# ACCELERATOR-BASED MEDICAL ISOTOPE PRODUCTION: AN OVERVIEW OF EMERGING TRENDS AND NOVEL INITIATIVES

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## Abstract

Recent advances in drug development and radionuclide research have notably expanded the role of nuclear medicine in treating cancer over the past decade. Throughout such research and development efforts, the list of drug moieties and cancer types under investigation is paralleled by a similarly expansive list of radionuclides. This is because the suitability of a radionuclide for a therapeutic radiopharmaceutical application will depend on many factors including, but not limited to, the decay mode (e.g. $\alpha$- vs $\beta$-emitter), the particle emission range, the matching of its half-life to the pharmacokinetics of the drug, and the co-emission of gamma rays of appropriate energy for imaging. Moreover, the successful adoption into clinical practice hinges on sustained, reliable, and cost-effective access to these radionuclides – a task which is not trivial. To this end, this work provides an overview of emerging trends in radionuclides, alongside novel initiatives for accelerator-based production strategies.

## INTRODUCTION & NUCLIDE TRENDS

The application of radionuclides to theranostics, i.e. the combination of diagnostics and therapeutic nuclides emerged in the 1940s using radioiodine for imaging and treatment of thyroid cancer [1]. In the past decade theranostics has, however, made an inflection point with significant increase in the research and clinical implementation of radionuclide theranostic pairs for several clinical indications. Two notable examples include the approvals of $^{68}$Ga- and $^{177}$Lu-based radiopharmaceuticals for diagnosis and therapy (respectively) of neuroendocrine tumors and prostate cancer [2, 3]. Clinical trials with $^{68}$Ga and $^{177}$Lu expand, however, beyond these applications with the numbers of clinical trials using these nuclides increasing ~5 and 10-fold, respectively, in the past decade (Fig. 1).
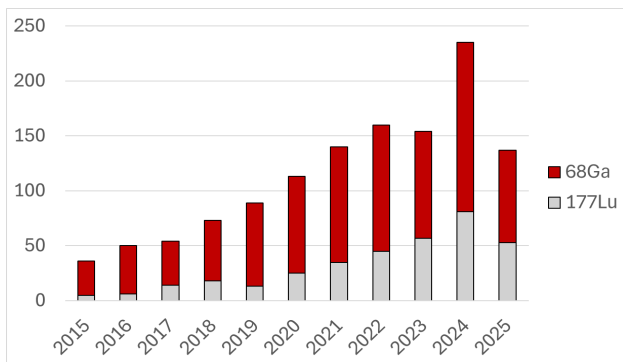


Figure 1: Number of clinical trials by starting year as reported on clinicaltrials.gov [4] for $^{68}$Ga and $^{177}$Lu search terms (accessed August 3, 2025).

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$^{68}$Ga and $^{177}$Lu are not, however, "magic bullet" nuclides for all applications. Instead, the decay characteristics of the nuclides must be considered in conjunction with the application (e.g. tracer kinetics, physical tumor characteristics, targeting properties, radiolabeling strategies, etc.). As such, and accompanied by new technologies for nuclide production, it is of no surprise that the "menu" of candidate nuclides of interest is ever-expanding. To this end, Fig. 2 highlights the growth of clinical trials using emerging radionuclides, while Fig. 3 summarizes select decay and chemical characteristics of these nuclides.
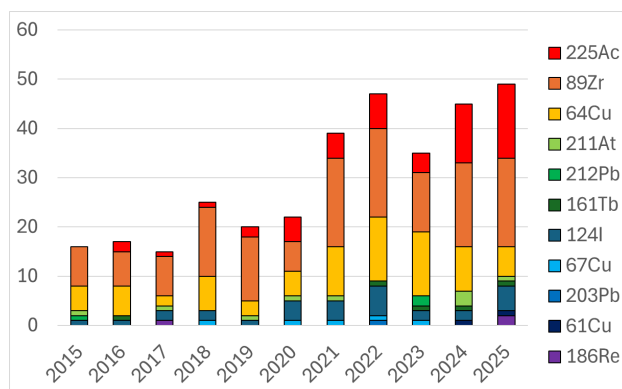


