INFN-LNL-256(2019)

Report 2017 - PASTA Project

Production with Accelerator of Scandium-47 for Theranostic Applications

OUTLINE

1. PASTA project - 2017: FTE, Finanziamento e rendicontazione di spesa
2. Scientific Activity (year 2017)
   - TEST TO REALIZE METALLIC TARGETS OF ENRICHED TITANIUM
   - IRRADIATION RUN AT ARRONAX FACILITY
   - CHEMICAL TEST
   - THEORETICAL STUDIES ON NUCLEAR CROSS SECTIONS
3. MILESTONE 2017
4. Congress, workshop, pubblications

1. PASTA project – 2017

	FTE (LNL)		FTE (FE)		ARRONAX
Gaia Pupillo	1.0	Micòl Pasquali	0.8	Ferid Haddad	-
Liliana Mou	0.5	Alessandra Boschi	0.5	Cyrille Alliot	-
Petra Martini	0.5	Adriano Duatti	0.5	Thomas Sounalet	-
TOT FTE - PASTA 2017 – 3.8					

Funding – year 2017	LNL (k€)	FE (k€)
MISSIONI* - Irradiation runs at Arronax (Nantes, Francia)	8	-
CONSUMO – Enriched material for thin targets, radiochemicals and consumables	12	8
TRASPORTO – Radioactive transport from Arronax (Nantes) to LNL (PD, Italy)	3	
Total	23	8
Total – PASTA Project 2017	31 k€	

I fondi della voce TRASPORTO sono stati stornati su INVENTARIABILE (1 k€, per l'acquisto di un Personal Computer) e su CONSUMO (2 k€).

Rendicontazione spese CONSUMO – Sezione LNL (14 k€)

Materiale / Ditta	Spese IVA inclusa
500 mg Ti-48 Trace Sciences International Corp.	7.378,53
Goodfellow Al 250 um, 10 um 100 um – giugno 2017	476,35
Goodfellow Al 50 um, 25 um (credit card) settembre 2017	252,57
Alfa Aesar 10 g Ti-nat metallico mesh 325 (Arronax)	106,80
Prodotti Gianni (vari foils) – 30/10/2017	2.077,00
Materiale vario per realizzazione porta-target – RS + ABC tools	2.631,33
Fustella + pressa Venturini store SRL – 18/10/2017	106,80
RDO - No.4 hard disk esterni 2 TB – ottobre 2017	273,28
RDO - Materiale radiochimico vario – ottobre 2017	749,29
Total	**€ 14.051,95**

Rendicontazione spese CONSUMO – Sezione di Ferrara (8 k€)

Materiale / Ditta	Spese IVA inclusa
Scatoline porta target	239,12
Sep Pak - Waters	490,81
Resine - Triskem	3.142,72
Dispencer HF - Di Giovanni	683,20
HF, Mn Acetato, Mn Cloruro -Sigma-Merk	408,82
Colonne per separazione - BGB	447,74
Materiale - Radius	2.427,07
Total	**7.884,48**

2. Scientific Activity (year 2017)

➢ TEST TO REALIZE METALLIC TARGETS OF ENRICHED TITANIUM

Since it was not possible to purchase enriched Titanium isotopes in crystal bar form (easy to laminate to the desidered thickness), different tests were made to find out the best solution to realize thin target foils. These tests were performed by using both natural titanium oxide powder ($^{nat}TiO_2$) and natural metal titanium powder (^{nat}Ti).

Figure 1. shows the results obtained by using a 10 Ton press, tests performed in collaboration with Stefano Corradetti, SPES project, INFN-LNL:

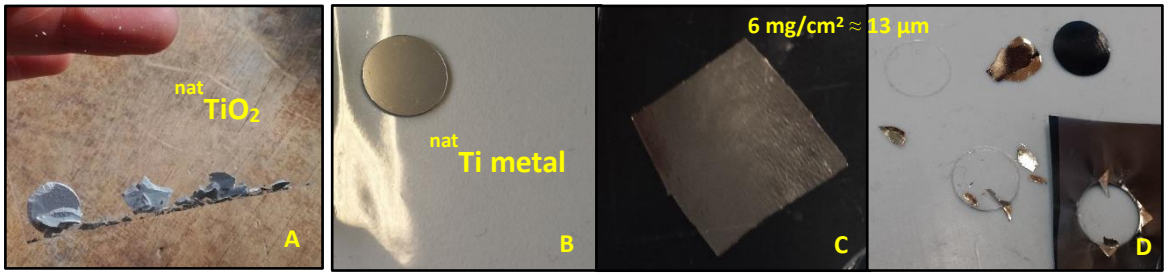
- Figure 1.A shows a typical result obtained by using titanium oxide powder: the final pellet was not self-sustainable and it needed a dedicated capsule. Considering the goal of our project (*i.e.* cross section measurement by using thin foil with precise knowledge of their thickness), this sintering method with $^{nat}TiO_2$ seemed to be unsuitable.

