REMIX
Research on Emerging Medical radIonuclides from the X-sections

Proposta sperimentale in CSN5

(2021 – 2022 – 2023)

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Responsabile Locale: Andrea Fontana

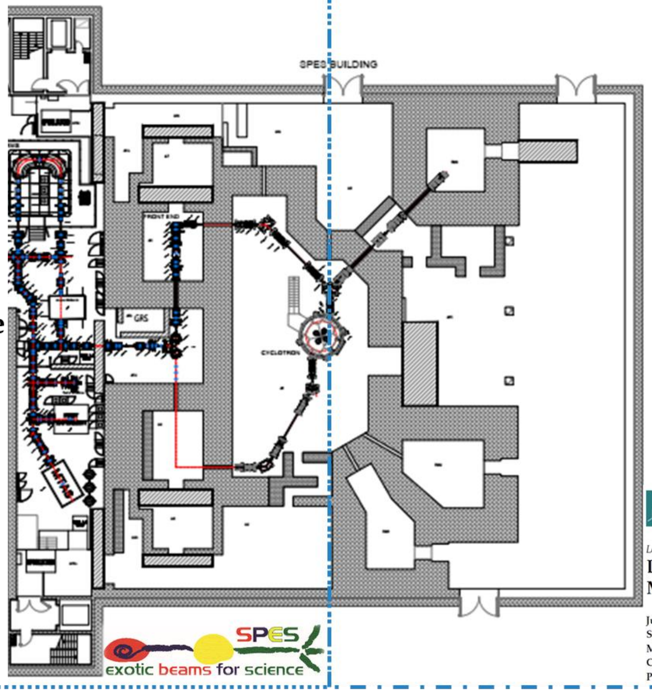
Sezioni INFN partecipanti: LNL, MI, PD

Aim of the project:

Study the production of **theranostic radionuclides** for innovative radiopharmaceuticals, considering the future LNL facility

Production of Medical-Radio-Isotope using the **ISOL technique**

ISOLPHARM
SPES exotic beams for medicine



Production of Medical-Radio-Isotope Using the **direct activation**

LARAMED

molecules **2019** MDPI

Letter

LARAMED: A Laboratory for Radioisotopes of Medical Interest

Juan Esposito [1], Diego Bettoni [1,2], Alessandra Boschi [3], Michele Calderolla [1], Sara Cisternino [1], Giovanni Fiorentini [2], Giorgio Keppel [1], Petra Martini [1,3,*], Mario Maggiore [1], Liliana Mou [1], Micòl Pasquali [1], Lorenzo Pranovi [1], Gaia Pupillo [1], Carlos Rossi Alvarez [1], Lucia Sarchiapone [1], Gabriele Sciacca [1], Hanna Skliarova [1], Paolo Favaron [1], Augusto Lombardi [1], Piergiorgio Antonini [1] and Adriano Duatti [1,4]

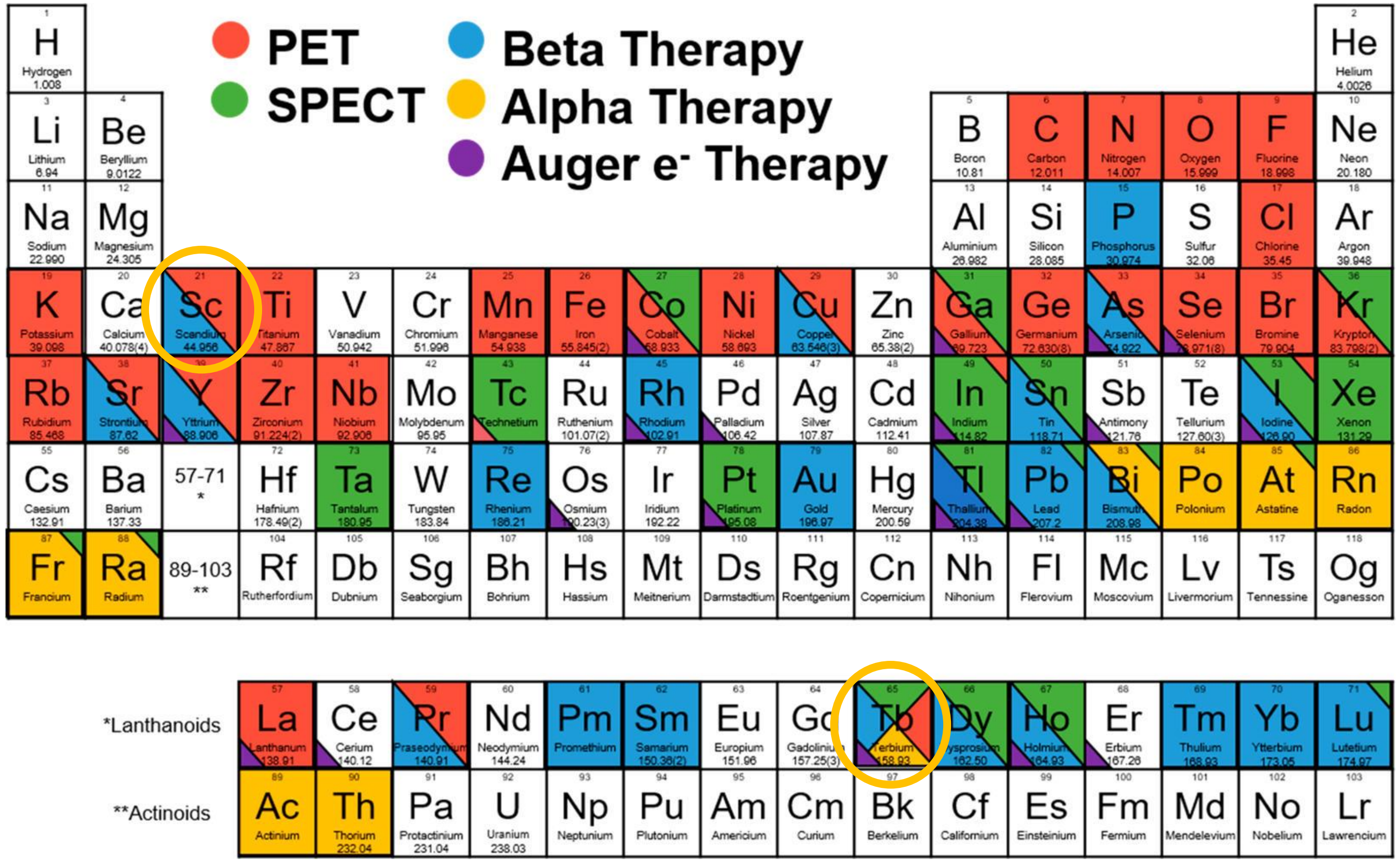
[*] Esposito J et al., Molecules **2019**, 24, 20; doi:10.3390/molecules24010020

