Cyclotron Production of Non-conventional Theranostic Radionuclides and Radiopharmaceuticals

Theranostic radiopharmaceuticals have become a driving force in nuclear medicine for the detection and treatment of human diseases and especially various cancers. Though many radionuclides have been historically used as theranostic agents (e.g., I-131), the application of radioisotope pairs has catalyzed production of radiotracers using Ga-68 (from cyclotrons and Ge-68 generators), Cu-64 and carrier- and no-carrier-added Lu-177 (from research reactors), and Y-90 (mainly from Sr-90 generators).

The global constellation of accelerators used for radionuclide production provides a prolific supply network and unparalleled opportunity for academic, clinical, and research institutes worldwide. The network is chronicled in the International Atomic Energy Agency (IAEA) database titled “Cyclotrons used for Radionuclide Production,” [1]. The network is capable of producing a tremendous diversity of useful radioactive synthons. Apart from the conventional theranostic radionuclides mentioned above, new routes for the production of approved nuclides, such as Ga-68, as well as the introduction of newcomers in theranostics (e.g., Cu-61, Cu-64, Cu-67, Sc-43, Sc-44g, and Sc-47) reveal new horizons for the “palette of PET tracers” for research and development of future clinical applications. These horizons are explored broadly in this special issue, with a particular focus on production methods.

Although the Ga-68 generator was instrumental in the development of many PET radiopharmaceuticals, its availability and cost stimulated the pursuit of alternative Ga-68 production methods. Cyclotron-produced Ga-68 has been approved in the United States and European Union and is discussed here by Becker and coauthors in the article entitled “A review of accelerator-produced Ga-68.” Liquid targets make cyclotron-production routes conveniently available to facilities that do not have solid target systems—many such systems were pioneered by the Mayo Clinic and are discussed by Pandey and coauthors in an article titled “Cyclotron Production of PET Radiometals in Liquid Target: Aspects and Prospects.” Due to the importance of Ga-68 radiopharmaceuticals, IAEA has recently published a technical document on the subject with the title “Gallium-68 Cyclotron Production” [2] and initiated an interesting international Coordinated Research Project (CRP) with the title of “Development of Ga-68 based PET-Radiopharmaceuticals for Management of Cancer and Other Chronic Diseases” in 2021 [3].

Copper radionuclides, including Cu-64 and Cu-61, have been the most studied cyclotron-based metal positron emitters (before new developments for Ga-68) and have attracted huge attention in the recent years. Avila-Rodriguez and coauthors from the Universidad Autonoma de Mexico (UNAM) thoroughly review the production of copper radionuclides in the article titled “A review on the production of copper radionuclides in compact medical cyclotrons” and cover the status and situation of these radioisotope in the world. Various copper-64 radiopharmaceuticals are produced worldwide for clinical trials, including small molecules and peptides, perhaps most successfully as peptide radiolabels. Mirzaei and coauthors discuss their exemplary experience with the Cu-64/F-18/Lu-177 triplet in prostate cancer in the article, “Theranostics of Metastatic Prostate Cancer Applying 64Cu/18F PSMA PET-CT and 177Lu Radiopharmaceuticals”. In 2016, the IAEA initiated a Coordinated Research Project (CRP) with the title “Copper-64 Radiopharmaceuticals for Theranostic Applications” that was successfully completed in 2020, integrating international experience from several laboratories on the production and application of [64Cu]CuCl2, as well as other radiolabeled molecules [4]. Though Cu-64’s 12.7 h half-life enables convenient radiopharmaceutical quality control and distribution, the half-life is too slow for some peptide imaging, and production requires expensive separated 64Ni target material. This motivated recent work with Cu-61 (t1/2 = 3.3 h) using deuteron irradiation of inexpensive 65Ni targets. Alves and coauthors describe their efforts on this topic in an article titled “GMP automated purification of copper-61 produced in cyclotron liquid targets: methodological aspects.”

Several scandium radionuclides (Sc-43, Sc-44, and Sc-47) with emissions suitable for PET, SPECT, and therapy are of increasing interest in the community. Chernysheva and coauthors from multiple U.S. institutions cover the production of these nuclides using charged particle accelerators and photon-induced reactions in an article titled “Accelerator Production of Scandium Radioisotopes: Sc-43, Sc-44, and Sc-47.”

Exploration of new molecular targets is essential in novel radiopharmaceuticals’ development. Somatostatin analogs, PSMA-targeting agents, have generated headlines with regulatory approvals this decade, and other targets are in advanced stages of development. The biology, biochemistry, and radiopharmaceutical chemistry of a novel molecular target, cancer-associated fibroblasts, relevant for molecular imaging and theranostics, is reviewed by Dr. Zhuralev and coauthors from the Hevesy Laboratory, Denmark, in an article titled “Theranostic radiopharmaceuticals targeting cancer-associated fibroblasts.”

Beta- and alpha-emitting radiopharmaceuticals, to varying degrees, have the disadvantage of irradiating surrounding cells when applied as therapeutic radiopharmaceuticals. The limited range of Auger electrons theoretically limits ablation to intracellular and potentially intranuclear scales depending on the efficacy of pharmacokinetic targeting. Intense current interest in the production of Auger emitters for theragnostic approach stimulated Hoehr and coauthors to describe their topical contributions in an article titled “Auger emitters for targeted radionuclide therapy: Antimony-119 and mercury-197m/g.”
The IAEA, as a worldwide platform for dissemination and support of radioisotopes and radiopharmaceutical sciences, has initiated complementary investigative efforts to disseminate radionuclide production technology in conjunction with this special issue. The CRP entitled “Therapeutic Radiopharmaceuticals Labelled with New Emerging Radionuclides (\(^{67}\text{Cu}, {^{186}}\text{Re}, {^{47}}\text{Sc})” [5] successfully concluded in 2020, and a recent IAEA publication with the title of “Therapeutic Radiopharmaceuticals Labelled with Copper-67, Rhenium-186, and Scandium-47” summerizes the technical outcome and outputs of the project [6]. In this issue, a review article on the results of this project with a special focus on Re-186, Sc-47, and Cu-67 theranostic radiopharmaceuticals is presented by Jalilian and eighteen international coauthors.

REFERENCES