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PERSPECTIVE

A practical guide to the construction of radiometallated bioconjugates for positron emission tomography

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Positron emission tomography (PET) has become a vital imaging modality in the diagnosis and treatment of disease, most notably cancer. A wide array of small molecule PET radiotracers have been developed that employ the short half-life radionuclides ^{11}C, ^{13}N, ^{15}O, and ^{18}F. However, PET radiopharmaceuticals based on biomolecular targeting vectors have been the subject of dramatically increased research in both the laboratory and the clinic. Typically based on antibodies, oligopeptides, or oligonucleotides, these tracers have longer biological half-lives than their small molecule counterparts and thus require labeling with radionuclides with longer, complementary radioactive half-lives, such as the metallic isotopes ^{64}Cu, ^{68}Ga, ^{86}Y, and ^{89}Zr. Each bioconjugate radiopharmaceutical has four component parts: biomolecular vector, radiometal, chelator, and covalent link between chelator and biomolecule. With the exception of the radiometal, a tremendous variety of choices exists for each of these pieces, and a plethora of different chelation, conjugation, and radiometallation strategies have been utilized to create agents ranging from ^{68}Ga-labeled pentapeptides to ^{89}Zr-labeled monoclonal antibodies. Herein, the authors present a practical guide to the construction of radiometal-based PET bioconjugates, in which the design choices and synthetic details of a wide range of biomolecular tracers from the literature are collected in a single reference. In assembling this information, the authors hope both to illuminate the diverse methods employed in the synthesis of these agents and also to create a useful reference for molecular imaging researchers both experienced and new to the field.

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Introduction

Over the course of the past fifty years, advances in medical imaging have revolutionized clinical practice, with a wide variety of imaging modalities playing critical roles in the diagnosis and treatment

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Dr. Brian Zeglis received his B.S. in chemistry summa cum laude from Yale University (2004), where he worked under the guidance of Professor Robert H. Crabtree. For his graduate studies, he attended the California Institute of Technology as an NSF pre-doctoral fellow. At Caltech, Brian worked under the mentorship of Professor Jacqueline K. Barton, studying the synthesis and development of DNA-binding octahedral metal complexes. After receiving his Ph.D. (2009), Brian moved to Memorial Sloan-Kettering Cancer Center, where he works as an NIH post-doctoral fellow in the laboratory of Professor Jason S. Lewis. Currently, his research is focused on the design, synthesis, and evaluation of ^{64}Cu- and ^{89}Zr-based PET radiopharmaceuticals

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of disease. Today, clinicians have at their disposal a remarkable range of medical imaging techniques, from more conventional modalities like ultrasound, conventional radiography (X-rays), X-ray computed tomography (CT scans), and magnetic resonance imaging (MRI) to more specialized methodologies such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET).

In recent years, medical imaging research has experienced a paradigm shift from its foundations in anatomical imaging towards techniques aimed at probing tissue phenotype and function.[1] Indeed, both the cellular expression of disease biomarkers and fluctuations in tissue metabolism and microenvironment have emerged as extremely promising targets for imaging.[2] Without question, the unique properties of radiopharmaceuticals have given nuclear imaging a leading role in this movement. The remarkable sensitivity of PET and SPECT combines with their ability to provide information complementary to the anatomical images produced by other modalities to make these techniques ideal for imaging biomarker- and microenvironment-targeted tracers.[3,4] Both relatively young modalities, SPECT and PET have had an impact on medicine (and oncology in particular), which belies their novelty, and both have been the topic of numerous thorough and well-reasoned reviews.[5–9] Both modalities have become extremely important in the clinic, and while PET is generally more expensive on both the clinical and pre-clinical levels, it also undoubtedly possesses a number of significant advantages over its single-photon cousin, most notably the ability to quantify images, higher sensitivity (PET requires tracer concentrations of ~10^{-8} to 10^{-10} M, while SPECT requires concentrations approaching 10^{-6} M), and higher resolution (typically 6–8 mm for SPECT, compared to 2–3 mm or lower for PET). Therefore, in the interest of scope, the article at hand will limit itself to the younger and higher resolution of the techniques: positron emission tomography.

