Wales Research and Diagnostic Positron Emission Tomography Imaging Centre

"PETIC"

Research Opportunities

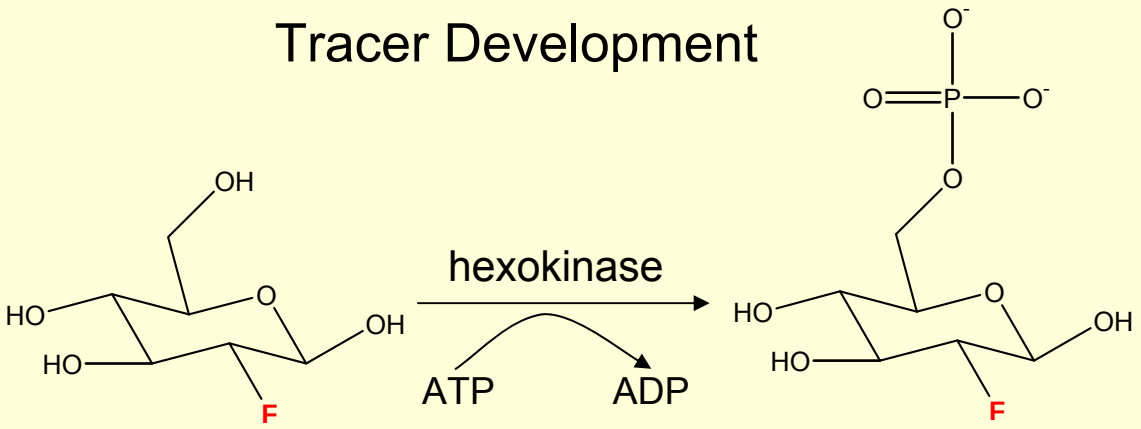
Stephen Daniels
Research Director

Research Priorities

- New PET/SPECT Tracers
  - Target driven development
  - Chemical properties: design, synthetic methods, ligands, metals
  - Physical properties: understanding and measuring
  - structure/activity/function, PK/PD, biodistribution
- Multi-modal Imaging
  - PET/MRI
  - SPECT/MRI
  - PET/Optical
- Pre-Clinical studies
- Clinical Research

  - cardiovascular
  - neuroscience
  - oncology

Tracer Development



^{18}Fluoro-deoxyglucose

Metabolic activity:- oncology, stroke, myocardial infarct, Alzheimer's disease, Huntington's disease

^{18}F-DOPA – dopamine activity / Parkinson's Disease

16α-^{18}F-17β-estradiol – oestrogen receptor / cancer

^{18}F-6-thia-heptadecanoic acid – fatty acid metabolism / myocardium

3-deoxy-3-^{18}F-thymidine – proliferation potential / cancer

^{18}F	^{11}C	^{13}N	^{15}O	
110min	*20min*	*10min*	*2min*	*half-life*

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Unconventional PET Isotopes

Isotope	Decay Mode	Half-life, min	Target Reaction	Potential Uses
^{66}Gallium	56% β^+ (EC)	569	^{66}Zn(p,n)^{66}Ga	Ga-citrate tumor imaging; antibody binding
^{120}Iodine	56% β^+ (EC)	95	^{120}Te(p,n)^{120}I	Organic molecule labelling
^{124}Iodine	24%β^+ (EC)	6048	^{124}Te(p,n)^{124}I	Organic molecule labelling
^{75}Bromine	73%β^+ (EC)	93	^{75}Se(p,n)^{75}Br	Organic molecule labelling (thymidine – tissue proliferation)
^{76}Bromine	55%β^+ (EC)	972	^{76}Se(p,n)^{76}Br	Organic molecule labelling

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Transition Metal PET Isotopes

Isotope	Decay Mode	Half-life, min	Target Reaction	Potential Uses
^{45}Titanium	85% β^+ (EC)	185	^{45}Sc(p,n)^{45}Ti	antitumor
^{60}Copper	93% β^+ (EC)	24	^{60}Ni(p,n)^{60}Cu	Cu chelators
^{61}Copper	61% β^+ (EC)	200	^{61}Ni(p,n)^{61}Cu	antibodies
^{62}Copper	98 % β^+	10	^{62}Zn/^{62}Cu gen	peptides
^{64}Copper	17% β^+ (39% β^-, EC)	762	^{64}Ni(p,n)^{64}Cu	Metabolism/therapy
^{86}Yttrium	32%β^+ (EC)	884	^{86}Sr(p,n)^{86}Y	Antibodies, chelating compounds
^{94}Technetium	70%β^+ (EC)	52	^{94}Mo(p,n)^{94}Tc	Cardiac imaging

