FIELD-LAB: advancing nuclear medicine

EURADOS

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EURADOS Webinar
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Medical isotopes are in use for decades, specifically for diagnosis

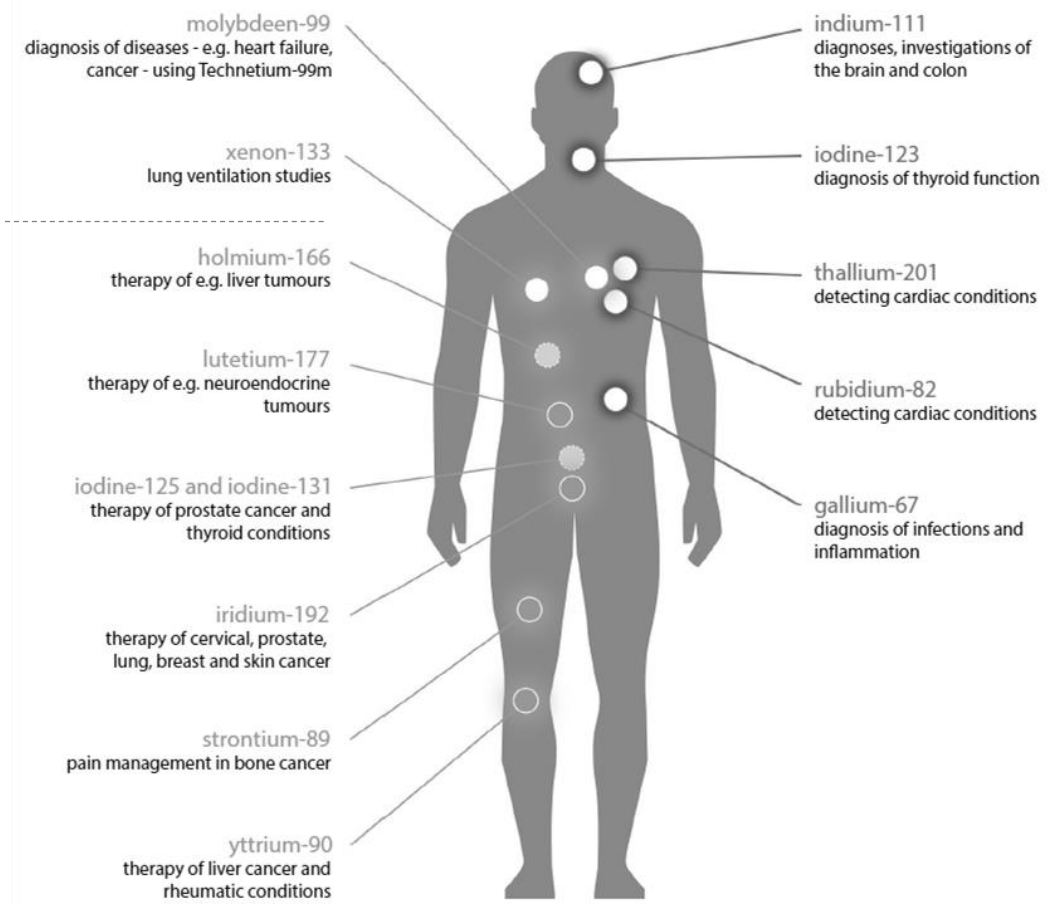
Current applications of medical isotopes in nuclear medicine – 2020

Diagnostics

40 million SPECT scans

Therapeutics

0.5 - 1 million procedures



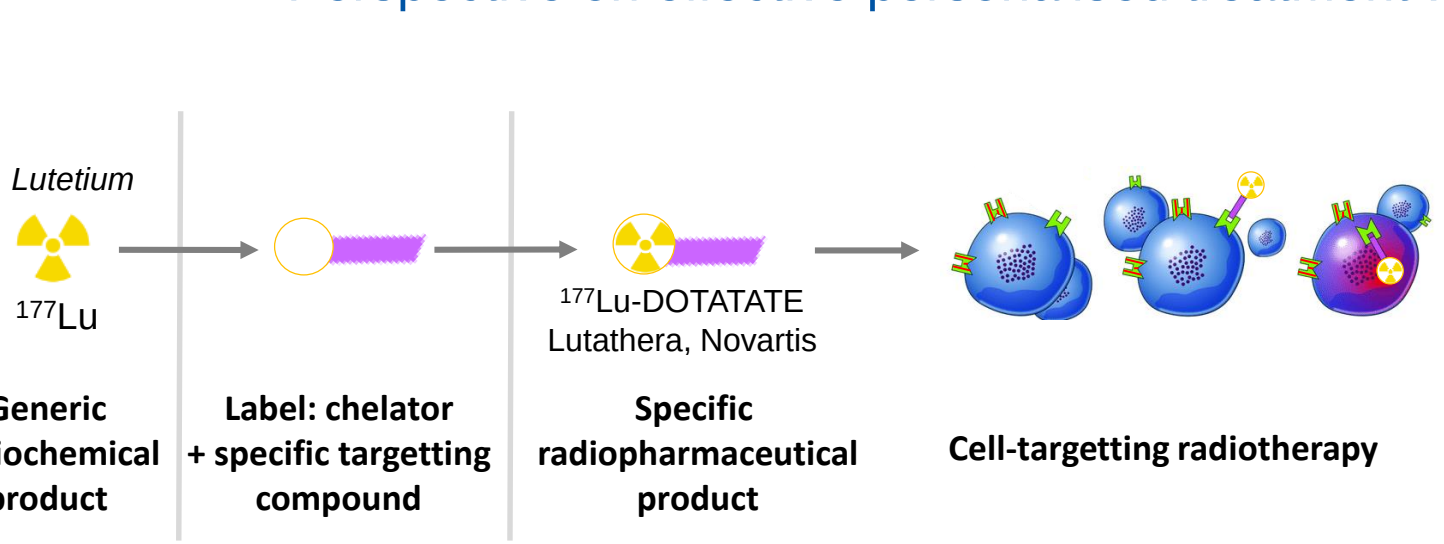
Diagnostics

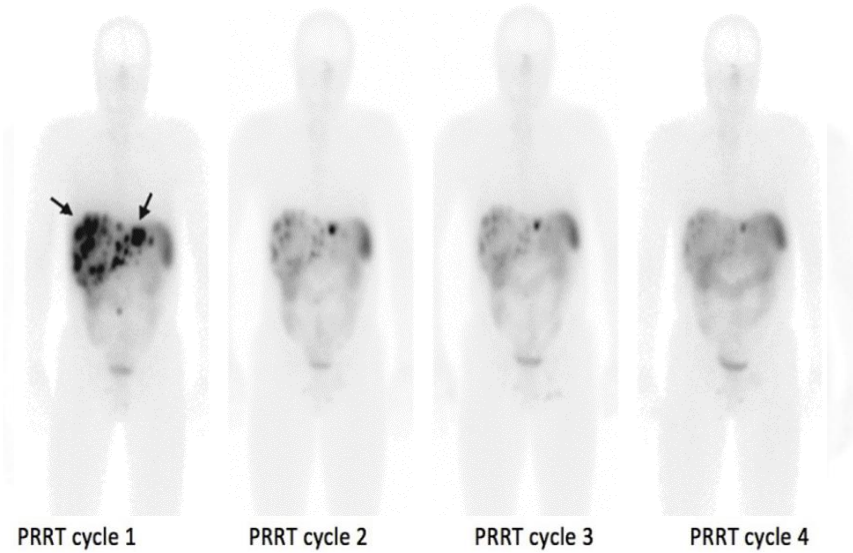
7.5 million PET scans

Source: *Medische isotopen, belang voor de wereld en kansen voor Nederland* (Nucleair Nederland 2017), MEDRaysintell 2019

Targeted radiotherapy: localized radiation at cell level

Perspective on effective personalised treatment with limited side effects



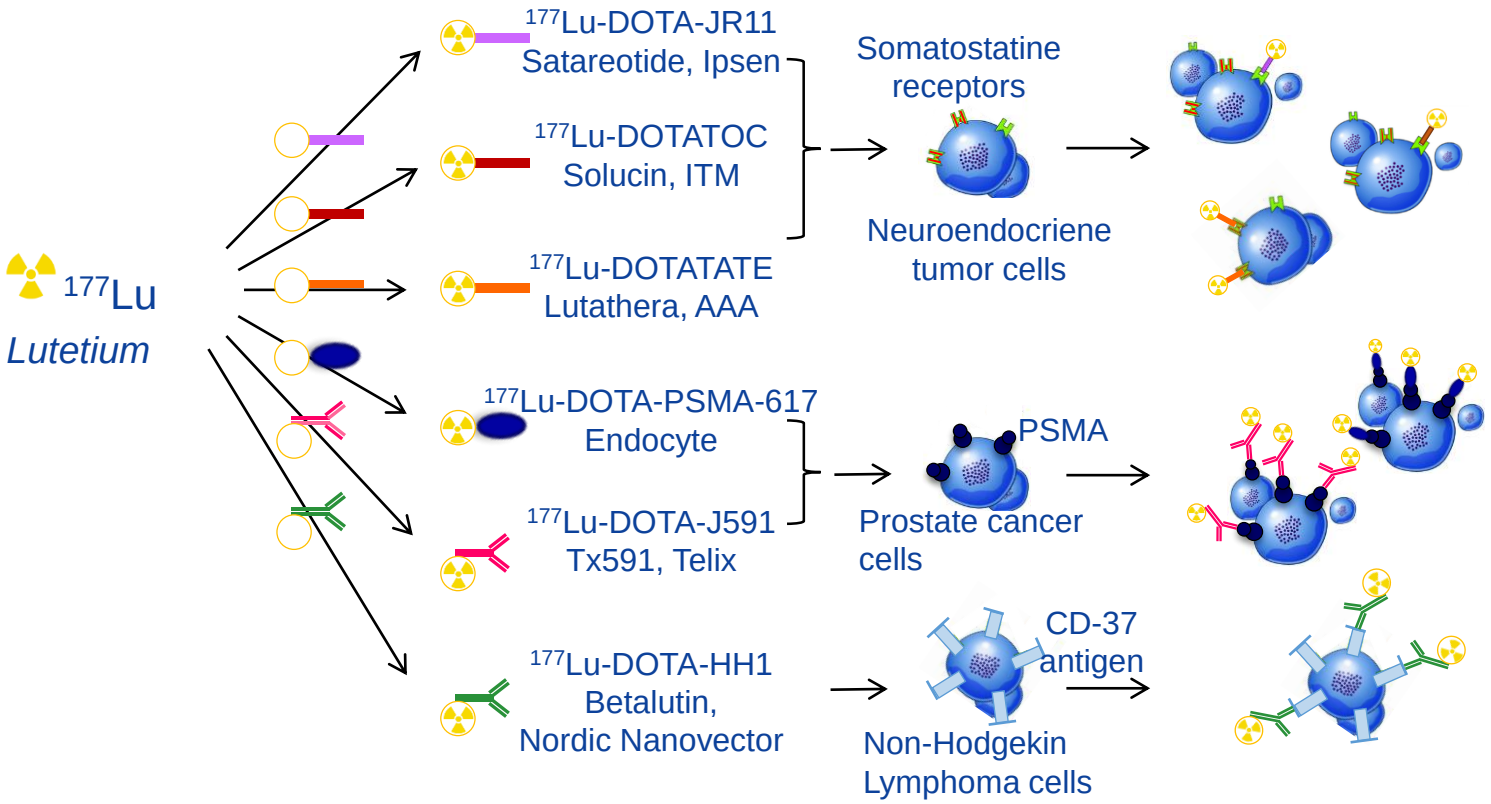


Treatment of a NET-patient with ^{177}Lu-labelled product
Source: Erasmus UMC, Kwekkeboom

- Therapeutic isotopes generate harmful radiation, that can damage cells, but over a short range.
- In the past decades many compounds have been discovered that connect specifically to receptors only found on cancer cells.
- By connecting these isotopes to these compounds, cancer cells (and not other cells) are damaged by radiation.
- This method offers perspective on effective treatment with minimized side effects.

One isotope, many applications

Over 30 different Lutetium-based products for different cancer indications are in or entering clinical stages



