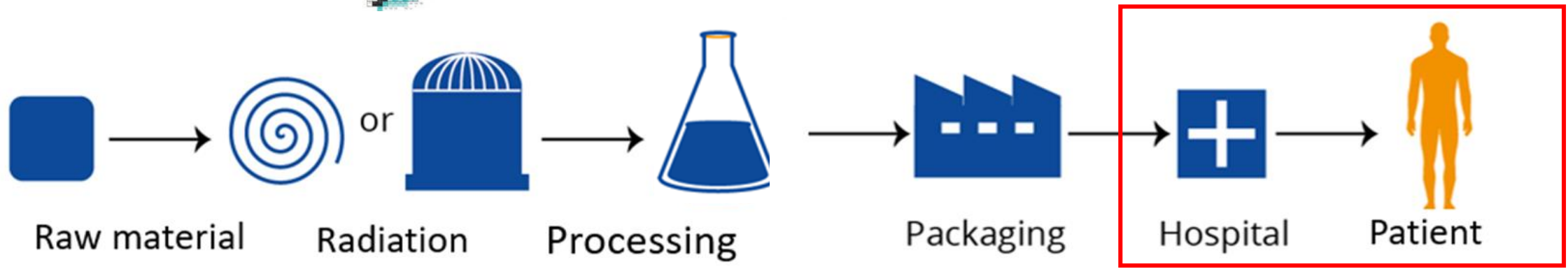
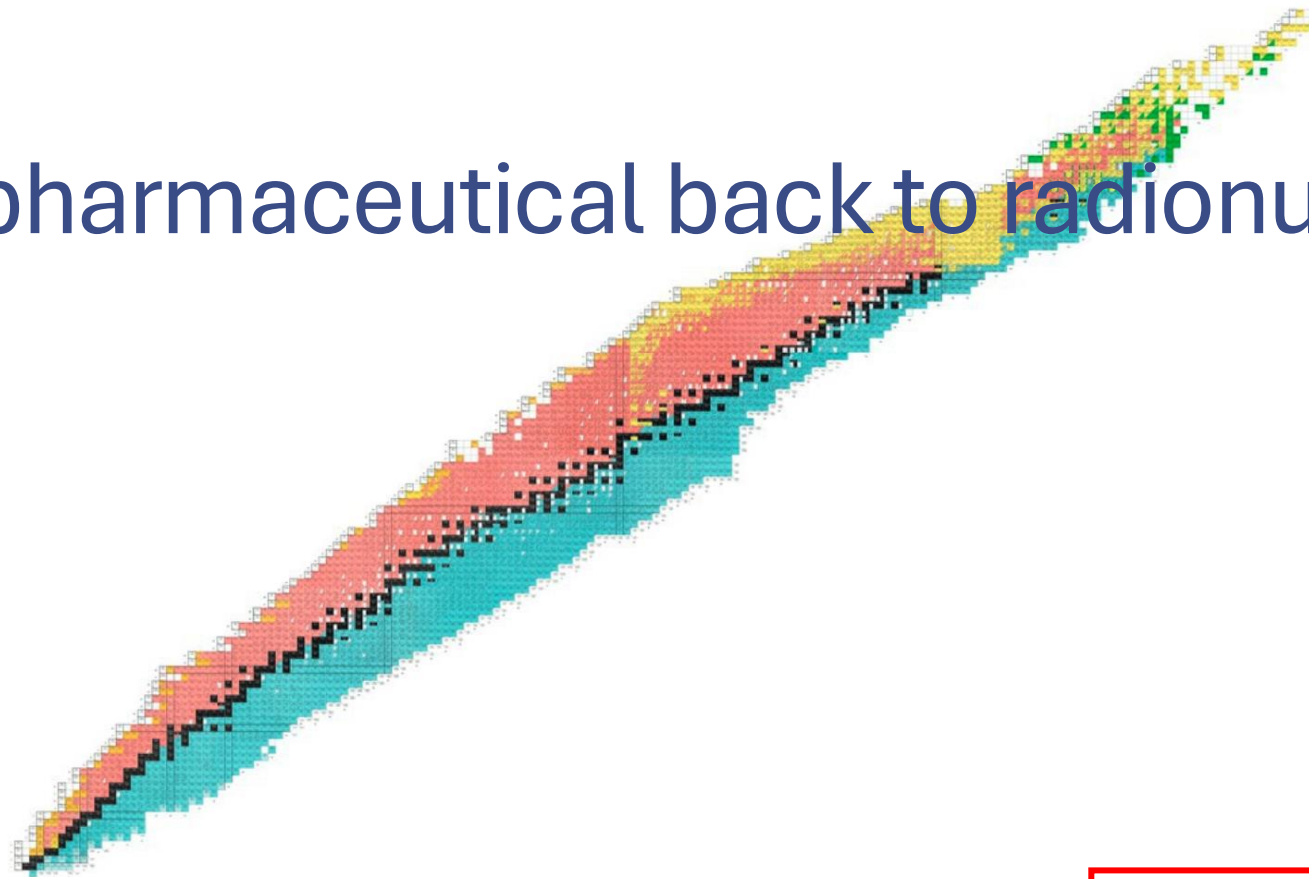


# Back-to-basics II: Basics of reactor production of radionuclides

Robin de Kruijff

# From radiopharmaceutical back to radionuclide



# Where are radionuclides produced?



research reactor

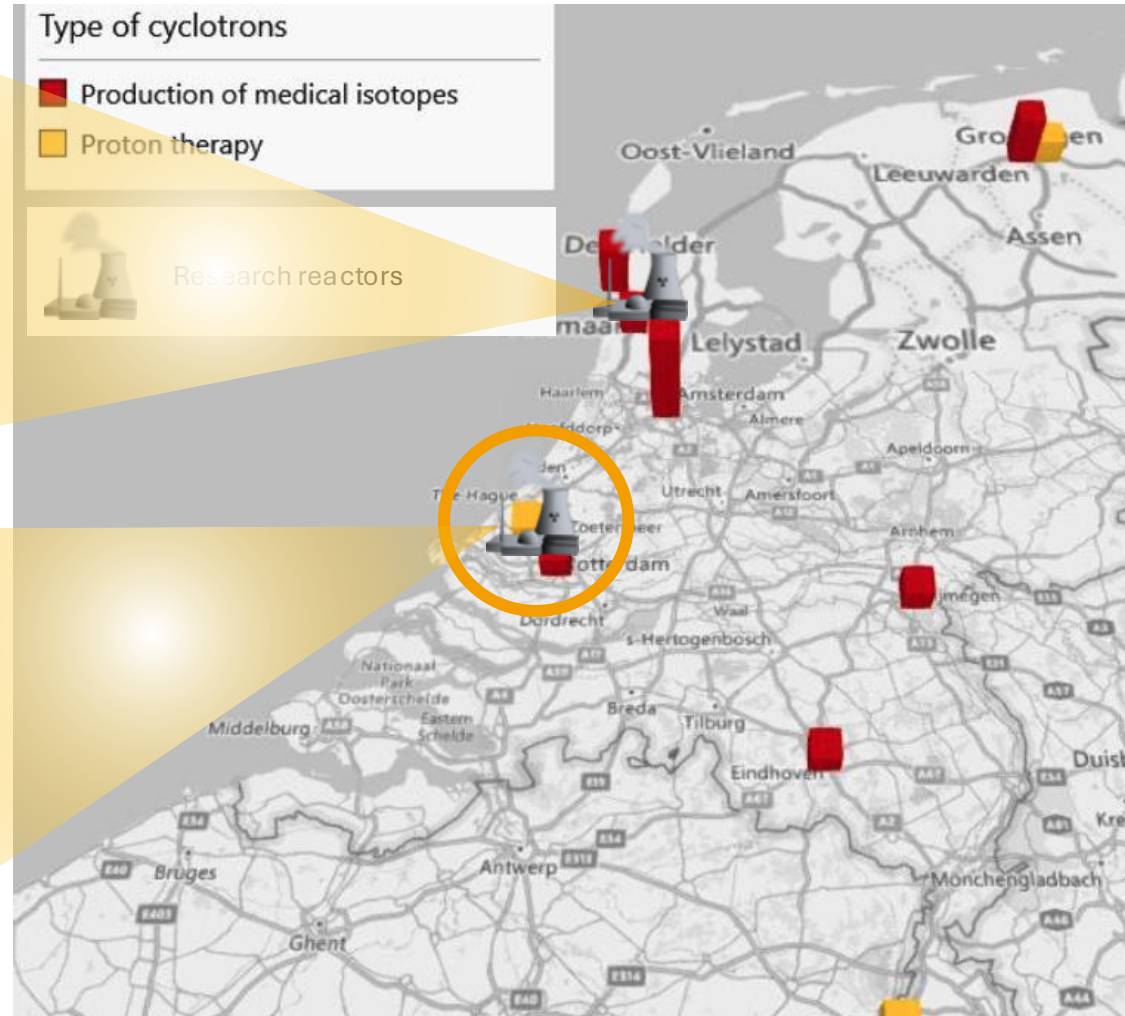


cyclotron



linear accelerator

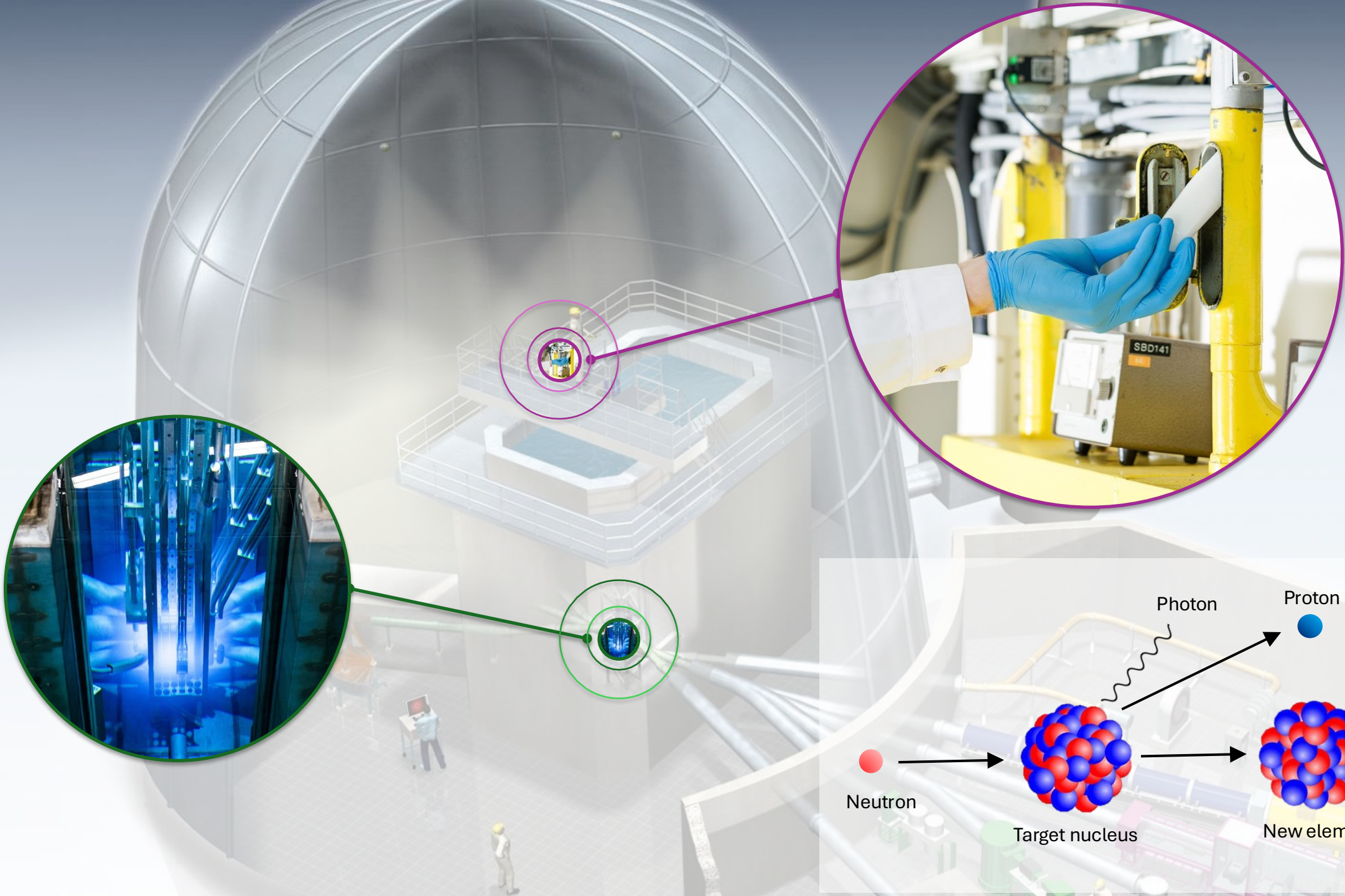
# Radionuclide production in the Netherlands



# Hoger Onderwijs Reactor (HOR)

- 2.3 MW pool-type research reactor (HFR is 45 MW)
- Reactor operates 5 days a week, 24 hours a day
- Primarily research irradiations with some exceptions



