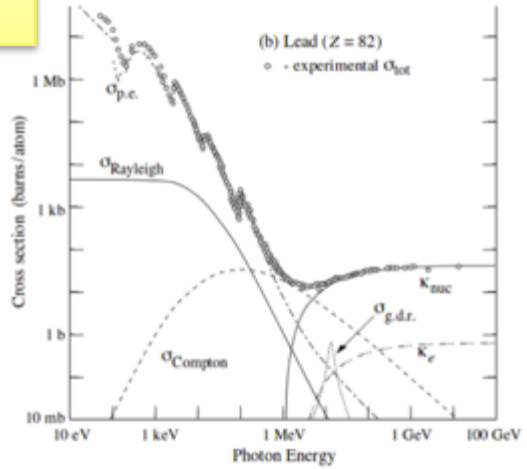
gamma-matter interactions (II)

A photon survives unchanged until it interacts → then it transforms

Photon beam attenuates exponentially

$$N(x)=N(0)e^{-\mu x}=N(0)e^{-n\sigma x}$$

μ=coefficiente di attenuazione
σ=sezione d'urto
n= # atomi per unita' di volume

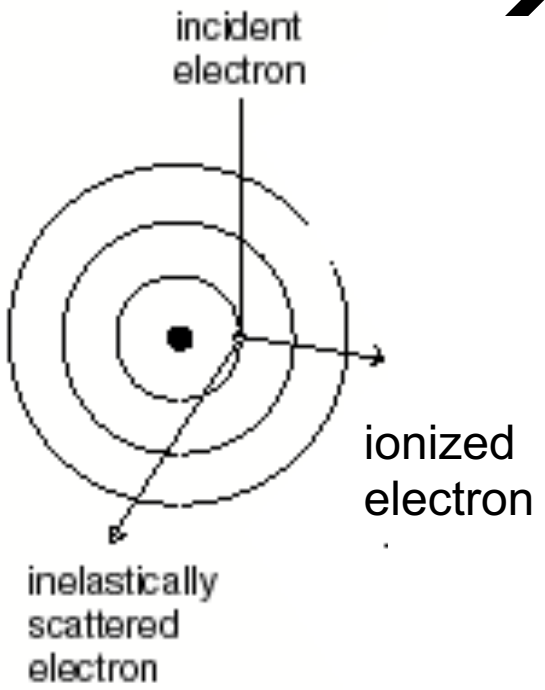


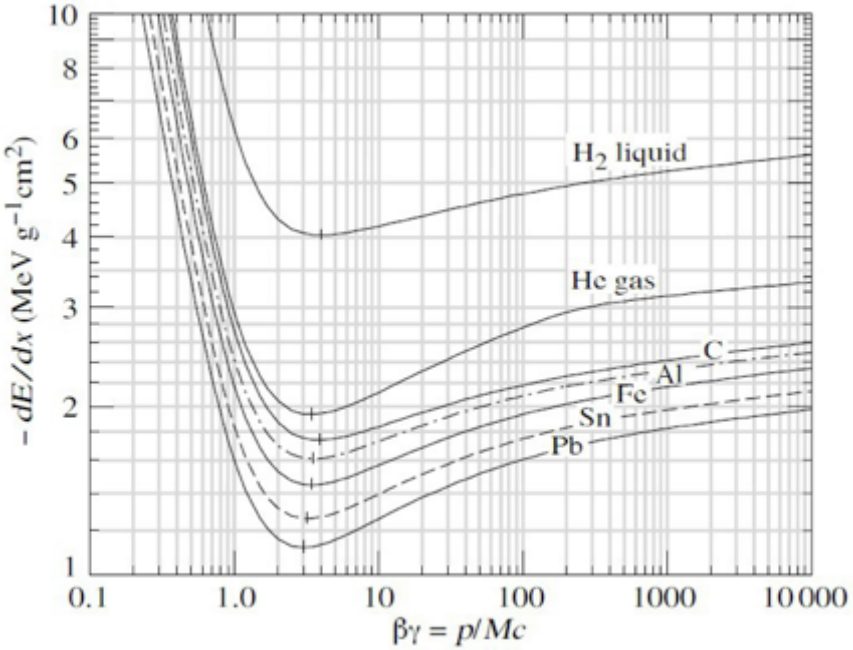
$\sigma_{tot}=\sigma$(p.e.)+
σ(compton)+
σ(pair)

Charge particles-matter interactions

Dominant interaction: ionization

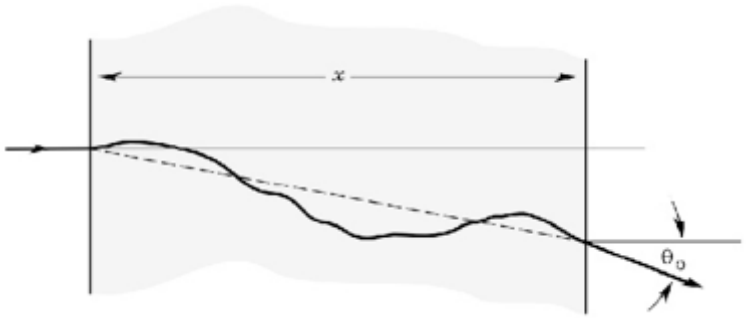
➔ continuous release of until particle stops

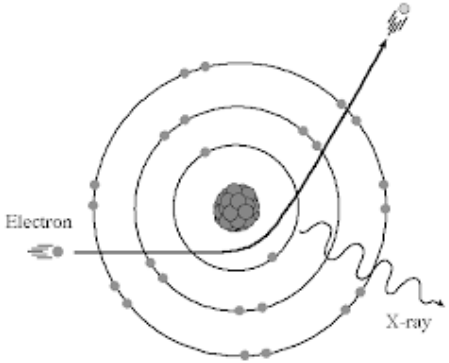


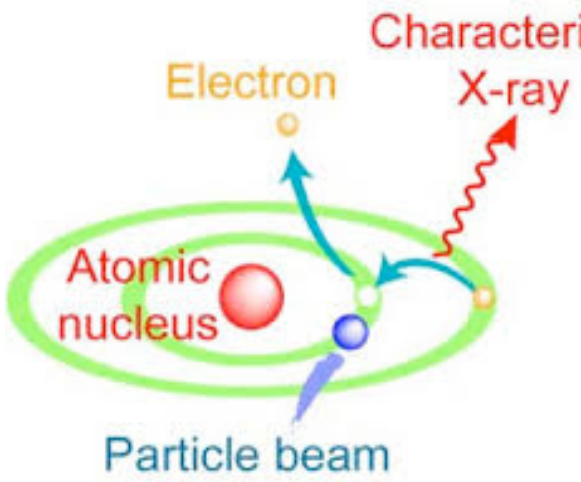


Multiple scattering

- Particles can also scatter on nuclei:
  - No energy loss
  - Angular deviation
- When traversing a thick material multiple scatterings occur

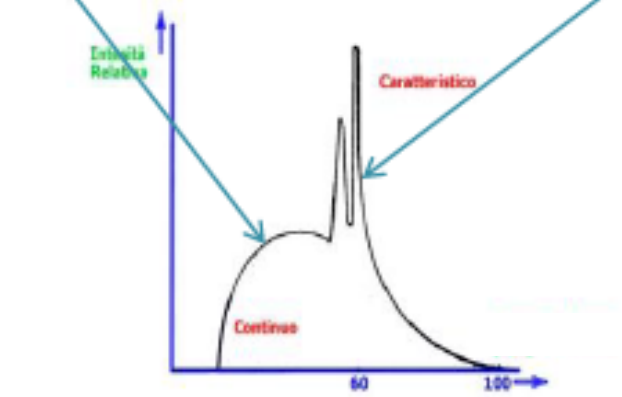






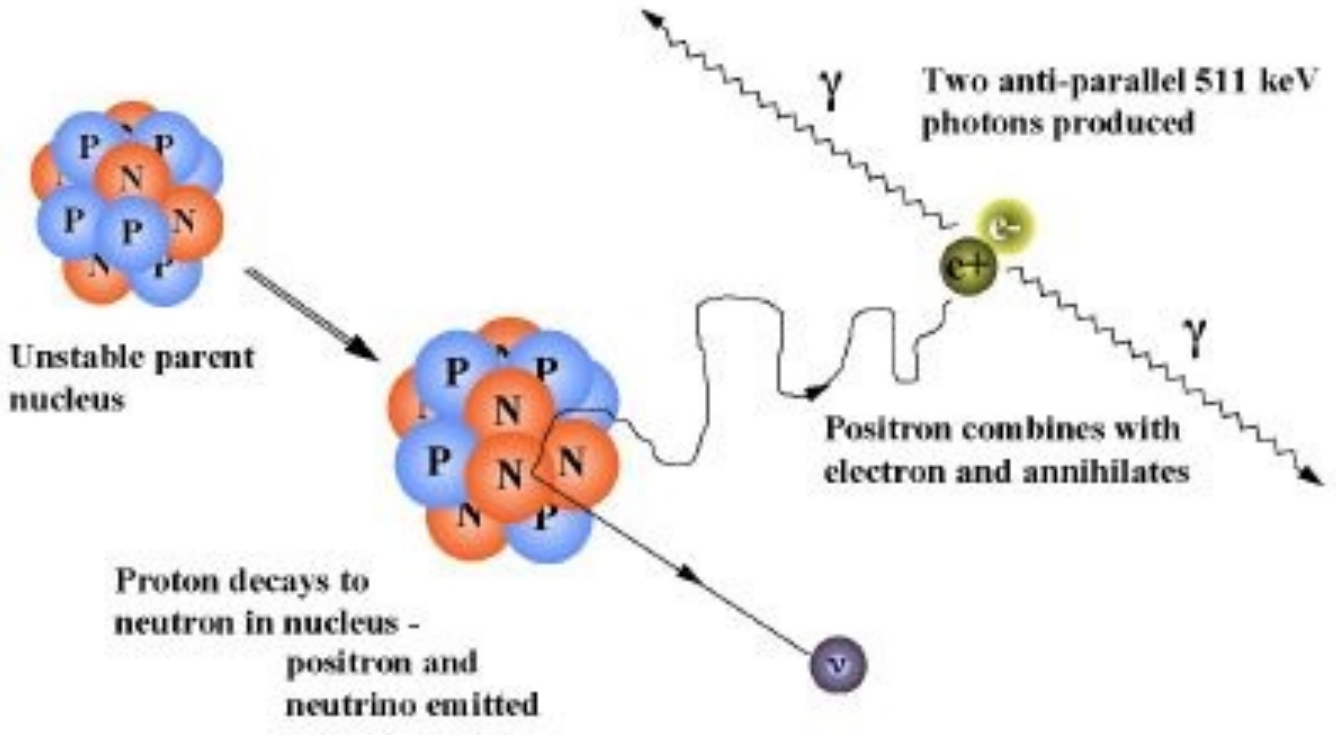
Bremsstrahlung → **Spettro continuo**

Diseccitazione → **Spettro caratteristico**



E_X[keV]

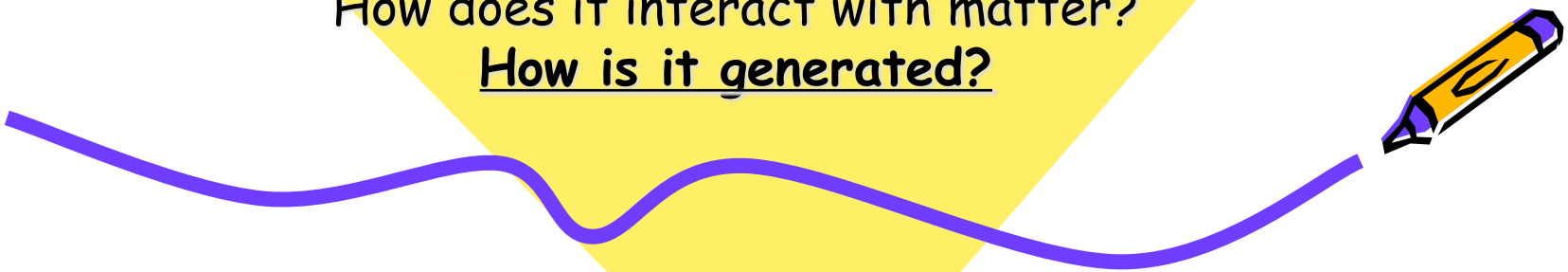
positron-matter interactions



In 80% of the cases there are two back-to-back mono-energetic photons

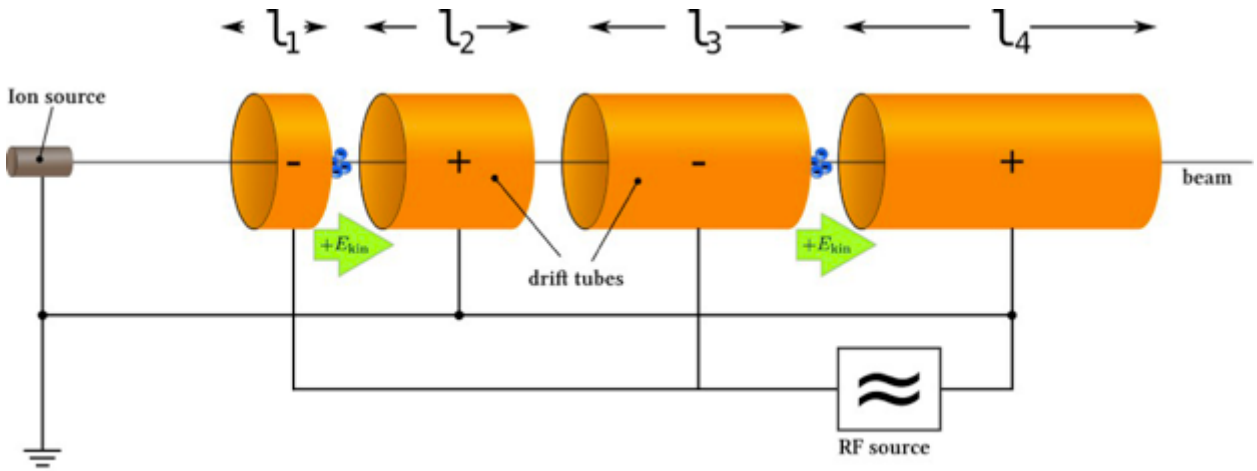
Introduction to radiation

Which one ?
How does it interact with matter?
How is it generated?

