In Vivo Screen using Chemical Inducers of Dimerization for Engineered Enzyme with Substrate Specificity

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Enzymes with Improved Activity and Novel Catalytic Functions require Screening and Selection Method Generating enzymes with both improved activity and novel catalytic function to study biological processes and to catalyze useful new reactions remains one of the most exciting prospects of chemical biology. The rational design of enzymes has proven to be difficult in practice due to the complexity of protein function. Recent studies have shown that an enzyme with the desired catalytic property can be isolated from a large pool of protein variants, which provides a promising alternative for generating enzymes with new functions. However, these directed evolution experiments are limited to reactions are inherently screenable or selectable. Therefore, there is a high demand for a general screening and selection method that does not limit the chemistry and that can readily be adapted to a new target reaction.

Chemical Inducer used to Dimerize Pair of Fusion Proteins for Engineered Enzyme with Substrate Specificity This method involves using a chemical inducer to dimerize a pair of fusion proteins. The dimerized fusion protein catalyzes bond cleavage in the chemical inducer which is read as a change in enzyme activity or gene transcription. In addition, it offers a method of evolving a protein with a new catalytic activity comprising screening proteins. The screening proteins are derived from a library of proteins which are mutants of a known protein, using the in vivo screening method. Furthermore, this technology provides an engineered enzyme having new substrate specificity and an engineered enzyme that functions with a cofactor which is different from the cofactors the enzymes naturally use. This high-throughput assay for protein function described here is a powerful tool for protein engineering and enzymology, drug discovery, and proteomics.

Applications:
• This method is useful in screening proteins having capability of catalyzing bond cleavage
• It offers a promising approach to screening cDNA libraries based on biochemical function
• It can be used to evolve a protein with a new catalytic activity and/or new substrate specificity

Advantages:
• A robust screen for enzymatic activities can be done in vivo and in both prokaryotes and eukaryotes
• The activity of thousands of protein variants can be measured simultaneously
• A novel method to evolve proteins with unique binding or catalytic properties

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