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A MINICYCLOTRON-BASED TECHNOLOGY FOR THE PRODUCTION OF POSITRON-EMITTING LABELLED RADIOPHARMACEUTICALS.

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INTRODUCTION

The use of short-lived positron emitters together with positron-emission tomography for probing the dynamics of physiological and biochemical processes in the normal and diseased states in man is presently an active area of research whose bounds continue to expand rapidly. Specifically, the use of compounds labelled with the positron emitters carbon-11, fluorine-18, nitrogen-13, and oxygen-15 have permitted the successful investigation of function and metabolism in the brain and myocardium (32). The methodology of positron computed tomography (PET) and tracer kinetic modelling and the application of these noninvasive nuclear – imaging techniques to the understanding and treatment of various pathologic states have been thoroughly reviewed recently from different perspectives (26,31,32,45).

Understandably, the pathway from production of the appropriately labelled precursor or final product to subject imaging in a diagnostic or research environment demands a multidisciplinary effort. One of the pivotal elements for the continued growth and success of PET, especially in a clinical setting, is the routine delivery of useful quantities of radioactivity incorporated in the desired positron emitting labelled compound. To date, the cyclotron remains the accelerator of choice for production of medically useful radionuclides. For the shorter lived isotopes, i.e., O-15 ($t_{1/2}$ = 2.03 min), N-13 ($t_{1/2}$ = 9.96 min), and even C-11 ($t_{1/2}$ = 20.38 min) this necessitates close proximity of the accelerator to radiochemical preparation systems, clinical facilities, and imaging hardware. Compounds labelled with F-18 ($t_{1/2}$ = 109.72 min) pose less of a restriction because of the longer half-life. However, as has been discussed elsewhere, (45) the more prudent strategy may still dictate an in-house accelerator facility, even for fluorine-18 labelled compounds.

SINGLE PARTICLE MINICYCLOTRONS

The development of PET has provided the capability of performing noninvasive local biochemical measurements in man that have never before been possible. The results from the applications of PET have provided a rapid increase in the number of positron emission tomography centers throughout the world. However, the major difficulty in the dissemination of PET is the cyclotron technology. Although progress has been made in the chemical synthesis of positron-emitting labelled radiopharmaceuticals, the design of cyclotrons required for the on-site production of those short-lived radionuclides has not changed significantly over the past two decades. This has stimulated a number of research investigators to explore this technology to meet the requirements of the medical environment.

Until recently, pragmatic concerns of physical size limitations and expense have limited the acquisition of cyclotrons to relatively large institutions having aggressive clinical programs and/or research objectives. However, with the advent of a new era of small, mini, or "baby" cyclotrons, (48) it is anticipated that a larger audience will be able to share in the benefits provided by PET. If the focus of the clinical program at hand is production of the four positron-emitters mentioned above, then several machines potentially capable of meeting existing production demands are either under contruction or commercially available (18,36,48). Machine parameters and physical descriptions of some of these accelerators have been given elsewhere (36,45). Most of these "baby" cyclotrons, however, have been developed in a conventional format of the physics cyclotron, with multiple particles and, for the most part, are not designed for low radiation shielding requirements, or to be used with computerized control.

For simplicity of design and operation, low radiation shielding requirements, low space and cost requirements, a low-energy single-particle machine is desirable. A small 8-10 MeV proton accelerator with 50-100 microamps of current meets these requirements and yet satisfy the needs for the production of sufficient quantities of radioactivity. The rationale for suggesting that a low energy, proton only machine is capable of providing the necessary levels of the four radionuclides in question was provided by an analysis of the available nuclear reaction yield data for proton bombardment of enriched stable isotopes (17,18,42). The proton reactions for production of the positron emitters of interest and their saturation yields of 8 MeV are given in Table 1.

Certainly, the yield of a given nuclear reaction at a particular energy is only part of the story. There are several other considerations that must be addressed before one arrives at the final radiolabelled product. Some of these factors include (33): 1) choice of target (i.e., solid, liquid, or gas) and ease of remote handling and transfer; 2) variables that affect efficiency of producing the theoretical maximum activity for a given set of machine parameters, including beam optics, small angle multiple scattering, and target gas density reduction (43); 3) generation of the desired chemical form of the labelled precursor by irradiation of the appropriate nuclear target, separation of this precursor from other unwanted labelled species, and their behavior and distribution as a function of irradiation conditions (9,10); and 4) precursor trapping and extraction efficiencies and radiochemical yields of the synthetic methods used. With these considerations in mind, a more realistic representation of cyclotron requirements based on user needs is given in Table 2. Here, we have transformed the current UCLA radiochemical activity level requirement per nuclide per production run into the theoretical end of bombardment (EOB) activity that is necessary to arrive at this desired

final product. In turn, the anticipated 8 MeV machine parameters based on these EOB activity levels are listed in column five. In both instances, CS-22 vs 8 MeV, the starting level of activity is more than sufficient to provide enough final product activity per patient study.