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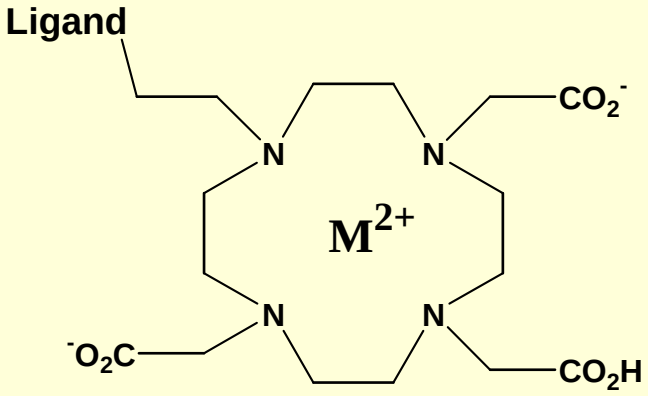
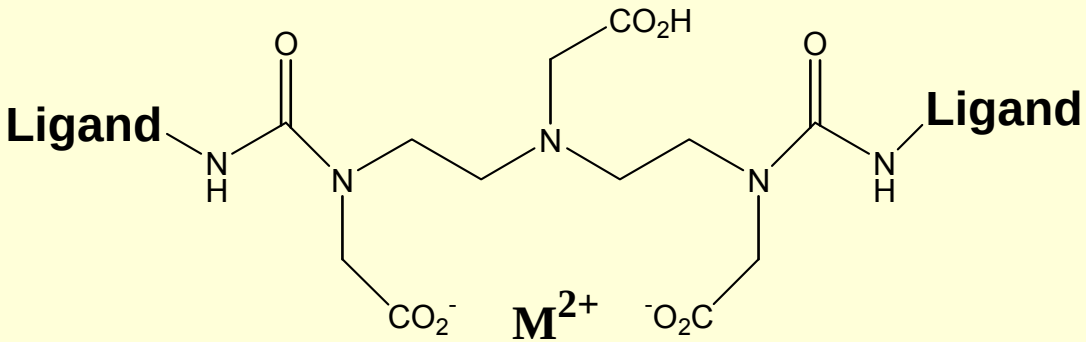
Tracer Development

Novel chemical structures



DOTA-based



DTPA-based

Metal:

^{64}Cu; $t_{1/2}$ *762min*, 17.5% β^+ 39% β^-
^{60}Cu; $t_{1/2}$ *24min*, 93% β^+
^{45}Ti; $t_{1/2}$ *185min*, 85% β^+
^{94}Tc; $t_{1/2}$ *52min*, 70% β^+

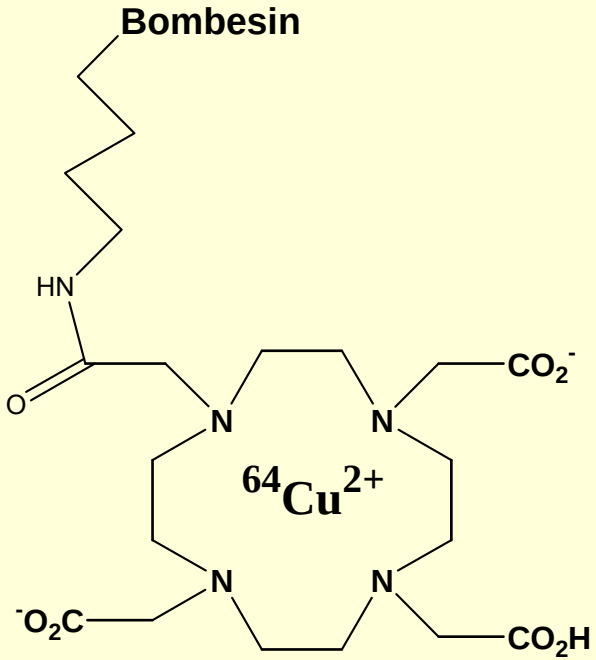
Ligand:

Receptor agonist/antagonist
e.g. raclopride, flumazenil
Antibody
e.g. anti-Aβ
Peptides
e.g. ^{18}F-benzoyl-c(RGDyK)