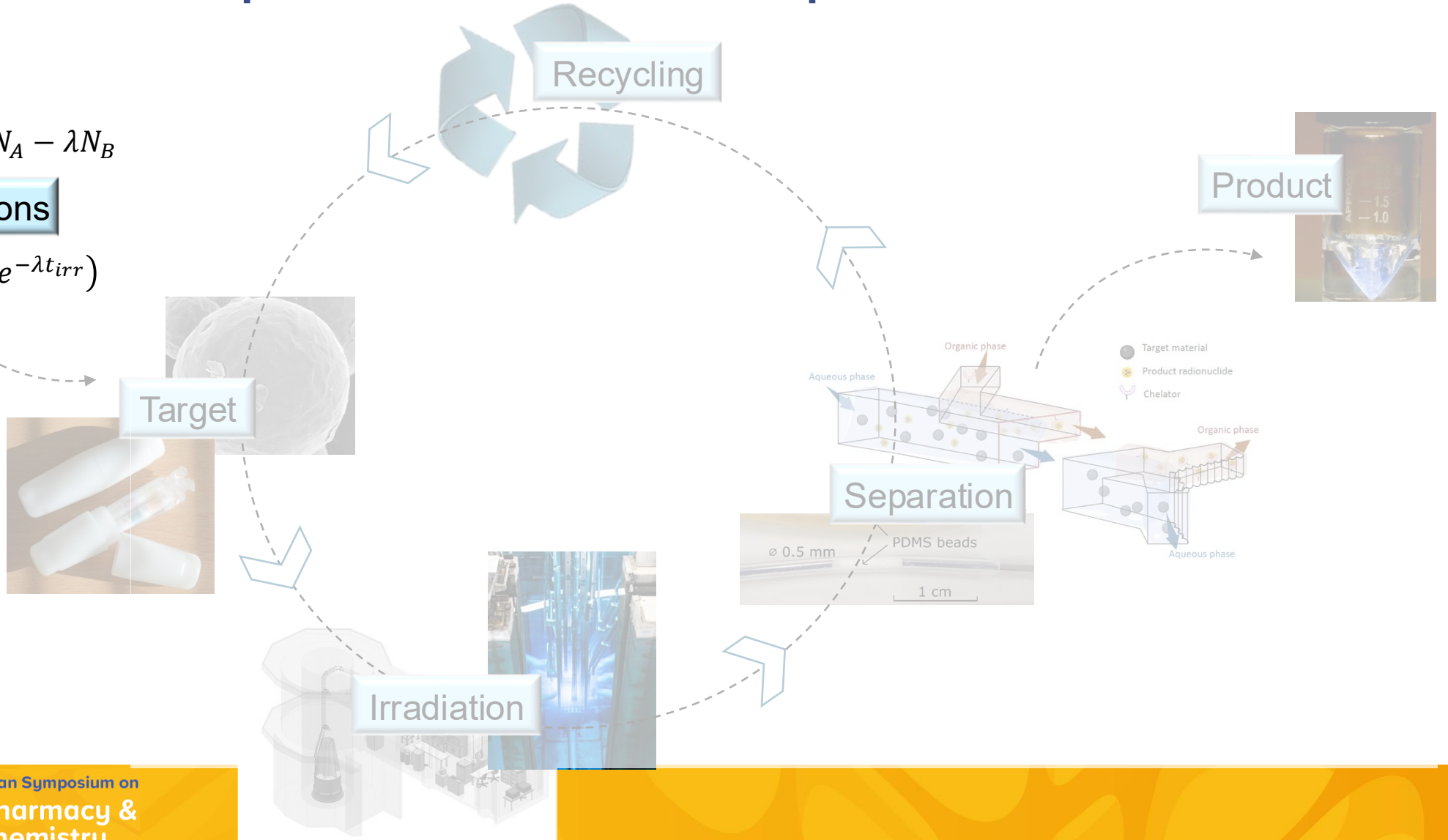


# Radionuclide production and separation

$$\left(\frac{dN_B}{dt}\right)_{Total} = \varphi\sigma N_A - \lambda N_B$$

**Calculations**

$$A_B = \varphi\sigma N_A(1 - e^{-\lambda t_{irr}})$$

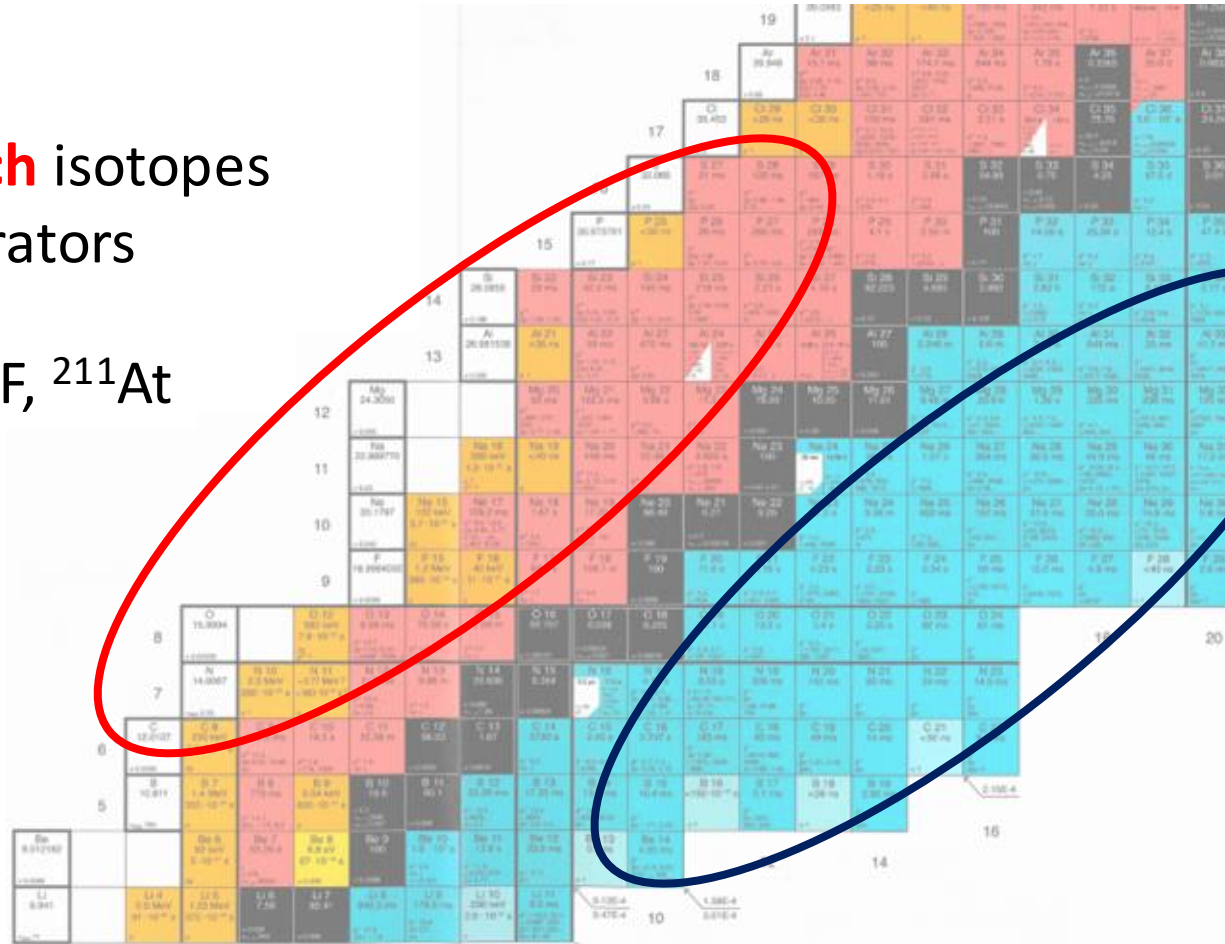


# Which radionuclides are produced?

**Proton-rich** isotopes

→ Accelerators

e.g.  $^{11}\text{C}$ ,  $^{18}\text{F}$ ,  $^{211}\text{At}$



**Neutron-rich** isotopes

→ Reactors

e.g.  $^{99}\text{Mo}$ ,  $^{161}\text{Tb}$ ,  $^{177}\text{Lu}$

# Production reactions

The produced activity ( $A_B$ ) after irradiation depends on:

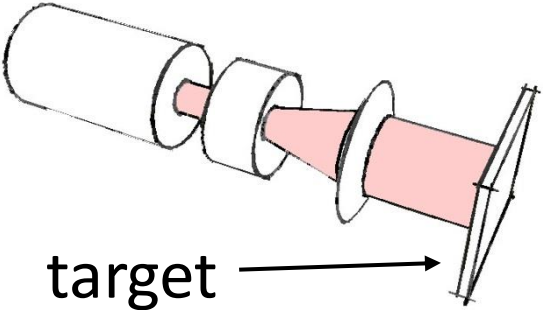
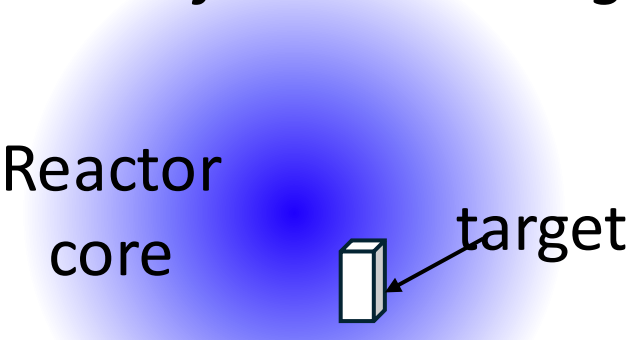
- Cross section ( $\sigma$ ) – Reaction probability
- Flux ( $\phi$ ) – Number of particles used for irradiation
- Number of target atoms ( $N_A$ )

$$A_B = \phi \sigma N_A (1 - e^{-\lambda t_{irr}})$$

Lu 175 97.401  $\sigma$ 16 + 8	Lu 176 2.599 3.68 h $\beta^-$ 1.2 3... 88... $\sigma$ 2 + 2100	Lu 177 160.44 d $\beta^-$ 0.2 $m_1$ $\sigma$ 1000	Lu 178 22.7 m   28.4 m $\beta^-$ 2.0... $\gamma$ 93, 1341 1310 1269... g
Yb 174 32.026 $\sigma$ 63 $\sigma_{n,\alpha} < 2E-5$	Yb 175 4.185 d $\beta^-$ 0.5... $\gamma$ 396, 283 114...	Yb 176 11.4 s   12.996 IT 96 $\gamma$ 293, 389 190, 82, $e^-$ $\sigma$ 3.1 $\sigma_{n,\alpha} < 1E-6$	Yb 177 6.41 s   1.911 h $\beta^-$ 4... 1080, 122 1241... g
Tm 173 8.24 h $\beta^-$ 0.9, 1.3... $\gamma$ 399, 461...	Tm 174 2.29 s   5.4 m IT 152, $e^-$ $\gamma$ 100, $e^-$	Tm 175 15.2 m $\beta^-$ 0.9, 1.9... $\gamma$ 515, 941 364...	Tm 176 1.9 m $\beta^-$ 2.0, 2.8... $\gamma$ 190, 1069 382... g

# Number of target atoms ( $N_t$ )

Difference between reactors and accelerators:

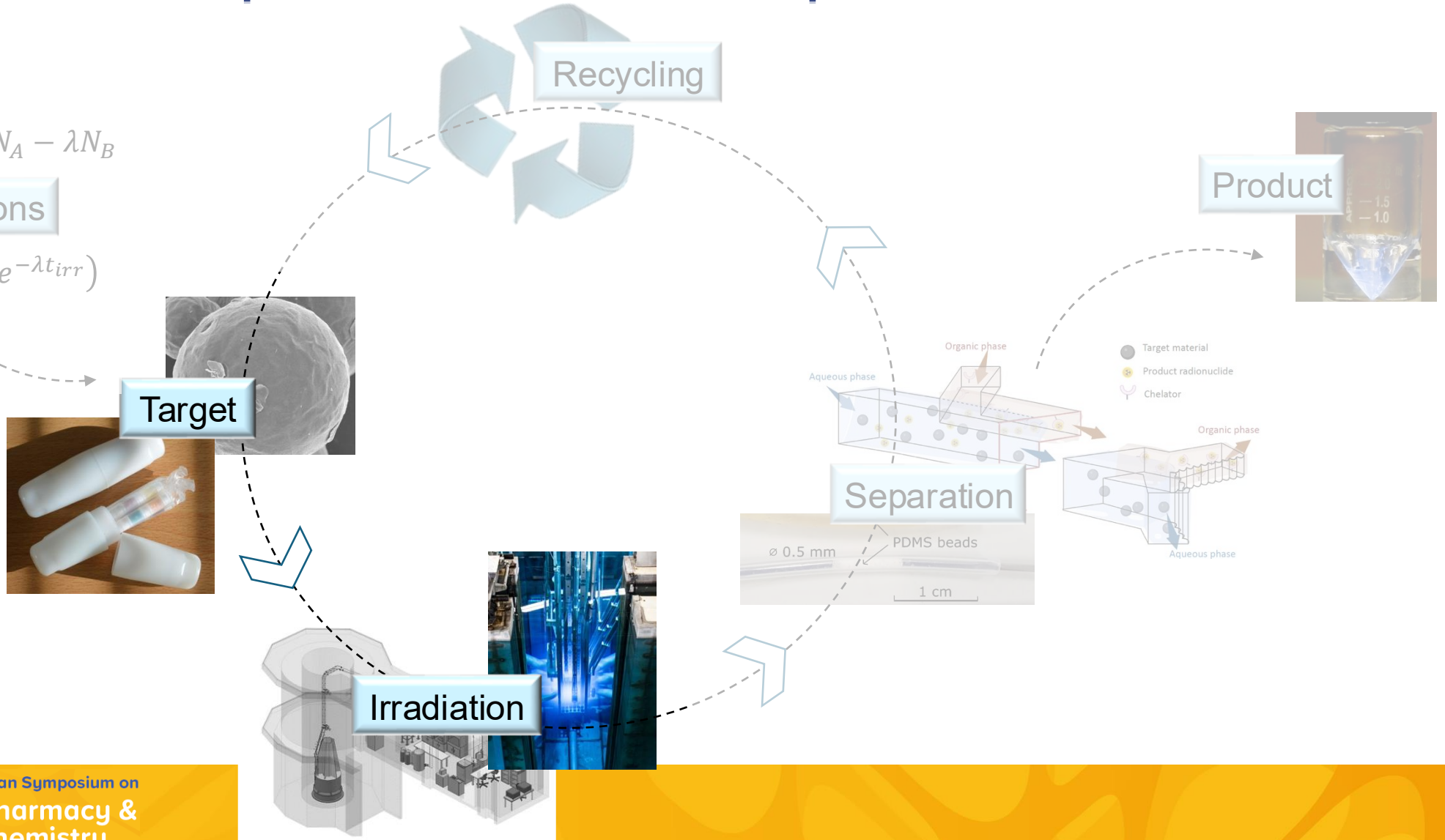
Accelerator	Reactor
<p>Beam smaller than target  <math>N_t = nr</math> of atoms in irradiated volume</p> 	<p>Small target in sea of neutrons  <math>N_t = total</math> nr of atoms in target</p> 

# Radionuclide production and separation

$$\left(\frac{dN_B}{dt}\right)_{Total} = \varphi\sigma N_A - \lambda N_B$$

Simulations

$$A_B = \varphi\sigma N_A(1 - e^{-\lambda t_{irr}})$$



# Target packaging (reactor)

## Encapsulation of target material

- Polyethelene capsules for short irradiations
- Quartz / aluminum for longer irradiations



## Transport systems

- Pneumatically (rabbits)
- Mechanically (cables)



$^{99}\text{Mo}$  production: 1 assembly (196 g) =  $\sim 1.5$  M patient doses

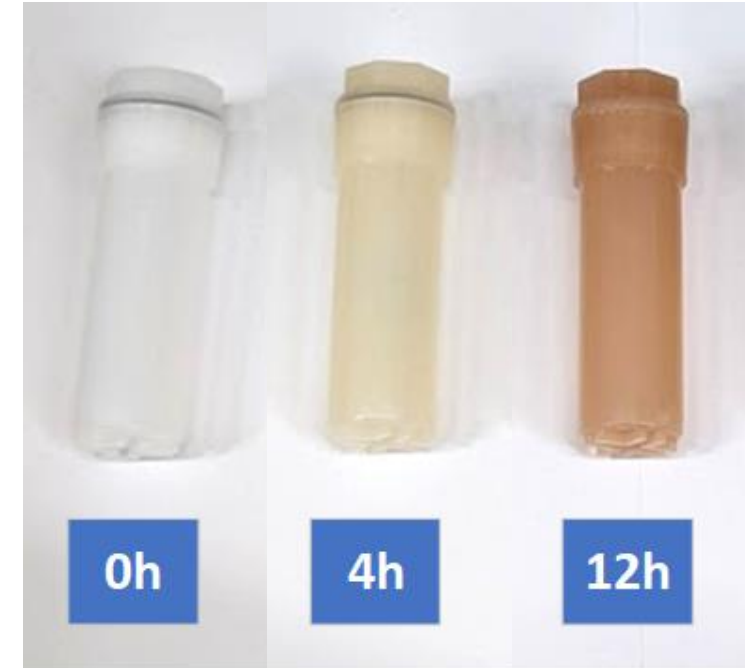
# Target considerations

## Elemental and isotopic content of target

- What other isotopes are made?
- Use of enriched targets

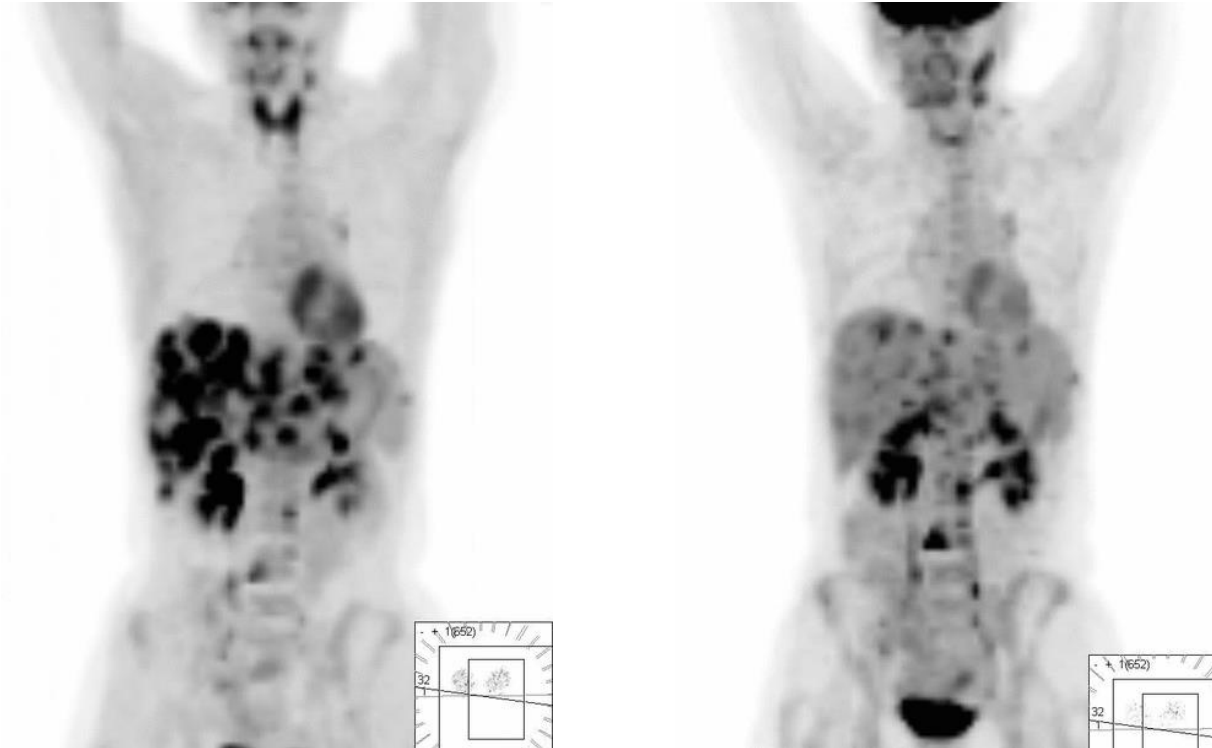
## Stability of target

- Thermal or chemical (radiolysis) decomposition
- Behavior of liquids under heating
- Chemical reactions with containment



