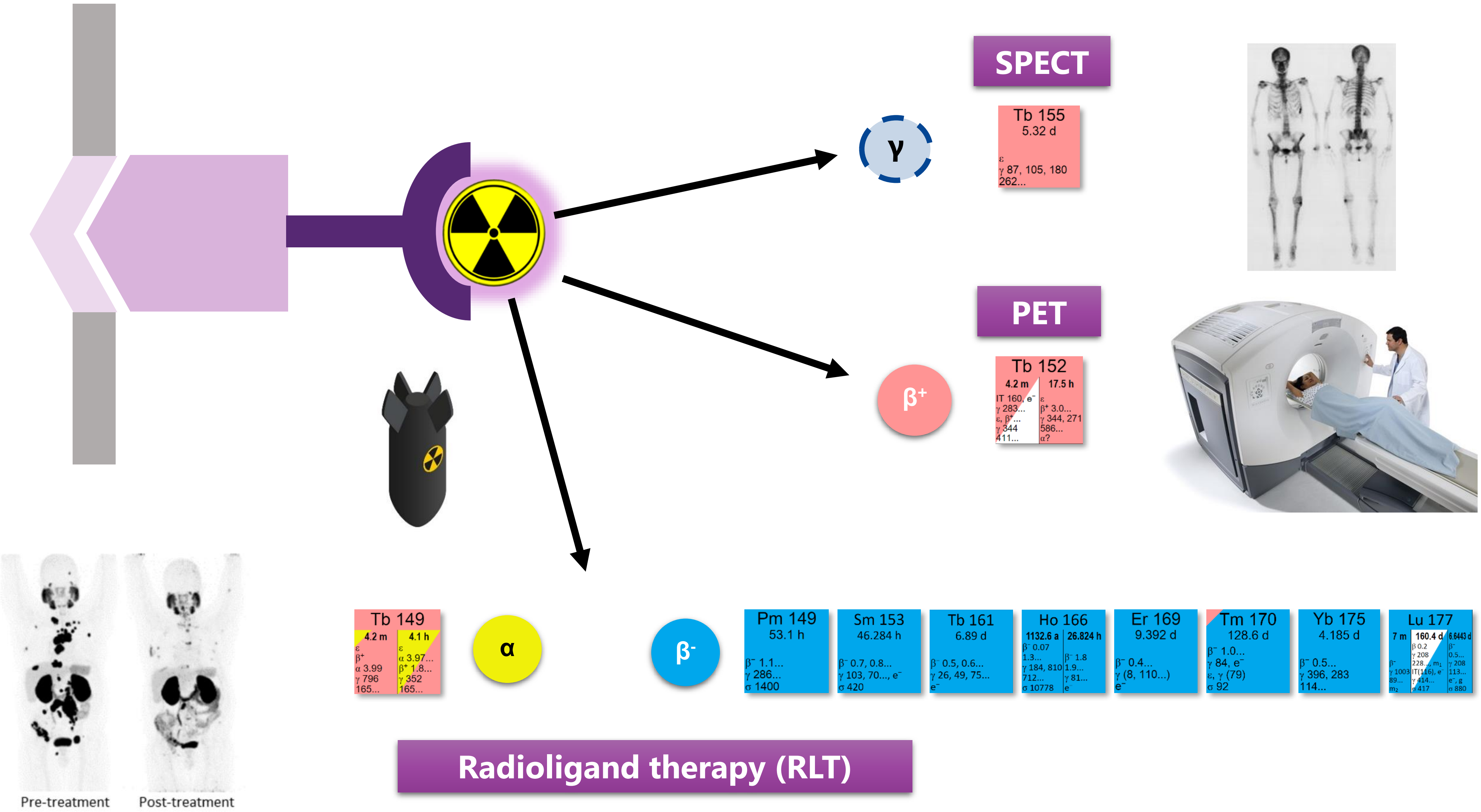
sck cen
Belgian Nuclear Research Centre

27 PRISMAP EU
Medical Radionuclides

(Reactor-based) production and radiochemical processing of medical radiolanthanides

Michiel Van de Voorde – PRISMAP Radiolanthanides Workshop – September 2024

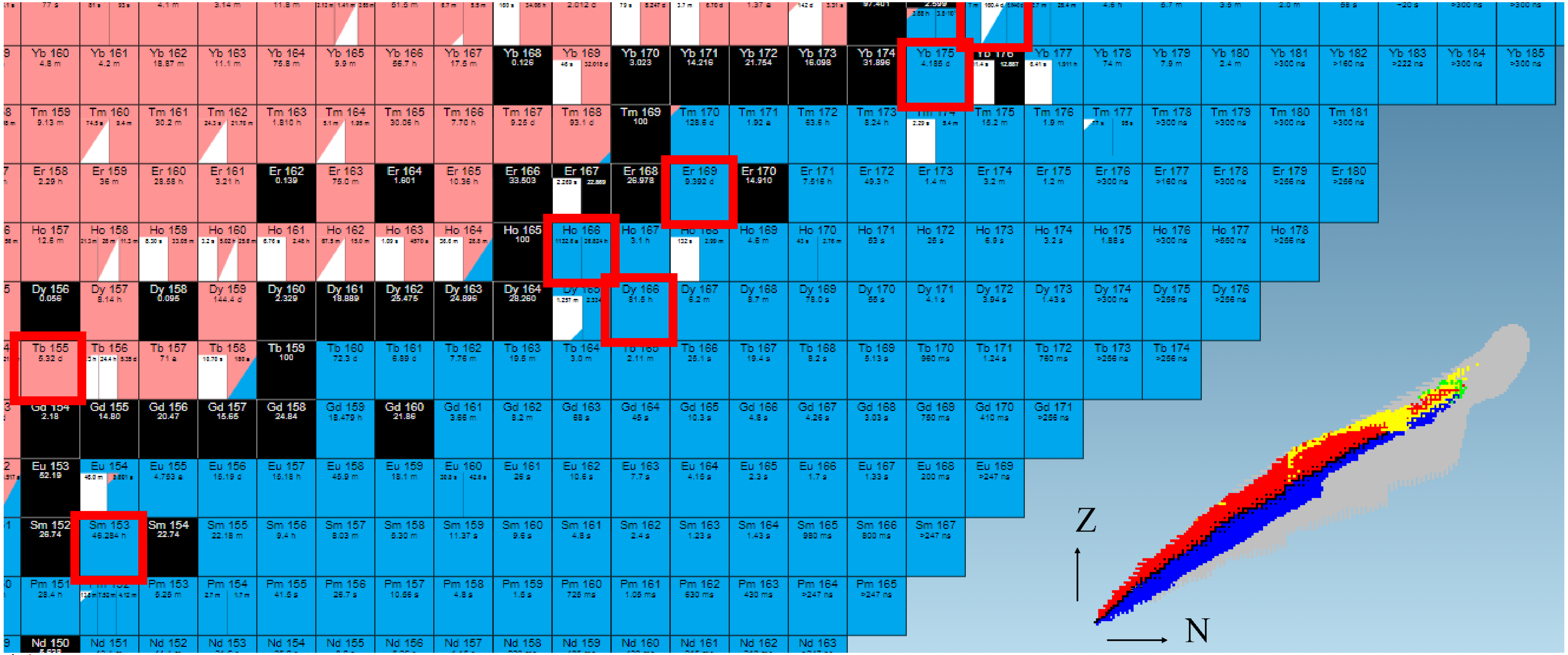

SPECT
Tb 155
5.32 d
γ
PET
Tb 152
β+
Tb 149
α
β-
Pm 149
53.1 h
Sm 153
46.284 h
Tb 161
6.89 d
Ho 166
Er 169
9.392 d
Tm 170
128.6 d
Yb 175
4.185 d
Lu 177
Radioligand therapy (RLT)
Pre-treatment
Post-treatment

