# Early phase PET research in the UK:

# Consensus opinion on prioritised research areas in oncology

The NCRI PET Research Initiative is funded by:

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# EXECUTIVE SUMMARY

There has been significant investment in PET infrastructure in the UK over the last 5 years following an acknowledgement that opportunities to enhance patient care using this technology were not being made. Following a recommendation from the NCRI PET Strategic Planning Group report ‘‘A framework for PET research in the UK’’ [1] the NCRI funded the NCRI PET Research Initiative to stimulate and support all aspects of PET research from radiotracer development to clinical trials to establish the role of PET in clinical care. Leadership is being provided by the UK PET Research Steering Committee and the NCRI PET Research Network (PRN) has been set up to provide an interface with the scientific and medical communities and the NHS and to catalyse action in priority areas.

This report focuses on early phase PET research and attempts to build a consensus from the research community on the priorities for action. Work has been undertaken to establish the existing infrastructure and research activity, identify the common goals and aspirations of the various research sites, summarise the problems and barriers to research, and to build relations with Pharma and commercial PET radiotracer companies to facilitate academic and commercial collaboration within the UK.

A structured questionnaire was sent to all Experimental Cancer Medicine Centre (ECMC) PET sites and commercial radiotracer companies followed by either a site visit or telephone interview. All participants were invited to a meeting in London in July 2009 where presentations and discussion groups were held. Most of the academic sites, all four commercial radiotracer suppliers and commercial NHS providers of PET services attended.

There is considerable variation in the extent and complexity of activity across the academic sites, dependent mainly on the length of time a unit has been established and proportional to the level of investment made. While there is some evidence of sharing of facilities across academic sites this is not the norm. There is limited use of the newer radiotracers (e.g. F-choline, FLT) and considerable frustration that these and other radiotracers are not more widely available. Some established sites produce their own radiotracers with a desire by some other centres to do the same, despite the recognition that this complex task is highly regulated and requires a large multidisciplinary team of experts. Commercial companies acknowledge the need for a broader tool kit of radiotracers but have not addressed how this can be effectively delivered in the UK.

A number of conclusions have been drawn from the PRN activities in this area, along with some key needs to address issues that are crucial to early phase PET research in the UK:

1. There is a shortage of skilled PET personnel in the UK, particularly radiochemists, physicists and qualified persons. **There is a need to increase PET expertise in UK by encouraging funding body initiatives (e.g. recent MRC PET in neuroscience call) and work with professional bodies (eg BNMS and Royal Colleges) to encourage more staff specialising in PET.**
2. Increased co-operation between PET centres could help alleviate shortfalls in specialised equipment, radiotracers and expertise, producing more efficient use of available equipment and expertise (e.g. radiotracer facilities), reducing the need for future capital investment and easing the shortage of skilled staff. **There is a need to promote collaborations across academic institutions to share equipment, radiotracers and expertise.**
3. There is no comprehensive catalogue of UK PET trials making it impossible to accurately assess the quantity and diversity of PET trials. **There is a need to create a register of early phase PET trials including pre-clinical activity that can be easily accessed by the PET community.**

4. There is a need for a toolkit of PET radiotracers to effectively address a range of clinical questions: **In priority order, there is a need for production of tracers for proliferation (FLT or other), hypoxia (Cu-ATSM or F-MISO), angiogenesis, apoptosis and perfusion, Ga-labelled peptide and F-choline.**
5. Need to generate produce proof of concept data and establish the clinical utility of each new radiotracer. **There is a need for qualification of response biomarkers for early phase drug discovery.**
6. There is currently a very limited range of radiotracers available in the UK and many of these are only produced by select academic PET centres. Moreover, some of the radiotracers sold by commercial companies are not available in all parts of the UK. **There is a need to encourage commercial companies to increase number and availability of new (i.e. other than FDG) radiotracers.**
7. There is limited availability of new radiotracers in the UK and it is likely that these will be considerably more expensive than FDG. A purchasing consortium could guarantee minimum demand for a radiotracer and produce economies of scale. Alternatively, radiotracer production could be promoted by academic, commercial or academic/commercial partnerships. **There is a need to explore new partnerships/consortia to purchase or produce new radiotracers for research**.
8. The complex and stringent MHRA regulations are perceived as a considerable barrier to PET research in the UK. Hurdles include the volume of paperwork involved, the time required to arrange a first in man microdosing trial, and uncertainty between the definition of a PET clinical trial and a mechanistic study. **There is a need to work with the MHRA to reduce regulatory hurdles.**
9. Many pharmaceutical companies recognise that PET can help with the development of new anti-cancer agents and there is considerable scope to increase in the number of UK PET studies. However, many PET studies are carried out in the USA or Europe, where there are less stringent regulations, access to a wider range of radiotracers or the potential to perform multi-centre trials. **There is a need to encourage Pharma to add PET to phase I/II drug studies and place this activity within the UK.**
10. There is currently a lack of clarity regarding potential funding opportunities (UK and international) for PET research. **There is a need to identify and highlight suitable funding opportunities that could be used to support common goals of the PET research community**

**Addressing needs in each of the areas outlined above is dependent on the commitment of a number of different organisations, bodies and researchers. The NCRI PET Research Network will work with stakeholders to try to catalyse and facilitate actions to take these priority areas forward.**

# 1. INTRODUCTION

Fluorodeoxyglucose (FDG) is the predominant tracer utilised in Positron Emission Tomography (PET) examinations in the UK, with applications ranging from clinical evaluation of patients to research use in developing new drugs. A number of new (i.e. non-FDG) PET tracers have been developed, including radiolabelled anti-cancer drugs, cell receptors and probes for biochemical pathways involved in glucose metabolism, proliferation, apoptosis, hypoxia, and angiogenesis. Together these form an adaptable toolkit for oncology research which could be utilised as predictive, prognostic, pharmacological and/or surrogate response biomarkers to facilitate the development of new anti-cancer agents and improve selection of patients for different treatments. However, these novel radiotracers have not been widely adopted to date, are generally not available from commercial producers and can only be made in relatively few centres in the UK at considerable expense.

The PET infrastructure in the UK has recently expanded to more than 20 static scanners and an extensive mobile service for NHS and research centres across the country. The new cyclotrons and radiochemistry facilities will increase capacity for radiotracer production in both the commercial sector and research institutions. More than £50million is being invested in four comprehensive cancer imaging centres in a key strategic initiative funded by CRUK/EPSCRC/MRC/NIHR, reflecting the importance of imaging in the development of new cancer treatments.

Pharmaceutical companies are exploring the use of PET to support the development of new anti-cancer agents, as demonstrated by increased collaboration with academia and investment in PET facilities. PET studies can generate important pharmacokinetic and pharmacodynamic data on new drugs, and surrogate response biomarkers can provide an early sign of drug efficacy, making valuable contributions to Go/No go decisions. Such studies often require specialised radiotracers to produce the applicable data and need to meet strict timelines, but can be of immense scientific value.

Despite recent investment, the infrastructure and resources available within the UK are still relatively limited. To fully realise the potential of academic PET centres, radiotracer companies and PET providers will need to collaborate and share knowledge and resources, to address the specialised complex problems. The National Cancer Research Institute (NCRI) recommended the creation of the NCRI PET Research Initiative to stimulate and coordinate PET research at the national level. Coordination is provided by the UK PET Research Steering Committee and the NCRI PET Research Network (PRN), with three network leads directing separate work streams. Stimulation and support of early phase PET research is a priority. The PRN has engaged with the PET community to agree priority areas for early phase PET research, stimulate research questions, develop collaborative projects and solve logistical problems.
Information and perspectives were obtained from the Experimental Cancer Medicine Centres (ECMC), pharmaceutical companies and commercial radiotracer companies via a survey, site visits, teleconferences and a PET workshop (for more information on the meeting visit www.ncri-pet.org.uk). The information obtained from these sources and the resulting consensus opinions from the PET meeting are summarised in this report.

