

Georgian-German Science Bridge Workshop 2026

Introduction to Nuclear Medicine

Institute for Neuroscience and Medicine, Nuclear Chemistry (INM – 5)

Davit Gabadadze



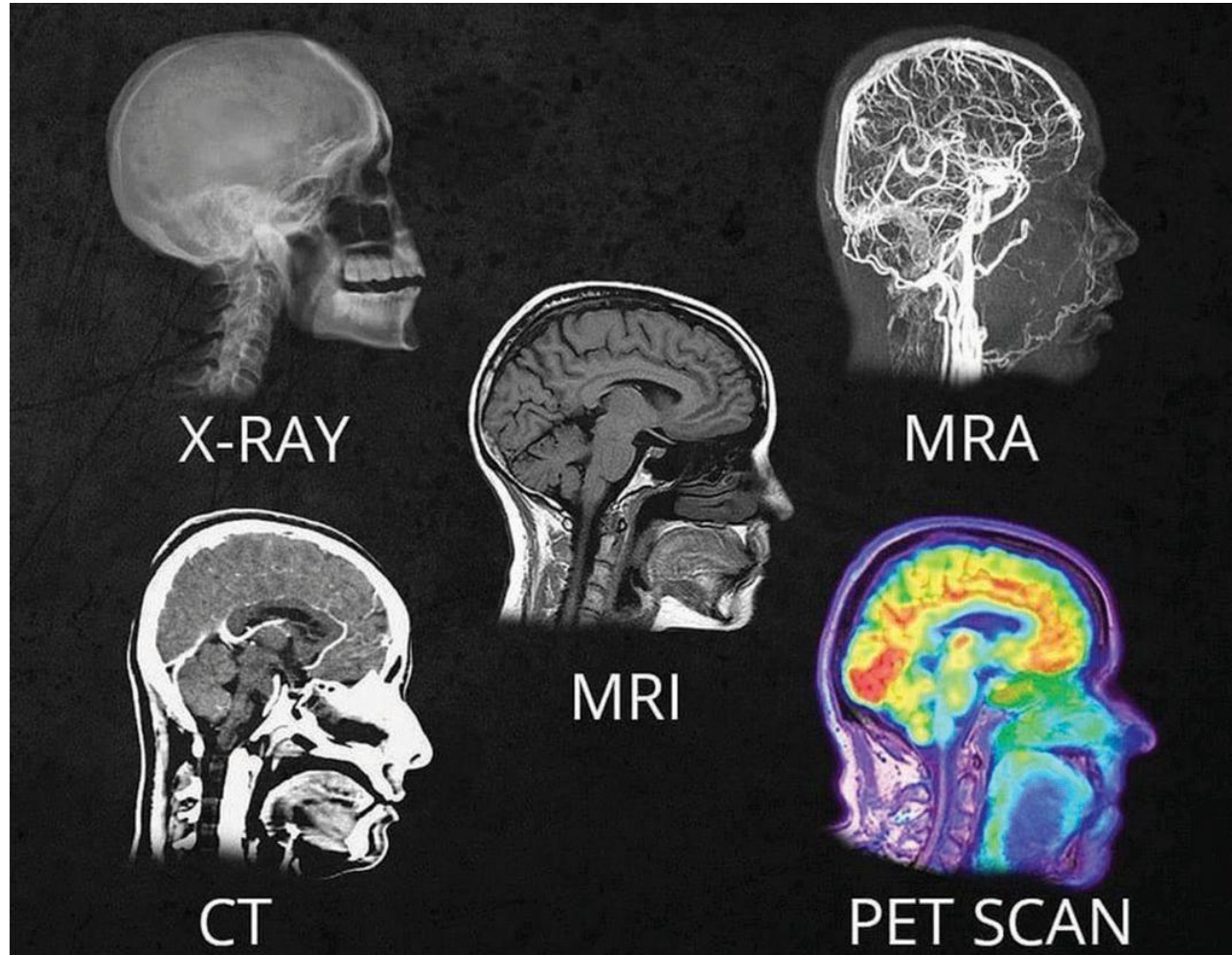
Nuclear Medicine uses **radioactive molecules** to assess body functions for diagnosis and therapy

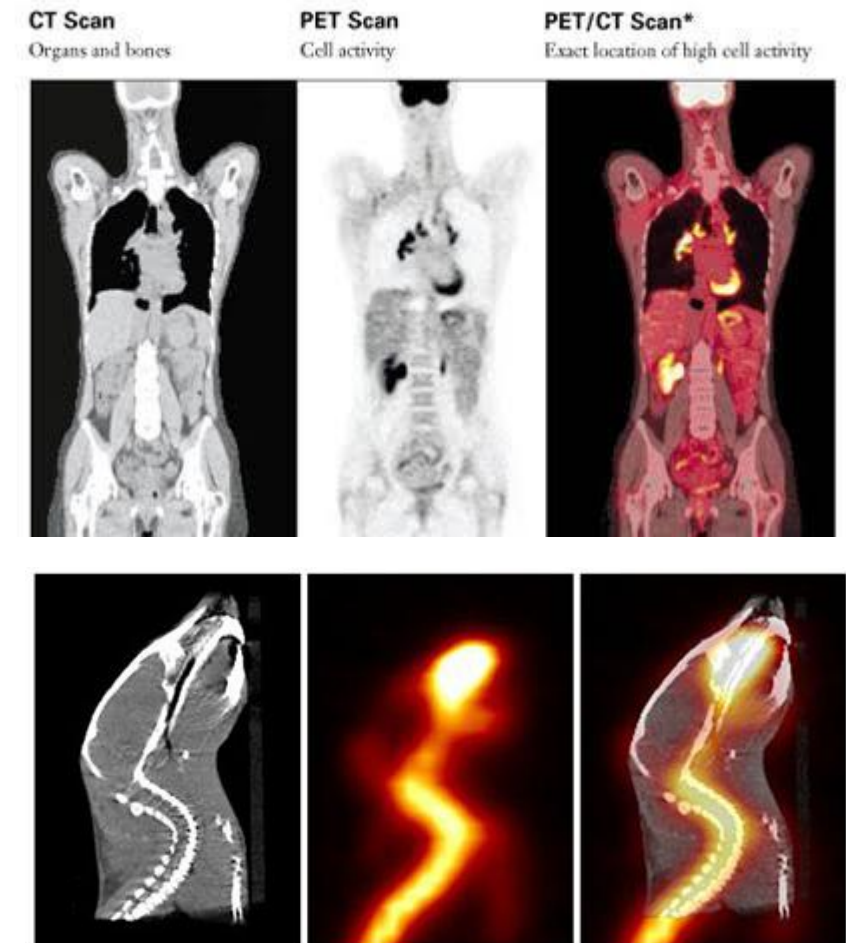
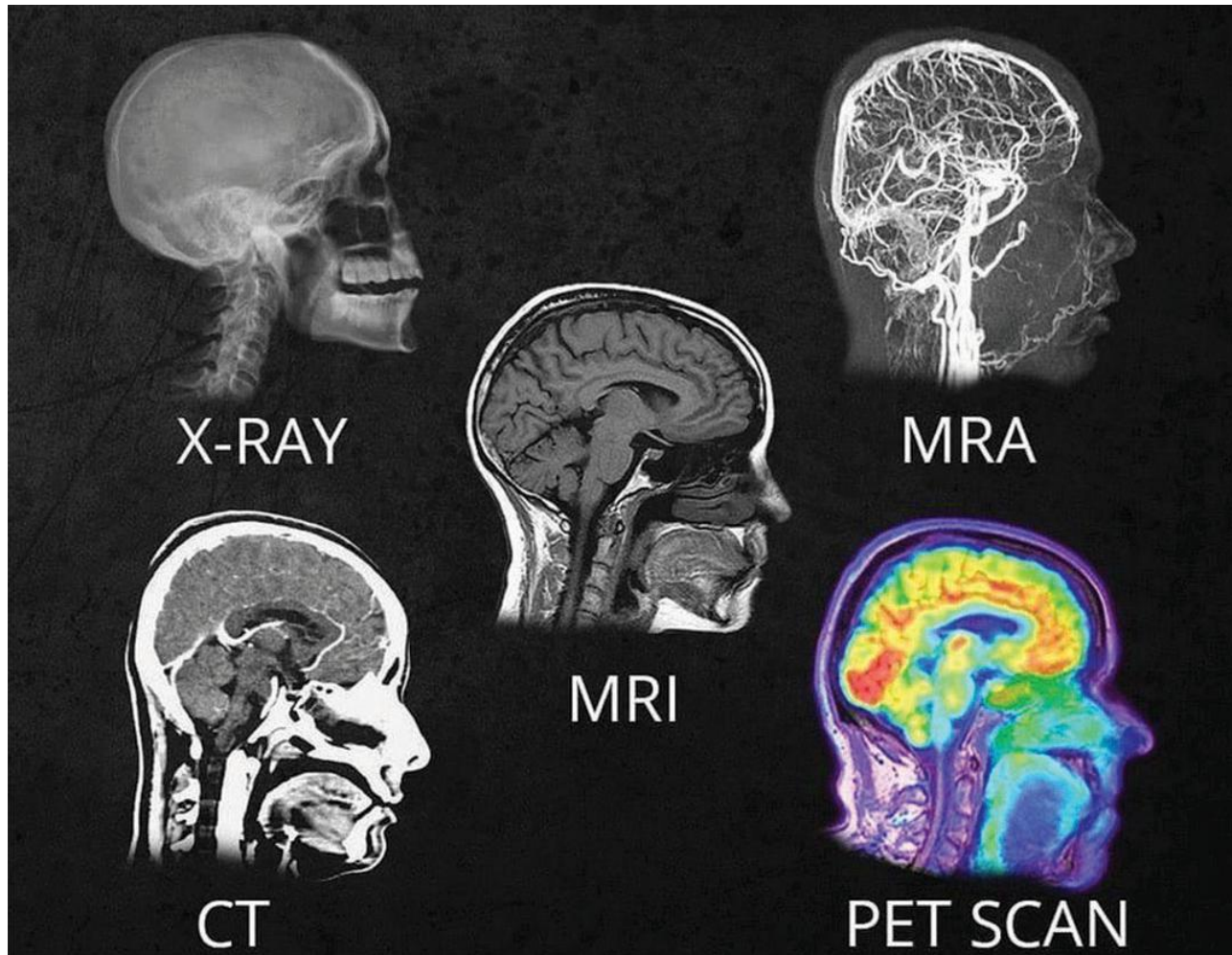
Molecular Imaging

Radiotherapy

Positron-Emission Tomography (PET)
Single Photon Emission Computed Tomography (SPECT)

➤ Different Imaging Modalities

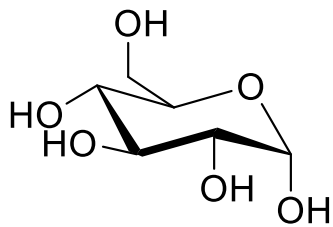




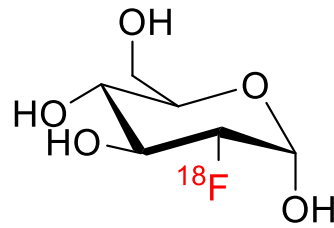
Tracer Principle

Radioisotopes behave like their stable counterparts.

They enable molecular tracking without changing biological behavior.



