THE DISCOVERY PROCESS

Human embryonic stem cells (hESC), proteomics, molecular profiling, and other cutting-edge technologies are generating excitement in the lab as scientists continue to balance scientific breakthroughs with ethical and safety development issues.

Before a drug even makes it into the clinic, much less to the market, teams of engineers, biologists, chemists, and physicists must spend long hours figuring out how to mass produce the results achieved by an individual scientist at his or her lab bench, according to the Pharmaceutical Research and Manufacturers of America (PhRMA).

There are a number of cutting-edge technologies that have emerged over the past several years that are allowing scientists to replicate experiments on a large scale to determine potential compounds for development. But even though these innovative tools are increasing the efficiency of drug discovery, companies continue to face a number of scientific challenges, as well as regulatory hurdles.

DISCOVERY AND TECHNOLOGY

One of the biggest opportunities for therapeutics and drug discovery can be realized through human embryonic stem cells (hESCs), according to William M. Caldwell IV, CEO of Advanced Cell Technology.

"HESCs offer the potential to grow virtually every cell found in the human body that could be used to replace diseased or ailing cells on future patients," Mr. Caldwell says. "Challenges, such as immune rejection and potential tumorgenecity, however, have to be addressed for hESCs to fulfill their promise therapeutically. In preclinical drug discovery, hESCs can be used to create lines of different cell types found in the human body that can then be used to test small-molecule compounds. In this way, drugs can be tested on human cells *in vitro* before ever being put into a patient."

Michael Hunt, CEO of ReNeuron Group Plc., believes firmly in the potential of stem cells for discovery, adding that the pharmaceutical and biotech industries are watching closely and are no doubt considering stem-cell therapies as a potential way to fill the gaps that currently exist in their pipelines.

"Companies will, in most cases, want to see good clinical data before investing," he notes. "There are more and more clinical stem-cell studies being conducted, and large pharma is becoming more attuned to the stem-cell field."

> In preclinical drug discovery, hESCs can be used to create lines of different cell types found in the human body that can then be used to test small-molecule compounds.This represents an interesting step forward in the way drugs are discovered and tested preclinically.
>
> William Caldwell IV
> Advanced Cell Technology

In a report issued earlier this year, analysts at Frost & Sullivan conclude that, despite lingering ethical, legal, and social concerns, a positive shift in government attitudes and encouraging public and private funding environments across several major healthcare markets worldwide offer support for stem cell-based research.

"While the United States is not the most friendly country to conduct stem-cell research in primarily because of the current administration's policies, in terms of stem-cell development and commercialization progress, how-

Thought Leaders

WILLIAM M. CALDWELL IV. CEO, Advanced Cell Technology Inc., Alameda, Calif.; Advanced Cell Technology is a biotechnology company applying human embryonic stem-cell technology in the emerging field of regenerative medicine. For more information, visit advancedcell.com.

KENNETH C. CARTER, PH.D. CEO and President, Avalon Pharmaceuticals Inc., Germantown, Md.; Avalon Pharmaceuticals is a biopharmaceutical company focused on the discovery and development of small-molecule therapeutics. For more information, visit avalonrx.com.

MICHAEL HUNT. CEO, ReNeuron Group Plc., Guildford, Surrey, United Kingdom; ReNeuron is a leading player in the stem-cell field, using human somatic stem cells to develop leading-edge therapies for neurodegenerative and other diseases. For more information, visit reneuron.com.

SUMITHA KANNAN. Research Analyst, Frost & Sullivan, San Antonio; Frost & Sullivan is a global growth consulting company. For more information, visit frost.com.

MICHAEL G. KAUFFMAN, M.D., PH.D. CEO, Epix Pharmaceuticals Inc., Lexington, Mass.; Epix Pharmaceuticals is a biopharmaceutical company focused on discovering, developing, and commercializing novel pharmaceutical products through the use of proprietary technology to better diagnose, treat, and

An exciting use of molecular profiling that has the potential to revolutionize drug screening is its use in the identification of drug candidates, rather than compound interactions with a specific target *in vitro*.

Dr. Kenneth Carter, Avalon Pharmaceuticals

We believe that the problem facing the industry is coming up with better medicinal chemical compounds — drug candidates — and moving them into and through human clinical trials expeditiously. Getting from a drug target to a good clinical candidate more effectively is where we believe the industry should focus.

Dr. Michael Kauffman, Epix Pharmaceuticals

ever, the United States is probably at the forefront, with California being home to many emerging companies in the field," Mr. Hunt says. "Despite challenges, the United States appears to be leading the race to commercialize new stem-cell therapies, a fact not lost on organizations based outside of the country."

According to Mr. Caldwell, there is perhaps no other scientific field as hampered by regulation as hESCs is today.

"State initiatives, such as California's Prop 71, are going to become very important to this field over the next five years," he says.

