Oncol Cancer Case Rep 2016,2:3(Suppl)
http://dx.doi.org/10.4172/2471-8556.C1.003

Development and evaluation of a tri-functional lipid nanoparticles for treatment of HER2-Positive breast cancer refractory to HER2 therapy

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Purpose: Breast cancer (BC) is the second leading cause of cancer deaths in women, and about 25% of BCs have overexpression of the HER2 receptor. Although HER2 targeted therapies have shown considerable improvement in HER2-positive BC patients' outcome, treatment resistance remains a clinical challenge. Here, we sought to develop and evaluate a novel Tri-Functional Lipid Nano-Particulate (TFLP) drug delivery system that overcomes HER2 treatment resistance by dually targeting HER2 on BC cells and CD3 receptors on cytotoxic T-lymphocytes (CTLs).

Material and methods: Anti-HER2 (Trastuzumab) and anti-CD3 (OKT-3) antibodies, were conjugated to lipid nanoparticles by the micelle-transfer method, and the resulting formulation was purified by dextran gradient ultra-centrifugation. Targeted lipid nanoparticles were formulated with a fluorescent lipophilic dye, DiD, for studying receptor binding and internalization. Studies were conducted with HER2-positive BT474 cells and CD3-positive Jurkat cells using flow cytometry analyses. Doxorubicin HCl (DXR) was encapsulated in the nanoparticles by the remote-loading technique for cell-kill experiments. *In vitro* cell-kill studies were conducted by co-culturing BT474 as the target cells, and peripheral blood mononuclear cells as the effector cells, at varying ratios.

Results: Purified formulations were successfully characterized for conjugation by determining protein to lipid ratio. Flow cytometry analyses demonstrated successful cell binding and/or internalization of the TFLP with both the HER2 and CD3-positive cell lines. Moreover, these dual-targeted nanoparticles were able to retarget T cells to kill HER2 positive BC cells, and showed improved efficacy compared to non-targeted and plain HER2-targeted formulations *in vitro*.

Conclusion: A novel TFLP drug delivery system that targets HER2 receptors on tumor cells, CD3 on CTLs, and is able to slowly release DXR was successfully developed and evaluated *in vitro* on HER2 overexpressing BC cells. Our findings show great promise at overcoming resistance to present HER2 targeted BC therapies, and may translate into improved anti-tumor activity clinically compared to other treatment options.

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Decavanadate contribution to vanadium biomarkers

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The levels of vanadium in urine and blood can be used as biomarkers of exposure, but the mechanism of vanadium toxicity is of major relevance in order to understand how biomarkes can be valuable. Our research group has performed *in vivo* and *in vitro* studies using fish and rat models to analysed and compare the toxicity effects induce by vanadium(V) species in the forms of vanadate (V1) and decavanadate (V10). Vanadium toxicological studies often disregarded the formation of decameric vanadate species (V10) known to interact, *in vitro*, with high-affinity with many proteins such as myosin, actin and sarcoplasmic reticulum calcium pump. Among different experimental *in vivo* conditions, it was analysed different: (i) mode of administration; (ii) fish species; (iii) metal concentration (1 and 5 mM); (iv) tissues; (v) subcellular fractions ; (vi) exposure time and particularly different metal ionic species, such as V1 and V10. It was observed that"decavanadate" promote different effects than other vanadate oligomers in catalase activity, glutathione content, lipid peroxidation, mitochondrial superoxide anion production and vanadium accumulation. Moreover, in *in vitro* studies using fish and rat liver mitochondria, it was observed that decavanadate impared respiration by depolarization of the mitochondrial membrane, wich altered the redox state of complex III. Putting it all together, it is suggested that decavanadate species are much more effective than monomeric vanadate species in inducing changes in several biomarkers. By changing mitochondrial functioning decavanadate migh provoke ROS formation, but further studies are needed to understand V10 contribution to vanadium biomarkers.

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