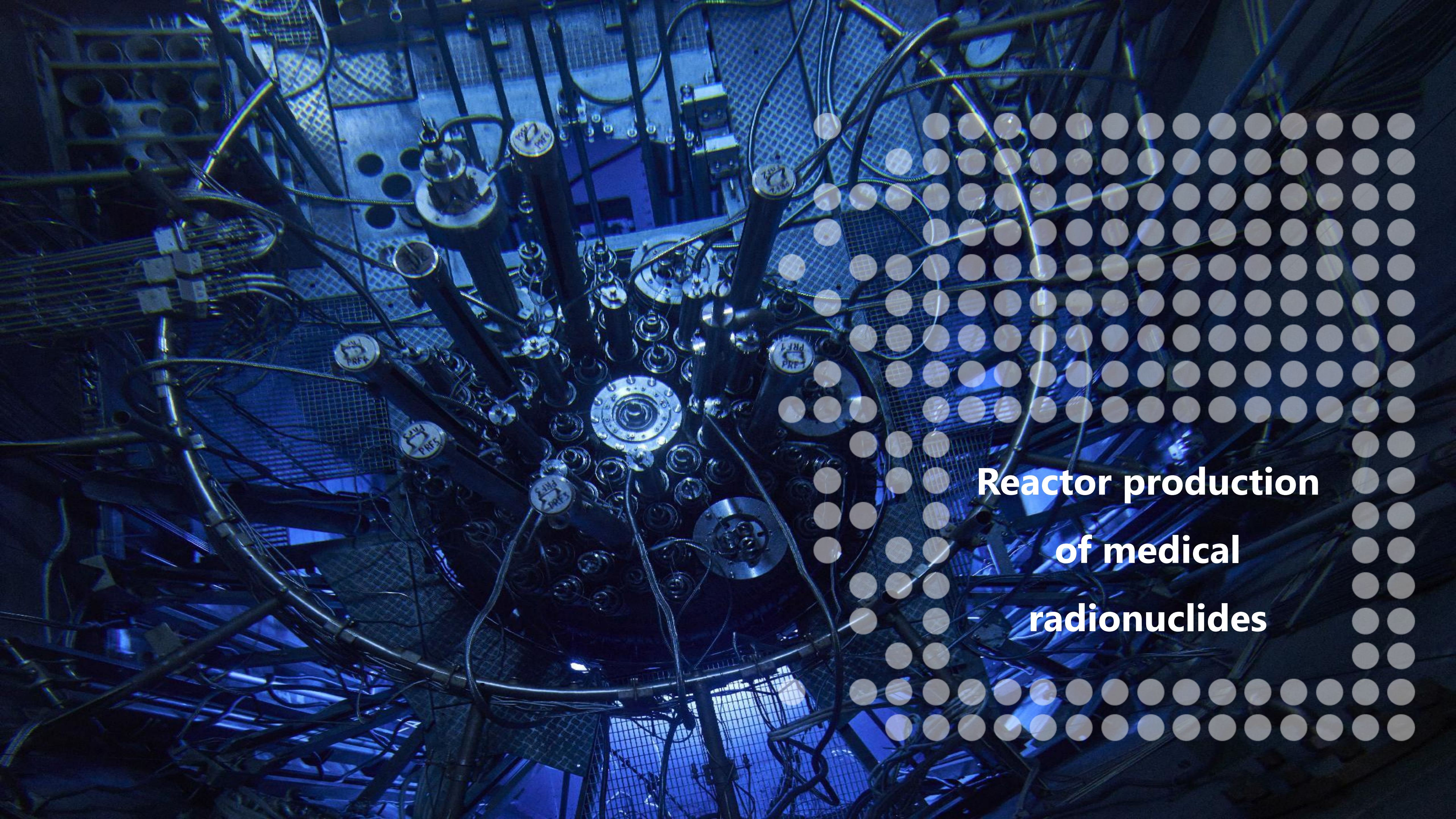
Neutron-deficient

Acquired by particle accelerators

Proton-deficient

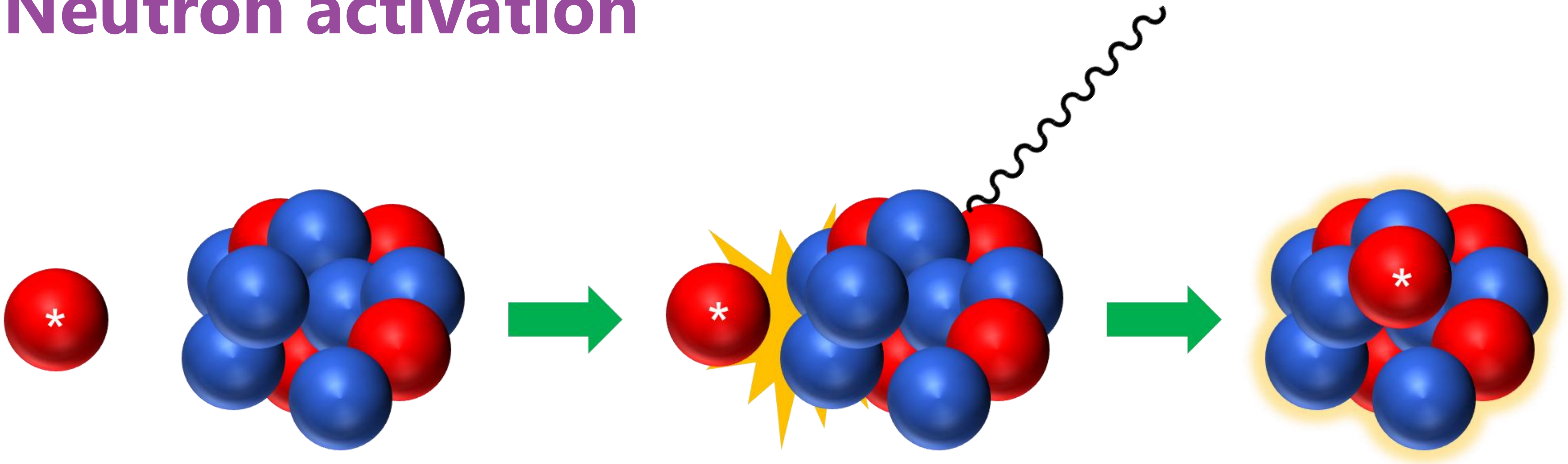
Acquired by thermal neutron flux in nuclear research reactors





Reactor production of medical radionuclides

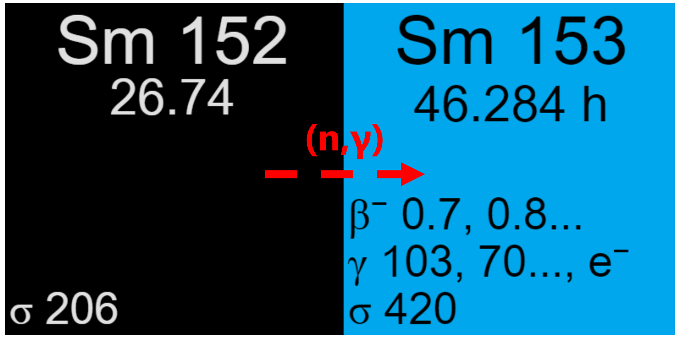
Neutron activation



Neutron bombardment

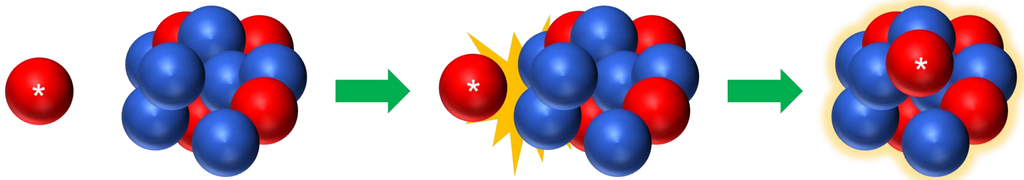
Neutron capture
Photon emission (n,γ)

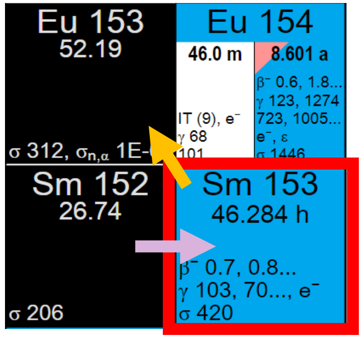
Unstable nucleus
Neutron excess
Beta decay