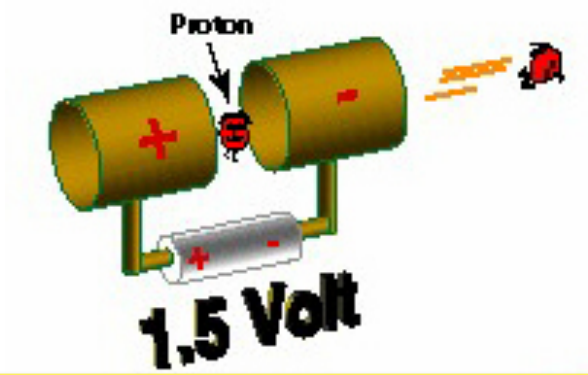


Accelerators: LINAC

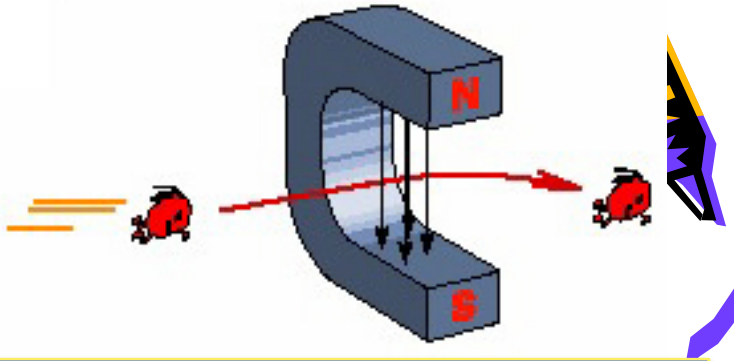
Used in medicine for electrons up to few MeV



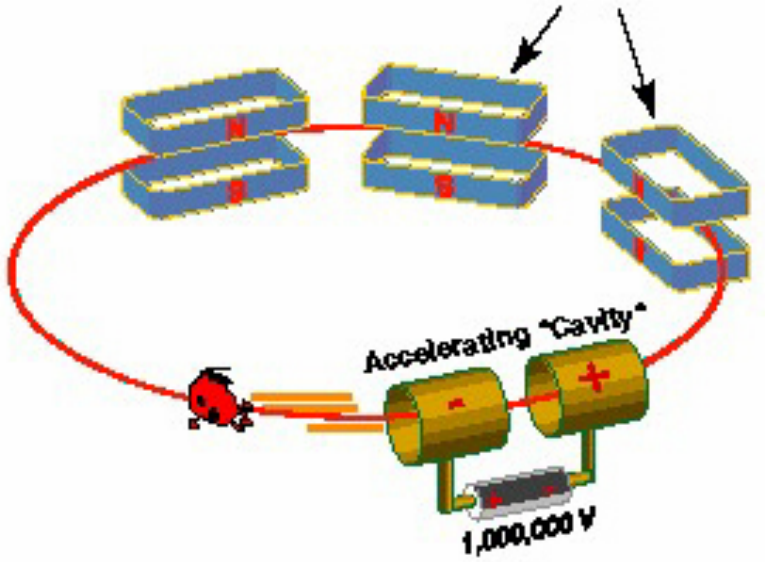
Accelerators: working principle



Accelration: electric field



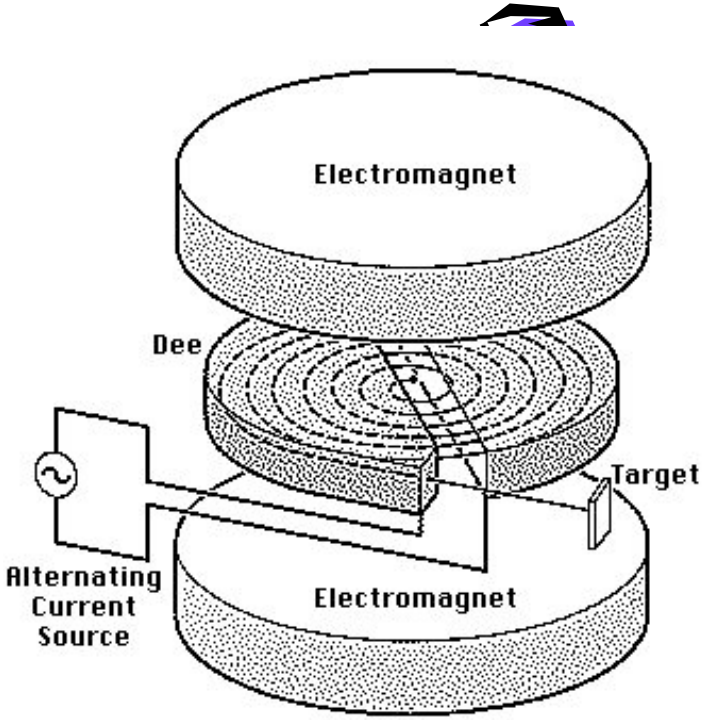
Bending: magnetic field

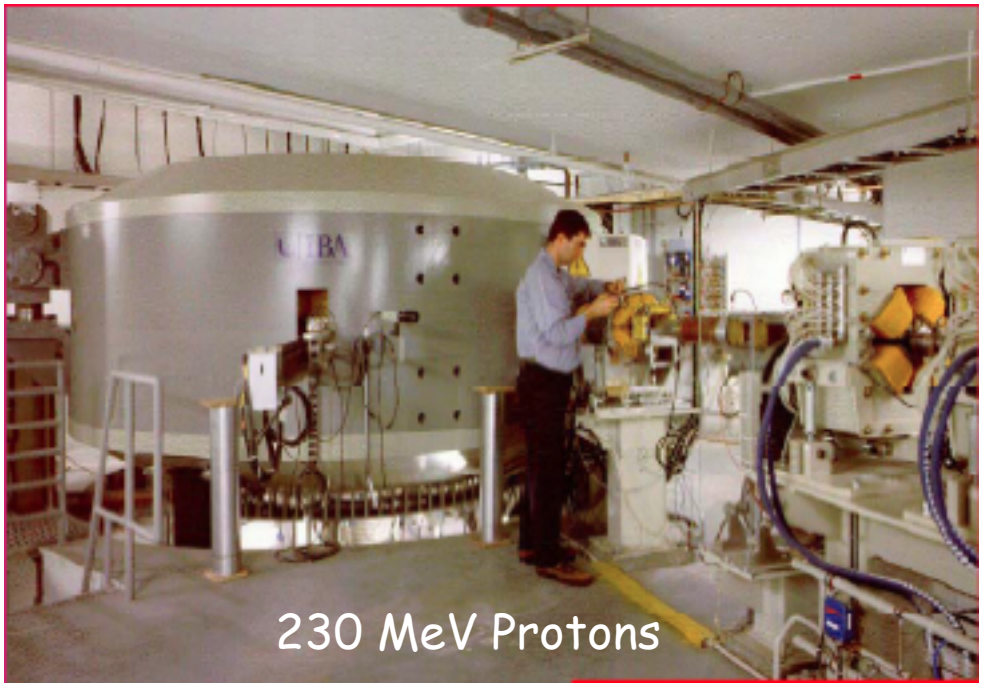


Accelerators: CYCLOTRON

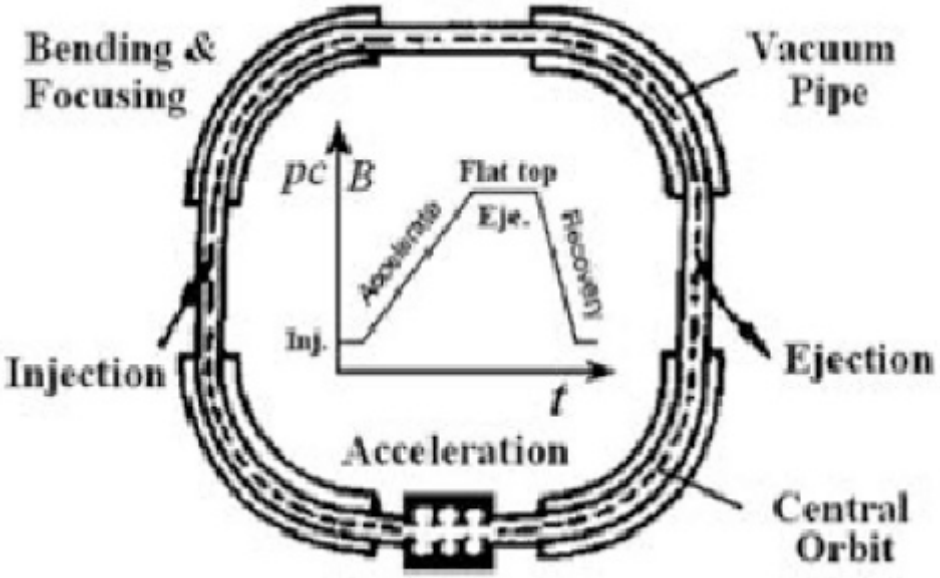
Used to accelerate protons/ions

- 10-30 MeV for radio-isotope production
- Up to 200 MeV for radio-therapy





Accelerators: syncrotrons

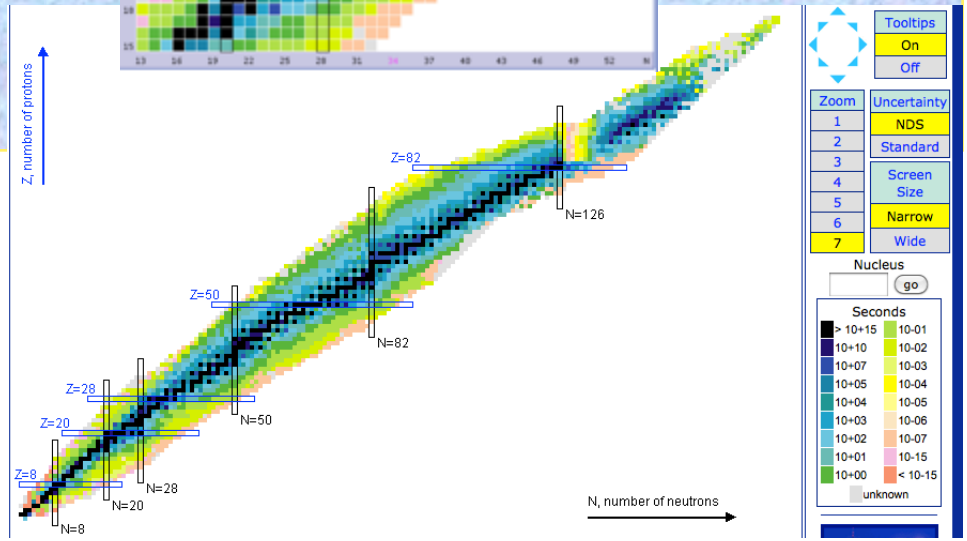


Accelerate protons/carbons for therapy up to 4800 MeV

Decadimenti nucleari

Possiamo classificare i diversi modi di emissione radioattiva di un nucleo instabile nel seguente modo:

- **Interazione nucleare forte**
  - Radioattività α
  - Radioattività da protoni o neutroni differenziati
  - Fissione spontanea
- **Interazione nucleare debole**
  - Radioattività β
  - Cattura elettronica (EC)
- **Interazione elettromagnetica**
  - Isomeria nucleare

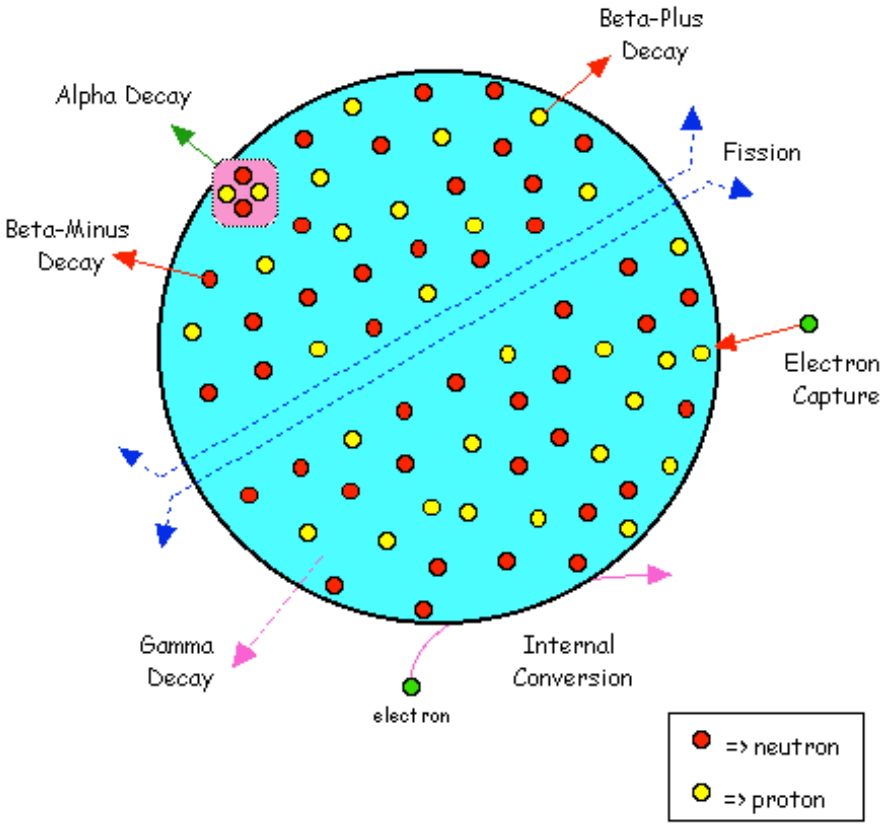


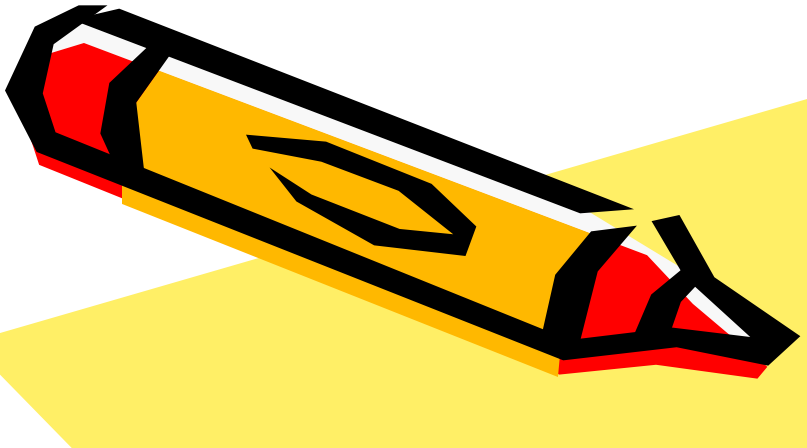
Radio-isotopes

Unstable nuclei that decay

Produced:

