Recruiting Endogenous Proteins for Site-Specific Transport: A Novel Workflow for Gene Carrier Design

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Nanoparticle-based drug carriers are promising, minimally invasive candidates for cancer treatment. However, the challenge remains in how best to specifically target transformed cells. Upon entering the body, nanoparticles are immediately covered with complex layers of blood proteins (protein coronae) which determine the resulting biological responses: signaling, accumulation, transport and toxicity. Thus, it is vital to control nanoparticle-protein interactions to ensure site-specific transport of therapeutic cargo. This study examined the effectiveness of a reverse engineering approach for corona modulation. For each derivative in a graphene library, proteins constituting corona isolates in human serum were identified and quantified through liquid chromatography-tandem mass spectrometry (over 300 proteins/derivative). A novel bioinformatics-based screening strategy was implemented to determine the most suitable corona protein to act as an endogenous carrier for targeting lung, breast, and colorectal cancer cells. Derivatives with favorable corona compositions were then conjugated with antibodies specific to these proteins and functionalized with siRNA. Gene carriers were evaluated for cellular uptake, cell viability, and gene silencing ability in A549, MCF7, and HCT 116 cells. With this new methodology, time allocated for gene carrier fabrication can be streamlined to find and validate the optimal carrier configuration in just four days – engineered carriers exhibit higher cellular uptake and superior gene silencing ability at a significantly lower cost in comparison to conventional counterparts. With its wide range of applicability, this novel methodology has the potential to save millions of lives while also saving the global healthcare system billions of dollars.