Nuclear medicine plans and collaborations @ Nuclear Futures Institute, Bangor University

Nuclear academics meeting
Coventry University (London) 2023

Dr Tim Smith and Dr Mark Ogden

Nuclear Medicine

Nuclear medicine: medical specialty that uses radioactive tracers (radiopharmaceuticals) to assess bodily functions and to diagnose and treat disease

Nuclear medicine imaging: detection of radiation introduced into the body and accumulated in regions of interest often using targeting molecules to which radionuclides are attached

Nuclear medicine therapy: administration of radionuclides/targeted radionuclides to destroy tumour or normal tissue

Radionuclide categories used in nuclear medicine

Emission	Range	LET	Examples (range in tissue)	Use
γ/positron			^{89}Zr, ^{203}Pb*	Imaging
β	Up to 10 mm	low	^{177}Lu (1mm), ^{198}Au, ^{90}Y (10mm)	MRT
α	Up to 100µm	high	^{212}Pb*, ^{223}Ra	MRT
Auger electrons	Up to 5µm	high	^{125}I, ^{89}Zr, ^{111}In	MRT

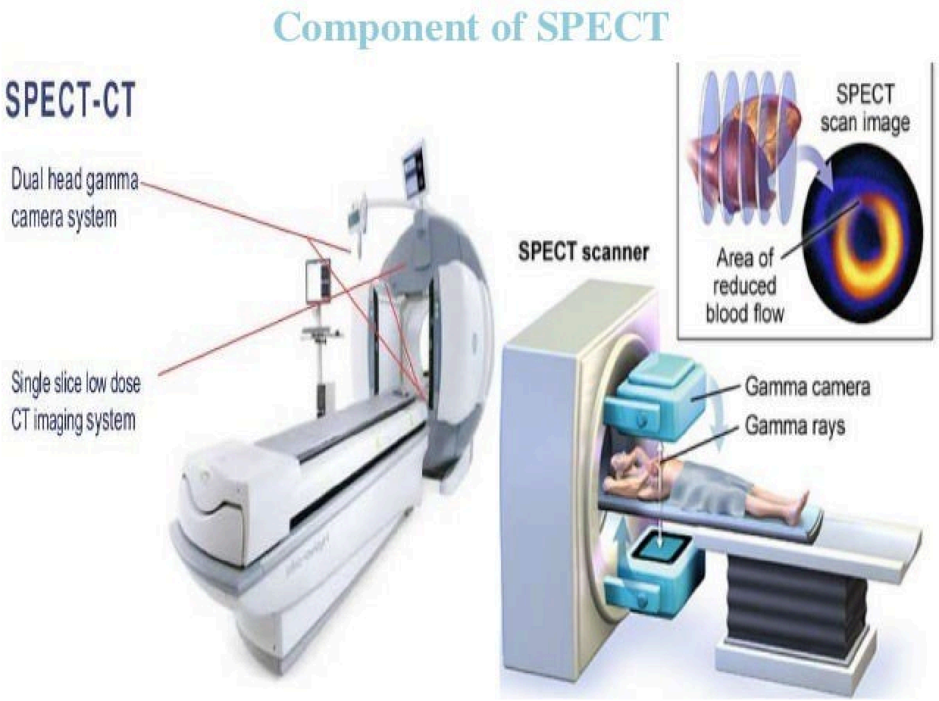
*theragnostic pair

Nuclear Medicine Imaging

Single photon emission computed tomography (SPECT)

