Agilent Case Study: University of California at San Diego

Pathways to Better Health

Agilent aids research into metabolic flux and disease mechanisms

Christian Metallo and his team apply systems-level modeling in their research for one reason—and it's not because they enjoy adding complexity to an already complex undertaking.

"We do it to keep us honest about what we can claim, what we can conclude about the data," he says. "If you look at one piece of data in isolation, that may suggest a certain conclusion. But by analyzing our data in the context of metabolic networks, we can reach a more robust conclusion."

The data that Metallo and his colleagues at the University of California at San Diego are collecting spans several areas of inquiry, including cancer metabolism, stem cell biology, and metabolic syndrome.

"The overarching goal of our research is to try to understand how metabolic dysfunction converts to disease processes," he says. "So, presented with a biological system—be it disease in clinical patients, samples from those patients, or a disease model in either animals or cell culture—we then try to explore how metabolism is functioning."

What makes Metallo's research especially compelling is a relentless focus on metabolic flux analysis.

"Rather than looking at static metabolites and static analytes, we use stable isotope tracers to quantify metabolic activity or enzyme activity," he says. "Then, by seeing which metabolic pathways are altered in a given biological system or disease model, we hope to identify the critical pathways or enzymes that could then be targeted via drugs or diet or what have you."

The indispensable tools of their research: "Tried-and-true instruments from Agilent."

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"Everything we do is all about quantitation and numbers," Metallo says. "If you don't have precision in your measurements, then you're pretty much worthless."

His lab relies primarily on three **GC/MS** systems from Agilent as well as a **triple quadrupole LC/MS** system, also from Agilent, that they use for targeted lipidomics.

"What gives me confidence in our results is the robustness of the instruments that we have and the sensitivity," Metallo says.

While Metallo has a clear preference for analytical instruments with proven precision and reliability, he and his team have also developed new methods to probe metabolic pathways in greater detail.

"Some of the processes are highly compartmentalized, so you have different components of a cell executing specific functions, and the challenge is to look at what's happening in one part of the cell as opposed to another," Metallo says.

"The deuterium tracing technique that we developed allows us to get at some of that information in terms of what's happening within a mitochondria or outside of the mitochondria in the cytoplasm of the cell. Otherwise, when you're dealing with metabolites that turn over very fast, it's not easy to separate out those different components of the cell."

Metallo explains that his team uses a combination of reporter metabolites and tracing with deuterium isotopes.

"That allows us to address questions of how cells are functioning in a more compartmentalized manner," he says. "It's one thing if you've got bacteria, which are basically a sack full of DNA and proteins, but mammalian cells are more complex. Our new techniques allow us to get a more detailed picture of how the cells operate."

An avenue of research that Metallo is increasingly excited about is profiling how lipids turn over and how they contribute to disease—especially neurological diseases.

"One of the recurring themes we're seeing is that there are alterations in lipid metabolism that are contributing factors to disease. In the case of the nervous system and the retina, they are known to have very distinct lipids and have very particular needs from those lipids."

In simple terms, certain cells crave certain nutrients. Some want more sugar, for example; others want more fat. Which means that both diet and genetics play their roles. As does age. In fact, Metallo points out, neurodegenerative diseases are becoming more prevalent as the population ages.

"Over time, metabolic exhaustion or defects in these processes ultimately cause a breakdown," he says, "and the first things that often break down are the higher-order tissues."

That is, the tissue in our hearts, eyes, brains.

"As we develop a more complete picture of the metabolome, metabolites that are potentially toxic or potentially beneficial are appearing—and we're able to quantify them and characterize their function in more detail," Metallo says.

"We're trying to identify mechanisms where dietary change has positive (or negative) effects. Once you do that, maybe you can go deeper and design a more tailored therapy."

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