Regardless of the broader perspective, any discussion of PET benefits from a brief description of the underlying physical phenomena. Starting from the beginning, a positron released by a decaying radionuclide will travel in a tissue until it has exhausted its kinetic energy. At this point, it will encounter its antiparticle, an electron, and the two will mutually annihilate, completely converting their mass into two 511 keV γ-rays that must, due to conservation of momentum, have equal energies and travel 180° relative to one another. These γ-rays will then leave the tissue and strike waiting coincidence detectors; importantly, only when signals from two coincidence detectors simultaneously trigger the circuit is an output generated. The two principal advantages of PET thus lie in the physics: the short initial range of the positrons results in high resolution, and the coincidence detection methodology allows for tremendous sensitivity.

In the early 1950s, Brownell[10] and Sweet[11] developed the first devices for creating images using the coincident detection of γ-rays emitted from positron-electron annihilation events. At the same time, these researchers and others were pioneering the oncologic applications of positron imaging, specifically the imaging of brain tumors.[10–14] Not until the 1970s, however, did the field take the next important practical step forward: tomographic systems and computer analysis were first applied to positron imaging, innovations which paved the way for the widespread clinical use of the modality.

Since the advent of PET in both the clinic and medical research laboratories, a number of positron-emitting isotopes have been developed for use in radiopharmaceuticals. For years, the field was dominated by small molecule tracers, radiopharmaceuticals whose short biological half-lives favor the use of non-metallic radionuclides with correspondingly short radioactive half-lives, such as ^{18}F, ^{15}O, ^{13}N, and ^{11}C (Table 1). In many ways, this is still true: [^{18}F]-fluoride and the ubiquitous [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) are the only FDA-approved PET radiopharmaceuticals commonly employed in oncology ([^{13}N]-NH_3 and [^{82}Rb]-RbCl are FDA-approved but are used principally for myocardial perfusion scans). Further still, an examination of the list of PET radiotracers currently in NIH-sponsored clinical trials reveals an overwhelming majority of agents with non-metallic radionuclides, including among others the promising agents [^{18}F]-FLT, [^{18}F]-FES, [^{18}F]-FDHT, [^{18}F]-FMISO, [^{18}F]-FACBC, [^{18}F]-fluoroethylcholine, [^{18}F]-deshydroxycholine, [^{18}F]-FMAU, [^{11}C]-acetate, [^{11}C]-choline, [^{11}C]-MeAIB, [^{11}C]-MET, [^{124}I]-IAZGP, and [^{124}I]-FIAU.[15]

Yet despite the significant successes of small molecule probes labeled with non-metallic isotopes, these radionuclides possess

Table 1 Physical decay characteristics of conventional PET radionuclides[158,159]

Radionuclide	Half-life	Decay mode (% branching ratio)	Production route	E(β⁺)/keV	β⁺ end-point energy/keV	Abundance, $I_{\beta+}$/%	E_γ/keV (intensity, I_γ/%)
^{11}C	1223.1 (12) s	β⁺ (100)	^{14}N(p,a)^{11}C	385.6 (4)	960.2 (9)	99.759 (15)	511.0 (199.5)
^{13}N	9.965 (4) m	β⁺ (100)	^{16}O(p,a)^{13}N	491.82 (12)	1198.5 (3)	99.8036 (20)	511.0 (199.6)
^{15}O	122.24 (16) s	β⁺ (100)	^{15}N(p,n)^{15}O ^{14}N(d,n)^{15}O	735.28 (23)	1732.0 (5)	99.9003 (10)	511.0 (199.8)
^{18}F	109.77 (5) m	β⁺ (100)	^{18}O(p,n)^{18}F ^{20}Ne(d,a)^{18}F	249.8 (3)	633.5 (6)	96.73 (4)	511.0 (193.5)
^{124}I	4.1760 (3) d	ε + β⁺ (100) β⁺ (22.7 [13])	^{124}Te(p,n)^{124}I	687.04 (85) 974.74 (85)	1,534.9 (19) 2,137.6 (19)	11.7 (10) 10.7 (9)	511.0 (45) 602.7 (62.9) 722.8 (10.4) 1,691.0 (11.2)

