



From lab to man

With the pharma industry's business model under heavy pressure, transforming the scientific interchange between the lab and the clinic is critical

by Michael D. Christel. April 2010

Knowledge silos between discovery and development segments, a rigid reliance on sequential drug development, and an emphasis on technology without truly understanding the molecular mechanisms of disease have contributed to soaring drug attrition rates. Compounds, while perhaps efficacious, are failing due to poor safety profiles, costing developers millions of dollars in the process.

Realizing the costly toll of drug attrition in late-stage testing, many pharmaceutical and biotechnology companies are turning to translational medicine strategies to aid so called "go/no-go" decisions in early development. The incorporation of advanced biomarkers and other predictive tools in Phase I and early Phase II studies are enabling companies to make quicker and smarter decisions on whether to pursue development of a compound or reinvest resources into more promising opportunities.

"By investing in experimental medicine, molecular profiling, and imaging, we have much greater capability to thoroughly validate the targets that we work on," says Gary Herman, M.D., VP of early stage development, Merck Research Laboratories (merck.com).

According to Dr. Herman, Merck established a focused effort in this area in 2006. Since then, he says, the company has dramatically increased the number of programs that are undergoing early critical go/no-go decisions before late-stage development.

Additionally, the more sophisticated technologies of today are helping sponsors demonstrate a drug's proof of concept earlier in the process, using data from patients and healthy volunteers.

"It's just as important to stop a useless drug as it is to find a good drug," says Professor Tim Mant, M.D., senior medical advisor, Quintiles (quintiles.com). The R&D veteran points out that in the past, the tendency was to focus more predominately on the toxicology of a compound in early development, where knowledge could be gained on its pharmacokinetics in healthy people, but the data did not necessarily translate well to the product's target population of patients.

The hope, Dr. Mant says, was that the candidate had linear pharmacokinetics and was being well-tolerated, but little was still known about its ultimate benefit, or lack thereof, in patients.

"It is difficult to translate efficacy seen in preclinical studies into humans," Dr. Mant says. "While preclinical studies remain a vital part of the drug-development process, what is really crucial is that we get evidence as early as possible that the drug works in man."

The role of biomarkers and personalized medicine in aiding such efforts is becoming even more crucial as the burden of disease grows across the globe. Personalized medicine is the practice of tailoring a medicine to a specific subset of patients based on their genetic profile. According to a report by PriceWaterhouseCooper (pwc.com), the U.S. personalized medicine market is estimated at about \$232 billion and is forecast to grow 11% annually. By 2015, the market could reach \$450 billion.

Realizing such potential, however, will depend on a healthcare system willing to expand the knowledge base of basic biological science and disease, and, aided by advances in information technology, translate those discoveries into evidence-based medicines.

According to a report by Global Business Intelligence (gbiresearch.com), the global biomarkers market generated \$6.3 billion in revenue in 2008, 44% of which was in pharmaceutical sector applications. Since the application of biomarkers in drug discovery has only been realized relatively recently, the market is expected to grow to \$22.2 billion by 2015, the report says.

Global Business Intelligence also notes that biomarkers can save companies roughly \$100 million in drug-development costs and shave three to four years off R&D timelines. Using conventional methods, the average drug-development project requires an \$800 million expenditure and a timeline of 12 to 15 years.

A human need

Conditions such as diabetes, Alzheimer's disease, and hepatitis C virus are rising in prevalence at alarming rates, only compounding existing challenges in treating cancer, bacterial infections, autoimmune diseases, and other conditions.

"There are thousands of diseases where there is no effective treatment," says Andreas Wallnoefer, Ph.D., head of the recently established Pharmaceutical Research and Early Development group at Roche (roche.com). "And in the areas we have effective treatment, the response varies between 20% to 90% depending on whether it's a cancer agent or a pain killer."

