Lutetium-177 Production in the Oregon State TRIGA Reactor

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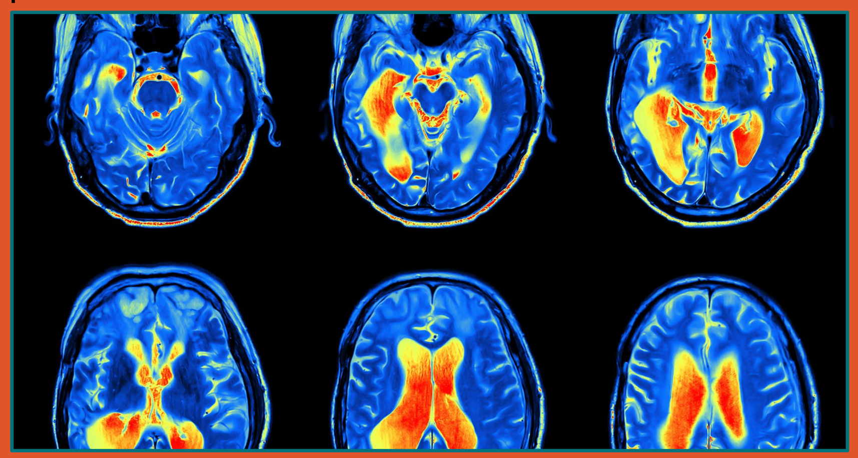
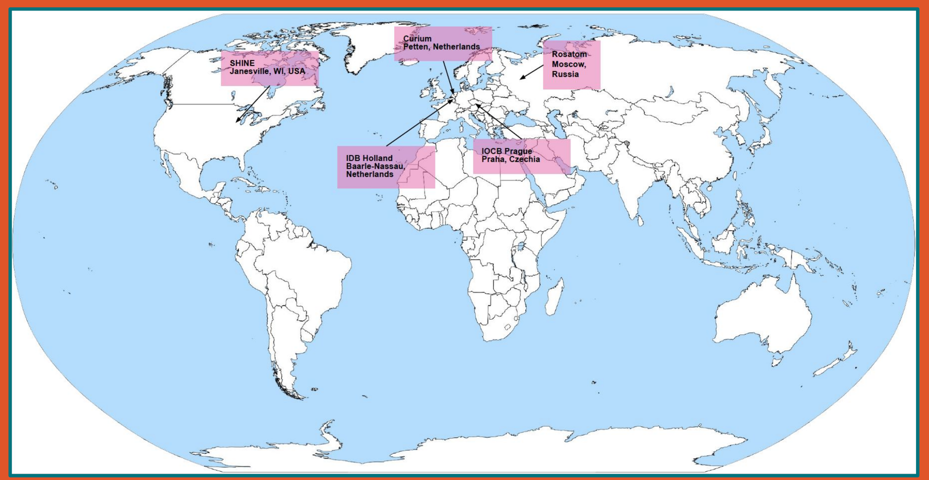
Purpose: The purpose of this project is to investigate the feasibility of the production of the radionuclide ^{177}Lu in the OSTR for use as a nuclear therapeutic treatment and diagnostic tool.

Background

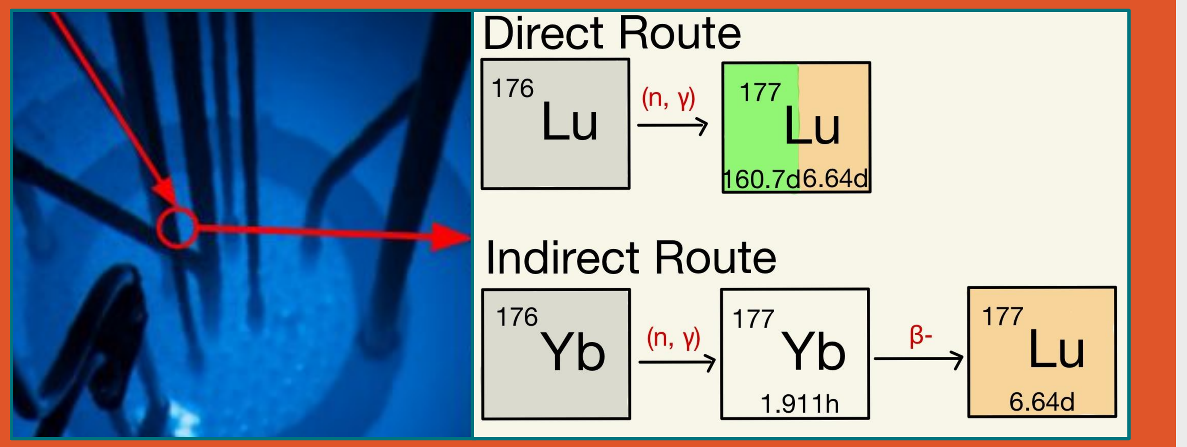
- Radionuclides are essential in medicine
- Demand for Lutetium (^{177}Lu) is rising due to its versatility in imaging and cancer treatment
  - It is particularly useful for digestive cancer treatment and palliative bone treatment



