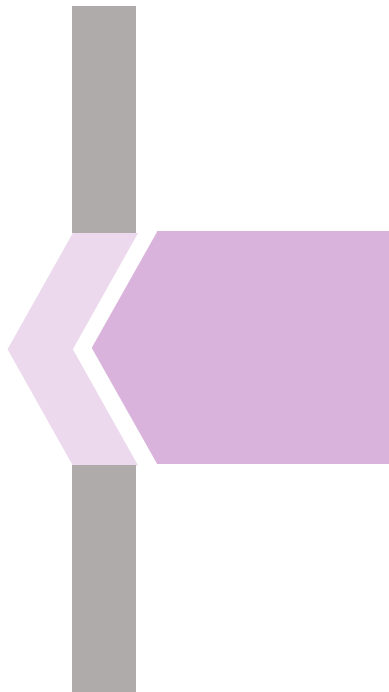


sck cen
Belgian Nuclear Research Centre



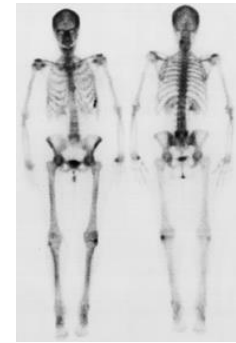
(Reactor-based) production and radiochemical processing of medical radiolanthanides

Michiel Van de Voorde – PRISMAP Radiolanthanides Workshop – September 2024



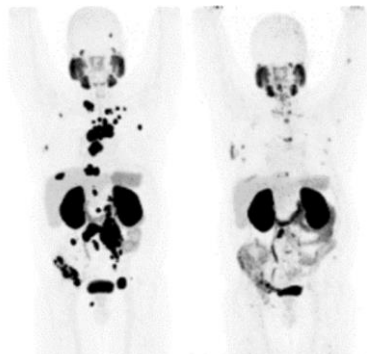
SPECT

Tb 155
5.32 d
ε
γ 87, 105, 180
262...



PET

Tb 152
4.2 m 17.5 h
IT 160, e⁻ ε
γ 283... β⁺ 3.0...
ε, β⁺... γ 344, 271
γ 344 586...
411... α?



Pre-treatment

Post-treatment

Tb 149
4.2 m 4.1 h
ε
β⁺ α 3.97...
α 3.99 β⁺ 1.8...
γ 796 γ 352
165... 165...



Pm 149
53.1 h
β⁻ 1.1...
γ 286...
σ 1400

Sm 153
46.284 h
β⁻ 0.7, 0.8...
γ 103, 70..., e⁻
σ 420

Tb 161
6.89 d
β⁻ 0.5, 0.6...
γ 26, 49, 75...
e⁻

Ho 166
1132.6 a 26.824 h
β⁻ 0.07
1.3... β⁻ 1.8
γ 184, 810 1.9...
712... γ 81...
σ 10778 e⁻

Er 169
9.392 d
β⁻ 0.4...
γ (8, 110...)
e⁻

Tm 170
128.6 d
β⁻ 1.0...
γ 84, e⁻
ε, γ (79)
σ 92

Yb 175
4.185 d
β⁻ 0.5...
γ 396, 283
114...

Lu 177
7 m 160.4 d 6.6443 d
β⁻ 0.2 β⁻
γ 208 m₁ 0.5...
β⁻ 228 m₂ γ 208
γ 1009 IT(146), e⁻ 113...
89... γ 411... e⁻ 8
m₂ γ 417 σ 880

Radioligand therapy (RLT)

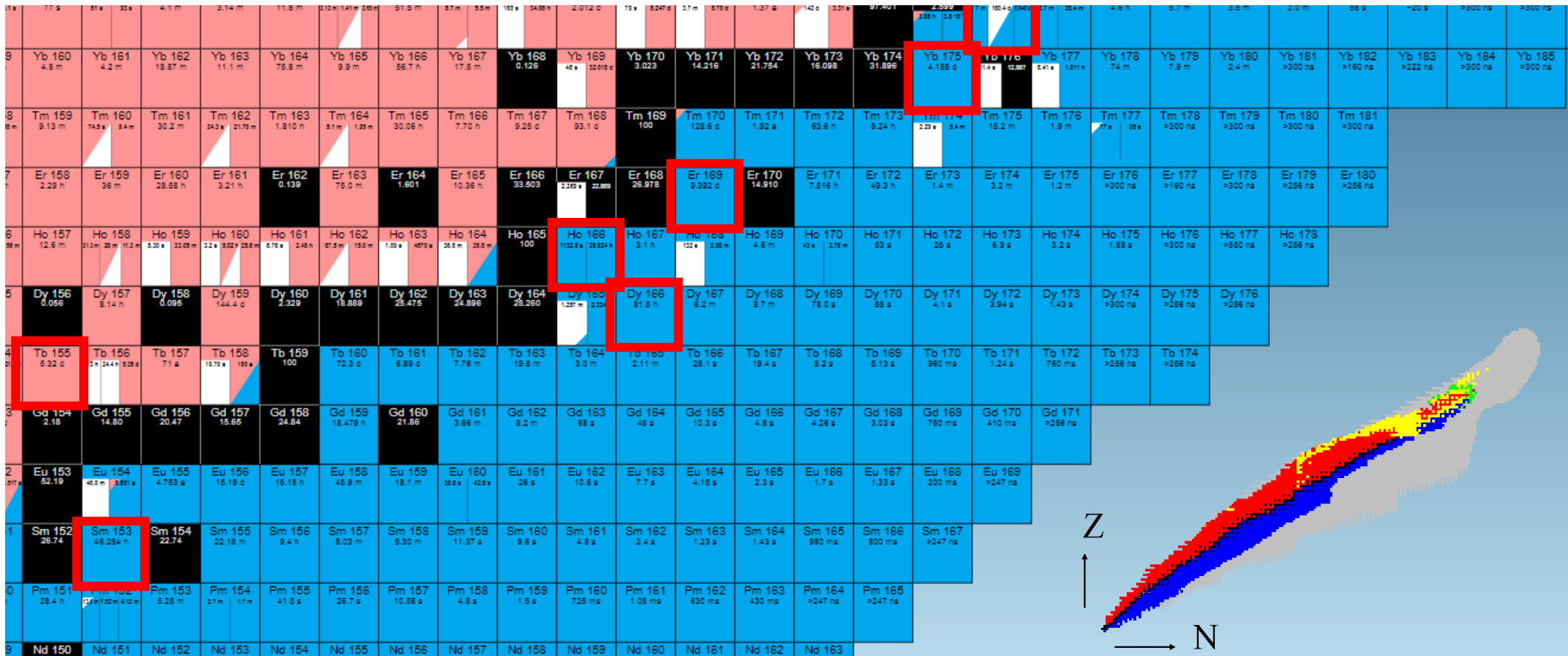
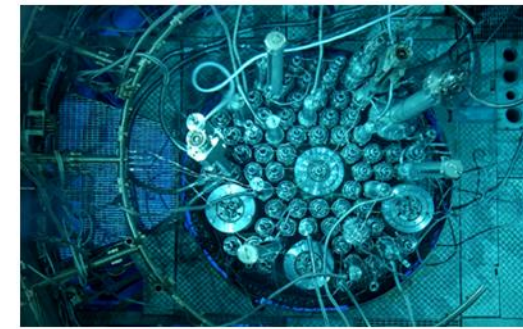


