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BIOENGINEERING BACTERIAL PROTEIN NANOCOMPARTMENTS AS MODULAR PLATFORMS FOR VACCINES AND DRUG DELIVERY

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In nature, prokaryotes can form supramolecular, self-assembling protein compartments, known as bacterial microcompartments (BMCs)[1] and nanocompartments which are associated with various metabolic processes. The modular nature and relative ease of recombinant production[2] of such systems has sparked interest into re-designing these structures with new functionalities. The design of robust platforms with different applications requires understanding and control over particle formation, protein display/encapsulation and stability of engineered variants. Using synthetic biology tools, we gain insights into those properties and the suitability of diverse nano- and microcompartment systems for versatile applications.

Here we will demonstrate two examples of protein nanoparticle engineering: (1) the design of a modular drug delivery platform and (2) a vaccine platform for the oriented display of antigens. The modular drug delivery platform was generated by fusing Designed Ankyrin Repeat Proteins (DARPins), a monoclonal antibody mimic for the specific binding to Human Epidermal growth factor Receptor 2 (HER2), to the capsid protein of the *Thermotoga maritima* encapsulin. The capsid was loaded with a photosensitive protein mini-Singlet Oxygen Generator (miniSOG). The entire drug delivery particle was generated by co-expression of two genes from a single plasmid and a simple purification step. The purified encapsulin-DARPin_miniSOG nanocompartment was shown to bind specifically to HER2-positive breast cancer cells triggering apoptosis after activation of miniSOG and release of reactive oxygen species, indicating that the system is functional[3]. The second application that we will present is a modular vaccine platform for the oriented display of antigens. Here, antigens of interest are displayed on the surface of the *T. maritima* encapsulin nanoparticle using non-covalent interactions with high-affinity picomolar-scale dissociation constants. The platform is tuneable and has the potential to be employed to generate mosaic vaccines composed of various antigens. Our work demonstrates proof of concept for the suitability of encapsulin systems as modular platforms for the bio-manufacture of future therapeutics.

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