BY DENISE MYSHKO

DRUG DISCOVERY: From Compound to Product Candidate

Pharmaceutical companies are using state-of-the-art technologies to understand the basis of disease as a way to bring product candidates to the clinic.

FAST FACT

DISCOVERY AND PRECLINICAL TESTING TAKE ABOUT 6.5 YEARS.

Source: PhRMA

The first step in finding a drug to bring to the clinic is screening chemical compound databases against a protein target. There are several phases that comprise early development, including target identification and validation, hit finding, and lead optimization. Activities during these steps, which aim to understand the underlying mechanism or cause of disease and screen for and create small molecules and biologics to increase their ability to address a target, are increasingly being driven by cutting-edge technologies.

Human genetic, genomic, and mass spectrometric bioanalytical technologies hold the most promise to define disease states by molecular pathway in individual patient populations, says Kalpana Merchant, Ph.D., chief scientific officer of the translational science group at Eli Lilly and Company.

"Advances in DNA sequencing technologies, including massive parallel sequencing, are reducing the cost of genotyping as well as providing deeper coverage of the genome," she says. "These technologies hold the promise to unravel the molecular basis for some of the most complex multigenic diseases, such as diabetes, as well as the identification of disease-causing somatic mutations in cancer tissues."

According to a recent report from Business Insights, the advent of DNA sequencing technologies has had a vast impact on the field of drug development and has played a key role in the success of the Human Genome Project. Furthermore, advanced technological developments in microarrays, bioinformatics, and similar tools have increased the scope of applications and services.

Similarly, Dr. Merchant says the application of technologies such as sensitive mass spectrometry can be used to characterize patient-derived tissues such as plasma, muscle, liver, cartilage, and brain, which will offer insights into key molecular pathways associated with different disease states, as well as the ability to distinguish patient populations based on molecular phenotypes.

Jean-Jacques Garaud, M.D., global head, pharmaceutical research and early development, at Roche, identifies the technologies of in silico modeling and simulation as key elements in discovery and early development.

"While highly fragmented in many different departments across the value chain, there is an opportunity for huge potential gains by integrating in silico processes across the spectrum and leveraging the knowledge gained to improve discovery and early development, from target validation through Phase II," he says. "This more integrated approach will result in quality decision-making."

A 2006 report from Frost & Sullivan finds that computational biology can effectively integrate data and enable accurate comparison of the information derived from discrete data sets. In addition, predictive models based on the systems approach of computational biology tools have enhanced their value for drug discovery.

New technologies will allow for enhanced portfolio management and more effective use of limited financial resources, while yielding substantial cost and time savings. In fact, Frost & Sullivan analysts predict that the elimination of false leads at the early stage rather than at the clinical trial stage can offer savings between $200 million and $300 million.

