

Functional interactions between different drug-metabolizing enzymes: a novel approach for variance in CYP3A4 activity

異種薬物代謝酵素間の機能的相互作用:
CYP3A4活性変動の新規機構

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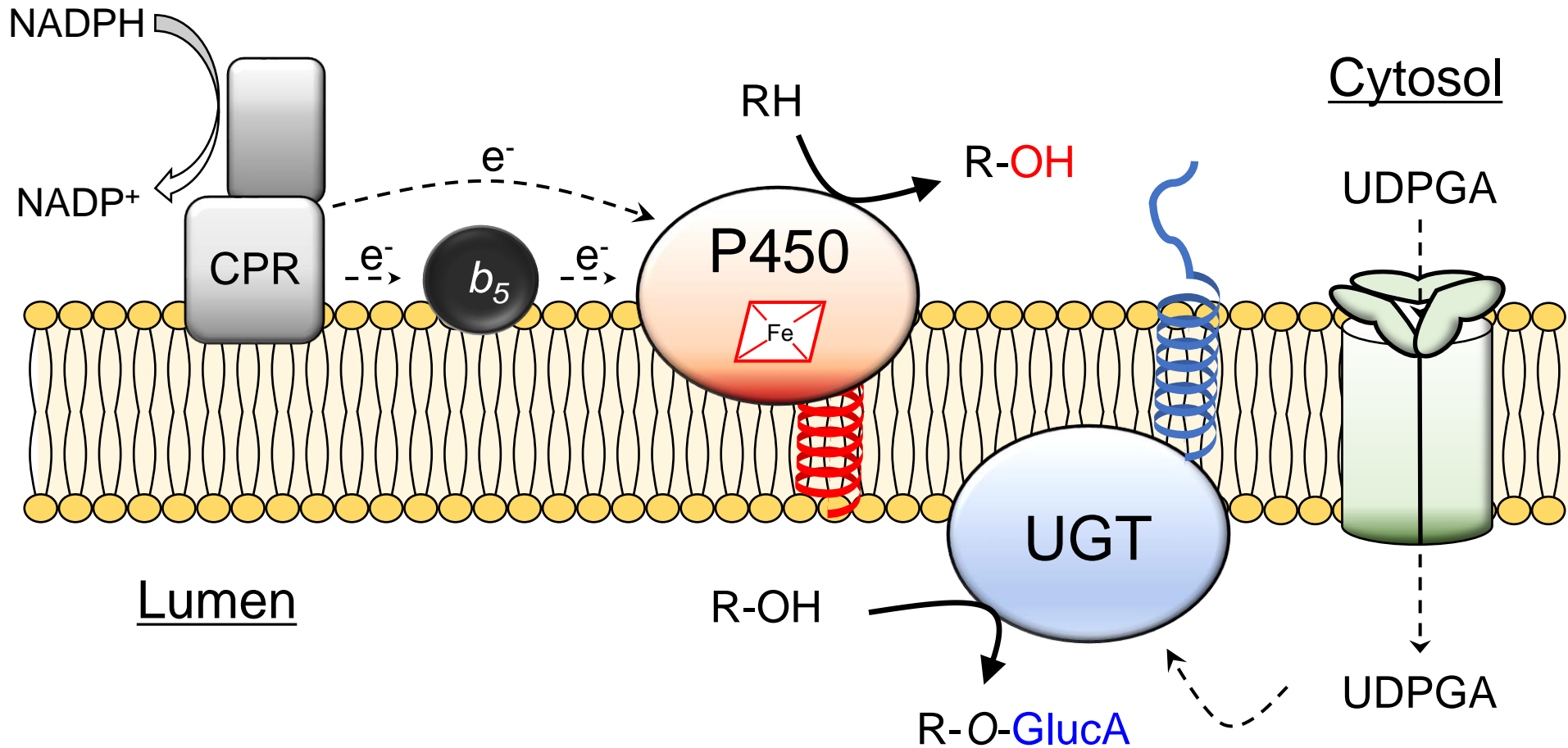
37th JSSX Annual Meeting

