THE PRODUCTION OF RADIONUCLIDES FOR THE BIOSCIENCES

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ABSTRACT

The use of cyclotrons for the production of radioisotopes used in the biosciences has experienced a renaissance during the last 20 years. A major factor for this renewed interest has been the development of the negative ion cyclotron permitting multiple simultaneous beams with differing energies and intensities. With these new cyclotrons, the commercial suppliers of radioisotopes could greatly expand their production capabilities with a single cyclotron. A look at future needs as expressed by the proposal by the United States Department of Energy to build a National Biomedical Tracer Facility are addressed.

In order to appreciate the issues surrounding radionuclide production one must first understand the *tracer principle* which is the basis for the use of these radioisotopes. The tracer principle requires that the tracer behave in a similar manner to the components of the system to be probed, that the tracer does not alter the system in any measurable fashion and that the tracer itself can be measured.

In assessing the radioisotopes that can be used to probe biological systems, there are but a few that have the requisite physical properties that enable them to be used in situations requiring external detection. Table 1 provides some examples. Included are the theoretical specific activities, a measure of the quantity of material that would be introduced into the system to be probed. It is evident that the higher the specific activity the greater the chance that the system will not be perturbed by the introduction of the tracer. For this reason, short-lived radionuclides are often the choice for the tracer.

The advantages associated with short-lived radioisotopes are the low radiation dose to personnel preparing the tracer and subject receiving the tracer, often serial studies can be performed on the same day, and there is little if any waste disposal problem. The disadvantages, on the other hand include the requirement of having an on-site accelerator such as a cyclotron and the burden of rapid chemistry in order to provide the radionuclide in a usable biochemically active form.

Table 1. Radioisotopes Used as Tracers

Radioisotope	$T_{1/2}$	Theoretical Sp. Act. (Ci/mmol)
^{3}H	12.4 y	29
^{14}C	5730 y	0.62
^{11}C	20.3 min	9.3×10^{6}
^{18}F	110 min	1.7×10^{6}
^{13}N	9.97 min	1.9×10^{7}

- 1 mCi $^{14}C = 9.6 \times 10^{18}$ atoms = 0.22 milligrams
- 1 mCi $^{11}C = 6.5 \times 10^{10}$ atoms = 1.5 picograms

In order to provide a radionuclide for use as a tracer there are a number of production considerations that need to be addressed as outlined below.

1. Energy required to initiate the reaction.
2. Energy where maximum cross section occurs.
3. Chemical form of the target nucleus.
4. Physical form of the target nuclei.
5. Chemical form of the product.
6. Physical form of the product.
7. Ease of separation of the product from the target.

As an example, the production of ^{18}F will be addressed using the above criteria.

Table 2 illustrates the possible reactions one can use to produce ^{18}F. Depending upon what type of accelerator is being used there are a number of reaction processes requiring different bombarding particles and energies.

The target materials cover the full spectrum including cryogenically frozen water targets. The chemical

Table 2. ^{18}F Production

Possible Reactions:

Reaction	E_{th}(MeV)	E_{max}(MeV)
^{18}O(p,n)	2.6	6.0
^{20}Ne(d,α)	0	5.5
^{16}O(^{3}He,p)	3.8	7
^{16}O(α,pn)	23.2	37
^{nat}Ne(p,X)	26	45

forms include elemental and simple compounds of oxygen as well as neon gas. The product is in two basic chemical states, either as aqueous fluoride or as fluorine gas. The ease of separation of product from target depends on the physical/chemical forms of the two. In the case of the neon, the target material is chemically inert and does not participate in any subsequent reactions. For the water targets, the fluoride ion is usually trapped to separate from the target material and then taken up in a non-protic solvent. The F_2/O_2 system is still under investigation but shows promise for use in a number of situations.

For many target configurations there is still controversy as to the target chamber materials that should be used. For the case of water targets, the choices include silver, titanium and nickel with silver or titanium being preferred. For gaseous fluorine it was long felt that the target chamber must be constructed of nickel or nickel alloys. Recent results indicate that aluminum may be just as useful.

The expected yield from a reaction is determined by integrating the cross section over the energy range of the bombarding particles. The yield also depends upon the particle flux and bombarding time. For short-lived radioisotopes the yield is adjusted by the saturation factor, $(1\text{-}e^{-\lambda t})$ to account for the fact that as the nuclei are produced these same nuclei are decaying.

