

# PRODUCTION OF RADIOISOTOPES FOR IMAGING AND THERAPY AT LOW ENERGY

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## 1 Introduction

The production of radioisotopes for use in biomedical procedures such as diagnostic imaging and/or therapeutic treatments is achieved through nuclear reactions in reactors or from charged particle bombardment in accelerators. In reactors the nuclear reactions are initiated with neutrons while in accelerators the typical charged particle reactions utilize protons although deuterons and  $\alpha$ -particles play a role. While the generation of the  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generator is performed in reactors and the procedures making use of this generator account for nearly 90% of all Nuclear Medicine procedures, this paper will focus on the use of low energy (<50 MeV protons) accelerators for the production of radioisotopes.

One clear advantage that accelerators possess is the fact that, in general, the target and product are different chemical elements making it possible to find suitable chemical or physical means for separation. This leads to the potential of high specific activities. In addition, at low energy there are fewer isotopic impurities that also contribute to higher specific activities.

The availability of accelerators fits into several categories. First there are university-based cyclotrons that are typically multi-particle machines with energies around 30-50 MeV. Then there are the hospital-based machines, which are generally dedicated to the production of the standard PET radioisotopes ( $^{11}\text{C}$ ,  $^{13}\text{N}$ ,  $^{15}\text{O}$ , and  $^{18}\text{F}$ ). These cyclotrons accelerate protons in the 10-19 MeV range and some also produce deuterons with an energy of about  $\frac{1}{2}$  that of the proton (5-9 MeV). The cyclotrons used by industry for large-scale production are typically 30 MeV proton only machines although there are some using lower energies for dedicated production of  $^{103}\text{Pd}$  (see below).

Several national labs from around the world are involved in the production of radioisotopes that are not produced by the commercial radioisotope producers such as the  $^{82}\text{Sr}/^{82}\text{Rb}$  generator and  $^{68}\text{Ge}$ . These machines are typically operated at greater than 100 MeV and accelerate protons with a beam current exceeding 150-200  $\mu\text{A}$ . The limitations of these high-energy facilities include the difficulty associated with scheduling since most of these facilities are machines that have been built around Nuclear Physics programs with medical applications using the accelerator in parasitic mode or when the physics program is not operational. Another problem is the range of products produced. Because of the high energy of the proton beam, the dominant reaction mechanism is spallation, which produces not only many different atomic species but also many isotopes of the same element. This not only provides possible radioactive contaminants but also stable species that can affect the specific activities of the desired product. A more detailed discussion of these facilities can be found elsewhere in these proceedings.

## 2 Radioisotopes for Imaging

While there is a wide range of radioisotopes that are used in imaging, a relatively small number make up the vast majority of all studies in SPECT and PET imaging. Table 1 lists the most widely used radioisotopes for imaging along with a couple of potentially useful radioisotopes.

SPECT	PET
$^{99\text{m}}\text{Tc}$	$^{11}\text{C}$
$^{123}\text{I}$	$^{18}\text{F}$
$^{201}\text{Tl}$	$^{64}\text{Cu}$
	$^{124}\text{I}$

Table 1. Radioisotopes used in imaging.

Table 2 provides the various low energy production routes along with the half-life of the radioisotopes. Technetium-99m is included since this isotope alone accounts for nearly 90% of all nuclear medicine imaging studies. There has been a number of proposals over time suggesting that  $^{99\text{m}}\text{Tc}$  could be produced at an accelerator. The economics of producing  $^{99\text{m}}\text{Tc}$  at an accelerator can never compete with the extremely low costs of producing it at a reactor. While there is concern about the ability to build new reactors and thus jeopardizing the availability of this important isotope, the recent construction of reactors in Canada dedicated to  $^{99}\text{Mo}$  production removes this concern for the present.

