Denise Myshko

Genomic **INNOVATION**

While much progress has been made in the area of genomics, developing drugs based on this information is still an emerging field.

Our understanding of disease and biology is growing every day, giving researchers even more power to develop new and better medicines. The area of genetics is taking off, industry experts say. The ability to sequence individual genomes and the genomes of diseases is providing new avenues of research and new ways to target patients.

This will impact pharma companies in a number of ways. The first is the ability to accurately determine the cause of disease and genes that might be involved, and this can help companies find targets to develop drugs against. The second is around selective biomarkers to provide information about which patients are likely to benefit. These data can then be used for selection in clinical studies.

By the end of 2011, there were 1,068 published genome-wide association studies, according to PwC. And about 100 products on the market now have genomic information available on their label, according to the FDA.

Giving the right drug to the right patients will be the key to success in the future, says Yoshi Oda, president of biomarkers and personalized medicine, at Eisai.

"Once we understand the role of genes in disease, we can find better targets," he says. "In the future, companies will have to provide both drug and diagnostics. If we can provide the right medicine, patients will have confidence to take their medications."

While some companies are investing in genomics in a big way — such as Amgen's December 2012 acquisition deCODE Genetics for $415 million in cash — genomics still plays a relatively small role in the lab.

Analysts from PwC estimate the industry spends just $6 billion a year — less than 7% of its total R&D investment in 2011 on genomic research. PwC researchers predict that by 2020, pharma could be investing as much as 20% of its R&D budget in genetics and genomics for discovering and commercializing new drugs.

Industry experts say every company will have to invest more heavily in genetics and genomics, and revise its R&D processes to improve its scientific productivity.

Genomics gives researchers better insight into disease, says Markus Warmuth, M.D., CEO of H3 Biomedicine.

"When I started my scientific career, we had very little information around mutations in the cancer genome," he says. "Very few oncogenes were known at that time. Now, next-generation sequencing platforms can turn around tens and hundreds of tumor samples. This is allowing researchers in the industry to get a better understanding of disease and tackle more meaningful targets, especially in oncology. We can clearly see this in the NIH's Cancer Gene Atlas. This is allowing a move beyond developing a cytotoxic drug that is going to be used for everyone with a particular cancer type to precision medicine that addresses the mutation that occurs in a subset of a particular cancer type."

The National Institutes of Health (NIH) established The Cancer Genome Atlas (TCGA) in 2009 to generate comprehensive, multi-dimensional maps of the key genomic changes in major types and subtypes of cancer. This catalogue serves as a resource for a new generation of research aimed at developing better strategies for diagnosing, treating, and preventing each type of cancer.

Industry experts say genomics is likely to have a great impact on the development of oncology therapeutics.

"Problems with DNA, or the ability to repair DNA, underlie the majority of cancers," says Stephen Gately, Ph.D., president of Translational Drug Development (T2), a TGen Company. "We now better understand the genetic basis of diseases. The area that is expected to receive the greatest benefit early on will be rare diseases, especially those with single genomic events that drive the disease process. For these patients, we may be able to design drugs to target those specific mutations."

DR. STEPHEN GATELY ▪
Translation Drug Development

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Genomics and Pharma

For a variety of reasons, the industry is investing more and more in technologies that enable the discovery and development of novel protein therapeutics, says Bill Newell, CEO of Sutro.

"We think this trend will continue, and that technologies focused on protein engineering will be particularly important to developing innovative new medicines," he says.

Genomics will allow pharmaceutical and biotechnology companies to design medicines specifically for unique genetic backgrounds, and identify genetic changes that sensitize patients' tumors to specific drugs, Dr. Gately says.

"This will create an enormous cost savings for the entire healthcare system by allowing us to very deeply refine new agents and determine who may benefit," he says.

Genetics and genomics have already and will continue to transform R&D, says Mara Aspinall, president of Ventana Medical Systems Inc.

"Genomics will help focus the discovery of new candidate medicines and their development in patient populations whose disease is being driven by the underlying gene or pathway abnormalities," she says. "It will help guide the selection of new drug candidates based on the rational molecular mechanisms of action. Most importantly, the study of genomics has created a new scientific discipline, and ultimately a clinical discipline, both of which rely critically on diagnostics."

Ms. Aspinall says diagnostic technology innovation will play an increasingly important role in the future.

"Most critical will be technologies that allow healthcare professionals to better molecularly interrogate patient disease, ranging from in vivo techniques to advanced screening methods to comprehensive methods for characterizing specific genetic drivers of disease," she says. "Specifically, we will develop techniques to 'multi-plex' or analyze a biopsy for several different biomarkers simultaneously."

Ms. Aspinall says personalized medicine, the development of drugs in specific and targeted populations based on a known biomarker, will accelerate drug development by reducing the number of patients needed to prove clinical efficacy in clinical trials.

"This reduces the time, expense, and risk associated with drug development," she says. "In turn, this new generation of drugs will have higher clinical efficacy, faster development time, and higher return on investment."

The ability to select the patients most appropriate for the investigational therapy improves the likelihood of success and may substantially reduce development cost, says Mike Sherman, chief financial officer of Endocyte. With therapies more targeted to the right patients, therapeutic benefit is likely to be more substantial, which also improves the likelihood of regulatory approval and reimbursement.

