Exploring hyaluronan nanocapsules as PARP inhibitor delivery systems: in vitro and in vivo studies (SPECT) in healthy mice

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Background: The goal of this research is to improve the biodistribution properties and tumour accumulation of poly ADP-ribose polymerase inhibitors (PARPis) via novel drug delivery systems for more efficient anti-cancer treatments. In this study we explored hyaluronan nanocapsules (NCs), as potential PARPi drug delivery systems *in vitro* and *in vivo* using [^{125}I]I-PARPi as a tracer for SPECT imaging.

Methods: I-PARPi was chosen after comparing the similar radiosensitising effects compared to Olaparib and F-PARPi, whilst allowing long-term tracking using ^{125}I SPECT imaging (Fig. 1A-C). [^{125}I]I-PARPi NCs were synthesised following previous methods and using [^{125}I]I-PARPi / I-PARPi in the organic phase.

Results: Size-exclusion chromatography indicated high (>80 %) encapsulation efficiency (EE) that was not affected by the amount of drug (I-PARPi) loaded in the NCs. Negative control studies verified the EE results. [^{125}I]I-PARPi NCs were colloidally and radiochemically stable in human serum and showed slow drug release over 72h *in vitro*. We then evaluated the biodistribution of [^{125}I]I-PARPi and [^{125}I]I-PARPi NCs in healthy Balb/c mice via SPECT imaging (2, 6 and 24 h) and ex vivo biodistribution studies (24h only). At early (2h) timepoints, the biodistribution of [^{125}I]I-PARPi and [^{125}I]I-PARPi NCs showed no significant differences in blood circulation, but significant differences in liver uptake, consistent with the behaviour of nanoparticulates. At later timepoints (24h), however, the biodistribution differed to what could be expected for a particulate drug delivery system with [^{125}I]I-PARPi showing higher levels of retention in liver/spleen, and higher thyroid levels for [^{125}I]I-PARPi NCs, which is likely the result of increased release of free [^{125}I]I-iodide.

Conclusions: Hyaluronan NCs appear to be a good system to encapsulate and slowly release PARPi in vitro. However, the [^{125}I]I-PARPi NCs seem to release the drug at a much faster rate in vivo making Hyaluronan NCs suboptimal for future applications as a PARPi delivery system. Future work will be looking for alternative nanocarriers for PARPi.