NON-CONVENTIONAL RADIONUCLIDES PRODUCED BY PARTICLE ACCELERATORS FOR THERANOSTIC APPLICATIONS

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Laboratories of Physics Applied to Health and Radiochemistry at LASA: Research Activity

	Radionuclides	Activation analysis	Radioactive counting techniques
RADIOCHEMICAL/ NUCLEAR METHODS →			
Research area →	Innovative Radionuclides for medical, toxicological and nanotoxicological use	Engineered nanoparticles (NPs)	Environmental radioactivity / Radioprotection
Project →	High Specific Activity RadioNuclides HSARN project	NAnoSafety Research NASAR project	RADioactivity Environ. Measurements RADEM project
Experimental activity →	Irradiations, Excitation functions, radioch. sep.	Radiolabelling/ NAA of NPs	Alpha, beta, gamma spectrometry
Studies carried out (examples) →	> 70; in the last 6 years ^{99m}Tc, ^{103}Pd; ^{89}Zr; ^{52g}Mn	^{51}TiO2 (Cosmetics) ^{110m} Ag (Food packaging) ^{59}Fe (Uptake by plants)	Measurements after NPP accidents; Measurements of ^{222}Rn indoor
Objectives →	Optimisation of radionuclide production (theranostic medicine)	Nanocharacterization, mechanisms of nanotoxicity, nanomedicine, support to industry	Radioprotection Education Dissemination

Theoretical SA(CF) :

$$SA(CF) = N_A \ \lambda / P_a \qquad [Bq\ g^{-1}]$$

Specific Activity, SA :

SA = Activity of a RN / mass isotopic carrier

Isotopic Carrier :

total number of atoms “isotopic” with main Radio-Nuclide (both radioactive and stable)

Isotopic Dilution Factor :

IDF = total number of isotopic atoms

divided

number of atoms of RN

Kinds of A_S

Alfred P. Wolf, Brookhaven National Laboratory, USA

J. Nucl. Med. 22 (1981) 392-393

Specific Activity
[Bq·g^{-1}]
[Bq·mol^{-1}]

- Carrier Free **A_S(CF)** — *theoretical only !* IN PRACTICE NOT ACHIEVABLE
- Carrier Added **A_S(CA)** — commonly used in "*classical*" radiochemistry
- No Carrier Added **A_S(NCA)** — "*modern*" radiochemistry *goal !!!*
- Nearly Carrier Free A_S(NCF) — non quantitative definition !

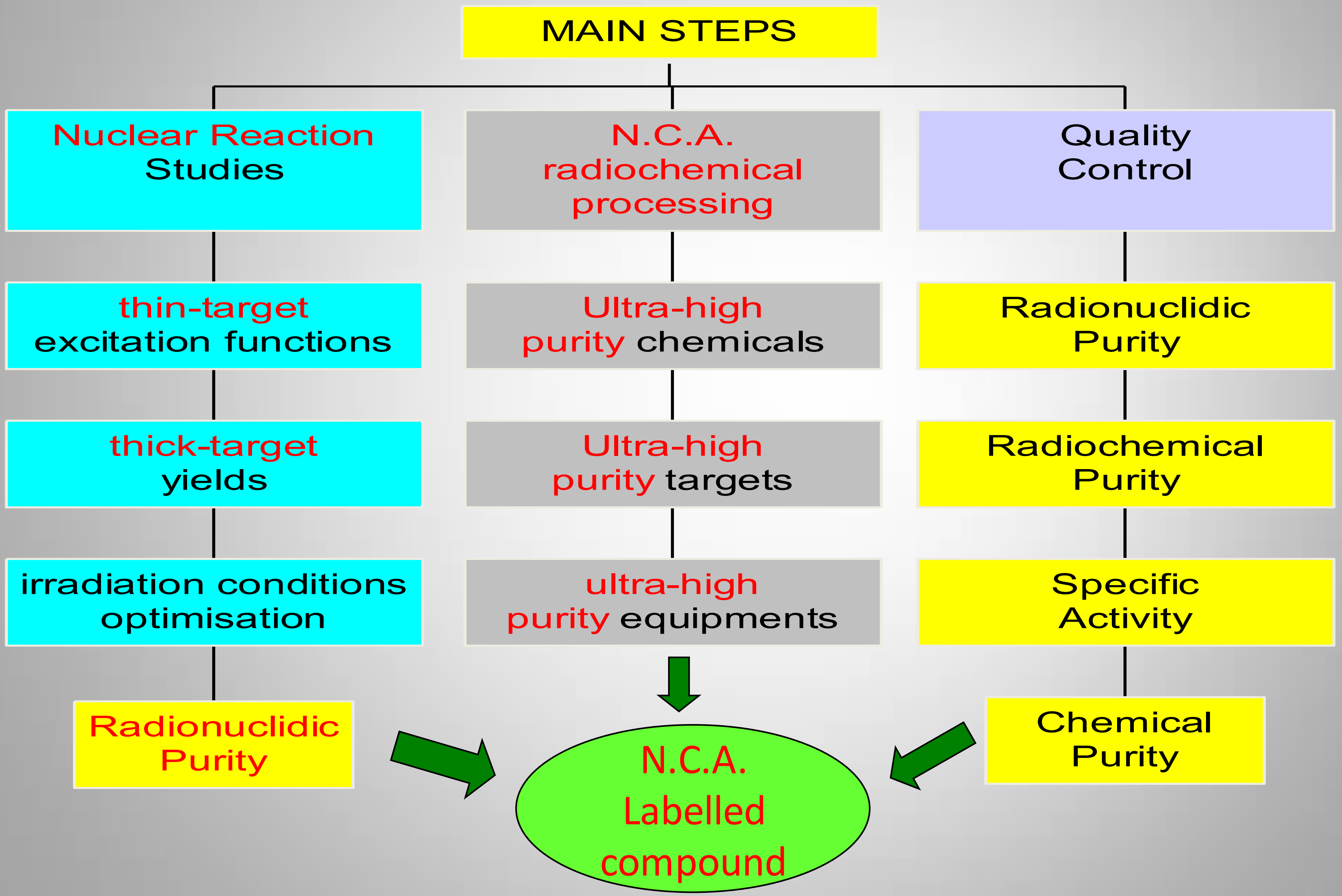
A_S must not be confused with
Radioactivity Concentration [Bq·g^{-1}]:
(same units but the meaning is completely different)

Origins of Isotopic Carrier (both stable and radioactive)

preparation pit falls in NCA radiotracer

- *target material* and *target holder* impurities
  - in practice "not avoidable"
- *side* nuclear reactions
  - very common in cyclotron irradiation
- *chemical impurities* in target radiochemical processing
  - use of *glassware* instead of inert materials (i.e: teflon-PFA)

Production, Radiochemical Processing and QC/QA of *No Carrier Added* (n.c.a.) labelled species



Quality Control/Assurance (QC/QA) of a radionuclide or labeled compound (e.g., radiotracer, radiopharmaceutical) means the experimental determination of:

- ✓ **Chemical Purity** — **CP**
- ✓ **Radiochemical Purity** — **RCP (%)**
- ✓ **Radionuclidic Purity** — **RNP (%)**
- ✓ **Specific Activity (i.e., IDF)** — A_S **(GBq.μg^{-1})**
- ✓ **Concentration of Activity** — C_A **(MBq.g^{-1})**

Moreover the experimental determination of:

- ✓ **Biological Purity (for applications in the life sciences, biological and human)**

- ✓ **Stability vs. Time of all previous parameters, both *in-vitro* and *in-vivo***

THERANOSTIC MEDICINE

- Theranostic medicine is a new integrated therapeutic system which can **diagnose**, **deliver targeted therapy** and **monitor the response to therapy**.
- the nuclear physician can **follow the real biodistribution of the radiopharmaceutical inside** the patient after the injection and the **follow-up during the repeated treatments**.
- The radioisotopes used for **metabolic radiotherapy are α, β and Auger electron emitters**. Many of them are also **γ** emitters and can be **detected by gamma-camera, SPECT or PET**.
- Many of these "neutron reach" radionuclides are produced by nuclear reactor with a very low A_S. In selected cases they can be produced by bombardment of targets by charged particle beams, in No Carrier Added Form – NCA - with very high A_S

Advantages if the irradiations are made with deuteron beams

- the **higher stopping power** in respect to the protons allows to employ targets with smaller thickness: the volume of reagents, the synthesis systems and the discharge of radioactive material for radioprotection purpose are smaller, the **A_S and chemical purity** of the final product **are higher**.

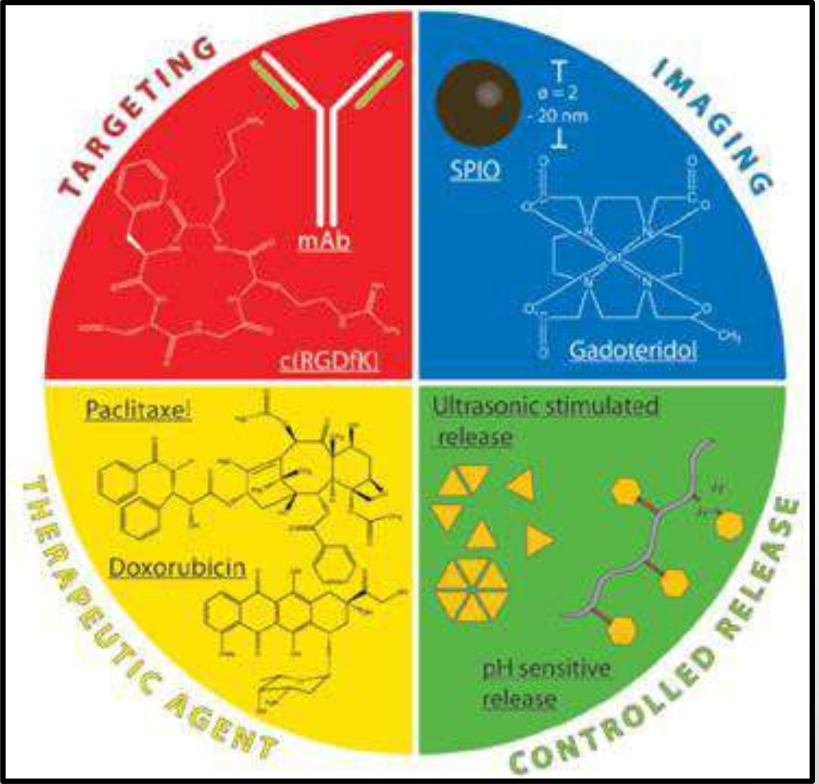
- deuterons usually present higher cross sections in compound nucleus region.

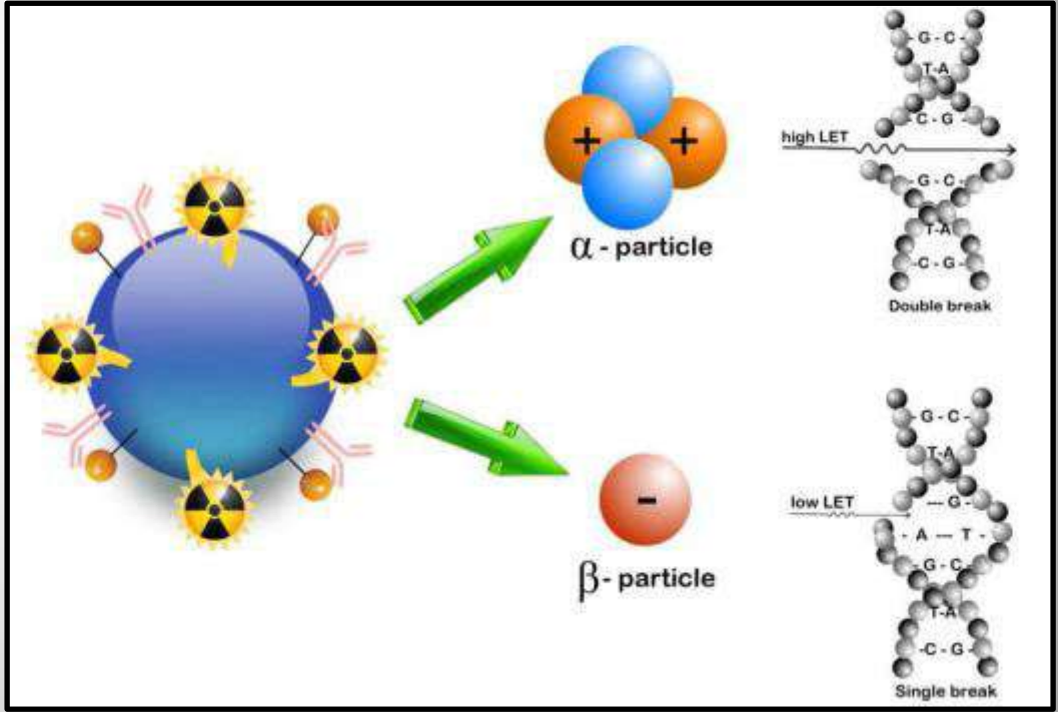
Radionuclides for metabolic radiotherapy and theranostics

radionuclide	Half-life days	β-max MeV	R soft tissue mm	Eγ keV
Dy-165	0.1	1.29 (83%); 1.19 (15%)	5.7	95 (4%)
Sm-156	0.4	0.7 (51%); 0.4 (44%)		none
Re-188	**0.7**	**2.12 (72%); 1.96 (25%)**	**11.0**	**155 (15%)**
Ho-166	**1.2**	**1.85 (51%); 1.77 (48%)**	**8.5**	**81 (6%)**
Rh-105	1.5	0.57 (75%); 0.25 (20%)		319 (19%)
Sm-153	**1.9**	**0.67 (78%); 0.81 (21%)**	**2.5**	**103 (28%)**
Au-198	2.7	0.96 (99%)	3.6	411 (96%)
Y-90	**2.7**	**2.28 (100%)**	**11**	**none**
Re-186g	**3.7**	**1.07 (74%); 0.93 (21%)**	**3.6**	**137 (10%)**
Yb-175	4.2	0.47 (87%)		396 (7%)
Lu-177g	**4.2**	**0.48 (78%)**	**1.7**	**208 (11%)**

Nanoparticles and theranostic nanomedicine

Multifunctional design of a micelle nanomedicine platform with cancer targeting, imaging, controlled release properties.



