NCRI PET Research Network

Meeting Report

How to Increase Availability of Non-Fluorodeoxyglucose Radiotracers for PET Research in the UK

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1. Introduction: Barriers that limit availability of non-FDG radiotracers for research and potential ways to overcome these

Increasing the availability of Positron Emission Tomography (PET) radiotracers in the UK is not a trivial task. It has taken a number of years for PET scanning with ^{18}F-fluorodeoxyglucose (FDG) to become well established throughout the UK and implementation of PET in the NHS has required robust scientific evidence to demonstrate the benefits of PET for oncology patients. Over the past 20 years a wide range of radiotracers have been developed in addition to FDG. Many of these may have a role in patient management and/or could facilitate the development of cancer therapeutics; however to date most have been evaluated in small research studies only. Some of these tracers are already produced in a small number of well-established academic PET centres and by commercial suppliers in the UK but availability remains very limited. A number of barriers have been identified that slow down, limit or prohibit potential suppliers from making these tracers widely available. Many of these barriers were highlighted in the recent NCRI PET Research

Network (PRN) report 'Early phase PET research in the UK: Consensus opinion on prioritised research areas in oncology' (see www.ncri-pet.org.uk), alongside some potential solutions to overcome them.

On 1st February 2010 a workshop was organised by the NCRI PET research network to bring together representatives from key academic sites, independent sector radiopharmaceutical companies and regulators in order to discuss and evaluate different radiotracer production and distribution models, and ascertain whether they could be used to increase the range and geographical availability of radiotracers in the UK. This report summarises the key outputs from the meeting.

2. Supply of radiotracers from industry

In order to permit more PET centres to participate in research studies involving non-FDG tracers it is necessary to improve their distribution and availability. A network of commercial facilities now exists throughout the UK (Fig. 1) which, in principle, has the capability to produce and distribute non-FDG radiotracers over a wide geographical area. The following were identified as key issues that need to be addressed if the supply of new radiotracers from commercial radiopharmaceutical suppliers and developers is to increase.

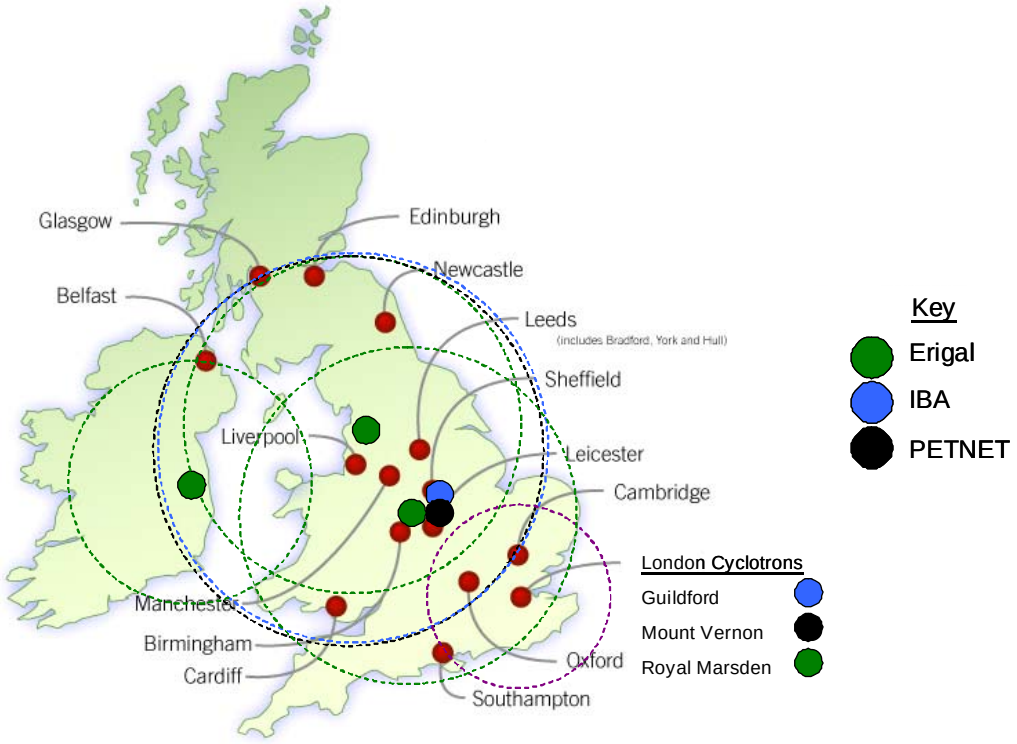

Fig 1. Commercial Facilities in the British Isles that manufacture and deliver radiotracers.
The dotted circles show the estimated delivery area from commercial sites. Commercial companies can deliver tracers to most of the PET centres in England. Commercial companies can also deliver radiotracers to Belfast, Edinburgh and Glasgow.

