

Review Article

Building on a 50-year legacy of the MRC Cyclotron Unit: the Hammersmith radiochemistry pioneering journey[†]

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Abstract: The Medical Research Council Cyclotron Unit (MRC CU) situated at Hammersmith Hospital, London, is widely recognised for its pioneering developments in radiochemistry. The MRC CU became one of the largest and most comprehensive PET centres in the world. More recently, under the umbrella of a public/private partnership between the MRC and Amersham Health (now part of GE Healthcare) this centre has continued to advance PET research.

This article reviews the 50-year history of radiochemistry development and application for medical research at Hammersmith. Copyright © 2007 John Wiley & Sons, Ltd.

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Introduction

The Medical Research Council Cyclotron Unit (MRC CU) situated at Hammersmith Hospital (HH) in London was one of the largest and most comprehensive facilities of its kind in the world. It has a long and distinguished 50-year history in the development and application of radioisotopes for medical research purposes.

A comprehensive history of the facility would require its own volume and this review focuses mainly on the achievements of the Radiochemistry group with some emphasis on radiochemistry with positron-emitting radionuclides for applications in medical research using positron emission tomography (PET).

As background a brief review of some of the important gamma-emitting radionuclides, as well as the early development of some positron emitters and their applications at the MRC CU, is presented and a list of landmarks in the history of the facility is presented in Table 1. Due to the huge amount of work that has been carried out at the MRC CU over the past 50 years, literature references to clinical applications, and some-

times original sources, of some of the tracers described herein will be kept to a minimum.

A personal view of the history of the MRC CU and summary of the methodological and technical developments, as applied to the brain programme at Hammersmith, can be found in a review by Terry Jones,¹ and a more general outline history of the centre can be found at the Imanet web site.²

For the purpose of this review, three periods are described in the evolution of the centre. They are: 1955–1979, the period following installation of the first medical cyclotron until the arrival of the first PET scanner at the MRC CU; 1979–2001, covering development of the PET radiochemistry programme; and 2001–2006 following privatization of the centre.

The first period involved some early work with positron emitters and the production of neutron-deficient gamma-emitting radionuclides suitable for human studies.

The second period followed the introduction of the first clinical PET scanner at the MRC CU and involved the incorporation of positron-emitting radionuclides into more complex molecules suitable for human PET studies.

The third period focuses on the continuation of the work after privatization of the centre by the formation of Hammersmith Imanet Ltd (HIL) through a public/private partnership between the MRC and Amersham Health and Amersham's subsequent incorporation into GE Healthcare.

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[†]Fiftieth Anniversary Special Issue, In memoriam John Jones.

Table 1 Landmarks in history at the Hammersmith Cyclotron building

Year	Landmarks
1934	MRC and the UK government establish the National Radium Beam Therapy Research Initiative based at Hammersmith Hospital, London
1941	MRC established the Radiotherapeutic Research Unit (RRU) at HH under Dr Constance Wood
1945	The MRC formed the Committee on Medical and Biological Applications of Nuclear Physics which recommended that a linear accelerator (1946) and a cyclotron (1948) should be developed by RRU
1946	Dr Hal Gray joined the RRU to widen its scope with basic radiological research
1953	The first patient was treated with the linear accelerator at HH
1955	Official inauguration of the first cyclotron at HH by HM Queen Elizabeth II
1958	The cyclotron first production of oxygen-15 using external beam
1959	Experiments begun on regional lung function using oxygen-15. Productions of fluorine-18 and carbon-11 begun
1962	Establishment of the MRC Cyclotron Unit at HH under Mr Derek Vonberg
1966	The first patient was treated with neutron therapy
1979	Installation of ECAT II – the first positron emission tomography scanner in the UK
1985–87	Replacement of the original cyclotron by the Scanditronix MC-40 Cyclotron and installation of new radiochemistry hot-cell facilities
1987	Installation of the first block detector PET scanner, the ECAT 931
1989	Development of the first small-bore PET scanner for small animal studies (RATPET)
1990	Installation of the first PET scanner with retractable septa, the ECAT 953B
1991	Installation of the IBA Cyclone 3 cyclotron for oxygen-15 production
1993	Incorporation of the Cyclotron Unit into the MRC Clinical Sciences Centre and Imperial College School of Medicine
1995	Spin off of the Functional Imaging Laboratory at Queen Square London
2001	MRC-Amersham plc joint venture – founding of Imaging Research Solution Ltd with formation of Imanet
2002	Installation of HR + PET scanner
2004	Acquisition of Amersham by GE Healthcare, HIL becomes part of GEHC
2005	Completed installation of GE PETtrace cyclotron and GMP hot-cell production facilities – ‘The Vonberg Suite’
2006	Installation of GE PET/CT Discovery RX

The MRC CU comprised a number of features which perhaps made it unique. In addition to supporting the various clinical research programmes in neurology, cardiology, oncology and pulmonary medicine resources were also devoted to producing radiotracers for supply to other hospitals and other centres, to a large extent acting as a national cyclotron for medical research.

1955–1979

The Medical Research Council (MRC), UK had the vision and foresight to install the world's first cyclotron dedicated to medical research at its Radiotherapeutic Research Unit at HH, London. It was officially opened by Her Majesty Queen Elizabeth II in 1955. The MRC has continued to support fundamental research in basic radiochemical science and the clinical application of radiotracers since that time. Details of other important developments during the first period are listed in Table 1.

During this early period, under the direction of Constance Wood, a radiotherapist (1941–1962) and subsequently Derek Vonberg, an engineer (1962–1985), the emphasis of the radiochemistry programme was on the development of production methods of radionuclides for research applications in the Royal Postgraduate Medical School (RPMS) at Hammersmith and other

hospitals within reach.³ During the latter part of this period, work was also carried out with positron emitters^{3–23} even before the installation of the PET scanner (see Table 2) and the development of cyclotron targetry for production of [¹⁸F]fluorine⁵ and [¹⁸F]fluoride.¹²

A lot of pioneering radiochemistry work was conducted during this early period under the leadership of David Silvester. John Clark led the targetry group and evolved automation strategies with Peter Horlock and Peter Buckingham. Ian Watson looked after radioisotope development and production, while Steve Waters looked after nuclear data²³ and quality control by GeLi gamma spectrometry and atomic absorption spectrophotometry.

Some examples of radionuclides produced between 1957 and 1979 for a variety of medical research projects are given below (see Table 2).

¹⁵O lung function studies ¹⁴N(d,n)¹⁵O, half-life 2 min, positron emitter

The first radiotracers to be produced were based on oxygen-15 after the inspiration of Mikael Ter-Pogossian from Washington University, St Louis. Several chemical forms, such as ¹⁵O₂, C¹⁵O, C¹⁵O₂ and H₂¹⁵O, were produced for use in pulmonary physiological studies by Colin Dollery (now Sir Colin Dollery) and John West.

Table 2 Chronological list of some radionuclides produced at the MRC CU 1957–1979²⁴

Date	Radionuclides and labelled compounds
1957	²² Na, ¹²⁴ I
1958	¹⁵ O (as O ₂ , CO, CO ₂); ⁴³ K; ⁵² Fe
1959	¹¹ C (as CO, CO ₂); ¹³ N (as N gas); ¹⁸ F; ⁷² As; ⁷⁴ As; ²⁰⁶ Bi
1960	¹⁵ O (as H ₂ O); ⁵⁷ Co; ⁸⁵ Sr; ⁷⁹ Kr; ¹²⁵ I
1961–62	⁷ Be; ⁵⁴ Mn; ⁶⁵ Zn; ⁶⁸ Ge/ ⁶⁸ Ga generators; ⁷² Se; ^{110m} Ag; ¹¹¹ Ag; 5-iododeoxyuridine, 5-iodouracil and 5-iodouridine labelled with ¹²⁵ I, ¹³¹ I or ¹³² I
1963	⁴⁸ V; ⁵² Mn; ⁶⁴ Cu; ⁹⁰ Nb; ¹¹⁵ Cd; ¹³ N (as N ₂ aqueous solution)
1964	²⁷ Mg; ⁴¹ Ar; ⁸⁴ Rb; ⁹⁵ Tc; ¹⁹⁷ Hg; ¹⁸ F-KBF ₄
1965	⁵¹ Cr; ⁸⁷ Y/ ^{87m} Sr generators; ¹²³ I; ¹²⁹ Cs; ¹³⁰ Cs; ¹³⁹ Ce; ¹²³ I-human serum albumin
1966	⁸¹ Rb; ^{82m} Rb/ ^{81m} Kr generators
1967	²⁰³ Pb
1968	⁷⁵ Se; ¹¹⁷ Sb; ¹²³ I-hippuran
1969	⁶² Zn; ⁶⁷ Ga; ^{69m} Zn; ⁷⁷ Br; ^{80m} Br; ^{85m} Kr; ¹⁹⁵ Au; ¹³¹ I-di-iodofluorescein; ¹³¹ I-tetra-iodofluorescein; ²⁰³ Hg-hydroxymercury-di-iodofluorescein
1970	¹¹¹ In; ¹²⁷ Xe; ¹⁵⁷ Dy
1971	K ¹¹ CN; ¹¹ C-glucose; ¹¹ C-fructose; DL- <i>p</i> -[¹⁸ F]fluorophenylalanine
1972	⁵⁶ Ni; ⁶² Zn-, ⁶⁷ Ga-, and ¹¹¹ In-bleomycin; [¹¹ C]benzoic acid; [¹¹ C]acetic acid; [¹⁸ F]-CCl ₃ F; [¹⁸ F]CCl ₂ F ₂ ; [¹⁸ F]benzoic acid
1973	³⁸ K; [¹¹ C]galactose; [¹¹ C]glycerol; [¹¹ C]methanol; [¹¹ C]methyl iodide; [¹⁸ F]KF; [¹⁸ F]SbF ₃ ; [¹⁸ F]AgF; ¹¹¹ In-DTPA; ¹¹¹ In-tetraphenylporphine; 4-(3-dimethylaminopropylamino)-7-[¹²⁵ I] iodoquinoline (NM113)
1974	[¹¹ C]mannitol; [¹¹ C]mannose; [¹⁸ F]DOPA; ¹¹¹ In-tetracyclin; ¹¹¹ In-EHDF; ¹²³ I-Conray; [¹²³ I]Hypaque; [¹²³ I]Rose Bengal; 4 analogues of NM113 (¹²⁵ I, ¹³¹ I)
1975	⁶¹ Cu; ⁹⁷ Ru; [¹¹ C]paraquat; <i>L-p</i> and <i>m</i> -[¹⁸ F]fluorophenylalanine; 2,4-di-[¹²³ I]iodo-oestradiol; ¹¹¹ In-oxine (for cell labelling)
1976	[¹⁸ F]SF ₆ ; [¹¹ C]formaldehyde; [¹¹ C]methylputrescine
1977	[¹⁸ F]CF ₄ ; <i>L-5</i> and 6-[¹⁸ F] fluorotryptophan; adenosyl-[⁷⁵ Se]selenomethionine
1978	[¹³ N]glutamate; 4-[¹⁸ F]fluoroestrone; 4-[¹⁸ F]fluoroestradiol; DL- <i>N</i> -acetyl- <i>p</i> -[¹⁸ F]fluorophenylalanine; DL- <i>N</i> -acetyl- <i>p</i> -[¹⁸ F]fluorotryptophan; ¹¹¹ In-acetylacetate (for cell-labelling); 4 analogues of NM113 (¹²⁵ I)
1979	[¹¹ C]palmitate; 2-deoxy-2-[¹⁸ F] fluoro-D-glucose

Where the chemical form is not stated, the radionuclides were prepared as a simple ionic species; otherwise the chemical names of labelled compounds are given. This style has been chosen to emphasize that the need moved, away from new radionuclides in simple ionic form, towards specific compounds labelled with a much narrower range of radionuclides.

