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New Methods for Targeted Alpha Radiotherapy

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Targeted radiotherapies based on alpha emitters are a promising alternative to beta emitting radionuclides. Because of their much shorter range, targeted α-radiotherapy (TAT) agents have great potential for application to small, disseminated tumors and micro metastases and treatment of hematological malignancies consisting of individual, circulating neoplastic cells. A promising approach to TAT is the use of the *in vivo* α-generator radionuclides ^{223}Ra ($t_{1/2}$ = 11.4 d) and ^{225}Ac ($t_{1/2}$ = 10.0 d). In addition to their longer half-lives, these two isotopes have the potential of dramatically increasing the therapeutic efficacy of TAT as they each emit four α particles in their decay chain. This principle has recently been exploited in the development of Xofigo®, the first TAT agent approved for clinical use by the U.S. FDA. Xofigo, formulated as $^{223}RaCl_2$, is used for treatment of metastatic bone cancer in men with castration-resistant prostate cancer. TAT with ^{223}Ra works, however, only in the case of bone cancer because radium, as a chemical analogue of calcium, efficiently targets bone. In order to bring the benefits of TAT with ^{223}Ra or ^{225}Ac to other tumor types, a new delivery method must be devised. Retaining the *in vivo* α generator radionuclides at the target site through the decay process is one of the major challenges associated with the development of TAT. Because the recoil energy of the daughter radionuclides from the α-emission is $\sim$ 100 keV – a value which is four orders of magnitude greater than the energy of a covalent bond - the daughters will not remain bound to the bioconjugate at the targeting site. Various approaches have been attempted to achieve retention of the α-generator daughter radionuclides at the target site, including incorporation of the *in vivo* generator into liposomes and fullerenes. Unfortunately, to date single wall liposomes and fullerenes are able to retain less than 10% of the daughter radionuclides. We have recently demonstrated that a multilayered nanoparticle-antibody conjugate can deliver multiple α radiations from the *in vivo* α-generator ^{225}Ac at biologically relevant receptor sites. The nanoparticles retained over 90% of the ^{221}Fr daughter over the course of three weeks in *in vitro* experiments. In *in vivo* experiments, approximately 90% of the ^{213}Bi was retained in the target tissue 24 hours after injection of the antibody labeled nanoparticle. An overview of the development and application of this promising, new approach to targeted alpha therapy will be presented.