Develepment of nanotechnology-based targeted drug delivery systems to treat triple negative breast cancer

Pegah Varamini, Sepideh Khazeni, Behdad Delavari, Bahareh Bigdeli*

School of Pharmacy, Faculty of Medicine and Health,
The University of Sydney,
Camperdown, NSW, Australia Address

pegah.varamini@sydney.edu.au

Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype. Due to the lack of sex-hormone receptors and HER2 overexpression, tumour does not respond to the available targeted drugs[1]. Hence, it is crucial to investigate the design of effective targeted drug delivery system (DDS) for the treatment of TNBC[2]. In this study, we have developed different nanotechnology-based DDSs to target overexpressing Luteinizing Hormone Releasing Hormone receptors (LHRH-R) on TNBC cells.

We studied the overexpression of LHRH-R by immunohistochemistry analysis using advanced Confocal Laser Scanning Microscopy (CLSM) on three different TNBC cells and normal breast cell lines. Uptake of different DDSs conjugated with a novel LHRH-R ligand (LHRH-DDS-n) was investigated by CLSM and IncuCyte® in these cell-lines. Using small interfering RNA (siRNA) against LHRH-R sequence, we knocked down the LHRH-R expression in TNBC cell lines with 85% knockdown efficiency and compared the uptake in these cells against wild-type TNBC cells. All *in vitro* models of TNBC for testing our DDSs confirmed the specific uptake by the targeted DDSs (e.g. Figure 1) and preferential cytotoxicity against cancer cells. Furthermore, we have shown a significant improvement in the physicochemical properties of the targeted vs. non-targeted nanoparticles in all DDSs which resulted in a more efficient antitumor activity against TNBC cells.

In conclusion, we have shown LHRH-based DDSs were selectively uptaken through LHRH-R overexpressed TNBC cells. These findings indicate that the developed DDSs are promising carriers to use for targeted delivery of anticancer agents for the treatment of TNBC. Furthermore, our developed methodologies allowed us to effectively investigate the *in vitro* behavior of this targeted DDS as a part of the preclinical studies.

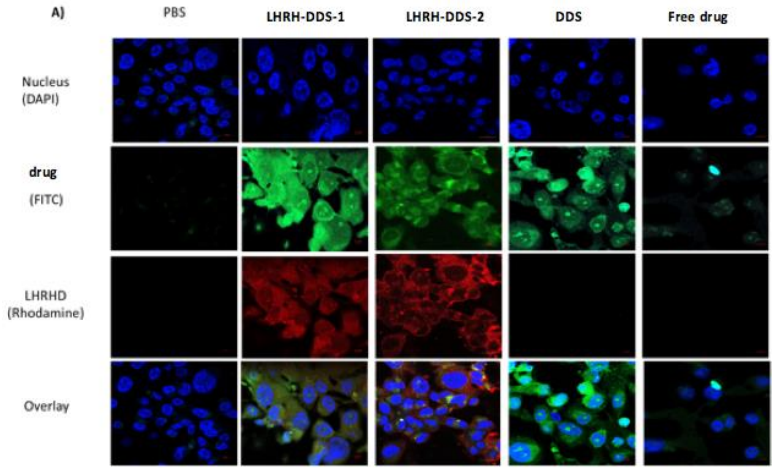

Figure 1: In vitro uptake study of targeted Cur-NPs in TNBC cell model (MDA-MB-231)

References;
1- Calderon, L. E. et al., *Bioconjugate Chemistry* **2017**, 28, 461-470
2- Khazeni, S. and P. Varamini, Gonadotropin Releasing Hormone. *Reference Module in Biomedical Sciences* , **2018** **(**https://doi.org/10.1016/B978-0-12-801238-3.98031-0)