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Identification of Genes that are Major Determinants and Predictors of Drug Tolerance and Toxicity

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Keywords: Adverse Drug Reactions (ADR), drug tolerance, toxic side effects, genetics, irinotecan.

Collaboration Research Opportunity: Roswell Park Cancer Institute is seeking research partners to help identify genes that control Adverse Drug Reaction (ADR) first in mice via the use of specialized mouse recombinant congenic strains, and subsequently to define and test their human homologues.

Summary: Adverse drug reactions (ADR) are a common complication of treatment of a variety of diseases. They cause damage which in many instances is permanent, impairs the quality of life, leads to additional hospitalizations, and frequently also impairs the outcome of treatment. In a number of instances, an approved drug has to be withdrawn from the market because of unacceptable ADRs, resulting in large financial losses.

Adverse reactions in cancer therapy often require reduction of dose, so that cancer is exposed to suboptimal drug levels and consequently the effects of therapy are seriously impaired. In fact, ADRs are the major cause of treatment failure of responsive cancers.

Prediction of individual susceptibility to ADRs would allow patients to be given the best tolerated drugs at optimal doses. ADR susceptibility is to a large extent genetically controlled. However, most searches for ADR-responsible genes used candidate gene approaches directed primarily at study of drug processing or transporting molecules (pharmacokinetics, PK) and direct drug targets (pharmacodynamics, PD), which turned out to be responsible only for a minority of ADRs, and hence the genetic basis of most ADRs remains unknown. Search for such unknown genes controlling ADR susceptibility requires a phenotype-based approach (as in GWA studies), but such studies of ADR reactions suffer from low statistical power and usually reveal only a few genes with a marginal statistical significance and poor reproducibility.

Technology: Researchers at Roswell Park Cancer Institute have developed a hybrid approach to the problem, which combines advantages of the high statistical power of candidate gene studies with the capacity of a phenotype-based approach to detect relevant genes of any type. Roswell researchers have produced special mouse strains that can perform the phenotype-based genetic analysis with very high efficiency, and thus, the genes discovered in these strains can be subsequently studied in humans using a statistically more powerful candidate gene approach.

As a proof of principle, Roswell researchers analyzed ADRs caused by the powerful and widely used anti-cancer drug irinotecan, whose PK/PD has been described in great detail. Surprisingly, this revealed that the majority of irinotecan-ADRs are caused by a number of novel genes (Adri-genes, for **A**dverse **d**rug **r**eaction – **i**rinotecan), that are distinct from all known irinotecan-PK/PD genes and DNA-repair genes. Adri-genes are drug-specific, organ-specific, and do not influence tumor therapy responses.

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Identification of Adri-genes in humans will allow for the identification of patients with very high ADR-risk who should receive a different therapy, and identification of patients with very low risk, who could receive a higher irinotecan dose, with a better treatment outcome.

However, there is a second, potentially more important benefit of definition of ADR genes. These presently unknown genes and their products could namely serve as targets for development of novel pharmacological products for prevention and therapy of ADRs. Also, as the mechanisms of drug- and organ-specific ADRs are to a very large extent unknown, the elucidation of the functions of ADR genes will also result in a much better understanding of the action of the studied drugs.

Our preliminary data with other drugs strongly indicate that this approach will be generally applicable to any drug, most likely including the prediction of ADRs by drugs targeted against specific proteins.

Potential Commercial Applications:

- This technology could lead to the production of possible diagnostic kits which could predict on the basis of ADR gene susceptibility of individual patients to toxic reactions to a planned therapy**.**
- The technology could lead to the development of improved drugs which would avoid predictable toxicities.
- Drugs targeting or counteracting these genes could be developed and used for prevention or treatment of adverse drug reactions.

Competitive Advantages:

- This technology is more efficient and cost effective than others in finding new genes for toxicity.
- This technology simplifies and facilitates testing and understanding of functions of new genes.

Development Status:

Inventor: Dr. Peter Demant, MD, PhD

Additional References: