

Biomarker Integration Necessary but Complex for Drug Discovery

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ATLANTA - The use of biomarkers is in its infancy, and early experience, particularly in cancer, is revealing a sea of complexity when it comes to their useful and productive application and integration into drug discovery.

A critical issue is that biomarkers are far from being able to address human variation, most notably in chronic diseases, where many different pathways lead to the same disease end state.

Lewis Bender, CEO of Interleukin Genetics, cautioned the idea that gene plus environment equals phenotype - for which read disease - is far from capturing the true complexity.

"It doesn't take account of genetic variation, environmental variation, gene-environment interaction or gene-gene interaction," Bender said as he introduced a session called "Integrating Genetic Markers in Drug Development" at the 2009 BIO International Convention.

The results of genome-wide studies that fish out genes associated with diseases, such as osteoarthritis or cardiovascular disease, need to be considered. The presence or absence of a genetic biomarker does not say anything about how it will be up- or down-regulated in response to different environments.

So while DNA-based biomarkers have the advantage over protein biomarkers of being static, it is hard to get a proper co-variant analysis based solely on DNA. Anyone consulting a doctor at risk of heart attack would be told to change his diet and do more exercise.

"Yet when you do a genome-wide association scan to find genes that are linked to risk of heart attack, there is no co-variant analysis for diet and exercise," said Bender, adding that if two people have the same bad genes and one diets and exercises and the other doesn't, different good and bad genes will be down- and up-regulated, resulting in different phenotypes.

Despite that and other reservations, there is a growing body of evidence showing biomarkers can be applied to shorten drug development times. They can be used to screen out patients who will not respond, leading to smaller clinical trials, fewer adverse reactions and improved efficacy. Bender suggested that the development of biomarkers is now advanced enough for them to be used for drug rescue and repositioning also.

"Maybe it was not quite positive in Phase IIb. How can you go back and identify responders and nonresponders to rescue drugs? As yet, that's really not being looked at to any significant degree."

Inflammatory pathways are the driving force behind all major age-related chronic diseases, and genetic biomarkers potentially could be of high value in trials for those drugs. For the same initiating event, for example, high cholesterol, the progress to a disease state could be very rapid, or very slow, depending on the genotype.

Bender noted that some people presenting at age 50 with osteoarthritis will progress very rapidly, others far more slowly. There is now a biomarker screen that can identify those with slow-developing disease, allowing them to be excluded, reducing what otherwise would be identified as a placebo effect, and increasing the chances of getting a positive result.

"Disease progression rates are really important in drug development," Bender said.

Similarly, it is now possible to identify rheumatoid arthritis patients who will respond to the interleukin-1 drug Kinaret. Whereas 40 percent of RA patients as a whole respond to Kinaret, 63 percent of those with the relevant genotype are responders. That has enabled Kinaret to be repositioned vis-à-vis TNF-alpha inhibitors, where the average overall response rate is 63 percent.

To date, the most famous biomarkers, such as Her2 overexpression, K-ras mutation and the EGFR mutation, are in cancer.

But even in oncology, the overall impact is low. They can help oncologists decide on the use of one particular targeted cancer therapy in a subset of the population, said Douglas Clark, chairman and chief scientific officer of Biomarker Strategies and a professor of pathology and oncology at Johns Hopkins Medical School.

"These high-profile biomarkers are a step in the right direction, but there is huge unmet need. As a pathologist, I can look at cells and say you have cancer, but I can't say which drug you should get."

There are 18 approved targeted cancer drugs, some of which have companion diagnostics, and 400 agents in the clinic spanning a range of cell biology - for example, eight are targeted at FLT-3 and five at src.

One way of finding responders to those drugs would be to test actual patient samples and see if the targeted pathway is blocked. "This would facilitate therapeutic decision-making," Clark noted.

At present, the systems and infrastructure for taking, processing and analyzing biopsies is unsuited to that approach. To apply biomarkers in that way, it will be necessary to handle samples in a completely different manner and bring the analysis closer to the patient.

Reid Leonard, executive director of licensing and external research at Merck Research Laboratories, said the company has "aggressive internal goals" around building biomarkers into its drug discovery strategy. One important aspect is their increasing adoption in toxicity testing of early stage compounds.

The eventual aim is to use information from biomarkers to pick targets that are least sensitive to genetic variation. "That is, rather than stratify the patient population, we will find a drug that a high proportion of the population react to," Leonard added.