ε = electron capture; m = minutes; d = days; s = seconds. Where positrons or γ-rays of different energies are emitted, only those with abundances of greater than 10% are listed. Unless otherwise stated, standard deviations are given in parentheses.

a few critical limitations. First, the short half-lives of the most common non-metallic radionuclides - approximately 20 min for ^{11}C, 10 min for ^{13}N, 2 min for ^{15}O, and 110 min for ^{18}F - allow only for investigations of biological processes on the order of minutes or a few hours using tracers with rapid pharmacokinetic profiles. Second, both the short half-lives of the radionuclides and the frequent necessity of incorporating the radioisotopes into the core structure of the tracer (rather than in an appended chelator or prosthetic group) often necessitate demanding and complex syntheses. Third, the clinical and pre-clinical use of short half-life, non-metallic radionuclides often requires a local cyclotron facility; in its absence, the radionuclide in question will undergo many half-lives of decay while in transit. Given the resources required for the construction and operation of medical cyclotrons, this is simply not an option in many locations.

These limitations have been brought into focus by the increasing study and development of biomolecular targeting agents for cancer, including short peptides, antibodies, antibody fragments, and natural and non-natural oligonucleotides. Given that Nature herself has designed or inspired these agents, they often show sensitivities and specificities for cancer cell biomarkers that far exceed those of their small molecule counterparts. However, these biomolecular tracers typically have biological half-lives that are much longer than the radioactive half-lives of the most common non-metallic positron-emitting radionuclides; further, though less pressing, many of these biomolecules are incompatible with the chemistry required for direct labeling with non-metallic radionuclides.[16–19]

Given the enormous potential of biomolecular imaging agents, significant effort has been dedicated to the production, purification, and radiochemistry of positron-emitting radioisotopes of the metals Zr, Y, Ga, and Cu. These isotopes, specifically ^{64}Cu, ^{68}Ga, ^{86}Y, and ^{89}Zr, have radioactive half-lives (roughly 12.7, 1.1, 14.7, and 78.4 h, respectively) that favorably complement the biological half-lives of many biomolecular targeting vectors (Table 2). Although all four radiometals emit positrons, each has a characteristic positron range, which is the principal factor in determining imaging resolution. ^{64}Cu and ^{89}Zr emit very low energy positrons, producing image resolution comparable to that of ^{18}F. ^{86}Y and ^{68}Ga, in contrast, emit higher energy positrons, which can result in slightly lower imaging resolutions, though this can be corrected through the use of mathematical algorithms.[20] Further still, and equally critical, all four metals form stable chelate complexes that may be employed for the radiolabeling of biomacromolecules. To be sure, not all biomolecular PET tracers are labeled with radiometals, nor are all radiometallated PET tracers biomolecules. An ^{18}F-labeled variant of the integrin-targeting RGD peptide[21] and an ^{124}I-labeled carbonic anhydrase-targeting antibody[22] have produced very exciting results and are currently being employed in human studies. Moreover, a few radiometal-based small molecule tracers have also proved extremely promising, most notably [^{64}Cu]-Cu(PTSM)[23] and [^{64}Cu]-Cu(ATSM),[24] with the latter currently in a multi-center clinical trial as an imaging agent for hypoxia.[25–28] Yet, despite these exceptions, the single most important application of positron-emitting radiometals is the development of tracers based on peptides, antibodies, and oligonucleotides.