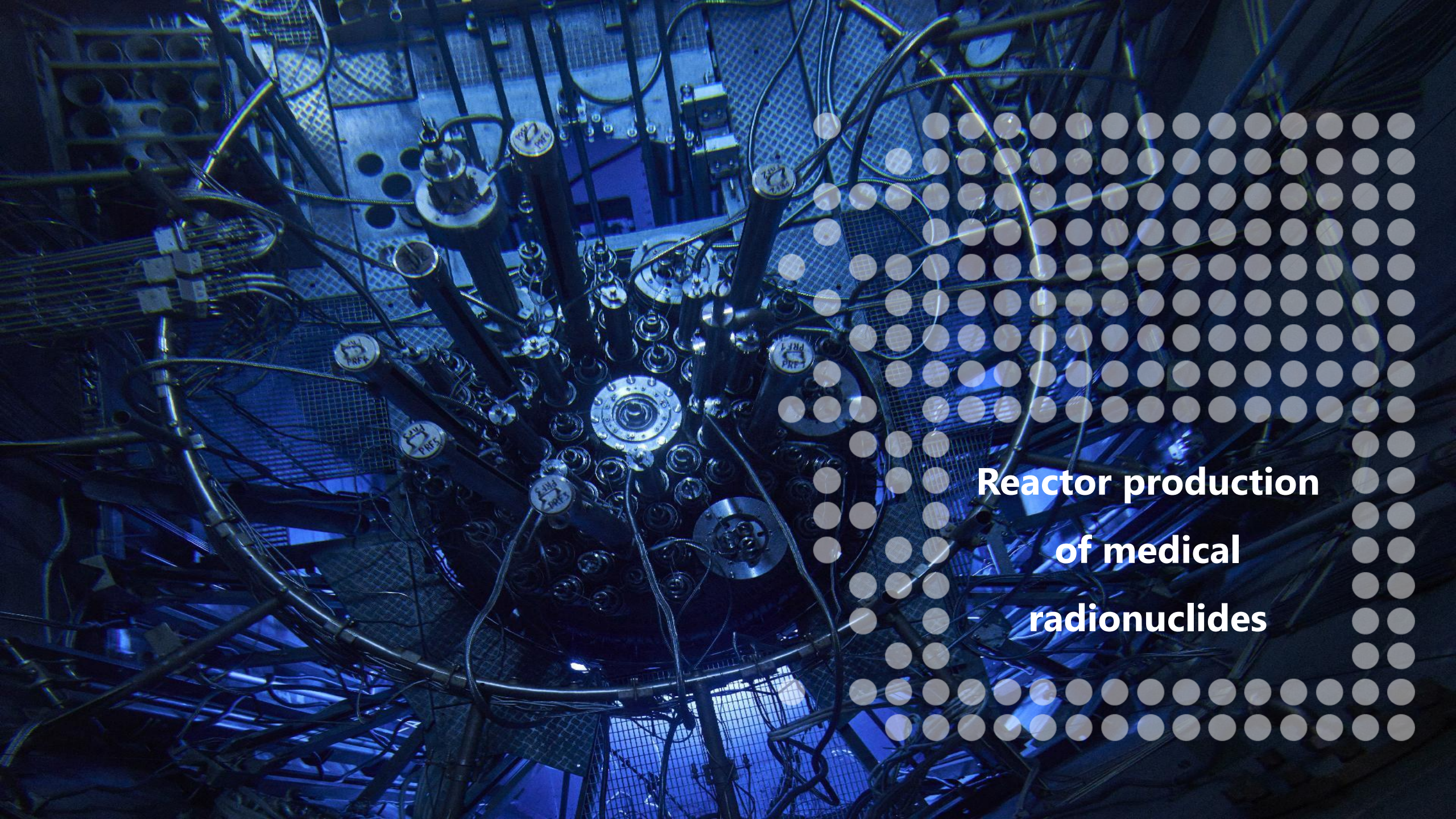
←
Neutron-deficient

Acquired by particle accelerators

→
Proton-deficient

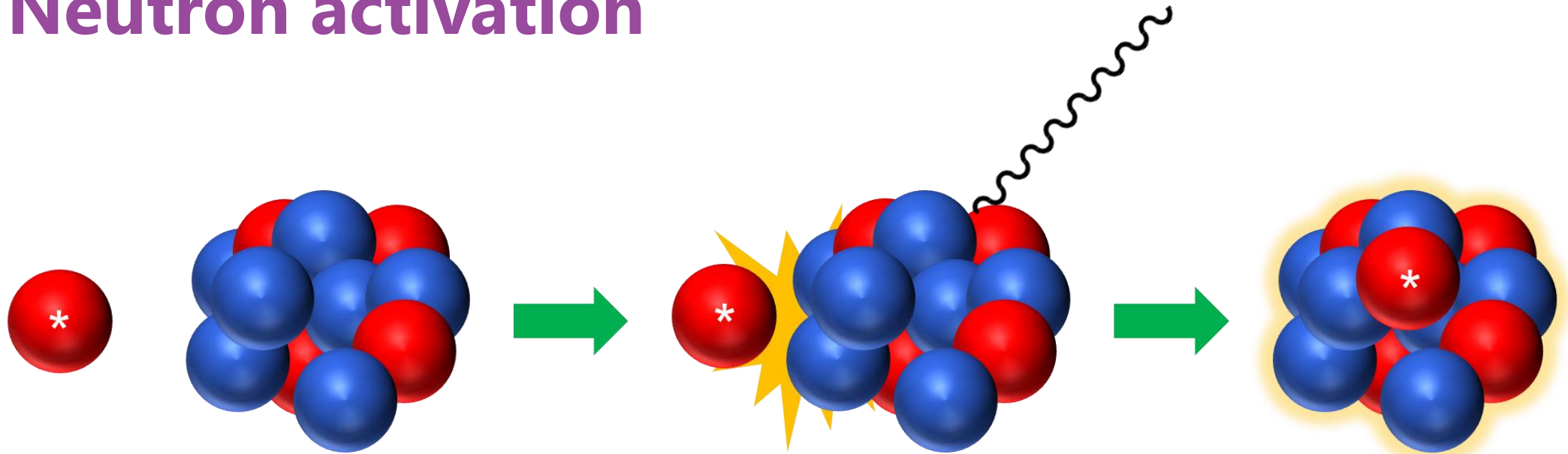
Acquired by thermal neutron flux in nuclear research reactors





**Reactor production
of medical
radionuclides**

Neutron activation



Neutron bombardment

Neutron capture
Photon emission (n,γ)

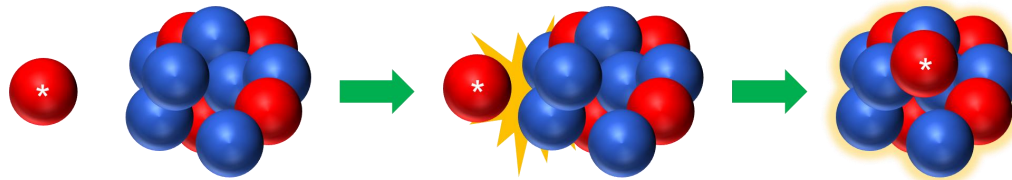
Unstable nucleus
Neutron excess
Beta decay