COI disclosure information

Author : Yuu Miyauchi

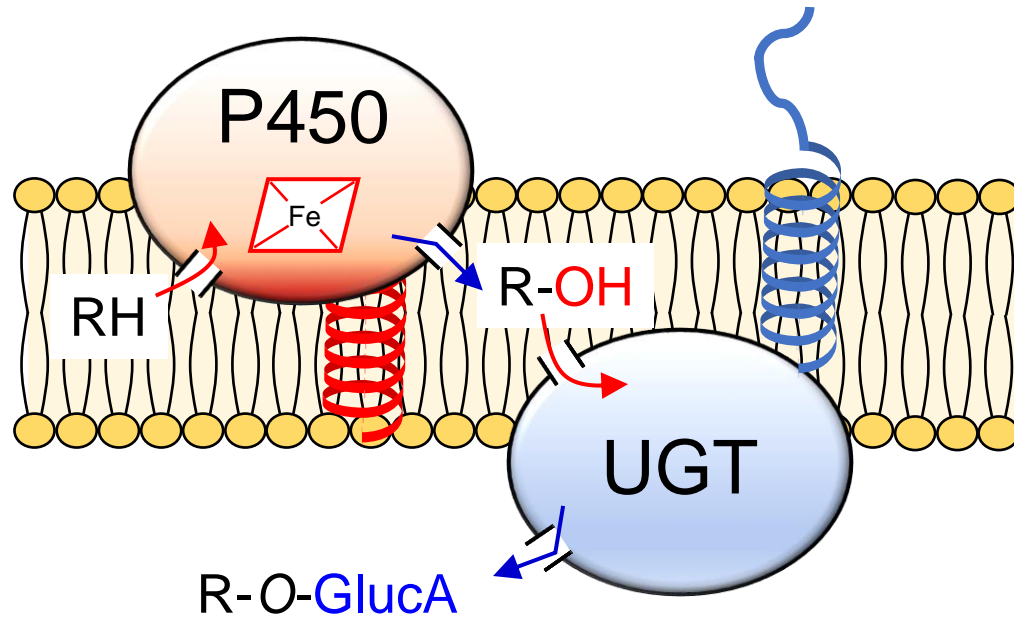
I have no financial relationship to disclose for my presentation contents.

P450 & UGT functions on the ER membrane



P450, CYP: cytochrome P450, CPR: NADPH-P450 reductase, *b*₅: cytochrome *b*₅
UGT: UDP-glucuronosyltransferase, UDPGA: UDP-glucuronic acid

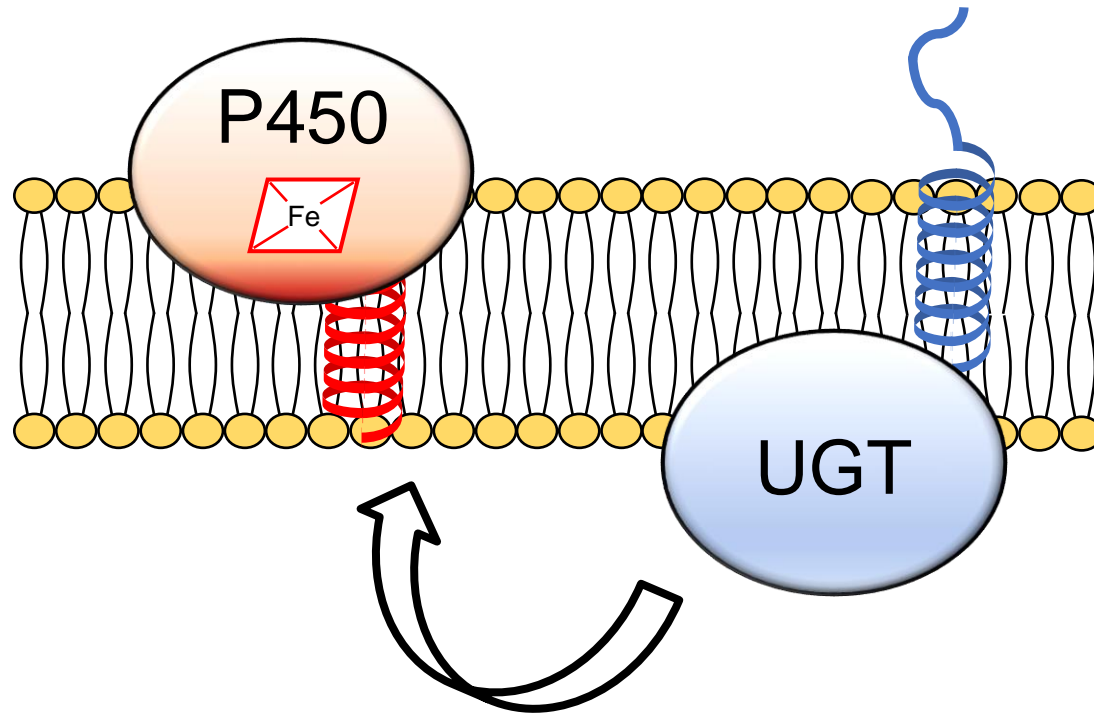
Do P450 & UGT really work separately??



Hypothesis

P450 & UGT form complex on the ER membrane and regulate each other via the interaction.