Discovery: The Biomarker Difference

Additionally, Dr. Garaud says biomarkers

DR. JEAN-JACQUES GARAUD ■ *Roche*

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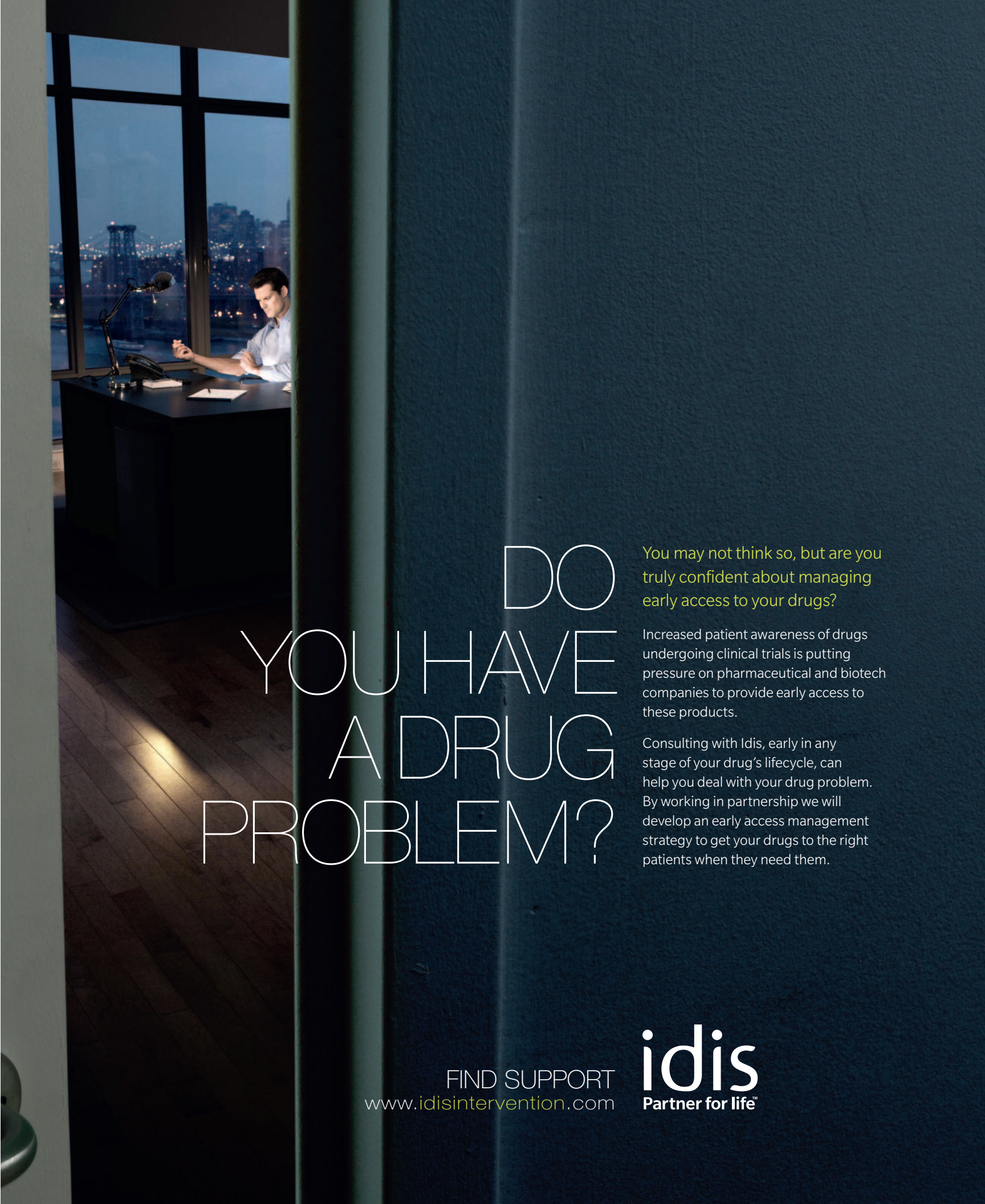

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are very important for advancing an effective personalized healthcare strategy.

"The discovery of new biomarkers will result from a greater understanding of target biology and the heterogeneity of disease," he says. "These can be extremely important in identifying subpopulations of patients who are more likely to respond to a treatment — a much more effective approach — and result in the development of highly differentiated medicines with more optimized benefit-risk ratios."

In oncology specifically, advanced biomarker technologies can produce better response rates to oncology drugs, while minimizing toxicity in patients, says Chip Gillooly, VP of capital at Quintiles.

"By increasing the efficiency of the screening process and eliminating patients who are unlikely to respond to a particular drug, researchers can greatly advance patient care, while reducing costs associated with unnecessary therapies," he says. "In addition, by refining biomarker capabilities, researchers can embark on the next step of patient treatment: understanding how to combine therapies. Through combinations — for example, chemotherapy plus a targeted therapy or two targeted therapies — researchers can truly begin treating patients via personalized medicine."

A recent report from Frost & Sullivan points out, however, that the process of biomarker discovery and assay development is costly. There is a lag between the discovery of biomarkers in the laboratory and commercialization because of major roadblocks in biomarker validation and assay development. Target validation, high-throughput compound screening, and lead discovery are processes that take place as a separate workflow, whereas biomarker discovery, assay development, and, much later, testing are a parallel workflow. Analysts say pharma companies need to find a way to converge the drug development workflow with the biomarker development workflow to facilitate cost-effective and accessible biomarker testing.

