Royal Society of Chemistry Radiochemistry Group- A Celebration of 50 Years

Past achievements, present innovation & future challenges-

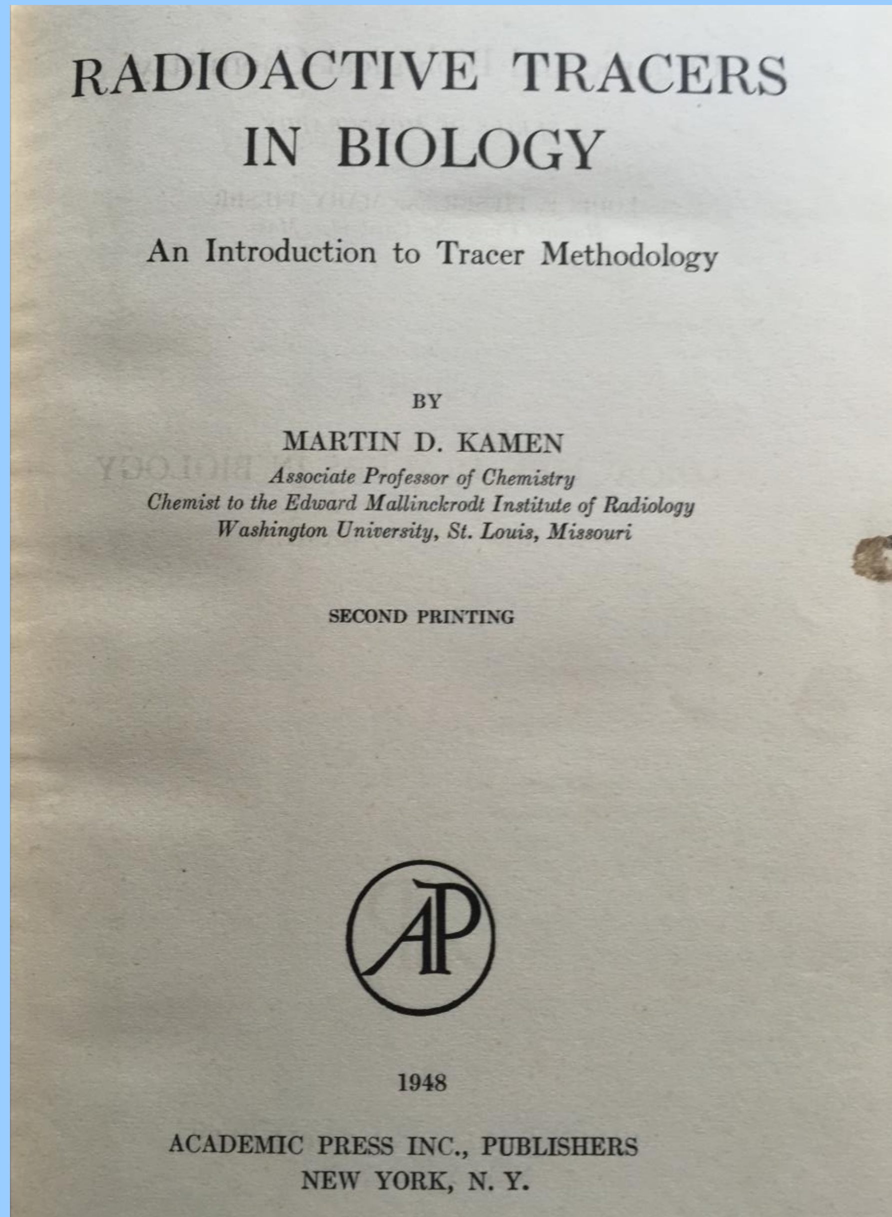
Nuclear Medicine

Terry Jones

1948

^{3}H

^{35}S


RADIOACTIVE TRACERS
IN BIOLOGY

An Introduction to Tracer Methodology

BY

MARTIN D. KAMEN

Associate Professor of Chemistry
Chemist to the Edward Mallinckrodt Institute of Radiology
Washington University, St. Louis, Missouri

SECOND PRINTING

1948

ACADEMIC PRESS INC., PUBLISHERS
NEW YORK, N. Y.

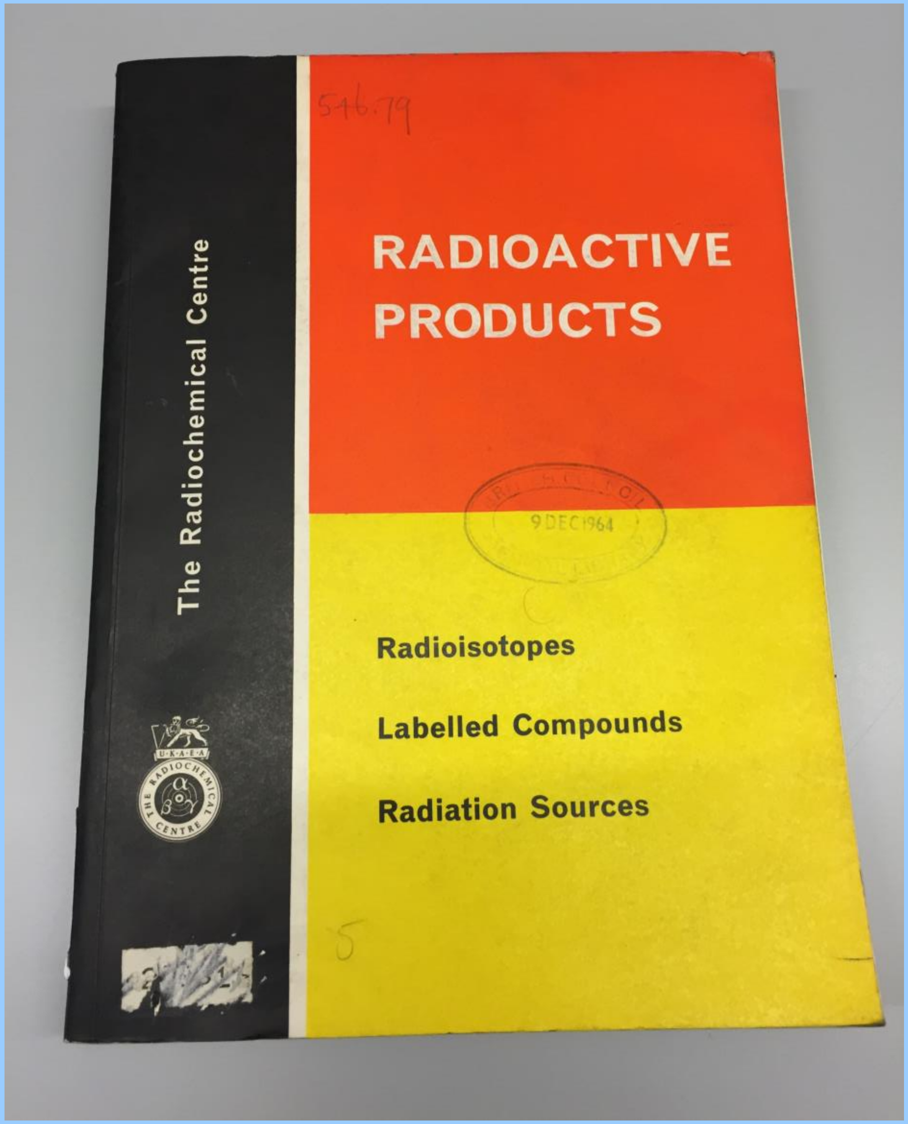
^{14}C

$[^{11}C]$

^{32}P

Ex-Vivo and *In-Vitro* assays

Amersham Catalogue-1964

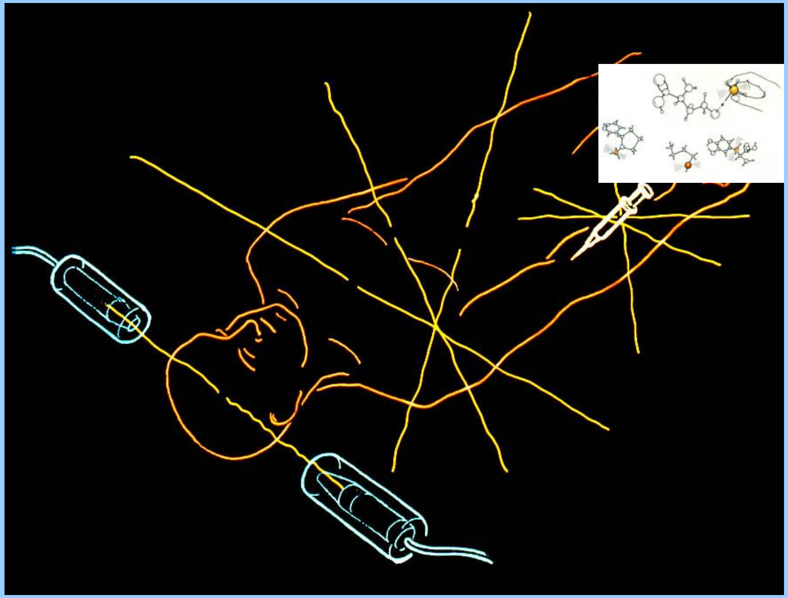


Tritium Labelling Service:
"Over 200 tritium compounds appear in the list of compounds and others may be prepared to special order"

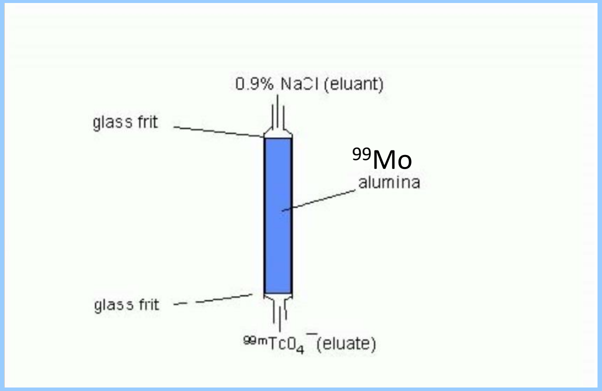
Carbon-14 labelling Service:
290 carbon-14 labelled compounds are listed

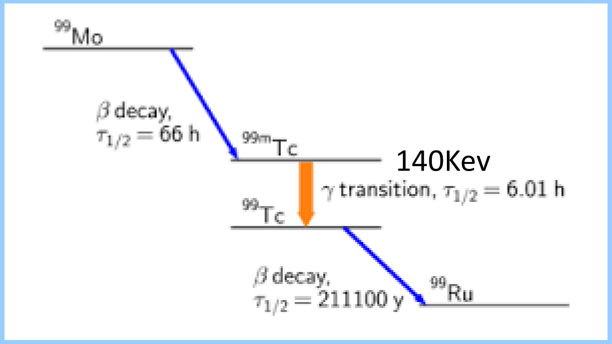
Radiochemistry for *in-vivo* measurements of regional tissue function for clinical research and healthcare

- Past achievements
- Present innovation
- Future challenges

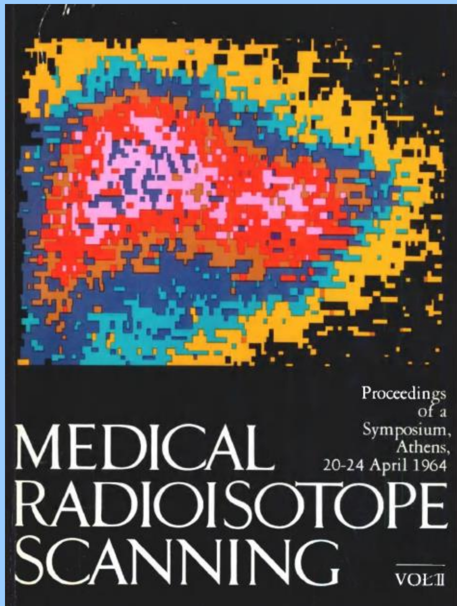


Technetium-99m Generator from the early 1960's





1964



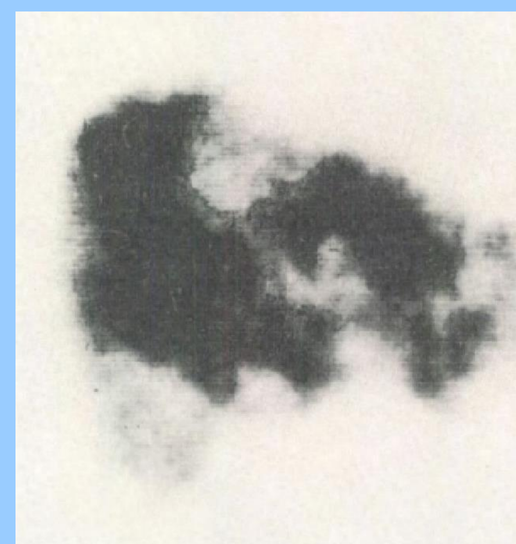
THE USE OF TECHNETIUM-99m
AS A CLINICAL SCANNING AGENT FOR THYROID,
LIVER AND BRAIN

P. V. HARPER, K. A. LATHROP, R. J. McCARDLE AND G. ANDROS
ARGONNE CANCER RESEARCH HOSPITAL*
AND THE DEPARTMENT OF SURGERY,
UNIVERSITY OF CHICAGO HOSPITALS AND CLINICS,
CHICAGO, ILL., UNITED STATES OF AMERICA

Brain tumour

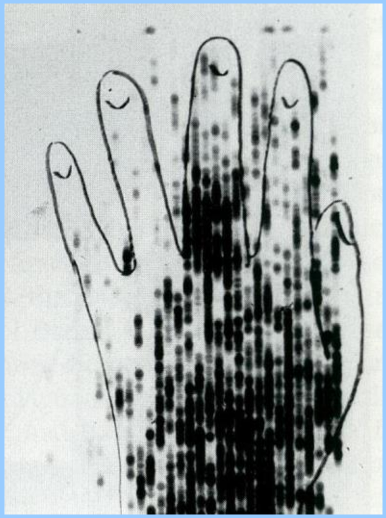
$^{99m}TcO_4$

Liver tumours

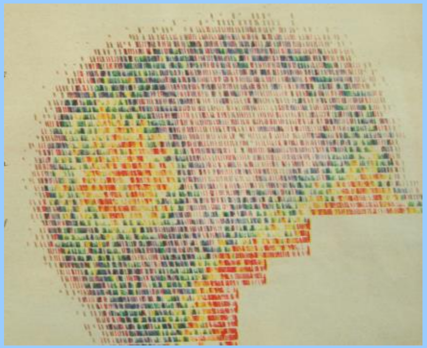


^{99m}Tc Sulphur Colloid

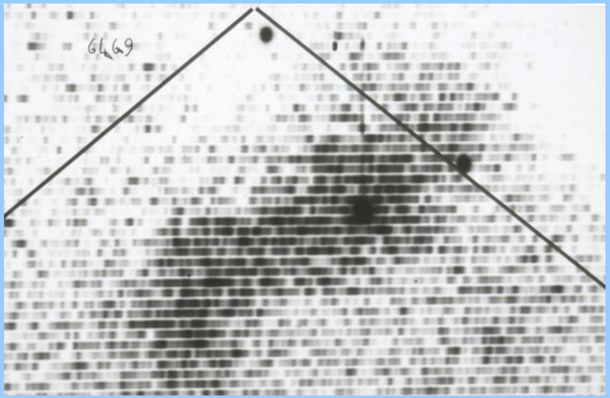
1966 Nuclear Medicine



Bone Scan
(^{18}F-Fluoride)

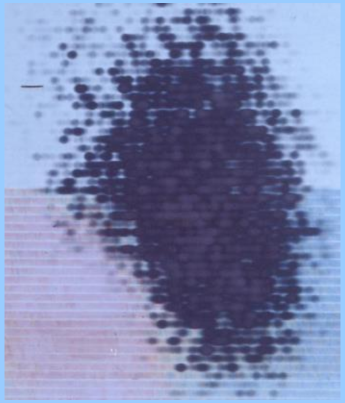


Brain tumour Scan
(^{99m}Tc-Pertechnetate)

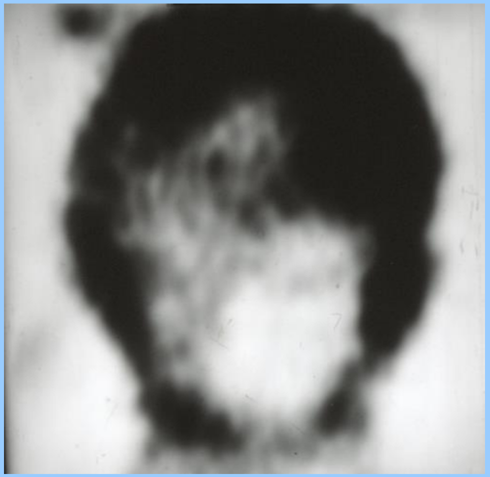


Pancreas Scan
(^{75}Se-Methionine)

Nuclear Medicine Scanning at The Royal Marsden Circ. mid 1960's
Curtesy of Dr Ralph McCready



Spleen Scan
(^{51}Cr denatured red Cells)



Placenta Scan
(^{131}I Albumin)

Past Achievements
1966-2016

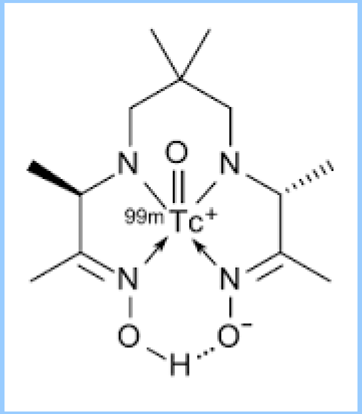
As assessed by the applications of the radiochemistry in humans

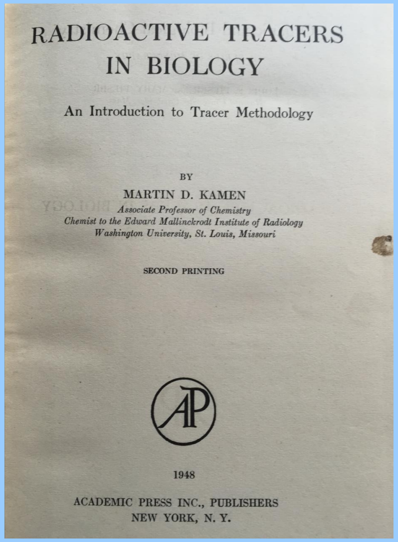
Single Photon Nuclear Medicine

THE RADIOPHARMACEUTICAL CHEMISTRY OF TECHNETIUM AND RHENIUM

JONATHAN R. DILWORTH
Department of Chemistry, University of Oxford, Oxford, UK
SOFIA I. PASCU
Department of Chemistry, University of Bath, Bath, UK

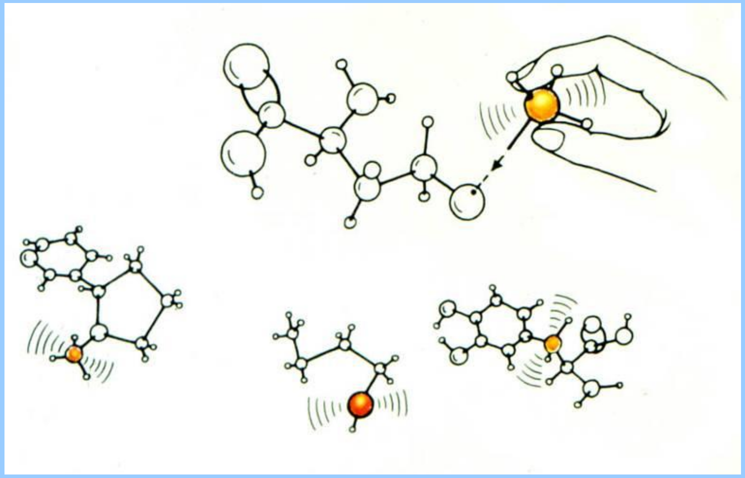
The Chemistry of Molecular Imaging
Ed: Nicholas Long & Wing-Tak Wong

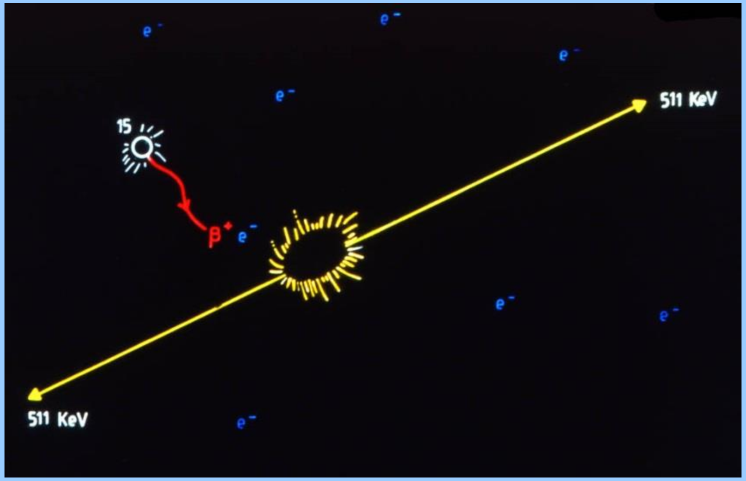




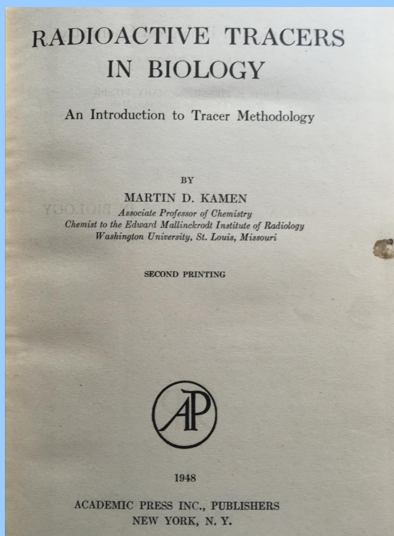
Translating → to *in-vivo*

Oxygen-15	2.1 min T½
Nitrogen-13	10 min T ½
Carbon-11	20.1 min T ½
Fluorine-18	1.7 hr T ½





CYCLOTRON PRODUCED POSITRON EMITTING ISOTOPES



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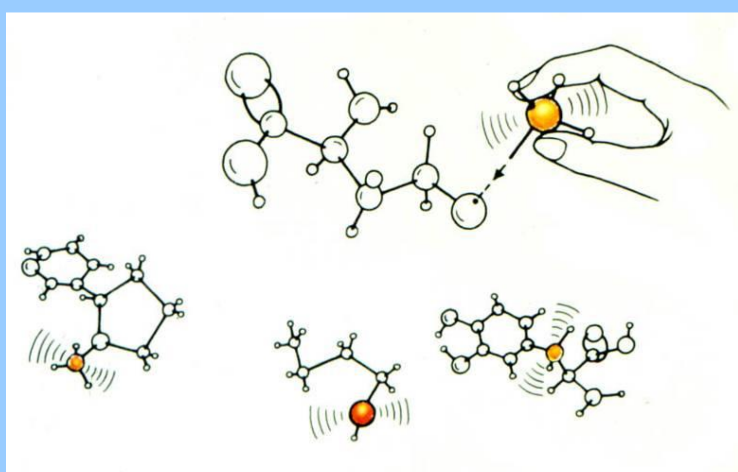
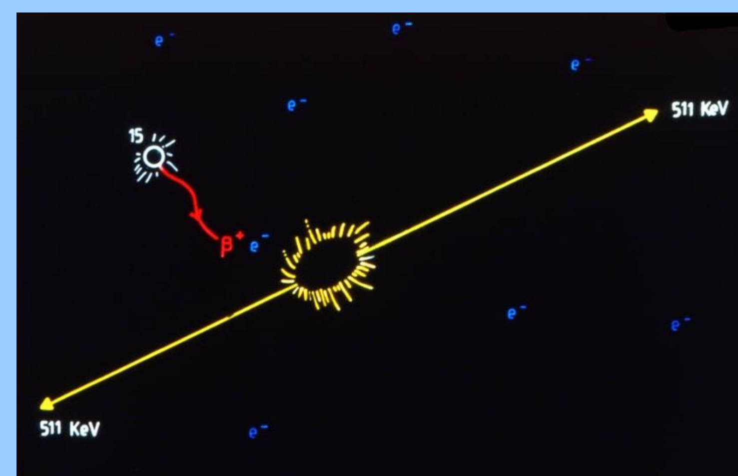
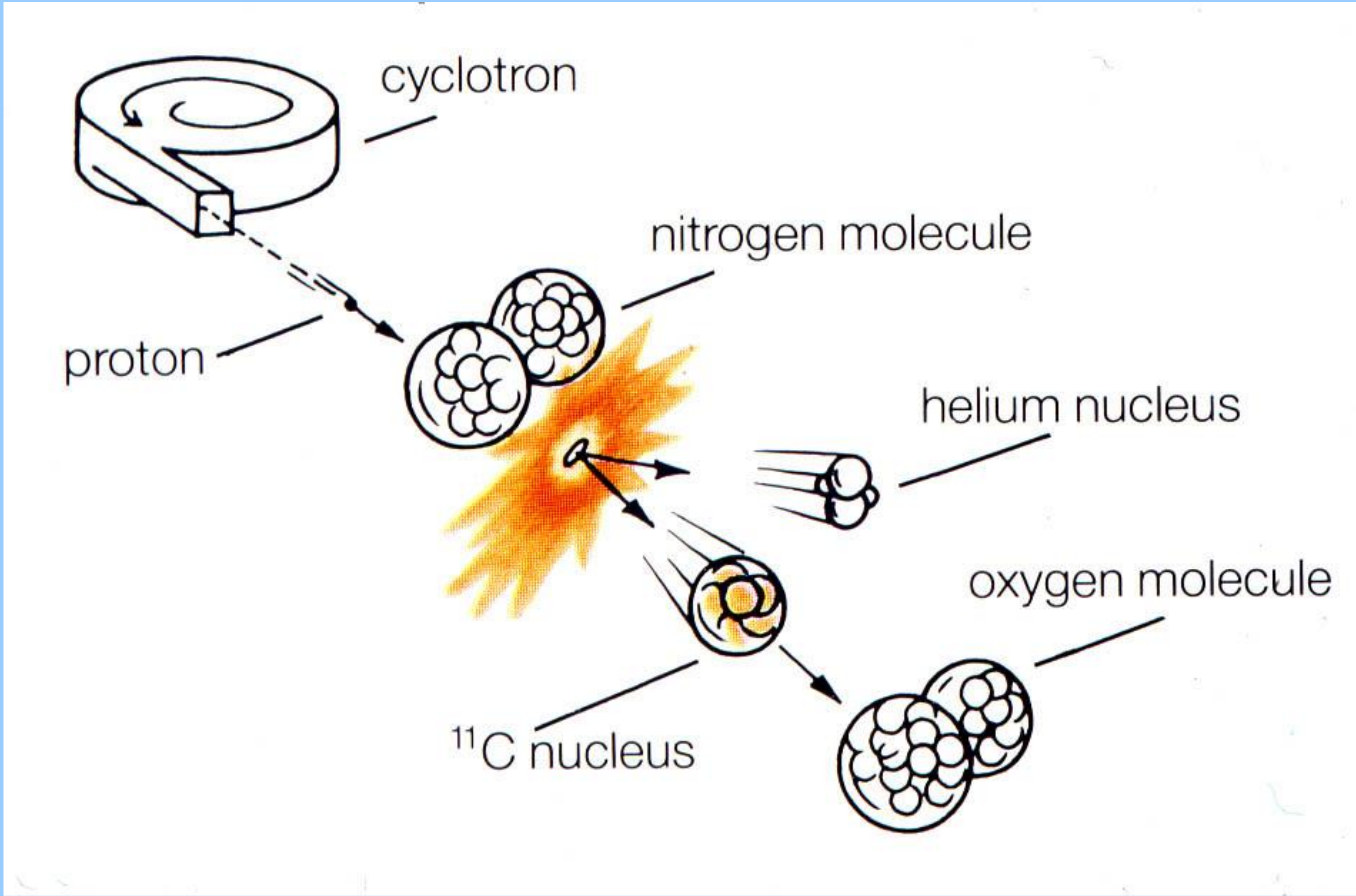


