Hybrid Lipid –Inorganic nanoparticles for drug delivery to the brain

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Drug delivery to the brain is challenging and relies on crossing a semipermeable membrane known as the blood−brain barrier (BBB). The BBB is an endothelial cell monolayer that separates the blood from the cerebral central nervous system (CNS). This tight junction in the BBB presents a physical barrier to the permeability of the majority of drugs from the blood to the CNS when administered intravenously.

Oxidative stress plays a significant role in the pathology of multiple neurodegenerative diseases such as Parkinson's disease, amyotrophic lateral sclerosis (ALS), Alzheimer's disease and stroke. Certain inorganic nanoparticles (NPs) are powerful antioxidants with robust activity and it was recently shown that they are promising candidates for novel therapy of neurodegenerative diseases involving oxidative stress that can neutralize several important pathological reactive oxygen species that can lead to neurodegeneration. Whilst they show great therapeutic promise, their small size (3-4 nm) means they are rapidly cleared from the body, accumulate in the liver and spleen, are unable to reach the brain and show off-target toxicity.

Lipid nanoparticles (LNPs) are a promising noninvasive strategy to protect drug payload and toxicity, and have been employed as delivery vehicles to treat many diseases such as cancer and recently in two COVID vaccine formulations. They can enhance penetration into the brain and although they show superior performance there are limited number of studies. LNPs offer advantages over current nanoformulations, including favourable drug payloads due to their high internal surface area, simple preparation protocols, superior ease of conjugation, biodegradability/ biocompatibility, and the ability to encapsulate hydrophobic and hydrophilic cargo.

The aim of this project is to create colloidally stable soft matter formulations that encapsulate inorganic NPs into various novel LNPs (100-200 nm) developed in our labs. These hybrid lipid-inorganic NPs will be characterized using Dynamic Light Scattering, Small Angle X-ray Scattering and cryo-TEM and long term stability studies. Encapsulation and release of the inorganic NPs will be assessed spectroscopically. The inherent heterogeneity within a nanomedicine formulation can lead to a range of behaviours and properties that influence the overall functionality of the product. We will investigate the heterogeneity of these soft matter formulations by asymmetric flow field flow fractionation (AF4) to separate LNPs into distinct subpopulations based on their size and shape, which are characterised by in-line multi-angle light scattering, UV-Vis spectroscopy and dynamic light scattering. The fractionated LNP subpopulations will also be characterized off-line to elucidate heterogeneities in drug-loading and release, which is crucial for performance.

The most promising LNPs will be tested *in vivo* in the USA in Dr. Leiter's lab, which the student will have the opportunity to visit.