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DEVELOPMENTS IN RADIOISOTOPE PRODUCTION AND LABELLING OF RADIOPHARMACEUTICALS

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Abstract

Recent developments in both reactor and accelerator production of radioisotopes finding applications in nuclear medicine and in biomedical research are summarised. The priorities for the production of 48 different cyclotron radioisotopes; and for 42 reactor produced radioisotopes finding biomedical applications are identified. Each includes 5 generator systems. The rapid expansion of cyclotron based radioisotope production and automated synthesis of short-lived radiopharmaceuticals with the position-emitting radionuclides continues to gain momentum. Recent feasibility studies of the cyclotron production of ^{186}Re, ^{99m}Tc and of ^{99}Mo are cited as examples of motivation to develop accelerator alternatives to use of nuclear reactors for medical radioisotope production. Examples of SPET and PET radiopharmaceuticals labelled with ^{131}I, ^{123}I, ^{124}I, ^{18}F, and with therapeutic radionuclides are highlighted.

INTRODUCTION

Nuclear reactors have played a key role in the production of radioisotopes required for medical, industrial, agricultural applications, education in the nuclear sciences and research. Millions of people worldwide have benefited from the ^{99}Mo $\rightarrow$ ^{99m}Tc generator for diagnostic imaging, and ^{131}I for the treatment of cancer. Table I lists the important reactor-produced biomedical radioisotopes. Advances in accelerator and medical imaging technology are driving the demand for radioisotopes and radiopharmaceuticals required by nuclear medicine.

Circumstances such as public perception arising from concern for the environment either from radiation accidents or long term storage of nuclear waste, as well as the operating and replacement costs for aging reactors are factors influencing the prospects of future availability of radioisotopes. This is reflected in recent decisions taken to initiate the de-commissioning of a few research TRIGA reactor(s) that were installed in hospitals during the 1960's.

TRENDS

The number of cyclotron installations at national laboratories, universities and teaching hospitals has expanded [1], since 1970 due to commercial availability of user-friendly cyclotrons. (Fig. 1). There are >200 cyclotrons operating in 1998, with the highest concentration in the United States, European Union and Japan. National accelerator programmes often include use of parasitic beam for LINAC production of selected radioisotopes (e.g., ^{26}Al, ^{67}Cu, ^{68}Ge, ^{72}Se, ^{82}Sr ^{109}Cd, ^{7}Be).

The reactor produced radioisotopes in highest demand for endotherapeutic radiopharmaceuticals are: ^{32}P, ^{67}Cu, ^{89}Sr, ^{90}Y, ^{103}Pd, ^{117m}Sn, ^{153}Sm, ^{165}Dy, ^{166}Ho, ^{186}Re, ^{188}Re and ^{198}Au. The ^{188}W$\rightarrow$^{188}Re generator and ^{186}Re have great potential for cancer therapy, particularly in the form of organo-rhenium radiopharmaceuticals. The ^{166}Dy$\rightarrow$^{166}Ho *in vivo*

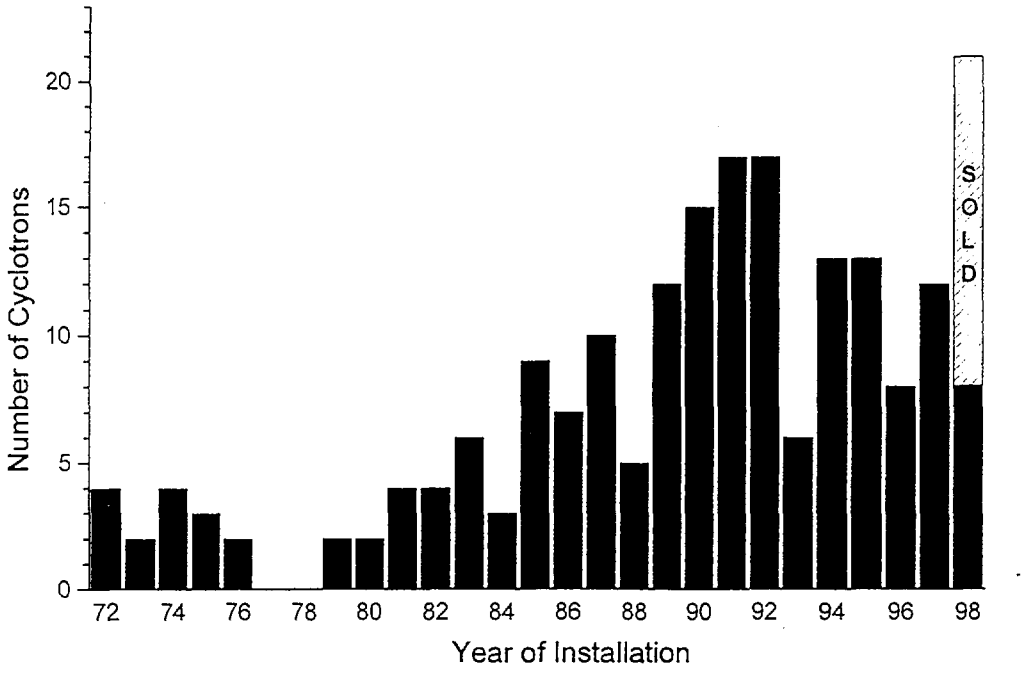

Fig. 1. Number of cyclotron installations commissioned between 1972 and 1997, and a projection for 1998 based upon the number of identified cyclotron orders.

