Advancing the management of adult solid tumours in 2023, and beyond: Unlocking the potential of radiopharmaceuticals

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Radiopharmaceuticals in principle: Mechanism of action and biological effects

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How do we design radiopharmaceuticals for clinical applications?

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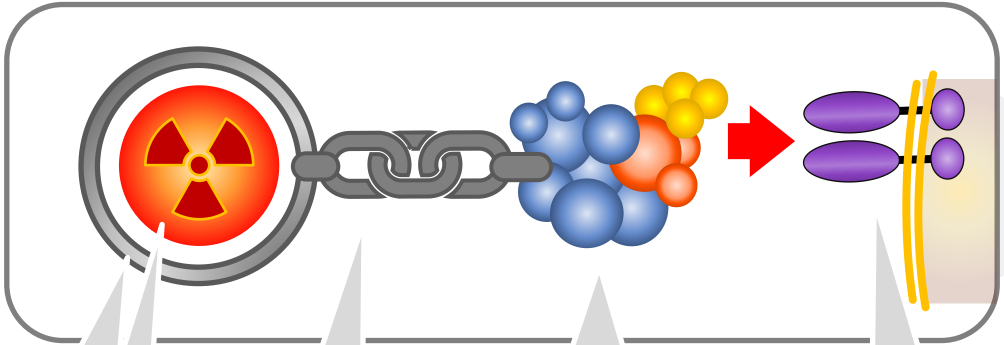
Design and construct of radiopharmaceuticals

Radionuclide, vector and target selection[1–4]



Chelator

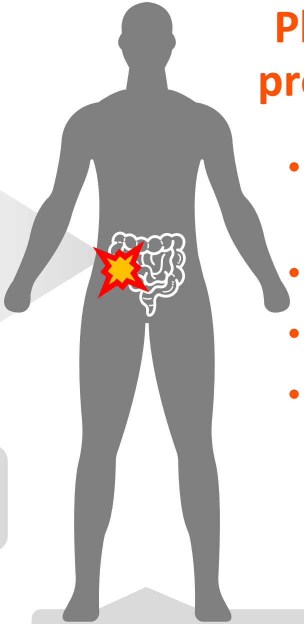
Radionuclide

Linker / spacer

Biomolecule / vector

- Antibodies
- Peptides
- Small molecules
- Microspheres
- Nanoconstructs

Tumour cell target



Required application

Molecular target location and type

Pharmacokinetics, decay profile and toxicity risks[2–4]

- Radiation type (α- or β-particles, or γ-rays)[2,4]
- Half-life[2,3]
- Daughter products[2]
- Biological clearance (e.g. renal)[4]

Image adapted from Holik HA, et al. 2022.[5]

1. Pouget JP, et al. *Nucl Med Biol.* 2022;104–5:53–64; 2. Kunos CA, et al. *Semin Radiat Oncol.* 2021;31:3–11; 3. Vermeulen K, et al. *Semin Nucl Med.* 2019;49:339–56; 4. Sgouros G, et al. *Nat Rev Drug Discov.* 2020;19:589–608; 5. Holik HA, et al. *Molecules.* 2022;27:3062.

What are the differences between α- and β-emitting radionuclides?

DNA damage mediated by α- and β-radiation

Particles with higher LET are more efficient at inducing DSBs

(normalized to tissue energy deposition)