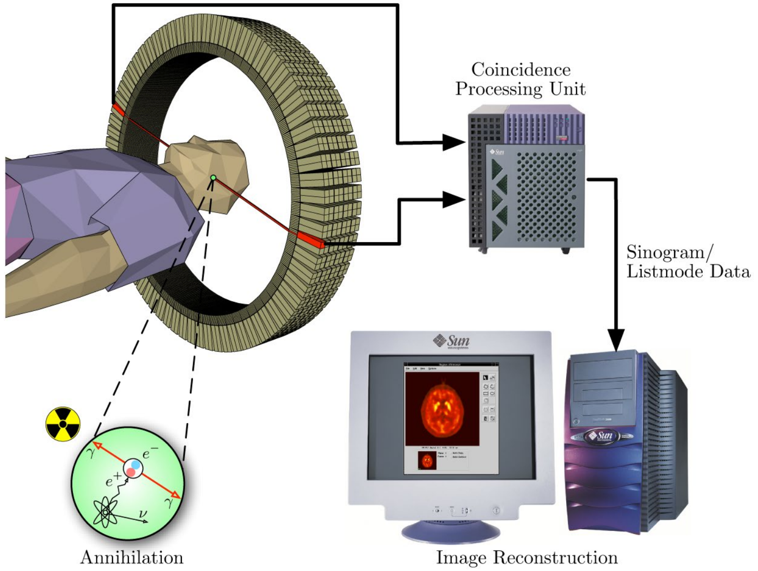
Usual isotope is ^{99m}Tc (140keV (low easily stopped)

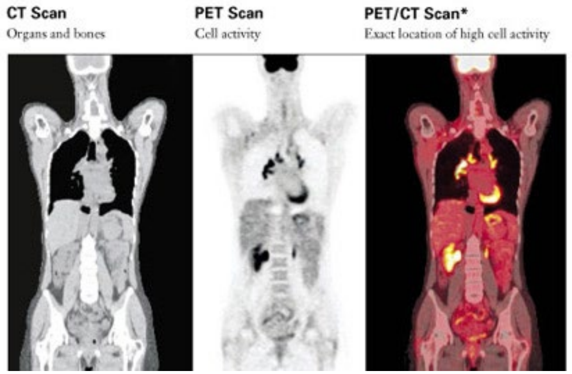
Many tracers e.g. Kidney function: ^{99m}Tc-DTPA dynamic scan



Positron emission tomography (PET)

- Coincidence detection of annihilation γs
- Usual isotope is ^{18}F
- Usual tracer [^{18}F]FDG (glucose analogue)



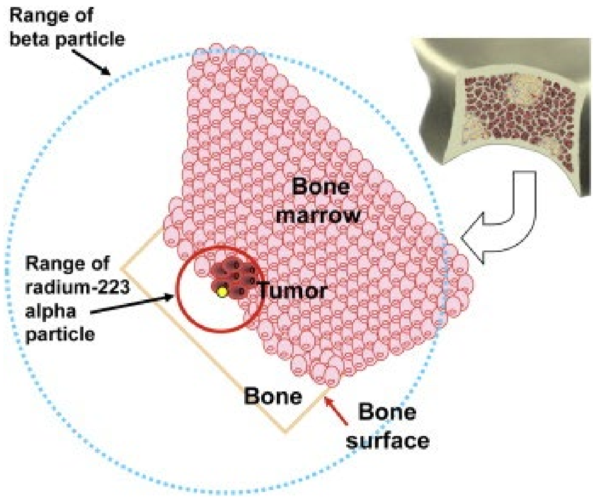


Nuclear Medicine therapy

Administration of cytotoxic radionuclides that themselves:
(a) target a disease process or (b) linked to targeting molecules (Molecular radiotherapy-MRT)

Examples of (a) radionuclides with affinity for target

1) For hyperthyroidism or medullary thyroid cancer [^{131}I]: Iodide specifically taken up by thyroid tissue
2) Bone metastasis ^{223}Ra is a Ca^{2+} mimic – accumulates in bone adjacent to bone metastasis

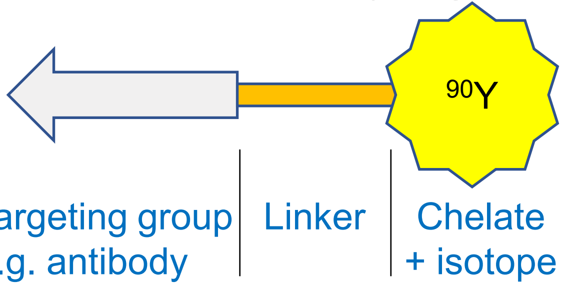


Shore et al Urology 2015

Molecular radiotherapy (MRT)

