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Strategies to optimize and use bacterial cytochromes p450 for drug discovery & development

Nico P E Vermeulen, H Venkataraman, D P Geerke and **J N M Commandeur**
VU University Amsterdam, Netherlands

Drug discovery and development is a costly and time-consuming process involving many steps, from target discovery up to clinical trials. Because drug metabolites often possess pharmacological or toxicological properties, theymay also play an important role in drug action and adverse drug reactions. It is thus important to investigate the metabolism of drugs and drug candidates and to characterize their pharmacological and toxicological properties.Also for the regulatory MIST guidelines, identification, quantification and characterization of major metabolites is considered important. Such studies require large quantities of pure metabolites, which are sometimes difficult to synthesize by conventional chemical methods. Innovative bio-catalytic strategies constitute an alternative for these purposes. Although human Cyt P450s are involved metabolism of many drugs, they are inefficient for the production of large quantities of drug metabolites. Engineered bacterial Cyt P450s, e.g. from Bacillus megaterium (P450s BM3), with high activities and selectivities have better perspectives for large-scale metabolite synthesis.

We have developed a '*metabolic production and profiling platform*' in which libraries of mutant P450 BM3 enzymes are employed for bio-catalytic purposes. Using random mutagenesis, saturation mutagenesis and (computationally guided) site-directed mutagenesis strategies, we have been able to generate versatile, highly active and highly selective and scalable P450 BM3 mutants. Thus we have generated with high turnovers, regio- and stereo-selective metabolites of ionones, pharmacologically active metabolites and toxicologically relevant chemically reactive metabolites. The strategies to engineer and optimize Cyt P450 BM3 mutants and their possibilities and limitations in drug discovery, development and safety studies will be illustrated with selected examples.

Biography

Nico P E Vermeulen did a Degree in Chemistry (1975, University of Nijmegen, NL), a PhD in Pharmacology (1980, University of Leiden, NL) and was appointed Professor of Molecular Toxicology in 1985 at VU University Amsterdam. He is Head of Department of Chemistry & Pharmaceutical Sciences. His general research interests are Roles molecular and computational toxicology can play in drug discovery, development and safety assessment. And he got the award like European ISSX Scientific Achievement Award (2006), an Honorary Doctorate (University of Copenhagen, 2011) and is a Life Time Honorary Member of ISSX. His work is taken up in the 2001 and 2014 list of Highly Cited Researchers in 'Pharmacology' i.e. the top 1% world-wide.

n.p.e.vermeulen@vu.nl