

OMICS

Exploiting the Value of Cancer Biomarkers

Expeditious Use Could Make Medicine More Personalized, Predictive, Preemptive, and Effective

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According to the Biomarkers Consortium at the Foundation for the NIH, “biomarkers are molecular, biological, or physical characteristics that indicate a specific, underlying physiologic state to identify risk for disease, to make a diagnosis, and to guide treatment.”

Thus, biomarkers are essential to personalized medicine. A number of researchers will be discussing their progress using biomarkers at CHI’s upcoming “TriMedicine Conference” to be held in San Francisco in late February. A preview of some of those presentations is provided in this article.

Lung Cancer

James L. Mulshine, M.D., professor at the Rush University Medical Center

in Chicago, will be describing his use of quantitative imaging as a biomarker of drug response in lung cancer.

Lung cancer is still the world’s leading cause of cancer death; however, drug development is slow and expensive. The primary barrier is the outdated and imprecise method of evaluating drug response. Dr. Mulshine advocates using 3-D tumor imaging as a “surrogate endpoint” of measuring drug responsiveness rather than the unidimensional measurements currently used, much the way cholesterol levels rather than the frequency of heart attacks are now used to evaluate the efficacy of lipid-lowering drugs.

Spiral, or helical, CT scanning is a quick way to measure changes in tumor volume with high resolution. It

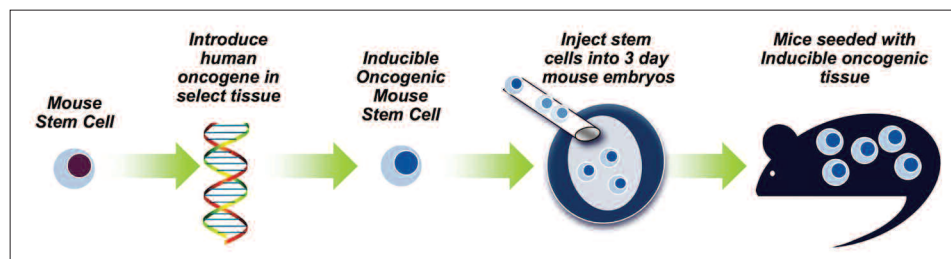
can, therefore, be applied to “window-of-opportunity” drug trials, in which tumors are imaged both before and after drug exposure. Changes in tumor volume and signaling pathways precipitated by the drug treatment can be measured.

Tumor reduction assessed by high-resolution CT was recently used successfully as an endpoint in a Phase II trial of pazopanib, an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-kit in patients with stage I-II non-small-cell lung cancer.

Breast Cancer

The laboratory of Thea Tlsty, Ph.D., professor at the University of California, San Francisco, studies the regulation of cancer initiation in human tissues. At the conference, she will be discussing the use of biomarkers to evaluate the risk of future breast tumor formation in women diagnosed with duc-

AVEO Pharmaceuticals’ Human Response Platform is based on the company’s genetically defined mouse models of human cancer, in which each model is engineered to contain signature genetic mutations that are present in human disease.



tal carcinoma in situ (DCIS).

Fifteen to thirty percent of women with DCIS go on to develop tumors within ten years after a lumpectomy. Unfortunately, many patients end up being treated too aggressively (needless mastectomies) or not aggressively enough.

Nuclear grade, surgical margins, and tumor size are all measured in the clinic, but none have been found to have strong enough predictive value to affect therapeutic decisions.

Interestingly, Dr. Tlsty found that cells expressing high levels of p16 and/or COX-2, when coupled with proliferation, go on to become basal-like invasive tumors. These particular biomarkers indicate an abrogated response to cellular stress; cells overexpressing them that continue to proliferate have bypassed pRb-mediated signals to senesce.

In contrast, cells with high p16 and/or COX-2, but low proliferation, have an intact Rb checkpoint and senescent program and do not go on to become tumorigenic. These biomarkers can be measured years before tumors actually arise, and thus can be used clinically to help dictate individualized treatment options.

Richard Bender, M.D., the chief medical director of **Agendia** (www.agendia.com), will be talking about the company's development of genomic biomarkers for prognosis and prediction in early-stage breast cancer. Agendia is marketing MammaPrint, which measures the expression profiles of 70 different genes in early-stage breast cancers.

MammaPrint was designed to specifically predict which 30% of patients are at a high risk of recurrence, which it does remarkably well, according to Dr. Bender; it has a hazard ratio of 10,

whereas most prognostics hover around 3–4. As a side benefit, these are the same 30% that are sensitive to chemotherapy. Dr. Bender notes that this type of gene-expression profiling is a “way of personalizing treatment for patients.”