- Figure 1.B shows a typical result obtained by using metal powder of ^{nat}Ti: 300 mg were sintered with approximately 730 MPa over a surface of about 13 mm diameter (30 minutes). The final pellet was self-sustainable but very thick (≈ 600 µm); teste were done with different amount of metal powder, finding that the lowest quantity for a self-sustainable pellet was 150 mg (≈ 310 µm thick).

- These foils were too thick for a cross section measurement, so they were laminated (test done in collaboration with Massimo Loriggiola, Laboratorio bersagli INFN-LNL); Figure 1.C shows a typical result: approximately a 10 µm thick metal foil, obtained from 150 mg of metal powder.

- Figure 1.D shows the result obtained cutting the foil to the desired dimensions (12 mm diameter): the foil fell to pieces, showing the unsuitability of this method. Moreover, it was very difficul to recover the material used and considering the cost of the enriched material this route was completely unsustainable (150 mg of enriched ^{48}Ti powder costs about 2.2 k€).

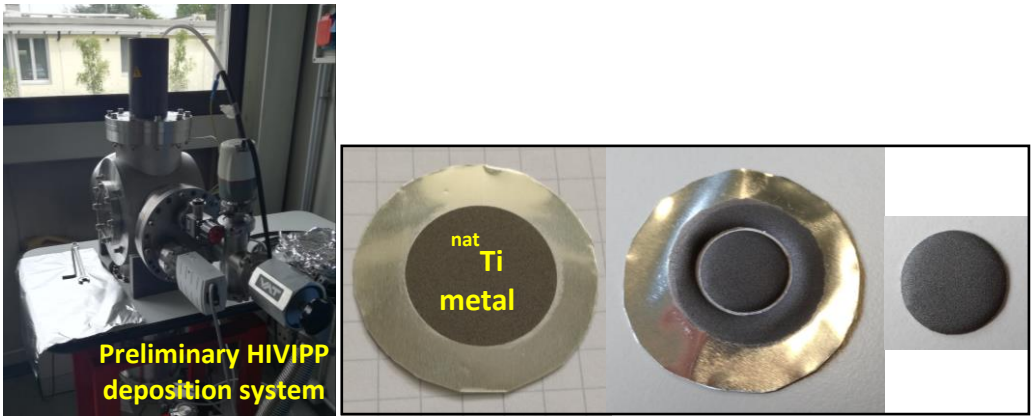
Figure 1. Test performed with natural metal and oxide titanium (collaboration with S. Corradetti and M. Loriggiola at INFN-LNL)



The HIVIPP method (HIgh energy VIbrational Powder Plating) was also explored in collaboration with Hanna Skliarova and Sara Cisternino (INFN-LNL) by using a preliminary system (Figure 2.A). Figure 2.B shows the result of a test performed by using 46.3 mg of metal ^{nat}Ti powder (325 mesh) deposited on a 100 µm thick aluminum support; after the deposition, 17.1 mg of powder were recovered, 9.6 mg were deposited on the foil "Up" and 8.7 mg on the foil "Low"; the powder losses were only 10.9 mg, approximately 24% of initial amount of ^{nat}Ti. Considering the density of natural metal titanium, the deposit was approximately 6 µm thick. Preliminary tests on target homogeneity were performed at AN2000 accelerator at INFN-LNL (in collaboration with Valentino Rigato), using Back-Scattering Rutherford method, showing that the deposit thickness was varying less than 10% on the entire surface. Figure 2.B also shows the target mechanical sustainability once cutted to 12 mm diameter.

These promising results obtained with HIVPP method and ^{nat}Ti powder on aluminium support were the fundamentals for the tests performed with enriched ^{48}Ti metal powder, purchased by TraceScience. The target foils obtained with enriched ^{48}Ti metal powder were used during the IV and V irradiation runs at Arronax facility (Nantes, France).

