

The Role of Biomarkers in Drug Discovery and Development

The United States Food and Drug Administration (FDA) defines a biomarker as a characteristic that is “objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic intervention.” Although biomarkers have been used in drug development and treatment of disease for a long time, the identification of new predictive safety and efficacy biomarkers is expected to reduce the time and cost of drug development. In addition, the use of novel, but less well-established, pharmacodynamic biomarkers can further facilitate decision-making from discovery through preclinical development and into clinical trials, while rapid advances in genomics and proteomics have increased the discovery of new biomarkers and their value in drug development and treatment of disease.

Biomarkers are currently being developed to identify patients at risk for disease and to predict potential treatment responders, adverse event occurrences, and favorable clinical outcomes for many disease states, particularly cancer. In fact, biomarkers have already established important applications in the selection of therapies in which the drug targets are also the biomarkers. As a result, tissue-based expression of the biomarker directs the molecularly targeted therapeutic course of treatment.

Figure 1: Examples of Tissue-Based Expression

CD20 positivity for treatment of lymphomas with rituximab (Rituxan)

HER2/neu positivity for treatment of breast cancer with trastuzumab (Herceptin)

BCR-ABL translocation for treatment of chronic myelogenous leukemia (CML) with imatinib (Gleevec)

Estrogen receptor (ER) or progesterone receptor (PR) positivity, which is a prerequisite for treatment of breast cancer with tamoxifen or aromatase inhibitors

Somatic mutations in the tyrosine-kinase domain of the epidermal growth factor receptor (EGFR), which have recently been shown to predict a greater efficacy of gefitinib (Iressa)

Biomarker measurements now support target validation and proof of target, mechanism, and efficacy, and they are being developed first in preclinical animal models of disease. The majority of biomarker research is done in clinical trials that test cancer drugs, which represent the single largest therapeutic class of drugs in development.

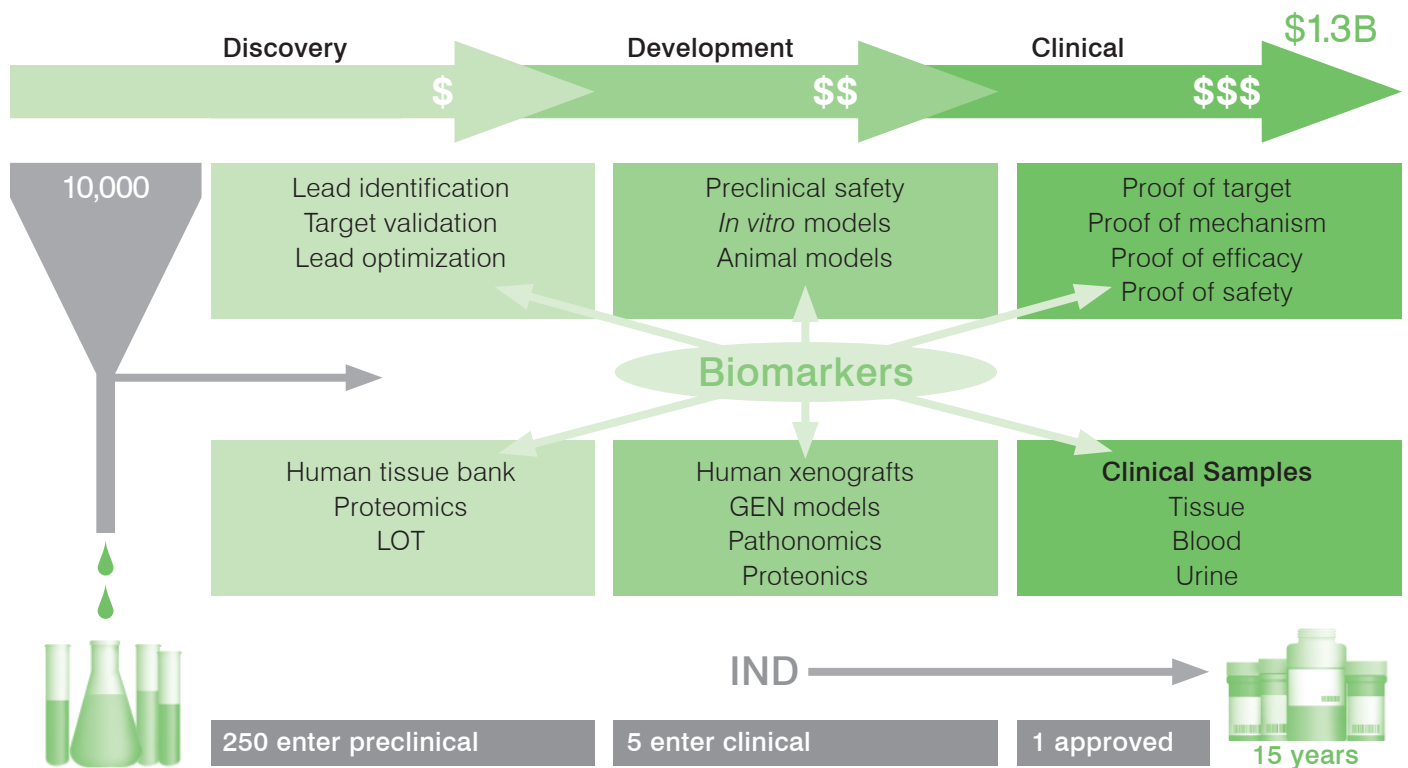
The Pharmaceutical Research and Manufacturers of America (PhRMA) recently reported a record 831 medicines and vaccines against cancer in development, including novel, mechanistically targeted drugs directed against molecular sites controlling cell growth, death, and recruitment. The progress in understanding the molecular biology of cancer has provided an enormous range of targets for drug discovery. Key to this understanding is pathology-based characterization of tissue changes at the cellular level.

