Universität Basel

Research Project

EMBO ALTF 194-2017, Long-Term Fellowship

Third-party funded project

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Organisation / Research unit
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Department
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The emerging field of synthetic biology offers new opportunities to address current biological and medical challenges, by providing tools to label and influence metabolic pathways as well as approaches for the development of novel therapeutic strategies. Particularly, a catalytic approach based on Artificial Metalloenzymes (AMs) could play a fundamental role in this endeavor.

This project outlines a strategy for the development of a new tumor treatment therapy. To this end, the cell surface tumor marker carbonic anhydrase IX (CAIX) is 'hijacked' as an AM by binding a CA-inhibitor, bearing a metallocofactor, to the Zn(II) ion in the active site of CA. Upon binding, the metallocofactor is activated and catalyzes the uncaging of a prodrug thus releasing a potent chemotherapeutic drug.

As a complementary approach, I seek to improve the performance of CA-based AMs in cellulo by combining protein design with in vivo evolution. AMs are designed and evolved to complement existing metabolic pathways. Specifically, to form the valine precursor α-ketovaline in an auxotrophic Escherichia coli knockout strain. This project is a proof of principle and blueprint for the development of AM-based tools for studying cellular regulation to answer basic biological questions.

Keywords Synthetic Biology / Protein Engineering / Directed Evolution / Drug uncaging / Artificial Metalloenzymes
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