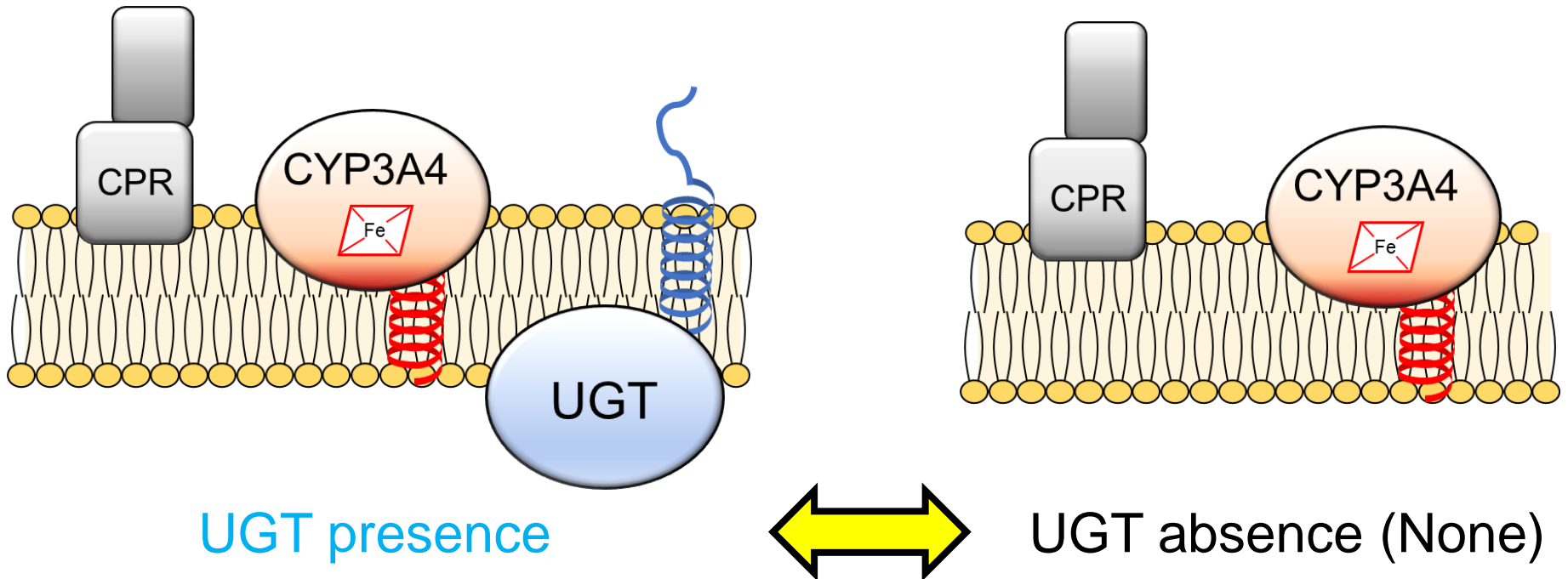
My research objective



UGT affects P450 function?

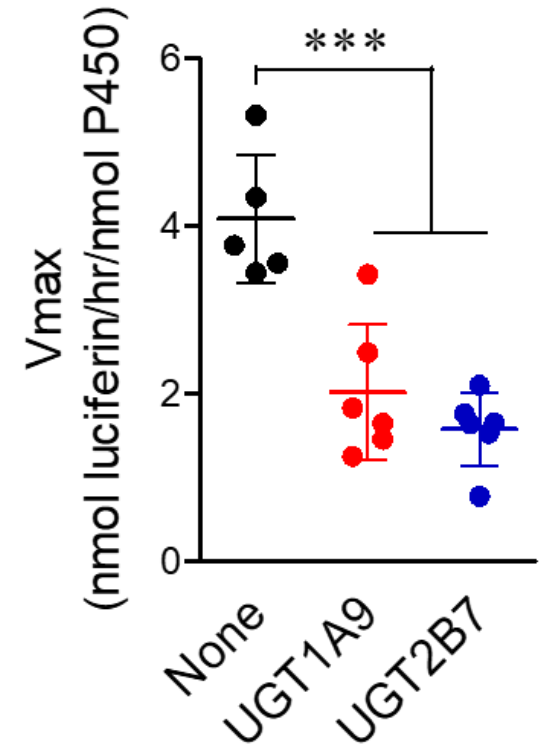
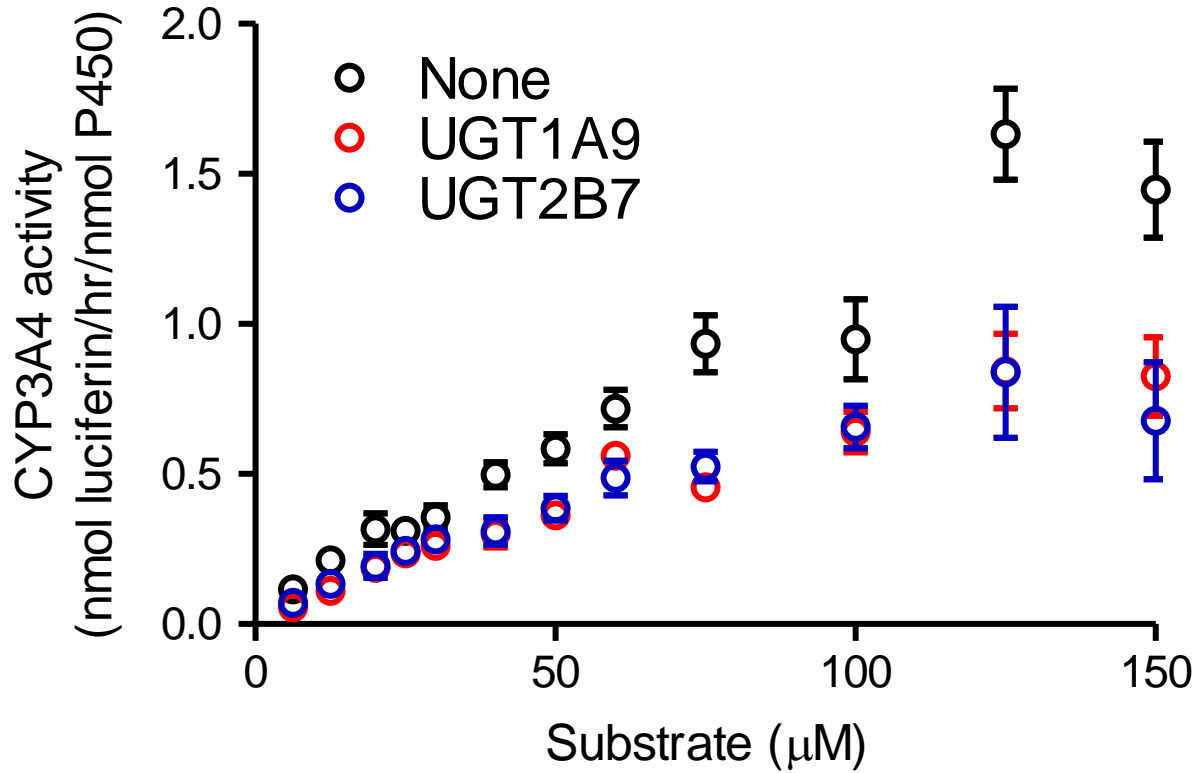
Methods