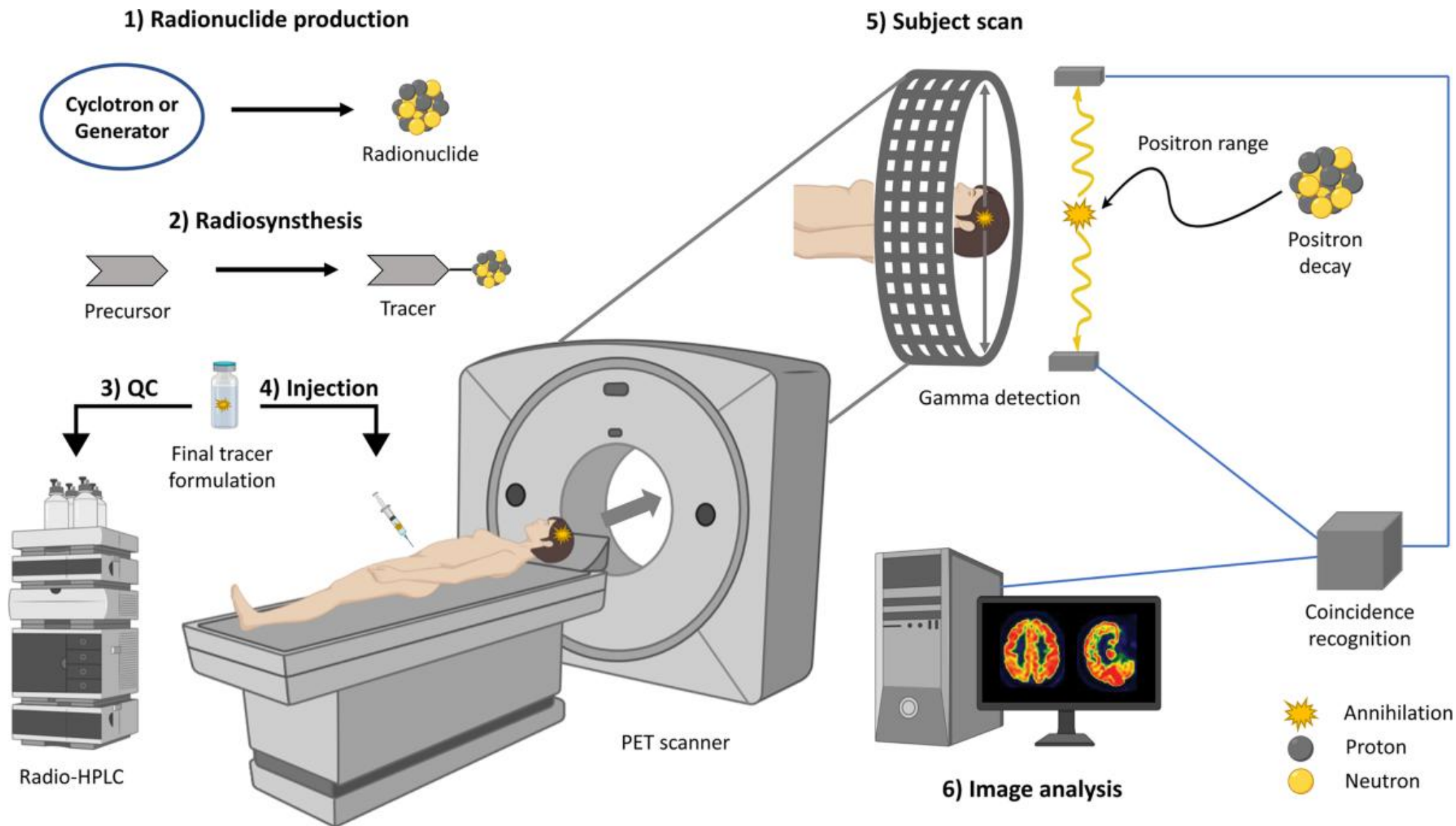
D-Glucose

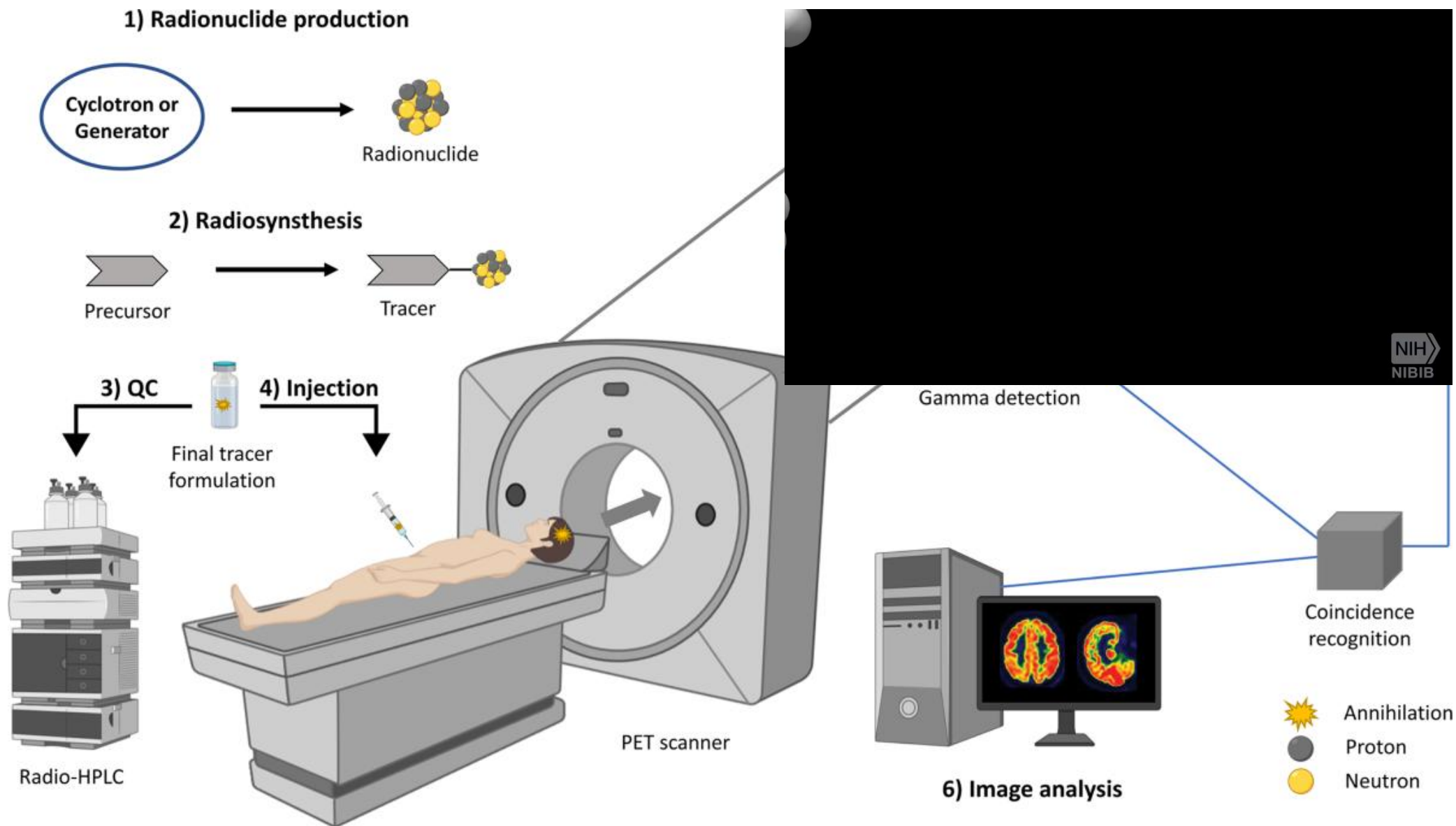


[¹⁸F]FDG

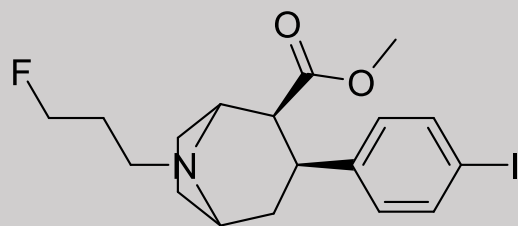


G. C. de Hevesy

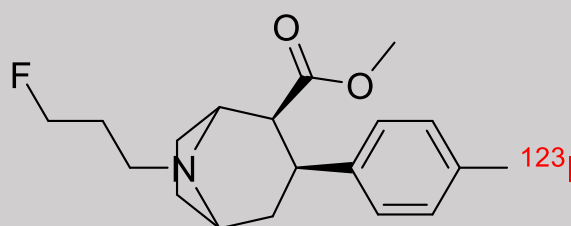




Isotopic Analog

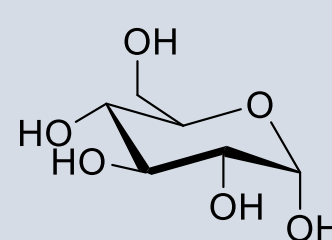


Ioflupane

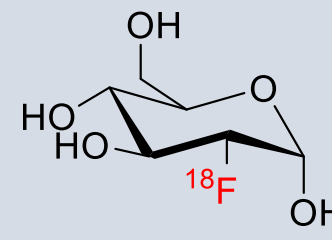


[¹²³I]ioflupane

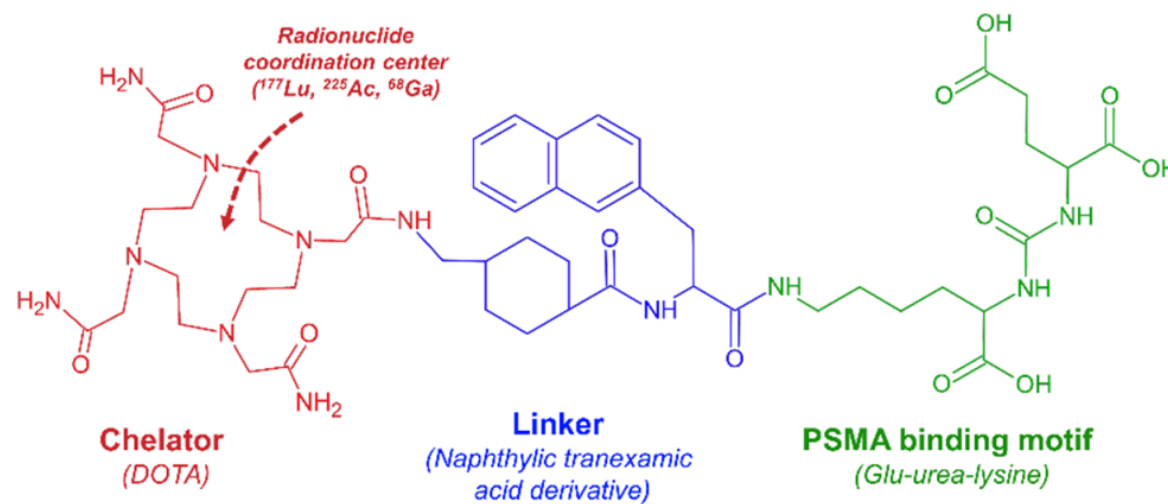
¹⁸F-Labeled Derivative



D-Glucose



[¹⁸F]FDG



Design and Development of Radiopharmaceuticals

WHAT CAN BE LABELLED?

- 1 Small molecules**
drugs, sugars and receptor ligands
- 2 Amino acids & metabolites**
natural substrates and analogues
- 3 Peptides**
compact, high-affinity targeting vectors
- 4 Peptidomimetics**
drug-like mimics of peptide recognition
- 5 Proteins & enzymes**
larger biological recognition systems
- 6 Antibodies & fragments**
high specificity; slower distribution
- 7 Oligos, nanoparticles & cells**
specialised or emerging platforms

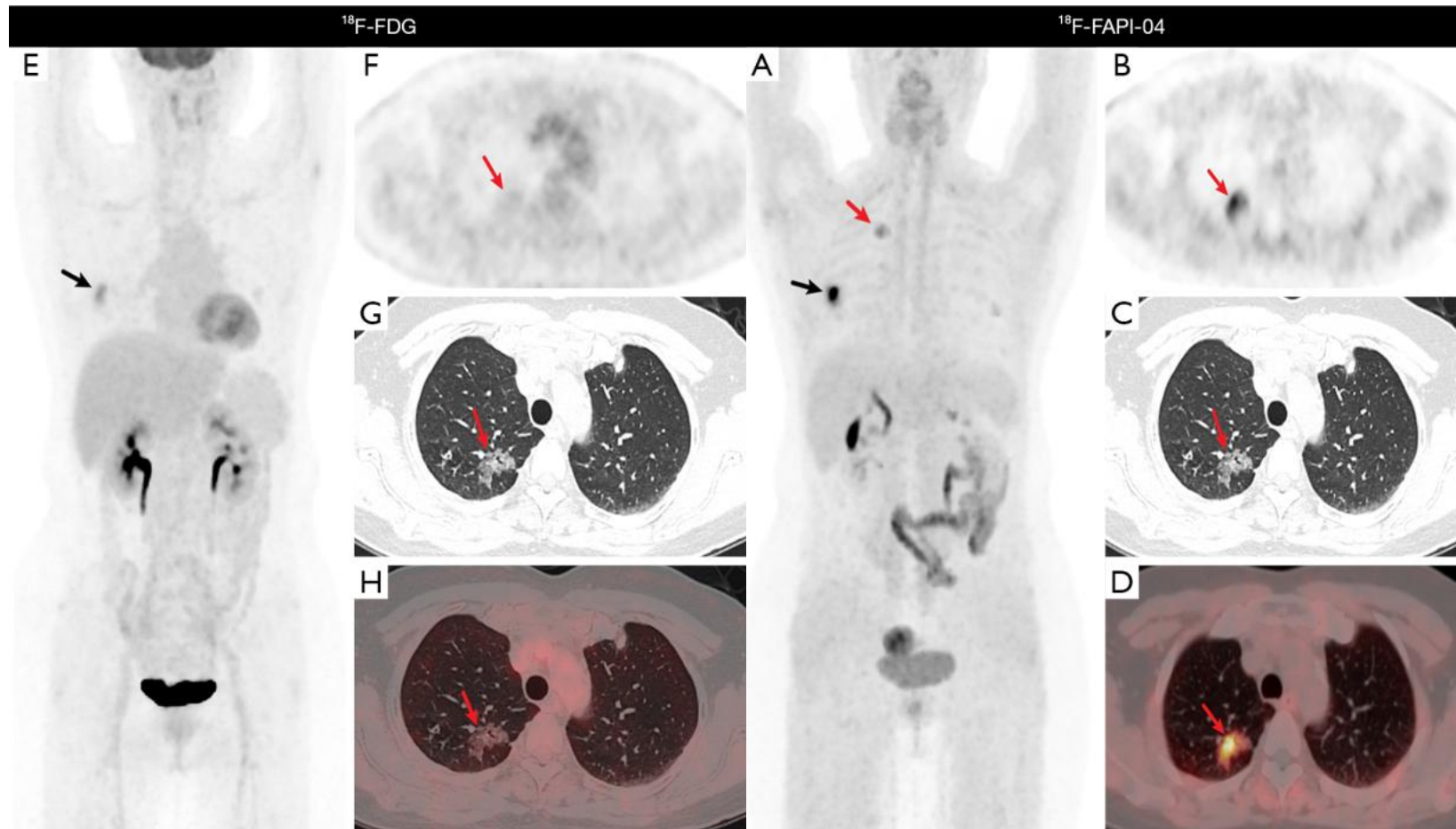
WHAT CAN BE VISUALIZED?

- 1 Metabolism & Perfusion**
[¹⁸F]FDG → glucose metabolism; [¹⁵O]H₂O → perfusion
- 2 Transport & Metabolic pathways**
Methionine/FET → amino-acid transport
- 3 Receptors**
DOTATATE → SSTR; GRPR peptides → GRPR
- 4 Enzymes & Cell-surface targets**
PSMA ligands → PSMA
- 5 Protein distribution / Enzyme localisation**
Labelled proteins/enzymes → their biodistribution/localisation
- 6 Cell-surface proteins**
Trastuzumab → HER2; anti-CD20 → CD20
- 7 Gene expression / Cell tracking / Microenvironment**
Oligos → Nucleic-acid targets; Cells → Migration; Nanoparticles → Microenvironment

Prerequisites of Radiopharmaceutical

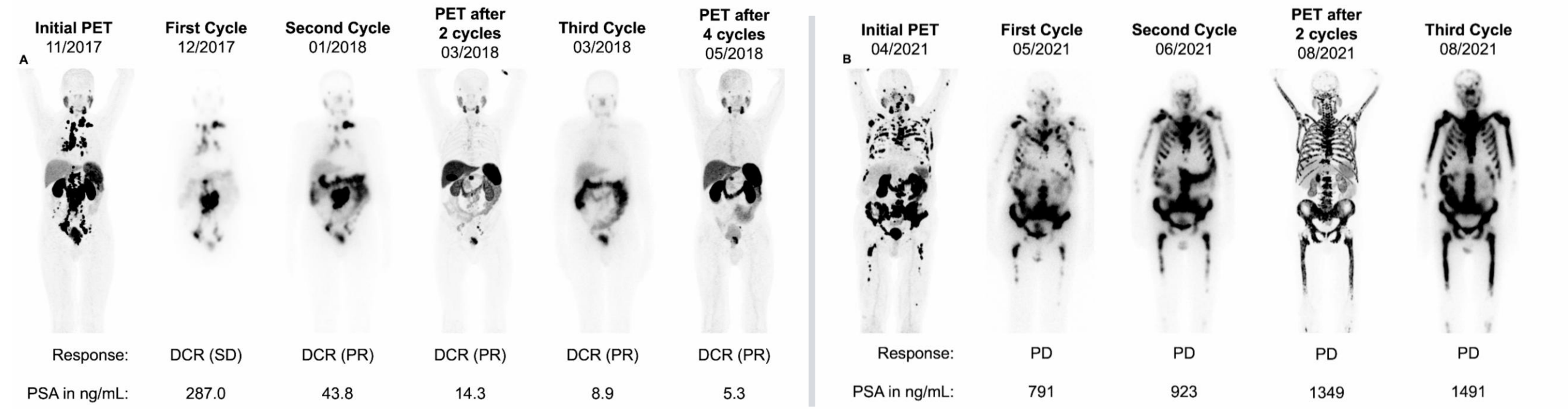
Clinical relevance	Answers a meaningful diagnostic or therapeutic question
Target selectivity	Target is abundant and accessible in diseased tissue but limited in important healthy organs
High affinity	Strong binding at the very low concentrations used for radiopharmaceuticals
Specific binding	Uptake is target-mediated and can be reduced in a blocking experiment
High target uptake	A sufficient fraction of administered activity reaches the intended tissue
Low nonspecific uptake	Minimal binding to unrelated proteins, membranes and healthy tissues
Favourable pharmacokinetics	Reaches the target efficiently and clears appropriately from blood and background tissues
High target-to-background ratio	Produces clear images or selective therapeutic irradiation
Adequate target retention	Remains at the target long enough for imaging or therapy
Suitable clearance	Preferably rapid and predictable elimination without excessive retention in kidneys, liver or other critical organs
Metabolic stability	Does not rapidly form radioactive metabolites with unwanted biodistribution
Appropriate lipophilicity and charge	Compatible with the required membrane passage, organ distribution and excretion
Low pharmacological mass	Diagnostic doses should not significantly disturb the process being measured
Low toxicity and immunogenicity	Vector, precursor, chelator, excipients and impurities must be safe

➤ Changing the tracer changes what becomes visible!



LIANG, H., HUANG, Q., HE, Y., MAI, Y., CHEN, Z., WANG, B., FANG, N., HU, J., LI, X., ZHANG, N., LIU, E., LI, X.. Comparison of the diagnostic accuracy between ^{18}F -FAPI-04 PET/CT and ^{18}F -FDG PET/CT in the clinical stage IA of lung adenocarcinoma. *Journal of Thoracic Disease*, North America, 17, feb. 2025. Available at: <<https://jtd.amegroups.org/article/view/96974>>. Date accessed: 03 Aug. 2026.