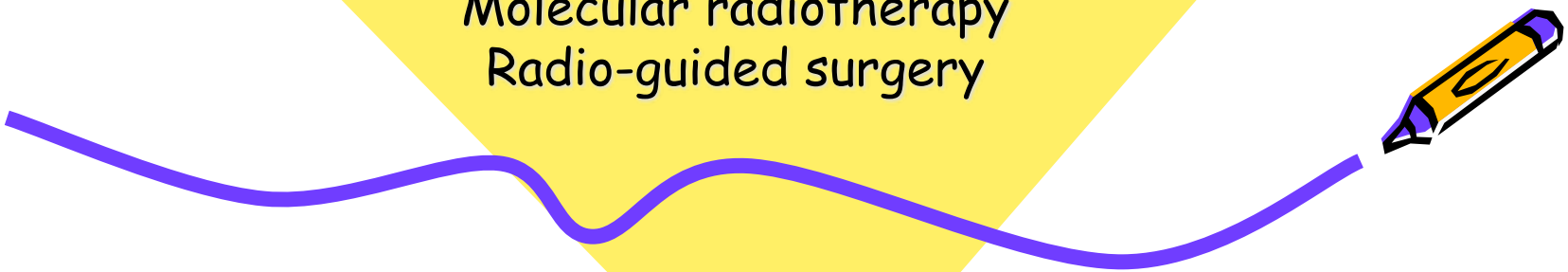
- by strong reactions (bombardment of stable nuclei with protons)
- as remnants from reactors





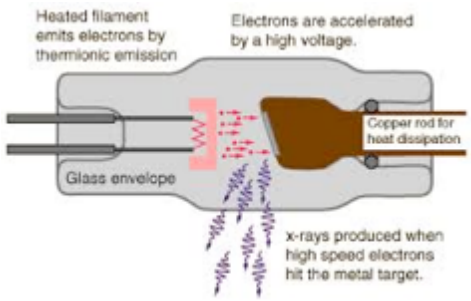
Diagnostics and Nuclear Medicine

Diagnostics (radiography, SPECT, PET,…)
Molecular radiotherapy
Radio-guided surgery

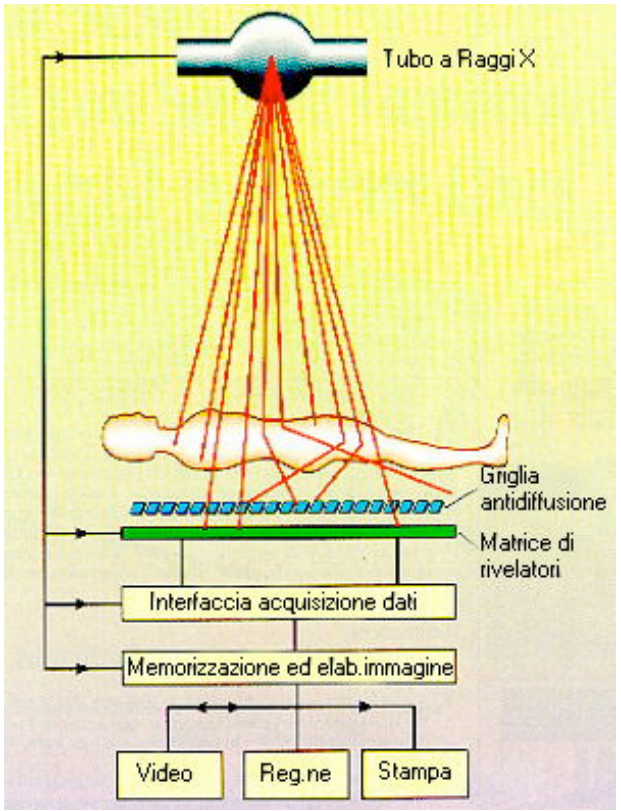


Diagnostics

- Two major categories:
  - Morphologic: sensitive only to densities
    - Radiography
    - TAC
    - ultrasound, …
  - Functional: sensitive to organ functionalities
    - PET
    - SPECT
    - …



Diagnostics: radiography



- X-rays produced with a cathodic tube by Bremsstrahlung
- Interaction between matter and patient
- X-ray detection

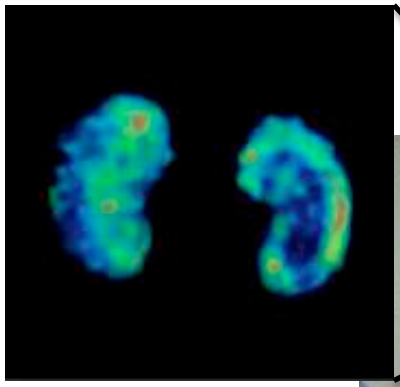
X-rays

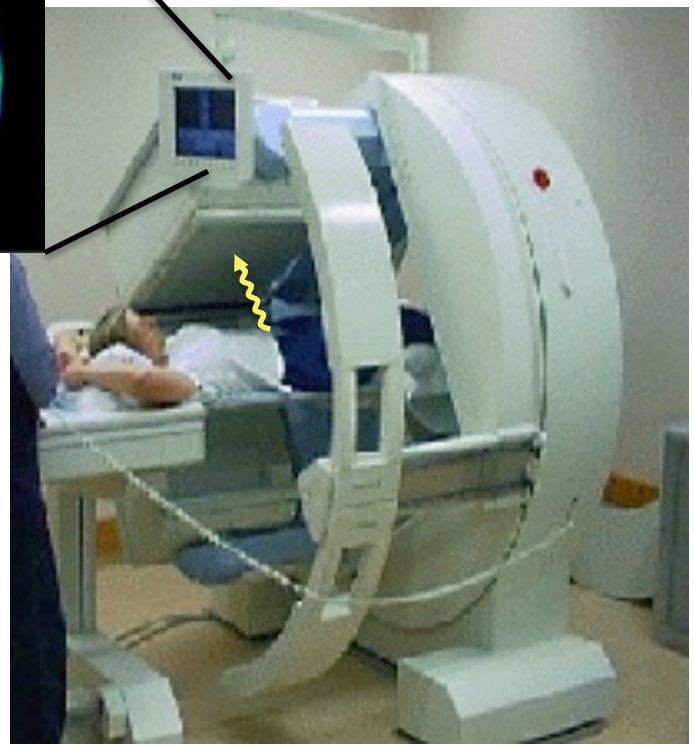
Radio-nuclides for imaging

- Administer, to patient (either systemically or locally) a drug which:
  - the tumor/organ of interest takes up significantly more than the rest.
  - is linked to a radio-nuclide that emits particles via nuclear decay
- Wait for the drug to diffuse
- Measure the emitted radiation and obtain information

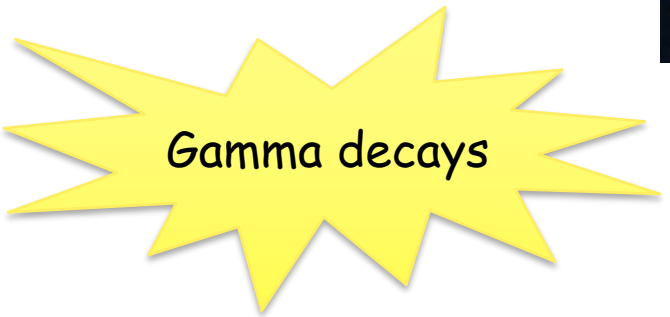
Diagnostics: SPECT

Single Photon Emission Computerized Tomography



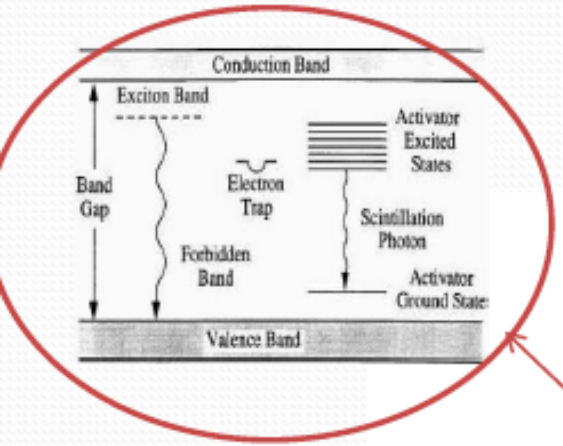


- Inject radionuclide (typically ^{99}Tc but also ^{131}I)
- Decays with single photon
- Detection ~50cm from source with anger camera



Detection principle

CRISTALLO SCINTILLANTE + TUBO FOTOMOLTIPLICATORE (PMT)



Raccolta di γ di scintillazione e trasmissione al PMT

Luce convertita in elettroni tramite effetto fotoelettrico e successiva elettromoltiplicazione

scintillatore

γ

uscita

Analisi del segnale raccolto attraverso un sistema elettrronico

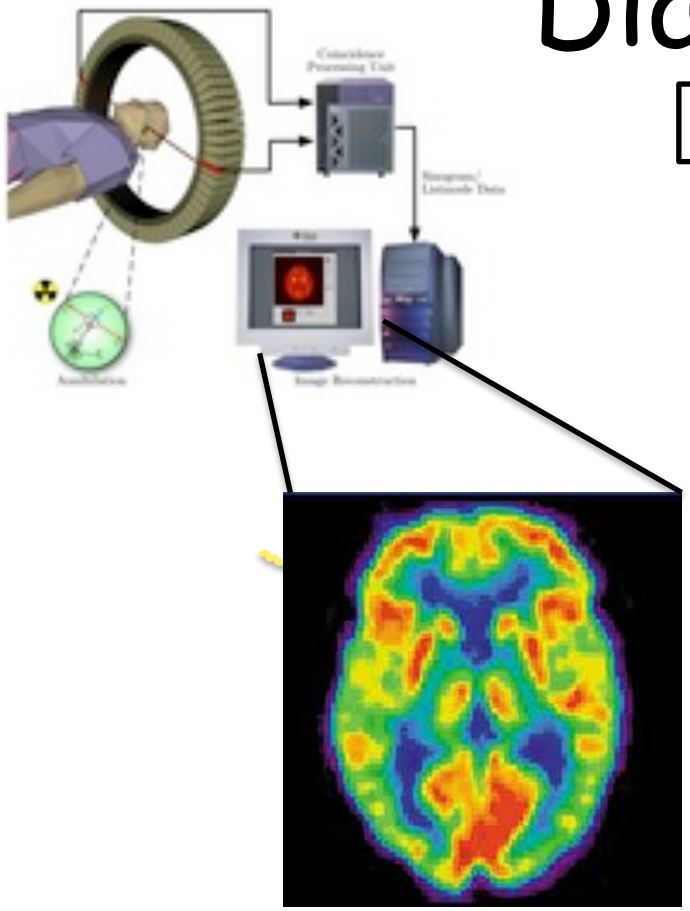
Tubo fotomoltiplicatore

Cessione di energia di γ nel cristallo tramite effetto Fotoelettrico o Compton

Eccitazione di atomi e molecole dello scintillatore che diseccitandosi emettono luce

Diagnostics: PET

Positron Emission Tomography



- Inject radionuclide (^{18}F in FDG, FET, 11C in methionine, choline)
- β+ decay
- Detect the two gammas in coincidence outside patient

Beta+ decays

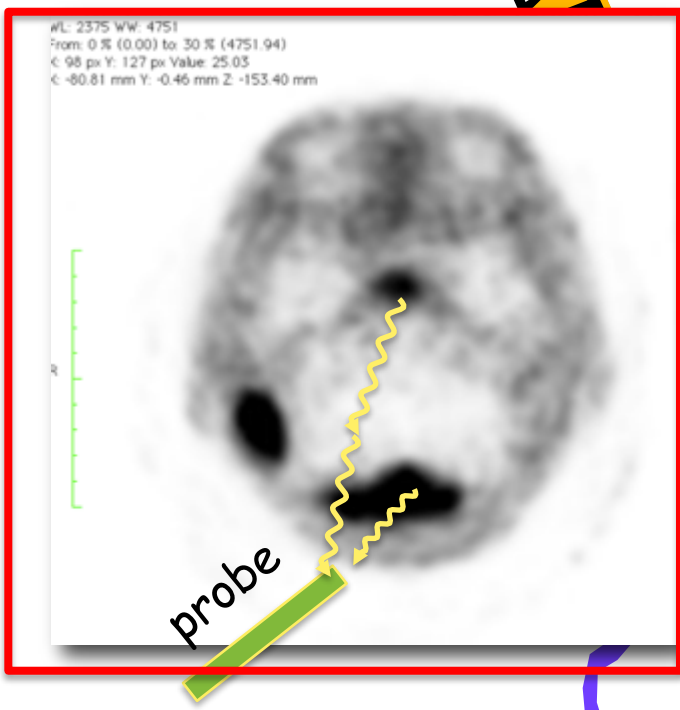
Radio-guided surgery

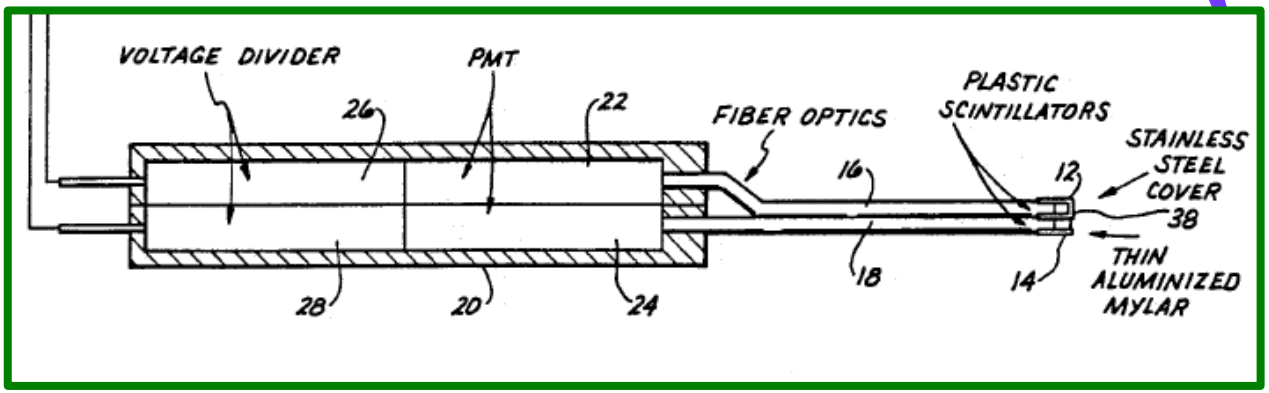
- Administer, before operation to patient (either systemically or locally) a drug which:
  - the tumor takes up significantly more than the healthy tissue.
  - is linked to a radio-nuclide that emits particles via nuclear decay
- Wait for the drug to diffuse to the margins of the tumor
- Start operation
  - Remove the bulk of the tumor
  - Verify with a probe that detects the emitted particles the presence of:
    - Residuals
    - Infected lymph nodes