A nitrogen gas target was bolted straight onto the cyclotron dee chamber where the new beam extraction system had been installed, together with what would now seem primitive on-line chemical processing system assembled from readily available parts including 'wartime surplus'! Most of this 'string and sealing wax' work was achieved in a very short time by Les Baker, Gerry Forse and Peter Buckingham.⁸

¹²⁴I for therapy ¹²¹Sb(α, n)¹²⁴I, half-life 4.15 d, positrons EC and gammas

In vivo radiotherapy was in its infancy in the 1950s and the reactor produced (fission product) ¹³¹I was being used in thyroid cancer therapy; however, the dose distribution was not ideal due to the fairly short range of the beta particles. It was suggested that the higher energy positrons of ¹²⁴I might give some advantages in dose distribution. An antimony target was devised with a plasma-sprayed copper plate being found to be quite effective for irradiation inside the cyclotron (internal beam). Post-irradiation processing using wet chemistry

was carried out by Phil Reasbeck initially at Birmingham University where handling facilities were available until similar facilities were installed at Hammersmith. The radiotherapy was undertaken by Alan Goolden, one of whose students in those pioneering days was Henry Wagner Jr.

⁷⁴As for brain tumours using positron scanning. ⁷⁴Ge($d, 2n$)⁷⁴As, half-life 17.8 d, ~28% positrons EC and gammas

One of the earliest radionuclide imaging challenges was the detection of brain tumours. Rectilinear scanners had been built by physicists and engineers to image radionuclides *in vivo*. John Mallard had built such a scanner at the HH Medical Physics Department. Together with members of the MRC CU, a coincidence detector scanner was assembled to improve the sensitivity and resolution of the device. In order to exploit these developments, positron-emitting radiotracers were needed. Small ions were thought to be able to cross the disrupted blood brain barrier around brain

tumours; hence ^{74}As arsenate was produced for this purpose. A plasma-sprayed germanium target was produced of similar design to the earlier antimony target for ^{124}I (see above). A wet chemical process was developed based on sequential distillation of volatile halides resulting in radionuclidically pure ^{74}As for clinical use.

^{72}As brain tumours using positron scanning. $^{69}\text{Ga}(\alpha, n)^{72}\text{As}$, half-life 26 h, ~75% positrons EC and gammas

Following the successful use of ^{74}As , the shorter half-life and more abundant positron emitter ^{72}As was developed. Due to the very low melting point of gallium (30°C) an alloy with silver was employed for the internal alpha beam irradiation. Wet chemistry and halide distillation were again employed to recover ^{72}As arsenate for brain tumour imaging. Processing of both ^{74}As and ^{72}As was carried out by Nesta White.

^{22}Na $^{24}\text{Mg}(\text{d},\alpha)^{22}\text{Na}$, half-life 2.60 y, positrons and gamma

^{22}Na can be produced only using a cyclotron and in the 1950s the only cyclotrons in the United Kingdom were at Birmingham University and HH. The Radiochemical Centre (TRC) at Amersham set up by the UKAEA to exploit radioisotopes for peaceful uses, including medical applications, needed a supply of ^{22}Na . Both cyclotrons undertook to irradiate magnesium targets, and the chemical processing was carried out by TRC Amersham, thereby establishing a longstanding and lasting relationship between the centres (see ^{111}In , ^{67}Ga and $^{87}\text{Y}/\text{Sr}^{87\text{m}}$ below).

^{206}Bi for *in vivo* radioimmunization. $^{206}\text{Pb}(\text{d},2\text{n})^{206}\text{Bi}$, half-life 6.24 d, betas and gammas

HH pioneered human organ transplantation in the 1950s and 1960s. This was before immunosuppression was achieved safely using chemical methods, but immunization by external irradiation was actively being explored. *In vivo* irradiations using radioisotopes targeted at the immune system would offer the chance of a more selective and controllable means of immunosuppression. ^{206}Bi colloids were known to concentrate in the lymph nodes and the cyclotron was employed to provide the ^{206}Bi . Lead melted onto copper plates was used for the internal target to be irradiated with the 15 MeV deuteron beam. Wet chemistry involving co-precipitation of carrier-free ^{206}Bi followed by ion-exchange chromatography resulted in sufficient material for research immunizations to be undertaken in

animal models. The radiochemical processing was carried out by Nesta White.

^{13}N for N_2 fixation studies. $^{12}\text{C}(\text{d},\text{n})^{13}\text{N}$, half-life 10 min, 100% positrons

The production of $^{13}\text{N}_2$ was developed for use, primarily for pulmonary lung volume studies in conjunction with oxygen-15 radiotracers (see above); however, Dr Nicholas, an agricultural scientist, was interested in exploring the mechanisms of nitrogen fixation in bacteria and plants using the only radiotracer available, ^{13}N . These experiments brought some interesting challenges to the radiochemist David Silvester, but the pioneering work, which also involved fast autoradiography was successful and led other groups to employ the methodology elsewhere. The target consisted of an activated charcoal-filled metal box with a thin beam entry window. Helium was passed continuously through the box during the deuteron irradiation resulting, after on-line purification, in $^{13}\text{N}_2$ suitable for the biological studies.

^{52}Fe for haematopoietic studies. $^{50}\text{Cr}(\alpha,2\text{n})^{52}\text{Fe}$, half-life 8.3 h, positrons and gammas

Iron is very important in blood chemistry and the Unit was asked to provide an alternative to ^{59}Fe (half-life 44.6 d beta gamma) which was not appropriate for imaging studies of the haematopoietic system. Natural chromium targets were made by electroplating Cr onto aluminium target plates using a specialist process. After alpha particle irradiation in the cyclotron internal beam, Cr was removed by electrochemically assisted etching with HCl. After adjustment of the HCl concentration, the ^{52}Fe was purified by solvent extraction using *di-isopropyl* ether and finally back extracted into water. The system used to carry out this separation was devised by David Silvester and Jeff Sugden.¹⁹

^{90}Nb tumour targeting. $^{90}\text{Zr}(\text{d},2\text{n})^{90}\text{Nb}$, half-life 14.6 h, positrons EC and gammas

As the arsenic radionuclide brain tumour imaging studies described above was developed, a systematic study of various radionuclides was undertaken by Dr Christine Matthews in the unit. ^{95}Nb was found to yield good target-to-background ratios in experimental tumours. For translation into humans, evaluation of the positron-emitting ^{90}Nb was developed. Titanium targets were prepared by plasma spraying onto copper. After deuteron irradiation using the internal cyclotron beam, the target surface was milled off using a custom-designed radioactive milling machine in a hot cell. The resulting metal particles were digested in concentrated

HF to dissolve the Ti. There followed an ion-exchange chromatographic purification of the ^{90}Nb for clinical use. This difficult separation was undertaken by Geoff Sugden.

^{43}K for myocardial imaging and whole body potassium estimations. $^{40}\text{A}(\alpha, p)^{43}\text{K}$, half-life 22.2 h, betas, gamma

Myocardial metabolism was known to depend on alkali metals, especially potassium. The application of potassium for imaging was proposed. The estimation of the total body exchangeable potassium is a measure often required by endocrine researchers and ^{43}K was found to offer some advantages over ^{42}K in multi-tracer studies.

The gas target for alpha irradiation was initially operated using a pulsed beam with a high-voltage cathode rod in the irradiation volume.⁷ The aim was to capture the radiogenic cations ($^{43}\text{K}^+$) with subsequent recovery by washing the cathode. The method suffered several drawbacks and was subsequently replaced with a circulating gas system where the radiogenic ^{43}K was captured on a glass filter continuously. Recovery post-irradiation involved a simple wash of the filter with dilute HCl (0.001 M). The system was devised by John Clark and engineered with the help of Jack Sharp and the staff of the cyclotron workshop.⁶

^{62}Zn for prostate imaging and ^{62}Cu radionuclide generator. $^{60}\text{Ni}(\alpha, 2n)^{62}\text{Zn}$ half-life 9.13 h parent of ^{62}Cu 9.76 m, positrons EC and gammas

In the basis of the finding that prostate tumour samples were high in zinc, the possibility of imaging this accumulation using radioactive zinc was suggested by the Genitourinary surgeons at HH. Nickel targets were prepared by electroplating methods using a variety of metal underlayers aimed at limiting the dissolution of the copper support plate during the recovery of the nickel target material by acid etching. ^{62}Zn was recovered and purified using mixed solvent (acetone/HCl) ion-exchange chromatography devised by Adrian Nunn.

A radionuclide generator based on ion-exchange chromatography was also developed to separate the 9.76 min half-life ^{62}Cu . This endeavour was too early for effective medical exploitation as the development of 'smart' chelating ligands with valuable biological properties, e.g. PTSM and ASTSM, would not take place for about another 25 years!

^{123}I iodohippuran for kidney studies and Rose Bengal for liver studies. $^{121}\text{Sb}(\alpha, 2n)^{123}\text{I}$, half-life 13.2 h, EC 159 keV gammas

When Anger gamma cameras became available, the gamma ray of ^{123}I was almost an ideal match for the instrument. $^{99\text{m}}\text{Tc}$ also had a good gamma ray energy of 141 keV, but little was known about its chemistry. However, iodination of bio-molecules was well established. Production of ^{123}I was set up using a similar target to that used for ^{124}I but in order to control the irradiation energy and energy loss in the antimony, thereby controlling the ^{124}I radionuclidic impurity, irradiations were carried out using the cyclotron's external beam. Wet chemical separations were used for the recovery of ^{123}I iodide.

Rose Bengal and hippuric acid were iodinated for liver and kidney function studies, respectively. Ian Watson and Peter Horlock looked after the chemistry and Les Baker devised a novel 'Rotary Chemistry' processing system which was a hot cell space saving idea.

Production of ^{123}I was eventually transferred to Harwell variable energy cyclotron (VEC) where higher yield and radionuclidic purity were possible using the $^{127}\text{I}(p, 5n)^{123}\text{Xe} \rightarrow ^{123}\text{I}$ reaction and was supplied as sodium iodide-123 for estimation of thyroid function.

^{203}Pb for lead tetraethyl combustion engine research Harwell and toxicity studies in children exposed to lead-based paints. $^{203}\text{Tl}(d, 2n)^{203}\text{Pb}$, half-life 52.1 h, EC and gammas

Environmental exposure to lead was and continues to be a cause of concern. The use of radiotracers of lead was required to aid the research into the mechanisms of lead sequestration from various sources and methods of exposure. A target was developed for the deuteron irradiation of thallium oxide together with a wet chemical separation of radionuclidically pure ^{203}Pb . In one application this was converted by researchers at UKAEA, Harwell into lead tetraethyl which was then added to gasoline (petrol) and used to generate exhaust fumes from a combustion engine thereby simulating the discharge of lead into the atmosphere by car exhausts. Ian Watson and Matthew Thakur looked after the radiochemical processing and Steve Waters product QC.

^{18}F fluoride, $^{16}\text{O}(\alpha, pn)^{18}\text{F}$, half-life 109.7 min, positrons

^{18}F -fluoride was initially required for dental studies but was soon found to be a valuable aid for bone metastases imaging using rectilinear scanners.

A water target was designed, manufactured from titanium to minimize loss of fluoride. As the extracted alpha particle was quite wide, a 'letter box'-shaped target was fitted. In order to avoid excessive pressures that might burst the thin Ti beam entry window, a Pd catalyst was introduced into the target headspace to recombine the radiolytic gases. Delivery of ^{18}F to many of the major London hospitals continued until other agents e.g. $^{99\text{m}}\text{Tc}$ polyphosphates were developed by Amersham and others. A further use of ^{18}F -fluoride was in the investigation of the mechanisms responsible for the incorporation of fluoride into plant toxins, trifluoroacetate in particular. This work was carried out at The University of Oxford. The target was devised by John Clark and David Silvester¹² and Ian Watson undertook the routine operation for the distribution service.

