The pursuit of the perfect radionuclide for imaging or therapy is ongoing, as no single choice can universally meet all applications. The field of nuclear medicine has seen significant advancements in radiotheranostics, particularly in neuroendocrine tumors (e.g., [18F]F-DCFPyL and [177Lu]Lu-PSMA-617) (1). In recent years, numerous new radiopharmaceuticals and radionuclides have emerged (1). Factors such as rising demand, costs, and availability must be considered when selecting a radionuclide for clinical use. To maximize benefits, it is also crucial to ensure compatibility between the radionuclide's physical properties and the ligand's pharmacokinetic properties, such as biologic half-life.

Copper radioisotopes, namely 61Cu and 64Cu for PET imaging and 67Cu for therapy, are highly desirable because of their suitability for their respective applications (2,3). 61/64Cu/67Cu offers a superior theranostic match compared with the commonly used 68Ga/177Lu pair, thanks to chemically identical structures shared between the imaging and therapeutic radiotracers (Cu-ligand). Of note, a few alternatives also have this elementally matched pair attribute, such as the emerging pairs 203Pb/212Pb and 152Tb/160Tb. This allows for consistent biodistribution and pharmacokinetics, essential for precise pretherapeutic dosimetry. Among copper radioisotopes, 64Cu is commonly used for PET imaging because of its longer half-life (12.7 h) and commercial availability. In 2020, [64Cu]Cu-DOTATATE received approval, and clinical trials are evaluating various [64Cu]-labeled PSMA.

**WHY 61CU VERSUS OTHER PET RADIONUCLIDES?**

In Table 1, the physical properties of 61Cu are compared with other established PET radionuclides, and Figure 1 illustrates the PET image resolution using a phantom. 61Cu (half-life, 3.33 h; 61% β⁺-fraction; mean positron energy [Eγ⁺], 500 keV; maximum Eγ⁺, 1,216 keV) exhibits more favorable characteristics than 64Cu. Even though 64Cu has a lower positron energy (maximum Eγ⁺, 655 keV) with intrinsically better spatial image resolution, 61Cu has a higher number of positrons (β⁺) emitted per decay (61% compared with 17.9%), leading to improved sensitivity, as already indicated by the pioneer work of McCarthy et al. (4). This provides the opportunity for a lower injected activity or a shorter scanning time to achieve adequate photon count statistics. Furthermore, the shorter half-life and absence of β⁻ particles (which account for 39% of decays in 64Cu) result in a reduced radiation dose to the patient. In daily clinical practice, using 61Cu may offer greater convenience for patient management, especially in countries with stricter radioprotection regulations.

Because of its intermediate half-life between 68Ga (68 min) and 64Cu (12.7 h), 61Cu enables PET scans to be conducted 3–6 h after injection, offering improved diagnostic performance due to higher image contrast and tumor-to-background ratios over time, compared with 68Ga-labeled tracers. This can enhance sensitivity and accuracy while avoiding false-positive signals. In addition, multiple-time-point scans enable pretherapeutic dosimetry estimations. 61Cu-labeled tracers are less susceptible to delays that may occur after administration to a patient than are 68Ga-labeled tracers. Certainly, in daily routine the 24-h availability of the generator-produced 68Ga is convenient, and scans at early time points are preferable. Nevertheless, the limited production capacity of the 68Ga tracers (2–3 patient doses) raises certain concerns, and multiple serial production is hampered by the waiting time between 2 consecutive elutions of the generator. 61Cu brings more flexibility in performing radiosynthesis, shipping from a central producer to satellite institutions, and scheduling patients, especially because of its longer half-life.

