Pre-targeting of PEG-based nanomedicines: precise delivery of potent payloads

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Molecular radiotherapy (MRT) involves targeted delivery of ionising radiation to trigger localised cell death. Targeted irradiation is achieved using alpha (α) or beta (β-) emitting radionuclides that are incorporated into a radiopharmaceutical. While most MRT research to date has focused on the delivery of β--emitting radionuclides (e.g. ^{177}Lu), growing interest has been focused on α-emitting radionuclides such as ^{225}Ac and ^{212}Pb. Highly ionizing α-particles deposit 100–1000 times greater energy per unit path length than the current clinical standard β- particles, which gives them the ability to produce lethal DNA double-strand breaks within the cell nucleus while reducing the amount of unwanted radiation to surrounding tissues. To achieve targeted delivery of this potent radiotherapeutic payload, a targeting nanomedicine platform was produced.

This current work reports PEG-based hyperbranched polymers (HBP) which can bind and deliver ^{212}Pb payloads. Further, through our previously reported[2] pre-targeting approach utilizing bispecific antibodies (BsAb), we are able to selectively enhance tumour uptake resulting in improved therapeutic efficacy. Herein we report in vitro assays validating cellular targeting as well as preclinical studies utilizing Single Photon Emission Computed Tomography (SPECT) and ex vivo biodistribution analysis demonstrating a 3-fold increase in tumour accumulation of ^{212}Pb payload using pre-targeting. We further applied this system to a preclinical breast cancer model and showed targeting to greatly improve therapeutic outcomes for ^{212}Pb HBP while also demonstrating good tolerability profiles in terms of general animal health and haematological toxicity.

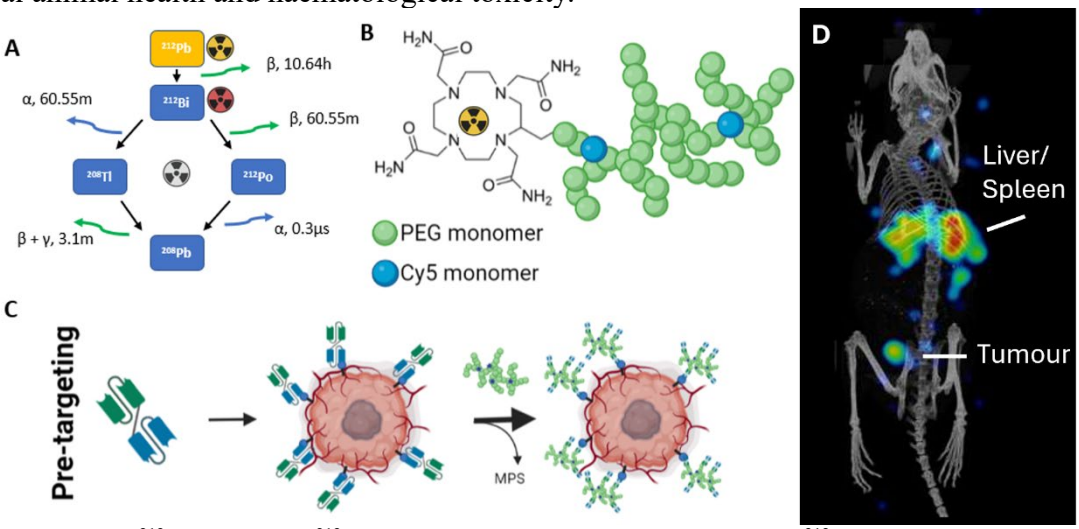

Figure 1; A) ^{212}Pb decay, B) [^{212}Pb]HBP, C) Pre-targeting approach and D) ^{212}Pb-SPECT imaging of nanomedicine tumour delivery in preclinical breast cancer model

References:

[1] Harrison, M. R.; Wong, T. Z.; Armstrong, A. J.; George, D. J.,. *Cancer Manag Res* **2013,** *5*, 1-14
[2] Fletcher NL, Prior A, Choy O, Humphries J, Huda P, Ghosh S, Houston ZH, Bell CA, Thurecht KJ.. Chem Commun (Camb). 2022 Jul 14;58(57):7912-7915..