^{18}F fluoride and ^{18}F fluorine, $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$, half-life 109.7 min, positron

For applications where anhydrous fluoride was needed, neon gas was irradiated with deuterons in a similar system to that of the one described above for ^{43}K . However, organic compounds were absorbed onto the glass filter and studies were carried out to estimate the incorporation of ^{18}F into the organic molecules e.g. protected amino acid tetrafluoroborate precursors. The method was more successful than the classical wet chemistry approach and was used for the preparation of a series of fluoroamino acids for biological evaluation as imaging agents. John Clark devised the target system and Ron Goulding developed the radiolabelling methodology.⁵

As part of a study on the *in vivo* fate of inhaled chlorofluorocarbons (CFCs) used as propellants in drug inhalers at the time, the $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$ reaction was employed to incorporate ^{18}F into AgF_2 which was then used in an heterogeneous synthesis of Freon-11. The work was commissioned by Colin Dollery and his colleagues in the Department of Clinical Pharmacology, RPMS. Tony Palmer carried out the radiochemistry and John Clark devised a method for filling drug inhalers with the radioactive Freon-11.

Finally, when molecular $^{18}\text{F}_2$ was required for 'electrophilic' fluorinations of compounds, such as [^{18}F]FDG, [^{18}F]FDOPA and [^{18}F]5-fluorouracil, a nickel target and gas handling system were built. The target was built by John Clark and most of the electrophilic fluorinations were undertaken by Tony Palmer. The system remained in use until the introduction by Andy Roberts of the much higher yield 'two shoot' $^{18}\text{O}_2$ target methodology at the MRC CU in the mid-1990's.

^{77}Br for extracellular space. $^{75}\text{As}(\alpha,2\text{n})^{77}\text{Br}$, half-life 56 h, EC and gammas

^{82}Br had been used for some time in the estimation of whole body extracellular space using isotope dilution analysis. In order to enable a multi-radiotracer *in vivo* estimation of whole body sodium, potassium and extracellular space, ^{77}Br was developed. Gamma-ray spectroscopy on plasma samples would enable simultaneous estimation if the gamma ray could be resolved. Targets were prepared from As_2O_3 pressed into a grooved aluminium plate and irradiated in the external alpha particle beam. Wet chemical separation with distillation was used to recover ^{77}Br bromide by Adrian Nunn. He subsequently developed a high-beam current target based on a Cu/As alloy.

^{127}Xe , ^{79}Kr and $^{85\text{m}}\text{Kr}$ for cerebral blood flow and pulmonary ventilation studies. $^{127}\text{I}(\text{d},2\text{n})^{127}\text{Xe}$, half-life 36.4 d, EC gamma; $^{79}\text{Br}(\text{d},2\text{n})^{79}\text{Kr}$, half-life 34.5 h, positron EC and gammas; $^{84}\text{Kr}(\text{d},\text{p})^{85\text{m}}\text{Kr}$, half-life 4.48h, beta and 151 keV gamma

^{127}Xe and ^{79}Kr were both produced using fused sodium halide (NaI and NaBr, respectively) targets. The salt was melted onto grooved copper plates using induction heating under a mildly reducing atmosphere of 5% H_2/N_2 . Irradiation conditions were carefully controlled so as to avoid melting and subsequent loss of the rare gases. Solution of the target salt in a closed system allowed recovery of the rare gases in an inert gas. $^{85\text{m}}\text{Kr}$ was produced by the deuteron irradiation of natural krypton in a gas target. The target contents were recovered cryogenically leaving rubidium side products on the target walls. All the rare gas productions were carried out by John Clark.²⁵

^{111}In for infection imaging and white blood cell labelling. $^{109}\text{Ag}(\alpha,2\text{n})^{111}\text{In}$, half-life 2.83 d, EC and gammas

Silver electroplated onto a copper target plate was irradiated in the internal alpha particle beam of the cyclotron. Wet chemical recovery and purification yielded high radionuclidic purity and low trace metal contamination both essential for the effective radiolabelling of cells using either oxime or latterly tropolone. The methodology for radiolabelling blood cells in buffer with [^{111}In]oxime was first introduced and developed for imaging of inflammation and various infections¹⁷ and later extended using [^{111}In]tropolonate to labelling cells in plasma to help preserve cell integrity.²⁶ The crystal structure of the cell-labelling agent indium-tropolonate

was also determined.²⁷ The cell-labelling techniques developed at MRC CU are now widely used in hospitals worldwide. Matthew Thakur and John MacAfee¹⁴ and recently Frank Brady were responsible for the radiochemistry and Heather Danpure and Safiye Osman for the cell labelling.²⁶

The production of ¹¹¹In was subsequently transferred to the TRC at Amersham where a commercial cyclotron had been installed. As it was a proton-only machine, the ¹¹¹Cd(p,n)¹¹¹In reaction was employed using enriched ¹¹¹Cd.

⁶⁷Ga for soft tissue tumour imaging. ⁶⁵Cu(α,2n)⁶⁷Ga, half-life 78.3 h, EC and gammas

Copper targets were irradiated with alpha particles in the internal beam. Wet chemical recovery of gallium from the copper target chemical etch solution was carried out by using solvent extraction. The production of ⁶⁷Ga was transferred to TRC at Amersham where the proton route employing enriched ⁶⁷Zn(p,n)⁶⁷Ga reaction was used.

¹²⁹Cs and ¹³⁰Cs for myocardial blood flow studies. ¹²⁷I(α,2n)¹²⁹Cs, half-life 32 h, EC and gammas and ¹²⁷I(α,n)¹³⁰Cs, half-life 29.9 min, 46% positron EC

NaI powder pressed into a grooved aluminium target plate was irradiated with the external alpha particle beam with careful selection of the incident energy being controlled using aluminium degrader foils. Wet chemical recovery was carried out by solvent extraction of Cs from the NaI solution into an amyl acetate solution of sodium tetraphenyl boron. Back extraction into water returned the Cs radionuclides to the aqueous phase. Ian Watson developed the radiochemistry and Peter Horlock subsequently devised a method for making radioactive scrambled eggs using ¹²⁹Cs bound to zirconium phosphate, an inorganic ion exchanger, for use in stomach clearance studies.

⁸⁷Y/^{87m}Sr generator for bone imaging. ⁸⁵Rb(α,2n)⁸⁷Y/^{87m}Sr, half-lives 80.3 and 2.8 h, respectively. ^{87m}Sr IT gamma 388 keV

Fused RbCl targets were made by induction heating of the copper target plate. After irradiation in the external alpha particle beam the RbCl was dissolved and ⁸⁷Y coprecipitated with Fe carrier. Ion-exchange chromatography was then employed to separate the ⁸⁷Y from the Fe. An ion chromatographic radionuclide generator was developed using a dilute citric acid eluant to recover the ^{87m}Sr. Barry Hine and John Clark developed both the separation chemistry and the generator.

The demand for the generator soon outstripped the production capacity of this route and commercial production was undertaken by TRC at Amersham using ⁸⁸Sr(p,2n)⁸⁷Y reaction.

⁶⁸Ge/⁶⁸Ga generators. ⁶⁸Ge via ⁶⁶Zn(α, 2n)⁶⁸Ge half-life 275 d and Los Alamos LAMF spallation material

Radionuclide generators based on Al₂O₃ chromatography for ⁶⁸Ga (half-life 68 min) were available for many years, but the eluant contained EDTA which posed many problems in the subsequent chemistry to incorporate ⁶⁸Ga into potentially useful biomolecules. A SnO₂-based chromatographic generator was developed in collaboration with Los Alamos who were also able to supply the spallation-produced ⁶⁸Ge parent radionuclide. Some early attempts to produce ⁶⁸Ge by the alpha particle irradiation of Zn were limited in yield particularly as the target material was unsuitable for internal beam irradiation. The resulting radionuclide generator was eluted with dilute HCl, which could readily be removed from the ⁶⁸Ga solution, thereby allowing its usage with bi-functional chelating agents. Peter Horlock and John Clark collaborated with Hal O'Brien of Los Alamos on this project. A similar radionuclide generator was produced commercially by NEN.

²³⁷Pu for bioburden studies

The fate of ²³⁹Pu (half-life 2.45 × 10⁴ y) when it has entered biological systems, especially man, is of crucial importance as it is both chemically highly toxic and also radiotoxic. It occurs as a by-product of the operation of nuclear fission reactors.

Irradiations of ²³⁵U targets with alpha particles were undertaken in collaboration with the biotoxicity team at AERE Harwell. The aim was to produce high specific radioactivity ²³⁷Pu, half-life 45.6 d. The highly enriched ²³⁵U target was prepared at Harwell by welding an aluminium/uranium alloy foil to an aluminium target plate. As no facilities were available at MRC CU for processing alpha emitters, the whole target was returned to Harwell for processing.

²¹¹At (half-life 7.2 h) alpha EC for *in vivo* radiotherapy

Alpha emitters are highly radiotoxic and if suitable radionuclides and biological forms could be synthesized, targeted *in vivo* radiotherapy might be achievable.

Astatine was thought to be a suitable candidate for these purposes and MRC CU was asked to explore the production of ²¹¹At. Bismuth targets were irradiated in

the external alpha particle beam. Initially, chemical recovery of the astatine was carried out by the off-site users where the incorporation of astatine into the targeting agent was also undertaken.

^{81}Rb for myocardial imaging and $^{81\text{m}}\text{Kr}$ radionuclide generator. $^{79}\text{Br}(\alpha,2n)^{81}\text{Rb}$, half-life 4.56 h, positron gamma, daughter $^{81\text{m}}\text{Kr}$, half-life 13 s, gamma 190 keV

Initially, ^{81}Rb was prepared for evaluation as a myocardial imaging agent as part of the continuing search for alkali metal radionuclides with suitable biological and radiation characteristics.

It was discovered that the radiogenic $^{81\text{m}}\text{Kr}$ gas could be harvested either in the gas phase or, with a novel inorganic ion-exchange column, in solution phase. Both forms were of interest for evaluation as ventilation and perfusion agents, especially as the newly introduced Anger Gamma cameras were well suited to the gamma emission energy of 190 keV.¹³

The demand quickly grew and generators were supplied to hospitals all over the UK and Europe and on several occasions were sent to Baltimore by Concorde, the supersonic airliner operated by the British Airways. The $^{81\text{m}}\text{Kr}$ generator has been available from MRC CU for subsequent 30 years, aided by the VEC at Harwell and the University of Birmingham cyclotron, during shutdown periods at MRC CU.

$^{81\text{m}}\text{Kr}$ became the gold standard along with $^{99\text{m}}\text{Tc}$ microspheres for perfusion/ventilation imaging and still remains the method of choice for detection of pulmonary embolism. Over 1 000 000 patients have benefited. The production ended in 2005 and was transferred to Birmingham University to ensure continuity of supplies.

A brief review of this nature cannot do full justice to the immense amount of original work that has been carried out at MRC CU on the production and applications of short-lived radioactive gases. In 1975, however, the two key figures in this work, John Clark and Peter Buckingham, published a monograph²⁵ on the production methods they were chiefly responsible for developing, and this has since then been recognized internationally as a standard reference work on the subject.

1979–2001

General

The Period following the introduction of the first PET scanner at the MRC CU in 1979 was one of intense activity which led to major achievements in both the

radiochemistry and the clinical PET programmes. It was also a period of ongoing change in terms of both management and remit with Terry Jones becoming Acting Director with Keith Gibson as Administrative Director following retirement of Derek Vonberg in the mid-1980s.

By the end of the previous period, and under the continuing leadership of David Silvester, a core organic chemistry group was emerging with Tony Palmer and Ron Goulding complemented by Vic Pike. This group was enlarged soon afterwards by the addition of Frank Brady, Dave Turton, Sajinder Luthra and Farah Shah.

The cell-labelling programme was run under the guidance of Heather Danpure and Safiye Osman.

Bruce MacKay, Malcolm Simpson and Mike Renton were responsible for running and maintaining the cyclotrons (Scanditronix MC 40, IBA Cyclone 3D) following the retirement of Geoff Burton.

The targetry and automation group led by John Clark was strengthened by the addition of Cyril Brown, Colin Steel and Keith Dowsett.

The Operations Group, under Ian Watson, was responsible both for routine production for the in-house clinical PET programme and 'off-site' sales of radiopharmaceuticals, while the quality control aspects were managed by Steve Waters and Malcolm Kensett initially.