Analysts hypothesize that stem cells represent a promising solution for addressing several unmet medical needs, particularly neurodegenerative diseases, cancer, and cardiovascular conditions. Other potential patient target groups include diabetics, those requiring treatments for spinal repair, and those with genetic diseases. Organ transplants are another prospective application, with efforts focused on tissue engineering for use in bone implants and cartilage regeneration. Moreover, with researchers having begun to obtain insights into stem-cell differentiation mechanisms, there will likely be even greater understanding of the treatment potential of stem cells.

Nevertheless, analysts say even with significant scientific progress, stem cell-based therapies remain in the preclinical stage for a variety of reasons. Pharmaceutical companies are adopting a cautious approach toward realizing the commercial potential of stem cell-based discoveries.

"Competitively, the field of stem-cell research and commercialization of therapies is wide open," Mr. Hunt says. "Currently, there are not a large number of stem-cell companies, and many of these companies are very small. The overall field is extremely promising and has great potential. There are plenty of opportunities for companies to make a mark clinically or commercially with stem cells."

For pharmaceutical companies, stem cells contribute to drug discovery through their application in finding novel drug targets and through the development of new technology platforms. Therefore, pharmaceutical compa-

ABOUT STEM-CELL THERAPY

Stem cells are nonspecialized cells with a remarkable potential for both self-renewal and differentiation into cell types with a specialized function, such as muscle, blood, or brain cells. Stem cells can be harvested from fetal or embryonic tissue or from adult tissue reservoirs such as bone marrow. Use of embryonic stem cells is at the center of significant ethical and moral debate. In contrast, use of adult stem cells does not provoke the same moral or political controversy. Stem-cell therapy aims to "cure" disease by replacing the diseased cells with healthy cells derived from stem cells. This approach has the potential to revolutionize medicine and, if successful, the implied commercial opportunities are great. Currently, scientists are exploring both embryonic stem cells (ESC) and adult stem cells (ASC) as the potential basis for multiple cell therapy products.

Source: BrainStorm Cell Therapeutics Inc., New York. For more information, visit brainstorm-cell.com.

manage patients. For more information, visit epixmed.com.

PETER A. KIENER, D.PHIL. Senior VP, Research, MedImmune, Gaithersburg, Md.; MedImmune is dedicated to advancing science and medicine to help people live better lives and is focused on the areas of infectious diseases, cancer, and inflammatory diseases. For more information, visit medimmune.com.

JAMES KLING. Author, CHA Advances Reports, Waltham, Mass.; CHA Advances Reports partners with industry experts to offer reports that evaluate the salient issues in pharmaceutical technology, business, and therapy markets. For more information, visit advancesreports.com.

G. JOHN MOHR. Chief Business Officer, Topigen Pharmaceuticals Inc., Montreal; Topigen is a biopharmaceutical company focused on developing new classes of inhaled drugs for respiratory disorders. For more information, visit topigen.com.

ROBERT J. MULROY. CEO and President, Merrimack Pharmaceuticals Inc., Cambridge, Mass.; Merrimack Pharmaceuticals is an integrated biopharmaceutical company committed to the innovation of life-enhancing medicines for the treatment of autoimmune diseases and cancer. For more information, visit merrimackpharma.com.

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Michael Hunt
ReNeuron Group

nies will increasingly explore the different methods in which stem cells can be used to accelerate the discovery of novel drug molecules.

"There are still disparate views regarding how long it will take for us to see real results from stem-cell therapies," Mr. Hunt says. "Today, there are a number of clinical-stage studies being conducted, and these therapies may not be as far off as people believe. The overall perception of the field as being very early stage or highly experimental is masking the good progress being made by many companies, including ReNeuron. Overall, the stem-cell field is grossly misunderstood and frequently characterized by hype and misunderstanding from the media and others. This is unfortunate for both the scientific and business communities working in the field."

There are a number of other technologies that are pushing discovery forward, such as bioinformatics, which will increasingly become a necessity for a wide spectrum of life sciences, pharmaceutical, and biotechnology companies, according to Frost & Sullivan experts. From being solely a science of comparison and analysis of gene and protein sequences to a more advanced tool that eliminates the need to perform long and sometimes potentially hazardous experimentation, bioinformatics has significantly expanded its application scope.

Other advances that are beginning to have a major impact on drug discovery include molecular profiling, the use of genomics and other "omics"-related technologies, according to Kenneth C. Carter, Ph.D., president and CEO of Avalon Pharmaceuticals Inc.

"There are a few companies now pursuing the use of molecular profiling for pharmacogenomic and toxicology studies," he says. "But over the next few years, this trend will become a universal practice. Also, the use of molecular profiling using a signature of genomic or proteomic response as a foundation for high-throughput screening will gain wider acceptance and open up a whole new avenue for drug discovery."