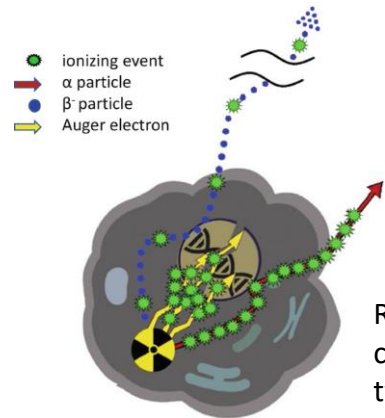
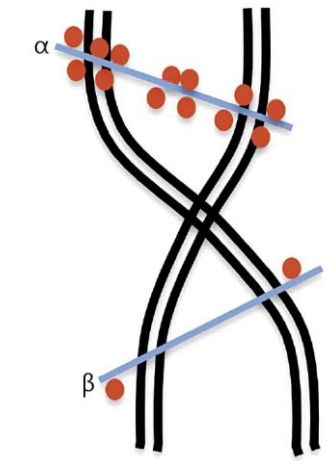
➤ See what you treat and treat what you see



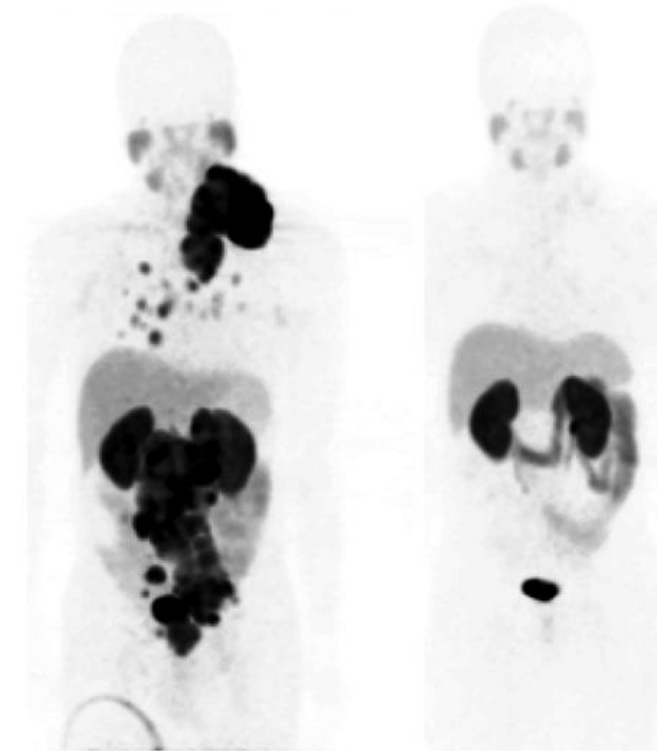
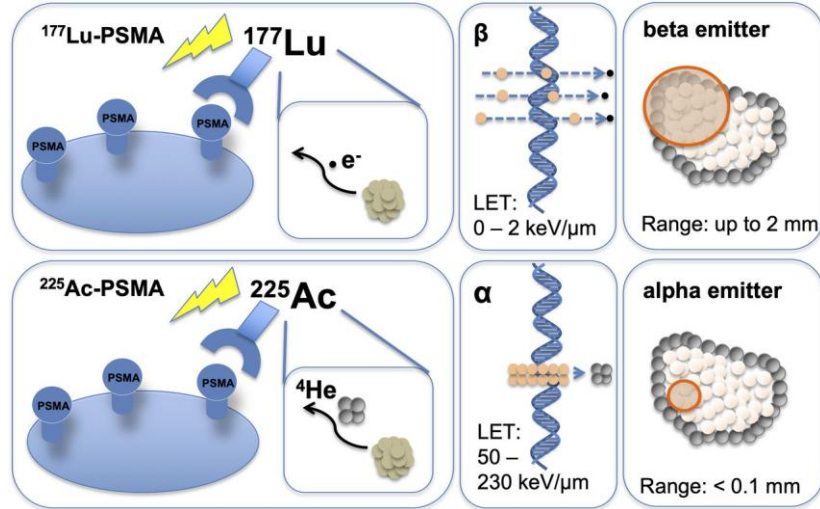
$^{68}\text{Ga}/^{18}\text{F}$ -PSMA PET → confirm PSMA expression → ^{177}Lu -PSMA therapy → post-therapy imaging

Ventura, D., Rassek, P., Schindler, P. et al. Early treatment response assessment with [^{177}Lu]PSMA whole-body-scintigraphy compared to interim PSMA-PET. *Cancer Imaging* **24**, 126 (2024). <https://doi.org/10.1186/s40644-024-00773-w>

➤ Targeted Alpha Particle Therapy



Range of different emissions in comparison to the size of a typical cell



^{68}Ga -PSMA studies in a patient with metastatic prostate cancer prior to (left) and after (right) ^{225}Ac -PSMA TAT. There was an excellent functional response to treatment with concurrent clinical and biochemical response (prostate-specific antigen decreased from 1,301 to 0.05 ng/L).

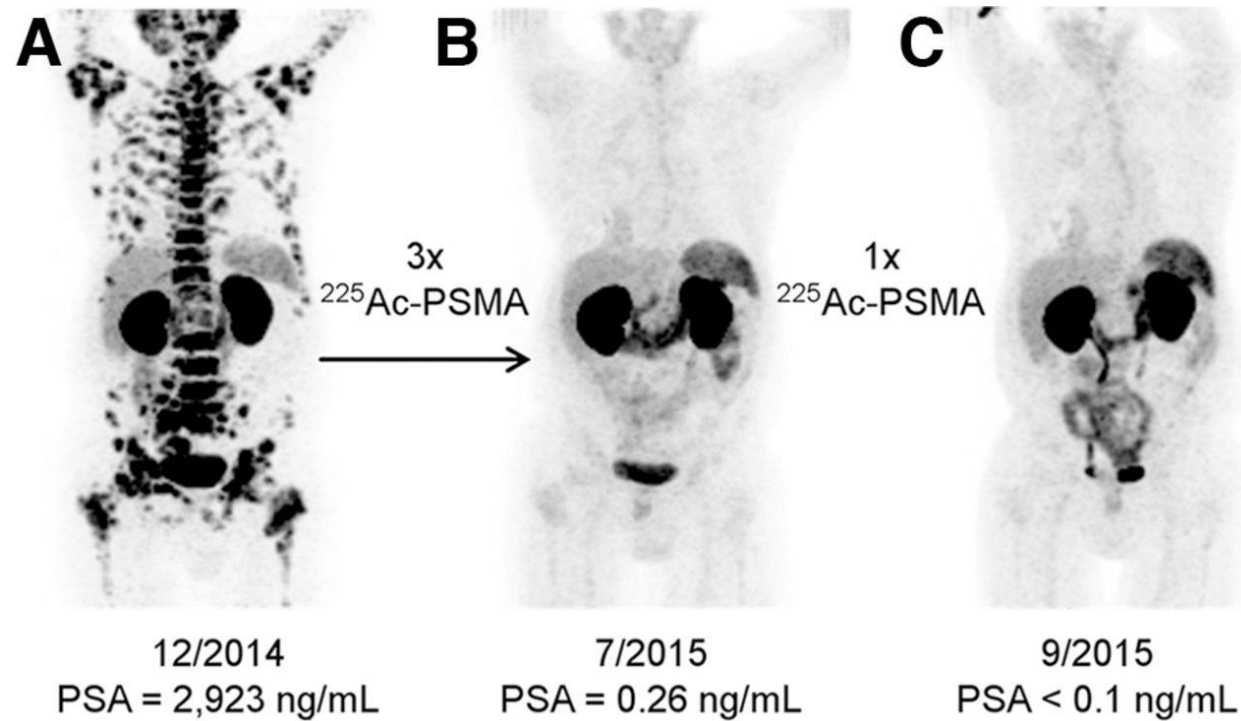
Images courtesy of Prof. Mike Sathekge, Department of Nuclear Medicine, Steve Biko Academic Hospital, University of Pretoria, Pretoria, South Africa. PSMA, prostate-specific membrane antigen; TAT, targeted alpha particle therapy.

Navalkisoor, S.; Grossman, A., Targeted Alpha Particle Therapy for Neuroendocrine Tumours: The Next Generation of Peptide Receptor Radionuclide Therapy. *Neuroendocrinology* 2019, 108 (3), 256-264.

Benedikt Feierecker, Clemens Kratochwil, Hojjat Ahmadzadehfar, Alfred Morgenstern, Matthias Eiber, Ken Herrmann and Kelsey L. Pomykala *Journal of Nuclear Medicine* May 2023, 64 (5) 685-692; DOI: <https://doi.org/10.2967/jnumed.122.265353>

Hoehr, C. (2023). The Next Generation of Therapeutic Radionuclides. In: Bodei, L., Lewis, J.S., Zeglis, B.M. (eds) *Radiopharmaceutical Therapy*. Springer, Cham. https://doi.org/10.1007/978-3-031-39005-0_23

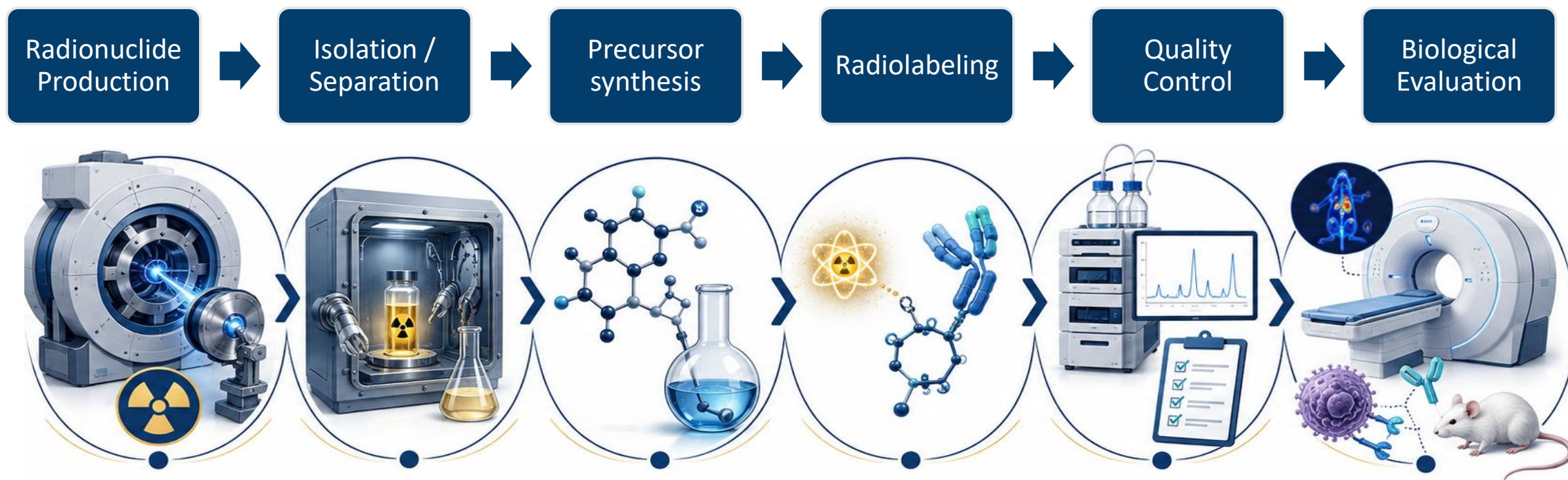
➤ Targeted Alpha Particle Therapy For Prostate Tumors



^{68}Ga -PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 month after third cycle of ^{225}Ac -PSMA-617 (B), and restaging 2 month after one additional consolidation therapy (C).

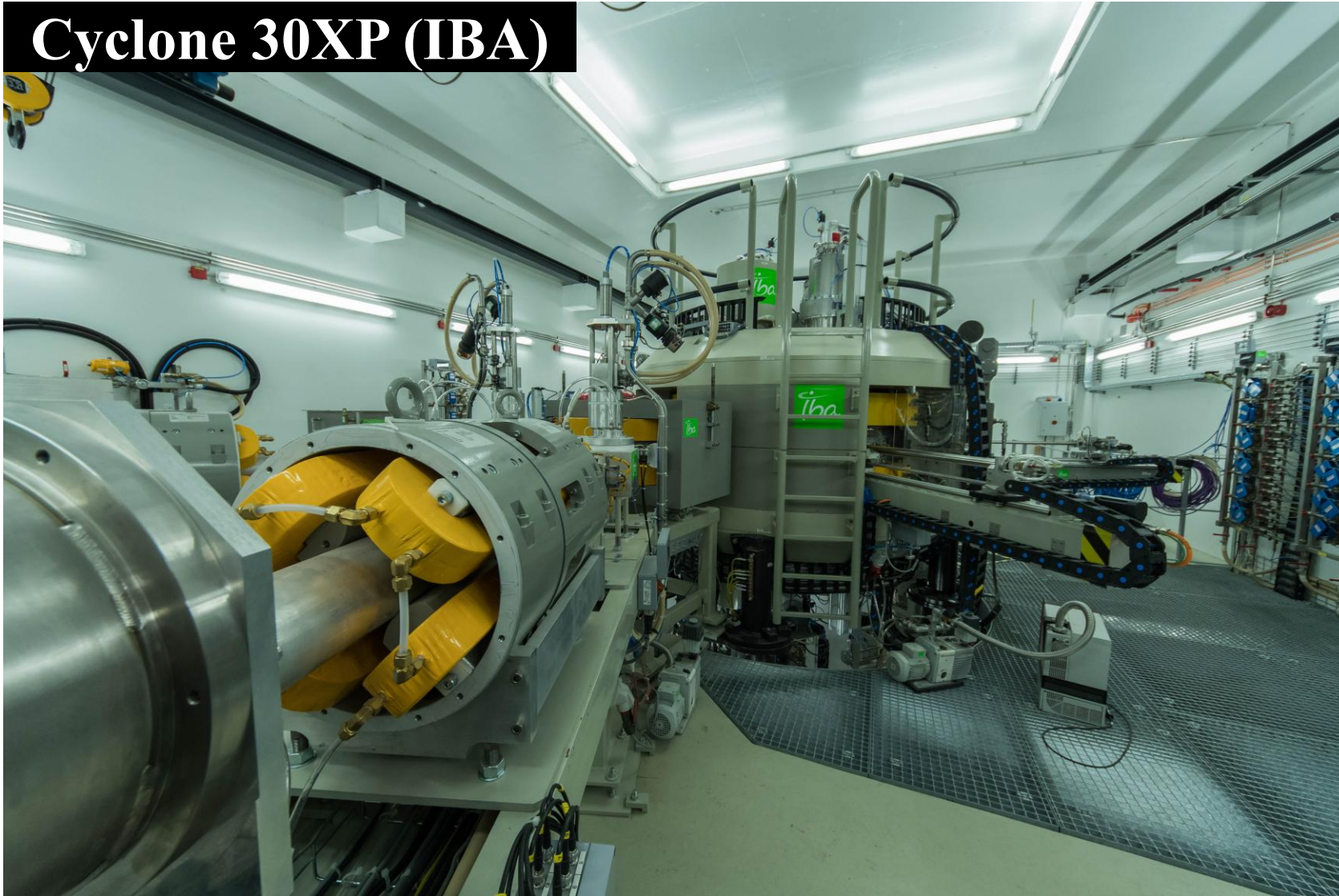
Clemens Kratochwil, Frank Bruchertseifer, Frederik L. Giesel, Mirjam Weis, Frederik A. Verburg, Felix Mottaghy, Klaus Kopka, Christos Apostolidis, Uwe Haberkorn, Alfred Morgenstern. *Journal of Nuclear Medicine* Dec 2016, 57 (12) 1941-1944; DOI: 10.2967/jnumed.116.178673