All these people played a pivotal role, in this and the subsequent period, in establishing the CU as a centre of excellence in PET chemistry. The group was successful in making available a range of radiopharmaceuticals and in initiating a metabolite analysis programme in support of increasingly demanding clinical PET studies.

Meanwhile, PET had evolved into a more powerful technique. It had achieved higher sensitivity, higher resolution, greater field of view and significantly improved quantification. It had also advanced with respect to the range and specificity of radiotracers that could be used with respect to the types of measurements that could be carried out. As a consequence, the technique attracted increasing interest from research clinicians for a wide range of disciplines both within the MRC, the RPMS and further a field. The pharmaceutical industry and medical charities began to appreciate the scientific and economic potential and value that PET could have in drug development. With the encouragement of the MRC CU, they increasingly sought to be involved in exploitation of PET. The MRC CU strengthened its role as a national resource and it was vital for it to respond to these challenges for the general good of health care and wealth creation by building from existing foundations towards excellence in radiopharmaceutical science.

During this period, the existing facilities were upgraded and new methodologies and technologies developed to allow radiolabelling of specific molecular imaging probes. This required the installation of new hot cells to house remotely controlled and semi-automated radiosyntheses systems such as those required for [^{18}F]FDOPA, [^{18}F]FU and [^{18}F]FDG, as well as for the daily production of ^{81}Rb and for subsequent production of $^{81\text{m}}\text{Kr}$ generators.

A great deal of the clinical research with the PET scanners focussed on the use of oxygen-15 for brain studies during this time. A range of carbon-11-labelled compounds were produced during this period despite an ageing cyclotron and only an 8 MeV proton beam.

During 1985–1987, a new MC40 Scanditronix cyclotron (multiple particle and variable energy) with a large and complex system of beam lines and radioactive gas delivery systems was installed.

This period also presented an opportunity for some staff members to undertake sabbaticals abroad to consolidate experience. Sajinder Luthra, Vic Pike, John Clark and Peter Horlock spent a year either living in or commuting to Orsay PET Centre and Frank Brady went to Sendai PET centre at Tohoku University for a year, working on $^{18}\text{F}^{28,29}$ and $^{11}\text{C}^{30,31}$ radiochemistry. These were complemented by a number of other non-chemistry scientists in the MRC CU visiting other PET centres. The results of these sabbaticals meant that new concepts and ideas flowed back into the unit when the programmes re-started after installation of the new cyclotron.

The Chemistry section of the MRC CU evolved considerably after the installation of the new cyclotron. At that time, the immediate needs were to set up the production of a range of valuable, positron-emitting radiotracers for the growing clinical PET programmes (see Table 3). These tracers were requested to drive the clinical research programmes in Neurology directed by Richard Fracowiack and later David Brooks and

Table 3 Some examples of Radiotracers produced at the MRC CU/HIL for preclinical and clinical studies

<i>Neurosciences</i>	
[^{11}C]Flumazenil	Central benzodizepine
[^{11}C]SCH 23390	D ₁
[^{11}C]Raclopride	D ₂
β -[^{11}C]CFT	DA transporter
β -[^{11}C]RTI-55	DA transporter
[^{11}C]CNS 5161	NMDA – ion channel site
[^{11}C]DASB	Serotonin reuptake site
L-[^{11}C]Deprenyl	Monoamine oxidase B
[^{11}C]Diprenorphine	Opiate receptors
[^{11}C]FLB 457	Dopamine D ₂ receptors
[^{11}C]GR 205171	Neurokinin NK ₁ receptors
[^{11}C]MDL 100907	Serotonergic 5-HT _{2A} receptors

[^{11}C]PIB or 6-OH-[^{11}C]BTA-1	Fibrillar amyloid marker
R-[^{11}C]PK 11195	PK-binding site
[^{11}C]Ro 15-4513	GABAA (α -5 subunit)
[^{11}C]RTI 32	Dopamine re-uptake site
[^{11}C]SCH 442416	Adenosine A _{2A} receptors
[<i>carbonyl</i> - ^{11}C]WAY-100635	Serotonergic 5-HT _{1A} receptors
[<i>methyl</i> - ^{11}C]WAY-100635	Serotonergic 5-HT _{1A} receptors
[^{18}F]FDOPA	Presynaptic dopamine neurons
[^{18}F]FMT	Presynaptic dopamine neurons

Cardiology

[^{11}C]Microspheres	Blood flow
<i>m</i> -[^{11}C]Hydroxyephedrine	Noradrenaline uptake site
[^{11}C]Acetate	Mycocardial oxygen metabolism
[^{18}F]5-Fluoro thymidine	Antisense probe precursor
6-L-[^{18}F]Fluorodopamine	Experimental tracer
[^{18}F]Fluoroethyl analogue of thymidine	Antisense probe precursor
[<i>N-methyl</i> - ^{11}C]Acetyl-L-carnitine	Metabolite
[<i>N-methyl</i> - ^{11}C]L-Carnitine	Metabolite
[1- ^{11}C]Propionate	Metabolite
[^{11}C]Propionyl-S-CoA	Metabolite
S-[^{11}C]CGP 12177	β -Adrenergic receptors
[^{11}C]GB-67	α_1 -Adrenoceptors

Oncology

[^{11}C]DACA	Anticancer drug
Analogues of DACA	
[^{11}C]SN23490, [^{11}C]SN 23719 and [^{11}C]SN 23935	Anticancer drugs
[<i>N-methyl</i> - ^{11}C]Temozolomide	Anticancer prodrug
[<i>carbonyl</i> - ^{11}C]Temozolomide	Anticancer prodrug
2-[^{11}C]Thymidine	Cell proliferation
2-[^{11}C]Thymine	Metabolite
[^{11}C]Bicarbonate	Metabolite
[^{11}C]Choline	Choline metabolism
[^{18}F]Fluoroetanidazole	Hypoxia marker
[^{18}F]Fluorothymidine (FLT)	TK-1 (proliferation)
5-[^{18}F]FU	Anticancer drug
Na ^{124}I	Gene expression

Pharmaceutical Industry

[<i>N-methyl</i> - ^{11}C]PLC	Drug
[<i>ester</i> - ^{11}C]PLC	Drug
[^{18}F]Fluticasone propionate	Drug
1-[^{18}F]HFA 134a	Drug propellant
2-[^{18}F]HFA 134a	Drug propellant
1-[^{18}F]HFA 227	Drug propellant
2-[^{18}F]HFA 227	Drug propellant

Pulmonary

[^{15}O]CO	Blood volume
S-[^{11}C]CGP 12177	β -Adrenergic receptors
R-[^{11}C]PK 11195	Inflammation

General Tracers

H ₂ ^{15}O	Blood flow
C $^{15}\text{O}_2$	Blood flow
C ^{15}O	Blood volume
[^{15}O]O ₂	Oxygen consumption
[^{18}F]FDG	Glucose metabolism

Cardiology (Paolo Camici) with a smaller Pulmonary component (Mike Hughes, Phillip Ind, HH). Ray Dolan, Peter Liddle, Karl Friston, Kris Frith and later Paul Grasby led the introduction of the Psychiatry programme. Pat Price was responsible for the clinical PET Oncology programme. The chemistry R&D group worked closely with the PET Biology (Sue Hume and Ralph Myers), Modelling (Adrian Lammertsma and Vin Cunningham) and Physics (Terry Spinks, Peter Bloomfield and Chris Rhodes) groups underpinning the MRC clinical PET programmes. It also fostered collaborations with external research programmes such as those involving the pharmaceutical industry, medical charities and academia. It also supported the in-house chemistry Operations group which provided a regular and safe supply of high-quality radiopharmaceuticals for the clinical PET programmes.

With a firm operational base in place, it was possible to place more emphasis on basic radiochemical research, particularly as the research chemists Vic Pike, Frank Brady and Sajinder Luthra were successful in obtaining major external support from pharmaceutical industry and medical charities. The Cancer Research Campaign through its New Anti-Cancer Agents Committee also helped them to establish a PET Oncology clinical programme led by Pat Price.

With the retirement in 1994 of the Group Head, David Silvester, after a long and distinguished service, Vic Pike was appointed as Head of Chemistry & Engineering in October 1996 and was awarded an honorary chair at the University of Sussex.

Towards the end of this period John Clark moved to Cambridge to set up the Wolfson Brain Imaging centre at the University of Cambridge, joined shortly thereafter by Franklin Aighibirio from the MRC CU. Colin Steel took on the role of leading the automation and targetry group. Terry Jones relocated to establish the Wolfson Molecular Imaging Centre, University of Manchester, while Vic Pike moved to the USA to set up a group at NIMH at Washington. Frank Brady and Sajinder Luthra remained to steer the PET chemistry programme. Matthias Glaser, Yongjun Zhao and Ed Robins joined the chemistry group during this period.

Chemistry group remit

Under the remit of the MRC during this period, the main scientific and technical objectives of the Chemistry-Engineering Group were to:

- (i) advance core radiochemical science to provide a strong methodological foundation for the in-house PET programmes

- (ii) develop specific radiotracers for PET studies of biochemical pathways and of the disposition and pharmacokinetics of drug entities and
- (iii) develop radioligands specific for binding sites or receptors *in vivo* for the MRC clinical research programmes in Neurology, Cardiology, Psychiatry and Oncology and in-house Neurobiology as well as projects for Pharmaceutical industry.
- (iv) carry out the organic chemistry needed for developing the radiochemistry and providing precursors for radiolabelling.
- (v) advance cyclotron targetry, automation of radio-syntheses and systems for metabolite analysis.
- (vi) maintain viable QC and metabolite analysis programmes.
- (vii) provide a supply of important radionuclide tracers through the Chemistry Operations Group to other hospitals and research centres, mainly in the UK but occasionally in Europe or the US.

The following section will describe some key developments in PET radiochemistry and automation including metabolite analysis and analytical chemistry during this period.

Chemistry developments

Carbon-11

The vast majority of organic radiopharmaceuticals used for PET are labelled with carbon-11 (half-life 20.4 min). At the MRC CU, low-volume gas targets were used routinely for producing carbon-11 as either [¹¹C]carbon dioxide or [¹¹C]methane.

Apart from radioactive gases, some of the first carbon-11 labelling agents used at the CU were [¹¹C]formaldehyde and [¹¹C]Grignard reagents. The latter was used to prepare [¹¹C]acetate³² and other [¹¹C]fatty acids³³ for cardiology of PET studies. [¹¹C]Formaldehyde was used to radiolabel the antibiotic Erythromycin³⁴ (Figure 1) by reductive alkylation for pulmonary studies. This was probably the first pharmacokinetic PET study commissioned by the Pharmaceutical industry.

In 1981, a system for the production of [¹¹C]iodomethane was assembled and used by Dave Turton. This was soon applied for labelling of [¹¹C]albumin and [¹¹C]microspheres³⁵ which overcame the problems associated with trying to attach chelated positron-emitting cations such as ⁶⁸Ga to protein microspheres since the latter were prone to rapid de-metallation *in vivo* by transferrin. Around this early period, [¹¹C]methylglucose and uniformly labelled [¹¹C]glucose were prepared for clinical studies in cardiology.

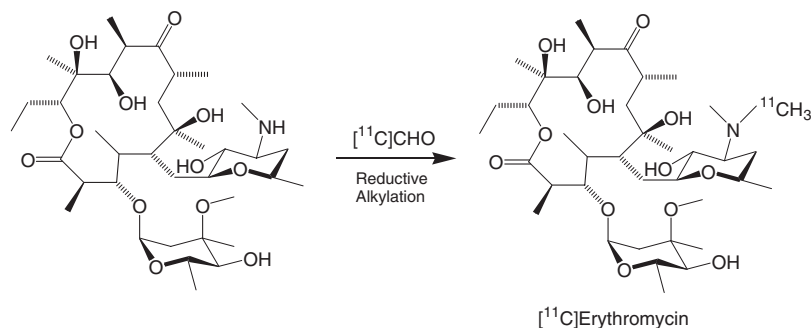


Figure 1 Synthesis of [¹¹C]Erythromycin.