Figure 2. HIVVPP preliminary deposition system and and test performed with ^{nat}Ti powder on aluminum support (collaboration with H. Skliarova and S. Cisternino at INFN-LNL)



➢ IRRADIATION RUNS AT ARRONAX FACILITY

During all the experiments performed at Arronax facility the stacked-foils target technique was used, in order to obtained multiple measurements of the cross section (at different energies) during an unique irradiation run. The number of target foils, inserted in the stacked-target and separated by aluminium foils used as beam energy degrader, is reported in Table 1. In order to measure the proton beam current, a monitor foil was used and the recommended cross sections by IAEA were taken into account in data analysis. Since enriched metal targets of ^{48}Ti were not available before September 2017, the first three irradiation runs were dedicated to the measurement of the ^{nat}V(p,x)^{47}Sc nuclear reaction. This is a promising route for the production of ^{47}Sc for medical applications: in fact the co-production of isotopic impurities (such as ^{46}Sc) seemed to be reduced in comparison with other nuclear reactions and the target material is available in metal form and low price, since it is mainly composed by the V-51 isotope (99.75% abundance, V-50 0.25%).

During the 4° and 5° irradiation runs the target of enriched ^{48}Ti foils realized by HIVIPP method were used. Two deposit of ^{48}Ti on aluminium support were very thin (< 1 µm) and for this reason they were inserted in contact in the stacked-foils target structure used in the 4° run (Figure 3) and considered as a unique target foil in data analysis.

In order to follow the decay of the radionuclides of interest, it is necessary to perform γ-spectrometry measurements of the same sample at different times after the End Of Bombardment (EOB). At least No. 5 acquisition of the same target foils were taken at each irradiation run; in particular, in order to measure the activity of the long-lived ^{46}Sc isotope (83.79 d half-life), all the target foil of each irradiation run were measured again during the first days of the following run, during the preparation of stacked-fois target and alignment procedure on the beam line (Figure 4).

Table 1. Characteristics of the irradiation runs performed at ARRONAX facility during the year 2017

Irradiation run	Date	Reaction	No. Target foils	Proton Energy (MeV)	Duration (minutes)	Proton Current (nA)
1	11/4/2017	$^{nat}V(p,x)^{47}Sc$	3	70.3	90	≈ 100
2	27/6/2017	$^{nat}V(p,x)^{47}Sc$	3	54.0	90	≈ 100
3	4/7/2017	$^{nat}V(p,x)^{47}Sc$	3	61.0	90	≈ 100
4	10/10/2017	$^{48}Ti(p,x)^{47}Sc$ $^{nat}V(p,x)^{47}Sc$	3* 3	34.0	90	≈ 120
5	22/11/2017	$^{48}Ti(p,x)^{47}Sc$ $^{nat}V(p,x)^{47}Sc$	4 1	40.0	50	≈ 130

Figure 3. Schematic structure of the stacked-foils target used in the IV irradiation run at ARRONAX facility

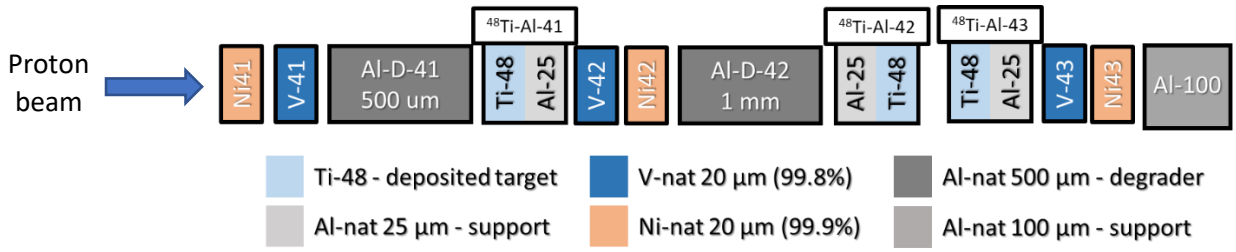
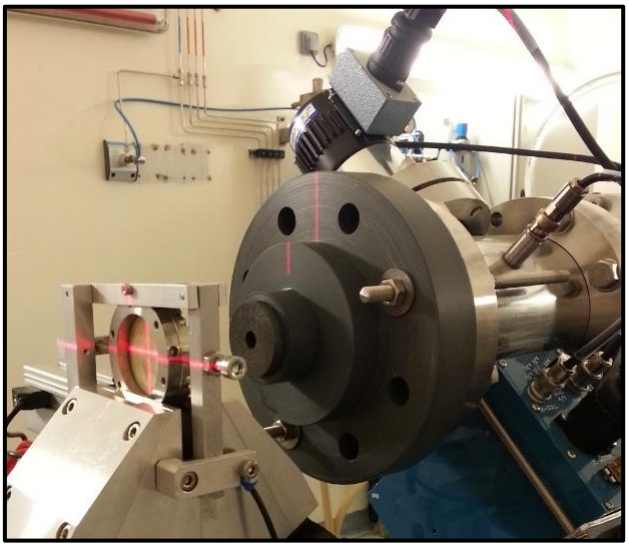