Workflow



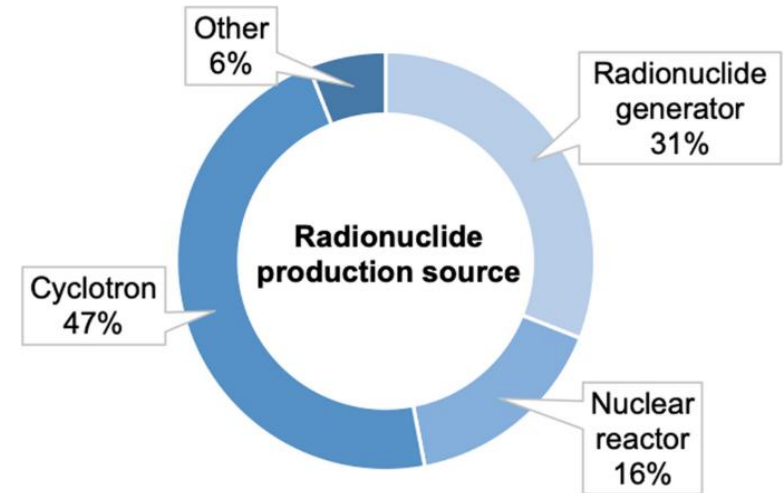
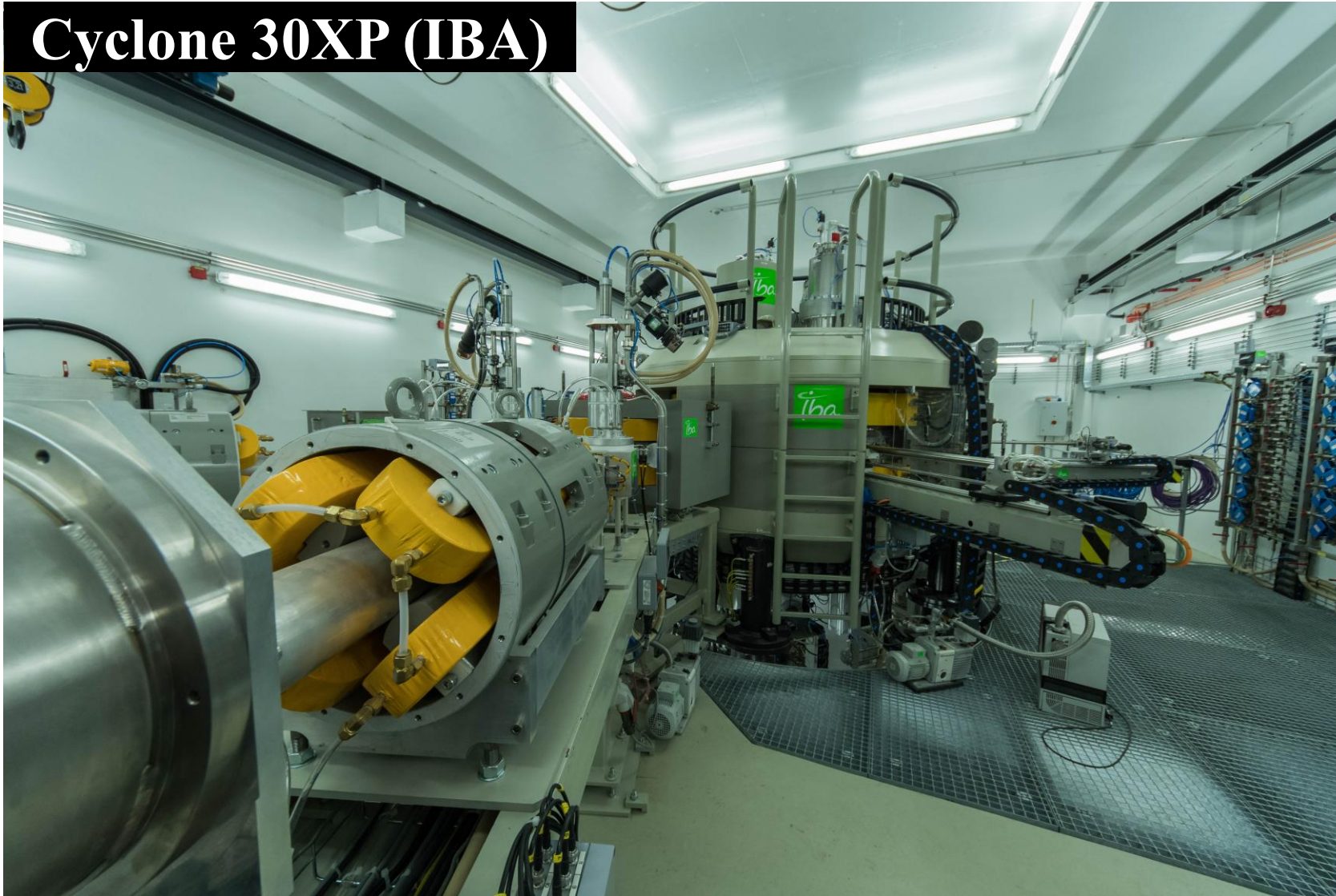
Radionuclide Production

Cyclone 30XP (IBA)

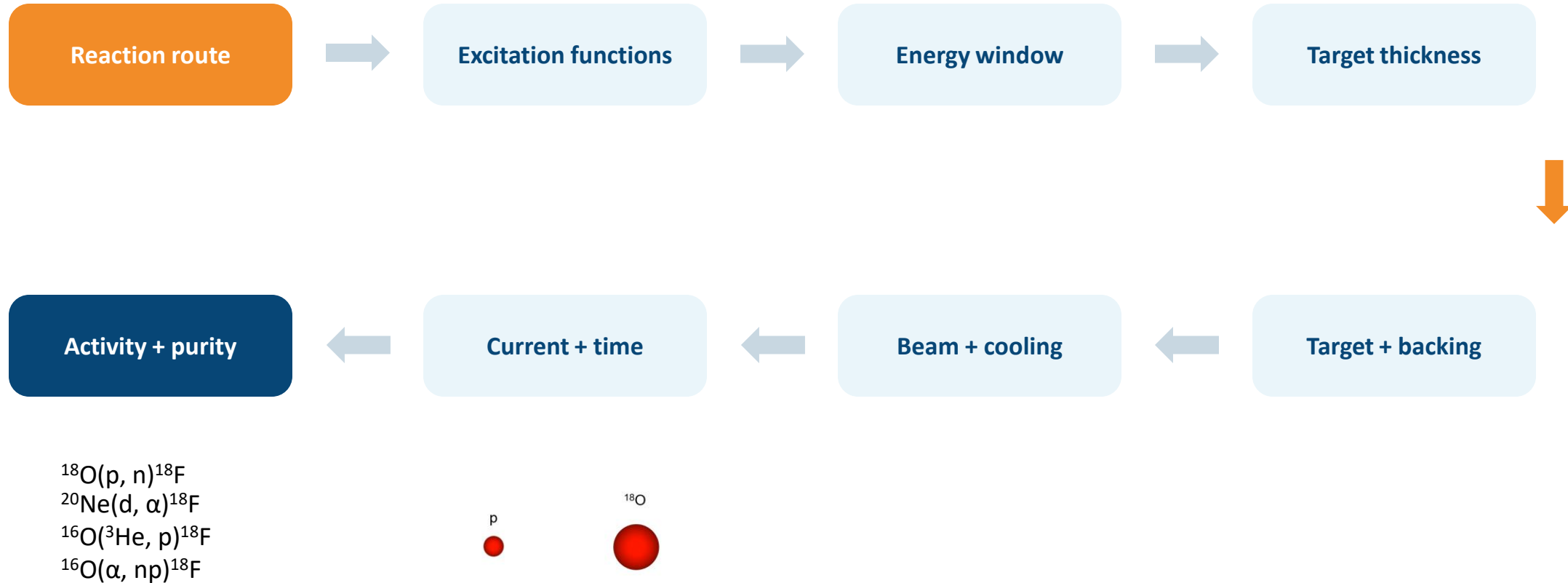


Radionuclide Production

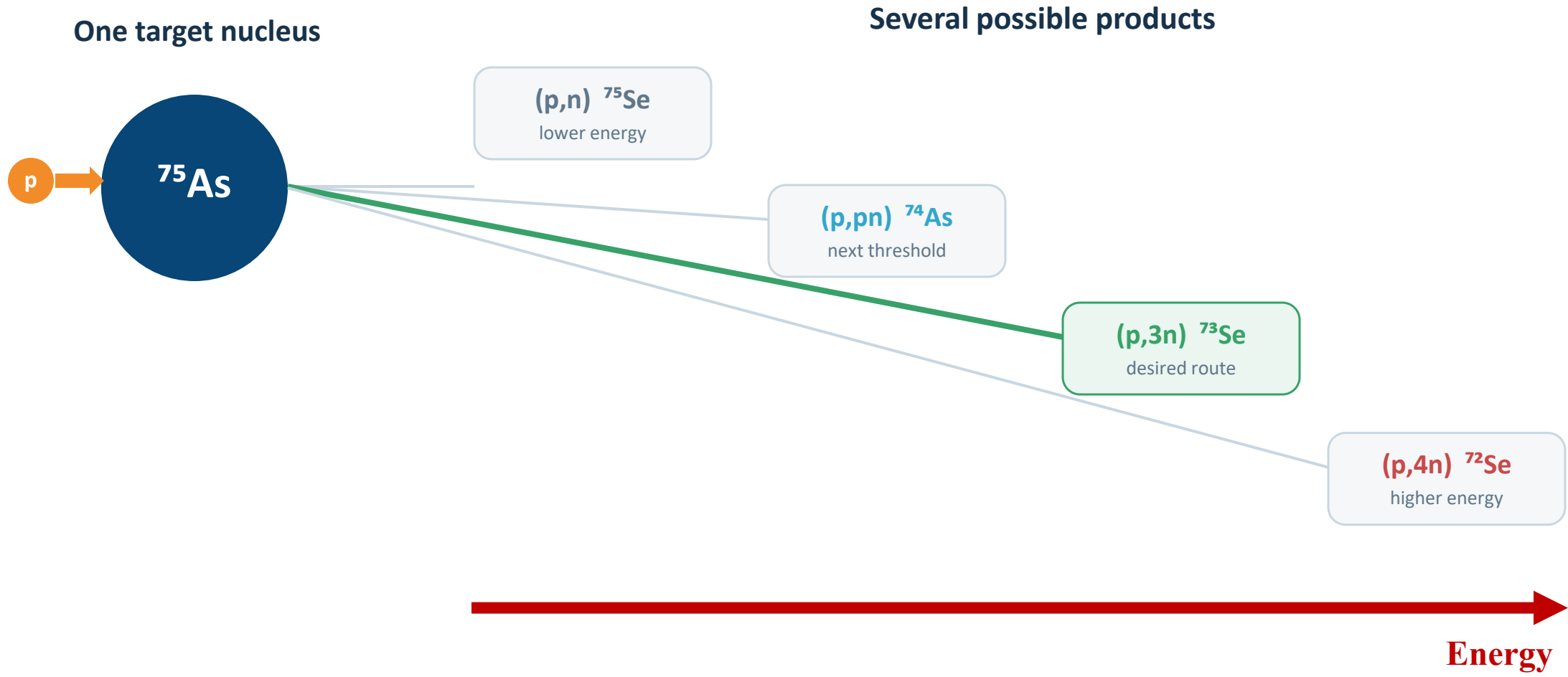
Cyclone 30XP (IBA)



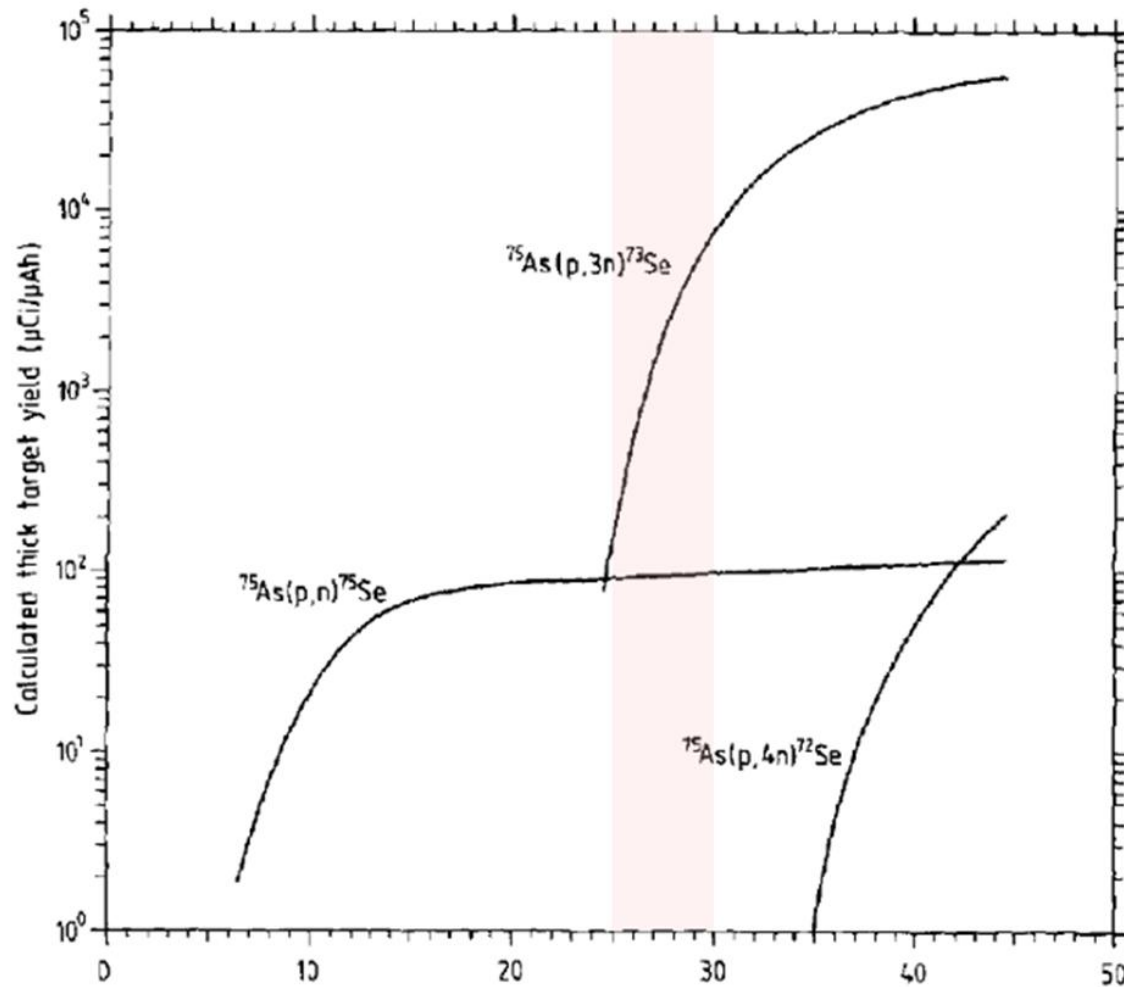
Radionuclide Production



Radionuclide Production



Radionuclide Production



Suitable energy window

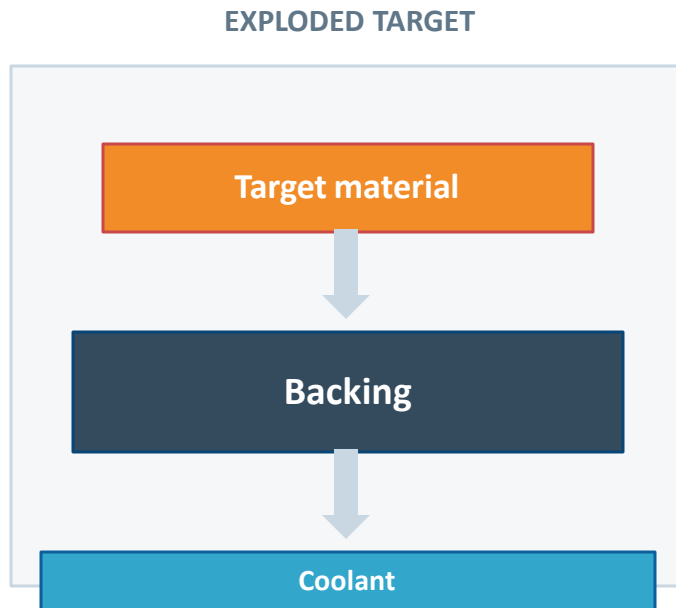
High ^{73}Se production while the other channels remain suppressed

Why impurities matter

^{72}Se , ^{73}Se and ^{75}Se share the same chemistry and cannot be separated conventionally

Energy controls radioisotopic purity.