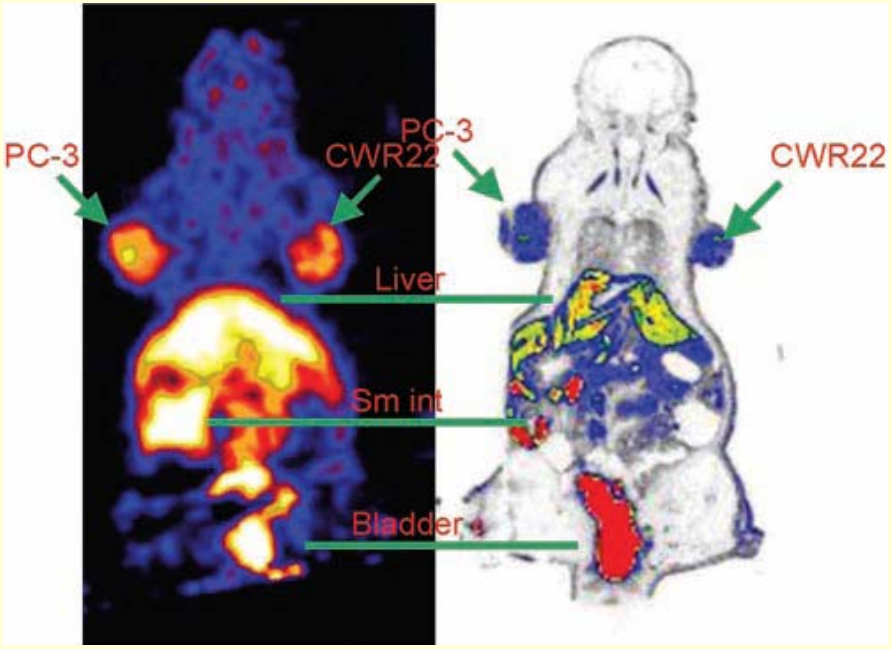
$^{68}Ge/^{68}Ga$ generator

Tracer Development

gastrin-releasing peptide receptor ligand



^{64}Cu-DOTA-[Lys^3]BBN



Coronal image of tumor-bearing mouse: human prostate cancer cells:

PC-3 androgen independent
CWR22 androgen dependent

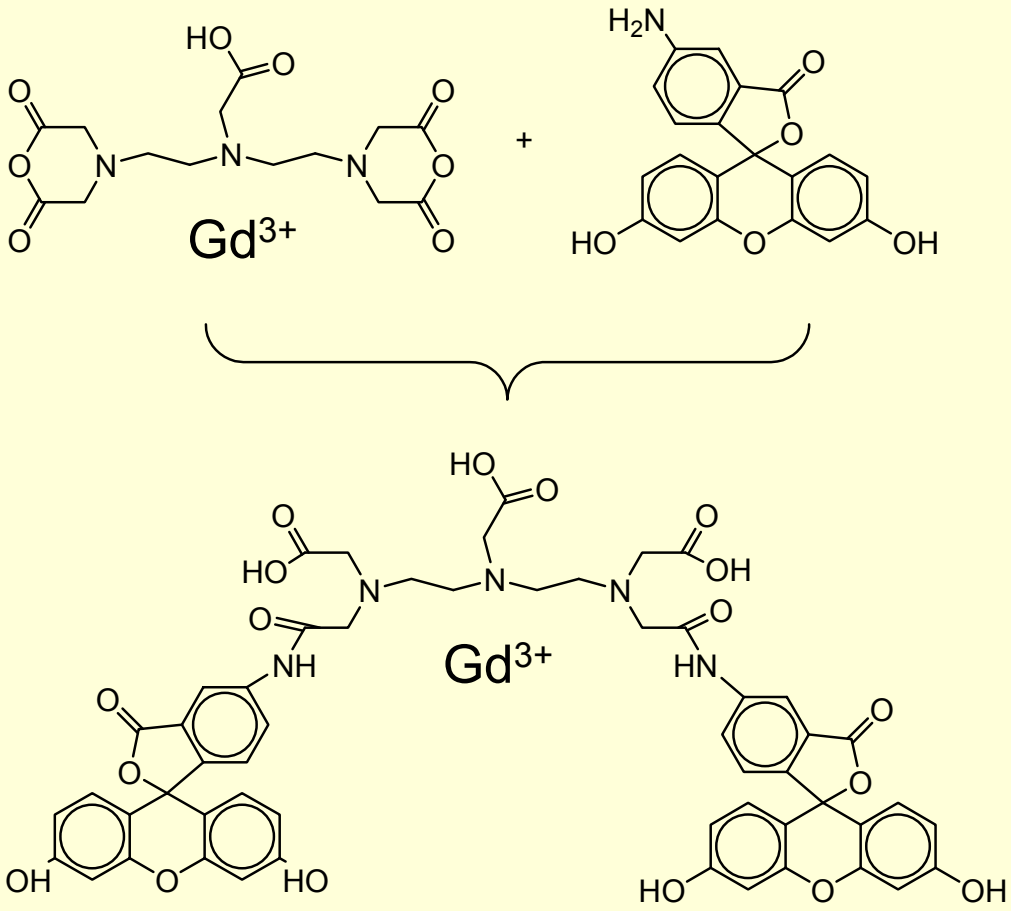
1 hr post-administration

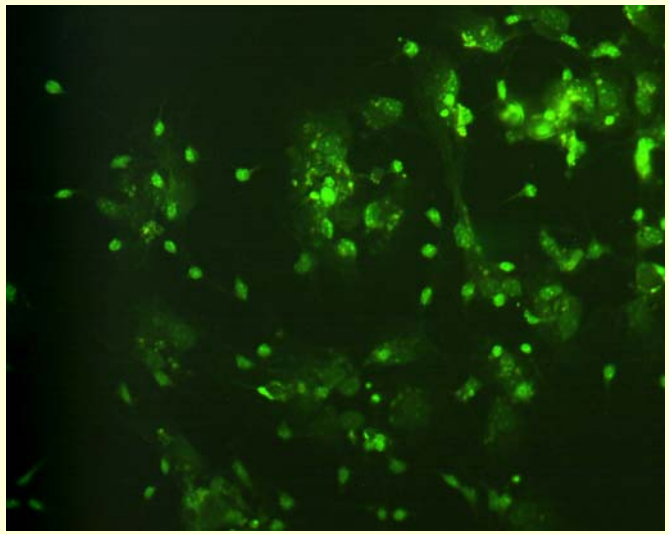
(Right) Digital autoradiograph

Chen *et al*., J. Nucl. Med. (2004), 45(8), pp1390

Multi-modal Imaging

MRI **fluorescence**





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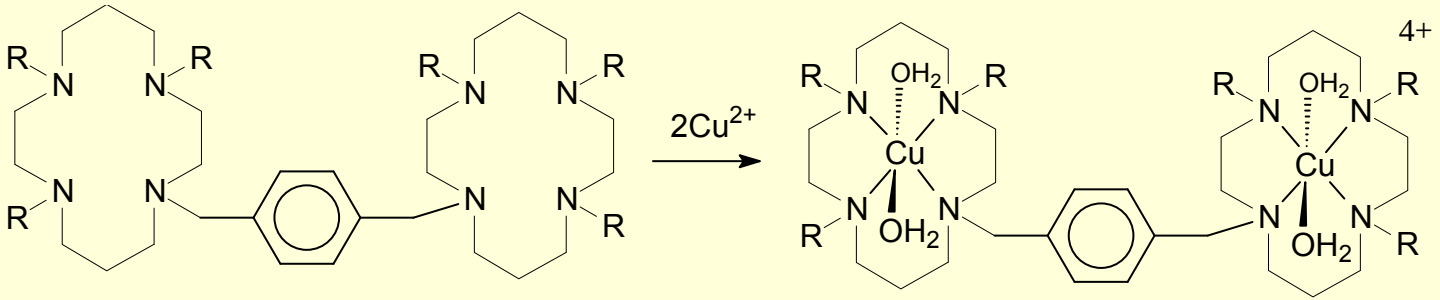
Multi-modal Imaging



AMD3100

- AMD3100 binds tightly and selectively to the CXCR4 co-receptor (fusin) and may represent a novel marker for inflammation
- AMD3100 is a strong copper binding compound and retains its receptor binding strength as the copper complex
- Copper(2+) is paramagnetic and can act as a T_1 contrast enhancing agent in MRI
- ^{64}Cu is a PET isotope

Tracer Development

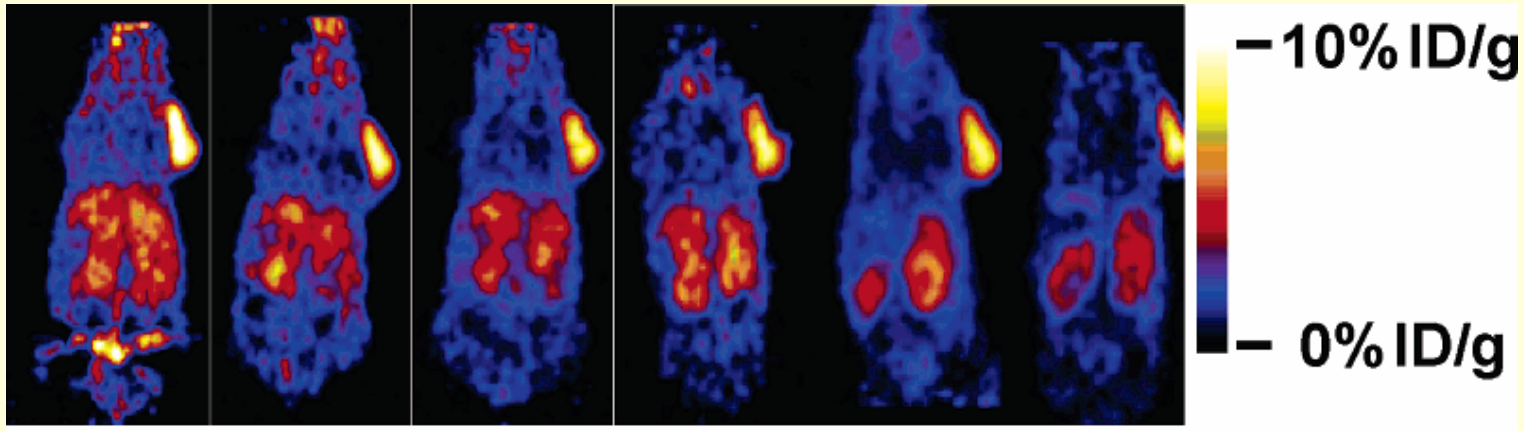
Antibody-based tracers:

- Expression of variable regions from antibody libraries using bacterial phage technology
  fragments reacting with the target selected on the basis of affinity, then mass produced
- Selected fragments converted into low molecular weight constructs; usually
  Single Chain Variable Fragment (scFv) or Fragment Antigen Binding (Fab)

advantages of using radiolabeled small peptides:

- natural binding units for interactions between integrins and extracellular matrix proteins
  e.g. vitronectin, fibronectin, fibrinogen, lamin, collagen, adenovirus particles
- can tolerate harsh conditions for radiolabeling and chemical modification
- compared to antibodies, less likely to be immunogenic
- rapid blood clearance because of small size
  faster blood clearance results in better target-to-background ratios