Figure 4. Photograph of the alignment procedure of target-holder and collimator on the beam-line at ARRONAX facility



➢ CHEMICAL TEST

Considering the medical application of cyclotron-produced Sc-47, the development of a target processing to extract the desired product in an injectable form is mandatory. The process should accomplish the separation in high yield of Sc-47 from the Ti bulky metal target and the purification of the isolated product from others trace stable/unstable contaminants and solvents. Moreover, the procedure time should be minimized to reduce as much as possible the decay loss.

The very first step of a separation procedure applied to a solid target is the target dissolution and eventual conversion of the solutes into a chemical form suitable for the separation (*e.g.* formation of cationic or anionic complex). The dissolution step optimization strictly depends on target characteristics (*e.g.* composition, mass, thickness, deposition method etc.). As described above, the targets used in the cross section measurements are composed by a thin deposit of enriched ^{48}Ti metal powder on a 25 µm thick Al support. This kind of target with an aluminum backing plate is useful for cross-section experiments but not in the view of a Sc-47 production for medical application. For this reason, during the 2017 of the PASTA project it was decided to keep the target processing task independent from the cross-section study and to start building the dissolution, separation and purification process by using commercial natural titanium metal foils. The chemical study started by considering an amount of titanium mass (of the order of dozens mg) in view of scaling up the procedure (dissolution and separation methods) once defined the proper titanium target configuration (mass, thickness, surface, enrichment, chemical purity etc.).

The dissolution step in case of metal titanium is very challenging, since this material is known to be physically inert to most acid at room temperature. The majority of literature data reports dissolution/separation procedures for Sc production from titanium dioxide targets (TiO_2) and only one paper, according to our knowledge, reports scandium production from titanium in metal form. In all cases, hydrofluoric acid (HF) has been used for the dissolution and separation process. In order to manage hydrofluoric acid, that is very reactive with glass, silica and silicates by forming silicon tetrafluoride, dedicated chemical accessories (vials, funnels, bottles etc.) were purchased. Considering the toxicity of the fluoride anion and the difficulties related to the use of HF, some dissolution tests were also performed by using different solvents to find out an alternative to hydrofluoric acid employment. Table 2 reports the solvent and solvent mixtures tested on metallic natural titanium samples (purity 99,6%; thickness 0.125 mm; mass 12.0 ± 1.7 mg); tests were performed by heating at 100°C for 4 hours and then let the solution react overnight.

As described in Table 2, only four samples were completely dissolved overnight, in particular when using highly concentrated hydrochloric acid (12 or 9 M) and mixture of sodium hydroxide and hydrogen peroxide in different ratio (4:1 and 1:1). However, it is important to choose the dissolution step taking into account also the following separation method that has to be applied. For this reason, the literature on Sc/Ti separation was studied, founding four different methods:

- ion exchange method, by using one resin such as DGA or 50W-X8 resin or a combination of ion exchanger such as DGA and 50W-X8 or AG1-x8 and AG50W-X8;
- solvent extraction method with Di-(2-ethylhexyl)phosphoric acid as extractant;
- ion exchange-solvent extraction combination.

After a deep evaluation of the literature on separation and purification of Sc from Ti, it was decided to purchase three resins suitable for ion exchange chromatography: DGA, LN and ZR resins. A cation and an anion exchange resin, *i.e.* AG50W-X4 and AG1-X8 respectively, were already available (project COME, funded by CSN3 - Dotazioni LNL for the year 2016).

Further chemical experiments are planned to find out different combinations of those resins (DGA, LN, ZR, AG50W-X4 and AG1-X8) and the available options for the dissolution step, in order to evaluate the best separation and purification procedure to obtain an injectable product.