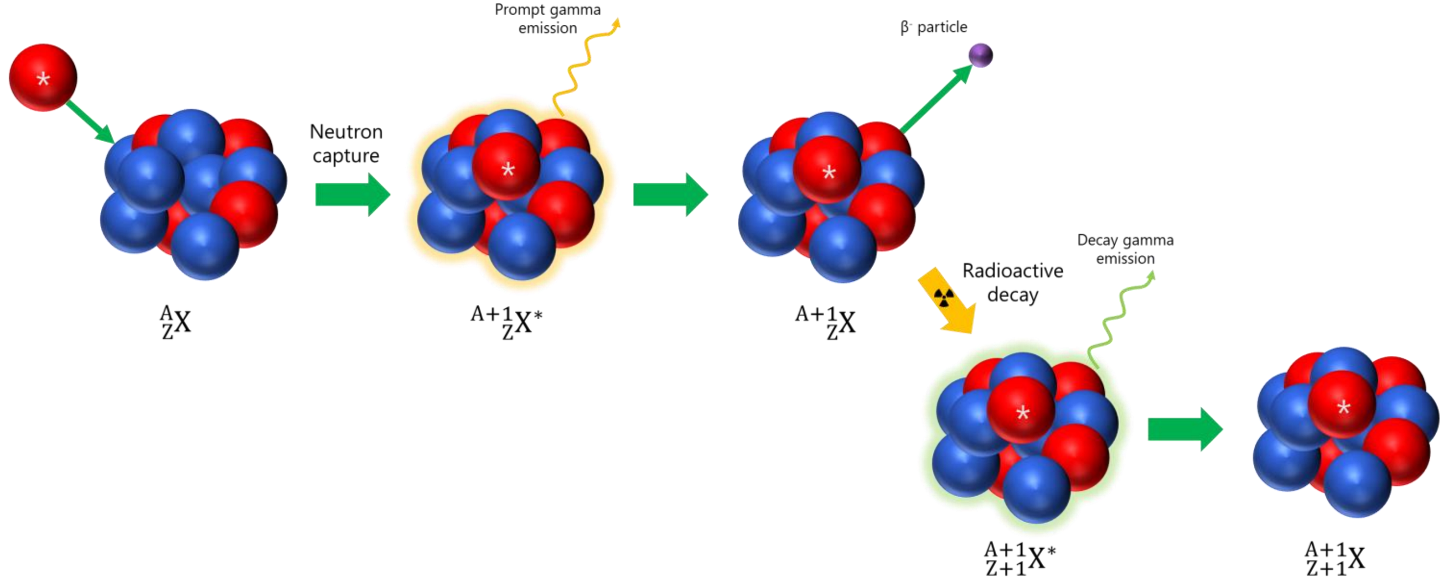
Neutron activation

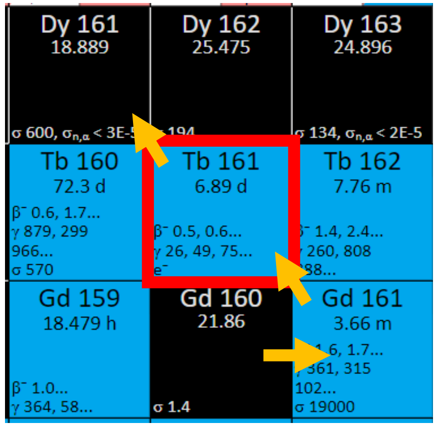
Carrier added





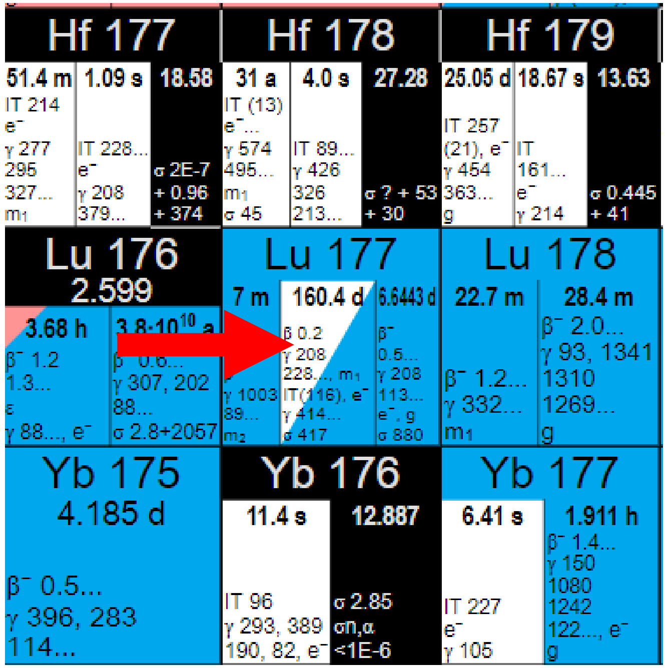
Non-carrier added





Production strategies – ^{177}Lu example

Direct route



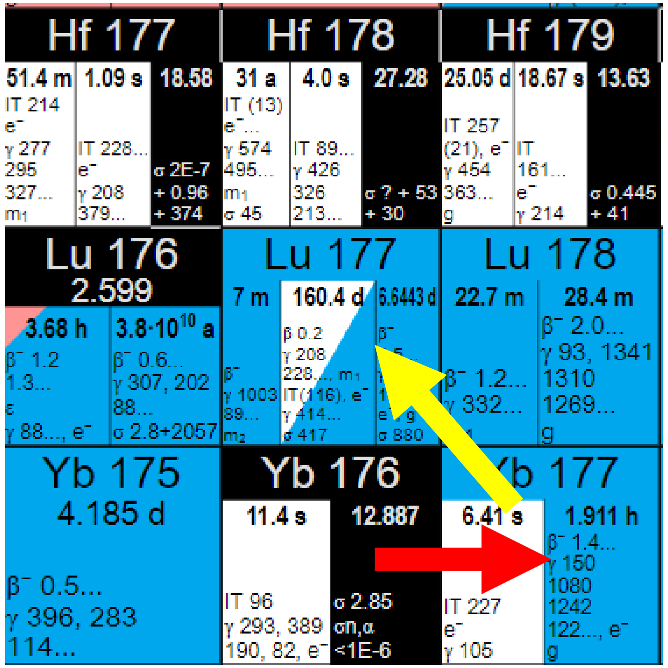
$^{176}Lu(n,\gamma)^{177}Lu$ (σ_{th} = 2057 barn)

High Cross section = high yield

Low molar activity

$^{176}Lu(n,\gamma)^{177m}Lu$ (σ_{th} = 2.8 barn)

Indirect route



$^{176}Yb(n,\gamma)^{177}Lu$ (σ_{th} = 2.85 barn)

Lower cross section = lower yield

Much higher molar activity

No coproduction of Lu-177m

Production strategies – ^{177}Lu example

	Direct route	Indirect route
Activity ^{177}Lu (EOI)	1115 TBq	1.5 TBq
Specific Activity (EOI)	1115 GBq/mg	4106 GBq/mg
Specific Activity (EOI+7d)	527 GBq/mg	4106 GBq/mg
^{177m}Lu content (EOI)	86 GBq	

Activation parameters

- 100% enriched target
- Φ_{th} = 3E14 neutrons/cm^2/s
- No epithermal or fast neutrons
- No self-shielding
- 7 days irradiation
- 1 g target

LuMark® Lu-177 chloride

SA ≥ 500 GBq/mg at ART

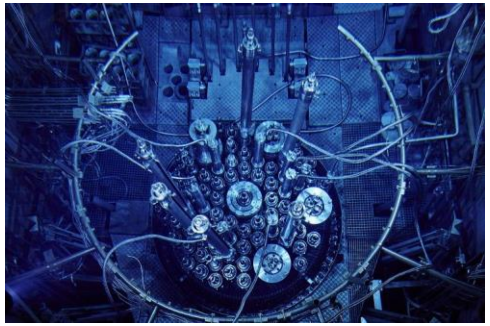
endolucin beta

SA ≥ 3000 GBq/mg at ART


Radiochemical processing
Target manufacturing and irradiation
Radiochemical processing
Quality control
Target recovery and recycling
Waste management

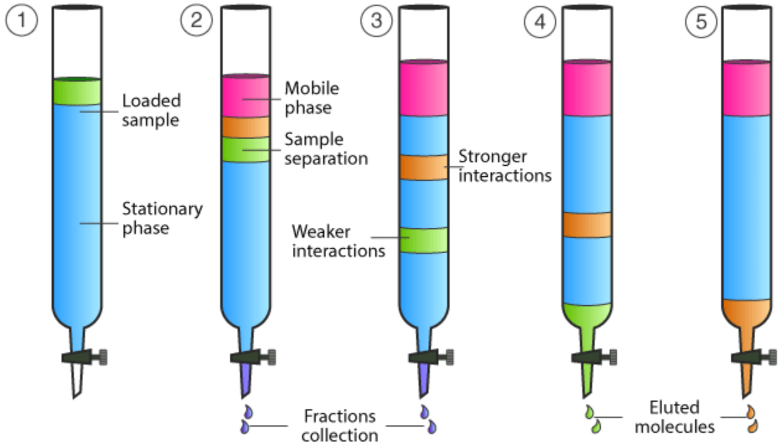
Production n.c.a. radiolanthanide – General approach

Transport



Transport

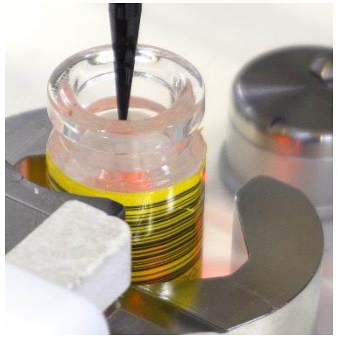
1. Ampoule crushing
2. Target dissolution



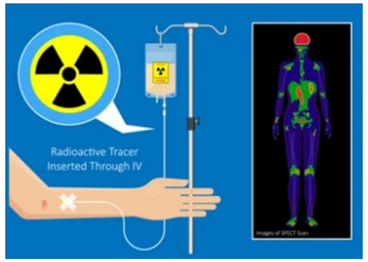
yyyYy   xxxXx

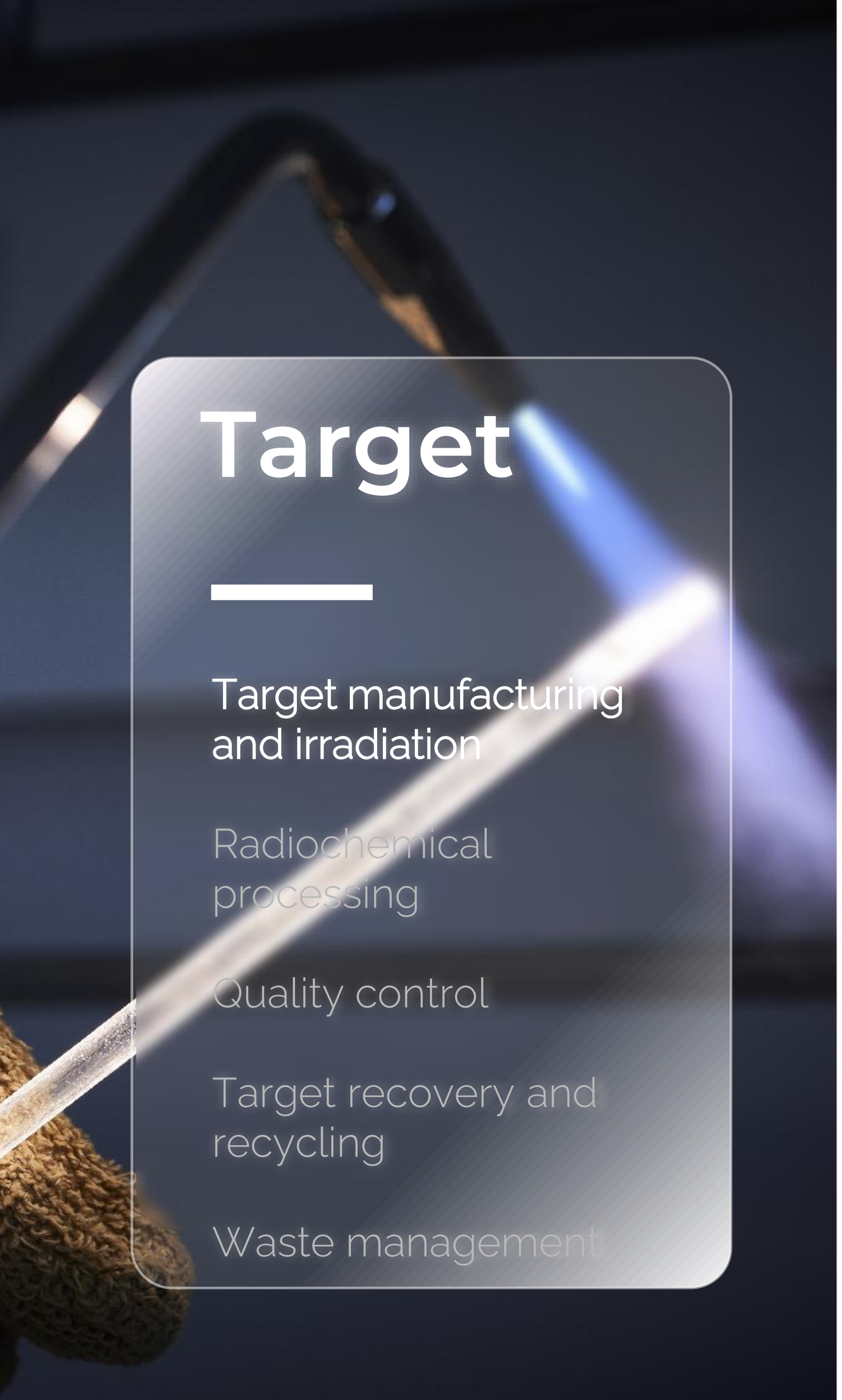
- yyyYy conversion to chloride
- Final [yyyYy]YyCl$_3$ for dispensing
- QC