Uniformly labelled [¹¹C]glucose was made from [¹¹C]CO₂ using green algae. This filled the lab with bottles of green slime, in the process of developing co-labelling with ¹¹C and ¹³C in order to get enough material for the first carbon-13 NMR, at the then enormously high frequency of 100 MHz, to demonstrate the positions of incorporation of the carbon-11 radiolabel.³⁶

The work on the use of alkylating agents also continued and the D₂ receptor ligand [¹¹C]methylspiperone was radiolabelled using [¹¹C]iodomethane produced by the wet method. The world's first human combined PET study of dopamine storage and D₂ receptor density was carried out using [¹⁸F]DOPA and [¹¹C]methylspiperone, respectively. The normal volunteer was Norman Veal, the veteran and pioneer of medical applications of radionuclides. In common with other centres [¹¹C]CH₃X (X = iodide, triflate) has been employed for labelling a wide range of radiopharmaceuticals. Another illustrative example was labelling the potential anti-cancer agent, topoisomerase I and II inhibitor, DACA³⁷ and some of its DNA-intercalating analogues³⁸ at the request of the drug development group at the University of Auckland (Baguley and Denny) as a potential aid to their drug development programme. The work with DACA was the first example of the use of a radiolabelled anticancer drug being studied in man prior to phase one clinical trials,³⁹ a concept later termed as microdosing.⁴⁰ More efficient methods of ¹¹CH₃I production were under development and during a sabbatical at The University of Washington, Seattle, USA, John Clark contributed to the work on developing the radiosynthesis of [¹¹C]CH₃I from methane.⁴¹

The availability of a wide range of labelling agents is crucial for providing synthetic versatility allowing PET chemists to tackle the radiolabelling of a greater range of structural types. Throughout the period, we continued to extend the range of ¹¹C, ¹⁸F and ¹²⁴I labelling agents for both small and macromolecules and this work went hand in hand with and underpinned the

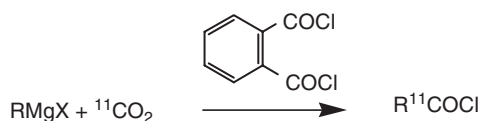


Figure 2 Synthesis of [¹¹C]acid chlorides.

development of novel tracers. Some of the ¹¹C-labelling agents developed and introduced are described below and some examples of their application are outlined. Examples for ¹⁸F and ¹²⁴I are given under the appropriate sections.

[¹¹C]acid chlorides. The radiosyntheses of a range of important [¹¹C]acid chlorides^{42,43} was developed (Figure 2) and these were applied to the radiosynthesis of the opiate antagonist, [¹¹C]diprenorphine⁴⁴ as well as the mixed agonist/antagonist, [¹¹C]buprenorphine³⁰ (Figure 3), and the selective α₁-adrenoreceptor ligand, [¹¹C]prazosin³¹ by acylation followed by reduction of the carbonyl group (Figure 2).

The production of [¹¹C]diprenorphine enabled the first imaging of the opiate receptor system at the MRC CU. However, this route was somewhat problematic as it produced large amounts of alum, an intractable material, during the reduction step which tended to clog apparatus and the synthesis was later superseded by an improved method using [¹¹C]methylation.⁴⁵ (Figure 4).

The effective production and use of [¹¹C]Grignards and [¹¹C]acid chlorides was extended by introducing an innovative technique, based on [¹¹C]carboxylation of 'immobilized' aryl or alkylmagnesium halides.^{46–52} The technique was applied to the production of a wide range of [¹¹C]acid chlorides, regardless of volatility. Very high specific radioactivities were obtained, even when using commercial organomagnesium halides. Such agents were applied to the labelling of many compounds, such as [¹¹C]acetate and propionyl-L-carnitine⁴⁸ for myocardial fatty acid metabolism. The first successful radioligand for imaging the 5-HT_{1A} receptors,

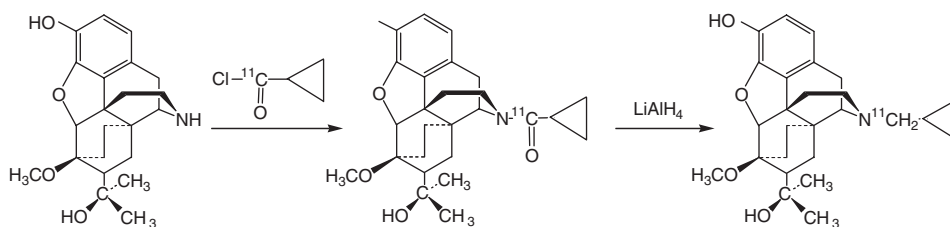


Figure 3 Synthesis of [carbonyl- ^{11}C]diprenorphine using [^{11}C]cyclopropanecarbonyl chloride.

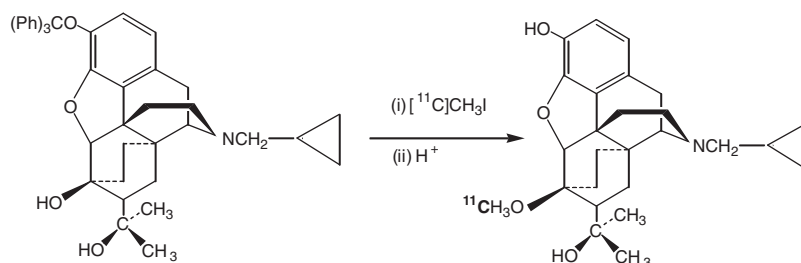


Figure 4 Synthesis of [methyl- ^{11}C]diprenorphine from [^{11}C]methyl iodide.

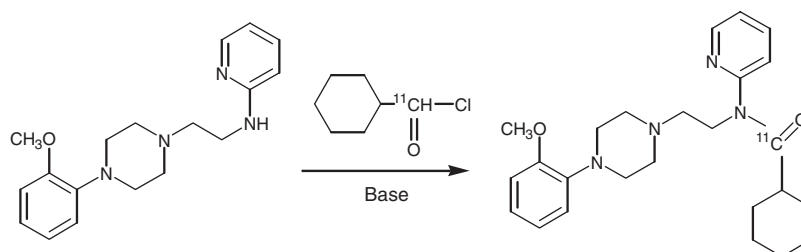


Figure 5 Synthesis of [carbonyl- ^{11}C]WAY 100635.

[methyl- ^{11}C]WAY-100635⁵¹, was developed by Vic Pike. The synthesis of this radioligand was subsequently improved⁵² by a rational approach taking into account findings on *in vivo* metabolism. [carbonyl- ^{11}C]WAY-100635 was synthesized using [^{11}C]cyclohexyl acid chloride (Figure 5) and this permitted the exquisite delineation of the 5-HT_{1A} receptors in human brains.⁵² [^{11}C]WAY 100635 has initiated the development of a wide range of ^{11}C and ^{18}F analogues at PET centres worldwide.

[^{11}C]phosgene. This was recognized early as an important synthon and the synthesis of [^{11}C]phosgene was introduced to the MRC CU in 1987.⁵³ This proved to be a troublesome and difficult radiosynthesis to reproduce as many groups have since found out. The grade and quality of the iron catalyst used was one of the major associated problems at the time, resulting in a lot of development work to optimize the radiosynthesis initially applied to the synthesis of the β -adrenergic ligand, [^{11}C]CGP-12177 by heterocyclic ring formation.⁵⁴ The importance of chirality for

improving the *in vivo* efficacy of PET radiotracers was already evident and the significant success in organic chemistry contributed to the development of improved homochiral radioligands and S-[^{11}C]CGP 12177 was an example.

Subsequent improvements to the radiosynthesis of [^{11}C]phosgene were carried out using liquid ammonia for the synthesis permitting more reliable production of and applying it to the synthesis of [^{11}C]isocyanates⁵⁵ (see below) and 2-[^{11}C]thymidine,⁵⁶ a marker of cellular proliferation in oncology. The synthesis of 2-[^{11}C]thymidine is a challenging multi-step procedure which pushes the limits of what is currently achievable with ^{11}C .

[^{11}C]isocyanates. Organoisocyanates are versatile reagents particularly useful for cyclization reactions forming heterocyclic rings. Additionally, ^{11}C can be incorporated into either the organo or the carbonyl group. The radiosyntheses of a series of [^{11}C]alkyl isocyanates⁵⁵ (RN ^{11}C O, R = Me, Et, Pr, Ph) by reaction of *N*-organosulphonyls (A) or *N,N*-organoureas (B) with [^{11}C]phosgene have been developed (Figure 6).

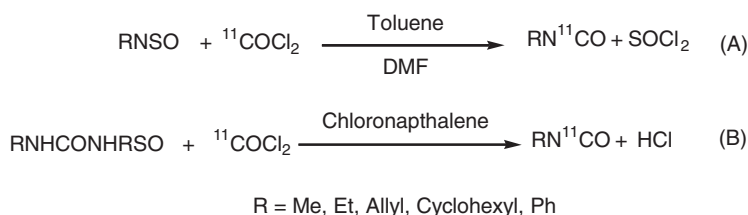


Figure 6 Synthesis of [carbonyl- ^{11}C]isocyanates.

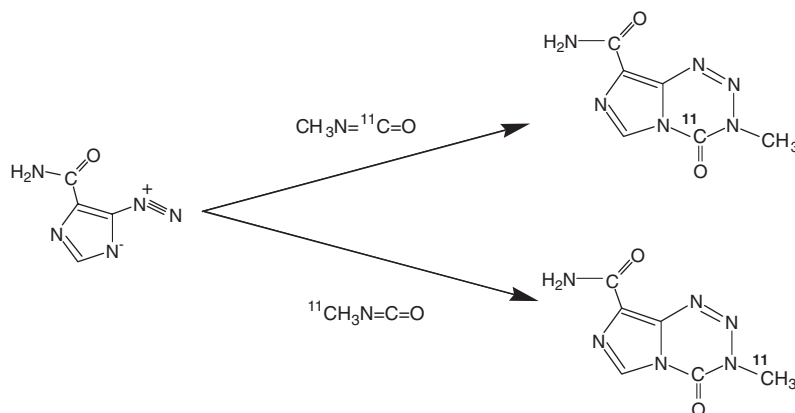


Figure 7 Synthesis of [carbonyl- ^{11}C] and [methyl- ^{11}C]Temozolomide.

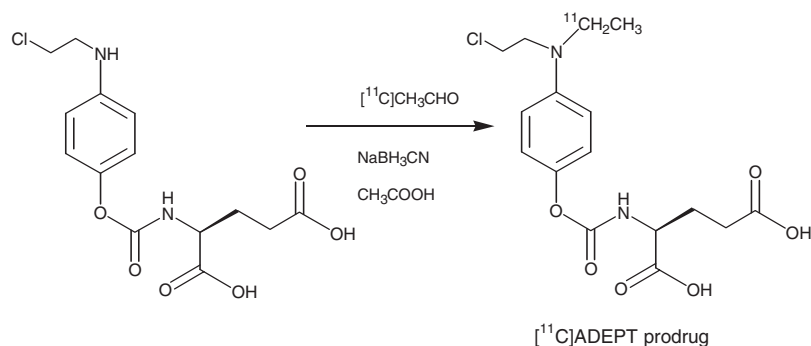


Figure 8 Synthesis of [^{11}C]ADEPT half-mustard prodrug.

[^{11}C]isocyanates have been used to radiolabel the anti-glioma and melanoma prodrug temozolomide in two different positions, either in the *N*-methyl or 4-carbonyl position using [^{11}C -methyl]isocyanate or 4-[^{11}C -carbonyl]methylisocyanate⁵⁷ or 4-[^{11}C -carbonyl]methylisocyanate, respectively (Figure 7). This was as part of a study to validate the proposed mode of action of this DNA-alkylating prodrug which was postulated to act by ring opening with loss of CO_2 to form an alkylating diazo species and we were able to confirm this *in vivo* by comparison of the methyl and carbonyl labelled forms.⁵⁸ Studies with [^{11}C]temozolomide also paralleled a clinical Phase II study. Temozolomide is now

the frontline agent for treating brain gliomas in conjunction with radiotherapy.