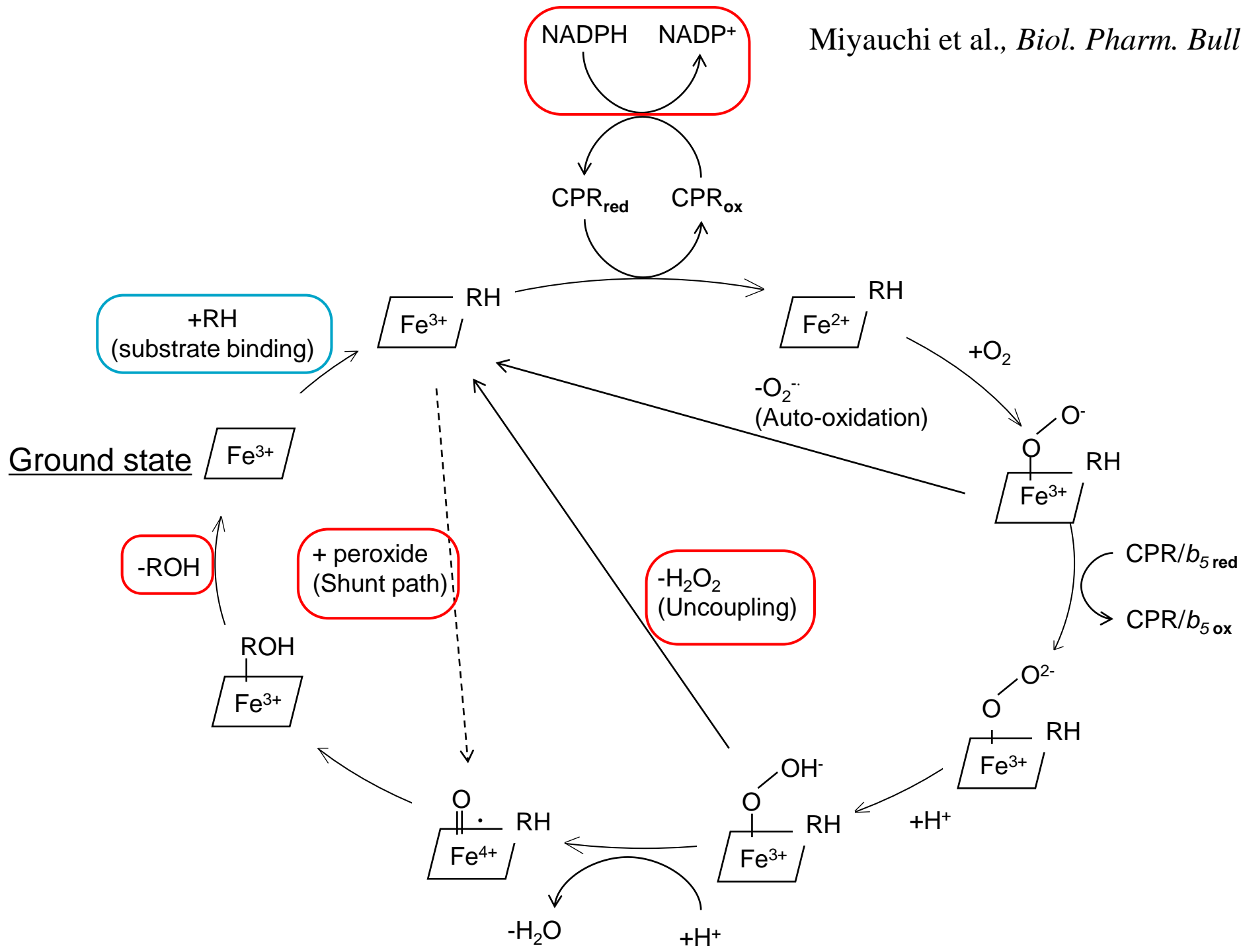
CYP3A4, CPR, and UGT were co-expressed with a baculovirus-insect cell expression system