Targeting receptors overexpressed on cancer with cytotoxic radionuclides

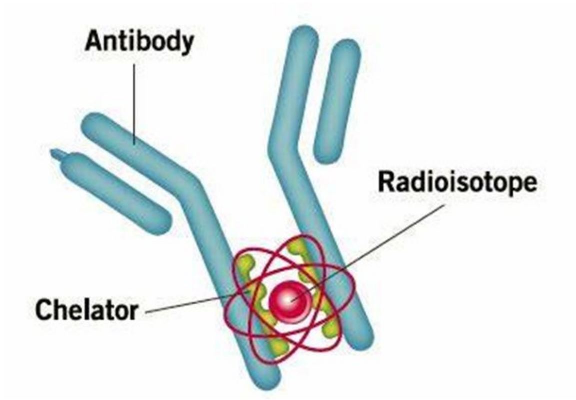
Targeted radiotherapy agents



Targeting group e.g. antibody

Linker

Chelate + isotope



Emission	Range	LET	Examples (range in tissue)	Use
β	Up to 10 mm	low	^{177}Lu (1mm), ^{198}Au, ^{90}Y (10mm)	MRT
α	Up to 100μm	high	^{212}Pb*, ^{223}Ra	MRT

Advantages

1) Systemic – treats primary and metastasis
2) Low normal tissue dose (c.f. EBRT)
3) Easy to administer

MRT limitations

1) Cancer types

- Molecular radiotherapy currently limited to a few cancer types
- Cancers that universally express a receptor type: Lymphoma CD20, Prostate PSMA and neuroendocrine somatostatin receptor

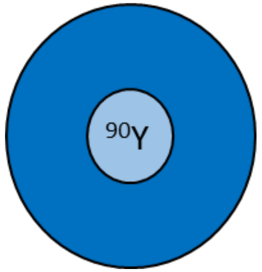
2) Heterogeneous intra-tumour dose distribution

- Perfusion and receptor expression across tumours – highly variable
- Use of a single radioisotope

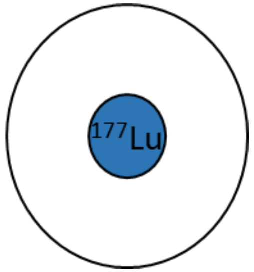
3) Lack of accurate dosimetry to inform on dose

Approaches

1. Optimising molecular radiotherapy based on target distribution:
    a. minimising tumour dose heterogeneity
    b. selecting suitable radionuclides based for target