2.1. Need to stimulate demand for existing and new tracers

Erigal, GE Healthcare, IBA and PETNET Solutions agreed that it was necessary to increase both existing demand for FDG and demand for new compounds that are already available. Several issues were raised on this theme:

1. Production of FDG provides the main income stream for the commercial suppliers. The current price of FDG is very low and not sustainable in the long-term. Companies need to increase income from FDG sales and recoup some of their recent expenditure before investing in setting up production of non-FDG tracers
2. Funding for FDG PET scans needs to be increased. Companies have formed a trade association and plan to lobby the Department of Health (DoH) on this issue
3. There are a limited number of PET scanners in the UK. The PRN survey of PET centres in 2009 revealed that there is a need to increase and/or optimise existing scanning capacity to permit research to take place in some regions. However, there is also some evidence that PET scanners in some centres are not fully utilised
4. There is a need to develop the market for non-FDG tracers that may have widespread clinical use. This requires robust evidence of the clinical benefit of these tracers.
5. Industry/academic collaborations may be a good way to establish the clinical utility of non-FDG radiotracers

	Erigal	GE Healthcare	IBA	PETNET
FDG	All sites	*	All sites	All sites
NaF	All sites	**	Dinnington (may expand)	Mt Vernon (may expand)
FLT	In development	**	In development	Nottingham
F-choline	Marsden (may expand to Keele)	-	In development	-
Hypoxia	In development	-	-	In development (Nottingham, HX4)
Angiogenesis	-	In development (GE135)	-	-
Apoptosis	In development	-	In development (Aposense)	-
Amino-acid metabolism	-	In development (GE148)	-	-
Renal cancer	-	-	In development (Redectane)	-

Fig 2. Radiotracer supply from commercial companies in the UK.
The table includes generic and proprietary radiotracers that companies are either currently supplying or developing for the UK market. Sites that manufacture particular tracers are indicated and shown in Fig 1. Erigal has sites at Keele, Preston & Sutton. IBA has sites at Dinnington & Guildford. PETNET has sites at Mount Vernon & Nottingham. GE is developing the Fastlab system and no longer manufactures and delivers radiotracers around the country but provides cassettes to PET centres.
* Fastlab cassette available. ** Fastlab cassette in development.

2.2. Need to minimise cost of radiotracers

1. The current price of non-FDG radiotracers is very high. This is due to the limited demand for these tracers at present and the fact that there are significant costs associated with setting up a new production line. Many academic grants have a maximum value, so high tracer costs could make these impractical/unattainable for funding PET studies. Therefore, reducing the cost of non-FDG tracers could increase the chance of getting funding for research trials and help to develop the market for the tracer. Some companies were receptive to this idea, whilst others need to consider this further. It is easier to justify reduced prices for proprietary tracers than generic ones.
2. The creation of purchasing consortia might allow a sufficient volume of a radiotracer to be requested to allow companies to build a business case for production at a lower price. Consortia could be organised in various ways:
    - The Principal Investigator for a study could negotiate with a company on behalf of all centres involved in the study.
    - Principal investigators from different studies that are employing a particular radiotracer could form a purchasing consortium
    - Purchasing consortiums may best be organised on a regional basis (e.g. southern England, northern England, Scotland) in parallel with trials networks
    - A funding body could agree a contract with a radiotracer company to purchase a specific number of doses of a particular radiotracer over a set time period and then invite academic groups to submit grant proposals that aim to use the radiotracer
    - Academic sites could collaborate to agree joint contracts with a commercial supplier
3. In some regions transportation costs contribute significantly to the cost of purchasing a radiotracer, so reducing delivery costs would be advantageous. ^{18}F-labelled FDG and ^{18}F-F can be manufactured at the same time, so could be delivered via the same transport
4. Unit cost of radiotracers could be limited by encouraging patients to travel to PET centres that specialise in performing scans with a particular radiotracer. However, in most cases this is not practical as patients are often in poor health, or do not understand the benefits of imaging trials, so are not willing to travel long distances

2.3. Technical issues

1. Make more effective use of each production run; some commercial manufacturers now produce particular radiotracers on specific days so that several orders for a particular tracer can be supplied from one production run
2. A technical solution could be standardised production modules (e.g. the GE 'Fastlab' system), allowing reproducible production to GMP standards on site. This could provide a good opportunity for industry to collaborate with academic sites.