# 2. CURRENT STATUS OF EARLY PHASE PET RESEARCH IN THE UK

## 2.1 Current UK PET facilities, existing toolkit and capacity in the UK

The 2007 NCRI report "A framework for PET research in the UK" [1] highlighted the need to determine the proper place of PET in both the clinical management of patients and in experimental medicine and break down the barriers to undertaking PET research. Since 2007 there has been significant investment in PET infrastructure. This report focuses on the NCRI funded ECMC centres. There is research activity being conducted at a number of other sites (see 2.1.4); these were not surveyed or visited but were invited to the consensus meeting.

### 2.1.1 PET infrastructure and staff in the ECMC network

Nineteen ECMC research sites were established to develop biomarkers and new anti-cancer treatments. This translational network of laboratory based and clinical research have different levels of PET infrastructure as summarised in appendices 1A and B.

Appendix 2 lists PET staff currently employed at each ECMC centre. Limited availability of trained staff, especially radiochemists, kinetic modelling expertise and qualified persons (QP) remains a problem. Qualified persons ensure that every batch of radiotracer released complies with its specification and has been made according to good manufacturing practice. The projected shortage of QP's is due to strict qualifying guidelines and retirement.

### 2.1.2 ECMC centres as suppliers of new PET radiotracers

Probes for numerous targets can be labelled and used as PET radiotracers (Fig. 1).

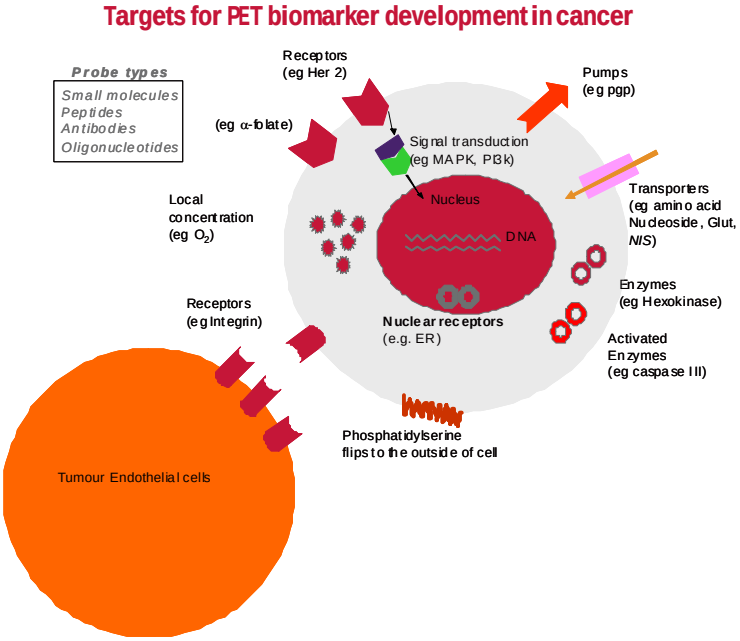



**Figure 1: Targets for PET biomarker development in cancer** (courtesy of Prof Eric Aboagye, Imperial College London)

Targets include DNA and proteins, and probe types can be small molecules, peptides, antibodies or oligonucleotides. Potential roles for PET tracers: Imaging biomarkers in dosimetry, biodistribution and metabolism studies; Study drug pharmacokinetics or pharmacodynamics; Assess response; Investigate tumour biology; and therapy planning.

Three centres currently have capacity to make GMP grade radiotracers to supply other centres; although King's College London (KCL) only has limited capacity. Several GMP-grade radiotracers with a half-life longer than 2 hours could in principle be supplied by the following ECMC sites:

- Cambridge: $^{18}$F-fluorothymidine (FLT) and $^{18}$F-Fluoromisonidazole (FMISO)
- KCL: $^{18}$F-Fluoride (F), FLT, $^{64}$Cu-(diacetyl-bis(N4-methylthiosemicarbazone) (ATSM), $^{18}$F-FMISO and $^{18}$F-methylcholine (F-choline)
- Manchester: FLT and 3,4-dihydroxy-6-$^{18}$F-fluoro-L-phenylalanine (F-DOPA)

### 2.1.3 Current PET Research at ECMC centres

While the majority of PET examinations are for clinical care (Fig. 2), many centres undertake 1-10 research scans/week. Factors limiting research scans are access to new radiotracers, funding and restricted scanner time for research.

There is a need for an accurate register of UK PET trials to avoid the unnecessary repetition of studies and highlight UK activity. A number of phase I and II PET clinical trials are underway (appendix 3A) with established and new anti-cancer drugs in solid tumours and leukaemia (appendix 3B). This is an underestimate of activity as some sites were reluctant to divulge information due to commercial and academic sensitivities. The majority of phase I/II PET trials are likely to be funded by pharmaceutical companies with limited need to publish data.

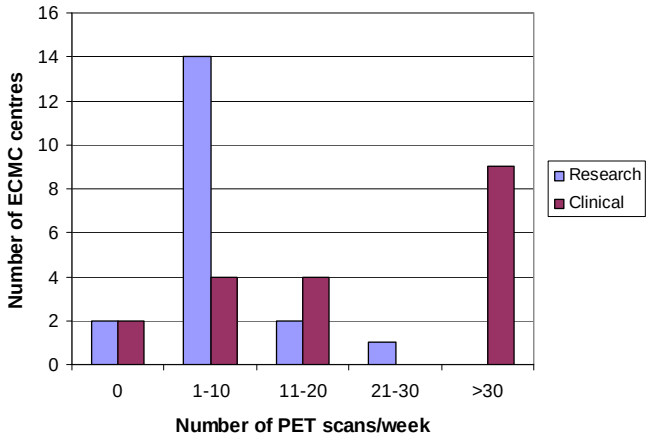



**Figure 2: Number of PET scans in ECMC centres.**
Each ECMC centre was asked to estimate the number of research and clinical PET scans (early and late phase) that are being performed at their ECMC PET centres each week.

### 2.1.4 Academic PET centres outwith the ECMC network

There are a number of PET centres outwith the ECMC network with well established PET oncology research and could participate in multi-centre trials involving new radiotracers or FDG. Centres with a static PET/CT scanner (+/- cyclotron) are listed in appendix 4.

## 2.2 The needs and aspirations of ECMC PET centres

The ECMC PET centres in the UK are in different phases of maturity with different imaging capabilities, resources, aspirations, opportunities for collaboration and obstacles that restrict research. Most of the new PET centres have a static PET/CT scanner and excellent supporting facilities, but most have no cyclotron or facilities to make GMP grade radiotracers. Established PET centres typically have one or more static PET/CT scanners, a cyclotron and facilities to make GMP-grade radiotracers. However, some established centres have no access to small animal PET, no spare capacity to synthesise additional radiotracers, insufficient trained staff and limited PET methodology expertise.

### 2.2.1 New PET radiotracer demand at ECMC centres

Sites were asked to prioritise their demand for new radiotracers. Centres were keen to access new radiotracers to increase their research options, apart from those sites that could either supply their current needs from their own facilities or were not yet ready to use new radiotracers.

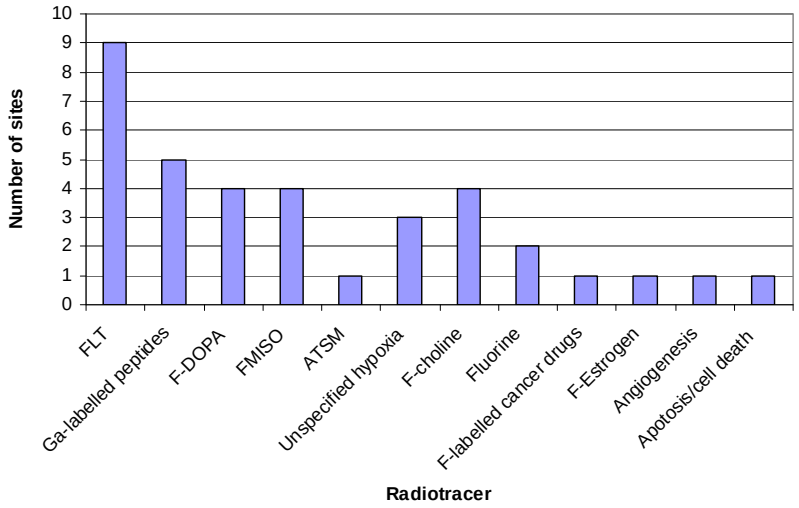



**Figure 3: New radiotracer demand in the ECMC centres.**
Each ECMC centre was asked to indicate which radiotracer(s) that they do not currently have access to, but would like to use in their research in the next two years.