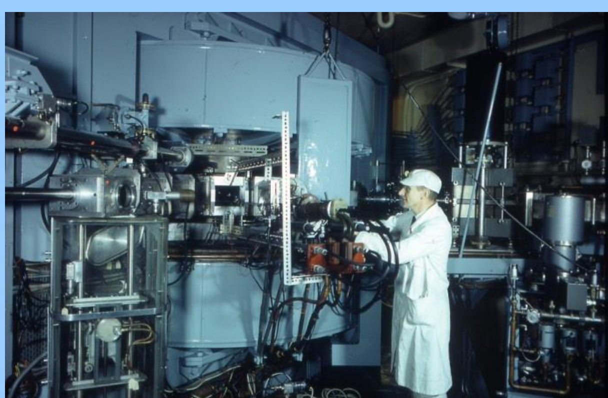


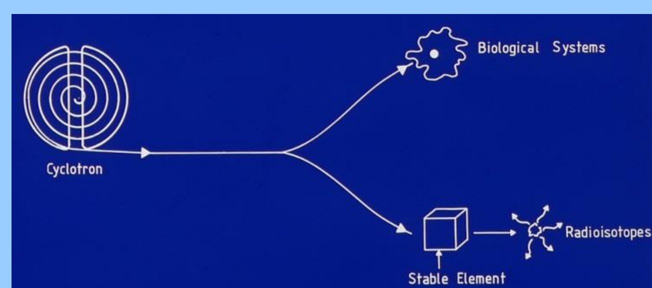

cyclotron
nitrogen molecule
proton
helium nucleus
oxygen molecule
11C nucleus

Hammersmith Hospital London

1955

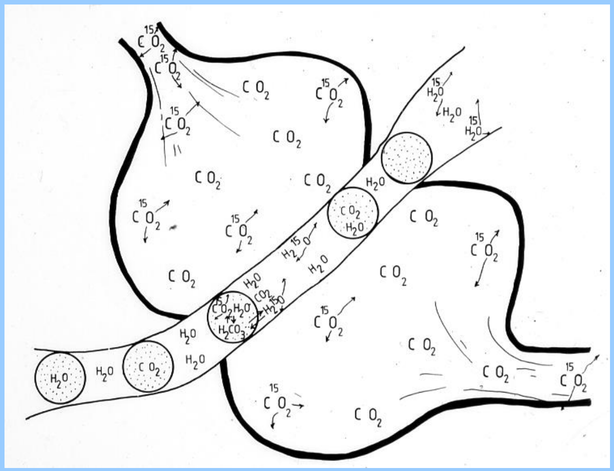
The first, & in 1966, the only operational hospital based cyclotron

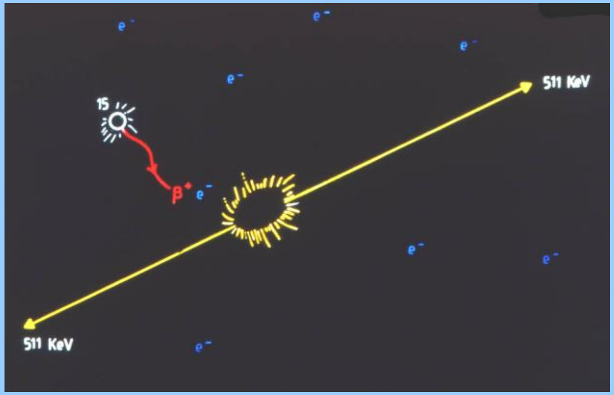


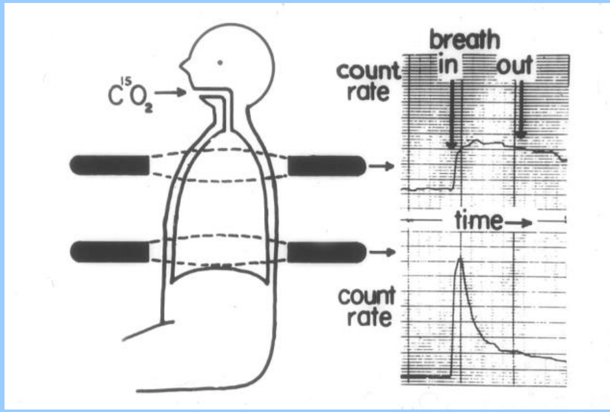


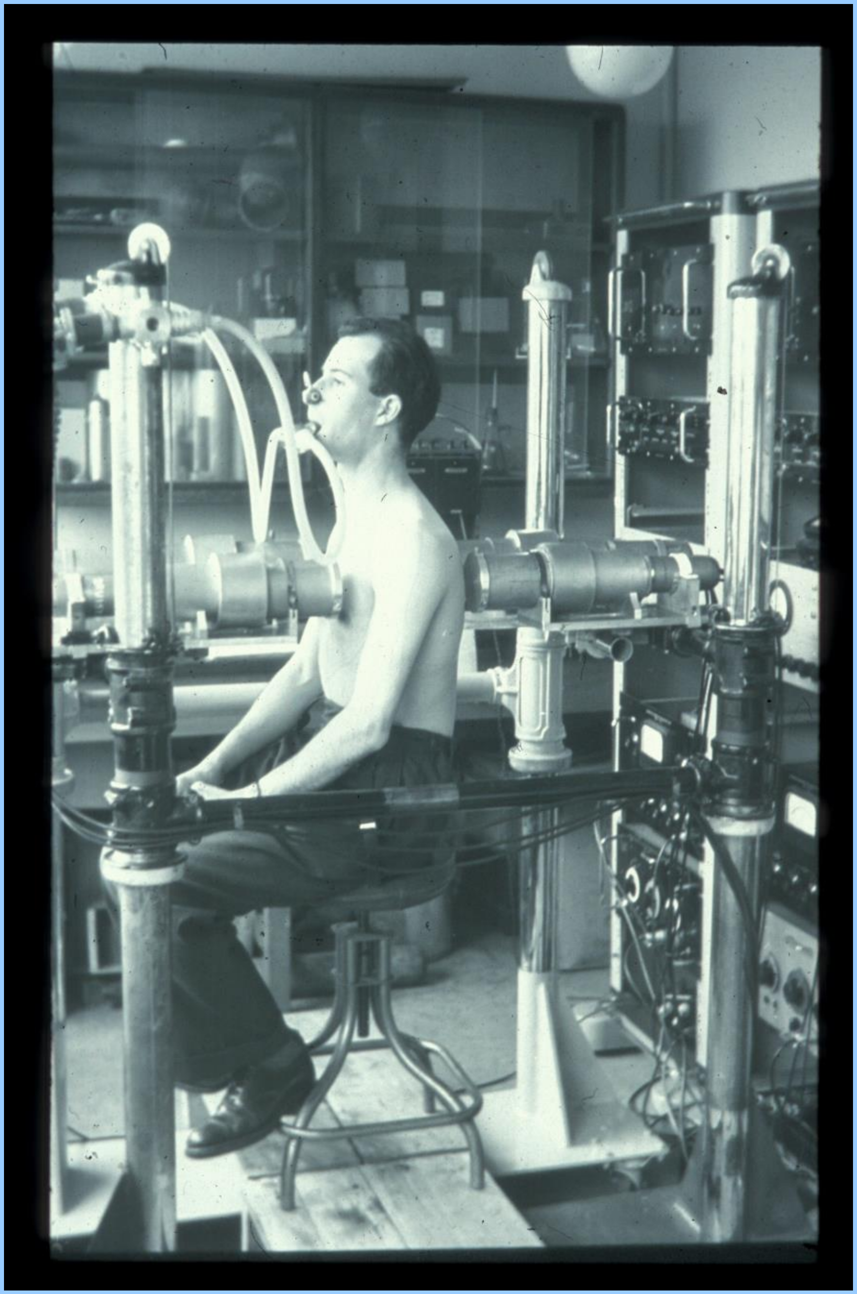
Medical Research Council Cyclotron Unit

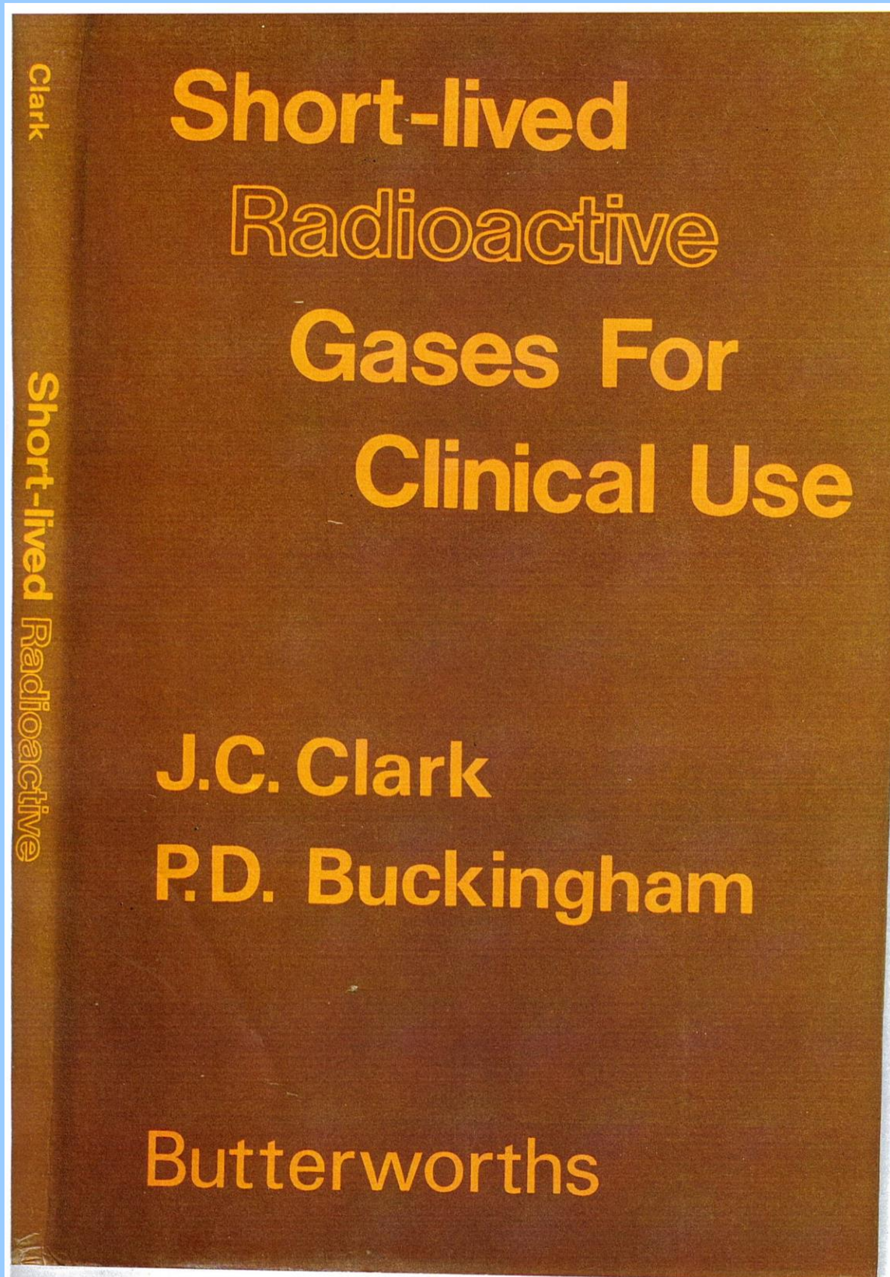
1958 Lung blood flow










Clark
Short-lived Radioactive
Short-lived
Radioactive
Gases For
Clinical Use
J.C. Clark
P.D. Buckingham
Butterworths

Circ. 1970

Labelling organic compounds with ^{15}O, ^{13}N, ^{11}C & ^{18}F for *in-vivo* functional biochemistry, physiology and pharmacology- the position:

- ^{11}C - easiest but too short lived
- ^{18}F - better half life, but not so accommodating with respect to organic chemistry

1971

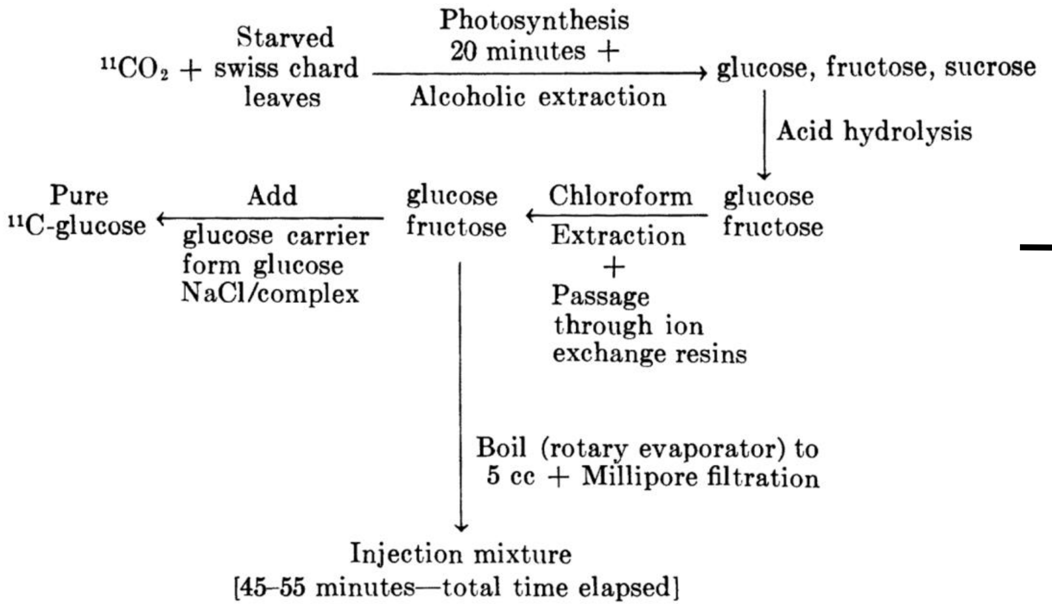
RADIATION RESEARCH 45, 35–40 (1971)

Preparation of Glucose Labeled with 20-Minute Half-Lived Carbon-11[1]

JUDITH F. LIFTON AND MICHAEL J. WELCH

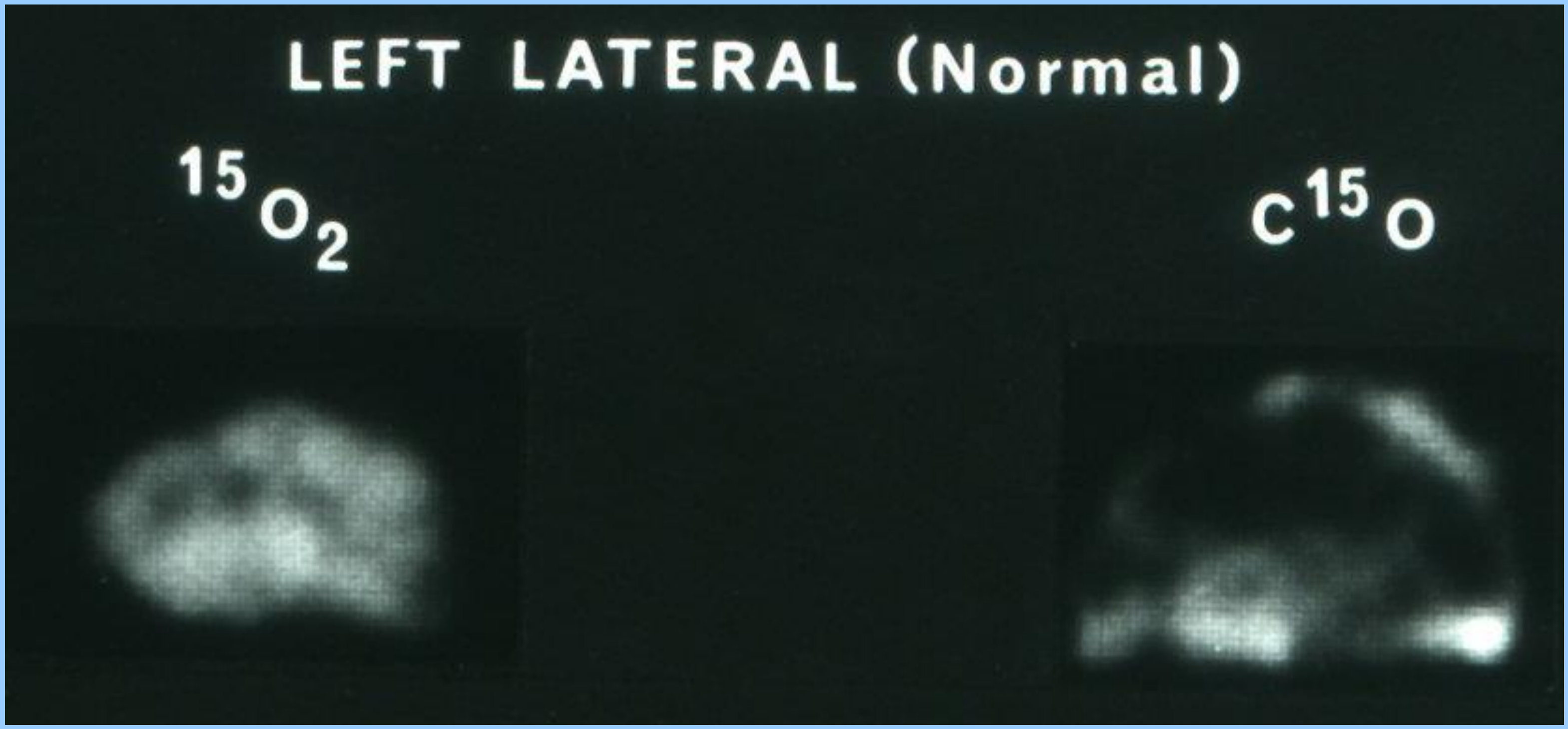
The Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, 510 South Kingshighway, St. Louis, Missouri 63110

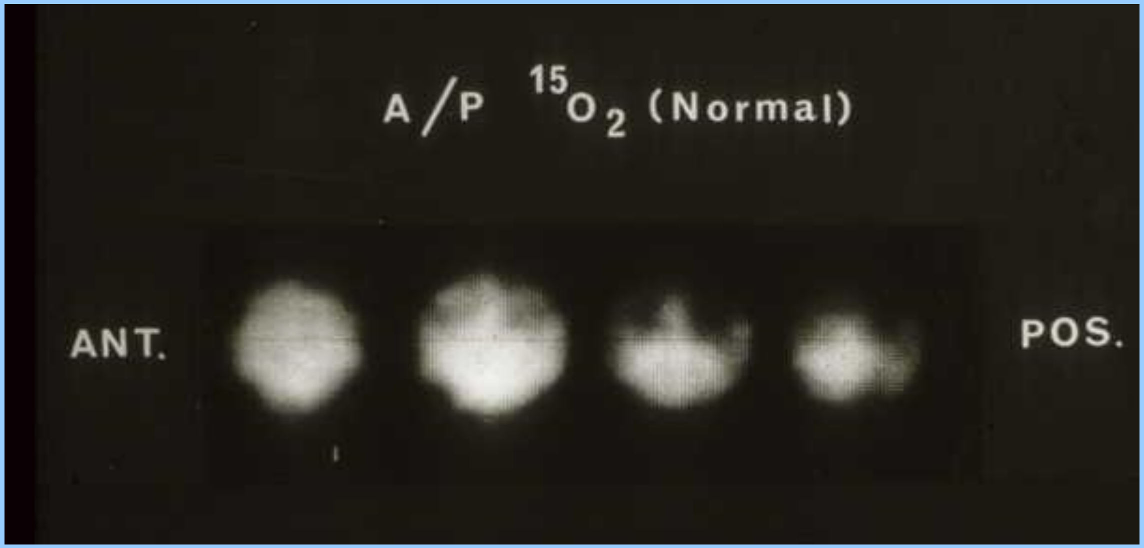
Production of ^{11}C-glucose



[^{11}C]-Glucose *in-vivo* uptake very complex to analyse and interpret

The first reported image of regional human brain metabolism



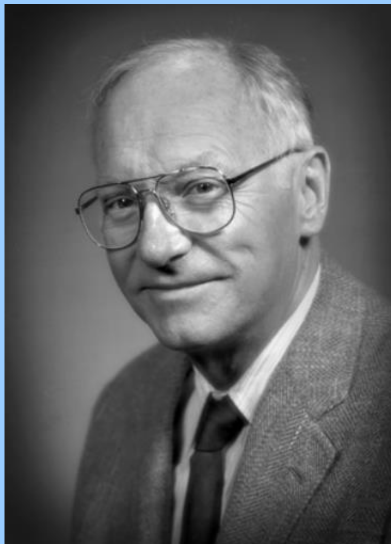


1973

MGH Boston

Brookhaven

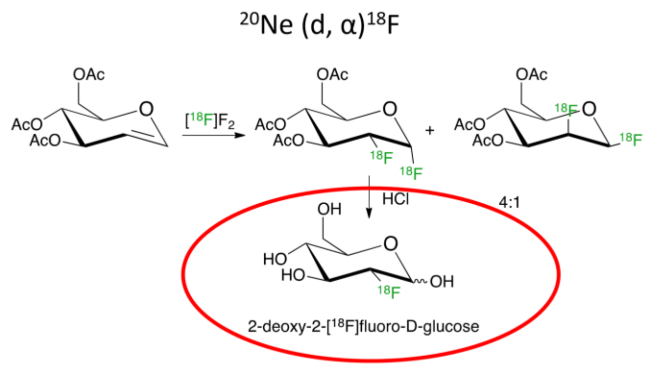
1976



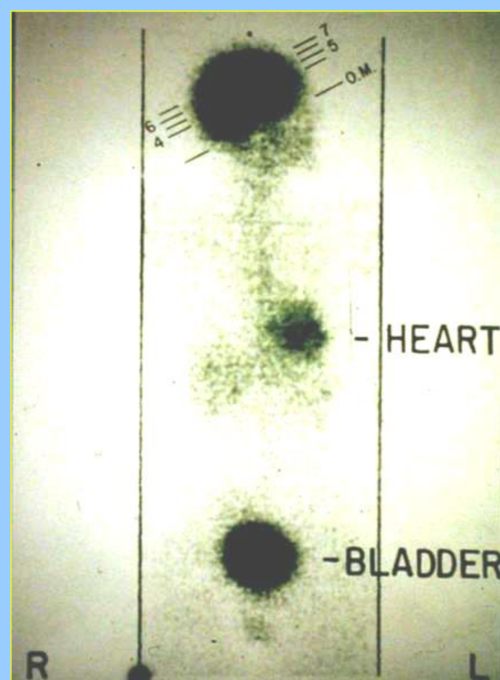
Al Wolf

Tatsuo Ido

First ^{18}FDG Synthesis for Humans (1976)



Synthesis time 2 hr: prepared according to a protocol that had been shown to produce a sterile, pyrogen free product.



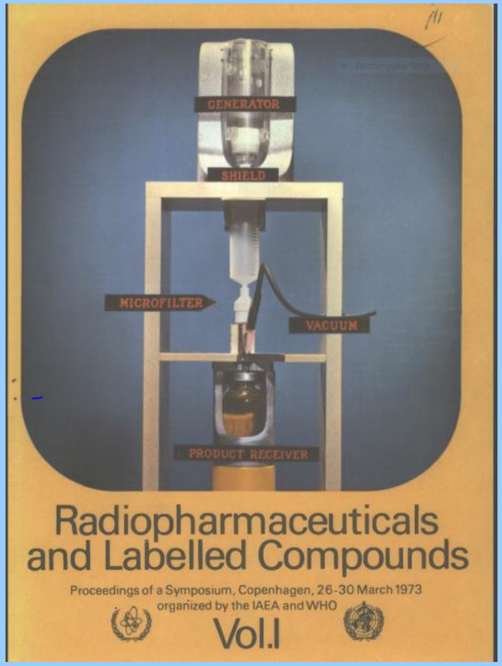
The first whole body ^{18}FDG image with a rectilinear scanner

Philadelphia

August 1976

1973

Carbon-11 labelling by methylation



IAEA-SM-171/22

SYNTHESE ET METABOLISME DE L'IODOMETHYLATE DE CHLORPROMAZINE-^{11}C

D. COMAR, M. MAZIERE*, C. CROUZEL
CEA, Département de biologie,
Service hospitalier Frédéric Joliot,
Orsay, France

Abstract–Résumé

SYNTHESIS AND METABOLISM OF ^{11}C-CHLORPROMAZINE METHIODIDE.

Of the short-lived radioelements produced in cyclotrons, ^{11}C ($T_{1/2}$ = 20 min) occupies a privileged position in that it is easily obtained in quantity as $^{11}CO_2$ or ^{11}CO and can be used directly in human subjects for investigating pulmonary function or, after incorporation in a natural or synthesized organic molecule, as a medical diagnostic agent or as a means of investigating the metabolism of a medicinal agent. *Synthesis of ^{11}C-chlorpromazine methiodide* involves the following stages: continuous production of $^{11}CO_2$ by bombarding nitrogen containing 4% oxygen with 16.5 MeV protons, the radioactivity obtained being of the order of 2 mCi/μA per min; conversion of $^{11}CO_2$ into methanol using the reaction scheme described by Nystrom; conversion of $^{*}CH_3OH$ into $I^{*}CH_3$ by reaction with hydriodic acid; synthesis of chlorpromazine methiodide through the action of gaseous $I^{*}CH_3$ on excess chlorpromazine in solution in tributyl phosphate. These reactions are performed continuously until after less than 40 min several millicuries of $I^{*}CH_3$ are produced. The yield of the synthesis was measured and the radiochemical purity was controlled at each stage by gas chromatography and thin-layer chromatography using silica gel. The chlorpromazine methiodide produced was dissolved in physiological solution, sterilized by Millipore filtration and injected intravenously into rabbits. The sequential images obtained with a gamma camera as well as the qualitative distribution of the molecule between different organs are presented.

1)-Fabrication du $^{11}CO_2$

$$^{14}_{7}N\ (p,\alpha)\ ^{11}_{6}C \xrightarrow{O_2} {}^{11}CO_2 + {}^{11}CO \xrightarrow[850\,^{\circ}C]{CuO} {}^{11}CO_2$$

2)-Fabrication de $^{11}CH_3OH$

$$-\ 4\ {}^{11}CO_2 + 3\ LiAlH_4 \longrightarrow LiAl(O^{11}CH_3)_4 + 2\ LiAlO_2$$

$$-\ LiAl(O^{11}CH_3)_4 + 4\ ROH \longrightarrow LiAl(OR)_4 + 4\ {}^{11}CH_3OH$$

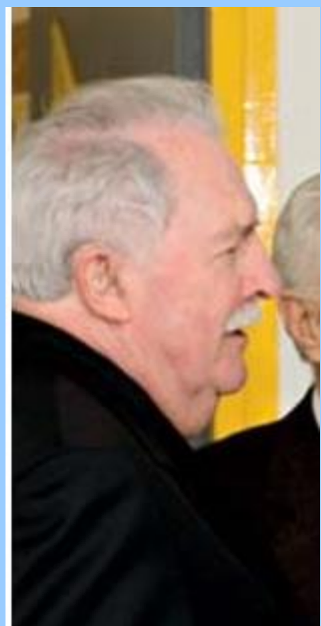
$$LiAlH_4 + 4\ ROH \longrightarrow LiAl(OR)_4 + 4\ H_2$$

3)-Fabrication de $I^{11}CH_3$

$$-\ {}^{11}CH_3OH + HI \longrightarrow {}^{11}CH_3I + H_2O$$

Dominique Comar
Orsay France

Carbon-11 labelling by methylation



Dominique Comar
Orsay France

1974

PROCEEDINGS OF A SYMPOSIUM ON DYNAMIC STUDIES WITH RADIOISOTOPES IN CLINICAL MEDICINE AND RESEARCH HELD BY THE INTERNATIONAL ATOMIC ENERGY AGENCY IN KNOXVILLE 15-19 JULY 1974

A METHOD FOR INVESTIGATING REGIONAL VARIATIONS OF THE CEREBRAL UPTAKE RATE OF ^{11}C-LABELLED PSYCHOTROPIC DRUGS IN MAN

C. RAYNAUD, A.E. TODD-POKROPEK, D. COMAR, S.M. PIZER, A. KACPEREK, M. MAZIERE, C. MARAZANO, C. KELLERSHOHN*

^{11}C-Chlorpromazine, ^{11}C-Impipramine, ^{11}C-Diazepam

1977

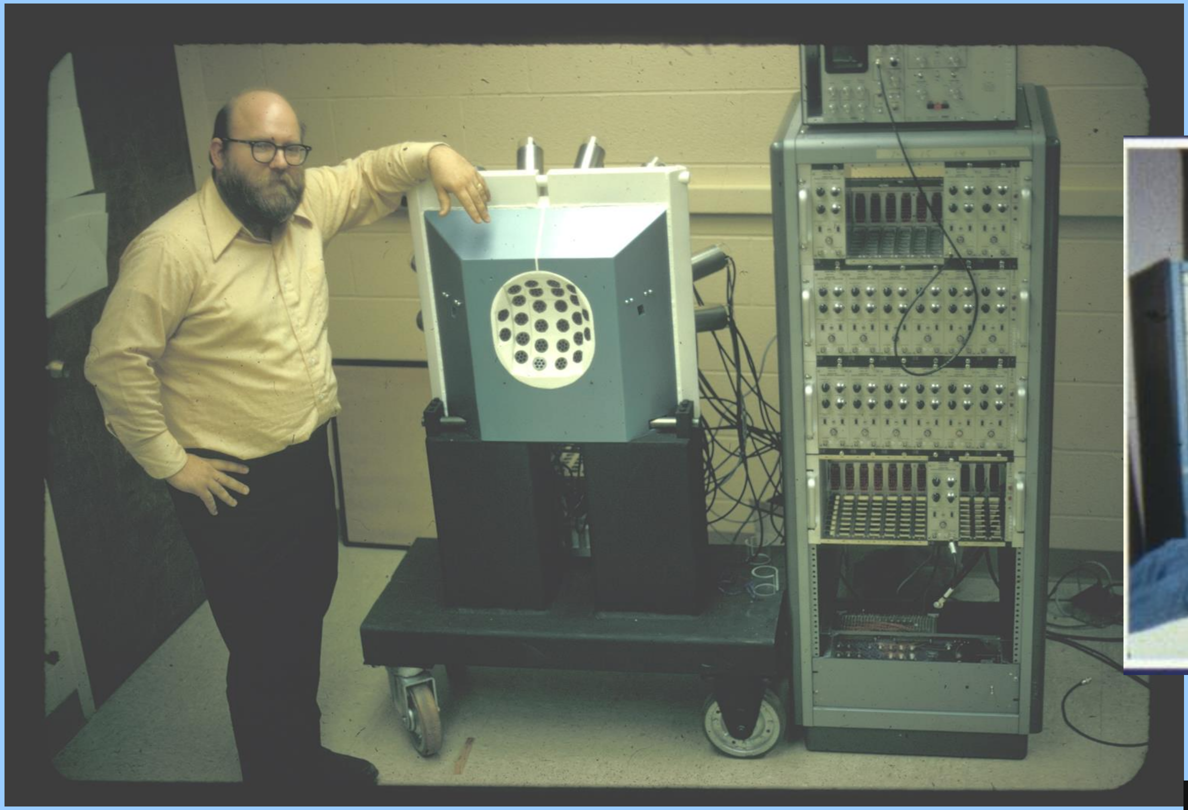
International Journal of Applied Radiation and Isotopes, 1977, Vol. 28, pp. 49 – 52. Pergamon Press. Printed in Northern Ireland