- Most of the production facilities are outside of the US as seen in the map below
  - Causes variability in price and availability
- Domestic production is needed
  - Stabilize the supply chain to reduce the cost of treatments and increases availability.
  - ^{177}Lu has a short half-life (6.64 days), making it important to reduce the transportation time post production



Production Routes



Pros and Cons	
Direct Method	Indirect Method
High cross section (2090 b)	Low cross section (2.85 b)
Limited handling and processing	Complicated chemical processing
Long irradiation times (5-30 days)	Long irradiation times (10-40 days)
Low natural abundance of ^{176}Lu (2.6%)	Low natural abundance of ^{176}Yb (12.76%)
Production of ^{177m}Lu	Negligible production of ^{177m}Lu
^{176}Lu & ^{177}Lu feasibly inseparable	^{176}Yb & ^{177}Lu chemically separable
Max specific activity proportional to flux	Specific activity independent of flux

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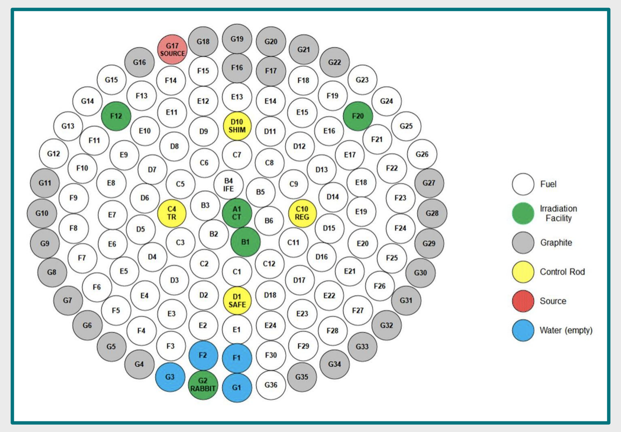
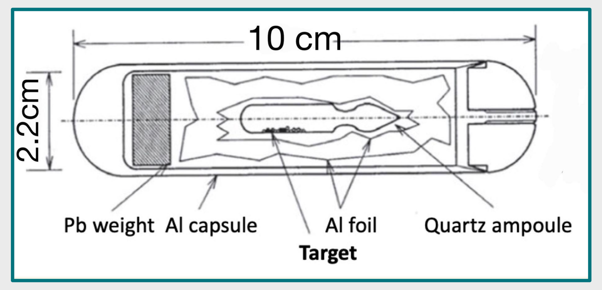
Irradiation Setup

- Oregon State TRIGA Reactor In-Core Irradiation Tube (ICIT)
  - Thermal Flux: $1.1*10^{13}$ n/cm^2/s
  - Epithermal Flux: $1.4*10^{12}$ n/cm^2/s
  - F12 core position
  - 3.175 cm diameter aluminum tube
- Sample: Yb_2O_3
  - Powder is placed in a quartz ampoule and flame-sealed
    - Ampoule is about 8 cm long with 6mm outer diameter
  - Ampoule is enclosed in outer aluminum irradiation tube
    - 10 cm long with a 2.2 cm diameter



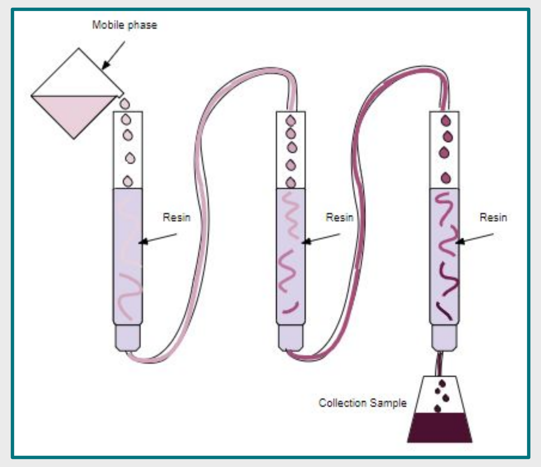


Left: TRIGA Core Map, ICIT facility (F12)
Right: Top: Example of irradiation vial with small inner quartz ampoule
Bottom: Example OSTR outer aluminum irradiation tube with the top and bottom separated

