Production and Purification of Titanium-45 for Positron Emission Tomography Imaging

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TRISKEM International

Cancer Diagnostic

1 in 2 Canadians will develop cancer

1 in 4 Canadians will die from cancer

Cancer is the

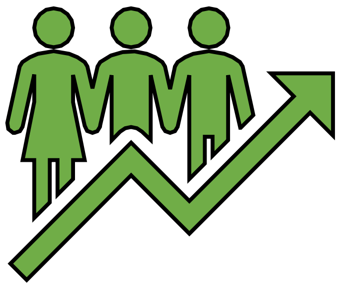
#1

cause of death in Canada

Survival rates increased from

55%-63%

From 1992 to 2014



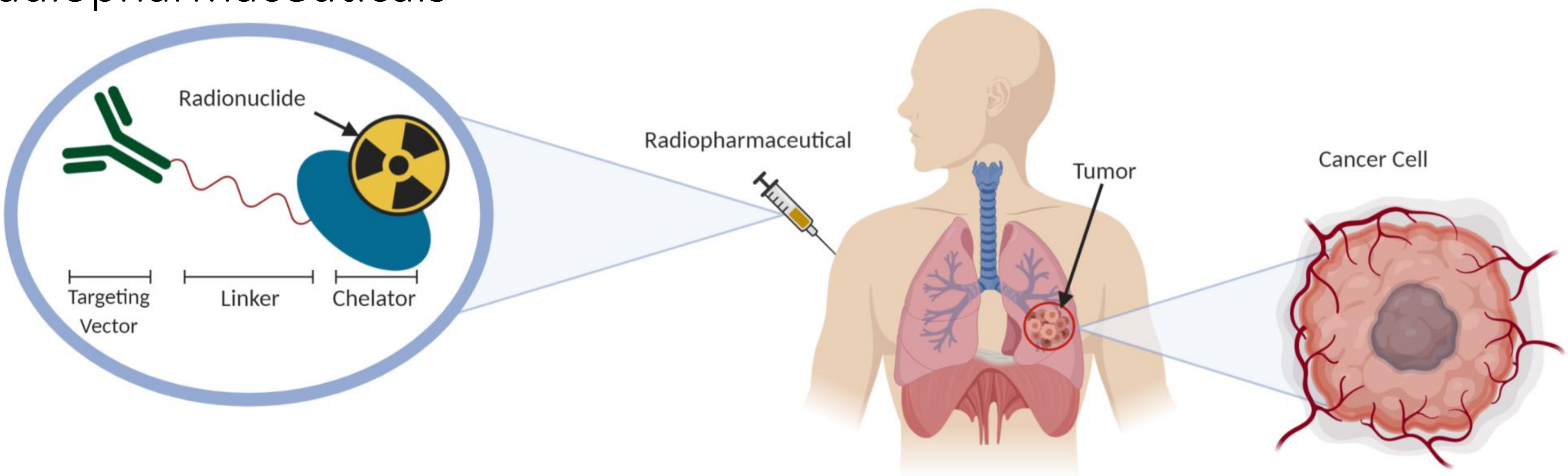
Impact of Early Detection

Survival rate based on cancer stage detection

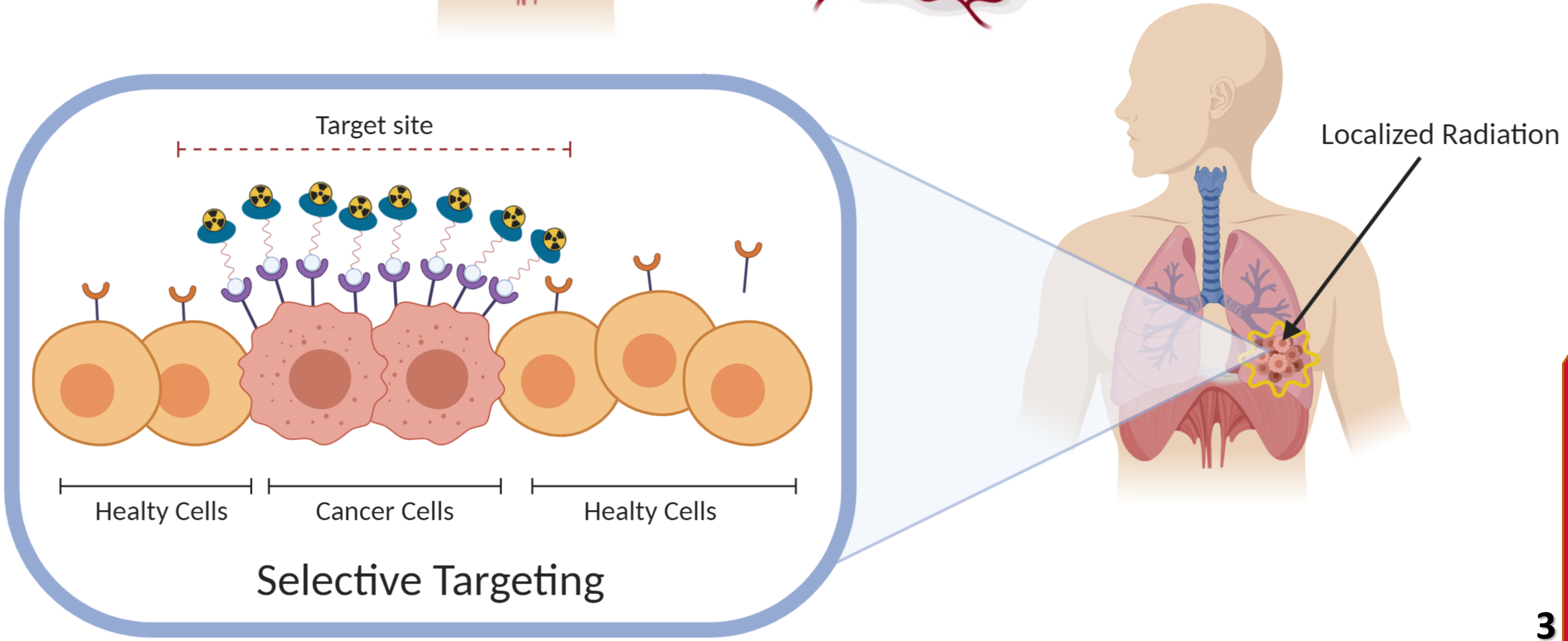
Type of cancer	5-year survival rate (%)	
	Stage I	Stage IV
Breast Cancer	90%	15%
Ovarian Cancer	90%	5%
Lung Cancer	80%	15%
Cervical Cancer	93%	15%

- Cancer Research UK website
- Canadian Cancer Statistics 2019, Canadian Cancer Society