Importantly, the basic strategy for the incorporation of a radiometal into a biomolecule differs somewhat from the synthesis of a small molecule radiotracer containing a non-metallic PET radionuclide. In small molecule tracers, the radionuclide most often replaces an isotopologue (*e.g.* [^{11}C]-acetate or [^{15}O]-H_2O) or is incorporated into the basic structure of a molecule with either the intent of strategically altering the behavior of the parent molecule (*e.g.* [^{18}F]-FDG) or, more likely, disturbing the activity of the parent molecule as little as possible (*e.g.* [^{18}F]-FDHT or [^{18}F]-FES). In contrast, in biomolecular tracers, the radiometal is almost never directly attached to the biomolecule itself. Rather, the radionuclide is bound to a chelating moiety (*e.g.* DOTA[29] or EDTA[30]), which is first covalently appended to the biomolecule with the intent of altering the vector's biochemical properties as little as possible.[31,32]

Table 2 Physical decay characteristics of common PET radiometals[40]

Radionuclide	Half-life	Decay mode (% branching ratio)	Production route	E(β^+)/keV	β^+ end-point energy/keV	Abundance, $I_{\beta+}$/%	E_γ/keV (intensity, I_γ/%)	Ref.
^{64}Cu	12.701(2) h	ε + β^+ (61.5 [3]) β^+ (17.6 [22]) β^- (38.5 [3])	^{64}Ni(p,n)^{64}Cu	278.21 (9)	653.03 (20)	17.60 (22)	511.0 (35.2)	84, 85
^{68}Ga	67.71 (9) m	ε + β^+ (100) β^+ (89.14 [12])	^{68}Ge/^{68}Ga	836.02 (56)	1889.1 (12)	87.94 (12)	511.0 (178.3)	160, 70, 161
^{86}Y	14.74 (2) h	ε + β^+ (100) β^+ (31.9 [21])	^{86}Sr(p,n)^{86}Y	535 (7)	1221 (14)	11.9 (5)	443.1 (16.9) 511.0 (64) 627.7 (36.2) 703.3 (15) 777.4 (22.4) 1076.6 (82.5) 1153.0 (30.5) 1854.4 (17.2) 1920.7 (20.8)	77
^{89}Zr	78.4 (12) h	ε + β^+ (100) β^+ (22.74 [24])	^{89}Y(p,n)^{89}Zr	395.5 (11)	902 (3)	22.74 (24)	511.0 (45.5) 909.2 (99.0	79, 83, 162–164

ε = electron capture; m = minutes; h = hours; s = seconds. Where positrons or γ-rays of different energies are emitted, only those with abundances of greater than 10% are listed. Unless otherwise stated, standard deviations are given in parentheses.

As new targets are described and radiometals become more available to the wider molecular imaging community, the amount of research into radiometal-based PET tracers has exploded in recent years. For example, over 60% of all publications describing ^{89}Zr-PET have been published in the last four years (with well over 20% in 2010 alone).[33] Indeed, the dramatic growth in this area and the expansion in the availability of radiometals have had the dual effects of broadening the appeal of biomolecular PET imaging and opening the field to investigators who previously may have left the development of PET probes to dedicated radiochemistry and molecular imaging laboratories. However, the frenetic pace of the field and the array of choices in chelation, conjugation, and metallation strategies may serve as an obstacle to those who are interested in the development of radiometallated PET tracers but lack significant bioconjugation or radiochemical experience.

This perspective aims at lowering this barrier. Here, we strive to create a practical guide to the synthesis of radiometal-based PET tracers. To this end, we have compiled the experimental details of chelator choice, conjugation strategy, and radiometallation conditions from the syntheses of a wide array of ^{64}Cu-, ^{68}Ga-, ^{86}Y-, and ^{89}Zr-labeled PET agents. Typically, reviews discuss the structure, behavior, biology, and imaging applications of these agents, with the experimental details touched upon only briefly or simply referenced.[7,16,34–37] All too often, however, the search for a specific conjugation or metallation protocol results in an elongated, and in some cases circuitous, trek through the literature to find a simple incubation time or buffer concentration. Importantly, we do not strive for an exhaustive review of the radiochemistry or imaging applications of radiometal-based PET tracers. Others - most notably Carolyn Anderson and her coworkers at the Washington University School of Medicine and Martin Brechbiel and his coworkers at the National Cancer Institute - have produced well-written and remarkably thorough reviews on these topics.[3,30,34,38–45]