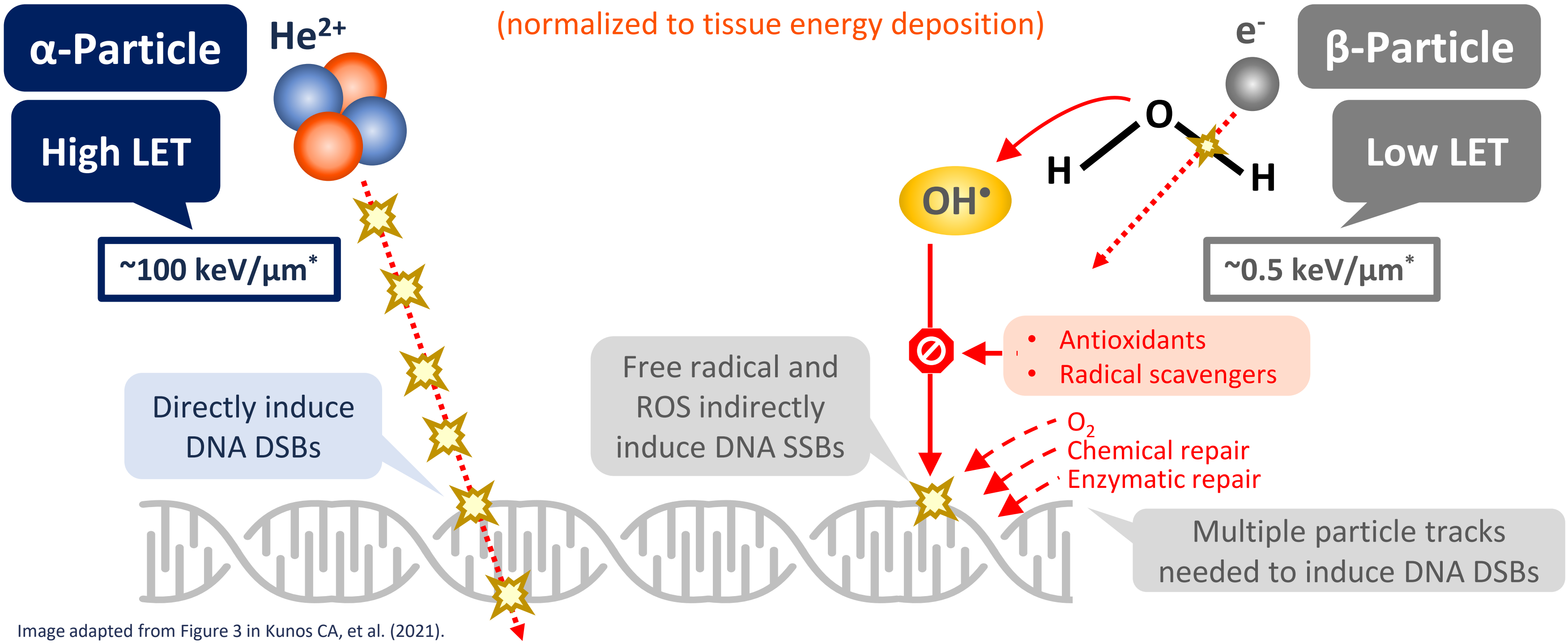


Image adapted from Figure 3 in Kunos CA, et al. (2021).
*Kiloelectronvolts per micrometre (keV/µm) is the standard LET unit of measure.
DSB, double-strand break; e, electron; LET, linear energy transfer; ROS, reactive oxygen species; SSB, single-strand break.
Kunos CA, et al. *Semin Radiat Oncol.* 2021;31:3–11.