<p>Sm 152 26.74</p>	<p>Sm 153 46.284 h</p>
<p>σ 206</p>	<p>β⁻ 0.7, 0.8... γ 103, 70..., e⁻ σ 420</p>

(n,γ) →

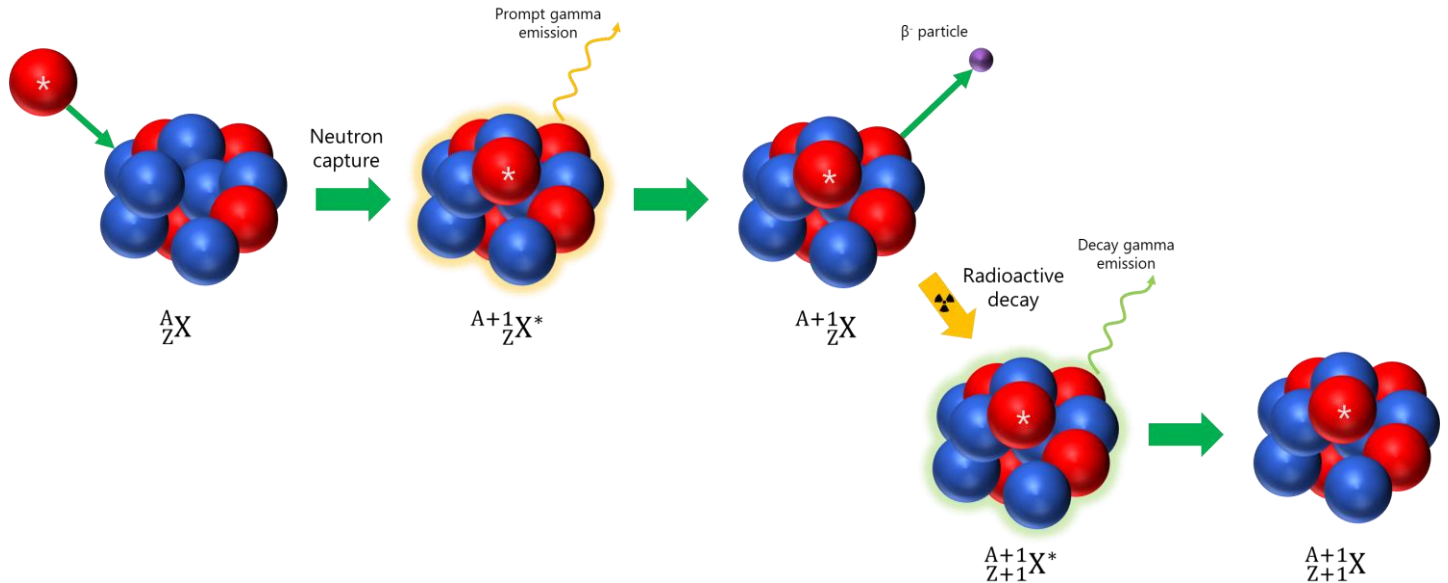
Neutron activation

Carrier added



Eu 153 52.19	Eu 154 46.0 m	Eu 154 8.601 a
		β^- 0.6, 1.8...
		γ 123, 1274...
		γ 723, 1005...
σ 312, $\sigma_{n,\alpha}$ 1E-		ϵ^- 1446
Sm 152 26.74	Sm 153 46.284 h	
		β^- 0.7, 0.8...
		γ 103, 70..., e^-
σ 206		σ 420

Non-carrier added

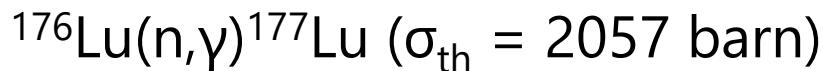


Dy 161 18.889	Dy 162 25.475	Dy 163 24.896
σ 600, $\sigma_{n,\alpha}$ < 3E-5	σ 194	σ 134, $\sigma_{n,\alpha}$ < 2E-5
Tb 160 72.3 d	Tb 161 6.89 d	Tb 162 7.76 m
β^- 0.6, 1.7...	β^- 0.5, 0.6...	β^- 1.4, 2.4...
γ 879, 299	γ 26, 49, 75...	γ 260, 808
966...	e^-	98...
σ 570		
Gd 159 18.479 h	Gd 160 21.86	Gd 161 3.66 m
		β^- 1.6, 1.7...
		γ 361, 315
β^- 1.0...		102...
γ 364, 58...	σ 1.4	σ 19000

Production strategies – ^{177}Lu example

Direct route

Hf 177			Hf 178			Hf 179		
51.4 m	1.09 s	18.58	31 a	4.0 s	27.28	25.05 d	18.67 s	13.63
IT 214			IT (13)			IT 257		
e ⁻			e ⁻ ...			e ⁻ ...		
γ 277	IT 228...		γ 574	IT 89...		(21), e ⁻	IT	
295	e ⁻	σ 2E-7	495...	γ 426		γ 454	161...	
327...	γ 208	+ 0.96	m ₁	326	σ ? + 53	363...	e ⁻	
m ₁	379...	+ 374	σ 45	213...	+ 30	g	γ 214	σ 0.445
								+ 41
Lu 176			Lu 177			Lu 178		
2.599			7 m	160.4 d	6.6443 d	22.7 m	28.4 m	
3.68 h	3.8·10 ¹⁰ a		β 0.2			β ⁻ 2.0...		
β ⁻ 1.2	β ⁻ 0.6...		γ 208	0.5...		γ 93, 1341		
1.3...	γ 307, 202		228... m ₁	γ 208		β ⁻ 1.2...	1310	
ε	88...		γ 1003	IT(116), e ⁻		γ 332...	1269...	
γ 88..., e ⁻	σ 2.8+2057		m ₂	σ 417		g		
Yb 175			Yb 176			Yb 177		
4.185 d			11.4 s	12.887		6.41 s	1.911 h	
β ⁻ 0.5...			IT 96	σ 2.85		IT 227	β ⁻ 1.4...	
γ 396, 283			γ 293, 389	σ n, α		e ⁻	γ 150	
114...			190, 82, e ⁻	<1E-6		γ 105	1080	
						g	1242	
							122..., e ⁻	
							g	



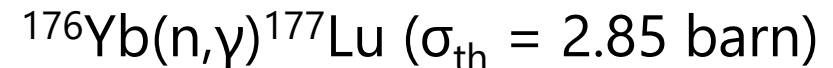
High Cross section = high yield

Low molar activity



Indirect route

Hf 177			Hf 178			Hf 179		
51.4 m	1.09 s	18.58	31 a	4.0 s	27.28	25.05 d	18.67 s	13.63
IT 214			IT (13)			IT 257		
e ⁻			e ⁻ ...			e ⁻ ...		
γ 277	IT 228...		γ 574	IT 89...		(21), e ⁻	IT	
295	e ⁻	σ 2E-7	495...	γ 426		γ 454	161...	
327...	γ 208	+ 0.96	m ₁	326	σ ? + 53	363...	e ⁻	
m ₁	379...	+ 374	σ 45	213...	+ 30	g	γ 214	σ 0.445
								+ 41
Lu 176			Lu 177			Lu 178		
2.599			7 m	160.4 d	6.6443 d	22.7 m	28.4 m	
3.68 h	3.8·10 ¹⁰ a		β 0.2			β ⁻ 2.0...		
β ⁻ 1.2	β ⁻ 0.6...		γ 208	0.5...		γ 93, 1341		
1.3...	γ 307, 202		228... m ₁	γ 208		β ⁻ 1.2...	1310	
ε	88...		γ 1003	IT(116), e ⁻		γ 332...	1269...	
γ 88..., e ⁻	σ 2.8+2057		m ₂	σ 417		g		
Yb 175			Yb 176			Yb 177		
4.185 d			11.4 s	12.887		6.41 s	1.911 h	
β ⁻ 0.5...			IT 96	σ 2.85		IT 227	β ⁻ 1.4...	
γ 396, 283			γ 293, 389	σ n, α		e ⁻	γ 150	
114...			190, 82, e ⁻	<1E-6		γ 105	1080	
						g	1242	
							122..., e ⁻	
							g	