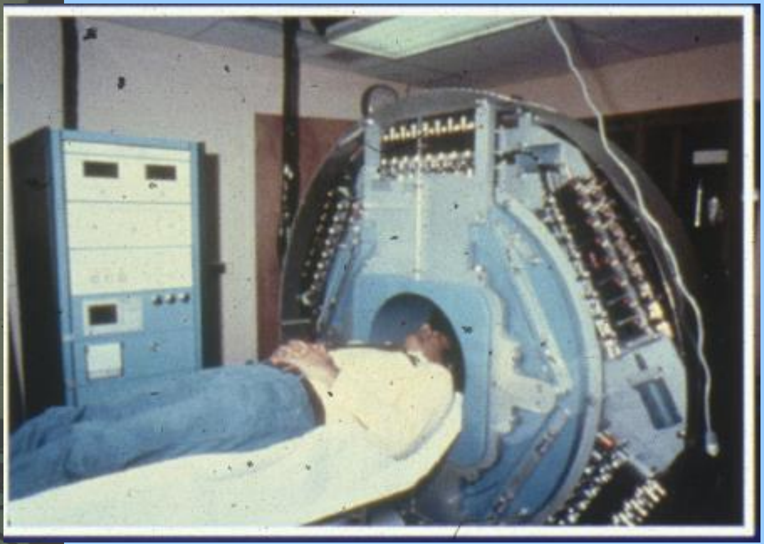
Synthesis of Methyl Iodide-^{11}C and Formaldehyde-^{11}C

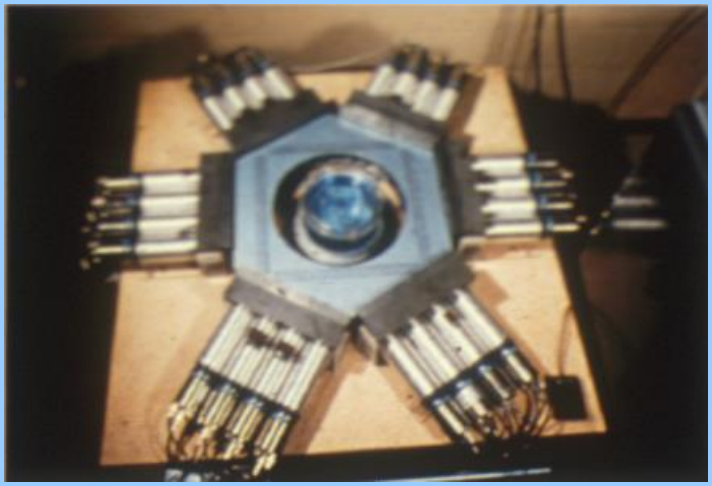
CHRISTIAN MARAZANO, MARIANNICK MAZIERE, GÉRARD BERGER and DOMINIQUE COMAR
Service Hospitalier Frédéric Joliot, Département de Biologie, Commissariat à l'Energie Atomique. 91406 Orsay, France

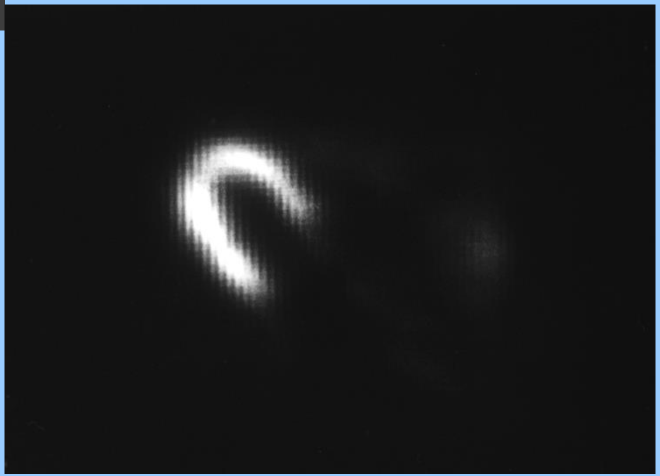
1973-76 St Louis

Positron Emission Tomography

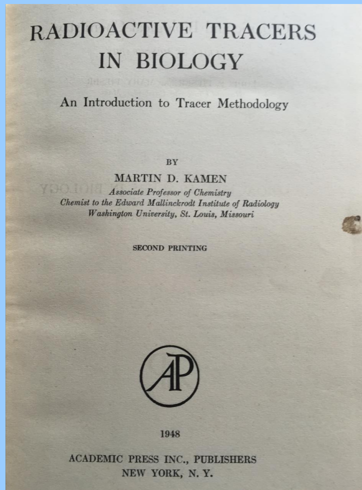








$[^{11}C]$ Palmitate-Myocardium

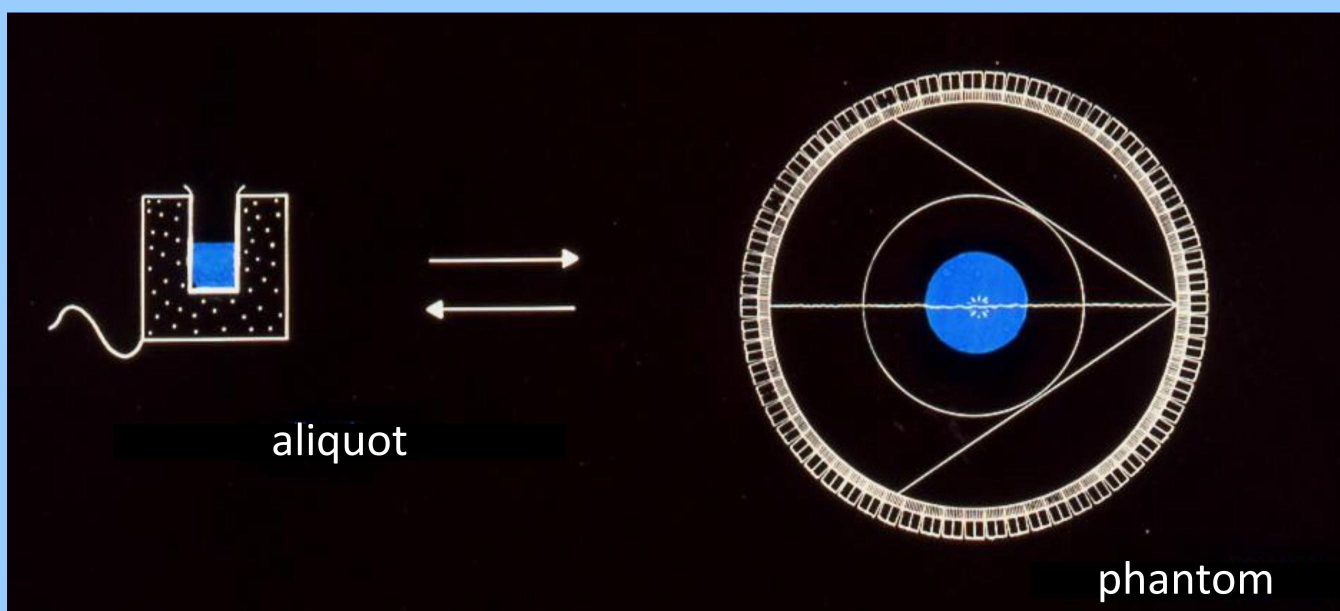


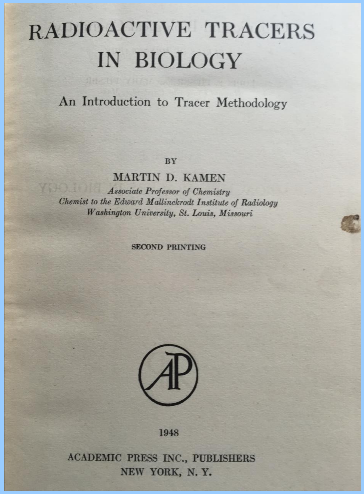
Translating
to *in-vivo*

Quantification of tissue tracer concentration

WELLCOUNTER
Counts/ml/sec.

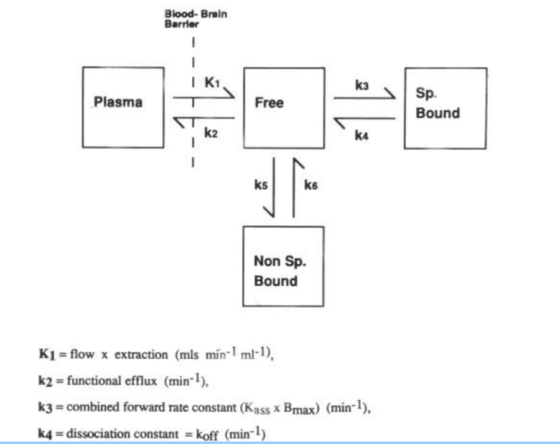
PET SCANNER
Voxel element counts/sec.





Translating to *in-vivo*

Application of classical compartmental modelling



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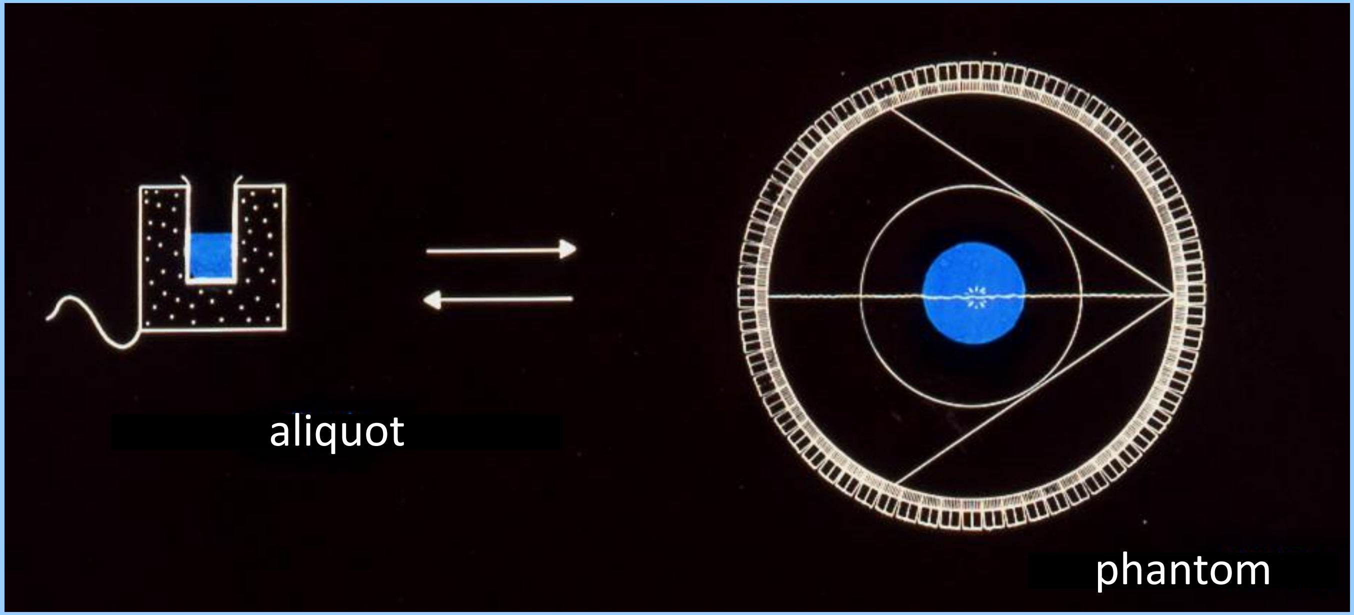
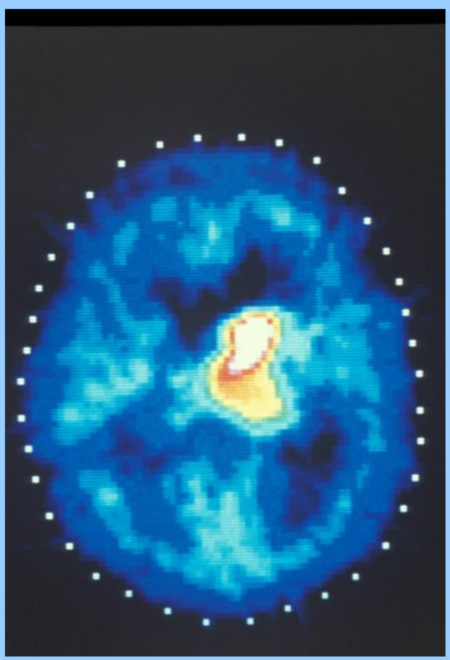
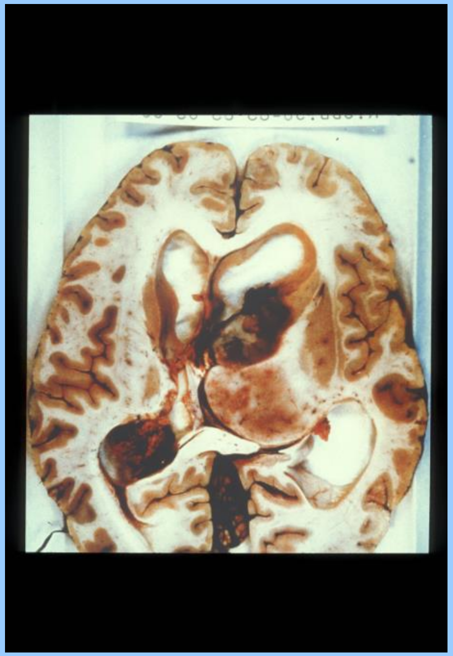


Late 1970's

Amino Acid Metabolism
[^{11}C]-Methionine-Brain Tumours



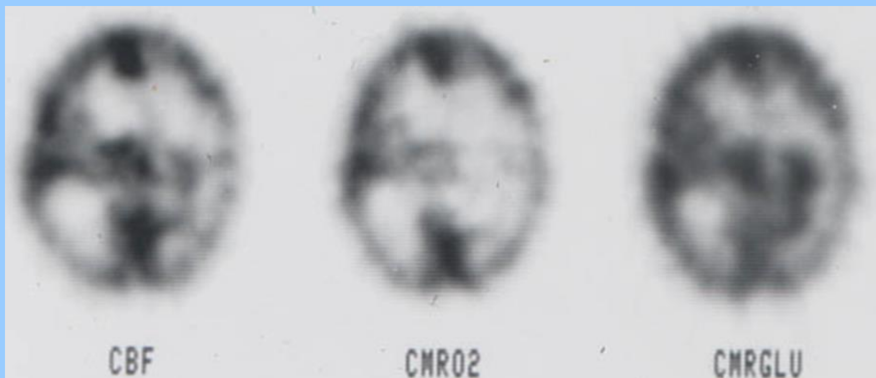


Lars Eriksson & Mats Bergstrom
Karolinska, Sweden

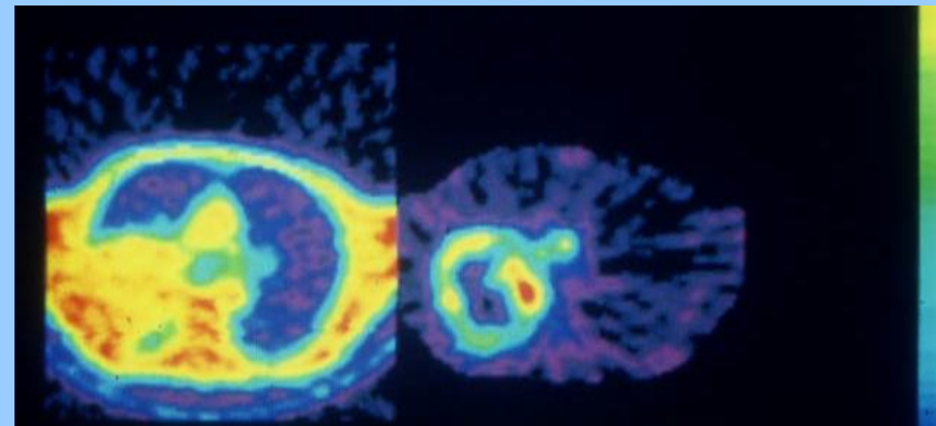
↔ 40 Kilometres

Bengt Langstrom
Uppsala, Sweden

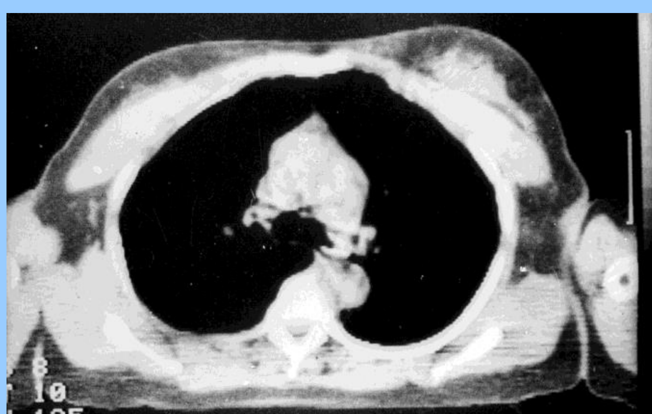
Imaging Glucose Utilisation in Tumours-^{18}FDG



Brain-1982



Lung-1984



Breast-1984

Hammersmith

Use of ^{18}FDG and PET in Oncology

At least 95% of PET scans world wide currently rest on the use of ^{18}FDG combined with X-Ray CT to:

- Detect focal cancers
- Stage patients-re the extent of the cancer
- Assess tumour response to therapy

Whole Body ^{18}FDG

1982

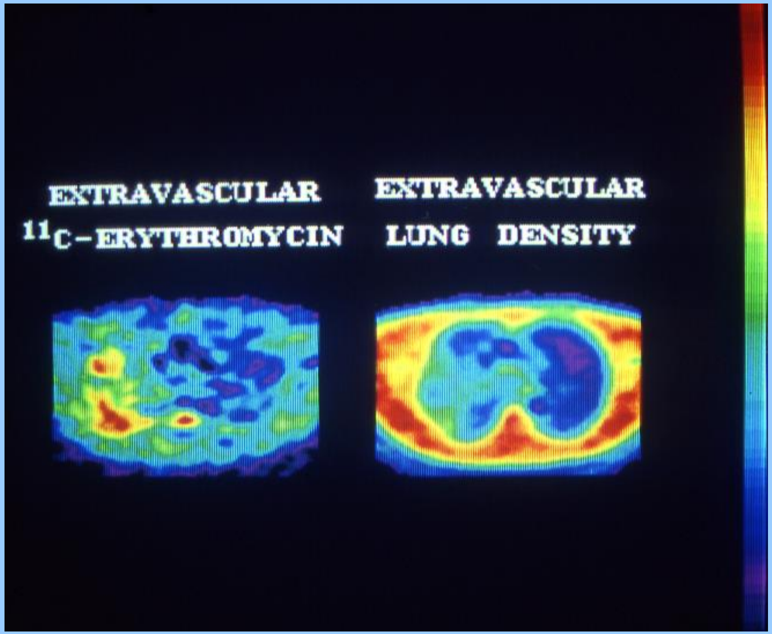
The First Labelled Drug PET Study

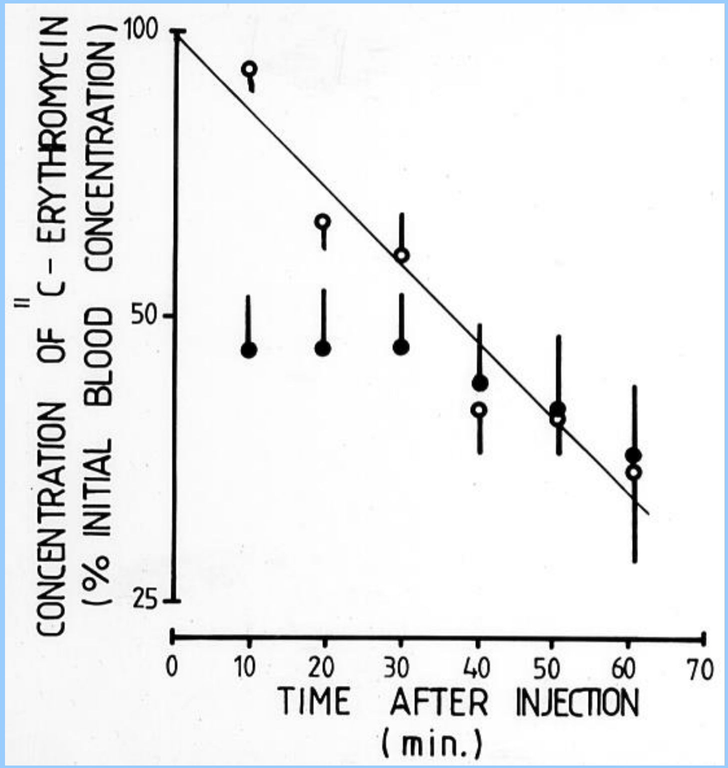
THE LANCET, DECEMBER 18, 1982

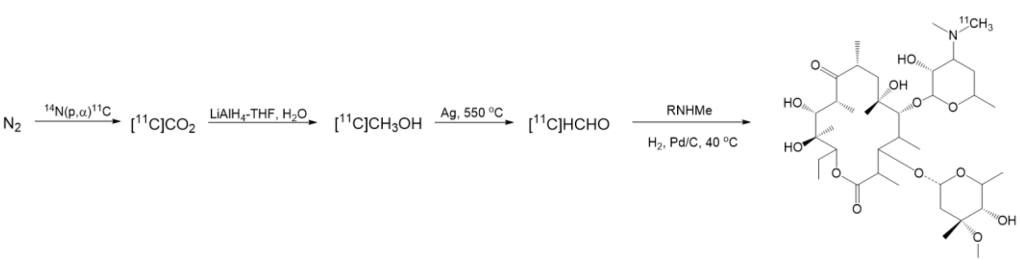
MEASUREMENT OF PULMONARY ERYTHROMYCIN CONCENTRATION IN PATIENTS WITH LOBAR PNEUMONIA BY MEANS OF POSITRON TOMOGRAPHY

PER WOLLMER* NEIL B. PRIDE
CHRISTOPHER G. RHODES ABRAHAM SANDERS
VICTOR W. PIKE ANTHONY J. PALMER
DAVID J. SILVESTER ROBERT H. LISS

Medical Research Council Cyclotron Unit and Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, and Arthur D. Little Inc., Acorn Park, Cambridge, Massachusetts, U.S.A.





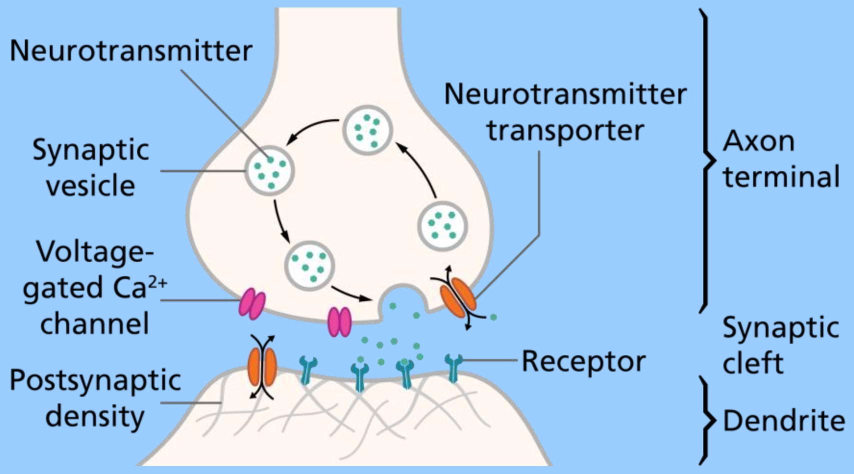


Pike, V. W., A. J. Palmer, P. L. Horlock, T. J. Perun, L. A. Freiberg, D. A. Dunnigan and R. H. Liss (1984). "Semi-Automated Preparation of a C-11-Labelled Antibiotic - [N-Methyl-C-11]Erythromycin-a Lactobionate." International Journal of Applied Radiation and Isotopes **35**(2): 103-109.