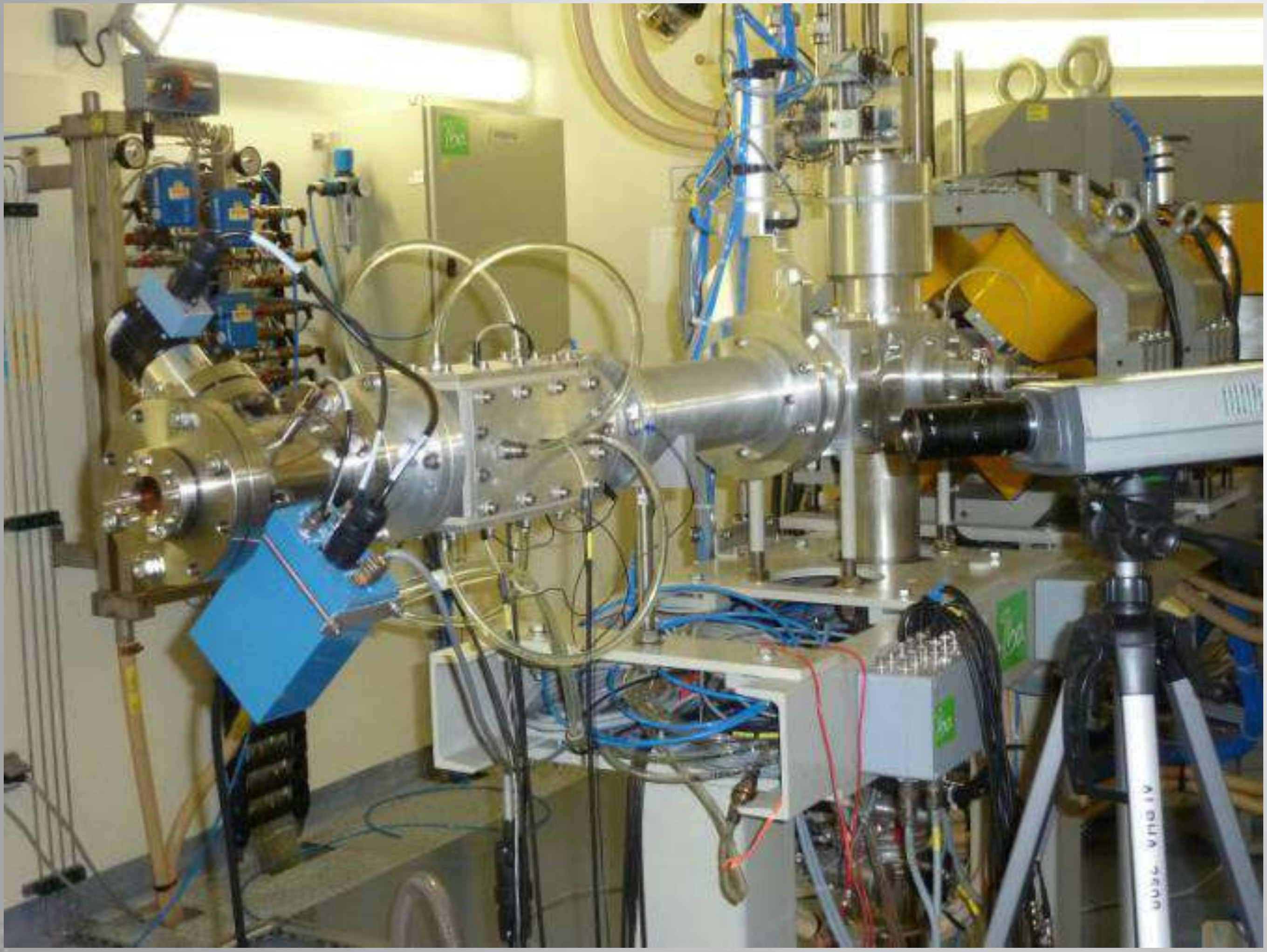


Blanco et al.,
Exp.Biol. Med.2009, 234:123-131

E. Morales-Avila et al. Radiolabeled Nanoparticles for Molecular Imaging (2012) in Molecular Imaging Ed. by B.Schaller, InTech

ARRONAX Cyclotron
Nantes - France

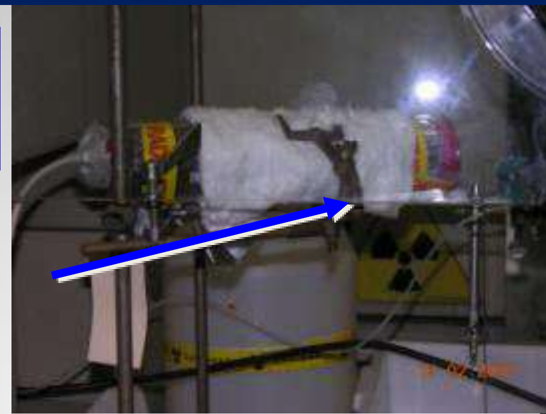
☢	Protons	35 - 70 Mev	up to 750 µA
☢	Deuterons	15 – 35 Mev	
☢	Alpha	70 MeV	



Nuclear Physics Measurements Laboratory
2 alpha, 2 beta, 9 HPGe (rel. eff. 15 – 40 %) spectrometers
LN_2 filling automatic system

Typical radiometric equipment, at LASA-Segrate

9 analog and digital HPGe gamma spectrometry



2 Liquid Scintillation Counting Spectrometry beta-alpha emitters

NaI(Tl) on-line gamma-X emitters

2 Si (SB or PIPS) for alpha emitters

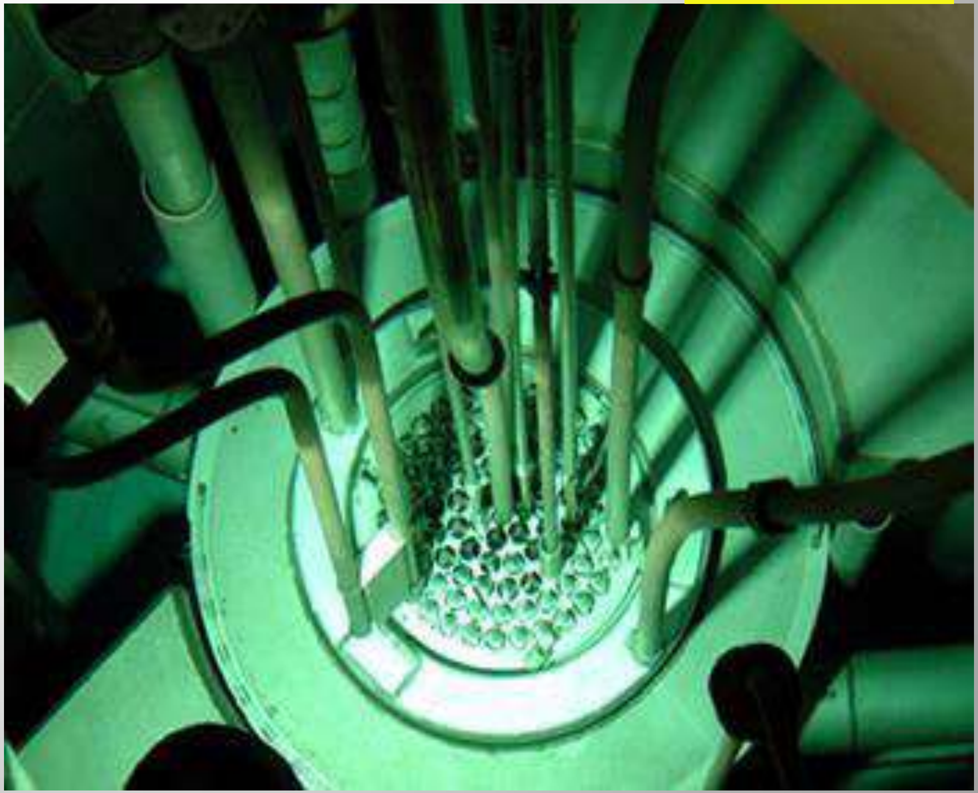
Cyclone® Plus Storage Phosphor System 2D imaging for gamma-beta emitters

Hot Radiochemistry Laboratory:
ISO Class II; UNICEN 7815

Low and medium activities of γ,β,α radionuclides are radiochemically processed

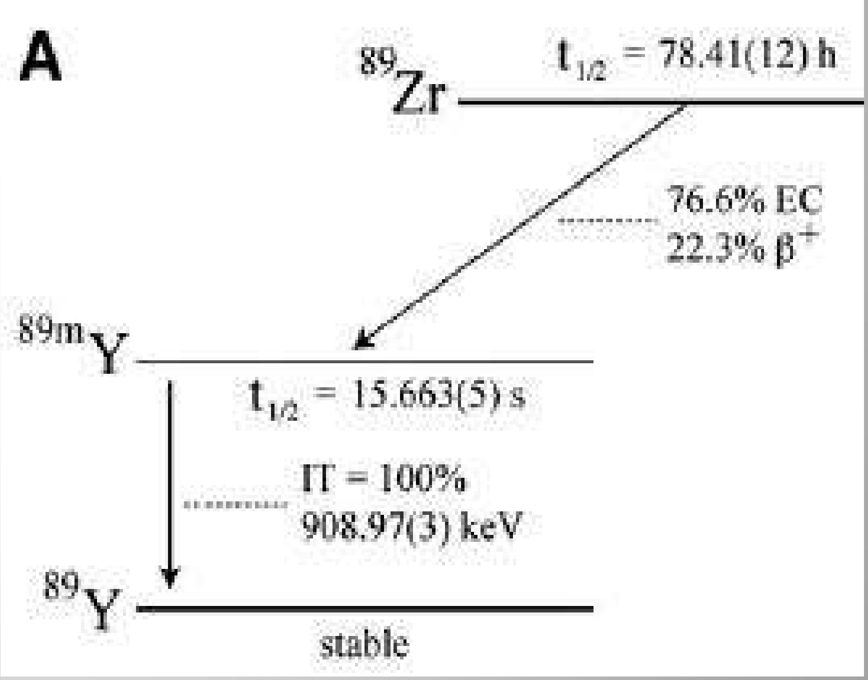
Research thermal/ephithermal nuclear reactor TRIGA Mark II, University of Pavia, Italy

critical 1965
requalified 2002

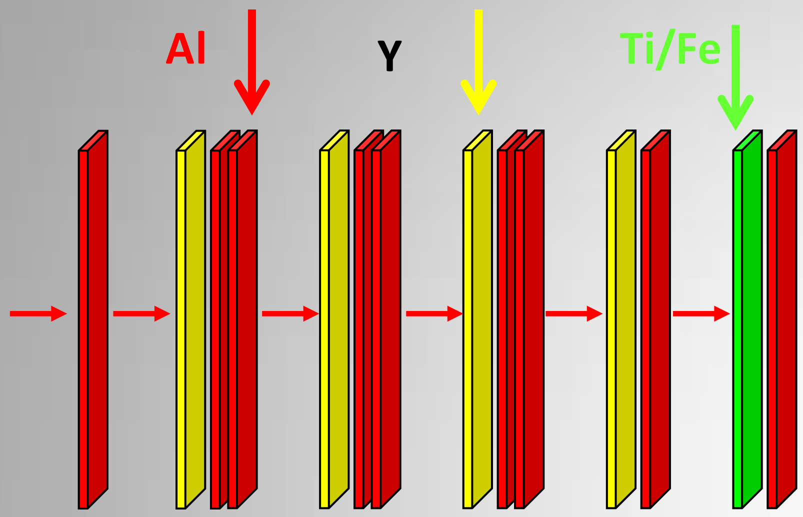


^{89}Y (d,2n) ^{89}Zr NCA

- Zr-89 is one of the most promising radionuclide in Nuclear Medicine for **labelling monoclonal antibodies** for **bio-distribution studies** and for **immuno-PET imaging**. Furthermore **Zr-89-labelled octreotide liposomes** can be used for simultaneous **PET and magnetic resonance** tumor imaging in **theranostics applications**.
- Zr-89 (**$T_{1/2}$ = 78.41 h**) decays by **β^+** (22.3%; E_{max} energy = 900 keV) and **EC** (76.6%) to the **stable isotope Y-89** - γ emission at **908.96** kev (Iγ = 99.87%) which is the main contribution to the absorbed dose. The longer-lived radioisotope Zr-88 ($T_{1/2}$ = 83.4 d) has a single γ-ray emission at **392.87 keV** is the only one radioisotopic impurity.