Radiopharmaceuticals



1
Radiopharmaceuticals' action pathway



2
Target site is saturated with radionuclides

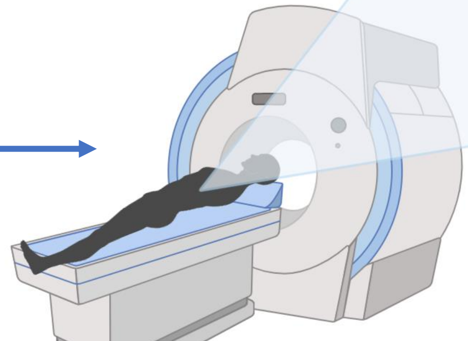
▪ Chem. Rev. 2019, 119, 902–956

Cancer Diagnostic: Imaging Modalities

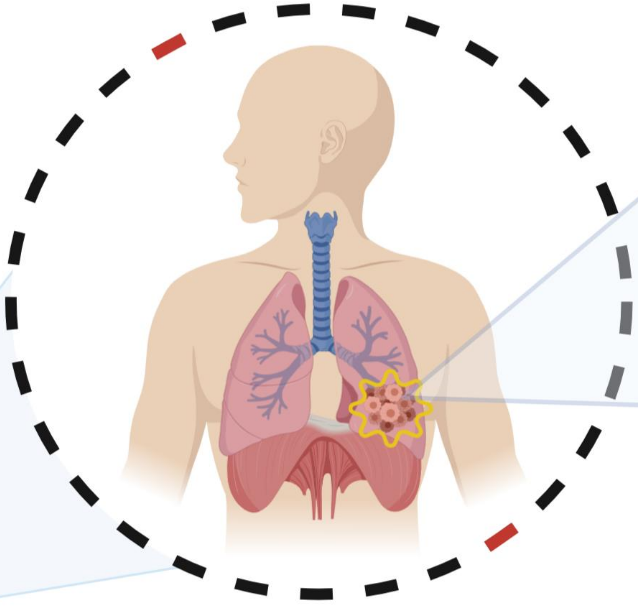
Types of Imaging Modalities

- Single-Photon Emission Tomography — SPECT
- Positron-Emission Tomography — PET

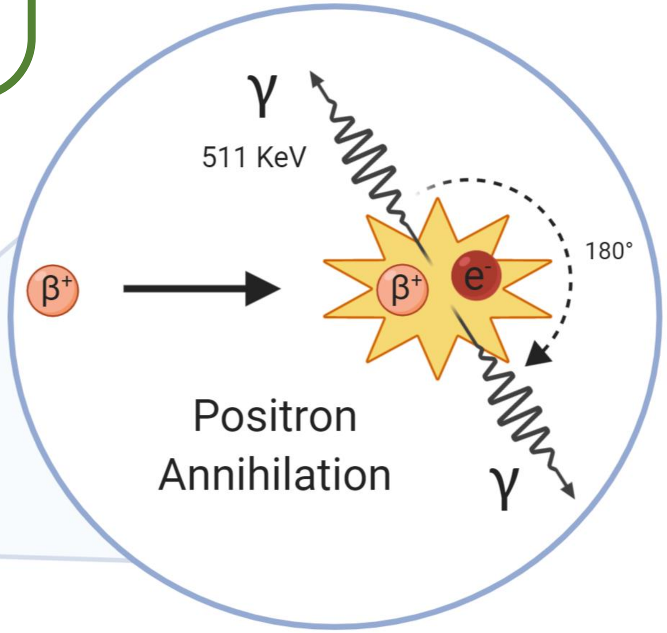
Current radionuclides used for PET



PET Scanner



Circular scanner detecting 2 gamma-rays simultaneously



Positron emitted from unstable nucleus with a certain energy

Low-energy positrons preferred for this modality

- Chem. Commun., 2013, 49, 4720
- FDA Approved Radiopharmaceuticals, Cardinal Health, 2019

PET Radionuclides

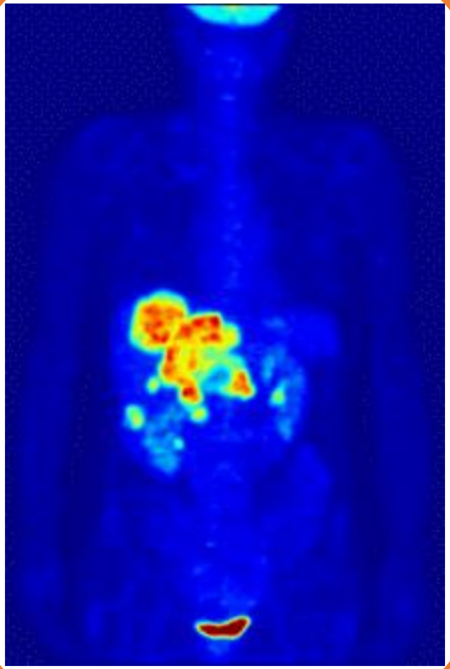
Organic Radionuclides

^{18}F
Half-Life: 109.77 min
β+ emission: 96.7%
$E_{\beta+}$: 0.249 MeV

^{11}C
Half-Life: 20.36 min
β+ emission: >99%
$E_{\beta+}$: 0.3857 MeV

^{13}N
Half-Life: 9.96 min
β+ emission: >99%
$E_{\beta+}$: 0.491 MeV

PET Image



β+: intensity of emission (%)
$E_{\beta+}$: Mean β^+ energy

Metallic Radionuclides

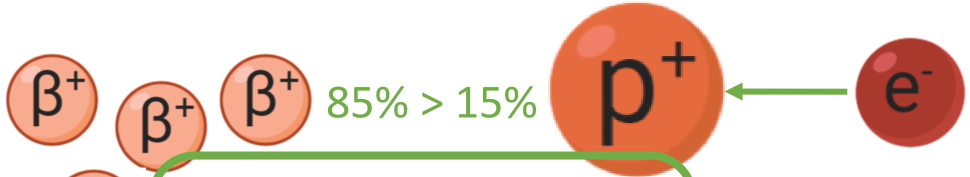
^{89}Zr
Half-Life: 78.5 hr
β+ emission: 22.7%
$E_{\beta+}$: 0.396 MeV

^{68}Ga
Half-Life: 67.71 min
β+ emission: 88.9%
$E_{\beta+}$: 0.839 MeV

^{82}Rb
Half-Life: 1.27 min
β+ emission: 95.4%
$E_{\beta+}$: 1.481 MeV

Chem. Soc. Rev., 2013, 10, 1039 ▪ FDA Approved Radiopharmaceuticals, Cardinal Health, 2019 ▪ www.nndc.bnl.gov

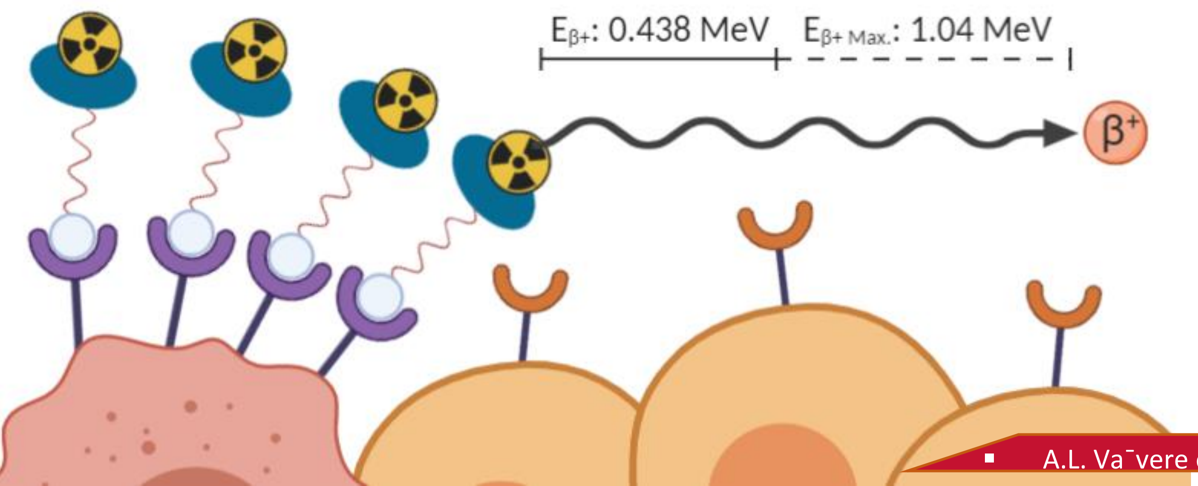
What makes Titanium-45 special?

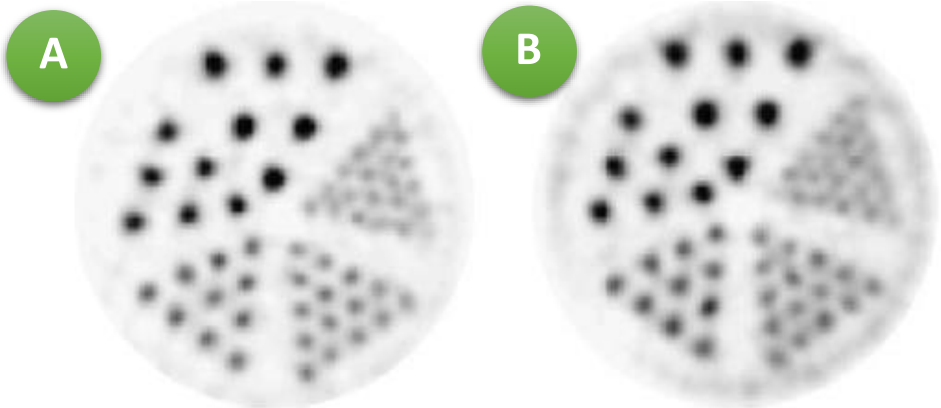


β+ emission: 85%
Electron Capture: 15%

$$p \rightarrow n + \beta^{+} + \upsilon \quad > \quad p + e^{-} \rightarrow n + \upsilon$$

$E_{\beta+}$: 0.3857 MeV
$E_{\beta+\ Max.}$: 1.04 MeV





Miniature Derenzo phantom imaged on microPET-R4 resolution comparison between (A) ^{18}F and (B) ^{45}Ti

Half-Life: 184 min

Produced from a single isotope, Scandium-45, with 100% natural abundance

Low energy cyclotrons can be used for its production. Mean proton beam energy required: 10 – 14 MeV

▪ A.L. Vaˉvere et al. / Nuclear Medicine and Biology 32 (2005) 117–122 (phantom images) ▪ Instruments 2018, 2, 8

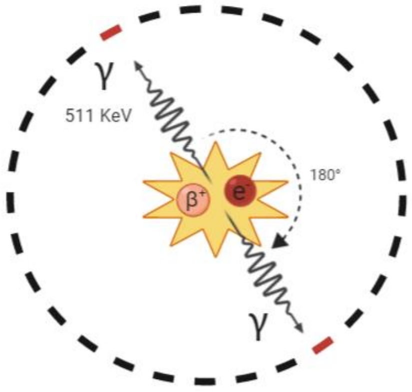
Project's Premise

Production

Produce ^{45}Ti from ^{45}Sc using a low energy cyclotron…

Purification

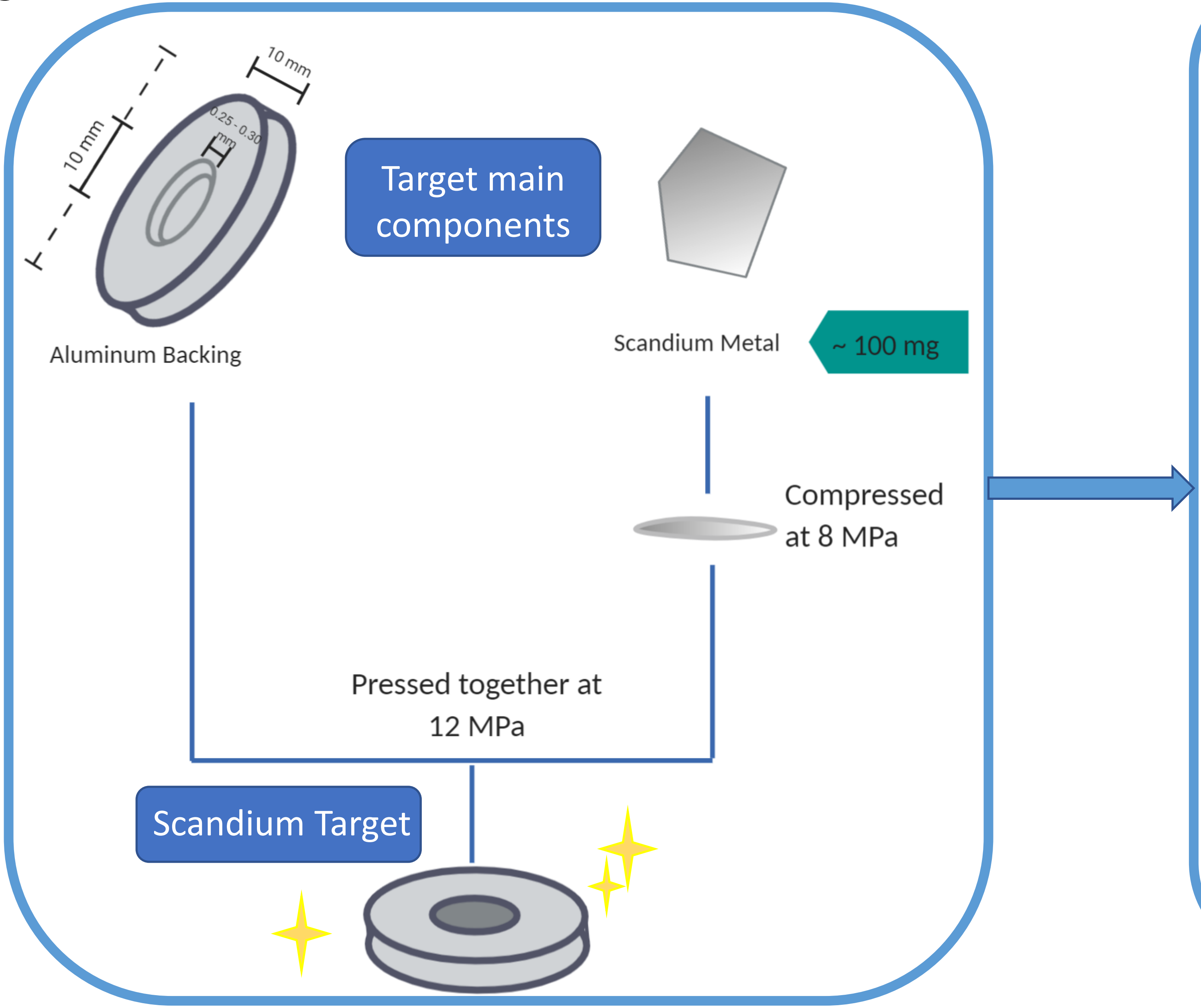
… and define a procedure to separate and purify this radionuclide from impurities…



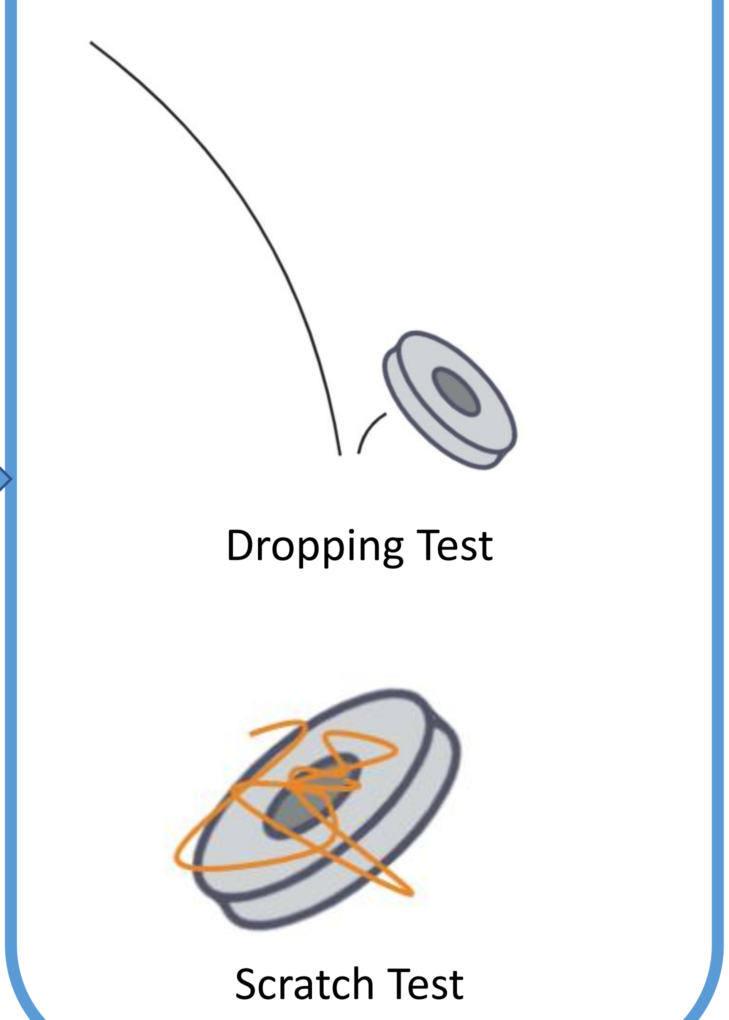
PET Imaging

…to be used for Positron Emission Tomography, given it's promising properties.

Target Production

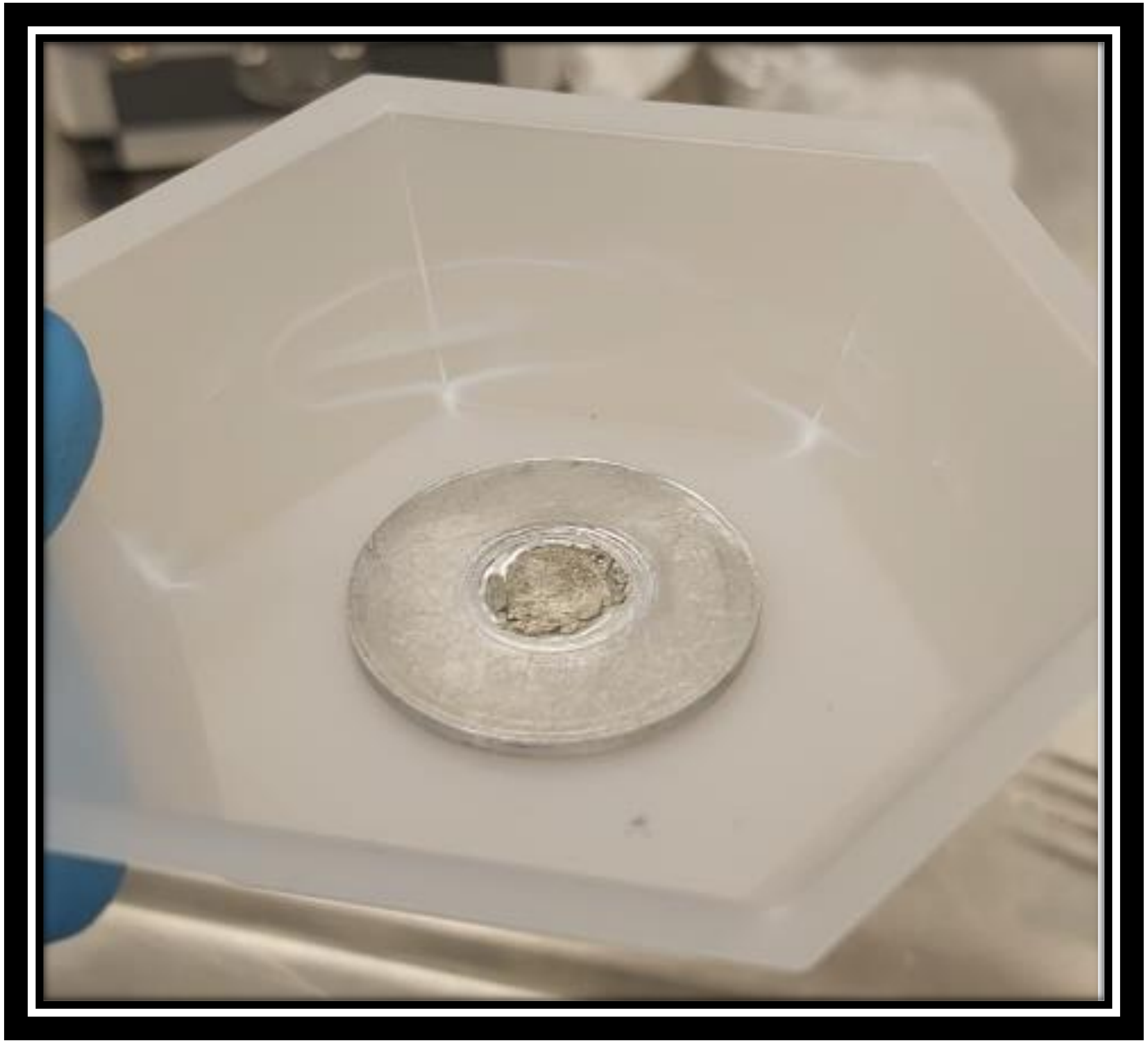


Quality Tests

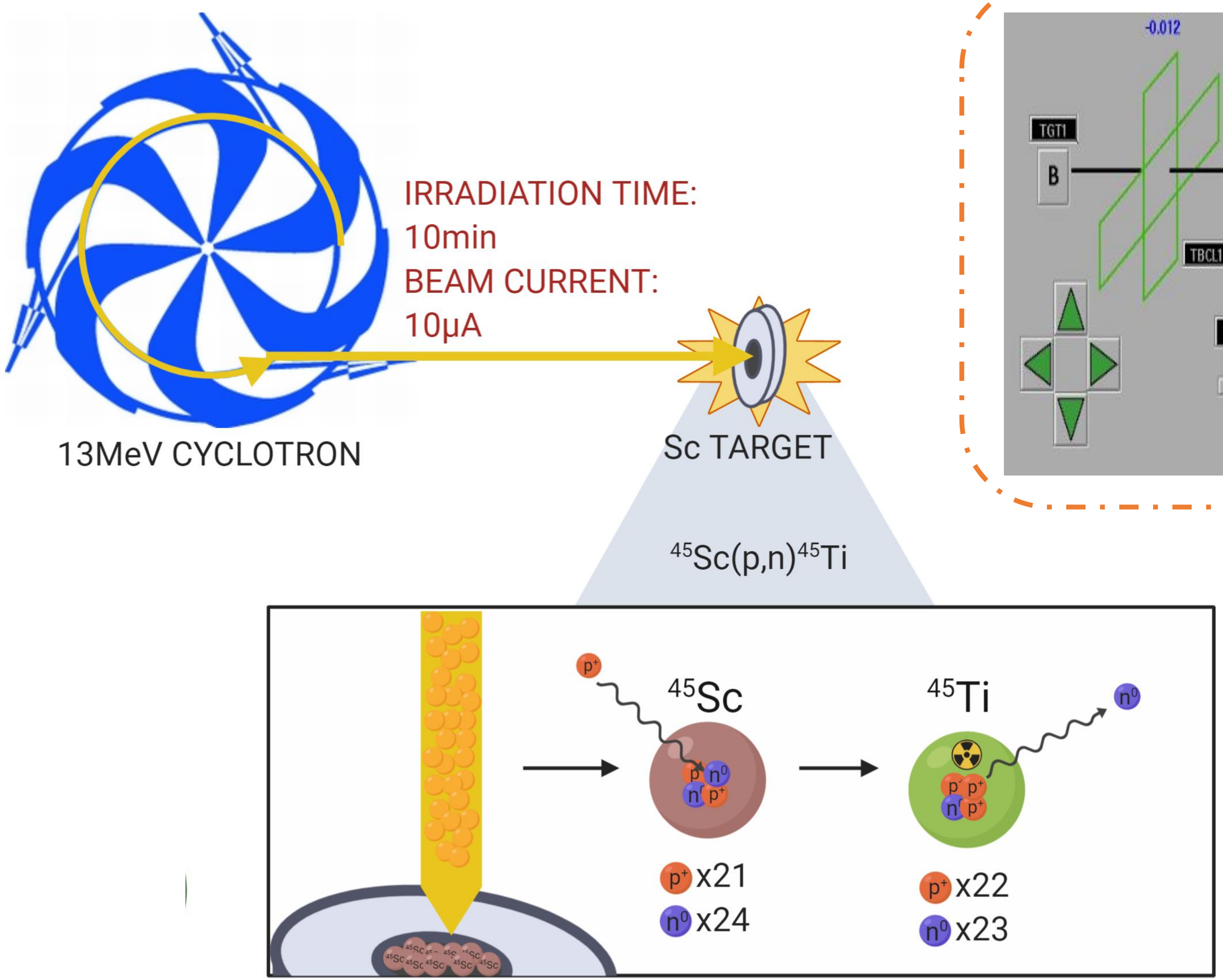


- TRIUMF Memo LS126, TRIUMF, 2018.

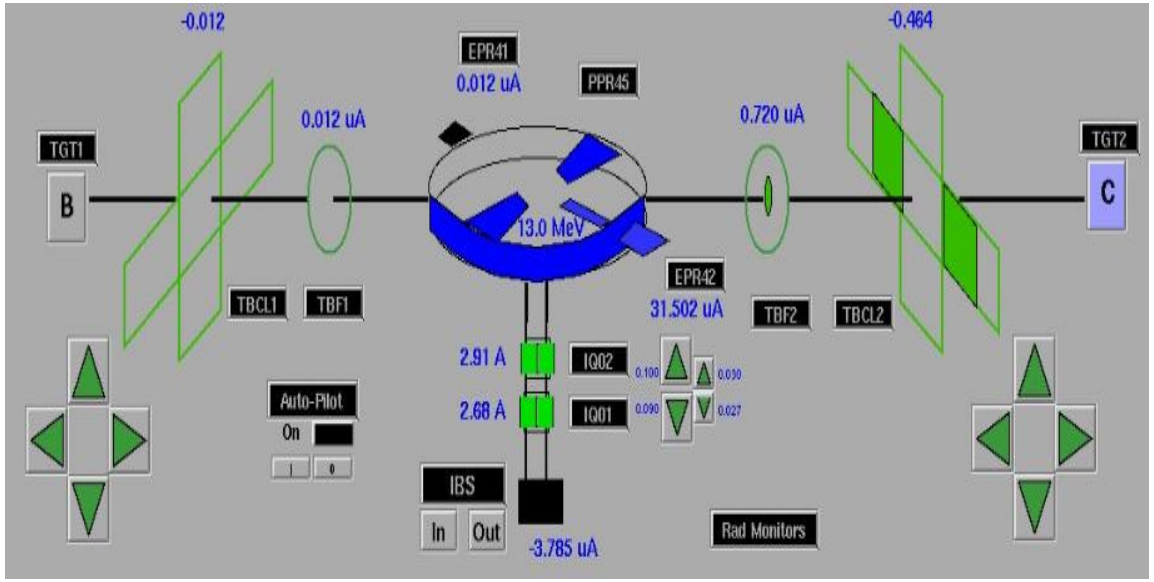
Scandium Target



Cyclotron and Irradiation Reaction

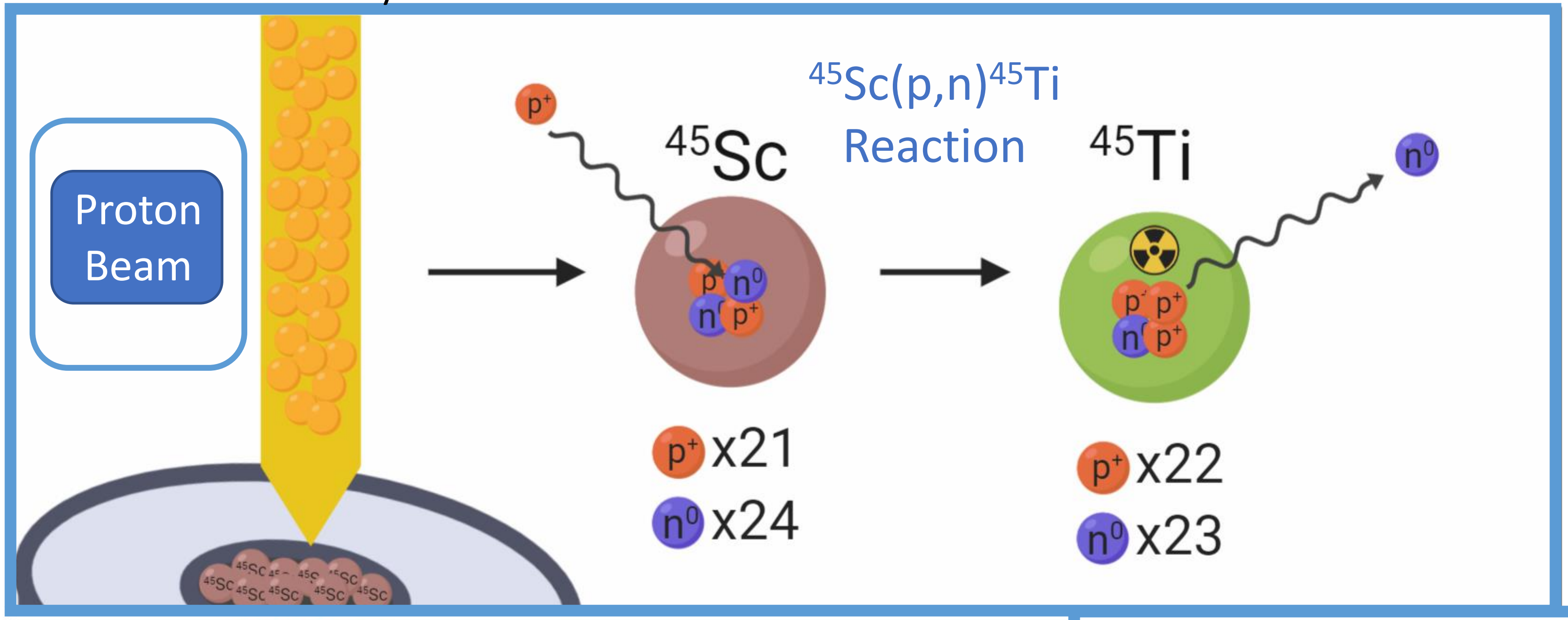


Actual TR13 Cyclotron Operation Diagram

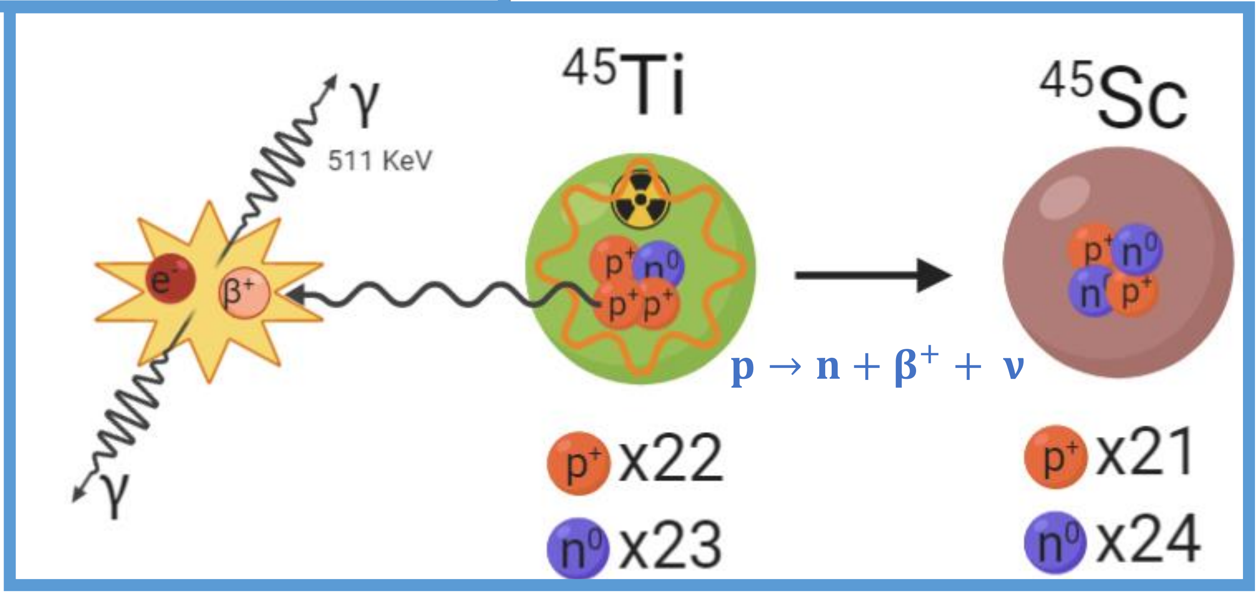


Nuclides and particles involved

Activation of Nucleus and Radioactive Decay



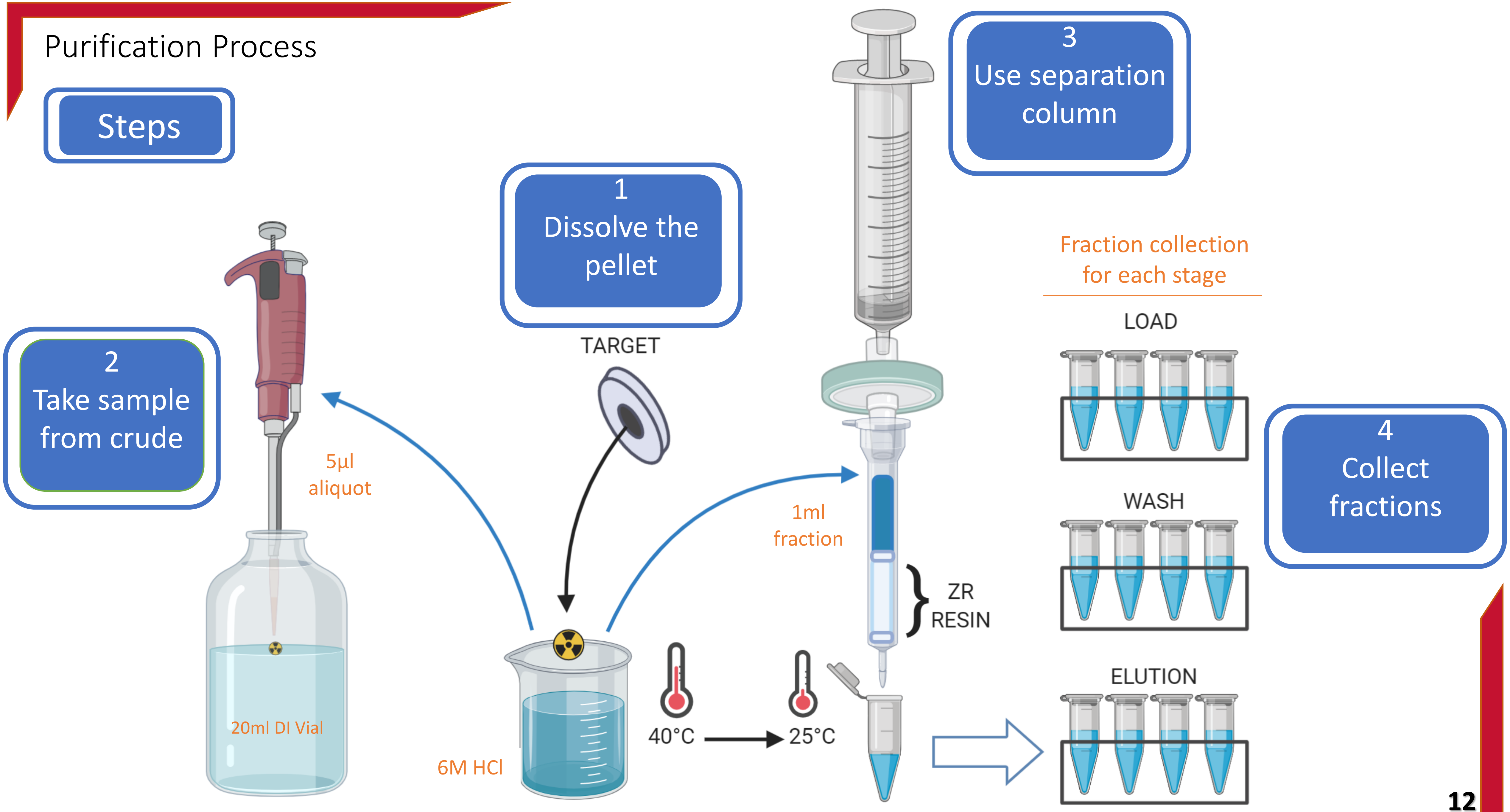
Radioactive decay of ^{45}Ti to ground state goes back to ^{45}Sc



The irradiation of Sc Target with a proton beam generates ^{45}Ti