CYP3A4 function was compared.

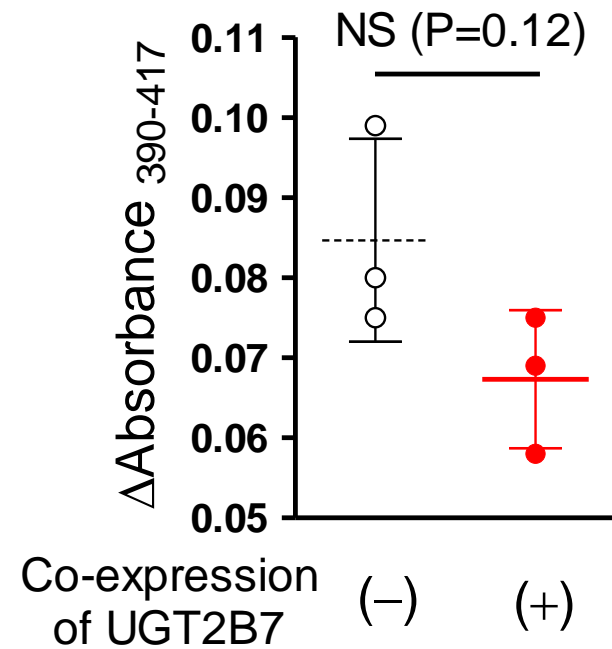
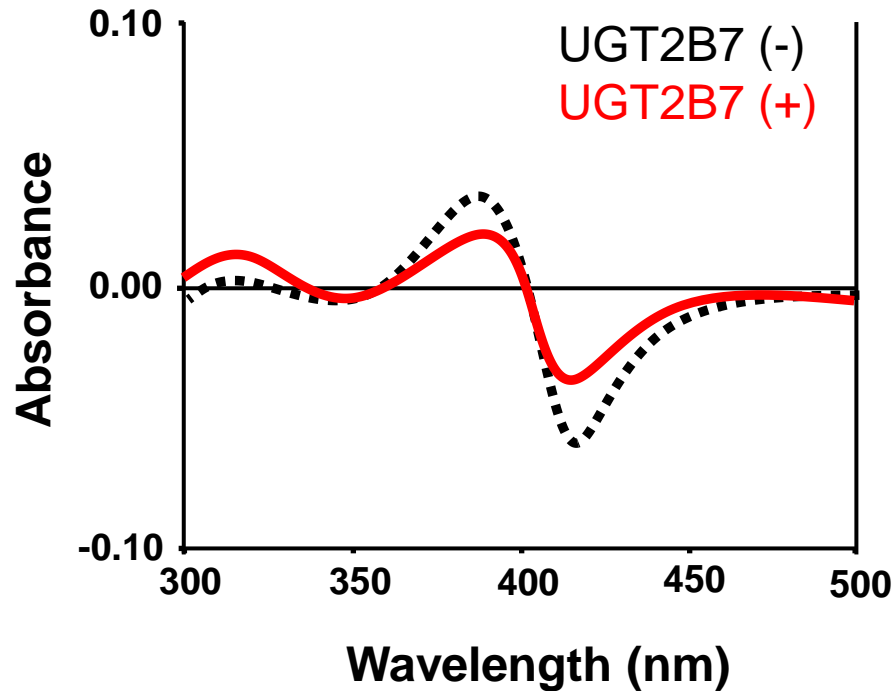
UGTs suppress CYP3A4 activity.



