

Biomarkers at Novartis

Innovation in Novartis R&D



“The pharma industry has been discussing customized therapy for more than a decade. Now the science has caught up with the promise and it is becoming a reality.” –Joanne Meyer, Global Head, Biomarker Development

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Biomarkers: The Promise of Customized Therapy

Patients diagnosed with the same disease can show marked differences in individual response to treatment: some clearly benefit while others have no positive response and yet others may experience adverse reactions. To identify the basis for these different responses, Novartis has an extensive program of biomarker discovery to pinpoint patients suitable for a given therapy; verify initial response; and monitor subsequent therapy and possible disease progression. At Novartis Institutes for BioMedical Research (NIBR), identification of biomarkers is a mandatory part of proposals for all new drug targets.

The term “biomarker” is widely used but frequently misunderstood. Biomarkers are measurable biological factors, such as gene activity, proteins, or chemical compounds that can act as indicators for how a disease or therapy is progressing. For instance, the abnormal Bcr-Abl protein can act as a biomarker for chronic myeloid leukemia (CML), a cancer of the blood and bone marrow. Increasingly sophisticated biochemical or genetic markers are under development – from amyloid deposition in the case of Alzheimer’s disease or prostate specific antigen, a risk factor for prostate cancer – and used to diagnose and track progression of a disease.

In the area of drug toxicity, major research initiatives are underway to understand the molecular mechanisms causing adverse drug reactions and, ultimately, to find biomarkers that identify people at risk. This research builds on recent advances in multiple scientific disciplines such as bioinformatics, genomics, imaging technologies and materials science.

Novartis recently established Molecular Diagnostics, a new business unit which is focused on leveraging these internal strengths

and capabilities to commercialize biomarkers for use as diagnostics in specific patient populations.

Novartis and the FDA

For decades, the pharmaceutical industry has struggled to curb high attrition rates for experimental drugs. Eight of every ten medicines that advance to full development fail to complete clinical testing required to receive regulatory approval. According to the US Food and Drug Administration (FDA), liver toxicity is the most common single adverse effect responsible for clinical failures or post-marketing withdrawal of approved drugs from the market.

As a more predictive approach to pharmaceutical discovery takes the spotlight, both the FDA and the European Medicines Agency (EMA) have been encouraging biomarker research and have been discussing regulatory processes to handle the resulting data. In 2004, the FDA launched a visionary program – the Critical Path Initiative – in an effort to improve efficiency of pharmaceutical R&D industry-wide. Biomarker research represents a key opportunity for industry and academia to partner with the FDA under this initiative.

From the industry side, Novartis has played a leading role in applying biomarker concepts to pharmaceutical R&D under this unprecedented cooperation between health authorities, industry, and academia. For example, Novartis was one of the first companies to forge a Cooperative Research and Development Agreement (CRADA) with the FDA to identify new safety biomarkers that predict drug effects on kidney function. Efforts conducted under the CRADA resulted in publication of the first pilot framework for a preclinical regulatory biomarker qualification process, an achievement likely to have a broad

“We’re looking at a paradigm shift. Identifying those subsets of patients with the same underlying cause of disease will lead to effective treatment of unmet medical need with the next generation of targeted therapeutics.” –Timothy Wright, Head of Translational Sciences at the NIBR

impact on qualification of safety biomarkers far beyond the initial partnership. Moreover, preclinical data provided evidence of the superiority of new renal biomarkers over the standards used by regulators for decades to assess renal injury in drug testing.

In addition, Novartis joined seven other pharmaceutical companies and an affiliate institute of the FDA in forming the Predictive Safety Testing Consortium (PSTC), which enables partners to share internally developed laboratory methods used to predict the safety of new treatments before they are tested in humans. Under the consortium, partners test and validate each other’s methods and results of those comparisons are submitted to the FDA.

Novartis and a second pharmaceutical company identified seven new biomarkers, tested them to prove their accuracy and usefulness and then shared their findings with other members of the PSTC.

According to FDA scientists the newly developed tests, measuring levels of these

biomarkers found in urine, may provide important advantages over the two blood tests traditionally used to evaluate kidney toxicity. The new tests are more sensitive and can detect cellular damage within hours and unlike the older tests also can pinpoint which parts of the kidney have been affected. More standardized methodologies are needed to fully realize benefits from this new molecular understanding. Through our Molecular Diagnostics business unit, we are working towards a future where we can provide important information to help physicians select the best treatment options for their patients.

Finding biomarkers for safety and efficacy enables the FDA and its industry partner to more reliably assess the benefit-risk balance of a drug through the development process and after it is launched. By playing a leading role in the biomarker field, Novartis will be able to apply these new concepts quickly and effectively to other R&D projects in its portfolio.

Glivec Case Study

As one of the first targeted anticancer treatments, Glivec took much of the guesswork out of matching medicines with patients most likely to benefit.

Prescribing has traditionally been a trial-and-error process. Even successful blockbuster medicines don’t work in a significant proportion of patients – leaving physicians without an explanation for that failure.

Glivec, by contrast, works with exquisite selectivity to inhibit a defective gene known as BCR-ABL and halt malignant cell growth characteristic of chronic myeloid leukemia (CML), one of the most common forms of leukemia. A diagnostic test enabled physicians to identify patients who carried the aberrant BCR-ABL – a biomarker – and were likely to benefit from Glivec. Another diagnostic tool – white-blood-cell counts – was used to confirm the efficacy of treatment and also sound the

alarm if patients developed resistance to Glivec, requiring a shift in treatment to a next generation Novartis drug, Tasigna.

Buoyed by the success of Glivec and other targeted medicines, the promise of customized therapy is revolutionizing drug discovery and development at Novartis.

