Sepideh Khazeni et al., J Clin Trials 2018, Volume 8
DOI: 10.4172/2167-0870-C2-025

Development of *in vitro* methodologies to study the behaviour of LHRH-receptor targeted drug delivery systems

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Statement of the Problem: Triple-Negative Breast Cancer (TNBC) is an aggressive breast cancer subtype. Due to the lack of sex-hormone receptors and HER2 overexpression, tumor does not respond to the available targeted drugs. Hence, it is crucial to develop effective targeted drug delivery system to treat TNBC. For the successful development of these delivery systems (DDS), various *in vitro* models need to be designed to allow successful translation of preclinical to clinical investigations. Many times, preclinical experiments are tested in a very narrow set of experimental conditions. We believe that the introduction of target-specific approaches to preclinical science and design of more relevant biological models to the specific delivery system under investigation, leads to more robust preclinical studies which in turn results in translation to more robust clinical trials. In this study, we have developed several *in vitro* models to test the behavior of different DDSs based on the Luteinizing Hormone Releasing Hormone Receptor (LHRH-R) targeting.

Experimental Design: We studied the overexpression of LHRH-R by immunohistochemistry analysis using advanced Confocal Laser Scanning Microscopy (CLSM) on three different TNBC cell line (MDAMB-231) and LHRH-R negative control cell-line (SKOV-3). Uptake of different DDSs conjugated with LHRH-R ligand was investigated by CLSM and IncuCyte® live cell imaging in these cell lines. By IncuCyte® live cell imaging, we also evaluated the uptake via LHRH-R with receptor binding competitive assay in which the uptake was examined in the presence and absence of a competitor of the LHRH receptor ligand.

Results: We observed the overexpression of LHRH-R in TNBC cells but not in the control cells. We detected a high uptake of LHRH-based DDSs by the TNBC cells using CLSM and IncuCyte®. The live cell imaging of the receptor binding competitive assay showed that LHRH- based DDSs were only up-taken in the absence of the competitor.

Conclusion: We successfully designed different experiments that could reveal the potential biological behavior and selectivity of our LHRH-based DDSs. These experiments showed that the LHRH-based DDSs are selectively up-taken through LHRH-R overexpressed TNBC cells. These findings indicate that LHRH-R ligands are promising carriers to use for future targeted drug design for the treatment of TNBCs. Furthermore, our developed methodologies allowed us to effectively investigate the *in vitro* behavior of this targeted DDS as an important part of the preclinical studies.

Biography

Sepideh Khazeni is a research student in The University of Sydney, Australia. She is currently working on projects focusing on Pharmacological evaluation of a peptide-based drug delivery system for targeted therapy of Triple Negative Breast Cancer.

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