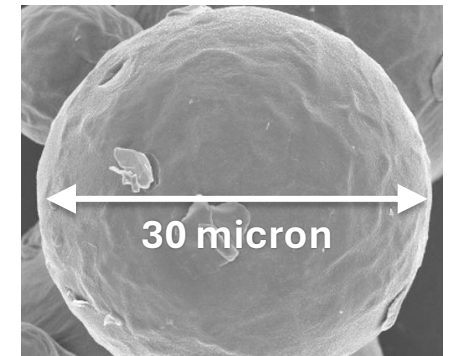
Irradiated target capsules

# Holmium microspheres



$^{99m}\text{Tc}$  in a tumor-seeking compound as tracer

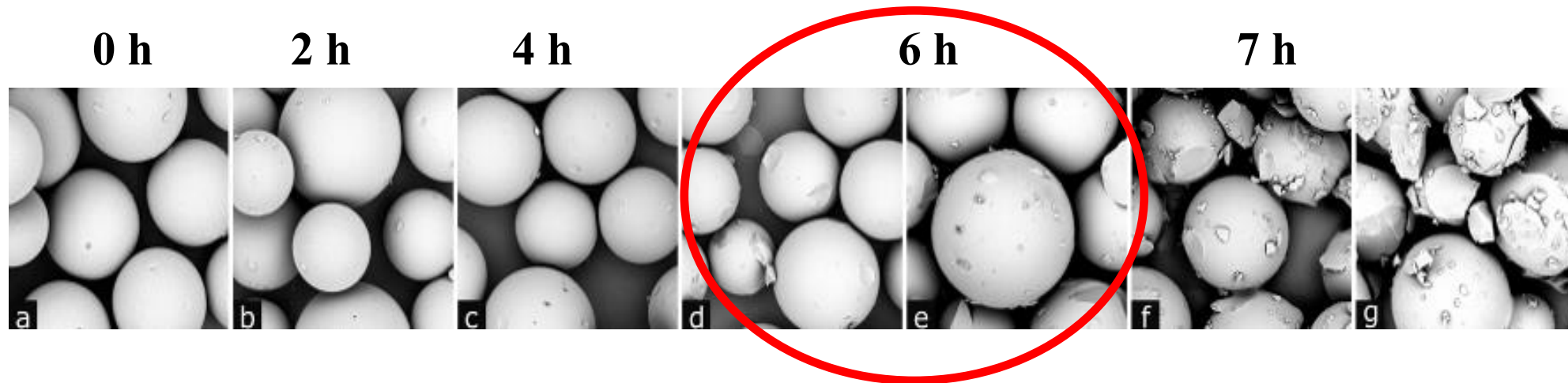
$^{166}\text{Ho}$ -containing  
microspheres



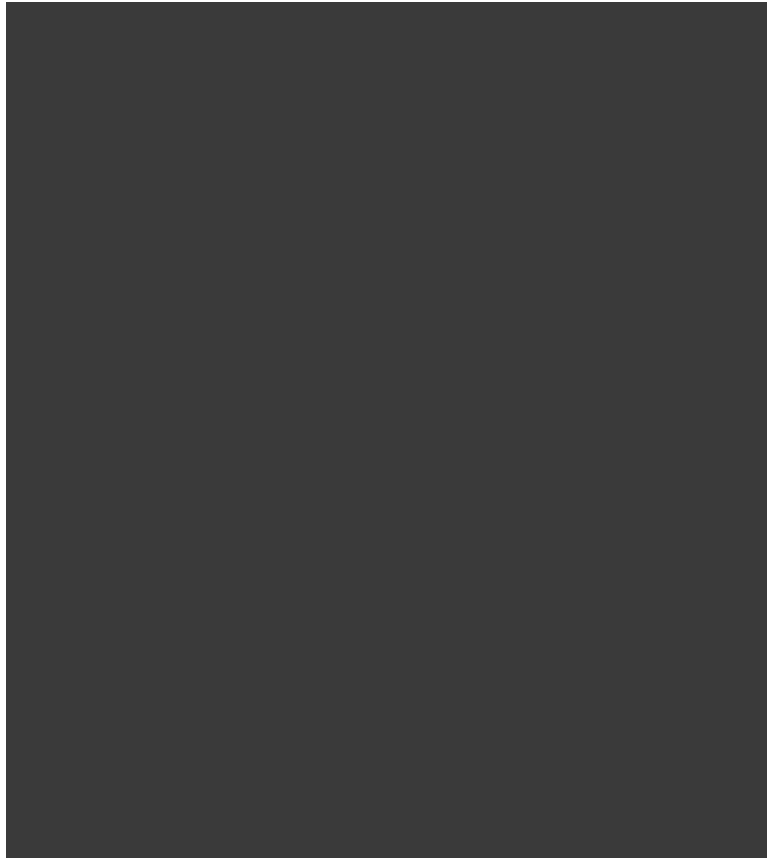
# New flexible irradiation facility

Irradiation times limited to about 6 h, spheres break down at longer irradiation times

→ **Damaged by gamma rays!**



# Lead as shielding material



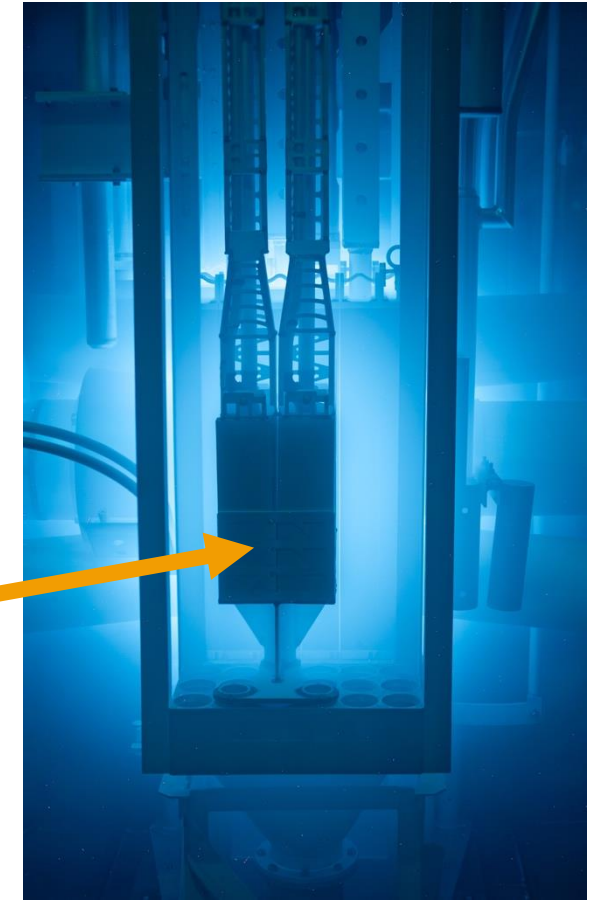
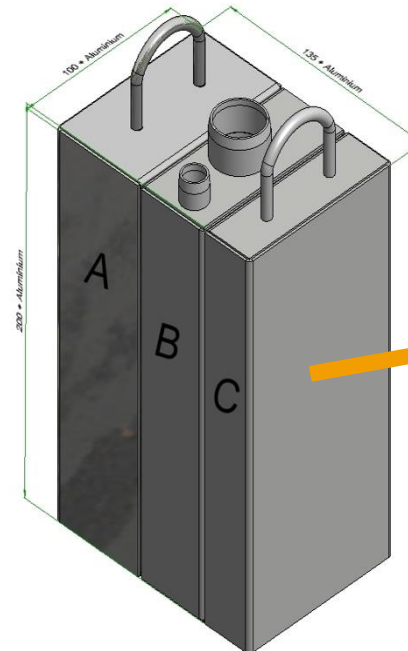
X-ray image



Neutron image

# Design of the facility

- Consists of three blocks which can be exchanged
- The material in block A and C can be adjusted
- Currently using lead blocks



# Irradiation up to 28 hours!

Configuration	Gamma dose (kGy/h)	Neutron flux ( $n\text{ cm}^{-2}\text{ s}^{-1}$ )
0 cm lead	265	$5.2 \times 10^{12}$
CBA (3 cm lead)	105	$6.6 \times 10^{12}$
ABC (6 cm lead)	70	$5.4 \times 10^{12}$
ACB (9 cm lead)	42	$3.9 \times 10^{12}$

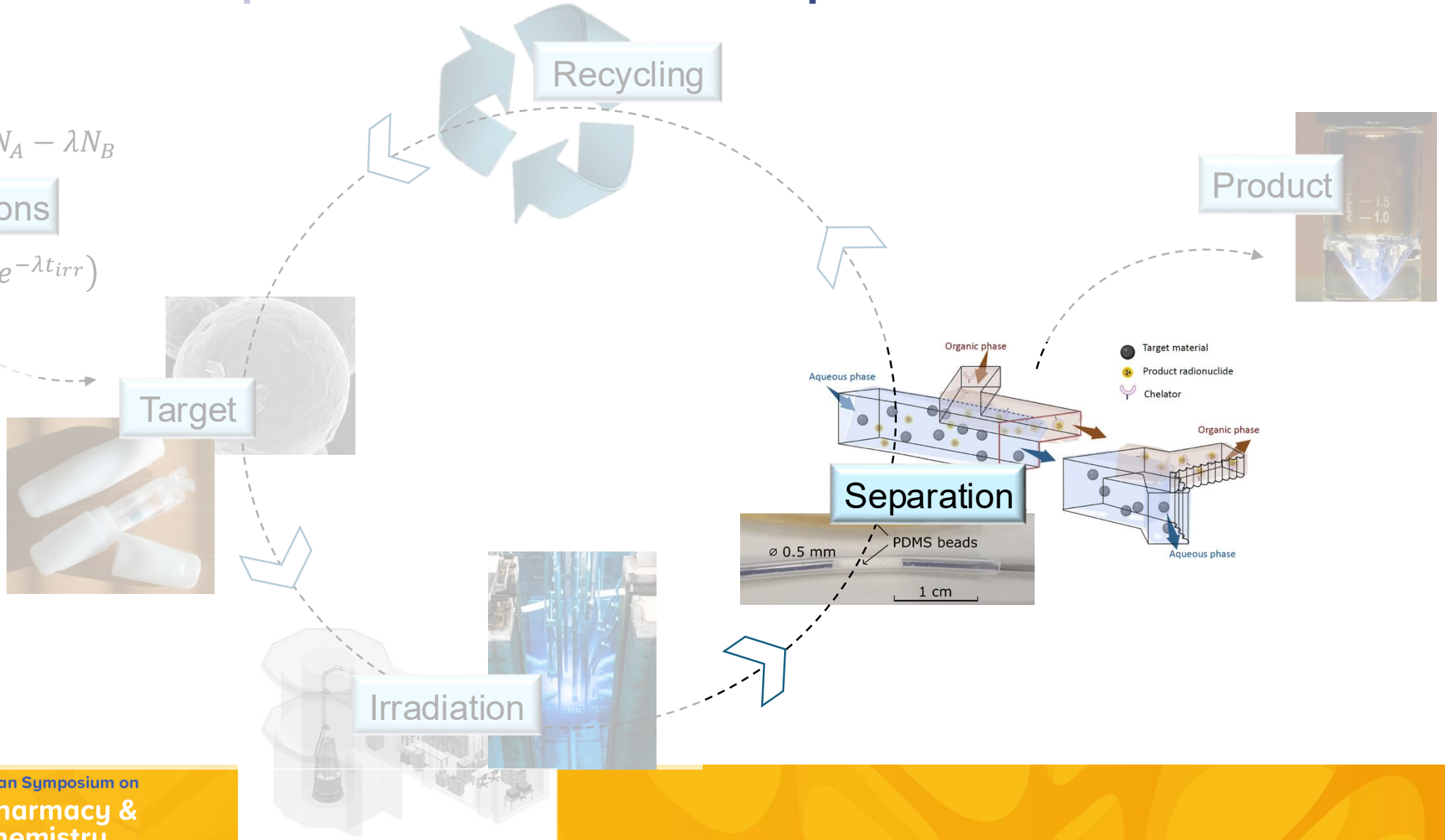


# Radionuclide production and separation

$$\left(\frac{dN_B}{dt}\right)_{Total} = \varphi\sigma N_A - \lambda N_B$$

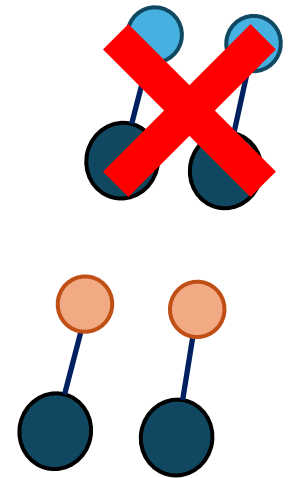
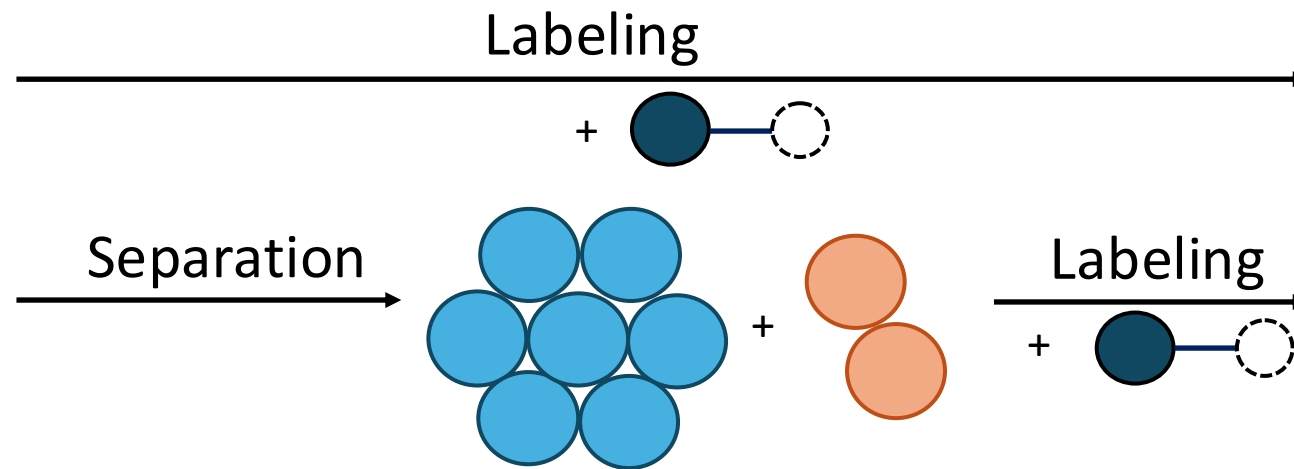
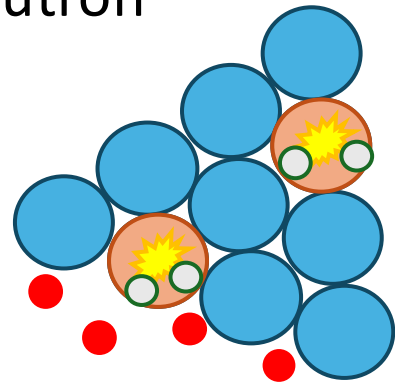
Calculations