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
$^{177\text{m}}\text{Lu}$ content (EOI)	86 GBq	

Activation parameters

- 100% enriched target
- $\Phi_{\text{th}} = 3\text{E}14$ neutrons/cm²/s
- No epithermal or fast neutrons
- No self-shielding
- 7 days irradiation
- 1 g target

 LuMark®
Lu-177 chloride

SA \geq 500 GBq/mg at ART

 endolucin[®]
beta

SA \geq 3000 GBq/mg at ART



Radiochemical processing

Target manufacturing
and irradiation

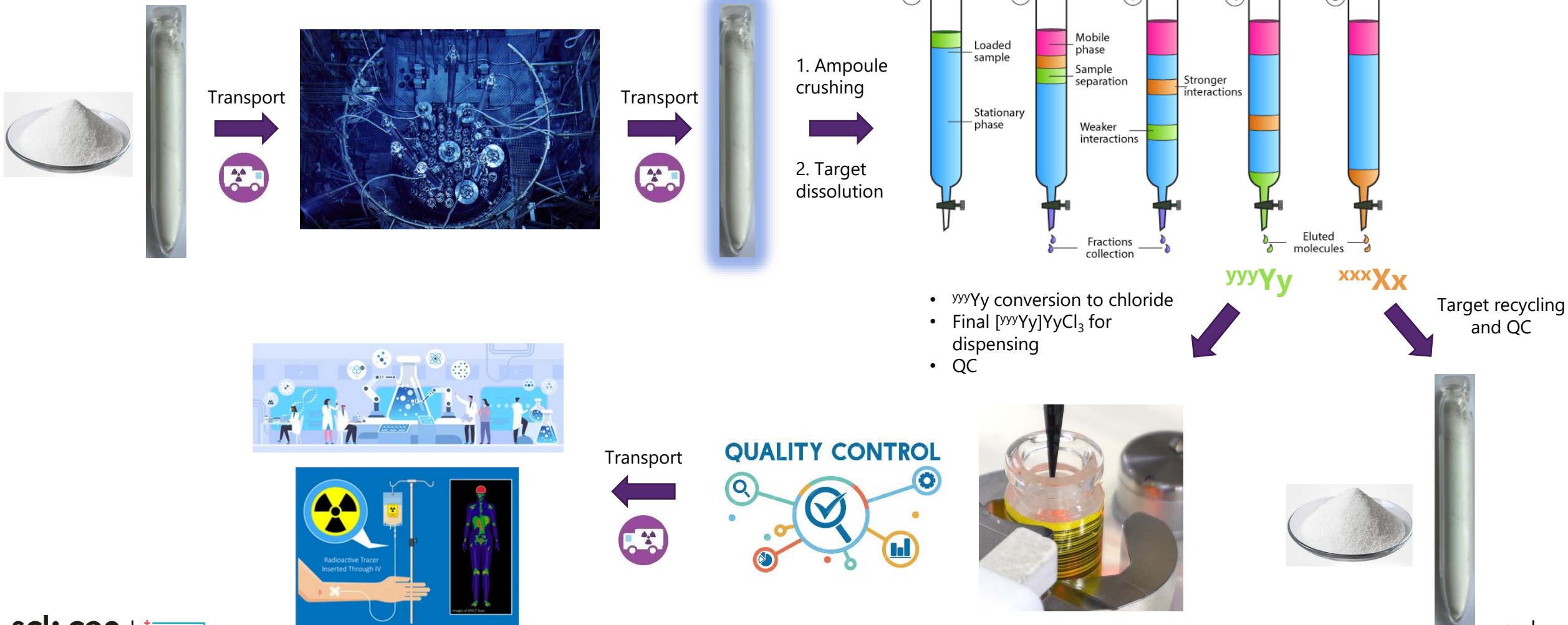
Radiochemical
processing

Quality control

Target recovery and
recycling

Waste management

Production n.c.a. radiolanthanide – General approach



Target

Target manufacturing
and irradiation

Radiochemical
processing

Quality control

Target recovery and
recycling

Waste management

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 compound

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

Target

Target manufacturing and irradiation

Radiochemical processing

Quality control

Target recovery and recycling

Waste management

$\text{Ln}(\text{NO}_3)\cdot x\text{H}_2\text{O}$		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