The core of this perspective lies not in the text but rather in the series of tables containing the practical details of chelator conjugation and radiometallation from a diverse collection of ^{64}Cu-, ^{68}Ga-, ^{86}Y-, and ^{89}Zr-labeled bioconjugates. We have elected not to include two types of macromolecular radiopharmaceuticals, bispecific antibodies and biomolecule-based nanoparticles, in the interest of space and scope, though these have been addressed well elsewhere.[46–49] Further, it is important to note that some of the conjugation strategies described herein are now, for the most part, obsolete with respect to their original vector; for example, a number of syntheses for DOTATOC will be outlined, though this DOTA-modified somatostatin analogue is now widely commercially available. Yet we believe it is important to detail these conjugation methods nonetheless, for the synthetic routes themselves may prove useful in the future for the creation of conjugates with different biomolecular vectors. In collecting these techniques in one place, we hope not only to shed light upon the diverse methods employed in the synthesis of these agents but also, and perhaps more importantly, to create a useful reference for both experienced molecular imaging scientists and researchers new to the field.

The anatomy of a PET bioconjugate

A radiometallated PET bioconjugate has four component parts, each of which must be carefully considered during the design and the radiometal, (3) the chelator, and (4) the linker connecting the chelator and the biomolecule (Fig. 1). A detailed discussion of the possible targeting vectors lies outside the scope of this work, though biomolecules ranging from cyclic pentapeptides and short oligonucleotides to 40-amino acid peptides, antibody fragments, and full antibodies have been employed.[30] Of course, the most important facet of the biomolecule moiety is its specificity for its biomarker target. Indeed, a wide array of biomarkers have been exploited. Most often, the chosen target is a cell surface marker protein or receptor, such as the somatostatin receptor family (SSTr),[50] integrin family (*e.g.* $\alpha_v\beta_3$),[51] gastrin-releasing peptide receptor (GRPR),[52] and epidermal growth factor receptor (EGFR).[53] In more specialized cases, disialogangliosides (*e.g.* GD2), mRNA gene products, and even the low pH environment of tumors have been targeted by antibodies,[54] oligonucleotides,[55] and short peptides,[56] respectively. Targeting cytosolic proteins and enzymes with antibodies and oligopeptides is rare due to the considerable difficulty of getting large biomolecules into the cytoplasm. However, significant progress is being made in the development of cell- and nucleus-penetration strategies, and this technology may prove productive for intracellular or intranuclear PET imaging agents in the near future.

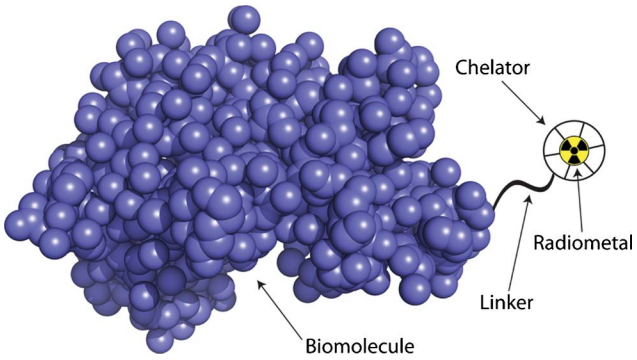

Fig. 1 The anatomy of a PET bioconjugate.