Radionuclide Production



Nuclear

- Isotopic enrichment
- Trace-element purity
- Target density

Thermal / mechanical

- Conductivity & melting point
- Vapour pressure
- Adhesion & expansion

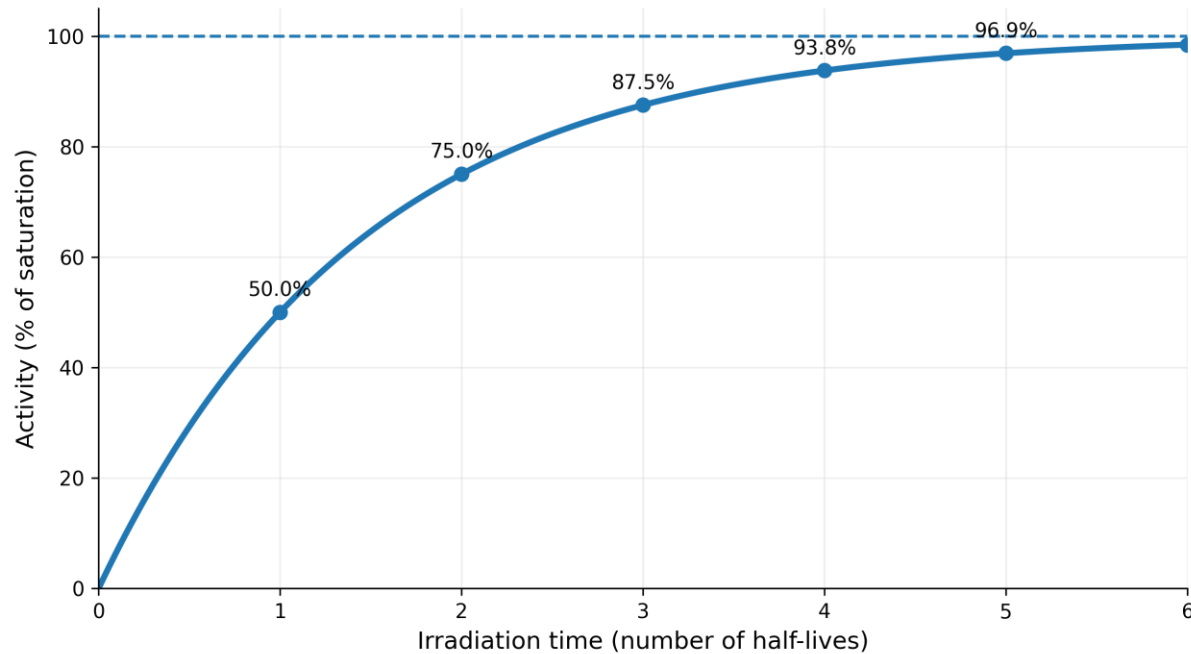
Chemical

- Rapid dissolution
- Product separation
- Target recovery

No backing is universally best: thermal performance, activation and chemistry must be balanced.

Radionuclide Production

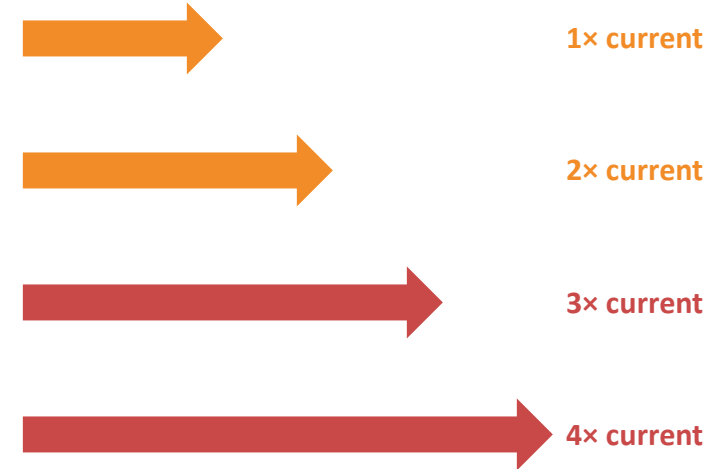
Increase irradiation time



$$\frac{A(t)}{A_{sat}} = 1 - e^{-\lambda t}$$

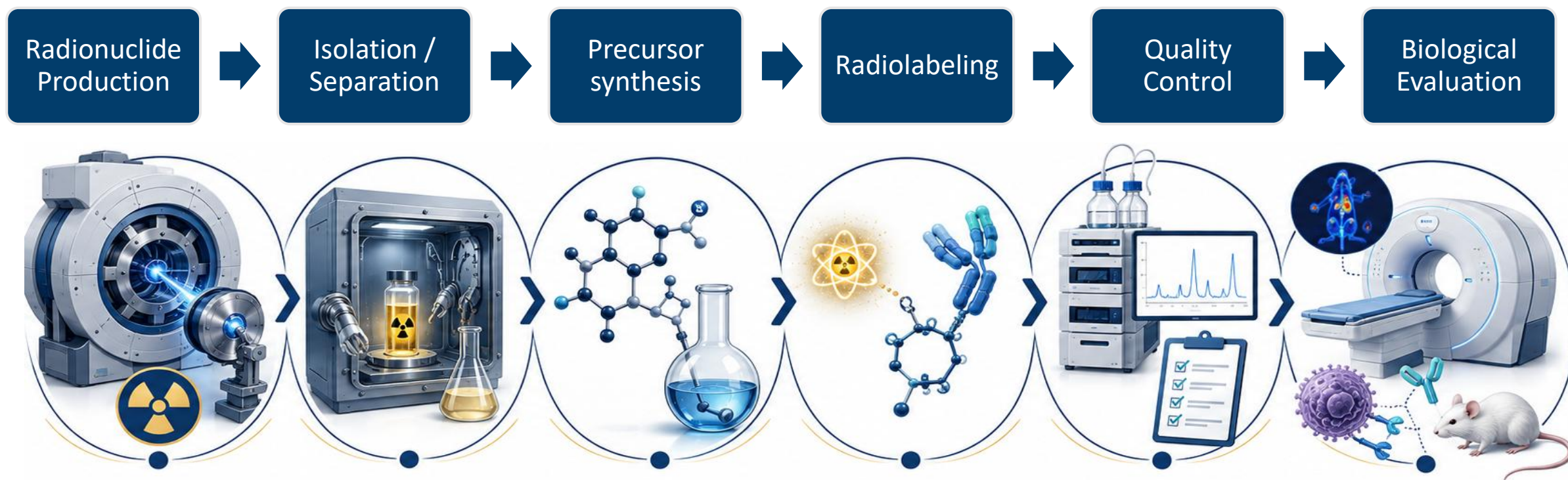
Increase beam current

raises production rate approximately linearly

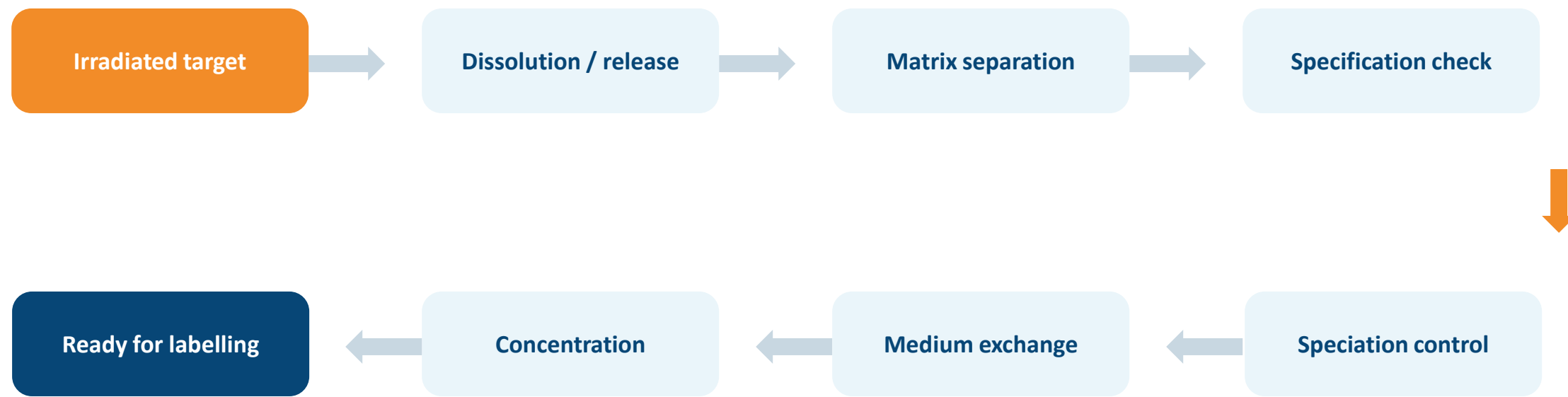


Higher current also raises power density, temperature and failure risk.

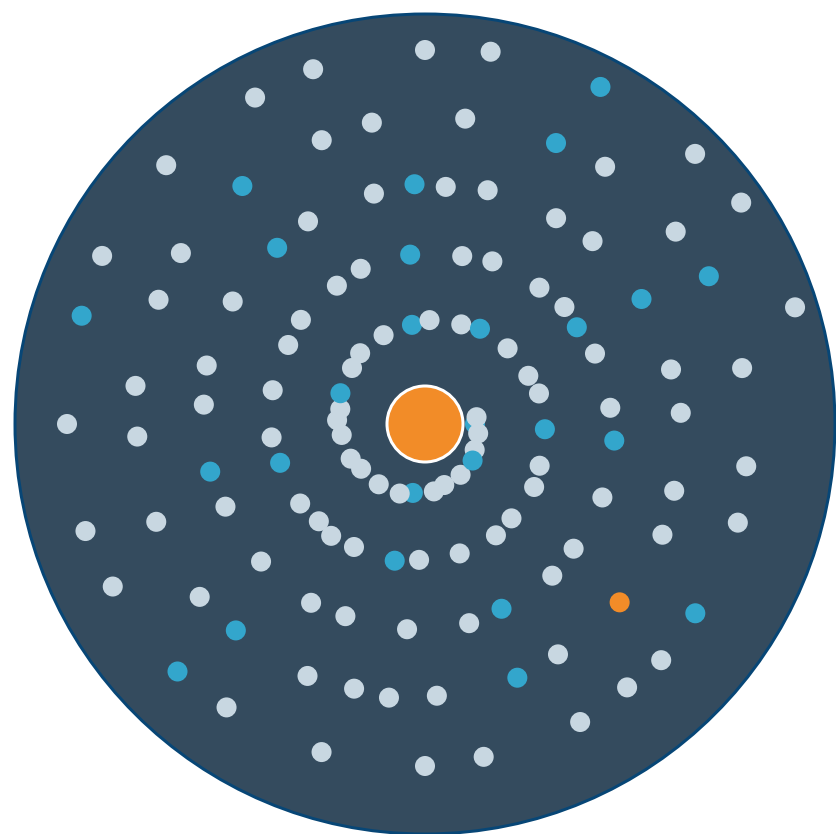
Workflow



Chemical Processing



Chemical Processing



Radioactive
product

Target matrix

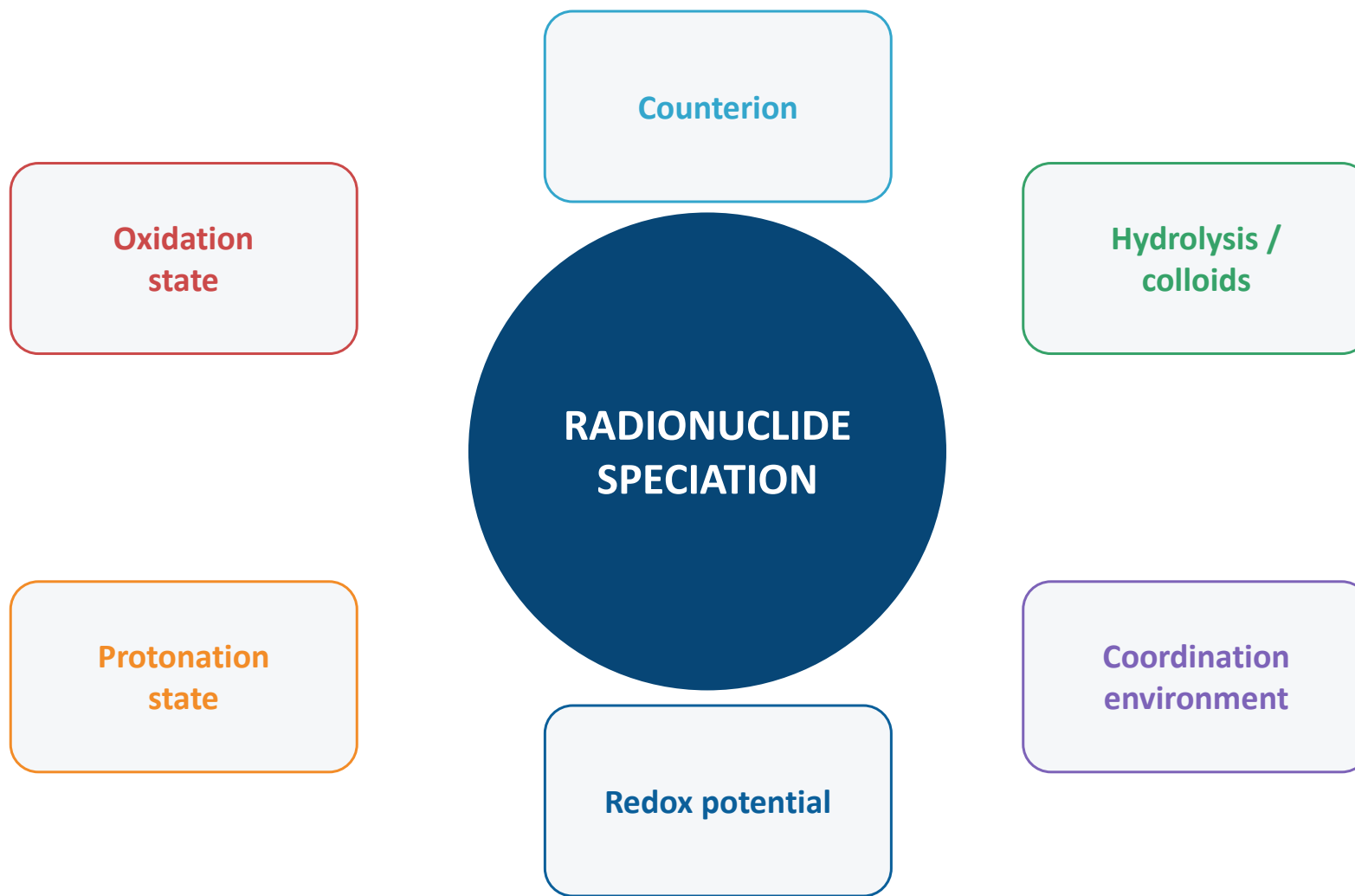
milligrams to grams

Desired radionuclide

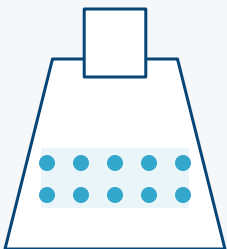
often picogram-to-nanogram mass

Small surface losses and trace-metal contamination
can impair subsequent radiolabeling.