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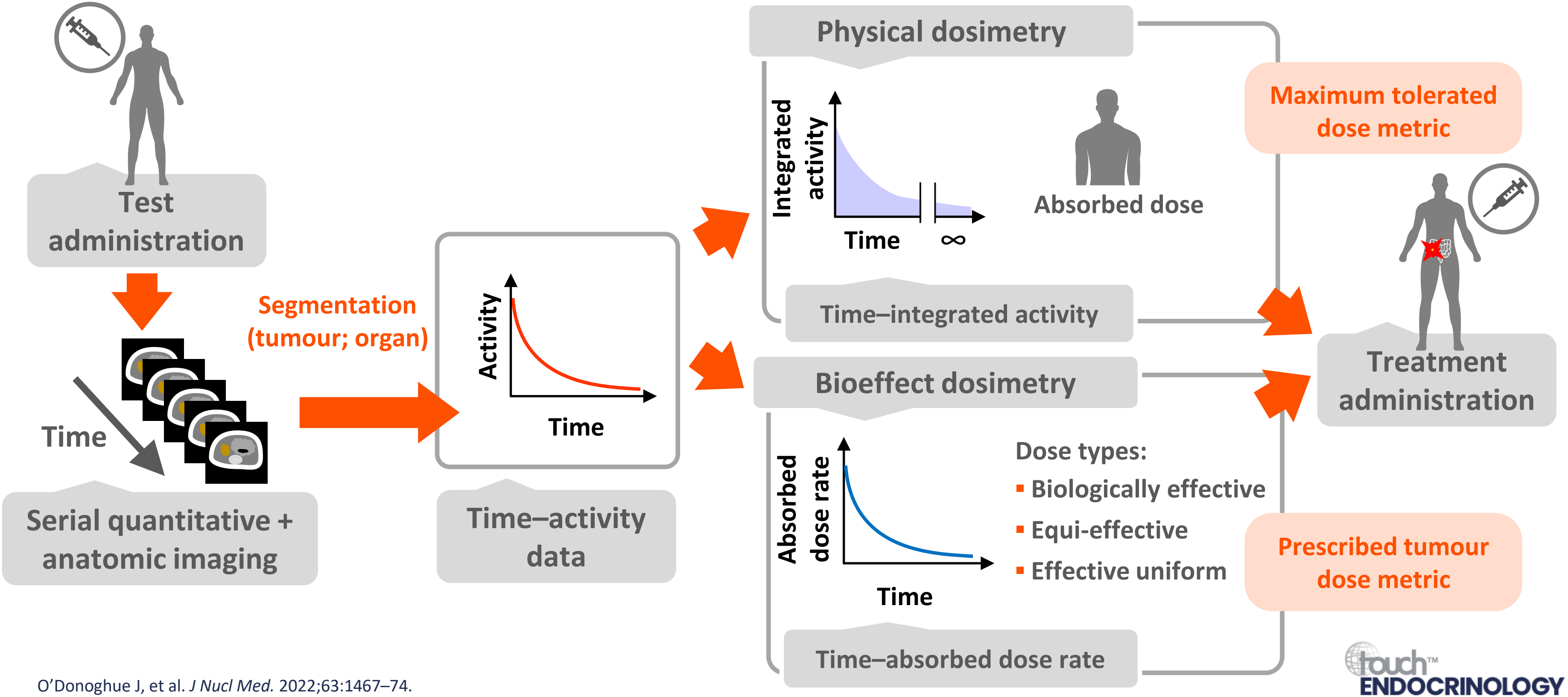
What are the current approaches to dosimetry when using radiopharmaceuticals?

Patient-specific dosimetry paradigm

Generalized workflow to support individualized dosimetry with radiopharmaceuticals



O'Donoghue J, et al. *J Nucl Med.* 2022;63:1467–74.

What are the potential side effects and off-target effects to consider when using radiopharmaceuticals?

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Off-target effects and side effects to consider

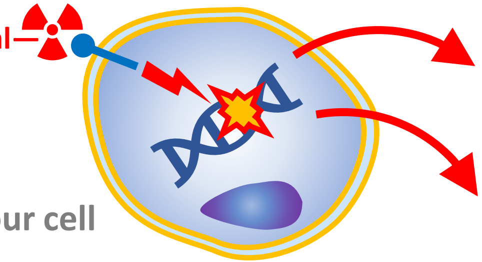
Considerations to maximize clinical benefit and minimize off-target and side effects[1]

Dosimetry based on absorbed dose to:[1]
- Target tumour tissue?
- Non-tumour tissue (at-risk organs)?

Dose-limiting tissues to consider:[2]
- Bone marrow
- Kidneys
- Liver
- Lungs
- Salivary glands

More clinical evidence is needed to understand implications of RPTs for dose-limiting tissues, and off-target and side effects[2–4]

Off-target effects[3,4]



Modulation of cell DNA repair response to radiation[3,4]

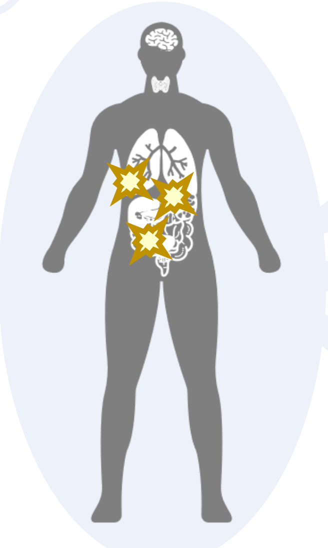
Deterministic effects		Stochastic effects
Repair	No repair	Misrepair
Cell survival	Cell death	▪ No meaningful change in cell biology ▪ Risk of carcinogenesis?