Target recycling and QC



Transport

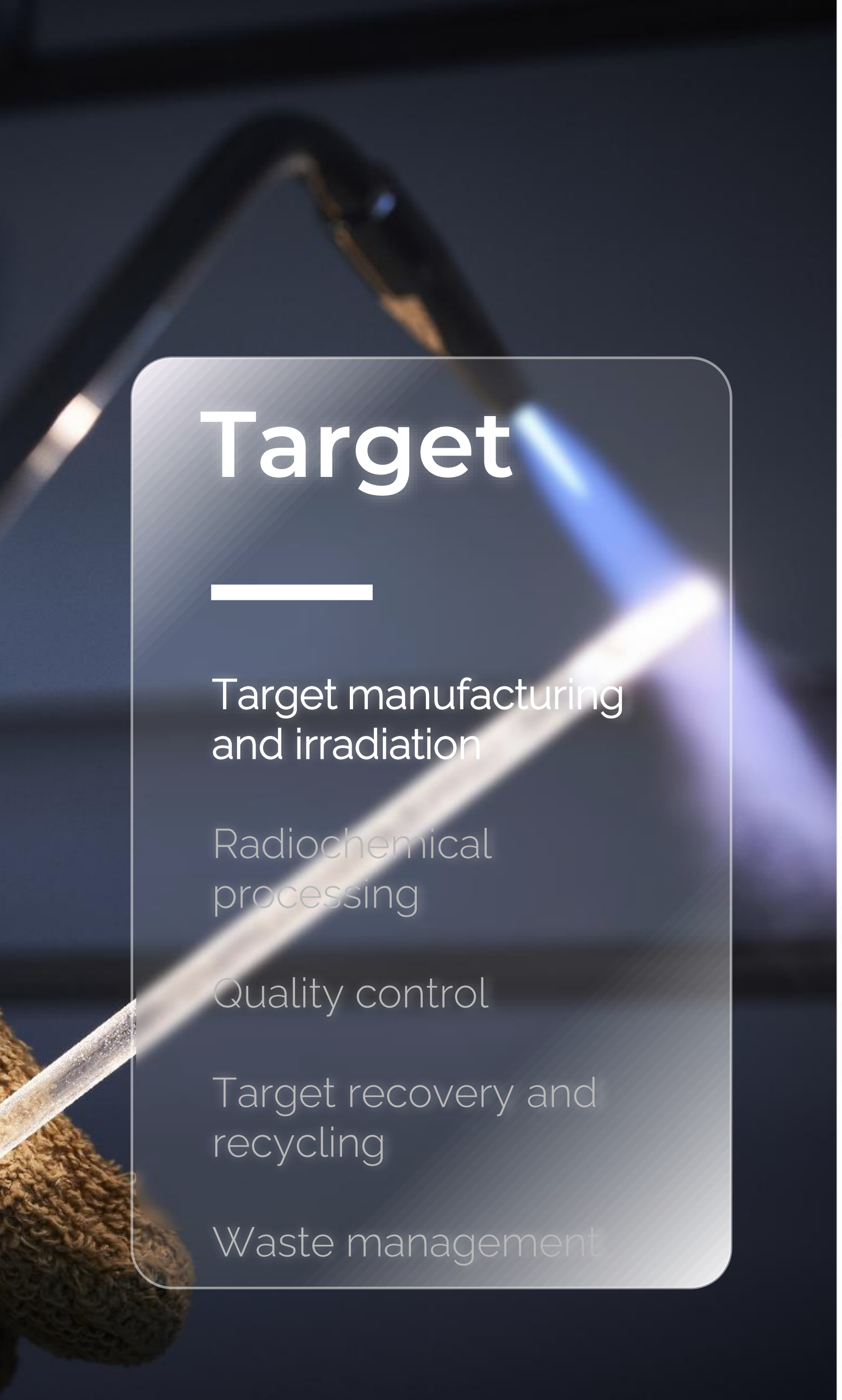




Target preparation

Target criteria

- **Properly sized**
  - fit into the irradiation position/canister
  - Sufficient volume to produce desired amount of activity
- **Good heat transfer properties** to prevent over-heating during irradiation
- **Provide a barrier** to the release of radioactive products during and after irradiation
- **Thermally stable compounds** to prevent pressure build-up and target failure → typically metal or oxide compounds
- Target material must be **compatible with chemical processing steps** to recover and purify desired radioactive compoud



Target preparation

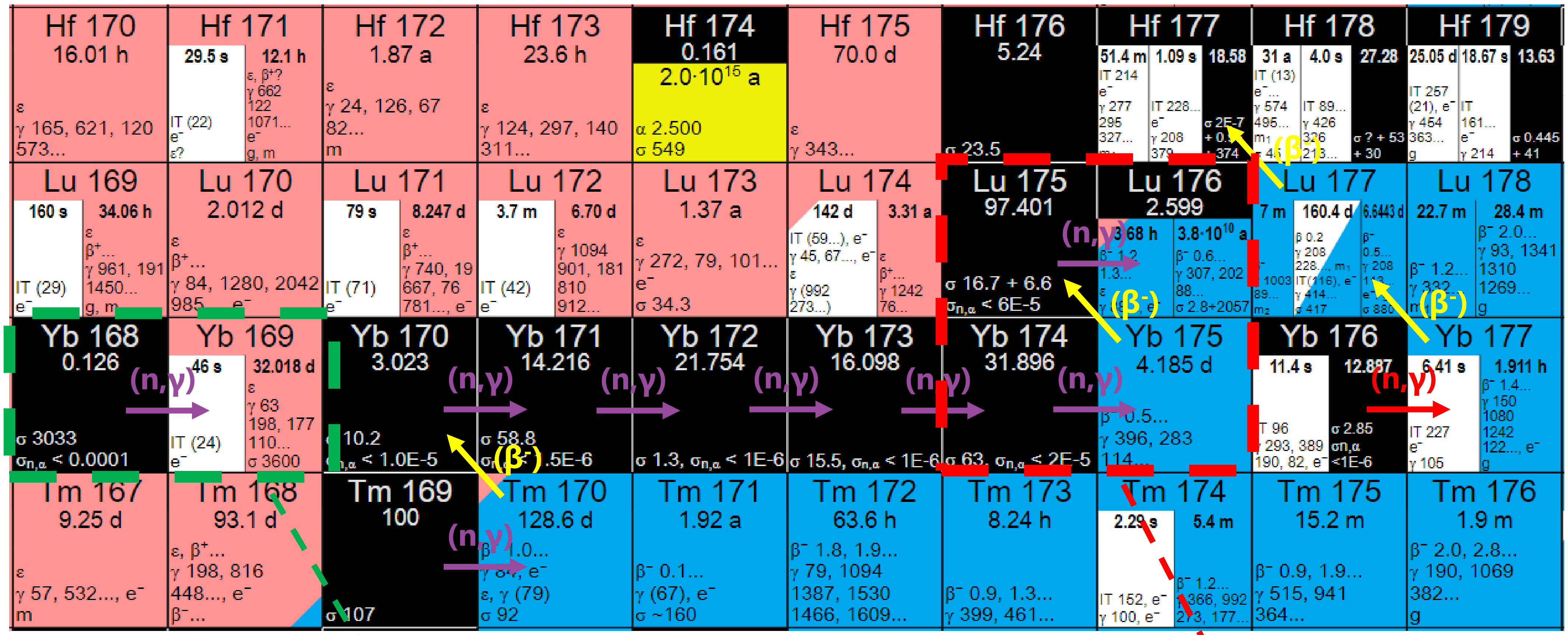
Target matrix should be suitable for neutron activation

→ **Radiolanthanides**: typically Ln_2O_3 target material sealed in a quartz glass ampoule (1 mm wall thickness) in cold welded aluminium irradiation can

$Ln(NO_3)\cdot xH_2O$		Ln_2O_3	
More time-consuming target preparation	☹	Simple target preparation	☺
Easy to dissolve for chemical separation	☺	More challenging to dissolve	😐
Hygroscopic nature	☹	Not hygroscopic	☺
Low thermal stability, increased risk of ampoule failure	☹	High thermal stability, enhancing target stability	☺
Lower density = lower loading capacity	☹	Higher density = higher loading capacity	☺

