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Production and radiochemistry of theranostic radioscandium nuclides

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Introduction

Theranostics incorporates the same targeting compound with different radionuclides. The clinical theranostic pair, ^{68}Ga and ^{177}Lu, can exhibit different pharmacokinetics between the diagnostic and therapeutic compounds, respectively. An elementally matched theranostic pair will result in identical complexation, *in vitro* binding, and *in vivo* pharmacokinetics, as the diagnostic and therapeutic compounds are chemically identical. A target recycling method was developed for high purity ^{43}Sc and ^{47}Sc using enriched [^{46}Ti]TiO_2 and [^{50}Ti]TiO_2, respectively. The produced ^{43}Sc/^{47}Sc will be used for exploring their theranostic potential.

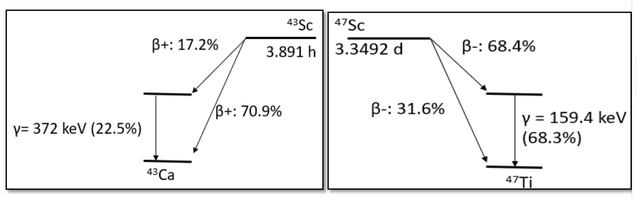

Figure 1: The decay scheme the radioscandium isotopes of medical interest: ^{43}Sc and ^{47}Sc

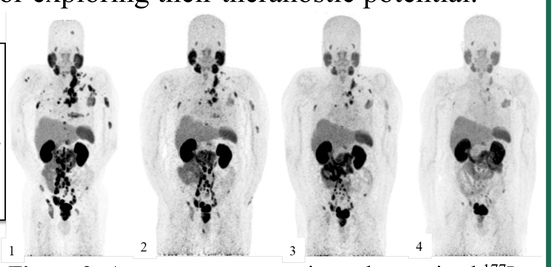

Figure 2: A prostate cancer patient who received ^{177}Lu-PSMA-617 therapy while being monitored using ^{68}Ga-PSMA-11.

Development of enriched TiO_2 target lifecycle

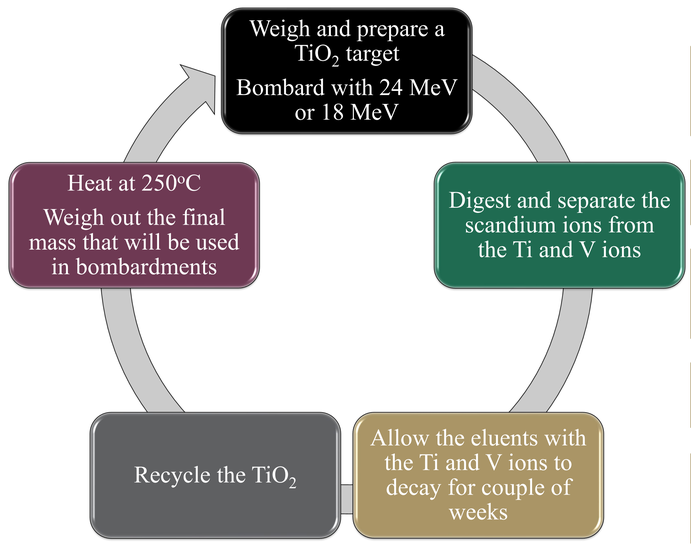

Figure 3: The target lifecycle of enriched TiO_2 for radioscandium production

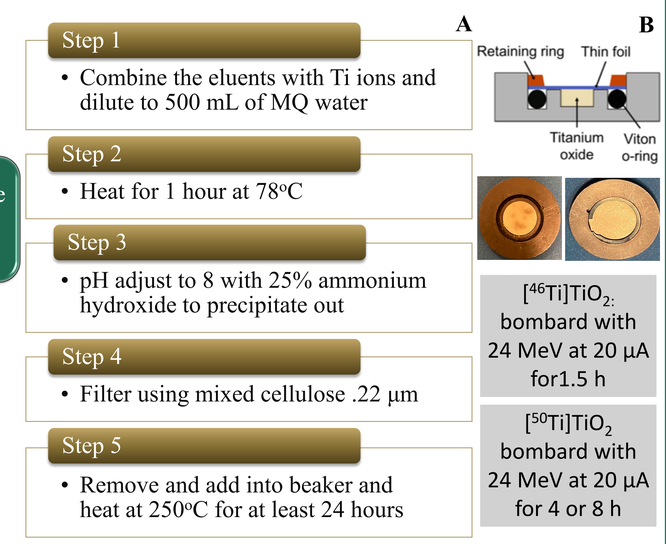

Figure 4: The titanium target recycle procedure (A). The titanium dioxide target design, pressed [^{50}Ti]TiO_2 and target bombardment parameters (B).