Radioguided surgery

Three approaches

- Gamma: well established, e.g. sentinel lymph-node
- Beta+: based on the dual probe approach
- Beta-: future fronteer





LIMITS OF γ-RGS

140 keV photons

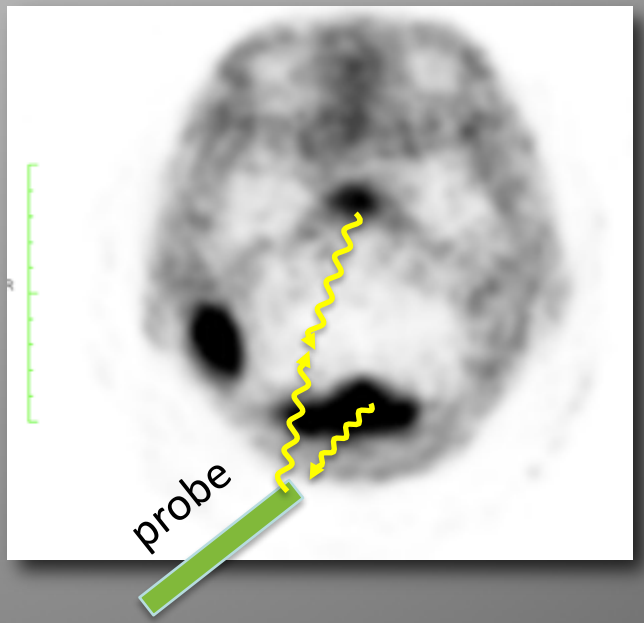
➔ attenuation in body ~8cm

Long range of gamma's involve:

- exposure of medical personnel
- Background from healthy organs

Difficult to apply in:

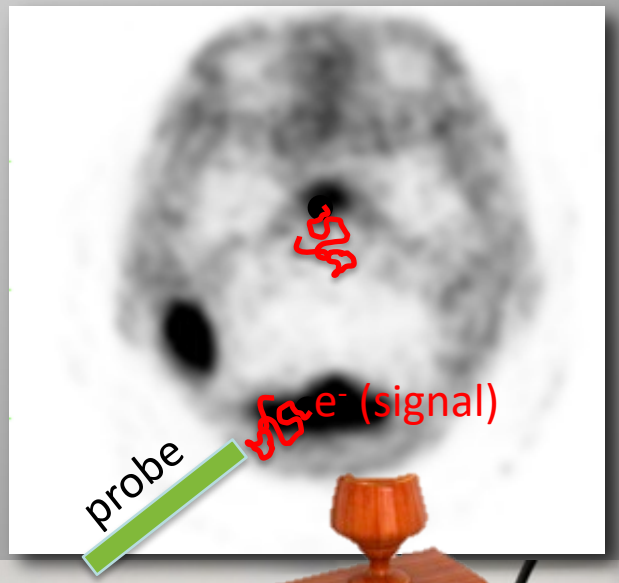
- Brain tumors
- Abdominal tumors
- Pediatric tumors



A CHANGE IN PARADIGM

- 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
    - reduced effect of nearby healthy tissues
    - Reduced dose to medical staff

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



NOTE: only detection at contact is possible

EXTEND RGS TO MORE CLINICAL CASES

The probe prototype

Compact, easy to handle, local measurement

Simple technology:
- scintillating crystal
- Light sensor (SiPM)

Most stringent constraints:
- Mechanics
- electrical safety
- sterilization

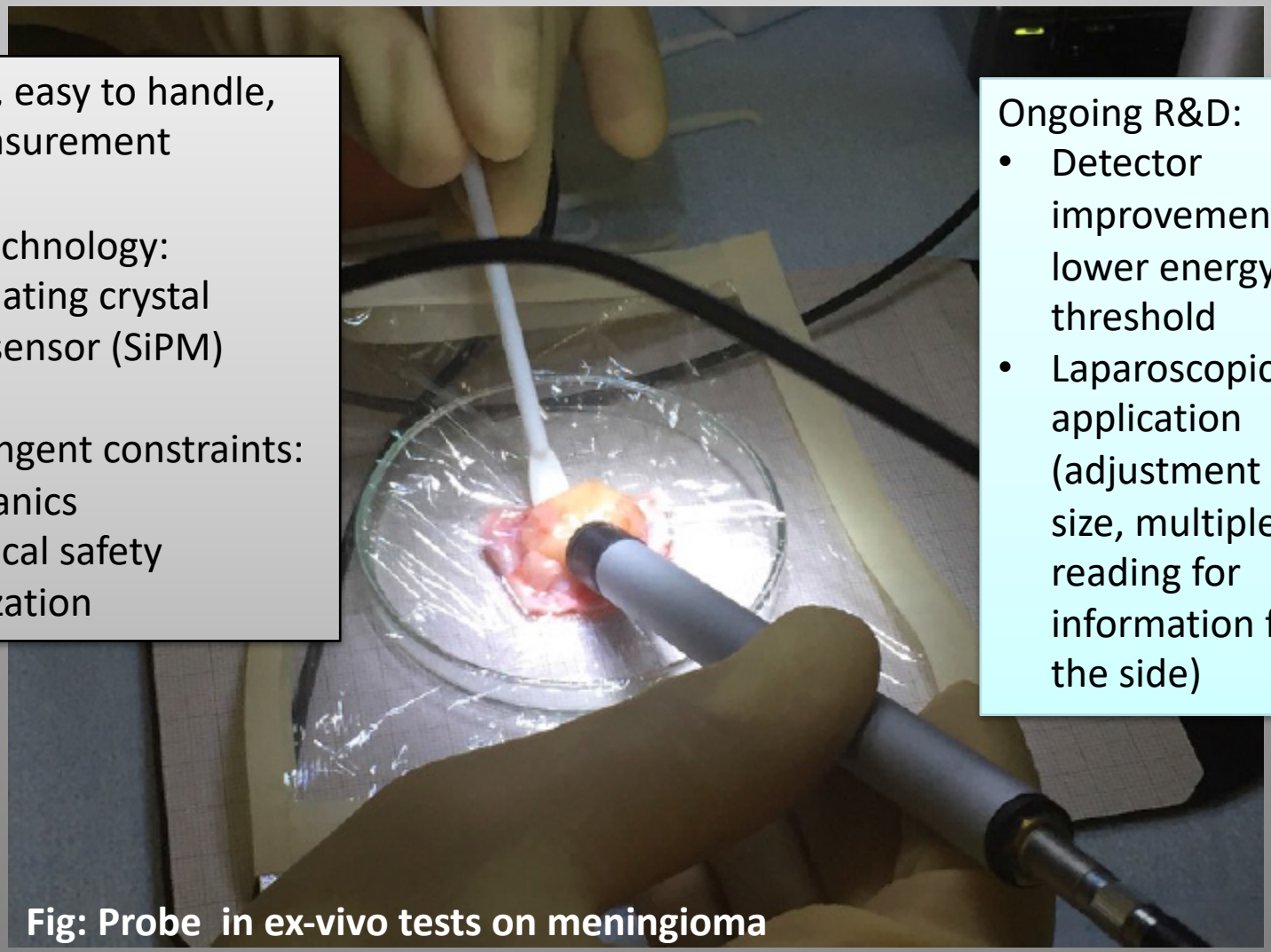
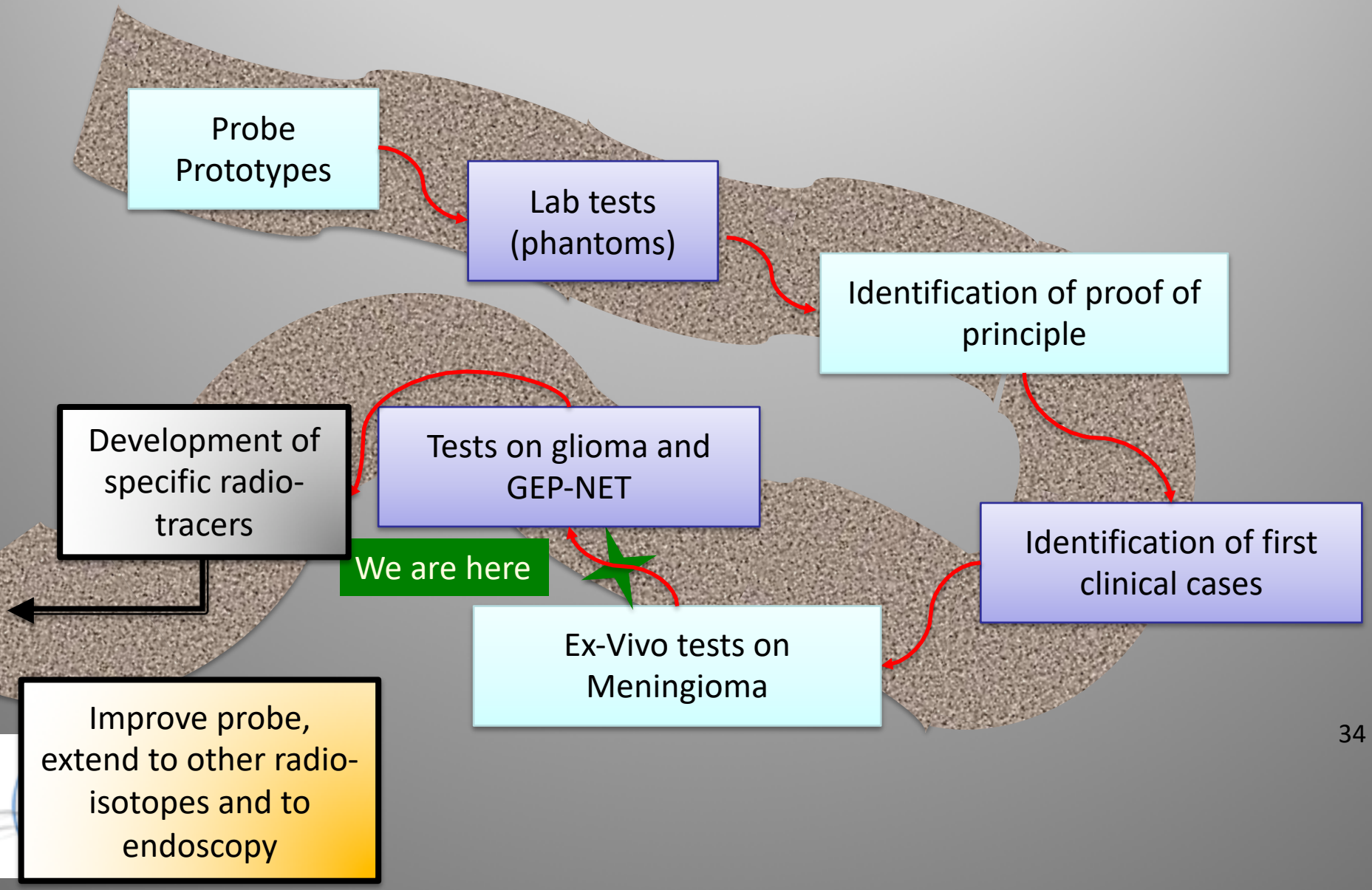


Fig: Probe in ex-vivo tests on meningioma

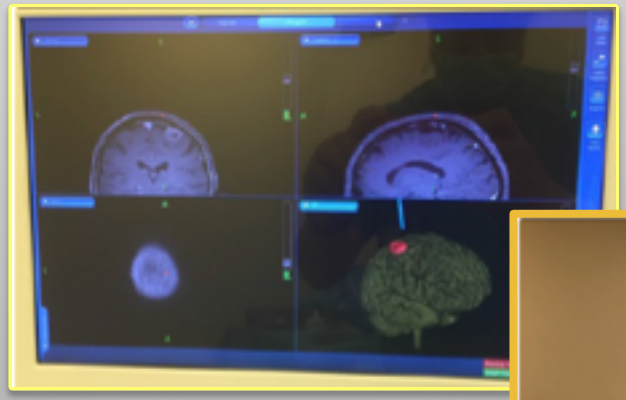
Ongoing R&D:
- Detector improvements to lower energy threshold
- Laparoscopic application (adjustment in size, multiple reading for information from the side)