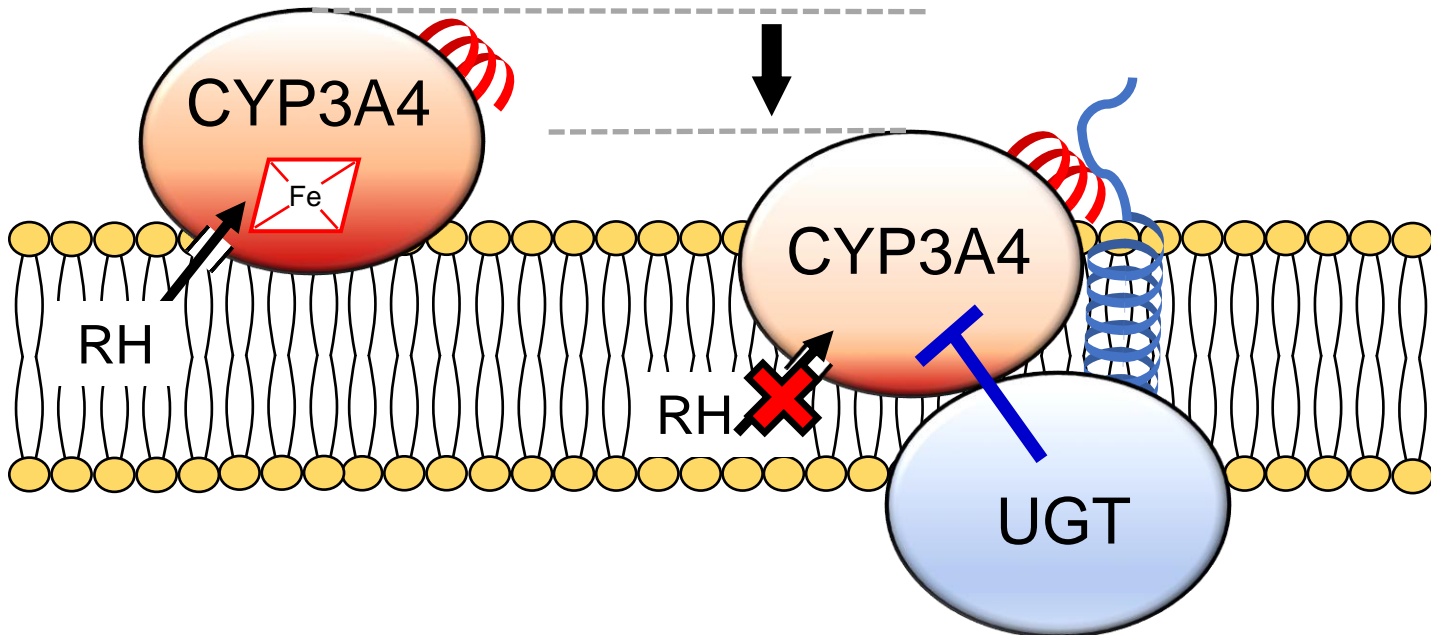


UGT may inhibit substrate-binding to P450.

Substrate-binding differences spectra of CYP3A4 (substrate: testosterone)