biomedical generator has been suggested as offering advantages for bioconjugated monoclonal antibodies. Both ^{188}W and^{166}Dy are produced by double neutron capture reaction, and therefore production is limited to a few high power nuclear reactors. The applications of neutron-rich radioisotopes include: treatments of cancer with radioimmunospecific radiopharmaceuticals, bone pain palliation, radiation synovectomy for treatment of rheumatoid arthritis, bone marrow ablation for treatment of myloma.

It is essential to develop accelerator technology for the production of neutron rich radioisotopes that are needed for therapeutic and industrial purposes. Since 1993 there has been considerable progress at a few laboratories to meet this objective, and to reduce reliance on research nuclear reactors for medical radioisotopes. For example, there are 16 cyclotrons that will be dedicated to operating 24 h at 7 d per week year round only for the production of ^{103}Pd. It is used as a brachytherapy source for treatment of prostate cancer. Interestingly, the worldwide shortage of highly enriched ^{102}Pd was the driving force to abandon (n,γ) production of ^{103}Pd. The cyclotron production of ^{186}Re, ^{64}Cu and ^{183}Ta has been demonstrated. There is a technological challenge to develop cyclotron targets that can withstand 1 to 5 mA beam currents, as will be required for certain of the nuclear reactions that have a small cross section. Current targetry technology limits beam currents to ~1.2 mA.

Cyclotron radioisotope production uses nuclear data such as decay schemes, excitation functions and thick target yields. Recently a multi-institutional study [2,3] was completed to evaluate the feasibility of the cyclotron production of ^{99m}Tc, and of the ^{99}Mo-^{99m}Tc generator. There are various conflicting reports in the scientific literature. The study was motivated because of the continuing concern about the future supply of ^{99}Mo which is produced with nuclear reactors. Both theoretical calculations using the Hybrid-ALICE code, and experimental measurements of the ^{100}Mo(p,pn)^{99}Mo nuclear reaction with 30-50 MeV protons indicated that the approach was not a viable alternative. However, detailed

TABLE I. IMPORTANT REACTOR - PRODUCED BIOMEDICAL RADIOISOTOPES

^{99}Mo-^{99m}Tc	^{131}I	^{32}P	^{133}Xe	^{60}Co	^{153}Sm
^{188}W-^{188}Re	^{169}Y	^{153}Gd	^{117m}Sn	^{186}Re	^{165}Dy
^{166}Dy-^{166}Ho	^{166}Ho	^{90}Sr	^{89}Sr	^{47}Sc	^{59}Fe
^{199}Hg-^{199}Au	^{198}Au	^{192}Ir	^{82}Br	^{51}Cr	^{55}Fe
^{125}Xe-^{125}I	^{64}Cu	^{177}Lu	^{42}K	^{109}Cd	^{105}Rh
^{212}Bi	^{213}Bi	^{33}P	^{24}Na	^{137}Cs	^{75}Se
^{14}C	^{3}H	^{35}S	^{47}Ca	^{152}Eu	^{170}Tm

TABLE II. PRIORITIES FOR PRODUCTION OF ACCELERATOR RADIONUCLIDES

Application		Radionuclide
PET and 511 KeV SPET		
	Emphasis on:	^{11}C, ^{13}N, ^{15}O, ^{18}F
	Emerging	^{64}Cu, ^{124}I, $^{82}Sr \rightarrow {}^{82}Rb$
	Research Interest	^{38}K, ^{45}Ti, $^{62}Zn \rightarrow {}^{62}Cu$, ^{73}Se, ^{75}Br, ^{76}Br, ^{82m}Rb, ^{94m}Tc
SPET	Clinical	^{67}Ga, ^{111}In, ^{123}I, ^{201}Tl
Therapeutic		^{64}Cu, ^{67}Cu, ^{103}Pd, ^{186}Re, ^{211}At
Standards and Sources		^{22}Na, ^{57}Co, ^{139}Ce
Commercial -Medical		^{18}F, ^{13}N, ^{67}Ga, $^{81}Rb \rightarrow {}^{81m}Kr$, ^{103}Pd, $^{123}Xe \rightarrow {}^{123}I$, $^{201}Pb \rightarrow {}^{201}Tl$
	Emerging	^{124}I
	Various	^{22}Na, ^{57}Co, ^{88}Y
Others		^{7}Be, ^{10}C, ^{26}Al, ^{28}Mg, ^{48}V, ^{75}Se, $^{87}Y \rightarrow {}^{87m}Y$, ^{93}Mo, ^{99}Mo, ^{109}Cd, ^{99m}Tc, ^{147}Gd, ^{195}Au, ^{206}Bi