1. Lawhn-Heath C, et al. *Lancet Oncol.* 2022;23:e75–87; 2. Wahl RL, et al. *J Nucl Med.* 2021;62(Suppl. 3):23S-35S; 3. Pouget JP, et al. *Nuclear Med Biol.* 2022;104–5:53–64; 4. Pouget JP, et al. *Antioxid Redox Signal.* 2018;29:1447–87.

Why are radiopharmaceuticals suited to the management of solid tumours?

Addressing unmet needs in solid tumours

Radiopharmaceuticals offer scope for personalized approaches in cancer management[1–6]



- **Clinical benefit demonstrated in SSTR+ GEP-NETs,[4,5] mCRPC[6] and mPPGLs[7]**
- **Systemic therapy able to localize to low volume metastatic disease not amenable to conventional therapy or not visible on radiographic imaging[8,9]**
- **Biological by-stander effects can induce immune response to systemic disease[9–11]**

Radiopharmaceuticals is an expanding field, with multiple agents in clinical development[12]

GEP-NET, gastroenteropancreatic neuroendocrine tumour; mCRPC, metastatic castration-resistant prostate cancer; mPPGLs, metastatic pheochromocytomas and paragangliomas; SSTR, somatostation receptor.
1. Kunos CA, et al. *Semin Radiat Oncol.* 2021;31:3–11; 2. Divgi C, et al. *Int J Radiat Oncol Biol Phys.* 2021;109:905–12; 3. Lawhn-Heath C, et al. *Lancet Oncol.* 2022;23:e75–87; 4. Strosberg J, et al. *N Engl J Med.* 2017;376:125–35; 5. Clement D, et al. *Eur J Nucl Med Mol Imaging.* 2022;49:3529–37; 6. Parker C, et al. *N Engl J Med.* 2013;369:213–23; 7. Severi S, et al. *ESMO Open*. 2021;6:10017; 8. Salih S, et al. *Molecules.* 2022;27:5231; 9. Sgouros G, et al. *J Nucl Med.* 2021;62(Suppl. 3):12S–22S; 10. Pouget JP, et al. *Nuclear Med Biol.* 2022;104–5:53–64; 11. Pouget JP, et al. *Antioxid Redox Signal.* 2018;29:1447–87; 12. Sgouros G, et al. *Nat Rev Drug Discov.* 2020;19:589–608.

Understanding radiopharmaceutical therapy: One modality, many entities

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When should we consider radiopharmaceuticals in the diagnosis and treatment of adult solid tumours?

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Using radiopharmaceuticals in solid tumours

Applications and purpose

Imaging[1–4]
- Diagnostic
- Monitoring

Treatment[2,5,6]
- Curative intent
- Palliative management

Theranostics[1,2,5]
- Imaging and/or treatment
- Image-guided therapy

Clinical considerations

Molecular targeting[1,2,7,8]
- Tumour target(s)
- Tissue specificity

Biodistribution[1–3,5,6]

Clearance and uptake[1–3]

Absorbed dose[1–3,6]
- Tumour response
- Potential toxicities

Image provided by corresponding faculty (Dr AP Kiess).

1. Korde A, et al. *EJNMMI Radiopharm Chem.* 2022;7:18; 2. Sgouros G, et al. *Nat Rev Drug Discov.* 2020;19:589–608; 3. Lawhn-Heath C, et al. *Lancet Oncol.* 2022;23:e75–87; 4. Schillaci O. *J Nucl Med.* 2014;55:357–9; 5. Kunos CA, et al. *Semin Radiat Oncol.* 2021;31:3–11; 6. O'Donoghue J, et al. *J Nucl Med.* 2022;63:1467–74; 7. Solnes LB, et al. *J Nucl Med.* 2020;61:311–8; 8. Salih S, et al. *Molecules.* 2022;27:5231.