As an organization with a longstanding emphasis on preclinical testing programs, Charles River Pathology Associates has led the expansion into biomarker support of clinical trials. Our biomarker services involve immunohistochemical detection of marker proteins within target tissues, and entry into a biomarker program generally begins with a referral from a discovery/early development scientist to a clinician or pharmacologist in the clinical department. Our pathologists and scientists work closely with the client to identify what markers to assess, design a scientifically rigorous approach to testing of samples, and provide a bridge between the preclinical and clinical.

Reliable assessment of exposure-response relationships is contingent on the application of rugged assay methodologies, an understanding of how biological factors and sample collection conditions affect variability, and scientifically rigorous evaluation and interpretation of results. Concomitant with the impact of pharmacogenomics on biomarker development, a huge push for biomarker development is underway in every major pharmaceutical company.

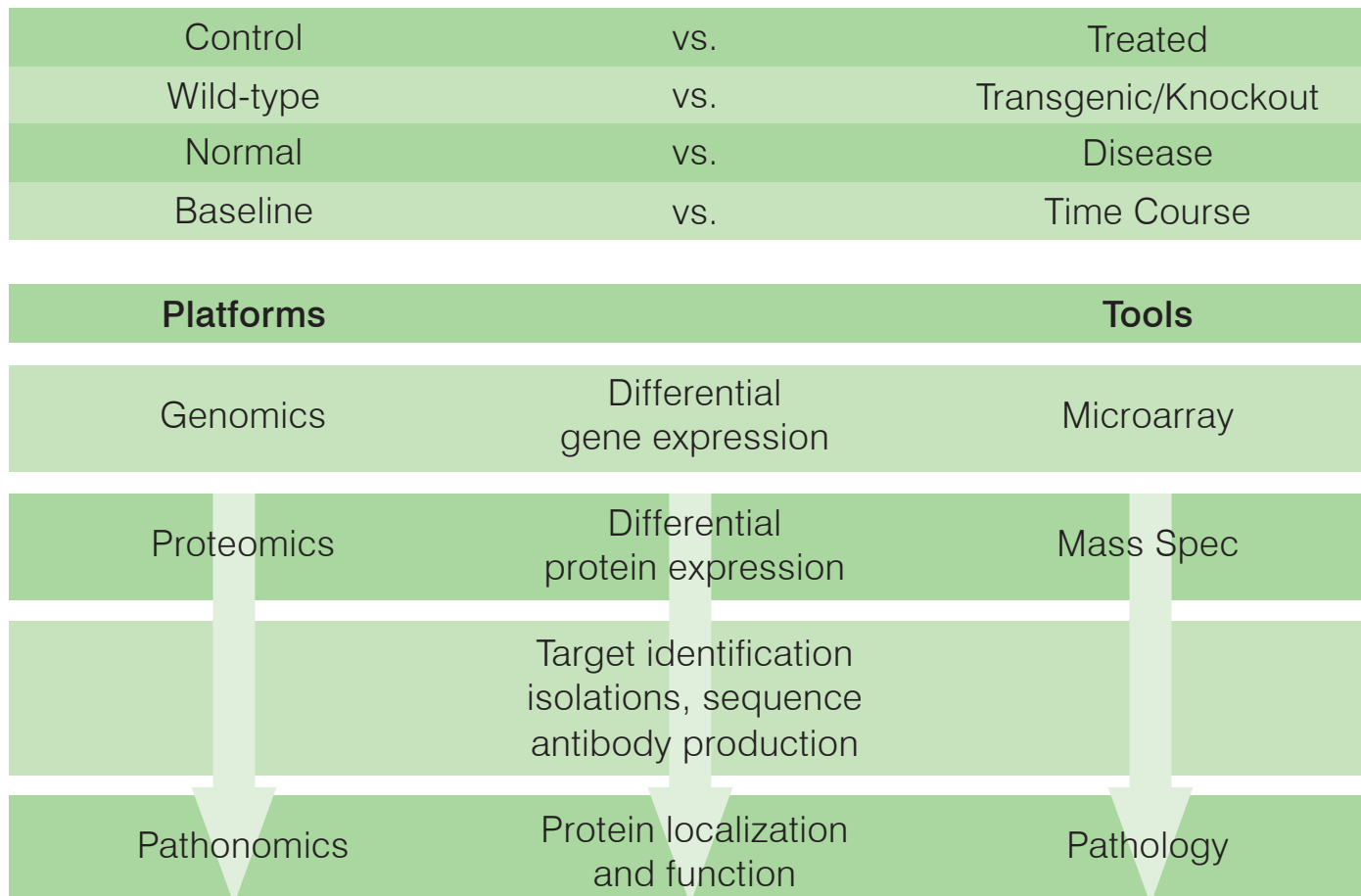
Of course, the drug discovery funnel continues to be inundated with novel compounds (Figure 2). High-throughput screening (HTS) is under escalating pressure to screen more targets against more compounds. Although HTS strives to provide high-quality “hits” in the fastest time, the probability of identifying quality leads that will become drug candidates has largely not improved. For example, it is reported that out of 35 million compounds screened, 5,000 hits are identified. Of these 5,000 hits, only five become drug candidates that make it to human testing. Only one of those five is approved for human use. More importantly, the probability of a lead candidate achieving regulatory approval has remained unchanged in over 30 years of pharmaceutical development.

Figure 2: Role of Biomarkers in Drug Discovery and Development



On the average, it takes 10-15 years at an estimated cost of \$1.3 billion to get one new drug from molecule to medicine. A primary goal within Charles River is to help our customers move their products into clinical trials faster and with greater probability for success. This goal is achieved by providing enabling technologies and products that can be incorporated into innovative multi-endpoint platforms, which facilitate more accurate predictive assays for safety and efficacy (Figure 2). Biomarkers offer a means to affect rational drug design early in the development process and accelerate translational drug development from animal to man.

Figure 3: Bridging “-Omics”



References

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technical sheet

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