Table 2. Solvents and solvent mixtures employed in the dissolution experiments of metallic titanium samples and eventual intermediate heating applied to the sample before adding the second solvent

Test	solvent#1	volumes#1	Intermediate heating	intermediate heating time	solvent#2	volumes#2	results
#	type and conc	ml	°C	min	type and conc	ml	
1	NaOH 6M	5.0					not dissolved
2	H_2O_2 30%	5.0					not dissolved
3	**HCl 12M**	**5.0**					**dissolved**
4	HCl 6M	5.0					not dissolved
5	**HCl 9M**	**5.0**					**dissolved**
6	NaOH 6M	4.0			H_2O_2 30%	1.0	not dissolved
7	HCl 12M	4.0	100	15	H_2O_2 30%	1.0	not dissolved
8	HCl 12M	1.0	100	15	H_2O_2 30%	4.0	not dissolved
9	HCl 12M	2.5	100	15	H_2O_2 30%	2.5	not dissolved
10	H_2O_2 30%	1.0	100	15	HCl 12M	4.0	not dissolved
11	H_2O_2 30%	4.0	100	15	HCl 12M	1.0	not dissolved
12	H_2O_2 30%	2.5	100	15	HCl 12M	2.5	not dissolved
13	**NaOH 6M**	**4.0**	**100**	**15**	**H_2O_2 30%**	**1.0**	**dissolved**
14	NaOH 6M	1.0	100	15	H_2O_2 30%	4.0	not dissolved
15	**NaOH 6M**	**2.5**	**100**	**15**	**H_2O_2 30%**	**2.5**	**dissolved**
16	HCl 12M	4.0			H_2O_2 30%	1.0	not dissolved
17	KOH 6M	5.0					not dissolved
18	NaOH 8M	5.0					not dissolved

➢ THEORETICAL STUDIES ON NUCLEAR CROSS SECTIONS

In the framework of the PASTA project a collaboration with experts in nuclear physics codes started, in order to:

- interpret the measurements of production cross-sections and to guide the measurements towards the most promising production regions (energy window, targetry, isotopic varieties);

- complete the measurements with the estimation of production of radioactive contaminants that are challenging to measure (*e.g.* very short half-life, radionuclides without characteristic γ-rays);

- provide estimates of stable isotopes that are difficult to measure if one relies on activation and/or radiochemistry techniques.

This collaboration involved Luciano Canton (INFN-PD) and Andrea Fontana (INFN-PV) that will both participate to the FTE of PASTA project for the year 2018. They used different nuclear codes (Talys, Empire and Fluka) to predict and compare results of the nuclear reactions of interest. Results were recently presented to the MCMA conference (Napoli, 15-18 October 2017 "Montecarlo calculation of reaction cross sections for the production of innovative radionuclides" A. Fontana, Pupillo G., Mou L., Rossi Alvarez C., Esposito J., Canton L.) and at the LANSPA & WONP-NURT 2017 conference (L'Havana, Cuba, 23-27 October 2017, "The modeling of reaction cross sections in the production of theranostic radionuclides" Fontana A., Pupillo G., Mou L., Rossi Alvarez C., Esposito J., Canton L.).

Considering the cost of enriched materials and the limited time of this project, it was not possible to measure all the possible nuclear reactions that produce ^{47}Sc with proton beams and enriched titanium targets. For this reason, the different nuclear codes (Talys, Empire and Fluka) were used to estimate the trend of the reaction of interest, *i.e*. ^{48}Ti(p,x)^{47}Sc, ^{49}Ti(p,x)^{47}Sc and ^{50}Ti(p,x)^{47}Sc – for all cases, it was important to evaluate the co-production of ^{46}Sc, the main contaminant radioisotope. The theoretical estimation of the ^{48}Ti(p,x)^{47}Sc reaction will be compared with experimental results, actually under analysis.

Figure 5 shows the estimations obtained with the three different codes, in case of the ^{49}Ti(p,x)^{47}Sc and ^{49}Ti(p,x)^{46}Sc reaction. Considering the final medical use of ^{47}Sc, it is important to reduce as much as possible the co-production of all contaminants, in particular ^{46}Sc.

Figure 5. Theoretical estimations of the production rates for ^{49}Ti(p,x)^{47}Sc (up) and ^{49}Ti(p,x)^{46}Sc (down) reactions. The brown curve describes the FLUKA results, the violet denotes the EMPIRE calculation, while for the TALYS results the two curves, black and blue, respectively, describe the results with standard input and with input modified to more modern pre-equilibrium and level density models, based on microscopic theories

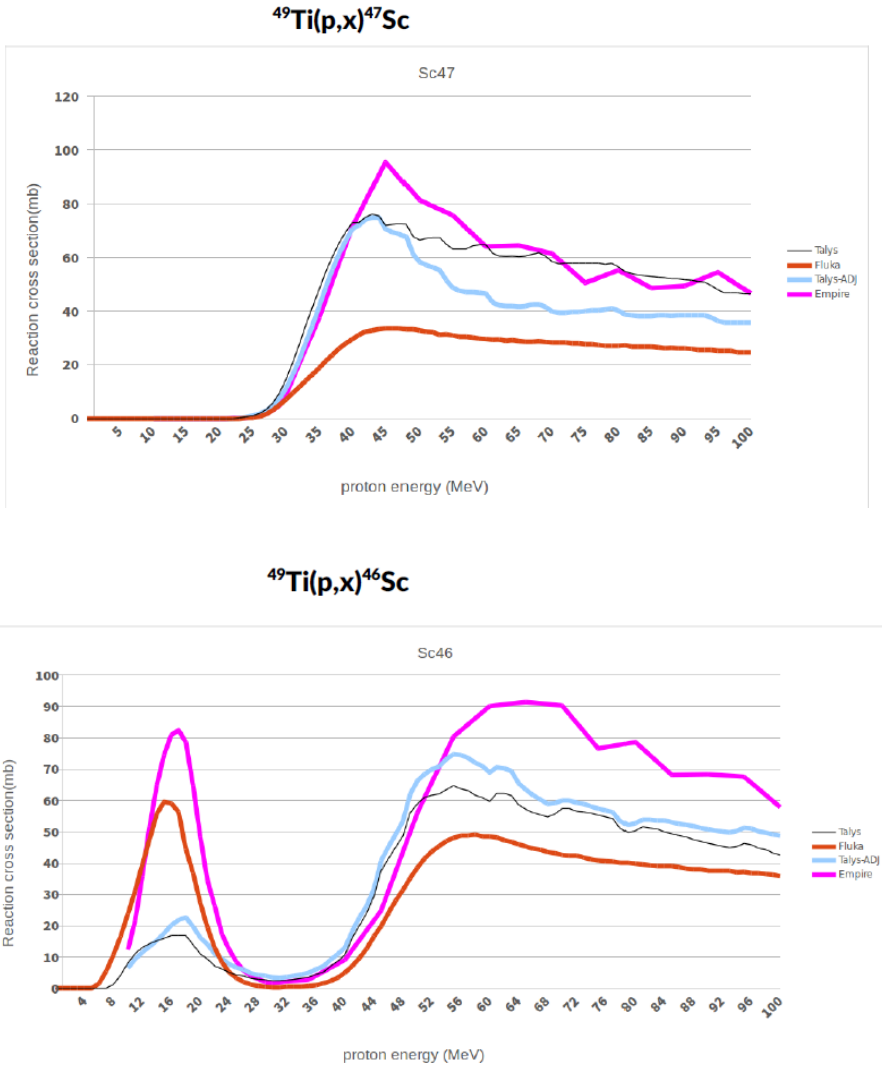
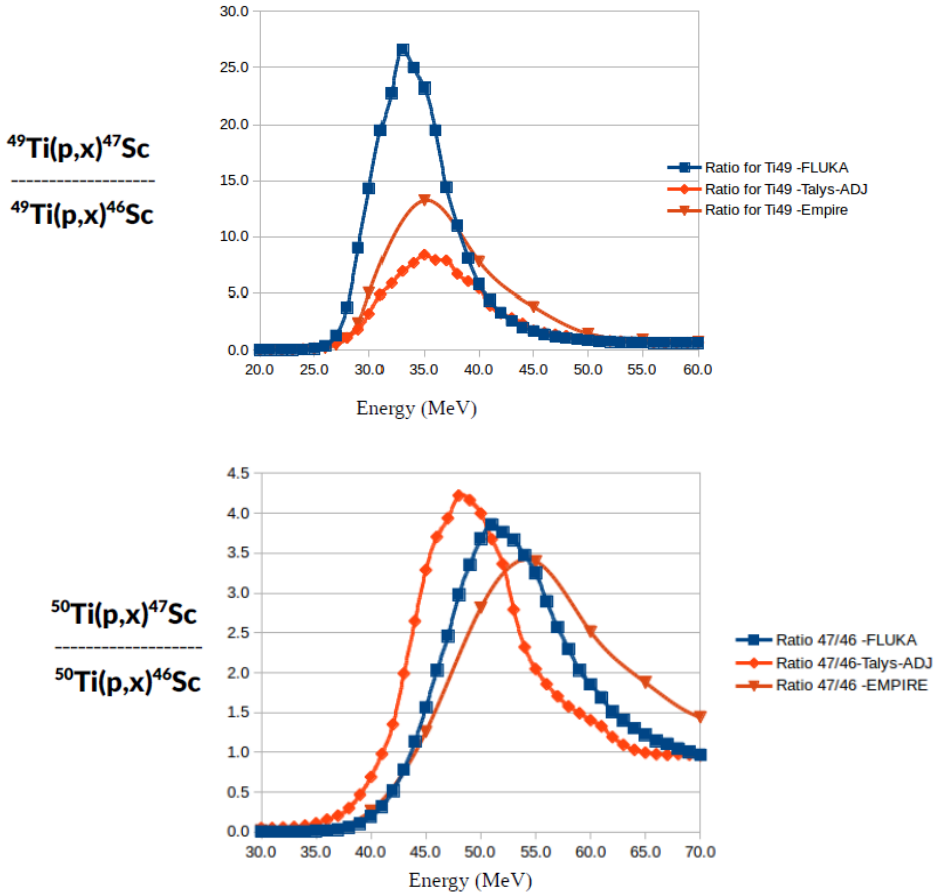


Figure 6 (up) shows the ratio of the estimated cross section for the production of ^{47}Sc and ^{46}Sc by using ^{49}Ti targets. It can be easily noted that all the codes indicate that in the energy range 40-25 MeV the production of ^{47}Sc is most favorable: the ratio varied from 8 to 28 (Figure 6 up). The same estimation was performed with ^{50}Ti targets, as shown in Figure 6 (down); in this case the codes indicate the energy region 70-40 MeV,

with a favorable ratio for ^{47}Sc production varying from 3.5 to 4.2. Considering the similar abundance of ^{49}Ti and ^{50}Ti (respectively 5.5% and 5.4%) and thus assuming a similar cost for these enriched materials, the investigation of the ^{49}Ti(p,x)^{47}Sc reaction may be more interesting than the ^{50}Ti(p,x)^{47}Sc one. Moreover, no data are available on international database for the ^{49}Ti(p,x)^{47}Sc, while the ^{50}Ti reaction was investagetd by Gadioli et al. (1981) by using oxide targets.

Figure 6. Prediction of the ratio of the production rates for ^{49}Ti(p,x)^{47}Sc, ^{46}Sc (up) and for ^{50}Ti(p,x)^{47}Sc,^{46}Sc (down). The different colors identify the different nuclear reaction codes used to formulate the predictions



3. MILESTONE 2017

31-12-2017 - PRIME MISURE DI IRRAGGIAMENTO

- No.5 run ad Arronax, per la misura delle reazioni nucleari ^{nat}V(p,x)^{47}Sc e ^{48}Ti(p,x)^{47}Sc (Table 1)

31-12-2017 - SVILUPPO DI PROCESSI CHIMICI DI ESTRAZIONE DELLO SC

- Studio della letteratura e test di dissoluzione Ti metallico e studio dei metodi di estrazione di Sc da Ti metallico (Table 2)

4. Congress, workshop, pubblication (year 2017)

- "Montecarlo calculation of reaction cross sections for the production of innovative radionuclides" - Poster presented at the MCMA conference (International Conference on Monte Carlo Techniques for Medical Applications) Napoli, 15-18 October 2017 - **A. Fontana**, Pupillo G., Mou L., Rossi Alvarez C., Esposito J., Canton L.

Abstract of the MCMA conference in press at the journal Physica Medica

- "The modeling of reaction cross sections in the production of theranostic radionuclides" - Oral presentation at the LASNPA & WONP-NURT 2017 conference (Latin-American Symposium on Nuclear Physics and Applications & Workshops on Nuclear Physics and Nuclear Related Techniques) L'Havana, Cuba, 23-27 October 2017 - Fontana A., Pupillo G., Mou L., Rossi Alvarez C., Esposito J., **Canton L**.

Proceedings of the LASNPA & WONP-NURT 2017 conference in press at the journal Nucleus