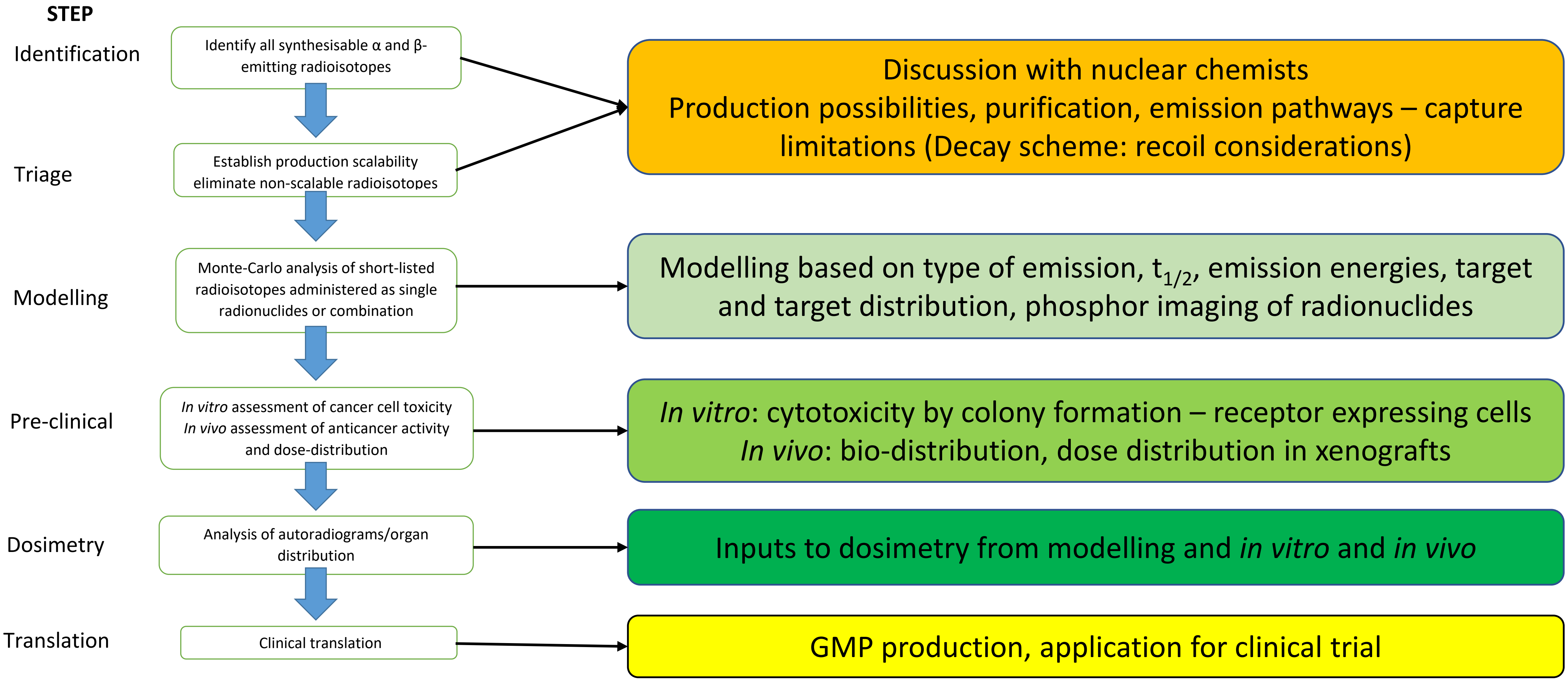
^{90}Y- high energy beta
- most dose
deposited mm from atom



^{177}Lu – low energy beta
emission – most dose
deposited within 1mm

2. Theragnostic pair:
    a) Particle with imaging radionuclide:
        Biodistribution and dosimetry - suitability of patient and tailored dose
    b) Chemically identical particle with therapeutic radionuclide
3. Metal amalgams for radionuclide capture (single and multiple)

Pathway to identify optimal radioisotopes for MRT



STEP

Identification

Identify all synthesisable α and β-emitting radioisotopes

Triage

Establish production scalability eliminate non-scalable radioisotopes

Discussion with nuclear chemists
Production possibilities, purification, emission pathways – capture limitations (Decay scheme: recoil considerations)

Modelling

Monte-Carlo analysis of short-listed radioisotopes administered as single radionuclides or combination

Modelling based on type of emission, $t_{1/2}$, emission energies, target and target distribution, phosphor imaging of radionuclides

Pre-clinical

In vitro assessment of cancer cell toxicity
In vivo assessment of anticancer activity and dose-distribution

In vitro: cytotoxicity by colony formation – receptor expressing cells
In vivo: bio-distribution, dose distribution in xenografts