Iodine-123 has been of interest for nearly 3 decades because of its unique chemistry that makes it possible to attach this isotope to a wide variety of molecules and the  $\gamma$ -

ray energy (159 keV) that is matched well to present day cameras. The ability to produce this isotope in high purity from enriched  $^{124}\text{Xe}$  targets made it possible to ship  $^{123}\text{I}$  over long distances and still have high specific activity  $^{123}\text{I}$  available for labeling. However, the production costs are still very high in comparison to other radioisotopes, which will make its use limited for the foreseeable future.

Radionuclide	t $\frac{1}{2}$	Reaction	Energy (MeV)
$^{99m}\text{Tc}$	6.0 h	$^{100}\text{Mo} (p,2n)$	30
$^{123}\text{I}$	13.1 h	$^{124}\text{Xe}(p,2n)^{123}\text{Cs}$ $^{124}\text{Xe}(p,pn)^{123}\text{Xe}$ $^{124}\text{Xe}(p,2pn)^{123}\text{I}$	27
$^{201}\text{Tl}$	73.1 h	$^{203}\text{Tl}(p,3n)^{201}\text{Pb} \rightarrow ^{201}\text{Tl}$	29
$^{11}\text{C}$	20.3 m	$^{14}\text{N}(p,\alpha)$ $^{11}\text{B}(p,n)$	11-19 10
$^{18}\text{F}$	110 m	$^{18}\text{O}(p,n)$ $^{20}\text{Ne}(d,\alpha)$ $^{\text{nat}}\text{Ne}(p,X)$	15 14 40
$^{64}\text{Cu}$	12.7 h	$^{64}\text{Ni}(p,n)$ $^{68}\text{Zn}(p,an)$ $^{\text{nat}}\text{Zn}(d,axn)$ $^{\text{nat}}\text{Zn}(d,2pxn)$	15 30 19 19
$^{124}\text{I}$	4.14 d	$^{124}\text{Te}(p,n)$ $^{125}\text{Te}(p,2n)$	13 25

Table 2. Nuclear reactions used to produce imaging radioisotopes.

Thalium-201 has been extensively used for more than 25 years. Over this period there have been numerous reports of its demise, yet the growth in demand for this isotope is still upwards.

The remaining isotopes listed are used in PET imaging. Carbon-11 is extremely attractive because, in principle, one can replace an existing carbon atom in the molecule of interest with the radioactive isotope. However, because of the short half-life, its availability will be limited to those sites possessing an accelerator or near to one. The demand for  $^{18}\text{F}$  exceeds its availability. To overcome this shortage, a number of central distribution centers have been placed in large metropolitan areas in North America, Europe and Japan. Although several nuclear reactions are provided, the (p,n) reaction is the route of choice for producing large quantities of

$^{18}\text{F}$ . If availability of  $^{18}\text{F}$  continues to grow,  $^{18}\text{F}$ -labeled compounds may begin to compete with other SPECT agents such as  $^{123}\text{I}$ .

The other two isotopes are candidates for both PET imaging and possible use in therapy (see below). The interest in these two is primarily related to the relatively long half-lives. Such properties would enable studies to be performed where the kinetics are slow and exceed the ability to image with  $^{18}\text{F}$ . The disadvantages include low production rate ( $^{124}\text{I}$ ) and the need for expensive enriched target material ( $^{64}\text{Ni}$ ,  $^{124}\text{Te}$ ). Recent results from Washington University in St. Louis have shown that even with the high-energy  $\beta$ -particles associated with  $^{124}\text{I}$  decay and other photons in coincidence with the  $\beta$ -decay, they can still be imaged at high resolution ( $^{64}\text{Cu}$ ).

### 3 Radioisotopes for Therapy

The idea of a radioisotope used in therapy is based on the desire to link a radionuclide which has a high linear energy transfer associated with its decay products such as Auger electrons,  $\beta$ -particles or  $\alpha$ -particles to a biologically active molecule that can be directed to a tumor site. Since the  $\beta$ -emitting radionuclides are neutron rich they have, in general, been produced in reactors. Table 3 lists some of the radionuclides that have been proposed as possible radiotoxic tracers.