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What radiopharmaceutical modalities are available and/or in development?

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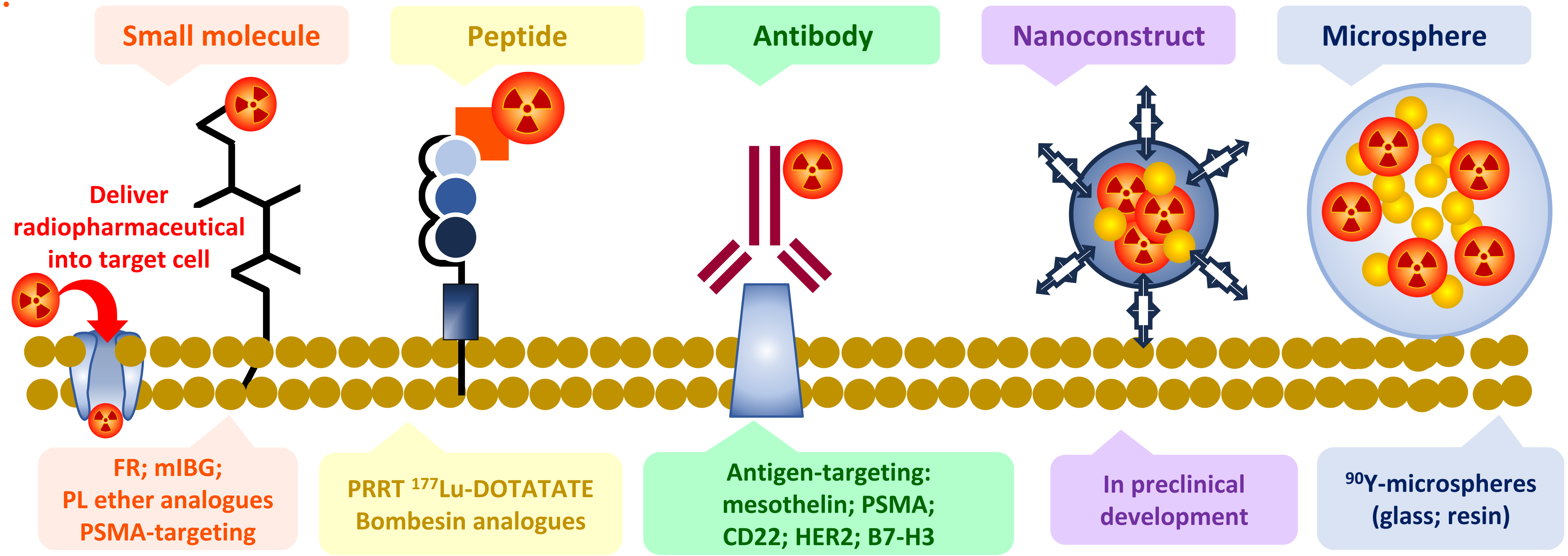
Radiopharmaceutical constructs



- Small molecules and peptides exhibit rapid targeting and clearance
- Shorter retention in target tissue

- Bivalent delivery
- Longer retention due to circulating half-life; may lead to off-target toxicities (e.g. haematological)

B7-H3, B7 homolog 3 protein; CD, cluster of differentiation; FR, folate receptor; HER2, human epidermal growth factor rececptor-2; Lu, lutetium; mIBG, meta-iodobenzylguanidine; PL, phospholipid; PRRT, peptide receptor radionuclide therapy; PSMA, prostate membrane-specific antigen; Y, yttrium.

Sgouros G, et al. *Nat Rev Drug Discov.* 2020;19:589–608.

What radiopharmaceuticals are currently approved in adult oncology indications?