Irradiation of thin Y targets with the stacked foil technique



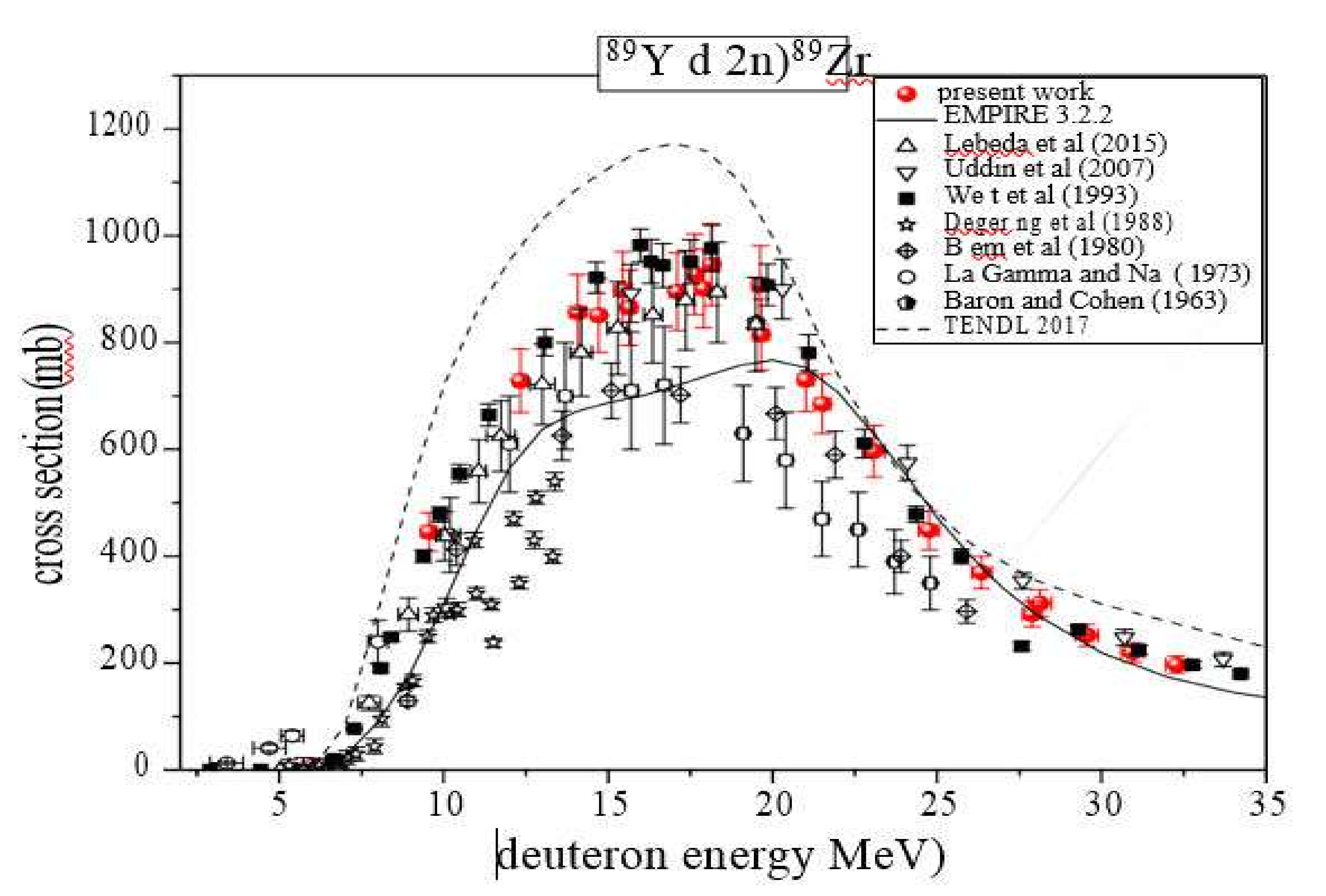
Al = degrader, catcher

Ti & Fe = monitors

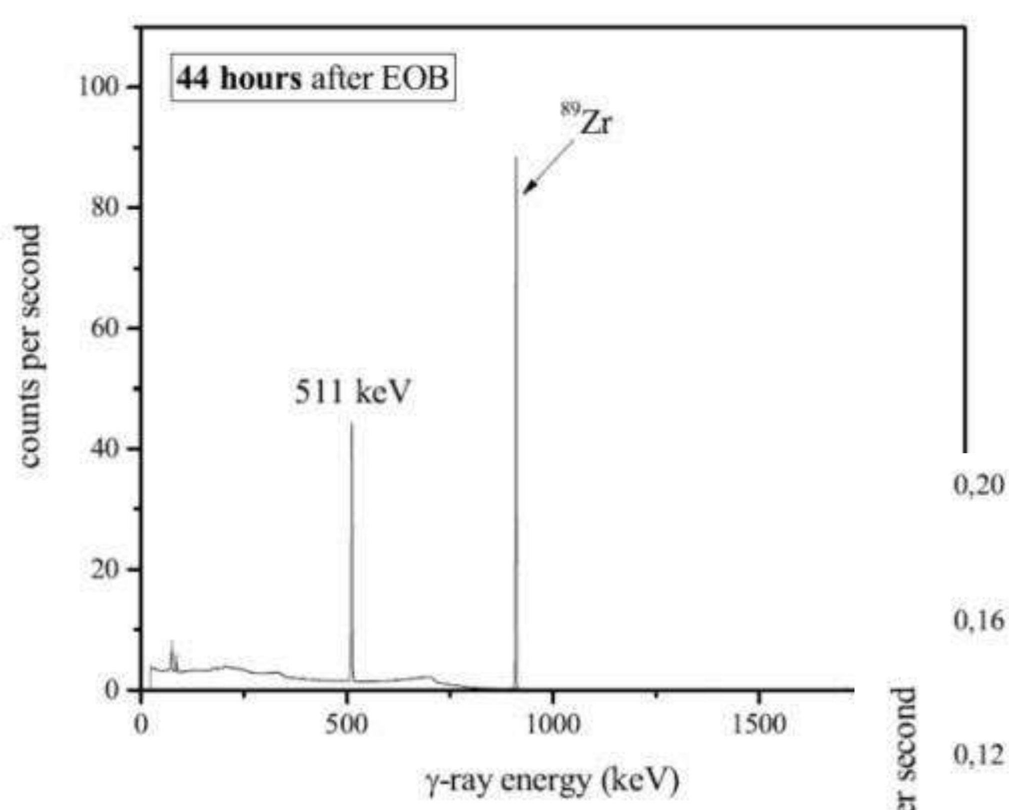
7 irradiations at ARRONAX, Nantes

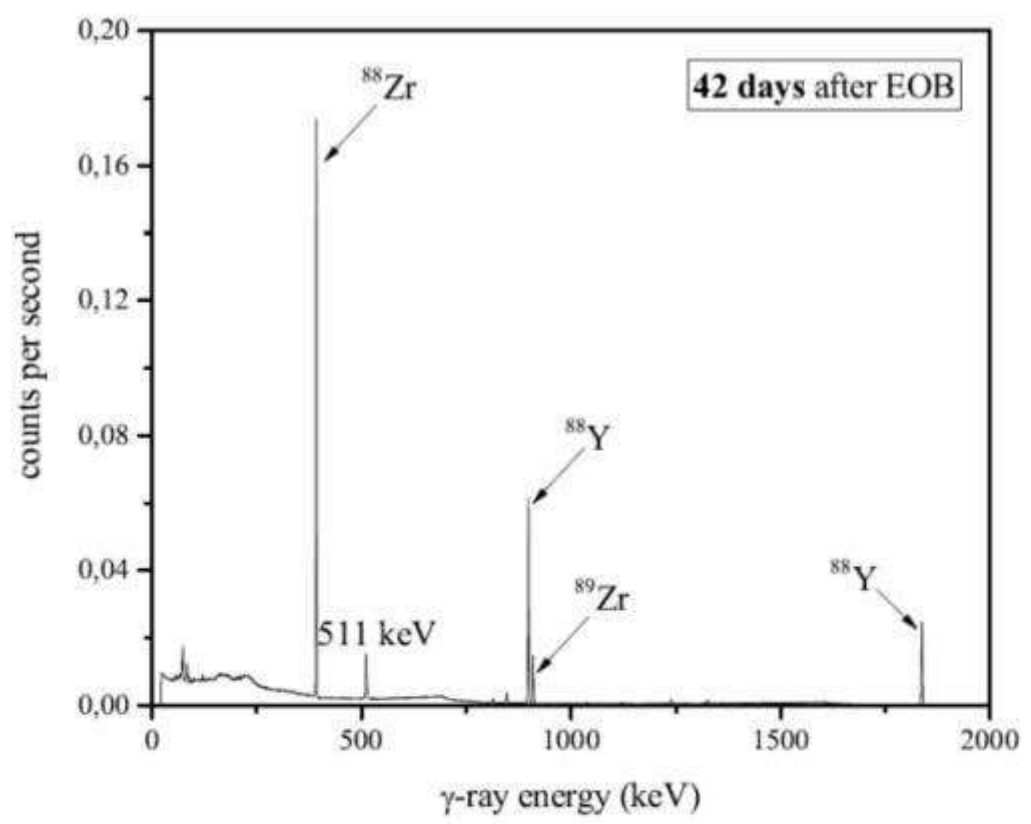
- **Thin natural Y targets: 22.35 mg/cm^2 and 44.70 mg/cm^2**
- **Incident Energies (MeV): 34; 28.7; 28.0; 24; 22.5; 19.5; 16.1**
- **Irradiation time: 60 min**
- **Beam current: 150 nA**

Cross Section of $^{90}Y(d,2n)^{89}Zr$ ($t_{1/2}$ = 78.41 h)