Processing

Extraction Chromatography

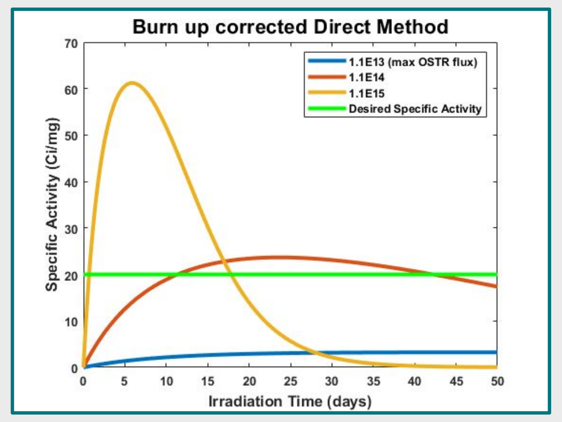
- Utilizes a long column filled with a stationary phase (resin) and a mobile phase
- Mobile phase flows between resin particles
- Basis of separation: different affinity to resin surface between ^{177}Lu and ^{176}Yb
  - ^{177}Lu is eluted first
  - ^{176}Yb follows much later
- Optimization depends on:
  - Resin selection
  - Composition of acidic solution of the target
- Purity:
  - Depends on the number of passes through the columns
  - >90% separation efficiency preferred
- Necessary tools:
  - Hot cell due to high doses



Example of the extraction chromatography setup

Calculations and Analysis

- MATLAB codes were written to calculate results such as the yield and specific activity as a function of irradiation time.
- The calculations for the **direct method** show that the maximum achievable activity of irradiated target is too low for therapeutic use as seen in the graph below
  - it requires a much higher flux value than possible at the OSTR.

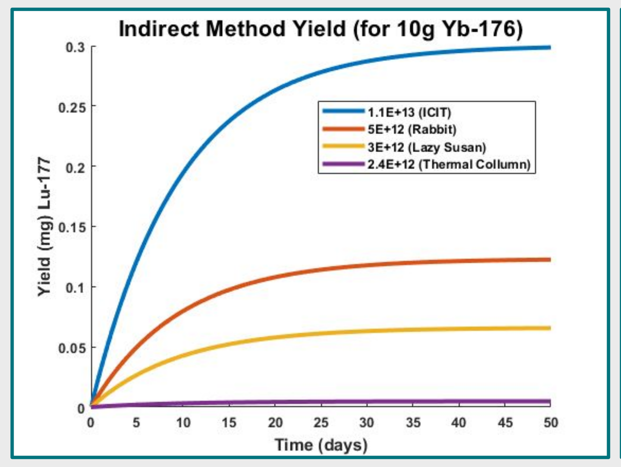


Direct method specific activity for different thermal fluxes. Blue = OSTR capability

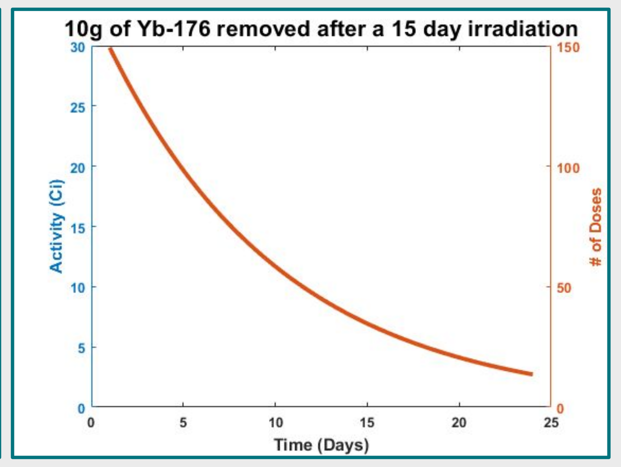
- The **indirect method** specific activity is independent of the flux as Yb and Lu are separable, so this method was chosen for further analysis.

^{177}Lu Production						
Irradiation time [d]	5	10	15	20	25	30
Yield of ^{177}Lu [μg per gram of target]	12.1	19.4	23.7	26.3	27.8	28.7
Example with an initial target mass of 10g						
Irradiation time [d]	5	10	15	20	25	30
Yield [mg] of ^{177}Lu	0.12	0.19	0.24	0.26	0.28	0.29
Activity [Ci]	13.4	21.5	26.3	29.2	30.8	31.8

- **One therapeutic dose is 200 mCi of ^{177}Lu**, which is applied to 20 ml of solution with the final concentration of 10 mCi/ml.
- For a 15 day irradiation period combined with seven days of decay, 0.1752 grams of 96% enriched $^{176}Yb_2O_3$ is required to achieve an activity of 200 mCi.
  - *# of doses produced =10 [g]/0.1752 [g/dose]= 57 doses*