INFN

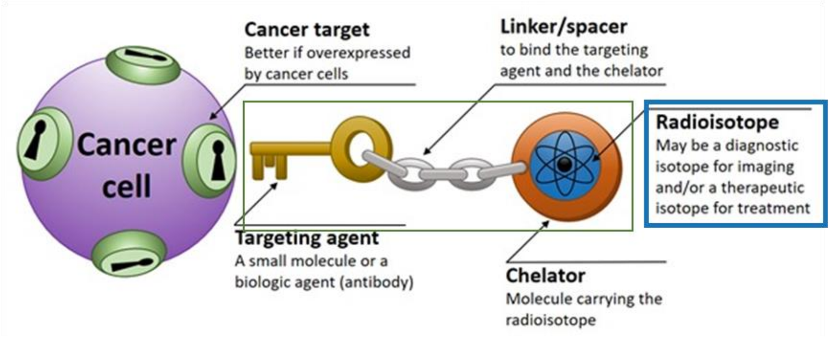
The LARAMED team has already investigated the nuclear cross sections for the production of the theranostic radionuclides:

- ^{67}**Cu** (COME project, 2016 and INFN Patent 2019)
- ^{47}**Sc** (PASTA project, 2017/2018)
- ^{52g}**Mn** (METRICS project, 2018/2021)
- ^{117m}**Sn** (ENSAR2 project, 2018/2020)
- …

Theranostic chart



Schematic structure of a typical **radiopharmaceutical**



The emitted radiation is the molecular probe:

- **Diagnosis:** γ-rays for SPECT and β^+ for PET imaging
- **Therapy:** β^-, Auger electrons and α particles

Why Scandium and Terbium?

		IMAGING		THERAPY		
Isotope	Half-life	β^+ $E_{average}$ [keV] (I)	x and γ with I > 10% E [keV] (I)	β^- $E_{average}$ [keV] (I)	Conv. & Auger electrons (>1 keV) $E_{average}$ [keV] (I)	α E [keV] (I)
^{43}Sc	3.9 h	476 (88%)	372 (23%)	–		–
^{44}Sc	4.0 h	632 (94%)	1157 (100%)	–		–
^{47}Sc	3.35 d	–	159 (68%)	162 (100%)		–
^{149}Tb	4.1 h	730 (7%)	42–50 (69%), 165 (26%), 352 (29%), etc.	–	32 (85%)	3967 (17%)
^{152}Tb	17.5 h	1140 (20%)	42–50 (65%), 344 (64%)	–	36 (69%)	–
^{155}Tb	5.32 d	–	42–50 (108%), 87 (32%), 105 (25%)	–	19 (204%)	–
^{161}Tb	6.89 d	–	45–53 (39%), 75 (10%)	154 (100%)	19 (227%)	–

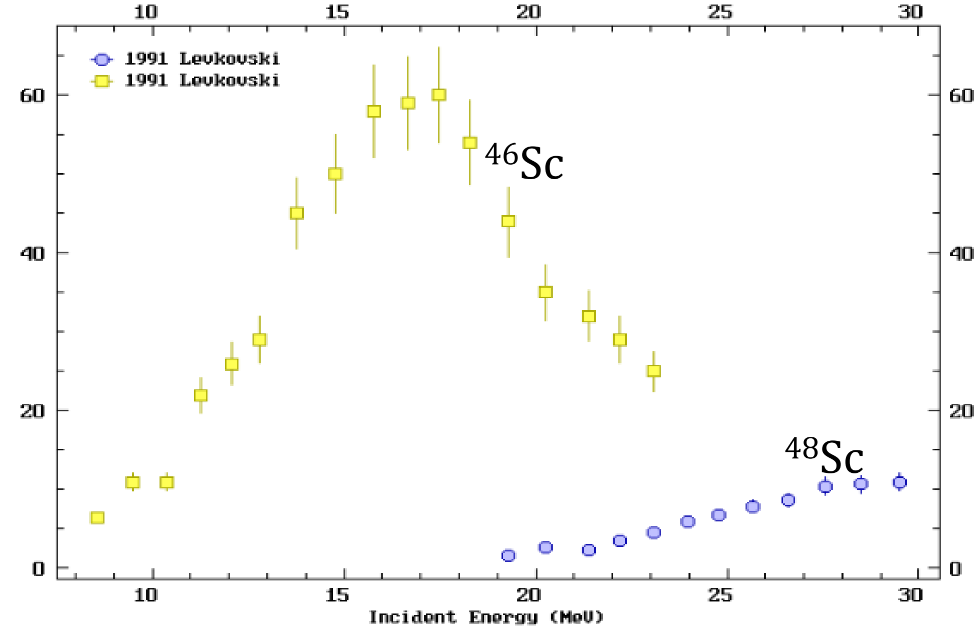
The goal of this project is to study the **production routes** of ^{47}Sc and Terbium-isotopes