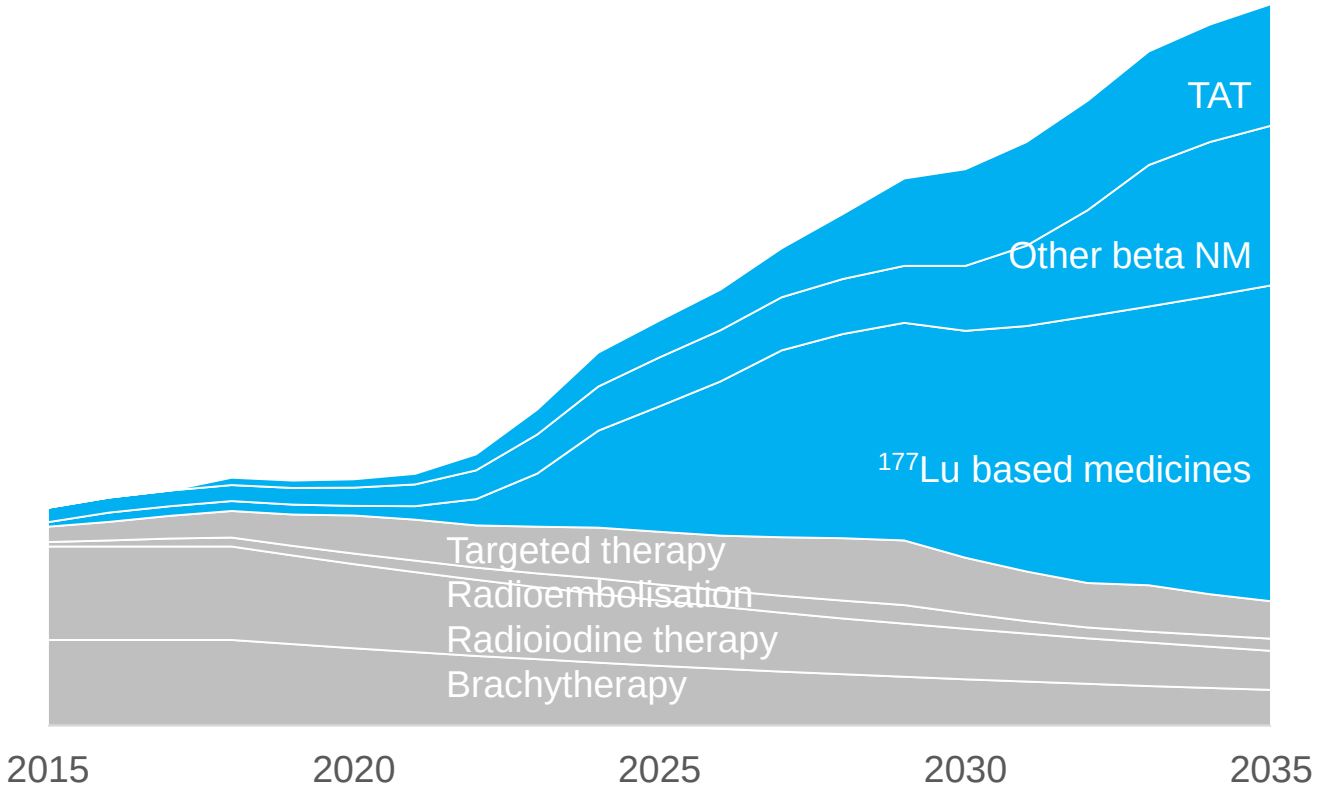
A large range of compounds is under development, allowing specific targeting, patient-specific → **Personalised treatment**

Main growth segment is therapeutics, to become mainstream

Possible growth in demand for nuclear medicine

Therapeutics

Medium growth scenario for worldwide therapeutic nuclear medicine doses



Source: MEDRaysintell, PALLAS business case, Novartis

Evidence:

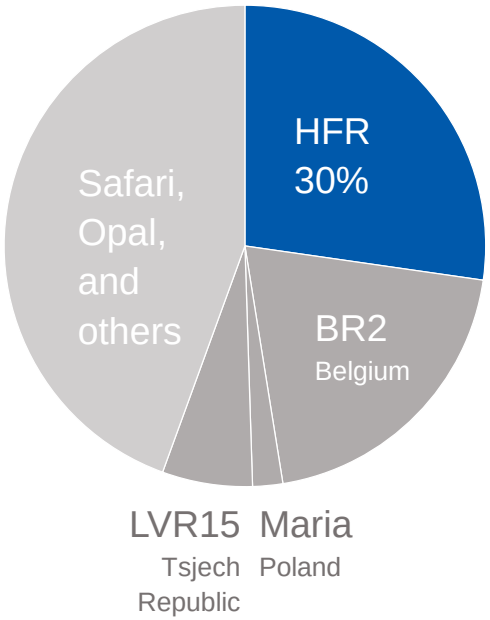
- 50-100 medicines in pipeline
- Increasing investment from pharma sector
- Nuclear medicine becoming mainstream
- High effectiveness potential: search-and-destroy of tumours and metastases, targeted, personalised, with few side effects

NRG - PALLAS prepare new infrastructure, not just a reactor

Position Petten / NRG - PALLAS in 2030

Current position

Share of global isotope irradiation volume



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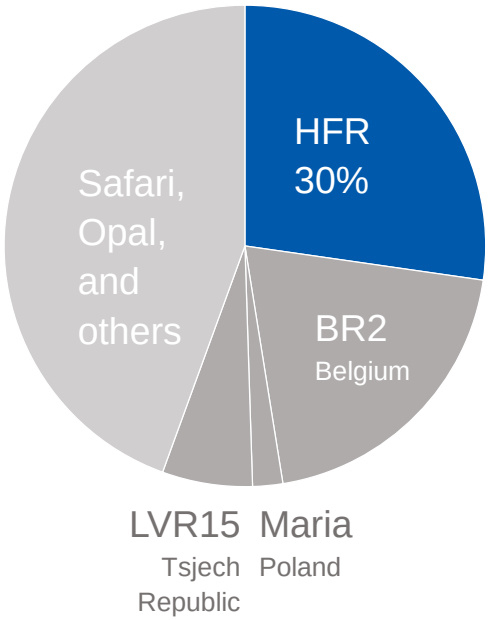
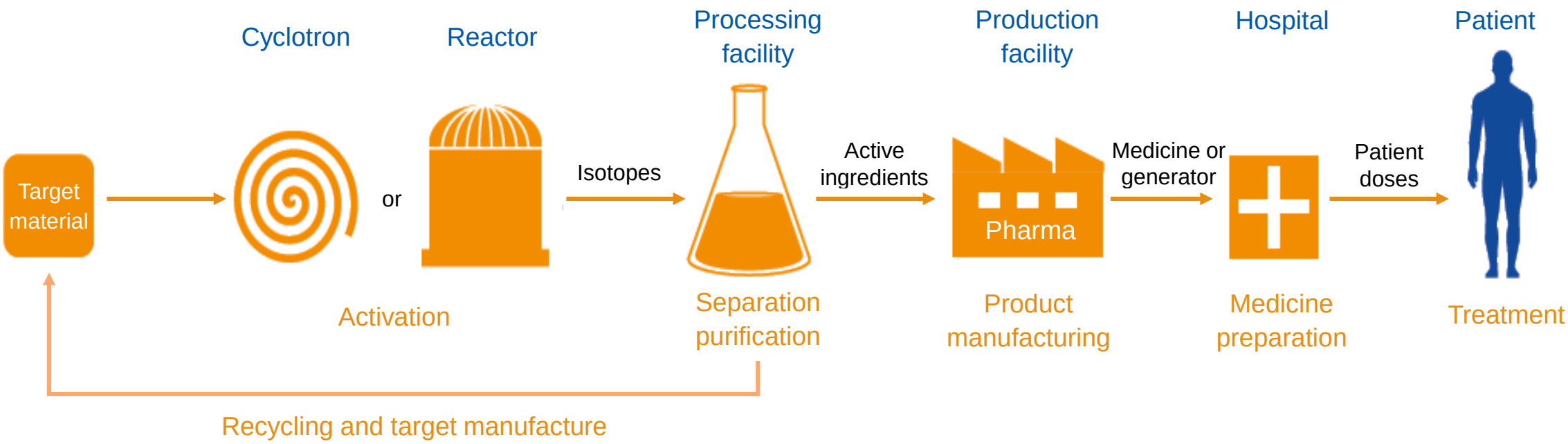