Table 1: Trace metal analysis of collected ^{47}Sc from recycled ^{50}Ti targets

	Cycle: 1 (ppb)	Cycle: 4 (ppb)	Cycle: 6 (ppb)
Zn	430	47	29
Cr	311	<15	<15
Mn	340	<15	<15
Fe	1,433	129	<15
Ni	189	<15	<15
Cu	263	11	<15
Pb	2,172	<15	<15
W	10,170	53	32

Table 2: The total activity yields decay corrected to end of bombardment for recycled targets

Production of ^{43}Sc from a single enriched ^{46}Ti target bombarded for 1.5 h			
Activity	Cycle 1	Cycle 2	Cycle 3
MBq	499	540	529
mCi	13.5	14.6	14.3
Production of ^{47}Sc from a single enriched ^{50}Ti target bombarded for 8-9 h			
Activity	Cycle 1*	Cycle 4	Cycle 8
MBq	110	85.1	84.7
mCi	2.97	2.3	2.29

Table 3: Activity of each radioscandium in the purified collection vial

Activity corrected to end of bombardment for the collected ^{43}Sc: **(n = 3)**							
Isotope	^{43}Sc	^{44m}Sc	^{44g}Sc	^{46}Sc	^{47}Sc	^{48}Sc	Total radioscandium
Activity mCi	13.6 ± 0.7	<0.01	0.14 ± 0.01	<0.01	0.01 ± 0.01	<0.01	13.9 ± .7
Percentage	98.5 ± 0.3	0.02 ± <0.01	1.02 ± 0.1	0.01 ± <0.01	0.07 ± <0.01	<0.01	100
Activity corrected to end of bombardment for the collected ^{47}Sc: (n = 3)							
Isotope	^{43}Sc	^{44g}Sc	^{44m}Sc	^{46}Sc	^{47}Sc	^{48}Sc	Total radioscandium
Activity mCi	Decayed	0.04 ± 0.01	0.04 ±0.01	0.04 ± 0.01	1.3 ± 0.17	<0.01	1.6 ± 0.3
Percentage	0	2.97 ± 0.6	2.97 ± 0.6	2.42 ± 0.4	91.1 ± 0.6	<0.01	100

Radioscandium purification

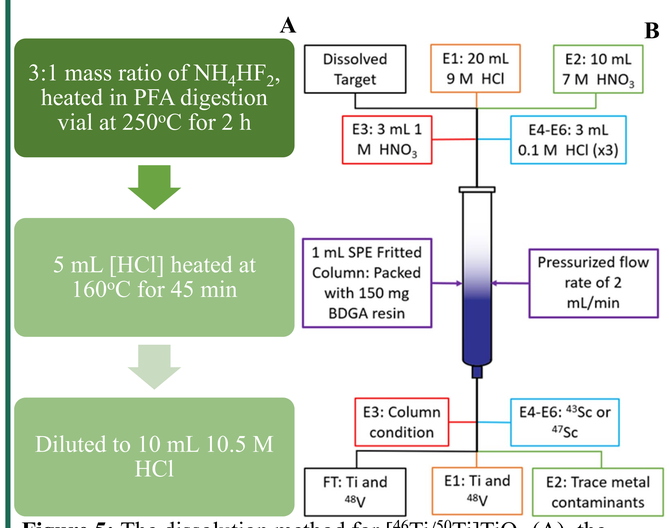

Figure 5: The dissolution method for [^{46}Ti/^{50}Ti]TiO_2 (A), the separation method (B).