FDA-approved radiopharmaceuticals

1971

^{131}I-radioiodine
Thyroid cancer[1,2]
- Active uptake via Na-I symporter
- β-emitter

1997*

^{153}Sm-lexidronam
Bone pain in cancer[1,2*]
- Binds hydroxyapatite matrix
- β-emitter

2002

^{90}Y-loaded resin microspheres
Hepatic metastases[1–3]
- Liver radioembolization
- β-emitter

2013

$^{223}RaCl_2$
mCRPC bone metastases[1,2]
- Ca analogue
- α-emitter

2018

^{131}I-mIBG
Adrenergic receptor+ tumours (mPPGLs)[1,2]
- Active uptake via adrenaline receptor
- β-emitter

^{177}Lu-DOTATATE
GEP-NETs[1,2]
- Binds SSTR
- β-emitter

2021

^{90}Y-loaded glass microspheres
Unresectable HCC[1,2]
- Liver microvasculature radioembolization
- β-emitter

2022

^{177}Lu-vipivotide tetraxetan
mCRPC[1,2]
- Binds PSMA
- β-emitter

*^{153}Sm-lexidronam has been discontinued (production terminated by manufacturer). Ca, calcium; GEP, gastroenteropancreatic; HCC, hepatocellular carcinoma; I, iodine; Lu, lutetium; mCRPC, metastatic castration-resistant prostate cancer; mIBG, meta-iodobenzylguanidine; mPPGLs, metastatic pheochromocytomas and paragangliomas; Na, sodium; NET, neuroendocrine tumour; PSMA, prostate-specific membrane antigen; $RaCl_2$, radium chloride; SSTR, somatostatin receptor; Y, yttrium.

1. Sgouros G, et al. *Nat Rev Drug Discov.* 2020;19:589–608; 2. FDA prescribing information available and searchable by agent at https://www.accessdata.fda.gov/scripts/cder/daf/ (accessed 23 March 2023); 3. Stubbs RS, Wickremesekera SK. *HPB (Oxford).* 2004;6:133–9.

What’s on the horizon for radiopharmaceuticals in adult solid tumours?

Future of radiopharmaceuticals in solid tumours

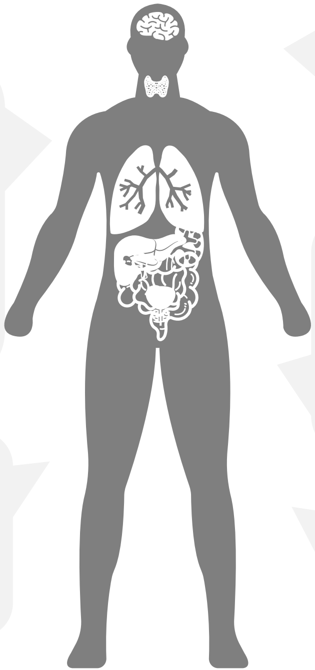
Prostate cancer/tumour neovasculature

- **^{177}Lu-PNT2002** (PSMA-targeting)[1,2]
- **^{227}Th-PSMA-TTC** (PSMA-targeting)[1,3]
- **^{225}Ac-PSMA-617** (PSMA-targeting)[4]
- **^{225}Ac-J591** (PSMA-targeting)[5]
- **^{225}Ac-DOTA-h11B6** (HK-2-targeting)[6]

GRPR+ advanced solid tumours

(e.g. breast, prostate and GISTs)

- **^{177}Lu-NeoBOMB1** (GRPR-targeting)[1,7]



Brain and CNS/DSRCT and other solid peritoneal tumours

- **^{131}I-omburtamab** (B7-H3-targeting)[1,8,9]

NETs

- **^{177}Lu-satoreotide tetraxetan** (SSTR-targeting)[1,10]
- **^{68}Ga-DOTA-JR11** (SSTR-targeting)[1,10]
- **^{68}Ga-satoreotide trizoxetan** (SSTR-targeting)[1,11]
- **^{212}Pb-DOTAMTATE** (SSTR-targeting)[1,12]

Advanced stage solid tumours/adenocarcinomas

- **^{177}Lu/^{90}Y-FAPI-46** (FAP-targeting)[13–15]
- **^{177}Lu-FAP-2286** (FAP-targeting)[13,16]