	Facilities 2021	New Facilities 2030	Role in nuclear medicine
Irradiation	 High Flux Reactor	 PALLAS-reactor	• 30% market share globally • 70% in Europa • Continuity security of supply
Processing	 Molybdenum Processing Facility	 Nuclear Health Centre	• Efficient production • Less logistics, less waste • Outsourcing, supply chain solutions
Innovation	 Laboratoria	 FIELD-LAB	• Development new isotope production and processing schemes • More efficient production technology

Supply chain of nuclear medicine

Dosimetry - radiation safety is of relevance in every step of the chain



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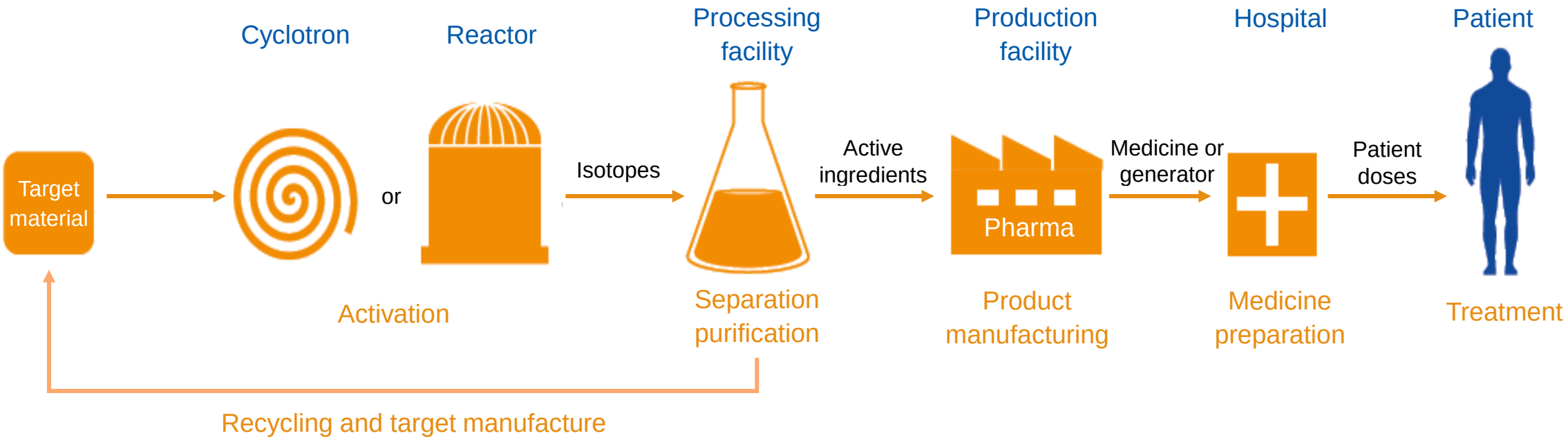

Therapeutic isotope application and demand will grow, this has large impact on dosimetry efforts for:

- Occupational exposure: (new) infrastructure to be established for the protection of (operator) employees
- Environmental exposure: optimisation of waste streams and accident scenarios for production and transport
- Medical exposure: determine the right balance between toxicity and efficiency for patients
- Occupational exposure: impact of (new) nuclear medicine treatment and protection of (medical) employees

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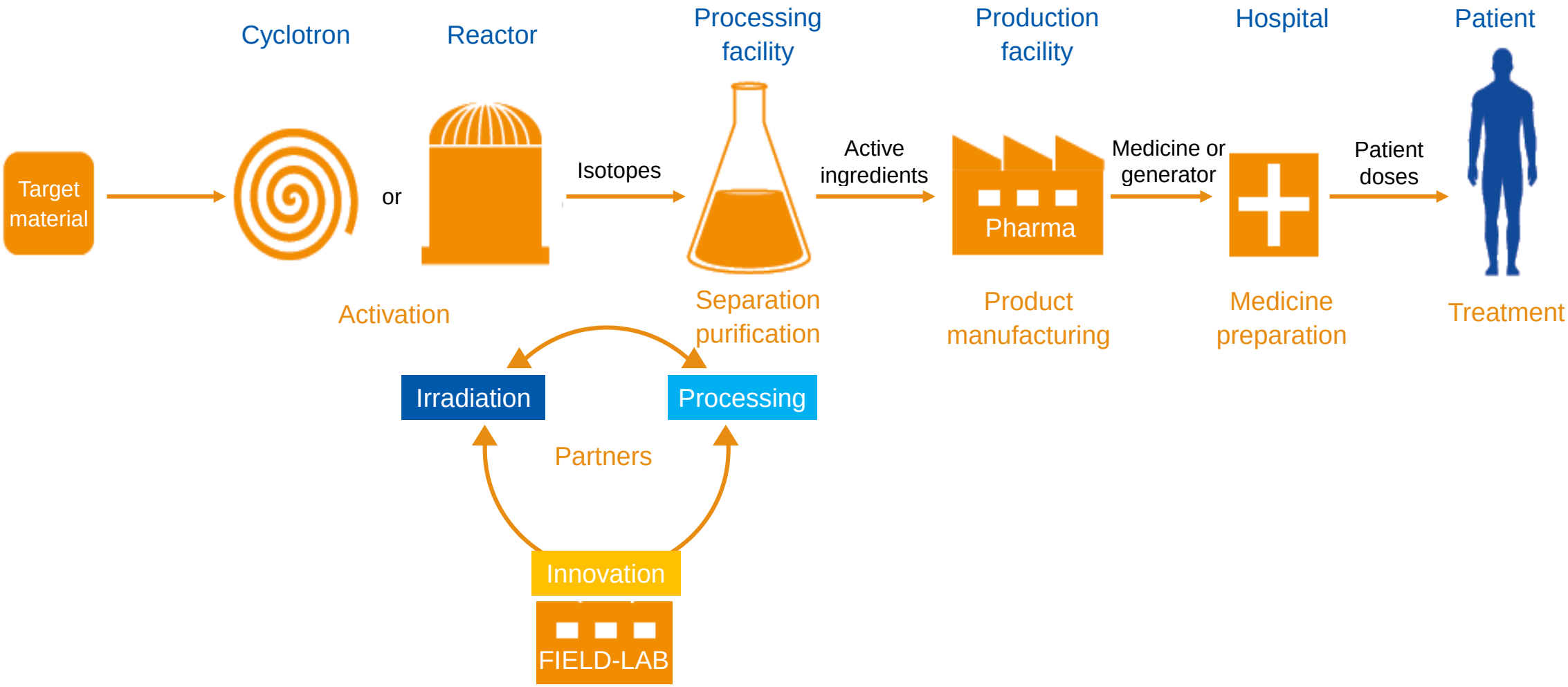

