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Theragnostics - Alternative production of terbium isotopes at the University of Birmingham using an MC40 cyclotron

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Abstract. In this work alternative methods for the production of terbium isotopes, and in particular ^{152}Tb and ^{155}Tb, have been investigated. These isotopes, which could be used for theragnostics, have been produced using an alpha and a proton beam incident on europium and gadolinium targets, respectively. The experimental results have been compared with the predicted cross-sections, calculated using TALYS and PACE4 code.

1. Introduction

Over time the diagnosis and treatment tools used to identify and remove cancer growths in patients have evolved. New ideas and techniques are continuously being investigated to improve the treatment of cancer. Table 1 lists some of the currently employed techniques to diagnose and treat cancer.

Table 1. Currently used techniques to treat and diagnose cancer.

Treatment	**Diagnostic Imaging**
Surgery	X-ray
Internal and External Radiation therapy	CT (Computerised Tomography)
Chemotherapy	MRI (Magnetic resonance imaging)
Immunotherapy	PET (Positron Emission Tomography)
Hormone therapy	Gamma Camera/SPECT (Single Photon Emission Computed Tomography)
Stem cell transplant	Ultrasound
Targeted therapy	Mammography

Internal radiotherapy, PET (Positron Emission Tomography) and SPECT (Single Photon Emission Computed Tomography) imaging are techniques classified under 'Nuclear medicine'.

Nuclear medicine works by introducing radioactive isotopes into the body and using the different forms of decay to either perform therapy or diagnostic imaging of a patient.

Therapy can be performed by using either beta or alpha emitting isotopes. The beta or alpha particles ionise the neighbouring cells causing damage to the DNA, often leading to either single- or double-strand breakages, respectively. Positron emitting isotopes are used to perform diagnostic PET imaging and isotopes which predominantly emit gammas are used for diagnostic SPECT imaging.

In nuclear medicine, cancer cells are located by attaching the radioactive nuclide to a biological targeting agent. For example, a glucose molecule can be replicated and modified such that a ^{18}F atom is attached to form FDG (fluorodeoxyglucose), see figure 1 . In this case the biological targeting agent reacts in the body as glucose does. Glucose is drawn into cells which are using up energy in metabolic processes i.e. the cells will break-down the glucose molecule to release energy for the cell's use. FDG will behave in the same way as glucose and will thus concentrate in areas of high activity, e.g. active areas of the brain and cancer lesions. It is the higher concentration of FDG in these areas which will be highlighted in a PET and SPECT images.

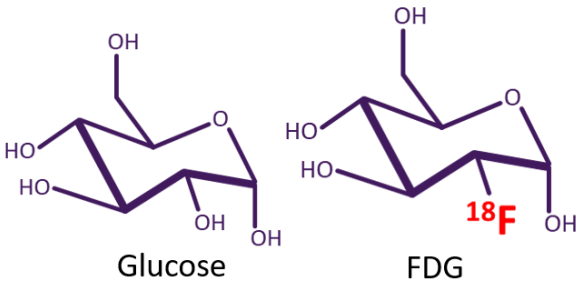

Figure 1. Molecular diagrams of Glucose and FDG (fluorodeoxyglucose)

A more specific method of cancer targeting is to use proteins (peptides). Cancer cells will have specifically shaped proteins on their outer membranes. If a complementary (i.e. fits like a glove over a hand) peptide is made, this will only attach to that specific cancer protein. A radioactive nuclide can then be attached to this complementary peptide using a chelator (linker) as shown in figure 2. This can be a more direct and tailored method of targeting cancer lesions.

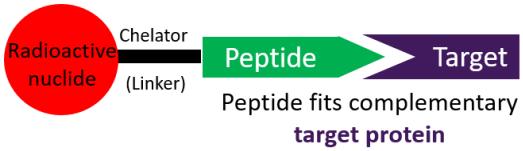

Figure 2. Schematic diagram of a radioactive nuclide attached to a peptide targeting molecule

It is the combination of **thera**py and dia**gnostic** imaging (**theragnostics**) which aims to provide a more tailored treatment to cancer. By monitoring therapy with diagnostic imaging the effectiveness of the treatment can be seen and changed according to need. The radiation dose received by a patient during treatment can also be monitored. Currently, a combination of Lu and Ga is commonly used in hospitals for β^-therapy and PET diagnostic imaging, respectively. These nuclei are different elements, hence, they will not necessarily chemically interact the same within the body. This provides uncertainty in the comparing diagnostic imaging to therapy,

which in turn provides doubt to the reliability of a theragnostic treatment. A way of resolving this issue would be to use different isotopes of the same element to perform the therapy and diagnostic imaging. Scandium, copper, arsenic and terbium are a few examples of proposed elements which have suitable properties for medical use. Some of the main properties to consider are half-life and energy of emitted radiation. The half-life of a medical isotope must be of reasonable length, so that it can be produced, transported, undergo radiochemical procedures and pass regulation tests before being administered to the patient. There must then be enough activity for the treatment or diagnostic imaging to be carried out effectively. However, the half-life must also be short enough that the isotope is not providing an unnecessarily large dose to the patient and their surroundings. In addition to the half-life requirements, the energies of the emitted radiation must also be suitable for the task. For example, a SPECT isotopes would ideally only emit gammas of a low energy (100-200 keV) which lie within a region of high efficiency for the gamma detectors; ideal PET isotopes would emit solely positrons and no gamma-rays other than 511 keV gammas from positron annihilation. In addition to this, for isotopes to be practical for hospital use, they should be able to be produced locally if not within the hospital. Hospital cyclotrons predominantly accelerate proton beams up to 17 MeV. This limits the type of isotopes that can be produced and is important to consider when developing new production methods.

Production of terbium by ISOLDE (Isotope Separator On Line DEtector) and MEDICIS (Medical Isotopes Collected from ISOLDE) [1] at CERN led to promising clinical trials over the past 8 years carried out by C. Müller et al. [2, 3, 4, 5] Consequently, these trials have motivated research into alternative production methods.

Table 2. The decay modes and most intense gamma transitions of the terbium isotopes used in theragnostics and their medical purpose. Here, E_α is the energy of the emitted α particle, E_β is the energy of the emitted β particle, E_γ is the energy of the emitted γ-ray and I_γ is the branching ratio of each γ-ray.

Isotope	Decay mode (Branching ratio)	Half life	E_α ***(MEV)*** / Average E_β (MEV)	E_γ (keV)	I_γ (%)	Use
149	α(16.7%) β^+ (7.1%)	4.12 h	***3.967(3)***	165.98(2)	26.4(8)	α therapy
				352.24(2)	29.4(9)	
			0.730(4)	388.57(2)	18.4(6)	
				652.12(2)	16.2(5)	
152	β^+ (20.3%)	17.5 h	1.140(13)	271.09(7)	9.53(21)	PET imaging
				344.278(1)	63.5(17)	
				586.27(7)	9.21(21)	
				778.904(2)	5.54(13)	
155	EC (100%)	5.32 d	N/A	86.55(3)	32.0(18)	SPECT imaging
				105.318(3)	25.1	
				180.169(9)	7.5(4)	
				262.27(1)	5.3(3)	
161	β^- (100%)	6.89 d	0.154(19)	25.6514	23.2(15)	β^- or Auger therapy
				48.9153	17.0(9)	
				57.1917(3)	1.79(10)	
				74.5667	10.2(5)	

The "quadruplet" of terbium isotopes (^{149}Tb, ^{152}Tb, ^{155}Tb and ^{161}Tb) proposed for theragnostic use possess the suitable properties for medical isotopes. These isotopes can be

used for all four aspects of nuclear medicine, α therapy, PET imaging, SPECT imaging and β^- therapy, respectively. Table 2 lists the half-lifes and energies of the emitted radiation from each isotope. Both the half-lifes and emitted energies for each isotope are suitable for medical purposes.

Looking at table 2, the terbium isotopes can be paired according to their half-lifes. Both the ^{149}Tb and ^{152}Tb have similar half-lifes of hours and ^{155}Tb and ^{161}Tb have similar half-lifes of days. The similar half-lifes of these pairs means that each pair can be used together to perform a more accurate form of theragnositcs for patient dose calculations.

Medical studies carried out by C. Muller, et al [2, 3, 4, 5] have provided the evidence required to further the investment into terbium production techniques. Their studies suggest that all four of the terbium isotopes would perform well for each of their designed functions. In addition to this, there is strong evidence [5] that, for example, in the case of prostate cancer ^{161}Tb will out perform ^{177}Lu because ^{161}Tb emits a β^- with a lower energy and thus has shorter range in tissue than ^{177}Lu so can target a more localised region.

2. Production

The MC40 cyclotron at the University of Birmingham is capable of accelerating proton and alpha particles up to 40 MeV and ^{3}He nuclei and deuteron particles can also be accelerated for isotope production. With these capabilities it is possible to produce ^{152} Tb and ^{155}Tb and potentially ^{149} Tb and ^{161}Tb [1].

The initial research focus was the production of the diagnostic imaging isotopes. The cross-section of interaction depends on energy. By varying the energy of the proton or alpha beam incident on the target the ratios of products produced changed. In order to create Tb isotopes, targets of either gadolinium or europium were used. Terbium isotopes can then be separated from the irradiate target using radio-chemical techniques being developed and NPL (National Physics Laboratory) [6].

For initial tests natural europium and gadolinium targets were used to identify which terbium isotopes could be produced using the MC40 cyclotron.

2.1. Europium target

The reaction mechanism for the production of ^{152}Tb and ^{155}Tb using and alpha beam on an natural europium target is as follows,

$$^{151}Eu(\alpha, 3n)^{152}Tb$$
$$^{153}Eu(\alpha, 2n)^{155}Tb$$

Initial investigations were done by looking at the PACE4 (Projection Angular-momentum Couples Evaporation Monte Carlo code) [7, 8] cross-section calculations for the interaction of alpha on a natural europium target (see figure 3(b)). The alpha beam energy was chosen by selecting the energy where the cross-section was a maximum for ^{152}Tb production. The irradiated Eu target was then place in front of a HPGe (High Purity Germanium) detector to identify products made using the emitted gammas. A small section of the gamma spectrum collected is shown in figure 4. Looking at this section alone, it can be observed that ^{154}Tb and ^{153}Tb were identified but more importantly ^{152}Tb in the ground state and excited isomer state were also identified. The isomeric state has a half life of 4 minutes compared to 17.5hrs for the ground state. Thus when gamma spectra were collected an hour later the purely isomeric ^{152}Tb states were no longer visible.

Although PACE4 was used for the initial investigation, the code does not differentiate between different isomers of terbium. An alternative code, TALYS (nuclear reaction code) [9] can differentiate between isomeric states. Comparing the PACE4 and TALYS cross-section (see

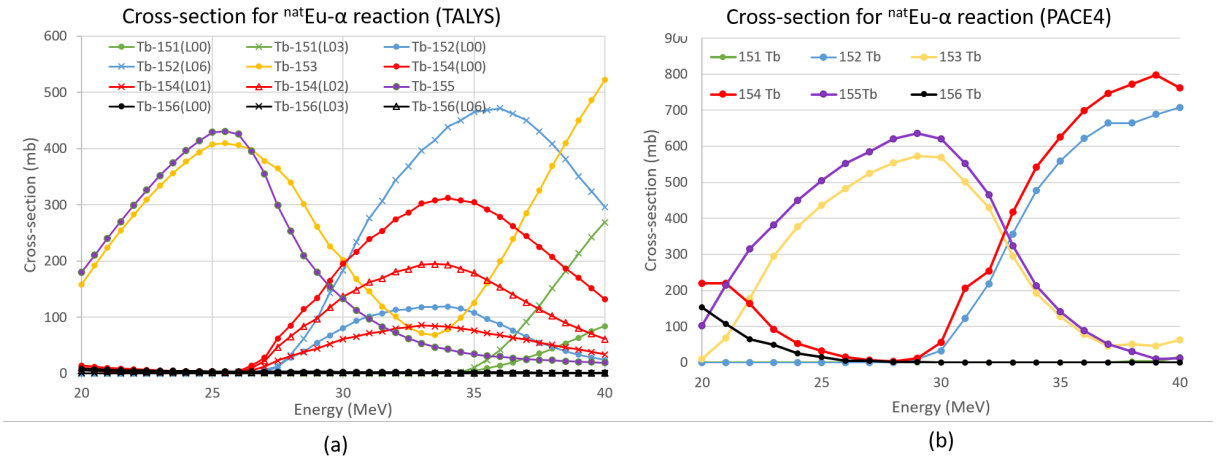

Figure 3. Cross-sections of interaction vs. energy of alpha beam on an natural Eu target (a)TALYS calculation (b)PACE4 calculation

figure 3(a)) there is a discrepancy between which alpha energy will produce the maximum cross-section for ^{152}Tb production. TALYS predicts a maximum cross-section at 34-36 MeV and PACE4 at 40 MeV. In the energy region for the initial production, TALYS predicts a much higher cross-section for the production of ^{153}Tb compared to PACE4. This was reflected in the gamma spectra data collected in figure 4 which displays the presence of ^{153}Tb. Therefore, for future investigation TALYS was used to calculate cross-sections to predict suitable beam energies.

An investigation to measure the cross-section of interaction for the production of terbium using an alpha beam incident on a europium target has begun. Preliminary results are currently being analysed.

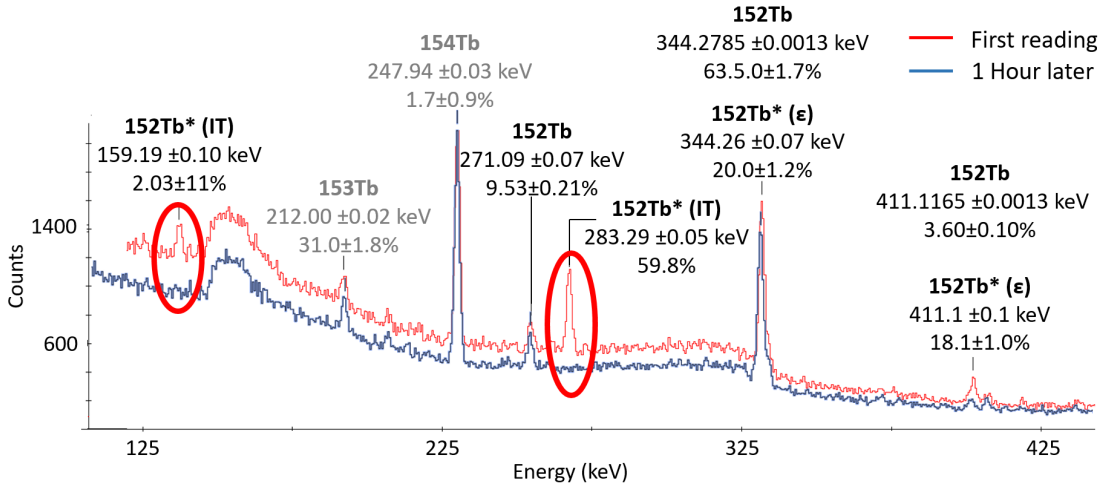

Figure 4. Calibrated section between 125 keV and 425 keV of the irradiated natural Eu foil gamma spectra, labelled with identified gamma energies and isotopes responsible for energy peaks

2.2. Gadolinium target

To identify which terbium isotopes could be produced using a proton beam incident on a gadolinium target, a natural gadolinium target was used. There are seven natural isotopes of gadolinium compared to the two of europium. This increases the complexity of production when comparing cross-section of interaction. The energy of the proton beam was selected using TALYS cross-section calculations. The energy select was to ideally produce a high yield of ^{155}Tb. A preliminary analysis of the gamma spectra collected of the target (see figure 5) revealed that ^{155}Tb was produced. The quantity of ^{155}Tb produced and the identification of the other isotopes present require further study.

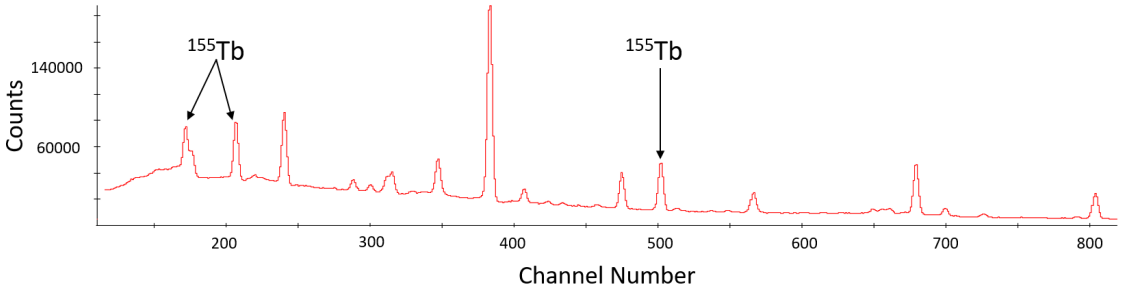

Figure 5. Preliminary identification of ^{155}Tb in an irradiated natural Gd foil

Summary

This preliminary study proved that the ^{152}Tb isotope can successfully be produced at the MC40 cyclotron using an alpha beam on a europium target, and the ^{155}Tb isotope could also be produced using a proton beam on a gadolinium target. The cross-section for the the production of terbium in each of these cases will be calculated from the spectra collected and compared to the predicted cross-section made by PACE4, TALYS and EMPIRE [10].

The optimal beam energy for the production of each isotope will then be determined from the cross-sections. Enriched targets will be used to gain a higher yield of the desired isotope and reduce other terbium isotope contaminants which can not be removed by radio-chemical separation at NPL.

References

[1] Formento Cavaier R and et al 2017 *Physics Procedia* **90** 157–163
[2] Müller C and et al 2012 *J Nucl Med* **53** 1951–1959
[3] Müller C and et al 2014 *J. High Energy Phys.* Nuclear Medicine and Biology **40** e58–e65
[4] Müller C and et al 2016 *EJNMMI Research* **35** 1–10
[5] Müller C and et al 2019 *EJNMMI Research* **49** 1919–1930
[6] Webster B and et al 2019 *Nature Scientific Reports* **9** 10884
[7] Tarasov O and Bazin D 2008 *NIM B* **266** 4657–4664
[8] Gavron A 1980 *Phys.Rev.* **C 21** 230–236
[9] Koning A, Hilaire S and Duijvestijn M 2008 *EDP Sciences* 211–214
[10] Herman M, Capote R, Carlson B, Obložinský P, Sin M, Trkov A, Wienke H and Zerkin V 2007 *Nucl. Data Sheets* **108** 2655