[^{11}C]aldehydes and [^{11}C]ketones. An on-line method for the useful and versatile synthons, aliphatic [^{11}C]aldehydes, was developed by oxidation of [^{11}C]alcohols and one of these, [^{11}C]acetaldehyde has been used to radiolabel a potential DNA-alkylating half-mustard, an anti-cancer ADEPT prodrug (Figure 8).⁵⁹

Iodonium salts have been introduced at the MRC CU for the novel syntheses of [^{11}C]ketones and [^{11}C]benzophenones via Pd-mediated [^{11}C]carbonylation using [^{11}C]CO.⁶⁰

[¹¹C]alkenes. Alkenes have a rich chemistry, but have been less explored as labelling agents. No-carrier-added (NCA) [¹¹C]ethylene was produced by pyrolysis of [¹¹C]ethanol and showed that a similar technique could be used to produce 1-[¹¹C]propene and 2-[¹¹C]propene and their 1,2-dibromo derivatives. Subsequently, an improved synthesis of [¹¹C]ethylene from [¹¹C]ethyl iodide. [¹¹C]Ethylene was converted into novel 1,2-disubstituted ethanes, namely [¹¹C]1,2-dibromoethane, 1-[¹¹C]chloro-2-iodoethane, 1-[¹¹C]chloro-2-triflate-ethane and 1-[¹¹C]chloro-2-tosylatoethane for application as labelling agents.^{61–64}

Meanwhile, development of novel PET tracers continued in parallel. At the time, the criteria required for successful PET tracers were less clear than they are today and many of those produced failed at one step or another during the development process as was common at many other centres. However, this lack of rationale for tracer selection was beginning to be addressed and some essential criteria were being established.⁶⁵ This of course still represents a major stumbling block in PET radiochemistry and efforts to overcome it by clarifying the physicochemical requirements for good tracers have continued. A computational approach was initiated at the MRC CU by setting up a database of PET radiotracers and associated physicochemical properties and attempts begun to correlate these with *in vivo* usefulness of the tracers concerned with a view to predicting efficacy based on physicochemical properties.^{66,67}

FLUORINE-18

Following the introduction of the method of cyclotron production of [¹⁸F]Fluoride from the cyclotron during the earlier period, [¹⁸F]fluoride continues to be produced in high yield and specific radioactivity by the ¹⁸O(p,n)¹⁸F reaction on ¹⁸O-enriched water. Record yields of molecular [¹⁸F]fluorine were produced by proton irradiation of oxygen-18 gas and re-irradiation in the presence of fluorine.^{68,69} This development was a key factor with regard to greatly increasing the yield of some radiotracers e.g. [¹⁸F]FDOPA. Fluorine-18 has

been used for numerous radiolabelling projects and illustrative contributions are described here.

[¹⁸F]MK 801 analogues. One of the earliest projects at MRC CU with [¹⁸F]fluoride was the synthesis of fluoro analogues [¹⁸F]fluoromethyl- and [¹⁸F]fluoromethyl MK 801, an NMDA ion channel blocker and a putative neuroprotective agent, for human PET studies.⁷⁰ This was a ring opening and displacement reaction on cyclic sulphamates as shown in Figure 9. This work was in collaboration with MSD Neurosciences R&D centre at Terlings Park, UK.

Iodonium chemistry. Iodonium salts are useful compounds that have allowed the introduction of ¹⁸F by [¹⁸F]fluoridation⁷¹ reactions (Figure 10). In collaboration with Imperial College, a novel facile synthesis of iodonium salts by reaction of aryltributylstannanes with Koser's reagent⁷² or aryl boronic acids⁷³ has been developed. The iodonium approach has been used to carry out [¹⁸F]fluoridation of aromatic and aromatic and heteroaromatic compounds including pyrimidines⁷⁴ which are not activated for nucleophilic substitution. An investigation into the mechanism of stereoselective control of fluoridation of iodonium salts using molecular modelling gave a better understanding of the behaviour and use of these reagents.⁷⁵

[¹⁸F]xenon difluoride. In collaboration with University of Keele, a synthesis of [¹⁸F]XeF₂ from [¹⁸F]fluoride⁷⁶ was developed giving access to a 'non-nucleophilic' source of [¹⁸F]fluorine.

[¹⁸F]fluorohaloxylens. Synthesis of ¹⁸F synthons suitable for easy attachment to peptides and other

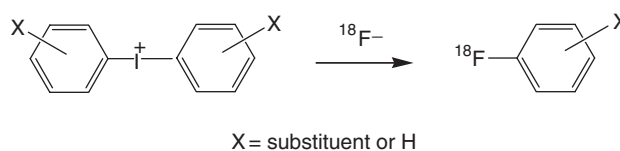


Figure 10 [¹⁸F]Fluoridation via iodonium salts.

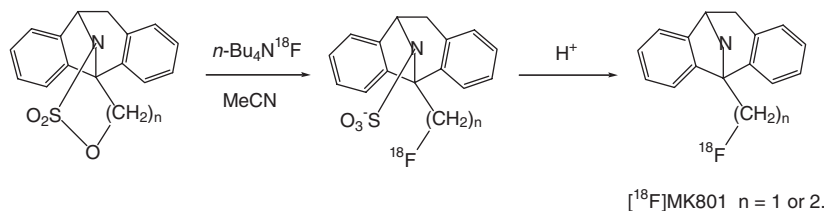


Figure 9 Synthesis of [¹⁸F]fluoroanalogues of MK 801.

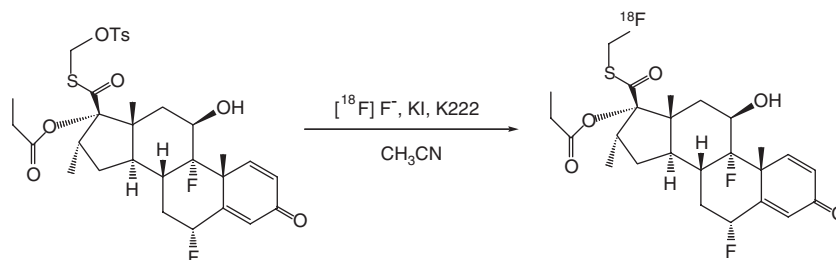


Figure 11 [^{18}F]Fluticasone propionate.

macromolecules is highly desirable. To extend the limited range of those available for this purpose, methods have been developed for synthesizing a series of *ortho*-, *meta*- and *para*-[^{18}F]fluoromethylhaloxylens.⁷⁷

[^{18}F]fluoroalkanes. The labelling of aerosol propellants as alternatives to CFCs was explored with Glaxo Wellcome. Simple hydrofluoroalkanes (HFA) were labelled with [^{18}F]fluoride⁷⁸ by either nucleophilic substitution or nucleophilic addition to give the aerosol propellant 1,1,1,2-tetrafluoroethane ([^{18}F]HFA 134a).⁷⁹ The deposition of inhaled [^{18}F]HFA 134a was investigated in man using PET.

[^{18}F]fluticasone. One example of [^{18}F]fluoridation was radiolabelling of fluticasone propionate (FP), a potent anti-inflammatory synthetic steroid, used for the treatment of asthma. FlixotideTM is a formulated pressurized metered-dose inhaler (pMDI) that contains small micronized FP particles in a blend of CFC propellants. A method of labelling FP in FlixotideTM pMDIs with ^{18}F was developed (Figure 11).^{80,81} FP particles from Flixotide pMDIs were mixed with [^{18}F]FP formulated into a pMDI and sonicated at room temperature. The drug delivery of [^{18}F]FP pMDI was assessed for particle size distribution and dose uniformity. The distributions of [^{18}F]FP was used for the regional measurement of lung deposition for inhaled FP in human subjects with PET. Vic Pike, Franklin Aigbirhio, Steve Waters and Maria Constantinou were the main contributors to this project in collaboration with Glaxo Wellcome.

IODINE-124

A dedicated facility for the production and safe handling of the positron emitter ^{124}I ($t_{1/2} = 4.2$ days) was set up. An improved [^{124}Te]TeO₂ target and recovery system for the production and recovery was established.⁸² ^{124}I was also supplied to a number of other PET centres (e.g. Memorial Sloan-Kettering, Melbourne and Aarhus).

Improved [^{124}I] synthons. The synthesis of the *N*-succinimidyl-3-trimethyltetramethylstannyl benzoate (mMeATE) precursor has been considerably improved through the use of *O*-(*N*-succinimidyl)-1,1,3,3-tetramethyluroniumtetrafluoro borate. *N*-succinimidyl-3-[^{124}I]iodobenzoate ([^{124}I]m-SIB) was prepared from mMeATE8.^{83,84} Examples of the use of ^{124}I -labelled tracers synthesized by Matthias Glaser were annexinV⁸⁵ for apoptosis, an anti-VEGF antibody⁸⁴ for angiogenesis and iodinsulin⁸⁶ for biological evaluation in cardiac work (Figure 12).

Radiochemistry automation

Automated 'on-line' delivery of ^{15}O -labelled radiotracers

Oxygen-15-labelled tracers provide some of the most fundamental and useful measurements with PET, for example, of blood flow in studies of 'brain activation' and coronary flow reserve with [^{15}O]water. The very short half-life of oxygen-15 ($t_{1/2} = 2$ min) poses its own challenges for controlled production and delivery of acceptable radiopharmaceutical forms ([^{15}O]water, [^{15}O]oxygen, [^{15}O]carbon dioxide, [^{15}O]carbon monoxide) to human subjects. In 1991, the importance of oxygen-15 radiotracers in the PET programme at the CU warranted the purchase of a compact low-energy, 3 MeV, cyclotron (the IBA Cyclone 3D) to be dedicated to its production.

In 1979, ^{15}O -labelled gases were delivered to only one PET scanner with manual quality control but advanced to a sophisticated servomechanism and with limited quantitation. The labelled gases are now delivered to three PET scanners. The simplification of the system design provides a 3- to 4-fold increase in yield. Quality control was now on-line and extensively automated.

A 'bed-side' device for the safe hands-off infusion of [^{15}O]water to human subjects in PET experiments was developed, by John Clark and Henri-Tochon Danguy, *de novo*.⁸⁷ The device is based on palladium-catalysed conversion of [^{15}O]oxygen gas into [^{15}O]water at the

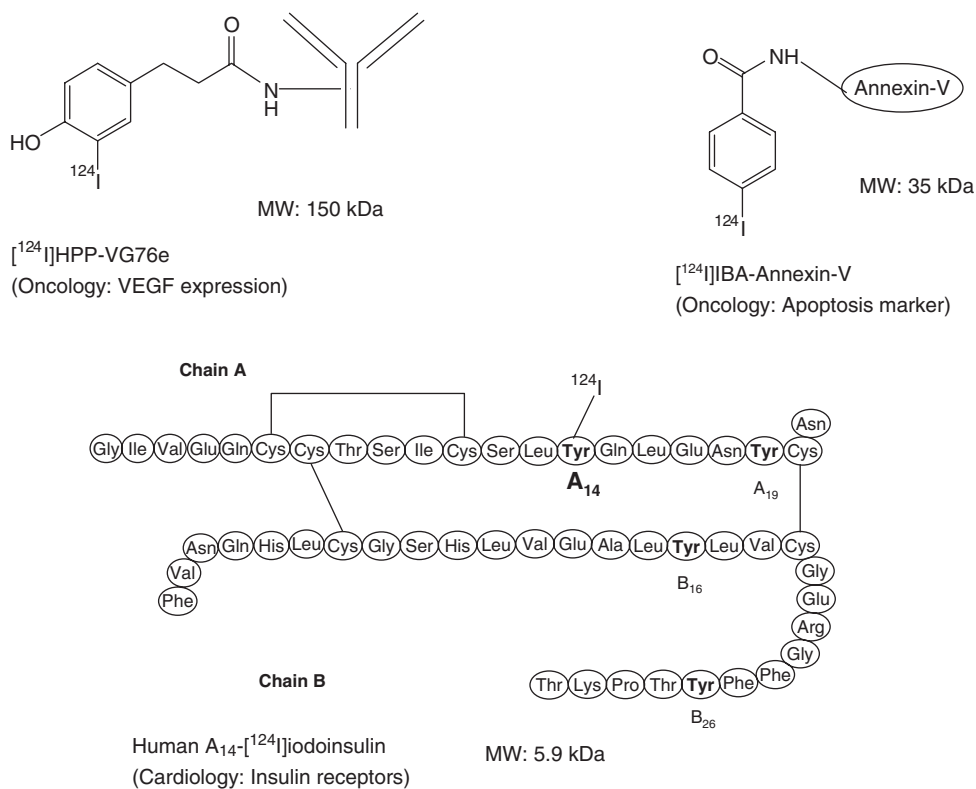


Figure 12 Some I-124-labelled tracers.