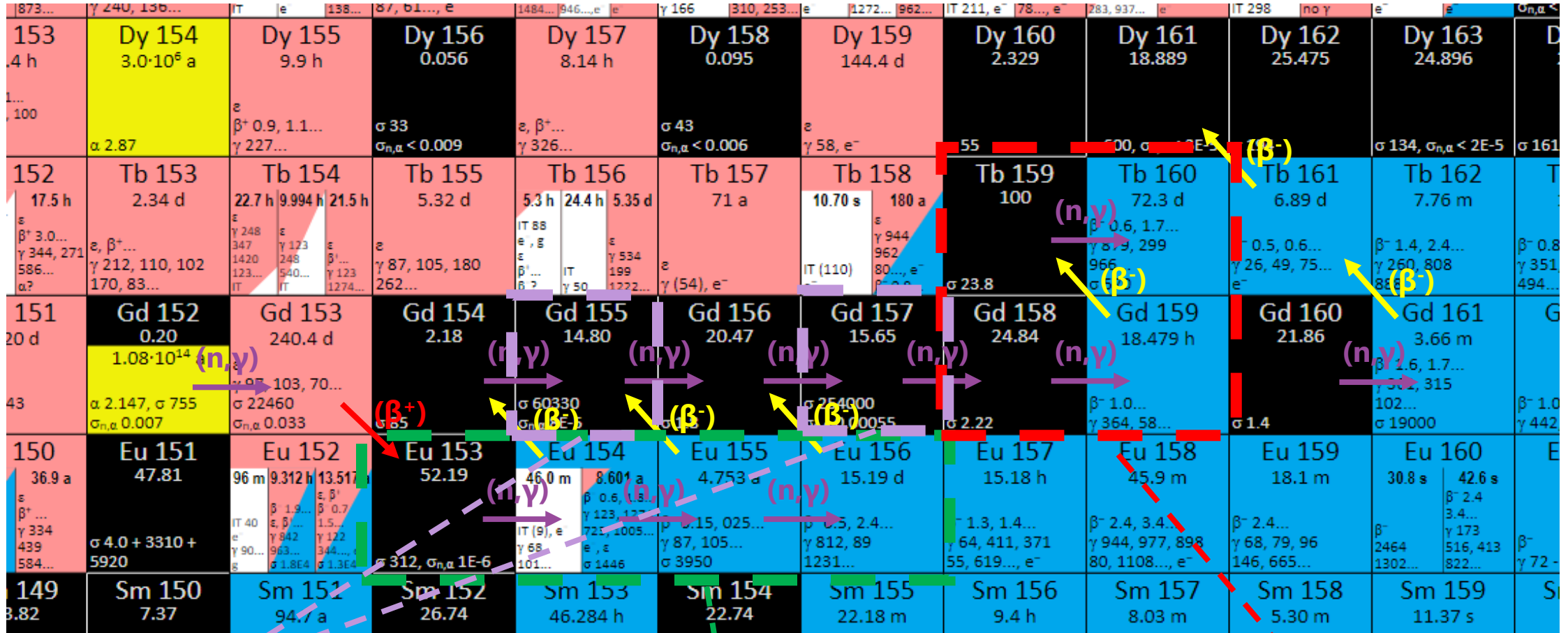
^{177}Lu production – Target quality

Hf 170	Hf 171	Hf 172	Hf 173	Hf 174	Hf 175	Hf 176	Hf 177	Hf 178	Hf 179
16.01 h	29.5 s, 12.1 h	1.87 a	23.6 h	0.161, $2.0 \cdot 10^{15}$ a	70.0 d	5.24	51.4 m, 1.09 s, 18.58	31 a, 4.0 s, 27.28	25.05 d, 18.67 s, 13.63
ϵ γ 165, 621, 120 573...	IT (22) ϵ ? ϵ, β^+ ? γ 662 122 1071... e^- g, m	ϵ γ 24, 126, 67 82... m	ϵ γ 124, 297, 140 311...	α 2.500 σ 549	ϵ γ 343...	σ 23.5	IT 214 e^- γ 277 295 327... IT 228... e^- γ 208 379 σ 2E-7 + 0.374	IT (13) e^- γ 574 495... 326 γ 213... IT 89... γ 426 326 σ ? + 53 + 30	IT 257 (21), e^- IT γ 454 161... e^- γ 214 σ 0.445 + 41
Lu 169	Lu 170	Lu 171	Lu 172	Lu 173	Lu 174	Lu 175	Lu 176	Lu 177	Lu 178
160 s, 34.06 h	2.012 d	79 s, 8.247 d	3.7 m, 6.70 d	1.37 a	142 d, 3.31 a	97.401	2.599	7 m, 160.4 d, 6.6443 d	22.7 m, 28.4 m
ϵ β^+ ... γ 961, 191 1450... IT (29) e^- g, m	ϵ β^+ ... γ 84, 1280, 2042 985... e^-	ϵ β^+ ... γ 740, 19 667, 76 781... e^-	ϵ γ 1094 901, 181 810 912... IT (42) e^-	ϵ γ 272, 79, 101... e^- σ 34.3	IT (59...), e^- γ 45, 67... e^- β^+ ... γ 1242 76... e^-	σ 16.7 + 6.6 $\sigma_{n,\alpha} < 6E-5$	β^- 3.68 h β^- 0.6... γ 307, 202 88... σ 2.8+2057	β^- 0.2 γ 208 228... 1003 IT (116), e^- γ 414... σ 417	β^- 2.0... γ 93, 1341 β^- 1.2... γ 332... 1269... g
Yb 168	Yb 169	Yb 170	Yb 171	Yb 172	Yb 173	Yb 174	Yb 175	Yb 176	Yb 177
0.126	46 s, 32.018 d	3.023	14.216	21.754	16.098	31.896	4.185 d	11.4 s, 12.897	6.41 s, 1.911 h
σ 3033 $\sigma_{n,\alpha} < 0.0001$	(n,γ) IT (24) e^-	10.2 $\sigma_{n,\alpha} < 1.0E-5$	(n,γ) σ 58.8 (β^-) .5E-6	(n,γ) σ 1.3, $\sigma_{n,\alpha} < 1E-6$	(n,γ) σ 15.5, $\sigma_{n,\alpha} < 1E-6$	(n,γ) σ 63, $\sigma_{n,\alpha} < 2E-5$	β^- 0.5... γ 396, 283 114...	IT 96 293, 389 190, 82, e^- σ 2.85 $\sigma_{n,\alpha} < 1E-6$	IT 227 e^- γ 105
Tm 167	Tm 168	Tm 169	Tm 170	Tm 171	Tm 172	Tm 173	Tm 174	Tm 175	Tm 176
9.25 d	93.1 d	100	128.6 d	1.92 a	63.6 h	8.24 h	2.29 s, 5.4 m	15.2 m	1.9 m
ϵ γ 57, 532..., e^- m	ϵ, β^+ ... γ 198, 816 448..., e^- β^- ...	σ 107	(n,γ) β^- 1.0... γ σ , e^- ϵ, γ (79) σ 92	β^- 0.1... γ (67), e^- σ ~160	β^- 1.8, 1.9... γ 79, 1094 1387, 1530 1466, 1609...	β^- 0.9, 1.3... γ 399, 461...	IT 152, e^- γ 100, e^-	β^- 0.9, 1.9... γ 515, 941 364...	β^- 2.0, 2.8... γ 190, 1069 382... g