Indirect method yield in different irradiation facilities



Decay of the Lu-177: 10g sample of Yb-176 after a 15 day irradiation period

Projected Costs and Profit

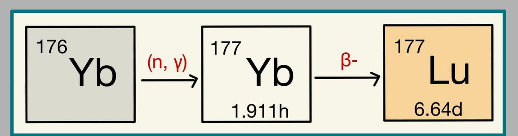
10g ^{176}Yb	BuyIsotope.com ($16,220/g of 97.7% ^{176}Yb): $162,200	American Elements ($19,630/g of 96% ^{176}Yb): $196,300
15 day reactor run at $5,780.83/day	$86,700	$86,700
Cost of Hot Cell	$360,000	$360,000
Total Material and Operational Costs	$608,900	$643,000

Selling Price: $56,092.28/dose with 57.07 doses	$3,201,600
Costs(96% enriched)	$643,000
Profit* for one 15 day irradiation with 10 g	$2,558,600

*Numbers calculated with 10 g of 96% enriched $^{176}Yb_2O_3$ irradiated for 15 days with seven days of decay and a 90% separation efficiency. This does not include the cost of processing or radiolabeling and is subject to change.

Conclusions

- Production of ^{177}Lu **is possible** in the OSTR through the **indirect production route.**

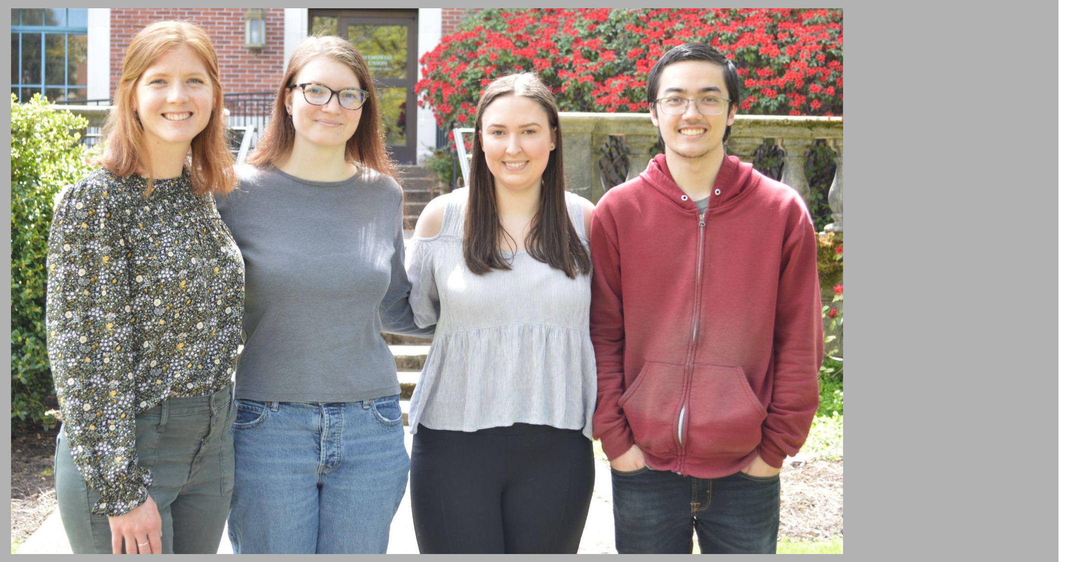


- For one dose (200 mCi of ^{177}Lu) to be produced, 0.1752 grams of 96% enriched $^{176}Yb_2O_3$ is required and irradiated in the ICIT for 15 days.
- Assuming 90% efficiency for Lu/Yb separation, the number of the doses that can be produced by irradiation of a 10 gram target may reach up to **57 doses** after seven days of decay.
- Based on our calculations, the estimated total costs would be $196,300 for 10 grams of 96% enriched ^{176}Yb (supplied by American Elements) and $86,700 in operational expenses for one irradiation trial, totaling $643,000 to produce 57 doses of ^{177}Lu dotatate of 10 mCi/ml concentration.
  - Processing, radiolabeling, and additional irradiations trials will incur further expenses.

Future Research

As the process of producing ^{177}Lu is relatively new, we have many recommendations for future research.

- Expand the computational analysis used, or use a radiation transport code to re-analyze feasibility.
- Investigate optimizations for the irradiation capsule and setup.
- Expand research on extraction chromatography and increase efficiency by testing the resins used in separation.
- Research reprocessing methods to recover the leftover ^{176}Yb material to form a new target.
- Identify radiolabeling capabilities at OSU or outsource a radiolabeling facility.



Pictured left to right: Brooke Konstanczer, Anneli Brackbill, Brianna Ashing, Jordan Northrop