Artificial Metalloenzymes for Molecular Nanofactories

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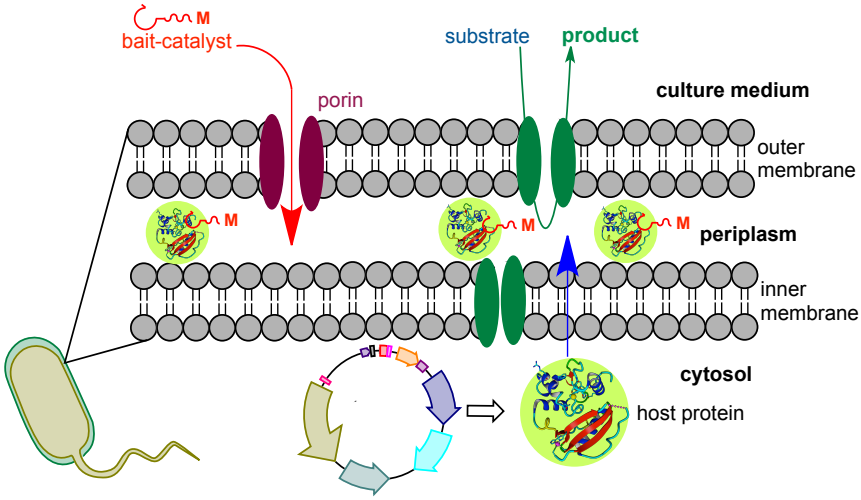
Artificial metalloenzymes (AME) have emerged as attractive alternatives to chemo- and biocatalysts. AME result from incorporation of organometallic cofactors within a protein and thus potentially combine the chemical diversity of homogeneous catalysis with the capacity for acceleration through fine-tuning reaction space in an evolvable protein scaffold.[1] Importantly, we have shown that such AME are compatible and complementary with natural enzymes, thus opening fascinating perspectives towards the implementation of non-natural reaction cascades for *in vitro* and *in vivo* selection.[2] It is proposed to exploit the periplasm of Gram-negative bacterial cells, such as E. coli, to compartmentalize the AME, thus minimizing deleterious interactions with cellular components present in the cytosol and at the same time maintaining a genotype-phenotype linkage that is instrumental to evolving the protein scaffold of the AME (Scheme 1). This innovative approach could ultimately lead to the development of molecular nanofactories for the production complex molecules resulting from non-natural reaction cascades. As a proof-of-principle, it is proposed to compartmentalize a ring closing metathesis reaction.



Scheme 1. Molecular nanofactories result from compartmentalization of artificial metalloenzymes within the periplasm of E coli. The host protein is produced in the cytosol and exported to the periplasm. The catalyst bearing a selective bait for the host protein is added in the culture medium. Following translocation through the outer membrane by diffusion through a porin, it is is firmly anchored to the host protein yielding the artificial metalloenzyme. The AME transforms a substrate into a product which can either be released from the cell or act as a substrate for a reaction cascade within E. coli (Scheme 3).

We are looking for candidates with a strong background in biomolecular engineering or organic chemistry, keen to work in a highly interdisciplinary environment.

[1] T. R. Ward, *Acc. Chem. Res.* 2011, 44, 47; T. Hyster, L. Knörr, T. R. Ward, T. Rovis, *Science*, 2012, *338*, 500.
[2] V. Koehler, Y. M. Wilson, M. Dürrenberger, D. Ghislieri, E. Churakova, T. Quinto, L. Knörr, D. Häussinger, F. Hollmann, N. J. Turner, T. R. Ward, *Nature Chem.* 2012, *4*, DOI: 10.1038/NCHEM.1498.