Agendia also has TargetPrint, which quantitates ER, PR, and HER2 expression in breast cancer. In contrast to MammaPrint, this test was designed to determine which drugs should be given to which patients.

Drug Response and Resistance

The human xenograft tumor model has been the standard preclinical model for testing the efficacy of new cancer drugs. However, many promising drugs, including the latest antibodies and kinase inhibitors that were so effective in these models, have failed in the clinic.

Murray Robinson, Ph.D., svp of oncology at **AVEO Pharmaceuticals** (www.aveopharma.com), notes that his whole company is predicated on the premise that we “can do better figuring out which patients are going to respond to which drugs. The biggest problem in oncology development is that we have little understanding of who will respond to a drug and how to test it.”

AVEO has developed the Human Response Prediction Platform to tackle this. It genetically engineers various tumor-initiating mutations (for example HER2 and EGFR) into human cells, then introduces them into mice and allows secondary mutations to arise spontaneously. These tumors end up with 100 different causative mutations, rather than just the two or three seen in xenografts, and, thus, more closely mimic the range of genetic heterogeneity observed in human tumors.

This population-based approach should help specify the important causative mutations that account for the variability seen in drug responses. Each tumor is extensively characterized by microarray analysis, so researchers can correlate sensitivity or resistance to drugs with expression information and other changes in biomarkers.

This is, in fact, what the company has done with AV-951, its highly potent triple VEGFR inhibitor. The molecule is in Phase II trials for treatment of metastatic renal cell carcinoma because all xenograft models responded to it. Less than half of patients did, however. Using its HRP platform, AVEO scientists correlated a panel of 33 genes with lack of response—and found all of them are involved in a very specific biology, non-VEGF driven angiogenesis. “The hope and promise,” Dr. Robinson comments, “is that using more accurate models will help us gain insight into responsive populations and promote cheaper and faster drug approval.”

Critical Path Initiative

Many tests currently used for diagnostic purposes and drug evaluations are over 100 years old. This is primarily because there is not yet an FDA guidance document for the regulation or approval of a method. Recognizing the problem, the FDA established the Critical Path Initiative (C-Path) in 2004. Its mission statement is “to create innovative collaborations in research and education that enable the safe acceleration of the process for developing new medical products.”

According to Raymond Woosley, Ph.D., the president and CEO of the Critical Path Institute, it is focused on “trying to address the process of getting

science into commercialization.” It wants to make sure that “better, more modern methods and tools are qualified for use in drug development.” He stressed that it does not deal with products, only processes.

Dr. Woosley will review a few examples of biomarkers being used clinically in oncology. C-Path would like to expedite the development of diagnostic and other assays to follow these.

Irinotecan, marketed by **Pfizer** as **Camptosar**, is a topoisomerase I inhibitor used clinically against colon cancer. Its active metabolite is inactivated in the body by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Patients with the otherwise benign Gilbert’s syndrome have insufficient UGT1A1, and therefore, when treated with irinotecan receive an effectively higher dose and suffer toxicity. An invader assay has been developed to detect this genotype in colon cancer patients, making irinotecan the first chemotherapy agent individually dosed by genotype.

Approximately 15–20% of breast cancers overexpress HER2/neu. Trastuzumab (Herceptin, **Genentech**) is only effective in these cancers, so breast tumors are routinely tested for this overexpression to determine the appropriate course of treatment.

Erlotinib hydrochloride, marketed as **Tarceva** (**Genentech**, **OSI Pharmaceuticals**), is used to treat non-small-cell lung cancer. As it targets the EGF recep-

tor, a test for EGFR mutations in cancer patients would probably help predict who will best respond to it and similar kinase inhibitors.

As an independent third party, C-Path has induced 18 pharmaceutical companies to share their methodologies, then summarized and compared them. This cooperation will determine if EGFR is in fact a valuable biomarker and, just as importantly, which test is best for predicting efficacy of drugs targeting it. Speeding up the trial process in this way could reduce the number of costly failed drugs and lower the price of prescription drugs in general.

Dr. Woosley opines that “biomarkers are not being fully utilized for drug development.” They could be used to predict, and thereby prevent, a new drug’s side effects and to account for variability in efficacy.

The representative examples mentioned here are only that; the uses for biomarkers need be limited only by researchers’ creativity. For instance, a group at the Technion in Israel recently described a novel technology for cancer biomarker discovery that they dubbed “humoral proteomics,” based on the fact that cancer patients have expanded antibody repertoires with abnormal specificities. Biomarkers have the potential to make medicine more like it should be: more personalized, more predictive, more preemptive, and ultimately more effective. **GEN**