

MOLECULAR PROFILING: Using the Genome to Identify Effective Cancer Agents

by Shannon M. Nixon, PhD

With molecular profiling paving the way to identify genomic disease signatures, could better drugs with lower treatment failure rates be far behind?

Drug discovery has historically relied on in vitro screening methods. However, at the genomic level, such a targeted approach overlooks the complexity of disease since in vitro methods do not allow the study of biological processes in the context of a living system. Often, in vitro screening is not physiologically relevant or not even possible to conduct if the target to be tested is unstable in a biochemical environment. These limitations have resulted in a shortage of drugs that yield high efficacy and low toxicity, which in turn, has led to an emerging shift in approaches to drug discovery toward more physiologically relevant models.

Advances in Genomic Technologies

The Human Genome Project and other genomic technologies have opened the door for these significant advances in drug development to occur. Having the capacity to monitor genome-wide expression patterns in normal and disease states has enabled researchers the ability to define better disease biomarkers and molecular profiles that aid drug discovery and development.

With new molecular profiling techniques, human cancers can be characterized by assigning a genetic signature. According to Todd Golub, MD, Chairman and Member of the Scientific Advisory Board of Avalon Pharmaceuticals, Inc. and Director of Cancer Research at the Broad Institute of MIT and

Harvard, this assigning allows a more precise definition of cancer.

“Identification of subtypes of human cancers will allow one to identify a discreet patient population that is most likely to respond to a particular treatment regimen,” said Golub.

Consequently, new molecular profiling techniques that identify genomic disease signatures could facilitate the design of better drugs with lower treatment failure rates and could greatly decrease the cost and time for the drug development process.

Molecular Profiling vs. Targeted Approaches

The idea behind molecular profiling is to shift the focus away from specific targets of disease and look more generally at the affected biologic pathways. Using this approach to drug discovery, the actual target becomes less important than the broader genomic effects of the disease.

“Many commercial and academic investigators try to use microarrays to classify patients and identify patient populations that are most likely to respond to a particular drug,” said Golub. “This approach involves identifying a critical target in advance and then doing a biochemical assay of some sort—which is fine, unless you happen upon a class of molecules that are not amendable to this type of assay.”

Unfortunately, up to 80 percent of the proteins that have been identified to play critical roles in disease progression are not “druggable” with traditional in vitro approaches because they are not stable in a biochemical environment (Hopkins AL, Groom CR. *Nat Rev Drug Discov.* 2002;1(9):727-730). For example, myc, stat3, and beta-catenin are clearly defined

With new molecular profiling techniques, cancers can be assigned a genetic signature

oncogenes that when misregulated play critical roles in cancer progression. However, due to their instability in a biochemical setting, drugs have not been developed for any of these validated disease targets.

Since molecular profiling methods monitor drug effects from a broader biological perspective, they serve to identify physiologically relevant endpoints of drug-target interactions. Therefore, validated targets such as myc, stat3, and beta-catenin can be studied again, but in a setting that is physiologically relevant and more likely to lead to the discovery of more effective drugs.

Molecular Profiling Model: How It Works

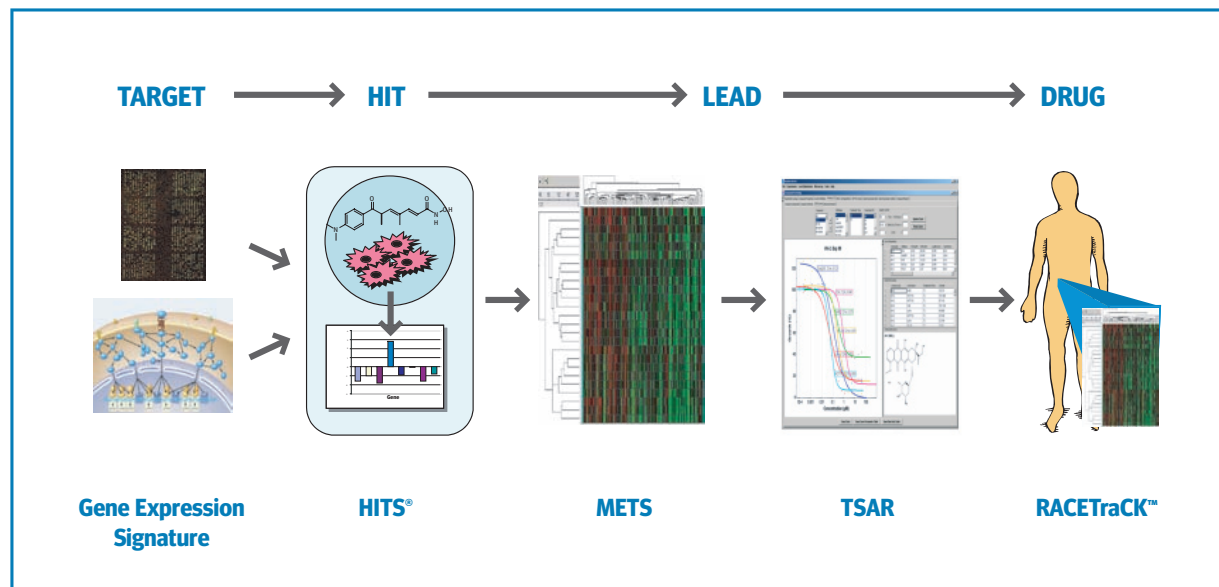
As an example, Avalon Pharmaceuticals, Inc. has developed the AvalonRx™ Gene Expression Based Drug Discovery Engine. The engine uses molecular profiling to identify disease biomarkers in an effort to tailor treatment regimens that target cancer by defining predictable patient responses. The approach begins by establishing a gene expression signature that would likely provide a beneficial therapeutic response. For instance, the gene