Figure 2: Number of clinical trials by starting year as reported on clinicaltrials.gov [4] for select theranostic nuclide search terms (accessed August 3, 2025).
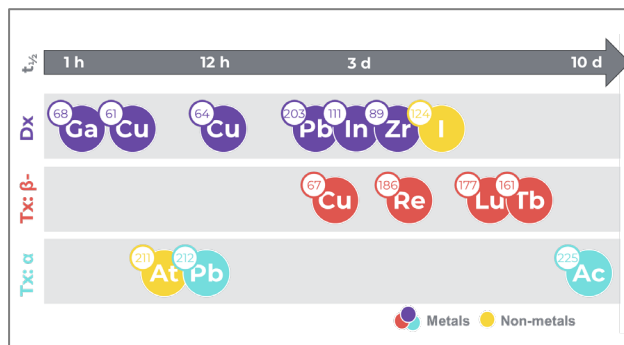


Figure 3: Properties of select theranostic nuclides based on half-life ($t_{1/2}$), diagnostic (Dx) or therapeutic (Tx) primary application, $\alpha$- vs $\beta$-emitter, and considerations for radiolabeling (e.g. metal/non-metal).

## NUCLIDE PRODUCTION

Translating this growing menu of nuclides of interest from research into widespread use requires a reliable and cost-effective supply chain of these nuclides. Although select nuclides (e.g. $^{177}$Lu) require a nuclear reactor for large-scale production, many nuclides (i.e. the majority outlined in Fig. 2) require an accelerator.

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To this end, the increase in accelerator-based production of radionuclides has similarly paralleled the trends observed with clinical trials. For example, the number of cyclotrons (i.e. the dominant technology for accelerator-based nuclide production) has increased from 262 to 1297 from 2006 to 2020 [5, 6]. As reported in Ref. [5], the profile of these cyclotrons has been as follows with a similar distribution assumed for present systems:

- Protons: > 99%; >80% at <30 MeV
- Deuterons: ~13% > 10 MeV; 0.4% > 20 MeV
- Alphas: ~10%; 4% > 20 MeV

While non-cyclotron accelerator-based technologies also significantly contribute to nuclide production, especially for reactions at higher proton energies as well as electron-based accelerators driving photonuclear reactions, access to high intensity alpha and deuteron beams continues to be limited. To further explore this limitation, $^{211}$At and $^{186}$Re are used as case-studies.

## Case Study #1: $^{211}$At

Although nuclides can often be produced from several different reactions and incident particles, the production of $^{211}$At is, in practice, limited to the alpha irradiation of $^{209}$Bi – i.e. via the $^{209}$Bi$(\alpha,2n)^{211}$At reaction. This is due to the lack of stable natural abundance target material at a proton number (Z) of 84 (Fig. 4).



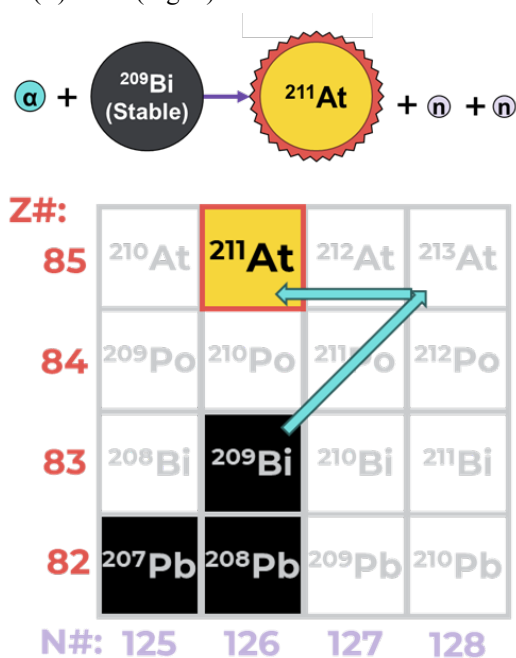Figure 4: The $^{209}$Bi$(\alpha,2n)^{211}$At reaction pathway.

In addition to requiring alpha particles, the energy of the alpha particles is critical. Namely, the alphas must be of adequate energy for $^{211}$At production, however, the energy must be restricted to below 29 MeV to limit the co-production of $^{210}$At. To date, $^{211}$At production has been limited as the acceleration of alphas in this energy range for nuclide production has been limited to a total cumulative intensity of ~350 µA [7].