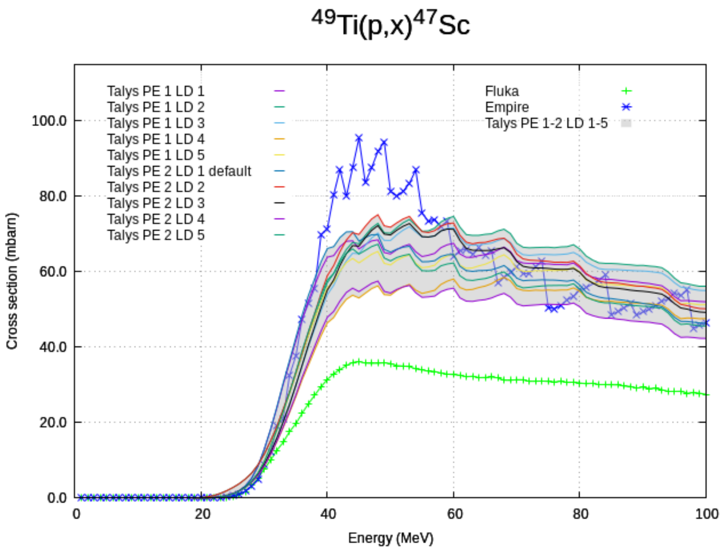
Production routes for ^{47}**Sc**: Ti-49 and Ti-50

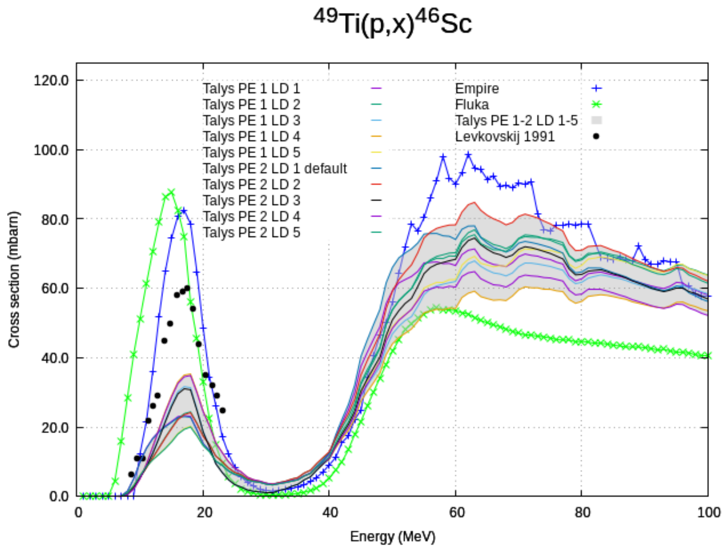
Target (abundance)	**Measured cross section**	**Comment**
Ti-48 (73.73%)	• *Gadioli et al* (1981): **Sc-47**, Sc-46, Sc-44, Sc-43 (V-48, V-47, K-43, K-42, Cl-39, Cl-34m) ▪ *Levkovskij* (1991): **Sc-47**, Sc-44m, Sc-44 (V-48, V-47)	Experiments done with oxide Ti-48 (99.1%) Not all the contaminant radionuclides were measured → **It is important to verify the cross sections** by using updated nuclear data and metal targets (highest available enrichment)
Ti-49 (5.41%)	▪ *Levkovskij* (1991): Sc-48, Sc-46 (V-48)	**No experimental data for Sc-47!**
Ti-50 (5.18%)	• *Gadioli et al* (1981): Sc-48, **Sc-47**, Sc-46, Sc-44, Sc-43 (K-43, K-42, Cl-39, Cl-38)	Experiments done with oxide Ti-50 enriched 69.7% and corrected with exp data for contamination of Ti-48 (23%) and theoretical data for Ti-49 (2.0%), Ti-47 (2.4%) and Ti-46 (3.1%)
V-nat (V-51: 99.750%)	➢ **Many authors**: Sc-48, **Sc-47**, Sc-46, Sc-44m, Sc-44, Sc-43 (V-48, Cr-48, Cr-49, Cr-51, K-43, K-42)	Very interesting due to the **low cost** and **highly available material**; it is important to **verify quantity and quality of produced Sc-47**

