PART 1 Research Radionuclide Availability in North America

Inadequate North American supplies of research radionuclides limit research opportunities for radiochemists and other nuclear medicine investigators in the United States and Canada. If basic and clinical scientists lose confidence in the long-term domestic availability of research radionuclides, the future practice of nuclear medicine may never realize its full potential for diagnosing and treating disease with radiolabeled compounds that target specific molecular sites. Since the "Atoms for Peace" effort in the 1950s, the U.S. government has funded the production of investigational isotopes that are not available from commercial suppliers. The U.S. Department of Energy (DOE) plays a vital role in funding the production of such radionuclides in research reactors and accelerators, as did its predecessor federal agencies (the Atomic Energy Commission and Energy Research and Development Agency).

Mounting pressures to reduce government spending, however, have created a crisis in the North American supply of radionuclides. The current availability of research radionuclides often fails to meet the needs of researchers. This failure results from intermittent production schedules and very limited resources devoted to production of "new" radionuclides for pilot studies. Programs to secure adequate, stable sources of research radionuclides are not in place, a problem made more acute by the aging of national laboratory facilities with limited efforts to renovate or rebuild. Because the DOE facilities involved in radionuclide distribution produce materials only in a "parasitic" operating mode, the future of such operations is inextricably linked to the ongoing viability of very expensive scientific programs, such as high-energy physics research, that are largely unrelated to biomedical research. The supply of radionuclides to the nuclear medi-

Table 1
U.S. REACTORS AVAILABLE FOR PRODUCING RESEARCH RADIONUCLIDES

Reactor, Location	Energy (MW)	Maximum Neutron Flux ($N/cm^2/sec$): Thermal	Maximum Neutron Flux ($N/cm^2/sec$): Fast	Produces Isotopes for	Comments
ATR Idaho National Engineering Laboratory	250	1×10^{15}	5×10^{15}	Commercial applications primarily	Main source of DOE-supplied reactor-produced radionuclides (^{60}Co, ^{192}Ir, ^{153}Gd, ^{89}Sr); no capabilities for production of short-lived radionuclides.
HFIR, Oak Ridge National Laboratory	100	2.5×10^{15}	1.2×10^{15}	Research/ commercial applications	Research/commercial applications Major upgrades planned that would expand capacity for radionuclide production; currently operates at 85 MW.
HFBR, Brookhaven National Laboratory	30	7.5×10^{13} to 4.2×10^{14}	3.8×10^{11} to 1.5×10^{14}	Research applications primarily	Currently does not produce radionuclides for sale; recently produced biomedical isotopes (^{47}Sc, ^{64}Cu, ^{117m}Sn, ^{153}Sm, ^{191}Os, ^{198}Au, ^{199}Au).
MURR, University of Missouri	10	4.5×10^{14} (flux trap) 8×10^{13} (graphite reflector)	1×10^{14} (flux trap) 6×10^{12} (graphite reflector)	Research/ commercial applications	Logged >90% online time since 1977; largest university research reactor in the U.S.; capable of power upgrade to 25 to 30 MW.

The Fast-Flux Test Facility (FFTF) at Hanford National Laboratory may become available for radionuclide production if the DOE decides to reactivate ^{3}H production.

ATR = Advanced Test Reactor; HFIR = high-flux isotope reactor; HFBR = high-flux beam reactor; MURR = Missouri University Research Reactor.

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Table 2
Shipments of Radionuclides from High-Flux Isotope Reactor (Fiscal Year 1996)

Radionuclide	Activity Shipped Ci	Activity Shipped GBq	Units Shipped
^{192}Ir	600,000	22,000,000	
^{63}Ni	160	6000	
^{89}Sr	1.5	55	
^{209}Po	1.1 x 10-6	0.4 x 10-6	
^{252}Cf	13*	500*	25 mg
^{99}Tc	8000	300,000	470 g
^{188}W			7 batches of solution
^{186}Re			2 batches
$^{188}W/^{188}Re$			1 generator

*Theoretical activity.

If researchers lose confidence in the long-term domestic availability of radionuclides, they will not devote their careers to radiopharmaceutical chemistry.

cine research community, therefore, has become untenably dependent on extrinsic federal programs and funding priorities.

In response to this growing crisis, the DOE commissioned the Institute of Medicine (IOM), of the National Academy of Sciences, to undertake an intensive examination of radionuclide production and availability. In 1995, the IOM Committee on Biomedical Isotopes issued its report, which emphasized the need to establish a reliable domestic supply of both reactor- and accelerator-produced radionuclides for medical practice and biomedical research (*1*). At this time, most of the recommendations of this report, including final design and construction of the National Biomedical Tracer Facility (NBTF), have not been implemented.

The crisis in radionuclide availability coincides, ironically, with an era of unprecedented opportunities for developing disease-specific radiotracers that could lead to promising advancements in nuclear medicine. Scientists worldwide are designing and evaluating radiolabeled biomolecules to target specific receptors and other cellular sites such as deoxyribonucleic acid (DNA) (*2*). These "designer" compounds serve as the foundation for novel radiopharmaceuticals that could develop into highly effective weapons against cancer and other diseases.

The Society of Nuclear Medicine's Committee on Isotope Availability held a workshop on June 6, 1996, to examine current radionuclide availability and to explore currently untapped sources of research radionuclides. This effort to find alternative sources of research radionuclides in no way diminishes the need to implement the recommendations of the IOM Committee on Biomedical Isotopes. Rather, the workshop focused on ways innovatively to overcome problems resulting from delays in developing dedicated federal production facilities, such as the proposed NBTF.