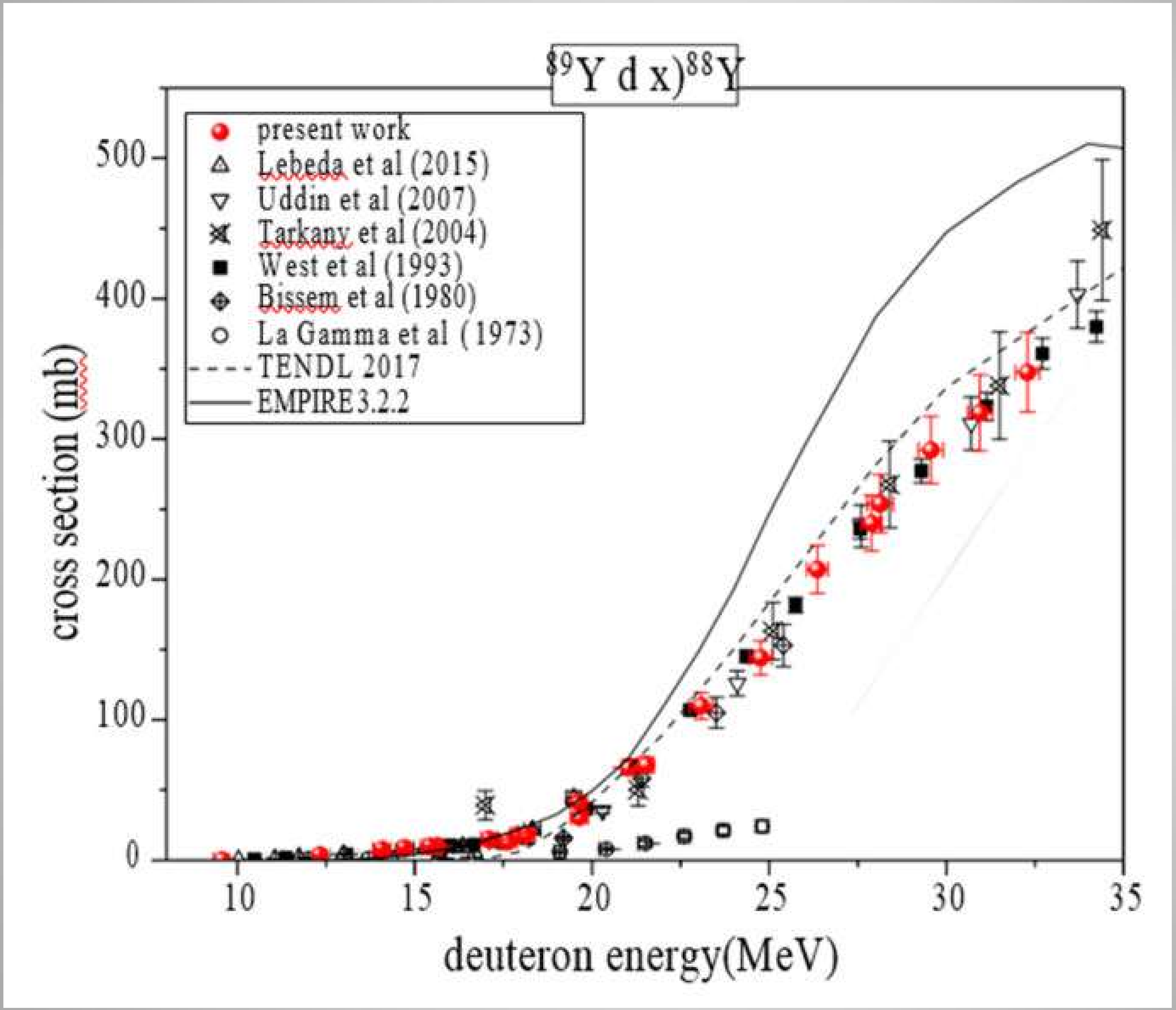


Examples of γ-ray spectra, E = 17.9 MeV

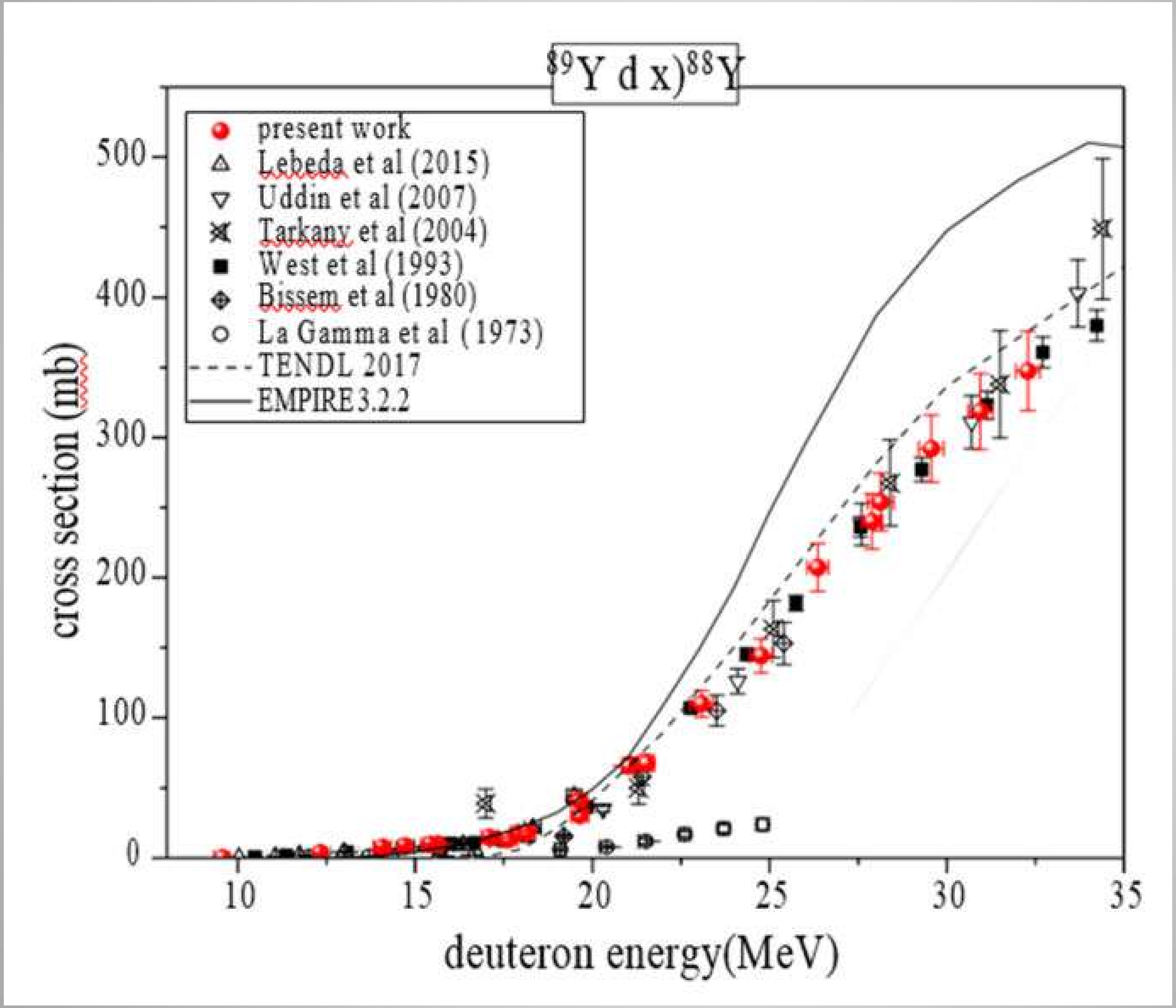




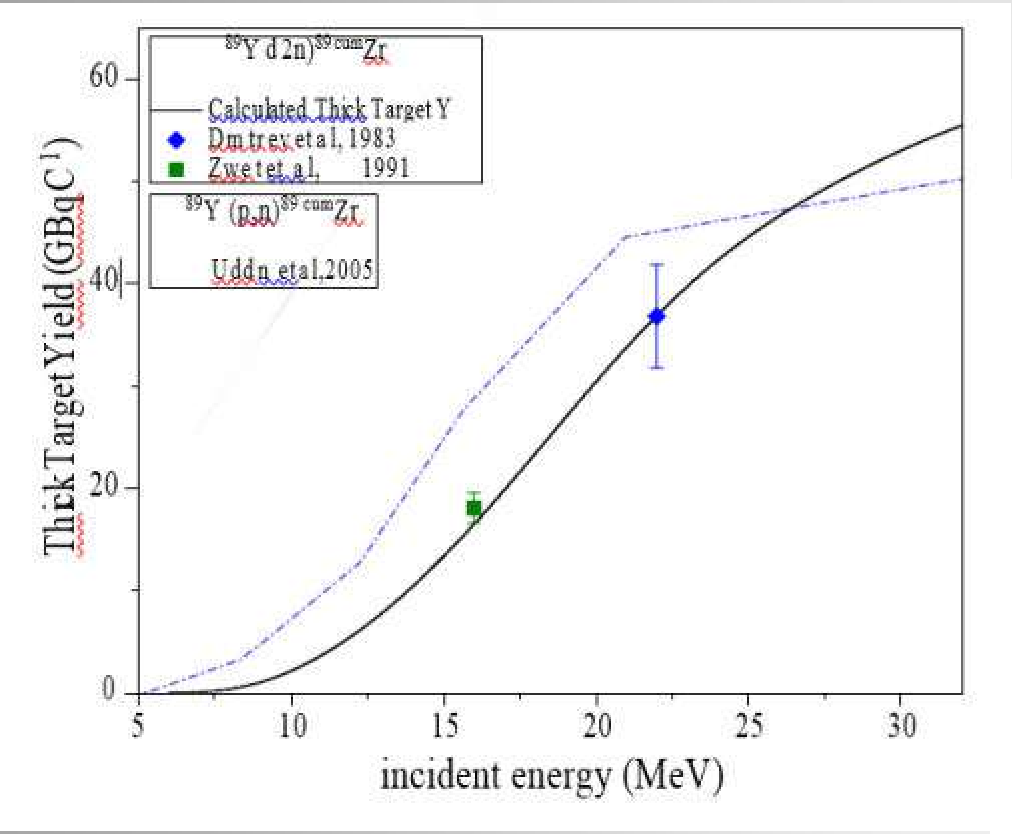
Excitation functions of $^{89}Y(d,3n)^{88}Zr$ ($t_{1/2} = 83.4$ d)

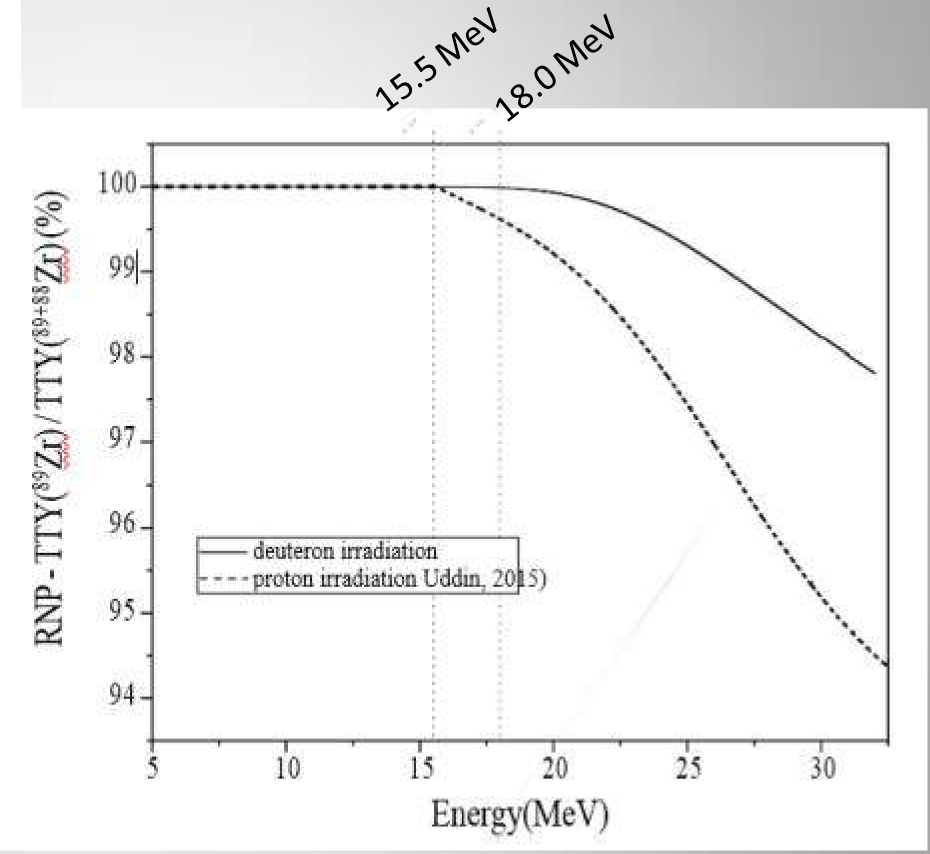


Excitation functions of $^{89}Y(d,x)^{88}Y$ ($t_{1/2}$ = 106.65 d)



TTY and RNP for $^{90}Y(d,2n)^{89}Zr$ ($t_{1/2}$ = 78.41 h)





^{52}Cr (d,2n) ^{52}Mn NCA

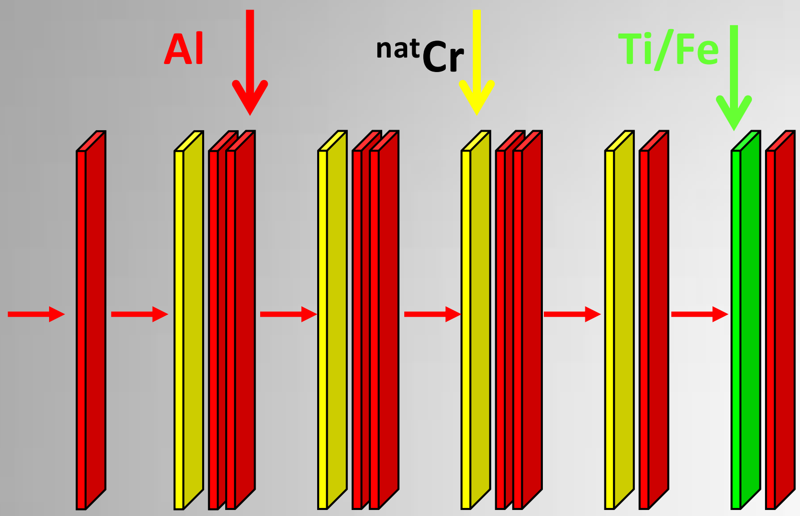
- ^{52g}Mn ($T_{1/2}$ = 5,59 d) is the radioactive isotope with useful nuclear properties **for PET imaging** like ^{18}F (i.e average $E_{\beta+}$ ~ 250 keV and similar β^+ spectrum energy range) or ^{51}Mn ($T_{1/2}$ = 46.2 min) with higher β^+ energy spectrum;
- The transition element Mn has moreover stable isotopes (Mn^{2+}) having useful paramagnetic properties to be used **as MRI contrast agents**.