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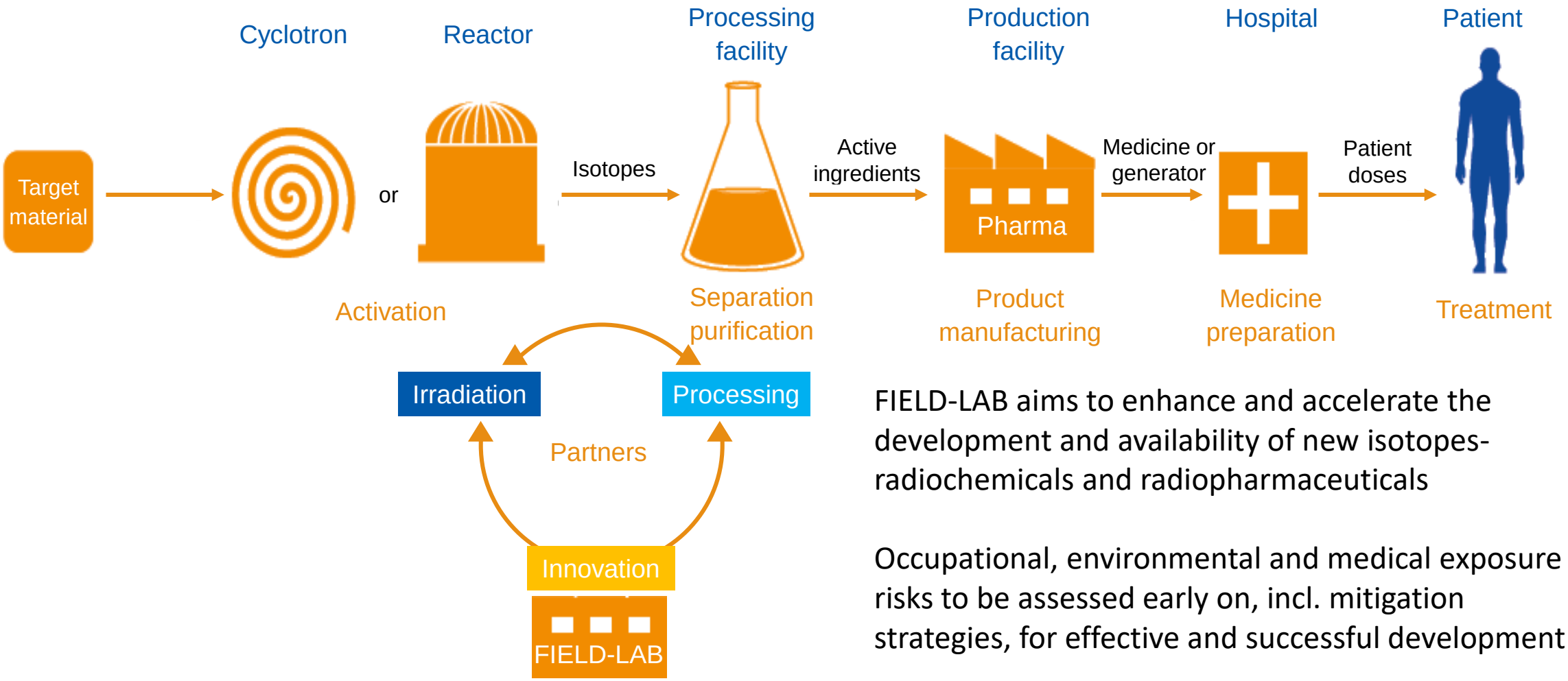
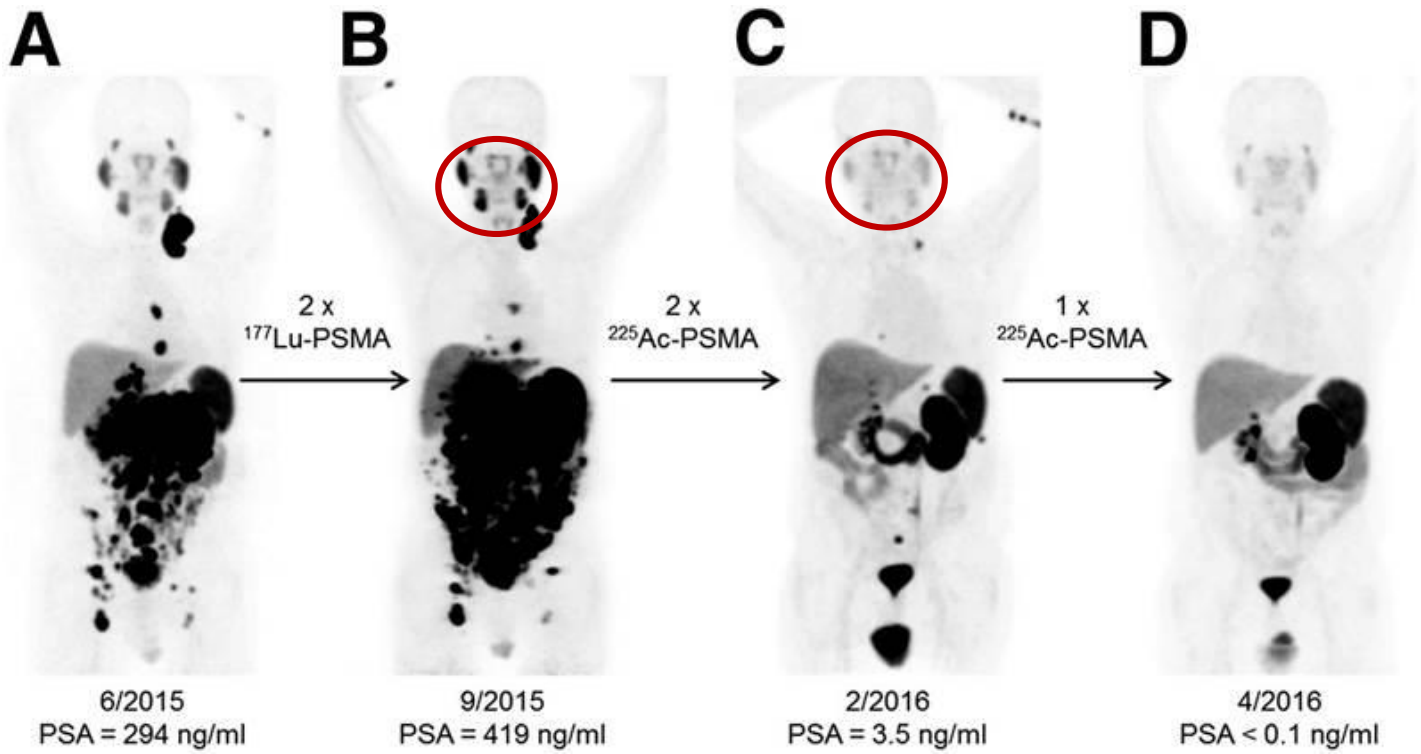


FIELD-LAB aims to enhance and accelerate the development and availability of new isotopes-radiochemicals and radiopharmaceuticals

Occupational, environmental and medical exposure risks to be assessed early on, incl. mitigation strategies, for effective and successful development

Targeted Alpha-Therapy could be the next step

Similar to Lutetium, one isotope can be associated with a multitude of targeting compounds



- Therapy with ^{177}Lu is not effective for 20-25% of the patients.
- In addition, cancer becomes resistant to beta-emitter treatment over time.