Although 61Cu does not possess better physical properties than 18F, it does offer advantageous chemical properties due to its ability to be labeled using chelators. As a result, radiosynthesis for 61Cu is simple, allowing for kit (shake-and-bake) formulation without requiring expensive infrastructure such as module-assisted radiosynthesis or purification systems commonly used for 18F radiotracers. These qualities make it well suited for daily routine use. Moreover, the notable structural differences between chelator-based therapeutics and 18F-based PET tracers bear a high risk of variations in biodistribution between the diagnostic and the therapeutic radiotracer. The increasing adoption of chelators, such as the NOTA chelator used in the Al18F strategy, in developing 18F-labeled tracers is a step toward solving this disparity. 61Cu offers the possibility of a chemically identical therapeutic companion (61Cu-labeled tracer) or a similar one (e.g., [64Cu]Cu/[177Lu]Lu-DOTATATE, in analogy to [68Ga]Ga/[177Lu]Lu-DOTATATE).

Copper chemistry is widely understood and straightforward (2,3,5). However, the challenge in developing 61Cu-based radiotracers lies in the in vivo stability of the 61Cu-chelator complex (3). This challenge is due to the risk of 61Cu(II) decomplexation (e.g., transchelation or transmetallation) (5) and the bioreduction of 61Cu(II) to 61Cu(I).
Cu(I) may be released from the chelator and incorporated into endogenous copper-binding proteins, followed by accumulation in the liver and other off-target tissues. Thus, a range of chelators has been specifically designed for Cu-based radiotracers (5). In contrast to the widely used DOTA and its derivatives, which demonstrate the in vivo instability of the copper-DOTA complex, chelators such as sarcophagine and NODAGA have shown promise in circumventing this issue. Additionally, these Cu-tailored chelators offer the advantage of room temperature labeling within a few minutes (shake-no-bake approach), making the production of radiotracers even faster and simpler.

WHICH LIGANDS MAY BENEFIT FROM 61Cu?

The favorable properties of 61Cu make it suitable for delayed imaging with ligands that exhibit peak tumor uptake 1–2 h after injection and have fast body clearance. This is especially relevant for small molecules or peptides. Indicative ligands in combination with 61Cu are somatostatin analogs (SSA), which have a peak tumor uptake of between 4 and 24 h. Currently, 68Ga-SSA PET/CT imaging is acquired 45–90 min after injection, which might be sub-optimal. Thus, delayed imaging using 61Cu could better exploit the pharmacokinetic properties of SSA and further enhance image contrast and sensitivity. However, the benefit of delayed imaging with [64Cu]Cu-DOTATATE compared with 68Ga-SSA PET or 18F-SSA PET scans at 1 h after injection is still uncertain (6,7).

WHERE DO 61Cu PRODUCTION, DISTRIBUTION, AND AVAILABILITY STAND?

Despite its favorable physical properties, the development of 61Cu has been limited by availability constraints. Recently, 2 methods for large-scale production of 61Cu using liquid (12) and solid (13) targets have been developed for commercial production on a standard medical cyclotron (16.5- or 18-MeV proton capability). The main routes of production involve proton bombardment of inexpensive natural zinc, or enriched 64Zn or 61Ni and deuteron bombardment of natural nickel or enriched 60Ni. Although liquid targets offer easy processing, their lower production yields and longer irradiation times may restrict widespread use, especially in view of interference with the routine 18F production. Yet, simultaneous production of 61Cu and 18F is possible using a dual-proton-beam setup. On the other hand, solid target production through an 8.4-MeV deuteron bombardment of natural Ni or enriched 60Ni has been limited by availability constraints. Recently, 2 methods for large-scale production of 61Cu using liquid (12) and solid (13) targets have been developed for commercial production on a standard medical cyclotron (16.5- or 18-MeV proton capability). The main routes of production involve proton bombardment of inexpensive natural zinc, or enriched 64Zn or 61Ni and deuteron bombardment of natural nickel or enriched 60Ni. Although liquid targets offer easy processing, their lower production yields and longer irradiation times may restrict widespread use, especially in view of interference with the routine 18F production. Yet, simultaneous production of 61Cu and 18F is possible using a dual-proton-beam setup. On the other hand, solid target production through an 8.4-MeV deuteron bombardment of 60Ni or a 12- to 14-MeV proton bombardment of 61Ni required shorter times and can be scaled from 4 to 60 GBq by increasing the
companion therapeutic 67Cu via chelator-based radiochemistry, radiolabeling, provides the potential for theranostics using the 67Cu ion. Furthermore, it allows for quick and convenient cold kit manufacturing, and distribution. With its relatively long half-life, expensive trace-metal data available. Clinical studies with 61Cu-labeled somatostatin and (NCT00585117) has been registered (in 2008), but there are no sustainabilty of 61Cu production. The Table 2.

