The National Medical Cyclotron - An Australian Experience in Technology

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SUMMARY

The establishment of the National Medical Cyclotron (NMC) in the early 1990's was the practical outcome of a vision, held by nuclear medicine professionals, to complement the available neutron-rich radionuclides produced in Australia, with neutron-deficient radionuclides. The NMC is operated by the Australian Nuclear Science and Technology Organisation (ANSTO) in collaboration with the Royal Prince Alfred Hospital (RPAH) in Sydney where the PET department is able to use the short-lived radiotracers to good advantage. Neutron-deficient radionuclides, produced by the NMC laboratories are used in over 70,000 patient studies per year. The NMC has achieved the status of a national facility.

1. INTRODUCTION

Australia's first nuclear reactor was commissioned in the outer suburbs of Sydney in the late 1950's. Australia can fairly claim that it was one of the pioneering countries involved with the reactor-production of neutron-rich radioisotopes, particularly technetium-99m, for application in nuclear medicine.

However, Australia lagged behind the rest of the developed world, in that it could not manufacture neutron-deficient radionuclides, to complement reactor produced radionuclides for the indigenous nuclear medicine community. Cyclotron-produced radionuclides had to be imported.

The first documented experience in Australia of using neutron deficient isotopes as a diagnostic tool occurred in 1960 when researchers from the Medical School of Sydney University used imported, positron emitting 74As, in conjunction with a simple coincidence detection system, for brain studies (1), (2). These studies resulted in the first request to government for an Australian Cyclotron in 1962 (3).

The Australian requirement in the 1980's for imported, cyclotron-produced isotopes plus the rapidly evolving diagnostic modality of Positron Emission Tomography (PET) at the international level, saw a renewed effort on behalf of the nuclear medicine professionals to establish a local cyclotron facility (4), (5).

A decision was made by the Federal Government in 1986 to establish a national cyclotron facility at the Royal Prince Alfred Hospital, Sydney. The $20 million complex was completed in 1991 and is currently operated by the Australian Nuclear Science and Technology Organisation (ANSTO) in collaboration with the Royal Prince Alfred Hospital (RPAH).

The cyclotron complex has the dual role of, (a) producing short-lived radiopharmaceuticals for immediate use in PET and (b) to produce the longer-lived neutron-deficient isotopes for Australia's nuclear medicine requirements.

2. NUCLEAR MEDICINE IN AUSTRALIA

Nuclear medicine in Australia has evolved from the early 1960's to the present in which a population of 18 million is well served by the 160 nuclear medical centres throughout the country. These combined centres are equipped with over 300 gamma cameras, 2 PET cameras and 2 coincidence detectors. They perform in excess of 430,000 patient studies per year.

3. THE NATIONAL CYCLOTRON FACILITY

3.1 The National Medical Cyclotron Complex

The ANSTO facility was built on land, leased from the Central Sydney Area Health Service. The complex houses the radionuclide production laboratories, cyclotron, independent beam rooms for target irradiations and pneumatic transport dispatch system for the RPAH PET department.

There are two radioisotope processing laboratories. One for producing PET-based radiopharmaceuticals and one for the longer lived SPECT (Single Photon Emission Computerised Tomography) radionuclides. . The cyclotron laboratories are located three hundred and sixty metres from the RPAH Department of PET and Nuclear Medicine. The PET radiopharmaceuticals are transferred from the laboratories to the PET camera facilities by an underground pneumatic transfer systems. Radioactive gases can be transferred to the RPAH diagnostic centre using underground stainless steel transfer lines.

ANSTO and RPAH staff have developed the quality procedures and protocols for the Cyclotron Complex to gain a licence, from the Australian Therapeutic Goods Administration, to manufacture both radiochemicals and radiopharmaceuticals for diagnostic requirements.

3.2 The Cyclotron

Nuclear reaction cross sections for the formation of the more common medical radioisotopes are such, that proton-energies of less than 30 MeV can be used. Radionuclides for PET diagnostics are formed at beam-energies generally less than 15 MeV.

Given these facts it was decided to install a 30 MeV compact cyclotron, designed by a Belgian company, Ion Beam Applications.

This cyclotron accelerates negative hydrogen ions to energies necessary to produce the relevant nuclear reactions. The negative ions are produced in a vertically mounted ion source, located external to the cyclotron . They are axially injected into the central region of the cyclotron where they are bent into a horizontal plane by a set of inflector electrodes.

When the beam of ions has reach the required energy inside the cyclotron, the negative ions are 'extracted' by passage through a carbon foil, located at a convenient radius in the cyclotron chamber. The two electrons on the negative hydrogen ion are removed or 'stripped' to form a positively charged hydrogen nucleus or proton. The proton beam can be directed onto a selection of targets using magnets

The cyclotron now operates one hundred hours per week with ninety percent of bombardment time devoted to producing the long-lived commercial radioisotopes. Ten percent of operation time is devoted to the production of short-lived (T1/2 < 2 hours) PET isotopes and related radiopharmaceuticals.

The cyclotron can be operated in a dual-beam mode in which two targets are simultaneously bombarded with the same energy and current.