Tracer Development



Mouse with U87MG, human glioma xenografts

250 μCi of integrin $\alpha_v\beta_3$ binding ^{64}Cu-DOTA-E-[c(RGDyK)]$_2$

Liu, S. Molecular Pharmaceutics (2006) 3(5), 472-487

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Tracer Development

Oligonucleotide-based tracers:

- (~10kDa) designed with 3-D structure to bind to the target protein.
- relatively large

  may have limited stability and slow clearance
- Naturally occurring oligonucleotides cannot be used for *in vivo* imaging

  rapidly degraded *in vivo* by endonucleases and exonucleases
- "designer"-oligonucleotide may degrade more slowly
- Peptide Nucleic Acids (PNAs)

  are completely resistant to both nucleases and proteases

  will accumulate at the site of internalisation

Tracer Development

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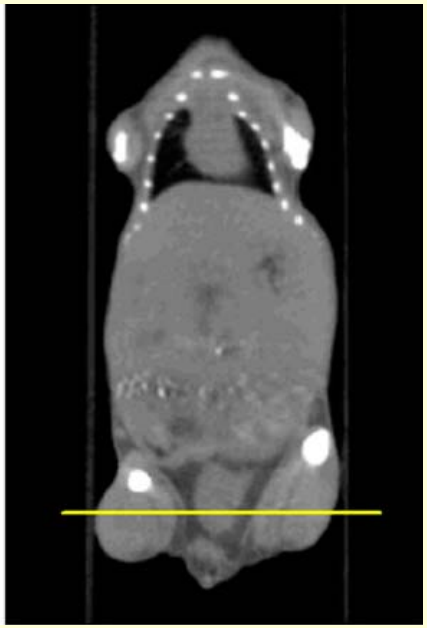
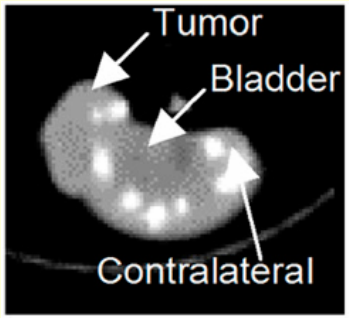
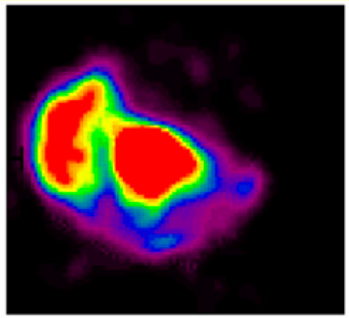
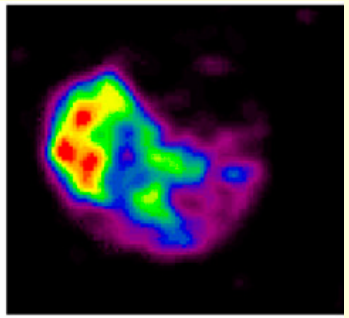
CT 4hr **CT 4hr** **PET 4hr** **PET 24 hr**









MCF7 estrogen-dependent, receptor-positive xenografts

4 μg (1 nmol) of [^{64}Cu]DOTA-PNA-peptide; 3.7–7.4MBq (100–200 μCi)

^{64}Cu-DOTA-link-CTGGTGTTCCAT-link-D-[Cys-Ser-Lys-Cys]-$CONH_2$

PET-trace Cancer marker-**PNA** sequence, hybridises with CCND1 mRNA; proto-oncogenic regulator of the G1/S checkpoint in the cell cycle

IGF1 analog, binds to receptor enabling internalisation

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Tian *et al.* J. Nucl. Med. (2007), 48, 1699–1707

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Clinical Research

Clinical research will:

- promote the use of PET for clinical conditions where evidence-based research is limited
- provide diagnostic and functional data to confirm clinical efficacy in clinical studies that have moved beyond “proof-of-principle” and into Clinical Trials.

PET Imaging underpinning Oncology Research:

- A number of UK clinical trials, funded by CR UK, are based in Cardiff.
- Cardiff investigators are also members of NCRI Clinical Studies Groups
- Cardiff also has strong links with the major UK Clinical Trials Committees.