$^{49}Ti(p,x)^{47}Sc, ^{xx}Sc$

EXFOR: $^{49}Ti(p,x)$





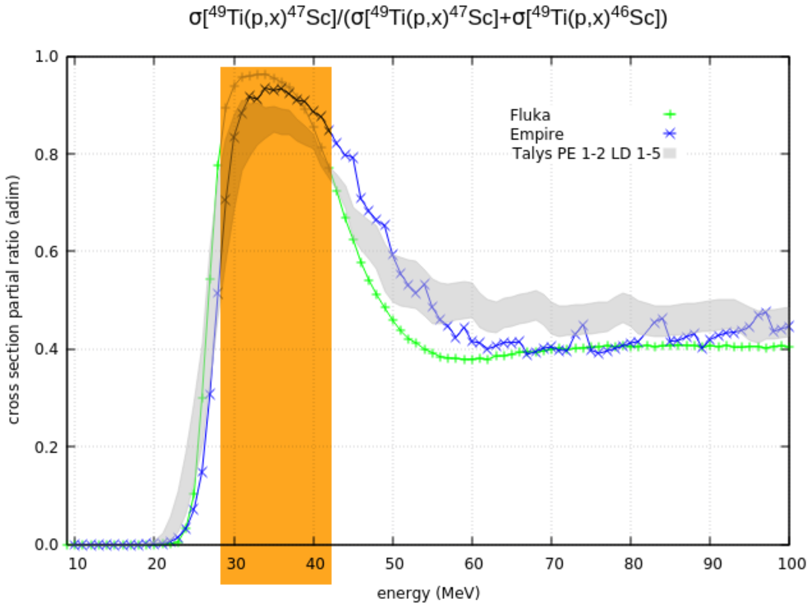


Modeling calculations

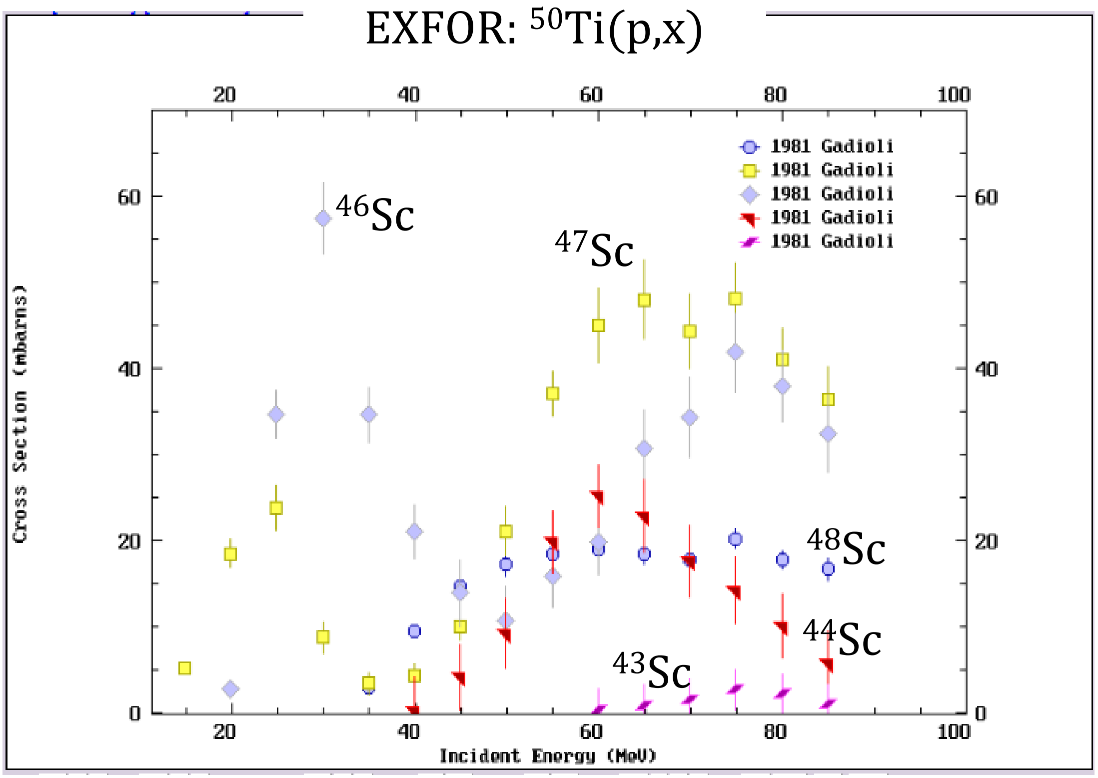
(TALYS, FLUKA, EMPIRE)