The survey results and discussion at the meeting produced the following prioritised list of radiotracers, to form the basis of a toolkit for PET research:

- Proliferation marker (FLT or other)
- Hypoxia marker ($^{18}$F-FMISO or $^{64}$Cu-ATSM or other )
- Angiogenesis marker
- Apoptosis marker
- Perfusion marker
- $^{68}$Ga-labelled-peptides
- $^{18}$F-choline

Increased availability of proliferation and hypoxia markers should be prioritised before other tracers due to the potential collaborative studies with pharmaceutical companies. In contrast, $^{68}$Ga-labelled-peptides will not have broad utility in early phase PET research, so have lower priority. Similarly MRI, CT and $^{15}$O-$H_2O$-PET are well developed to study perfusion, making a new perfusion radiotracer lower priority.

Most ECMC centres indicated that they would be happy to source new radiotracers from either academic or commercial centres, assuming that the desired quantity could be delivered at a suitable quality and price. Estimated demand for FLT ranged from 0-20 doses/week (Fig. 4). This range reflects different research objectives and opportunities. Eight centres would like to purchase FLT from a commercial company, 7 centres prefer to make FLT themselves and 4 are undecided.

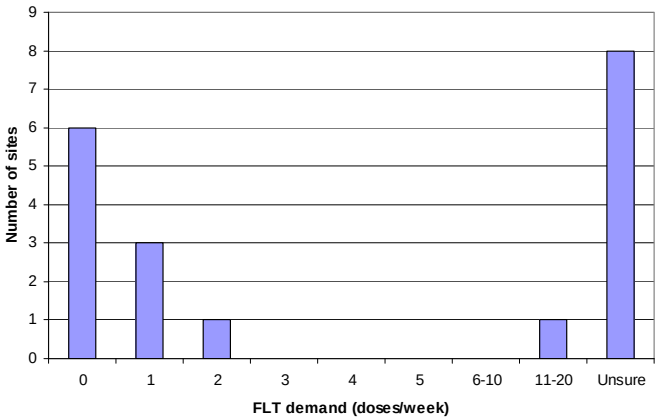



**Figure 4: Estimated demand for FLT in the ECMC PET centres.**

### 2.2.2 ECMC centres and radiotracer qualification studies

There was very strong interest from ECMC centres in working together to participate in qualification studies on new radiotracers. The ability to perform multi-centre studies would also be attractive to pharmaceutical companies.

### 2.2.3 Early phase research: Aspirations, obstacles and opportunities

The aspirations of most of the ECMC centres are quite varied (Table 1).

| Aspiration of PET centre | Number of centres |
|---|---|
| Use tracers for response assessment | 5 |
| Use tracers for early diagnosis | 4 |
| Develop new tracers | 4 |
| Increased access to new tracers | 3 |
| Obtain static PET/CT scanner for research | 3 |
| Generally upgrade PET facilities/capacity | 3 |
| Develop PET techniques/analysis methods | 3 |
| Increase PET R&D programme | 2 |
| Study tumour biology/disease processes | 2 |

**Table 1: Aspirations of ECMC PET centres (data from responses to PRN survey)**

The obstacles to PET research are somewhat ECMC centre-specific, although include several common topics (Table 2).

| Obstacles impeding PET research | Number of centres |
|---|---|
| Limitations of PET infrastructure at centre | 9 |
| Shortage of skilled staff | 6 |
| Limited funding/identify suitable funding stream | 5 |
| Complex regulatory framework | 5 |
| PET perceived as being too complex/expensive | 2 |
| Limited radiotracer availability | 2 |

**Table 2: Obstacles impeding PET research (data from responses to PRN survey)**

NCRI-badged studies are funded, but there is a tension between timely service delivery and additional PET scans undertaken for research purposes. Including PET sub-studies in trials can make the study too expensive. In addition, several potential barriers to collaboration between sites were identified:

- Academic competition between centres
- Lack of financial incentives
- Lack of consistent quantification/ standardisation of methods

Many opportunities were recognised by the ECMC centres.

| Opportunities for PET research | Number of centres |
|---|---|
| Good local research groups | 8 |
| Good phase I trials units/ NHS | 8 |
| Collaborations with pharmaceutical companies | 3 |
| Collaboration (nationally or internationally) | 3 |
| Collaboration with imaging/radiotracer companies | 2 |
| PET applicable in oncology, neurology & cardiology | 2 |

**Table 3: Opportunities for PET research (data from responses to PRN survey)**

### 2.2.4 How can the PRN help?

The responses to the questionnaire suggested a number of ways that that the PRN could assist academic PET research (Table 4).

| How can the PRN help with PET research | Number of centres |
|---|---|
| Collaboration/Networking | 9 |
| Increase access to radiotracers or help each centre to make their own | 6 |
| Help with multi-centre trials | 4 |
| Protocol standardisation/sharing best practise | 4 |
| Help reduce paperwork/regulatory burden | 3 |
| Training of skilled PET staff | 3 |

**Table 4: How can the PRN help with PET research? (data from responses to PRN questionnaire)**

Discussion at the early phase meeting also highlighted other areas where the PRN could help:

- Increase capacity at centres that could provide radiotracers to other sites
- Identify funding opportunities that could be used to support common goals of the PET research community

## 2.3 Requirements of pharmaceutical industry for PET radiotracers

There is a need to improve current drug development paradigms in oncology and PET is well placed to contribute to this, by providing valuable data to assist the development of new drugs. In particular there is a need to:

- Move away from maximum tolerated dose (MTD) driven phase I studies
- Offer patients in trials an opportunity for therapeutic response
- Develop ways of understanding tumour-host heterogeneity in more depth
- Define ways to rationally determine drug doses and dose-scheduling

- Use tools from monotherapy studies to design more efficient combination trials

### 2.3.1 Importance of imaging in drug development

PET can optimize drug utilization before the agent progresses to confirmatory studies. Small molecular and mechanistic trials with innovative design and explorative methodology to demonstrate efficacy in man would be helpful(Fig. 5).

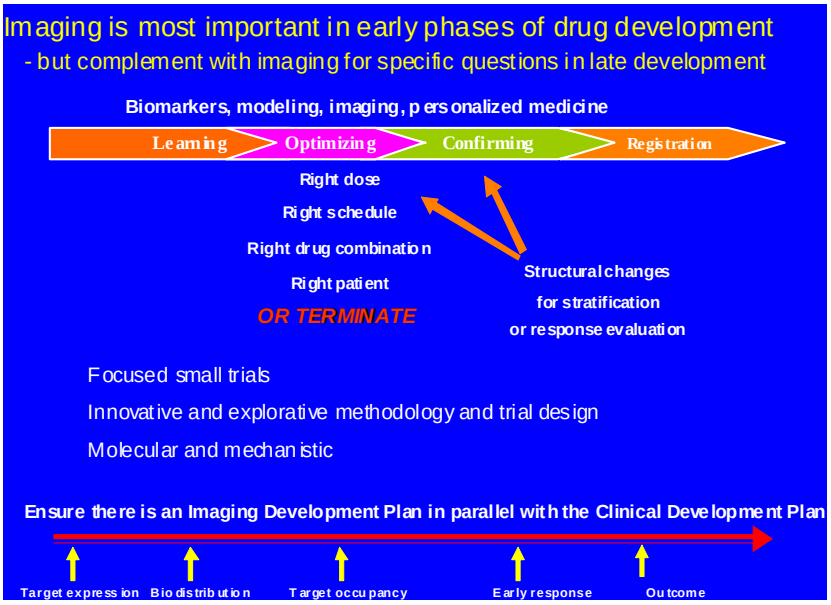



**Figure 5: Imaging in early phases of drug development** (courtesy of Prof Mats Bergstroem, Roche)

It may be better to introduce a rational step by step approach to studies (Fig. 6). In later phase studies PET radiotracers can be used as surrogate response markers, or additional clinical endpoints, to help confirm drug efficacy.