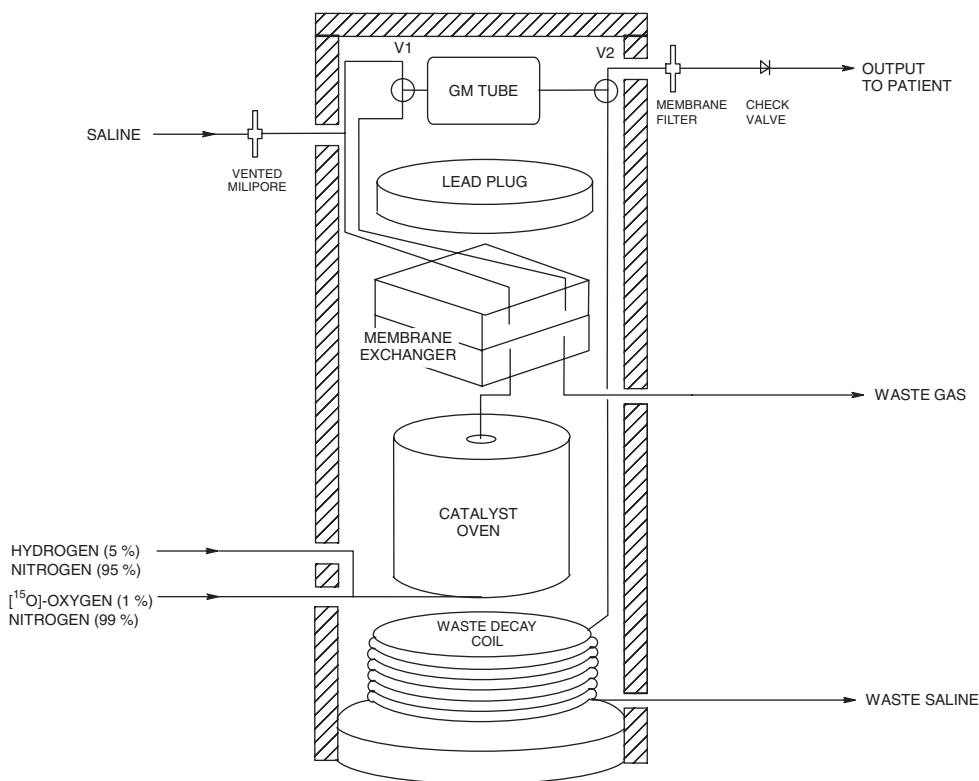


Figure 13 [¹⁵O]water generator.

PET scanner bedside. The [^{15}O]water is introduced into sterile saline across a semi-permeable membrane exchanger for administration by intravenous infusion (Figure 13). A stand-alone microcontroller accurately times the delivery of the [^{15}O]water and Windows software provides a user-friendly PC-based operator interface.

The device can be operated repeatedly for accurate dose preparation, measurement and delivery and is well accepted by patients and volunteers. The quiescent nature of the process allows its use in sophisticated studies of blood flow during brain activation paradigms. Three such devices were built and were operating intensely in the Unit. With our cooperation and assistance, this device has been copied or installed at number of other centres worldwide. This is now a commercial device with GMP compatible components (HIDEX).

Automation of radiotracer syntheses

The group has been successful in the complete automation of the production of a large range of ^{11}C - and ^{18}F -labelled radiopharmaceuticals, regardless of the complexity of radiosynthesis. This enabled the CU to produce a wide range of radiopharmaceuticals continuously available to clinical and biological researchers. Table 4 lists the radiotracers available at the centre.

Most radiosyntheses with short-lived ^{11}C and ^{18}F must begin with high levels of radioactivity (0.5–3 Ci) to achieve either practically useful yields or high specific radioactivity. Automation of the control of cyclotron targetry and radiochemistry hardware, contained within shielded environments, is crucial for safe experimentation by radiochemists and for the safe, efficient and reliable synthesis of radiopharmaceuticals for the PET programme. The automation team developed considerable skill in the construction of microchemical apparatus and in its control allowed the automation of all our routine radiosyntheses. Most commercial radiosynthesis devices are limited to accomplishing the simplest radiochemistry, whereas automation of complex multi-stage radiochemistry including that for 2- ^{11}C thymidine from ^{11}C methane was successfully achieved at this centre.

During the period 1980–1985, the production of radiopharmaceuticals for PET studies was carried out using semi-automated and manual remote control. In the late 1980s, the Unit was the first to introduce industrial programmable logic controllers (PLCs) to automate targetry operation and radiosyntheses without manual intervention, initially with Toshiba PLCs. This automation philosophy was used extensively to

achieve a high degree of operational safety and reliability. From 1985 onwards, systems were replaced by tracer-specific automated syntheses system under programmable logic control (PLC) which led to more reliable production and increased capacity of tracers.^{88,89}

Radioanalytical chemistry for QC

Radioanalytical methods were developed and implemented for ^{11}C and ^{18}F radiopharmaceuticals^{90,91} administered to human subjects. Methods were also developed for a range of others tested in biology. These analyses provide crucial information on radiochemical purity, chemical purity and specific radioactivity for each batch of radiopharmaceutical.

Metabolite analysis system

Metabolite analysis is an essential component for the evaluation of candidate radiotracers and radioligands in animals and human subjects. It is also vital for the implementation of bio-mathematical models and the interpretation of clinical PET data. The research of the metabolite analysis team, now under Safiye Osman, focussed on the development of methodology for measuring radioactive metabolites in biological samples and on characterizing the metabolic profiles of existing or developmental radiopharmaceuticals.

A versatile system was designed and constructed for the automated analysis of radioactive metabolites in serial biological samples from animal and human subjects.⁹² This system is based on solid-phase extraction and reverse-phase HPLC, with on-line radioactivity and UV absorbance detection and PC-based integration. Two further systems were built in response to the increasing demand for analyses during PET experiments, and a fourth for experimental use in the development of analytical methodology. Analyses ranged from those of moderately lipophilic radioligands (e.g. [^{11}C]PK 11195) to polar radiotracers (e.g. [^{18}F]FDOPA). The importance of metabolite analysis in the tracer development process is exemplified in the development of [^{11}C]WAY 100365, underpinned the use of [*carbonyl*- ^{11}C]WAY 100365 rather than the analogue [*methyl*- ^{11}C]WAY 100365 by identifying demethylation as the route of metabolism in the latter.⁵²

2001–2006

During The 1997 peer review of the MRC CU it had become clear to the MRC that the future development of PET imaging at HH required a new approach. George Radda, then the MRC's CEO, took the step of instigating

a search for a commercial partner with compatible aims and objectives. After a lengthy search and negotiation, Imaging Research Solutions Ltd (IRSL) was established in February 2001 as a public-private partnership (PPP) between the MRC and Amersham plc. The staff of the MRC CU who were not directly part of the clinical PET imaging programmes were transferred to the new company. The clinical PET imaging groups were incorporated into the MRC Clinical Sciences Centre (CSC) which by then was well established on the Hammersmith site.

IRSL became the first member of 'Imanet', network of imaging centres and its name was quickly changed to HIL. In 2004, Amersham plc, including Imanet, was incorporated into GE Healthcare. Imanet currently comprises HIL (UK), Uppsala Imanet (Sweden) and Turku Imanet (Finland). Imanet continues to have strong interactions with its academic links as well as those with the pharmaceutical industry. Already substantial new investment has been made at HIL including, new cyclotron, a new suite of GMP compliant hot cells for radiosyntheses as well as a PET-CT scanner.

John Thornback was appointed as the first Managing Director of HIL and oversaw the transition from an academic to a commercial operation, ensuring that there was a continuation of basic research and tracer development. During to increased regulatory demands, the provision of routine PET tracers as well as the development of new radiotracers/radioligands for human PET studies has required implementation of increasingly stringent quality assurance procedures. These include process validation studies and validation of automated syntheses systems.⁹³ A Development group was established under Dave Turton with Kawai Yau to link the chemistry research (Sajinder Luthra and Frank Brady) and operations programmes (Farah Shah). Colin's Steel's automation group was also expanded. Ian Watson retired towards the end of this period but remained for some time in a consultative role to help establish the new hot lab facilities in the Vonberg suite of new hot cell facilities. Frank Brady left in 2005 after 25 productive years at the centre. Erik Arstad joined the chemistry research group and Sajinder Luthra was appointed as Research Director of Imanet.

The close interactions established between the research chemists and the clinical groups (David Brooks, Paul Grasby and Paolo Camici, Pat Price (until 2001) and Eric Aboagye have been maintained since the formation of HIL. It is this interaction which has helped foster the identification of important molecular targets in clinical research areas and led candidates for development as potential PET radiotracers. During this period, work has continued on novel radiochemistry, automation and development of tracers as well as continuing to provide tracers (see Table 3) for the clinical PET programmes. Selected examples from each of these areas are given below.

Carbon-11

Glutamate system

***N*-methyl-D-Aspartate (NMDA).** The NMDA subclass of glutamate receptors play an important role in many brain diseases, including stroke, Parkinson's disease, Alzheimer's disease (AD), schizophrenia and epilepsy. To image the PCP-binding site of the NMDA ion channel we have radiolabelled⁹⁴ the highly potent and selective antagonist CNS 5161 (*N*-[2-chloro-5-(methylthio)phenyl]-*N'*-(3-(methylthio)phenyl)-*N'*-methyl guanidine) with carbon-11 (Figure 14). This is the first PET radioligand to show an *in vivo* signal for the NMDA receptor in rats. Clinical PET studies are in progress. The success of this radioligand will open many new areas in clinical research.

AMPA. 2-Acetyl-1-(4'-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, one of the most potent non-competitive AMPA antagonists described to date, has been labelled with carbon-11 and tritium and was evaluated as a potential ligand for *in vivo* imaging of AMPA receptors using PET.⁹⁵ This particular tracer showed rapid clearance from the CNS and low specific binding. Work is in progress to develop further candidates for studying the role of AMPA in synaptic plasticity.

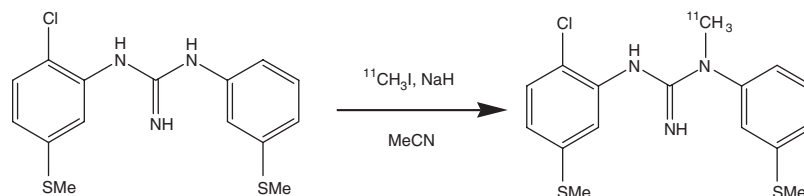


Figure 14 Synthesis of [*N*-methyl-¹¹C]CNS 5161.

Alzheimer's probes

PIB

The availability of radiotracers for imaging amyloid has important implications for studying disease progression in AD and assisting the development of drugs for treatment. A programme centred around the benzothiazole lead 6-OH-BTA-1 or [^{11}C]PIB and other structural analogues that can be radiolabelled with ^{11}C or ^{18}F has been initiated. The first phase of this work has been to bring [^{11}C]PIB⁹⁶ on-line for the PET Neurology research programme to assess the sensitivity and specificity of [^{11}C]PIB for measuring amyloid in early ADs. This work is in collaboration with University of Pittsburgh and Uppsala and Turku Imanet PET centres. Work is underway to evaluate a series of fluoro-analogues.