At Merrimack Pharmaceuticals, cutting-edge research is focusing on systems biology.

"Systems biology has the potential to change the entire scope of drug discovery and preclinical research by incorporating truly dynamic molecular data into targeting, validation, and patient stratification," says Robert Mulroy, president and CEO of Merrimack. "Our Network Biology approach has enabled a host of novel discoveries underlying complex biology that we are translating into integrated medicines, combining a best-in-class therapy with precise patient selection. Our Network Biology platform couples a proprietary, quantitative, proteomic profiling capability with computational modeling to gain a better understanding of the complexity of disease."

For Michael G. Kauffman, M.D., Ph.D., CEO of Epix Pharmaceuticals Inc., the ability to develop transgenic human systems, essen-

FUTURE DIRECTIONS OF PROTEOMICS

Proteomics is a rapidly evolving field that is rife with commercial opportunities as the technology achieves ever-higher throughput at lower cost and greater sensitivity. A new CHA Advances report, Proteomics: Current State and Future Directions, finds that 69% of respondents are using proteomics to discover novel biomarkers. Given the increased use of the technology, antibody/protein arrays and solution arrays will begin to gain ground as detection platforms over the next three years.

CHA surveyed 81 people involved with proteomics at biopharmaceutical and diagnostic firms, vendors of equipment and services, and academic research departments to shed light on current practices and future directions in the use of proteomics in pharmaceutical research and development.

"Proteomics is poised to become one of the leading technologies to usher in personalized medicine, which will feature diagnostic tests that precisely diagnose disease and use the patient's genetic profile to tailor a specific medication," says James Kling, author of the study. "The study of protein dynamics and protein interactions in normal and diseased tissues will drive the discovery of biomarkers that will form the basis of such tests."

But he says the field has not yet matured.

"Researchers continue to come up with new methods for protein separation and identification and there are few reliable methods for analyzing post-translational modifications, which can alter protein function," he says.

He notes that it is also critical to improve the reproducibility of proteomics studies and to standardize methods of sample preparation and protein fractionation. For example, blood samples are widely used for diagnostic purposes, but different proteins may vary in concentration by as much as a factor of 1 billion.

"Current techniques cannot study this entire dynamic range, so researchers must fractionate blood samples to simplify them," Mr. Kling says. "A common approach is to remove albumin, which is the single most abundant protein in blood. But it is also a carrier protein that moves fatty acids, hormones, and other physiologically important molecules, which may be the sought after biomarkers. This is the type of uncertainty that researchers face as they attempt to transform proteomics into a mature technology."

Source: CHA Advances Reports, Waltham, Mass. For more information, visit advancesreports.com.

They remind us of most online marketing programs. Cool to look at but they never fly.

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COMPASS

healthcare communications

Maximizing both safety and efficacy in a drug is another key challenge in drug discovery. A drug needs to be as potent as possible without reaching unacceptable toxicity levels, and striking that balance as early as possible in clinical development is important, both in terms of patient safety and continued development of the drug.

Dr. Peter Kiener, MedImmune

tially putting human genes into animals to conduct preclinical testing, will have the greatest impact on discovery and preclinical testing.

"This model is used in limited preclinical testing and could provide improved insights into how human biology responds to drug candidates very early in the development process," Dr. Kauffman says.

DISCOVERY CHALLENGES

According to Mr. Mulroy, the biggest challenge for drug discovery is improving the "hit rate" of potential products in specific patient populations.

"To counter this challenge, the industry needs to focus on better target selection early on so drugs advance into the clinic with a higher probability of success," he says.

Finding the right patient population is another challenge for drug discovery, according to Peter Kiener, D.Phil., senior VP of research at MedImmune.

"Drug-discovery efforts are targeting increasingly narrow patient populations, because individual patient responses can be examined and characterized in the early stages of clinical development through translational research," he says. "As a result, patients with a particular profile may be shown to have elevated response rates when compared with the broader patient population. Continued development can then be focused on matching the drug to the patients who respond to it. But a critical balance must be struck. If a drug is developed to treat only a small subset of the initially targeted patient population, it must also be a large enough group for the drug to be commercially viable."

Dr. Kauffman says determining how to move good, viable drug candidates from preclinical to human testing is another challenge.

"There is no such thing as a perfect drug, but it is important to determine which candidates have the right properties," he says. "Put another way, if there are 10 properties associated with a drug candidate, researchers need to determine which of those 10 are the most crucial to evaluate and which may prove to be the most predictive of how the human body may respond. That is a major challenge because the results seen in preclinical testing often are not the same as those seen in clinical trials."

"Maximizing both safety and efficacy in a drug is a key challenge in drug discovery," Dr. Kiener says. "A drug needs to be as potent as possible without reaching unacceptable toxicity levels, and striking that balance as early as possible in clinical development is important, both in terms of patient safety and continued development of the drug."

