COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Non-ionic Surfactant Vesicles (NISV) Have Host Directed Therapeutic Potential And Can Be Targeted To The Brain

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It is widely recognised that uncontrolled immune responses and neuroinflammation contribute to the pathogenesis of many infectious diseases including encephalitic alphaviruses. Therefore, host directed therapies, capable of controlling the immune response and inflammation could contribute to disease resolution. However, a major challenge to such treatments is getting therapies across the blood brain barrier (BBB) and downregulating inflammation.

We have recently developed a formulation of non-ionic surfactant vesicles (NISV) that have inherent immunomodulatory properties that can down regulate inflammation. We also previously demonstrated that a variant of these vesicles; NISV coated with glucosamine (gNISV) can efficiently cross the BBB. These vesicles bind to overexpressed GLUT1 receptors on the BBB and proved effective in delivering anti-alphavirus antibodies into the brain, improving mice survival.

Here we describe the formulation and characterisation of NISVs coated with either ascorbic acid (ascNISV), transferrin (tNISV) or angiopep-2 (apNISV), which each target unique receptors and use alternative mechanisms of cell entry. We determined the ability of each formulation to modulate macrophage activation in vitro and test their abilities to traverse the blood brain barrier us an in vitro transwell system. Regardless of coating, all vesicle formulations were non-toxic to bone marrow derived macrophages (BMDCs) and retained immunomodulatory properties previously shown with un-coated NISV. Cytometric Bead arrays demonstrated that NISVs modulate a number of key inflammatory products dependent on Toll Like Receptor (TLR) stimulation examined. Transcriptomic analyses reveal that NISV downregulate NF-kB and NLRP3 inflammasome following stimulation with viral mimetic ligands for TLR7 or TLR8. NISVs coated with either, transferrin or angiopep-2 but not with ascorbic acid had enhanced BBB crossing ability relative to NISV, but all formulations significantly increased transport compared to free drug (mAb). These data demonstrates that each of these formulations have potential to target host specific receptors to direct therapeutics to the brain. Our most promising candidates, have been shown to increase BBB crossing of therapeutic cargo by over 10 fold. NISV formulations have been shown to entrap both biologics and small molecule anti-microbials, raising the possibility of using the NISV platform in a combined host directed and pathogen directed therapy. NISVs are a flexible, adaptable drug delivery platform technology with inherent host directed therapeutic abilities, that can be engineered to target specific, difficult to access host tissues. Their ability to entrap anti-infectives or host directed biologic therapies provides further multimodal therapeutic potential.

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