Chemical Processing



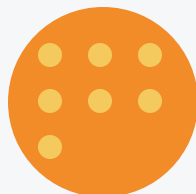
Chemical Processing



Soluble salt

Water or dilute acid

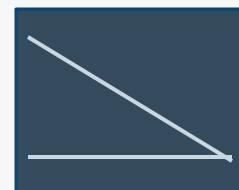
rapid dissolution



Metal oxide

Acid + heat or ligands

rate depends on density



Metal

Strong or oxidizing acid

backing compatibility matters

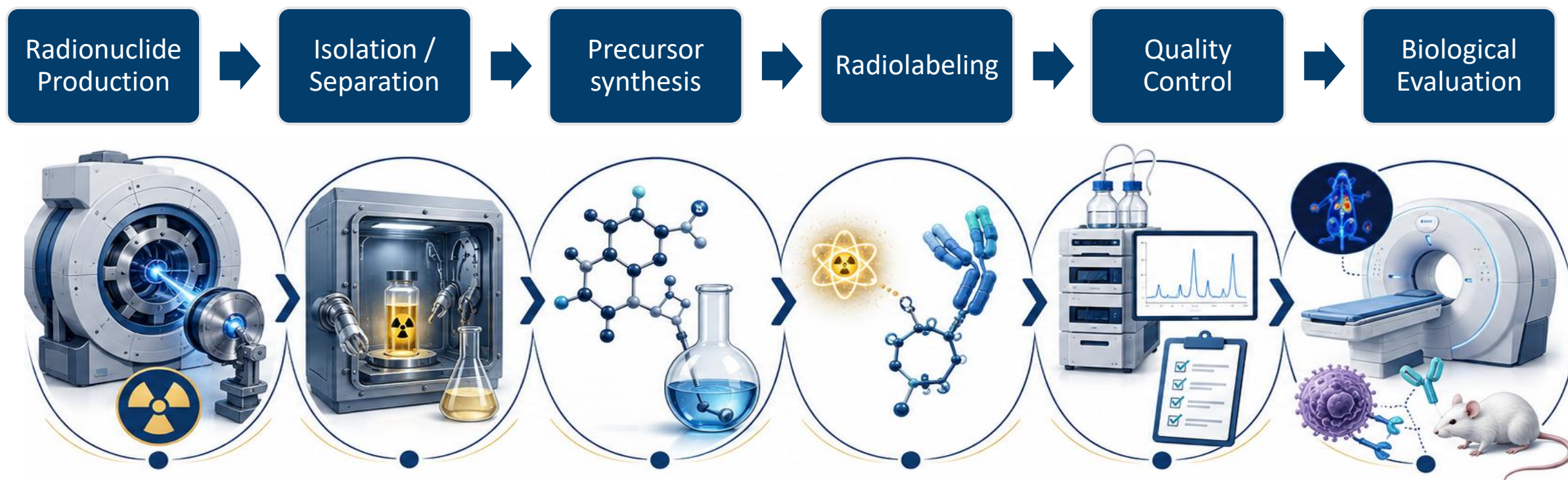


Volatile product

Thermal release /
distillation

matrix may remain intact

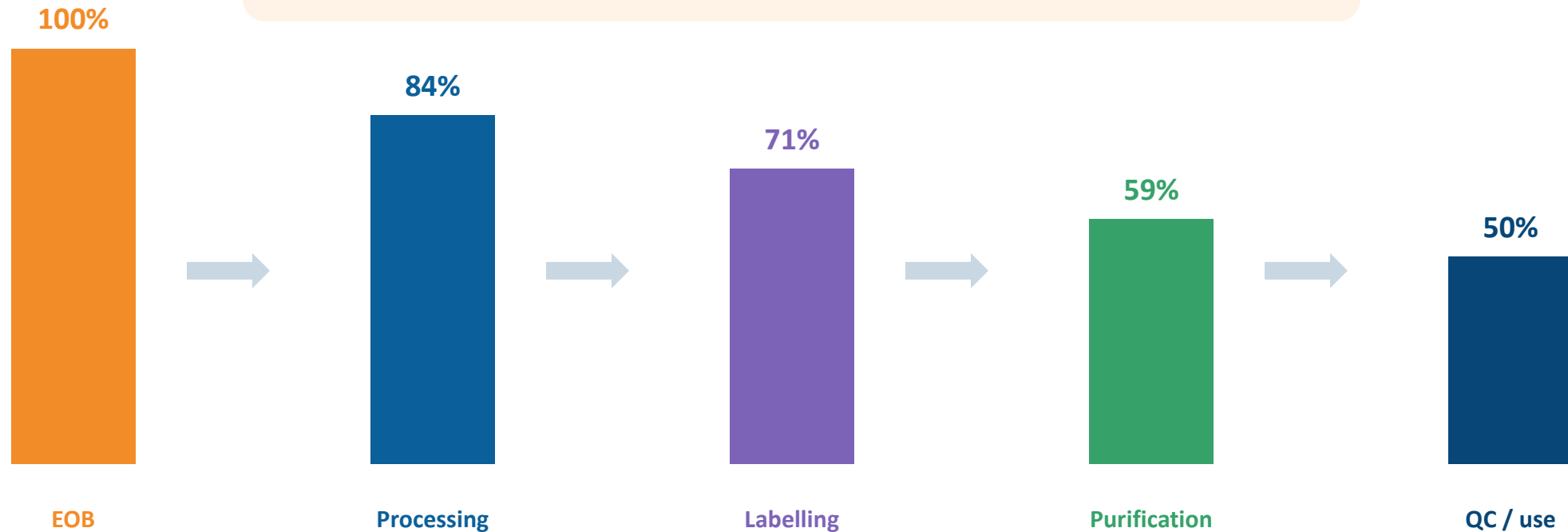
Workflow



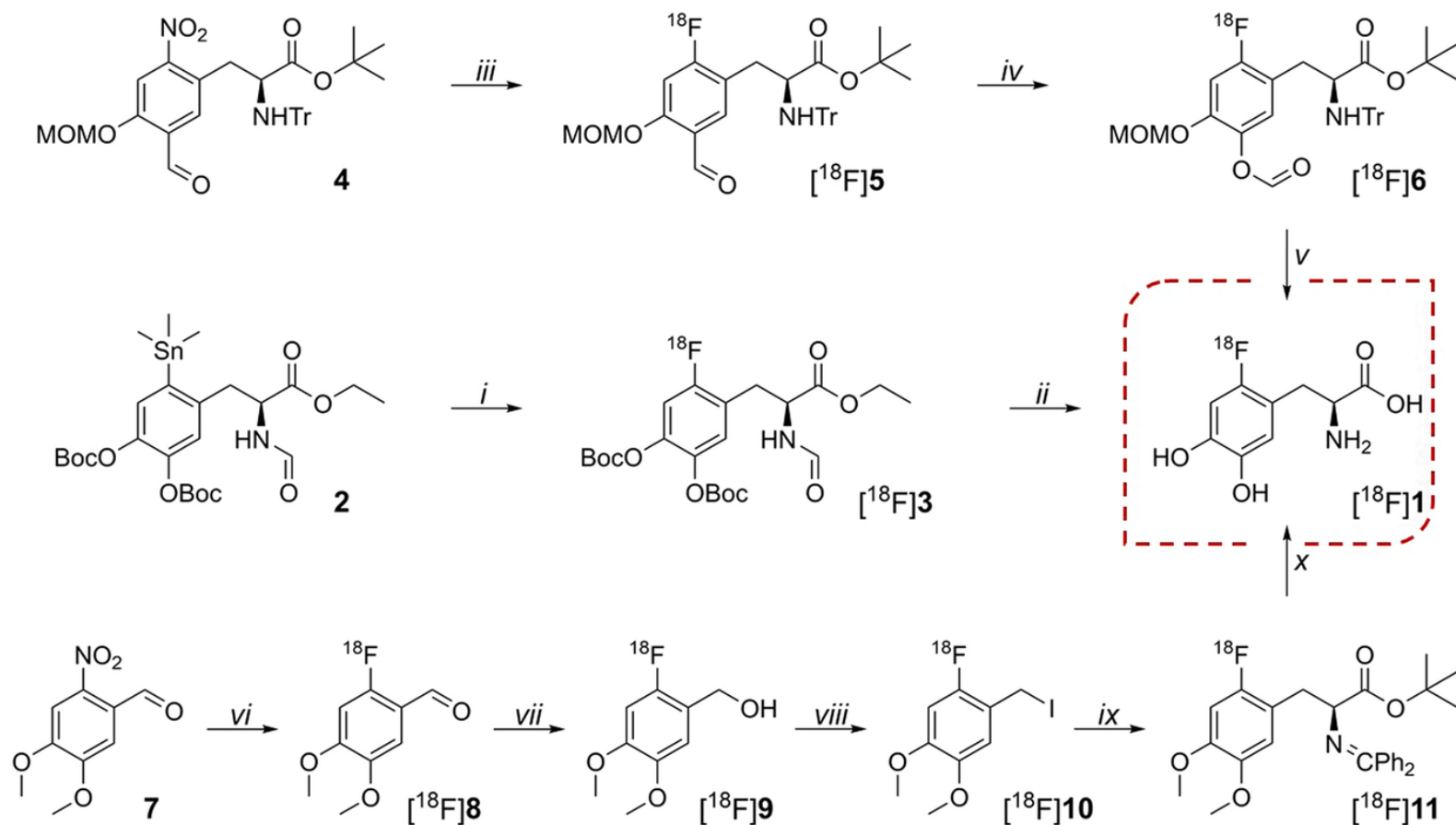
Precursor Synthesis

$$A_{\text{Final}} = A_{\text{EOB}} \times 2^{(-t(\text{total}) / T_{1/2})} \times \eta_{\text{process}} \times \eta_{\text{labeling}} \times \eta_{\text{purifying}}$$

Decay loss and chemical recovery multiply; they do not occur independently.

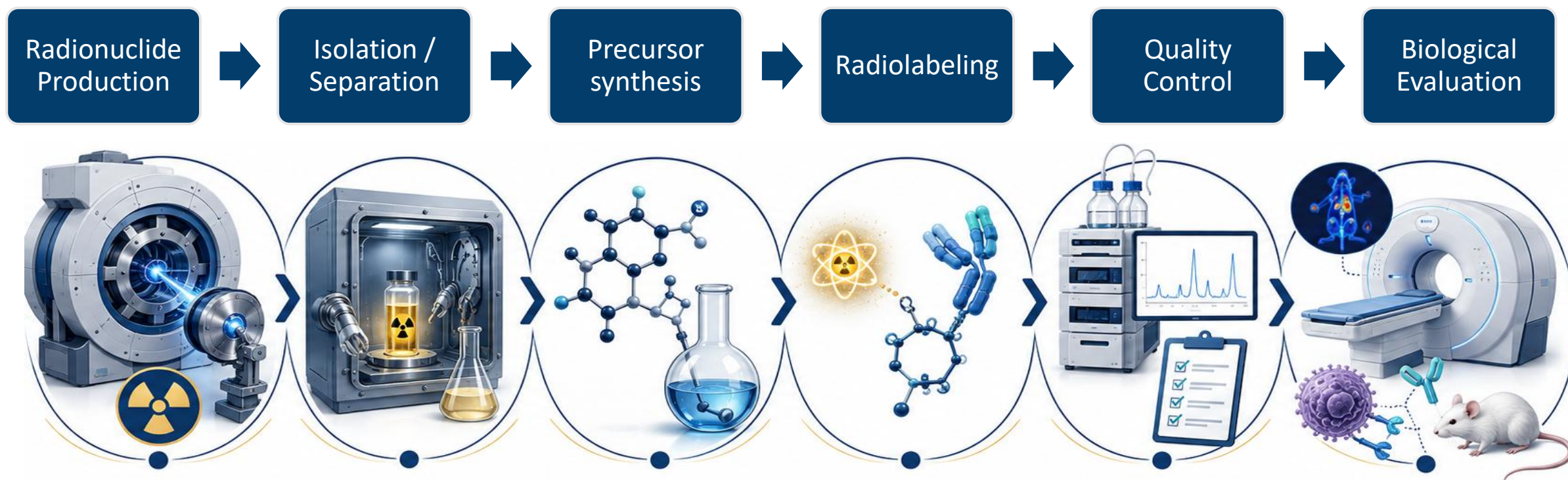


Precursor Synthesis



The three different synthetic pathways to $[^{18}\text{F}]\mathbf{1}$. *i*, $[^{18}\text{F}]\text{F}_2$, CHCl_3 , RT; *ii*, 57% HI, 150 °C; *iii*, $[^{18}\text{F}]\text{TBAF}$, DMSO, 110 °C; *iv*, *m*-CPBA, MeCN, 55 °C; *v*, 30% HCl, EtOH, 50 °C; *vi*, $[^{18}\text{F}]\text{KF}/\text{K}_{222}$, DMF, 165 °C; *vii*, NaBH_4 , H_2O @ tC18, RT; *viii*, 57% HI @ tC18, RT; *ix*, $\text{Ph}_2\text{C}=\text{NCH}_2\text{Boc}$, DCM, cPTC, KOH, -20 °C; *x*, 57% HI, 165 °C..

Workflow



Radiolabeling

pH



Radionuclide and precursor are reactive while the molecule remains stable.

TEMPERATURE



Reach the required conversion within the available time without damaging the product.

PRECURSOR AMOUNT



Use enough for fast, reproducible labelling—but no more than necessary.

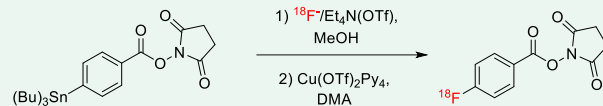
Radiolabeling

DIRECT COVALENT LABELLING



The radionuclide becomes part of the molecular skeleton.

INDIRECT: PROSTHETIC GROUP



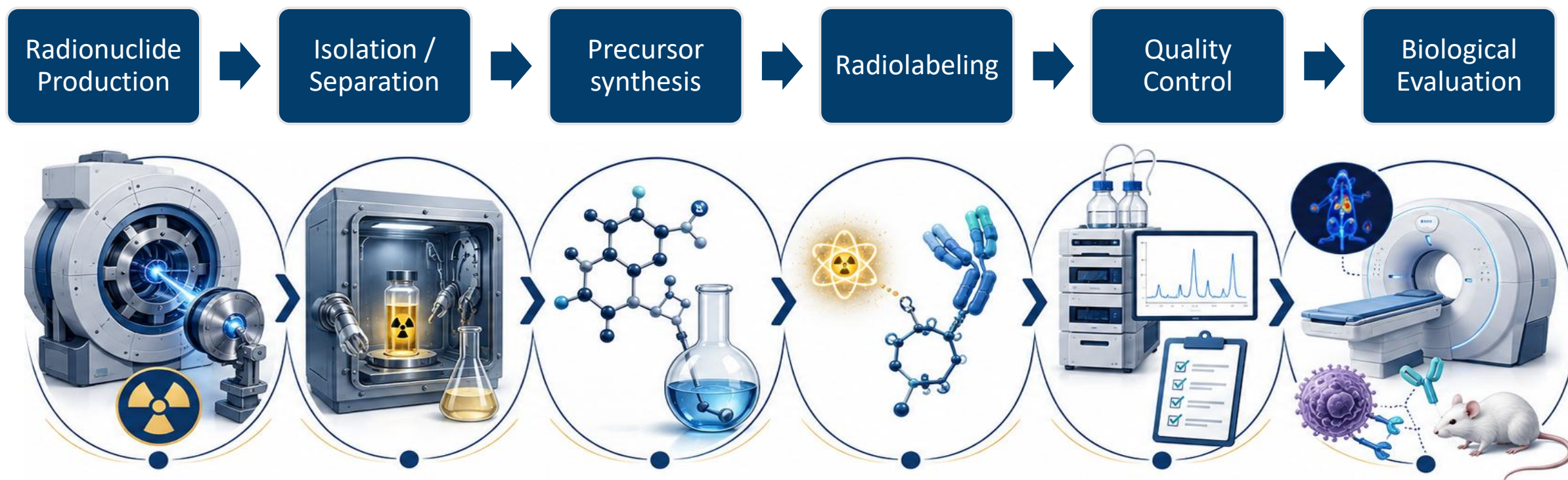
A small labelled synthon is conjugated under mild conditions.

RADIOMETAL CHELATION



M* radiometal • C chelator • L linker • V targeting vector

Workflow



Quality Control

CHEMICAL PURITY

What nonradioactive material remains?

precursor • solvents • metals • by-products

HPLC–UV / LC–MS / GC / ICP–MS

RADIOCHEMICAL PURITY

Where is the desired radionuclide chemically?

free [^{73}Se] species vs [^{73}Se]tracer

radio-HPLC / radio-TLC / SEC

RADIONUCLIDIC PURITY

Which radionuclides produce the activity?