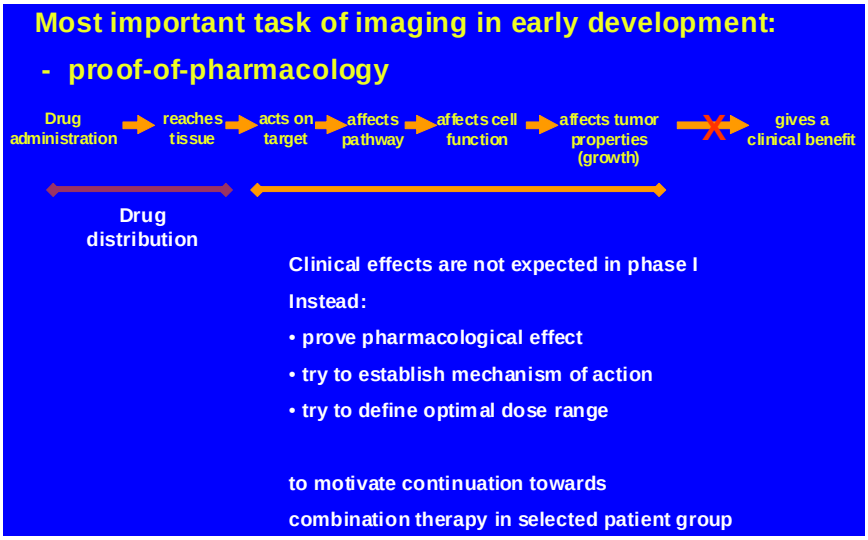



**Figure 6: Most important task of imaging in early phase drug development** (courtesy of Prof Mats Bergstroem, Roche)

The microdosing concept is ideal for taking a PET tracer into man but time-lines need to be shortened (Fig. 7). Antibodies and micro-molecules should also be considered in PET, but the complex metabolism of antibodies *in vivo* makes data interpretation very difficult.

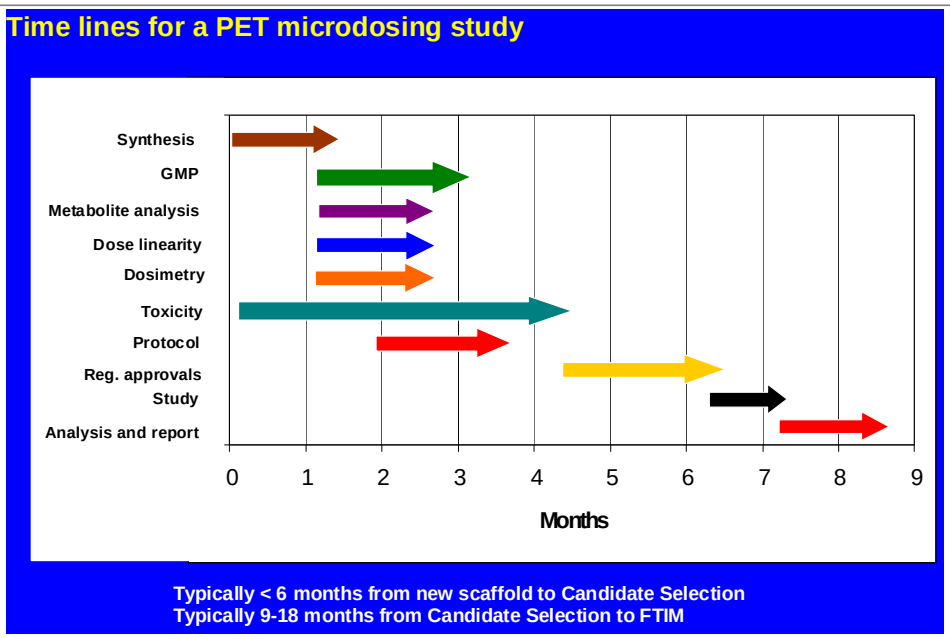



**Figure 7: Timelines for a PET microdosing study** (courtesy of Prof Mats Bergstroem, Roche)

It will be important to investigate target expression and drug-target interaction in oncology where the drug target is known (extracellular, intracellular, kinases). However, pharmacodynamic readouts close to the target are needed and pharma is currently lacking the appropriate tools. In the meantime good tools are necessary to examine the secondary aspects of pharmacological action such as cell cycle kinetics, proliferation and apoptosis. Fortunately, PET is suitable for studying both receptors and enzymes.

A number of different classes of anti-cancer agents are undergoing development (Figure 8). There is a specific need for tools to study cell cycle arrest and apoptosis. Pharma would like access to a PET toolkit with more than one imaging tool to study each process.

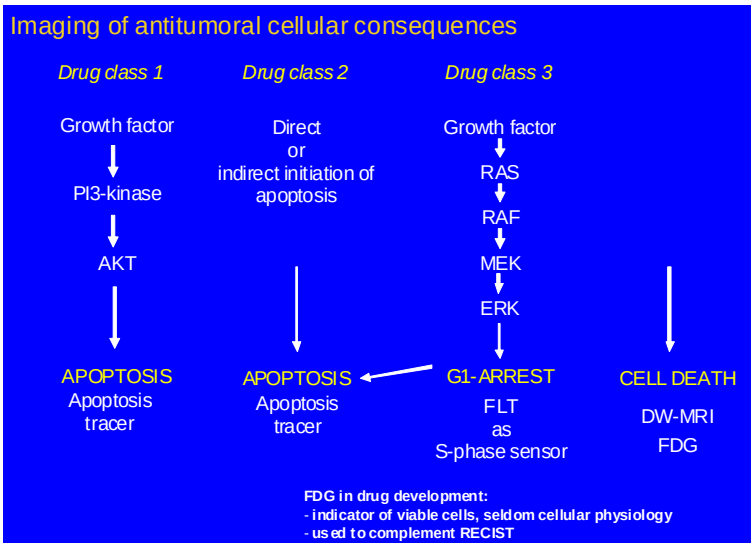



**Figure 8: Imaging of anti-tumoral cellular consequences** (courtesy of Prof Mats Bergstroem, Roche)

### 2.3.2 Why is PET imaging not further integrated into oncology drug development?

- Too few PET tracers and these are not widely available
- No qualified PET tracers tools for key processes (e.g.cell cycle arrest and apoptosis)

- Can not study the cascades driving tumour growth (e.g. MAP kinase), angiogenesis or the main targets for antibody therapeutics and inflammatory cells in tumours
- Not yet accepted by FDA as biomarkers

### 2.3.3 Opportunities for academia to work more closely with industry

A few big Pharma companies have PET and many medium sized (biotechnology) companies would benefit from PET. Academia can lead discovery of new PET probes, undertake validation and provide the infrastructure for clinical PET. Pharma needs to works with academia to develop and design new types of clinical trials with imaging endpoints. Collaboration between industry and academia will be encouraged by the Innovative Medicines Initiative (IMI) to develop imaging biomarkers for proliferation and apoptosis.

## 2.4 Commercial radiotracer companies in the UK

Erigal, GE Healthcare, IBA and PETNET Solutions, have radiotracer production sites at various UK locations (appendix 5). Commercial companies have expanded their UK presence to meet an increase in demand for FDG and are now starting to supply some other radiotracers/radioisotopes to academic PET centres.

### 2.4.1 Erigal

Erigal is a joint venture between M2i Holdings (Dublin) and Alliance Medical Limited. Production facilities are sited in Dublin, Royal Marsden Hospital at Sutton, Keele and Preston. Erigal supplies FDG and will supply new radiotracers soon (Table 5).

### 2.4.2 GE Healthcare

GE Healthcare operates the Hammersmith facility, London (25% owned by the Medical Research Council (MRC)) making 15-20 different radiotracers for research use (most for neurology applications and with short half-lives). The Grove Centre, Amersham is focused on the development and production of novel PET imaging agents.

### 2.4.3 IBA

IBA owns two UK sites that manufacture radiotracers: Guildford and Dinnington, Sheffield. IBA is actively involved in new radiotracer research and is planning to make a range of new radiotracers available in the next three years.