Clinical Research

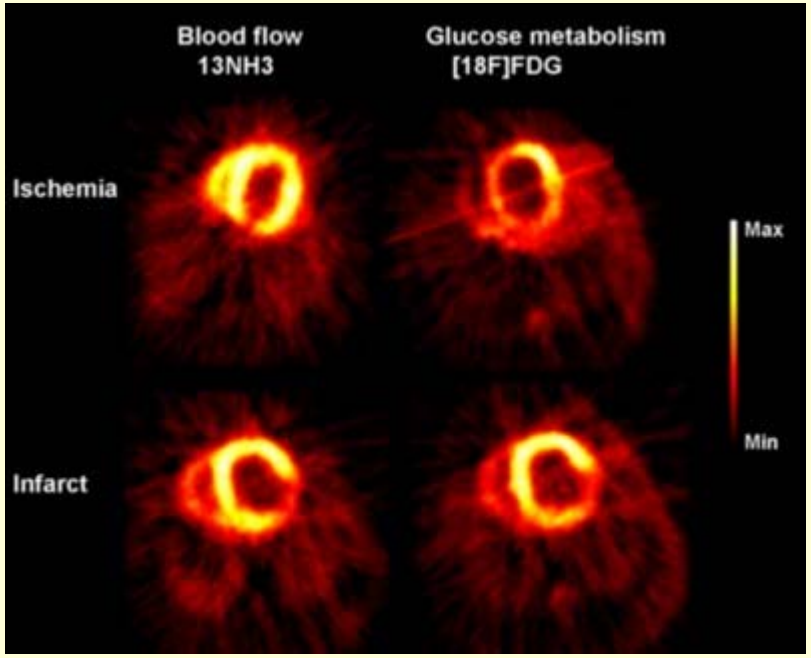
Cardiac

- Diagnosis of hibernating myocardium ~ poor LV function before revascularisation
- Patients with a fixed SPECT ~ may benefit from revascularisation
- Prior to referral for cardiac transplantation
- Diagnosis of CAD or assessment of known coronary stenosis *if*
  - other investigations (SPECT, ECG etc.) are equivocal

Neuropsychiatry

- Presurgical evaluation of epilepsy
- Suspected recurrence or failed primary treatment of primary malignant brain tumours. - most have MR and CT with equivocal results
- Early diagnosis of dementia - especially younger patients (particularly Alzheimer's disease) MR or CT is either normal or equivocal
- Differential diagnosis of dementia

Clinical Research



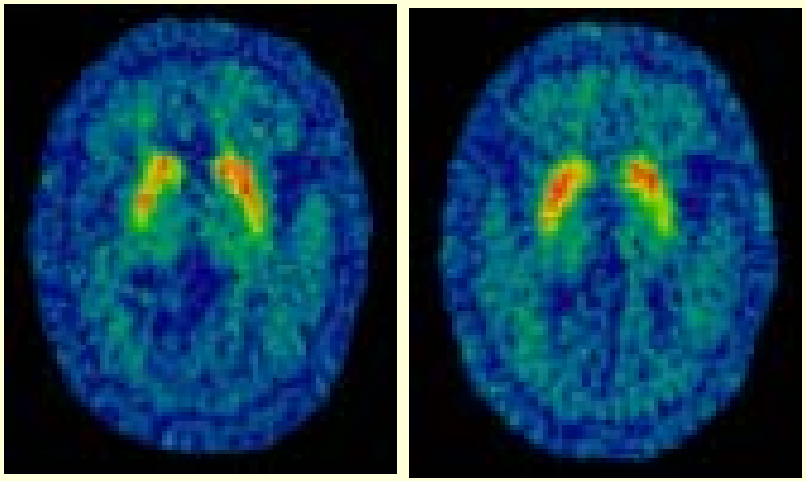
mismatch of blood flow and glucose utilization indicating an ischemic heart condition.

decreased blood flow and glucose utilization indicating an infarct.

NEST-UK trial in Huntington's

Prof. Stephen Dunnett &
Prof Ann Rosser

human fetal striatal tissue implantation in the brain of Huntington's patient

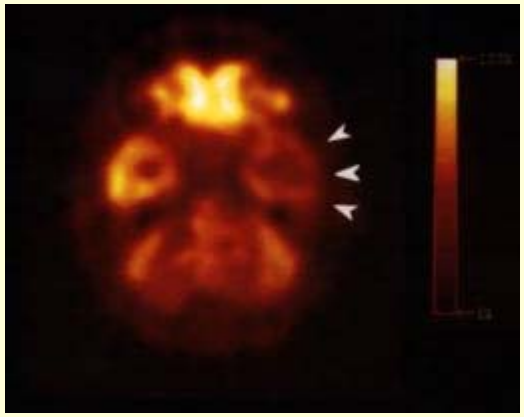


pre-op 1 year post-op

^{11}C-Raclopride

Clinical Research

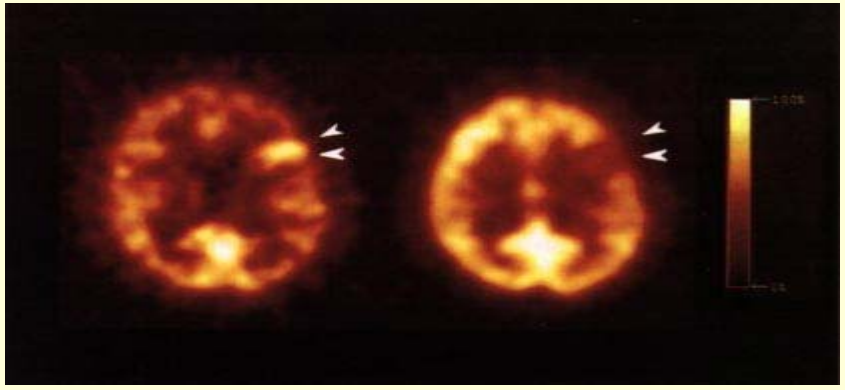
Epilepsy



Temporal lobe epilepsy

The left temporal lobe shows reduced ^{18}FDG uptake in the interictal period (arrowheads).