- Actinium (^{225}Ac) holds a large promise
- However, ^{225}Ac is a relatively long-lived high damage multiple alpha-emitter:
  - Medical concerns regarding off-target and longer term side effects

- Other alpha-emitters can be considered
  - Shorter half-live
  - Less alpha's in the decay chain

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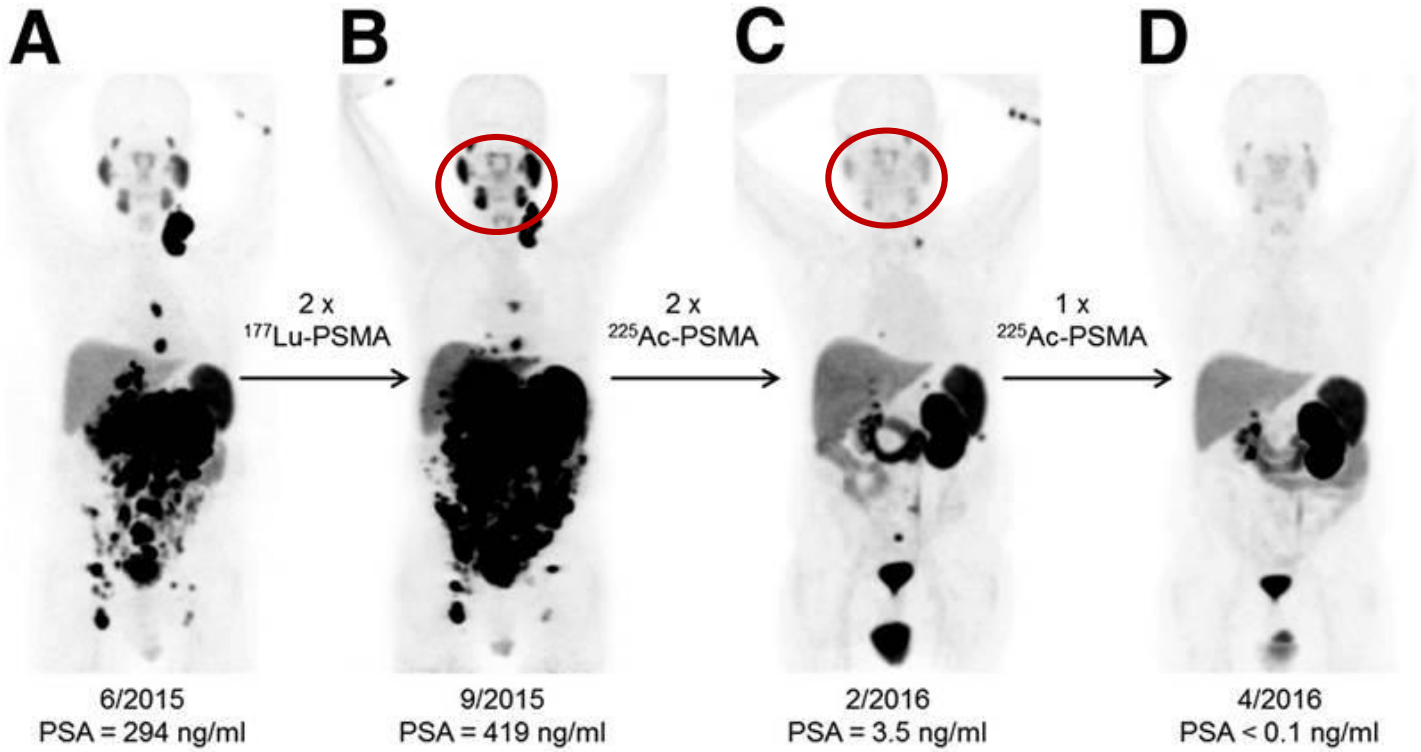

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Significant research and development still needed, specifically on targetting efficiency, and compound related off-target effects

Dosimetry coupled to compound biodistribution and kinetics?

Various alpha-emitters to be considered

Which one depends largely on the targetting compound specifics, and availability

Isotope	Source	Half-life	Decay
Bismuth-212	Pb212 (Ra224)	60 m	1 α
Lead-212	Ra224 (Th228)	10 h	1 β -> 1 α
Bismuth-213	Ac225 (Th229)	45 m	1 β -> 1 α
Actinium-225	Th229 (Ra225)	10 d	4 α
Radium-223	Th227 (Ac227)	11 d	4 α
Radium-224	Th228	4 d	4 α
Thorium-227	Ac227	19 d	5 α
Astatine-211	*Cyclotron*	*7.2 h*	*1 α*
Terbium-149	*Cyclotron*	*4 h*	*1 α + 1 β+*
More alpha isotopes and more production methods…			

- Alpha-emitter selection: balance between decay-time (half-life) and damage profile (number of alpha's emitted in the decay chain)
- After alpha-decay, the isotope is no longer bound to the targetting compound (recoil): this can lead to off-target effects (side effects) of multi-alpha isotopes
- The half-life needs to match with the targetting compound characteristic: long enough to ensure the compound+isotope reaches target locations, not too long to avoid isotope distribution (residence time)
- Short-lived isotopes: challenge to produce, process, distribute and administer very quickly
- Availability & cost are critical for large scale application (often neglected in R&D phases)

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Targetting efficiency, and decay-related off-target effects

Free isotopes due to recoil: **Dosimetry coupled to biodistribution and kinetics of decay daughters?**