Dr. Wallnoefer believes that a great need exists for the industry to get better at translating basic science into actual application in man, not only from a pharmaceutical R&D perspective, but a humanity perspective. "The industry has to change, because the business model is under pressure," he says. "There is opportunity for change because we have a better understanding of the molecular mechanisms of disease, and we have new technologies. There is an opportunity to really focus medicine and create differentiated medicines."

Dr. Wallnoefer notes that the bottleneck in R&D productivity originating at the translational stage is occurring at the same time researchers are achieving notable strides in areas such as genomics, proteomics, metabolomics, digital pathology, molecular diagnostics, bioinformatics, and computational sciences. These tools hold the potential to reduce development timelines and costs as well as pave the way to new approaches in personalized medicine.

Progress and caution

Some big pharma companies have restructured their R&D operations to better harness their capabilities in translational research. Roche, for instance, since buying out longtime partner Genentech Inc. (gene.com) more than a year ago, has integrated the research and early development arms of both companies, creating two distinct units – Pharmaceutical Research and Early Development and Genentech Research & Early Development. These groups work closely with Roche’s previously established Clinical Research and Exploratory Development division, known as CRED. Last month Roche opened a translational research hub in Singapore where the company will work with 16 institutes on expanding knowledge of disease biology to develop new personalized treatment approaches.

The goal of these approaches, executives say, is to first understand the disease heterogeneity and molecular mechanisms in active therapeutic areas of focus. Researchers then identify and develop relevant biomarkers for a targeted therapy, stratify patient populations that are most likely to benefit from the drug, and demonstrate improved benefit/risk ratio in larger clinical trials. Roche is considered a top pharmaceutical player in the personalized healthcare space. The company possesses an internal diagnostics division and is the marketer of the popular breast cancer drug Herceptin, which targets patients who overexpress the HER2 gene mutation. According to Dr. Wallnoefer, all 58 molecules in Roche’s pipeline are being developed with a biomarker or companion diagnostic strategy.

In oncology, multiple biomarkers are often examined to gain an understanding of the pathways that are being activated or blocked in the cancer cell.

Dr. Wallnoefer cites the example of the regulatory pathway p53, which he calls the “Holy Grail” of cancer activation. p53 is a major suppressor gene protein that induces programmed cell death in tumors. The activity of p53, however, is naturally inhibited by another protein, murine double minute 2, or MDM2, which when overexpressed can bind to p53, contributing to the growth and survival of cancer cells.

Aided by biomarkers that can predict the efficacy of p53 gene therapy from patient to patient, Roche and others are developing molecules designed to specifically block the interaction between p53 and MDM2 proteins in various cancers.

Other big pharma companies are increasingly recognizing the value of partnering with diagnostic companies. Pfizer Inc. (pfizer.com) recently entered an agreement with DxS (dxsdiagnostics.com), a unit of Qiagen (qiagen.com), to develop a companion diagnostic test kit for PF-04948568, an immunotherapy vaccine in development for the treatment of glioblastoma multiforme.

Several collaborations between industry, academic institutions, and government agencies around translational medicine have been established recently as well. Last month, The Biomarkers Consortium (biomarkersconsortium.org), a public-private partnership that includes the National Institutes of Health, FDA, and major pharmaceutical companies, launched the I-SPY 2 breast cancer trial, which will use biomarkers from patient tumors to test five experimental cancer drugs simultaneously. The five-year, \$26 million study will match patients to current Pfizer candidates figitumumab and neratinib, Abbott

Laboratories' (abbott.com) drug veliparib, and Amgen Inc.'s (amgen.com) conatumumab and AMG 386. The trial could cut several years off drug approval timelines, experts say, by using DNA to tailor therapy more quickly and toss out approaches that do not work or are too toxic.

Earlier this year, NIH and FDA established a partnership bridging the disciplines of translational science with regulatory science to help speed up decision making in the drug review process. The partnership will focus on equipping FDA regulators with the latest science and tools needed in order to assess drugs and other products coming from fields such as genomics, nanotechnology, and stem cell therapy.

