Simulation of Human Cytochrome P450-membrane Interactions

Ghulam Mustafa[a], Prajwal P. Nandekar[a,b], Goutam Mukherjee[a,c], Rebecca C. Wade[a,b,c,*]

[a] Molecular and Cellular Modeling Group, Heidelberg Institute of Theoretical Studies (HITS), [b] Center for Molecular Biology (ZMBH), DKFZ-ZMBH Alliance, [c] Interdisciplinary Center for Scientific Computing (IWR), Heidelberg University, INF 368, 69120 Heidelberg, Germany

Email: rebecca.wade@h-its.org

Human cytochrome P450 (CYP) enzymes play an important role in drug metabolism, steroid biosynthesis and xenobiotic degradation. They form a large superfamily of heme-containing enzymes that catalyze substrate monooxygenation. Human CYPs are membrane-anchored proteins and the active site is buried inside the globular domain. We have developed a systematic protocol to build and simulate a CYP-membrane complex using coarse-grained (CG) and all-atom (AA) MD simulations and applied this to several drug-metabolizing CYPs.[1], [2] We observed that different CYPs can display different interactions with the membrane, caused by primary sequence and three-dimensional structure differences.

Furthermore, we employed our multiscale simulations protocol to study the steroidogenic CYPs, CYP17 and CYP19, to assess the effects of mutations in the N-terminal transmembrane (TM) region used in *in-vitro* studies on the interactions between the protein and the membrane. For CYP19, a slight difference in orientation of the globular domain in the membrane was observed due to the truncation of the N-terminal TM-helix residues. For CYP17, our observations suggest that the mutations, particularly W2A and E3L, increase the likelihood of the TM-helix being pulled out of the membrane core and lying parallel to the membrane, behaving as an amphipathic helix. The mutations thereby disrupt CYP-membrane interactions, affect the degree of insertion of the globular domain in the membrane and the position of linker in mutant CYP17, obstructing the substrate access tunnel from the membrane to the active site, could affect the catalytic activity.

References:

[1] V. Cojocaru, K. Balali-Mood, M. S. P. Sansom, and R. C. Wade, *PLoS Comput. Biol.* **2011,** 7, e1002152

[2] G. Mustafa, P. P. Nandekar, X. Yu, and R. C. Wade, *J. Chem. Phys.*, **2015**, 143, 243139.