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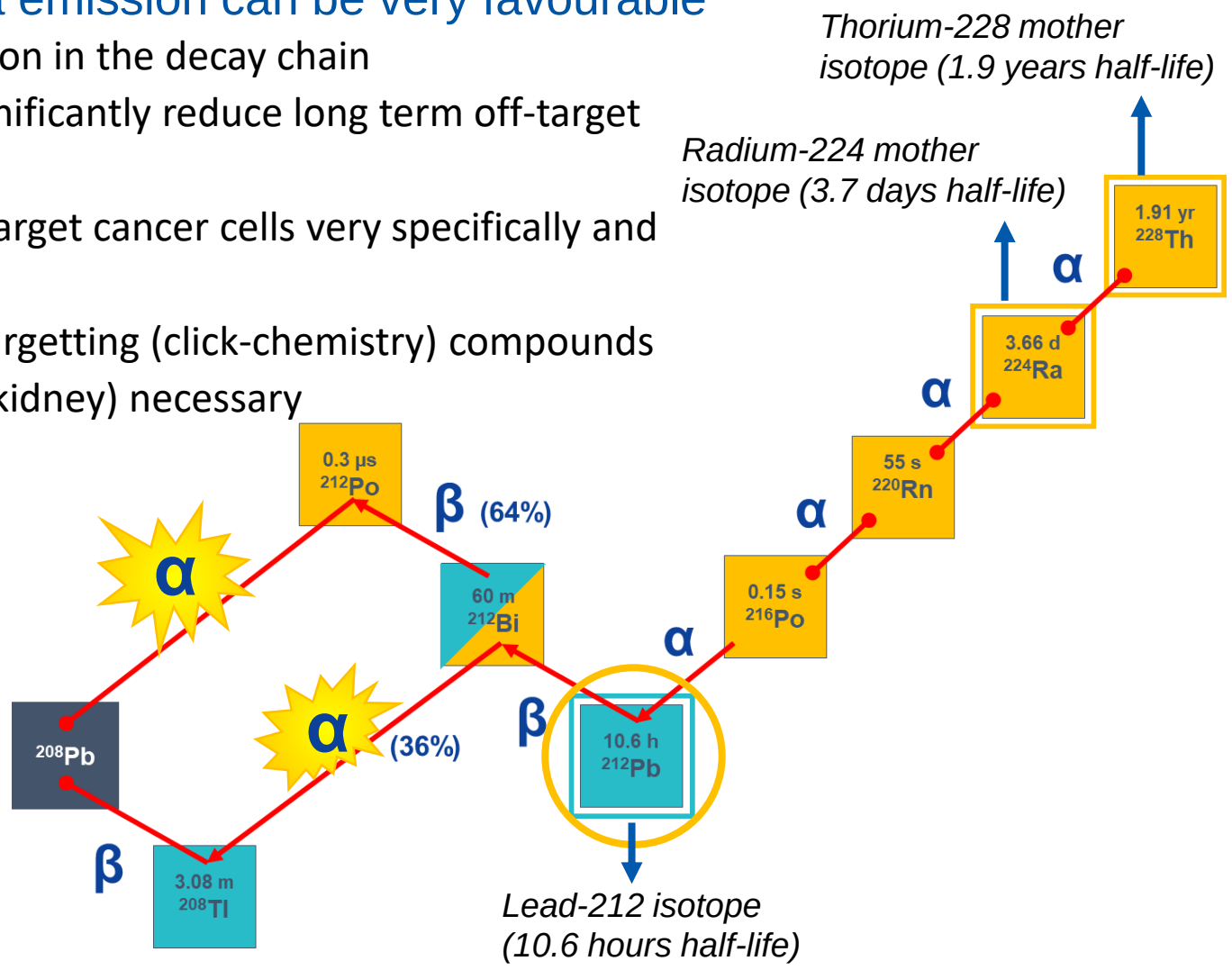
Example: ^{212}Pb (Lead-212)

Half-life and single alpha emission can be very favourable

- Lead-212 is a beta emitter, with a single alpha emission in the decay chain
- Single alpha and relatively short half-life (11 hrs), significantly reduce long term off-target effects
- Short half-life limits application to compounds that target cancer cells very specifically and quickly:
  - Suitable for small molecules, peptide and pre-targetting (click-chemistry) compounds
  - High initial activity can make organ protection (kidney) necessary

- Long-lived mother isotopes enable centralized production, and distribution via generators
- Source isotope is ^{228}Th (Thorium-228), which can be produced via multiple routes, large scale most conveniently via reactor



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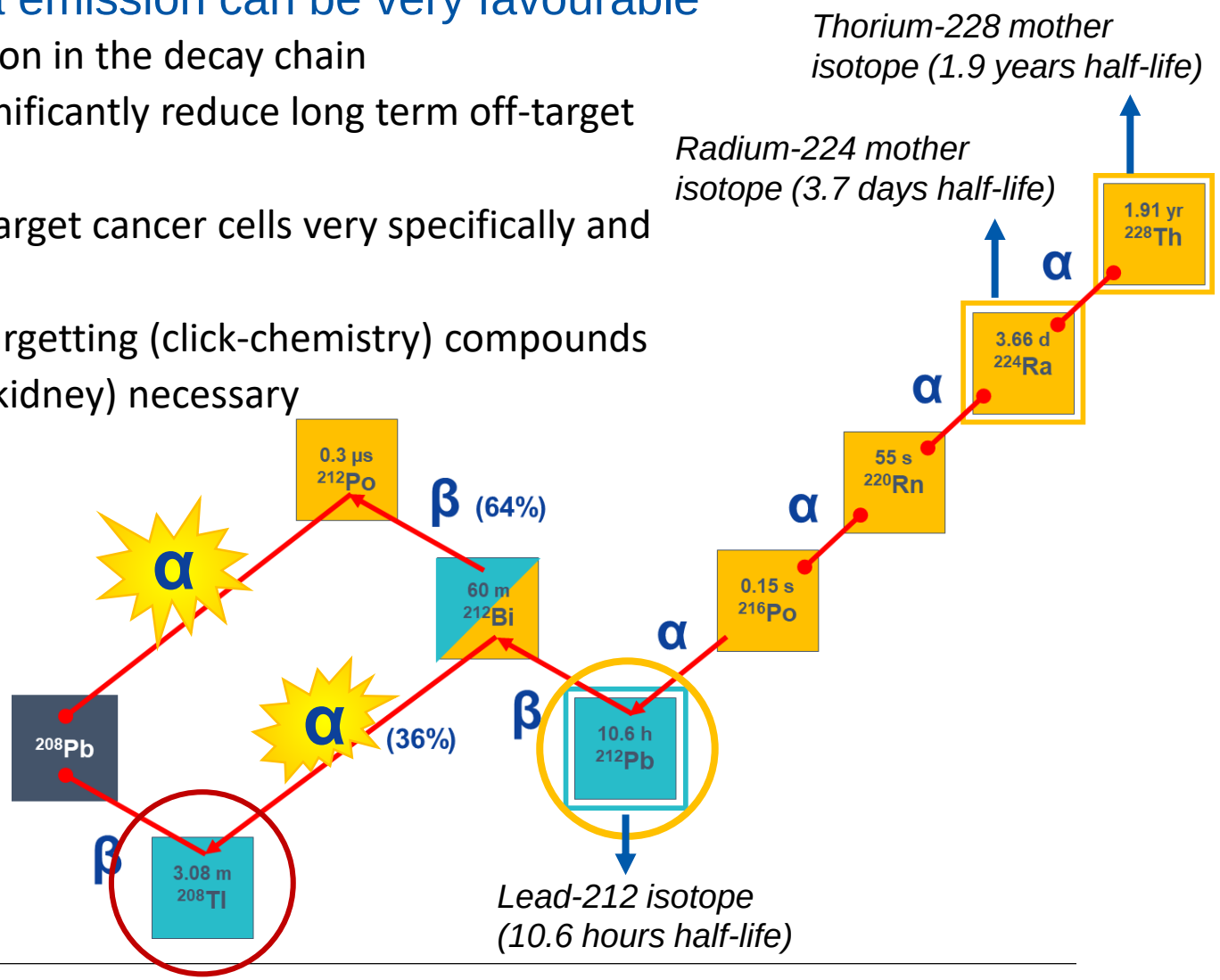
- The decay chain produces a strong gamma (^{208}Tl, Thallium-208), which is difficult to shield

Dosimetry challenge: occupational exposure



Auger emitters: holy grail of TRT?