expression patterns of several genes under normal and disease conditions are compared to identify the specific genomic changes associated with the disease state. Efforts can then be aimed at designing and testing compounds that “correct” these changes.

Next, active compounds are screened with high-throughput methods to determine their genomic effects in living cells. This screen allows the study of drug-target interactions and the identification of compounds that may give a desired therapeutic response.

Microarray technology is then used to monitor “on target” and “off target” effects of the test compounds on the expression patterns of thousands of genes to gain a broader idea of a compound’s activity, cross-reactivity, and specificity for the intended pathway.

Structure-function studies are then conducted to determine the ability of the test compounds to alter the regulation of core genes that represent desired “on target” and “off target” effects. [cont. on pg 34 >>](#)



The AvalonRx™ Gene Expression Based Drug Discovery Engine is a new strategy for the efficient discovery, characterization, and optimization of candidate drug compounds. A gene expression signature associated with a particular disease is identified and used to determine a desired therapeutic response, to identify candidate drug compounds that may achieve this response (HITS®), to determine compound specificity and cross-reactivity (METS), to monitor “on target” and “off target” effects (TSAR), and to study in vivo efficacy and appropriate dosing levels (RACETraCK™).

MOLECULAR PROFILING

Finally, the compounds are evaluated in *in vivo* models to establish the physiological effects of treatment. Specifically, murine tumor models are treated with test compounds and the gene expression profile generated in response to treatment is monitored. These studies can give information on efficacy and appropriate dose levels of a particular compound in a physiologically relevant setting.

Avalon Pharmaceuticals is currently developing its lead drug candidate, AVN944 (IMPDH inhibitor) for treatment of hematologic cancers. Comprehensive molecular profiling strategies have shown AVN944 to be more selective and less toxic than previous IMPDH inhibitors. AVN944 has also been shown to be effective and to inhibit its target at sub-toxic doses in preclinical and clinical studies.

A complete data report from Phase I clinical trials of AVN944 for treatment of hematologic cancers is expected in 2007.

Looking Toward the Future

While traditional approaches to drug discovery have been burdened with difficulty, there have been some successes that can teach a lot about the future of drug development. Notably, Gleevec® [imatinib mesylate, Novartis] has had unprecedented success in the treatment of patients with CML. CML is a relatively homogenous disease in terms of its genetic signature, a feature that contributed greatly to the identification of a successful treatment regimen.

Brian Druker, MD, discoverer of Gleevec, explained, “Every cancer is ultimately homogenous...Right now, we think of breast cancer

as one disease. There may be 20 different subtypes of breast cancer and each of those 20 subtypes is a homogenous disease.” The ability to define a molecular signature and use that signature to classify homogenous subtypes of cancer may in fact result in more successful treatments.

Tarceva® [erlotinib, Genentech/OSIP] is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that was recently developed as a cancer therapy. This treatment resulted in a 73 percent response rate in a subtype of patients with non-small cell lung cancer (NSCLC) who had a similar molecular disease signature—namely a somatic EGFR mutation.

Most of the EGFR-mutated patients who responded to Tarceva therapy were never-smoking women of Asian descent (Byrne BJ, Garst J. *Curr Oncol Rep.* 2005;7(4):241-247; von Eyben FE. *Crit Rev Clin Lab Sci.* 2006;43(4):291-323). Now, many patients who fit this disease profile are placed on Tarceva therapy and survival rates in these patients have been significantly greater than previously seen in NSCLC cases.

The drug had only a 10 percent response rate in NSCLC patients with wild-type EGFR.

The key to successful treatment of NSCLC patients with wild-type EGFR, and cancer patients in general, may be molecular profiling approaches that monitor gene expression patterns and identify genetically homogenous subtypes of the disease. Then, treatments can be tailored to more specifically target that disease signature. **SMN**

“Every cancer is ultimately homogenous...”

>>OBR DAILY NEWS FLASH

November 23 - The U.S. Food and Drug Administration (FDA) expanded the approved use of Herceptin®, a biological cancer drug. The new indication is for Herceptin, in combination with other cancer drugs, for the treatment of HER2 positive breast cancer after surgery (lumpectomy or mastectomy). (*FDA News*)