Might affect target recycling

Might affect specific activity ^{177}Lu

^{161}Tb production – Target quality



Might reduce production yield

Might create long-lived waste

Might affect specific activity and radionuclidic purity of ^{161}Tb

Neutron activation

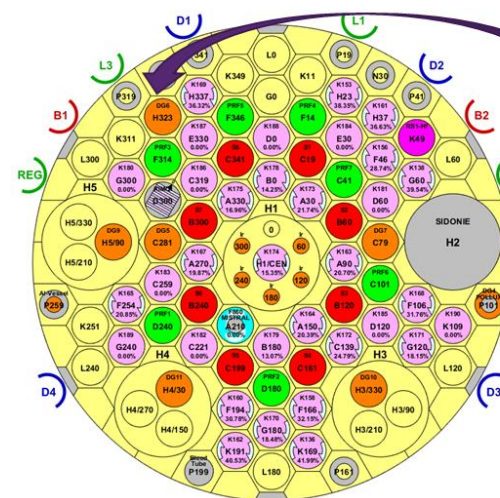
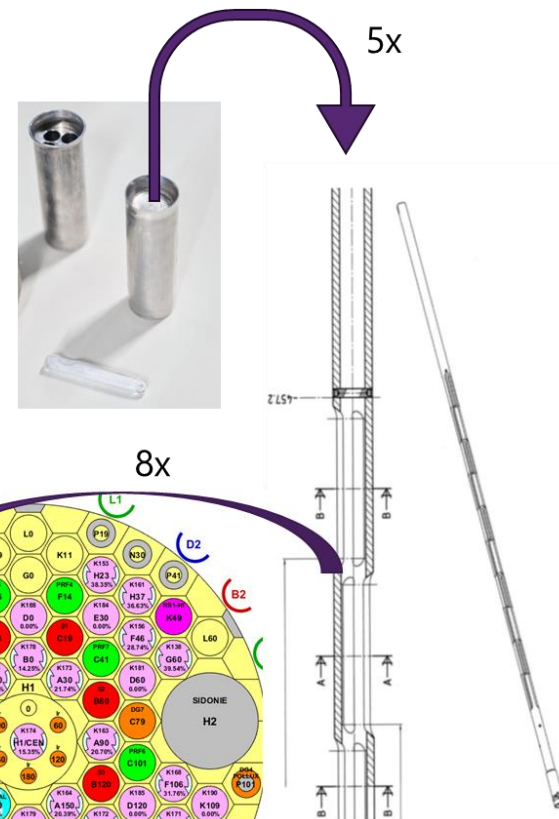
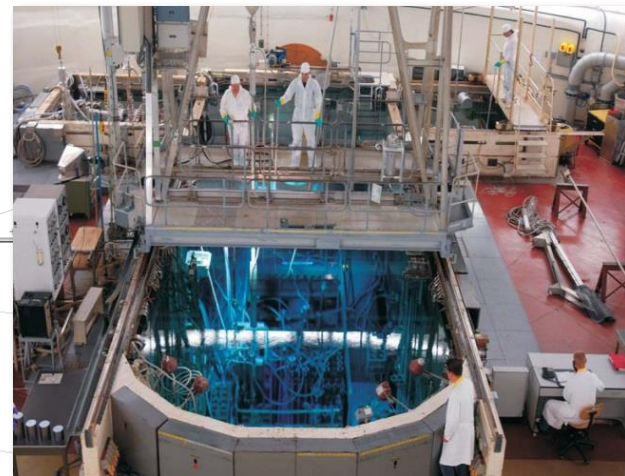
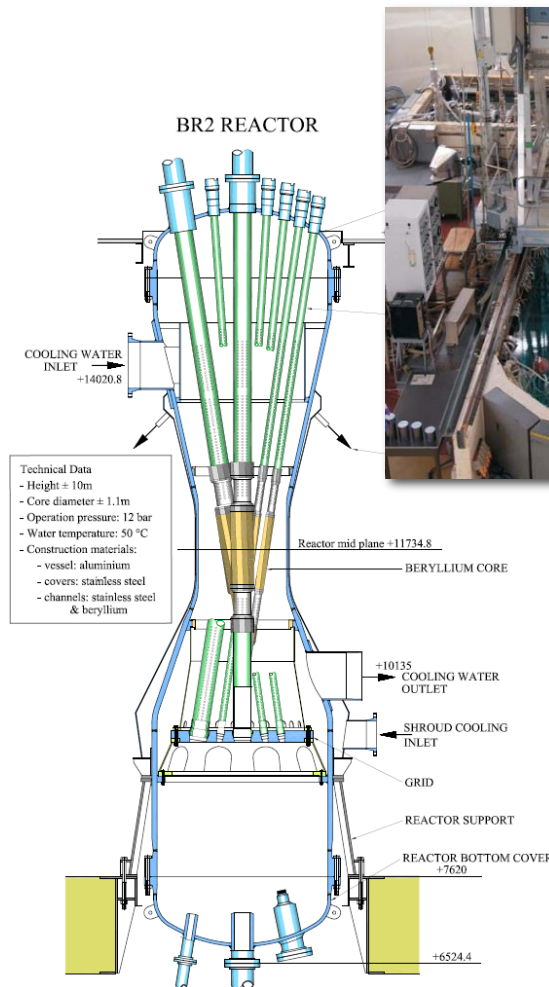
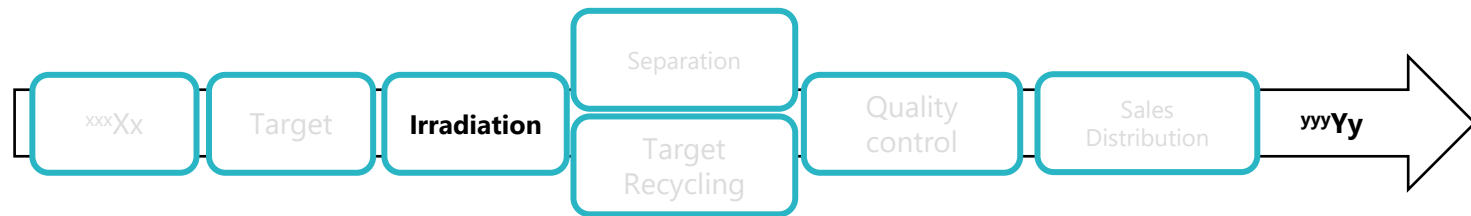
Target manufacturing and irradiation

Radiochemical processing

Quality control

Target recovery and recycling

Waste management



Neutron activation

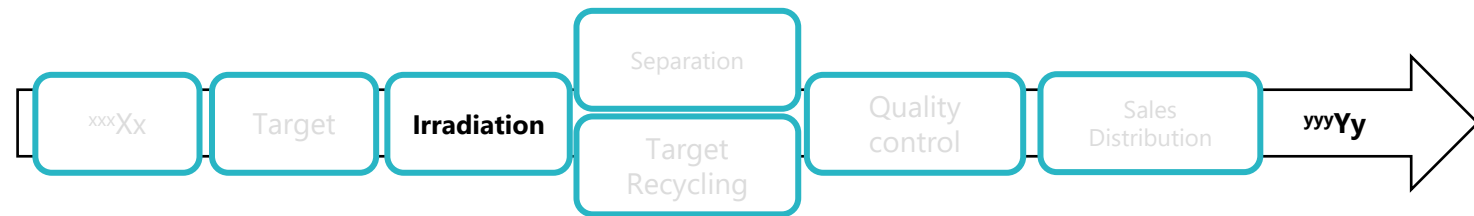
Target manufacturing and irradiation

Radiochemical processing

Quality control

Target recovery and recycling

Waste management



Transfer of irradiated targets to hotcell for decanning

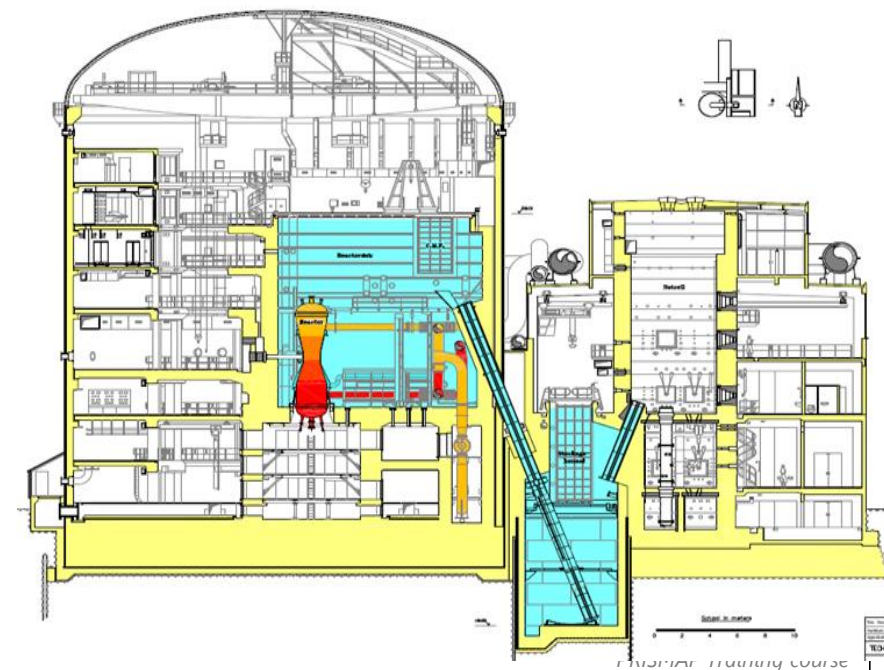
- Cooling of irradiated targets → *decay of short-lived radio-contaminants*
- Opening of aluminium irradiation can
- Preparation for shipment in dedicated transport containers



Type A (≤ 700 GBq ^{177}Lu)



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



RADIO CHEMISTRY

Target manufacturing and irradiation

Radiochemical processing

Target recovery and recycling

Quality control

Waste management

Separation method: What to look for?