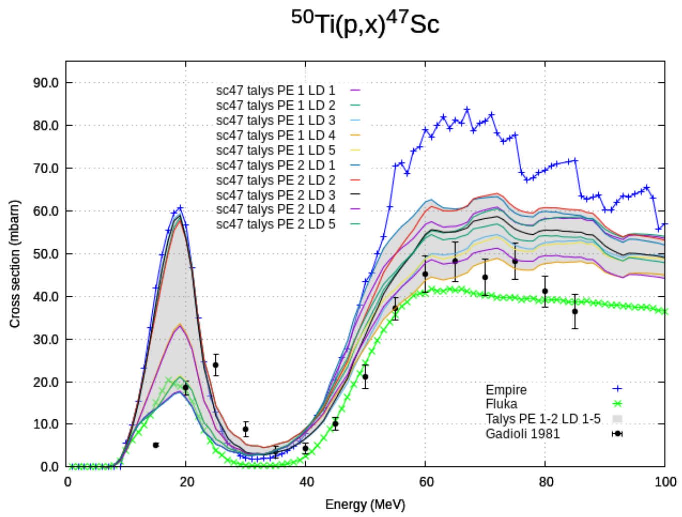
Ti-49

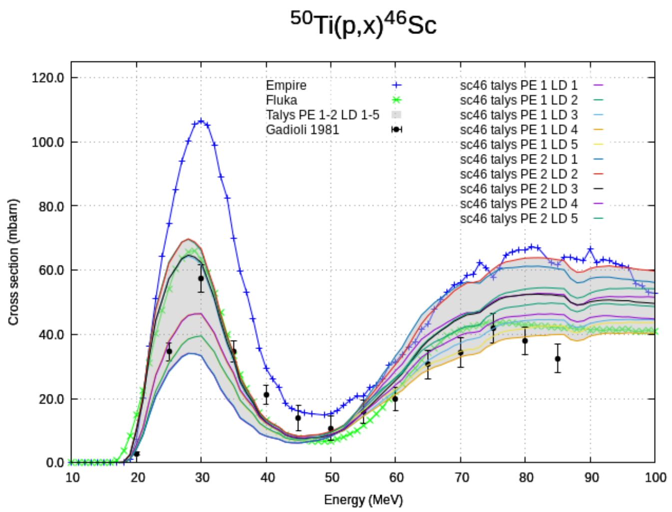
25-40 MeV



$^{50}Ti(p,x)^{47}Sc,^{xx}Sc$





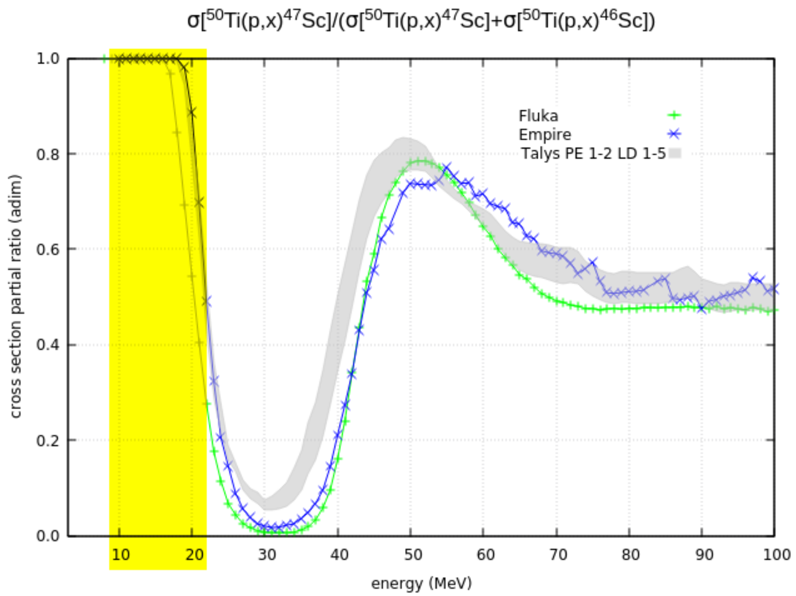


Modeling calculations

(TALYS, FLUKA, EMPIRE)

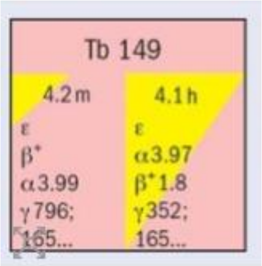
Ti-50

10-20 MeV



Terbium: *Swiss army knife for nuclear medicine*

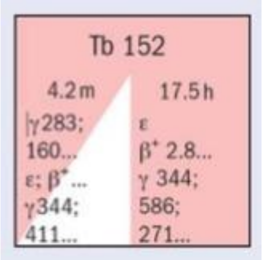
https://cerncourier.com/a/terbium-a-new-swiss-army-knife-for-nuclear-medicine/



Radiation:
α , β+ , Auger e- , γ

Ground and isomeric state information for $^{149}_{65}$Tb

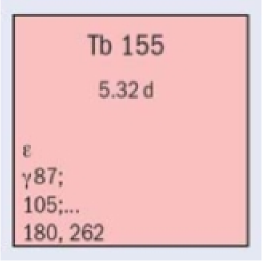
E(level) (MeV)	Jπ	Δ(MeV)	$T_{1/2}$	Decay Modes
0.0	1/2+	-71.4886	4.118 h *25*	ε : 83.30 % α : 16.70 %
0.0358	11/2-	-71.4528	4.16 m *4*	ε : 99.98 % α : 0.02 %



Radiation:
β+ , Auger e- , γ

Ground and isomeric state information for $^{152}_{65}$Tb

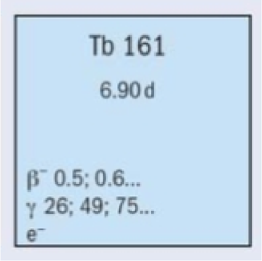
E(level) (MeV)	Jπ	Δ(MeV)	$T_{1/2}$	Decay Modes
0.0	2-	-70.7169	17.5 h *1*	ε : 100.00 % α < 7.0E-7 %
0.5017	8+	-70.2152	4.2 m *1*	IT : 78.80 % ε : 21.20 %



Radiation:
Auger e- , γ

Ground and isomeric state information for $^{155}_{65}$Tb

E(level) (MeV)	Jπ	Δ(MeV)	$T_{1/2}$	Decay Modes
0.0	3/2+	-71.2500	5.32 d *6*	ε : 100.00 %



Radiation:
β- , Auger e- , low energy γ
(74 keV, 10%)

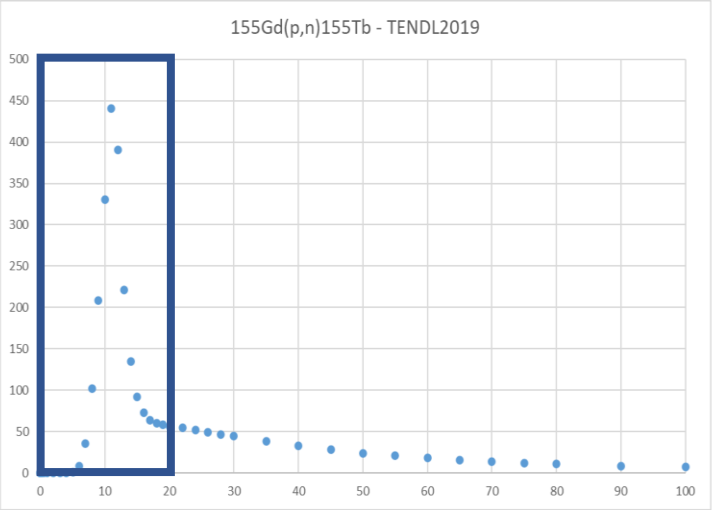
Ground and isomeric state information for $^{161}_{65}$Tb

E(level) (MeV)	Jπ	Δ(MeV)	$T_{1/2}$	Decay Modes
0.0	3/2+	-67.4615	6.89 d *2*	β^- : 100.00 %

