Development of a nano-based novel drug delivery platform for treatment of Triple Negative Breast Cancer.

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Background: Triple-negative breast cancer (TNBC) is an aggressive form of cancer, and there are yearly around 2500 new cases of TNBC in Australia. TNBC is not amenable to anti-hormone therapy or anti-HER2 targeted therapy, due to the lack expression of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2).[1] Chemotherapy is the most common treatment for TNBC. However, despite an initial response, many patients experience tumour relapse. Additionally, chemotherapy is associated with harmful side effects and is often ineffective in treating metastatic TNBC, highlighting the urgent need for more targeted and effective therapies.[2] Moreover, TNBCs were found to be enriched in cancer stem cells (CSCs), which are relatively quiescent and intrinsically resistant to chemotherapy leading to the metastasis and relapses.[3] It is, therefore, an urgent need to develop drug delivery systems that would specifically deliver the cytotoxic compound to the tumour site and overcome chemotherapy resistance at the same time. Targeting luteinising-hormone releasing hormone receptor (LHRH-R) (expressed in 70-100% of TNBCs) is one approach by which targeted delivery of chemotherapy can be achieved.[1] Combing the benefits of this approach with a CSCs inhibitor by conjugating both to a nanoparticle platform and using them as a combination is expected to improve the treatment efficacy and clinical outcomes of TNBC patients. Plasma polymerized nanoparticles (PPNs) are a new class of nanoparticles synthesized through plasma polymerization, allowing for a single-step functionalisation with molecular cargo without the need for linker intermediates. In this process, a plasma field is used to polymerize monomers, forming nanoscale particles with surface functionalities that enable direct cargo attachment.[4]
Aim: The aim of this project is to optimize a method for the synthesis and characterization of PPNs conjugated to a novel CSC inhibitor (7C)[5] and a previously developed novel LHRH-based peptide-drug conjugate (PDC) (Patent ID: WO2020220085A1) and evaluate the effectiveness of combining the developed conjugates.
Methodology: PPNs incorporating 7C and PDC have been characterised using High Performance Liquid Chromatography (HPLC), X-ray photoelectron spectroscopy (XPS), and dynamic light scattering (DLS). Biological studies including antiproliferative studies and colony formation assay were conducted.
Conclusion: The conducted studies revealed the efficacy of the compounds involved in these studies (PDC and 7C). Characterization of the developed conjugate has been completed. However, the conjugated platform will be further evaluated via cell-based pharmacological studies including antiproliferation study and uptake in 2D and 3D culture.

References:

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