Concept: Nick Van der Meulen/Jan-Rijn Zeevaart

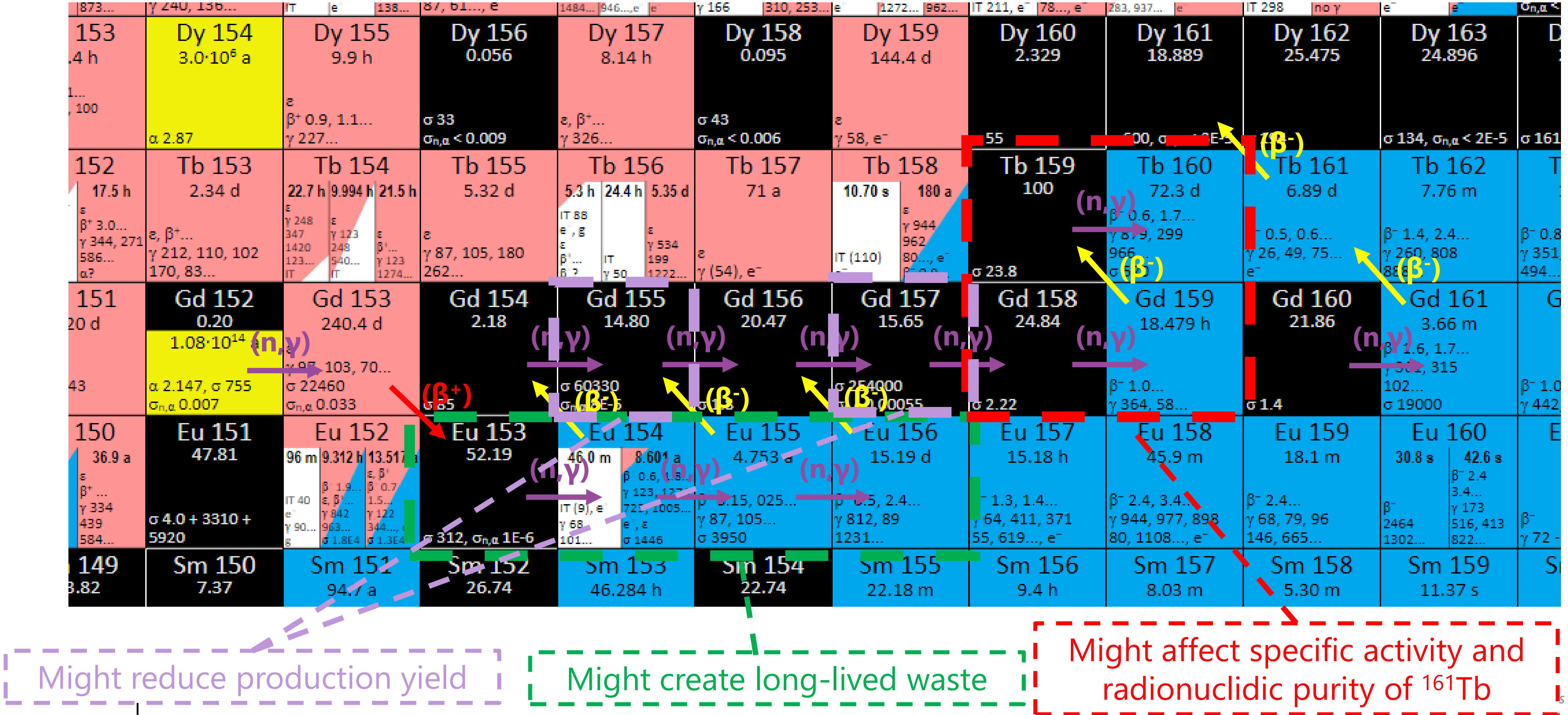
^{177}Lu production – Target quality



Might affect target recycling

Might affect specific activity ^{177}Lu

^{161}Tb production – Target quality



Neutron activation

Target manufacturing and irradiation

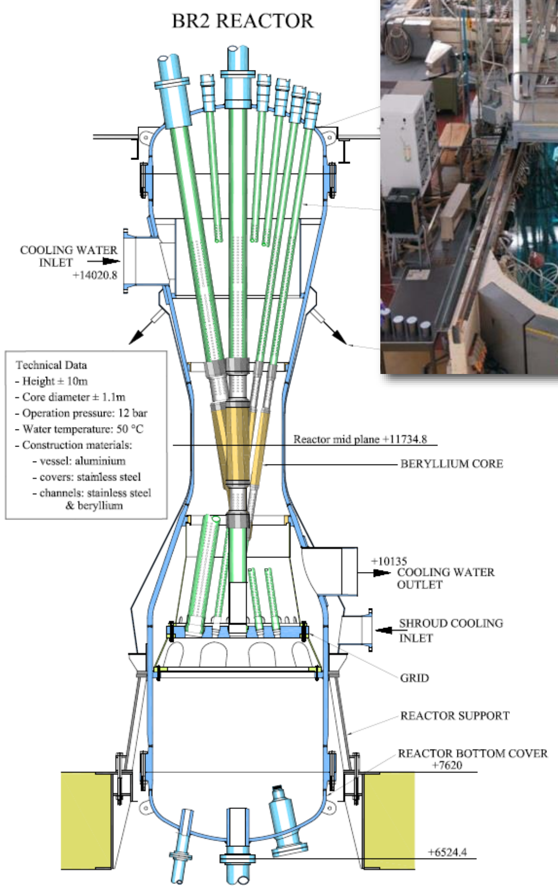
Radiochemical processing

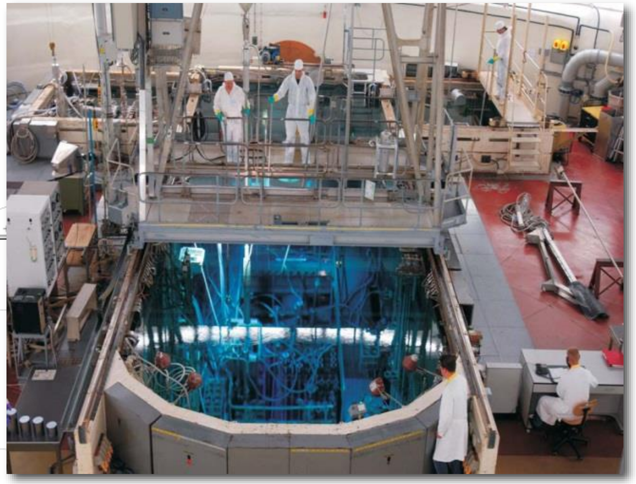
Quality control

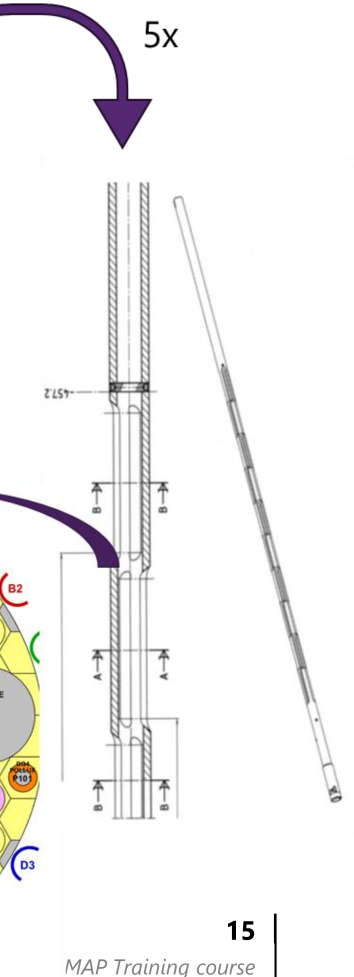
Target recovery and recycling

Waste management

xxxXx → Target → **Irradiation** → Separation / Target Recycling → Quality control → Sales Distribution → yyyYy