3.3 Radionuclide Production by the National Medical Cyclotron

The production of radionuclides in a particle accelerator such as a cyclotron differs significantly from the procedures used in a fission reactor. Cyclotrons require a different approach in target technology. In particular, cyclotron targets have to dissipate high levels of thermal energy generated , as the energy of charged particles is dissipated in matter.

For instance, to produce 201Tl at the NMC, requires a proton-beam of energy 30 MeV and a current of 300 A to bombard the solid, internal target. The target must therefore dissipate 9 kW of heat otherwise the electrodeposited target material under bombardment would melt. Heat dissipation is achieved by cooling the back surface of the solid copper target plate with water, flowing at a rate of 25 L.min-1.

External liquid targets, used in the cyclotron production of PET isotopes, are typically bombarded with a beam power 0.4 kW. In addition to water cooling, with a flow rate of 6 L.min-1, these targets also have the front surface cooled by jets of compressed helium.

The radionuclides and nuclear production routes which, to date, have been produced at the cyclotron complex can be seen in Table 1.

TABLE 1. RADIOISOTOPES PRODUCED BY THE NMC

Isotope	Half-life	Production Route
18F	109.8 m	18O (p,n) 18F
11C	20.3 m	14N (p,) 11C
13N	9.97 m	16O (p,) 13N
15O	122.2 s	16O (p,pn) 15O
201Tl	72.9 h	203Tl (p,3n) 201Pb- 201 Tl
67 Ga	78.2 h	67Zn (p,n) 67Ga
123I	13.2 h	124Xe (p,2n)123Cs 123Xe 123I
111In	67.3 h	112Cd (p,2n) 111In

Production of 201Tl and 67Ga commenced at the NMC in 1993. These relatively long-lived radiochemicals are produced in bulk and transported to Australian Radioisotopes, at Lucas Heights, some 40 km south-west of Sydney, for processing and conversion to radiopharmaceuticals, ready for injection.

The major use for 201Tl in Australia is to contribute to the diagnoses of coronary artery disease and tissue viability in addition to indicating to the nuclear medicine practitioner, the to decide the most appropriate patient management regimes over a broad range of coronary disease.

Gallium-67 radiopharmaceuticals are mainly used for diagnosing the extent of Hodgkins Disease and monitoring the effects of chemotherapy used to treat the disease.

The original expectations for an Australian cyclotron facility (3) is now being realised with over 70,000 patient studies per year being conducted with long-lived radionuclide being produced in this facility.

3.4 PET-Based Radiopharmaceutical Production

Whereas the long-lived radiotracers are processed at the Lucas Heights Laboratories, the PET-related preparations are produced at the NMC. These pharmaceuticals are produced, using ANSTO facilities, by radiochemists working for the Royal Prince Alfred Hospital

From an institutional perspective, RPAH comes within the purview of the State of NSW and ANSTO under the Commonwealth. An "in-house" arrangement exists between the two collaborating organisations for the manufacture of these pharmaceuticals. This arrangement enables the ANSTO PET-production laboratories to be considered as a hospital central pharmacy. An Ethics Review Committee of RPAH assesses the technical and ethical questions of PET-pharmaceutical administration for that institution.

From a manufacturers view-point, radiopharmaceuticals for general use are terminally sterilised by autoclaving. Because of time constraints with short-lived PET preparations, filtration sterilisation is favoured over autoclaving. Australian Standards for filtration sterilisation define that this operation must be performed in an environment supplied with filtered air, containing not greater than 3.5 particles per litre with particle diameters less than 0.5 m. The routine PET production laboratoriethe NMC were built to meet these stringent specifications.

Diagnostic PET makes use of positron emitting radionuclides of the essential elements of life: carbon, nitrogen, oxygen and fluorine (as a substitute for hydrogen in organic molecules).

The pharmaceuticals which are being administered to patients at the RPAH Department of PET and Nuclear Medicine include:

* 13N-ammonia; used in diagnosing coronary perfusion abnormalities
* 15O-water: used in measuring regional blood flow in heart and brain
* 18F -FDG: can be classified as the work-horse of PET (6). It was used in cardiac and brain imaging in the early 90's but is now used extensively in oncology in the late 1990's..

At a recent international conference, held in the USA, Australian work conducted at the RPAH with 18F-FDG, was considered to have made a valuable contribution to the use of positron emission tomography in nuclear medicine (6).

The numbers of studies now being conducted by the RPAH PET Department exceed the forecasted 1200 studies per year, estimated by the Australian Institute of Health in the early 90's (7).

Evolving positron-detection technologies have resulted in comparatively inexpensive PET scanners. As these scanners are introduced into Australian nuclear medicine departments 18F-based radiopharmaceuticals are expected to be supplied, from the NMC, to support this evolving technology.

4. CONCLUDING COMMENTS

An Australian cyclotron facility, first mooted in the early 1960's became a reality in the 1990's. This national facility is operated by ANSTO in collaboration with RPAH.

Since the first proton beam was generated at the National Medical Cyclotron on 9 July 1991 several significant improvements were made by ANSTO staff to the cyclotron so that it now exceeds the manufacturers specifications in a number of areas.

The National Medical Cyclotron Laboratories are licensed by the Australian Therapeutics Goods Administration to produce radiochemicals and ethical pharmaceutical formulations for the nuclear medicine profession

The benefits created by this facility touch the well-being of over 70,000 Australians per year

5. REFERENCES

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