

Programming the cytosolic fate of magnetic nanoparticles: fusogenic delivery, extracellular vesicle encapsulation, and hydrodynamic-driven bioproduction

Abstract

Magnetic iron oxide nanoparticles (MNPs) are interesting candidates for imaging and therapy due to their magnetic responsiveness and physicochemical versatility. Yet, once internalized by cells, MNPs are predominantly trapped within endosomes. This confinement restricts their cytosolic bioavailability, limits functional interactions with cellular machinery, and results in progressive degradation and iron recycling. In parallel, cells naturally secrete extracellular vesicles (EVs), lipid bilayer-delimited nanoparticles that mediate intercellular communication and are emerging as highly promising therapeutic nanocarriers due to their intrinsic biocompatibility and targeting capabilities. However, if MNPs could be interesting cargos for EVs, their sequestration into endosomes leads to extremely poor encapsulation into EVs.

This project proposes a strategy to enable the efficient encapsulation of MNPs into extracellular vesicles (EVs). To achieve this, the first bottleneck is for MNPs to access the cell cytosol after internalization. This can be achieved through two different systems: surface functionalization of MNPs with peptides that allow endosomal escape, or MNP encapsulation into fusogenic liposomes that can directly fuse with the cell membrane to deliver their cargo into the cytosol. These approaches will be optimized during this project to enhance internalization and cytosolic delivery, validated through advanced imaging and physicochemical characterization.

A second critical challenge is scalable production of loaded EVs. Here, physics plays a pivotal role: we leverage a patented hydrodynamic bioproduction system to stimulate EV secretion and modulate cargo composition. By integrating cytosolic MNP programming with hydrodynamic control, we aim to generate high-yield, multifunctional EVs co-loaded with magnetic nanomaterials and functional RNA, establishing a novel nano-RNA combinatorial platform.

This interdisciplinary project bridges chemical design, biological understanding of EV biogenesis, and physical control of membrane processes. It seeks to transform how inorganic nanomaterials interface with living cells and how EVs can be engineered as next-generation therapeutic vectors.