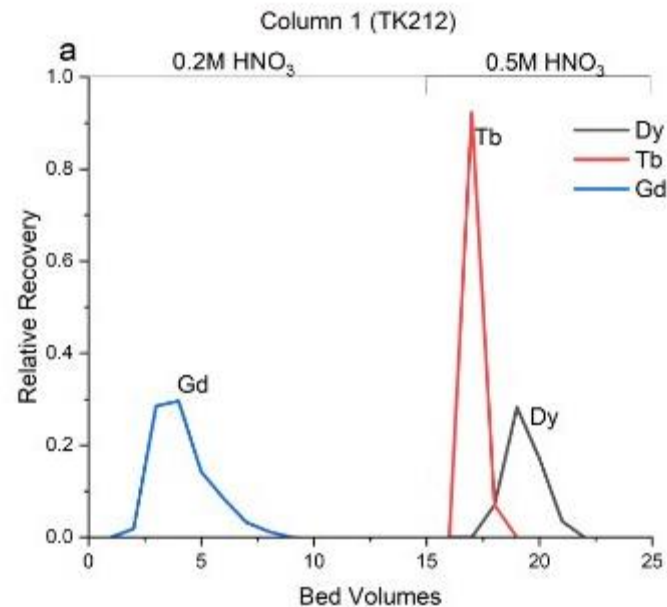
- Separation of micro amounts from macro amounts
- Method must yield
 - High purity fractions
 - High target recovery and regeneration
- Easy scale-up and cost-efficient
 - MBq scale → GBq scale
 - GBq scale → TBq scale
 - Simple, robust and fast
 - Automated and remote-controlled
 - Insensitive to target contaminants



Lu:Yb ratio 1:10⁴-10⁶

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

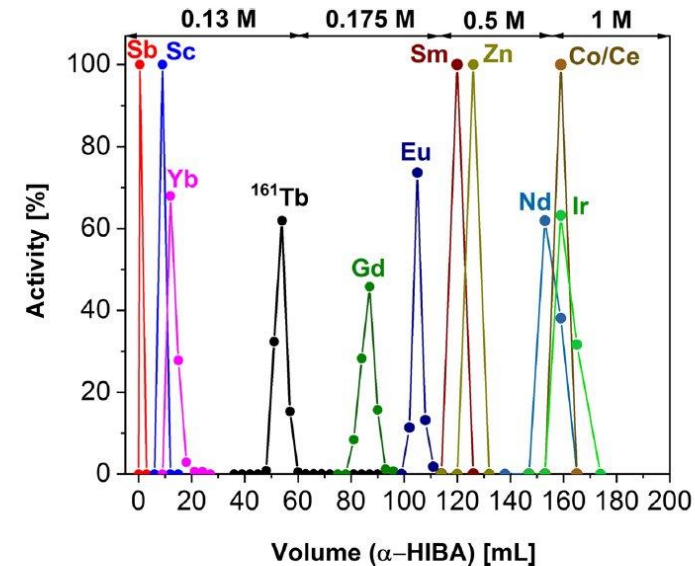


Fig. 1 Elution profile of ¹⁶¹Tb separation from the irradiated target material and side products (10 mm x 170 mm Sykam resin column, 8 mg ¹⁶⁰Gd₂O₃, 0.6 mL/min eluent flow rate)