Comparison with some already used positron-emitting radionuclides in NM

Currently ^{89}Zr and ^{64}Cu are the common radiometals of choice for labelling proteins and monoclonal antibody with a slow bio distribution kinetics. They might be easily replaced by ^{52}Mn **compounds.**

^{52}Mn		^{89}Zr and ^{64}Cu
Higher β^+ branch ($I_{\beta+}$ = 29.4%) longer half-life ($T_{1/2}$ = 5.6 d)	^{64}Cu	β^+ branch ($I_{\beta+}$ = 17.6%) half-life ($T_{1/2}$ =12.7 h)
	^{89}Zr	β^+ branch ($I_{\beta+}$ = 22.7%) half-life ($T_{1/2}$ =3.3 d)
lower mean energy $<E_{\beta+}>$ =241.6 keV PET superior resolution	^{64}Cu	$<E_{\beta+}>$ = 395.5 keV
	^{89}Zr	$<E_{\beta+}>$ = 278.2 keV
Easy and more stable aqueous chelation chemistry	hard ligands like oxalate are needed to keep ^{89}Zr	

Irradiation of thin ^{nat}Cr targets with the stacked foil technique



Al = degrader, catcher

Ti & Fe = monitors

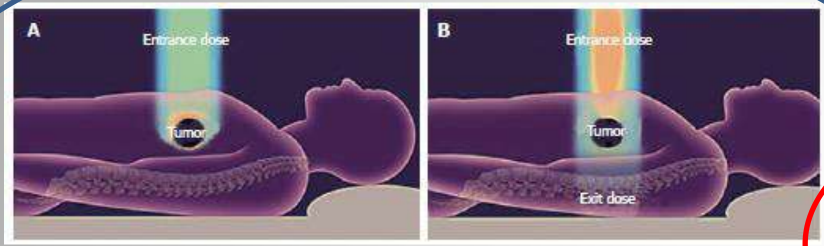
1 irradiation at ARRONAX, Nantes - 10 October 2018

- **Thin natural ^{nat}Cr targets (prepared at POLIMI by elettrodeposition on Al support): 22.79 mg/cm^2 and 17.95 mg/cm^2**
- **Incident Energies (MeV): 28.7; 24**
- **Irradiation time: 60 min**
- **Beam current: 150 nA**

THE DATA ARE UNDER ANALYSIS

Hadron Therapy and Magnetic Hyperthermia

The goal is the investigation of the possible combined action of the **Hadron Therapy** with **Magnetic Hyperthermia**, two different therapeutic techniques, for going one step beyond the state of art of **pancreatic cancer therapy**.



(A) targeted proton therapy deposits most energy on target; (B) conventional radiation therapy deposits

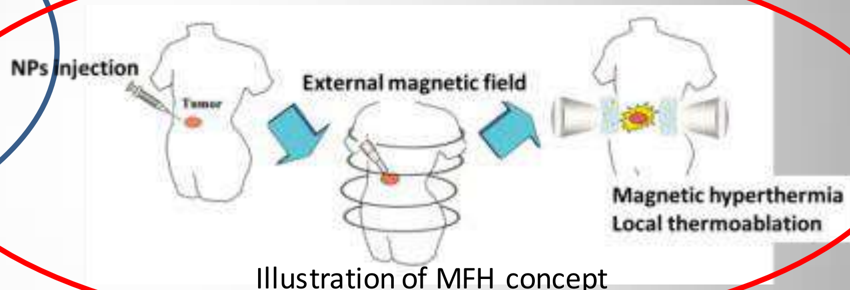


Illustration of MFH concept

Magnetic Fluid Hyperthermia allows to strictly controlling the region under treatment by using Magnetic Nanoparticles (MNPs) as heating elements.

Used in clinics (Germany, USA)

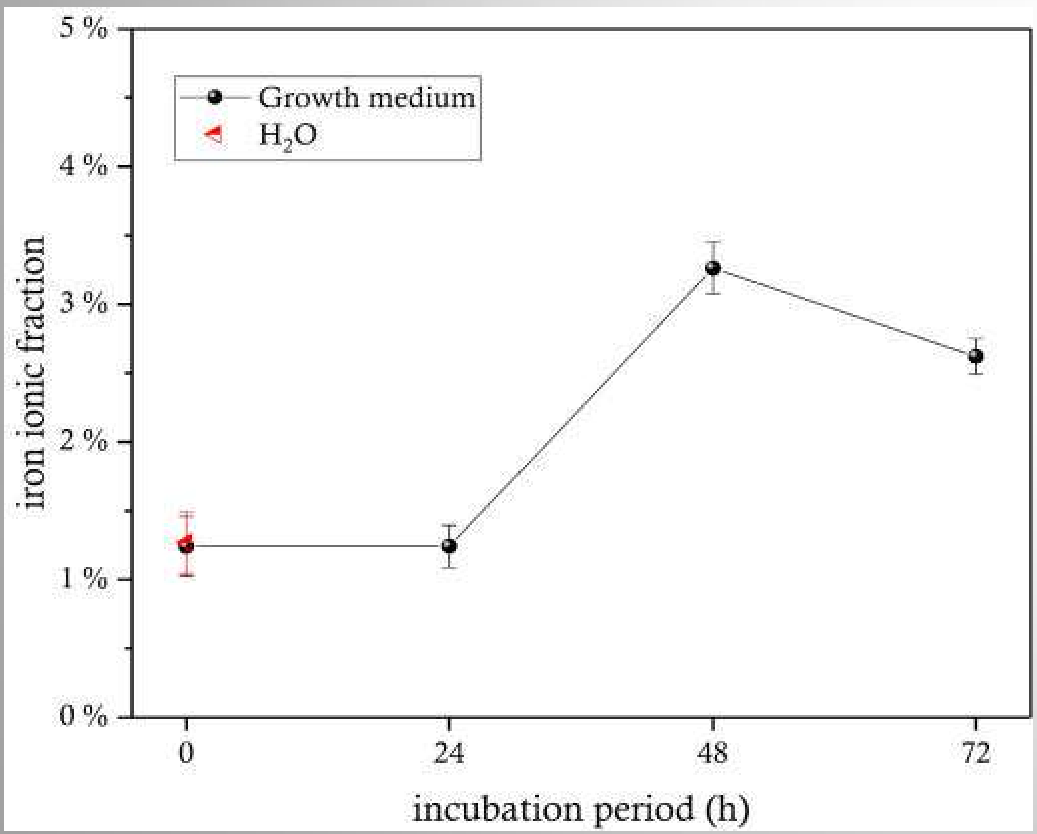
Heating through application of AC magnetic field via activation of MNPs directly injected in the tumour mass at high doses (ca. 50 mg/cm^3).

- Typically: f ~ 100 kHz, amplitude 10 kA/m.
- Minor side-effects

Dissolution of MNPs in cells

The MNPs solution and Fe ion samples used as standard were irradiated **for 12 hours at the TRIGA Mark II reactor of the LENA** Laboratory in Pavia.

1. **0.5 mL of radioactivated MNPs solution, in Petri glass plates, was added to 10 mL of culture medium**. **After 0 h, 24 h, 48 h and 72 h**, nanoparticles were removed by means of filtration from the culture medium. **At the time t = 0 h** a test was also performed with **bidistilled H_2O** in order to evaluate any different behavior in the use of the two different medium.
2. The fraction of **free Fe ion** on the total as a function to the exposure time is shown in the figure.



a) With regard to the MNPs supplied it **can be stated that there is no dissolution in the culture medium**.

b) It will redesign the experiment in **function of MNPs of different sizes and different coatings**.

c) The next experiments should be carried out using the same plastic flasks of the experiment since the dissolution of the MNPs may also depend on the environment in which the culture medium is incubated.

d) 1.2% of the ion at zero time can be interpreted as impurities in the preparation of NPs or transformation into ion after irradiation. In order to be able to discriminate between the two hypotheses, MNPs would be the same as those used as "cold", building them starting from radioactive Fe-59.

CONCLUSIONS

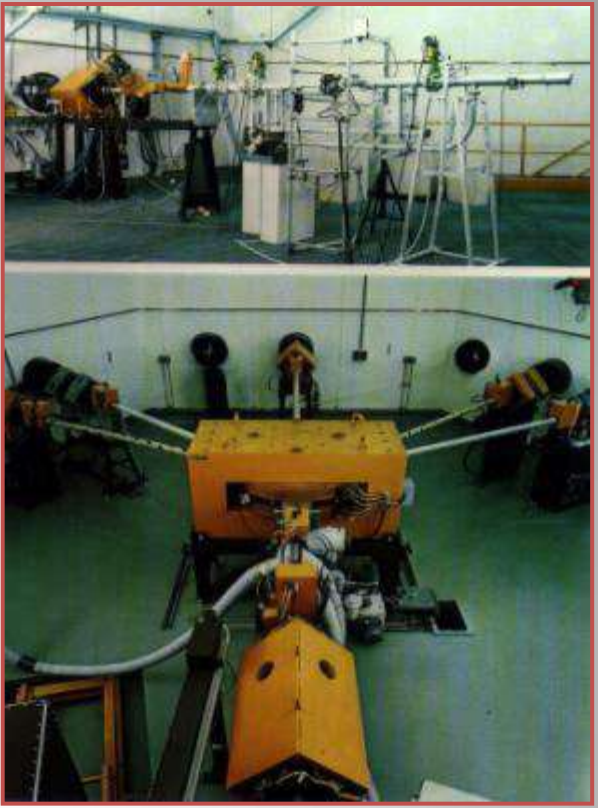
- There are different possibility to produce and to have theranostic radionuclides;
- The deuteron induced nuclear reactions can be a real challenger to obtain radionuclides with very high specific activity
- The problem is that the number of cyclotrons that can deliver deuterons with the suitable energies and beam current is very scarse.


SPES
www.lnl.infn.it
13/11/2014
13:00

HINPw5

Thank you for your kind attention

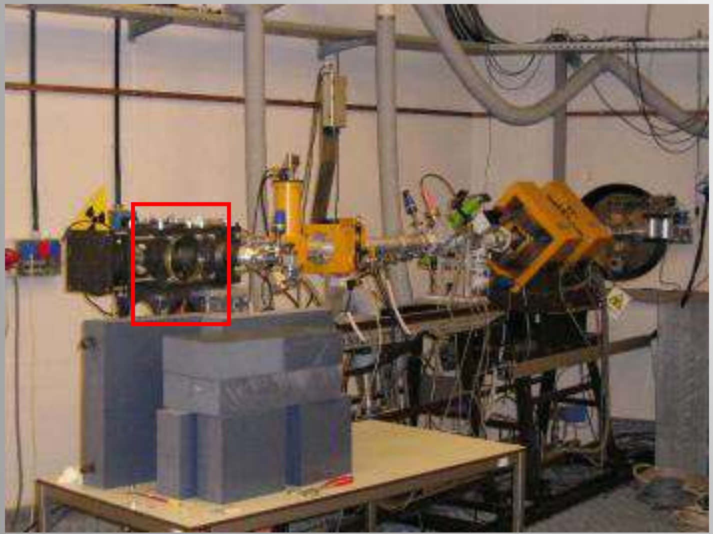
Typical Compact Cyclotron of Class II IHCP, JRC-Ispra of EC-Euratom



$$\frac{T_{max}(MeV)}{A} = K \cdot \left(\frac{Z}{A}\right)^2$$

- 2014: the only one accelerator in Italy at variable energy that can accelerate protons and alpha particles at energies up to 38 MeV and deuteron up to 19 MeV with a current up to 60 μA
- **NOW is SHUTTED DOWN**

Beam line 2



Irradiation Chamber

Solid Target Holder

Available online at www.sciencedirect.com

Applied Radiation and Isotopes 68 (2010) 1595–1601

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

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journal homepage: www.elsevier.com/locate/apradiso

Review

Production study of high specific activity NCA Re-186g by proton and deuteron cyclotron irradiation

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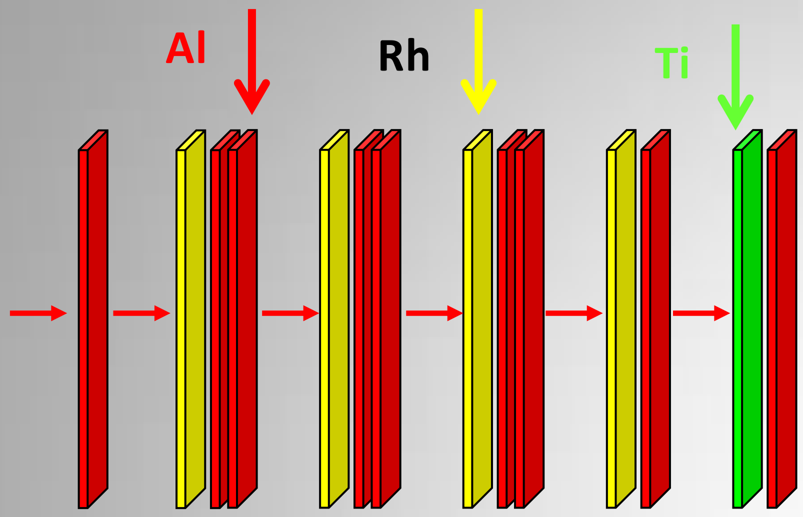
^{103}Pd production methods on ^{103}Rh target

- ^{103}Rh (p,n) **^{103}Pd** **NCA**
- ^{103}Rh (d,2n) **^{103}Pd** **NCA**

- The ^{103}Pd ($t_{1/2}$ = 17 d) is an effective alternative to ^{125}I ($t_{1/2}$ = 60 d) for brachytherapy of prostate cancer by implantation of seeds into the gland.