Clearly, we will need a variety of radionuclides with various physical and chemical properties to create the sophisticated radiopharmaceuticals of the future. As Wynn Volkert, PhD, Associate Research Career Scientist, H.S. Truman Memorial VA Hospital, Professor of Radiology, University of Missouri, Columbia noted in the workshop introduction, the future of nuclear medicine depends on the long-term, uninterrupted availability of research radionuclides on a routine basis at reasonable costs. If researchers lose confidence in the long-term domestic availability of radionuclides, warned Volkert, they will not devote their careers to radiopharmaceutical chemistry, and they will not build research programs to design the sophisticated molecular radiotracers that hold so much promise for the future practice of nuclear medicine.

Nuclear Reactors

Four reactors currently produce most of the research radionuclides used in North America (Table 1). The DOE and the University of Missouri operate these reactor facilities.

DOE Facilities

The DOE operates several research reactors, including:

• Idaho National Engineering Laboratory, Advanced Test Reactor (ATR) routinely produces radionuclides, but primarily for commercial applications.

• Oak Ridge National Laboratory (Tennessee), High-Flux Isotope Reactor (HFIR) routinely produces radionuclides for research (Table 2) and commercial applications. In the core's hydraulic tube facility, seven to nine targets can be irradiated for anywhere from a few seconds to the full 25-day cycle.

• Brookhaven National Laboratory (New York), High-Flux Beam Reactor (HFBR) recently became available for small-scale irradiations. As this reactor operates, seven vertical thimbles can be accessed for the production of short-lived radionuclides.

Owen W. Lowe, Associate Director for Isotope Production and Distribution, Office of Nuclear Energy, DOE, reported that each DOE reactor has the capability to produce radionuclides that cannot be produced elsewhere. The DOE reactors, together with the University of Missouri's research reactor (MURR), comprise most of the total production capability available in the United States to provide reactor-based radionuclides. At the Hanford National Laboratory (Washington state), the Fast-Flux Test Facility (FFTF) may become available for radionuclide production if the DOE decides to reactivate the reactor for tritium [^3H] production.

University of Missouri

As recognized in the recent IOM report (*1*), the MURR Center provides an outstanding example of the role a university-based facility can play in meeting national and international demands for research radionuclides. MURR, a 10-MW nuclear reactor, has an annulus-pressure vessel with a central flux trap and operates 155 hours (6.5 days) per week at full power. Alan R. Ketring, PhD, Interim Scientific Director, MURR, Leader, Radiopharmaceuticals Group, University of Missouri, Columbia, reported that MURR, the largest university research reactor in the U.S., has logged >90% online time since 1977 and is capable of a power upgrade to 25 to 30 MW.

MURR serves as the primary non-DOE source of research radionuclides in the U.S. (Table 3). The MURR Center believes it is capable of supplying North American researchers with adequate amounts of most short-lived ($t_{1/2}$ < 7 days), reactor-produced radionuclides "at a reasonable cost on a routine and reliable basis."

Table 3
Shipments of Research Radionuclides from MURR (July 1992 to June 1993)

	Radionuclide	Activity Shipped	
		Ci	GBq
> 50 Ci > 1850 GBq	^{32}P	7960	295,000
	^{192}Ir	5920	219,000
	^{35}S	5060	187,000
	^{198}Au	2840	105,000
	^{186}Re	1480	54,600
	^{51}Cr	697	25,800
	^{169}Yb	344	12,700
	^{103}Pd	179	6630
	^{31}Si	172	6360
	^{55}Fe	115	4260
	^{166}Ho	79	2930
	^{63}Ni	76	2810
	^{177}Lu	54	2010
	^{170}Tm	54	1990
	^{153}Sm	51	1870
1–50 Ci 35–1850 GBq	^{175}Yb, ^{191}Os, ^{45}Ca, ^{75}Se, ^{24}Na, ^{86}Rb, ^{113}Sn, ^{141}Ce, ^{204}Tl, ^{58}Co, ^{59}Fe, ^{124}Sb, ^{97}Zr, ^{153}Gd, ^{46}Sc, ^{188}Re, ^{165}Dy, ^{199}Au, ^{64}Cu, ^{199}Pt, ^{110m}Ag, ^{103}Ru, ^{203}Hg, ^{85}Sr, ^{95}Zr		
< 1 Ci < 35 GBq	^{71}Ge, ^{195m}Pt, ^{160}Tb, ^{131}Cs, ^{60}Co, ^{133}Ba, ^{105}Rh, ^{131}Ba, ^{145}Sm, ^{109}Pd, ^{65}Zn, ^{123m}Te, ^{182}Ta, ^{119m}Sn, ^{115}Cd, ^{187}W, ^{193m}Pt, ^{188}W, ^{154}Eu, ^{67}Cu, ^{129}Te, ^{125m}Te, ^{166}Dy, ^{47}Ca, ^{239}Np, ^{129m}Te, ^{210}Bi		

MURR = Missouri University Research Reactor.

Nordion International Inc.

Nordion International Inc., of Kanata, Ontario, Canada, operates its NRU reactor, which produces ^{99}Mo, at Chalk River. Because of cost and logistical issues, the NRU does not produce small amounts of research radionuclides. Ivan C. Travena, PhD, Vice President, Isotope Products, Nordion International Inc., Kanata, Ontario, Canada, reported that the company is building two new reactors Maple 1 and Maple 2 to replace the NRU, scheduled to shut down in 1999. Maple 1 (for routine production) and Maple 2 (for backup production) will be used to produce commercially viable radionuclides.

Although ATR, HFIR, HFBR and MURR are all capable of producing research radionuclides, there are several limitations. ATR, for example, produces radionuclides primarily for commercial applications. HFBR produces biomedical research radionuclides, but they are not for sale; instead, they are available only to DOE-affiliated investigators. Currently, only MURR and HFIR routinely supply research radionuclides to any qualified investigator, regardless of DOE affiliation.

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