

Artificial Protein Corona for Enhanced LNP Gene Delivery to Glioblastoma

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The biological performance of nanocarriers is strongly influenced by their interactions with the surrounding biological environment. Upon exposure to biological fluids, nanoparticles rapidly acquire a layer of adsorbed proteins, known as the protein corona (PC), that redefines their biological identity, affecting cellular recognition, uptake, and intracellular fate [1,2]. While PC formation has traditionally been regarded as an uncontrolled process, engineering this bio-nano interface offers an opportunity to actively modulate nanocarrier behaviour and improve therapeutic delivery [3,4].

Here, we exploit this concept to enhance lipid nanoparticle (LNP)-mediated gene delivery to glioblastoma (GBM). Through *ex vivo* plasma conditioning, we generate a stable artificial PC enriched in apolipoproteins, which are key mediators of lipid transport and receptor-mediated cellular interactions. This composition is particularly relevant in GBM, where altered lipid metabolism and lipoprotein uptake represent prominent features of tumour biology. This engineered biological interface functionally redirects endocytic routing in GBM cells, enhancing intracellular trafficking and ultimately increasing functional gene delivery.

We investigated this strategy across a hierarchy of GBM models of increasing biological complexity, including 2D cell cultures, 3D tumour spheroids, patient-derived GBM organoids, and *in vivo* xenograft models. The enhanced functional delivery observed across these experimental systems indicates that the beneficial effects of plasma conditioning are maintained in increasingly complex biological settings.

Overall, our findings demonstrate the potential of engineering the PC as a functional component of LNP design to modulate their biological identity and intracellular fate. *Ex vivo* plasma conditioning provides a simple and potentially scalable strategy to enhance LNP-mediated gene delivery, offering a promising framework for the development of more effective nanotherapeutic approaches for GBM.

Reference

- [1] Monopoli et al., Nature Nanotechnology, 2012
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