Terbium: very rich production and decay network

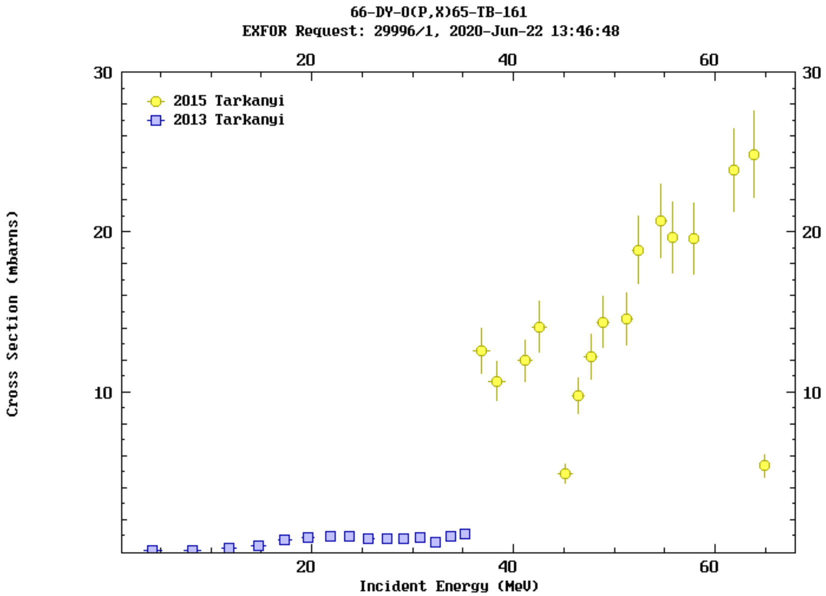
List of priorities:

Experimental measurements of the reactions during the years 2022 - 2023:



- **^{155}Gd(p,n)^{155}Tb** (half-life 5.32 d ; Auger e- , γ) → No experimental data on EXFOR (Ep < 20)
  - Comparison with the **^{nat}Gd(p,x)^{155}Tb** route (experimentally and theoretically)

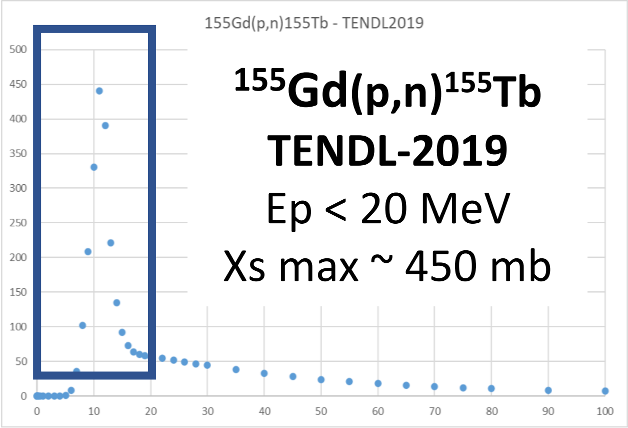
- **^{nat}Dy(p,x)^{161}Tb** (half-life 6.91 d; Auger e- , γ @ 74 keV) → Experimental data with questionable trend up to 70 MeV
  - Study of the co-production of contaminant **^{xxx}Tb**



Theoretical and dosimetric calculations are necessary to compare the production of **^{xxx}Tb isotopes** by using **^{nat}Gd and/or ^{nat}Dy** targets

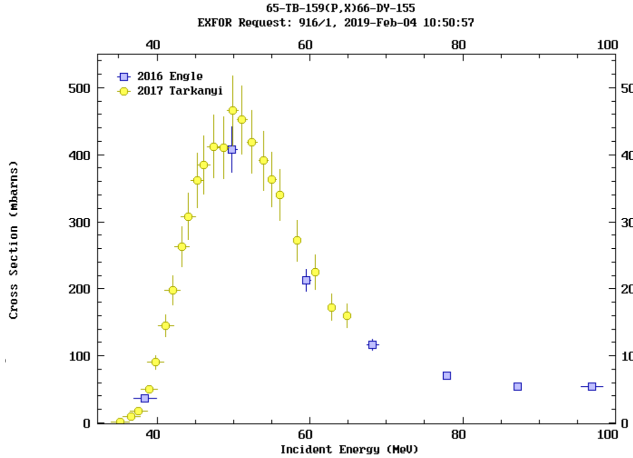
Tb-155 .

Gd-155 oxide with I.E. 90,4atom%: ~ US$10.00 per mg of Gd-element weight;
Gd-155 metal foils with I.E. 91,7atom%: ~ US$29.00 per mg (ISOFLEX June2020)



- **^{155}Gd(p,n)^{155}Tb** interesting to **measure the TTY @ Sacro Cuore Don Calabria hospital**
  - We can try to test SPS with $^{nat}Gd_2O_3$ and then $^{155}Gd_2O_3$
    - → It is important to have @ LNL the SPS machine and infrastructure!
  - The economical quotation for **$^{155}Gd_2O_3$ is expensive**, but not prohibitive

- **^{nat}Gd(p,x)^{155}Tb** it is ok to measure it, with all the co-produced contaminants; no issue for thin target foils

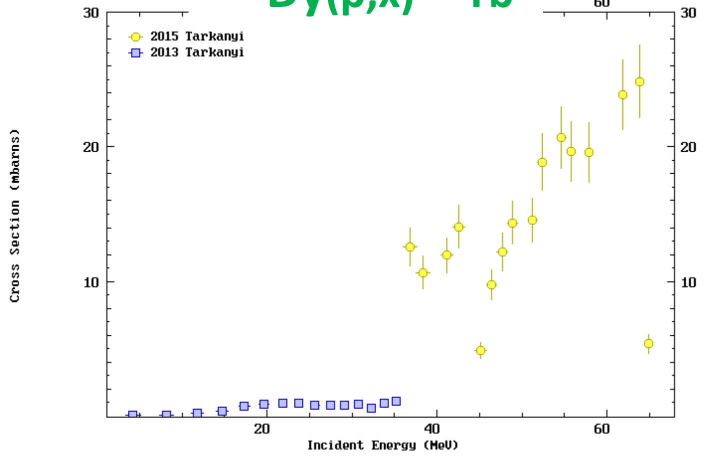


- ^{159}Tb(p,5n)^{155}Dy (half-life 10.0 h) → ^{155}Tb . Advantages: natural target material and need of a 70 MeV proton beam. Disadvantages: complicated chemistry and need to study the co-production of ^{xxx}Dy radionuclides that may decay to ^{xxx}Tb (e.g. ^{157}Dy, half-life 8.14 h→^{157}Tb, half-life 71 y), affecting the radionuclidic purity of ^{155}Tb.

