# A NEW APPROACH TO TARGETRY AND CYCLOTRON PRODUCTION OF $^{45}$Ti BY PROTON IRRADIATION OF $^{45}$Sc

by

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**Titanium-45 with a half-life of 3.09 hours decays by emission of positrons (85%) and the electron capture process (15%). These properties make this radionuclide useful in the diagnosis of tumors by positron emission tomography. In this study, after having considered the excitation functions for the $^{45}$Sc(p, n)$^{45}$Ti reaction using TALYS and ALICE/ASH codes and after the comparison with other experimental data, $^{45}$Ti was produced by dint of the pressing method and a newly designed and manufactured shuttle and capsule, resulting in an experimental yield of 403.3 MBq/μAh. Essential target thickness and physical yield were calculated. The scandium oxide target was irradiated at a 20 μA current and a 21 MeV proton beam energy for 1 hour.**

*Key words: $^{45}$Ti, $^{45}$Sc, proton, excitation function, physical yield*

## INTRODUCTION

$^{45}$Ti with a half-life of 3.08 h is a positron-emitting radioisotope with a positron branching of 85% and a decay of 15% by electron capture with $E(\beta^+_{max})$, *i. e.*, 1.04 MeV decays to $^{45}$Sc [1]. In the $\beta^+$-decay process, the proton in the nucleus is transformed into a neutron with the emission of a $\beta^+$-particle and a neutrino. The range of the positron in the tissue is a few millimeters, up to the moment it encounters its antiparticle, the electron. When that happens, the electron-positron pair is annihilated and transformed into two oppositely directed 511 keV-photons. These photons can be detected by the coincidence technique used in positron emission tomography (PET). Nuclear medicine, particularly PET, is important in the diagnosis, treatment planning, and evaluation of the treatment response in patients with cancer, so a high $\beta^+$-yield, short half-life and a stable daughter make $^{45}$Ti a suitable candidate for PET imaging [2, 3].

As shown in fig. 1(a), there are four methods for the production of a $^{45}$Ti radionuclide: (a) $^{45}$Sc(p, n)$^{45}$Ti, (b) $^{46}$Ti(p, n + p)$^{45}$Ti, (c) $^{46}$Ti(n, 2n)$^{45}$Ti, (d) $^{45}$Sc(d, 2n)$^{45}$Ti [4-11]. According to fig.1(b) and (c), to avoid isotopic impurities of $^{45}$Ti, the $^{45}$Sc(p, n)$^{45}$Ti method was employed. The aim of this study is to design and manufacture a new shuttle and capsule target for the direct production of $^{45}$Ti *via* a $^{45}$Sc (p, n) $^{45}$Ti-reaction by means of the pressing method. The theoretical calculation of the physical yield and target thickness were done by using the stopping and range of ions in matter (SRIM) Code [12]. To determine the aberration amount of the acquired and experimental data, they were compared with each other.

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## MATERIALS AND METHODS

The production of $^{45}$Ti was performed at the Nuclear Medicine Research Group (AMIRS) 30 MeV cyclotron (Cyclone-30, IBA). Chemicals and alloys were purchased from the Aldrich Chemical Co. (Germany), and ion-exchange resins from Bio-Rad Laboratories (Canada). The radioactivity of the sample was determined by counting a Canberra$^{TM}$ high-purity germanium detector (HPGe, model GC1020-7500SL) and a CRC Capintech Radiometer was used for activity measurements of the samples. All simulation studies were done by SolidWorks 2010 software [13].

## CALCULATION OF THEORETICAL PHYSICAL YIELD AND BEAM ENERGY

According to all calculation methods using ALICE, TALYS, and ALICE/ASH codes shown in fig. 1

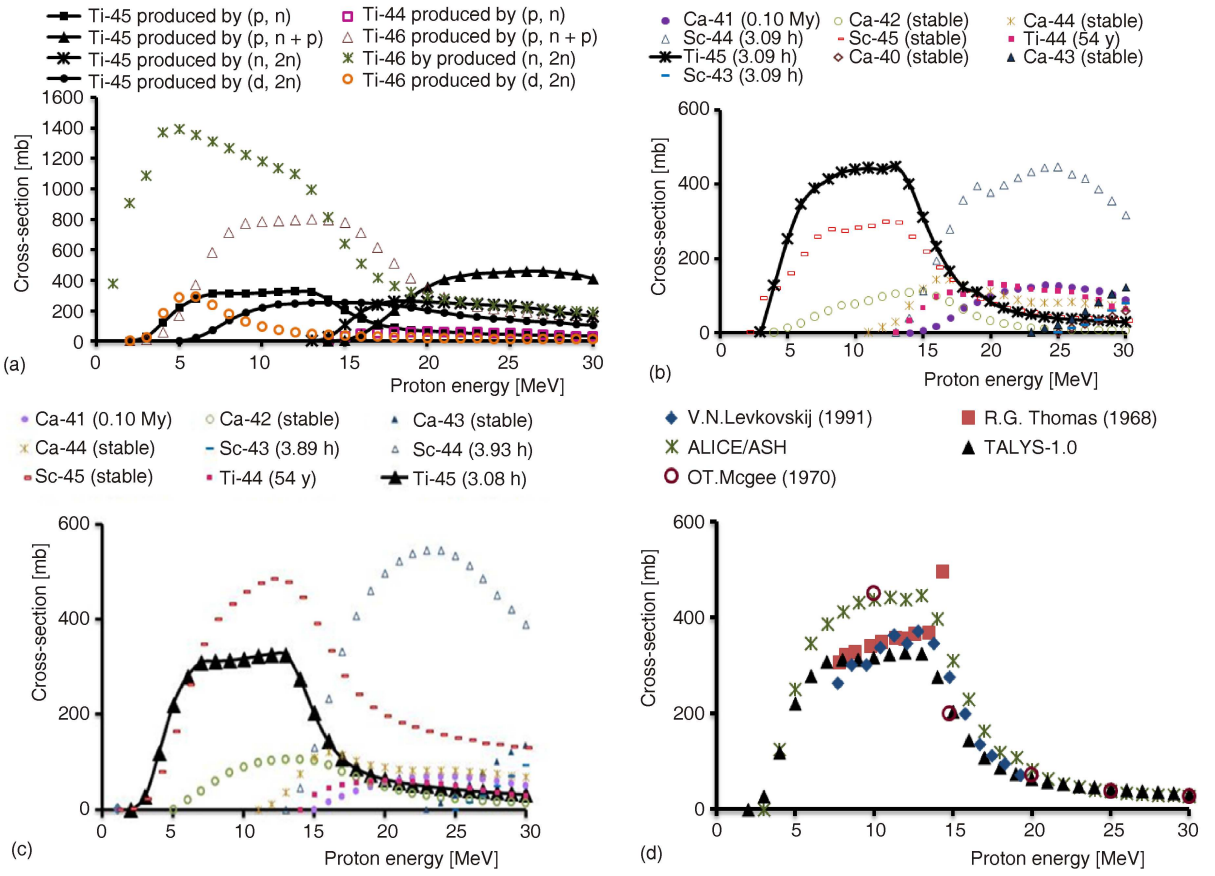


**Figure 1. Ti-45 radioisotope production based on calculations by the TALYS code for all possible reactions ($^{45}$Sc(p, n)$^{45}$Ti, (b) $^{46}$Ti(p, n + p)$^{45}$Ti, (c) $^{46}$Ti(n, 2n)$^{45}$Ti, (d) $^{45}$Sc(d, 2n)$^{45}$Ti) and the evaluation of possible impurities resulting from these reactions [4-11] (a); $^{45}$Sc(p, n)$^{45}$Ti reaction calculated by the ALICE/ASH code in order to evaluate possible impurities (b); $^{45}$Sc(p, n)$^{45}$Ti reaction calculated by the TALYS code in order to evaluate possible impurities (c); and comparison of the calculated excitation function of $^{45}$Sc(p, n)$^{45}$Ti reaction by the TALYS and ALICE/ASH code to experimental code (d)**

[14-21], the $^{45}$Sc(p, n) $^{45}$Ti method had the best reaction due to the capacity of our cyclotron machine in which the proton energy beam is within the range of less than 30 MeV and the best range of energy is 5-14 MeV.

The following equation was used to calculate the physical yield of nuclear reactions in this study

$$Y = \frac{N_L H}{M} I(1 - e^{-\lambda t}) \int_{E_1}^{E_2} \frac{dE}{d(\rho x)} \sigma(E)\, dE$$

where $Y$ [MBq/μAh] is the yield product, $N_L$ – the Avogadro's number, $H$ [%] – the isotope abundance of the target nuclide, $M$ [g] – the mass number of the target element , $\sigma(E)$ [mb] (1 mb = $10^{-31}$ m$^2$) – the cross-section at energy $E$, $I$ [μA] – the projectile current, $dE/d(\rho x)$ [MeVmg$^{-1}$cm$^2$] – the stopping power, $\lambda$ [h$^{-1}$] – the decay constant of the product, and $t$ [h] – the time of irradiation. The cross-sections are calculated by TALYS and ALICE/ASH codes and the stopping power of projectile particles in the target material is calculated by the SRIM code [10].

## DESIGN OF THE NEW SHUTTLE AND CALCULATION OF THE THEORETICAL BEAM ENERGY

In this study, a specific shuttle is required for the bombardment of the capsule target (fig. 2). The shuttle is designed in such a manner that a water layer with a thickness of 1 mm is situated in front of it, while a layer of the same thickness is situated at the back (fig. 3)

Water with an outlet mass flow of 0.75 kg/s is used for target cooling, so that part of the energy is consumed through the water and aluminum foil used to separate the target material ($Sc_2O_3$) from the aqueous environment. Thus, the proton beam lost a part of its initial energy in the aqueous environment. The wasted energy was obtained by the interpolation of projected range-energy curves (fig. 4).

As the energy of the proton entering the $Sc_2O_3$ layer should be 14 MeV, proton energy after passing the aluminum layer with a thickness of 200 um should also be 14 MeV. The corresponding projected range to 14 MeV is 1122.25 μm. The thickness of the water layer located in front of the aluminum is 1 mm. The en-

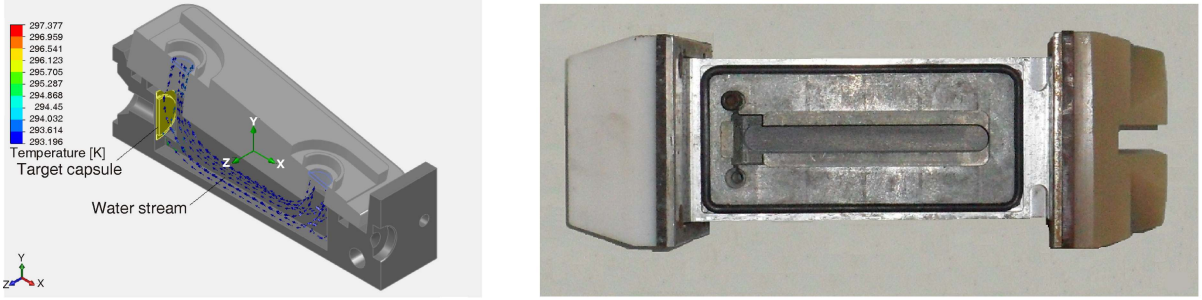


**Figure 2. Schematic picture and snapshot of the shuttle**

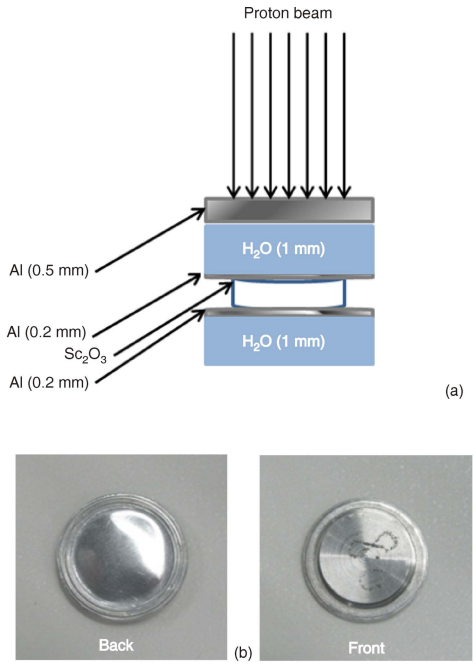


**Figure 3. Schematic picture of the target capsule**

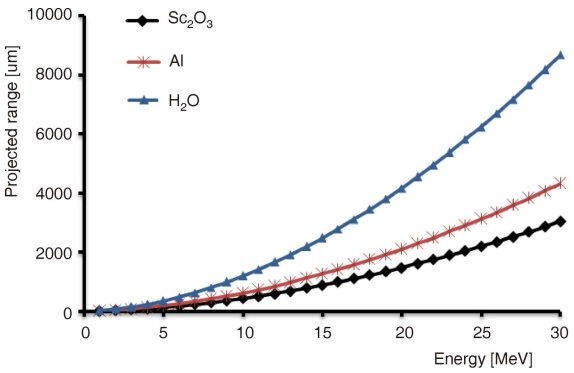


**Figure 4. Projected range-energy curves for $Sc_2O_3$, $H_2O$, and Al**

ergy of the protons coming out of the water layer should, therefore, also amount to 15.36 MeV. The projected ranges in each environment and their corresponding energies are mentioned in tab. 1.

**Table 1. Calculated energy and projected range in $Sc_2O_3$, $H_2O$, and Al layers**

| Environment | Energy [MeV] | Projected range [μm] |
|---|---|---|
| $Sc_2O_3$ | 5 | 133.09 |
| $Sc_2O_3$ | 14 | 789.99 |
| Al | 14 | 1122.25 |
| Al | 15.36 | 1322.25 |
| $H_2O$ | 15.36 | 2587.91 |
| $H_2O$ | 18.40 | 3587.91 |
| Al | 18.40 | 1822.38 |
| Al | 21.08 | 2322.38 |

## TARGET PREPARATION

Making use of existing facilities, among the possibilities to produce $^{45}$Ti, we have employed the $^{45}$Sc (p, n)$^{45}$Ti reaction in order to test target preparation. Medical application requires a highly enriched $^{45}$Sc target. The natural Sc target was prepared by the stack foil technique reported by Folkesson for 3-6 MeV[1] and a 7 mm × 7 mm titanium foil (Alfa Aesar), used for processing the Sc target for proton bombardment at 14.5 MeV by Vavere *et al.*, [22]. In this study, we have employed the pressing technique to prepare the $^{nat}$Sc target.

For the preparation of the target, scandium-oxide powder should be formed as a pellet. Thus, 360 mg of $Sc_2O_3$ powder were pressed at 50-60 bar by a hydraulic jack and the prepared pellet then put into an aluminum shield for bombardment.

The proton of 21.08 MeV comes out of the beam line, loses 2.68 MeV of its energy in the first aluminum layer (0.5 mm) and enters the water with a charge of 18.40 MeV. About 3.04 MeV of the beam energy is wasted in this environment before the proton enters the aluminum foil (0.2 mm) with a charge of 15.36 MeV and, upon entry, loses 1.36 MeV before finally reaching the scandium oxide with a charge of 14 MeV. As shown in fig. 5, thermal simulations for the shuttle and target capsule determine that the maximum heat values for the beam power of about 300 W on the target capsule are 384.2 K (front) and 338.2 K (back).The maximum heat resistance for beam power of about

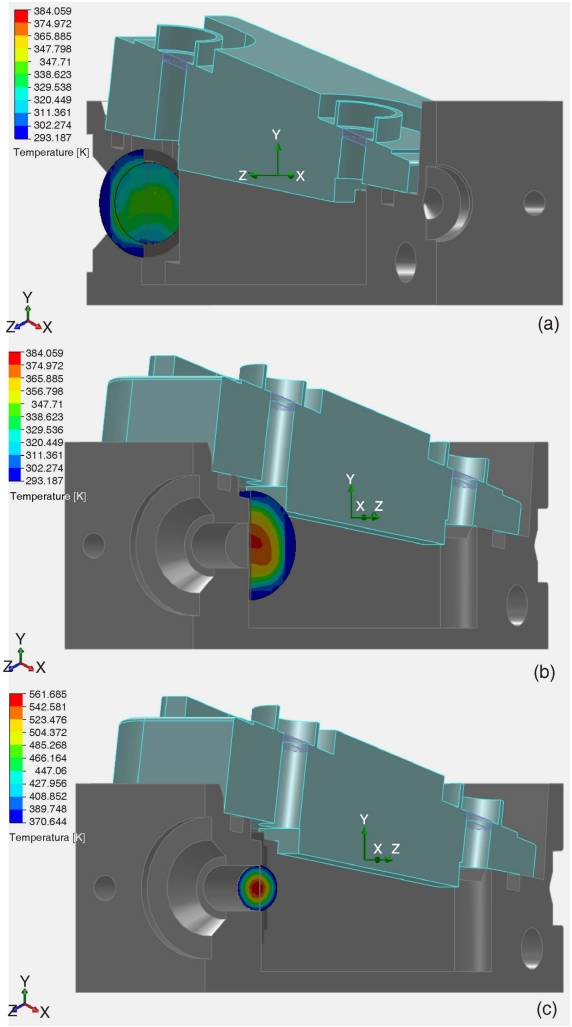


**Figure 5. Schematic picture of the maximum heat resistance for beam power of about 300 W on the target, front (a) and back (b), and the aluminum window (c)**

1000 W on the aluminum window is also calculated and the maximum heat value determined to amount to about 563 K, far from the melting point of aluminum (933.47 K) (fig. 5).

## IRRADIATION

Irradiation was carried out at the agricultural, medical, and industrial research school (AMIRS) by means of a Cyclone-30 (IBA, Belgium) cyclotron machine. The $Sc_2O_3$ capsule was used as a target and bombarded with 21 MeV protons at a current of 20 μA per 1 hour.

## CHEMICAL SEPARATION

Upon successful irradiation, the scandium-oxide pellet was dissolved in 2.5 mL of concentrated HCI to give $^{45}TiC1_4$, upon which a drop of concentrated $HNO_3$ was added to ensure the oxidation of the $^{45}Ti$ to the + 4 state. Then, the solution was evaporated to dryness and dissolved in 6 m HC1, again. The step was repeated three times in order to completely remove $HNO_3$. The $^{45}Ti$ dissolved in 2 mL of 6 M HCI was loaded on an AG 50 W 8 column (100-200 mesh, Bio-Rad, 1 cm i. d. 18 cm) prewashed with 6 M HCI. $^{45}Ti$ was then eluted with 6 M HC1, while the scandium was eluted with 4 M HC1 containing 0.1 M HF. After the drying of the $^{45}Ti$ fraction, $^{45}Ti$ was dissolved in 1 mL-2 mL of 1 M HCI.

## RADIOACTIVITY MEASUREMENTS

The radioactivity of the sample was determined non-destructively, using high-resolution HPGe detectors. The distance from the sample to the detector was 30 cm, counting time adjusted according to the half-life of the product nuclide so as to get a reasonable counting statistic. All the major gamma lines of the resulting radionuclide were identified. $^{45}Ti$ activity was determined using a 720 keV $\gamma$-ray (fig. 6). Note that the 720 keV $\gamma$-ray has the highest $I\gamma$ [%] in gammas from $^{45}Ti$. The 511 keV $\gamma$-ray cannot be used in calculation due to the Doppler Broadening Effect which results in an incorrect width of the peak. Detector efficiency for the target material is set based on a container with a fixed geometry that includes one drop of the final product in 10 ml of the solvent.

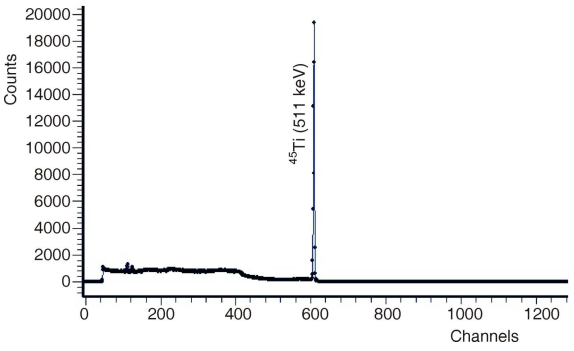


**Figure 6. $\gamma$-ray spectrum of proton-irradiated $Sc_2O_3$ after separation of $^{45}Ti$ from $^{45}Sc$**

## RESULTS AND DISCUSSION

The only stable isotope of natural scandium can transmute to a titanium-45 radioisotope through the $^{45}Sc(p, n)^{45}Ti$ reaction. In this work, the scandium-oxide capsule target was prepared using the pressing method. According to calculation, a thick target of 800 μm was bombarded. Incident proton energy was 21 MeV. For 1 h, no target material loss was observed at the current beam of up to 20 μA. With this method, the production of titanium-45 provides an opportunity

**Table 2. Calculated thickness and physical yield**

| Reaction | Beam energy [MeV]* | Target thickness [μm] | Calculated yield [MBq/μAh] | References |
|---|---|---|---|---|
| 45Cs(p, n)$^{45}$Ti | 14 5 | 656.9 | 526.88 | Theoretical calculation by TALYS-1.0 |
| | 14 5 | 656.9 | 710.03 | Theoretical calculation by ALICE/ASH |
| | 14.5 | – | 422 30 | Vavere *et al*., [21] |
| | 14 5 | 652 | 403.3 | This work |

*Incident energy on target material; exit energy after target material

to apply high beam power of about 300 W (20 μA), under the condition that the target material can withstand the current beam while demonstrating stability at the same time. Folkesson's samples were prepared using scandium foils. The targets were bombarded with beams of up to 18 μA and the time of irradiation was about 3 h [3], while a Vavere's target consisting of a natural scandium foil was irradiated with a proton beam of 14.5 MeV at 5 μA over a period of 1 h [22].

The advantage of this production method is that, by the use of scandium oxide which is economical, as well as the use of a pressed scandium oxide target in an aluminum shield, the beam current can increase as much as needed, based on the utilized cyclotron (in our case, 150 μA) and total heat produced on the window (referring to the aluminum window resistant to a beam power of up to 1000 W). The presented shuttle was tested in an experiment with a 100 μA current and 25 MeV energy for 1 h, with no errors being observed (above the requirements set by our experiment). The measured yield of $^{45}$Ti at the end of bombardment (EOB) was 403.3 MBq/μA h (tab. 2).

## CONCLUSIONS

After considering the excitation functions of a $^{45}$Sc(p, n)$^{45}$Ti reaction using TALYS and ALICE/ASH codes and the comparison with other experimental data, $^{45}$Ti was produced by dint of the pressing method and a newly manufactured shuttle which resulted in an experimental yield of 403.3 MBq/μAh. Essential target thickness and physical yield were calculated by SRIM codes. The scandium oxide target was irradiated at a 20 μA current and 21 MeV proton beam energy for 1 h and a highly pure $^{45}$Ti in the form of chloride was achieved. In this type of the pressing method, any environmental contamination which may result from the sedimentation production method and toxic elements due to the electroplating bathe *via* the electroplating production method, are non-existent. Taking into account the ability to determine a desirable beam current accompanied by a lower risk of environmental pollution by means of a shielding target material contained within a capsule, we have come to the conclusion that this approach to targetry might prove to be a suitable candidate for the production of radiopharmaceuticals.

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## AUTHOR CONTRIBUTIONS

The theoretical analysis was carried out by Y. Fazaeli, F. Bayat, K. Yousefi, and T. Kakavand. The experiments were carried out by Y. Fazaeli, M. Aboudzadeh, and K. Aardaneh. All authors analyzed and discussed the results. The manuscript was written by Y. Fazaeli and the figures were prepared by Y. Fazaeli, F. Bayat, and K. Yousefi.

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## НОВИ ПРИСТУП ПРОИЗВОДЊИ $^{45}$Ti ПРОТОНСКИМ ОЗРАЧИВАЊЕМ $^{45}$Sc У ЦИКЛОТРОНУ

Титанијум-45, са временом полураспада од 3.09 часова, распада се емисијом позитрона (85%) и процесом захвата електрона (15%). Ова својства чине $^{45}$Ti корисним за дијагностификовање тумора позитронском емисионом томографијом. По претходном разматрању ексцитационих функција реакције $^{45}$Sc(p, n)$^{45}$Ti, помоћу програмских кодова TALYS и ALICE/ASH и после поређења са експерименталним подацима, произведен је $^{45}$Ti методом притиска и са пројектованим и начињеним шатлом и капсулом, уз експериментални принос од 403.3 MBq/μAh. Прорачунати су основна дебљина мете и физички принос. Мета од скандијумоксида озрачивана је током једног часа протонским снопом енергије 21 MeV, јачине струје 20 μA.

*Кључне речи: $^{45}$Ti, $^{45}$Sc, протон, ексцитациона функција, физички принос*