Neutron activation

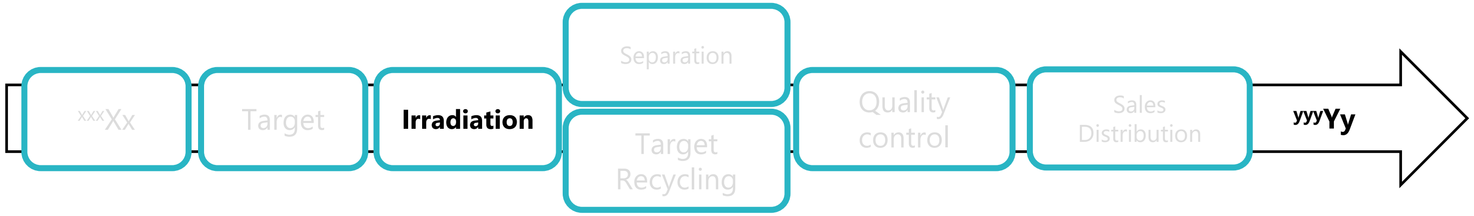
Target manufacturing and irradiation

Radiochemical processing

Quality control

Target recovery and recycling

Waste management

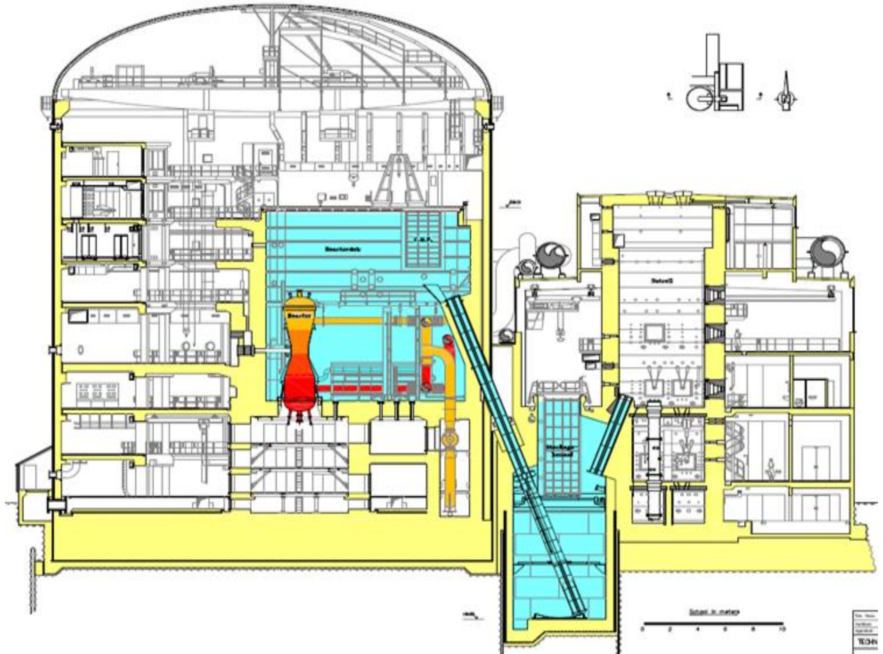


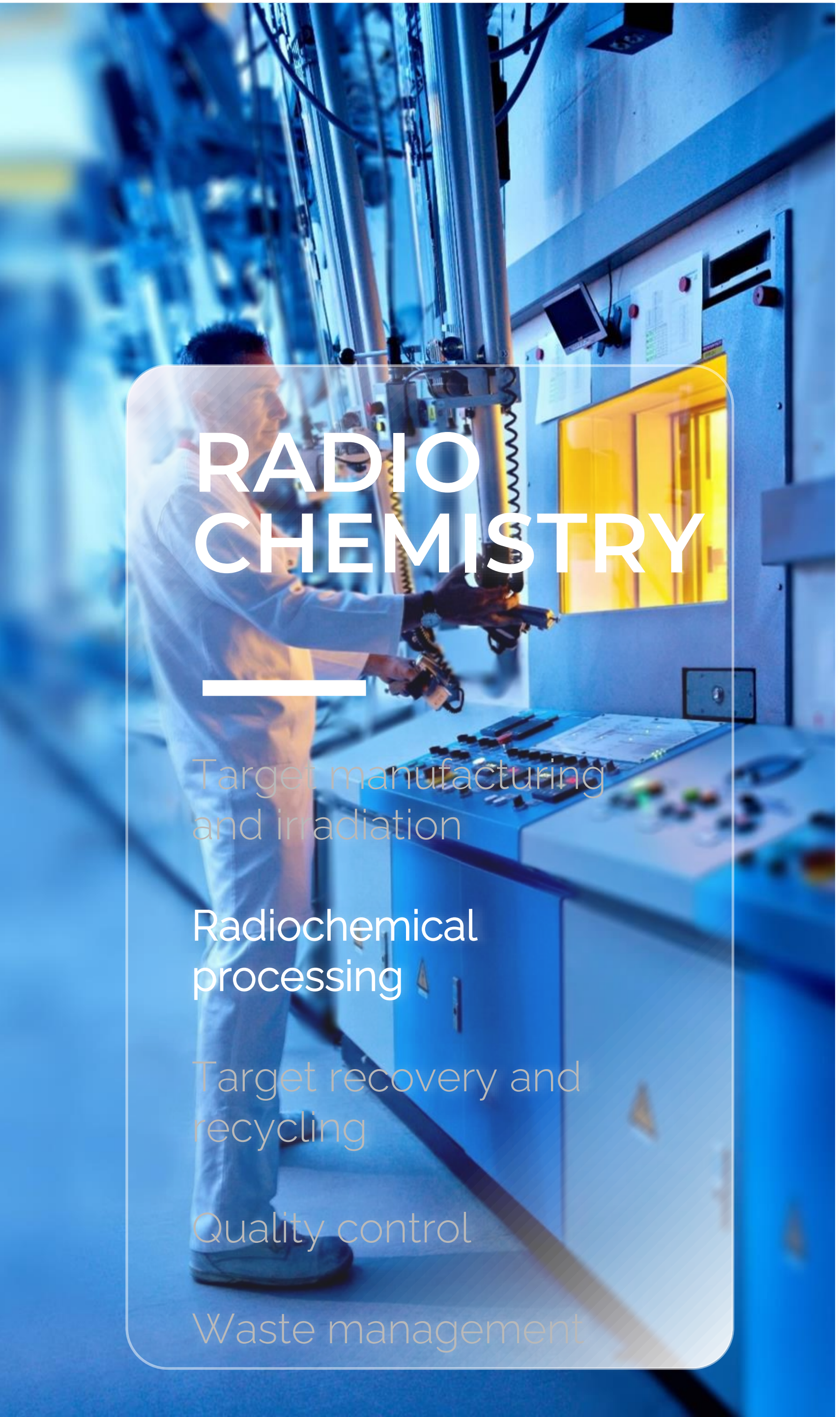
Transfer of irradiated targets to hotcell for decanning

- → Cooling of irradiated targets → *decay of short-lived radio-contaminants*
- → Opening of aluminium irradiation can
- → Preparation for shipment in dedicated transport containers

Type A (≤700 GBq ^{177}Lu)

Type B (>700 GBq ^{177}Lu)

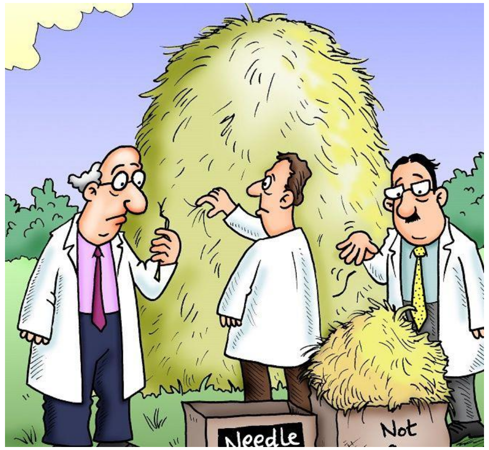




Separation method: What to look for?

- Separation of micro amounts from macro amounts
- Method must yield
  - High purity fractions
  - High target recovery and regeneration

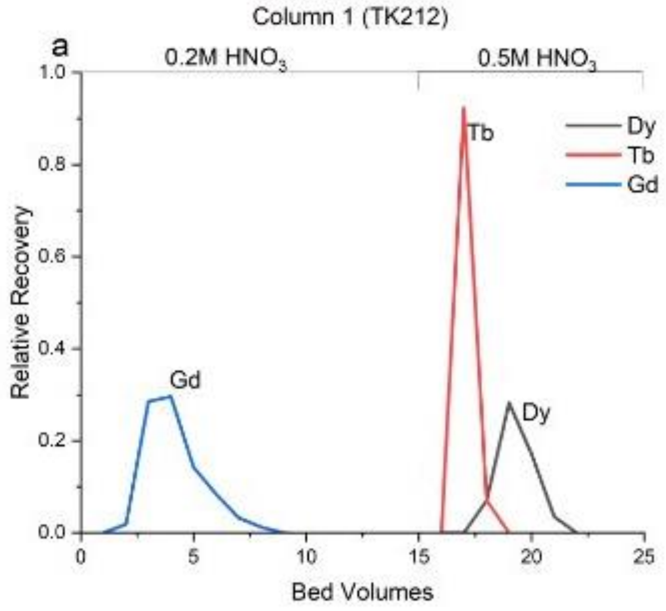
- Easy scale-up and cost-efficient
  - MBq scale → GBq scale
  - GBq scale → TBq scale
  - Simple, robust and fast
  - Automated and remote-controlled
  - Insensitive to target contaminants



Lu:Yb ratio 1:10^4-10^6

Lanthanides – Separation strategies

Extraction chromatography



- Extractant physically impregnated onto solid support
- **Lighter lanthanide elutes first**

S. McNeil et al., EJNMMI Radiopharm. and Chem., 2022

Ion Exchange chromatography

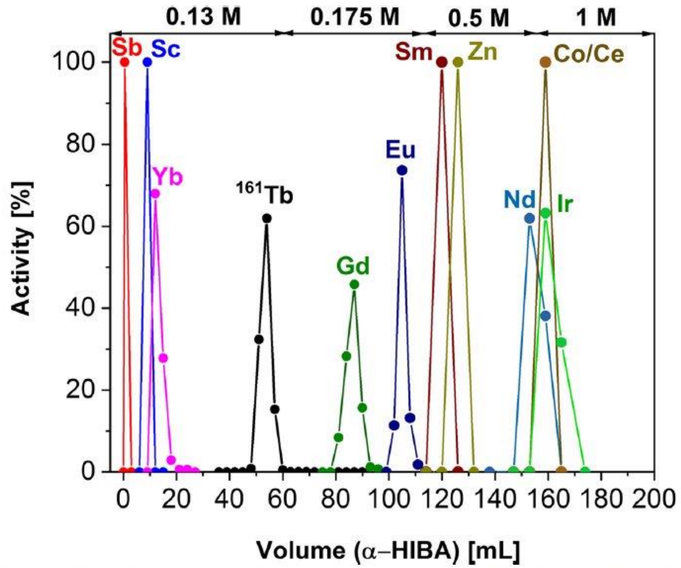
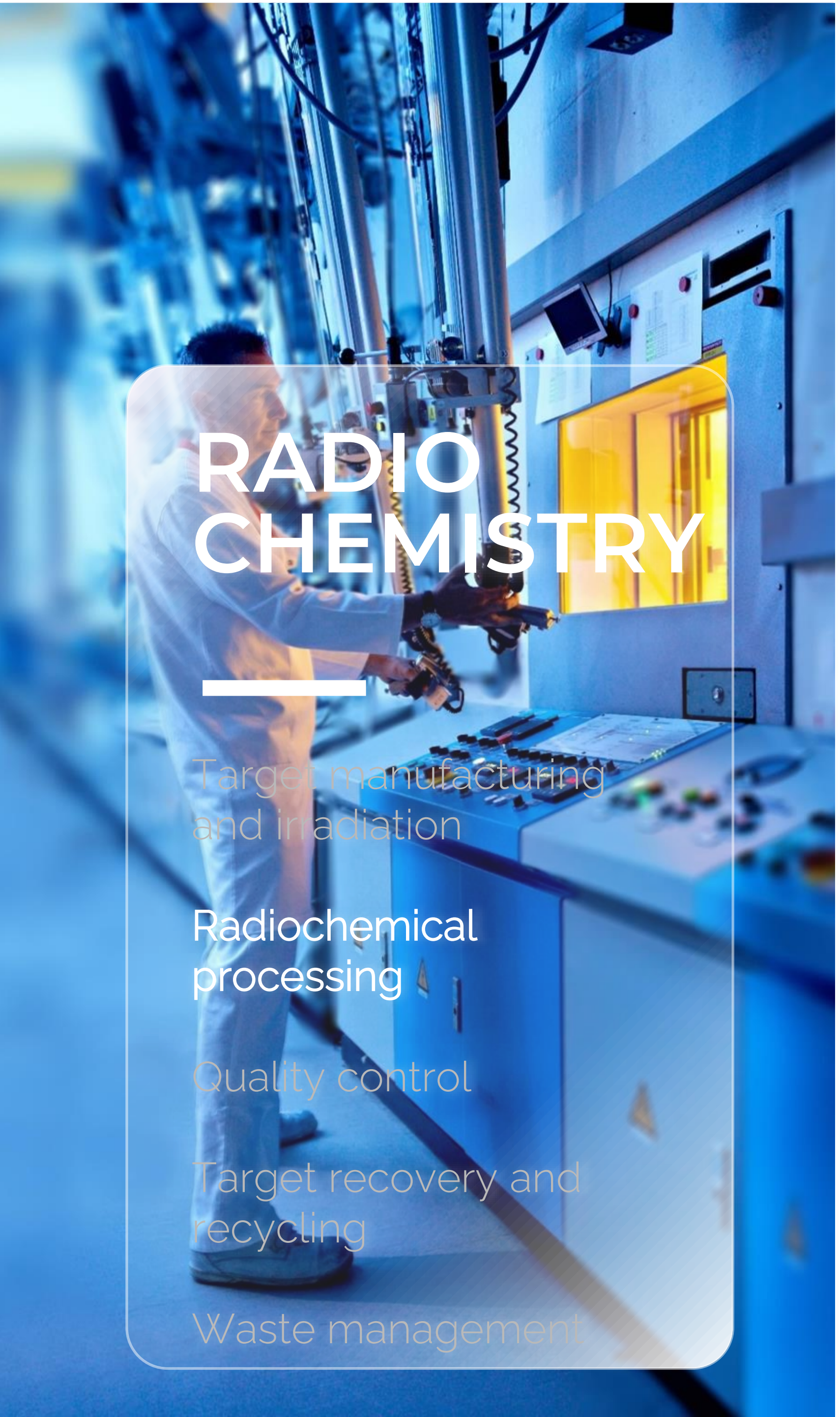
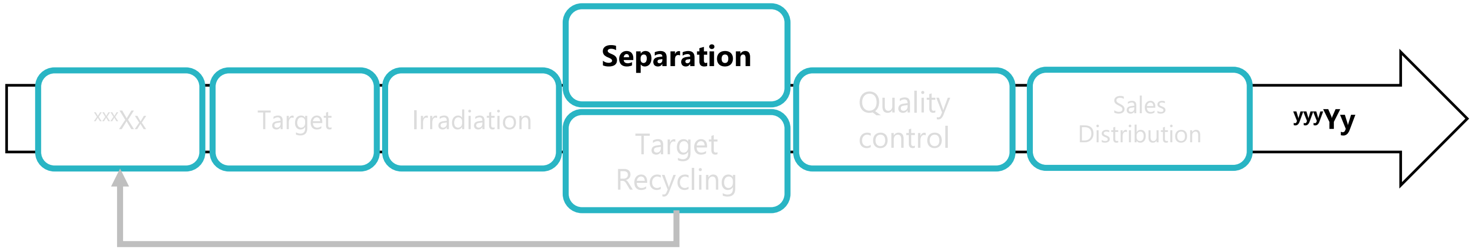