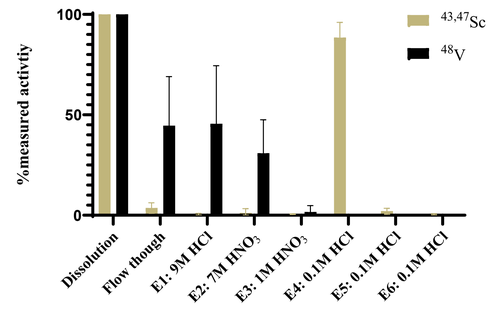

Figure 6: The separation profile of ^{43}Sc/^{47}Sc from enriched [^{46}Ti/^{50}Ti]TiO_2

Table 5: The separation results

Isotope	Starting	FT & Washes	E4	E5	E6
^{43}Sc (mCi)	14±0.6	1.3±0.1	12.±0.1	0.1±0.08	0.2±0.01
^{48}V (µCi)	67±7.7	74±15.7	0	0	0
^{47}Sc (mCi)	1.4±0.1	0.1±0.02	1.2±0.1	0.1±0.01	0.1±0.01
^{48}V (µCi)	224±11	256±10	0	0	0

Radiochemistry of ^{43}Sc and ^{47}Sc

Methods

Radiolabeling

Radiolabeling was performed in 0.25 M ammonium acetate buffer pH 4.7, at 95°C, shaking at 800 rpm for 30 minutes. Either DOTA or PSMA-617 was used for complexation. A DOTA titration with 80-100 µCi was used for determining apparent molar activates for different target cycles. The molar activities of [^{43}Sc]Sc-PSMA-617 was 208 µCi/nmol. [^{4x}Sc]Sc-DOTA was confirmed using iTLC-SG in 1 M citrate buffer. [^{43}Sc]Sc-PSMA-617 was confirmed using HPLC.

In vivo analysis

Athymic nude male mice were implanted with either LNCaP (PSMA+) or PC3 (PSMA-) cells and allowed time for tumor growth. Mice were injected (tail-vein) with either [^{43}Sc]Sc-PSMA-617 or [^{43}Sc]Sc-PSMA-617 with 5 mg/kg of 2-PMPA. Mice were scanned for 30 min at 1 or 4 h on Sofie PET scanner, followed by CT and Biodistribution

Table 6: The apparent molar activity of [^{43}Sc]Sc-DOTA and [^{47}Sc]Sc-DOTA

Isotope	Target cycle	Apparent molar activity	Target cycle	Apparent molar activity
^{43}Sc	2nd	160.3 mCi/µmol	6th	628 mCi/µmol
^{47}Sc	3rd	34 mCi/µmol	6th	91.7 mCi/µmol

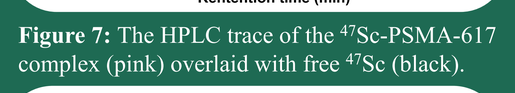

Figure 7: The HPLC trace of the ^{47}Sc-PSMA-617 complex (pink) overlaid with free ^{47}Sc (black).

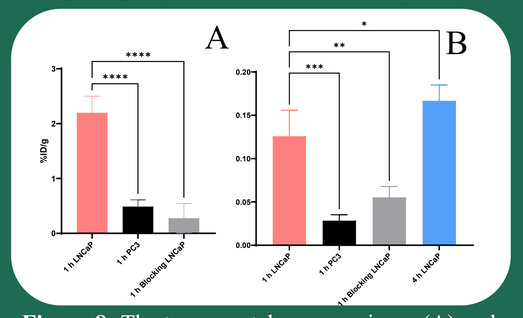

Figure 8: The tumor uptake comparisons (A) and SUV comparisons (B) of ^{43}Sc-PSMA-617 in Figures 9 and 10.

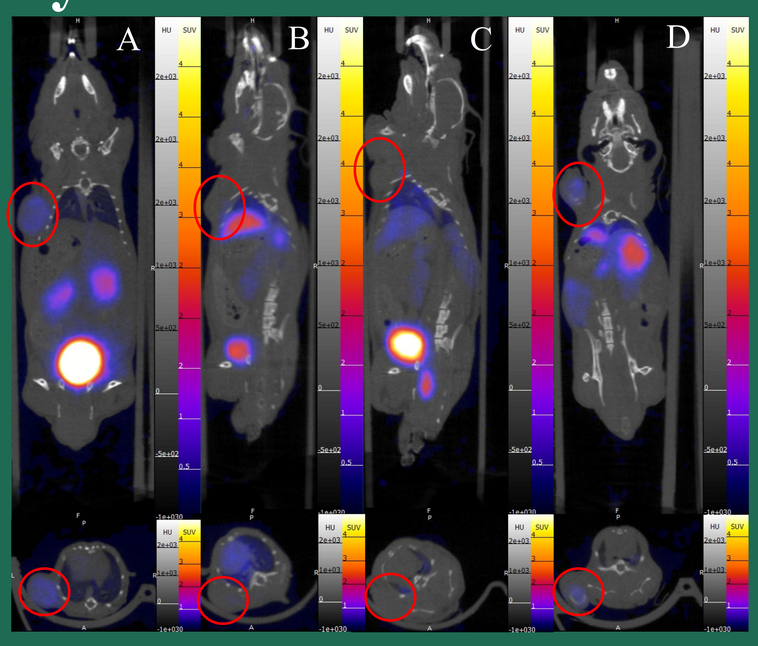

Figure 9: The 1 h coronal and transversal PET image of PSMA+ mice (A), PSMA+, co-injected with 5 mg/kg 2-PMPA mice, (B), PSMA- mice (C), and 4 h PSMA+ mice. (D)