## Case Study #2: $^{186}$Re

The most common route to $^{186}$Re is via a reactor, using the $^{185}$Re$(n,\gamma)^{186}$Re reaction, however, this results in a low specific activity product. While low specific activity has its utility, there are applications for which high specific activity would be required. High specific activity $^{186}$Re is possible via accelerator routes. As exemplified in Fig. 5, however, the (d,2n) production route has far superior cross sections when compared to the (p,n) reaction.
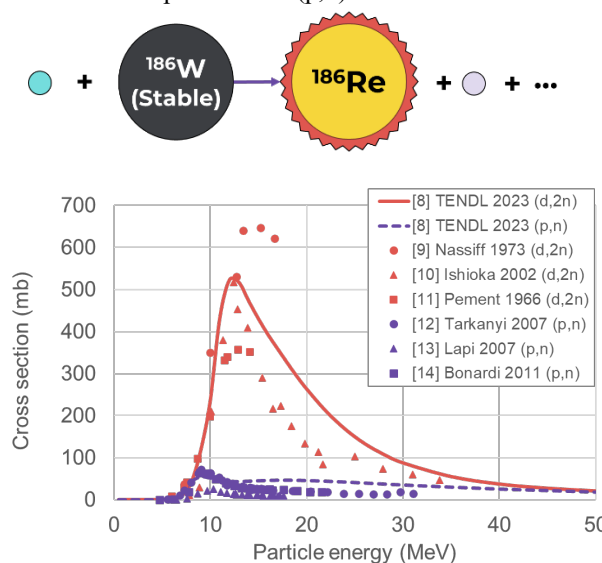


Figure 5: Deuteron (red), and proton (purple) excitation functions for the production of $^{186}$Re from $^{186}$W via the (d,2n) and (p,n) reactions, respectively [8-14].

Although not to the same extent as observed for $^{186}$Re, the direct production cross sections for $^{64}$Cu, $^{67}$Cu, $^{89}$Zr, and $^{123}$I are similarly higher with deuterons vs. protons (Fig. 6). This suggests that higher production yields with potentially with lower target mass could be possible. Once again, however, access to deuteron beams of suitable energy and intensity have been limited.
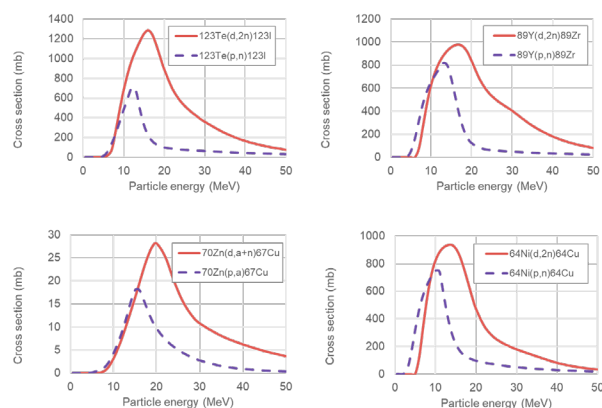


Figure 6: Deuteron (red), and proton (purple) excitation functions for the direct production of $^{123}$I, $^{89}$Zr, $^{67}$Cu, and $^{64}$Cu, as taken from [8].

## NOVEL PRODUCTION TECHNOLOGY

To address shortages in the supply of key radionuclides, our efforts are focused on developing and implementing novel ion source and accelerator technologies. To this end, the installation of our accelerator in our new purpose-built isotope production facility is well underway. Our initial focus includes the acceleration of deuterons (to 25 MeV) and alphas (to 50 MeV), each with average currents of ~3-5 mA. These beams will be used for simultaneous irradiation of up to twelve targets across four target bays (Fig. 7).

With such unprecedented beam currents in these energy ranges (e.g. >10-fold of the cumulative global alpha beam current to date [7]) we believe these efforts will play a key role in facilitating translation of the growing menu of desired radionuclides of interest from research into widespread use.
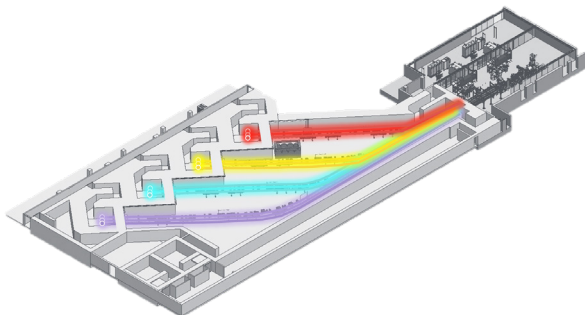


Figure 7: Floor plan showing Nusano's LINAC hall (upper right) supplying beam to up to 12 targets across 4 target bays.

## CONCLUSION

The past decade has been met with growth in both the utility and diversity of radionuclides in medicine. To ensure reliable, and cost-effective access, new technologies and infrastructure is required, including access to high energy and intensity deuteron and alpha beams.

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