Engineering pathogen super-mimics as vaccines using ester bond molecular superglues

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Bacterial cell-surface adhesins facilitate host cell attachment to establish infection. In Gram-positive bacteria, these adhesins are long, thin molecules that contain repetitive domains featuring intramolecular covalent bonds to provide resistance to mechanical stresses in the host environment [1]. These bonds are autocatalytically generated in enzymatic-like mechanisms and hold great potential in biotechnology applications including vaccine design [2, 3].

The biotechnological utility of such spontaneously forming intramolecular covalent bonds was first realised in the SpyTag/SpyCatcher system using a split adhesin repeat domain which re-ligates to join disparate proteins together [2]. We have more recently engineered a toolkit of orthogonal ester bond molecular superglues that are non-cross-reactive with each other and that hold great promise in the assembly of highly complex vaccine particles. Each of our split molecular superglue domains is near identical in structure to our original C. perfringens construct and we have employed X-ray crystallography to understand why they do not cross-react, or conversely, why they are promiscuous [4, 5]. My focus on two known ester bond molecular superglues suggests a small number of specific sites direct specificity.

We are using our toolkit of molecular superglues to build new vaccine constructs that incorporate the best features of contemporary vaccine platforms to safely mimic a whole-pathogen immune response and elicit long-lasting protection. In this endeavour we will covalently join antigenic protein and mixtures of adjuvants or cell receptor-targeting molecules to platforms such as protein cages where our unique molecules can be displayed on the surface, or in other arrangements within lipid nanoparticles. Structural characterisation by electron microscopy shows discrete particles with obvious and regular surface modification.

Our modular and flexible approach to vaccine design allows us to “pick-and-mix” components to elicit a robust and tailored immune response. While mRNA approaches have been a revelation, assembled subunit vaccines, particularly those that could stimulate very specific immune pathways, could be valuable therapeutics in targeting infectious disease and even in personalised cancer vaccines [6].

Figure 1. (A) Cartoon representation of a ligation domain’s structure. The last strand, which is split from the rest of the domain, is coloured yellow. (B) Negative stain electron microscopic image of protein cage nanoparticles.