### 2.4.4 PETNET Solutions

PETNET Solutions (Siemens) has two sites to manufacture radiotracers: Mount Vernon London and Nottingham. FLT is available and new radiotracers are being developed.

### 2.4.5 Radiotracers that can be sourced from commercial companies

There is currently a limited range of oncology radiotracers from commercial companies (Table 5).

| | **Widely available in UK** | **Limited availability in UK** | **In development** | **Available in USA or Europe** |
|---|---|---|---|---|
| **Erigal** | $^{18}$F-FDG; $^{18}$F | $^{18}$F-choline | $^{18}$F-FLT; $^{68}$Ga-DOTA | |
| **GE Healthcare** | | | $^{18}$F-GE135 (angiogenesis); $^{18}$F-GE148 (amino-acid metabolism) | |
| **IBA** | $^{18}$F-FDG; $^{18}$F | | $^{18}$F-FLT; $^{18}$F-DOPA | $^{18}$F-FLT; $^{64}$Cu; $^{89}$Zr; $^{124}$I |
| **PETNET Solutions** | $^{18}$F-FDG | $^{18}$F-FLT | $^{18}$F; $^{18}$F-HX4 (hypoxia) | $^{18}$F; $^{18}$F-FLT; $^{18}$F-DOPA |

**Table 5: GMP-grade oncology radiotracers/radioisotopes available from commercial companies (>1h half-life)**

## 2.5 Issues around access to existing and new radiotracers and how to use tools more effectively

Effective models to increase the availability of tracers, and appropriate funding streams to develop new tracers, will facilitate their progression into clinical use. This will permit multi-centre studies of diagnostic effectiveness to be undertaken.

### 2.5.1 New radiotracers: Development and commercialization

Development of a new PET radiotracer is an involved and expensive process and can be funded by industry, academia, or an industrial/academic partnership. A molecule or pathway may be a promising target, but could have intellectual property (IP) issues. The principles behind developing radiotracers with or without IP coverage are the same: There needs to be a sufficient level of demand for manufacturers to justify obtaining a manufacturing license and to sell the radiotracer at a competitive price. However, the IP status of the tracer can have an effect on the return on investment and therefore affects the development costs that organisations are prepared to incur: A radiotracer with no IP coverage could be developed either by academia and /or industry, whereas when a company holds the IP rights the early phase trial costs will tend to be commercially funded. This may not be the optimal model, since the market return for a new radiotracer may not justify funding a clinical trial. Indeed, development of a new tracer may not always be commercially feasible, as outlined using the following exemplar from the USA.

There are many parallels between the traditional drug development process and the development of new PET radiotracers, but there are some significant differences in their economics:

- In the USA, traditional drug development costs are approximately $1 billion per product, whereas an imaging agent costs $300-400 million
- Imaging agents are used in much smaller quantities than drugs with the dose being approximately 1% of that of a pharmaceutical agent
- The production cost of a PET agent is approximately 75% of the revenue, compared to 5-10% for a pharmaceutical
- The market for imaging agents is smaller than for a therapeutic

Since PET radiotracers generally produce a smaller profit margin than therapeutics, it will be necessary to find mechanisms to alleviate this unfavourable economic barrier.

### 2.5.2 Models for increasing access to radiotracers

Demand for new PET tracers is driven by both research and clinical needs. A number of factors need to be considered when designing models to increase access to new radiotracers: Which radiotracers are needed; Estimate demand; Identify which institutions require the product; Determine which institutions can supply each tracer and their production capacity; Identify cost-effective models. It will then be possible to consider the development of regional supply centres:

- **Academic collaboration**: Academic sites could work together to increase the availability of new tracers. This may require infrastructure investment to increase production capacity or a financial incentive
- **Commercial supply**: Commercial radiotracer companies could contribute towards increasing radiotracer availability. However, it is currently uncertain whether each tracer can be supplied at a competitive price
- **Industrial/academic partnership**: This could involve commercial companies providing laboratory space for production of new radiotracers. Facilities for production of GMP-grade

radiotracers could be arranged at Sutton (Erigal), Nottingham (PETNET) and Guildford (IBA)

- **Mobile hotlab**: This could make new radiotracers available over a wide geographical area
- **Make more effective use of each production run** (e.g. distribute each batch to multiple sites; set aside a specific day of the week for studies with each radiotracer)
- **Encourage patients to move to key centres for scans** (especially for short half life $^{11}$C radiotracers)

### 2.5.3 Models for the cost-effective supply of new radiotracers

New radiotracers are likely to be significantly more expensive than FDG, since the FDG production process has been optimised, strong demand for FDG produces economies of scale, and there is a competitive marketplace as FDG is routinely synthesised by all of the commercial companies and many academic centres.

The cost of production of $^{18}$F-FLT, $^{64}$Cu-ATSM and $^{18}$F-choline is likely to be similar. FLT yield is much lower than for FDG (20 doses/batch) suggesting that production is not optimised; commercial companies routinely make 2-4 doses/batch of FLT, and some academic PET centres make 4-5 doses/batch. The high cost of $^{64}$Cu makes a significant contribution to the price of $^{64}$Cu-ATSM. There is IP associated with $^{18}$F-choline, but production is relatively efficient (15 doses/batch). Radiotracers to study apoptosis are generally harder to produce, so will be more expensive. The short half-life of $^{11}$C-labelled tracers generally makes their distribution unfeasible.

Although many centres have expressed a desire for their own cyclotron and PET radiopharmacy, this may not be the best solution as it is unlikely to be cost-effective, and the recruitment and retention of specialised key staff has proven to be problematic in the UK.

#### 2.5.3.1 Exploiting economies of scale

Collaborations can succeed if economies of scale are maximised. Set-up costs for a new radiotracer production line are significant and escalate dramatically for a new centre. Approximately 100-200 doses/year are required to keep the cost/dose acceptable. This could be achieved by an agreement between multiple users to guarantee to purchase sizeable quantities from a supplier. However, it will be necessary to have a competitive and accurate estimate of radiotracer cost for grant applications, and each academic PET centre will only be able to commit to a consortium when funding is available.

#### 2.5.3.2 Academic centres as suppliers of new radiotracers to a consortium

If the supplier is an academic centre a number of factors need to be considered:

<u>Potential advantages</u>:

- Revenue stream
- Robustness afforded by increasing the production size of the centre
- Facilitation of locally-led multi-centre trials

<u>Potential disadvantages</u>:

- Distraction from the “core business” (fewer publications)
- Space and staff required

#### 2.5.3.3 Commercial companies as suppliers of new radiotracers to a consortium

In the UK market, an initial tender of 100 patient doses per annum may be sufficient for a radiotracer to be commercially viable. A commercial company needs to consider a number of factors:

Potential advantages:

- Competitive advantage
- Defraying the costs of developing new products
- Robustness afforded by more extensive facilities
- Economies of scale

Potential disadvantages:

- Distraction from the profit-making "core business" of the company
- High risk if tracer not adopted for wider use
- Potential losses unless purchasing consortium commits to minimum number of doses

#### 2.5.3.4 The purchasing consortium

A robust well funded purchasing consortium is crucial to reassure suppliers. The NCRI, ECMC network or the CCRN could provide co-ordinating function to give solidity and reliability to the consortium, co-ordinate the choice of tracers and co-ordinate and channel funding.

### 2.5.4 Funding and collaborative options for developing new radiotracers

There are a number of funding options and strategies that could contribute towards the development of a new radiotracer.

