

PHARMACOGENOMICS— *the roadmap* TO PERSONALIZED MEDICINE

Since the race to sequence the human genome was won in 2001, new knowledge gleaned from human gene “mapping” has opened many doors that may lead to health benefits. One of those doors is marked “pharmacogenomics.”

Pharmacogenomics, the science of custom fitting drug treatment to an individual’s genetic profile, promises to optimize patient treatment when scientists can recognize how drugs interact with genes. The knowledge can lead to more efficacious, safer therapies.

Hongbing Wang, PhD, assistant professor in the Department of Pharmaceutical Sciences, has been focusing on ways to better understand how genes affect drug uptake and how genes and their regulators may affect drug-to-drug interaction. One group of genes, called Cytochrome P450, is of high interest.

“How P450 is expressed—high or low expression—affects how certain drugs are metabolized,” explains Wang. “One of our studies looks at establishing standards regarding how genetic variance, or polymorphs, can affect drug performance.”

Getting answers means collaboration with a number of other School of Pharmacy scientists, including those working in the Computer-Aided Drug Design Center (CADD) with Alexander MacKerell, PhD, the lab’s director. The search for new reagents and potent inhibitors is aided and accelerated by CADD’s ability to rapidly identify the structure of compounds and match them to biological targets. The expectation is that when pharmacogenomics researchers and those engaged in drug design and delivery work more closely with those in the open CADD labs in the upper floors of the Pharmacy Hall, everyone will benefit.

“Our focus on drug metabolism will benefit absolutely from closer collaboration,” says Wang.



Hongbing Wang

Among the many questions his group is trying to answer is how drugs become therapeutic or toxic based on gene expression. For example, a recent study by Wang and colleagues targeted genes and their regulators in human liver cells to determine rates at which compounds induced or inhibited responses.

“We know that P450 plays a role in metabolism in the human liver,” says Wang. “In some cases, P450 is beneficial. But it can also induce toxicity.”

The role P450 plays in metabolizing acetaminophen in the liver is a case in point, says Wang. The gene’s receptors help induce toxicity in the presence of alcohol, and toxicity can kill liver cells.

“Expression of Cytochrome P450 is tightly controlled by a group of transcription factors including nuclear receptors such as CAR [constitutive androstane receptor] and PXR [pregnane X receptor],” says Wang.

According to Wang, the identification of a human CAR selective activator or deactivator helped delineate human CAR targets in human liver cells.

“CAR and PXR regulate an overlapping set of target genes,” says Wang. “Significant progress has been achieved in our understanding of CAR’s role in the regulation of P450 and other drug metabolizing enzymes.”

To advance the School’s research in pharmacogenomics, the beginning of a center devoted to enhancing campuswide collaboration in pharmacogenomics is on the drawing board.

—*Randolph Fillmore*

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