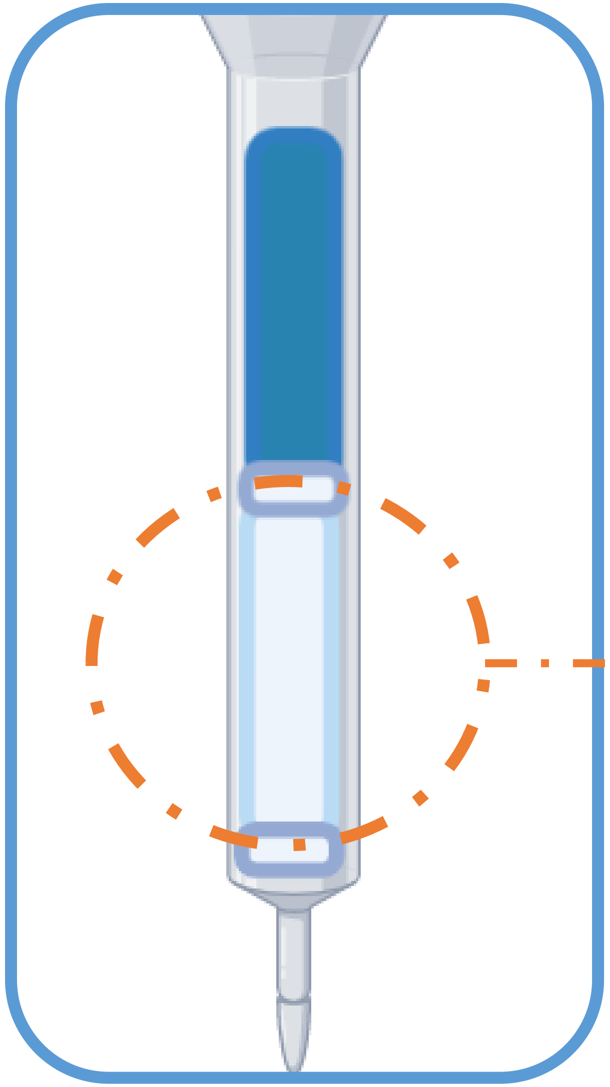
- Schmitz, R. E. et al. "The Physics of PET / CT scanners." (2013).

Purification Process



Zirconium Resin Significance

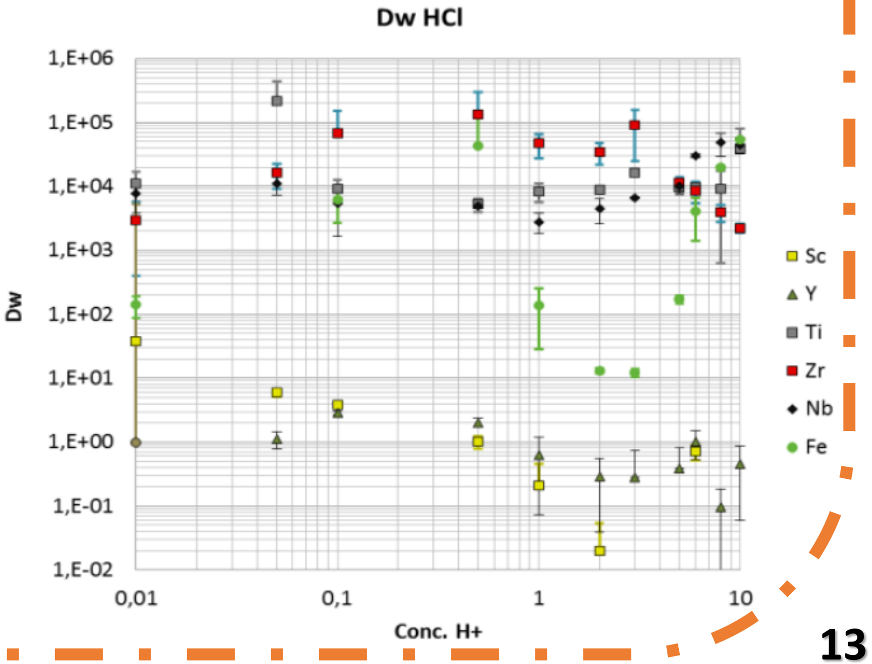
Why ZR resin?



It contains hydroxamate functional groups, often used as metal chelators.

Previous research on ^{44}Sc production supported the viability of hydroxamate based ZR resin for Sc/Ti separation.