In addition, the NIH's National Center for Research Resources gathered together more than 400 government researchers and officials and senior industry executives to explore potential projects with academic clinicians funded by the Clinical and Translational Science Awards, a national consortium launched in 2006 that creates academic homes for clinical and translational science at research institutions across the United States (see page 16 for more).

Collaborations between the NIH and smaller, specialty drug developers on novel mechanisms have advanced lately as well. Massachusetts-based Seaside Therapeutics LLC, supported by translational research grants from the NIH and others, recently launched a Phase I trial for a potentially disease-modifying treatment for fragile X syndrome, the most common known cause of autism, for which there are no approved therapies.

Seaside hopes its drug, known as STX107, which was able to knock out the fragile X gene in mouse models, will have application in a broad range of developmental brain disorders.

"Personalized medicine is going to be important in autism, much like it is in oncology right now," says Randy Carpenter, M.D., co-founder, president, and CEO, Seaside (seasidetherapeutics.com). "Because when someone doesn't respond to your treatment, you now have the ability to sequence a thousand other genes and look at a number of other circuit functions non-invasively in the brain and try to understand why that person is not a responder. It may lead you to new therapeutics."

Several global CROs have made significant investments in translational medicine collaboration abroad. Icon is slated to open a new translational hub in Manchester, United Kingdom, in the second quarter of this year, and Quintiles recently opened an expanded Phase I research unit at Guy's Hospital in London as part an alliance with Guy's and King's College London. Quintiles, a company originally born out of academia, employs about 150 people at the site, providing small molecule and biologic translational medicine solutions.

According to Dr. Mant, who is the principal investigator at the Quintiles site, a significant push is under way in the United Kingdom to bolster translational research in an effort to speed the development of safe and effective treatments into the market.

"Drug discovery from laboratory into man is slow and expensive at the moment," Dr. Mant says. "We all recognize that science has moved ahead quicker than medicines in many ways; the clinical medicine

needs to catch up with scientific advances, medical academics need to catch up. Academia has to work with the pharmaceutical industry to develop new drugs. We're getting cleverer – the industry and academia – at targeting disease. We have learned more about the pathology of the disease, what the problem is, and how we can fix it. My job is to put these new agents into man safely for the first time and try to get as much information as I can.”

Life sciences companies active in discovery research have a similar responsibility in translating science from the in vivo to the preclinical in vitro stage. With increased demand for genetic and biochemical information, companies are focused on developing high-throughput technologies such as next-generation DNA sequencing; multiplex assays; microarray-based and chip-based genotyping and proteomic profiling tools; and metabolic tools that better assess the safety and efficacy of drugs.

“In the past, what might take you three or four weeks to get an answer, it now takes minutes,” says Kevin Hrusovsky, president and CEO, Caliper Life Sciences (caliper.com), a technology provider that specializes in microfluidics, lab automation and liquid handling, and optical imaging solutions.

Caliper recently launched LabChip GX, a microfluidics platform that, according to Mr. Hrusovsky, allows companies to conduct precise high-throughput tests on DNA and RNA samples 70 times faster than conventional methods. “You can now get a lot more information in a more broad-based way to see if you can learn something that you would never have been able to learn in the past because you couldn't explore that level of landscape,” Mr. Hrusovsky says.

He notes that challenges still remain for companies in pursuing high-throughput screening tools, which in the past have failed to identify potential safety issues associated with a drug.

“Historically, people were willing to compromise translation for throughput and efficiency, and that certainly hurt them relative to wasting a lot of money on a lot of compounds that ended up not having safety,” Mr. Hrusovsky says. “Because once you get into the animals, you start learning about all the side effects. Everyone has done really well with efficacy, but it's the side effects that the bigger biology systems teach you. Being able to create a much better translation in a high throughput has enabled a lot of new strategies.”