Radiometals: properties and production

The principal radiometals employed for the labeling of biomolecular tracers are ^{64}Cu, ^{68}Ga, ^{86}Y, and ^{89}Zr. Of course, these are not the only positron-emitting radiometals. Some metallic radioisotopes, such as ^{60}Cu, ^{61}Cu, ^{62}Cu, ^{82}Rb, ^{52m}Mn, and ^{94m}Tc, have been used in PET studies to varying degrees, but their half-lives make them far better suited for small molecule tracers (*e.g.* [^{60}Cu]-Cu(ATSM)).[57–60] Other positron-emitting radiometals, including ^{45}Ti ([^{45}Ti]-transferrin[61]), ^{52}Fe ([^{52}Fe]-citrate/transferrin[62]), ^{55}Co ([^{55}Co]-antiCEA F(ab′)$_2$[63,64]), ^{66}Ga ([^{66}Ga]-octreotate[65]), ^{110m}In ([^{110m}In]-octreotate[66]), and ^{74}As ([^{74}As]-bavituximab[67,68]), have been employed in the synthesis of biomolecular radiopharmaceuticals.[41] However, these will not receive more than a brief discussion here, due to either the lack of more than one or two radiotracers per isotope, the limited availability of the radionuclide in question, or decay characteristics that make the isotope sub-optimal for use in a clinical PET radiopharmaceutical.[40]

The selection of a radiometal from the four main candidates, ^{64}Cu, ^{68}Ga, ^{86}Y, and ^{89}Zr, is a critical factor in determining the ultimate properties of a PET bioconjugate. In this regard, one

half-life of the isotope to the biological half-life of the biomolecule. For example, ^{68}Ga is an inappropriate choice for labeling fully intact IgG molecules, for the radionuclide will decay through a number of half-lives before the antibody reaches its fully optimal biodistribution within the body. Therefore, the longer lived radiometals ^{64}Cu, ^{86}Y, and especially ^{89}Zr are most often employed for immunoPET with fully intact mAbs. That said, ^{68}Ga has been used successfully in the construction of PET bioconjugates based on antibody fragments with shorter biological half-lives. Conversely, ^{89}Zr would be an inappropriate choice for a short peptide radiotracer; in this case, the multi-day radioactive half-life of ^{89}Zr would far exceed what is typically a multi-hour biological half-life of the peptide, resulting in poor PET counting statistics and unnecessarily increased radiation dose to the patient. Thus, ^{64}Cu, ^{86}Y, and ^{68}Ga are most often employed for oligopeptide PET tracers. It is important to note that ^{64}Cu and ^{86}Y occupy a favorable middle ground with respect to radioactive half-life, allowing these radionuclides to be utilized advantageously in both antibody- and peptide-based based tracers.

The production of radiometals in high radionuclidic purity and specific activity is essential to the development of effective bioconjugates for PET imaging, and while an in-depth understanding of the nuclear reactions and purification chemistry behind their production may not be necessary for the biomedical use of these isotopes, a brief overview of the processes surely has merit. The production methods for radionuclides fall into three general categories: generator, cyclotron, and nuclear reactor (Fig. 2). Of the positron-emitting radiometals addressed in this perspective, ^{68}Ga is generator-produced, while ^{64}Cu, ^{86}Y, and ^{89}Zr are produced using a medical cyclotron.

^{68}Ga is produced *via* the electron capture decay of its parent radionuclide, ^{68}Ge. In the laboratory and clinic, ^{68}Ga can be produced using a compact, cost-effective, and convenient ^{68}Ge/^{68}Ga generator system, which is capable of providing ^{68}Ga for PET tracers for 1–2 years before being replaced.[69] The ^{68}Ga is eluted from the generator in 0.1 M HCl, providing a $^{68}GaCl_3$ starting material for radiolabeling.[70] Despite its convenience, the system does have some limitations, most notably high eluent volumes that often must be pH-adjusted prior to radiolabeling reactions, ^{68}Ge break-through from the generator, and metal-based impurities. However, a number of purification techniques have been developed to circumvent the problems presented by the trace impurities in the ^{68}Ga eluent.