- In particular ^{103}Pd is used for tumors with larger Gleason Index than ^{125}I

Irradiation of thin Rh targets with the stacked foil technique



Al = degrader, catcher
Ti = monitor

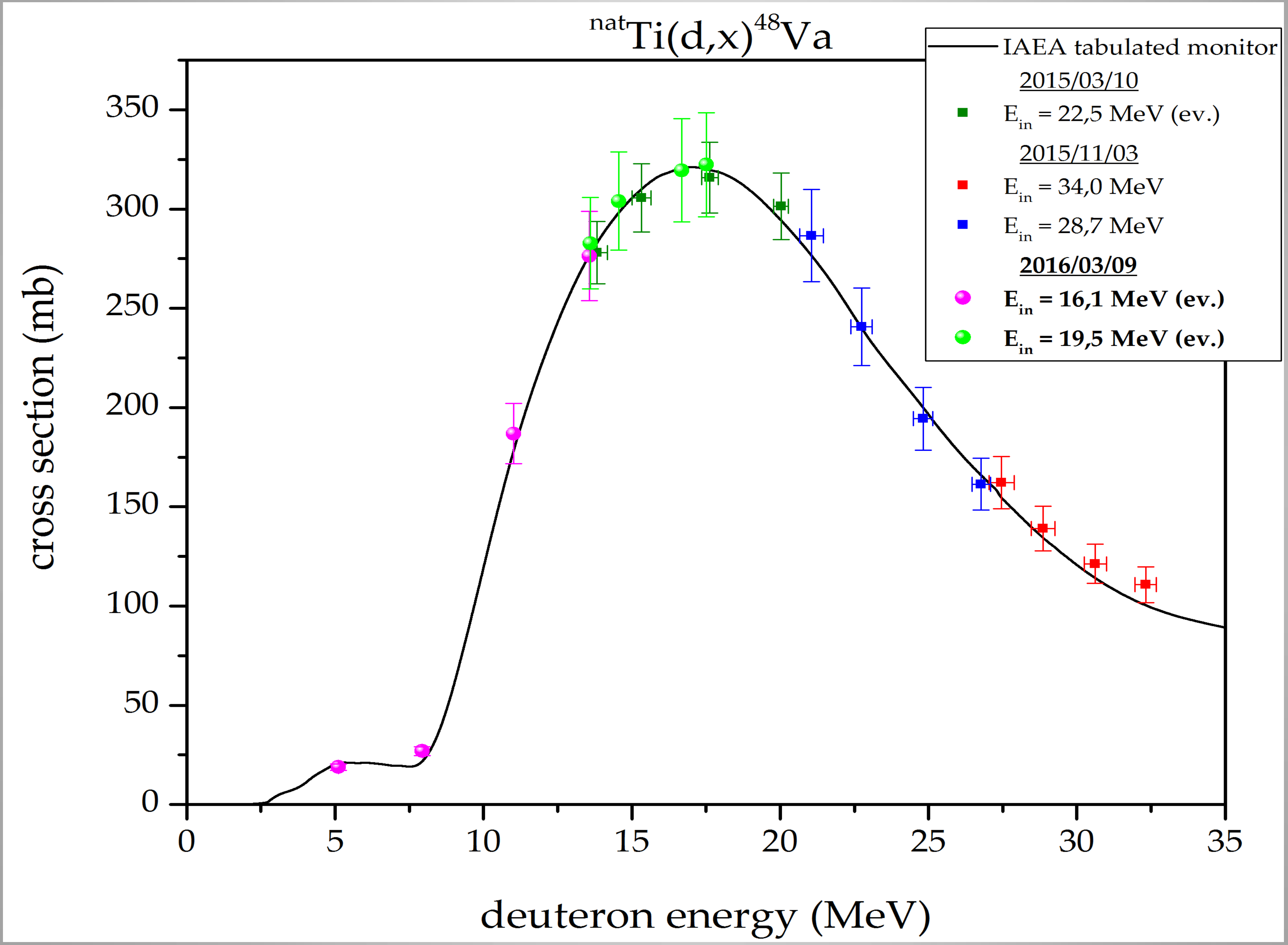
6 irradiations at Ispra Cyclotron

- **Thin natural Rh targets:** ***15.25 mg/cm^2***
- ***Irradiation time : 1 h***
- ***Beam current: 100 nA***

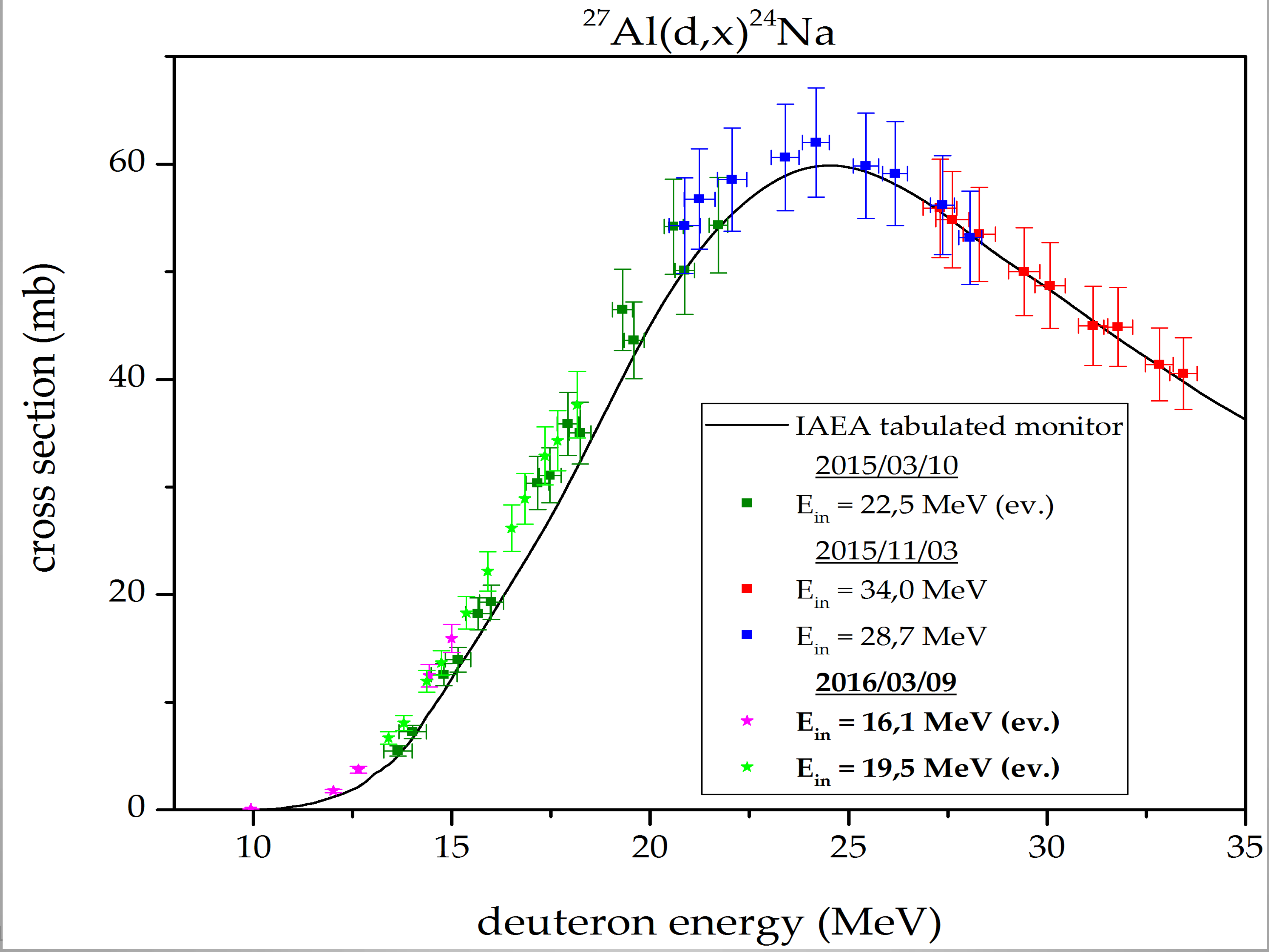
5 irradiations at ARRONAX, Nantes

- **Thin natural Rh targets:** ***15.25 mg/cm^2 and 31.75 mg/cm^2***
- ***Irradiation time: 160 min / 120 min***
- ***Beam current: 175 nA / 100 nA***

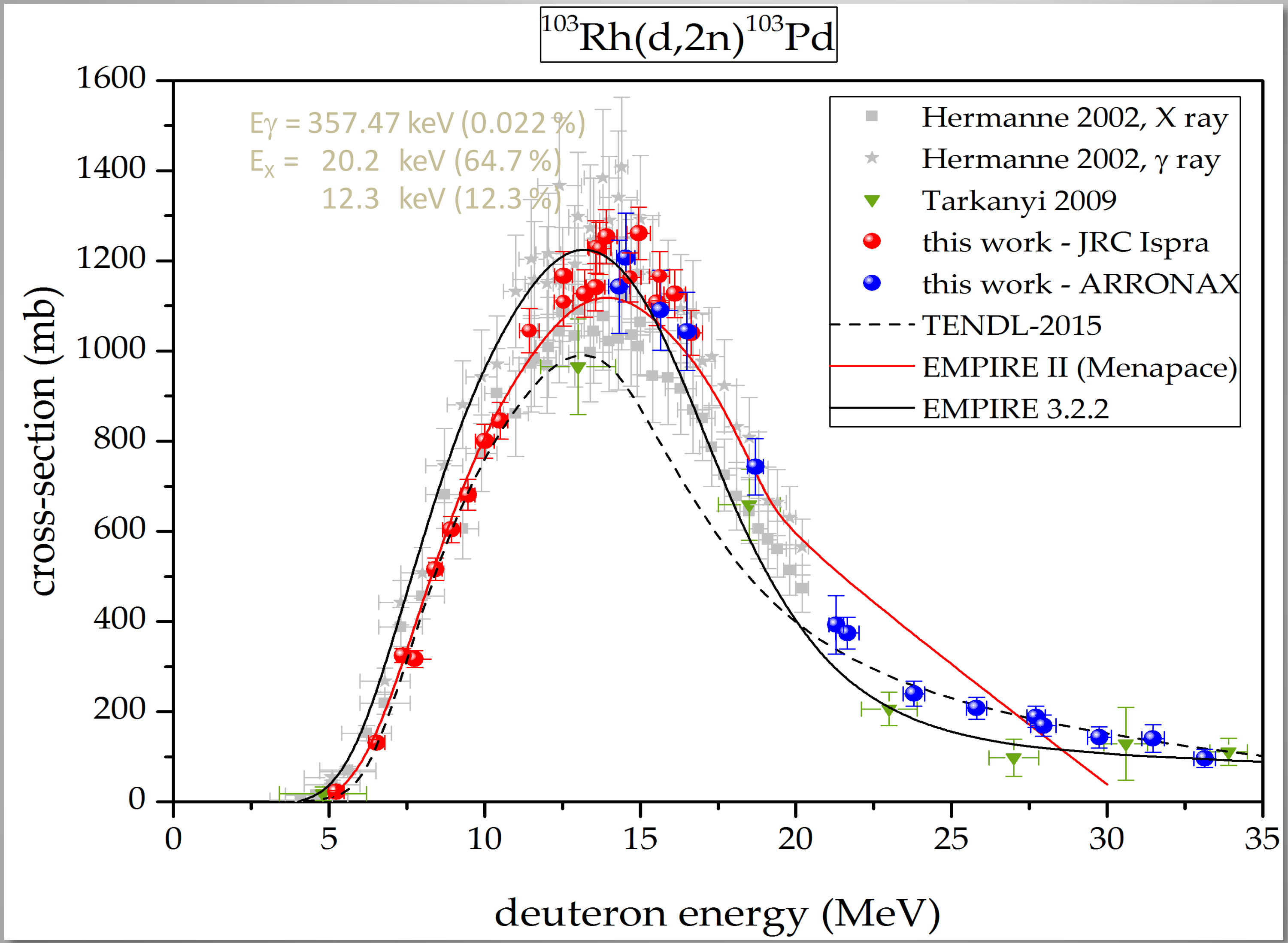
Cross Section of $^{nat}Ti(d,x)^{48}V$ monitor reaction