Imaging post and pre synaptic neuro-transmission

Challenges in the early 1980s to produce radiolabelled tracers and ligands with:

- A sufficient specific to non-specific ratio in tissue
- Sufficient specific activity (very potent molecules)
- Sufficient yields



I983-Sept

RESEARCH ARTICLE

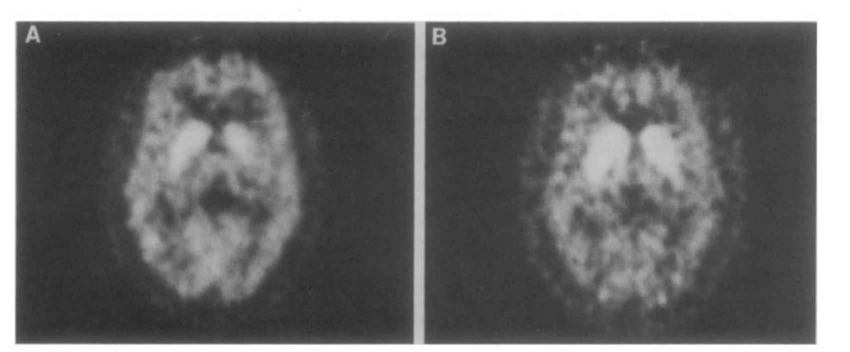
Science 221, 1264 (1983)

Imaging Dopamine Receptors in the Human Brain by Positron Tomography

Henry N. Wagner, Jr., H. Donald Burns, Robert F. Dannals
Dean F. Wong, Bengt Langstrom, Timothy Duelfer, J. James Frost
Hayden T. Ravert, Jonathan M. Links, Shelley B. Rosenbloom
Scott E. Lukas, Alfred V. Kramer, Michael J. Kuhar

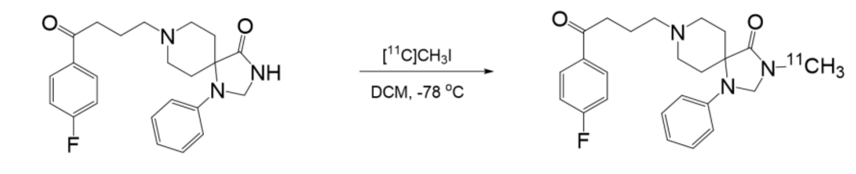
Henry Wagner Jnr

3-N-[^{11}C]methylspiperone-D_2



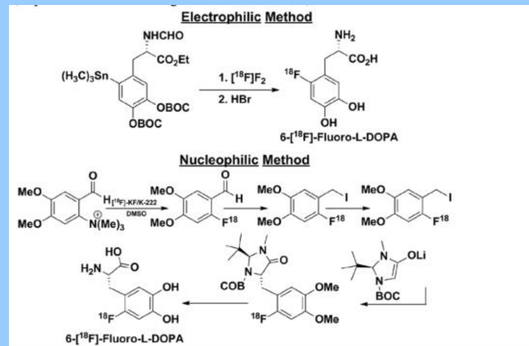
40-60 mins

70-130 mins



Bengt Langstrom

1983 Sept



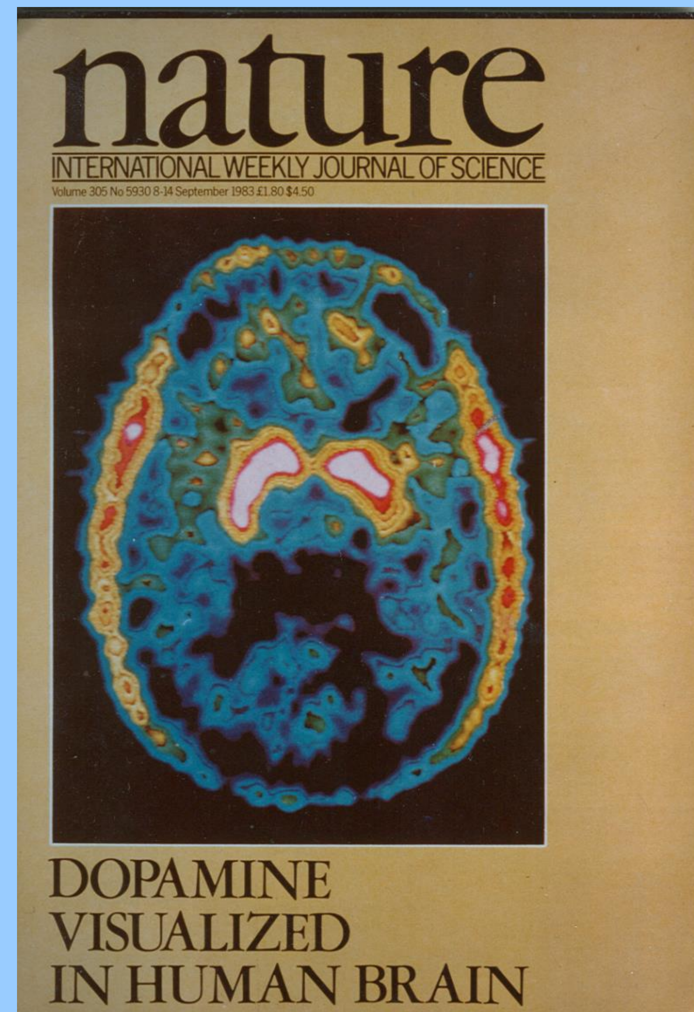
[18F]F-DOPA

NATURE VOL. 305 8 SEPTEMBER 1983

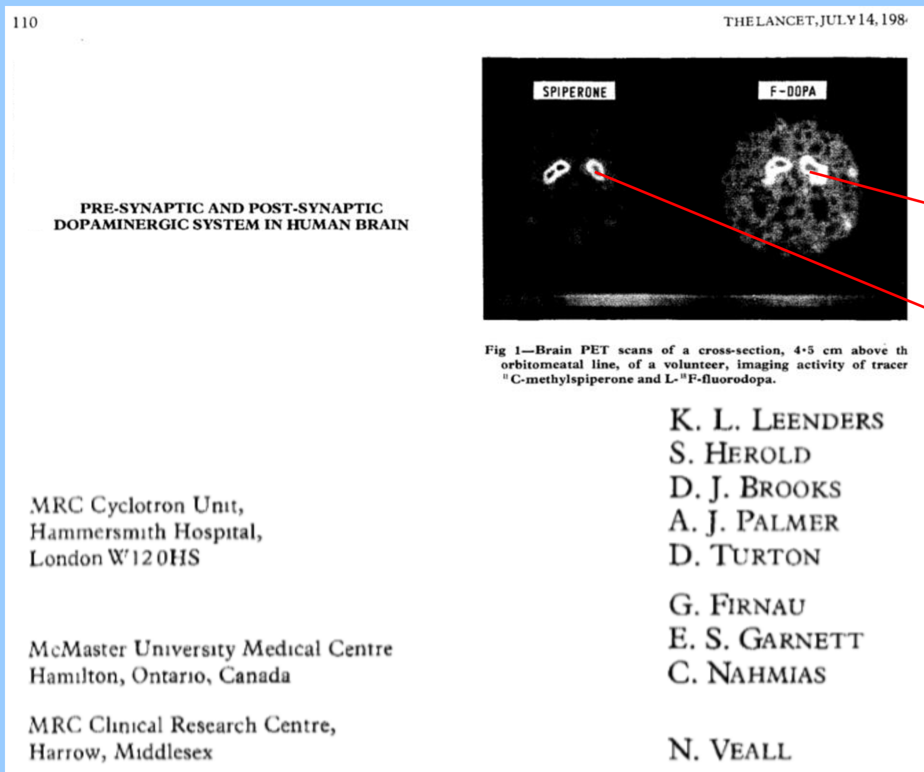
Dopamine visualized in the basal ganglia of living man

E. S. Garnett, G. Firnau & C. Nahmias

Department of Nuclear Medicine, McMaster University Medical Centre, 1200 Main Street West, Hamilton, Ontario, Canada L8N 3Z5



1984


110 THE LANCET, JULY 14, 198

SPIPERONE F-DOPA

Fig 1—Brain PET scans of a cross-section, 4·5 cm above th orbitomeatal line, of a volunteer, imaging activity of tracer ^{11}C-methylspiperone and L-^{18}F-fluorodopa.

PRE-SYNAPTIC AND POST-SYNAPTIC DOPAMINERGIC SYSTEM IN HUMAN BRAIN

MRC Cyclotron Unit,
Hammersmith Hospital,
London W12 0HS

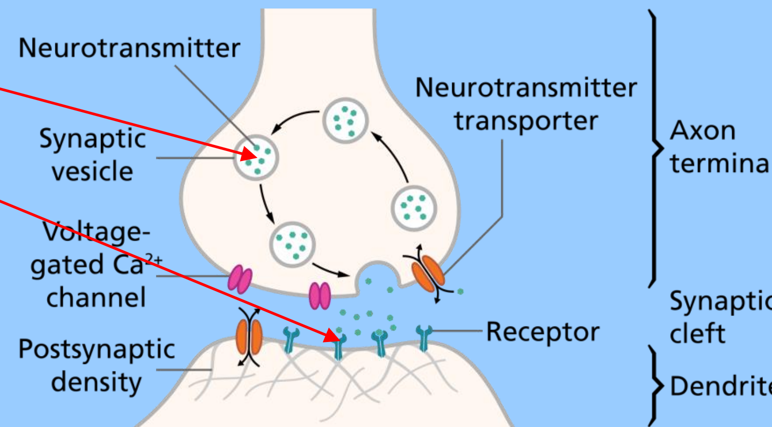
K. L. LEENDERS
S. HEROLD
D. J. BROOKS
A. J. PALMER
D. TURTON

McMaster University Medical Centre
Hamilton, Ontario, Canada

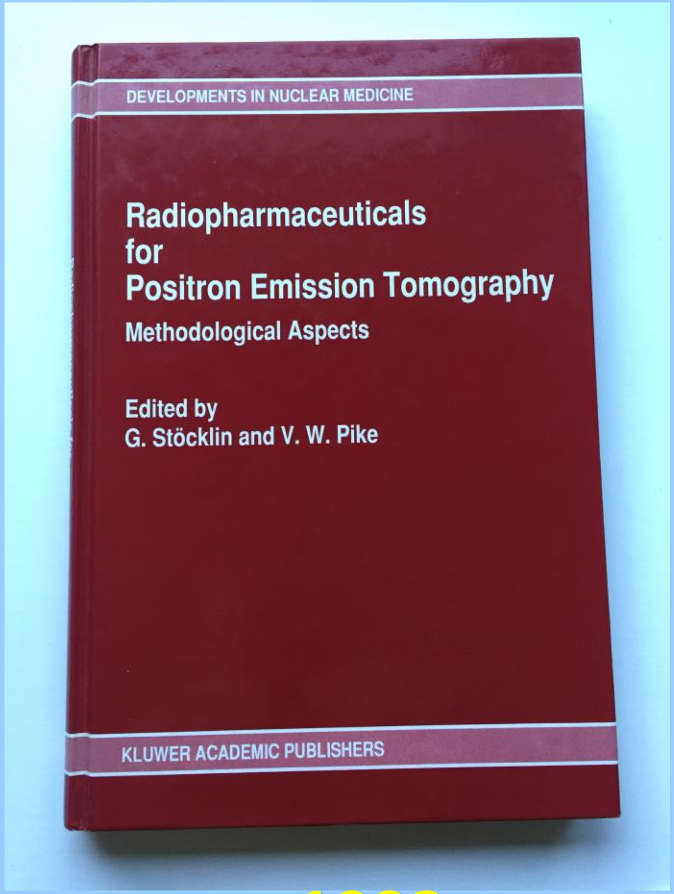
G. FIRNAU
E. S. GARNETT
C. NAHMIAS

MRC Clinical Research Centre,
Harrow, Middlesex

N. VEALL



Explosion of radiolabelled compounds with positron emitting radionuclides 1983-1993

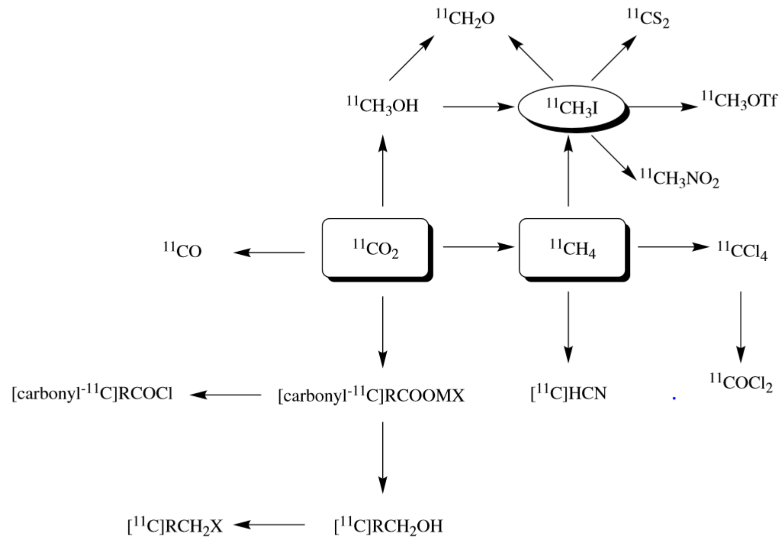


1993

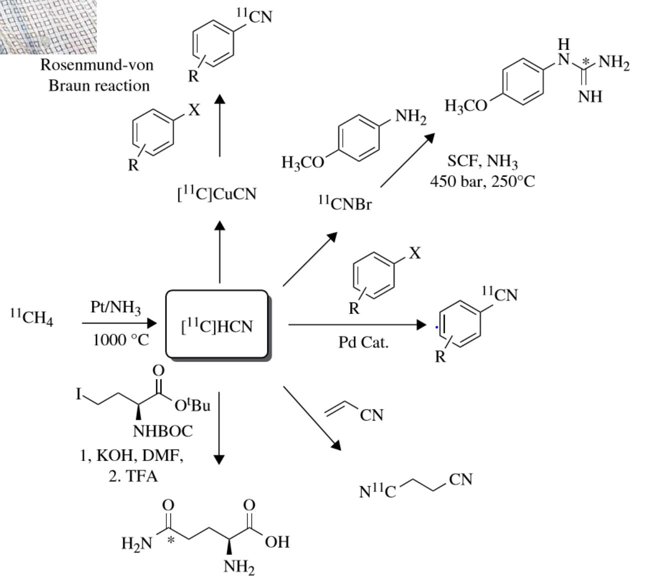
Carbon-11 Labelling

Philip W. Miller
Koichi Kato
Bengt Långström

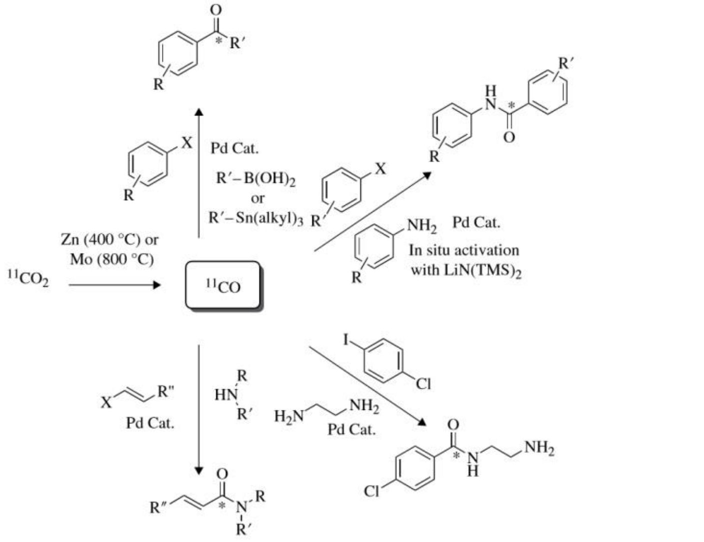
The Chemistry of Molecular Imaging
Ed: Nicholas Long & Wing-Tak Wong



SCHEME 4.1 The major ^{11}C-precursors used in the synthesis of ^{11}C-labelled compounds produced from either $^{11}CO_2$ or $^{11}CH_4$.

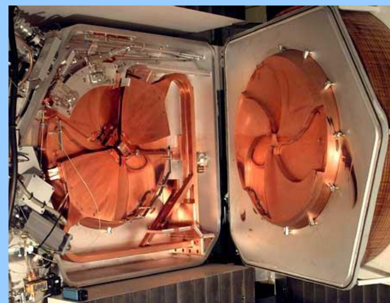


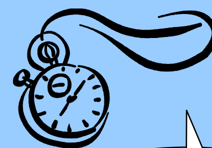
SCHEME 4.18 Synthesis of [^{11}C]HCN and selected [^{11}C]cyanation reactions.

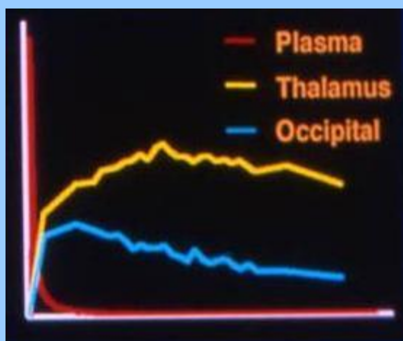


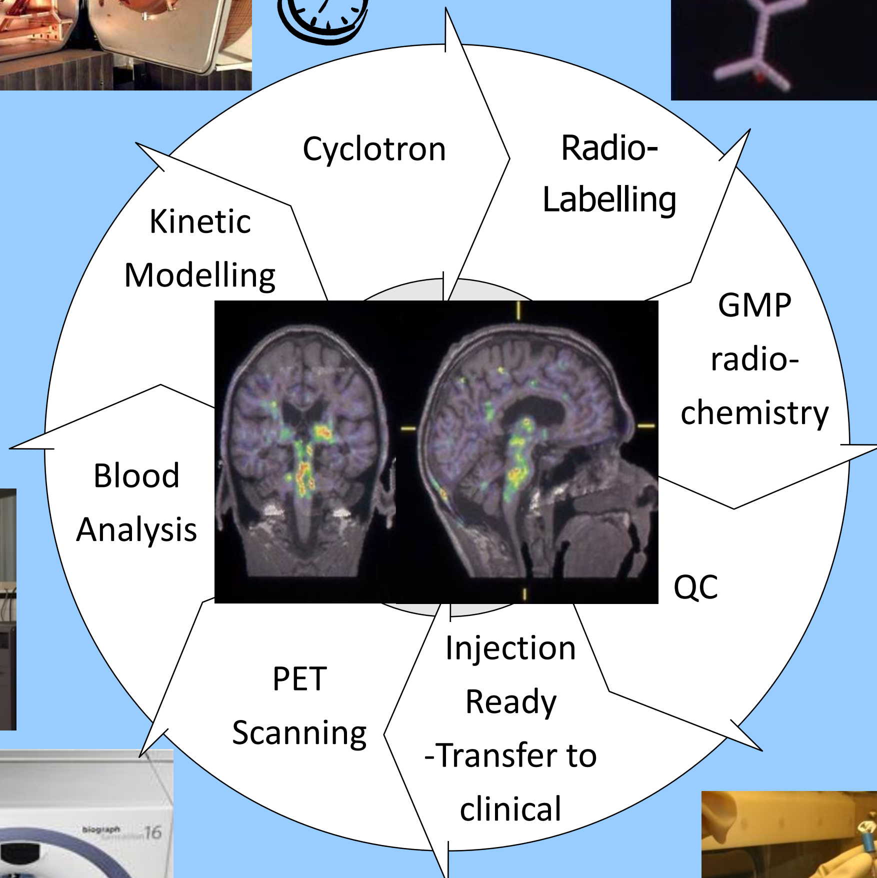
SCHEME 4.19 Selected palladium-mediated [^{11}C]carbonylation reactions using high pressure micro-autoclave system.

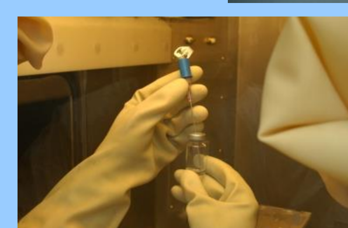
The PET Procedure using a Carbon-11 labelled compound – A complex process done in 1 hour!







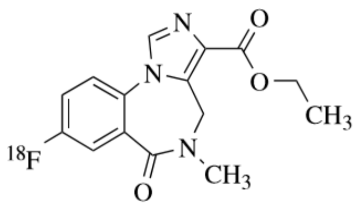




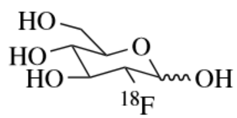
RECENT DEVELOPMENTS IN THE CHEMISTRY OF [^{18}F]FLUORIDE FOR PET

DIRK ROEDA AND FRÉDÉRIC DOLLÉ

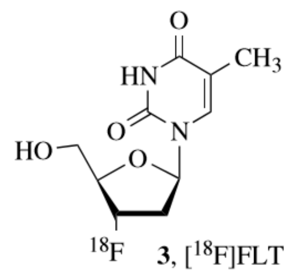
CEA, I2BM, Service Hospitalier Frédéric Joliot, Orsay, France



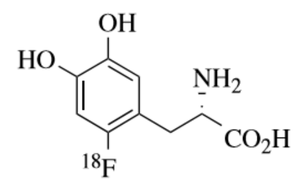
1, [^{18}F]Flumazenil



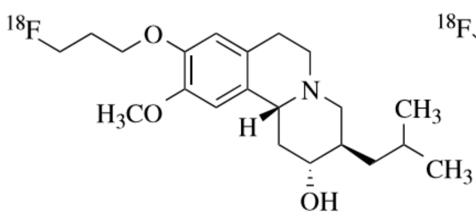
2, [^{18}F]FDG



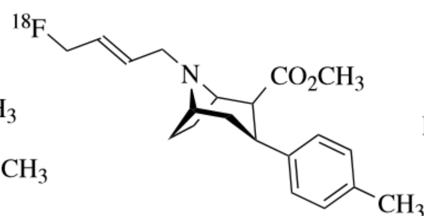
3, [^{18}F]FLT



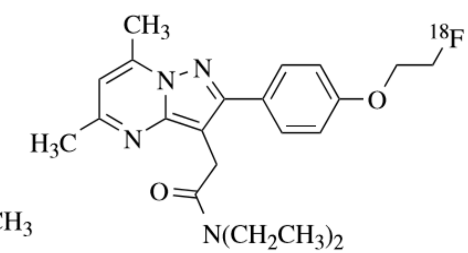
4, 6-[^{18}F]fluoro-L-DOPA



5, [^{18}F]AV-133



6, [^{18}F]LBT-999

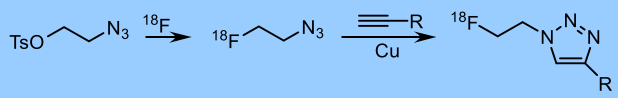


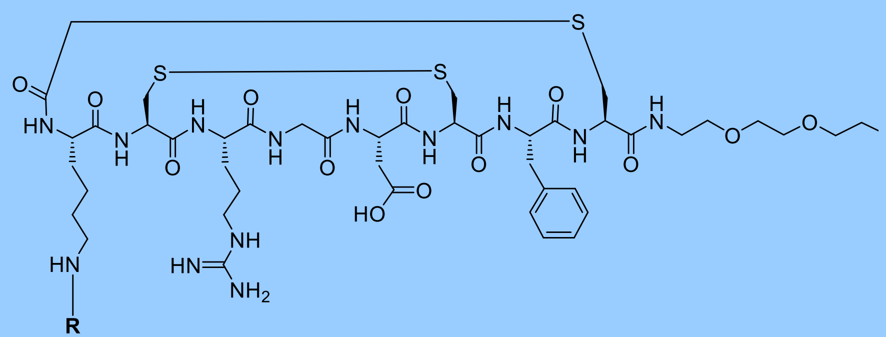
7, [^{18}F]DPA-714

FIGURE 3.1 Three categories of radiopharmaceutical design: True labelling (**1**), H- or OH mimicking by a [^{18}F]fluorine atom (**2–4**) and prosthetic labelling (**5–7**).

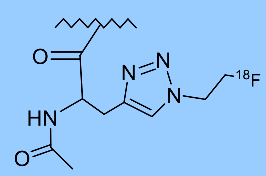
The Chemistry of Molecular Imaging
Ed: Nicholas Long & Wing-Tak Wong

Click labelling of RGD peptide with [^{18}F]fluoroethyl azide



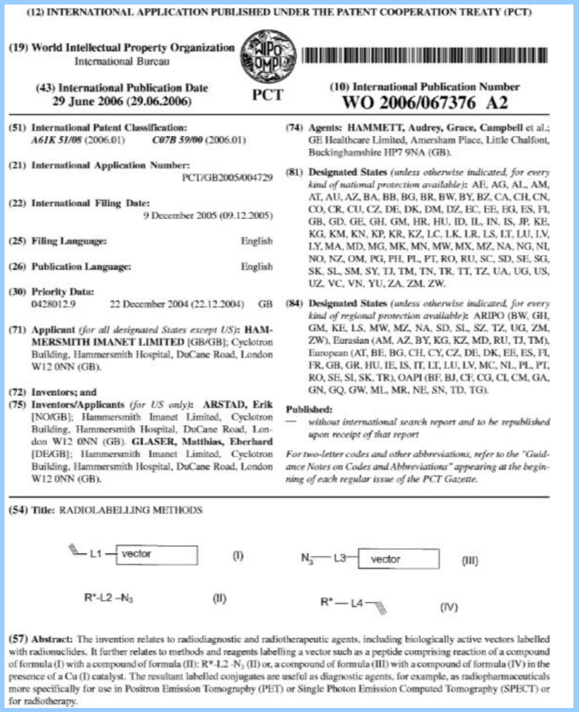


R =



	isolated r.c.y.
$CuSO_4$/ascorbate:*	70 ± 5 % (*n* = 3)
Cu powder:	42 ± 14 % (*n* = 5)
One-Pot:*	**46 ± 7 %** (*n* = 4)
Synthesis time:	**105 min**

Filing date: 22 December 2004



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WO 2006/067376 A2

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(25) Filing Language: English

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0428012.9 22 December 2004 (22.12.2004) GB

(71) Applicant (*for all designated States except US*): **HAMMERSMITH IMANET LIMITED** [GB/GB]; Cyclotron Building, Hammersmith Hospital, DuCane Road, London W12 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **ARSTAD, Erik** [NO/GB]; Hammersmith Imanet Limited, Cyclotron Building, Hammersmith Hospital, DuCane Road, London W12 0NN (GB). **GLASER, Matthias, Eberhard** [DE/GB]; Hammersmith Imanet Limited, Cyclotron Building, Hammersmith Hospital, DuCane Road, London W12 0NN (GB).

(74) Agents: **HAMMETT, Audrey, Grace, Campbell** et al.; GE Healthcare Limited, Amersham Place, Little Chalfont, Buckinghamshire HP7 9NA (GB).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: RADIOLABELLING METHODS

L1 — vector (I)

N_3 — L3 — vector (III)

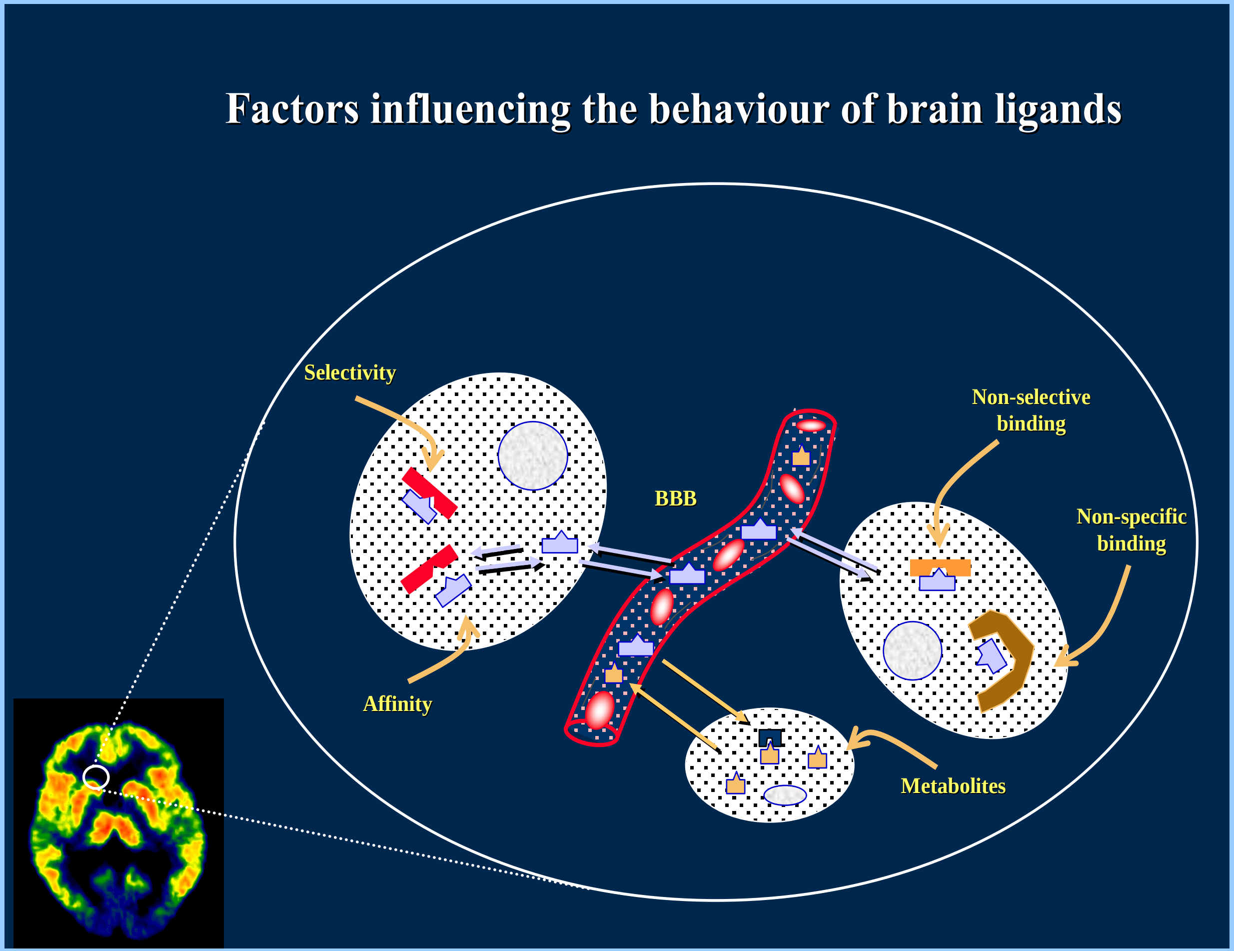
R*-L2 –N_3 (II)

R* — L4 (IV)

(57) Abstract: The invention relates to radiodiagnostic and radiotherapeutic agents, including biologically active vectors labelled with radionuclides. It further relates to methods and reagents labelling a vector such as a peptide comprising reaction of a compound of formula (I) with a compound of formula (II): R*-L2 -N_3 (II) or, a compound of formula (III) with a compound of formula (IV) in the presence of a Cu (I) catalyst. The resultant labelled conjugates are useful as diagnostic agents, for example, as radiopharmaceuticals more specifically for use in Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) or for radiotherapy.