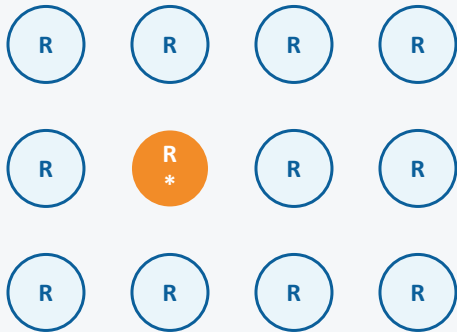
^{75}Se • ^{72}Se • ^{74}As

gamma spectrum / measured half-life

Quality Control

HIGH MOLAR ACTIVITY

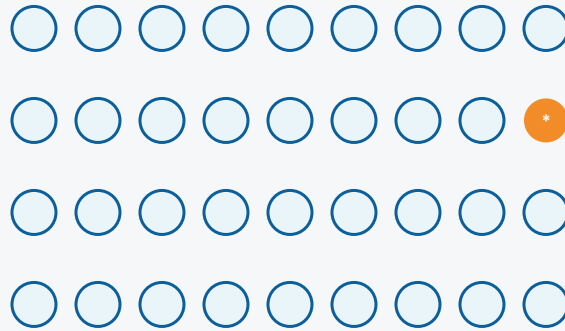
1 GBq



few molecules

LOW MOLAR ACTIVITY

1 GBq



many molecules

$$A_m = \text{activity} / \text{amount}$$

Bq/mol • commonly GBq/ μ mol

Why biology cares

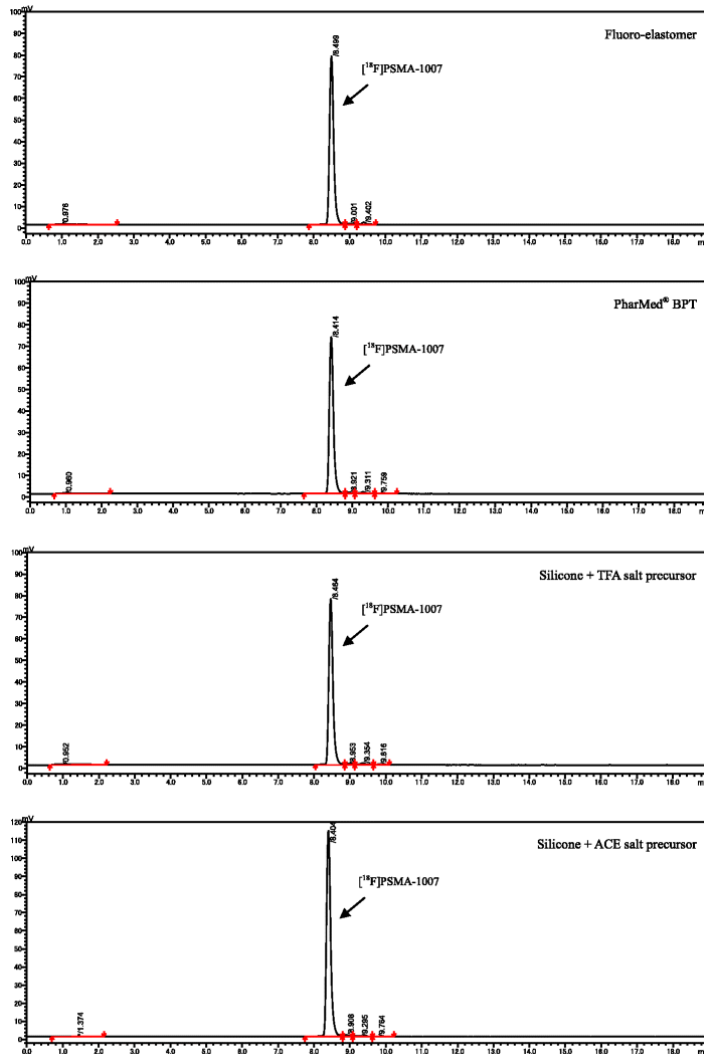
Non-radioactive ligand can occupy a finite number of receptors before the radiotracer arrives.

More precursor lowers A_m only when competing or nonradioactive material remains in the final sample.

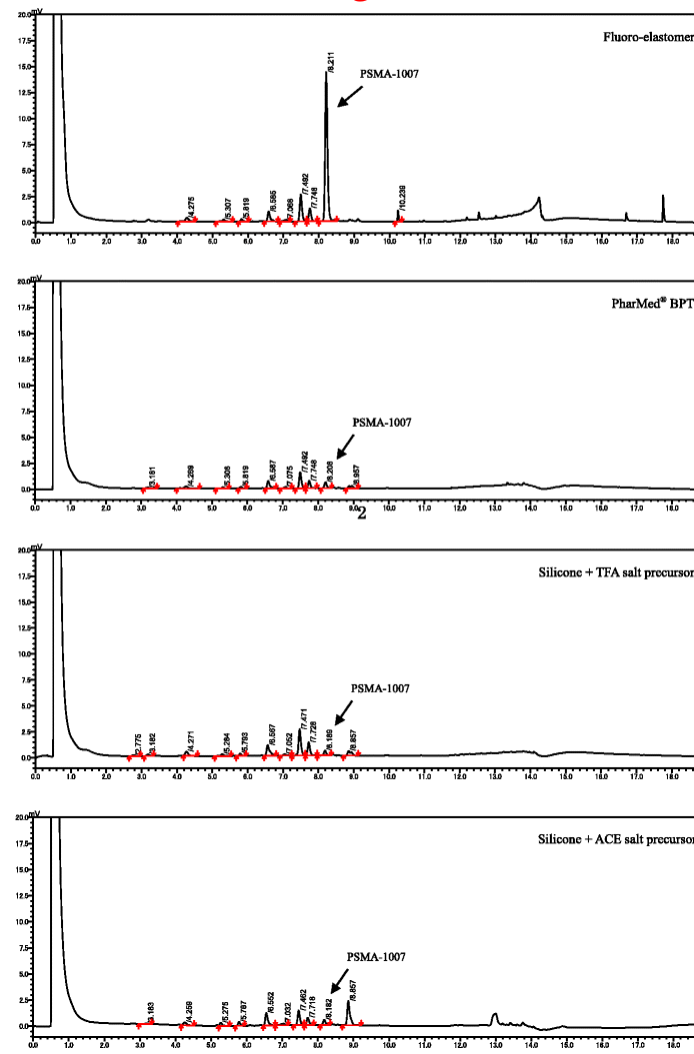
Quality Control

(a)

Radio-chromatograms of [^{18}F]PSMA-1007



UV-chromatograms of the PSMA-1007



Residual precursor lowers A_m only when competing or nonradioactive product remains in the final sample.

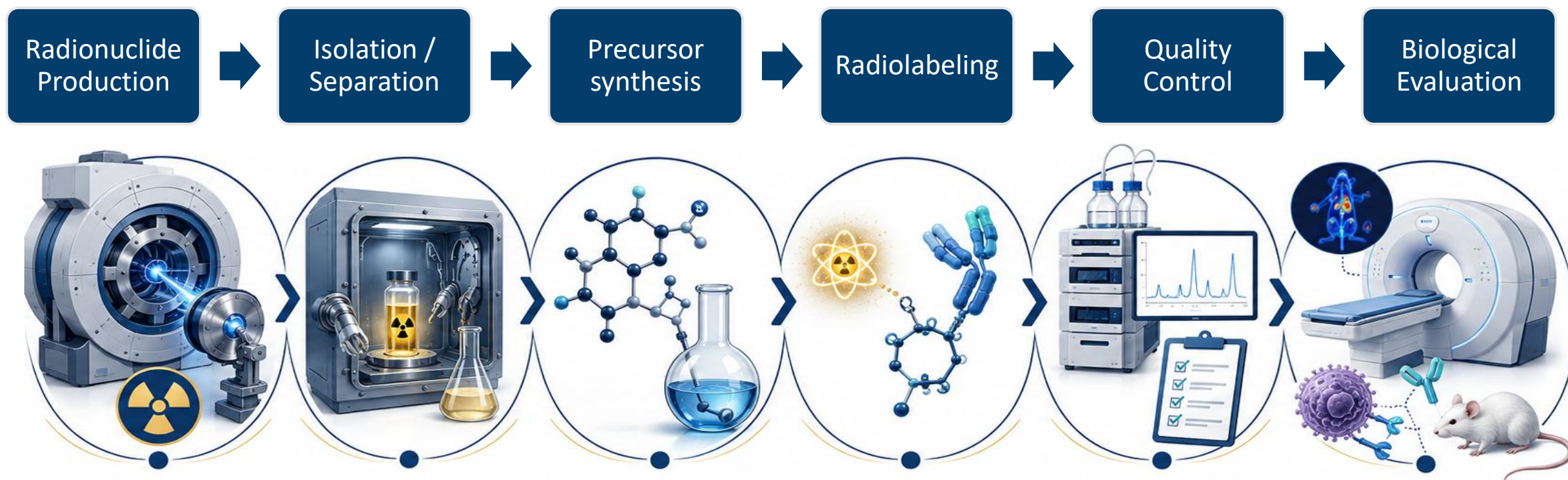
Fluoro-elastomer: 46 GBq/ μmol $\rightarrow$ low A_m

PharMed BPT: 1184 GBq/ μmol $\rightarrow$ high A_m

Silicone: 1411 GBq/ μmol $\rightarrow$ high A_m

Naka, S., Watabe, T., Kurimoto, K. *et al.* Automated [^{18}F]PSMA-1007 production by a single use cassette-type synthesizer for clinical examination. *EJNMMI radiopharm. chem.* **5**, 18 (2020). <https://doi.org/10.1186/s41181-020-00101-0>

Workflow



Biological Evaluation

QC PASS

- ✓ Correct radionuclide
- ✓ Correct chemical form
- ✓ Acceptable formulation



Metabolic Stability

Serum / plasma

Does the parent tracer remain intact?

Protein binding

What fraction remains freely available?

**Challenge
molecules**

Does the label survive realistic competition?

The final biological question

Does the radioactive signal behave like the biology of the target?

Biological Evaluation

n-OCTANOL



radioactivity distribution

BUFFER pH 7.4

$$\log D_{7,4} = \log_{10}(C_{\text{octanol}} / C_{\text{buffer}})$$

LIPOPHILICITY

membrane permeability

nonspecific membrane binding

renal vs hepatobiliary clearance

blood–brain barrier potential

PLASMA PROTEIN BINDING

protein-bound

free fraction

Longer circulation may increase—but free tissue access may decrease.

Biological Evaluation

Blocking

“Does excess ligand remove the signal?”

Specificity / receptor-mediated uptake

Saturation

“How does the tracer fill the receptor pool?”

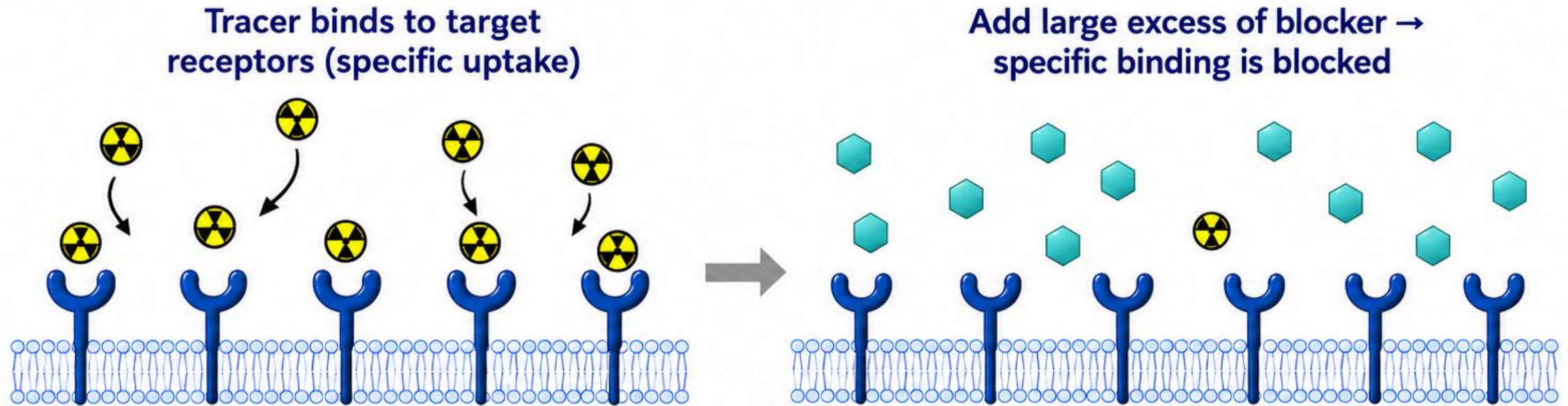
$K_d + B_{max} \rightarrow$ tracer affinity + capacity

Competition

“Can cold molecules fight off the tracer?”

$IC_{50} / K_i \rightarrow$ apparent affinity of competitor

Biological Evaluation, Blocking Experiment



How it works: Measure tracer uptake or binding with and without a large excess of a known blocker or cold ligand.

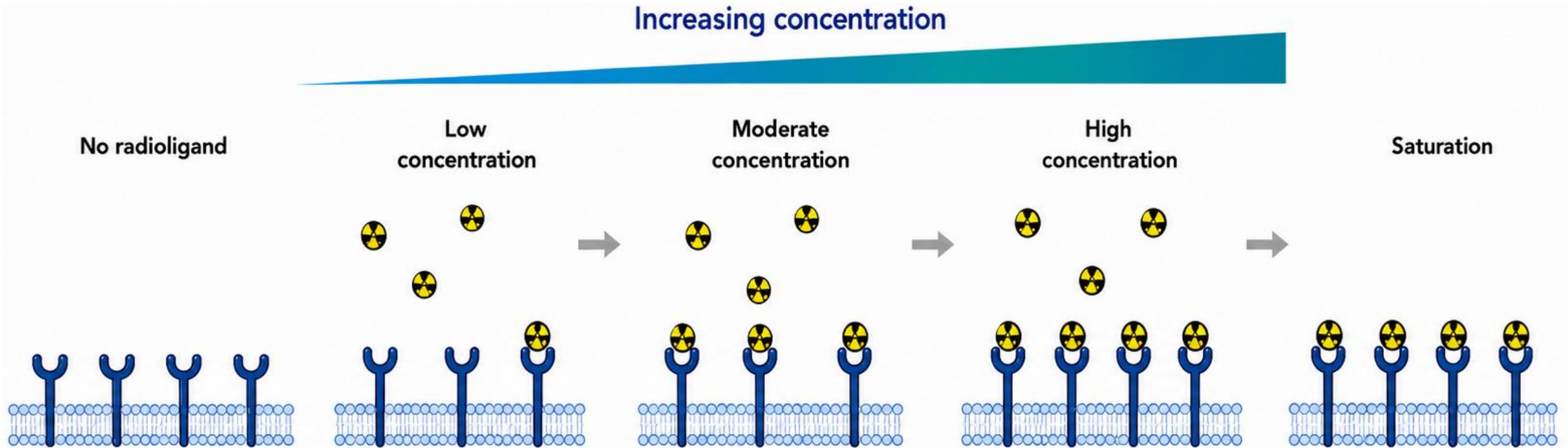


What question it answers: Is the observed signal target-specific or mostly non-specific?



A strong drop after blocking demonstrates receptor-specific uptake.

Biological Evaluation, Saturation assay



How it works: Gradually increase the concentration of the tracer and measure total binding and non-specific binding to determine specific binding.



What question it answers: What is the tracer's affinity for the target and how many binding sites are available?