Dosimetry

Analysis of autoradiograms/organ distribution

Inputs to dosimetry from modelling and *in vitro* and *in vivo*

Translation

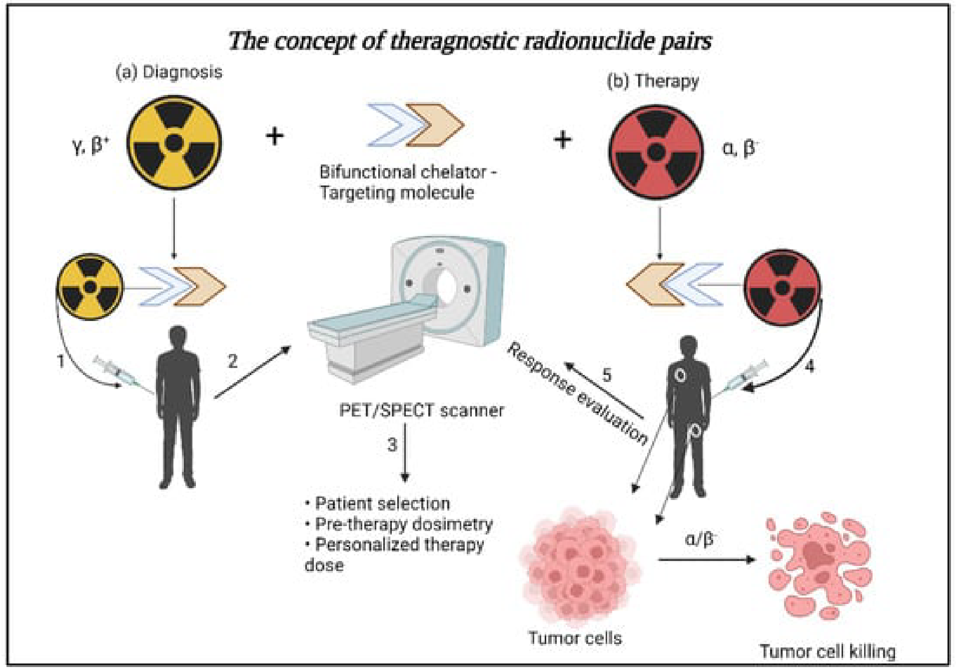
Clinical translation

GMP production, application for clinical trial

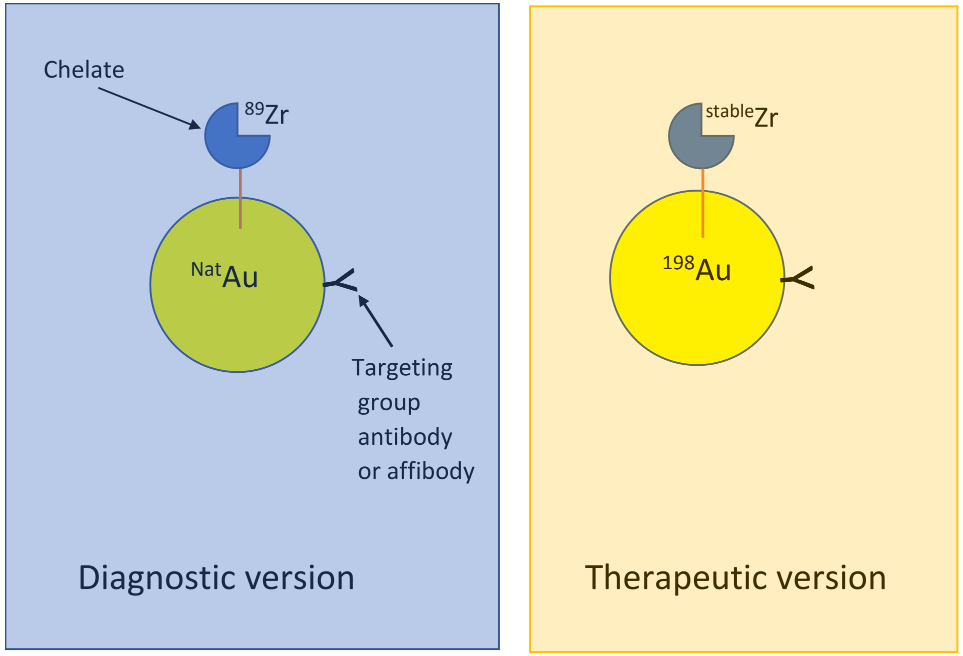
- Implement pipeline

Theragnostics

- Imaging and treatment
- Enables dosimetry prior to delivery of therapeutic radionuclides



Chhabra and Thakur Biomedicines 2022

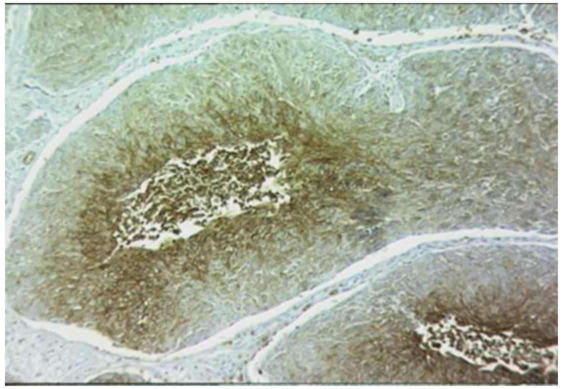


- Fabrication of gold nanoparticles
- ^{89}Zr – positron emitter
- ^{198}Au – β-emitter
- Collaboration: Fred Currell DCF University of Manchester Zeljka Krpetic University of Salford