Large dosimetry challenges to predict efficiency/toxicity

Human cell diameters are between 5-150 micron:

Alpha-particle: range 40-100 micron (5000-9000 keV)

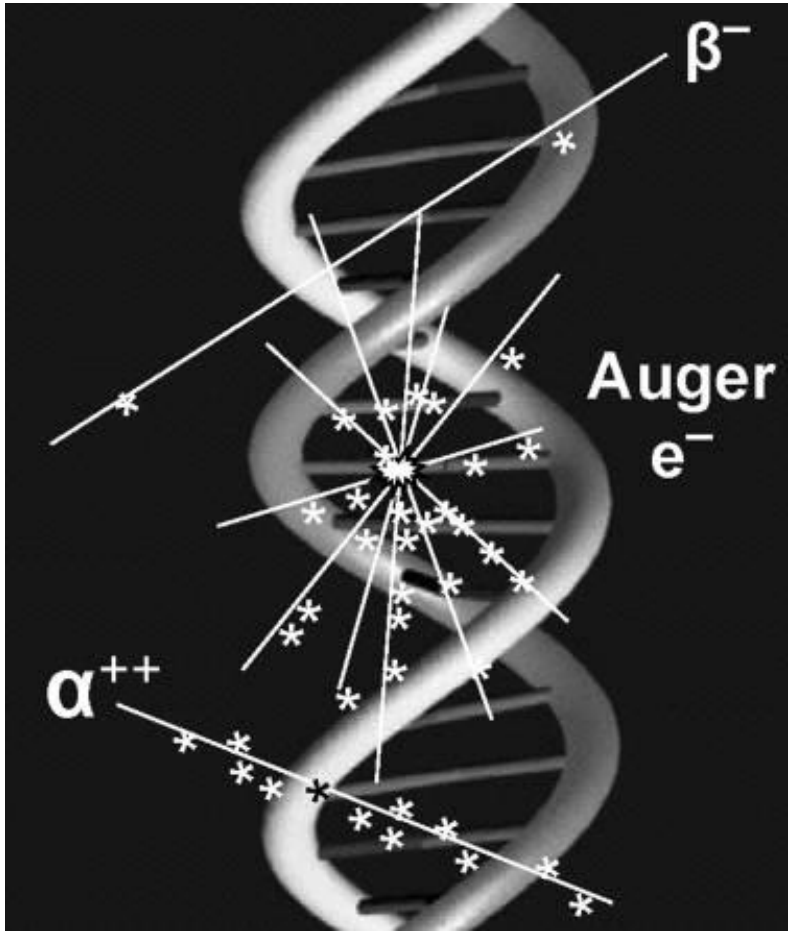
Beta-particle: range 50-12000 micron (50-2300 keV)

Auger-emission: range 0.002-0.5 micron (0.001-1 keV)

Auger-emitters hardly generate damage if not specifically located at DNA or cell membrane. However, **very effective if well targeted**:

Perspective of ^{161}Tb (Terbium) instead of ^{177}Lu (Lutetium)

Other (pure) Auger-emitter isotopes require significant development, specifically on the medical (targetting) side



Source: therapeutic Radionuclides: Biophysical and Radiobiologic Principles, Admin I. Kassis, Semin Nucl Med sep 2008, 38(5)-358-366

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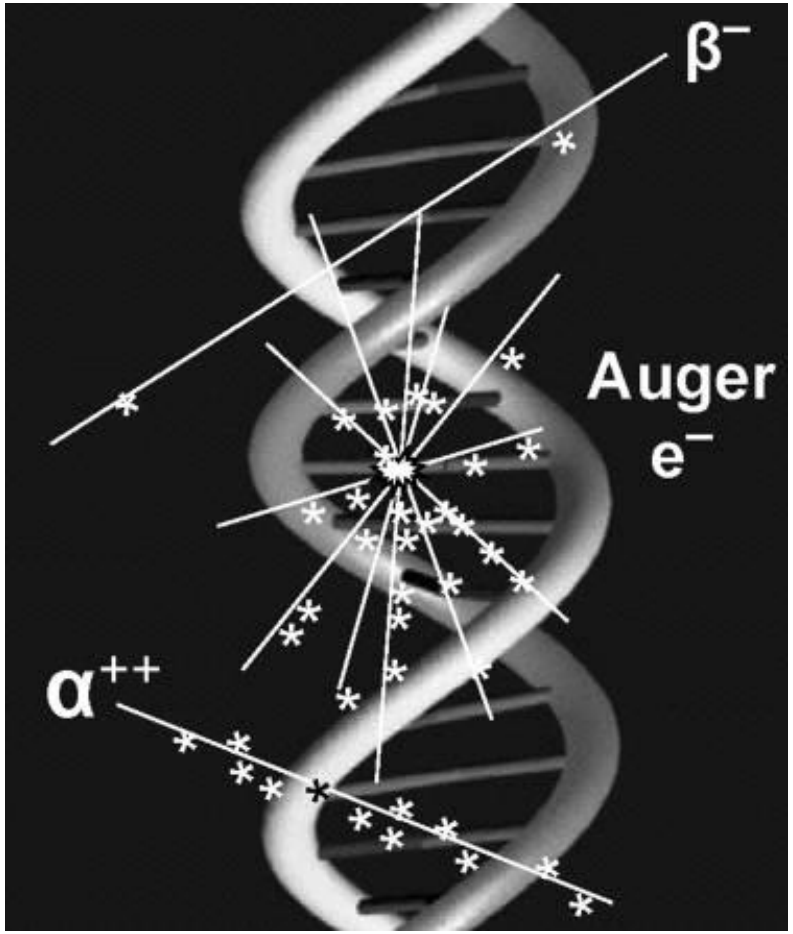
Biokinetics in the cell environment critical to success or failure of Auger emitters: in-cell nano-dosimetry in combination with in-cell (bio)kinetics required? Also to assess off-target effects (kidney-liver toxicity)?



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Future of reactor isotopes

Targetted radiotherapy has a bright future, but development and proof is still needed

- MOLYBDENUM: ^{99}Mo-^{99m}Tc (SPECT diagnosis)
- PAIN RELIEF ISOTOPES: ^{89}Sr-^{169}Er-^{117m}Sn (beta)
- LUTETIUM: ^{177}Lu (targetted therapy work horse)
- TERBIUM: ^{161}Tb (therapy additional benefit, metastases and resistance remediation)
- ALPHA EMITTERS: ^{225}Ac, ^{212}Pb, ^{227}Th …? (depending on compound availability/cost, application, clinical outcomes)
- AUGER EMITTERS? (depending on medical targetting development, availability/cost)

Therapeutic isotope application have a very bright future, this brings dosimetric opportunities:

- Dosimetry in combination with biokinetics can help to predict and optimize product performance and assist determining the balance between efficiency and toxicity of the new generation of nuclear medicine

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- Dosimetry in combination with biokinetics can help to predict and optimize product performance and assist determining the balance between efficiency and toxicity of the new generation of nuclear medicine

and dosimetric challenges:

- Upscaled production leads to radiation safety and protection concerns at production level, for logistics and at the hospital: protection of worker, environment and patient
- Dosimetry in combination with biokinetics most likely already useful for beta-emitters, more complicated for alpha-emitters, possibly very complicated for Auger emitters

Thank you for your attention

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