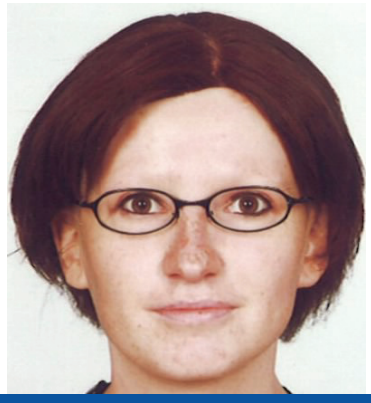
# Biomarkers for Nephrotoxicity: Putting Data into Functional Context

At the Innsbruck Medical University, scientists are using QIAGEN's Ingenuity Pathway Analysis (IPA) to study how chemical and environmental stressors affect cultured human kidney cells.



At the Innsbruck Medical University (IMU) in Austria, scientists hope to build better predictive models for human drug and chemical safety and to advance biomarker discovery to inform treatment protocols or find more useful targets for medical intervention.

These researchers, based in the lab of nephrology expert Paul Jennings, are studying how chemical and environmental stressors affect cultured human kidney cells. These organs are particularly vulnerable to damage from medications and other chemicals and can be compromised or shut down completely by such exposure. For example, each year some 5 percent of people who take non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen will develop renal toxicity, with many requiring hospitalization.

With higher blood flow than the brain, liver, or heart, the kidneys are the main regulatory organ in the human body. As our acting garbage collectors, the kidneys remove the waste we create (such as urea, ammonia, and other toxic substances) and help regulate our absorption of essential elements like salt, electrolytes, water, and glucose.

"The kidney has a critical job in keeping us healthy," says Lydia Aschauer, a scientist in the Jennings lab. "The more we understand how it processes different chemicals and compounds and how those things affect it, the better equipped we'll be to treat and care for this vital organ."

Aschauer and her colleagues think that compound-induced cell stress and toxicity likely compromise normal kidney function as a consequence of cell dedifferentiation related to their response to toxins. To test this hypothesis, they have developed a maturation data set evaluating kidney function over time that they are comparing to nephrotoxin-induced molecular signatures. Their aim is to set a basis that supports the identification of novel biomarkers of stress, dysfunction, or functional impairment of the kidney's proximal tubule. If all goes well, these tissue-specific biomarkers may allow a better classification of compounds and could improve the predictive value of *in vitro* nephrotoxicity test models.

Powering the lab's research are molecular assays and state-of-the-art technologies that generate transcriptomic, proteomic, and metabolomic data. By integrating all this information together with high-value analysis tools, the IMU team is assembling a more global view of how nephrotoxins impact the mechanisms underlying kidney function and dysfunction.

To bring these seemly disparate data sets together, Aschauer and her colleagues have chosen QIAGEN's IPA platform. IPA is an all-in-one, web-based software application that enables users to analyze, integrate, and understand data generated by many different technologies including microarrays and next generation sequencing, as well as other small-scale experiments that generate gene and chemical lists.

"A great advantage of IPA is that we can easily compare different data sets in a format that provides a high degree of interlinking," Aschauer says. "For example, with transcription factor analyses, there are bioinformatic tools that are based on overrepresentation of conserved transcription binding sites. But for some transcription factors, these binding sites are not very specific or are not well characterized, making the analysis with other tools more difficult." IPA is powered by the Ingenuity Knowledge Base, a repository of molecular interactions, regulatory events, signaling and metabolic pathways, and

gene-to-phenotype associations that provide the building blocks for pathway construction. IPA contains millions of findings from the full text of the life sciences literature that describe relationships between chemicals, proteins, genes, cells, drugs, and clinical phenotypes, among others. IPA also has extensive libraries of metabolic and cell signaling pathways, a robust synonym library, and extensive contextual details, including species specificity, localization, mutations, epigenetic modifications, and experimental conditions. The structured, detailed content in the Ingenuity Knowledge Base enables researchers using IPA to analyze and interpret combined 'omics data, visualize metabolite and gene interactions, and place data in a proper biological and chemical context.

"Most recently, we've been working on the characterization of *in vitro* maturation and differentiation processes of the renal epithelial monolayer. For example, we've used transcriptomics to elaborate molecular signatures of the maturation process," Aschauer says. "This analysis included transcription factor prediction analysis from IPA in order to unravel the transcription factors that regulate this process. In addition, we measured the activity of a subset of these transcription factors in order to verify the predicted activity."

Prior to using IPA, Aschauer and her colleagues used free pathway enrichment tools such as PANTHER or DAVID, but they found that these tools did not have the highly integrative, complex functions of IPA -- nor could they manage the larger number of genes under review in many projects. To gain a more integrated view of their transcriptomic, proteomic, and metabolomic data, the IMU scientists have utilized IPA's pathway analysis and transcription factor prediction tools to find significantly perturbed pathways, novel biomarkers, and metabolic regulators.

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*Lydia Aschauer*

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