Arstad E and Glaser M, patent WO2006067376 (A2)

Radiochemists addressed the challenges to discovering and developing imaging biomarkers



Principal radiotracers used for human brain PET studies 1974 - 1996

Radiotracer	Targets	Reference
[^{11}C]psychotropic drugs	Drug Pharmacokinetics	*Raynaud et al (1974)*
[^{18}F]FDG	Glucose Utilisation	*Kuhl et al (1976)*
[^{11}C]methionine	Amino Acid Transport	*Comar et al (1976)*
[^{11}C]unnatural amino acids	Amino Acid Transport	*Hubner et al (1979)*
[^{15}O]Oxygen	Oxygen Utilisation	*Frackowiak et al (1980)*
[^{15}O]Water	Blood Flow	*Frackowiak et al (1980)*
[^{11}C]leucine	Protein Synthesis	*Barrio et al (1983)*
[^{18}F]F-DOPA	Dopamine Synthesis	*Garnett et al (1983)*
[^{11}C]methyl-spiperone	Dopamine and Serotonin Receptors	*Wagner et al (1983)*
[^{11}C]PK-11195	Peripheral Benzodiazepine Receptors	*Camsonne et al (1984)*
[^{11}C]BCNU/carmustine	Drug Pharmacokinetics	*Diksic et al (1984)*
[^{11}C]diprenophine	Non-Selective Opiate Receptors	*Jones et al (1985)*
[^{11}C]carfentanil	μ-Opioid Receptor	*Frost et al (1985)*
[^{11}C]flumazenil (FMZ)	Central Benzodiazepine Receptors	*Samson et al (1985)*
[^{11}C]raclopride	Dopamine type 2 (D_2) Receptor	*Ehrin et al (1985)*
[^{11}C]Schering-23390	Dopamine type 1 (D_1) Receptor	*Halldin et al (1986)*
[^{11}C]nomifensine	Dopamine Transporter (DAT)	*Aquilonius et al (1987)*
[^{11}C]deprenyl	Monoamine Oxidase type B (MOAB)	*Fowler et al (1987)*
[^{11}C]McNeil 5652	Serotonin Transporter (SERT/5-HTT)	*Suchiro et al (1993)*
[^{11}C]WAY 100635	Serotonin 5-HT1A Receptor	*Pike et al (1994)*
[^{11}C]FBL 457	Dopamine ($D_{2/3}$) Receptors	*Halldin et al (1995)*
[^{11}C]MTBZ	Vesicular Monoamine Transporter (VMAT2)	*Kilbourn et al (1995)*
L-1-[^{11}C]tyrosine	Brain Tumor Protein Synthesis	*Willemsen et al (1995)*
[^{11}C]MDL 100907	Serotonin 5-HT2A Receptor	*Lundkvist et al (1996)*
[^{11}C]β-CIT-FE	Dopamine Transporter	*Halldin et al (1996)*
[^{11}C]PMP	Acetylcholinesterase (ACE)	*Kilbourn et al (1996)*
[^{11}C]verapamil	P-glycoprotein (P-gp) substrate	*Elsinga et al (1996)*

Adapted from Jones and Rabiner *J Cereb Blood Flow and Metab* 2012

Principal radiotracers used for human brain PET studies 1997 - 2014

Radiotracer	Targets	Reference
[^{11}C]MP4A	Acetylcholinesterase (ACE)	*Iyo et al (1997)*
[^{11}C]NNC112	Dopamine (D_1) Receptor	*Halldin et al (1998)*
[^{18}F]A-85380	Nicotinic Acetylcholine Receptors	*Horti et al (1998)*
[^{18}F]fallypride	Dopamine (D_2) Receptor	*Mukherjee et al (1999)*
[^{11}C]α-methyl-l-tryptophan	Tryptophan Activity	*Shoaf et al (2000)*
[^{11}C]DASB	Serotonin transporter (SERT/5-HTT)	*Ginovart et al (2001)*
[^{11}C]Ro15 -4513	GABA-Benzodiazepine Receptors	*Lingford-Hughes et al (2002)*
[^{11}C]temazolomide	Temazolomide Pharmacokinetics	*Saleem et al (2003)*
[^{18}F]SPA-RQ	Neurokinin-1 Receptor	*Solin et al (2004)*
[^{11}C]PIB	β-Amyloid	*Klunk et al (2004)*
[^{18} F]fluoroethyl-L-tyrosine	Brain Tumor Protein Synthesis	*Pauleit et al (2005)*
[^{18}F]fluorothymidine	Brain Tumor Proliferation	*Chen et al (2005)*
[^{11}C]harmine	Monoamine Oxidase Type-A (MAO-A)	*Ginovart et al (2006)*
[^{18}F]MK-9470	Cannabinoid Receptor Type 1 (CBR-1)	*Burns et al (2007)*
[^{11}C]ABP688	Glutamate Receptor 5 (mGluR5)	*Ametamey et al (2007)*
[^{11}C]methylreboxetine (MRB)	Norepinephrine transporter (NET)	*Logan et al (2007)*
[^{11}C]PBR28*	Translocator Protein (TSPO)	*Imaizumi et al (2008)*
[^{18}F]fluoromisonidazole	Brain Tumor Hypoxia	*Spence et al (2008)*
[^{11}C]AZ10419369*	Serotonin 5HT1B Receptor	*Pierson et al (2008)*
[^{18}F]SP-203*	Glutamate Receptor 5 (mGluR5)	*Brown et al (2008)*
[^{18}F]galacto-RGD	Brain Tumor Angiogenesis	*Schnell et al (2009)*
[^{11}C]SB-207145	Serotonin 5HT4 Receptor	*Marner et al (2009)*
[^{11}C]GSK189254*	Histamine-3 Receptor	*Ashworth et al (2010)*
[^{11}C]P943*	Serotonin 5HT1B Receptor	*Gallezot et al (2010)*
[^{11}C]GSK931145*	Glycine Transporter 1 (GlyT1)	*Passchier et al (2010)*
[^{11}C]GSK215083*	Serotonin 5HT6 Receptor	*Parker et al (2012)*

Adapted from Jones and Rabiner *J Cereb Blood Flow and Metab 2012*

Imaging Enzymes in the brain: Three Types

1. Platonic (reversible binding)
2. Metabolic trapping
3. Suicide/mechanistic inhibitors

Curtesy of Alan Wilson
Toronto

Enzyme Imaging:
Type 2: Metabolic trapping of the label

Radiotracer (T) + Enzyme (E) $\rightleftharpoons$ T:E

T:E $\xrightarrow{\text{enzyme in action}}$ P + E

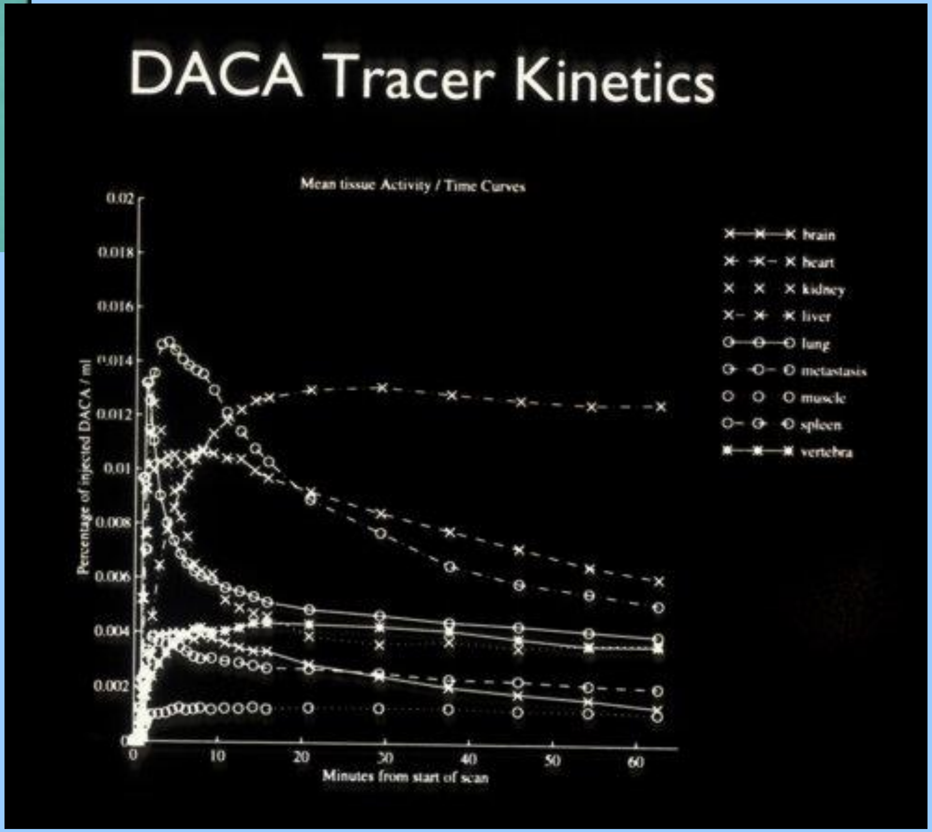
- New product
- Enzyme unchanged
- Product "trapped" where produce

Examples: Many
$[^{18}F]$-FDG, $[^{18}F]$-FDOPA,
$[^{18}F]$-FMT,
$[^{11}C]$-MP4A, $[^{11}C]$-PMP
$[^{18}F]$-FMISO, $[^{18}F]$-FAZA

Curtesy of Alan Wilson
Toronto

Using PET to study the uptake and distribution of new anti-cancer Drugs

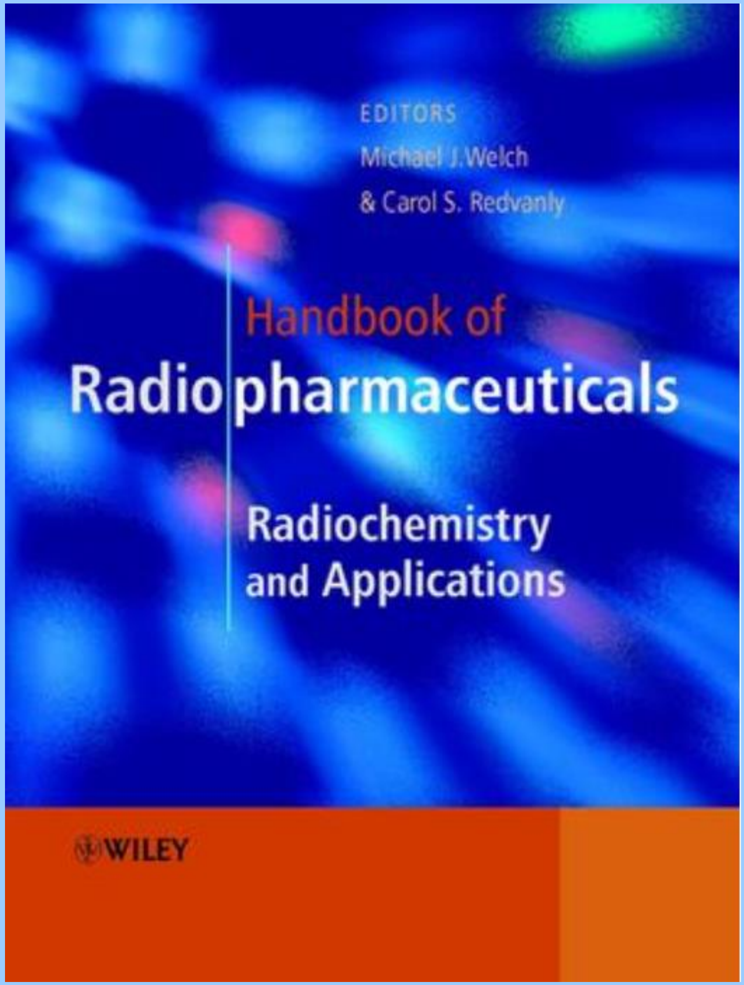
Micro dose PET 6 months before the Phase 1 of an anti-cancer drug started



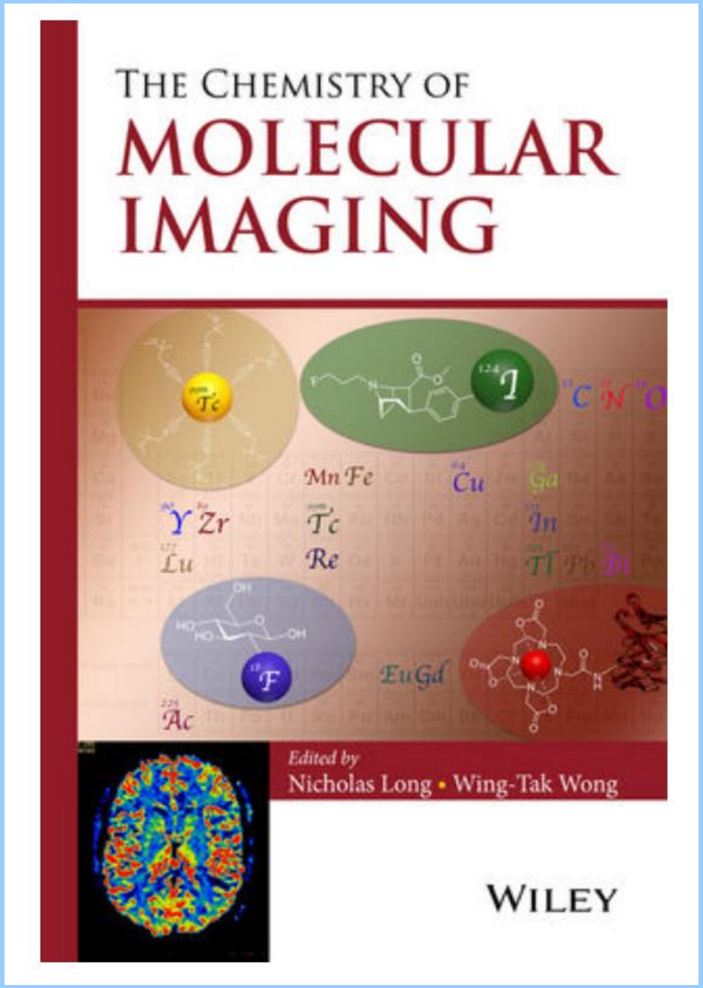
Tissue	VD	K_1 (min^{-1})	$t_{1/2z}$ (min)
Liver (n=7)	858	0.42	41
Lung (n=24)	131	0.66	1.2
Brain (n=4)	20.6	0.24	12.2
Tumour (n=20)	203	0.42	22.9

Pharmacinoketics of [^{11}C]DACA

Two text books on radiochemistry



2003



2015

Labelled Cells for Single Photon Imaging

Indium-111-Labeled Autologous Leukocytes in Man

Mathew L. Thakur, J. Peter Lavender, Rosemary N. Arnot, David J. Silvester, and Anthony W. Segal

Hammersmith Hospital, London, England

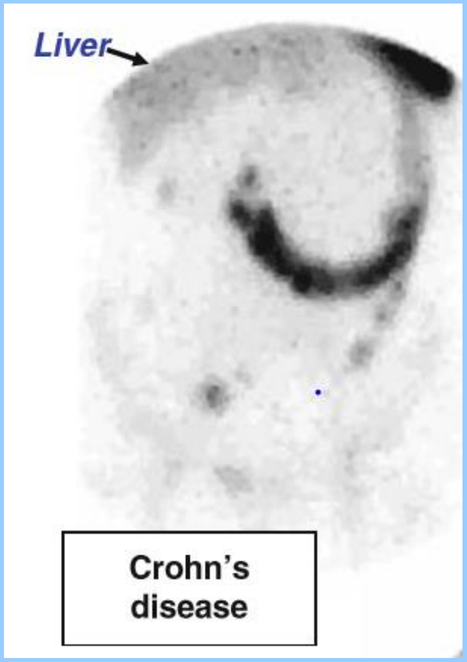
J Nucl Med 18: 1012–1019, 1977

Indium-111 chelated with 8-hydroxyquinoline (oxine)

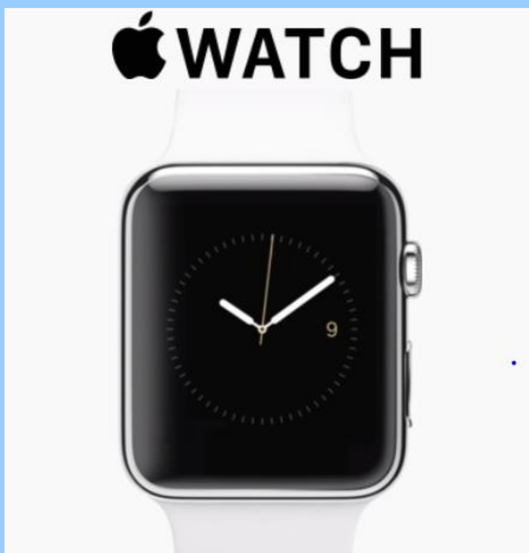
CLINICAL EXPERIENCE WITH ^{99m}Tc-HEXAMETHYLPROPYLENE-AMINEOXIME FOR LABELLING LEUCOCYTES AND IMAGING INFLAMMATION

A.M. Peters, S. Osman, B.L. Henderson, J.D. Kelly, H.J. Danpure, R.J. Hawker, H.J. Hodgson, R.D. Neirinckx, J.P. Lavender

Lancet. 1986;2:946–9.



Present Innovations

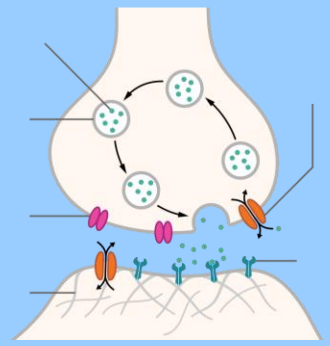


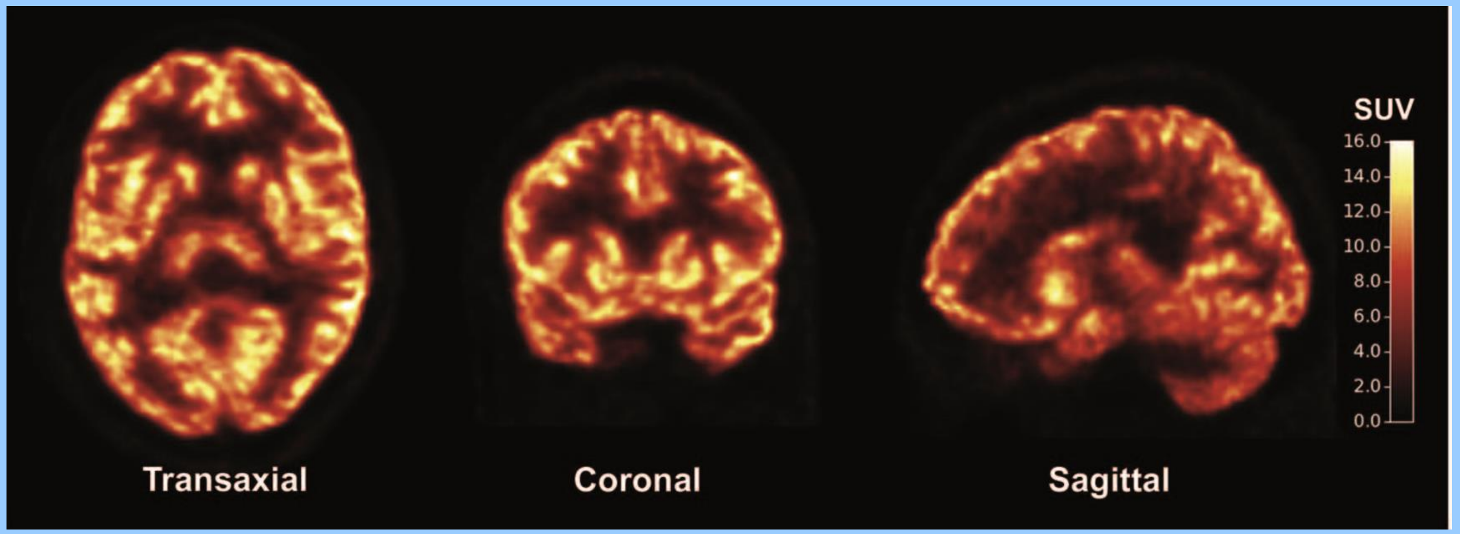
Synapse Imaging

Imaging synaptic density in the living human brain

Sjoerd J. Finnema,[1]* Nabeel B. Nabulsi,[1] Tore Eid,[2] Kamil Detyniecki,[3] Shu-fei Lin,[1] Ming-Kai Chen,[1] Roni Dhaher,[2] David Matuskey,[1] Evan Baum,[1] Daniel Holden,[1] Dennis D. Spencer,[4] Joël Mercier,[5] Jonas Hannestad,[5†] Yiyun Huang,[1] Richard E. Carson[1,6]

www.ScienceTranslationalMedicine.org 20 July 2016 Vol 8 Issue 348 348ra96





Synaptic Vesicle Glycoprotein 2A (SV2A) radioligand-[^{11}C] UCB-J

Fig. 1. Mean tau and Aβ topographies.

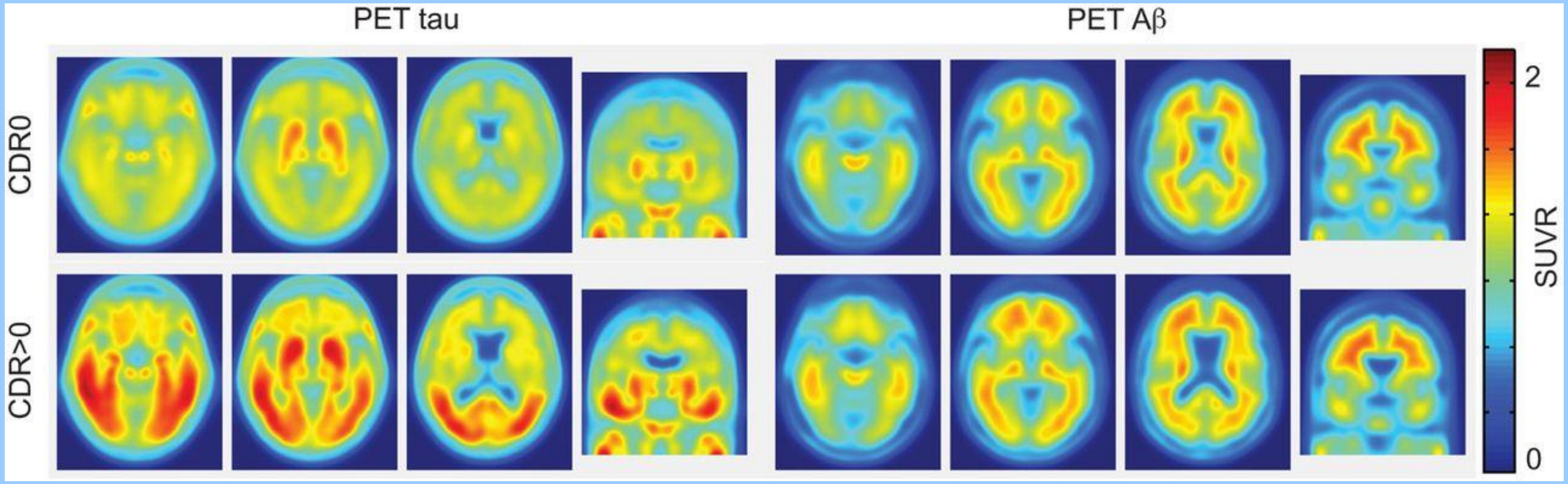
Dementia

18F-AV-1451 (T801)

18F florbetapir

36 Controls

10 MCI



Clinical Dementia Rating-CRO

Matthew R. Brier et al., Sci Transl Med 2016;8:338ra66

Science Translational Medicine AAAS

Zirconium-89 [78.5 hours $t_{1/2}$] labelling

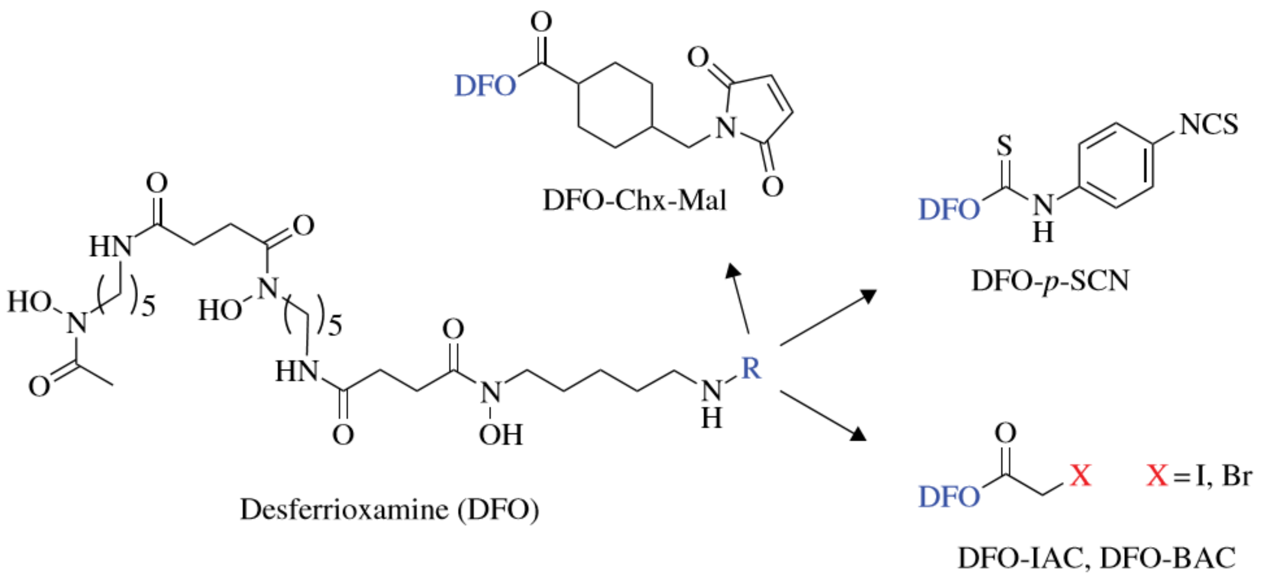
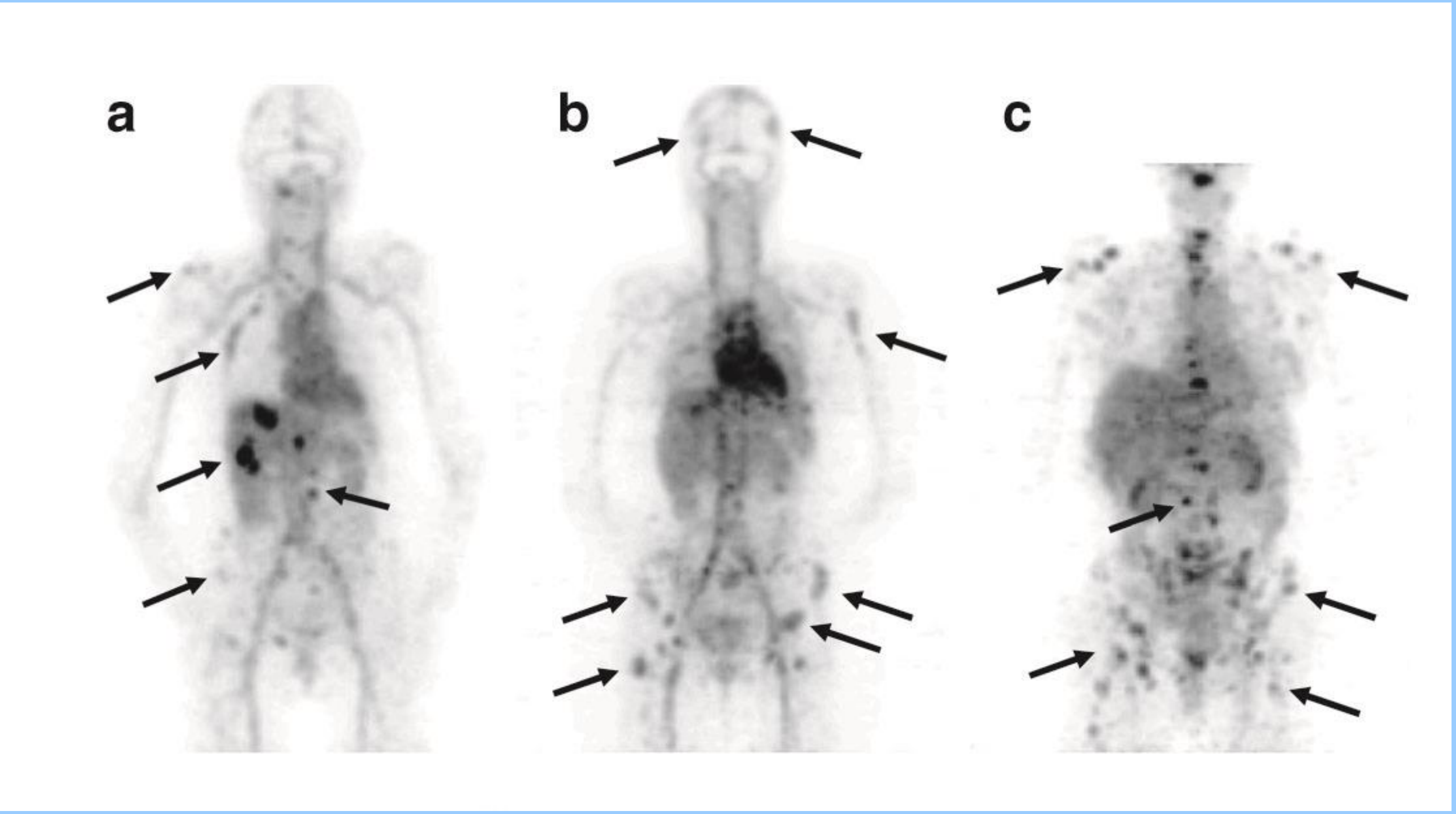


FIGURE 5.14 The most commonly used ^{89}Zr chelator, desferrioxamine (DFO), with various BFC precursors.

Eric W. Price and Chris Orvig

The Chemistry of Molecular Imaging
Ed: Nicholas Long & Wing-Tak Wong

Antibody Labelling with ^{89}Zr (78.4 hour half life)



^{89}Zr-trastuzumab uptake **5 days** after the injection.
(**a**) A patient with liver and bone metastases,
and (**b** and **c**) two patients with multiple bone metastases.

