Lawrence Lesko was given a perfect opportunity to embark on a new research project where the risks would be high, but so would the potential rewards.

Renowned for his work as a system pharmacologist, Lesko received an Agilent Thought Leader Award last year and decided to use the resources to search for biomarkers that could better predict the side effects of new medicines.

Lesko chose to focus on drug-induced renal toxicity because this side effect is one of the many reasons pharmaceutical companies halt drug development projects and doctors discontinue certain chemotherapy and antimicrobial treatments.

His aim: Use Agilent systems and software to develop a metabolomic profile that could provide early warning that a drug is harming the kidneys.

Lesko notes that the current lab test indicators for impaired renal function are changes in serum creatinine, blood urea nitrogen, and creatinine clearance. “The problem,” he says, “is the changes in these biomarkers occur after the drug substantially damages the kidney, where you can’t necessarily reverse it, and the patient has to endure long-range suffering.”

He used Agilent instruments (a combination of highly accurate liquid chromatography and mass spectrometry systems) to gather mountains of data, then used Agilent software (MassHunter, Mass Profiler Professional, and Pathway Architect) to analyze it.

Lesko and his team at the University of Florida in Lake Nona then created a model—a physiologically based, pharmacokinetic model—that enables them to simulate scenarios they weren’t able to test, including a novel new approach to mitigate risk that they hope to validate through in vivo intervention studies.

“We know that cisplatin, a chemotherapy drug widely used in oncology, gets into the kidneys through a transport mechanism called OCT 2 (short for organic cation transporter 2), which takes it from the blood into the renal cortex,” Lesko explains. “Now here’s the really cool thing. We figure, ‘OK, the drug is taken up by OCT 2, What if we gave an antidote that blocks OCT2 transport before the cisplatin?’”

They chose cimetidine, an over-the-counter remedy for gastric upset, as a possible solution.
"Using our model, we simulated co-administration and were able to simulate cisplatin plasma levels and show a significant reduction of cisplatin in the renal cortex. Where we have to go next is an opportunistic in vivo study, probably in rodents, to validate our simulation, but ideally in patients," he says.

The end game? “Reduce the toxicity of a drug by giving a second drug a priori that minimizes the toxicity mechanistically—in this case by blocking the OCT 2 pathway,” Lesko says.

"No one has done this before. It’s very innovative.”

In metabolomics, the key obstacle, he notes, is deciphering the functionality of vast quantities of data.

“You get terabytes of data from Agilent MassHunter and so on, so our main challenge now is to interpret the data in a mechanistic way that would give us insight into how these drugs become toxic. What are the off-target and on-target pathways that are being affected by the drug and what is the mechanism by which these pathways are being affected? Is it the drug binding to receptors or proteins? Are there stress pathways of these drugs? What exactly are the metabolites—the end products of the pathways—telling us? How can we be sure that these metabolite changes are due to kidney damage versus heart damage, for example?” Lesko says.

“We’re looking at the pathways and asking questions: If we see a change in lipids, are the kidney and lipid metabolism in the organ associated with toxicity, or if there’s a change in amino acids is this reflecting mitochondrial damage in the kidney? So that’s where we are. Those are our biggest challenges right now: looking at the data and correlating metabolite changes with the mechanisms.”

Innovations in science, Lesko and others have noted, tend to come at the intersection of different disciplines, in this case, clinical pharmacology and pharmacometabolomics.

“The intersection between metabolomics, physiologically based modeling, and molecular-level pharmacology is what brought us to this point, to have something pretty exciting. There’s still a lot of work to be done, but we got this far by virtue of that intersection,” Lesko says.