**Efficient intracellular delivery of nucleic acids by NUVEC® silica nanoparticles**

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In recent years, there has been a surge in the development of diverse range of therapeutic modalities to treat disease, initiating a shift from a drug discovery of small and large molecule medicines. This includes but is not exclusive to nucleic acid therapeutics. However, the limitations of delivery are restricting translation of therapeutic mRNA, siRNA, and DNA to the clinic. In a quest to tackle this issue, N4 Pharma has developed NUVEC®, a next-generation, complex silica nanoparticle with the capacity to deliver nucleic acids efficiently into a broad spectrum of cell types. NUVEC® has an intricate structure with a unique spiky surface coupled with positively charged polyethyleneimine that entrap, deliver, and protect the cargo from nuclease-mediated degradation. At MDC, we have developed a pipeline of advanced techniques and assays that we have applied to characterise NUVEC® bound with either plasmid DNA or siRNA cargo. We assess physical properties via Zetasizer and demonstrate effective loading of cargo onto NUVEC® particles via mass spectrometry. High-resolution microscopy and genetic engineering techniques have been employed to better understand NUVEC® and its mechanisms of intracellular trafficking. Our data demonstrates cellular internalization, endosomal escape followed by release of functional cargo into the cytoplasm. Subsequently, we observe target gene silencing comparable to lipid transfection with a leading commercial reagent; ~80% knockdown of both endogenous (EHMT2) and overexpressed (GFP) genes. Furthermore, NUVEC® particles have the capacity to simultaneously bind and deliver two different siRNA at an efficacious concentration. Our data demonstrates the therapeutic potential for NUVEC in oncology and other disease areas where dual inhibition of undruggable targets is required to improve clinical outcomes. Furthermore, the techniques and assays used to characterise NUVEC® particles can be applied to characterise other complex medicines.