Gallium-68 [68 mins $T_{1/2}$] labelling

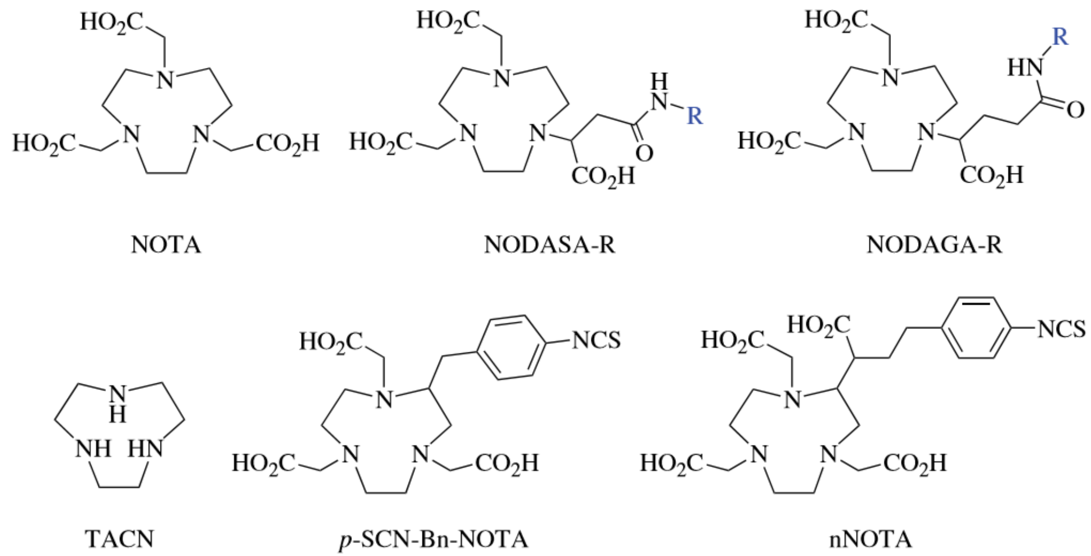


FIGURE 5.9 The macrocyclic chelating agent TACN and the TACN derivative NOTA, which is currently the 'gold standard' for gallium complexation, along with several NOTA-based BFC derivatives (**R** = biovector).

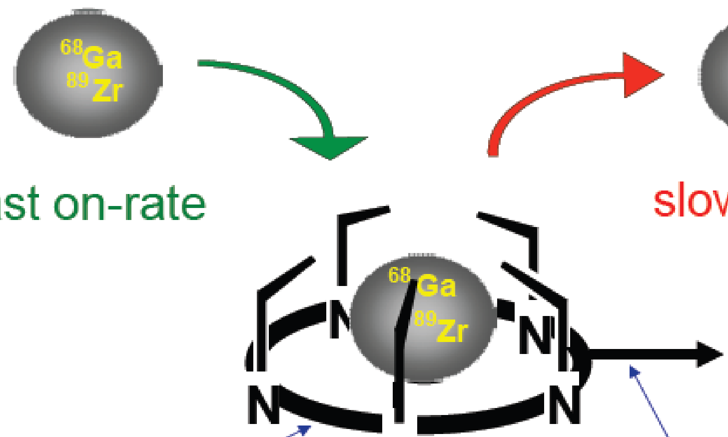
Eric W. Price and Chris Orvig
The Chemistry of Molecular Imaging
Ed: Nicholas Long & Wing-Tak Wong

^{68}Ge (271 days T1/2)/^{68}Ga (68 mins T1/2) Generator

Fundamentals of radiolabeling

(Bifunctional) Chelating Agents

$$M^{3+} + HL \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} ML + H^{+} \qquad K_{ML} = \frac{[ML]}{[M^{3+}]\cdot[L]}$$



"The Chelator makes the difference"

Helmut Maecke

Theranostics 2014, Vol. 4, Issue 4 386

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

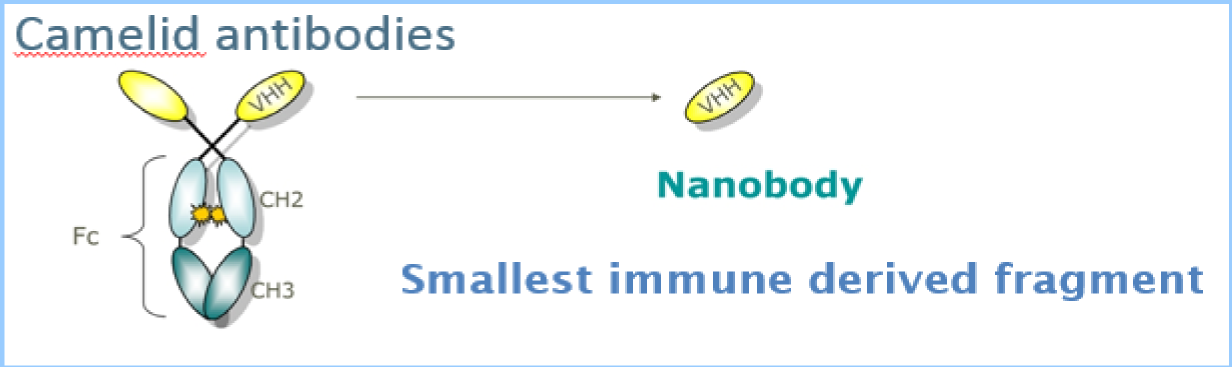
2014; 4(4):386-398. doi: 10.7150/thno.8006

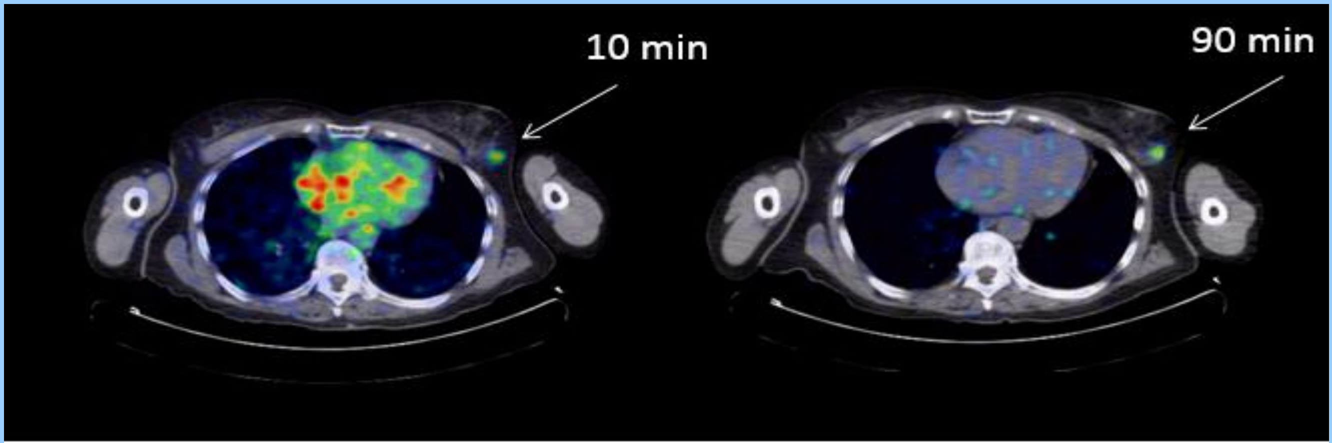
Review

Nanobody: The "Magic Bullet" for Molecular Imaging?

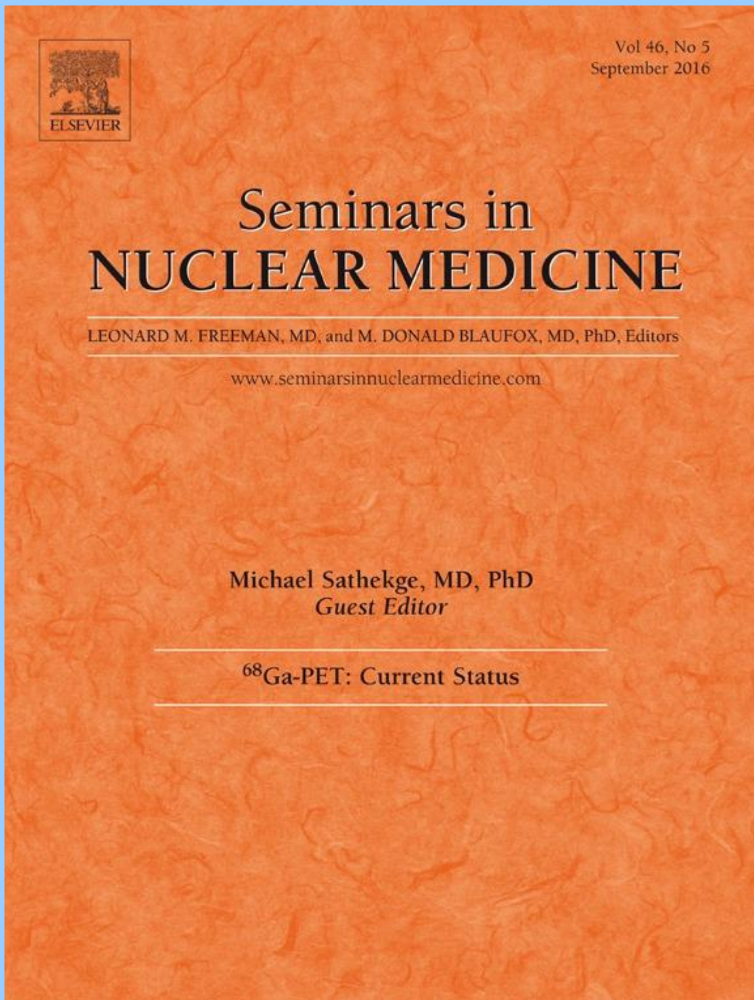
Rubel Chakravarty [1, 2, ✉], Shreya Goel [3], Weibo Cai [1, 3,4,5, ✉]

1. Department of Radiology, University of Wisconsin - Madison, WI, USA





HER2 imaging in breast cancer
Ga-68 label


Vol 46, No 5
September 2016
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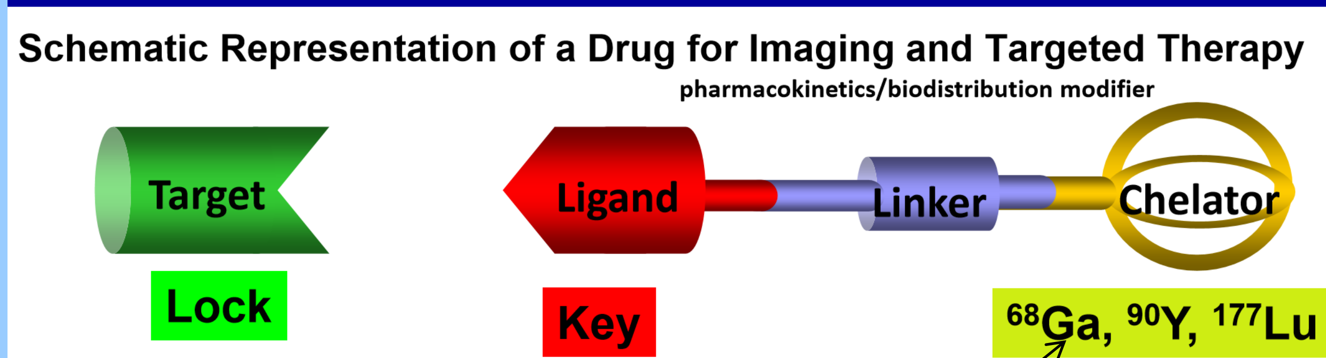
NUCLEAR MEDICINE
LEONARD M. FREEMAN, MD, and M. DONALD BLAUFOX, MD, PhD, Editors
www.seminarsinnuclearmedicine.com
Michael Sathekge, MD, PhD
Guest Editor
68Ga-PET: Current Status

Theranostics:
Combination of a diag*nostic* tool to define the right *thera*peutic tool*

THERANOSTIC – we see what we treat
Targeted Molecular Imaging and Therapy
The Key-Lock Principle



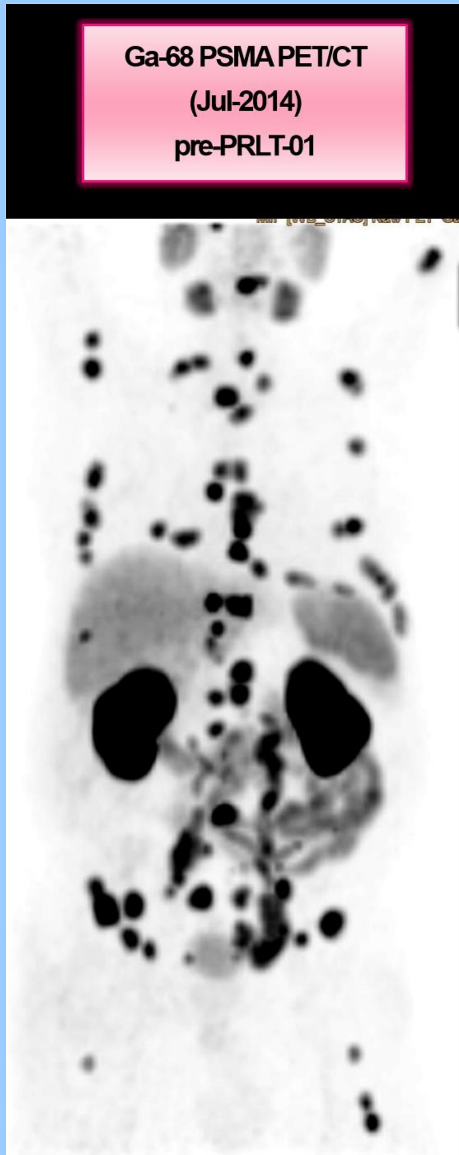
The reporting unit
positron emitter- 68 min $t_{1/2}$

The toxic unit
Beta energy 490 Kev

*Radioiodine treatment of thyroid cancer 1947 ⟶

FIG. 25.—Perspex jig used to position collimated G-M counter for thyroid scanning.

Seidlin SM, Marinelli LD, Oshry E. Radioactive iodine therapy; effect on functioning metastases of adenocarcinoma of the thyroid. Journal of the American Medical Association. Dec 7 1946;132(14):838-847.



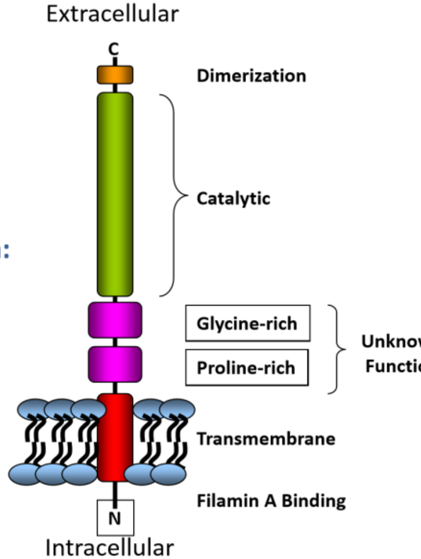
Metastatic Prostate Cancer

Schematic of prostate-specific membrane antigen.

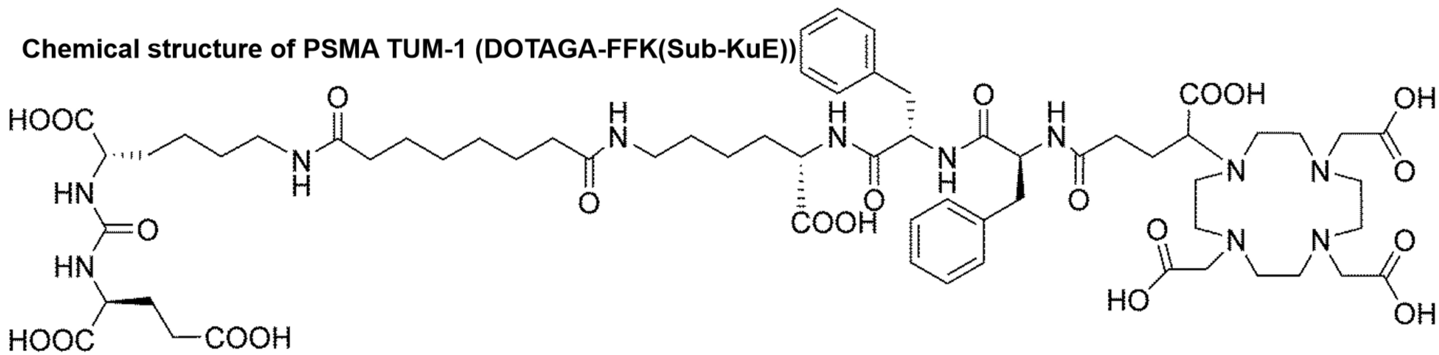
PSMA for Targeting Prostate Cancer

Henry N. Wagner: FDG – the molecule of the (last) century
Richard P. Baum: PSMA – the target of the next decade

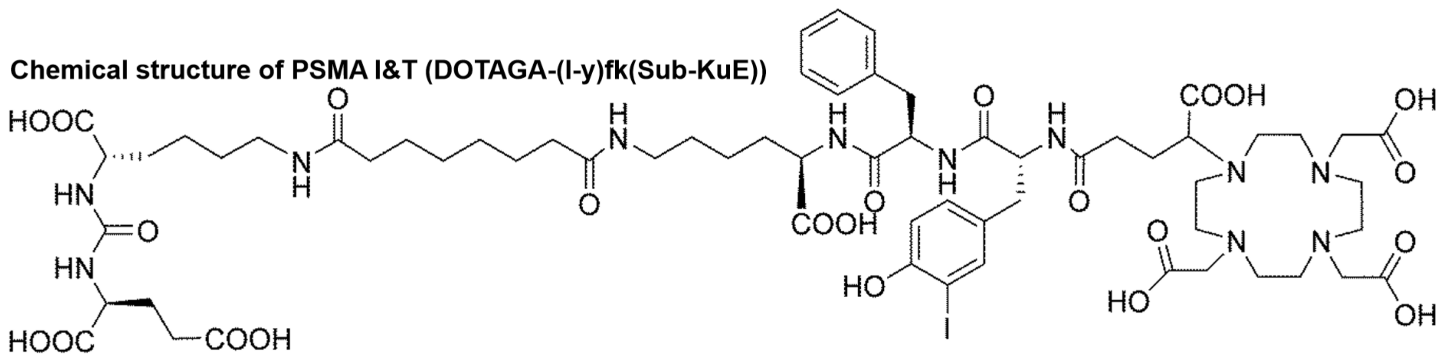
- **A cell surface enzyme that's continually internalized.**
- **Glutamate carboxypeptidase II (GCP-II) activity**
- **Folate hydrolase (FOLH1) activity**
- Hydrolyses y-peptide bonds between N-acetylaspartate and glutamate
- **PSMA expression increases progressively in:**
  - Higher grade tumors
  - Metastastic disease
  - Hormone-refractory prostate cancer
  - Present also in tumor neovasculature
- PSMA thought to play a role in tumor invasiveness
- Target validated with anti-PSMA antibodies (J591)



Chemical structure of PSMA TUM-1 (DOTAGA-FFK(Sub-KuE))

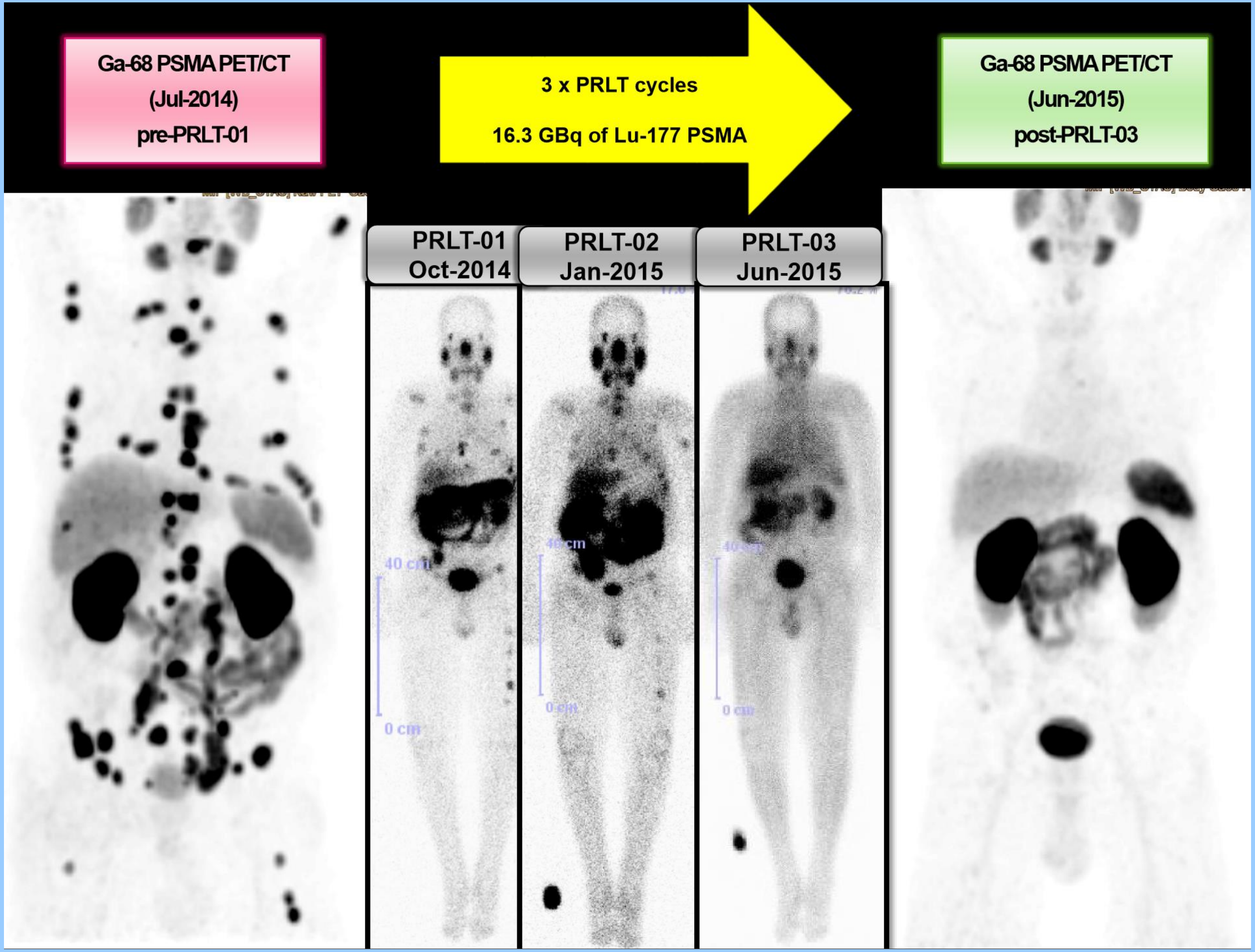


Chemical structure of PSMA I&T (DOTAGA-(I-y)fk(Sub-KuE))



The DOTAGA PSMA small molecules (PSMA TUM-1 and PSMA I&T) were labeled with Lu-177 at the Radiopharmacy of Zentralklinik Bad Berka and utilized after appropriate quality control (purity > 99 %)

Image guided treatment of metastatic prostate cancer with ^{177}Lu PSMA



Curtesy of Richard Baum Bad Berka Germany


Future Challenges

Logistics

PET Radiochemistry GMP: Amsterdam Free University Radiochemical Centre

Manufacturing Radio Labelled Molecules for Human Administration

Regulations

Regulations Governing WMIC

REGULATIONS

- Environmental Agency (Radiation)
- Clinical Research Governance (Experimental Medicine)
- Administration of Radioactive Substance Committee
- Good Manufacturing Practice (GMP)
- Good Clinical Laboratory Practice (GLP)
- UK Home Office (Pre-clinical animal suite)

World Wide PET Scanners & Cyclotrons 2014*

	Cyclotrons	PET Cameras
Asia	404	1123
Europe	231	806
Latin America	37	121
MEA	30	142
North America	257	1625
Oceania	13	54
	969	3871

* Data by curtsey of Medical Options

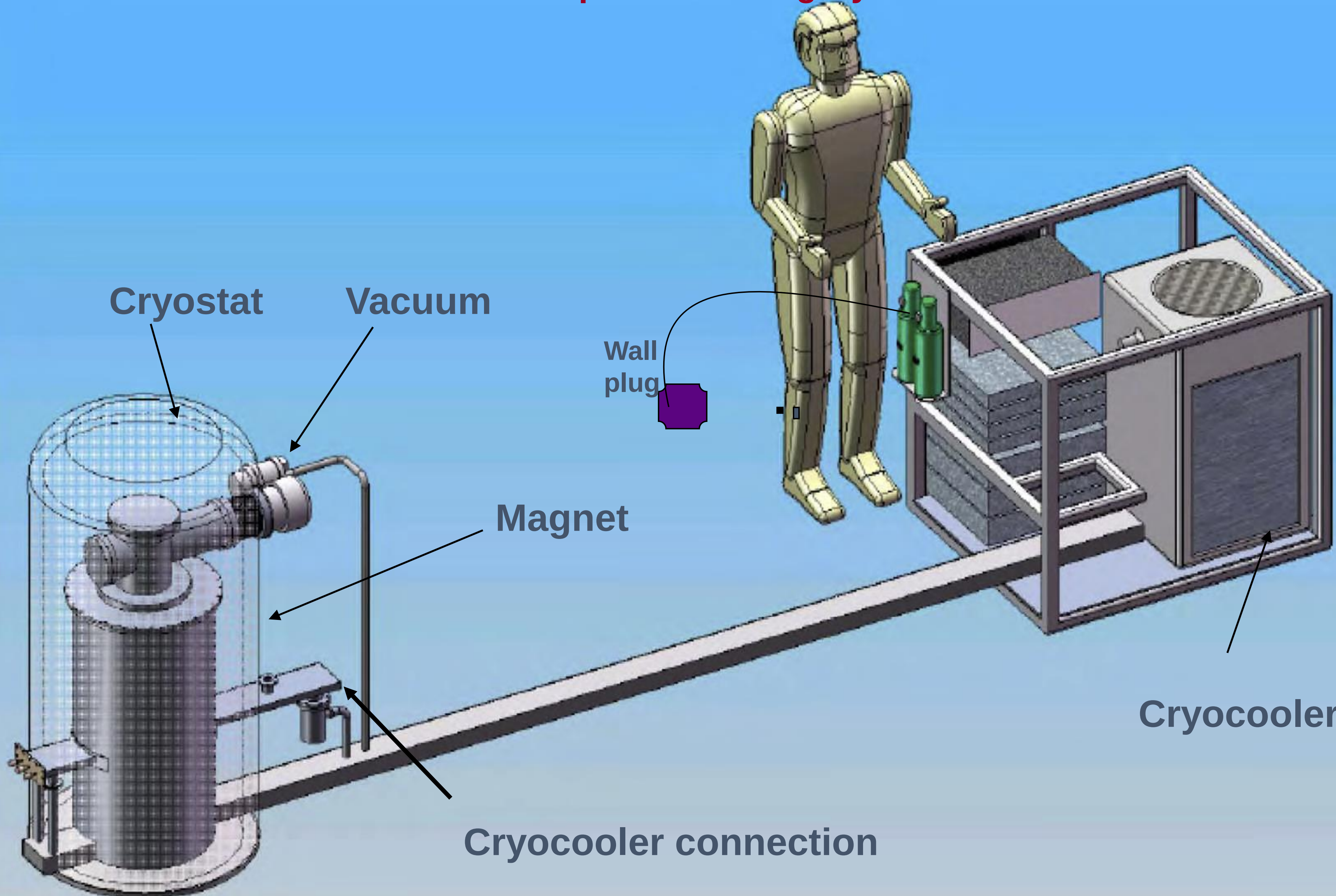
PET scanners without direct cyclotron access

Asia:	64%
Europe:	72%
Latin America:	70%
MEA:	79%
USA:	84%
OCEANIA:	76%

~~Oxygen-15~~	~~2.1 min T ½~~
~~Nitrogen-13~~	~~10 min T ½~~
~~Carbon-11~~	~~20.1 min T ½~~
Fluorine-18	1.7 hr T ½

2014

Five Tesla Superconducting Cyclotron



Fm. Timothy Antaya, MIT

Five Tesla Superconducting Cyclotron

Timothy Antaya

12 MeV 1800 kg cyclotron

Future Scientific Opportunities

The Human Brain

The Most Complex Biological Structure Known to Man

The Least Understood

The Most Investigated

A Major Frontier of Human Understanding

Brain Disorders
Cost Europe
800 Billion Euros per Year*

*Gustavsson et al. Oct 2011   The Greek Debt: 317Bn Euros

The Breakdown of the Costs of Brain Disorders (1)

Depression
(113Bn€)

Brain Tumours
(5Bn€)

Dementia
(105Bn€)

Movement Disorders
(14Bn€)

Schizophrenia
(94Bn€)

Epilepsy
(14Bn€)

Anxiety
(74Bn€)

Cerebral Vascular Disease
(64Bn€)

Addiction
(65Bn€)

Animal Models?