Cross Section of $^{27}Al(d,x)^{24}Na$ monitor reaction

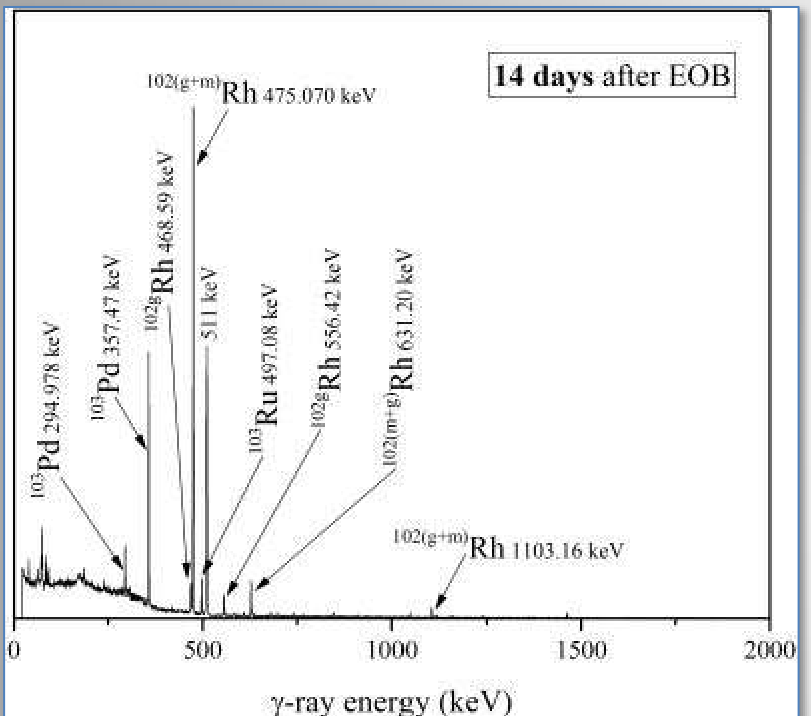


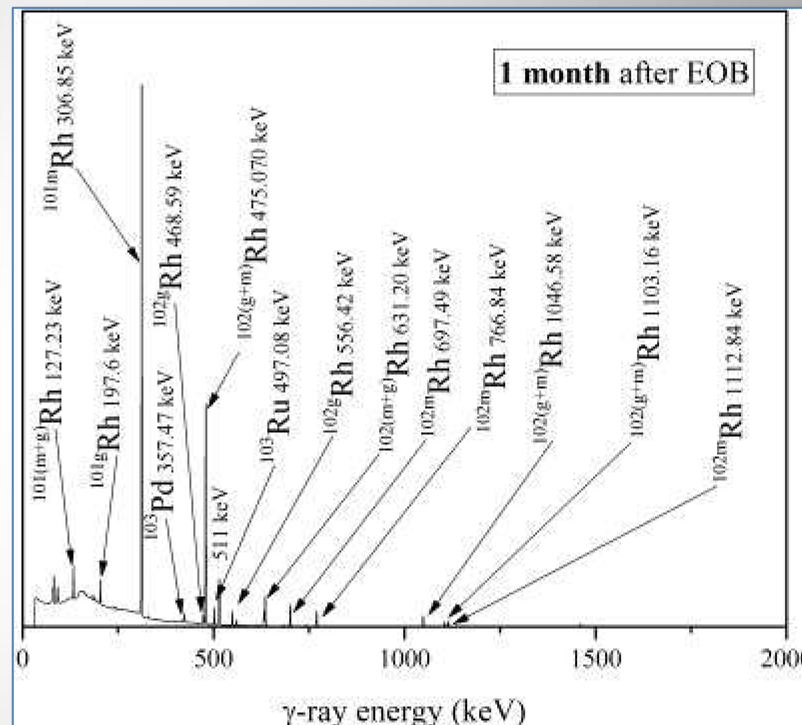
Cross Section of $^{103}Rh(d,2n)^{103}Pd$ ($t_{1/2}$ = 16.96 d)



Manenti, S., Alí Santoro, M.C., Cotogno, G., Duchemin,C., Haddad, F., Holzwarth, U., Groppi, F., 2017. Excitation function and yield for the $^{103}Rh(d,2n)^{103}Pd$ nuclear reaction: Optimization of the production of palladium-103, Nucl. Med. Biol., 49, 30-37

Examples of γ-ray spectra with the γ emissions of ^{103}Pd visible in spite of their low intensities



