# EDITORIAL
# The Potential for Generator-Based PET Perfusion Tracers

The power of positron emission tomography (PET) as a tool in medical research and diagnosis is well established and widely recognized. An increasing body of basic and clinical research involving PET imaging, combined with improving PET instrumentation and the prospects for third-party reimbursement for efficacious PET procedures, sets the stage for the research efforts of several groups seeking to develop PET radiopharmaceuticals labeled with generator-produced nuclides. While the cyclotron-produced nuclides around which PET has grown and flourished (Table 1) allow the study of an impressive array of discrete biochemical and physiologic processes, the expense associated with operation of an in-house cyclotron for production of these short-lived isotopes remains a significant obstacle to their more widespread application. There is hope that PET radiopharmaceuticals labeled with generator-produced nuclides could fuel the growth of PET imaging in somewhat the way the $^{99}Mo/^{99m}Tc$ generator played a central role in the tremendous growth of nuclear medicine following its introduction.

Unfortunately, only a very limited number of positron-emitting nuclides are available from parent/daughter generator systems (*2–5*); those that would seem to have the greatest prospects for clinical utility are listed in Table 2. While the nuclear properties of these parent/daughter pairs may prevent them from complementing PET imaging as ideally as the $^{99}Mo/^{99m}Tc$ generator serves traditional imaging with an Anger-type gamma camera, it is reasonable to believe that under the right circumstances some of these generators could be exploited to provide clinically useful tracers.

Three of the most frequent applications of PET imaging technology involve studies of regional tissue perfusion, regional tissue metabolism, and receptor-based tracer binding processes. In considering the potential role for generator-produced radionuclides in the clinical application of PET, it should be recognized that the unique strength of this technique derives not only from the ability of the imaging technology to provide quantitative images of tracer distribution with relatively high spatial resolution, but also from its ability to employ radiotracers that participate in distinct and well defined biochemical/physiological processes (*6*). The mainstay of PET imaging with the cyclotron-produced positron-emitters is the use of radiopharmaceuticals based on natural biochemicals or therapeutic drugs labeled by isotopic substitution or isosteric replacement. The generator-produced positron-emitting nuclides stand to have their greatest clinical impact in perfusion imaging with PET since the labeling of useful metabolic or receptor-based radiopharmaceuticals with these inorganic nuclides is probably precluded by their chemistry and/or physical half-lives. Perfusion imaging with these nuclides remains a viable prospect because, in principle, the organ uptake of a blood flow tracer should occur by passive diffusion without the involvement of any underlying biochemical processes in the tissue of interest.

Rubidium-82 ($^{82}Rb$) is the first of the generator-produced positron-emitters to make its way into clinical nuclear medicine. A $^{82}Sr/^{82}Rb$ generator system developed by Squibb Diagnostics was approved for use by the United States Food and Drug Administration in late 1989. The $^{82}Rb^+$ cation, eluted from the generator in isotonic saline, is useful for the study of myocardial blood flow since it is taken up by myocardial cells as a $K^+$ analog (similar to the basis for the traditional use of $^{201}Tl^+$ in nuclear cardiology). However, there are numerous problems with the use of $^{82}Rb^+$, leaving room for the advent of superior tracers derived from other generator systems. These problems include the expense associated with $^{82}Sr$ production (*7*), the need for generator replacement at 3–5 wk intervals, the non-linear relationship in myocardium between the rate of perfusion and the $Rb^+$ extraction

**TABLE 1**
Properties of Cyclotron-Produced Positron-Emitting Nuclides Most Frequently Used in PET Imaging*

| Radionuclide | Half-life (min) | Positron yield | Average energy per disintegration (MeV) |
|---|---|---|---|
| $^{15}O$ | 2.04 | 99.9% | 0.735 |
| $^{13}N$ | 9.96 | 99.8% | 0.491 |
| $^{11}C$ | 20.4 | 99.8% | 0.385 |
| $^{18}F$ | 109.8 | 96.9% | 0.242 |

* See Reference 1.