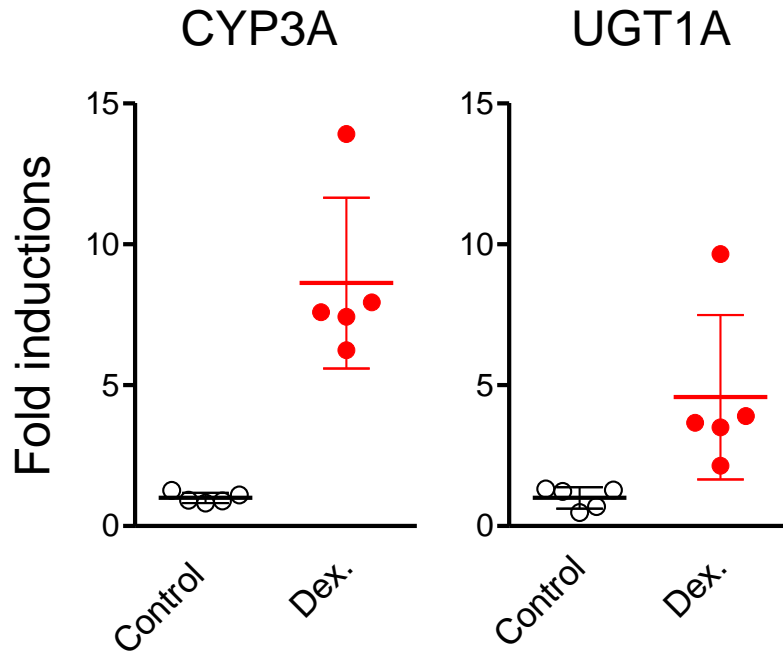


Postulated mechanism of UGT-mediated suppression of CYP3A4 function

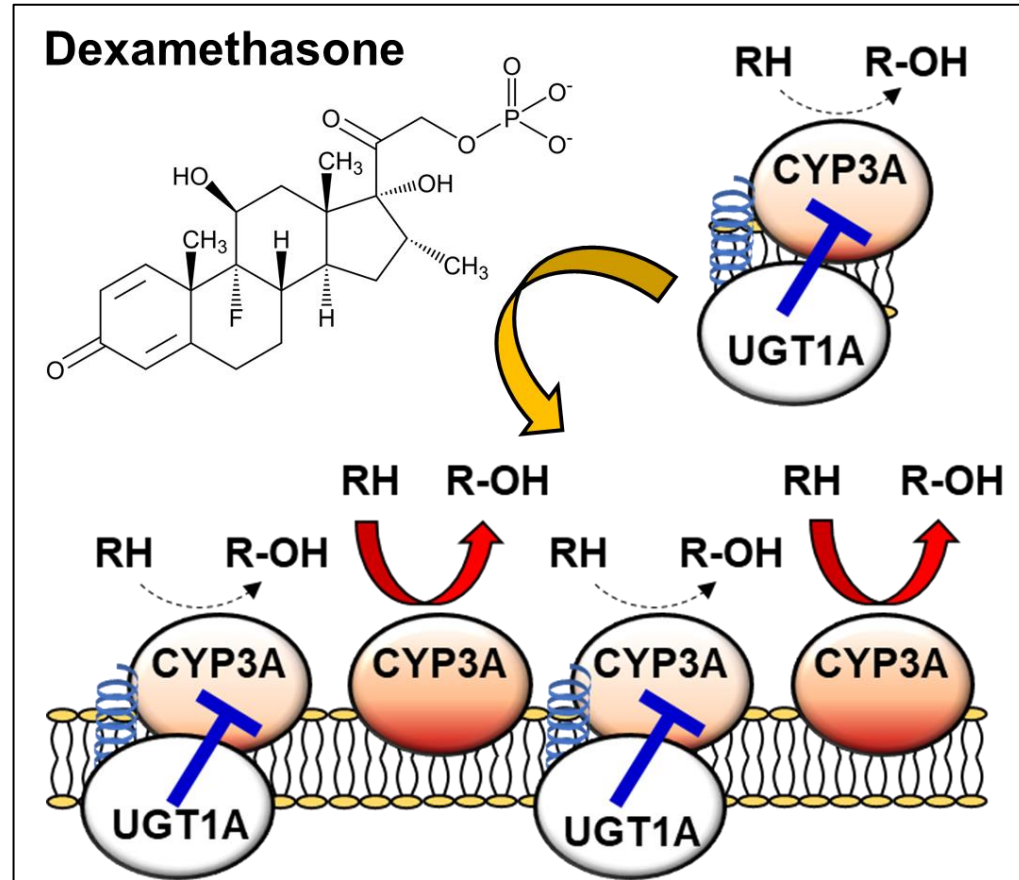


P450 is drawn in the ER membrane by the association with UGT. This positional alteration elicits suppressive effect on P450 function.

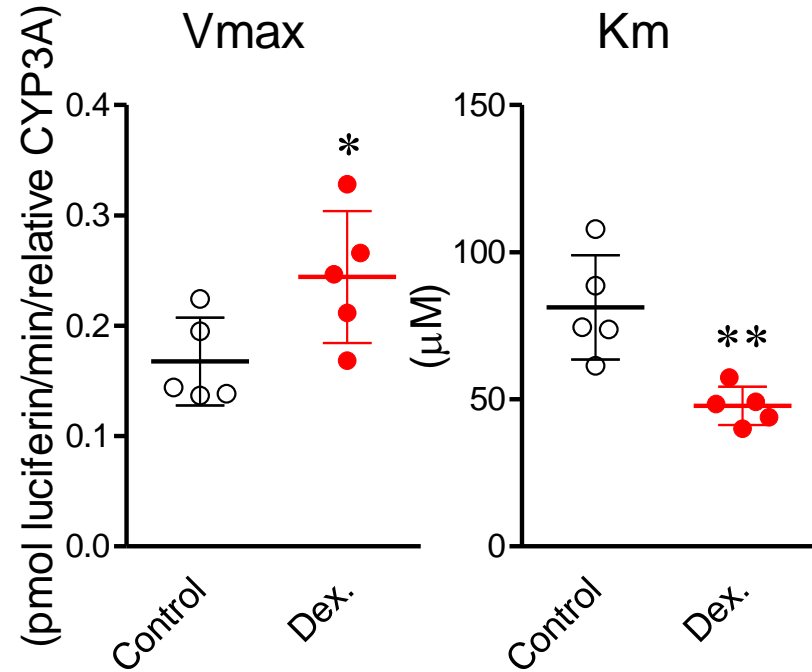
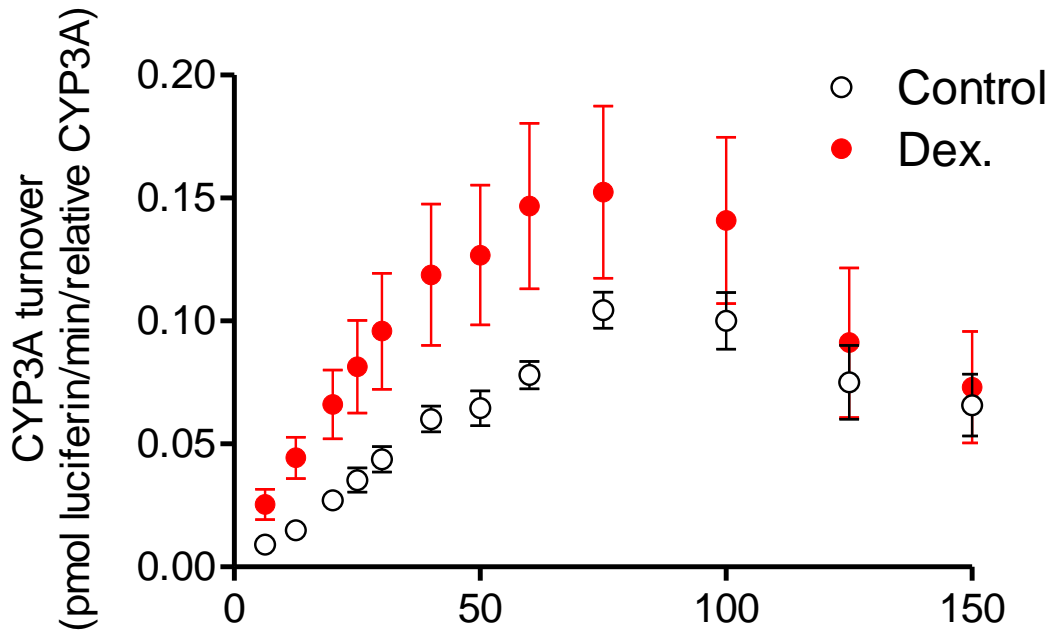
Dexamethasone-treatment can increase UGT1A-free (=not suppressed) CYP3A in rat liver



