Paving the way to provide the β⁻-emitting ^{161}Tb radionuclide for clinical studies: challenges and lessons learned

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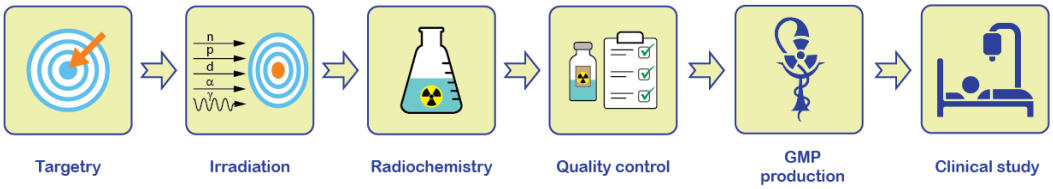
Targeted radionuclide therapy can be a potent means to treat cancer, as exemplified, among others, by therapeutic agents based on the β⁻-emitting radionuclide ^{177}Lu. It has been determined that ^{161}Tb has a decisive advantage over ^{177}Lu because it co-emits significant amounts of conversion and Auger electrons. The least energetic of these electrons, characterized by their short penetration path (≤ 1 µm) but high linear energy transfer, are expected to be selectively lethal for small tumors and even single cells as encountered in the metastatic progression of the disease.

To conduct clinical studies with ^{161}Tb, it needs to be reliably available on a regular basis and in a quality that meets the stringent requirements of the pharmacopeia and the medicinal control authorities. To reach this goal several steps, as shown in the following scheme, need to be taken.



It begins with sourcing the target material with the adequate chemical and isotopic composition for the irradiation, followed by partnering with irradiation facilities with high neutron fluxes (up to ≈$1\cdot10^{15}$ *n* $cm^{-2}s^{-1}$) to generate the radionuclide via the desired ^{160}Gd(n,γ)^{161}Gd→^{161}Tb nuclear reaction. A robust separation procedure, adapted to the remote handling of highly radioactive material, needed to be devised. In this case, this encompasses not only engineering challenges but also the notoriously difficult task of quantitatively separating two neighboring lanthanides (Gd and Tb), knowing that the desired ^{161}Tb is diluted in a ≈10'000-fold excess of the starting material [1]. Successful chromatographic separation is critical to achieving high radiochemical purity (≥ 99.0%, separation yield ≈80%) of the final product considering that the vector molecule to be radiolabeled is present in the micromolar range with only a minimal excess over the purified radionuclide. In addition, high radionuclidic purity (^{161}Tb ≥ 99.9%) is essential to minimize unnecessary radiation dose to the patient by other Tb radioisotopes or impurities [2]. Finally, the formulation of the final product must take place under Good Manufacturing Practice (GMP) conditions and pass the prescribed tests before release for use in humans.

With concerted efforts of a multidisciplinary team, the challenges have been mastered and all requirements met **for ^{161}Tb to become the first radionuclide fully developed in Switzerland to enter the clinical trial stage** as the SSTR antagonist ^{161}Tb-DOTA-LM3.

[1] Nadezda Gracheva et al. *EJNMMI Radiopharm. Chem.* **2019**, 4(1), 12. [2] Chiara Favaretto et al. *J. Nucl. Med.* **2023**, 64, #265268 online May 18, 2023.