Much Ado About Molecules

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By Meredith W. Salisbury

Metabolomics could well be the new darling of the large-scale biology community, with vendors, investment, and hype aplenty. There's already a Metabolomics Society hosting annual meetings, at least one metabolomics-focused research journal, and in Canada the Human Metabolome Project has been underway for almost two years.

"There's more buzz about it right now than people actually doing it," says Steve Fischer, senior applications scientist for LC/MS and go-to metabolomics guy at Agilent. The metabolomics market is predicted to be worth more than $2 billion by 2012, according to Research and Markets.

Those are some serious expectations — and a hefty amount of pressure — for a nascent field with a good number of bumps in the road ahead. Proponents of metabolomics, or the high-throughput analysis of cellular metabolites, say that these molecules could become even better biomarkers than SNPs or proteins, helping not only to diagnose illness but also to understand and predict off-target or toxic effects of therapeutics. But before that happens, scientists will have to overcome the biggest hurdle — the current difficulty in identifying the molecules that are found to be biomarkers — as well as several others that face any growing young field.

Growing Pains

Far and away the major challenge standing between metabolomics and its shiny future is the dilemma of identifying molecules discovered in these global studies. "In all metabolomic experiments carried out so far," says Oliver Fiehn, associate professor and metabolomics specialist in the University of California, Davis, Genome Center, "there are always compounds being relevant that remain unidentified." When a genomics experiment reveals a gene, you can Blast it against GenBank to figure out what it is; with an unidentified protein, you can compare mass spectra to a protein database to see what it is. But currently there's no comparable repository for metabolites, and no tool that can analyze and identify them. "We need a kind of sequencing tool … for *de novo* identification," Fiehn says.

Current means of compound identification are a little more by-guess-and-by-golly than most scientists feel comfortable with. The most common approach to metabolomics studies is "some sort of separation followed by a mass spectrometer," says Agilent's Fischer, noting that GC/MS, LC/MS,

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Young Investigator Profile

Julius Brennecke
Group Leader
Institute of Molecular Biotechnology

Parsing Nature's Elegant Solutions

Julius Brennecke is studying small RNA pathways in *Drosophila* using DNA sequencing technologies, genetics, bioinformatics, and cell biology. With this approach, he hopes to elucidate the main germline-specific piRNA pathway, thought to be partially involved in heterochromatin biology and telomere length control. His group is also focused on the roles of the microRNA pathway and the endogenous small interfering RNA pathway in germline development, and siRNA-centered pathogen defense.

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and CE/MS are all popular options with the metabolomics crowd. And for the relatively few molecules that are already well characterized, that could be the end of the story. But for the many experimental results that emerge unidentified, scientists must go through all sorts of contortions to pin the name on the molecule. Studies of MS/MS data can lead to a hypothesis of what the compound is, says Gary Siuzdak in the Center for Mass Spectrometry at the Scripps Research Institute. Researchers use that information to synthesize the molecules they suspect might be the answer and compare them to the original compound, hoping to find a match.

One way scientists are aiming to improve the situation is by building metabolite databases in the hopes that one day they will be far more comprehensive and useful than they are now. Siuzdak runs one of the best known such databases, METLIN. “When we first started this, there wasn’t too much out there,” he says. “We have about 4,400 compounds in there right now.” Estimates of the number of metabolites in existence are reminiscent of the early days of estimated human gene counts, and they range from 2,500 to 20,000, says Fischer. One gleam of hope, says Siuzdak, is that early studies indicate that it may be possible to do some rudimentary identification by matching unknown metabolites up to known ones with similar characteristics. “At least for a fair number of metabolites it may not be as overwhelming as we thought,” Siuzdak adds. “Many appear to be closely related to other metabolites. … There’ll probably be cases where they’re completely new structures, but probably a lot of low-hanging fruit out there that’ll let us identify at least some of the new molecules.” To that end, Siuzdak encourages pharmaceutical companies and other institutions with large compound libraries to begin making some of that data public to aid in the metabolite identification effort.

Identification isn’t the only hurdle for metabolomics. As with so many new ’omics fields, this one faced early confusion over reporting standards. Fiehn, who has been a vocal supporter of standards, says there have been “some bad papers published” due to lack of standards early on, but he’s optimistic that his and others’ efforts to encourage standards are helping add rigor to the field.

Also like disciplines that went before it, metabolomics has an uphill battle getting effective and useful software in place, says Fischer. “These are not single-point analyses. In metabolomics it’s a comparative analysis technique,” he says. “The net result of all this is software, software, software. … That’s where virtually every vendor who’s trying to service this marketplace is putting effort in.”

The Potential

Metabolomics scientists contend that these analytes could prove better biomarkers than those derived from proteins or SNPs — in large part because the molecules circulate and are more easily accessible through blood and urine than tissue-based biomarkers. “They’re more accessible, circulating, and usually higher quantity so they’re easier to detect,” says Fischer. Besides, examples of metabolite biomarkers have been around for a long time, and organizations like the FDA might be more comfortable with them. Fischer points to glucose, used as a biomarker for diabetes, as one example.

Siuzdak notes that metabolomics is in fact already being used in clinical environments for neonatal testing. Some 4 million or 5 million infants have been screened “using tandem mass spectrometry to quantify metabolite levels and tell the parents if their child has one of these 30 or so diseases,” he says.

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Metabolomics can also be used to evaluate whether a drug will have toxic or off-target effects, says John Ryals, president and CEO of Metabolon, a company partnering with big pharma for these kinds of studies. “We’ve done probably 60 or more projects with pharmaceutical companies over the past couple of years,” he says. Those projects often revolve around compounds that have been blocked for off-target effects or toxicity, and Metabolon’s role is to find new metabolite biomarkers that enable the pharma to predict which patients can safely take the drug — thereby rescuing the compound from the FDA gulag. Biomarkers can be chosen for on- and off-target effects, as well as for screening responders and nonresponders.

Ryals expects the upshot of much of this work to lead to clinical diagnostics, a path his company plans to travel. Working with pharma on their compound projects has been a massive learning experience for Metabolon, he says, and that knowledge is being put to use with the company’s first product offering: a service to help companies choose the most selective compound in preclinical studies. Beyond that, “we’re moving forward on a number of clinical diagnostics,” including one for ALS, he says. “Over the next couple of years we’re going to start looking more and more like a diagnostic company.”

Clearly, there’s no single goal for the metabolomics field, and its potential for impact in the scientific and medical community only expands as new uses are found. As Fiehn at UC Davis says, “[Metabolomics is] getting width and breadth. There are more and more people involved.”

Science

A recent study identified similar methylation patterns from opposite sides of the same tumors, suggesting that they arose all at once in a rapid burst, rather than in a series of expansions.

Business

Beckman Coulter plans to pay $800 million to acquire Olympus' diagnostics business. Beckman expects the business to provide revenues of around $500 million in 2010.

Funding

NINDS has set aside $3.6 million to support the Ischemic Stroke Genetics Consortium, which will identify genomic regions associated with ischemic stroke susceptibility.

Genome Technology Magazine

Check out the March issue of *Genome Technology*.