For now, cancer biomarkers and cardiovascular biomarkers have been found to have the greatest growth among the disease areas; CNS biomarkers are not far behind mainly because of the tremendous thrust in Alzheimer's biomarker research. The biomarker analysis market is set to grow exponentially for most of the next seven years.

Discovery: Challenges

Dr. Merchant says one of the challenges in the discovery phase is understanding the important role molecular pathways play in the etiology, progression, or pathophysiology of a disease. Once this challenge is tackled successfully, researchers will be able to find therapeutic targets within the molecular pathways.

"Because there is an absence of understanding and defining clinical disease states on a molecular level, we have relied on animal models, many of which have limited or questionable predictive value for human disease states," she says.

Discovery: Best Practices

Dr. Merchant says one best practice is to form consortia between the private and public sectors as well as within the private sector to collaboratively approach foundational translational studies aimed at elucidating disease biology in specific patient populations.

"The rationale is to break complex trait syndromic diseases into more homogenous, molecularly defined disease states, which is a highly resource-intensive endeavor that is best tackled by the combined intellectual and monetary resources of many groups," she says.

Another best practice is to perform clinical proof of principle studies with pharmacological probe molecules and objective disease state biomarkers to assess the relevance of a target to the disease state of interest.

"This type of clinical target assessment early on can de-risk a target and allow for prioritized resource allocation for drug discovery," Dr. Merchant says.

Alain Stricker-Krongrad, Ph.D., chief scientific officer at Charles River, says by focusing on the drug metabolism, efficacy, and toxicity aspects of the lead optimization process, relevant animal models can be used for lead generation for most major human diseases, such as mouse models to test novel oncology compounds.

"Endpoint analysis in cancer models typically involves the use of an imaging technology such as an MRI, bioluminescence, or PET scan to measure tumor growth, angiogenesis, or biochemical activity," he says. "Quantitative analysis of biomarkers is also critical. For each therapeutic indication, the combination of these technologies is used to provide a seamless transition to development, expediting the process of bringing better drugs to the clinic. Scientific and regulatory experience is essential to successfully incorporate these technologies in an integrated drug development plan, bringing added value to the more classical approach."

Dr. Stricker-Krongrad says it is essential to embrace the new, effective approaches to drug discovery and development.

"The costs of developing effective therapies are increasing, and for this reason it is critical to fully use any and all means of streamlining the process," he says. ✦

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THE PERSONALIZED MEDICINE MARKET

The U.S. market for personalized medicine is already $232 billion, and it is projected to reach $452 billion by 2015, according to a recent report by PricewaterhouseCoopers — The Science of Personalized Medicine: Translating the Promise into Practice.

Personalized medicine, which targets individualized treatment and care based on genetic variation, is creating a booming market, but it is a disruptive innovation that will create opportunities and challenges for traditional healthcare and emerging market participants.

What's ahead:

- The core diagnostic and therapeutic segment of the market — comprised primarily of pharmaceutical, medical-device, and diagnostics companies — is valued at about $24 billion and is expected to grow by 10% annually, reaching $42 billion by 2015.
- The personalized medical care portion of the market — including telemedicine, health information technology, and disease management services — is estimated at between $4 billion and $12 billion and could grow to more than $100 billion by 2015 if telemedicine takes off.

The growth of personalized medicine is one of the market forces driving the changing business model of big pharma away from the blockbuster drug model to a more collaborative model focused on outcomes and specialized therapies.

How payers approach personalized medicine will be critical, as their reimbursement schemes will influence the business models of pharma and diagnostics companies, as well as providers who depend on third-party payment. Insurance premiums today are based on actuarial statistics that apply to large, predictable populations. By contrast, personalized medicine targets small populations, which are far less stable and predictable from an actuarial standpoint.

Source: PricewaterhouseCoopers.
For more information, visit pwc.com.


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