RESEARCH PATH



E. Solfaroli et al., submitted to JNM

Ex-vivo test on meningioma

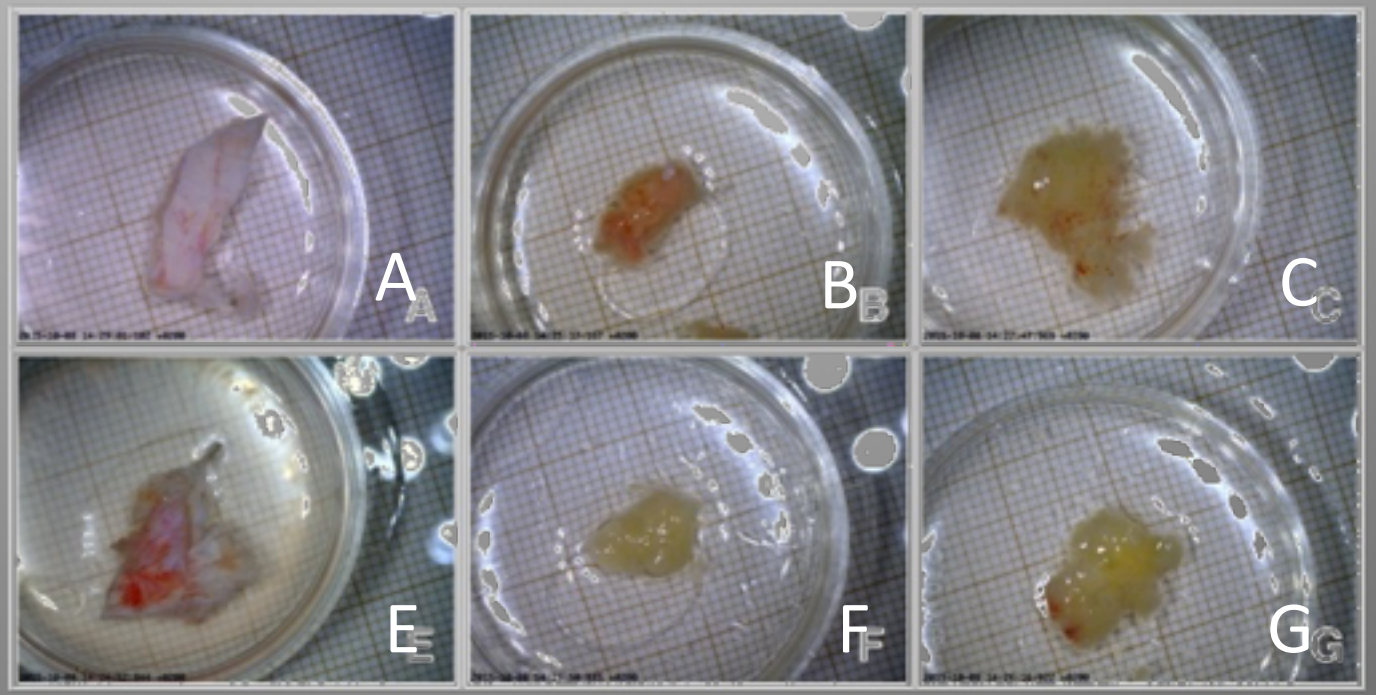


- PET with Ga68 on Sep 14th
  - Tumor SUV ~2g/ml (relatively low, but enough)
  - TNR ~ 14 (good)

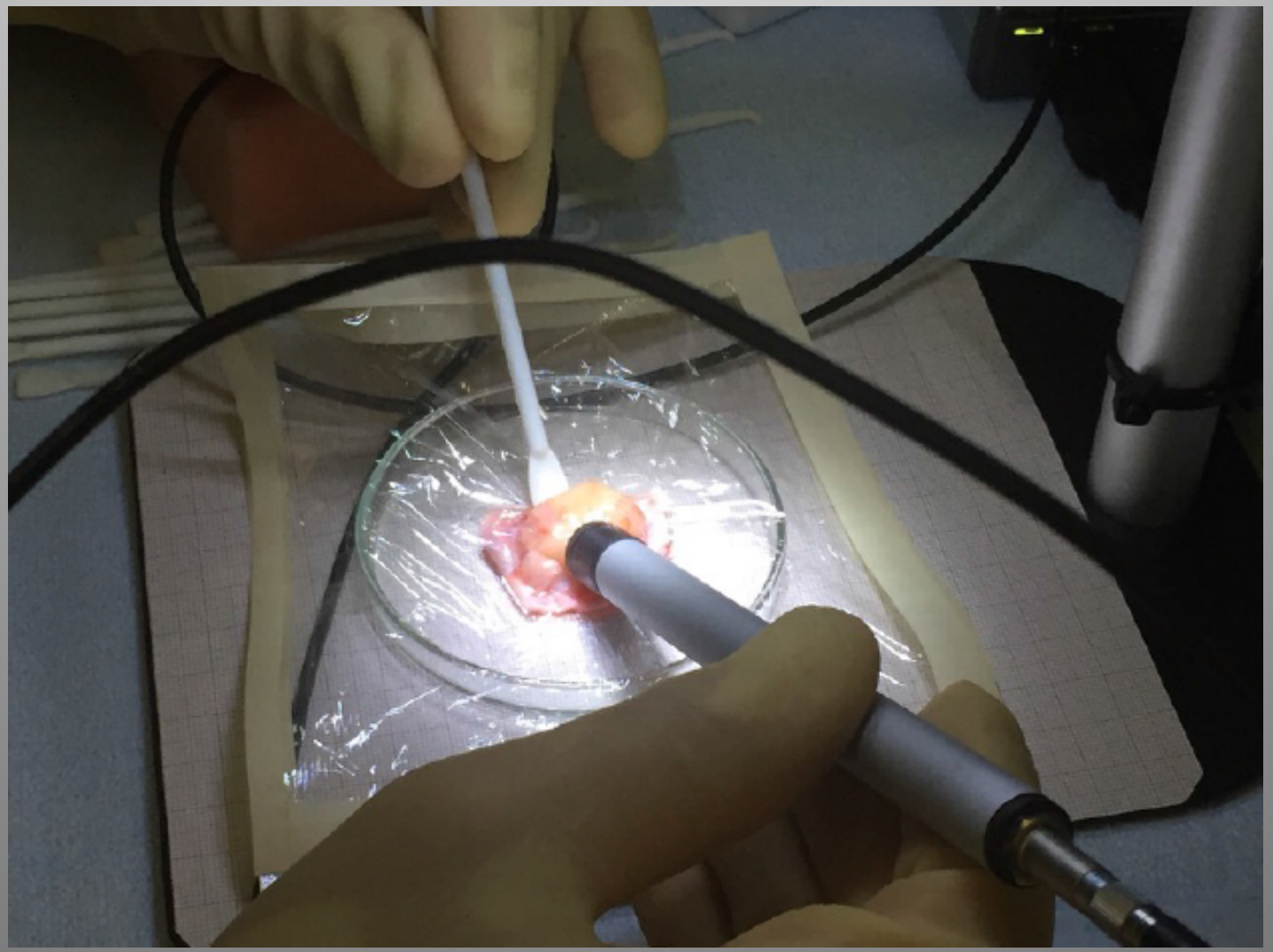
- 8mCi Y90—DOTATOC on Oct 9th
- Surgery on Oct 10th

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



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

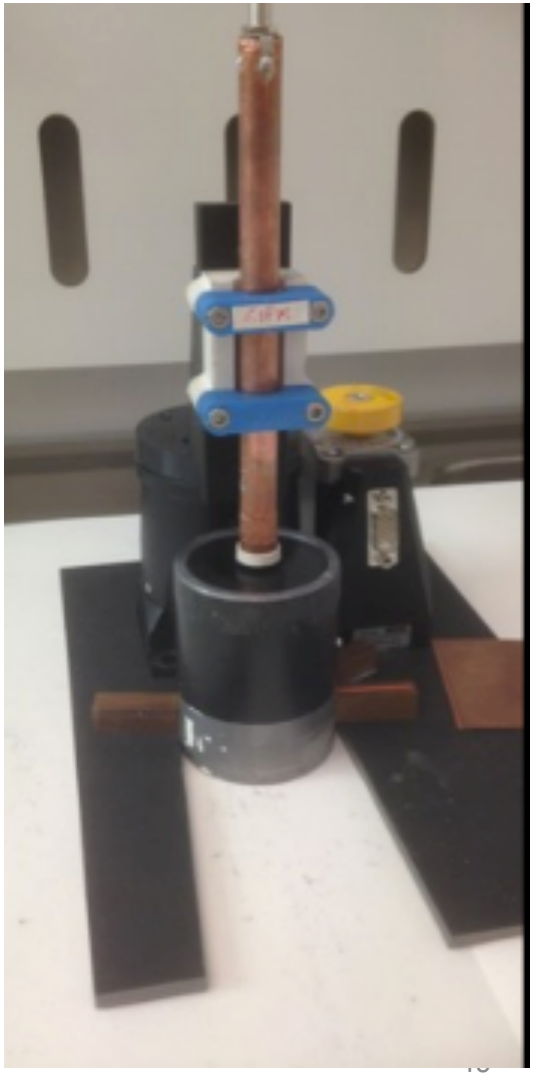
β^+ RGS: different isotopes

- ^{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 (II)

* 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

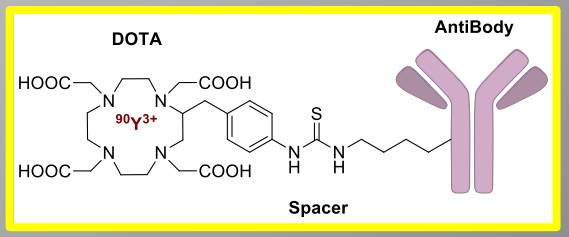
- OK with current probe
- High SUV and TNR required: improvements in γ rejection and energy threshold useful
- Significant improvements in γ rejection and energy threhold required

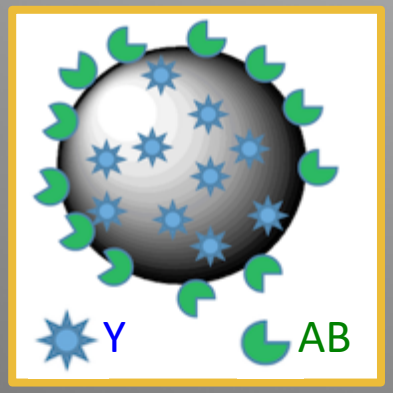
Extension to other tumors: new tracers

Mark existing tracers with Y90 or other beta- emitters. Examples of ongoing studies:

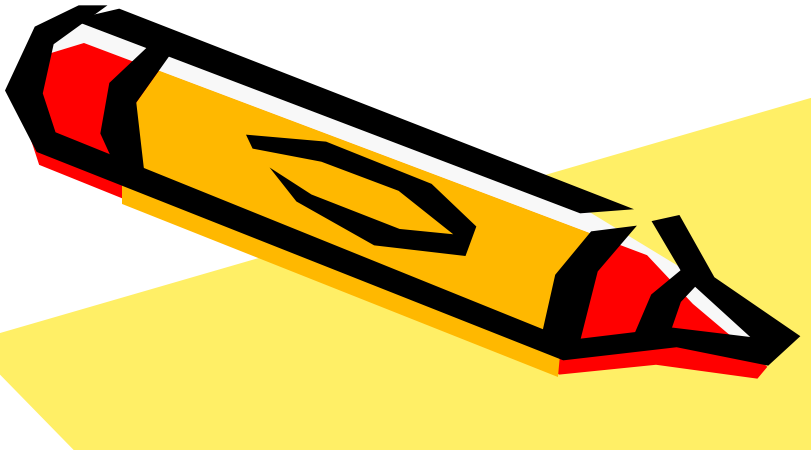
- Monoclonal antibodies

  (NIMOTUZUMAB) for EGFR receptors
- MIBG





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



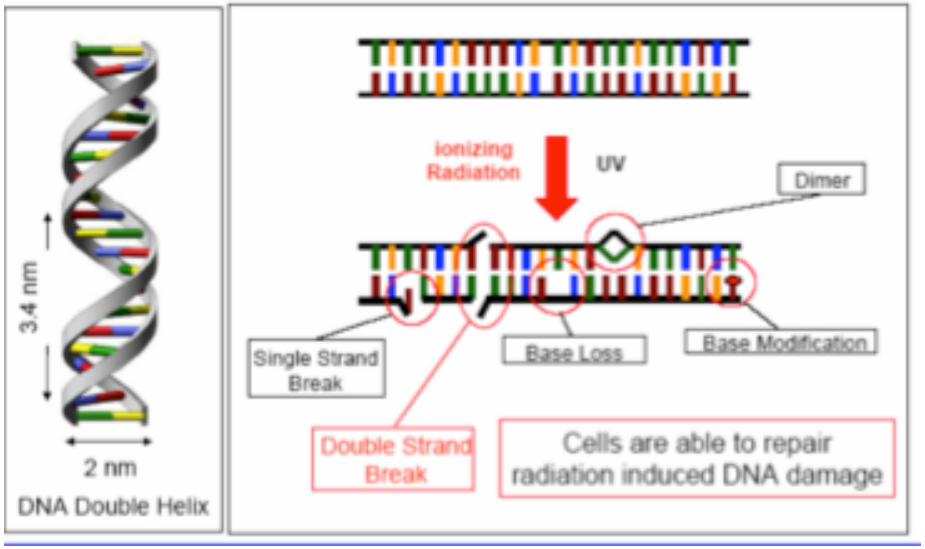
Radiotherapy

From conventional to Hadrotherapy

Radiotherapy

Goal:

- Deliver energy on tumor cells in order to break them in an irreparable way

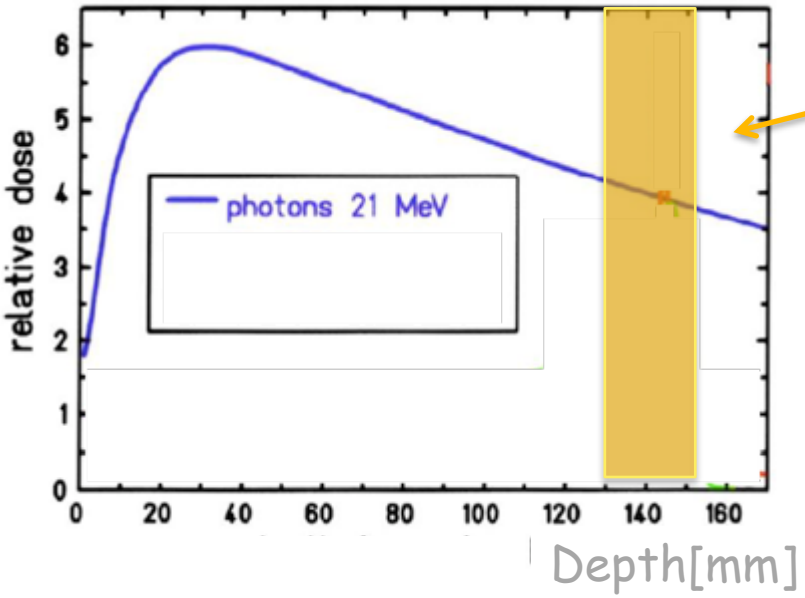


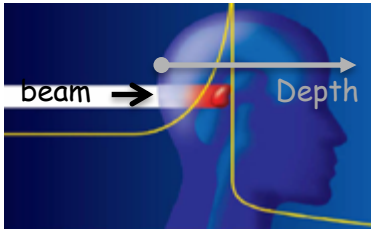
Large dE/dx
➔ DNA breaks irreparably

Moderate dE/dX
➔ chemical reaction due to free radicals

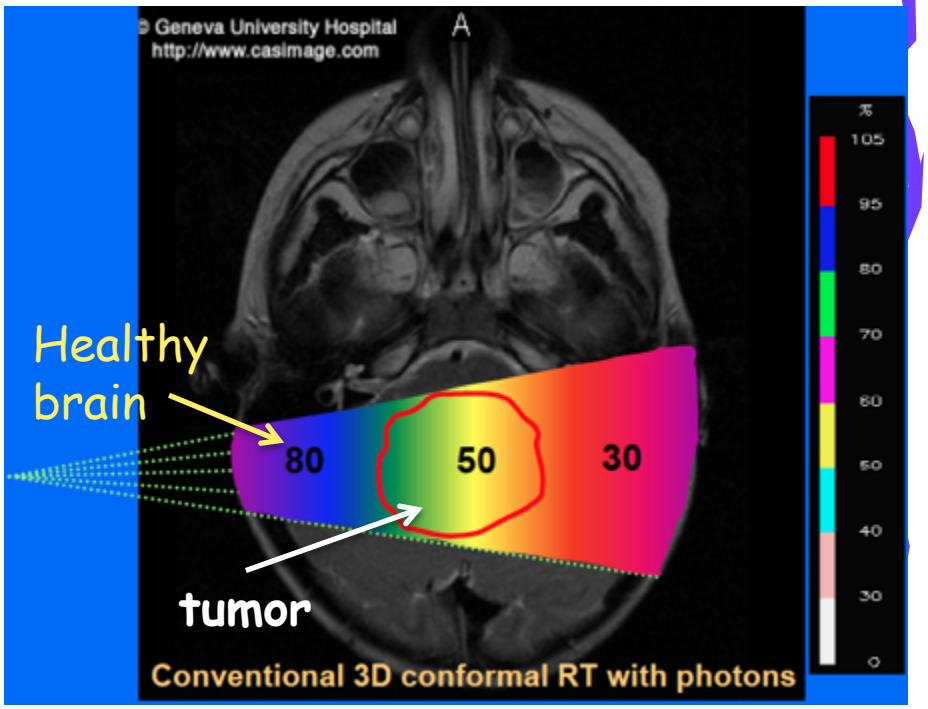
Conventional radiotherapy

Photon beams on patient

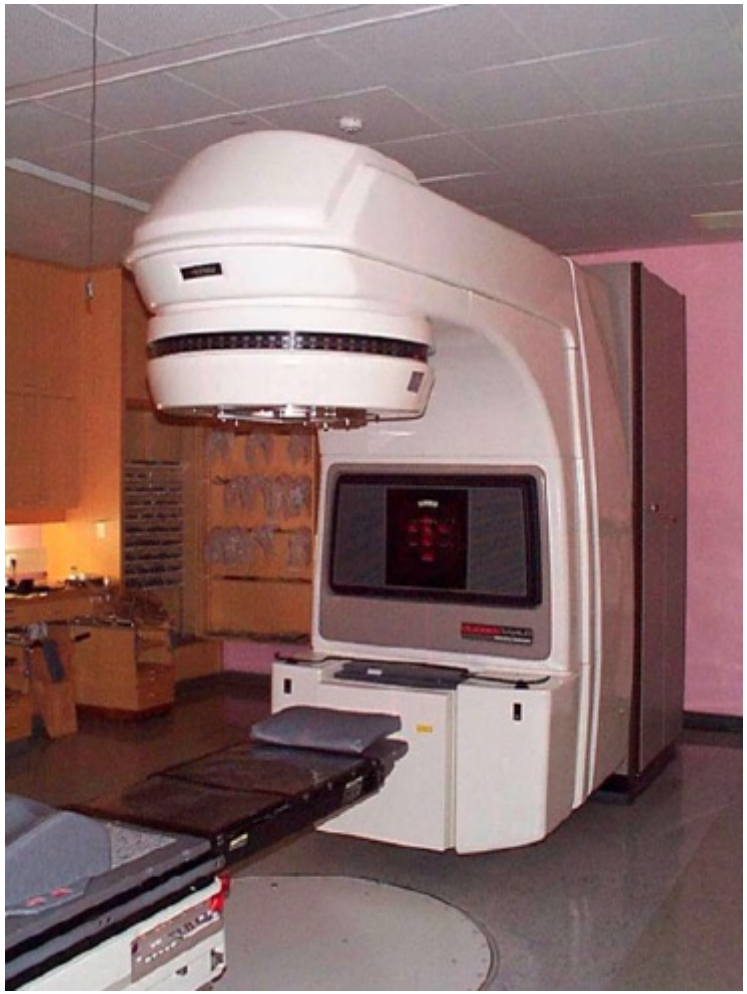


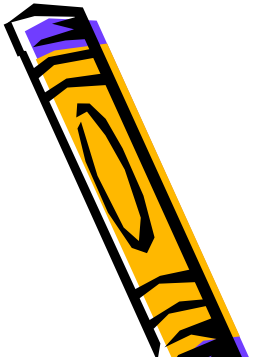


Large release of energy outside tumor

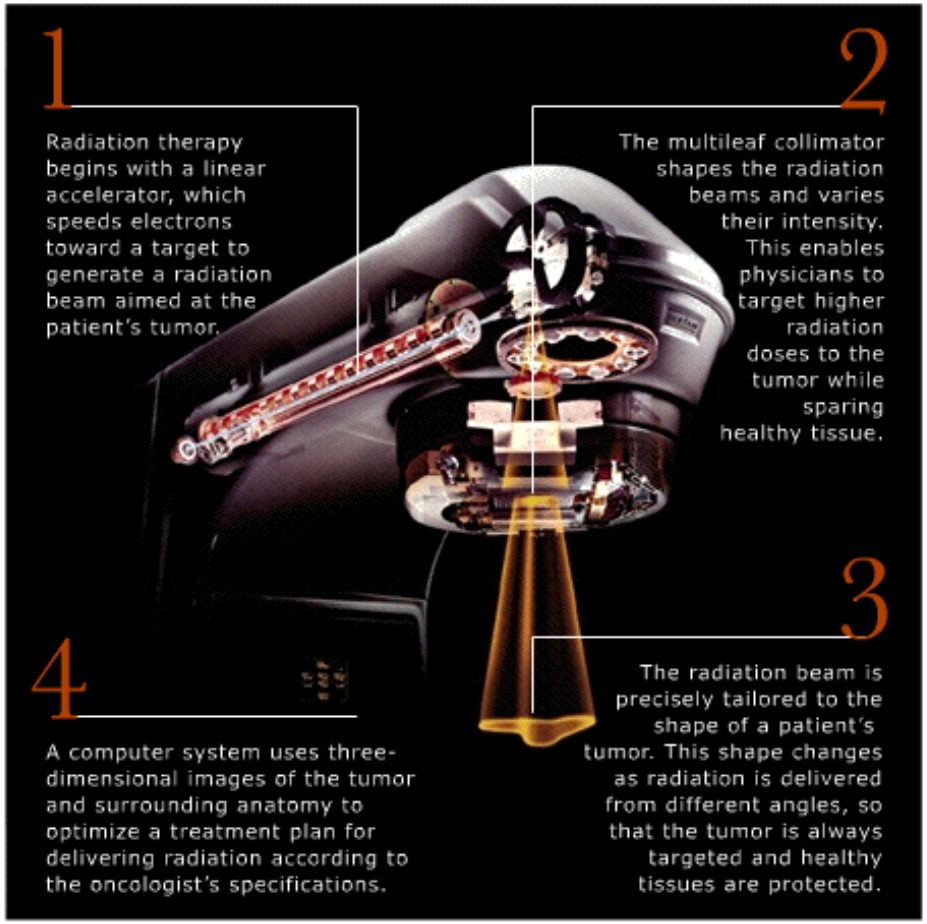


Radiotherapy LINAC



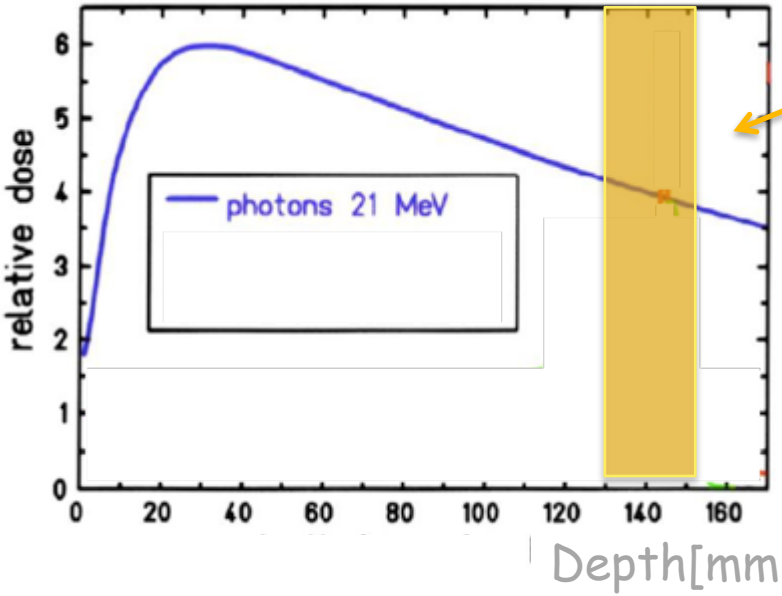


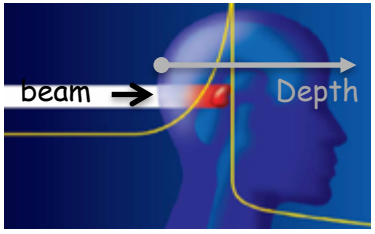
How a Linac Works



Conventional radiotherapy

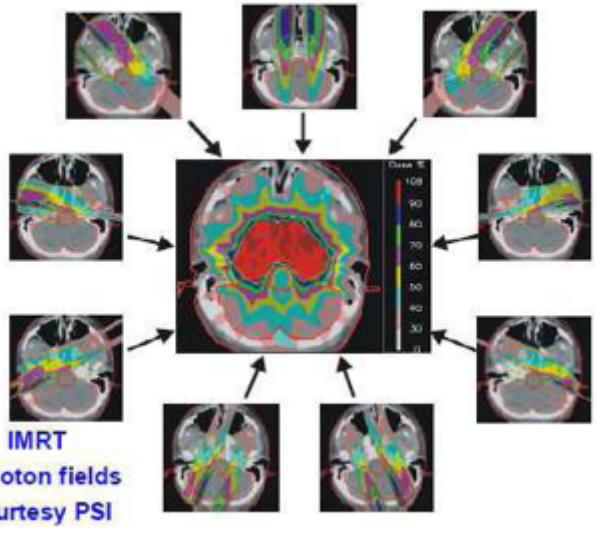
Photon beams on patient





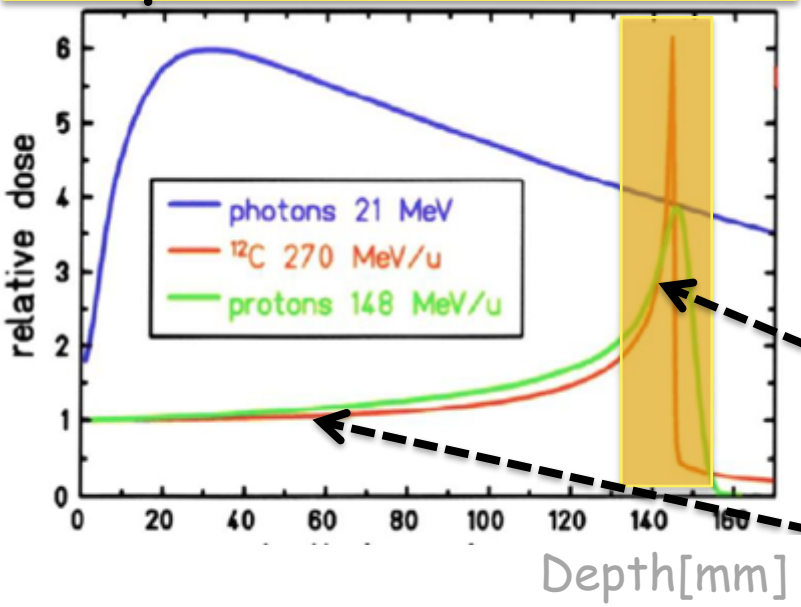
Large release of energy outside tumor

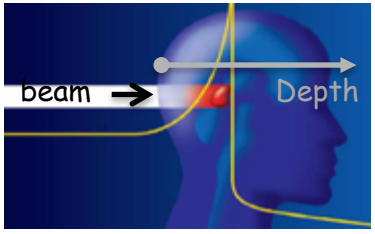
- Multiple beams each of smaller energy (IMRT)