"Even earlier in the development process, companion diagnostics can play a role in determining the potential viability of a therapy before substantial development of a therapeutic," he says.

Mr. Sherman says companion diagnostics will play a central role in the future of medicine.

"The most obvious benefits of companion diagnostics are related to patient selection," he says. "Understanding the specific nature of a patient's disease at the time therapeutic alternatives are being considered gives healthcare providers the greatest opportunity to personalize therapy. Patients will receive the therapies that are most likely to provide them benefit and patients who are not likely to benefit will be spared the lost time and potential side effects of a suboptimal therapy for their disease. This can also yield substantial cost savings to the healthcare system."

There is a potential for high returns in areas of unmet medical needs, says Nick Davies, Ph.D., U.S. pharmaceutical and life sciences advisory services, PwC.

BILL NEWELL ▪ *Sutro*

"For a variety of reasons the industry is investing more and more in technologies that enable the discovery and development of novel protein therapeutics."

"Increasingly as the technology advances we are starting to see, even in pharma with conventional modalities, an increase in interest in rare diseases," he says. "In fact, there are about 450 medicines against rare diseases in pharma's pipeline."

New Technologies, New Therapies

By using existing knowledge of molecular and cellular biology, researchers will continue to develop more sophisticated therapies with the goal of lengthening and improving the quality of life of patients, especially those with chronic diseases, says Ingmar Hoerr, Ph.D., co-founder and CEO of CureVac.

For example, he says messenger (m) RNAs vaccines could have a significant impact in the fight against cancer and pathogens.

"The safety of mRNA-based treatments supports the potential success of using mRNA vaccination for therapeutic or prophylactic approaches as well the possibility to combine mRNA with many existing therapy approaches," Dr. Hoerr says. "The immune-stimulatory potential of RNA was first observed in 1960s, and we have shown that the intradermal application of 'naked' RNA leads to induction of specific cytotoxic T lymphocytes and antibodies. Improved mRNA-based vaccines have already demonstrated their potential as cancer vaccines in clinical trials, inducing a balanced humoral, as well as T cell-mediated, HLA-independent immune response while having a favorable safety profile. As several antigens can be administered in combination, mRNA offers an effective, flexible and safe vaccination approach. It is also currently under investigation for the development of prophylactic vaccines for infectious diseases."

Another promising technology will allow for the rapid and systematic interrogation of protein structure activity relationships. This has and will continue to become more important as certain classes of biologics become more critical to treating disease, Mr. Newell says.

"For example, interest in developing ADCs and bispecific antibodies has grown substantially due to recent clinical and commercial successes for these therapeutics," he says. "We believe cell-free protein synthesis technology will play an important role in the creation of therapeutics of these types. In addition, this technology holds promise for producing a wide variety of additional biologics, including vaccines."

Mr. Newell says cell-free protein synthesis technology will translate into new therapies by allowing for the rapid design and development of best-in-class biologics, whether ADCs, bispecific antibodies or other classes of protein therapeutics.

"This technology enables candidates with optimized properties to be selected, resulting in the advancement to clinical trials of a candidate with an optimized safety and efficacy profile, which potentially translates to less clinical risk and more drug approvals," he says.

Challenges in Genomics

Dr. Gately says the quickly evolving nature of technology innovation creates a challenge in the application of genomics for patients.

"The major challenge will be the rate at which innovation is occurring in this space, and companies may be reluctant to select one particular technological approach," Dr. Gately says. "There is a little bit of inertia right now. The field is moving quickly, and there are many vendors currently. Once the technology improvements reach a plateau and federal regulators adopt standards for the application of genomic information, we'll likely see more broad application of genomic interrogation in drug development."

One of the main obstacles to the growth of personalized medicine has been cost of genetic sequencing technology, says David Fishman, president of Snowfish.

"Until very recently the devices used for genome sequencing cost $500,000 to $750,000," he says. "Additionally, the individual tests ran $5,000 to $10,000 and took days to produce results. Things are changing though. Just this past year, one company introduced a gene sequencer that is designed to map the entire human genome in a day for $1,000 and the machine costs $149,000 making it significantly more affordable. Clearly, the barriers to purchase are breaking down. It is not hard to imagine that the cost of a complete genomic test will be a few hundred dollars within a few years."

MARA ASPINALL ▪ *Ventana Medical Systems*

"Skills sets in medicine, molecular biology, chemistry, and bioinformatics are all critical to translating genomic discoveries into clinical diagnostic solutions."

The age of personalized medicine is upon us and it will completely revolutionize how treatment is determined. Today, clinicians choose therapies based on research done on thousands of people that have a diverse genetic profile and have only a limited ability to adjust therapy based on individual differences. In the case of cancer, treatment is currently based upon the tumor location.

Another challenge, says Dr. Warmuth, is managing data.

"This is why it is important for pharma to consider working with the IT industry and nonconventional partners," he says. "Cloud computing is something that every company in the space is already looking to. It can be very scary, especially for big pharma companies because they've been very conservative around protecting their data. But with many of the bioinformatics that we're running today, it's not always economical to have the computing power needed within internal systems." PV

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