

## Comparison of promising new short range therapeutic radiopharmaceuticals using $^{225}\text{Ac}$ , $^{213}\text{Bi}$ and $^{161}\text{Tb}$

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Prostate-specific membrane antigen is a prominent imaging biomarker in nuclear medicine. With Gallium-68 ( $^{68}\text{Ga}$ ) opportunely available to hospital radiopharmacies we recently developed a PSMA11 single kit vial radiolabeling solution which is now routinely used in the Steve Biko Academic hospital in Pretoria, South Africa. The most widely used therapeutic pendant for  $^{68}\text{Ga}$  is  $^{177}\text{Lu}$  but recent advances in radionuclide production methods have made  $^{225}\text{Ac}$ ,  $^{213}\text{Bi}$  and  $^{161}\text{Tb}$  available as alternatives to  $^{177}\text{Lu}$ . This created interesting opportunities to treat metastases with the short range Alpha or Auger and conversion electron emissions.

$^{225}\text{Ac}$  is a very promising radionuclide for targeted alpha therapy. With its relatively long half-life (9.9 d) it has enough time to target also less-easily accessible tumours, and the 4 emitted alpha's in the decay chain ensure effective cell killing once at the targeted site.  $^{225}\text{Ac}$  is produced by radiochemical extraction from  $^{229}\text{Th}$  at the Institute for Transuranium Elements, Karlsruhe, Germany. In a recent study by the Sathekge group in Pretoria, [ $^{225}\text{Ac}$ ]Ac-PSMA-617 radioligand therapy of chemotherapy-naïve patients with advanced metastatic prostate carcinoma led to a  $\geq 90\%$  decline in serum PSA in 82% of patients including 41% of patients with undetectable serum PSA who remained in remission 12 months after therapy.

In contrast the radioactive decay of  $^{213}\text{Bi}$  ( $T_{1/2} = 46$  min) results in the emission of two high-LET  $\alpha$ -particles releasing around 100 keV/ $\mu\text{m}$ . Due to the relatively short half-life of  $^{213}\text{Bi}$ , it can deliver a high radiation dose to the target within a short period of time.  $^{213}\text{Bi}$  is eluted from  $^{225}\text{Ac}/^{213}\text{Bi}$  Generator (ITG, Munich, Germany). In a recent study by the Sathekge group in Pretoria a first-in-human treatment with [ $^{213}\text{Bi}$ ]Bi-PSMA-617 in a patient with mCRPC that was progressive under conventional therapy, was undertaken. The patient was treated with two cycles of [ $^{213}\text{Bi}$ ]Bi-PSMA-617 and restaging with [ $^{68}\text{Ga}$ ]Ga-PSMA PET/CT after 11 months showed a remarkable response w.r.t. soft tissue metastases.

The use of these short range emitters does not go without challenges that will have to be overcome. Upon emission of an alpha particle, the daughter nuclide experiences a recoil energy which is several orders of magnitude larger than the energy of the chemical bond of the nuclide resulting in the daughter to be released from the targeting vector.

Terbium is a unique element, as it provides a quadruplet of radionuclides suited for diagnostics and therapy in nuclear medicine.  $^{161}\text{Tb}$  (Auger/conversion electron and  $\beta$ -emitter,  $T_{1/2} = 6.9$  d) was produced by neutron irradiation of enriched  $^{160}\text{Gd}$  in the SAFARI-1 research reactor from which no-carrier-added  $^{161}\text{Tb}$  was produced. In a recent study by the Müller group in Villigen-PSI, [ $^{161}\text{Tb}$ ]Tb-PSMA-617 showed superior in vitro and preclinical in vivo results as compared to [ $^{177}\text{Lu}$ ]Lu-PSMA-617 confirming theoretical dose calculations with regard to a positive effect of conversion and Auger electrons.

The various options & pros and cons for these three radionuclides/radiopharmaceuticals will be discussed.

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