

# TOXICOLOGY AND APPLIED PHARMACOLOGY

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### Genetic heterogeneity among slow acetylator N-acetyltransferase 2 phenotypes

Genetic polymorphisms in human N-acetyltransferase 2 (NAT2) modify the metabolism of numerous drugs and carcinogens. These genetic polymorphisms modify both drug efficacy and toxicity and cancer risk associated with carcinogen exposure. Previous studies have suggested phenotypic heterogeneity among different NAT2 slow acetylator genotypes. NAT2 phenotype was investigated *in vitro* and *in situ* in samples of human hepatocytes obtained from various NAT2 slow and intermediate NAT2 acetylator genotypes. NAT2 gene dose response ( $NAT2^*5B/^*5B > NAT2^*5B/^*6A > NAT2^*6A/^*6A$ ) was observed towards the N-acetylation of the NAT2-specific drug sulfamethazine by human hepatocytes both *in vitro* and *in situ*. N-acetylation of 4-aminobiphenyl, an arylamine carcinogen substrate for both N-acetyltransferase 1 and NAT2, showed the same trend both *in vitro* and although the differences were not significant ( $p > 0.05$ ). The N-acetylation of the N-acetyltransferase 1-specific substrate p-aminobenzoic acid did not follow this trend. In comparisons of NAT2 intermediate acetylator genotypes, differences in N-acetylation between  $NAT2^*4/^*5B$  and  $NAT2^*4/^*6B$  hepatocytes were not observed *in vitro* or *in situ* towards any of these substrates. These results further support phenotypic heterogeneity among NAT2 slow acetylator genotypes, consistent with differential risks of drug failure or toxicity and cancer associated with carcinogen exposure.

### Biography

David W Hein has served as a Principal Investigator/Co-Investigator/Mentor on over 75 grants and contracts. He has coauthored over 225 peer-reviewed journal articles and book chapters, 75 published gene sequences and about 600 abstracts. He serves as Peter K Knoefel Endowed Chair of Pharmacology, Professor and Chairman of the Department of Pharmacology & Toxicology, Distinguished University Scholar, and Vice Provost for Academic Strategy at the University of Louisville. He also directs the National Cancer Institute-funded Cancer Education Program. He previously served as the Founding Director of the NIH Minority Biomedical Research Support Program at Morehouse School of Medicine and the NIEHS T32 Pre- and Post-doctoral training program in environmental health sciences at the University of Louisville. He chaired Departments of Pharmacology & Toxicology at Morehouse School of Medicine and the University of North Dakota School of Medicine and Health Sciences prior to his recruitment to the University of Louisville in 1997. He has led development and implementation of Pharmacology and Toxicology PhD partnerships with Wenzhou Medical University, Jilin University, Cairo University and Ain Shams University. Numerous students have completed thesis and dissertation research training in his laboratory and he contributes towards instructing undergraduate, graduate and health professional students.

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