Quite often the yield from a particular reaction does not equal the calculated yield. Possible causes include the following:

- Wall interactions (low recovery).
- Target gas density reduction in beam path, also cavitation in liquid targets (low production).
- Bombarding energy not optimized (low production).
- Contaminates in the target mixture (low recovery).

In spite of these difficulties, a well designed target can produce yields that approach the theoretical maximum, even at high beam current. In using gas targets, the designs require the use of high gas pressure which presents its own problems, especially with respect to the thin target isolation foils. The construction of gas targets requires a good understanding of heat transfer and material sciences.

Table 3 gives the estimated use, in curies, for a variety of radionuclides used in nuclear medicine over the past decade. Beside the obvious conclusion that the ^{99}Mo/^{99m}Tc generator system dominates nuclear medicine usage, is the fact that there has been a tremendous growth in the use of ^{201}Tl and ^{123}I.

This increase in availability of radioisotopes has resulted from the manufacture of a new generation of cyclotron designed explicitly for radionuclide production. Up until the last 15 years or so most of the cyclotrons that were used as *medical* cyclotrons were multi-particle physics machines with fixed energy electrostatic deflection. For high current operation internal targets were utilized. In the late 1970's, The Cyclotron Corporation introduced the first commercially available negative ion cyclotron.

The negative ion cyclotrons accelerate H^- ions which makes it possible to extract the beam of protons at any energy and to also extract multiple beams simultaneously. These features have the advantage of simplicity of extraction with a thin graphite foil which is extremely efficient, nearly quantitative. And by placing the foil extraction system at various radii, the energy can be varied. With more than one extraction system multiple beams can be extracted simultaneously. Thus, a 30 MeV negative ion cyclotron becomes a highly efficient machine for producing radionuclides. Most of the major radiopharmaceutical companies now own at least one of these cyclotrons.

A less obvious trend is that the use of the chemically inert xenon continues to grow. In spite of the better decay properties of ^{127}Xe in comparison to ^{133}Xe, the latter still dominates in usage. The reason for this is the requirement for a high energy accelerator for producing ^{127}Xe (around 100 MeV). At the present time the only sources for ^{127}Xe are the large accelerators at the national labs in the U.S. and facilities like TRIUMF. Because these facilities use machines designed for physics programs the schedules preclude the routine, reliable production of medical radioisotopes.

Table 3. Estimated Usage of Selected Radioisotopes by Year (curies)

Nuclide	$t_{1/2}$	Retail Consumption 1982	Retail Consumption 1987	Retail Consumption 1990
^{99}Mo/^{99m}Tc	66 h/6 h	100,000 (^{99}Mo)	120,000	150,000
^{111}In	68 h	150	160	185
^{123}I	13.2 h	75	1,250	3100
^{127}Xe	36.4 d	100	100	100
^{133}Xe	5.2 d	25,000	25,000	45,000
^{201}Tl	73 h	500	2,500	6,000

In addition there are a number of other radioisotopes that are not readily available through the commercial route which have the potential of having importance in medical research as diagnostic or theraputic agents. The U.S. Department of Energy at the urging of the Society of Nuclear Medicine has organized a number of workshops to address ways these radioisotopes can be made available. At the most recent workshop at Purdue University, a draft mission statement was formulated which included the following aims.

- Production of research radionuclides
- Research – production, separation and purification of radionuclides
- Education and training
- Research in basic radiopharmaceutical chemistry
- Production of commercial radionuclides

In order to meet the mission the accelerator was to have the following design features:

- Proton beams
  - 30 - 100 MeV, variable to 1 MeV increments.
  - >750 μA.
- 2 High intensity beam lines
- 2 Low intensity beam lines
- Any 2 operational simultaneously
- Operation -
  - 24 hours/day
  - 7 days/week
  - Minimum of 46 weeks/year

The outcome of this movement awaits Congressional action.

This presentation began as a retrospective look at the roots of radionuclide production. If we are to be more than simple historians we need to examine the basis of this evolution and try and learn from the experience. Thus it seems fitting to speculate on the future of cyclotrons, as seen by this author and in doing so we can look forward to seeing cyclotrons in the following areas.

- (>100) Small cyclotrons (3–18 MeV) located at regional centres and large research hospitals.
- (10-20) Production cyclotrons (30 MeV) operated for commercial production and distribution of radionuclides.
- (1 or 2) High energy cyclotrons (100 MeV) located at national research centres.

So it is with these predictions that designers of cyclotrons are challenged to find ways to make this a reality so that biomedical research can continue to grow to the benefit of all.