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**TABLE 2**
Properties of Selected Parent-Daughter Generator Systems for Positron-Emitting Nuclides*

| Parent isotope | Parent half-life | Daughter isotope | Daughter half-life | Daughter positron yield | Daughter average energy per disintegration (MeV) |
|---|---|---|---|---|---|
| $^{68}$Ge | 271 days | $^{68}$Ga | 68.1 min | 89% | 0.740 |
| $^{82}$Sr | 25.6 days | $^{82}$Rb | 76.4 sec | 95% | 1.409 |
| $^{62}$Zn | 9.26 hr | $^{62}$Cu | 9.74 min | 97% | 1.280 |
| $^{52}$Fe | 8.27 hr | $^{52m}$Mn | 21.1 min | 97% | 1.133 |
| $^{122}$Xe | 20.1 hr | $^{122}$I | 3.62 min | 77% | 1.087 |

* See Reference 1.

fraction (*8*), and the influence of ischemia on tracer uptake (*9*). In addition, the 76-sec half-life of $^{82}$Rb imposes short image acquisition times, a factor that will be especially problematic with those PET cameras designed to operate at relatively low count rates. Finally, the synthesis of $^{82}$Rb radiopharmaceuticals for diverse imaging applications may be precluded by the relatively limited chemistry of the alkali metals, as well as the short physical half-life of the nuclide.

A $^{82}$Rb radiopharmaceutical for the study of cerebral perfusion would significantly increase the attractiveness and versatility of this generator, but poses substantial chemical challenges. The crown ethers and cryptates that are known for their size-selective complexation of specific alkali metal cations unfortunately have their least selectivity in differentiating the larger cations like $Rb^+$. The $^{82}$Rb-radiopharmaceutical problem is further complicated by the inherent toxicity of these ligands and the fact that tracer levels of $^{82}Rb^+$ must be coordinated in the presence of a very large excess of competing $Na^+$ ions. In this context the kinetic lability of the alkali metal-cryptate complexes, despite their considerable thermodynamic stability, poses further problems, although more kinetically inert complexes are now appearing. However, the chemical problems to be overcome in achieving the rapid synthesis of a stable $^{82}$Rb-ligand complex that will efficiently penetrate the blood-brain barrier following intravenous injection appear rather formidable.

In the current issue of *The Journal of Nuclear Medicine*, Dr. Kung's group at the University of Pennsylvania reports on a new lipophilic and cationic gallium-68 radiopharmaceutical, $Ga(BAT\text{-}TECH)^{1+}$, that appears to merit more detailed investigation for its potential as a tracer for myocardial blood flow (*10*). The $^{68}$Ga generator is commercially available and is attractive because the 271-day parent half-life provides a long generator lifespan. In addition, the 68-min half-life of the $^{68}$Ga daughter allows ample time for radiopharmaceutical synthesis, although it is rather long relative to the normal time frame of PET perfusion studies (especially those PET procedures that involve multiple tracer injections under a variety of physiologic conditions).

While the 68-min half-life of $^{68}$Ga is compatible with exploitation of the fairly extensive synthetic chemistry of this element for radiopharmaceutical purposes, the development of lipophilic $^{68}$Ga radiopharmaceuticals for perfusion imaging has proven a somewhat elusive goal (*11*). No gallium radiopharmaceuticals have been reported that can efficiently penetrate the intact blood-brain barrier to allow $^{68}$Ga studies of cerebral blood flow and only modest success has been obtained in the development of $^{68}$Ga-radiopharmaceuticals to study myocardial blood flow. We have reported on the synthesis, tissue distribution, pharmacokinetics, and PET imaging of a gallium-68 *tris*-(salicylaldimine) complex, $Ga[(5\text{-}MeOsal)_3tame]$, which showed promise as a myocardial perfusion tracer (*12, 13*). This unchanged, lipophilic $^{68}$Ga radiopharmaceutical resists ligand exchange with the plasma protein transferrin following intravenous injection and has allowed qualitative PET imaging of myocardial blood flow in the dog (*13*). However, $^{68}Ga[(5\text{-}MeOsal)_3tame]$ was judged unsuitable as a substitute for cyclotron-produced myocardial flow tracers, due to its clearance from myocardium and a need to correct the images for radioactivity remaining in the ventricular blood pool (*13*).