It should be noted that providing curie levels of positron emitters (18) is not as simple as offsetting the lower proton energy (and, thus, yield in some instances) with a higher beam current. The potential problem of radiation-induced complications has already been mentioned above. In addition, potential problems due to excessive target and target containment foil heating due to higher beam currents must be resolved. Also, the cost, recovery, and reuse of expensive enriched isotopes must be carefully considered.

RADIOPHARMACEUTICAL PRODUCTION

It is very little doubt that with the use of enriched targets sufficient quantities of F-18 (34), C-11 (8), N-13 (24,47), and O-15 (19) can be produced in the form of synthetically useful radiolabeled precursors. The more compelling issue upon which hinges the success of a low energy, proton only machine is provision of a suitable F-18 labeled precursor for electrophilic reactions (e.g. F-18 F_2).

The problem is not one of producing sufficient quantities of F-18 via 8 MeV proton bombardment. As can be seen in Figure 1, roughly 130 mCi/μA at saturation of F-18 can be produced 8 MeV using $^{18}O(p,n)^{18}F$ reaction. A similar yield for the $^{20}Ne(d,\alpha)^{18}F$ reaction requires in excess of 20 MeV deuterons. Because a single particle machine can produce F-18 only via the ^{18}O $(p,n)^{18}F$ reaction, some concern can be expressed over its ability to produce F-18 F_2 for F-18 labeled 2-deoxy-2-fluoro-D-glucose ((F-18)2-FDG) synthesis via electrophilic addition (20,21).

Only limited success was met in producing (F-18)F_2 by adding carrier to an O-18 O_2 target (33,34). Recent advances, however, in target chemistry have paved the way for demonstrating that the single energy, proton only machine can be used successfully in a clinical setting. The development of a two-step radiation-induced exchange of F-18 (from O-18(p,n)) deposited on the target wall with carrier F_2 added in the second step after recovery of the O-18 O_2 has resulted in production of more than 60 mCi of (F-18)F_2 (25,28). Preliminary results from this laboratory have shown that 25% of the theoretical yield of F-18 activity can be recovered as F_2 using this method, with specific activities that approximate those presently used for production of (F-18)2-FDG.

Moreover, the continued pursuit of new synthetic routes to [F-18]2-FDG has involved nucleophilic displacement by fluoride ion (23,39,41). The use of fluoride ion is attractive because all of the fluorine-18 produced could be incorporated into the final product. Furthermore, accelerator production of F-18 fluoride is more readily achievable, and at the no-carrier added level, than (F-18)F_2. Because of competing reactions, nucleophilic displacement at C-2 of carbohydrates is difficult and the reaction proceeds only with low yields using the appropriate 2-O-trifluoromethanesulfonyl-β-D-mannopyranoside as a substrates (23). The use of the 2,3-sulfate ester of 4,6-benzylidene-1-O-β-methyl mannopyranoside provides an elegant solution to the problem, giving excellent yields of the fluoro sugar upon treatment with fluoride ion (41). Similar encouraging results have been obtained by nucleophilic displacements on 1,2-anhydro-3,4:5,6-di-O-isopropylidene-1-C-nitro-D-mannitol with potassium hydrogen fluoride (39), a reaction being extended with modifications, to F-18 fluoride at our Laboratories (35).

Reactions with F-18 fluoride ion are particularly important when high specific activities are required for the F-18 labeled products. Exquisite

examples of these are radiotracers for the mapping of neuroreceptors, specifically F-18 labeled neuroleptics for central dopamine neurotransmission localization (4). A concentrated effort to label F-18 labeled neuroleptics (e.g. F-18 labelled spiperone and haloperidol) is presently taking place in various laboratories using nucleophilic aromatic substitution with non-carrier added F-18 fluoride (6,40) on a variety of organic substrates, e.g. 1-aryl-3,3-dialkyltriazenes, and nitroaromatics (46). This has provided a stimulus for the exploration and development of new methods of F-18 fluoride production (44). In fact the literature is replete with methodology for the production of "anhydrous" $H^{18}F$, (11-15,22) and aqueous or anhydrous fluoride ion (16). Thus, labelled fluoride ion can be provided either by proton bombardment of a) enriched $^{18}O_2$ gas target and subsequent recovery of F-18 HF (37,38) or $^{18}F^-$(aq), (27) or b) an enriched O-18 water target and recovery of $^{18}F^-$(aq) (44).

THE INTEGRATED REMOTE, AUTOMATED SYSTEM

The integrated radiopharmaceutical production system, designed to meet the needs of the medical research environment and to provide the capabilities for the dissemination of the technology in a clinical setting should have the following key features: i) operatior by a Nuclear Medicine Technician from an interactive video-terminal which exercises control on the cyclotron, radiation monitors, delivery lines and precursor modules, ii) efficient production of radiopharmaceuticals with automated chemistry modules, iii) low equipment cost, and iv) reduced cost of personnel and space (e.g. small size of the system).