Fig. 1 Elution profile of ^{161}Tb separation from the irradiated target material and side products (10 mm × 170 mm Sykam resin column, 8 mg $^{160}Gd_2O_3$, 0.6 mL/min eluent flow rate)

- Functional resin in combination with chelating ligand
- **Heavier lanthanide elutes first**

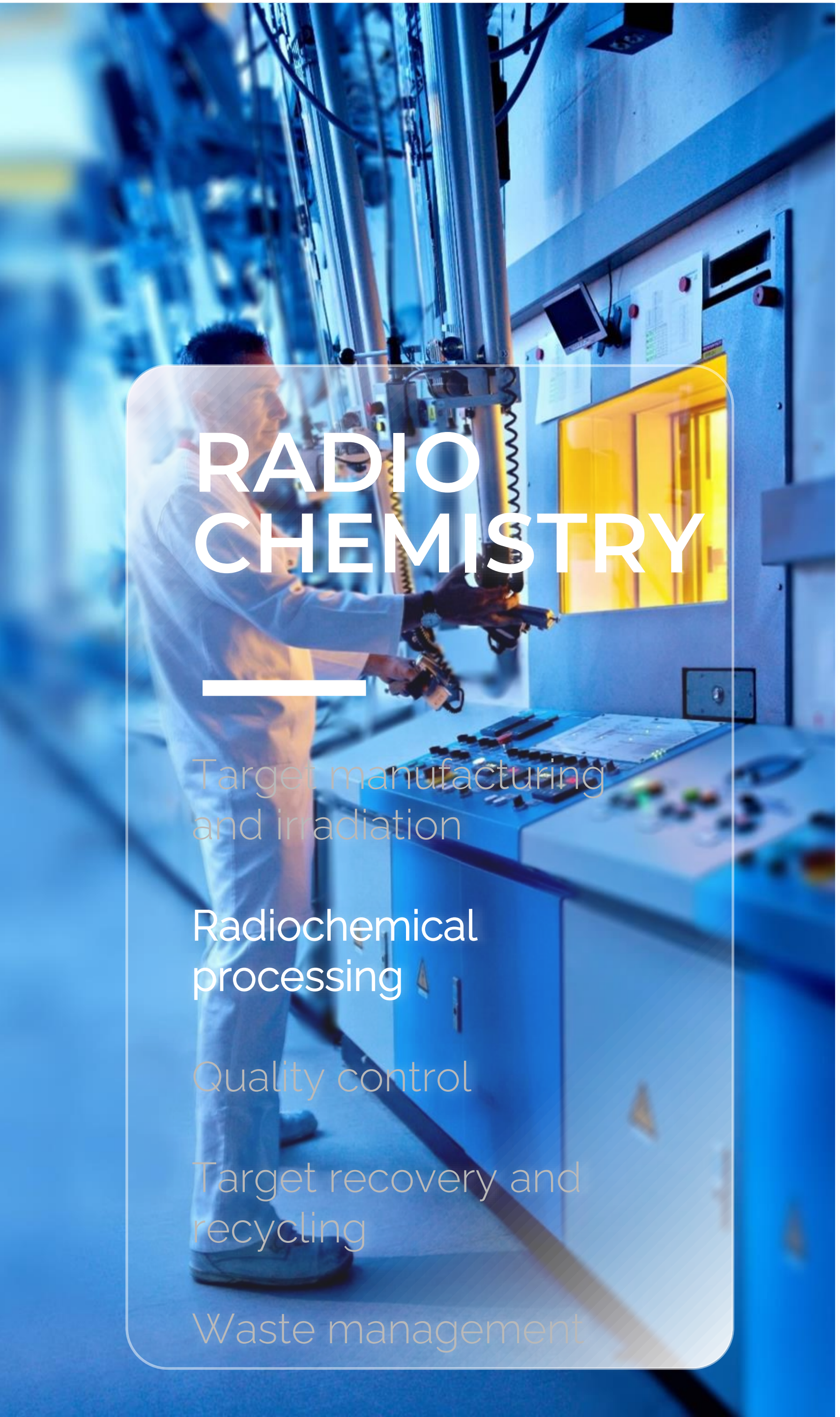
N. Gracheva et al., EJNMMI Radiopharm. and Chem., 2019

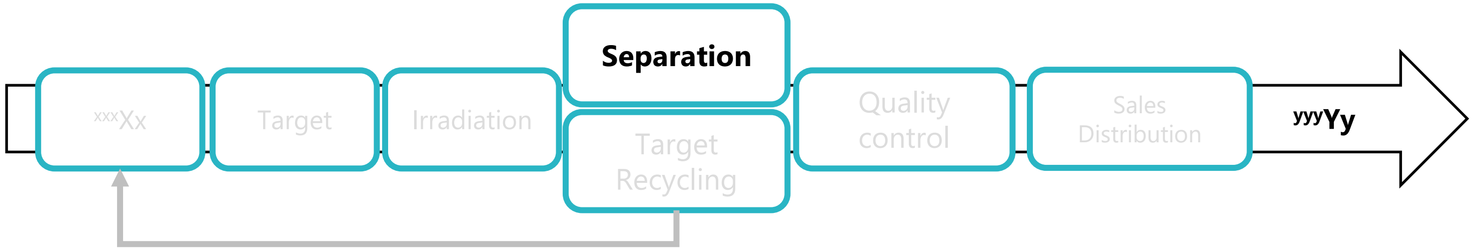




Typical production environment

- Lead shielded hot cells
- Processes (fully) automated
- Hot cells equipped with telemanipulators for remote handling
- In a clean room facility once GMP





Dispensing, sterilization and packaging

^{177}Lu bulk vial → Dose calibrator activity measurement → Dispensing into vials → Autoclaving vials → Activity measurement and packaging

Quality control

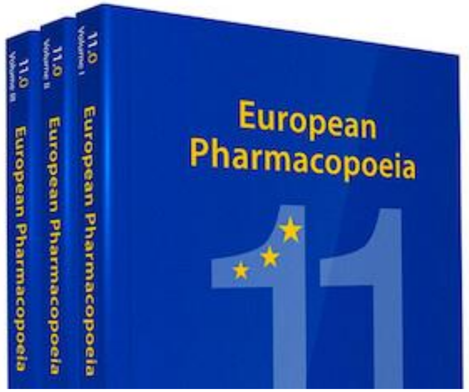
Target manufacturing and irradiation

Radiochemical processing

Quality control

Target recovery and recycling

Waste management



- Needed to guarantee product quality for medical use
  - Radionuclidic purity *(gamma spectrometry)*
  - Chemical purity *(ICP-MS/ICP-OES)*
  - Radiochemical purity *(radio-TLC)*
  - Activity concentration *(dose calibrator)*
  - Specific activity *(dose calibrator + ICP-MS/ICP-OES)*
  - Radiolabeling (apparent molar activity) *(radio-TLC)*
  - Biocompatible (endotoxin + sterility)