$$A_B = \varphi\sigma N_A(1 - e^{-\lambda t_{irr}})$$



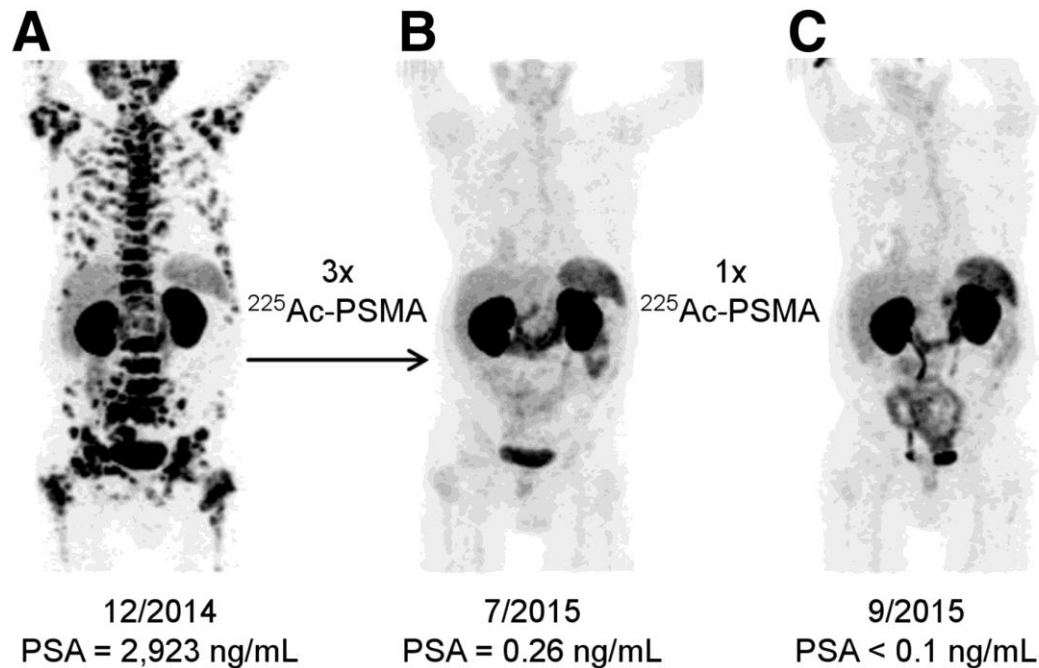
# Identifying targets is only half the work

- = Ra-226
- = Ac-225
- = proton
- = neutron



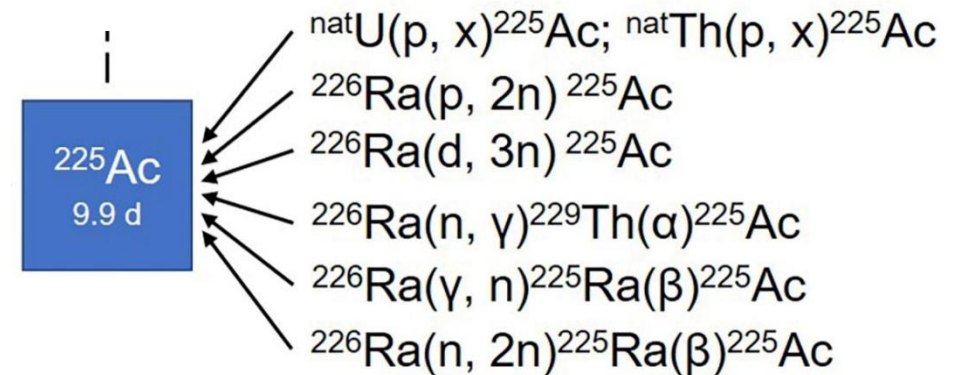
# Case study: extraction of $^{225}\text{Ac}$ from Ra targets

$^{225}\text{Ac}$  is a very promising radionuclide used for targeted alpha therapy



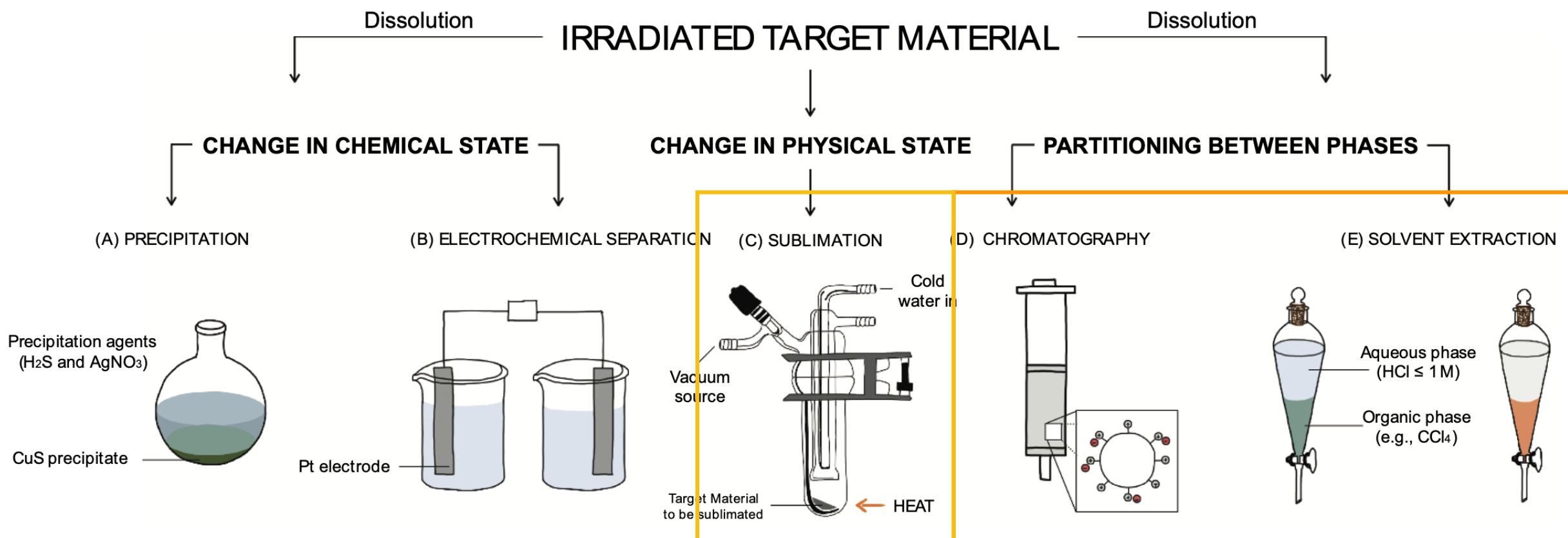
Kratochwil et al 2016

$^{225}\text{Ac}$  production routes:



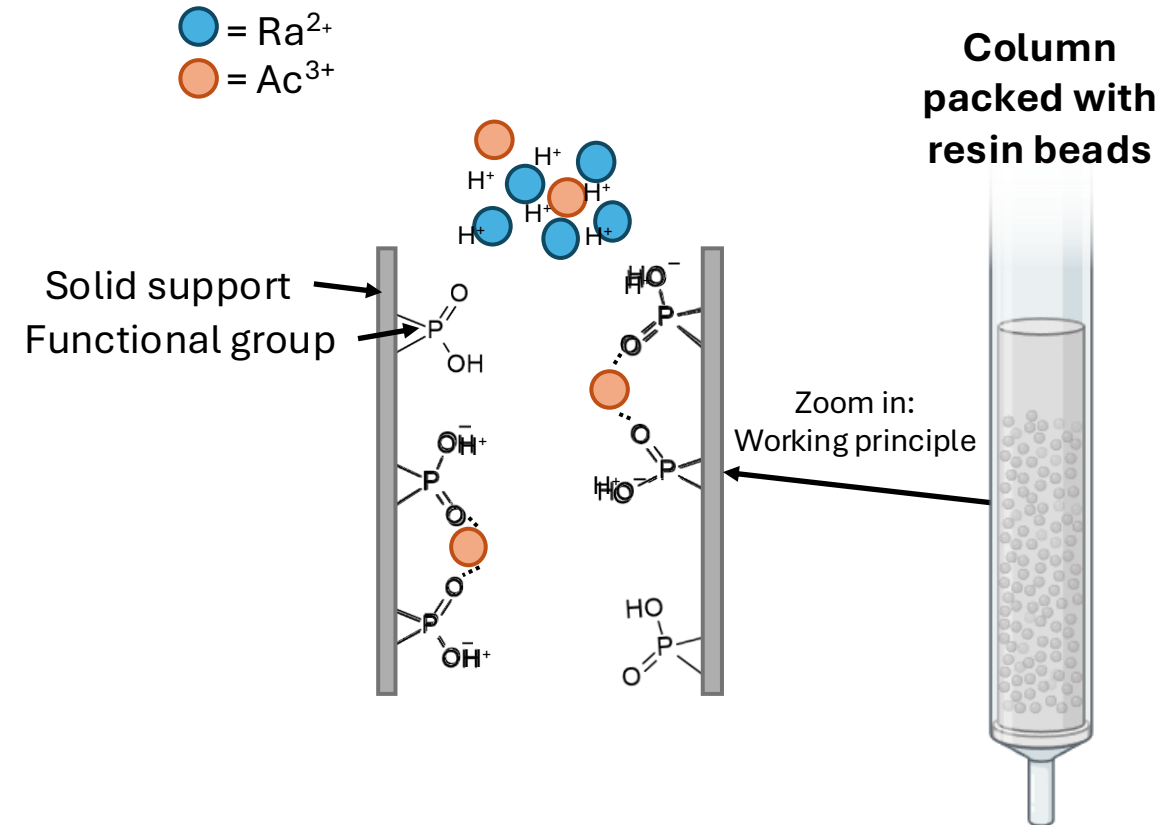
Shi et al 2022

# Separation / purification

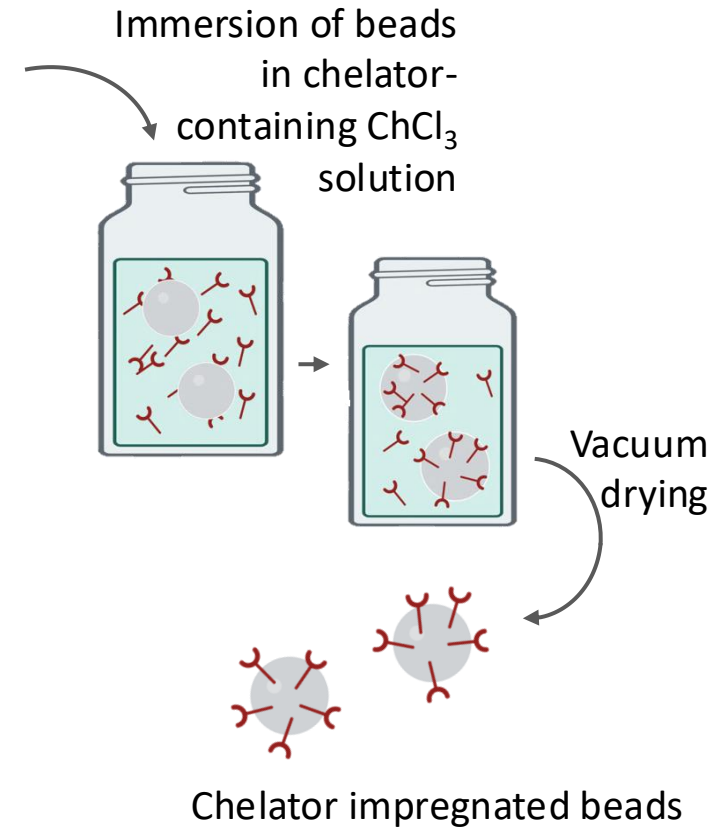
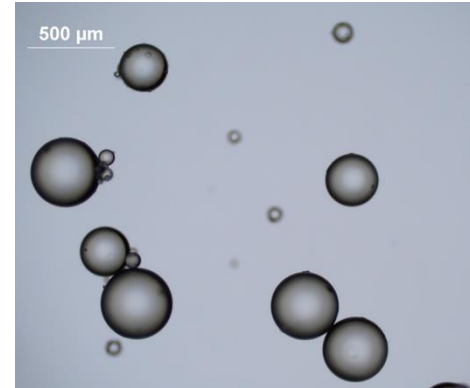
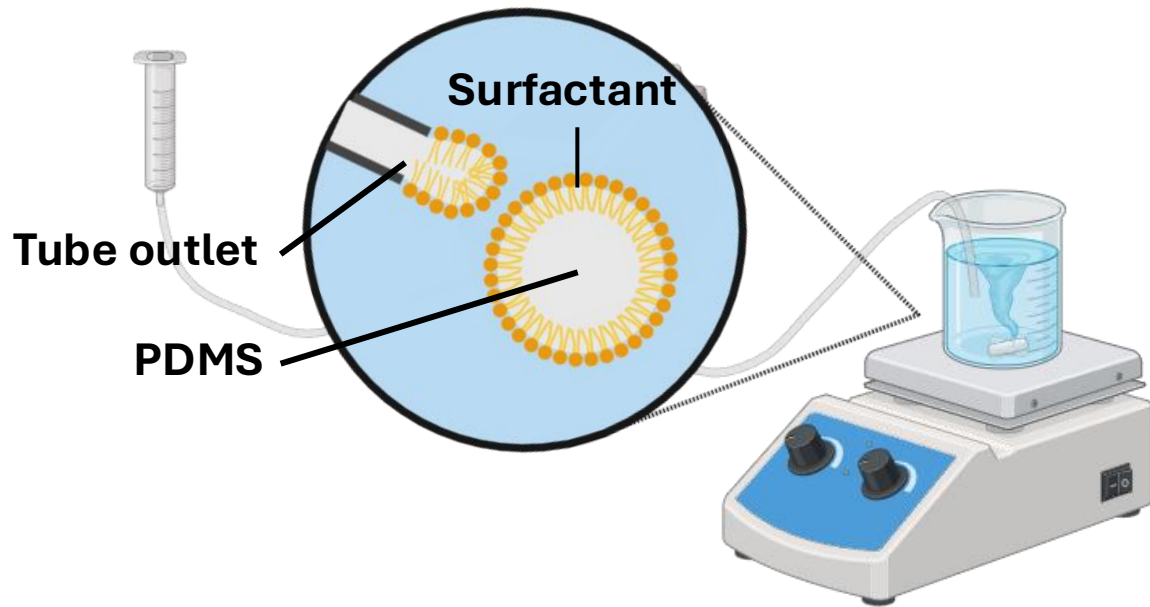


# Chelator-impregnated resins

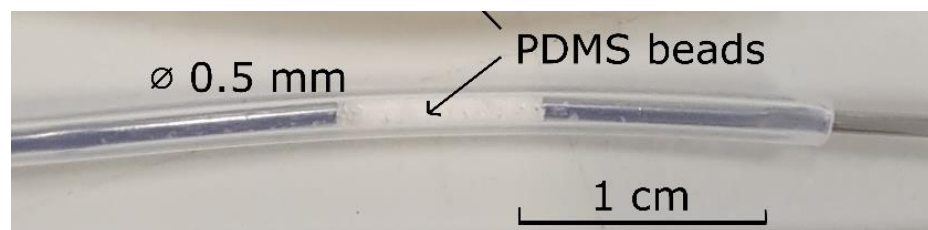
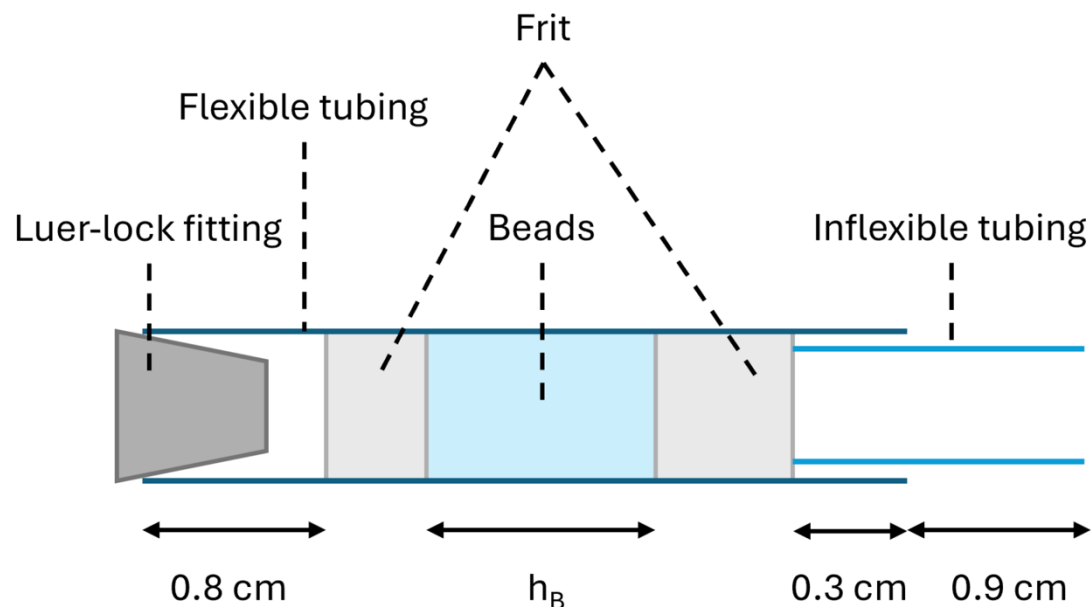
- Consist of a solid support, coated (or 'impregnated') with a chelator
- + Simple and quick to fabricate
- + Versatile applications
- Low chemical stability



