

**Engineered protein superstructures for the encapsidation of nucleic acid therapeutics**T. G. Edwardson<sup>1</sup>, D. Hilvert<sup>1\*</sup><sup>1</sup>ETH Zurich

The potential of proteins for the fabrication of new functional nanostructures is yet to be fully exploited. This is due to the permissive complexity of self-assembly information encoded in peptide chains. However, it is this diverse range of physical and chemical functionality which holds much potential for new technologies in a variety of fields. One example is proteins which self-assemble into hollow structures that can encapsulate cargo. These appear in nature with various roles, such as reaction vessels for catalysis, storage containers and delivery vectors. Recently, the first examples of artificially engineered protein containers have appeared, presenting an exciting opportunity to develop synthetic assemblies that mimic the structure and function of their biological counterparts. The research presented concerns the development of a protein cage which can load nucleic acids into its core, as a potential solution to the intracellular delivery of therapeutic nucleic acids. A protein-based carrier has distinct advantages over other nanoparticles, due to biocompatibility, atomic level structural control and potential for site-specific modification. Here electrostatic interactions are used, exploiting the anionic nature of nucleic acids and directing them to the positively charged cavity of the protein cage. The first challenge is the design and expression of a hollow protein structure with a positively charged lumen. Secondly, the capacity for loading is studied, with a focus on complex stability and capacity of the capsule to protect its cargo from degradation. Finally, the ability of the device to enter cells and regulate protein expression is investigated, including modification of the capsid surface to control cellular uptake and trafficking. This research focuses on nanomedicine but in a broader sense aims to show that a simple, rational approach combining supramolecular chemistry and biotechnology can be used to create new function in protein materials.