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Developing bioorthogonal smart polymers for cancer therapy

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The selective delivery and effective localisation of drugs is crucial in cancer therapy. Conventional chemotherapy is subjected to certain drawbacks, such as limitation of tumour-specific receptors that ensure efficient internalisation to enhance drug release as well as significant systemic toxicity to healthy tissues.1 The use of bioorthogonal chemistry is a versatile and promising tool to overcome such drawbacks as it expands the scope of using non-internalising receptors as targets for cancer therapy and selective extracellular release of the drug. Importantly, this drug release stimulus is controlled only by the addition of an exogenous molecule, providing more direct control over in vivo drug release.2 In this work, a 64Cu radiolabelled tetrazine probe (tetrazine-PEG-NOTA) was synthesised, that showed rapid pharmacokinetics in healthy mice when tested in positron emission tomography/computed tomography (PET-CT). Critically, almost all of the tetrazine radioligand was cleared into the bladder within 20 minutes. Additionally, another PET-CT study conducted using a 64Cu radiolabelled PEG-NOTA probe showed that tetrazine does not affect the clearance behaviour of the molecule from the bloodstream other than the pathway of clearance. Looking forward, a PEGylated hyperbranched polymer will be synthesised that is conjugated with bispecific antibodies as targeting ligands and trans-cyclooctene moieties bearing the anti-cancer drug doxorubicin. This will be administered to tumour-bearing mice, and following its accumulation at the tumour site, the fast clearing tetrazine probe will be administered. Selective bioorthogonal conjugation of the 64Cu radiolabelled tetrazine probe to trans-cyclooctene through rapid inverse electron demand Diels-Alder cycloaddition will then be monitored in real-time by PET-CT. In this way, the click reaction will facilitate pro-drug activation as well as provide a means to quantify the amount of drug administered at site.

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