Miyauchi et al., *Br. J. Pharmacol.* (2020)



Dexamethasone-treatment abrogates UGT-mediated suppression of CYP3A.

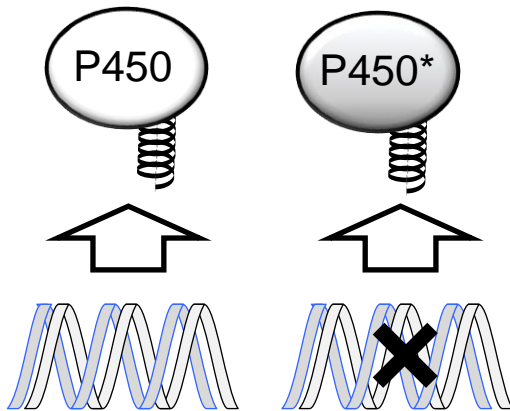


Miyauchi et al., *Br. J. Pharmacol.* (2020)

P450-UGT interaction as one of the post-translational factors for P450/UGT inter-individual differences

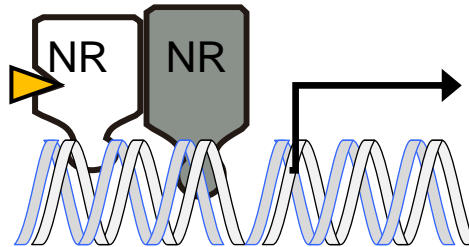
Genetic factor

SNPs

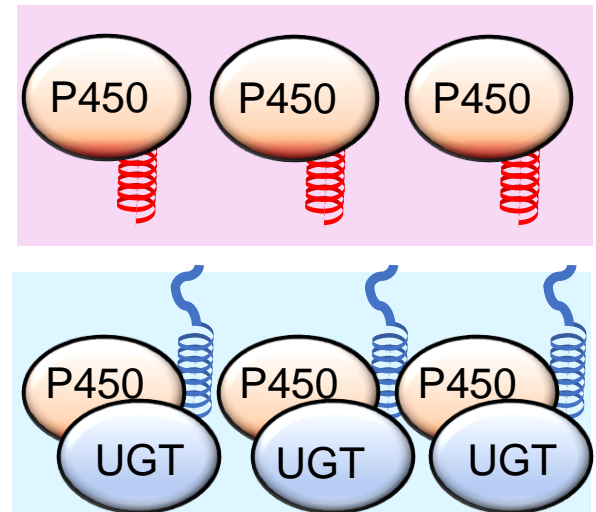


Transcriptional factor

Induction by nuclear receptors



Post-translational one



For more detail about our research, please refer to the reviews!

Ishii Y. et al., *Drug Metab. Rev.*, **42**(1): 145-158 (2010)

Miyauchi Y. et al., *Biol. Pharm. Bull.*, **44**(11): 1635-1644 (2021)

Miyauchi Y., *Yakugaku Zasshi*, **142**(11): 1169-1175 (2022)

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