The Breakdown of the Costs of Brain Disorders (2)

Child/Adolescent Disorders
(21Bn€)

Traumatic Brain Injury
(33Bn€)

Somatoform
(21Bn€)

Headache
(44Bn€)

Sleep Disorders
(35Bn€)

Mental Retardation
(43Bn€)

Multiple Sclerosis
(15Bn€)

Neuromuscular
(8Bn€)

Eating Disorders
(1Bn€)

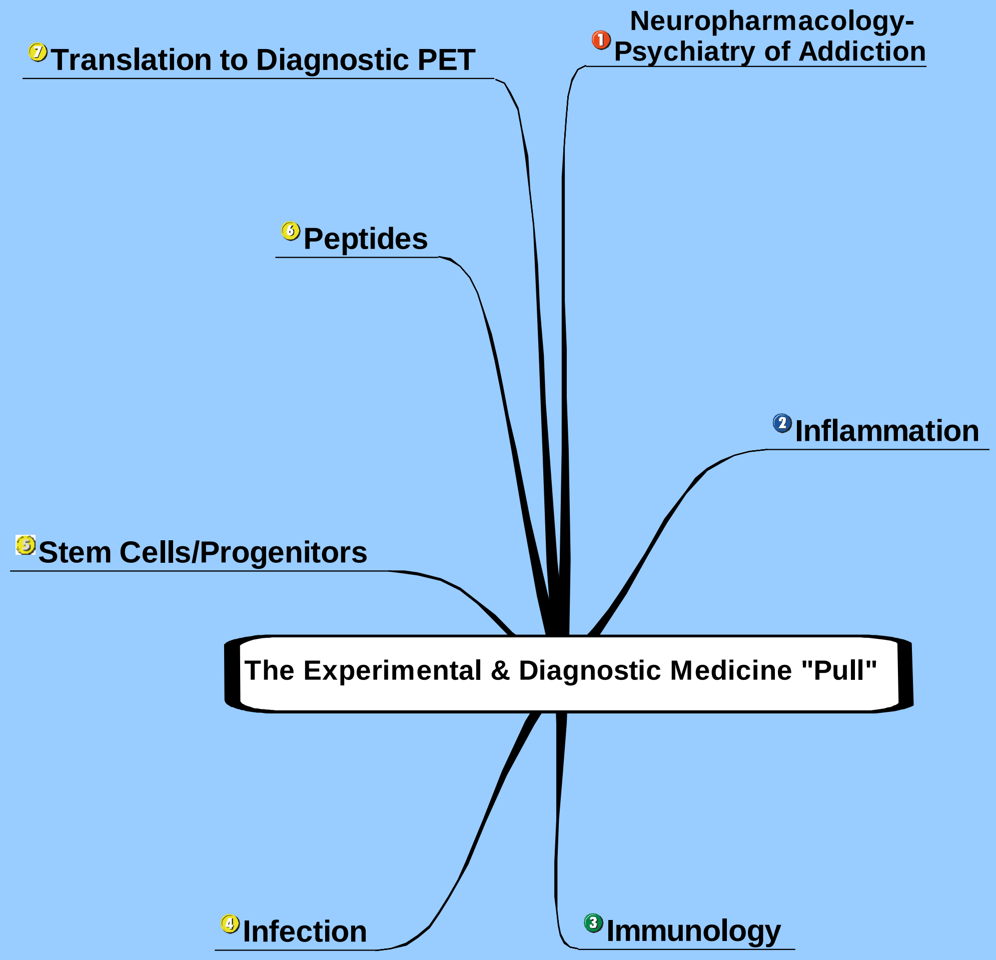
The World Wide Challenges

Brain Disorders
Costs approx:4.2 Trilion$

Drug Development Costs
for Brain Disorders: Y Bn$

Understanding the Normal Brain: 7.06 Billion People

More development of neuro-enzyme imaging biomarkers?



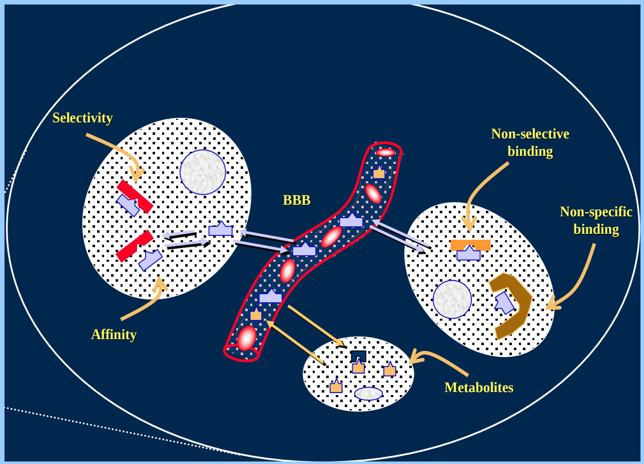
Report on a Review of the PET Molecular Imaging Strategy for the Imperial College London AHSC
July 2008

Challenges to Discovering and Developing Imaging Biomarkers

- Specificity/Affinity
- Metabolites
- Non-Specific Binding
- Blood Circulating Levels
- Endothelial Penetration
- Low Density Targets

"Relative Kinetics"

"CHEMISTRY"
&
"BIOLOGY"



Challenges to Discovering and Developing Imaging Biomarkers

↓

In-vitro testing of the tissue kinetics of candidate molecules

In-Vitro PET

A Systematic Approach for Developing Bacteria-Specific Imaging Tracers

Alvaro A. Ordonez, Edward A. Weinstein, Lauren E. Bambarger, Vikram Saini, Yong S. Chang, Vincent P. DeMarco, Mariah H. Klunk, Michael E. Urbanowski, Kimberly L. Moulton, Allison M. Murawski, Supriya Pokkali, Alvin S. Kalinda and Sanjay K. Jain

J Nucl Med.
Published online: September 15, 2016.

clinically. **Methods:** We systematic screened 961 random, radiolabeled molecules *in silico* as substrates for essential metabolic pathways in bacteria, followed by *in vitro* uptake in representative bacteria – *Staphylococcus aureus*, *Escherichia coli, Pseudomonas aeruginosa*, and mycobacteria. Fluorine-labeled analogs, that could be developed as positron emission tomography (PET)-based imaging tracers, were evaluated in a murine myositis model. **Results:**

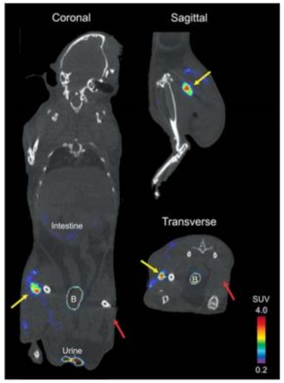
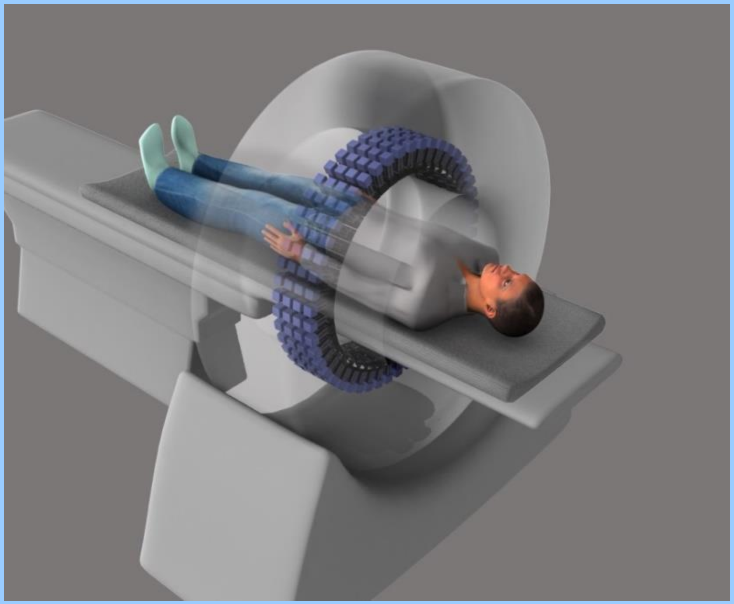


Figure 6. **^{18}F-FDS PET/CT imaging of *E. coli* murine myositis model.** A 15-minute

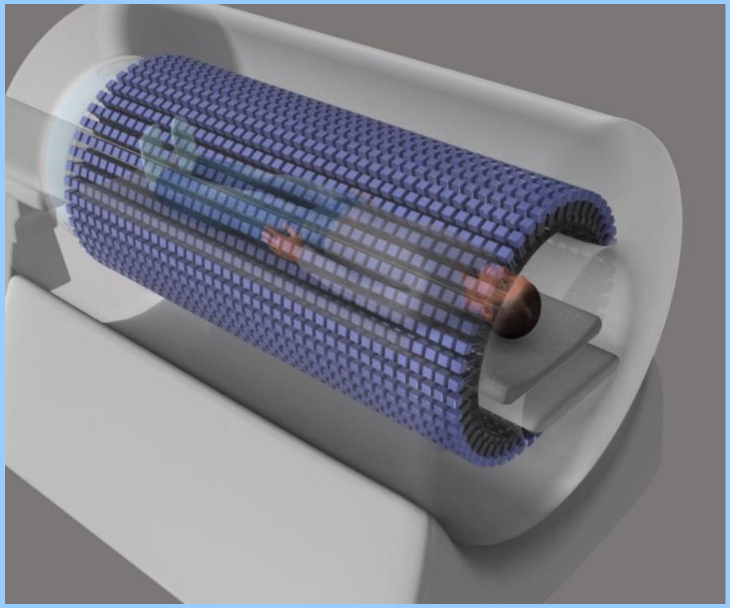
***In silico* Screen**

Commercially available libraries of ^{14}C, ^{3}H and ^{125}I molecules were obtained from Moravek Biochemicals, American Radiolabeled Chemicals, Perkin Elmer (Waltham, MA), ViTrax (Placentia, CA). Data was extracted from PubMed, PubChem, SciFinder and Google Scholar. *Escherichia coli folp* (dihydropteroate synthase)*, mtlD* (mannitol-1-phosphate dehydrogenase) or *srlD* (sorbitol-6-phosphate dehydrogenase) were queried against the UniProtKB database of bacterial species to calculate alignment and percentage identity using ClustalOmega (*5*).

Total Body PET Initiative

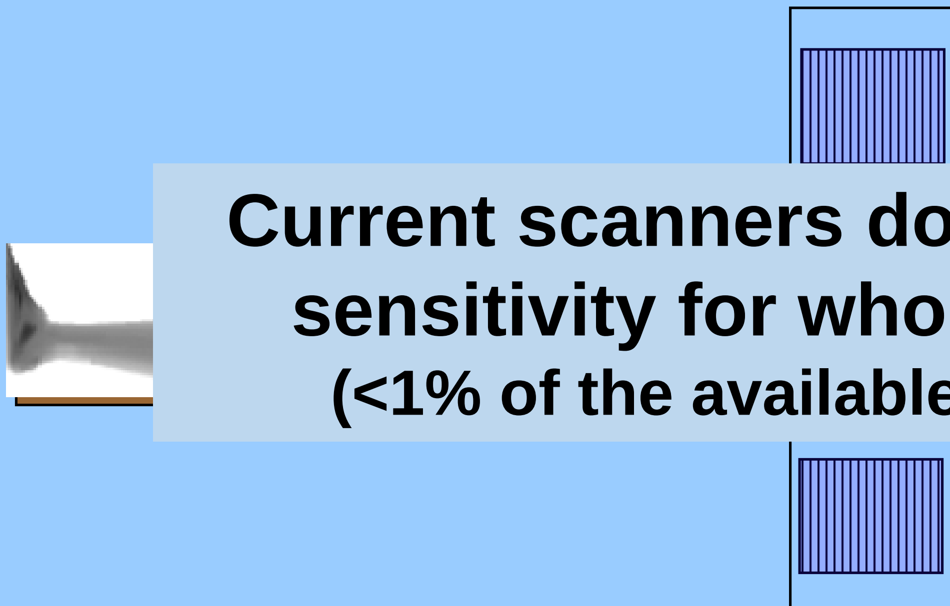


Conventional
PET Scanner
(2016)



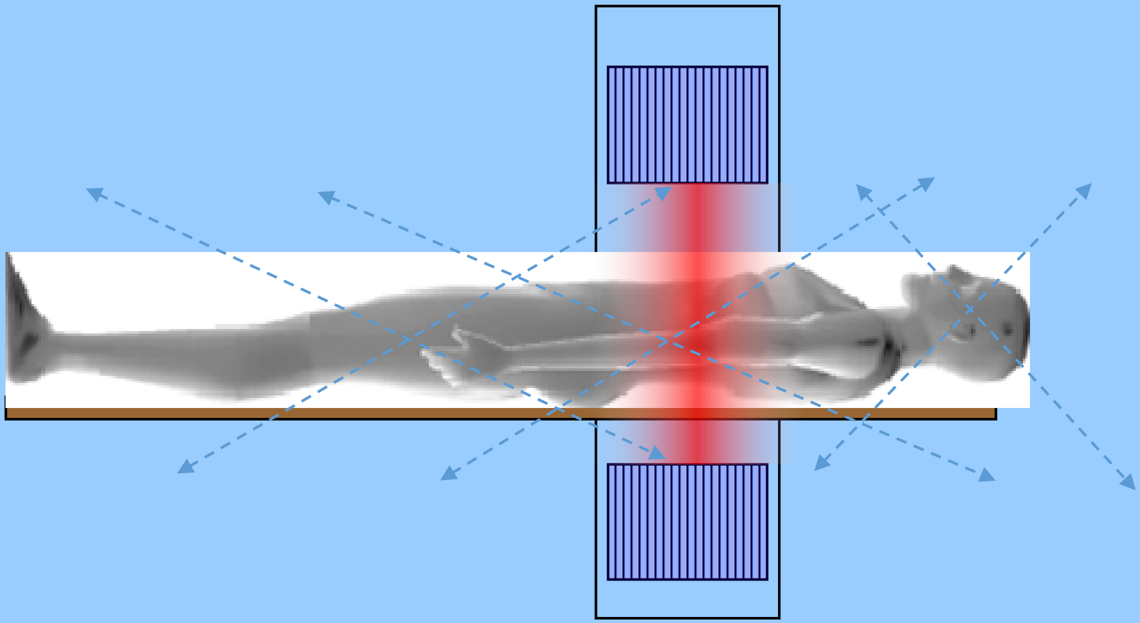
EXPLORER
Total Body PET Scanner
(2017)

All PET studies are limited by statistics, radiation dose, or both



Current scanners do not maximize the sensitivity for whole-body imaging

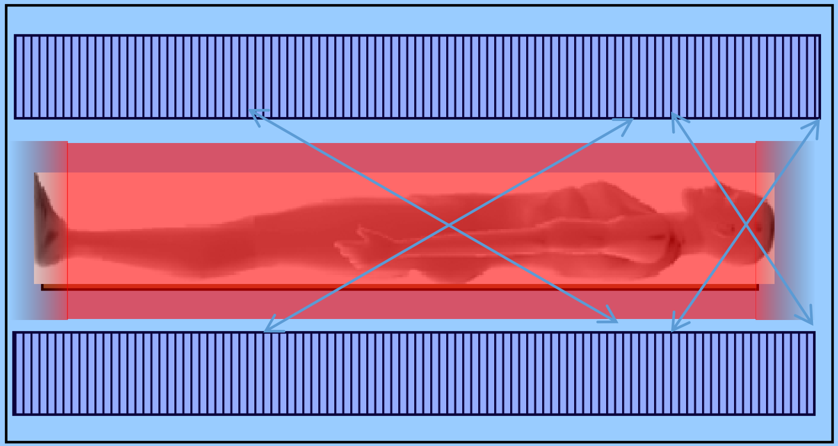
(<1% of the available signal collected)



<1% of the potential return on the investment in:

- Cyclotron operation
- Labelled tracer production
- PET scanning facilities and resources
- The radiation dose to the patient

Total-Body PET:
Maximizing sensitivity and simultaneously imaging the whole body



Needed to realise the potential of PET
In biomedical research and healthcare

EXPLORER Team

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Simon Cherry
Jinyi Qi
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David Mankoff (Univ. of Pennsylvania)
Michael Graham (Univ. of Iowa)
William Jagust (LBNL)
Pat Price (Imperial College)

Industry Advisory Panel:
Chuck Stearns (GE Healthcare)
Michael Casey (Siemens)
Matthias Schmand (Siemens)
Ling Shao (Philips Healthcare)

Senior Advisors:
Thomas Budinger
Michael Phelps

Total-Body PET: Maximizing Sensitivity

- 40x gain in effective sensitivity for total-body imaging!
- 4-5x gain in sensitivity for single organ imaging

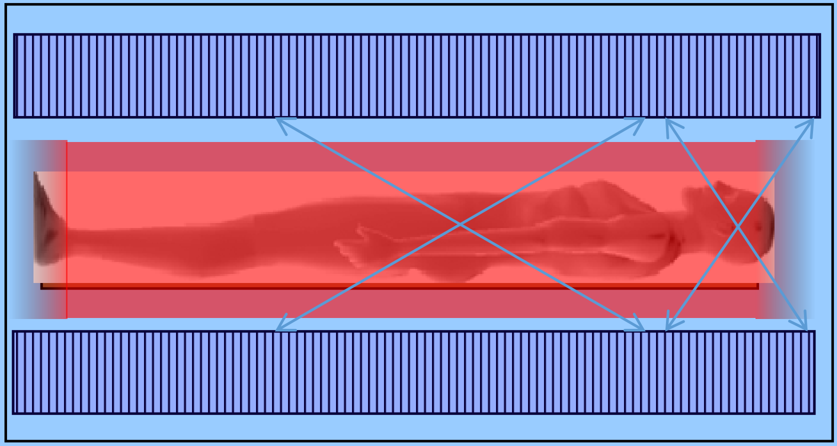
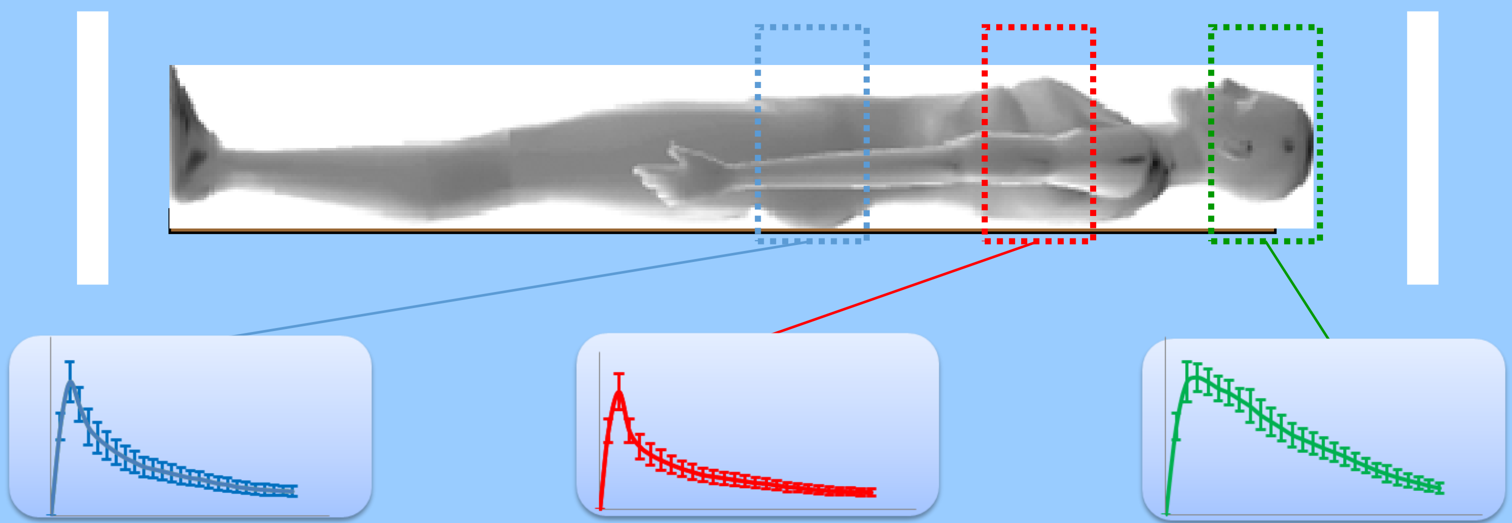


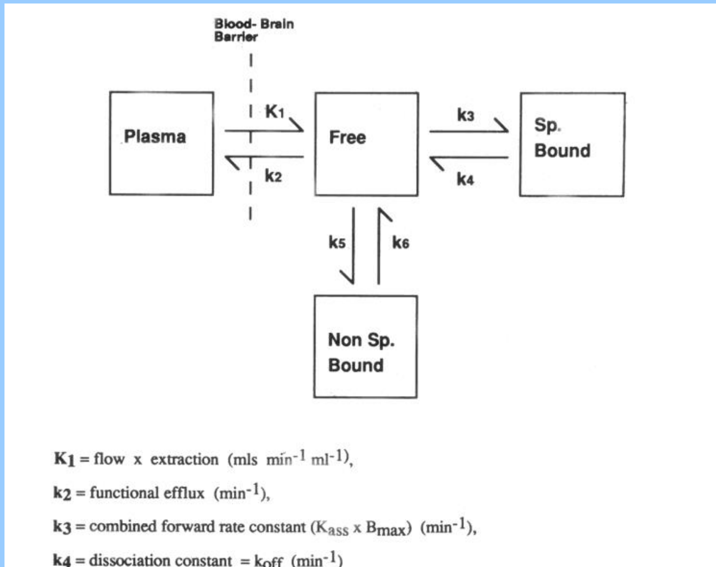
Image Kinetics

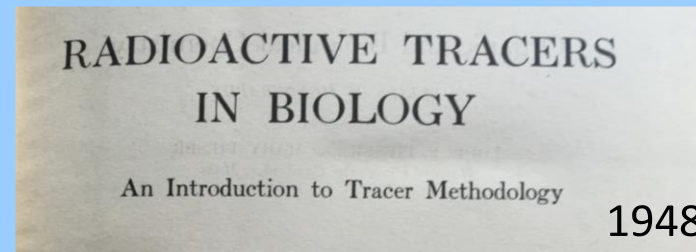
Kinetic Data from the whole Body Field of View

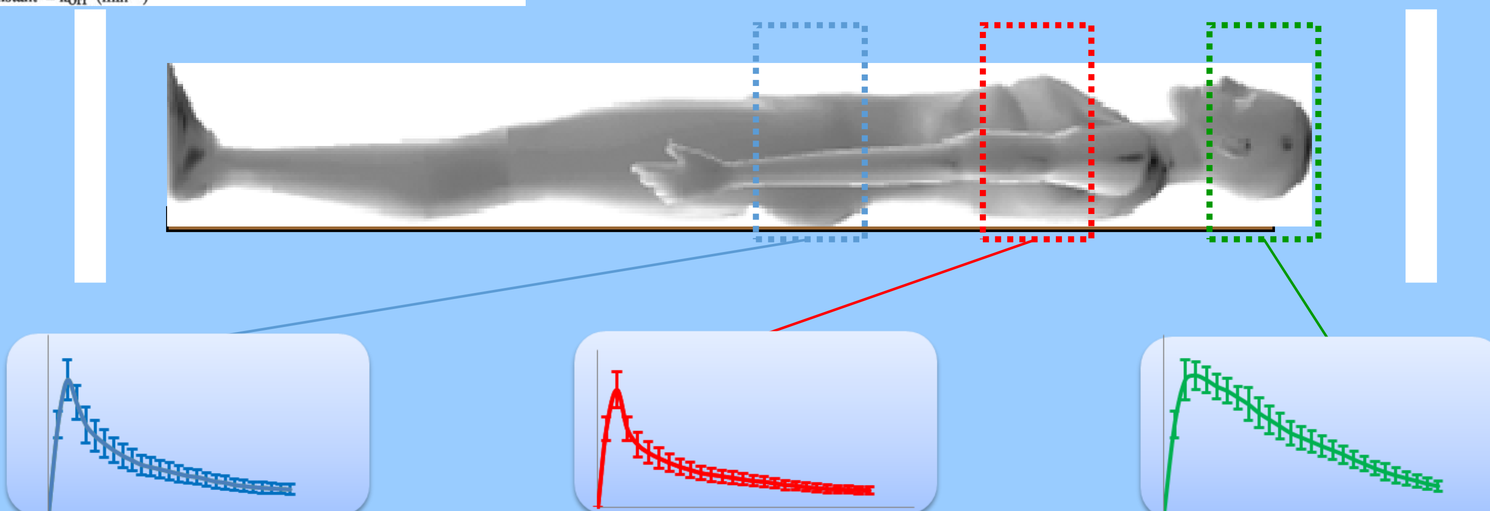


Regional tissue kinetics & arterial blood input functions with high statistical quality

Image Kinetics







Regional tissue kinetics & arterial blood input functions with high statistical quality

"Effecting the tracer principle for the whole body"

Image Longer

- **40-fold greater dynamic range**

  can image for 5 more half lives

- **^{11}C**

  > 3 hours

- **^{18}F**

  > 18 hours

- **^{89}Zr**

  > 30 days

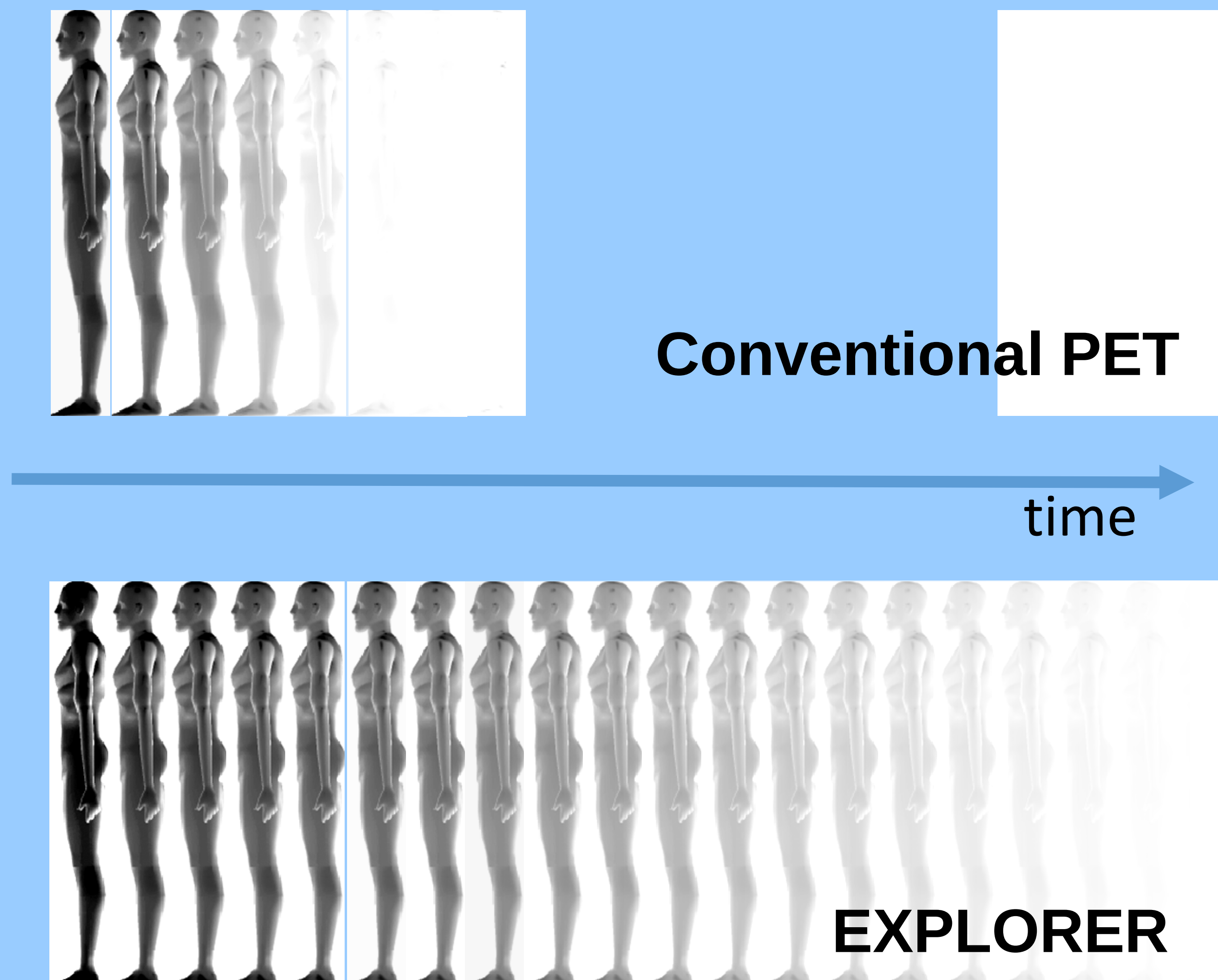


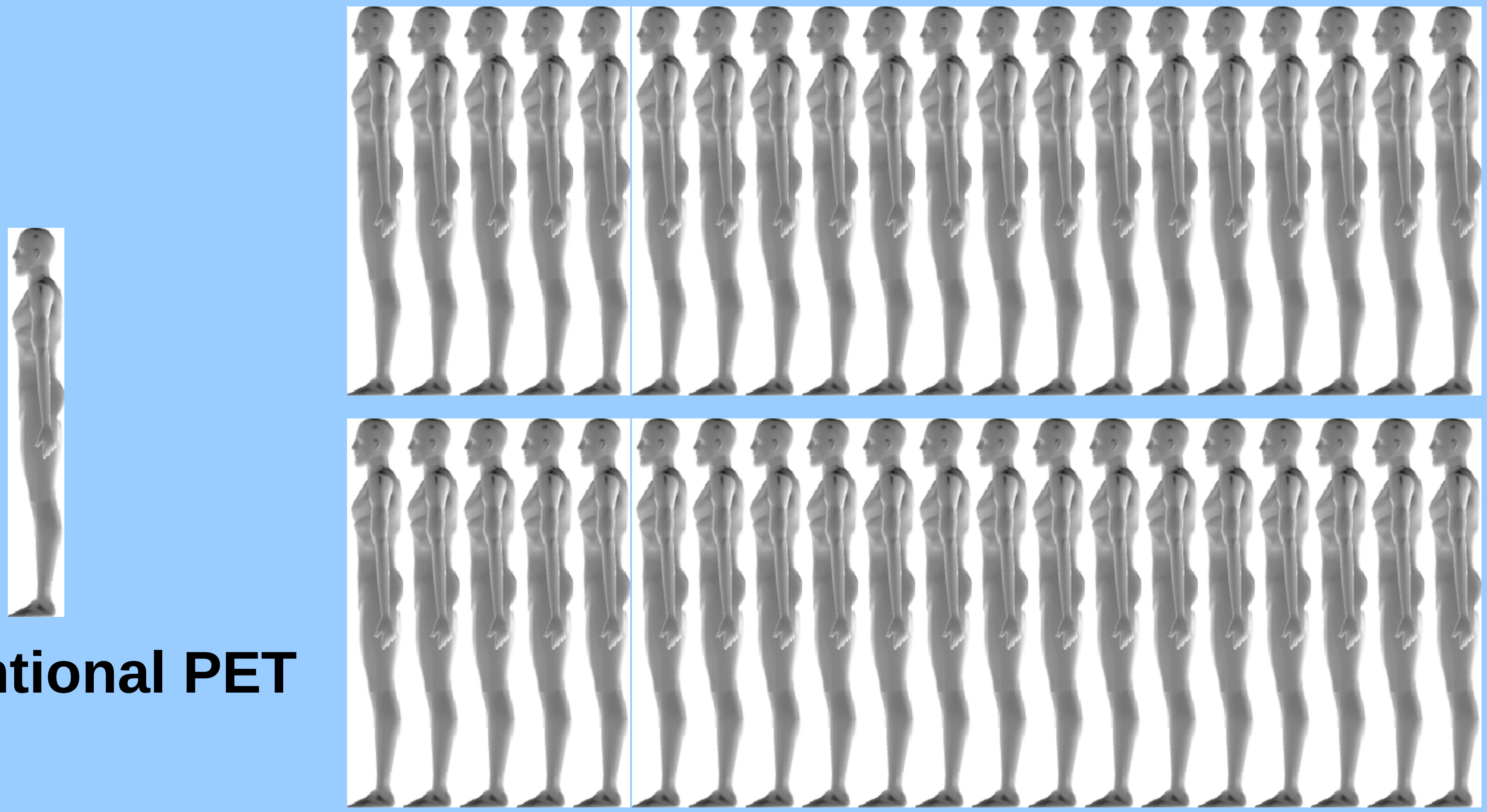
Image Gently (Low Dose)