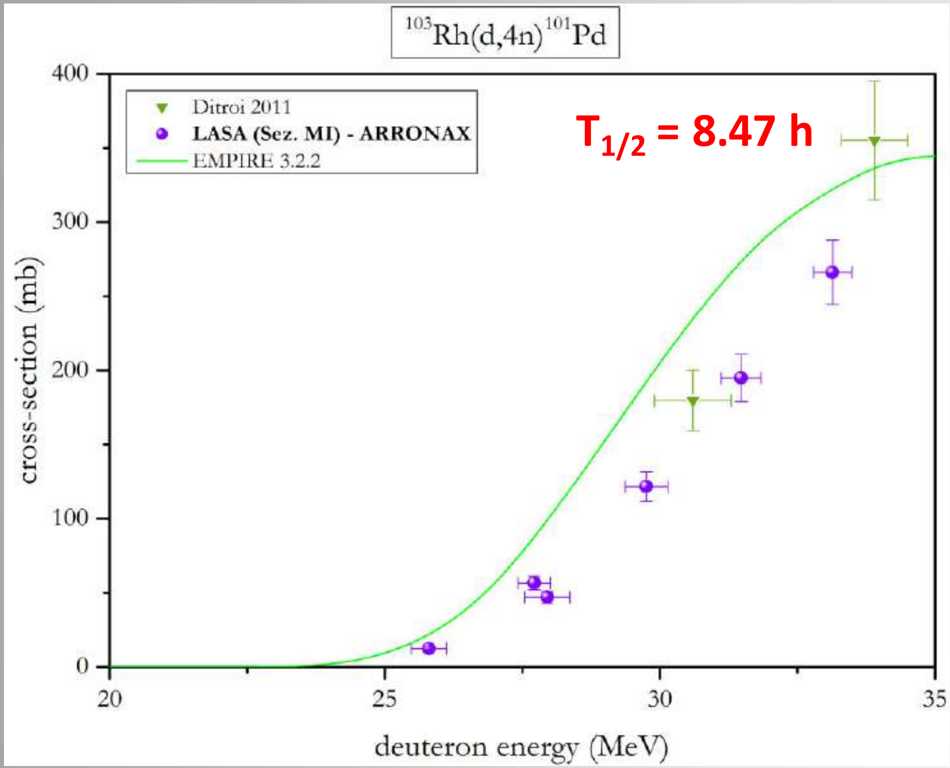


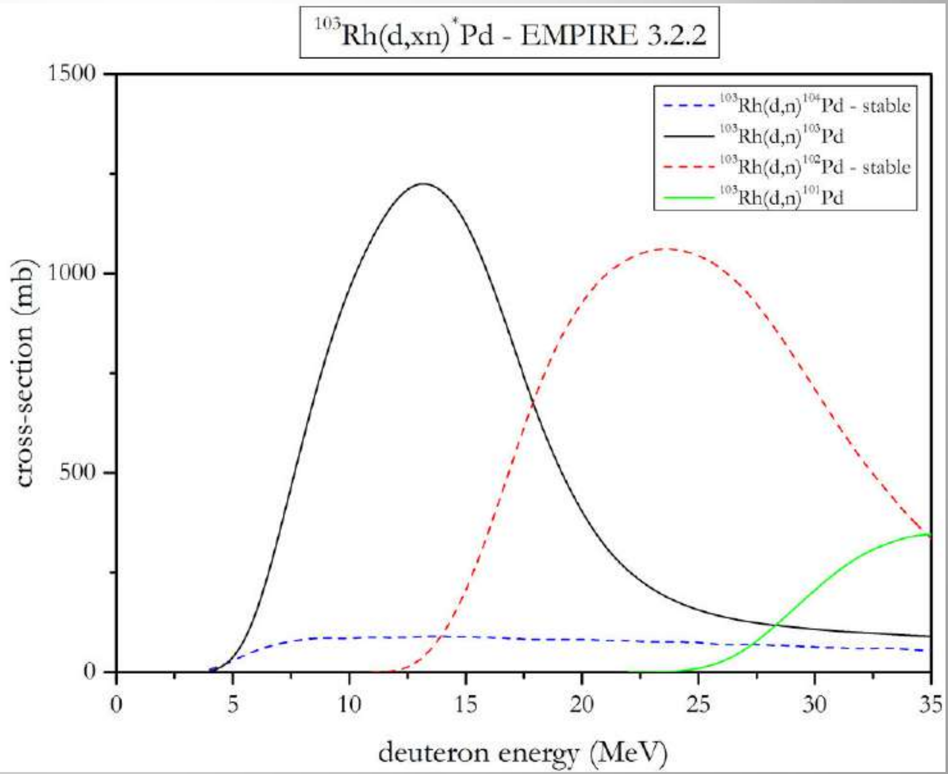
^{103}Pd

E_γ = 357.45 keV; I_γ = 0.0221 %

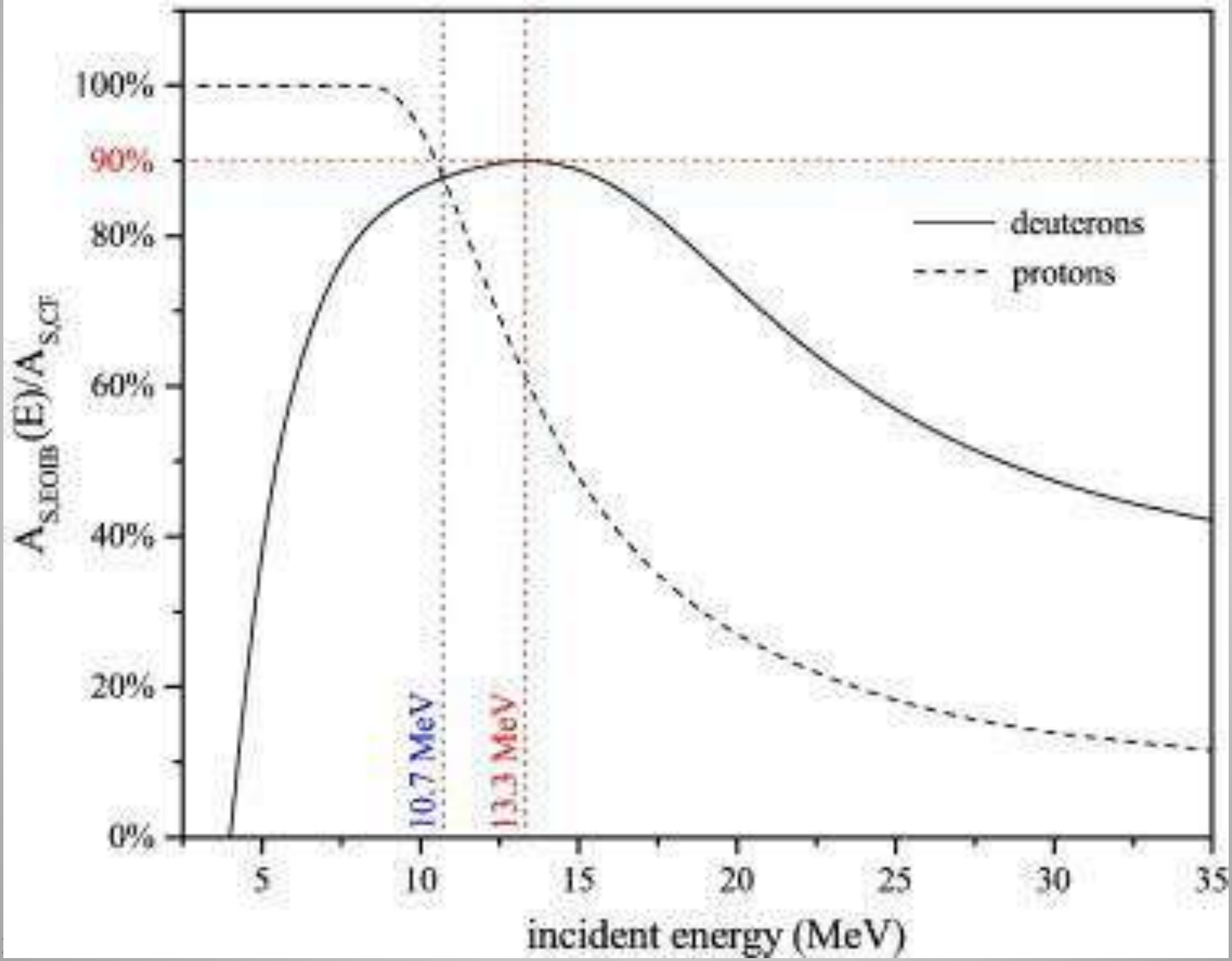
E_γ = 294.978 keV; I_γ = 0.00280 %

Radioisotopic impurities for AS determination in the ^{103}Pd production

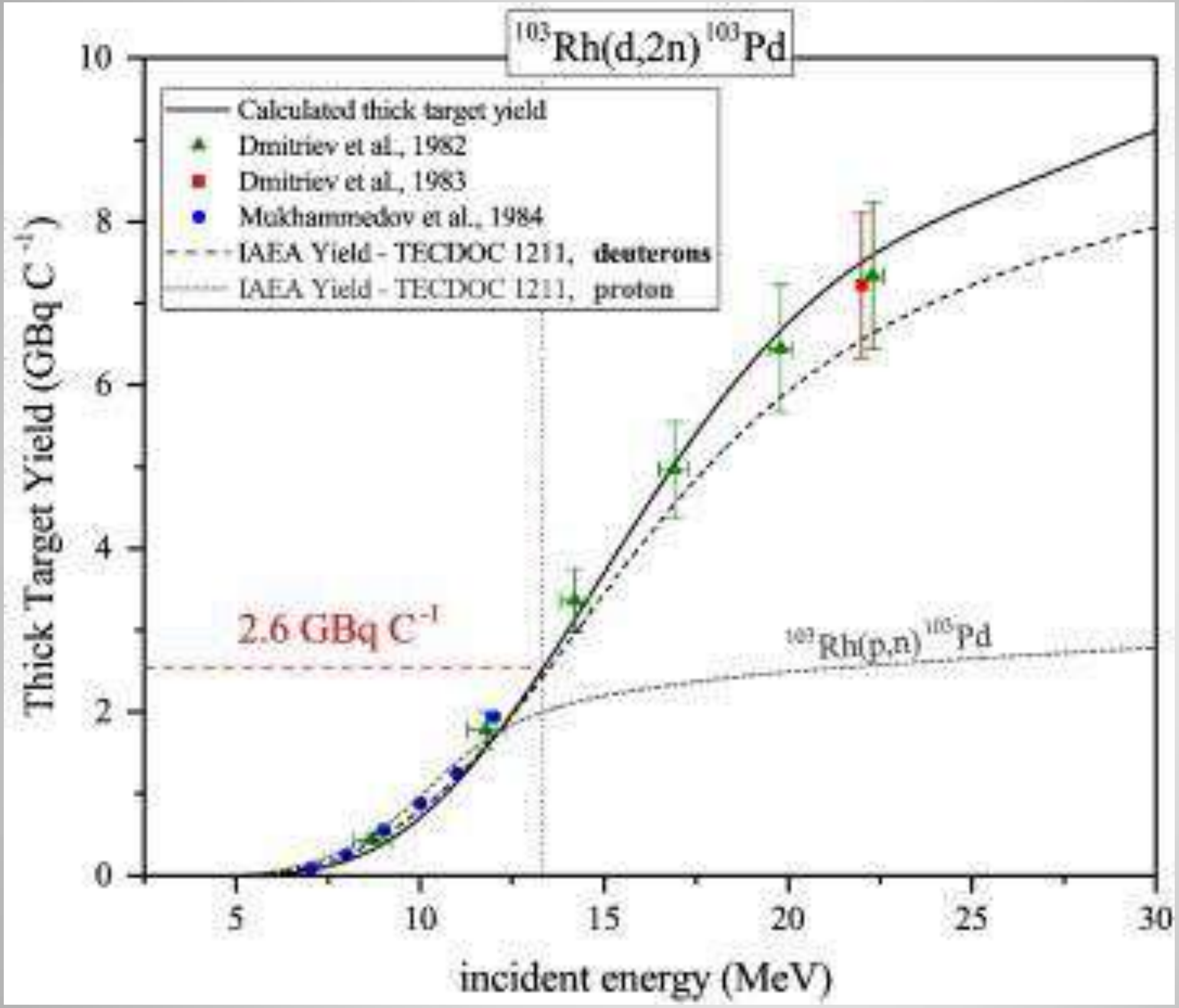




Ratio between the AS at the End Of an Instantaneous Bombardment and the AS(CF)

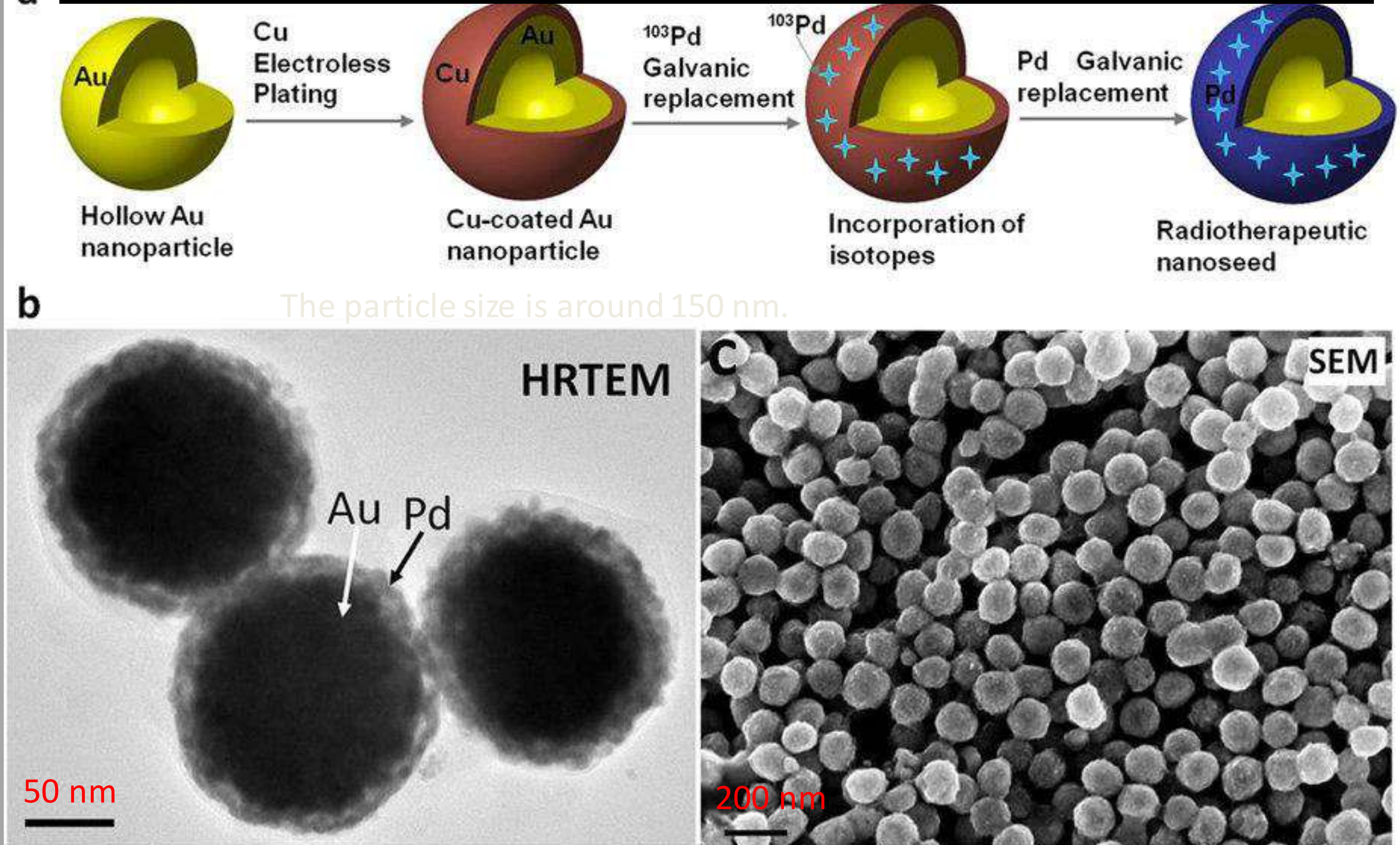


Calculated TTY for ^{103}Pd production



the TTYs obtained by protons are comparable up to 12 MeV with the one by deuterons but for higher particle energies the achievable TTY with deuterons is higher

Schematic of the process of incorporation of ^{103}Pd on hollow Au nanoparticles.

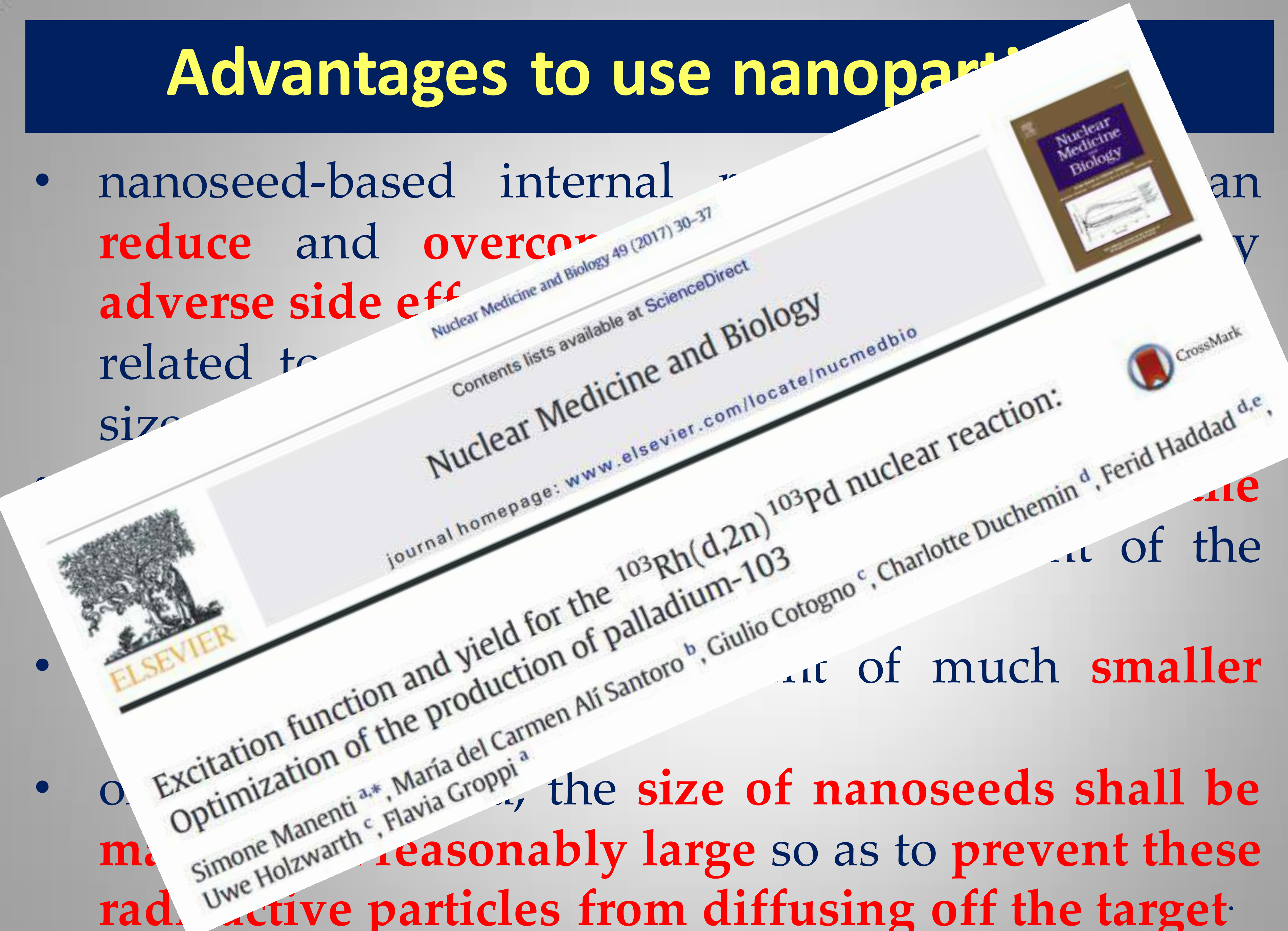


The particle size is around 150 nm.

Gently by: Moeendarbari, S. *et al.* Theranostic Nanoseeds for Efficacious Internal Radiation Therapy of Unresectable Solid Tumors, *Sci. Rep.* **6,** 20614; doi:10,1038/srep20614 (2016)

Advantages to use nanopart

- nanoseed-based internal … an **reduce** and **overco** … y **adverse side eff** … related to … size …
- … **the** … of the …
- … of much **smaller** …
- o… , the **size of nanoseeds shall be ma… reasonably large** so as to **prevent these rad… ctive particles from diffusing off the target**.


Nuclear Medicine and Biology 49 (2017) 30–37

Contents lists available at ScienceDirect

Nuclear Medicine and Biology

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CrossMark

Excitation function and yield for the $^{103}Rh(d,2n)^{103}Pd$ nuclear reaction: Optimization of the production of palladium-103

Simone Manenti [a,*], María del Carmen Alí Santoro [b], Giulio Cotogno [c], Charlotte Duchemin [d], Ferid Haddad [d,e], Uwe Holzwarth [c], Flavia Groppi [a]

Cross Section of $^{90}Y(d,2n)^{89}Zr$ ($t_{1/2}$ = 78.41 h)