Subsequent work with related *tris*(salicylaldimine) ligands (*14*) led to identification of one tracer, $Ga[(4,6\text{-}MeOsal)_3tame]$, that affords significant myocardial uptake and substantially better heart-to-blood ratios than $Ga[(5\text{-}MeOsal)_3tame]$, as does $Ga(BAT\text{-}TECH)^{1+}$ (Tables 3 and 4). However, $Ga[(4,6\text{-}MeOsal)_3tame]$ has not been pursued in imaging studies because its clearance from myocardium (Table 3) is expected to compromise the quality of the perfusion images it would provide. The same problem would appear to exist with $Ga(BAT\text{-}TECH)^{1+}$. With both of these tracers, image contrast in the ischemic heart can be expected to be progressively degraded with time, since the rate of tracer clearance is likely to be greater in high flow than in low flow regions. Thus, tracer clearance from myocardium will tend to impose short image acquisition times in order to maintain the best relationship between tissue counts and relative regional perfusion. In this context, the 68-min half-life of $^{68}$Ga appears undesirably long, since it may be substantially greater than the imaging time dictated by the pharmacokinetics of the

**TABLE 3**
Myocardial Levels of Various Radiopharmaceuticals in the Rat*

| Compound | % ID in heart | | | | |
|---|---|---|---|---|---|
| | 1 min | 2 min | 5 min | 30 min | 60 min |
| Ga[BAT-TECH]+ | — | 1.68 | — | 0.52 | 0.26 |
| Ga[(5-MeOsal)$_3$tame] | 0.97 | — | 0.66 | 0.23 | 0.14 |
| Ga[(4,6-MeOsal)$_3$tame] | 2.0 | — | 0.99 | 0.53 | 0.35 |
| Cu[PTSM] | 2.7 | — | 3.4 | — | 3.3† |

* See References 10 and 12–16.
† 120 min.

radiopharmaceutical. Table 4 also presents data from a preliminary report on another new gallium radiopharmaceutical, Ga[THM$_2$BED], that may show promise as a myocardial perfusion tracer (*17*).

In addition, it should be mentioned that albumin microsphere and macroaggregated albumin radiopharmaceutical kits, sold commercially for labeling with $^{99m}$Tc, can also be labeled with $^{68}$Ga for PET applications that can exploit a particulate perfusion tracer (*11,18*). Gallium-68-labeled albumin microspheres have been used in PET studies of pulmonary blood flow (*19*) and also as a reference tracer in the validation of $^{15}$O-water cerebral and myocardial blood flow techniques (*20,21*). However, practical problems inherent in the use of a particulate perfusion tracer for organs other than the lungs make this approach unacceptable for routine clinical cerebral and myocardial perfusion measurements.

The possible role for the $^{62}$Zn/$^{62}$Cu generator in clinical PET has led to its re-examination in recent years by several groups (*22–25*). The 9.7-min half-life of the copper-62 daughter is well suited to the time frame of perfusion imaging studies with PET. In addition, the physical half-life of $^{62}$Cu is attractive because it is short enough to allow repeat imaging at reasonably brief time intervals, yet still long enough to potentially allow the "kit-type" chemical synthesis of a variety of $^{62}$Cu-radiopharmaceuticals.

The only major, but by no means insignificant, disadvantage of the $^{62}$Zn/$^{62}$Cu generator is the rather short half-life of the $^{62}$Zn parent. This parent half-life would necessitate generator replacement at 1–2-day intervals, if $^{62}$Cu were to be used routinely for clinical PET (*26*). While generator replacement at this interval may be feasible, it is clearly not ideal. However, the inconvenience of frequent $^{62}$Zn replenishment is somewhat offset by the ease with which this nuclide can be produced in large quantities by the $^{63}$Cu(p,2n)$^{62}$Zn reaction using a medium-energy cyclotron (*25,26*). Thus, there are now numerous commercial cyclotrons and clinical cyclotron/PET facilities that could supply $^{62}$Zn to hospitals in their areas, should suitable uses of $^{62}$Cu be found to merit establishment of an appropriate distribution network.