- **40-fold reduction in dose**
  - Whole-body PET at ~0.15 mSv
  - Annual natural background is ~2.4 mSv
  - Return flight (SFO-LHR) is ~0.11 mSv
  - PET can be used with minimal risk – new populations

Conventional PET

EXPLORER

Image More Often



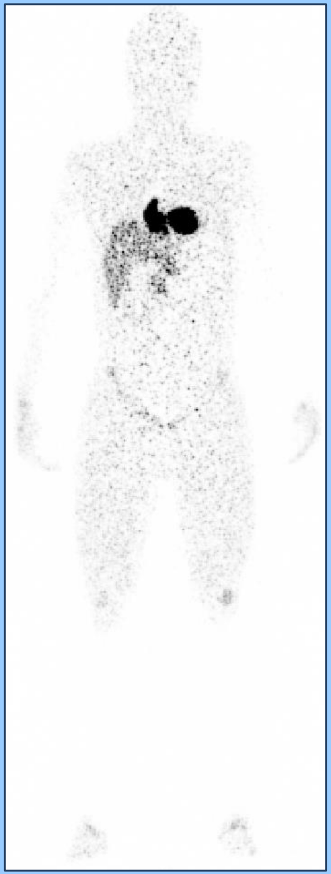
Conventional PET

EXPLORER

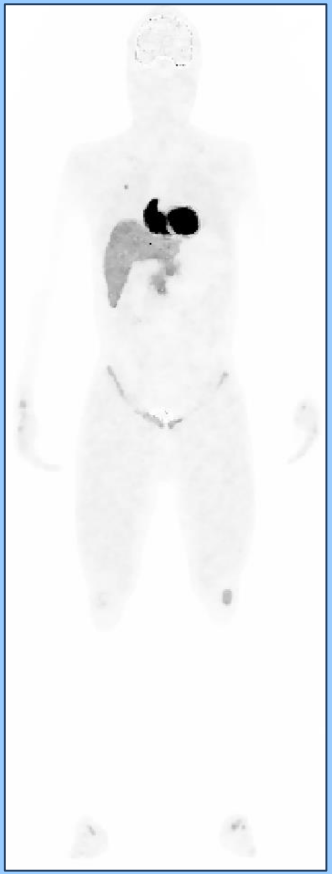
APPLICATIONS

Image Better

- **> 6-fold improvement in SNR-simulations**
  - Reconstruct at higher spatial resolution
  - Detect smaller lesions
  - Detect low-grade disease
  - Better statistics for kinetic modeling
- **> Whole body kinetic data**



Conventional PET



EXPLORER

October 2016

Practical/economical advantages of Total Body PET Scanning
40 times more sensitive for whole body imaging

Scan times of minutes:
More patient throughput per unit of time

Could do the clinical load of 3-4 conventional scanners:
Space and staff saving

Easily prescribe scan quality e.g. from 2-3 to 10's of mins duration

Prescribe scans with up to a factor of 40 lower radiation absorbed dose

Extend the working day

Provides time for extensive clinical & research activities on the one scanner

Extends the distance from a distribution centre of radio labelled tracers by a further 5 half lives
Avoids the cost of in house production

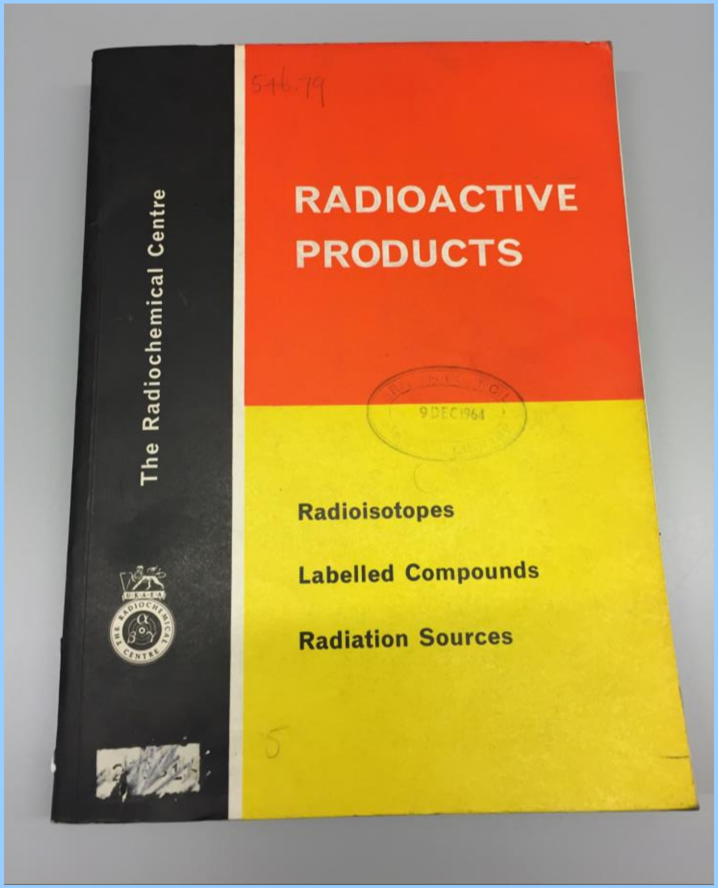
The 21st Century "Amersham Catalogue"

Centralized Radioisotope Production:

Radiochemistry for patient doses

GMP production

Regulatory Control



Zirconium -89 Custom Labelling Service of cells and antibodies

Fluorine-18 & Gallium-68 Custom labelling Service of macromolecules peptides, nanobodies

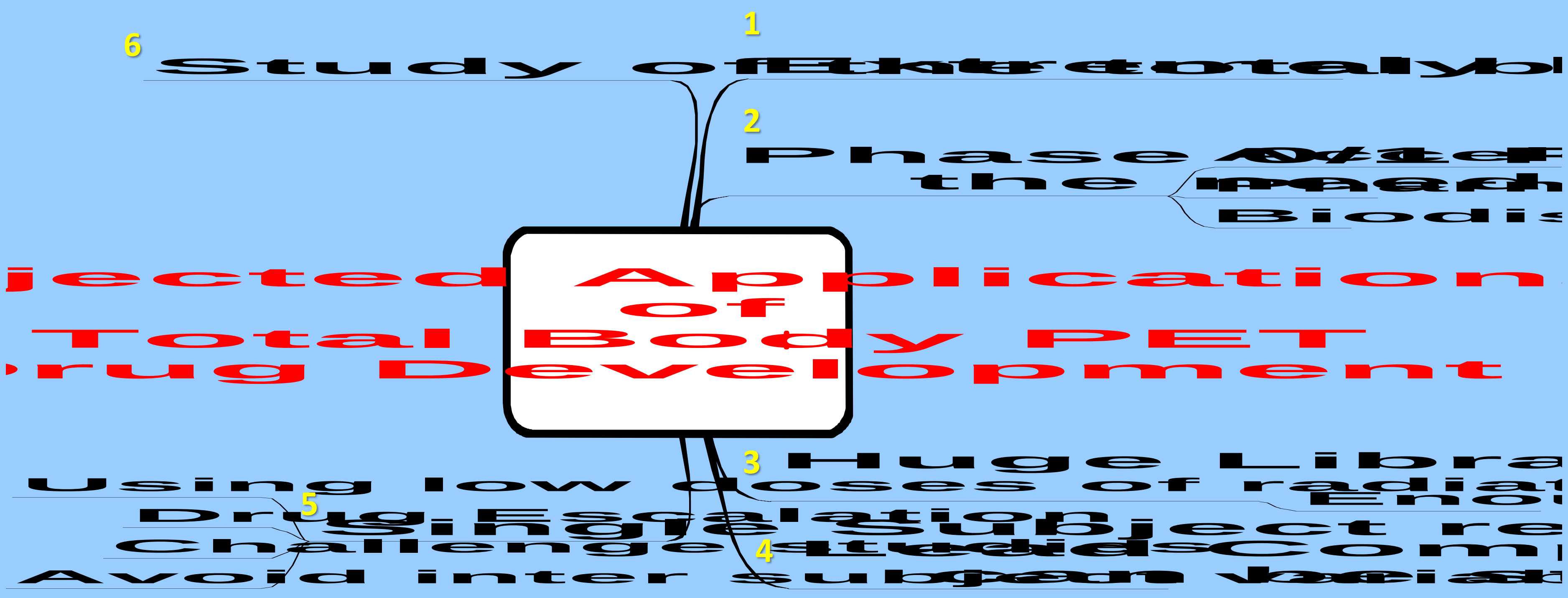
Fluorine-18 Custom labelling Service of small organic molecules

^{11}C labelled metabolic precursors-non specific activity dependant

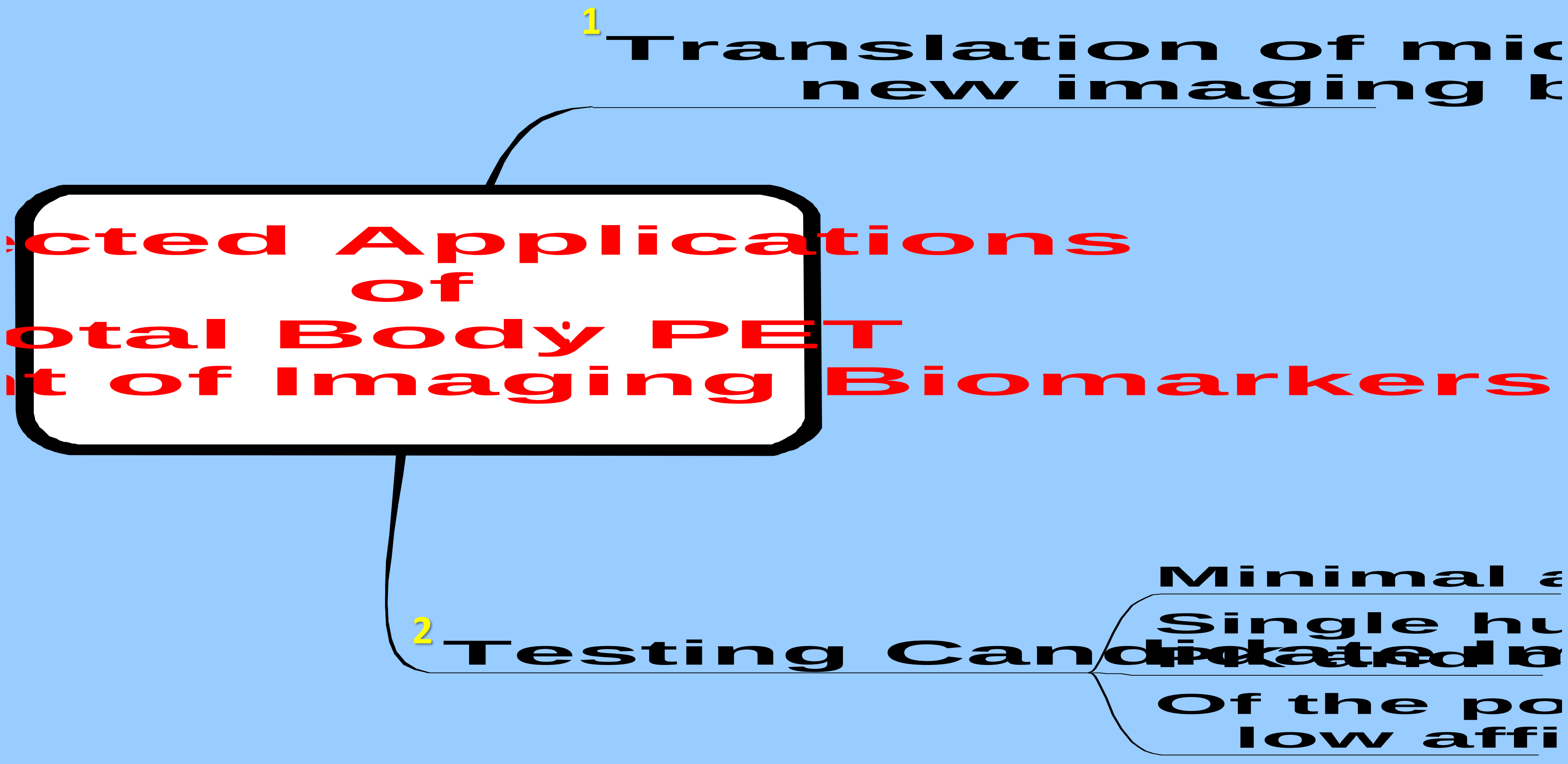
Transformative Areas of Investigation

- **Detecting occult low density multi-system disease**
  - Ultra-staging of micro-metastases
  - Plaques in atherosclerosis
  - Inflammation
  - Infection
- **Providing total body kinetics**
  - Drug delivery / extended time courses / physiologically based pharmaco-kinetic models
  - Translational pipe line for new radio-labelled imaging biomarkers
  - Toxicology
- **Studying the interactions between the body's organs**
  - Distribution of tissue blood flow
- **Enabling low radiation dose studies**
  - Repeat studies
  - Normal subjects
  - Young patients
  - Maternal-Fetal
- **Studying interactive regional pathologies brain: body**
  - Anxiety / Depression
  - Alzheimer's Disease
  - Metabolic syndrome / obesity
- **Expanding the commercial future**
  - Higher clinical throughput
  - New applications

Drug Development

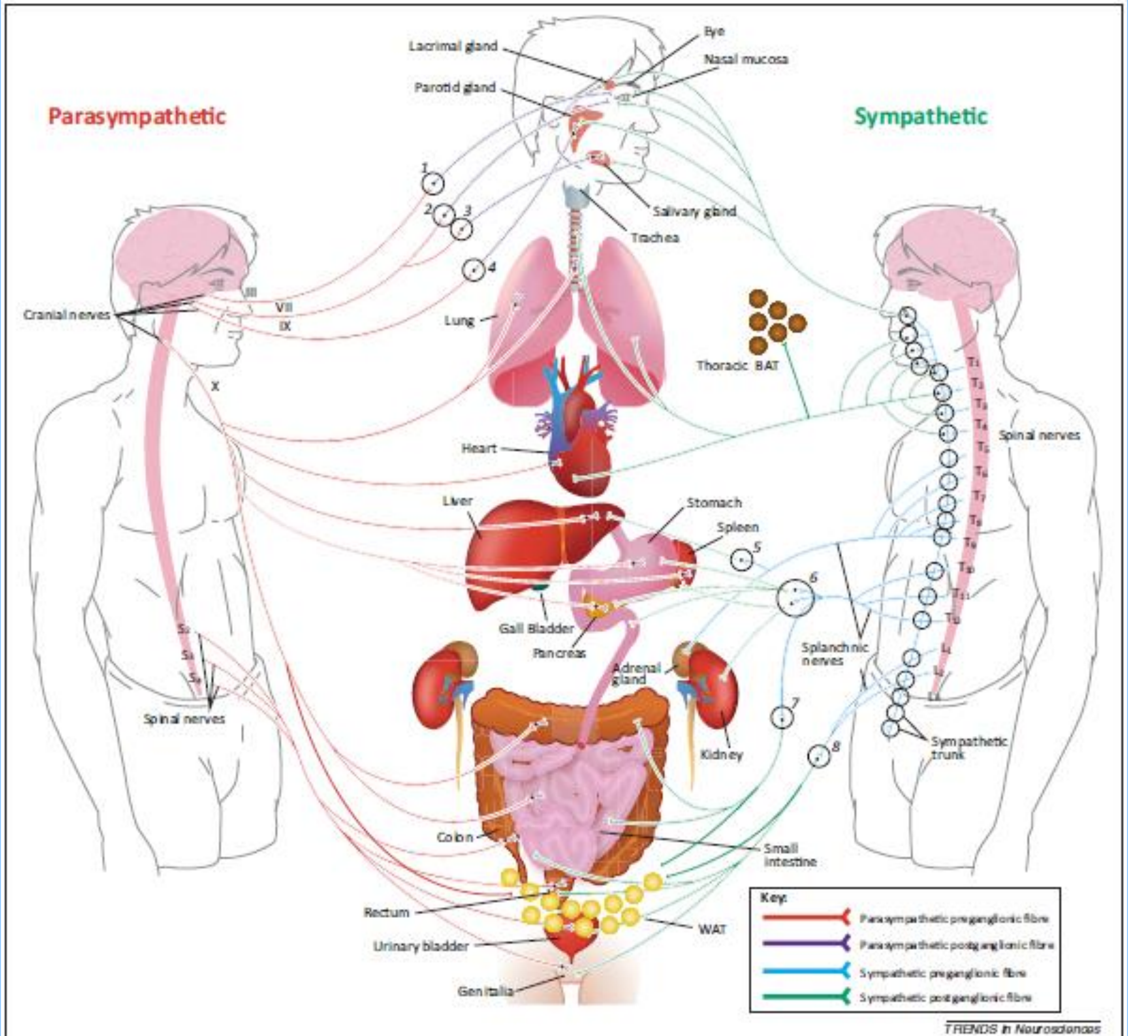


Development of Imaging Biomarkers

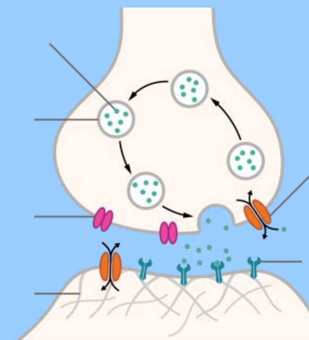


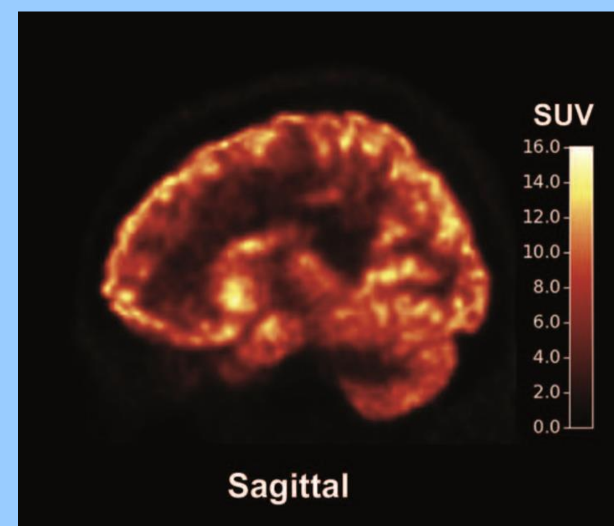
Total-Body PET:
Studying the interactive complexity of the Human Body

- Brain-Body
- Heart-blood circulation
- Hormone & Peptide producing organ: Pancreas/Adrenals/Thyroid/Gut/Gonads
- Cell trafficking
- <u>Systems Biology</u>



Synapse Imaging





"The synaptic basis of neuroimmune communication is also coming into focus, and this area is particularly exciting due to the potential to execute rapid changes immune status."

M L Dustin J Cli. Inv. vol 122.4. April 2012

Stress and disease

Major Depressive Disorder, Irritable Bowel Syndrome, Borderline Personality Disorder,

Bipolar Disorder

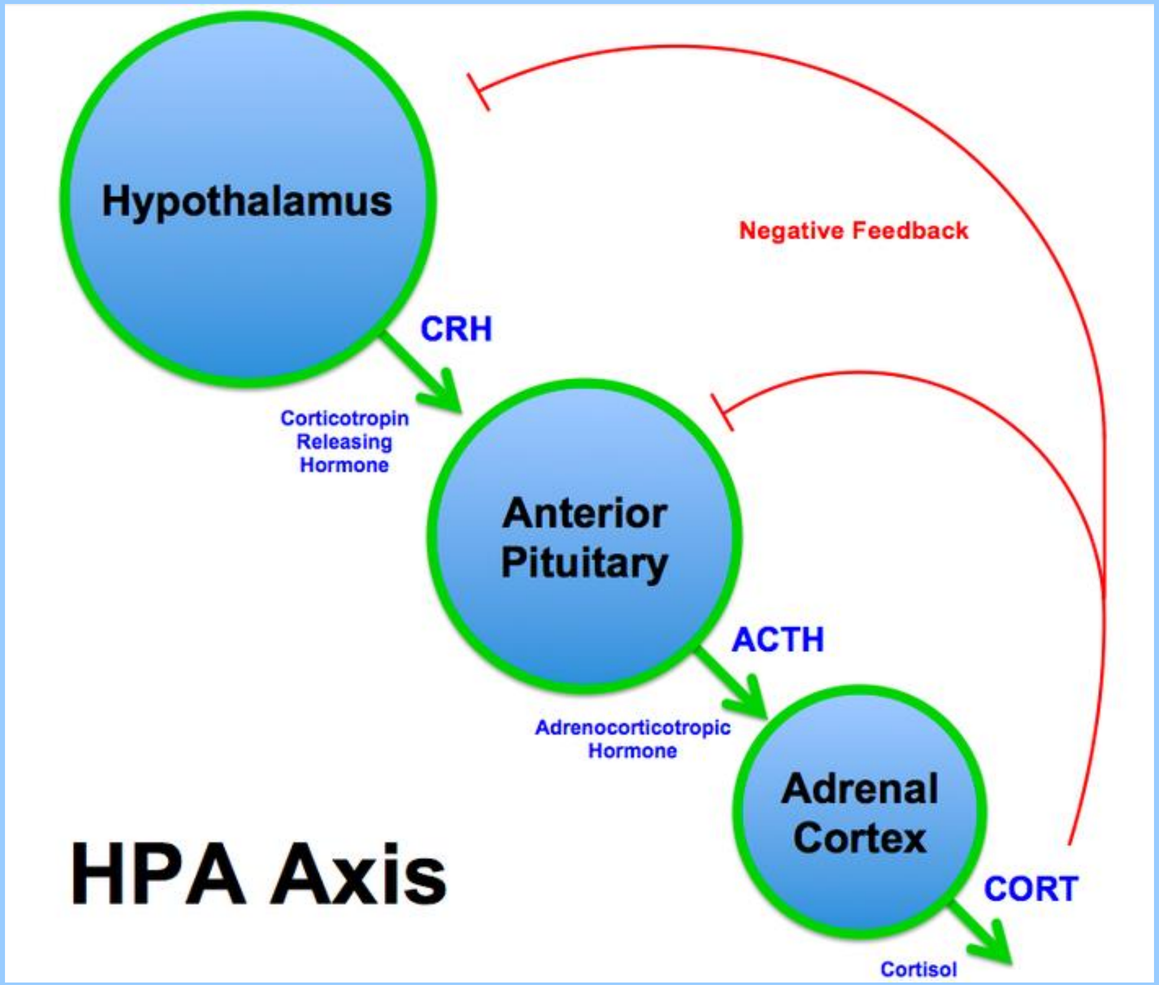
ADHD

Anxiety Disorder

Insomnia

Alcoholism

Fibromyalgia

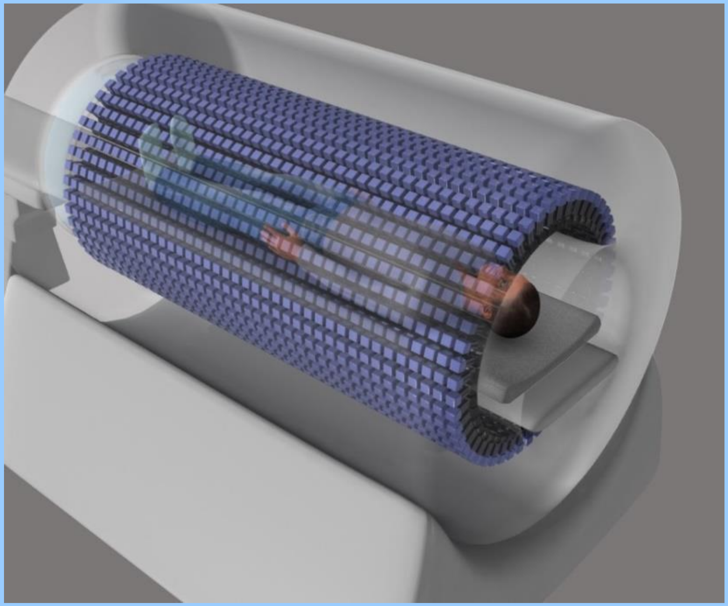


Posttraumatic Stress Disorder, Burnout, Chronic Fatigue Syndrome

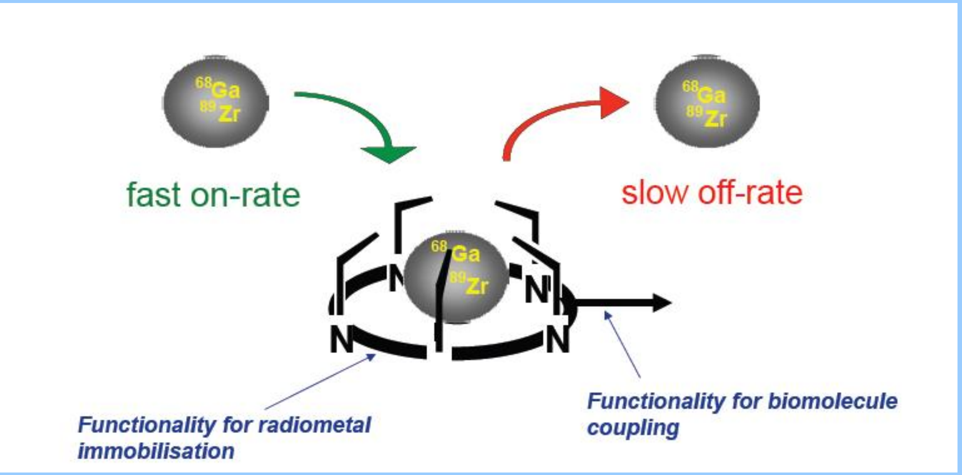
^{11}C labelled precursor –for cortisol synthesis in the adrenals?

Bio-distribution of cells over days/weeks

Total Body PET



^{89}Zr (78.5 hrs T1/2)



Synthesis and characterisation of zirconium complexes for cell tracking with Zr-89 by positron emission tomography

Trevor J. Ferris,[a] Putthiporn Charoenphun,[b] Levente K. Meszaros,[b] Gregory E. D. Mullen,[b] Philip J. Blower[bc] and Michael J. Went*[a]

Dalton Trans., 2014,**43**, 14851-14857

Total-Body PET: Opportunities for Radiochemistry

- In house non GMP radiochemistry labelling and pre-clinical testing
- Commercial customised GMP syntheses for human studies
- ^{11}C labelling of metabolic precursors body-brain interactions:
    - Leptin-obesity
    - Cytokines-dementia
    - Cortisol-depression, anxiety, etc.
- Low dose biomarker development in single human subjects
- Low dose first into human labelled drugs
- Labelling cells for long term trafficking
- Radiochemistry using significantly lower levels of activity- shielded fume cupboard

To the next 50 years

Thank you