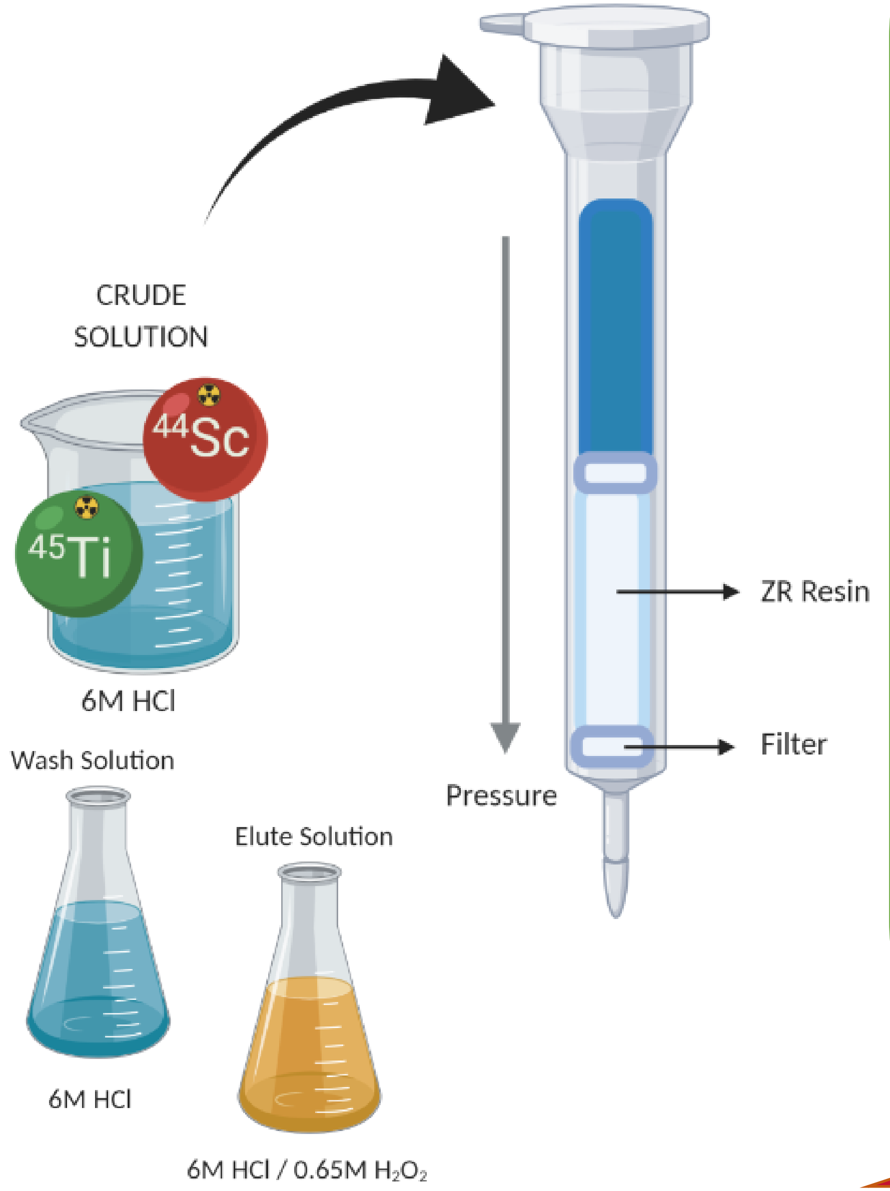
According to manufacturer's data, it shows high selectivity for titanium (compared to scandium) in acidic solution.



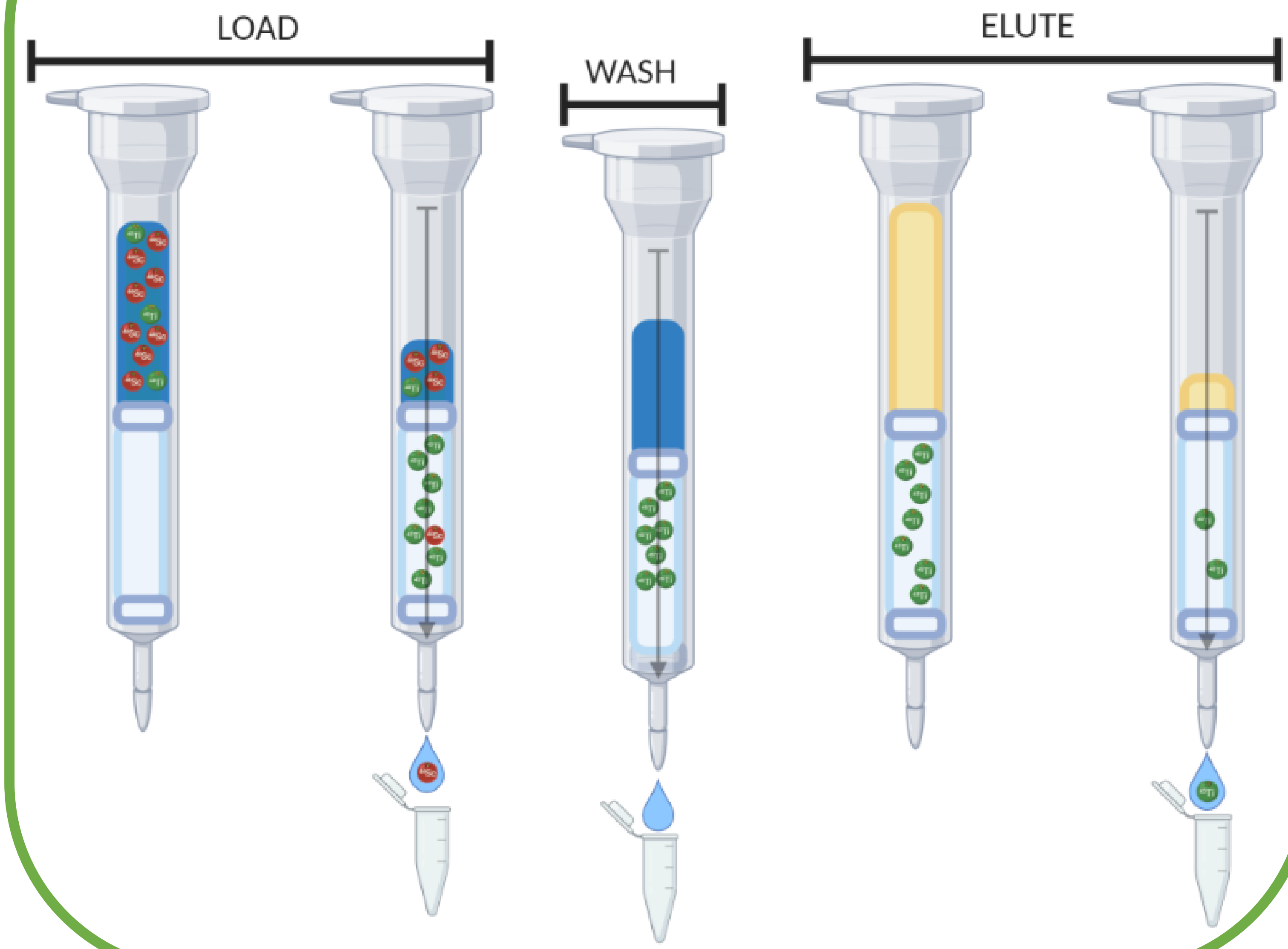
- J Chromatogr A. 2016 Dec 16;1477:3946
- ZR Product Sheet, TRISKEM, 2017.

