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Targeting xenobiotic receptors PXR and CAR in drug toxicity and resistance

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Xenobiotic receptors Pregnane X Receptor (PXR) and Constitutive Androstane Receptor (CAR) regulate drug toxicity and resistance, which are the leading causes of treatment failure and for which no clinically safe and effective remedy is available. PXR and CAR play central roles in activating the expression of CYP3A4, a major enzyme responsible for metabolizing more than 50% of clinically prescribed drugs, and ALAS1, a rate-limiting porphyrin biosynthesis enzyme that increases the levels of hepatotoxic Protoporphyrin IX (PPIX), both contributing to drug-induced liver toxicity. Elevated MDR1 level is associated with drug resistance. MDR1 expression is induced by CAR and PXR. While PXR is ligand-inducible, CAR is constitutively active. Therefore, inhibitors of PXR and CAR (i.e., antagonists of PXR and inverse agonists of CAR) may prevent drug-induced liver toxicity and overcome drug resistance. By using a chemical biology approach we have identified and optimized PXR antagonists and CAR inverse agonists, investigated their mechanisms of action by performing structural and functional analysis, and evaluated their *in vivo* activities by using humanized animal models. Our data indicate that it is feasible to prevent drug-induced liver toxicity and overcome drug resistance by targeting PXR and CAR using mechanism-guided chemical agents.

Biography

Taosheng Chen completed his PhD from the University of Vermont, and Postdoctoral studies from the University of Virginia. He is an Associate Member (Associate Professor) and Director of the High Throughput Screening Center at St Jude Children's Research Hospital. Prior to joining St Jude, he was a Senior Research Investigator at Bristol-Myers Squibb, and a Research Scientist at SAIC-Frederick, National Cancer Institute. He serves on the Editorial Boards of several journals and on NIH Grant Review Panels. He has authored more than 80 publications. His research laboratory studies the roles of nuclear receptors in therapeutic efficacy and toxic effects.

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