- **Commercial**: Have the benefits of large scale production and distribution
- **Industrial/academic partnership**: This could produce significant benefits by sharing of expertise or resources as well as combining key attributes of different business models (e.g. collaboration between GE and Imperial)
- **Funded early phase clinical trials**: This could potentially be an good way of developing and validating new radiotracers that have no IP
- **CRUK-NAC (feasibility studies)**: This is used for small studies to obtain some early clinical data on the utility of a new radiotracer (e.g. $^{11}$C vs $^{18}$F-choline for staging prostate cancer – see appendix 3)
- **Central database to speed up regulatory applications:** In the USA, the NIH operates a central database that makes data from Investigational Medical Product (IMP) dossiers available for subsequent applications. An equivalent model could support UK applications
- **NIHR Health Technology Assessment programme**: Could fund large multi-centre studies to ascertain the diagnostic efficacy of a radiotracer

## 2.6 Regulatory issues

The regulatory process for testing a new radiotracer in man is complex and expensive. A particular concern is that radiotracers are treated in the same way as drugs, even though they are used in much lower, sub-pharmacologically active amounts. The regulatory process is regarded as a barrier to the discovery and development of radiotracers. A comprehensive understanding, and some easing of the regulations, would be of significant benefit to the UK PET community.

### 2.6.1 Radiotracer regulations in the United States

Radiotracers with a United States Pharmacopeia (USP) monograph can be used clinically and do not require FDA approval. USP monographs exist for $^{18}$F-FDG and $^{18}$F-F.

PET radiotracers without a USP monograph are considered investigational PET products. Investigational use requires one of the following processes:

- Approval by FDA according to conditions described in an Investigational New Drug (IND) application
- Approval by FDA according to conditions in an exploratory IND
- Approval by a radioactive drug research committee

While tracers for clinical use need to be produced to GMP standards the FDA published guidance that reduced the GMP requirements for research use (http://www.fda.gov/cder/Guidance/5425dft2.htm) but this is likely to change. New regulatory guidance for pre-phase I studies with very limited human exposure and have no therapeutic or diagnostic purpose has been released (http://www.fda.gov/cder/guidance/7086fnl.htm). The guidance reduces the extent of pre-clinical testing required to gain regulatory approval in line with the reduced risk.

### 2.6.2 Radiotracer regulations in the European Union

The European Medicines Agency (EMEA) is the governing body that sets the guidelines for regulations for the EU. Some European countries have additional legislation or different interpretation leading to differences in practice across Europe. For example the regulations in Switzerland and Belgium are more lenient than in the UK. This could be a disadvantage for the UK. Updated EMEA guidelines for production of radiopharmaceuticals for commercial purposes, came into effect in May 2009 (http://www.emea.europa.eu/pdfs/human/qwp/30697007enfin.pdf - 2008-12-05).

### 2.6.3 Radiotracer regulations in the UK

PET research studies are either designated as mechanistic studies or clinical trials. The distinction derives from a legal basis (see Clinical Trials Directive 2001/20/EC; CTD) and seeks to protect patient safety and the quality of the data.

Clinical trials in the UK (and the EU) are defined as ‘investigations in humans intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of one or more IMP(s), and/or to identify any adverse reactions to one or more IMP(s) and/or to study adsorption, distribution, metabolism and excretion of one or more IMP(s) with the object of ascertaining its (their) safety and/or efficacy’. PET clinical trials need a CTA for the study, an IMP license for the tracer, and are subject to regulation by the MHRA, the Research Ethics Committee (REC) and ARSAC. The documentation involves considerable effort and resources and the radiotracers need to be prescribed by a QP. Mechanistic studies, and clinical studies with non-standard tracers that do not need an IMP license can be performed under a ‘specials’ license, which is unique to the UK: An unlicensed relevant medicinal product may only be supplied to fill a ‘special need’ and in response to a bona fide unsolicited order, formulated in accordance with the specification of a doctor, dentist or supplementary prescriber and for use by his/her individual patients on his/her direct responsibility. PET radiotracers for these studies can be prescribed by an ARSAC certificate holder, who prescribes the dose on a named patient basis.

### 2.6.4 UK radiotracer regulations: Practical issues

The regulatory process for a new radiotracer in the UK is complex as demonstrated by the following observations:

- Research using the same radiotracer can be classified either as a mechanistic study or a clinical trial depending on the role of the tracer
- The requirements set by the study sponsor can be more strict than those set by the EU CTD and MHRA
- It can sometimes take a long time from funding application to initiation of research

The PRN plans to put a PET specific algorithm on the website (http://www.ncri-pet.org.uk/) to define the process, which will be supported by a list of frequently asked questions. Moreover, the MHRA are willing to advise researchers whether their study comes under the CTD, and will respond to investigators within a week.

### 2.6.5 Timeline from funding application to research

The long timeline from funding application to research is a result of multiple regulatory and governance requirements (i.e. MHRA, NHS R&D, ARSAC and REC).

- The integrated research application system (IRAS) is helping to streamline the information requirements. However ARSAC still issues paper licences which makes it hard for other regulators to know when the licence has been issued and makes it more difficult to issue reminders when the licence is due to expire. (2) There is some duplication between REC and ARSAC, with both considering the radiation dose.
- Some early phase trials can be adversely delayed by regulatory requirements. A streamlined process or exemptions in this sort of scenario could be helpful (e.g. see EMEA public consultation paper on assessment of the functioning of the CTD), as protection of data quality is less of an issue for early phase trials.

## 3. PRIORITIES AND ACTIONS

The presentations and discussion at the early phase meeting and the information from the centre visits and responses to the structured questionnaire have produced an overview of current PET research in the UK, a consensus opinion of key issues that need to be addressed and some possible solutions that could help to deal with these issues. The main priorities are:

1. Increase number of trained staff to support PET in the UK, particularly radiochemists, medical physics/data analysis and QPs, but also PET scientists such as clinical fellows and biologists (see 2.1.1, 2.2.3.2 and 2.2.4)

2. Promote collaborations across academic institutions to share equipment, radiotracers and expertise, to ensure maximum return from existing investment in UK academic sites (see 2.2.4)

- Facilitate sharing of resources for making radiotracers between ECMC centres (see 2.2.4)
- Include non-ECMC PET centres (see 2.1.4)
- Consider model of Scottish ‘pooling’ initiative, which facilitates collaboration between academic sites by encouraging consortia to apply for funding support for research

3. Create register of early phase PET trials (see 2.1.3)

4. Produce oncology radiotracer toolkit. Increase availability of new radiotracers - in priority - FLT (or other proliferation marker), and tracers for hypoxia (Cu ATSM or F-MISO), angiogenesis, apoptosis and perfusion, Ga-labelled peptide and F-choline (see 2.2.1)

- Determine the exact assignment of current resources and capabilities available to produce the chosen radiotracer(s) within academia, industry or an industrial/academic partnership (including site specific barriers to increasing production)

5. Qualify response biomarkers (see 2.3.2)

6. Encourage commercial companies to increase number and availability of new radiotracers (see 2.5.2 and 2.5.3.3)

7. Explore potential partnerships/consortia to purchase/produce new radiotracers for research purposes (see 2.5.2 and 2.5.3)

- Increase use of production runs for new radiotracers (e.g. image with a specific radiotracer on a specific day for low volume radiotracer work (see 2.5.2)
- Set up research directories of radiotracer availability for pre-clinical and clinical research studies
- Identify which PET centres are willing to participate in multi-centre studies (see 2.2.2)

8. Oncology community should work with MHRA and MRC neuroscience representatives to reduce regulatory hurdles:

- Clarify definition of mechanistic study and clinical trial for radiotracer development and produce PET specific algorithm (see 2.6.3 and 2.6.4)
- Develop flowchart to help guide first-in-man PET studies
- Consider setting up a PET 'expert' group to act as an intermediary to provide advice on regulatory issues to PET users
- Consult with chair of QP panel of advisors to try to find mechanism to raise awareness of PET imaging among QP trainees and investigate whether it could be possible to replace QP requirement with local or regional 'quality supervisors/responsible persons' specialised in PET regulations
- Investigate potential mechanisms to share data on non-IMP compounds to avoid duplication of work (see 2.5.4)
- Establish mechanism to share good practise and enable other centres to develop novel radiotracers
- Organise workshop to guide PET research community on regulatory issues to streamline application process
- Shorten timelines for a microdosing study (approx 9 months or longer) to fit in with needs of Pharma (6 months) (see 2.3.1)

9. Encourage Pharma to add PET sub-studies to phase I/II drug trials in the UK

- Create register of PET sites (on web site) with their capacity to undertake studies with contact details and tumour types
- Facilitate meetings with academic sites and pharmaceutical companies e.g. Roche, AZ, GSK - need to foster sense of common mission of Pharma and academia