3. Supply of non-FDG radiotracers from academic sources

3.1. PET radiotracers in academia

Most non-FDG tracers produced in academic centres are used in research studies and clinical trials, and the funding to develop, validate and produce these is usually obtained through competitive peer review. Tracer production for other centres/external use is mainly:

1. To enable collaboration
2. To use spare capacity
3. A source of additional income

Tracer availability would be improved by targeted investment to optimise production at centres that have developed promising radiotracers. This would permit these centres to supply these experimental radiotracers to other PET centres and improve the impact of their research. Useful strategic investments would include:

1. A more accessible means of funding tracer development
2. Helping to establish capacity to manufacture GMP-grade radiotracers
3. Infrastructure (hot cells/staff to allow more frequent routine production in larger quantities
4. Simpler and more reliable methods for tracer production

The academic model is probably best for supplying small/medium scale demand of non-FDG tracers on a regional basis. This is an important role, as it makes experimental tracers available for studies to establish their clinical utility. There are several academic sites where a commercial production facility has been set up (e.g. Marsden, Nottingham). These sites should be encouraged to produce new radiotracers as part of the academic collaboration with the company and make them widely available. Infrastructure support may be required for this.

Large-scale commercial production can then take over as high levels of demand become established.

3.2. PET Trials Network

All but the smallest mechanistic studies and trials of new tracers will take place at more than one site, in order to maximise recruitment. Mechanistic and early phase studies require smaller numbers of subjects and sites with specific clinical expertise that are capable of performing complex imaging protocols. Larger phase II/III trials are likely to require larger number of subjects and sites, but generally use simpler protocols.

It is important to know which type(s) of clinical PET trial can be performed at each UK centre, which tumour types can be accessed, which radiotracers can be employed and whom to contact in terms of key staff (oncologist, chief radiochemist, lead PET scientist). The PRN aims to create functional mechanistic trials networks to perform detailed pharmacokinetic/pharmacodynamic studies to support the development of new therapeutic or imaging agents, and to investigate the clinical utility of new PET radiotracers. It is important that potential users can readily gain access to the network and understand how it is coordinated. This will be an extension of and complement the NCRI PET Clinical Trials Network that is already operational

3.3. Funding sources for academic/industry consortia

A number of funding sources were highlighted that could help academic/industry consortia to achieve specific goals. These can be viewed in the database section on the PRN website (www.ncri-pet.org.uk).

4. Summary of proposed actions for PET Research Network

Based on this report several key actions were identified as important to increase the availability of non-FDG radiotracers in the UK. These are summarized below and will be followed up by the PET Research Network in collaboration with other key stakeholders

Consulting with commercial tracer companies

1. Engage with the companies to determine what they would like to see in terms of clinical trials network and which projects may be suitable for academic/industry collaborations
2. Confer with companies to try to agree ways to reduce the cost of experimental tracers for initial studies to help develop the market

Review of existing data

3. Perform/organise a systematic review on new radiotracers to help establish clinical utility and identify research gaps
4. Try to build consensus on best tracer(s) to fill each clinical role e.g. hypoxia (^{18}F-FMISO, ^{64}Cu-ATSM, ^{18}F-AZA, ^{18}F-HX4), apoptosis, angiogenesis and proliferation
5. Identify key studies that should be performed and try to find ways of funding these

Organising purchasing consortia

6. Help to organise purchasing consortia for radiotracers on a regional basis

Developing partnerships

7. PRN website to provide up-to-date information on UK PET sites, to help academic and industry researchers identify PET centres that could contribute to specific studies,(e.g. early mechanistic or large phase II/III)

8. Establish which PET centres can perform mechanistic studies and extend and develop the NCRI PET Clinical Trials Network to be able to perform this type of trial

9. Organise meeting between individual companies and interested academic parties to form consortia and agree framework to tackle specific projects

Consulting with funding bodies

10. Having identified key areas for research, consult with funders to identify suitable way to fund key trials involving new radiotracers; academic, commercial or joint funding approach?

Increasing awareness of utility of PET

11. Work with PET experts and oncologists via Clinical Studies Group meetings to encourage PET substudies in clinical trial design

5. Appendix

List of participants

Surname	Forename	Affiliation
Aigbirhio	Franklin	Cambridge
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Brown	Ian	PETNET Solutions
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Fry	Nigel	Manchester
Gilbert	Fiona	Aberdeen
Godfrey	Elaine	MHRA
Groves	Ashley	University College London
Hagan	Jim	GMEC
Marsden	Paul	King's College London
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Mendizabal	Marivi	GE Healthcare
O'Donnell	Ruairi	Erigal
Owens	Jonathan	Glasgow
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Stratford	Rebecca	National Cancer Research Institute
Vivian	Gill	British Nuclear Medicine Society
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Wilson	Ian	GE Healthcare
Yon	Michael	IBA

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