S55-7 Directed Evolution of Catalytic Antibodies in Phage-displayed Combinatorial Libraries

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Advances in methods for conformational prediction, structural analysis and site-directed mutagenesis of proteins have contributed to the understanding of their structure and function. However, with the exception of a few successes, the generation of practical functional proteins solely by rational design remains a difficult challenge. The aim of our study is to investigate molecular design relying on evolutionary processes, called as "directed evolution", to generate a novel class of biofunctional molecules. This evolutionary approach consists of three steps; 1) constructions of protein libraries based on structural information, 2) expressions of the libraries on phage particles, and 3) selections with investigator-imposed selective pressures. In this work, I would like to introduce our strategy for directed evolution of catalytic antibodies in phage-displayed antibody (Fab) libraries.

To evolve abzymes toward higher catalytic activity, we have reconstructed an enzyme-evolutionary process *in vitro*. Thus, a phage-displayed combinatorial library from a hydrolytic abzyme, 6D9, generated by the conventional *in vivo* method with immunization of the transition-state analog (TSA), was screened against a newly devised TSA to optimize the differential affinity for the transition state relative to the ground state. This method was able to provide the evolved mutants which were 20 fold higher active than the parent antibody 6D9.