Boosting radiotherapy to hypoxic bladder cancer cells

Target discovery on hypoxic cells using Mass spectroscopy

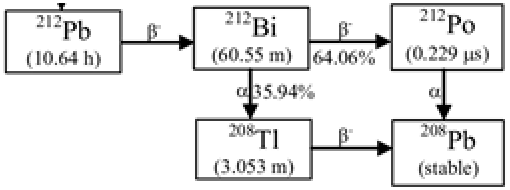
- Bladder cancer cell lines
- 21% O_2 vs 1% and 0.1% O_2 Mass spectrometry
- Candidate proteins 2X increase and $p<0.05$ in hypoxia
- Corroboration – e.g. w.blot



Pimonidazole bladder cancer
Hoskin et al Br J Cancer 2004

Suitability of α-emitters for targeting hypoxic cells

- Hypoxic regions: contiguous, focal and single cell within tumours
- Cell kill from most β-emissions – due to crossfire at a distance
- The range of α-particles 1-4 cell diameters
- Kill cells to which the radionuclide is attached and nearby.
- Targeted therapeutic armed with an α-emitter (via ^{212}Pb)



Source of ^{212}Pb

- National Nuclear Laboratories (NNL), Mithras and RadNet (City of London) initiative to increase supply of medically relevant radionuclides
- ^{212}Pb from legacy nuclear ‘waste’

Capturing single/multiple radionuclides using amalgams

Contents lists available at ScienceDirect

Journal of Alloys and Compounds

journal homepage: http://www.elsevier.com/locate/jalcom

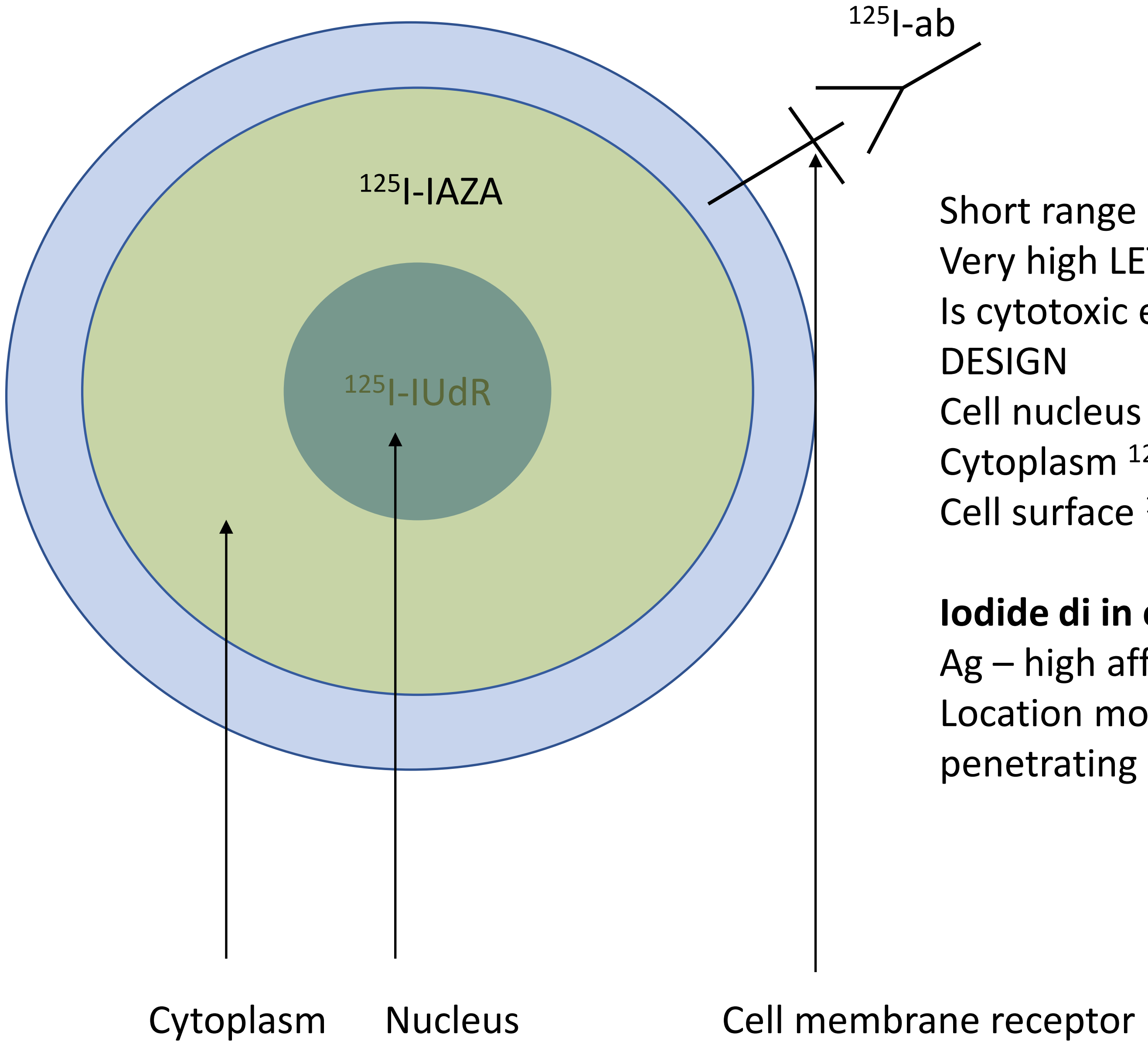
Cu@Au self-assembled nanoparticles as SERS-active substrates for (bio)molecular sensing

