Operation of PET Cyclotrons for Medical Imaging

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1 The Role of Cyclotrons for PET Studies

The attendees of this conference have their own views of the operation of a cyclotron. In the context of this paper it is viewed primarily as a source of positron emitting radioisotopes which are used for molecular imaging based on positron emitting tracers and positron emission tomography (PET). This form of imaging is the most sensitive and specific method for measuring, in life, molecular interactions and molecular pathways. It represents a fundamental bridge between basic molecular, cellular and experimental animal studies to those of measurements of diseased tissue function in the living patient.

The specificity of PET arises from the use of Carbon-11, Oxygen-15 and Fluorine 18 which can be used to label biochemicals and pharmaceuticals without disturbing their biological function. The sensitivity of PET arises from the fact that imaging is based on the coincidence counting of the annihilation photons emitted following positron capture. As a result of this electronic coincidence counting, high solid angle for detection is offered unlike the case where lead collimation is necessary for example in single photon detection.

Within the scope of this sensitivity and specificity it is possible to identify the role of PET within the spectrum of medical imaging (1). Here it is unrivalled by other methods in the detection of molecular pathways and specific binding and receptor sites where high sensitivity is necessary in order not to disturb the function of those sites with blocking doses of chemical. Within the long term, the role of PET is assured for studying neuro-transmitter pathways, receptors, drug binding and general pharmacology. As a research tool it is destined to be used to obtain new information on human disease, to assess the efficacy and mechanisms of therapies and for drug development and discovery.

2 The Cyclotron Program at Hammersmith Hospital

At the Cyclotron Unit at Hammersmith Hospital, two cyclotrons are in operation: the Scandatronix MC40-II and the IBA CYCLONE 3-D. The former produces beams of protons up to 40MeV, deuterons up to 20MeV, Helium-3 up to 53 MeV and Helium-4 up to 40 MeV. The IBA machine produces deuterons of 3.8 MeV and is used exclusively to produce Oxygen-15 primarily for radioactive water studies of tissue blood flow and thereby avoiding clashes with the production of Carbon-11 etc from the large Scandotronix machine.

At present, two PET scanners are in full operation within the Cyclotron Unit and typically in one week, up to 7-8 different C-11 labelled, compounds are used on at least one occasion for human PET studies. These are inter-weaved with F-18 labelled compounds, radioactive water and experimental C-11 radiochemistry and biology studies. Clinical research programmes, are based on investigations in neurology, psychiatry, cardiology and oncology. In addition, work is being undertaken in pulmonary studies and inflammation. The emphasis is to use a wide range of radiolabelled molecules to create dynamic sequences of images from which the kinetics of tissue tracer concentrations can be recorded tomographically.

3 Cyclotrons for Medical Institutions

The principle emphasis of modern cyclotrons dedicated to PET studies is epitomised by the CTI produced RDS-11. This is an 11 MeV, negative ion, proton only machine which comes with a self shielding facility. There are other manufacturers with similar types of medically dedicated cyclotrons in particular IBA, Ebco Oxford Instruments, Japanese Steel Company etc. To give as an example the flexibility of these machines for medical installations I draw your attention to the fact that at Pittsburg in the USA, they have installed one of the self shielding CTI machines on the 9th floor of a busy medical centre. RDS-11 machines have been installed at many centres in North America which comprehensively cover the country and this is given as an example as to how mature is the Cyclotron engineering for this area.

4 Future Challenges in the Design of Medical Cyclotron

It is interesting to note that although there are many cyclotrons in the field dedicated to produce positron emitting isotopes, very few of them are used to produce Carbon-11 which is perhaps the most interesting short lived with respect it chemical to flexibility and specificity for molecular imaging. Much of the emphasis on the use of these machines is on F-18 compounds and FDG in particular. However, it is worth reflecting that this application could be furnished fairly comprehensively from distribution centres strategically located within North

America. In effect many medical cyclotron installations are the equivalent of thorough bred race horses which are kept firmly locked in the stable. Maybe one of the reasons for this lack of exploitation rests on the high commitment necessary to introduce radiosynthetic labelling using Carbon-11 and the corresponding safety and quality control regulations which need to be overcome in their administration to human subjects.

With this observation it is appropriate to consider the future designs of cyclotrons for medical imaging. It could be considered that the location of cyclotrons for sophisticated molecular imaging is best considered to be that condusive to molecular biology, molecular medicine and pharmacology rather than radiology, the average department of which is certainly less molecularly orientated.

In considering the future potential of molecular imaging in medical research it is clear that its role in the translation from the laboratory to the bedside will be important. Hence one would anticipate that the future use of molecular imaging will focus primarily on large academic centres with a strong remit to exploiting molecular biology discoveries and drug development in general. In fact one could go far as to say that unless this translation from molecular biology to studies in human subject occurs, then many of the fundamental discoveries in the laboratory will be under exploited.

Having identified this future application, it is worth considering how one would extend the range of tracer studies in order to comprehensively embrace the requirements of the molecular biologist.

One area which requires immediate attention for development is how to radiolabel, with positron emitting isotrops, amino acids, proteins, peptides etc. Here one turns to radiochemistry which is being developed primarily in the single photon area namely the use of methods used for radiolabelling by direct halogenation and chelation techniques. In fact, this chemisty is far simpler to implement than that where one builds a molecule with Carbon-11 using chemical precursors. With this vision in mind, one requires positron emitting radio isotopes of suitable metals and halogens.

Table 1 shows a range of metals and halogens which emit positrons suitable for this type of study. It is of note that the identified routes for producing these type of nuclei involve the use of comparatively high energy accelerated beams and in particular the use of helium 3 and helium 4 particles.

Hence the challenge to the cyclotron manufacturers is that in order to fully exploit molecular imaging, the ideal cyclotron is one which is as user friendly and computer controlled as the small 11 MeV negative ion proton machines are but with the flexibility for producing beams of up to 30 MeV alpha particles. Such machines will be destined for academic centres of the highest order and also developmental departments within the pharmaceutical industry. There may be concern that the use of longer lived radiolabels would be restrictive because of excessive radiation dose to the subject investigated. However, I draw your attention to the fact that the technology of PET scanners is continuously developing with respect to improved sensitivity. This is based mainly on extending the axial length of the tomographs thereby increasing the solid angle for detection.

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6 Reference

T. Jones, The role of Positron Emission Tomography within the spectrum of Medical Imaging Eur J Nucl Med (1996) 23:207-211.

Table 1

	Positron emitting isotope	half life	Production primary	Routes alternate
	^{11}C	20m	$^{14}N(p,a)$	
Synthetic	^{13}N	10m	$^{16}O(p,a)$	
Radiolabelling	^{15}O	2m	$^{15}N(p,n)$, $^{14}N(d,n)$	
	^{18}F	110m	$^{18}O(p,n)$	
	^{73}Se	7.1h	$^{75}As(p,3n)$	$^{70}Ge(a,n)$
	^{75}Br	97m	$^{75}As(^{3}He,3n)$	$^{76}Se(p,2n)$
Chelation	^{76}Br	16h	$^{75}As(^{3}He,2n)$	$^{76}Se(p,n)$
and	^{94m}Tc	53m	$^{92}Mo(a,2n)$ (gen.)	$^{93}Nb(a,3n)$
Halogenation	^{110m}In	69m	$^{110}Cd(^{3}He,3n)$ (gen)	
Radiolabelling	^{120}I	1.4h	$^{122}Te(p,3n)$	
	^{124}I	4.2d	$^{125}Te(p,2n)$	$^{124}Te(p,n)$

Data kindly compiled by Dr. Andrew Roberts