CONTEXT MATTERS
MULTI-OMIC RESEARCH REVEALS NEW BIOLOGICAL PARADIGMS USING AGILENT TECHNOLOGY

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"We are literally rewriting textbooks," says Adam Rosebrock. "That's part of the fun here."

"Here," is the Donnelly Centre for Cellular and Biomolecular Research and the Department of Molecular Genetics at the University of Toronto, where Dr. Rosebrock and his team are using metabolomics to identify new biochemical reactions and understand how metabolism is controlled during cell growth and division.

"With metabolism, we don't have a comprehensive map to tell us what we should find in the cell," he says. "One of the most exciting aspects of what we're doing is discovering new metabolites and new reactions."

Rosebrock's work is expanding our knowledge by finding new metabolic reactions and identifying the proteins that catalyze them.

"Unlike a genome, from which we can read out mRNAs and encoded proteins, we can't predict the metabolome," Rosebrock says. "My group is working to directly identify the compounds that cells make and the enzymes responsible for these reactions."

Rosebrock and his team are able to look at metabolism more closely, thanks to a full complement of Agilent LC/MS solutions, along with new methods and tools developed in house.

"For our work, instrument reliability and run-to-run reproducibility are of paramount importance. We generate tens of thousands of data files in large projects that encompass months, even years, of samples. Robust chromatographic separations and mass spec reproducibility let us compare across these many, many runs and integrate data from different instruments," Rosebrock says.

"We use the entire range of Agilent LC/MS instruments. That includes high-resolution Q-TOFs including the 6550 and 6540, rock-solid triple quads like the 6490 and the 6460, and even a 6100-series single-quadrupole, all driven by ultra-high-pressure 1290 Infinity LCs. The sensitivity of the Agilent platform is excellent, enabling us to run precious and limited samples on multiple orthogonal instruments and chromatographies."

Agilent software gives the lab unified instrument control and easy-to-use analytical tools, enabling students and staff to generate and analyze data from fundamentally different types of mass spectrometers.

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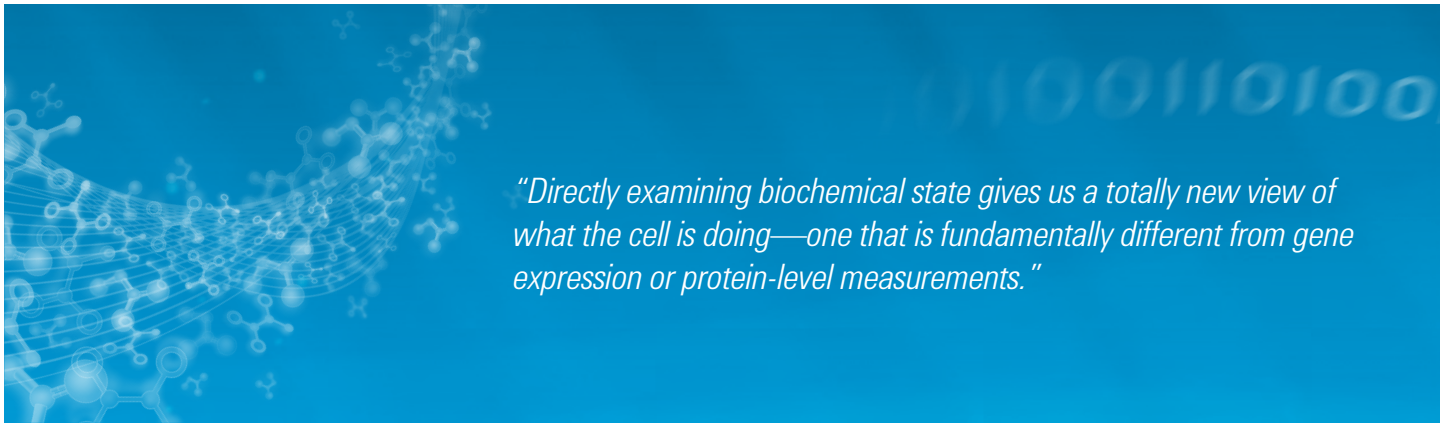

Rosebrock is not just a user of technology, though. Collaborating with Agilent, his group actively develops new chromatographies and methods to separate and unambiguously measure a wide range of analytes.

"A major challenge in metabolomics is that isomeric compounds often play fundamentally different roles in the cell. We're finding entirely new metabolic pathways, and we've been able to understand paradigms that haven't been seen before," Rosebrock says.

"Directly examining biochemical state gives us a totally new view of what the cell is doing—one that is fundamentally different from gene expression or protein-level measurements."

His key, overarching observation is that, in metabolomics, context matters.

"Research in my lab centers on how cells coordinate a genome worth of metabolic reactions that are separated in space and time. The biochemical state of actively growing cells is fundamentally different from cells that are quiescent, maintaining the status quo. Imagine the power of a reaction that only happens when cells are actively dividing. If we could stop that reaction, if we could specifically inhibit that process, we could then target only cells that are actively growing. In other words, cancer or inflammatory cells," Rosebrock says.

As it turns out, gene expression patterns are remarkably similar whether cancer tissue is grown in a dish or in rodent models. Metabolism, however, is fundamentally different.

"I came to metabolomics from a background in gene expression analysis. The fib we always told when measuring transcript levels, and it was a good fib at the time, was that we can predict what the cell is doing by looking at gene expression. My group's results now point to previously uncharacterized mechanisms to establish and maintain cellular biochemical state—post transcriptional, localization, and allosteric mechanisms that we'd missed using expression analysis," Rosebrock says.

"Because we can now directly measure that metabolic state, we can now directly examine biochemical phenotype. I view metabolomics as the ultimate assay of what cells are truly doing."

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Published in USA, October 30, 2015
5991-6421EN

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