Certificate of Analysis

EndolucinBeta 40 GBq/ml Radiopharmaceutical precursor solution

Lot No.:	Lu-22-346-01	**Time of Manufacturing [CET]:**	13.06.2022 11:00
Serial No.:	11103081-0-0		
Customer:	SCK-CEN		
Activity [GBq]:	9.3	**ART [CET]:**	20.06.2022 12:00
Volume [µl]:	238	**Expiry Date [CET]:**	22.06.2022 11:00
Chemical Form:	Lu (3+) in aqueous 0.04 M HCl solution		
Packaging:	2 ml type I glass vial, closed with fluorotec coated bromobutyl septum and center hole crimp cap		

Test	Specification	Unit	Result
Activity per Vial [1]	90 - 110 of the activity stated on the label	%	complies
Radioactivity Concentration (Dose Calibrator) [1]	36 - 44	GBq/ml	39
Appearance	Clear and colorless solution	n.a.	complies
Identity Lu-177 (Gamma spectrometry)	113 keV gamma line existing 208 keV gamma line existing	n.a.	complies
Identity Chloride (Ph. Eur.)	White precipitate visible	n.a.	complies
pH value (pH indicator strips)	1 - 2	n.a.	complies
Specific Activity (ICP-MS) [2]	≥ 3000	GBq/mg	3020
Chemical Purity (ICP-MS) corrected to Lu-177 activity at EOS	Fe ≤ 0.25 Cu ≤ 0.5 Zn ≤ 0.5 Pb ≤ 0.5 Yb-176 ≤ 0.14 Sum of impurities ≤ 0.5	µg/GBq µg/GBq µg/GBq µg/GBq µg/GBq µg/GBq	<0.01 <0.1 <0.1 <0.1 <0.01 <0.1
Radionuclidic Purity (Gamma spectrometry) corrected to Lu-177 activity at EOS [3]	Yb-175 ≤ 0.01 Sum of other impurities ≤ 0.01	% %	<0.01 <0.01
Radiochemical Purity (TLC)	≥ 99.0 as 177LuCl3	%	100.0
Radiolabeling Yield (TLC) based on radiolabeling with Lu-177 of DOTA-derivate, molar ratio 1:4	≥ 99.0	%	99.9
Bacterial Endotoxins (Ph. Eur.)	≤ 20	EU/ml	<2
Sterility (Ph. Eur.)	Sterile	n.a.	Sample taken

1 Result taken from In-Process Control, value decay-corrected to ART
2 Result taken from Release / Retest of API, value decay-corrected to ART
3 Result taken from Release / Retest of API, value decay-corrected to EOS

ART: Activity reference time
EOS: End of shelf life
** OOS Result

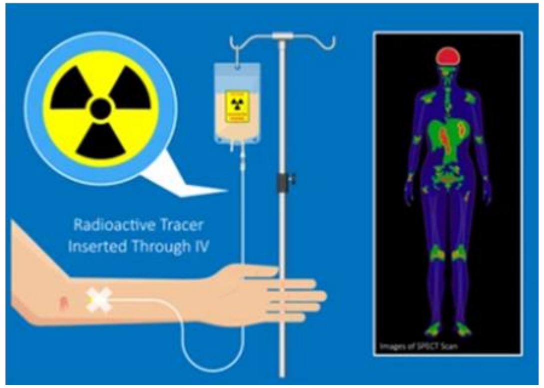
This batch complies with the specification.

Source: ITM EndolucinBeta CoA

Transport of purified radionuclide

Radiochemical processing facility

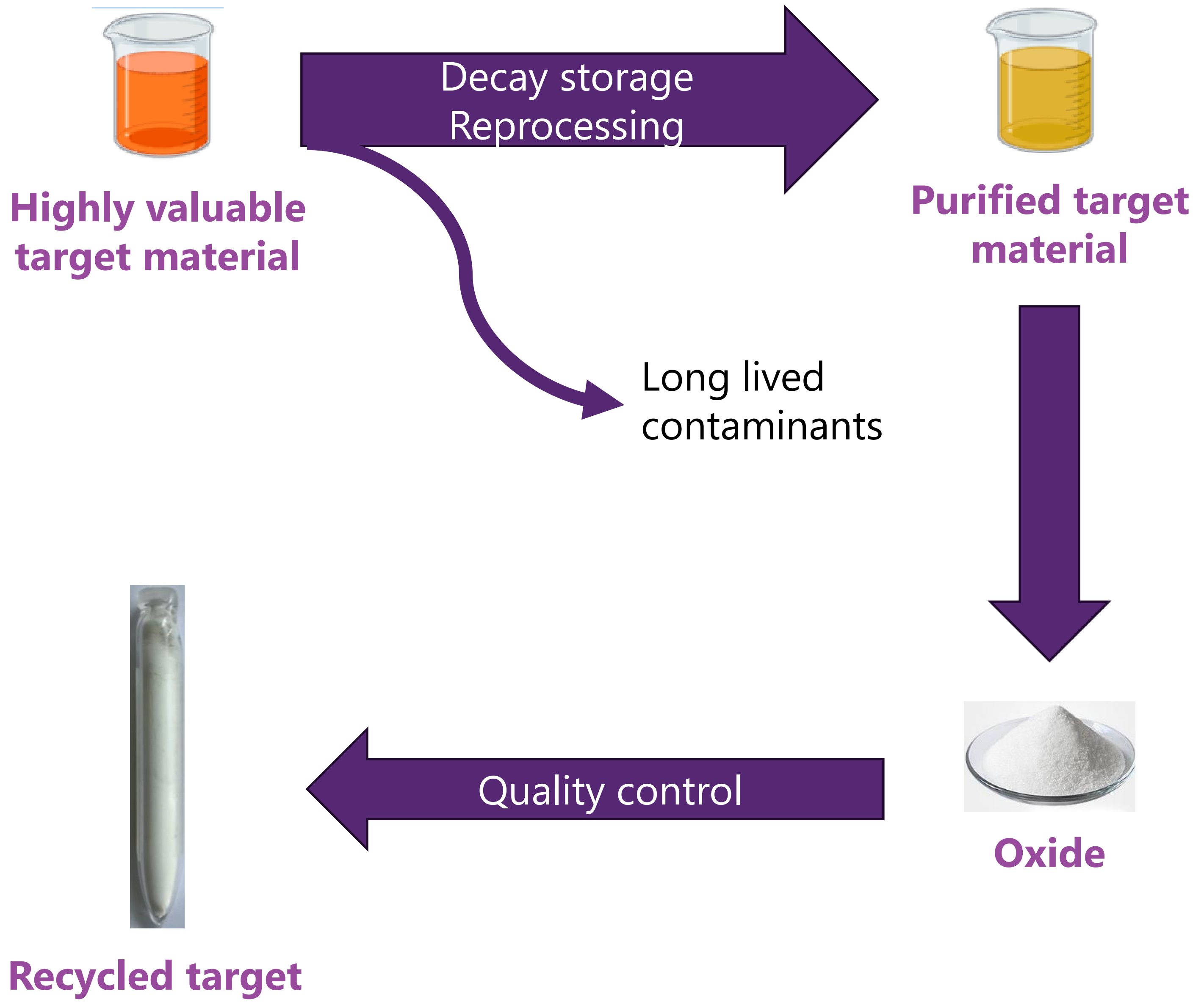
Radiopharmaceutical company



Hospital

Target recycling

- Target manufacturing and irradiation
- Radio-chemical processing
- Quality control
- Target recovery and recycling
- Waste management



Waste management

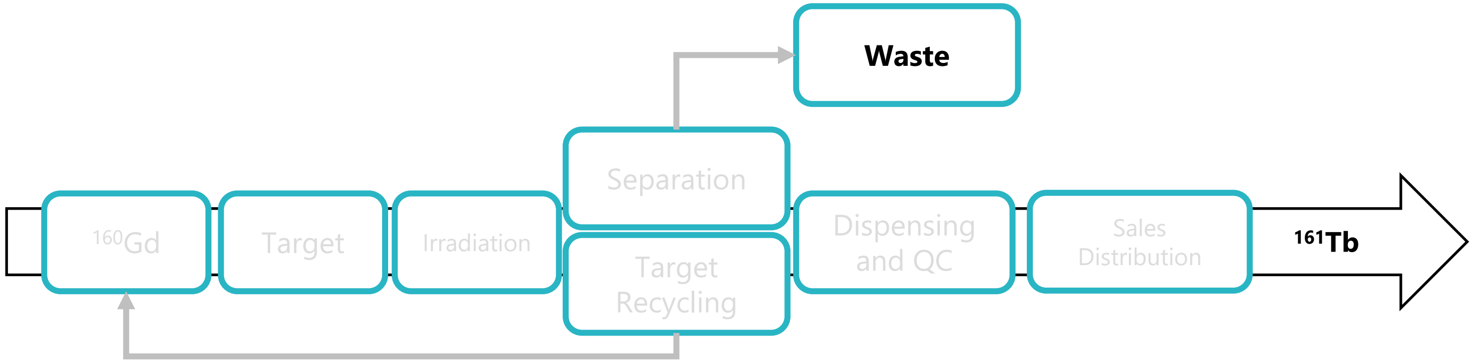
Target manufacturing and irradiation

Radio-chemical processing

Quality control

Target recovery and recycling

Waste management



- Identification of long-lived radio-contaminants in each fraction
  - Depends on purity of target material
- Appropriate waste collection and treatment strategies
  - Liquid waste
  - Solid waste
- Appropriate selection of materials used for irradiation (e.g. quartz quality)

→ To be considered during design of the radiochemical process and selection of appropriate target material!

Conclusions

- High thermal neutron fluxes are required for efficient production of radionuclides
- Two major production pathways
  - Carrier added
  - Non-carrier added
- Supply chain can be complex, and is a race against time
- Simple, robust and scalable radiochemistry steps
- High target quality is key

Nuclear research reactors are powerfull thermal neutron sources

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Crucial for manufacturing of therapeutic medical radionuclides

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PRISMAP PROJECT

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