Stroke



Left middle cerebral artery infarct 1 week after clinical onset. $^{13}NH_3$ scan (left) shows increased cerebral perfusion, whilst ^{18}FDG scan (right) shows decreased metabolism in the corresponding area.

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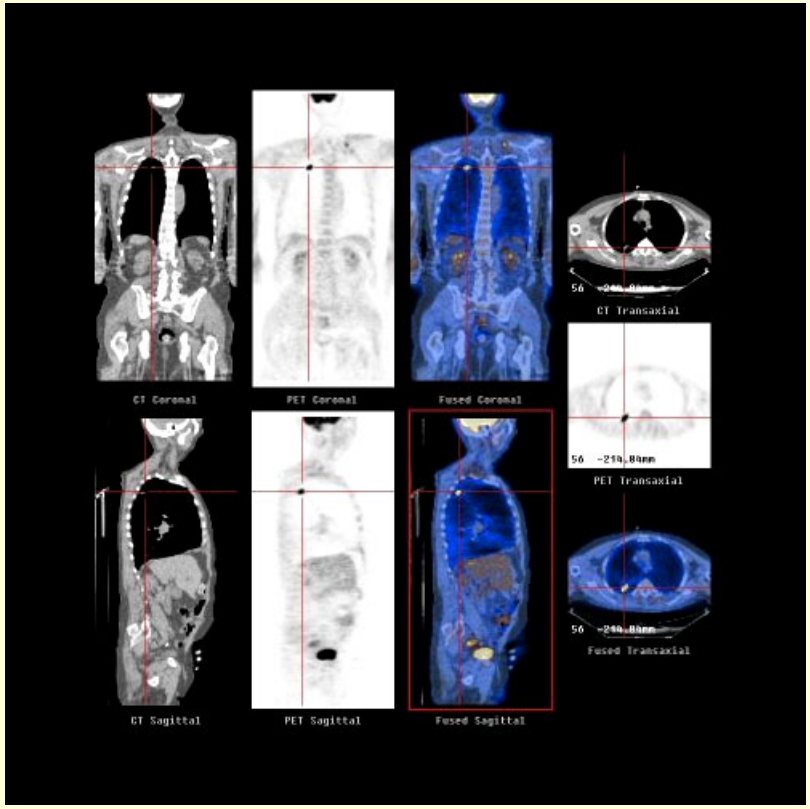
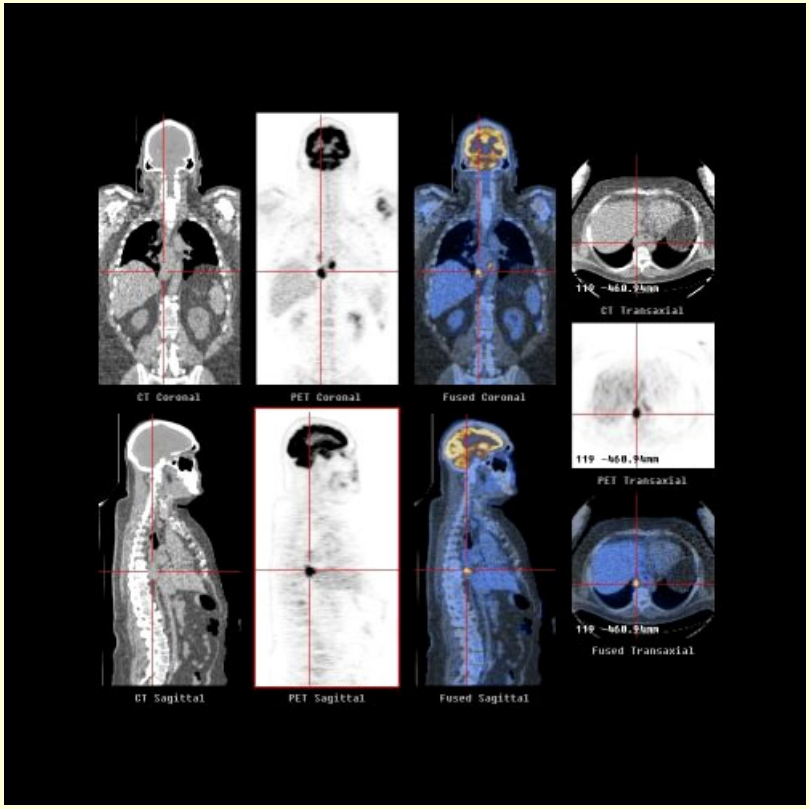
Clinical Research



Pulmonary Solitary Nodule
2x2cm solitary nodule in upper right lung



Gastro-esophageal cancer
left scapular bone FDG uptake

Images Medical College of Wisconsin, USA

Basic Research

To explore fundamental mechanisms underlying physiological and pathophysiological function and potential thrapeutic interventions:

PET enables studies of:

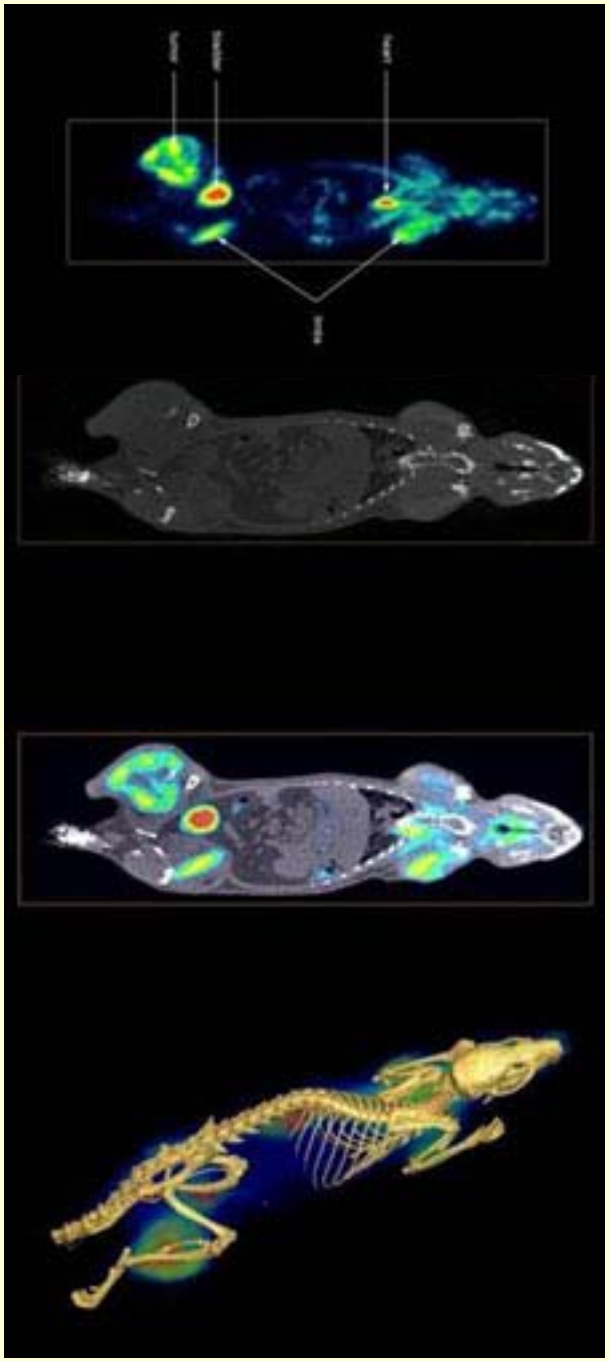
- Biodistribution
- PD/PK
- Toxicology

and, most crucially, it permits:

- Longitudinal studies

and

- Reduction Refinement Replacement



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Potential Research Areas for PET:

- Tissue Metabolic Activity
  - ^{18}FDG, $^{15}O_2$, ^{11}C-palmitic acid
- Blood Flow
  - $H_2{}^{15}O$, ^{15}O-butanol, ^{11}CO, $^{13}NH_3$
- Gene Expression
  - ^{18}F-penciclovir,
  - ^{18}F-antisense oligonucleotides
- Receptor Affinity
  - ^{11}C-raclopride, ^{11}C-carfentanil,
  - ^{11}C-scopalamine
- Neurotransmitter Activity
  - ^{18}fluorodopa, ^{11}C-ephedrine
- Enzyme Activity
  - ^{11}C-deprenyl, ^{18}F-deoxyuracil
- Protein Synthesis
  - ^{11}C-leucine, ^{11}C-methionine,
  - ^{11}C-tyrosine

Potential Research Areas for SPECT:

- Oncology
  - Bio-distribution (many ^{123}I-labelled tracers)
  - Apoptosis (^{99m}Tc-rh-Hynic-Annexin V)
- Cardiology
  - Myocardial perfusion (^{99m}Tc[myoview])
  - Cardiac gating (^{99m}Tc-pertechnetate)
- CNS and Brain Research
  - Parkinson's disease model ([^{123}I]-β-CIT)
- Cell migration (^{111}In oxine)

^{133}Xe, ^{99}mTe, ^{123}I, ^{111}In

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Translational Research

The μPET/CT system will facilitate the transfer of new imaging modalities to use in clinical studies.

Proof-of-principle studies will establish: targeting, biodistribution, pharmacokinetic, pharmacodynamic and toxicology, prior to transfer to man.

Experimental Cancer Medicine Centre:
mission to stimulate early phase clinical trials and first-into-man studies

Acute Myelogenous Leukemia (AML)

Clofarabine
Forodosine & Sunensis
PDK-1 inhibitors

Myeloma and prostate cancer

LC-1

Ovarian cancer

SJG136

Pharmaceutical companies:

- Small molecule libraries
- combinatorial chemistry
- not therapeutic
- tracer molecules ?

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