EVOLUTION OF A MODULAR, MULTI-FUNCTIONAL TARGETED DELIVERY NANOPARTICLE

James Swartz, Stanford University, USA
jswartz@stanford.edu
Maya Nagasawa, Stanford University, USA
Marcus Rohovie, Stanford University, USA
Rinchu Mathew, Stanford University, USA

In spite of hundreds of attempts over the last century, Paul Ehrlich's dream of the "magic bullet" targeted delivery system still has not been realized. Yet these studies have clearly identified the many technological barriers that prevent success. This presentation will describe a step-by-step progression that converted an unstable, non-functional viral capsid (a virus-like particle, VLP) into a sophisticated nanoparticle for targeted delivery of drugs, nucleic acids, and proteins.

Initial mutations reduced immunogenicity and antigenicity and provided a new conditional stability that still allows the VLP to disassembly inside the targeted cell to release its cargo. A hexa-histidine tag enables purification of cell-free produced VLP subunits while potentially also serving to trigger endosomal escape by the "proton sponge" effect. The subunits are also extended with a cargo adsorption domain so that simultaneous cargo loading and VLP assembly can be triggered by increasing ionic strength. Finally the VLP subunit protein was further mutated to incorporate non-natural amino acids which then enable precise surface modification by attaching scFv antibody fragments as targeting agents as well as the extracellular domain of the CD47 receptor to avoid immune system interception. To provide an authentic CD47 interactive surface, the ECD has a pyroglutamate N-terminus, two point attachment (mostly) to the VLP surface, and improved solubility. Functional evaluations using cultured cells are promising and results from initial animal studies will be described.