Despite advances in drug screening and characterization and increased collaborations centered on translational research, marked benefits for patients and their prescribing physicians are a long way from being realized. Many contend government and industry need to work much more deeply on drug development. Also, while new biomarkers are being identified in droves for a wide range of diseases, true successes in personalized medicine have been few to date, leaving its promise unfulfilled.

“Companies are starting to understand the needs of implementing biomarkers,” says Claudio Carini, M.D., who recently joined the Halloran Consulting Group (hallorancg.com) as a senior consultant leading the company's biomarker and translational medicine efforts. “What's happened very often is that there is a misconception. Either there are people who feel that biomarkers will solve the problems of the world or people who feel that biomarker evaluations are an extra expense, adds an extra layer of complication within clinical development, and they say, ‘Why [use them]?’”

Dr. Carini says such thinking may be shortsighted. He notes drugs such as Herceptin and Novartis' (novartis.com) blockbuster Gleevec, which specifically targets the abnormal protein BCR-ABL known to trigger the onset of Philadelphia chromosome-positive chronic myeloid leukemia, are evidence of the potential of targeting therapies in dividing responder populations from non-responders. Nevertheless, with most new projects still in their infancy, the jury remains out on the future influence of personalized medicine in mainstream drug development.

"We cannot come back in the next 10 years with the same two examples," says Jacky Vonderscher, Ph.D., head, translational research sciences, Roche, who worked on Herceptin and Gleevec, the latter during a previous stint at Novartis. "Only the very fantastic things that are coming will be visible, but that's something everybody can find. The real winner will be the people integrating the knowledge."

Bedside to bench

Most R&D executives agree that efforts in translational medicine would benefit from less dependence on the sequential process of developing drugs, one in which preclinical and clinical units often operate in silos. Leads are optimized, the usual assessments made and channels checked, but, according to some experts, after a product is handed off, valuable information is rarely shared between the preclinical scientists and the clinical physicians, and vice versa.

Translational medicine, practiced properly, attempts to foster closer interactivity between R&D segments, promoting the advantages of exchanging scientific and discovery information with clinicians, who, in turn, can feed back findings on adverse events and other outcomes to aid future discovery. "Instead of talking about from 'bench to bedside,' we're calling it from 'bedside to bench,'" Dr. Vonderscher says. "We should learn much more from our clinical experience."

Once an animal model for a drug is correlated with a human model, translational medicine strategies focus on the free flow of information between the clinical and preclinical settings. The goal is to design tighter, less time-consuming clinical trials, while also helping researchers enhance exploratory development because they have clinical data to validate their experiments.

"Academia and industry, as well as hospitals, should communicate much more, so in the ideal world there will be continuous exchange of information," Dr. Carini says. "This not only will abbreviate the [development] time, because better choices can be made regarding target populations and trial design, but most of all it will reduce cost by early targeting of drug candidates to patients they are most likely to help."

Dr. Carini notes such dynamics are particularly important for small and mid-sized biotechnology companies, who, despite recent improvements in venture capital funding, are still under pressure to save money while also accelerating potentially novel medicines through the pipeline.

For an industry ingrained in its ways, however, redrawing the blueprint for preclinical and clinical collaboration will not be an easy feat.

“Even if you merge them, it’s not happening over night,” Dr. Vonderscher says. “You have on one side molecular biologists, who are simply thinking in cellular, and then you have on the other side clinicians or medics, who are much more physiologically oriented. To link the dots is not a given. You need a good mix of people who are coming from both sides and who are a little bit out-of-the-box thinkers, thinking more in terms of efficiency of the process, in terms of theoretical approach.”

Finding individuals that fit such a mold will be a challenging task. Many in the highly specialized R&D community are not equipped with a firm understanding of translational medicine, creating a need in the field for more academic-oriented and scientific-oriented doctors.