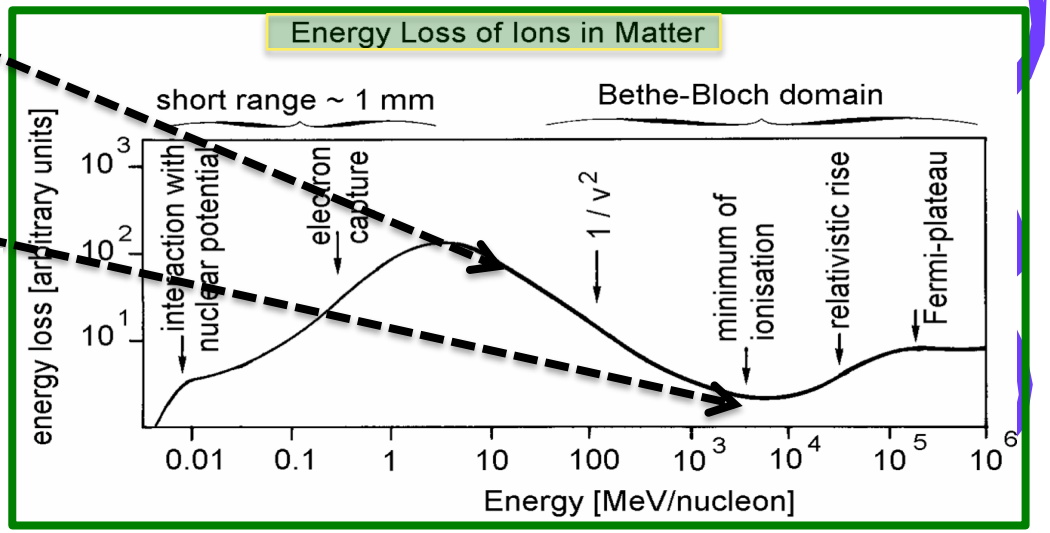
Hadrontherapy

Proton/ion beams on patient



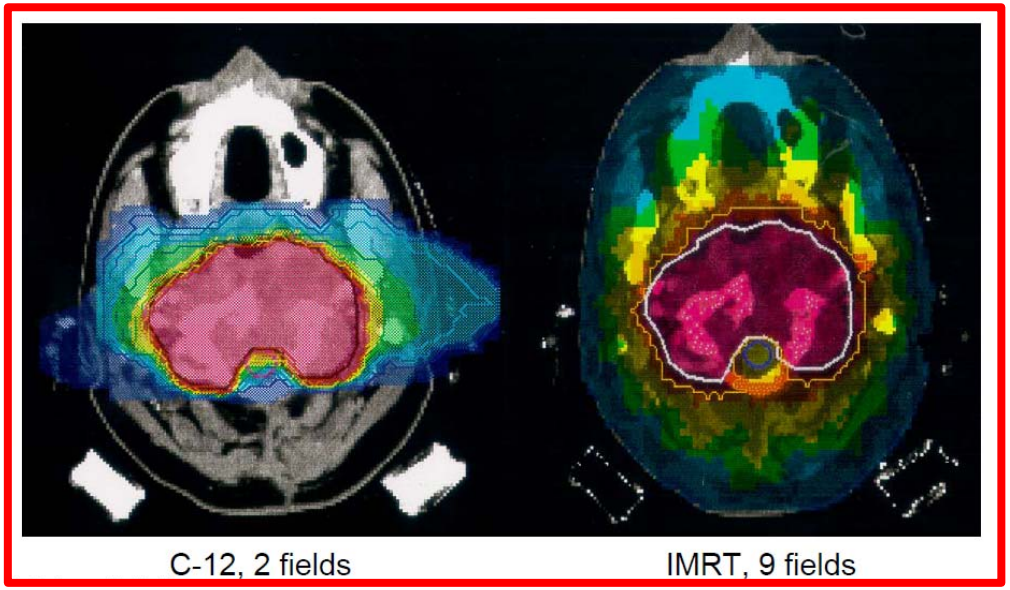


Concentrate release of energy inside tumor due to release of energy in ionization.

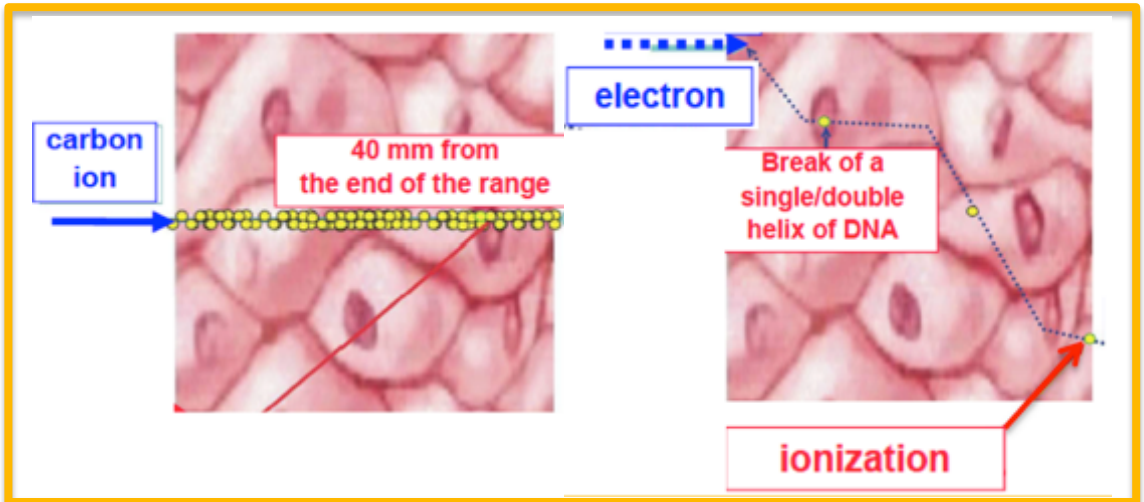


Comparison ^{12}C vs IMRT

Better confinement of energy release

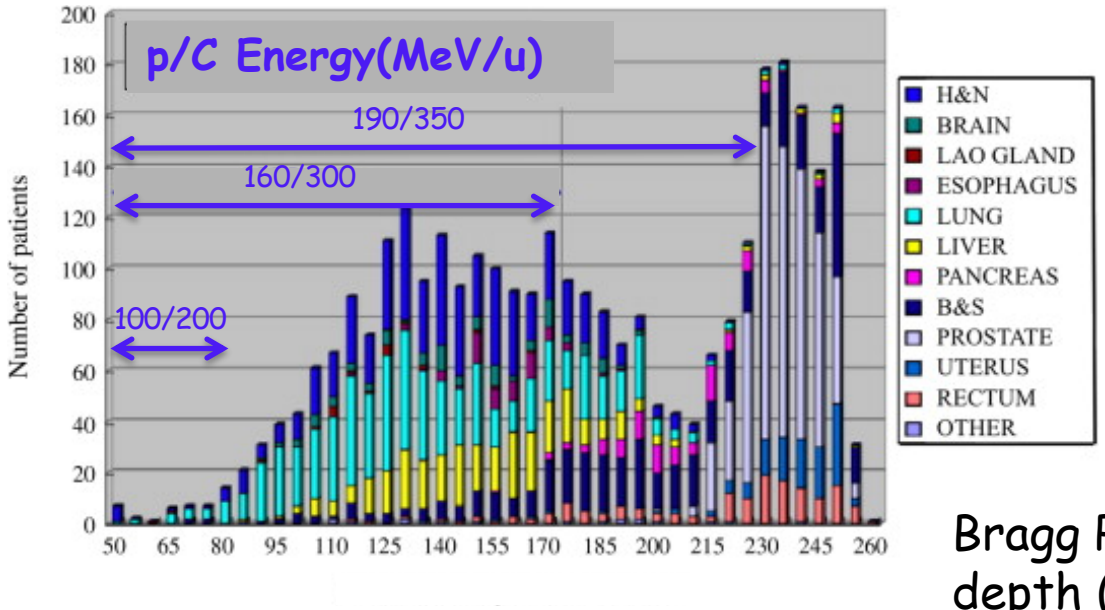


More effectiveness in killing cells



Accelerators

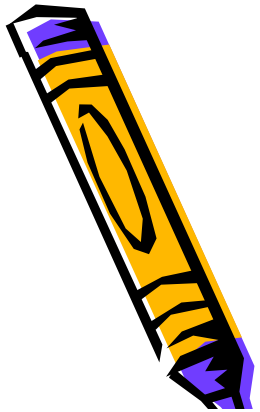
Required proton/Carbon energy



Bragg Peak depth (mm)

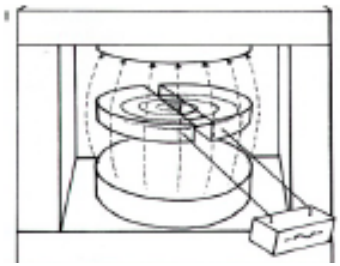
Proton Kinetic Energy between 100-250 MeV
Carbon Kinetic Energy between 200-400 MeV/u

Accelerators for hadrotherapy



therapy with protons (~ 200 MeV)

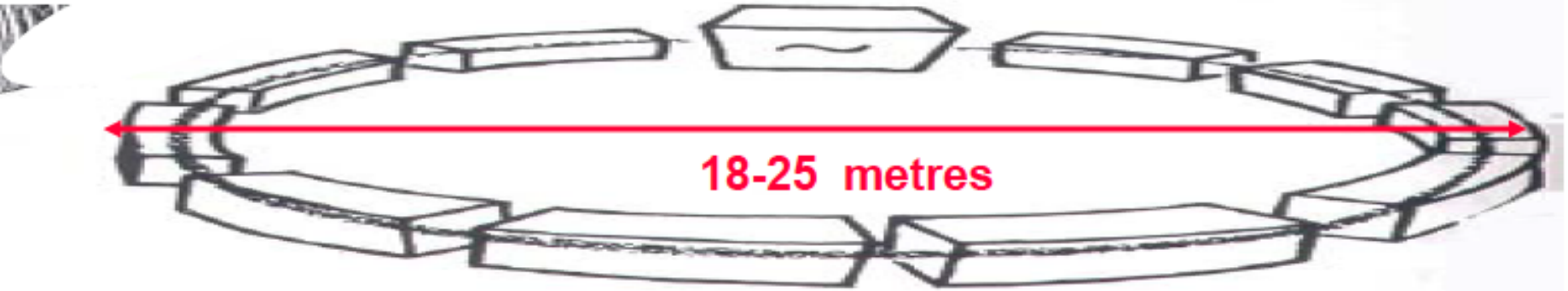
CYCLOTRONS (Normal or SC)



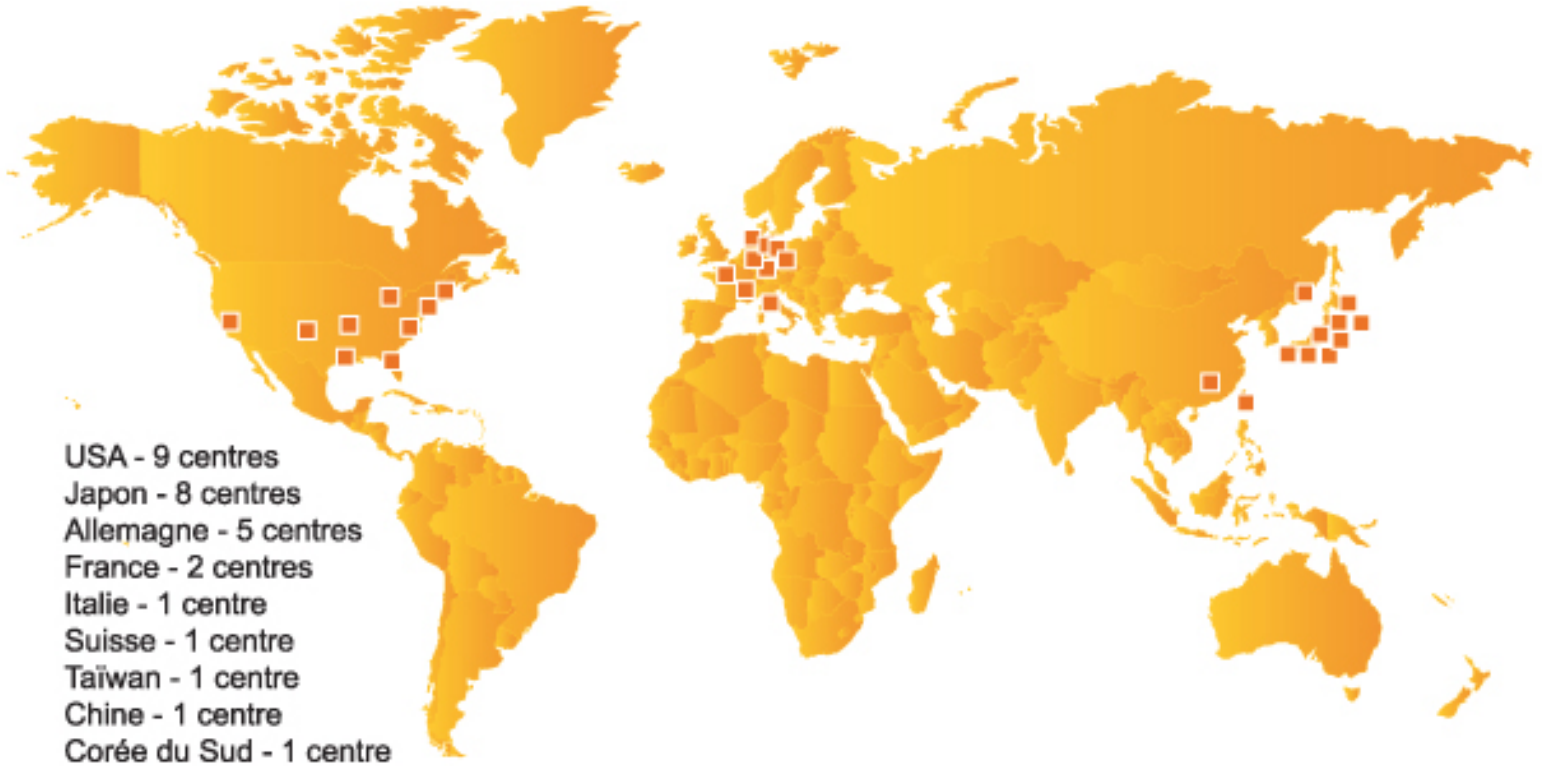
SYNCHROTRONS

therapy with carbon ions (~ 4800 MeV)