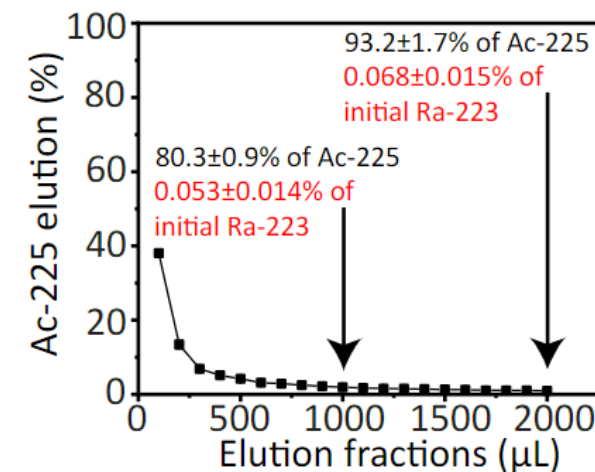
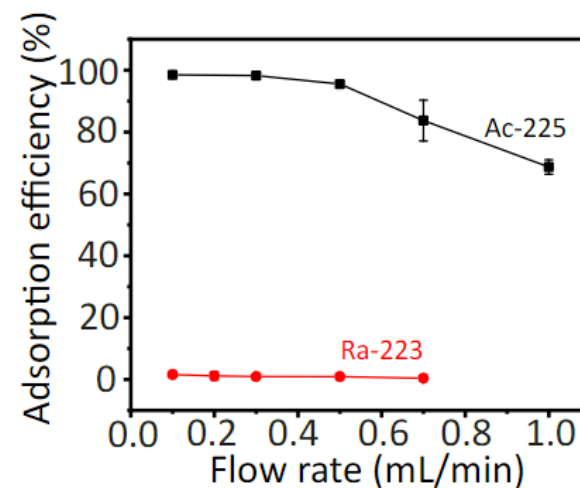
# Resin bead production



# Chelator-impregnated resins



Extraction takes less than 10 minutes!



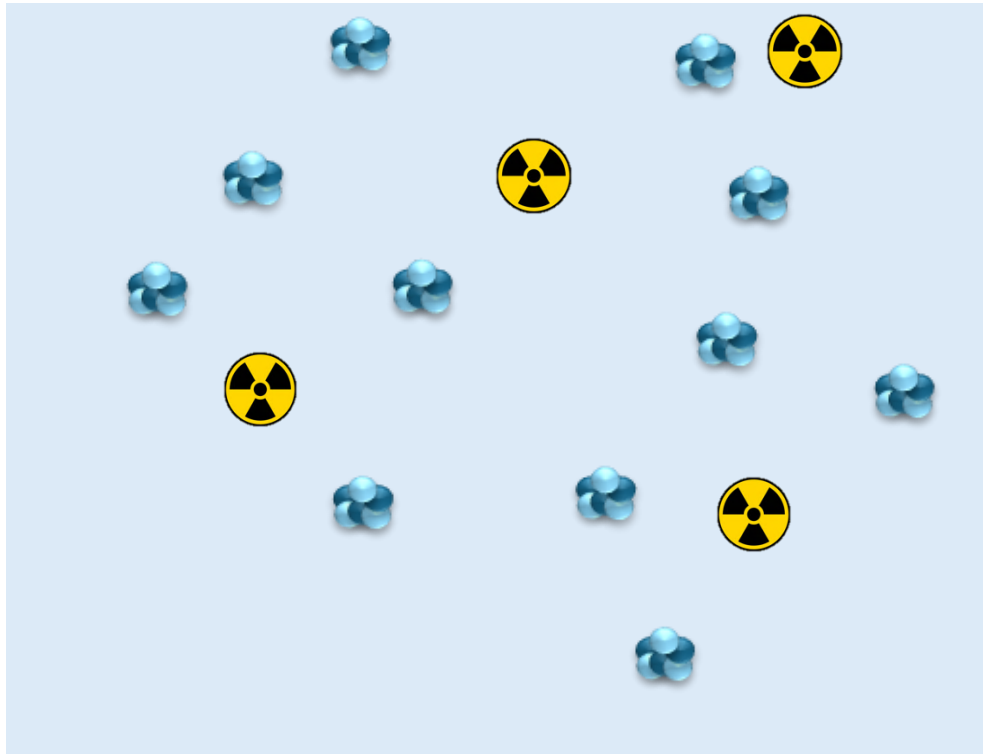
# Solvent (liquid-liquid) extraction

- Extraction based on solubility differences
- Enhanced with chelators
- Selective chelators form hydrophobic complexes → extraction to organic phase

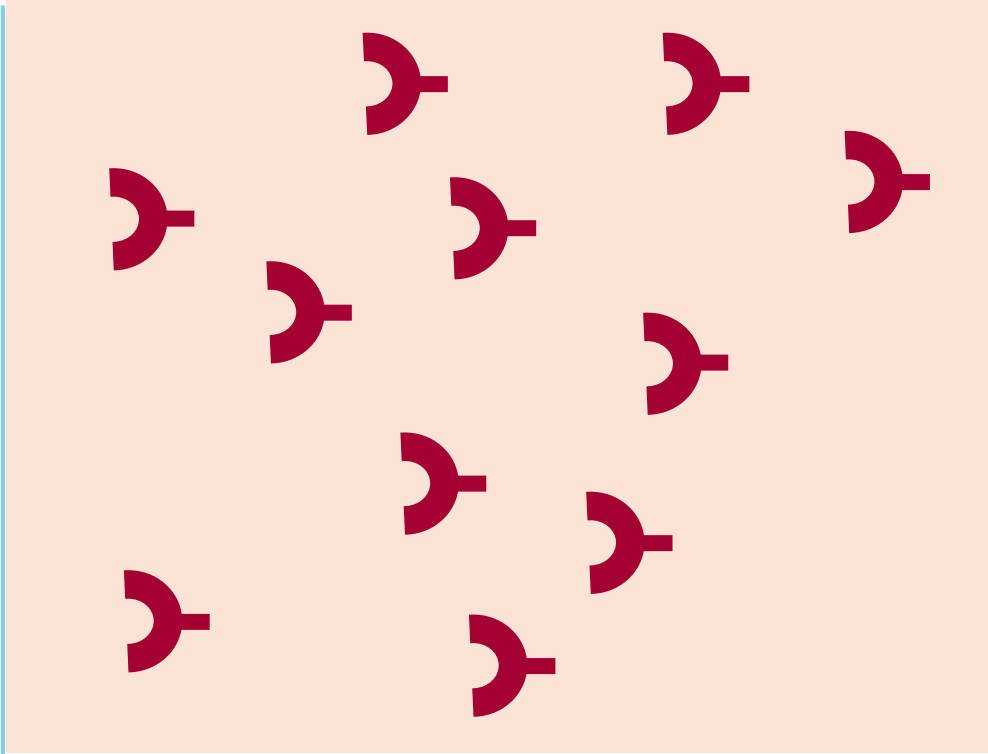



# Solvent extraction

aqueous phase (water based)



organic phase (e.g. chloroform)



 Target material (e.g. Ra-226)

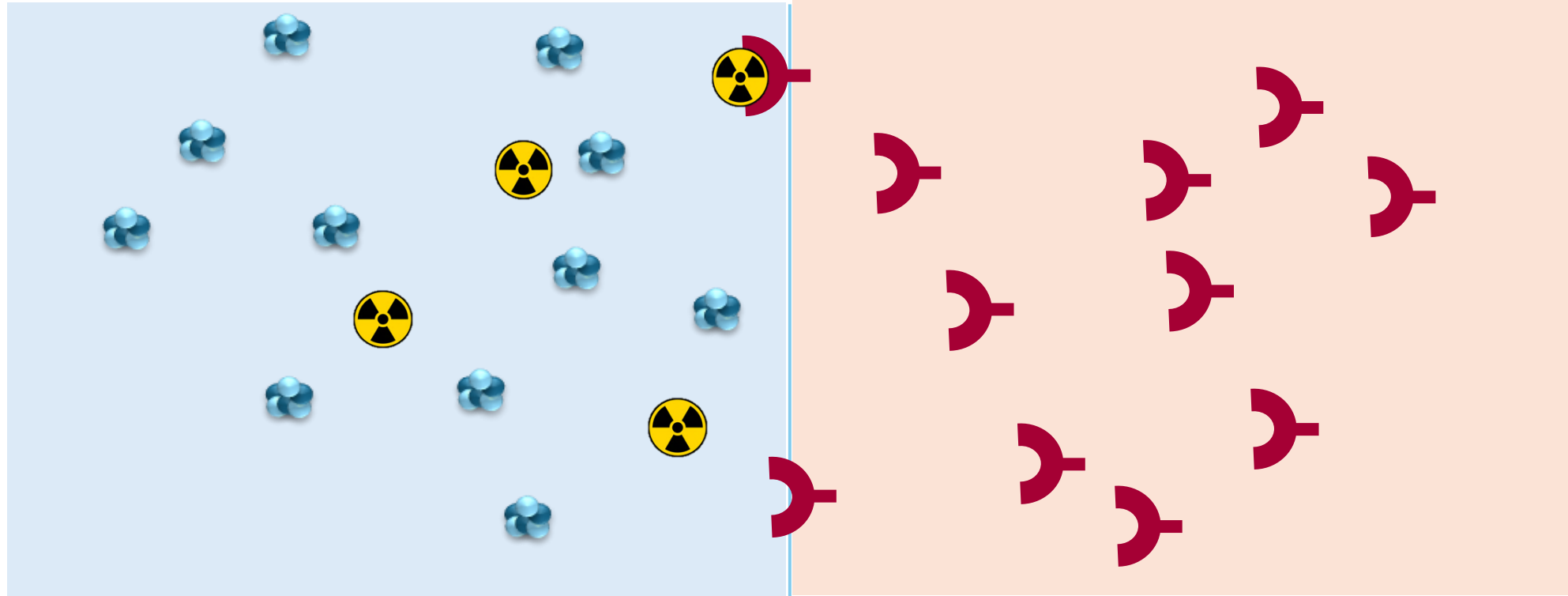
 Radionuclide (e.g. Ac-225)


 Chelator

# Solvent extraction

aqueous phase (water based)

organic phase (e.g. chloroform)



 Target material (e.g. Ra-226)

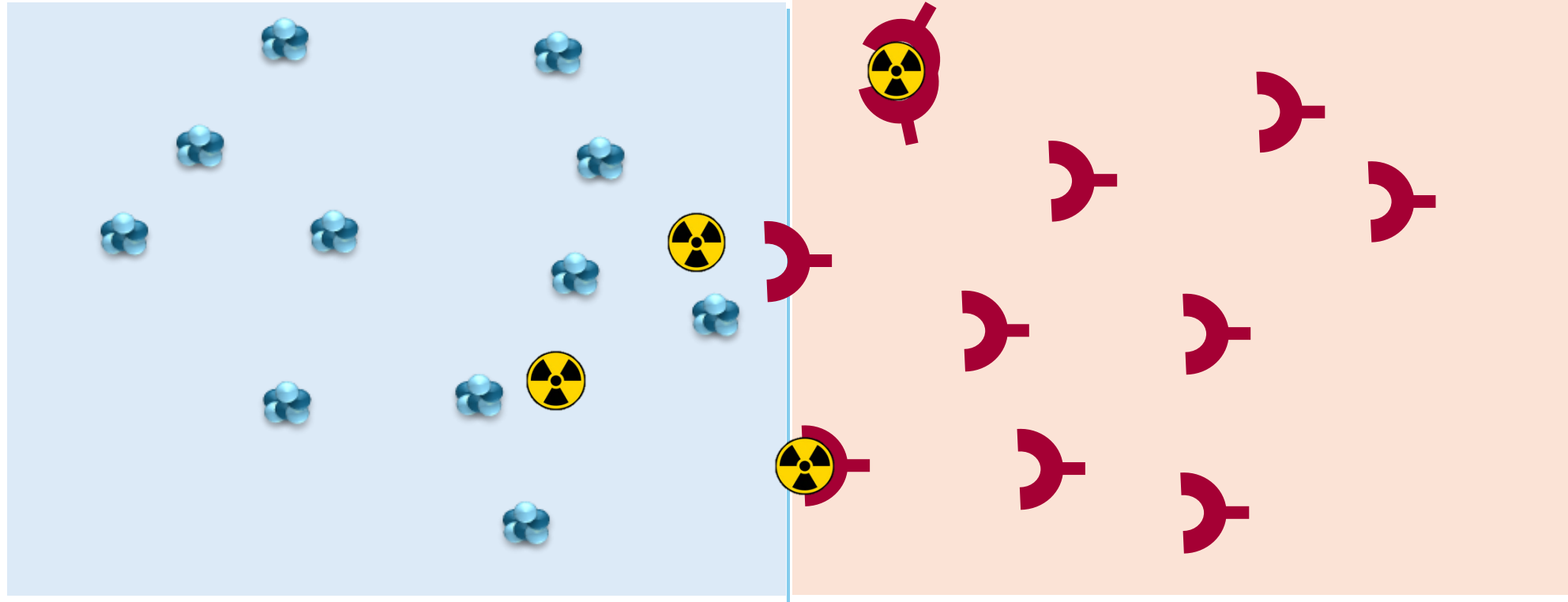
 Radionuclide (e.g. Ac-225)


 Chelator

# Solvent extraction


aqueous phase (water based)

organic phase (e.g. chloroform)



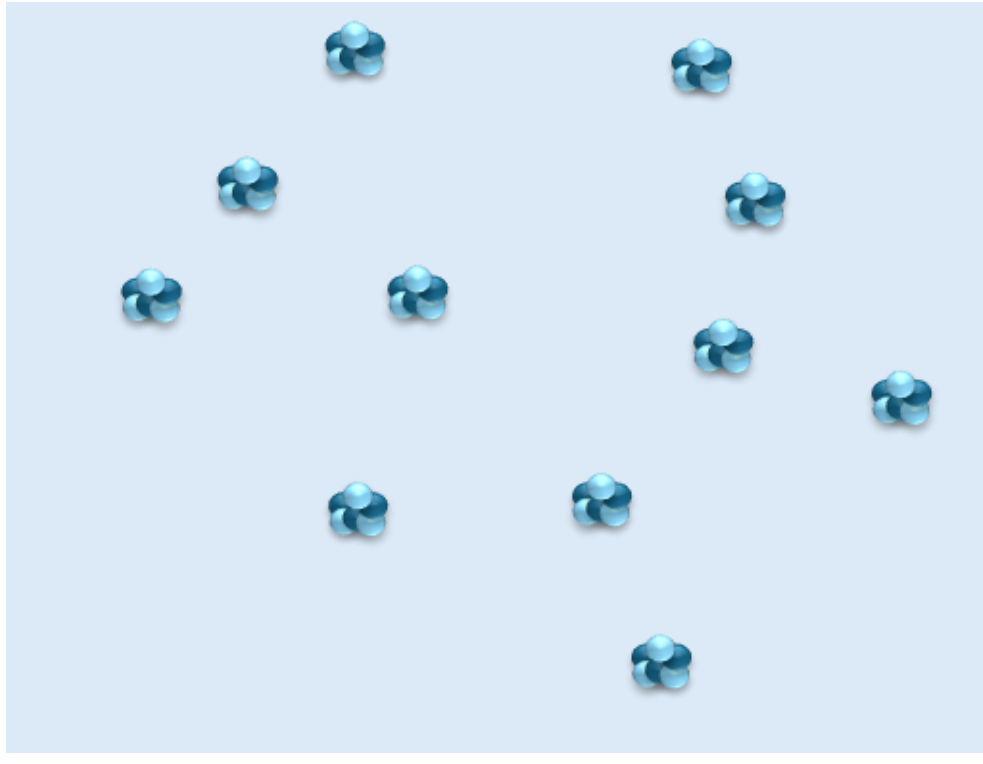
 Target material (e.g. Ra-226)