“We want to produce physicians who are curious, who ask, ‘Why?’” Dr. Mant says. “People who keep questioning, ‘Is this the right thing to do?’ Just because we have treated patients with a certain condition in a certain way for many years does not mean that it continues to be right. As disease understanding grows, as new diagnostic approaches are introduced, and as new medicines become available, we need physicians that will challenge the status quo to ensure medicine capitalizes on scientific advances.”

Marked for growth

According to a new report by BioCrossroads (biocrossroads.com), contract research organizations will become increasingly important in the development of biomarkers. According to the BioCrossroads report, CROs will enhance their position as research partners and play a key role in developing biomarkers that can be used as companion diagnostics to their clients’ drugs.

The report points to recent efforts by CROs such as Covance (covance.com) to bolster biomarker capabilities via internal and external means. Last year, Covance established a Biomarker Center of Excellence in Greenfield, Ind., as part of the company’s 10-year, \$1.6-billion drug development agreement with Eli Lilly and Co. (lilly.com), initially signed in August 2008. The center focuses on biomarker testing and validation and uses the services that already reside at the Greenfield site, including in vivo preclinical safety and efficacy assessment, and preclinical imaging modalities.

Covance, Icon Plc., and Quintiles are among the CROs making the largest investments in biomarkers, noting that demand for these tools is growing not only in oncology but also for poorly understood genetic disorders in neuroscience, cardiovascular disease, and other areas.

“Even today, we don’t have a good handle on whether drugs designed to bind to certain receptors in the brain actually get there in man, so the demand for imaging biomarkers such as [positron emission tomography] occupancy studies continues to rise,” says Cyril Clarke, VP, translational medicine, Icon Development Solutions, a unit of Icon (iconplc.com). “We have also seen an increase in the demand for integrated cardiovascular safety studies in which electrophysiology, cardiac contractility, and markers of platelet and vessel wall activation are related to exposures in early phase studies.”

Icon has its own imaging unit, Icon Medical Imaging, which provides biomarkers that enable the visualization of pharmacodynamic effects of drugs and responses to treatments. Technologies used include molecular probes such as fluorodeoxyglucose-PET, dynamic contrast-enhanced magnetic resonance imaging, and the use of tumor volumes for cancer trials.

Increasing the integration of molecular imaging from the lab to the clinic has the potential to streamline the drug-development process by allowing for new opportunities in treatment management of targeted therapies, including patient selection, dose optimization, and optimal drug regimen. Dr. Mant, whose Phase I unit in London has access to hospital imaging tools, points to the field's advancement in aiding cognitive disease trials.

“With PET scanning, you can look at receptor occupancy if you have the appropriate ligand,” Dr. Mant says. “Whereas in the past, it was almost like a blunderbuss technique – ‘We’ll try all these different doses and see what seems to be effective.’ With functional MRI – even more convenient – the possibilities are extraordinary in looking at how drugs affect the brain and your response to different therapy.”

Functional magnetic resonance imaging is a type of scan that measures the hemodynamic response related to neural activity in the brain or spinal cord of humans or other animals.

For the biomarkers market to demonstrate full value, it will need to produce more surrogate markers. These are measures that correlate statistically to clinical outcomes and can be used as surrogates in endpoint studies. Approved surrogates include blood pressure for hypertension, LDL cholesterol for atherosclerosis, prostate-specific antigen for prostate cancer, hemoglobin A1c for diabetic complications and diabetes, and viral ribonucleic acid for HIV.

Achieving new validated biomarkers in the vein of HER2, the genetic marker for breast cancer that spawned 1998's approval of Herceptin, has proved challenging. Advancing such measurements for surrogate candidacy often requires long and exhaustive clinical work, as well as stringent regulatory review. Agencies such as FDA, however, have encouraged increased exploration of validated biomarkers through such programs as the Critical Path Initiative.

“They realize this has been a challenging field and they've been very supportive,” Dr. Carpenter says.