10. Identify funding opportunities that could be used to support common goals of the PET research community (see 2.2.3.2, 2.2.4 and 2.5.4)

- Encourage applications to non-UK funding bodies e.g. IMI and National Cancer Institute (NCI) (see 2.3.3)

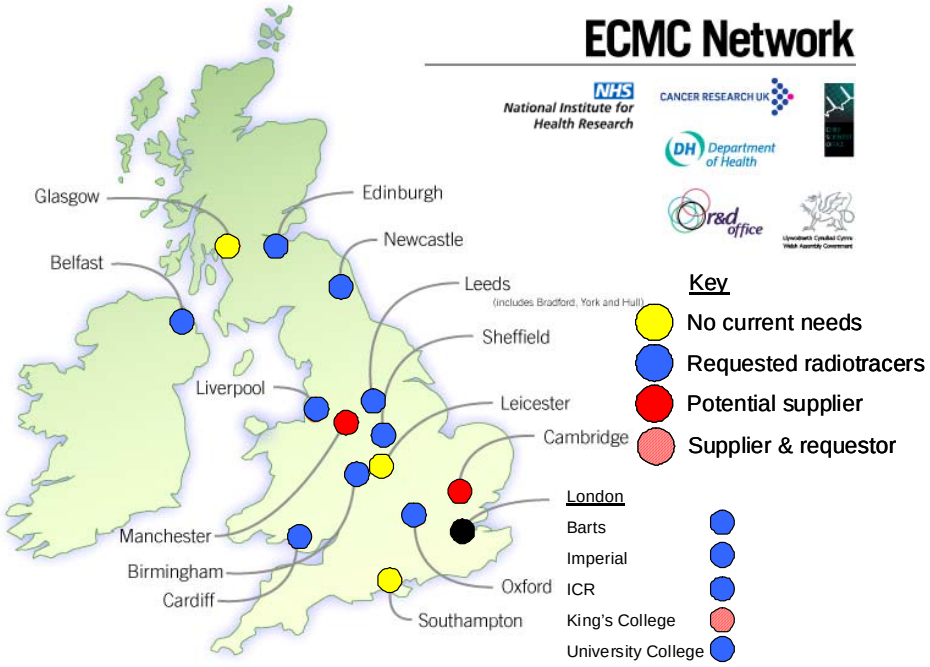
## *Appendix 1 – PET infrastructure in ECMC centres in the UK*

A.

| | Barts | Belfast | Birmingham | Cambridge | Cardiff | Edinburgh | Glasgow | ICR | Imperial College | King's College | Leeds | Leicester | Liverpool | Manchester | Newcastle | Oxford | Sheffield | Southampton | UCL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Will institution have cyclotron by end of 2009?** | N | Y | N | Y | Y | Y | Y | Y | Y | Y | N | N | N | Y | N | N | N | N | N |
| **Number of production hot cells** | 0 | 4 | 0 | 3 | 2 | 4 | 4 | 3 | 4 | 3 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 0 |
| **Number of research hot cells** | 2 | 0 | 0 | 7 | 3 | 0 | 1 | 2 | 6 | 2 | 0 | 0 | 0 | 7 | 2 | 1 | 0 | 0 | 2 |
| **Synthesis module available?** | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | N | N | N | Y | Y | N | N | N | N |
| **Clean room available?** | N | Y | N | Y | Y | Y | Y | Y | Y | Y | N | N | N | Y | N | N | N | N | N |
| **Dispensing cell/isolator available?** | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | N | N | Y | N | N | N | N | N |
| **GMP Grade facilities?** | N | Y | N | Y | Y | Y | Y | Y | Y | Y | N | N | N | Y | N | N | N | N | N |
| **Scanner type (Static/Mobile) at end of 2009** | S | S | S | S | S | S | S | S | S | S | S | M | M | S | S | S | S | M | S |
| **Make of research scanner (GE/Philips/Siemens)** | P | G | G | G | G | Si | G | P | Si | G | P | – | – | Si | Si | G | P | – | G |
| **Gamma counter available?** | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | N | Y | N | N | Y |
| **Small animal PET scanner available?** | Y | N | N | Y | Y | N | N | N | Y | Y | N | N | N | Y | Y | Y | N | N | N |
| **Arterial blood sampling available?** | N | N | Y | Y | Y | Y | Y | N | Y | Y | N | N | Y | Y | N | Y | N | N | Y |
| **Metabolite analysis available?** | Y | N | N | Y | Y | Y | Y | N | Y | Y | N | N | N | Y | N | Y | N | N | Y |

Abbreviations: ICR, Institute of Cancer Research; UCL, University College London; S, Static; M, Mobile; P, Philips; G, GE Healthcare; Si, Siemens; Y, Yes; and N, No.

B.




Geographical map showing the cyclotron and scanner status for each ECMC centre at the end of 2009.

## *Appendix 2 – PET Staff in ECMC centres in the UK*

| | Barts | Belfast | Birmingham | Cambridge | Cardiff | Edinburgh | Glasgow | ICR | Imperial College | King's College | Leeds | Leicester | Liverpool | Manchester | Newcastle | Oxford | Sheffield | Southampton | UCL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Radiochemists (research or clinical)** | Y | Y | N | Y | N | Y | N | Y | Y | Y | N | N | N | Y | Y | Y | N | N | Y |
| **Physics/data analysis** | Y | Y | Y | Y | N | N | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | N | Y |
| **Medical staff** | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y |
| **Access to QP (either at institution or via contract)?** | Y | N | Y | Y | Y | Y | N | Y | Y | Y | N | N | N | Y | N | Y | Y | N | Y |

Abbreviations: ICR, Institute of Cancer Research; UCL, University College London; Y, Yes; and N, No.

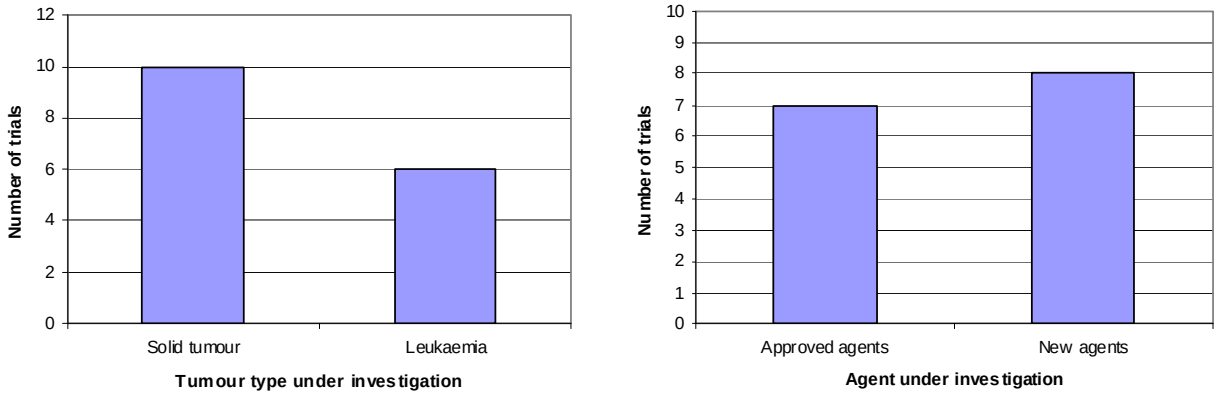
## *Appendix 3 – Current early phase PET trials and funding in the UK*