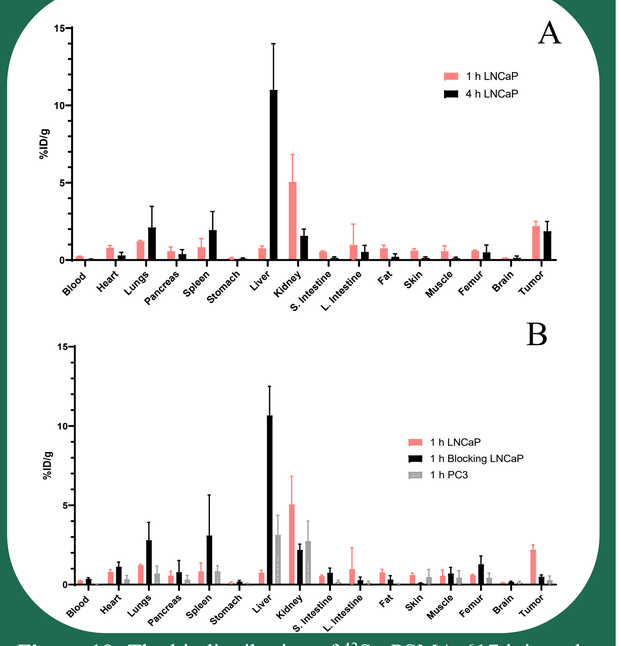

Figure 10: The biodistribution of ^{43}Sc-PSMA-617 injected mice at 1 h (pink) and 4 h (pink). (A) The 1 h biodistribution of ^{43}Sc-PSMA-617 PSMA+ (pink), blocking (black) and PSMA-(gray). (B)

Conclusions

An enriched [^{xx}Ti]TiO_2 lifecycle was developed that resulted in reproducible radioscandium yields, increased the purity of both target material and purified radioscandium. The AMA of ^{43}Sc and ^{47}Sc increased with the target cycle. ^{43}Sc-PSMA-617 *in vivo* results establishes stability and specificity for PSMA-targeted theranostic.

Future Directions

Continued analysis of titanium targets passed cycle 8. Analysis of additional chelators with high purity ^{43}Sc and ^{47}Sc. SPECT imaging of ^{47}Sc-PSMA-617 will be conducted at longer timepoints. An *in vivo* therapy study will follow with ^{43}Sc-PSMA-617 to be used for monitoring treatment response of ^{47}Sc-PSMA-617.

References

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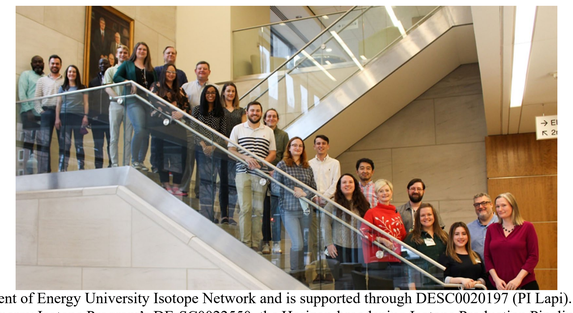
Acknowledgments

The authors would like to acknowledge the Lapi Lab group members, the Cyclotron Facility, the SAIF Facility and the UAB Machine Shop for their work in this project



The UAB cyclotron facility is a member of the Department of Energy University Isotope Network and is supported through DESC0020197 (PI Lapi). This work was supported in part by the Department of Energy Isotope Program's DE-SC0022550, the Horizon-broadening Isotope Production Pipeline Opportunities (HIPPO) program. This work was also supported by the Small Animal Imaging Core through O'Neal Cancer Center P30CA013148, and the Alabama Graduate Research Scholars Program (GRSP) funded through the Alabama Commission for Higher Education and administered by the Alabama EPSCoR.