SYNCHROTRONS

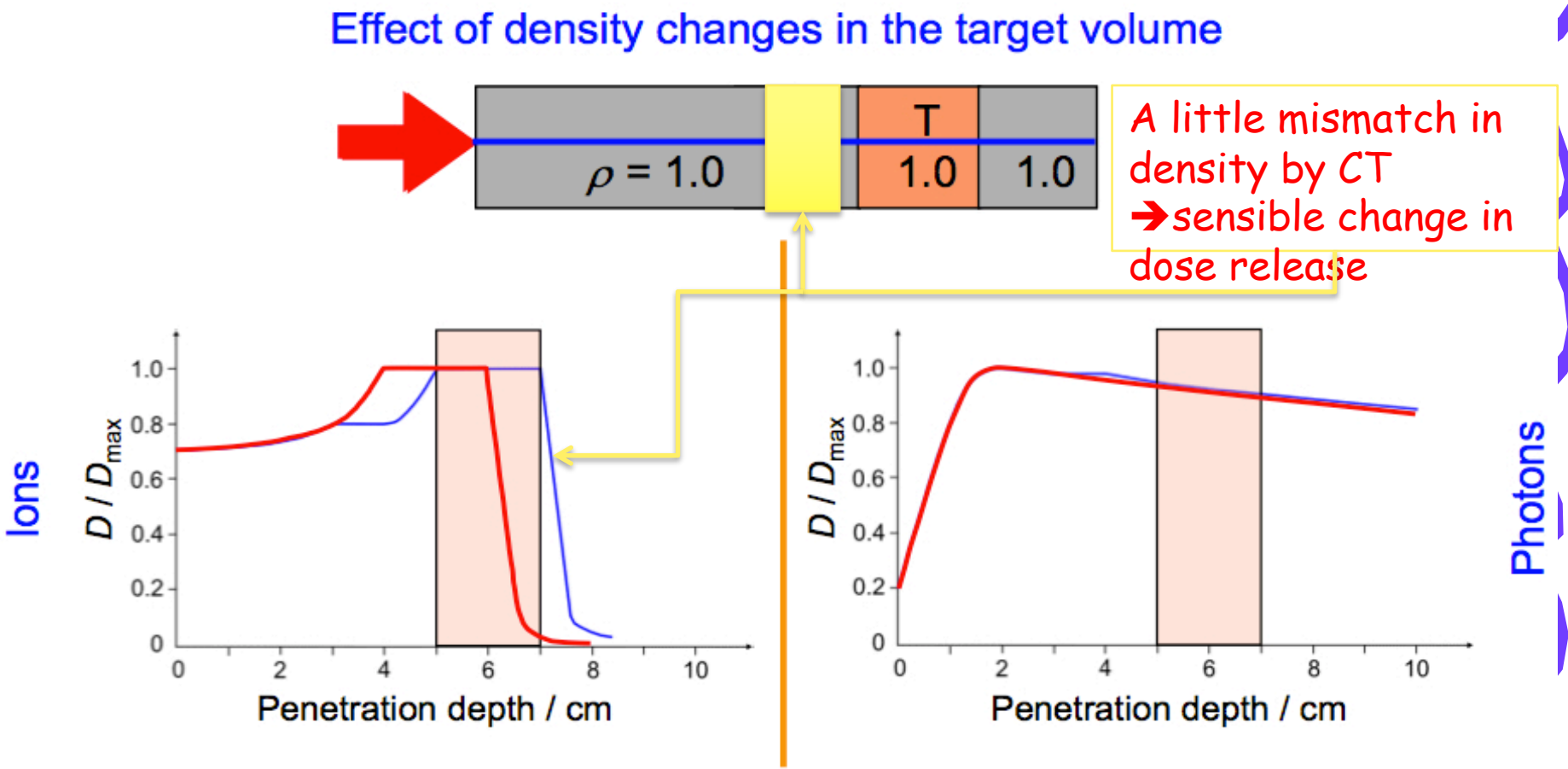


Present of hadrotherapy



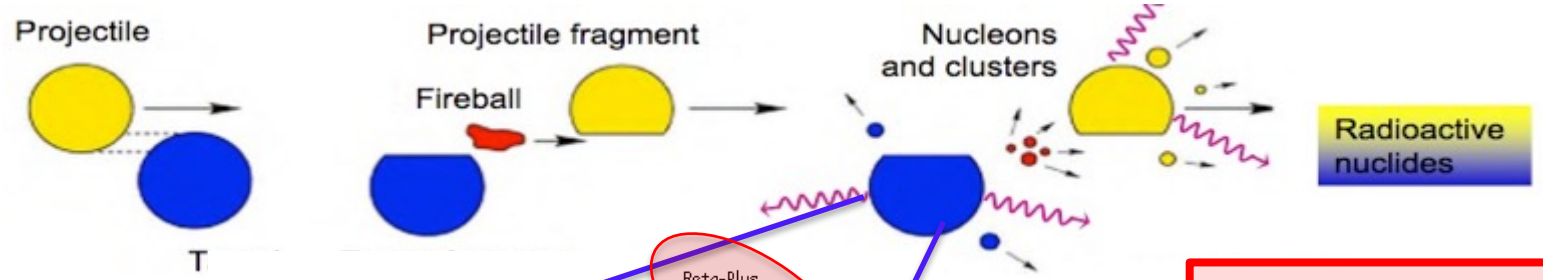
HT:Monitoring the dose

- Why is so crucial to monitor the dose in hadrontherapy ? Is like firing with machine-gun or using a precision rifle..

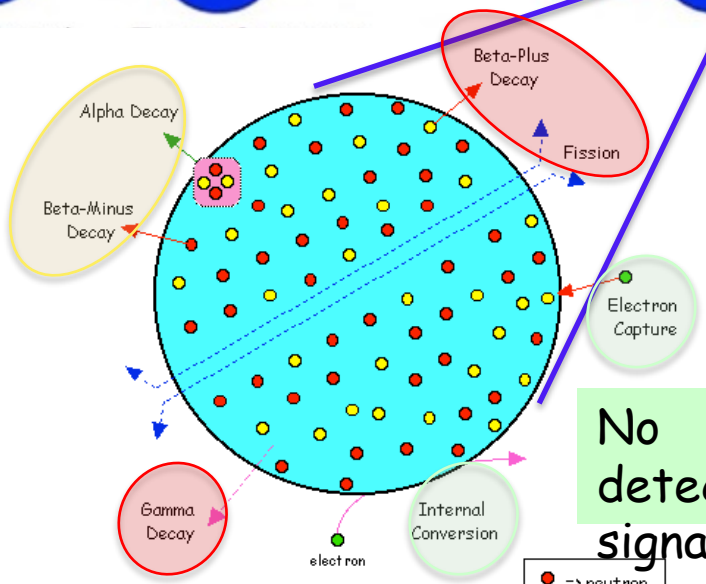


Measuring the dose

Based on nuclear reactions between the projectile and the patient



Don't exit patient



No detectable signal

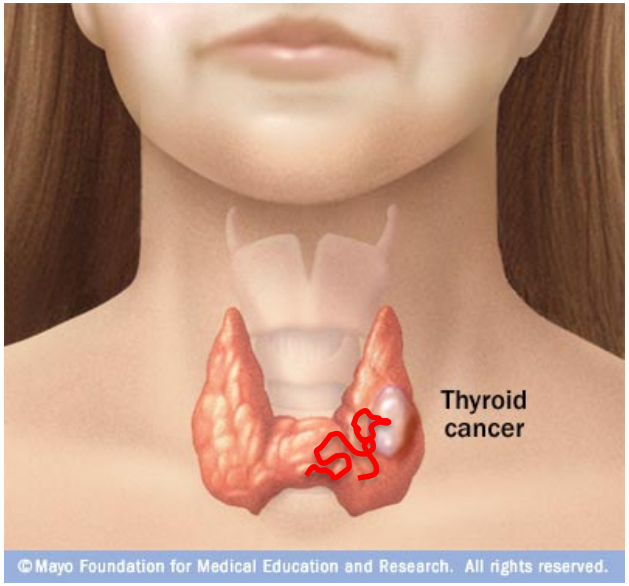
Possible nuclear reactions

Reactions of interest

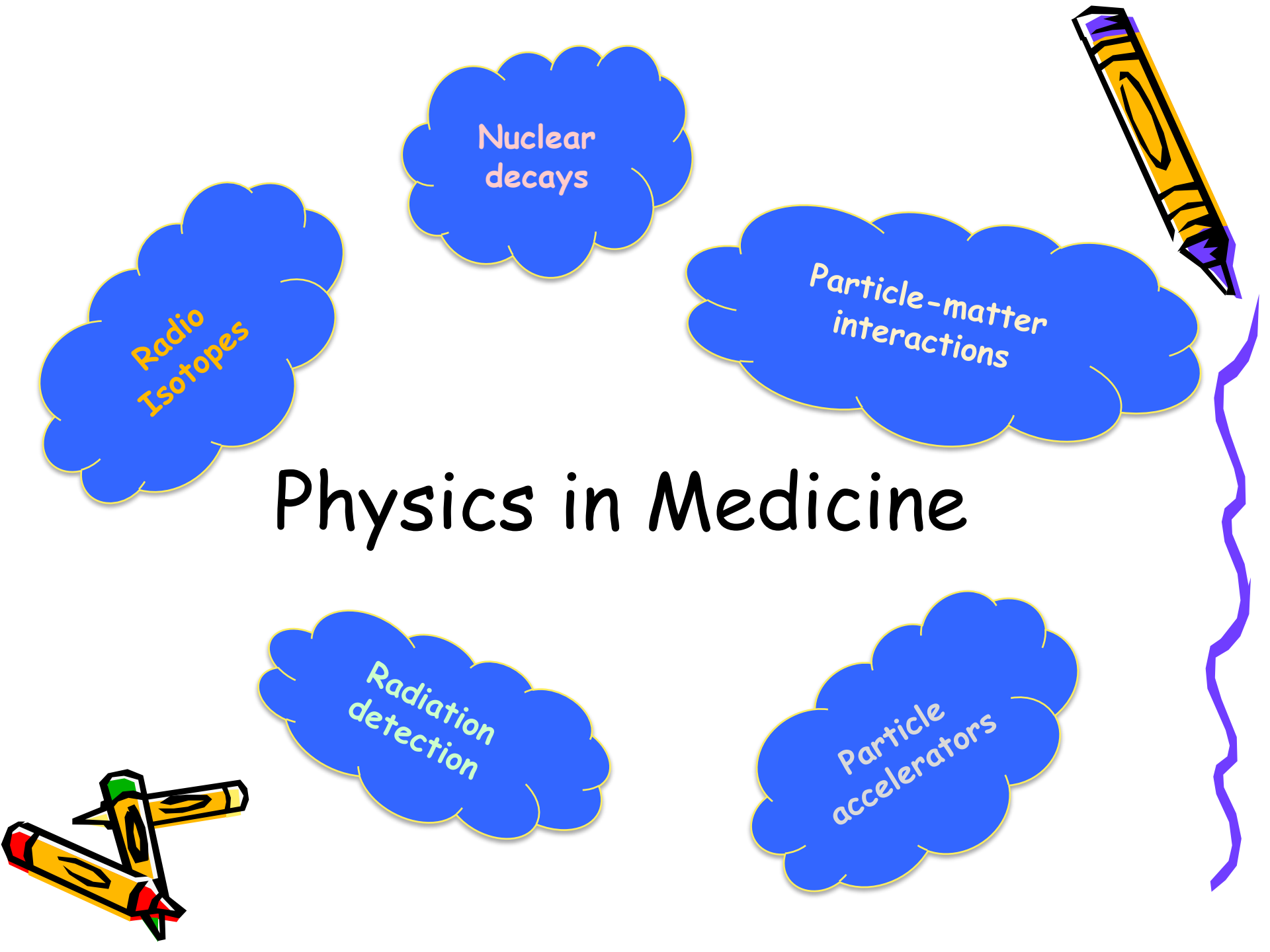
- β+ decays
- Prompt γ
- Charged products

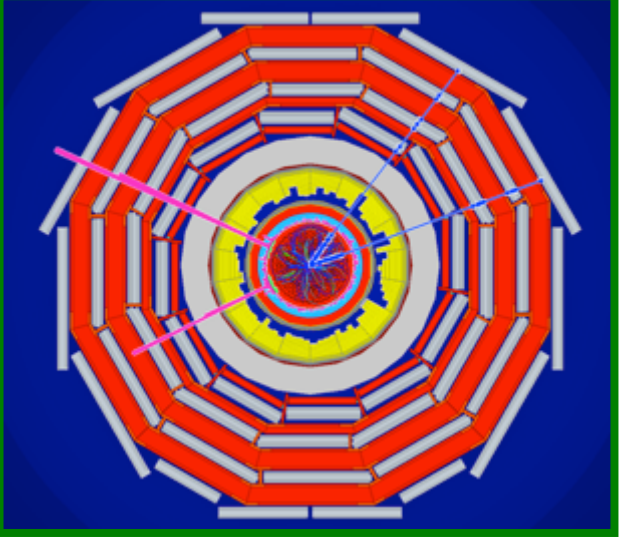
radiomethabolic/Brachithera py

- Inject/ position radionuclide (e.g. 131I)
- Beta- decays
- Electrons release energy in tumor locally



Beta- decays


Nuclear decays
Radio Isotopes
Particle-matter interactions
Physics in Medicine
Radiation detection
Particle accelerators



PHYSICS IS BEAUTIFUL …

… AND USEFUL

(U. Amaldi)