^{86}Y is the first of the three cyclotron-produced radiometals to be addressed here. ^{86}Y is most often produced through the ^{86}Sr(p,n)^{86}Y reaction *via* bombardment of an isotopically enriched $^{86}SrCO_3$ or ^{86}SrO target with 8–15 MeV protons.[71–74] A range of purification methods have been employed, including combinations of precipitation, ion exchange chromatography, chromatography with a Sr-selective resin, and electrolysis.[75–77]

^{89}Zr has been produced *via* both the ^{89}Y(p,n)^{89}Zr and ^{89}Y(d,$2n$)^{89}Zr reactions. In the past, these methods have been used to successfully produce the radiometal using 13 MeV protons and 16 MeV deuterons, respectively, though both pathways have been complicated and limited by problematic purification protocols.[78–80] A significant improvement upon these methods was provided by another production strategy that yielded ^{89}Zr *via* the bombardment of ^{89}Y on a copper target with 14 MeV protons, oxidation of Zr^0 to Zr^{4+} with H_2O_2, and purification *via* anion exchange chromatography and subsequent sublimation steps.[81,82] In the last few years, these methods have been improved upon further through the use of an ^{89}Y thin-foil target (99% purity, 0.1 mm width), the optimization of bombardment conditions (15 MeV, 15 μA, 10° angle of incidence), and an improved solid phase hydroxamate resin purification to produce ^{89}Zr reliably and reproducibly in very high specific activity (470–1195 μCi/mmol) and radionuclidic purity (>99.99%).[83]

Finally, ^{64}Cu can be produced with either a nuclear reactor or a cyclotron *via* a variety of reaction pathways.[3] In a nuclear reactor, ^{64}Cu can be produced through the ^{63}Cu(n,γ)^{64}Cu and ^{64}Zn(n,p)^{64}Cu pathways. On a biomedical cyclotron, carrier-free ^{64}Cu can be produced using the ^{64}Ni(p,n)^{64}Cu and ^{64}Ni(d,$2n$)^{64}Cu reactions.[84–88] The former pathway has proven more successful and is currently used to provide ^{64}Cu to research laboratories throughout the United States. In this method, the ^{64}Cu is processed and purified *via* anion exchange chromatography to yield no carrier-added $^{64}Cu^{2+}$. The expense of the enriched ^{64}Ni target is a limitation of this production pathway, though a technique for the recycling of ^{64}Ni has ameliorated this issue somewhat. In the last few years, a number of groups have worked to develop methods for the production of ^{64}Cu using Zn targets through the ^{64}Zn(d,2p)^{64}Cu,^{66}Zn(d,α)^{64}Cu, and ^{68}Zn(p,αn)^{64}Cu reactions.[89–92] These efforts have yielded some promising results but have failed to supplant the cyclotron-based ^{64}Ni(p,n)^{64}Cu pathway as the main route for ^{64}Cu production.

Radiometal chelation chemistry

With both the targeting vectors and radiometals in hand, the spotlight next falls on how to combine these two essential parts of the PET bioconjugate. Indeed, both the formation of a kinetically inert metal chelate and the stable covalent attachment of the

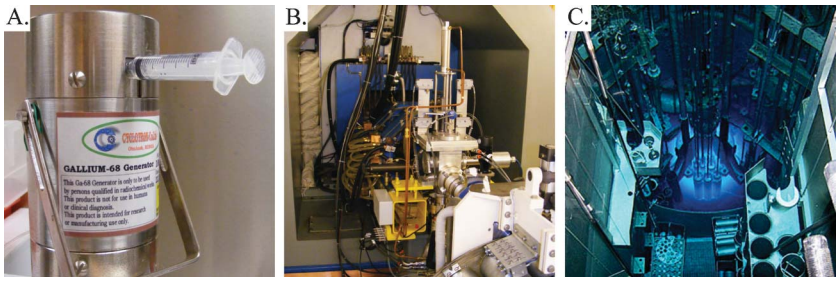

Fig. 2 Three methods for the production of radionuclides: (A) ^{68}Ga generator, (B) cyclotron, and (C) nuclear reactor. The authors acknowledge David

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