$^{47}\text{Sc}$	$^{64}\text{Cu}$	$^{67}\text{Cu}$	$^{77}\text{Br}$	$^{90}\text{Y}$
$^{105}\text{Rh}$	$^{103}\text{Pd}$	$^{111}\text{Ag}$	$^{124}\text{I}$	$^{142}\text{Pr}$
$^{149}\text{Pm}$	$^{153}\text{Sm}$	$^{159}\text{Gd}$	$^{166}\text{Ho}$	$^{177}\text{Lu}$
$^{186/188}\text{Re}$	$^{194}\text{Ir}$	$^{199}\text{Pt}$	$^{211}\text{At}$	$^{213}\text{Bi}$

Table 3. Listing of radionuclides that have been proposed for use as possible radiotoxic isotopes for treating cancer.

Most of these radionuclides are produced in a reactor although a few are best produced in via charged particle reactions. Table 4 provides the charged particle nuclear reactions that can be used for selected radiotoxic nuclides.

The attractive feature of  $^{77}\text{Br}$  is its chemical versatility in addition to its half-life. Production rates are relatively low and purity may be an issue since  $^{76}\text{Br}$  is often co-produced. The demand for  $^{103}\text{Pd}$ , which is used in treating prostate cancer, is continuing to grow. A large number of low energy (19 MeV) cyclotrons are dedicated solely to the production of this isotope.

Rhenium-186 is attractive for a number of reasons. It has the desirable physical characteristics of being a  $\beta$ -emitter with a useful half-life (90 hours) and a  $\gamma$ -ray

(137 keV) that can be imaged. In addition, Re is in the same chemical family as is Tc, thus much of the chemistry developed for Tc can be applied to Re. The production rates from all of the reactions listed in table 4 are very low. Thus the only practical route to this potentially important isotope is via neutron capture in a reactor. This route results in a very low specific activity product, which severely limits its utility.

Radionuclide	t ½	Decay Mode	Reaction	Energy (MeV)
<sup>77</sup> Br	2.4d	Auger electrons	<sup>75</sup> As(a,2n)	27
			<sup>77</sup> Se(p,n)	13
			<sup>78</sup> Se(p,2n)	24
			<sup>79,81</sup> Br(p,xn) <sup>77</sup> Kr	45
			<sup>nat</sup> Mo(p,spall.)	>200
<sup>103</sup> Pd	17.5d	Auger Electrons	<sup>103</sup> Rh(p,n)	19
			<sup>nat</sup> Ag(p,xn)	>70
<sup>186</sup> Re	90.6h	β <sup>-</sup>	<sup>186</sup> W(p,n)	18
			<sup>186</sup> W(d,2n)	20
			<sup>197</sup> Au(p,spall.)	>200
			<sup>nat</sup> Au(p,spall.)	>200
			<sup>nat</sup> Ir(p,spall.)	>200
<sup>211</sup> At	7.2h	α	<sup>209</sup> Bi(a,2n)	28
			<sup>209</sup> Bi( <sup>7</sup> Li,5n) <sup>211</sup> Rn	60
			<sup>232</sup> Th(p,spall.) <sup>211</sup> Rn	>200

Table 4. Charged particle production routes for therapy isotopes.

And finally, α-emitting isotopes have been of interest for use in therapy because of the high LET associated with the α-decay. Astatine is of interest because it possesses many properties of halogens and each decay of <sup>211</sup>At has an α-particle associated with it. Because of its short half-life multiple production sites would be required. Thus the interest in producing its parent radionuclide (<sup>211</sup>Rn) has been suggested as a way of producing and shipping <sup>211</sup>At to remote sites.

#### 4 Conclusions

The vast majority of radioisotopes used in imaging are widely available and in the cases where demand continues to grow, the private sector is expanding to meet those needs.

Many clinically relevant therapeutic nuclides cannot be produced in high specific activity from reactors and the accelerators cannot produce sufficient quantities for

large-scale usage. Thus a possible solution could be the use of off-line isotope separators. In such a situation, large scale production could be achieved in reactors, and the specific activity improved by using the isotope separator.