Fluorine-18

Solid-phase F-18 chemistry

There are a number of potential advantages of using reagents supported on solid phase for PET radiochemistry, especially for simplifying and facilitating automation of radiosyntheses. We have developed methods the immobilizing suitably protected precursors on solid supports in such a way that the [^{18}F]fluorination (either $^{18}\text{F}^-$ or $^{18}\text{F}_2$) releases only the labelled product into solution and retains the unreacted precursor on the solid phase.⁹⁷ This concept was applied to the development of disposable components for automated synthesis units. Initial work focused on 2-[^{18}F]FDG. A suitable traceless linker was developed (Figure 15) and 2-[^{18}F]FDG was pro-

duced in yields comparable to those obtained in solution.⁹⁷

[^{18}F]fluoro-organothiols

Two novel [^{18}F]fluoro-alkylthiols and one novel [^{18}F]fluoro-benzylthiol have been prepared by Matthias Glaser as labelling agents designed for site-specific labelling of suitably modified peptides.⁹⁸ This method is already showing promise as an efficient route to radiolabelling peptides with fluorine-18 for clinical PET studies.

F-18 click chemistry

The concept of 'click chemistry' to a novel and facile method of producing F-18-labelled synthons was particularly useful for applications in peptide and macromolecule labelling.⁹⁹ This chemistry is based on reaction of an azide with an acetylenic function to form an ^{18}F -synthon containing a heterocyclic ring as outlined in Figure 16. This approach has the potential to overcome major hurdles in macromolecule labelling as there is no need to protect sensitive functional groups and the reaction can be carried out in aqueous solution.

Automation of radiochemistry

The aim at HI has been to develop modular systems that are capable of performing a range of radiochemistry, more compact multi-tasking and intelligent (e.g. control system and feedback devices, self-diagnosing/reporting) and user-friendly (e.g. improved user interface, ease of maintenance). The whole approach was

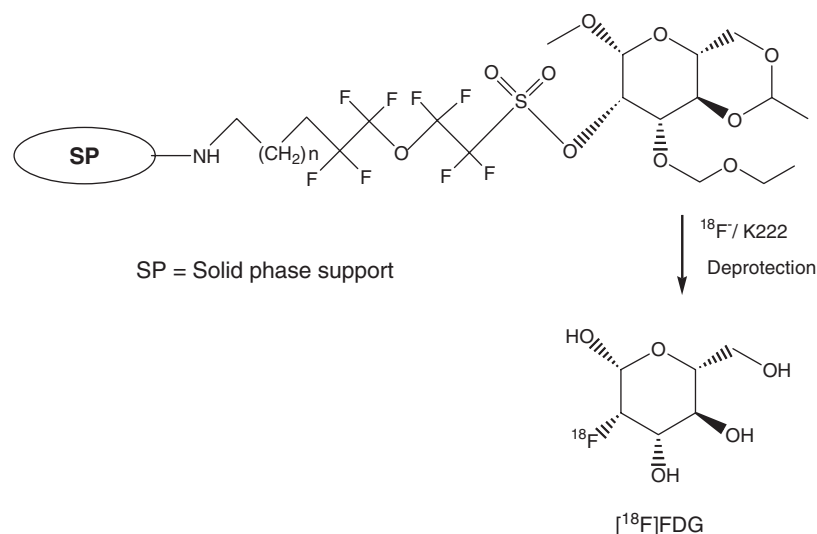


Figure 15 Synthesis of 2-[^{18}F]FDG on a solid-phase support.

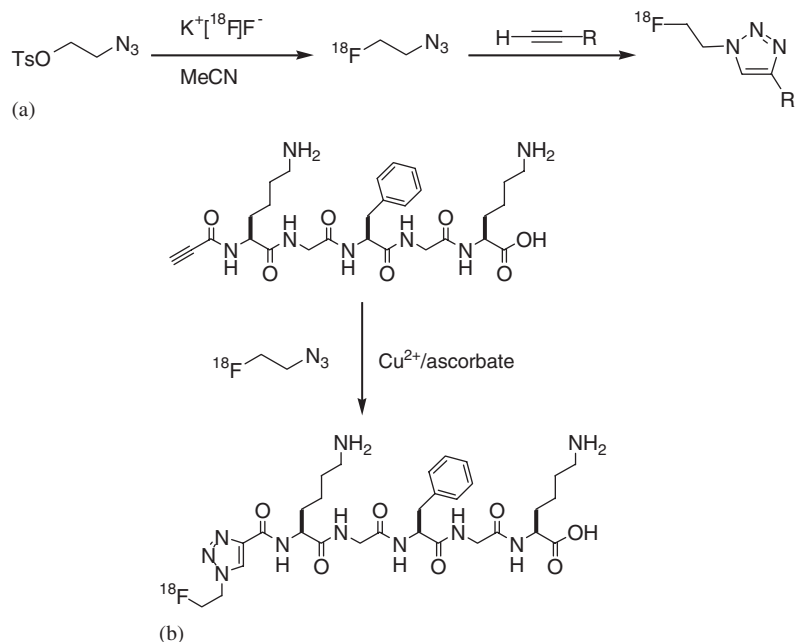


Figure 16 (a) Radiosynthesis of 2-[^{18}F]fluoroethylazide **2** and 1,3-dipolar cycloaddition with terminal alkynes and (b) labeling of model peptide, with 2-[^{18}F]fluoroethylazide using CuSO_4 /sodium ascorbate catalysis.

required to be compliant with GMP. The implementation of process validation required a radical change in our approach to the development of radiosyntheses and associated automated systems. Elements of this new approach have already been incorporated into our automated systems.

As part of implementing GMP (GAMP4) compliance, a validation framework has been established for all of the radiosyntheses systems used at HIL.⁹³

A powerful and flexible computer-based control system was developed (Beckoff interface terminal system). Aspects have already been applied to control a number of automated radiosyntheses including [^{11}C]WAY 100635, [^{11}C]choline and the NK_1 tracer, [^{18}F]L 829 165 and an experimental [^{18}F]fluoridation system. The same strategy is being used for operating the [^{15}O]H $_2$ O water generator system.

A gas phase system capable of delivering batches of [^{11}C]methylation agents every 15 min from [^{11}C]methane has been established. On-line synthesis systems have the potential of producing a large array of radiotracers with improved specific radioactivity.

Radiochemistry on microfabricated devices

The short half-lives of the radioisotopes used for PET radiochemistry require that radiosyntheses are carried out rapidly and efficiently using automated systems contained in large (ca. 1 m 3) lead-shielded hot cells to

prevent radiation exposure to the operator. Since radiosyntheses involve only physically minute quantities of radioactive material, it should be feasible to perform radiochemistry on microfabricated devices (ca. 1 cm 2) using the principle of laminar flow through a network of microchannels etched on glass, silicon or plastic substrates. We have developed suitable microfabricated devices and demonstrated the first radiosynthesis of 2-[^{18}F]FDG as well as [^{11}C]methylation using these.^{100,101} Fused silica capillary lines are used for input of reagents and removal of products. The concept of radiochemistry on a microfabricated device is illustrated in Figure 17. Work continues to achieve the goal of incorporating as many steps of the radiotracer synthesis process as possible onto a single microfabricated device. Several steps of this concept have already been achieved and work in this area is in progress.¹⁰²

Conclusions and vision for the future of PET radio-pharmaceutical chemistry

The last 50 years have seen tremendous advances in all aspects of PET radiochemical science. There have been improvements and much innovation in basic radiochemistry, automation of radiosyntheses and associated systems as well as development of radioligands and tracers for novel and specific targets. The MRC has played a key role in this by providing continuous

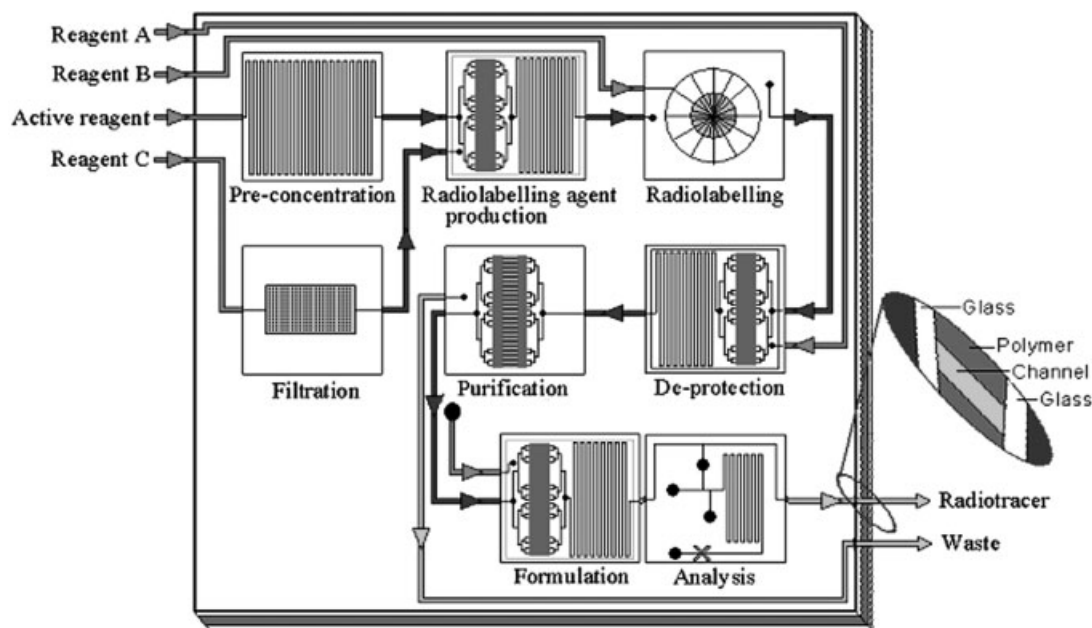


Figure 17 Concept of radiochemistry on microfabricated device. This figure is available in colour online at www.interscience.wiley.com/journal/jlcr

support for the centre in terms of funding, grants and studentships. The past success of the MRC CU had its foundation on the multi-disciplinary environment and synergistic culture driven by curiosity and imbued with a common purpose and desire to achieve advances in all aspects of PET science for the benefit of health care. Proximity to the academic environment and clinical science with its research culture on the HH site has been a stimulating influence. A constant flow of visiting workers provided steady intellectual progress and new ideas and ways of seeing, complemented with numerous national and international collaborations with academic centres of excellence. This stimulated a healthy degree of competition with other PET centres around the globe.

Improvements in radiochemistry will continue to play a pivotal role in advancing the PET science for the foreseeable future. One major bottleneck hindering more widespread application of PET is a dearth of selective and potent molecules which are successful as PET radioligands and tracers. The properties of molecules which make them suitable for such purposes is still poorly understood. Pharmaceutical companies may have failed drug molecules and analogues sitting in their inventories which may nevertheless serve as useful PET tracers or useful leads for development as such. The molecular descriptors that define good radioligands and tracers must be identified. Ways must be found to use these for interrogating chemical structure and drug structure/activity databases to

select lead candidates, in the same way that medicinal chemistry in the 21st century will be information led.

Improvements in automation of radiochemistry, and the trend to making systems smaller, will lead to more reliable, efficient and user-friendly devices for radio-syntheses. Such user-friendly devices could help reduce set-up costs and contribute to encouragement of more widespread application of the PET technique.

Such advances require farsighted provision of secure funding for basic radiochemistry, automation and tracer development and blue sky exploration in these areas. HIL will continue to consolidate, carry forward and fully exploit these advances for the benefit of clinical research and health care.

Acknowledgements

In a review of this size and scope the need for brevity makes it impossible to mention all the individuals who have made contributions to the success of the CU and without whose help it could not have functioned. These include numerous national and international collaborations involving post-doctoral fellows, visiting workers, short-term workers, PhD students, technicians and administrative staff whose contributions are gratefully acknowledged. Many of those involved or who were trained at this centre have gone onto establish and to work at many other PET centres worldwide. Opinions expressed in this review represent those of

the authors and not necessarily those of the other individuals mentioned by name.

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