Gema Cabello [a, *], Kenneth C. Nwoko [b], José F. Marco [c], María Sánchez-Arenillas [c],
Ana María Méndez-Torres [d], Jorg Feldmann [b], Claudia Yáñez [d], Tim A.D. Smith [a, **]

- Amalgams of gold and copper for carrying therapeutic $^{198/199}$Au and imaging $^{67/64}$Cu radionuclides
- Ideal size (<5nm) – renal excretion

- Explore other metal/amalgams particles to capture medically useful radionuclides

Auger emitters



Short range (<10μm)
Very high LET
Is cytotoxic efficacy related to nuclear accumulation?
DESIGN
Cell nucleus ^{125}I-IUdR
Cytoplasm ^{125}I-IAZA
Cell surface ^{125}I-labelled antibody

Iodide di in cell may be a problem
Ag – high affinity for iodide
Location modification using Ag nanoparticle-membrane penetrating peptides

Target manufacture

- Avoiding parasitic absorption
- Optimizing radionuclide production
- Proliferation resistant

Target irradiation

- Reactor
- Cyclotron
- Generator
- Optimizing radionuclide production

Target dissolution

- Benign conditions
- Sustainable
- Reduced co-contaminant

Isotope purification

- Removal of co-contaminants
- Concentration of isotope
- Sustainable & cheap
- Proliferation resistant

Radiopharmaceutical manufacture

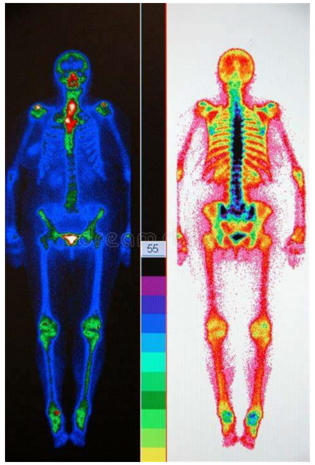
- Combined with a drug
- High purity
- Consistent quality
- Scale up of production

Radiopharmaceutical shipping

- Containment
- Safety
- Reduce losses in isotope
- Consistent quality

Radiopharmaceutical preparation

- Controlled dose
- Mixing with other drugs
- Optimized lifetime
- Easy administration to patient



Diagnostic and radiotherapy treatment

Collaborations

- Neutron bombardment of metal foils e.g. for production of ^{198}Au
  - Birmingham University
- Proton bombardment
  - DCF University of Manchester
- Funding partners