 Radionuclide (e.g. Ac-225)

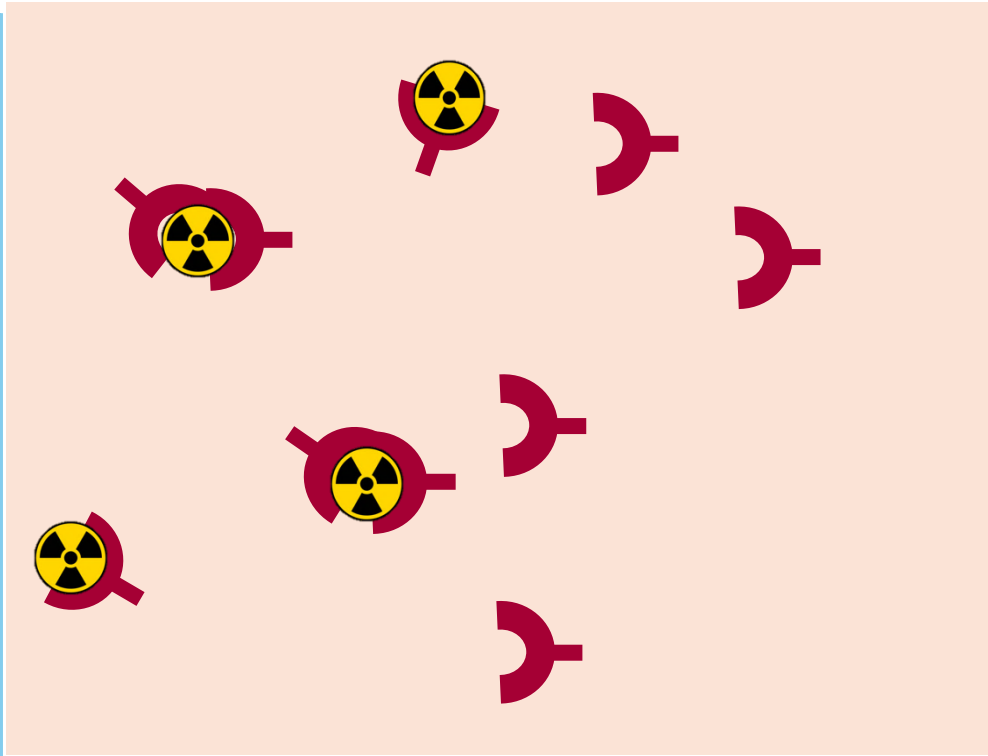
 Chelator


# Solvent extraction

aqueous phase (water based)




organic phase (e.g. chloroform)



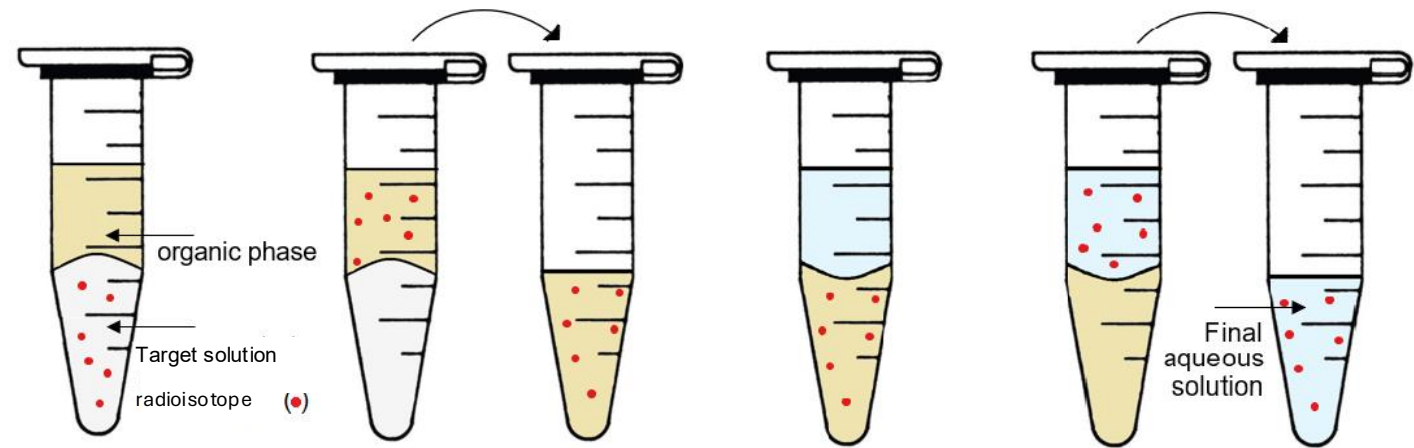
 Target material (e.g. Ra-226)

 Radionuclide (e.g. Ac-225)

 Chelator

# Solvent extraction - batch

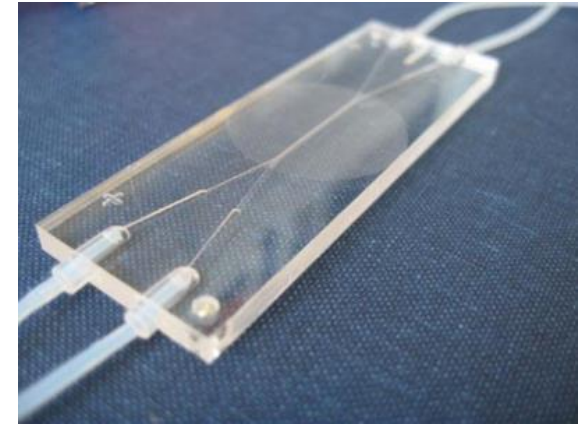
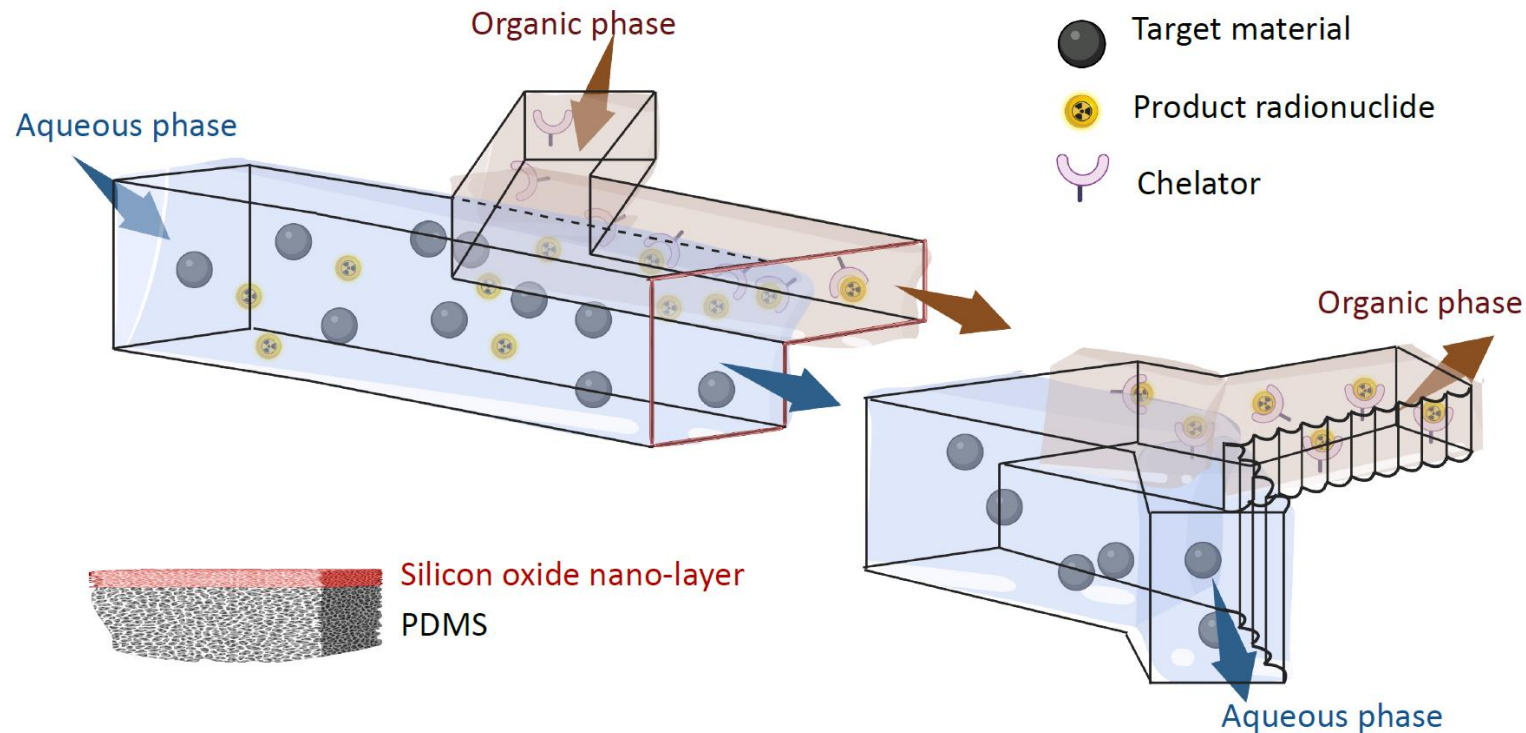
- In vials on vortex shaker
- Batch experiments are done to determine equilibrium extraction efficiencies!



→ Difficult to automate!

# Microfluidic solvent extraction

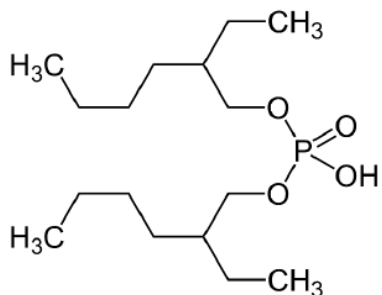
- High surface to volume ratio
- Enables direct target recycling



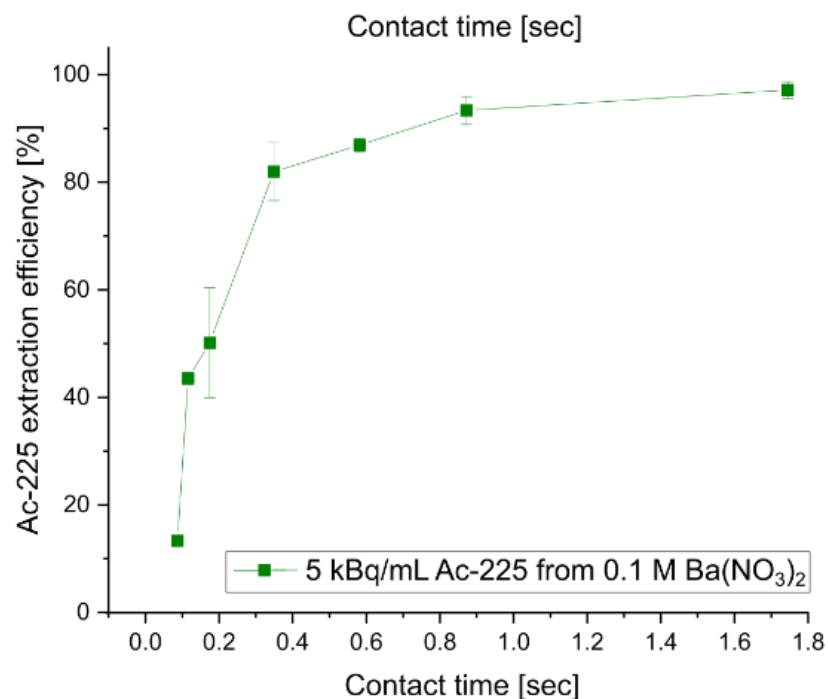
# Microfluidic extraction with D2EHPA

Extraction with:

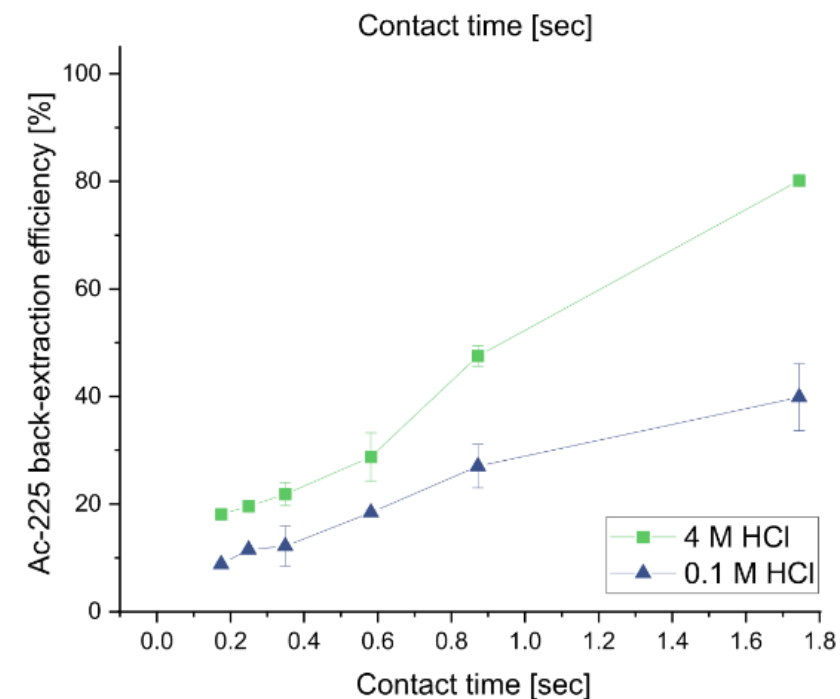
10v% D2EHPA in Chloroform



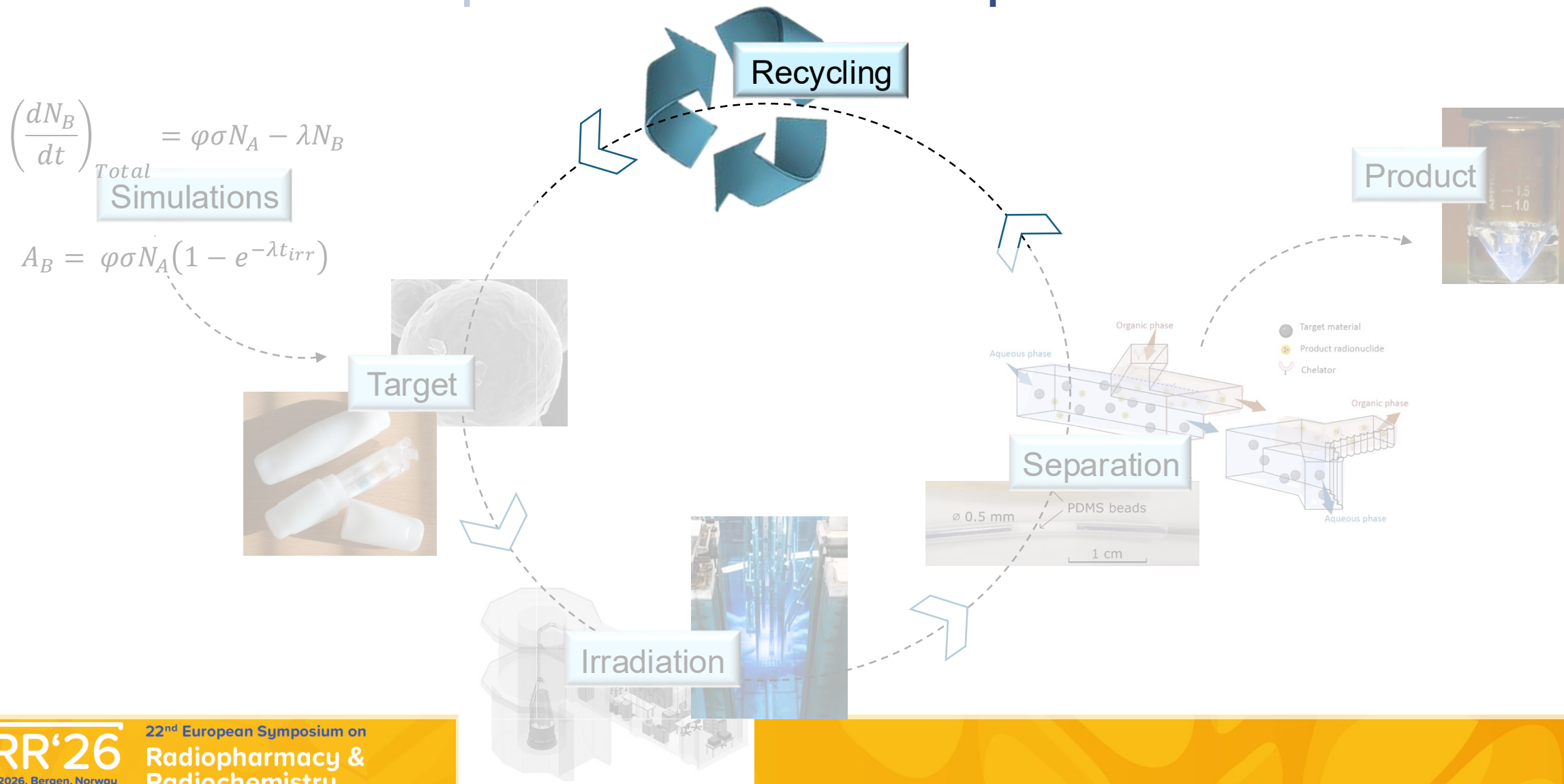
$^{225}\text{Ac}$  extraction



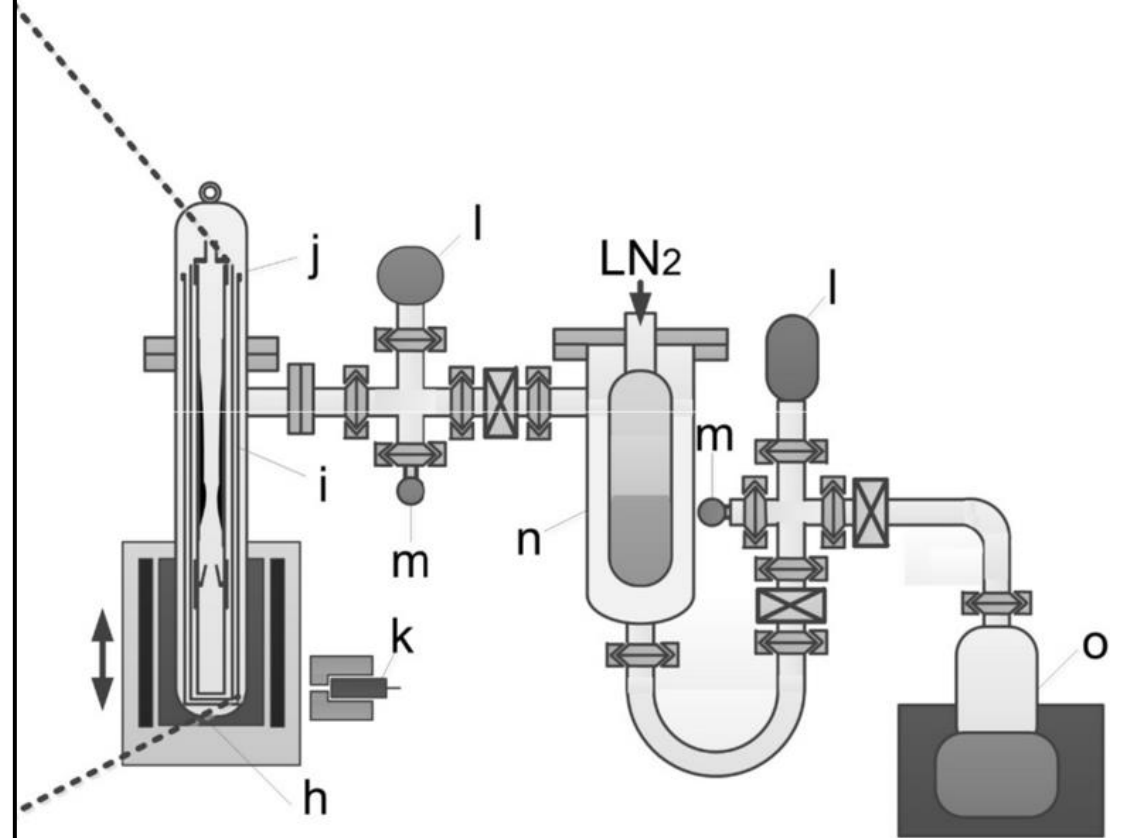
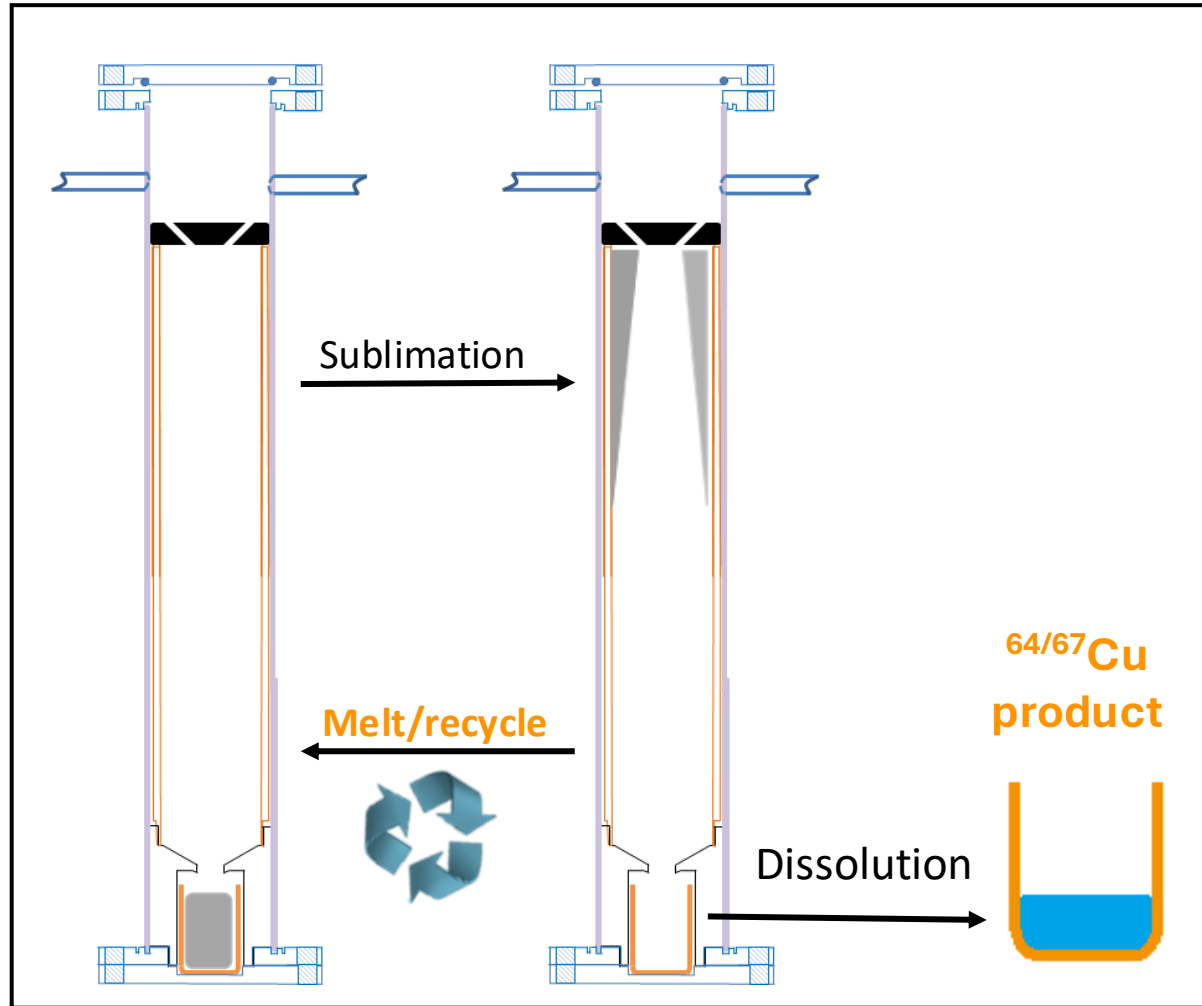
$^{225}\text{Ac}$  back-extraction



# Radionuclide production and separation



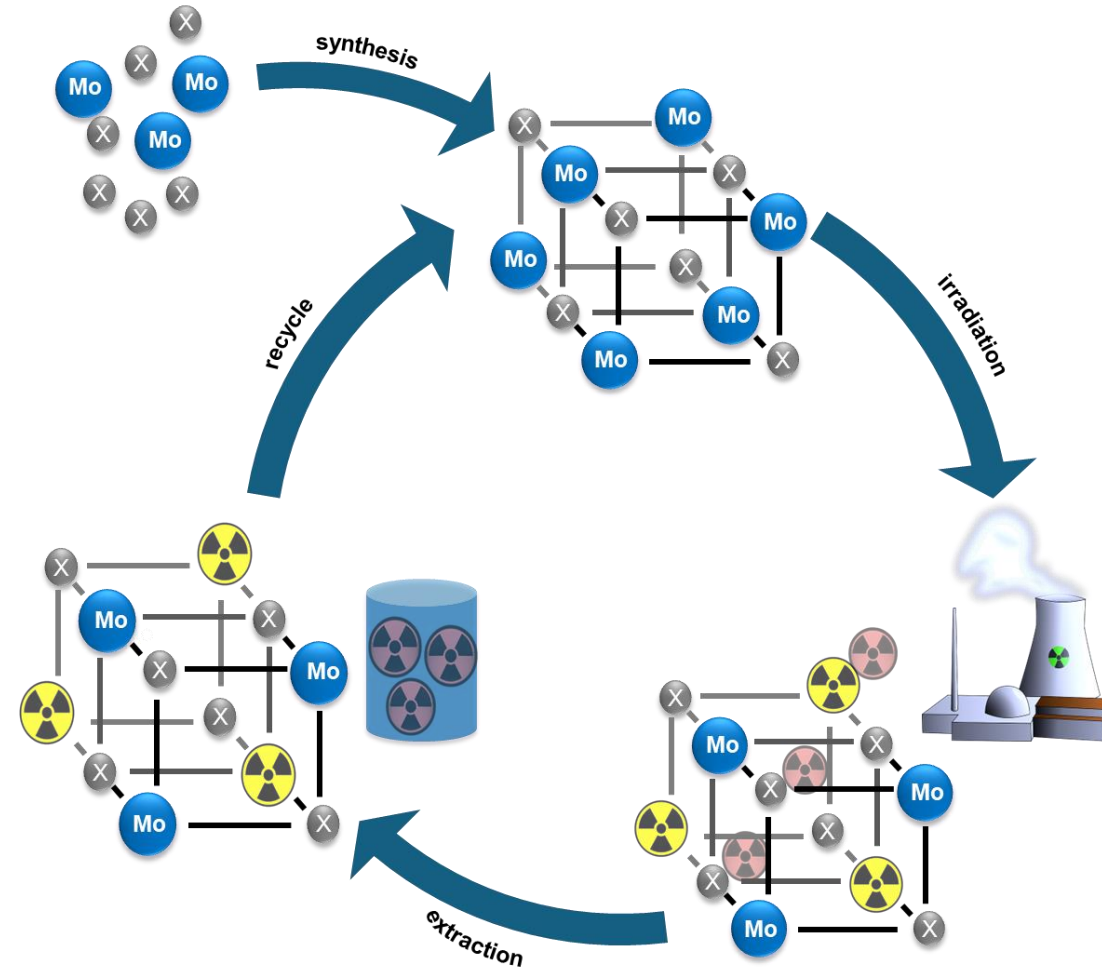
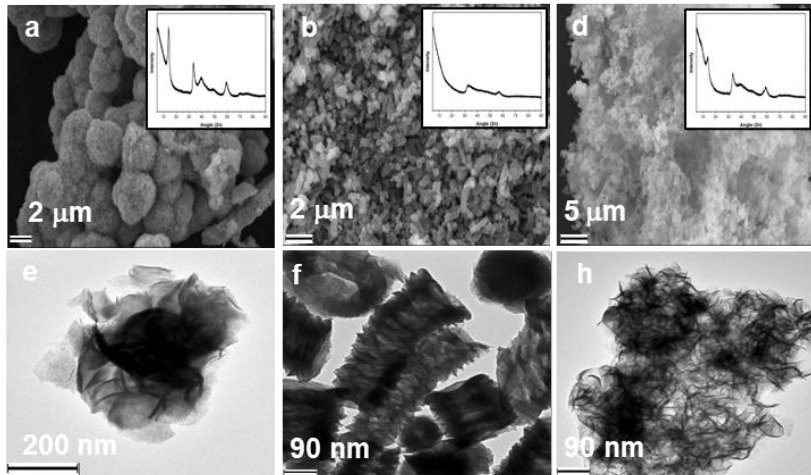
# Sublimation-based separation – recycling made ‘easy’!