A

| Main funding body | Trial name | Drug treatment/ aim of study | Tumour type | Phase | No of sites |
|---|---|---|---|---|---|
| MRC | | Docetaxel | Breast | other | 2 |
| CRUK | R-CHOP-21 trial | CHOP | Non-hodgkins | other | National |
| CRUK | ITEM | Glivec | Eye | 2 | 5 |
| Gloucester Pharmaceuticals | GPI-06-002 | Depsipeptide | Peripheral T-cell | 2 | 1 |
| CRUK | HD95 | OEPA vs COPP | Hodgkins | 2 | 4 |
| MRC | | chemo | Liver | pilot | 4 |
| CRUK & OXiGENE | PH1/098 | Oxi4503 | solid tumour | 1 | 4 |
| Eli Lilly & Co | The TS study | pemetrexed+cisplatin | NSCLC | 2 | National |
| Novartis | | LBH589 (panobinostat) | HER2+ Breast | 1 or 2 | 3 |
| Bayer-Schering | ORH/PIB/5336 | Sorafenib | Kidney | 2 | 1 |
| CRUK | IELSG26 | chemo/retixumab/radiotherapy | Diffuse large B-cell | 2 or 3 | 4 |
| CRUK | ReACH | RIC allograft using FMA conditioning | Hodgkins | 2 | Multi-centre |
| Leukaemia Research Fund | SelRICE | methylselenocysteine + R-Ice | Non-hodgkins | 1 or 2 | Multi-centre |
| | | Sunitinib (Sutent) | Metastatic renal | phase 2 pilot | 1 |
| | | CNTO328 (IL-6 antibody) | Epithelial ovarian | phase 2 | 1 |
| CRUK | | Evaluate $^{11}$C vs $^{18}$F-choline for staging | Prostate | 1 | 1 |

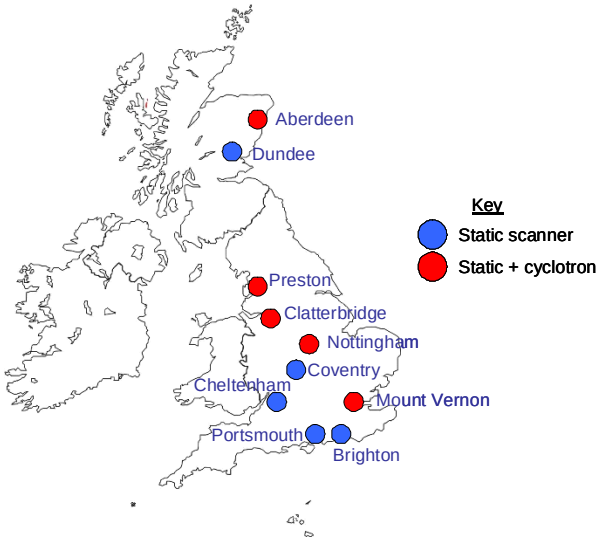
Selection of the early phase PET clinical trials underway in the UK. All of these trials utilise $^{18}$F-FDG, except the CRUK-funded prostate cancer study, and are included in the clinical trials databases. Please note that a number of phase I trials ongoing in the UK are not represented in the table, since they are funded by pharmaceutical companies and not registered in these databases. Abbreviations: CRUK, Cancer Research UK; MRC, Medical Research Council; CHOP, Cyclophosphamide + Hydroxydaunorubicin + Oncovin + Prednisone; COPP, Cyclophosphamide + Oncovin + Prednisone + Procarbazine; OEPA, Oncovin + Etoposide + Prednisone + Adriamycin.

B.



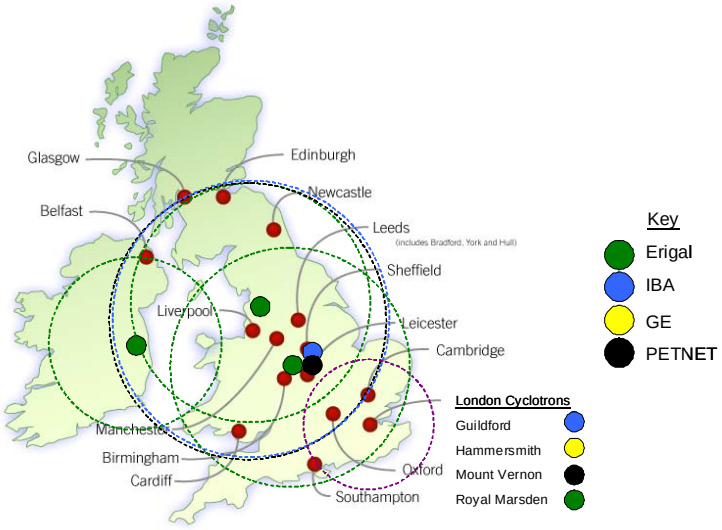

Early phase PET clinical trials by tumour type (solid tumour vs. leukaemia) and drug type under investigation (approved agent vs. new agent).

## *Appendix 4 – Infrastructure in non-ECMC PET centres in the UK*




Geographical map showing the non-ECMC PET centres in the UK that have a static PET scanner. Many of these centres also have access to an onsite cyclotron. Mount Vernon, Nottingham and Preston hospitals have cyclotrons that have been installed by commercial radiotracer companies.

## *Appendix 5 - Commercial delivery of $^{18}$F-FDG in the British Isles*




The dotted circles show the estimated delivery area from commercial sites. Commercial companies can deliver $^{18}$F-FDG to most of the PET centres in England. Erigal can deliver FDG to Belfast from its site at Dublin, and IBA currently delivers FDG to Edinburgh and Glasgow.

## Appendix 6 – Glossary of acronyms

| | |
|---|---|
| ARSAC | Administration of Radioactive Substances Advisory Committee |
| ATSM | $^{64}$Cu-(diacetyl-bis(N4-methylthiosemicarbazone)) |
| AZ | AstraZeneca |
| CCRN | Comprehensive Clinical Research Network |
| CRUK | Cancer Research UK |
| CT | Computed Tomography |

| | |
|---|---|
| CTA | Clinical Trials Authorisation |
| CTD | Clinical Trials Directive |
| ECMC | Experimental Cancer Medicine Centre |
| EMEA | European Medicines Agency |
| F | Fluorine |
| FDA | Food and Drug Administration |
| FDG | Fluorodeoxyglucose |
| FDOPA | 3,4-dihydroxy-6-$^{18}$F-fluoro-L-phenylalanine |
| FLT | Fluoro-L-thymidine |
| F-MISO | Fluoromisonidazole |
| GE | General Electric Healthcare |
| GMP | Good Manufacturing Practice |
| GSK | GlaxoSmithKline |
| HTA | Health Technology Assessment |
| IMI | Innovative Medicines Initiative |
| IMP | Investigational Medical Product |
| IND | Investigational New Drug |
| IP | Intellectual Property |
| IRAS | Integrated Research Application System |
| KCL | King's College London |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| MRC | Medical Research Council |
| MTD | Maximum Tolerated Dose |
| NCI | National Cancer Institute |
| NCRI | National Cancer Research Institute |
| NCRN | National Cancer Research Network |
| NHS | National Health Service |
| NIH | National Institute of Health |
| NIHR | National Institute of Health Research |
| PET | Positron Emission Tomography |
| PRN | PET Research Network |
| QA/QC | Quality Assurance / Quality Control |
| QP | Qualified Person |
| R&D | Research and Development |
| REC | Research Ethics Committee |
| SPECT | Single Photon Emission Computed Tomography |
| USP | United States Pharmacopeia |

**References**

[1] Report of the NCRI PET Strategic Planning Group (2007). A framework for PET research in the UK. http://www.ncri.org.uk/includes/Publications/reports/petreport_low.pdf

***Appendix 7 - Acknowledgments***

The PRN would like to thank all of the individuals who contributed to the PET meeting on July 21st 2009.

**Chairs & Presenters:**

Prof Eric Aboagye, Imperial College London
Prof Mats Bergstrom, Roche
Dr Ian Fleming NCRI PET Research Network & University of Aberdeen
Prof Fiona Gilbert, University of Aberdeen

Dr Paul Marsden, Kings College London
Prof Stephen Mather, Barts and the London School of Medicine
Prof Paul Matthews, GlaxoSmithKline, Imperial College London
Kevin McCarthy, PETNET Solutions
Prof Ken Miles, University of Sussex
Prof Herbie Newell, University of Newcastle-upon-Tyne
Dr Rowena Paul, St Thomas' Hospital Clinical PET Centre & Kings College London
Dr Michael Waller, University of Leeds

**Organisers:** All of the members of the NCRI PET Research Network and NCRI for organising the meeting

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