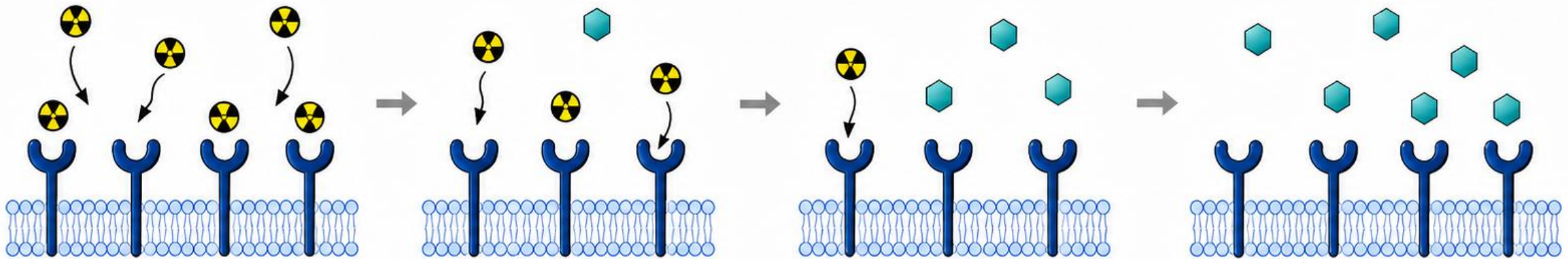
Key outcome: Determines affinity and the number of available binding sites.

K_d = Radioligand Affinity

B_{max} = Available Binding-Site Capacity

Biological Evaluation, Competition Binding

Increasing competitor concentration



How it works: A constant amount of signal is challenged with increasing concentrations of an unlabeled competitor.



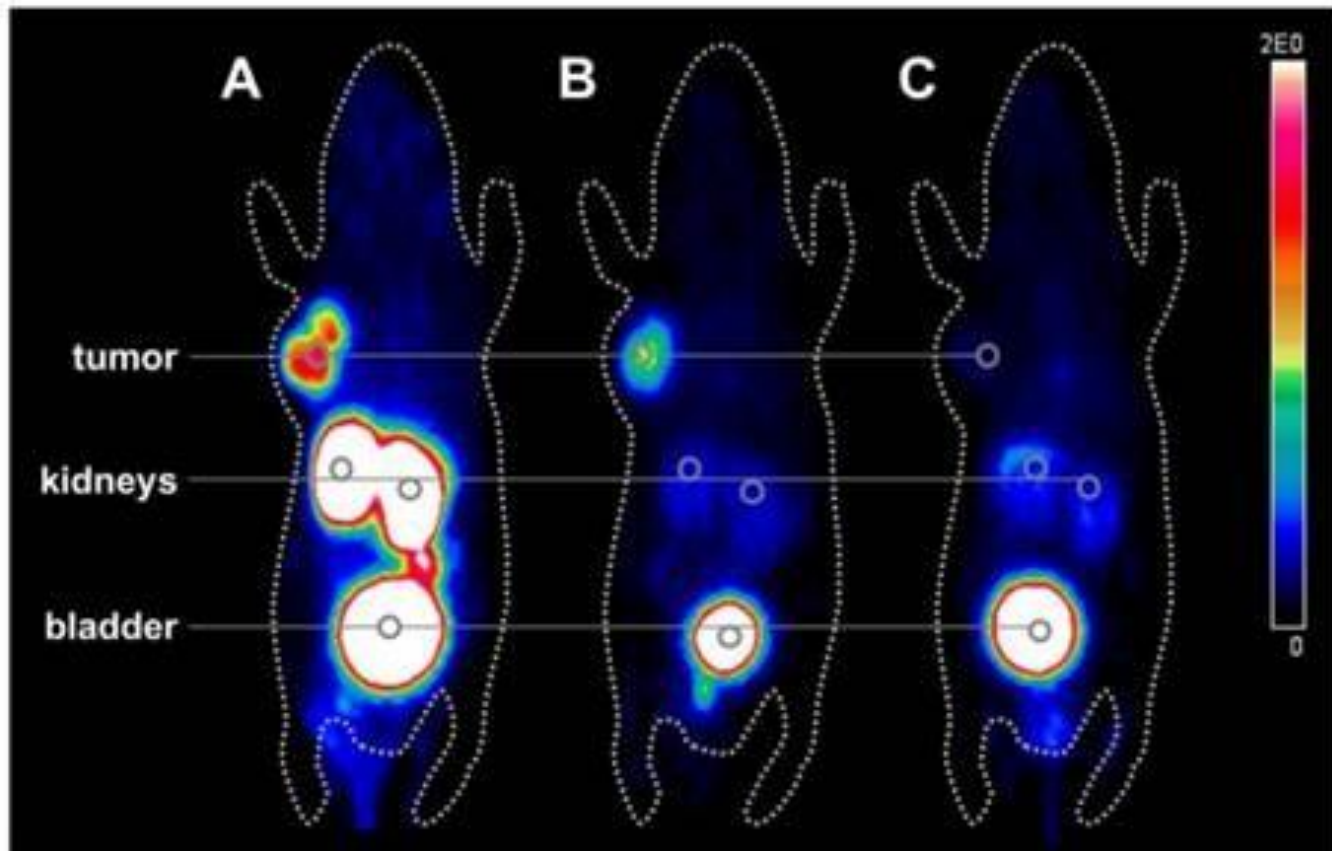
What question it answers: How effectively does the competitor bind to the same target site?



What it reveals: Stronger binding is reflected by less signal remaining at a given competitor concentration.

IC_{50} - Indicates the concentration of an inhibitor required to inhibit a biological or biochemical function by 50% *in vitro*

Biological Evaluation



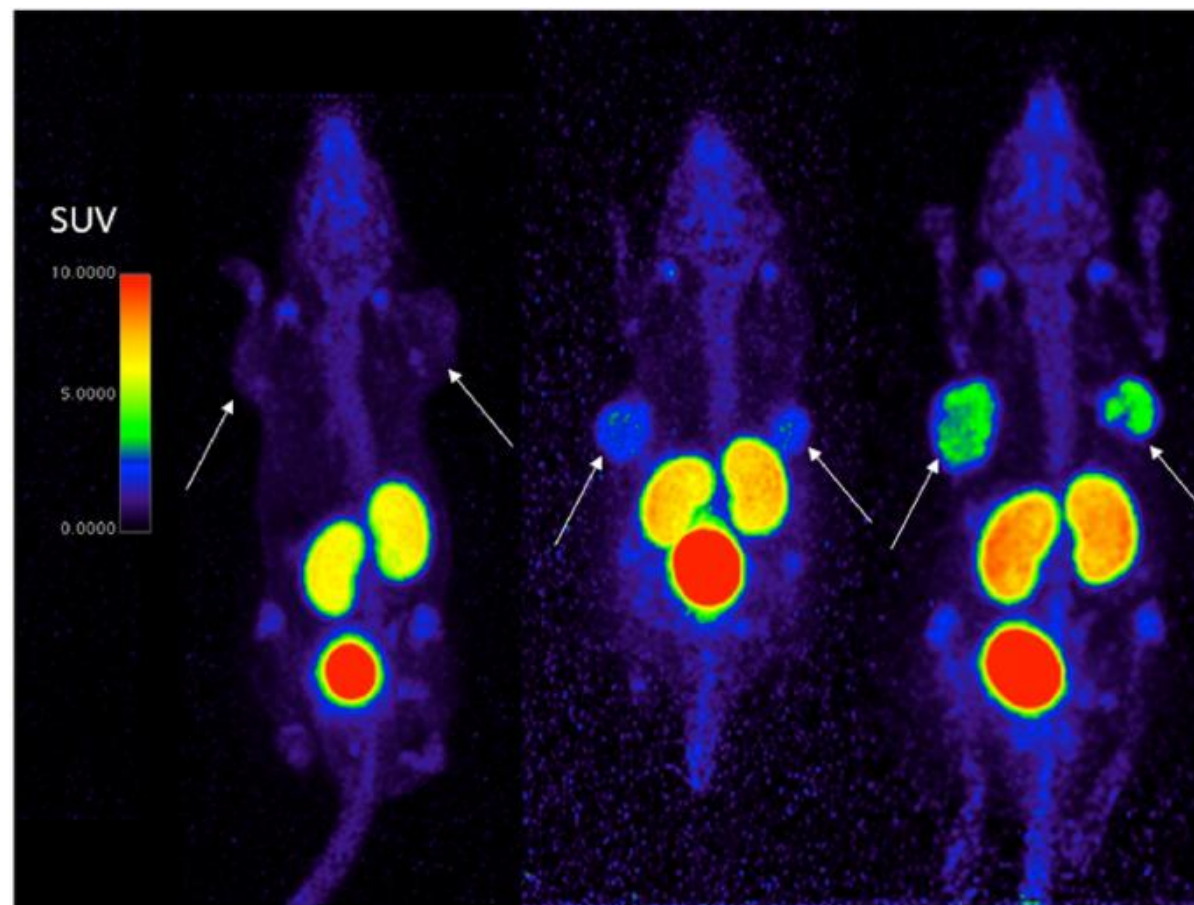
A / B: tracer alone

Tumor is visible because free receptors bind the radiotracer.

C: tracer + 100× unlabeled ligand

Receptors are occupied by nonradioactive compound, so the PET tumor signal collapses.

Biological Evaluation



Negative Control → PC-3

22Rv1

C4-2

→ Positive/High-expression model

Cell models in this example

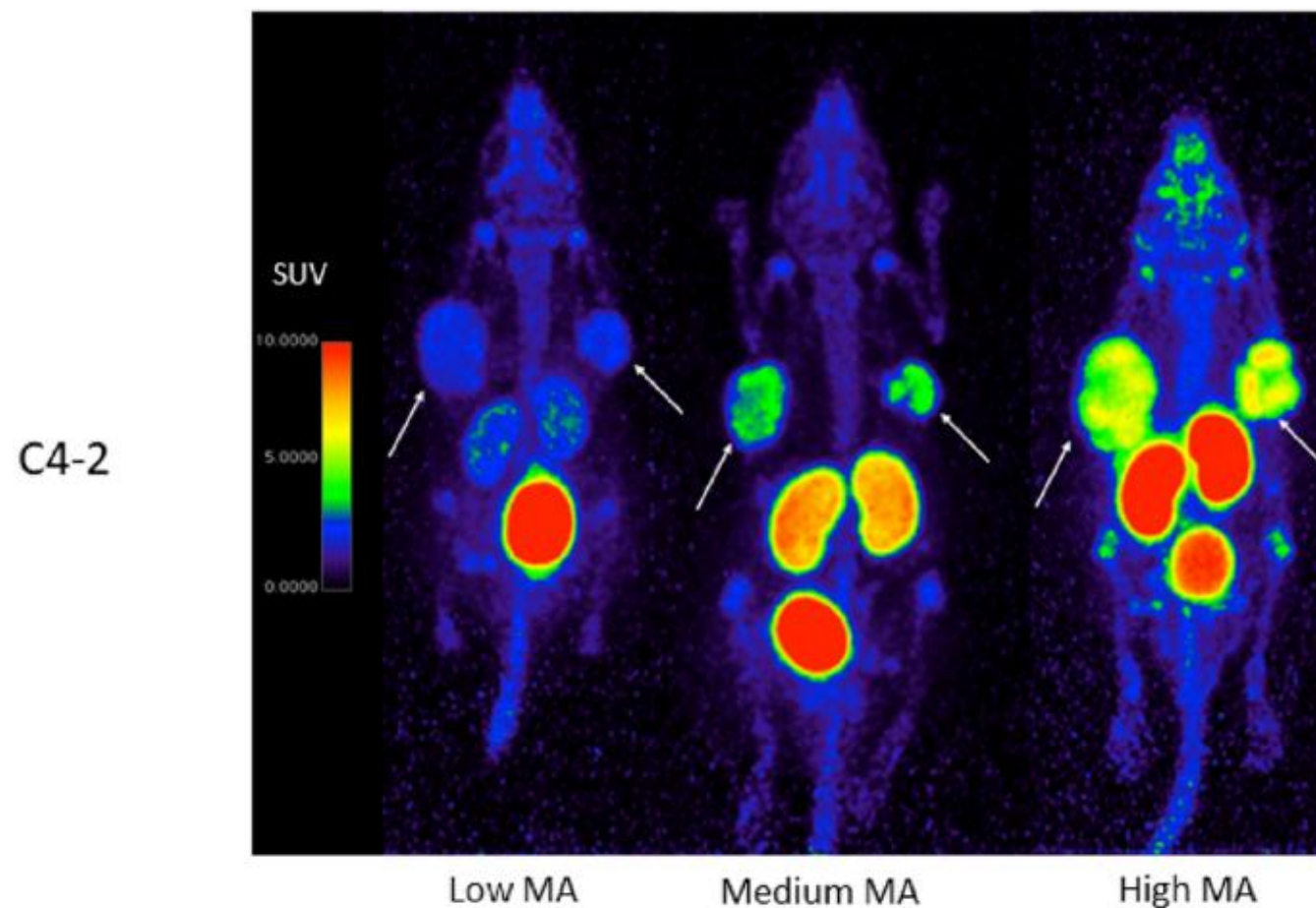
PC-3
PSMA negative
→ no clear tumor uptake

22Rv1
low PSMA expression
→ visible but weaker uptake

C4-2
high PSMA expression
→ stronger tumor uptake

Piron, S., Verhoeven, J., De Coster, E. *et al.* Impact of the molar activity and PSMA expression level on [^{18}F]AlF-PSMA-11 uptake in prostate cancer. *Sci Rep* **11**, 22623 (2021). <https://doi.org/10.1038/s41598-021-02104-6>

Biological Evaluation

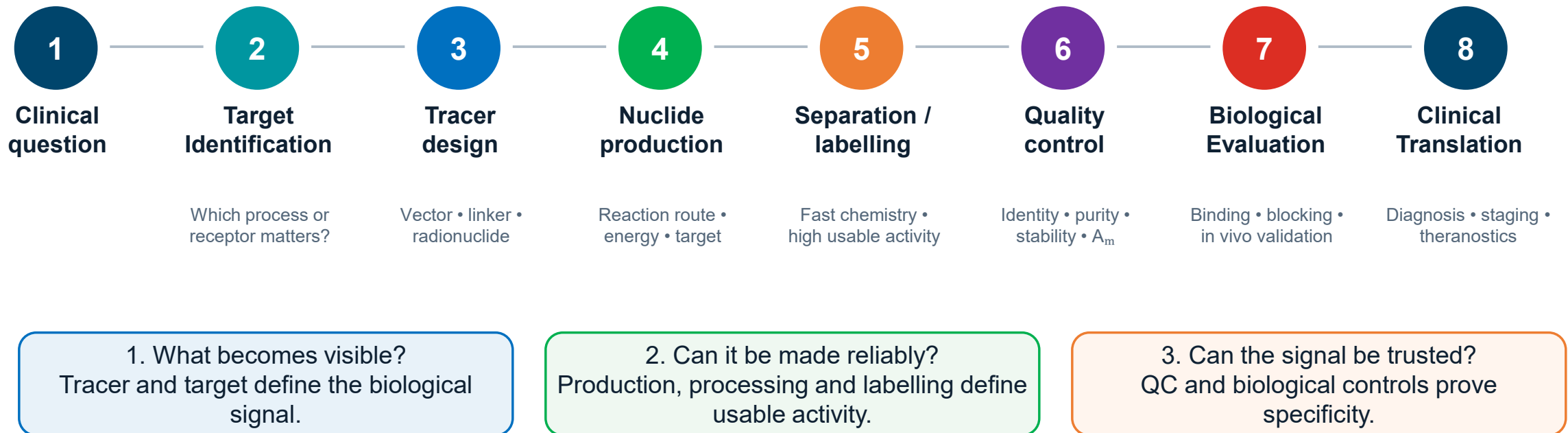


Same target, different mass dose

Low apparent molar activity
more cold PSMA ligand
→ receptors partially saturated
→ weaker tumor uptake

High apparent molar activity
less cold ligand
→ more free receptors for tracer
→ stronger tumor uptake

Summary



Thank You For Your Attention!