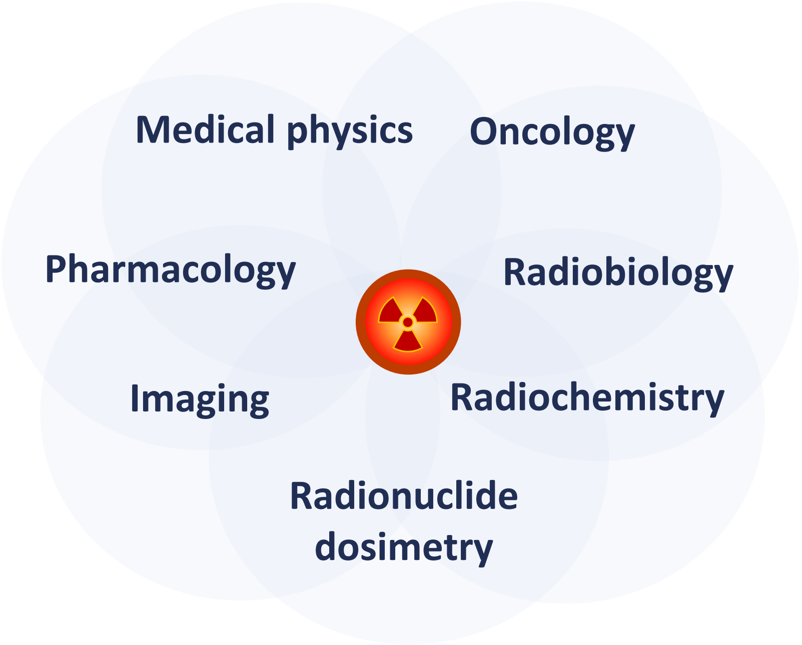
Ac, actinium; B7-H3, B7 homolog 3 protein; CNS, central nervous system;
DSRCT, desmoplastic small round cell tumour; FAP, fibroblast activation protein; Ga, gallium; GIST, gastrointestinal stromal tumour; GRPR, gastrin-resistant peptide receptor; HK-2, human kallikrein-2; I, iodine; Lu, lutetium; NET, neuroendocrine tumour; Pb, lead; PSMA, prostate-specific membrane antigen; SSTR, somatostatin receptor; TCC, targeted thorium conjugate; Th, thorium; Y, yttrium.

1. Sgouros G, et al. *Nat Rev Drug Discov.* 2020;19:589–608; 2. NCT04647526; 3. NCT03724747; 4. NCT04597411; 5. NCT03276572; 6. NCT04644770; 7. NCT03872778; 8. NCT05064306; 9. NCT04022213; 10. NCT02609737; 11. NCT03220217; 12. NCT03466216; 13. Calais J. *J Nucl Med.* 2020;61:163–5; 14. Liu Y, et al. *Eur J Nucl Med Mol Imaging.* 2022;49:871–80; 15. Ferdinandus J, et al. *J Nucl Med.* 2022;63:727–34; 16. Baum RP, et al. *J Nucl Med.* 2022:63;415–23. All trial information available at: https://clinicaltrials.gov/ (accessed 22 March 2023).

What more is needed to support integration of radiopharmaceuticals into clinical pathways in adult oncology?

Radiopharmaceuticals: An interdisciplinary endeavour

Expanding knowledge and multidisciplinary team involvement[1]



Steps to realizing the potential of radiopharmaceuticals

- Wider access to education and clinical training to expand access to expertise (e.g. training in radionuclide dosimetry)[2,3]
- Frameworks for multidisciplinary collaboration[1,3]
- High-quality evidence to support use[3]
- Addressing healthcare infrastructure needs (e.g. staff and additional imaging costs)[3]
- Optimizing patient communication[2–4]

1. Sgouros G, et al. *Nat Rev Drug Discov.* 2020;19:589–608; 2. Divgi C, et al. *Int J Radiat Oncol Biol Phys.* 2021;109:905–12;
3. Lawhn-Heath C, et al. *Lancet Oncol.* 2022;23:e75–87; 4. Kohl P, et al. *Front Nucl Med.* 2023;3:1127692.