



Contribution ID: 560

Type: Verbal

## Alpha Radionuclide Therapy Using Polymeric Nanocarriers

*Tuesday, 15 May 2018 16:15 (15 minutes)*

Alpha radionuclide therapy (ART) is a very powerful tool for the treatment of small tumour metastases. Due to their short range and high LET, alpha particles are much more efficient at killing cells than the commonly used beta radiation. Furthermore, their short range stops them from destroying neighbouring healthy cells. One of the main problems which still needs to be solved before ART can successfully be implemented in the clinic is the recoil problem: upon alpha-decay the daughter nuclide receives a recoil energy decoupling it from any targeting agent, allowing it to diffuse throughout the body to irradiate healthy tissue.

We have developed polymeric nanocarriers capable of retaining the recoiling daughters of the alpha-emitting radionuclide  $^{225}\text{Ac}$  and thus limit healthy tissue toxicity. Using a Monte Carlo-based simulation tool, a number of different polymersome designs have been simulated to optimize the recoil retention. Subsequently, polymersomes have been prepared with  $^{225}\text{Ac}$  co-precipitated with an  $\text{InPO}_4$  nanoparticle inside the vesicle, as the use of high-Z materials results in a much-reduced recoil range as compared to an aqueous environment. Using this new formulation, recoil retentions have improved significantly as compared to earlier published results by Wang et al., where  $^{225}\text{Ac}$  was encapsulated using a hydrophilic chelate [1].

Excellent results have been obtained in vitro, where the potential of  $^{225}\text{Ac}$ -loaded polymersomes has been evaluated in U87 glioblastoma multicellular spheroids. We have found that polymersomes distribute themselves throughout the spheroid after 4 days which, considering the long half-life of  $^{225}\text{Ac}$  (9.9 d), allows for irradiation of the entire spheroid. Our studies indicated that even at low radionuclide activity the  $^{225}\text{Ac}$  polymersomes deliver a very high dose, with spheroid growth inhibition was already observed at just 0.1 kBq of  $^{225}\text{Ac}$  added. The therapeutic efficacy upon intratumoural administration of  $^{225}\text{Ac}$ -polymersomes has been tested in vivo in BALB/c mice bearing an MDA-MB-231 tumour. The retention of the vesicles upon intratumoural administration has been shown to be very high ( $46.0 \pm 21.5\%$  and  $37.0 \pm 23.9\%$  at 1 day and 7 day p.i. respectively), whereas the tumours which have been injected with  $^{225}\text{Ac}$ -DOTA retained less than 1% (1 day p.i.), demonstrating the advantage of using the vesicles intratumourally. The accumulation of recoiled  $^{213}\text{Bi}$  in the kidneys was limited, with a kidney to tumour ratio of only 1:30. Immunohistochemical analysis of the tumours has shown an increase in double-stranded breaks in the group treated with  $^{225}\text{Ac}$ -polymersomes, indicating their suitability for tumour irradiation.

Large strides have thus been made towards the clinical implementation of polymersomes in ART. The incorporation of nanoparticles in polymersomes has allowed for high retention of the  $^{225}\text{Ac}$  mother and daughter nuclides, and both in vitro as well as in vivo their potential in destroying tumours has been demonstrated.

**Primary authors:** Dr DE KRUIJFF, Robin (Radiation Science and Technology, Delft University of Technology, Delft, the Netherlands); Dr HESKAMP, Sandra (Radiology and Nuclear Medicine, Radboud University Medical Centre; Nijmegen, the Netherlands); Mrs MOLKENBOER-KUENEN, Janneke (Radiology and Nuclear Medicine, Radboud University Medical Centre; Nijmegen, the Netherlands); Ms VAN DER MEER, Astrid (Radiation Science and Technology, Delft University of Technology, Delft, the Netherlands); Dr MORGENSTERN, Alfred (European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany); Dr BRUCHERTSEIFER, Frank (European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany); Dr SMINIA, Peter (VUmc Cancer Center Amsterdam, Amsterdam, the Netherlands); Prof.

WOLTERBEEK, Bert (Radiation Science and Technology, Delft University of Technology, Delft, the Netherlands); Dr DENKOVA, Antonia (Radiation Science and Technology, Delft University of Technology, Delft, the Netherlands)

**Presenter:** Dr DE KRUIJFF, Robin (Radiation Science and Technology, Delft University of Technology, Delft, the Netherlands)

**Session Classification:** RPH 1

**Track Classification:** Radiopharmaceutical Chemistry, Labelled Compounds