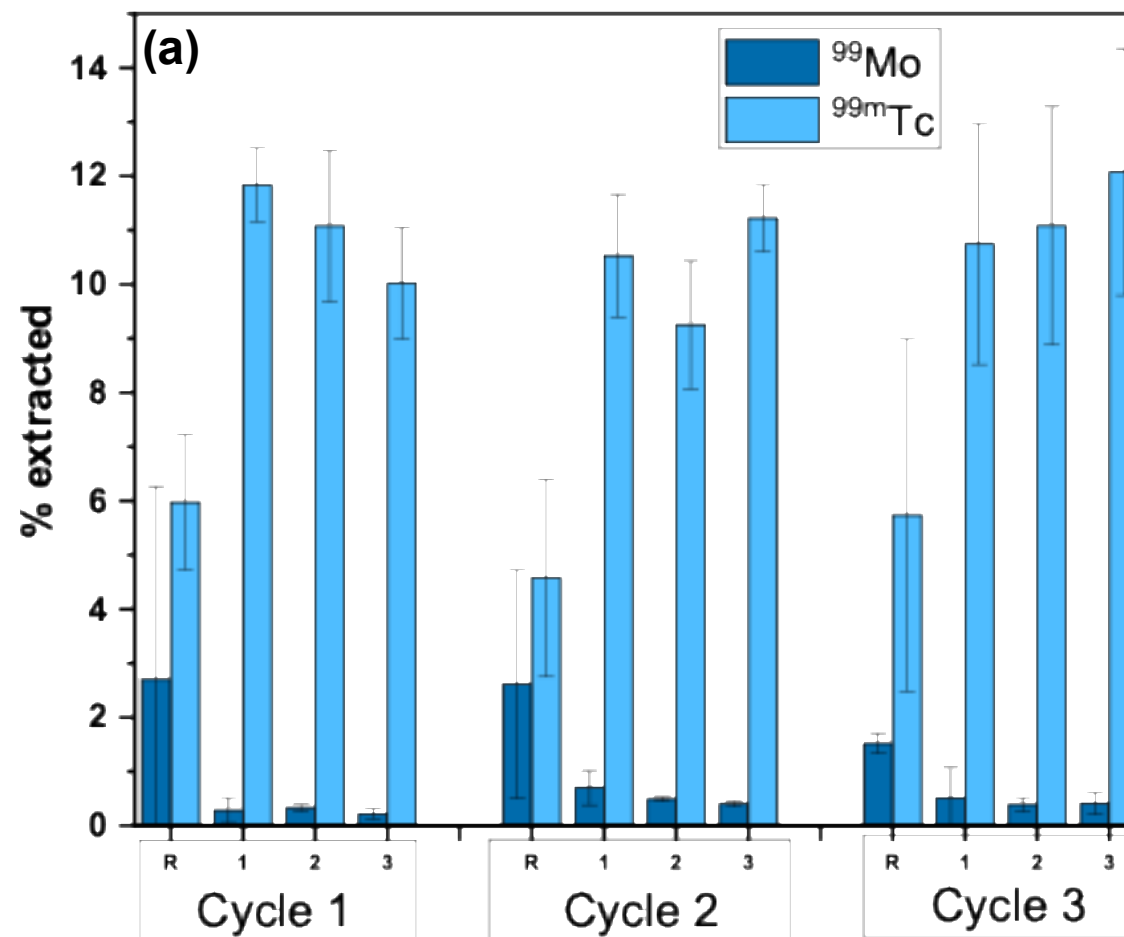
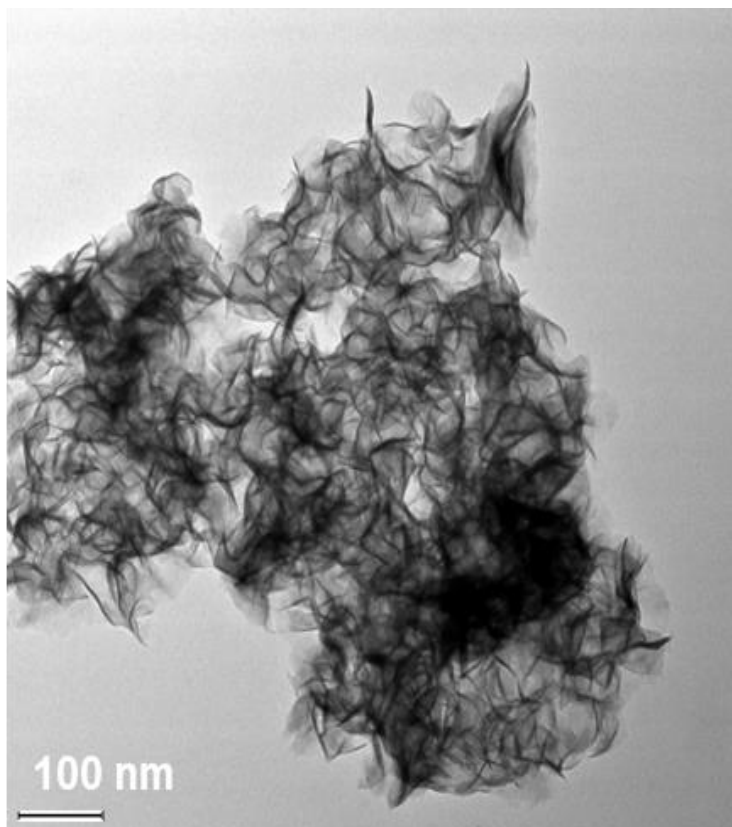
# Nanoparticle-based recyclable target materials

## Requirements

- Large surface area / porosity
- Chemical and radiation stability
- High  $^{99m}\text{Tc}$  extraction
- Low Mo breakthrough



# Multiple Irradiation Cycles of **NDS** in MEK

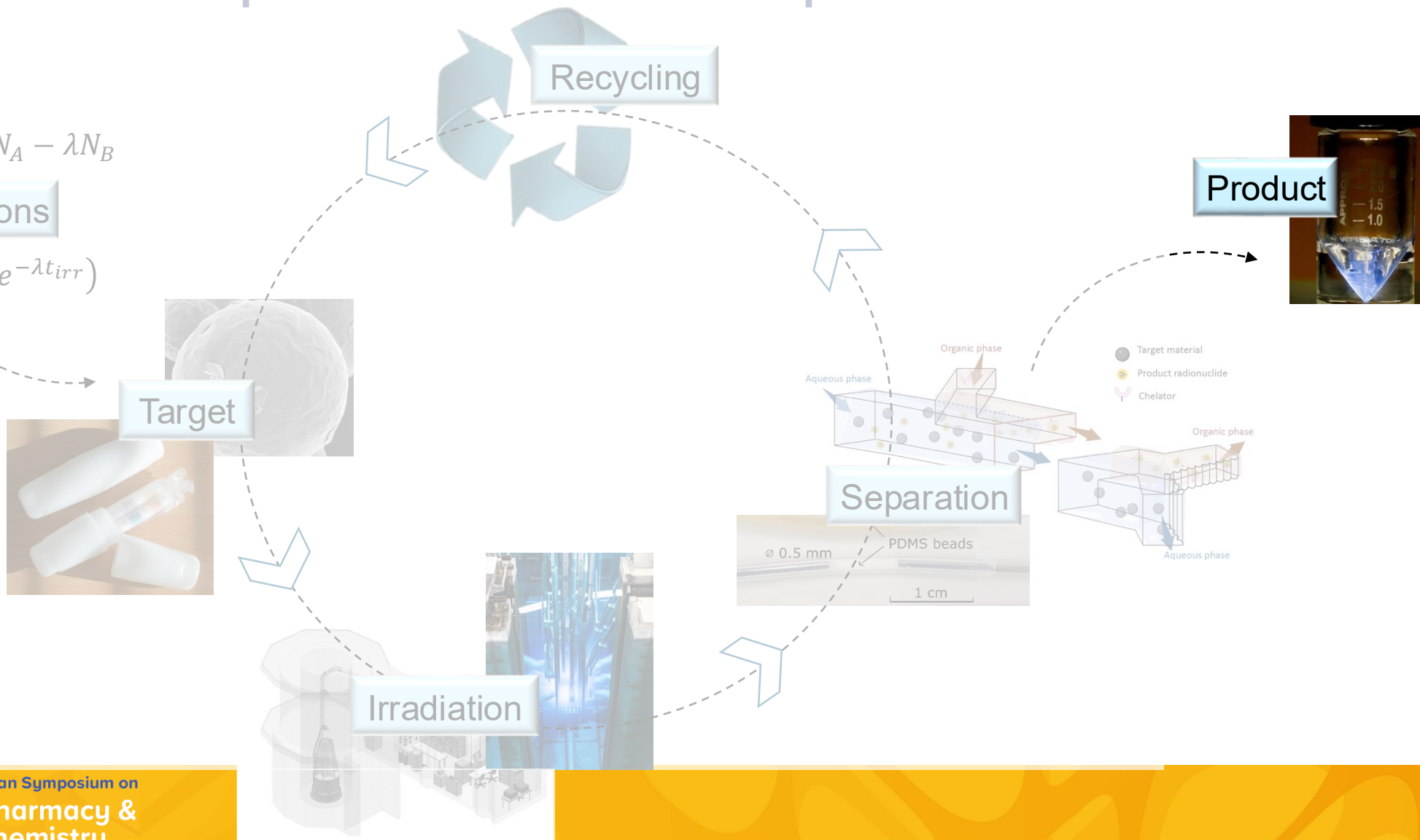


# Radionuclide production and separation

$$\left(\frac{dN_B}{dt}\right)_{Total} = \varphi\sigma N_A - \lambda N_B$$

Calculations

$$A_B = \varphi\sigma N_A(1 - e^{-\lambda t_{irr}})$$



# Specific activity – a matter of definitions



$$SA = \frac{A(t)}{m}$$

## Radionuclide production:

Specific activity

m = mass of same element

Effective specific activity

m = mass chemically similar elements

## Radiopharmacy:

m = mass / moles of chemical compound

## Radiological health physics:

m = total mass or volume of solution

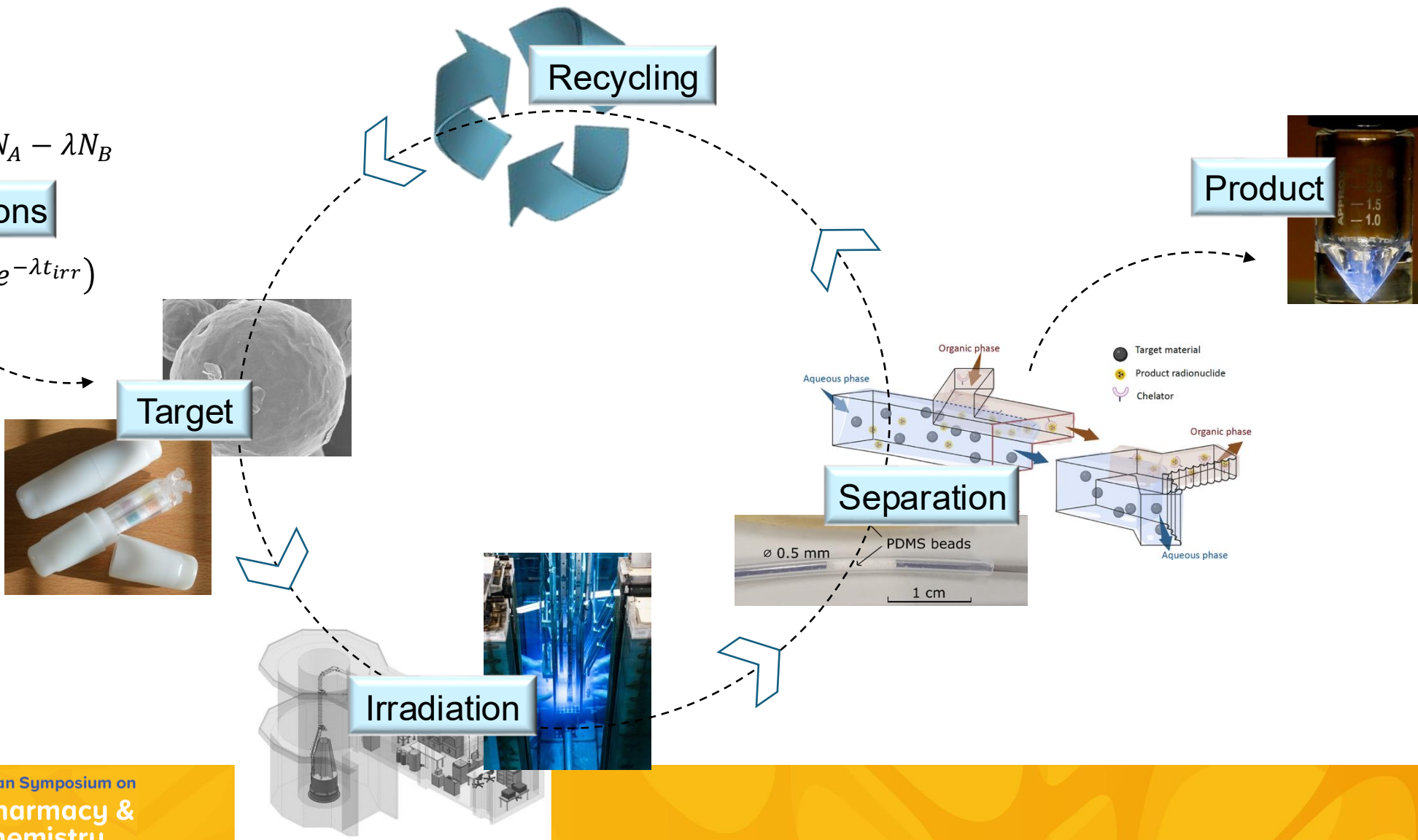
Make sure you talk the same language!

# RADIONUCLIDE PRODUCTION AND SEPARATION

$$\left(\frac{dN_B}{dt}\right)_{Total} = \varphi\sigma N_A - \lambda N_B$$

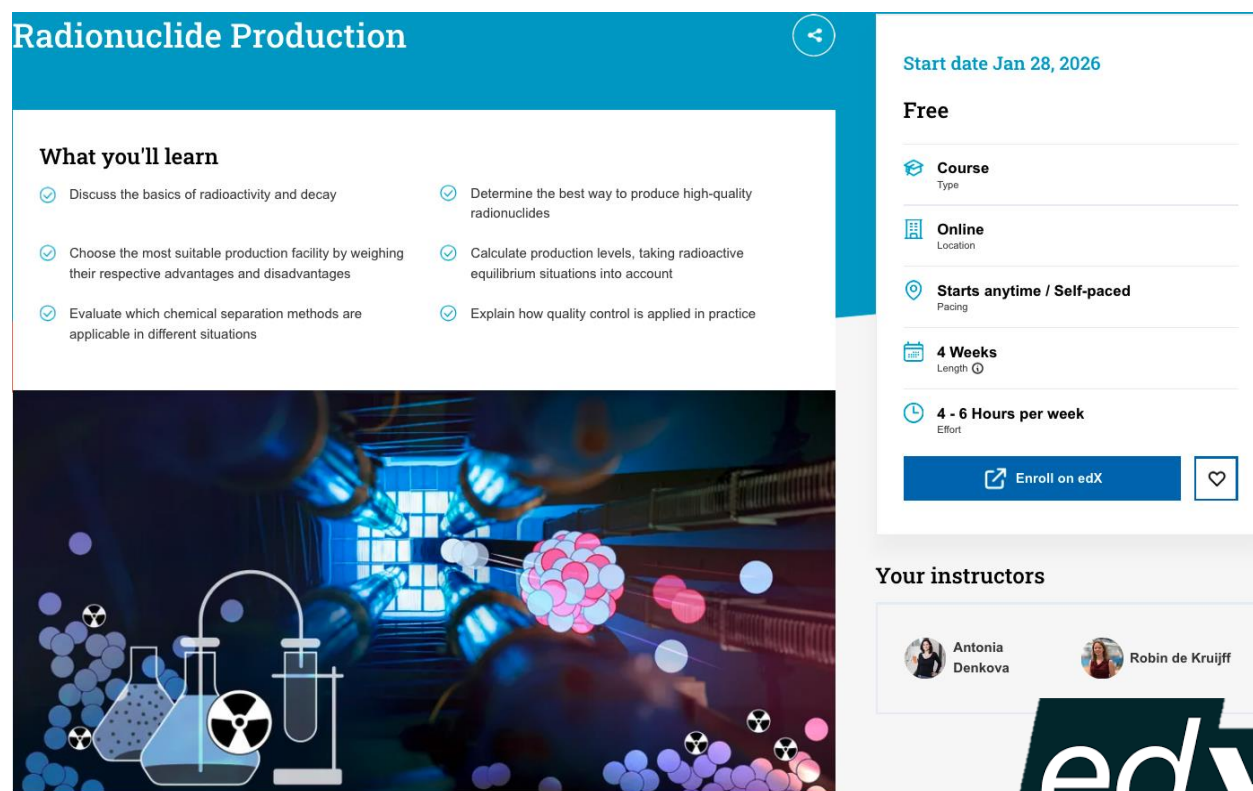
**Calculations**

$$A_B = \varphi\sigma N_A(1 - e^{-\lambda t_{irr}})$$



# Want to know more? Check our free online course on radionuclide production!

*“One of the most rewarding learning experiences I’ve had in a field I’m deeply passionate about”*



**Radionuclide Production**

Start date Jan 28, 2026

Free

Course Type

Online Location

Starts anytime / Self-paced Pacing

4 Weeks Length

4 - 6 Hours per week Effort

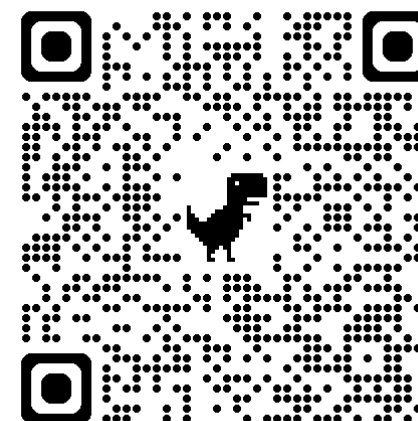
Enroll on edX

Your instructors

Antonia Denkova, Robin de Kruijff

**What you'll learn**

- Discuss the basics of radioactivity and decay
- Determine the best way to produce high-quality radionuclides
- Choose the most suitable production facility by weighing their respective advantages and disadvantages
- Calculate production levels, taking radioactive equilibrium situations into account
- Evaluate which chemical separation methods are applicable in different situations
- Explain how quality control is applied in practice



*“A well-structured and insightful course”*

*“Without a doubt, it was a challenging one, but this course was laid out with the utmost detail and structure.”*





Thank you!