Consequently, the system, can be viewed as having the following components; a) a small, microprocessor-video terminal controlled low-energy, single particle cyclotron, with physical size and weight significantly reduced compared with other small cyclotrons (45); b) electronically controlled exchangeable target system for production and delivery of C-11, F-18, N-13 and

O-15 in appropriate chemical forms, c) modules for conversion of these radionuclides into appropriate chemical precursors, and d) automated chemistry modules (unit operations) for the synthesis, processing and purification of the final radiopharmaceutical preparation, in a sterile and pyrogen-free form, suitable for injection into humans.

Thus, it should be clearly recognized that the development of the technology for production of a number of radiopharmaceuticals for the study of blood flow, membrane transport, metabolism, protein synthesis and neuroreceptor localization requires not only the development of a low-energy, single particle cyclotron, but also the targetry, delivery systems, the chemical methods for production of labeled compounds in an automated form, and, finally, the integration of all these components.

Although an integrated system, specifically designed for biomedical applications, has never been developed, a significant amount of groundwork has been laid for this technology. A small, simplified low-energy, only a proton cyclotron has been specifically designed and constructed for this purpose, and the data available demonstrate that with the use of enriched targets sufficient quantities of F-18, C-11, N-13 and O-15 can be produced in appropriate chemical form (Table 1).

At UCLA we have also developed and used remote semiautomated systems, with the ultimated goal of refining this approach to achieve complete automation of the synthetic process through total microprocessor control (1). This approach to the design of these systems was dictated by two requirements. First, the system must be composed of simple, interchangeable units, one for each type of operation being carried out (e.g., aqueous-organic extraction, column purification, sterilization, etc.) Second, these units are to be composed of common laboratory items whenever possible. Thus, any system initially constructed for the preparation of a specific compound may easily be

disassembled into its components, which can then be recombined in a different way to obtain another synthesis system. In line with these objectives, each unit (or step) of the synthetic procedure has been simplified as much as possible which makes the unit operations easily adaptable to a microprocessor control. The flexibility and reliability of this design approach is attested by the record of over 1200 production runs for the preparation of (F-18) 2-FDG (2), [1-^{11}C]2-DG (29), [1-^{11}C]palmitic acid (3), L-amino acids labelled with carbon-11 and nitrogen-13, produced enzymatically from (C-11) carbon dioxide (3) and (N-13) ammonia (7), and L-[1-^{11}C]leucine prepared using the Bucherer-Strecker reaction (5).

In summary, the development of this technology, which is within reach the human resources of Nuclear Medicine, entails building of a core cyclotron specifically designed for this purpose, and further research into the areas of nuclear reactions, targetry, isotope delivery, and rapid chemical and biosynthetic techniques. Thus a project of this kind requires the dedicated input of a multidisciplinary group of engineers, chemists, physicists, computer scientists and physicians, knowledgeable about each of these technologies and able to foresee the most important applications of PET now and in the future. The work already done in this area, and discussed above, demonstrates the feasibility of this technology and brings the concept of widespread use of small cyclotrons in a clinical atmosphere several steps closer to reality.

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Table 1. Proton Reactions and Yields for a 8 MeV Cyclotron

Nuclear Reaction	Saturation Yield(mCi/μA)
$^{14}N(p,\alpha)^{11}C$	40
$^{15}N(p,n)^{15}O$	47
$^{13}C(p,n)^{13}N$	82
$^{18}O(p,n)^{18}F$	129[a]
"	88[b]

[a] O-18 gas target

[b] O-18 water target

Table 2. Cyclotron Production of Radionuclides

TCC CS-22			H^+ only, 8 MeV fixed	
Reaction of Choice	Beam Conditions[a]	Theoretical EOB Activity[b]	Reaction	Beam Conditions[c]
$^{20}Ne(d,\alpha)^{18}F$	9.4 MeV 25 μA x 1 hr	450 mCi	$^{18}O(p,n)^{18}F$	16 μA x 1 hr
$^{14}N(p,\alpha)^{11}C$	12.3 MeV 30 μA x 10 min	1.1 Ci	$^{14}N(p,\alpha)^{11}C$	30 μA x 35 m
$^{16}O(p,\alpha)^{13}N$	20 MeV 20 μA x 15 min	700 mCi	$^{13}C(p,n)^{13}N$	15 μA x 15 m
$^{14}N(d,n)^{15}O$	9.4 MeV 30 μA x 8m min	1.3 Ci	$^{15}N(p,n)^{15}O$	30 μA x 3 m

[a]Dictated by user needs, reaction/trapping/extraction efficiencies, etc. Energies listed are "on target".

[b]Assumes a thick target.

[c]Assumes use of some targetry as for CS-22.

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