Modeling and dosimetric studies are necessary to evaluate a possible future production route of ^{155}Tb @ LNL

Tb-161 .

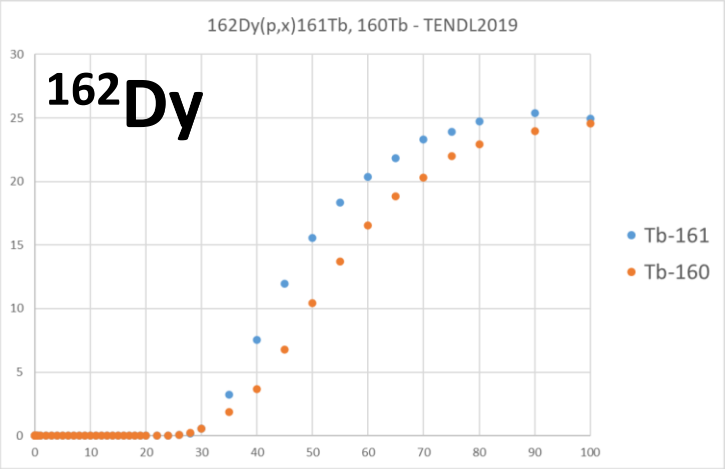
$^{nat}Dy(p,x)^{161}Tb$

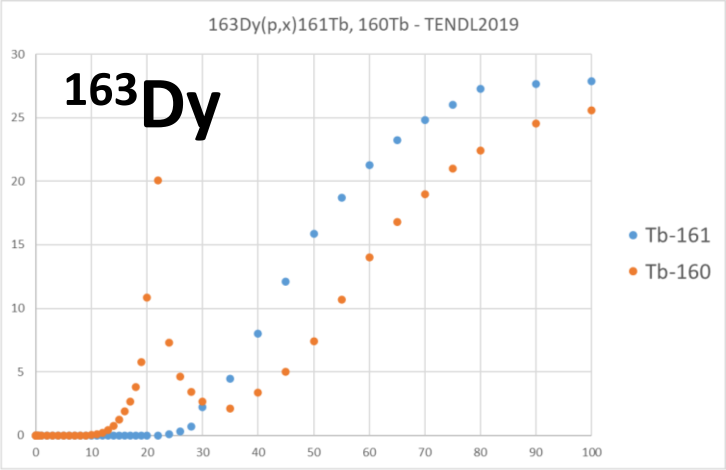


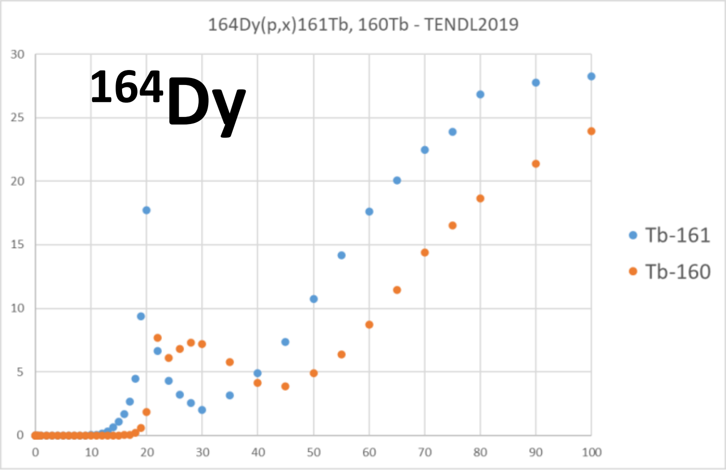
- $^{160}Gd(p,\gamma)^{161}Tb$ not interesting due to the very low predicted xs
- **$^{nat}Dy(p,x)^{161}Tb$** it is ok to measure it, with all the co-produced contaminants; no issue for thin target foils

^{nat}Dy commercial foils are available

- The reactions on enriched targets (^{162}Dy, ^{163}Dy, ^{164}Dy) have to be evaluated first by modeling and dosimetric calculations. It is not an experimental priority.







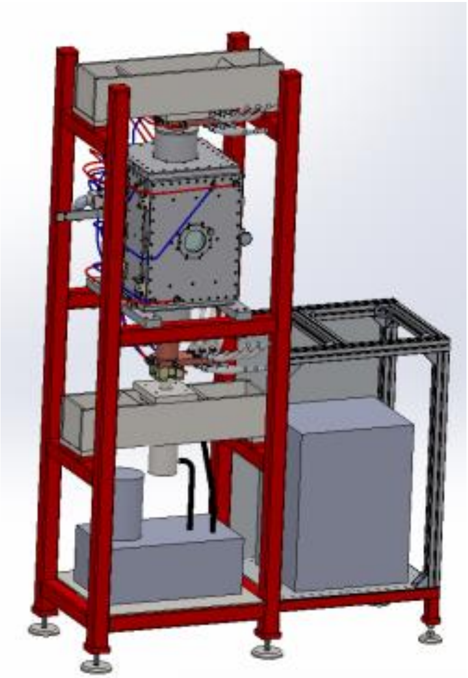
REMIX project activities plan:

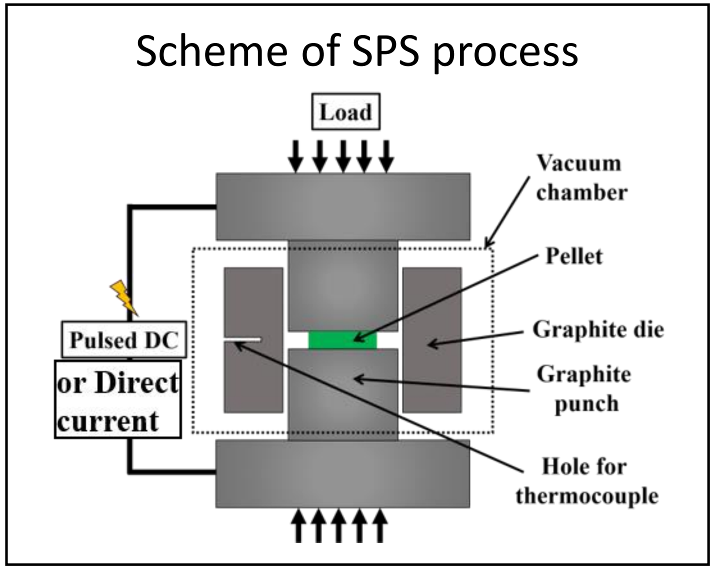
	2021	2022	2023
Theory			
PV-PD	^{47}**Sc** decay chain, isotopic and radionuclidic purities and yields.	^{155}**Tb** and ^{155}**Tb** decay chain, isotopic and radionuclidic purities. Development of a tool to handle complex decay chains and to identify the optimal conditions and experimental parameters for a production of radionuclides	Yields and purities for ^{155}**Tb** and ^{155}**Tb.** Assessment of theoretical uncertainties. Comparison with experimental data. Dosimetry calculations in collaboration with IOV.
Experiment			
LNL	^{49}**Ti(p,x)**^{47}**Sc,**^{xx}**Sc** xs measurement @ ARRONAX (no. 4 run)	^{50}**Ti(p,x)**^{47}**Sc,**^{xx}**Sc** xs measurement @ ARRONAX (no. 4 run) Target preparation and irradiation tests with ^{nat}**Gd**$_2$**O**$_3$ **targets** @ Sacro Cuore Don Calabria hospital (Negrar, VR)	^{nat}**Dy(p,x)**^{161}**Tb,** ^{xxx}**Tb** xs measurement @ ARRONAX (no. 4 run) No. 1 irradiation run with enriched ^{155}**Gd**$_2$**O**$_3$ **targets for** ^{155}**Tb** @ Sacro Cuore Don Calabria hospital (Negrar, VR) **Test @ LNL** with the new LARAMED L3c beam-line (100 nA)
MI	^{nat}**Gd(p,x)**^{161}**Tb,** ^{xxx}**Tb** xs measurement @ ARRONAX (no. 1 run)	^{nat}**Gd(p,x)**^{161}**Tb,** ^{xxx}**Tb** xs measurement @ ARRONAX (no. 2 run)	^{nat}**Gd(p,x)**^{161}**Tb,** ^{xxx}**Tb** xs measurement @ ARRONAX (no. 2 run)

SPS machine design

- Gd_2O_3 pellets (1 mm thick) will be manufactured by SPS technique [1] with SPS prototype machine that will be installed at LARAMED target laboratory: $^{nat}Gd_2O_3$ SPS parameters optimization and then $^{155}Gd_2O_3$ targets manufacturing

- La macchina SPS arriva a LNL (con manuali) a fine 2021.
- Durante il 2021 si potrà utilizzare, anche se resterà installata a Pavia (dato che a LNL il lab bersagli dell'edifice SPES non sarà terminato).
- E' previsto il collaudo della macchina SPS a Pavia entro 2020





[1] Awin, E. W et al., Structural, functional and mechanical properties of spark plasma sintered gadolinia (Gd_2O_3). *Ceramics International* **42**, 1384–1391 (2016).

Richieste economiche ed FTE

		missioni		consumo	trasporti	manutenzione	inventario	spservizi	TOTALI
	2021	estere	interne						
LNL		16	2	14			4	2	38
PD			2				2,5	2	6,5
PV			2				1,5		3,5
MI		3		2	3	2			10
								totale	58
	2022								
LNL		16	2	20				2	40
PD			2					2	4
PV			2						2
MI		4		5	6	2	2		19
								totale	65
	2023								
LNL		12	4	1,5				2	19,5
PD			2					2	4
PV			2						2
MI		4		5	6	2	2		19
								totale	44,5
								TOT	167,5

Lettere di supporto al progetto REMIX

Arronax Nantes

SACRO CUORE DON CALABRIA — Istituto Don Calabria IRCCS Ospedale Sacro Cuore Don Calabria — Presidio Ospedaliero Accreditato - Regione Veneto

I.O.V. — Istituto Oncologico Veneto I.R.C.C.S.

Forte interesse per le ricadute del progetto REMIX sia nel mondo scientifico che medicale

Nome	M/F	Sezione	2021	
<u>Pupillo</u>	F	LNL	0.8	**FTE LNL: 3.0** Misure sperimentali (ARRONAX, ospedale Sacro Cuore, LNL) e coordinamento del progetto
Mou	F	LNL	0.7	
Cisternino	F	LNL	0.6	
Martini	F	LNL	0.2	
Pasquali	F	LNL	0.2	
Sciacca	M	LNL	0.2	
Esposito	M	LNL	0.1	
Rigato	M	LNL	0.1	
Campostrini	M	LNL	0.1	
Groppi	F	MI	0.35	**FTE MI: 1.45** Misure sperimentali (ARRONAX)
Manenti	M	MI	0.4	
Cagnetta	F	MI	0.2	
Harki	F	MI	0.5	
Fontana	M	PV	0.6	**FTE PV: 1.8** Modellistica nucleare
Carante	M	PV	0.4	
Ballarini	F	PV	0.3	
Embriaco	F	PV	0.5	
Canton	M	PD	0.4	**FTE PD: 2.5** Modellistica nucleare e calcoli dosimetrici (IOV)
De Nardo	F	PD	0.5	
Melendez-Alafort	F	PD	0.8	
Turato	F	PD	0.8	