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

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

RADIO CHEMISTRY

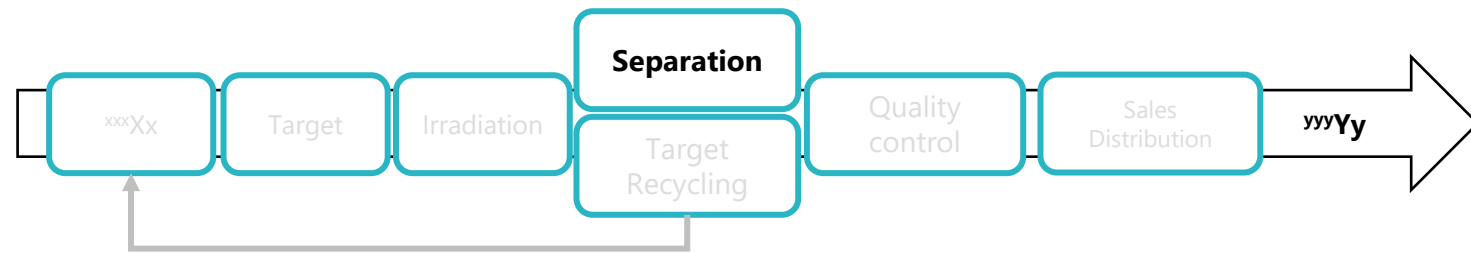
Target manufacturing and irradiation

Radiochemical processing

Quality control

Target recovery and recycling

Waste management



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



RADIO CHEMISTRY

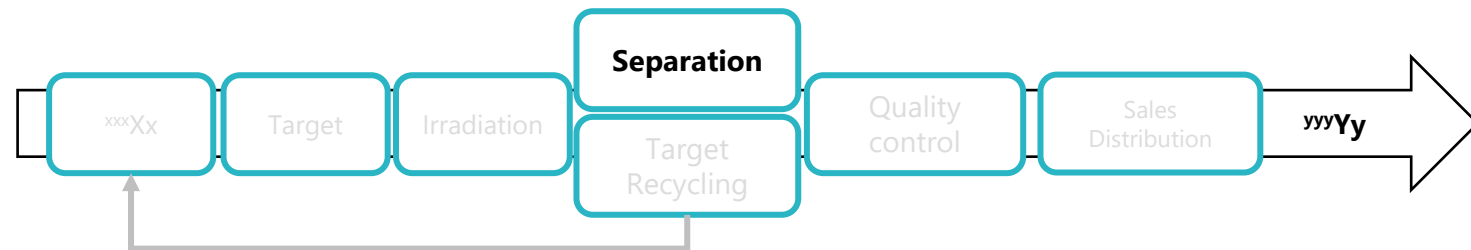
Target manufacturing and irradiation

Radiochemical processing

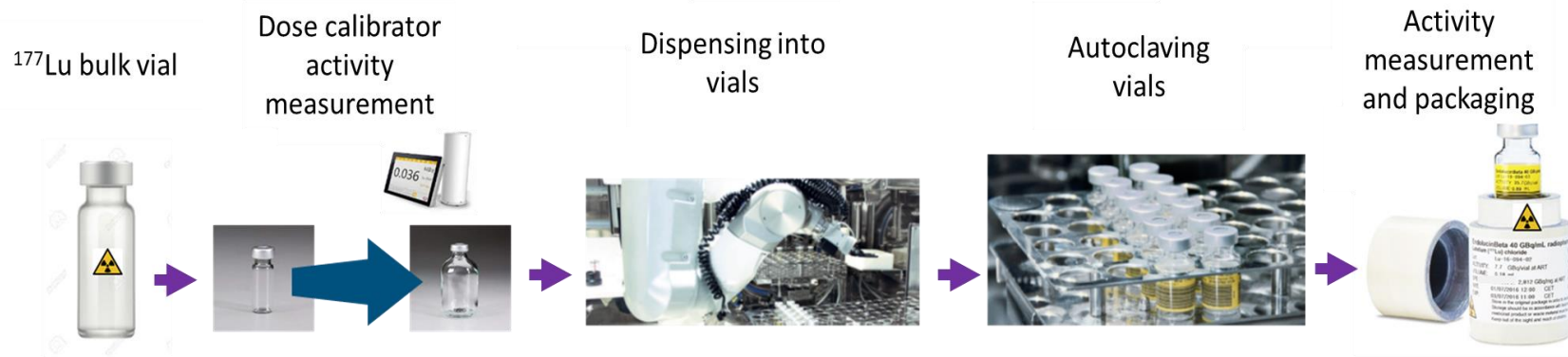
Quality control

Target recovery and recycling

Waste management



Dispensing, sterilization 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)

Quality control

Target manufacturing and irradiation

Radiochemical processing

Quality control

Target recovery and recycling

Waste management

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
Radioisotopic 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.



Transport of purified radionuclide



Radiochemical processing facility



Radiopharmaceutical company



Hospital

Target recycling

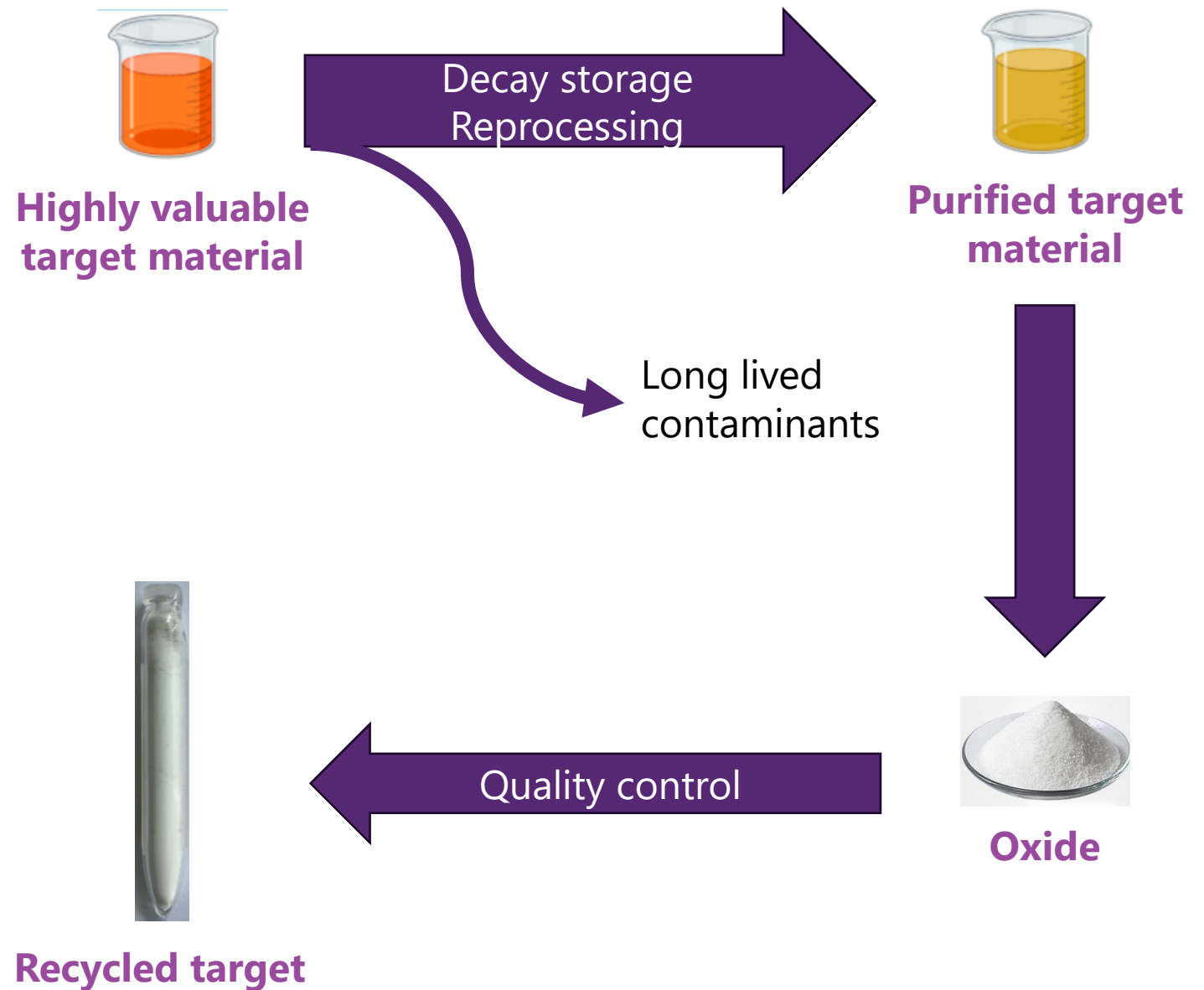
Target manufacturing and irradiation

Radio-chemical processing

Quality control

Target recovery and recycling

Waste management



Waste management

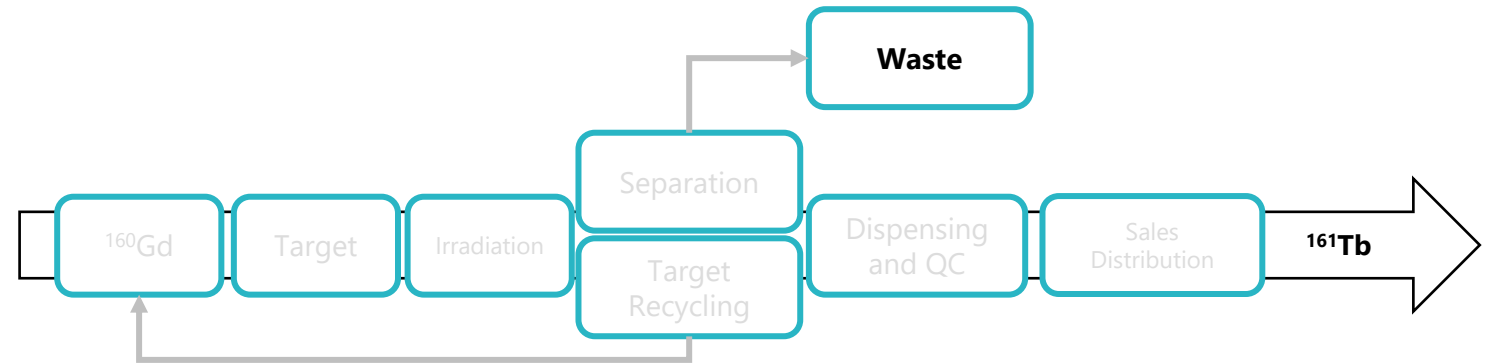
Target manufacturing and irradiation

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**

**Crucial for manufacturing of
therapeutic medical radionuclides**





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 PRISMAP PROJECT



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