Universität Basel

Research Project

Exploring Sequence-Function Landscapes of Therapeutic Enzymes using Single-Cell Hydrogel Encapsulation and Deep Sequencing

Third-party funded project

Project title Exploring Sequence-Function Landscapes of Therapeutic Enzymes using Single-Cell Hydrogel Encapsulation and Deep Sequencing
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Department
Project start 01.01.2021
Probable end 31.12.2024
Status Active

The pharmaceutical industry is rapidly transitioning from small molecule therapeutics towards biologics. Among the various classes of biologics under development, therapeutic enzymes are gaining attention as molecular entities that can catalyze specific chemical reactions in the body to achieve a therapeutic effect. Therapeutic enzymes can be delivered systemically as full proteins or incorporated into gene therapies to transduce target cells with specific functionality in vivo. In these envisioned applications, understanding sequence-function relationships of therapeutic enzymes will play a crucial role. There is therefore an urgent need for improved methods for molecular analysis and enhancement of therapeutic enzymes. Naturally occurring enzyme sequences are typically not suitable as biopharmaceuticals due to general lack of stability, developability, and/or activity. In this context, molecular enhancement by improvement of colloidal stability, catalytic turnover rate, substrate binding affinity, and/or sensitivity to environmental conditions are essential steps in enabling therapeutic enzymes to reach their full potential. The establishment of rapid design, build, test, and learn (DBTL) cycles and the analysis of large-scale sequence-function relationships for therapeutic enzymes will be crucial for the advancement of leading therapeutic strategies.The Nash Lab at the University of Basel/ETH Zurich focuses on engineering and biophysics of artificial biomolecular systems. We recently developed an ultrahigh throughput enzyme screening strategy that outperforms multi-well robotic assays and automation by several orders of magnitude. We are now able to screen genetic libraries of catalytic enzymes using a one-pot reaction followed by fluorescence activated cell sorting (FACS). Our system is based on localized enzyme-triggered polymerization of a hydrogel capsule around individual yeast cells. Our goal is to utilize the ultrahigh throughput nature of this system to analyze sequence-function landscapes of enzymes on an unprecedented scale.

Financed by
Swiss National Science Foundation (SNSF)

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