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Approaching polynomial biopolymer engineering- engineering enzyme, regulatory protein and cell membranetogether as a new biosynthetic molecular scaffold

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Abstract

Amidst millions of polymers that are used worldwide to catalyse synthetic reactions, drug delivery, energy science, molecular scaffolds and myriads of other purposes, polymers exploiting supramolecular chemistry have been gaining immense importance over the last few years due to their excellent host-guest interaction, non-covalent types of forces and value added properties over the molecules that are encapsulated within this polymers. Hence, polymers such as DNA or proteins have been undertaken as novel molecular host to encapsulate candidates for various value-added strategies. However, these approaches have two basic limitations. First, the stability of these complexes is compromised when extracted out of the cell and second, the innate biochemical pathways are lost when biopolymers are taken out of the cell. In order to solve this problem, we have adopted basic two strategies in our investigation. First, the enzymes or proteins are used intact within the cell to retain their tertiary structure as a crucial molecular scaffold. Second the whole system is retained within the cell for using the cell membrane as secondary polymeric gateway for tuning the reaction. The substrate is added outside the cell in organic solvent and is transported inside cell for the enzymatic reaction. The outer core polymeric membrane is further engineered by two-factor binomial engineering. First the transcriptional switches of the cell are carefully mutated to enhance the expression level of desired gene circuits that in turn, improved the cell membrane tolerance under such reaction conditions. Second transporters are added in the reaction medium to augment the cell membrane permeability for facilitating the substrate transport inside the cell. When we have exploited this approach for synthesizing one important pharmaceutical intermediate Ethyl-chloro-hydroxy-butanoate from its precursor Ethyl-chloro-oxo-butanoate*via*such engineered biopolymer based factories, our product titer shoot more than 5-6 times higher than those reported so far for this reaction. We propose that this kind of engineered biopolymer based cell factories can be successfully employed as molecular scaffold for catalyzing chemical reactions in other fields too.

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Development of Novel Synthetic Bioconjugates for Effective Diagnostics and treatment in different Autoimmune Diseases

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Abstract

Human autoimmune diseases involve an abnormal immune response of the body by the development of autoantibodies and auto-reactive cells. If it is not early diagnosed and treated, autoantibodies and auto-reactive cells destruct human tissues, induce abnormal organ growth and change organ function. Autoimmune diseases are very diverse (more than 80), can be fatal and affect the blood vessels, connective tissues, endocrine glands, joints, muscles, red blood cells, skin etc. Examples of autoimmune diseases include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (polyJIA), systemic juvenile idiopathic arthritis (sJIA), juvenile (type-1) diabetes, pulmonary fibrosis etc. These diseases involve development of autoantibodies against one's own double-stranded DNA and phospholipid-protein complexes.

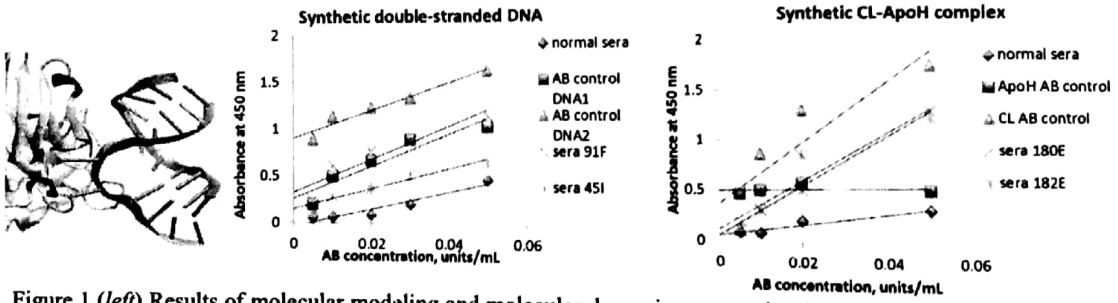

Figure 1 (*left*) Results of molecular modeling and molecular dynamics suggesting high binding affinity of autoantibodies to 5'-CT-3' rich oligonucleotide srand. (*right*) IgG ELISA for control antibodies (ABs), polyJIA patient samples and synthetic DNA/cardiolipin-apolipoprotein H (CL-ApoH) complex as biomarkers.

Early detection techniques are one of the major strategies to fight back this type of diseases which will help prevention from the disease development. However, currently applied heterogeneous and unstable natural biomarkers often result in poor repeatability and false results of the blood tests. **Synthetic biomolecules** have high purity and well-controlled chemical structure which makes them a promising tool for diagnostics and studies on autoimmune diseases. Moreover, rational design can be applied to optimize the structure for optimal properties of biomarker incl. stability, target binding etc. Recently we showed a unique selectivity and sensitivity of synthetic oligonucleotides containing locked nucleic acids (LNA) for recognition of nucleic acid targets and antibodies against double-stranded DNA. In our very recent studies, series of synthetic DNA and "clicked" cardiolipin-apolipoprotein H molecules selectively detected purified control autoantibodies, also within several SLE, sJIA and polyJIA patient samples (**Fig. 1**).