<table>
<thead>
<tr>
<th>Target</th>
<th>Target material</th>
<th>Target material cost/mg</th>
<th>Nuclear reaction</th>
<th>Target concentration or weight</th>
<th>Beam current (μA)</th>
<th>Irradiation time (min)</th>
<th>Activity produced (GBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid</td>
<td>natZn</td>
<td>$0.003</td>
<td>natZn(p,α)61Cu</td>
<td>200 mg/mL</td>
<td>70</td>
<td>180</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>Liquid</td>
<td>64Zn</td>
<td>$0.5–0.7</td>
<td>64Zn(p,α)61Cu</td>
<td>200 mg/mL</td>
<td>70</td>
<td>180</td>
<td>3.3 ± 0.4</td>
</tr>
<tr>
<td>Solid</td>
<td>natNi</td>
<td>$0.005</td>
<td>natNi(d,n)61Cu</td>
<td>80 mg</td>
<td>60</td>
<td>60</td>
<td>2.0 ± 0.2</td>
</tr>
<tr>
<td>Solid</td>
<td>61Ni</td>
<td>$20–25</td>
<td>61Ni(p,3n)61Cu</td>
<td>50 mg</td>
<td>40</td>
<td>30</td>
<td>3.5 ± 0.5</td>
</tr>
</tbody>
</table>

enrichment levels of the 64Ni. However, solid targets require additional steps such as target material dissolution but provide higher production yields at shorter irradiation times and scalability based on material enrichment. The choice between liquid and solid targets depends on production requirements, material availability, and commercial demand. A comparison of the production routes is listed in Table 2.

There are several major factors contributing to the cost and sustainability of 61Cu production. The first is the cost of the target material, especially when enriched isotopes are used. Although upscaling production is possible only with enriched isotopes, their higher cost and limited supply require target material recycling to minimize expenses.

A second factor is the operation and maintenance costs of the cyclotron. These costs directly impact the cost per hour of irradiation. Limiting the irradiation time and complexity of the production can be beneficial in contract manufacturing to minimize costs.

A third factor are the separation and purification costs, as specialized processes are required to isolate the desired 68Ga from the target material and other by-products. These processes require expensive trace-metal–free chemicals and consumables.

A final factor is radiopharmaceutical production and distribution: additional costs are involved in the final product’s formulation, manufacturing, and distribution. With its relatively long half-life, 61Cu provides a distribution range of over 400 km and the advantages of centralized manufacturing and longer shelf-life than for 68Ga or 18F radiopharmaceuticals.

CONCLUSION

Using cyclotron-produced 61Cu offers the advantage of streamlined production and logistics similar to centralized 18F production. Furthermore, it allows for quick and convenient cold kit radiolabeling, provides the potential for theranostics using the companion therapeutic 67Cu via chelator-based radiochemistry, and is a sustainable and cost-effective approach. So far, only 1 pilot clinical study with [61Cu]Cu-ATSM for imaging hypoxia (NCT00585117) has been registered (in 2008), but there are no data available. Clinical studies with 61Cu-labeled somatostatin and PSMA analogs are planned in 2024 that may indicate the role of 61Cu in clinical PET imaging. In the emerging era of radiopharmaceuticals and radiotheranostics, 61Cu radiotracers are a valuable alternative. Still, their future adoption as a preferred choice is yet to be determined.

DISCLOSURE

Melpomeni Fani is a scientific advisor of Nuclidium AG and co-inventor on 2 patent applications filed by Nuclidium AG and the University of Basel, Switzerland. No other potential conflict of interest relevant to this article was reported.

REFERENCES