Separation Column

Purification Reactants

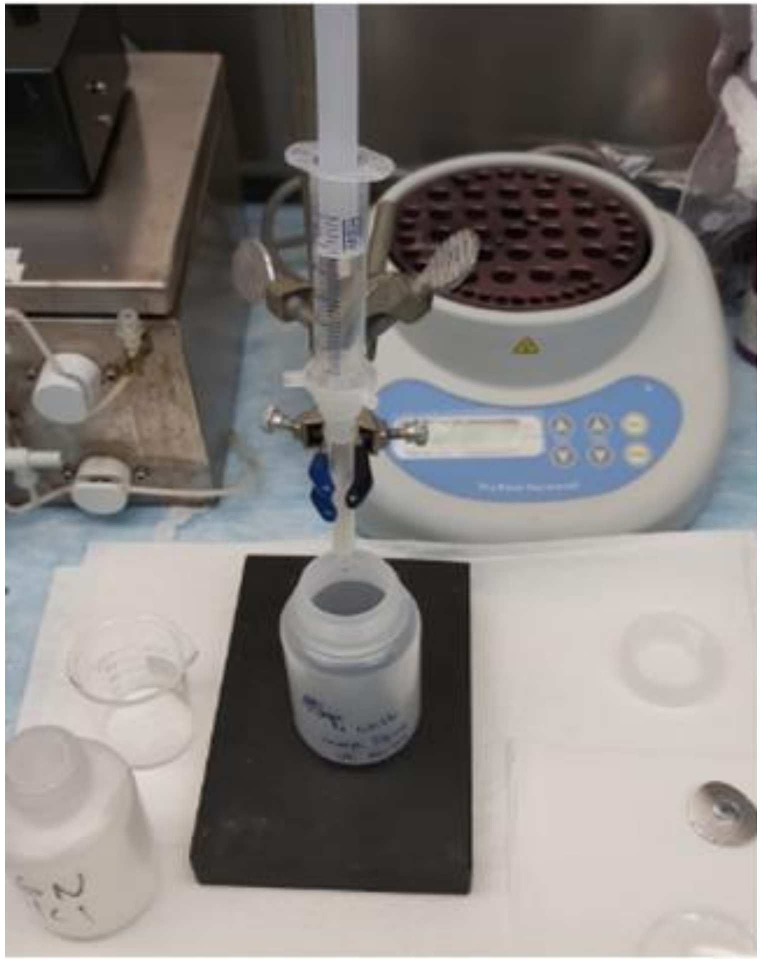


Separation Stages

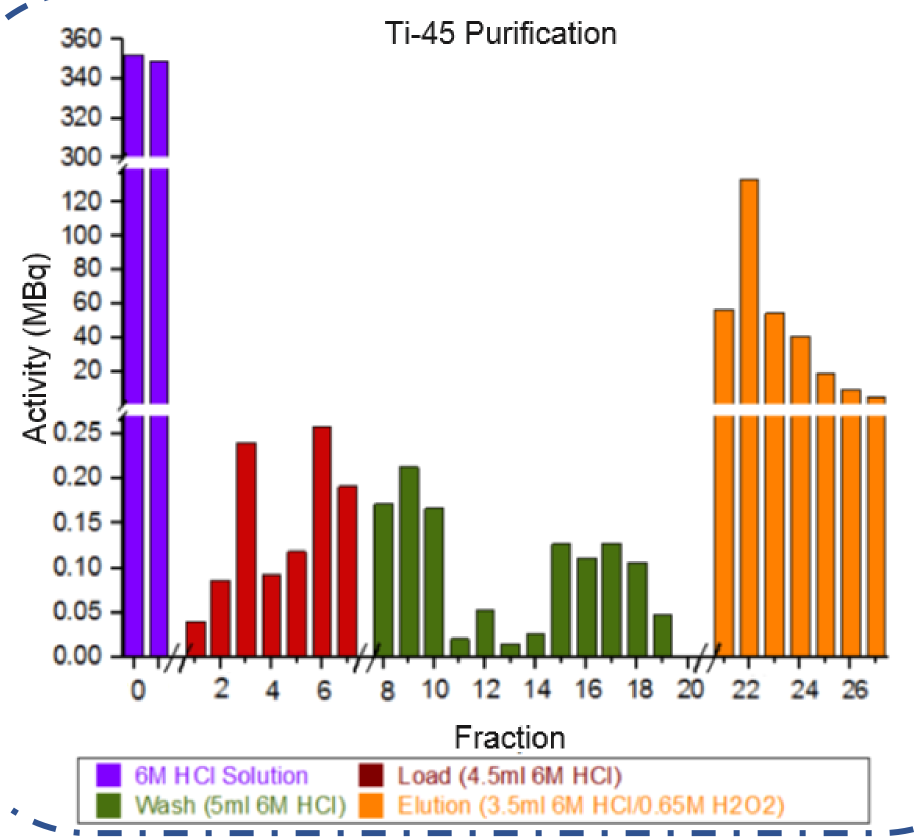


- TRIUMF Memo LS126, TRIUMF, 2018.

Results from Fraction Collection



Activity profile from each separation stage



The jumps in values are indicated by //

Activity measurements were performed on a Carpintec Dose Calibrator set for ^{44}SC

Fraction activity from Crude Solution		
Stage	**Activity (MBq)**	**Fraction (%)**
Crude Solution	350.32	100%
Load	1.41	0.40%
Wash	0.80	0.23%
Elute	319.38	91.17%
Column	28.72	8.20%

Experiments' results

Runs 6 - 7:

-Question where the remaining ^{45}Ti go

- ^{45}Ti loses at Load and Wash stage

-Amount of resin used doubled

- ^{44}Sc spikes of known activity on target purification process (no ^{45}Ti activity)

(Decay Corrected) Recovered Ti-45 (MBq)			
Run #	Crude	Purified	Recovery %
6	1197.18	956.81	80%
7	716.50	452.04	63%
8	1213.55	-	-
9	1008.53	994.92	99%
10	581.43	604.41	104%
11	532.14	498.10	94%
12	472.18	443.93	94%
13	532.35	467.26	88%
14	495.91	231.73	47%
15	522.57	467.34	89%
16	499.41	484.21	97%
17	497.60	313.85	63%
18	596.87	344.70	58%

First Experiments:

-Experiments 1-5 were not adequately measured with the right calibration number

Latest Experiments:

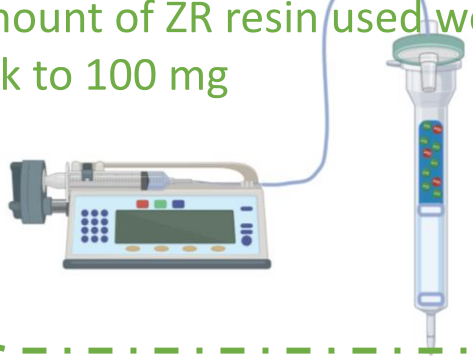
-Implementation of a syringe pump to regulate flow rate:

Run 6: 0.300 ml/min

Run 7: 0.100 ml/min

-Duplicate samples taken from total Load and Wash stages

-Amount of ZR resin used went back to 100 mg



Conclusion

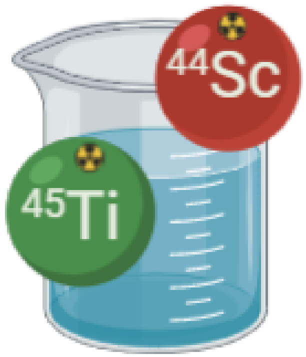
Production of ^{45}Ti from ^{45}Sc was achieved through irradiation of ^{45}Sc target for 10 min at 10 µA

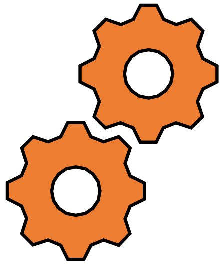
Production rates of ^{45}Ti activity seemed to closely match theoretical values at the beginning

Sc/Ti separation was possible, obtaining no ^{44}Sc mesurable but ICP-MS will be done for validation

^{45}Ti recovery was optimized from 65% to 99%, more runs will be performed using the last flow rate used (0.100 ml/min)

Future Steps





Short-Term Goals

Replicate experiment 3 times more using the same conditions and parameters from best recovery results

Medium-Term Goals

Design and define an automated system for the purification process

Standardize Process

Long-Term Goals

Define a potential chelator to bind with ^{45}Ti

Perform radiolabeling studies

In vitro studies / In vivo studies

Academic Progress

ITESO, Universidad Jesuita de Guadalajara

BSc Chemical Engineering

- Contributed to 2 research academic publications

MsC Chemistry

- Research project on inorganic chemistry applied to nuclear medicine
- Mitacs' Graduate Fellowship
- SFU Graduate Fellowship (Summer 2020)
- Teacher Assistant (Fall 2019)
- CHEM849 Special Topics in Analytical Chemistry (Fall 2019)
- CHEM842 Special Topics in Radiochemistry (Spring 2020)

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- TRISKEM