We have recently reported several studies of a copper radiopharmaceutical, Cu(PTSM), that shows considerable promise as a PET tracer for both cerebral and myocardial perfusion when labeled with $^{62}$Cu (*15,23,25,27–30*). This unchanged and lipophilic copper(II) *bis*(thiosemicarbazone) complex can be administered intravenously and is relatively highly extracted into both cerebral and myocardial tissues under diverse physiological conditions, whereupon the copper label is efficiently trapped and retained (*28–30*). The prolonged tissue retention of the copper label can be understood in terms of the known susceptibility of Cu$^{II}$(PTSM) to reductive decomposition by reaction with ubiquitous intracellular sulfhydryl groups, a process that liberates the label as ionic copper to be bound by intracellular macromolecules (*16,31*). Because the $^{62}$Cu label from $^{62}$Cu(PTSM) is trapped in tissues in a "microsphere-like" manner, image acquisition times with this radiopharmaceutical are limited only by the 10-min physical half-life of the radiolabel.

In animal as well as two preliminary human studies with $^{62}$Cu-(PTSM), high quality PET images of the brain and heart have been obtained that compare favorably to the images obtained with a validated, cyclotron-produced PET perfusion tracer, $^{15}$O-water (*25*). In sequential baseline/activation PET studies with an awake monkey, $^{62}$Cu(PTSM) has been shown to be a sufficiently sensitive tracer of cerebral blood flow to allow detection of focal areas of increased cerebral perfusion resulting from neurological stimulation (*25*). Based on these preliminary studies, it would appear

**TABLE 4**
Heart/Blood Ratios for Selected Radiopharmaceuticals in the Rat*

| Compound | Heart/Blood ratio | | | | |
|---|---|---|---|---|---|
| | 1 min | 2 min | 5 min | 30 min | 60 min |
| Ga[BAT-TECH]+ | — | 3.5 | — | 3.1 | 1.2 |
| Ga[(5-MeOsal)$_3$tame] | 1.5 | — | 2.0 | — | 1.6 |
| Ga[(4,6-MeOsal)$_3$tame] | 5.6 | — | 7.0 | 4.6 | 4.4 |
| Ga[THM$_2$BED] | — | — | — | — | 2.4 |
| Cu[PTSM] | 5.9 | — | 9.8 | — | 9.0† |

* See References 10 and 12–17.
† 120 min.

that $^{62}$Cu(PTSM) will be a sufficiently good tracer for cerebral and myocardial perfusion to test the clinical feasibility of using the $^{62}$Zn/$^{62}$Cu generator as a PET radionuclide source.

Of the two remaining generators listed in Table 2, $^{122}$Xe/$^{122}$I and $^{52}$Fe/$^{52m}$Mn, the $^{122}$I generator has been more extensively investigated as a PET radionuclide source and probably offers the greatest potential for clinical utility. In the opinion of this author, the $^{52}$Fe/$^{52m}$Mn generator presents no chemical or practical advantages over the $^{62}$Zn/$^{62}$Cu generator, which has similar parent and daughter half-lives, and presents a major disadvantage over the latter with regard to the relative difficulty of producing the $^{52}$Fe parent (*32*). However, the $^{52m}$Mn daughter, administered as either the chloride or acetate, has been used as a PET tracer for myocardial perfusion (*33*).

Iodine-122 is unique among these generator-produced positron-emitters in two respects: it is not a metallic element and it is the daughter of a nuclide that is an inert gas. While the customary use of column chromatography for parent/daughter separation will not be appropriate for $^{122}$Xe/$^{122}$I, suitable alternative means for this separation have been described (*34,35*). Although $^{122}$Xe requires higher accelerator energies than $^{62}$Zn for production, $^{122}$Xe is available as a by-product in the commercial production of $^{123}$I for nuclear medicine. However, the 20-hr $^{122}$Xe half-life is somewhat short and would stand to pose delivery problems similar to $^{62}$Zn in routine clinical use.

The 3.6-min half-life of $^{122}$I is attractive for many PET applications, as is the potential for labeling a variety of organic molecules with this isotope. Unfortunately, the chemistry of iodine is not particularly amenable to the rapid synthetic chemistry dictated by the physical half-life of this label. Nevertheless, at least two potential agents for $^{122}$I studies of cerebral perfusion have been described (*36,37*).

In conclusion, the increasing role of PET in clinical nuclear medicine will continue to motivate efforts to develop radiopharmaceuticals labeled with positron-emitting nuclides that can be obtained from parent/daughter generator systems. While limitations inherent in the nuclear properties of these parent/daughter pairs may prevent them from supporting clinical PET as effectively as the $^{99m}$Tc generator has supported single photon imaging, further development of their chemistry can be expected to produce new PET tracers to serve the nuclear medicine community.

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