TABLE III. OUTLINE OF ^{123}I-RADIOPHARMACEUTICALS

Tumours	Peptides and proteins Receptor-specific ligands Meta-iodobenzylguanidine (m-IBG) Hypoxia agents α-methyl-iodotyrosine 5-Iodo-2'-deoxyuridine
Heart	m-IBG Receptor-specific ligands, Fatty acids, e.g., BMIPP
Brain	Neuroreceptor specific ligands, e.g. IDEX, β-CIT, FP-CIT, Blood flow tracers
Infection and Inflammation	Monoclonal antibodies Cytokines
Other	Atrial natriuretic peptide Serum amyloid P component (SAP) Growth factors

measurements of the excitation function for the ^{100}Mo(p,2n)^{99m}Tc nuclear reaction determined that the 22-12 MeV proton energy range could be considered to produce a few Curies of instant ^{99m}Tc for local use provided that a ^{100}Mo target of high isotopic enrichment is used. The peak of the excitation function is between 16-18 MeV. The method may be considered by Member States that do not presently have a nuclear reactor, and have to rely upon imported ^{99}Mo in order to have ^{99m}Tc for nuclear medicine.

The priorities for the production of 48 different cyclotron radioisotopes including 5 generator systems are summarised in Table II. A classification as to applications include medical uses (diagnostic and therapeutic radiopharmaceuticals, stents for treatment of coronary restenosis); radioactive standards and calibration sources; industrial purposes, and environmental tracers, and research.

DESIGN OF RADIOPHARMACEUTICALS

The cyclotron produced radioisotopes used in nuclear medicine have a short half life and decay with a high abundance of photons (100 to 200 KeV) that are efficiently detected by medical imaging instruments such as SPET (Single Photon Emission Tomography) and gamma camera; or that decay with positron emission that permit quantitative imaging with PET (Positron Emission Tomography).

Iodine-123 is gradually displacing the use of ^{131}I for diagnostic applications. The major drawback to wider use of ^{123}I is the expensive targetry system involving the use of isotopically enriched ^{124}Xe as the target system. Table III outlines the range of ^{123}I-radiopharmaceuticals used for various applications [4].

Fluorine-18 ($T_{1/2}$ = 110 m), ^{11}C ($T_{1/2}$ = 20 m), ^{15}O ($T_{1/2}$ = 2 m), and ^{13}N ($T_{1/2}$ = 10 m), are the most popular PET radioisotopes. Over 1000 compounds have been labelled to study specific biochemical processes and physiologic function. Numerous of receptor-specific ligands, small molecules, growth factors are being evaluated [5]. The European concerted action [6] on new radiotracers is an excellent example of coordinated research efforts for quality assurance and technology transfer. The new frontier for radiopharmaceutical development is based upon the collaboration of radiopharmaceutical scientists and molecular biologists.

Radioisotope production has been optimised, but there is a continuing need for automation in radionuclide processing and radiopharmaceutical synthesis. Considerable synthesis automation is commercially available for the preparation of synthetic precursors and PET radiopharmaceuticals. The clinical applications in oncology, cardiology and neurology presently rely upon 25 different PET radiopharmaceuticals. However, most clinical PET centres routinely use only 2 to 5 PET radiopharmaceuticals. ^{18}FDG is the most popular PET radiopharmaceutical. There is an opinion the nuclear oncology with ^{18}FDG accounts for >80% of clinical PET applications.

An additional advantage of emission tomography is that low dose of short lived cyclotron radioisotopes is used to do individual patient radiation treatment planning prior to administration of a high dosage of reactor produced radioisotopes for endotherapeutic treatments. For example, the use of the positron emitter ^{124}I for PET studies as the prelude to high dose administration of ^{131}I; ^{64}Cu and ^{67}Cu; or ^{86}Y and ^{90}Y.

PROGRAMME DEVELOPMENT CONSIDERATIONS

The first question arising when an institution is considering to purchase a cyclotron relates to the decision of the scope of the program envisioned for radioisotope production. The next questions focus on all aspects of the radiochemistry, hot cell processing, automation for provision of radioisotopes, labelled synthetic precursors and preparation in the required radionuclidic purity and radiochemical form for use. Considerable information is available in topical books and review articles published during the past 5 years [7,8.9,10]. The Cyclotron Directory to be published in 1998 contains very useful information concerning cyclotron programs worldwide[1].

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