According to Dr. Carter, the single largest challenge in drug discovery is dealing with the complexity of human cells and tissues.

"This problem is the underlying cause of many roadblocks in the discovery and development process, ranging from off-target effects to difficult potency profiles," he says. "Again, molecular profiling as a tool to dissect the breadth of a drug's actions holds great promise." ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

APPLICATIONS ARE EXPANDING FOR BIOINFORMATICS

Bioinformatics will increasingly become a necessity for a wide spectrum of life-sciences, pharmaceutical, and biotechnology companies. As the number of market participants increases, purchasers will have an edge as the range of available tools expands. To succeed, market participants will need to offer cost-effective, easy-to-use and more widely applicable solutions, according to a Frost & Sullivan report, Opportunities for Outsourcing Bioinformatics (Europe).

From being solely a science of comparison and analysis of gene and protein sequences to a more advanced tool that eliminates the need to perform long and sometimes potentially hazardous experimentation, bioinformatics has significantly expanded its application scope.

"Using IT to solve scientific problems is extremely challenging and requires an in-depth knowledge of living systems, an all round understanding of structural, functional, and regulatory processes in living systems as well as familiarity with advanced computational power," says Frost & Sullivan Research Analyst Sumitha Kannan. "The bioinformatics market is positioned to achieve its maximum potential over the next three to seven years because biotechnology companies with bioinformatics operations, software firms in bioinformatics, as well as core computer hardware, peripherals, and IT companies will diversify into this area and make concerted efforts to realize its full value."

Informatics-based solutions that help solve biological puzzles will rationalize and streamline the drug-discovery process more than was previously possible. This will reduce the cost and time required to bring a medicine from research stage to real-world application.

One of the major challenges in the market will be to achieve cost competitiveness while simultaneously providing customized solutions. Developing higher flexibility and ease of use in software tools involves longer and more expensive development life cycles. Moreover, product customization typically implies proportionate pricing increases, which reduces affordability resulting in a restricted client base. At the same time, simple, attractively priced solutions often do not offer full value to customers.

Source: Frost & Sullivan, San Antonio. For more information, visit frost.com.

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OUTLOOK:
INCREASING EFFICIENCY AND QUALITY OF DISCOVERY EFFORTS

PHARMAVOICE ASKED EXPERTS INVOLVED IN THE DISCOVERY PHASE TO IDENTIFY THE STRATEGIES BEING EMPLOYED AT THEIR COMPANIES TO IMPROVE OVERALL EFFICIENCIES AND OUTCOMES.

William M. Caldwell IV
Advanced Cell Technology

We are focused on creating as many cell lines as possible using hESCs. This includes embryonic stem-cell lines as well as lines of differentiated cell types. We also have started work to produce hESCs under GMP conditions, which will be necessary to provide cells for human trials in the future. We believe having a diverse set of both hESC lines and differentiated cell lines will be a key accelerator to the development of therapeutic products over the next five to 10 years.

Kenneth C. Carter, Ph.D.
Avalon Pharmaceuticals

An exciting use of molecular profiling that has the potential to revolutionize drug screening is its use in the identification of drug candidates, rather than compound interactions with a specific target *in vitro*. This is an approach to drug discovery that uses our proprietary technology, which we termed AvalonRx. This technology allows Avalon scientists to screen for active compounds by monitoring genomic response profiles within living cells. One of the most important advantages of this approach is that it allows a straightforward way to design a screen for essentially any target or pathway.

Michael G. Kauffman, M.D., Ph.D.
Epix Pharmaceuticals

We employ a proprietary drug-discovery technology and approach using computational models to move a drug target through initial discovery to preclinical testing and into the clinic. In our experience, using a computational model has been the most efficient way to discover new drug candidates, optimize them, and efficiently drive them into the clinic. We have used our proprietary algorithms to discover and advance four drug candidates into the clinic. Now that the human genome is completely sequenced, we have an abundance of new potential drug targets.

We believe that the problem facing the industry is coming up with better medicinal chemical compounds and moving them into and through human clinical trials expeditiously. Getting from a drug target to a good clinical candidate more effectively is where we believe the industry should focus.

Peter A. Kiener, D.Phil.
MedImmune

We are intensely focused on maximizing the efficiency and quality of discovery efforts through translational science. With about 45 product candidates in our research and development pipeline, it is essential that resources are properly allocated within that broad portfolio. Our goal is to find out as much as we can, as early as we can, about a drug and its prospective patient population. We can apply the results of translational research, such as noninvasive imaging and biomarker analyses, to link preclinical and clinical findings. Understanding early in the drug-development process how a drug works and how its target patient population responds affords several key benefits.

Through these efforts we expand scientific knowledge and gain more and more expertise related to a particular disease state. As we can begin to characterize patients' individual responses to a drug and learn why some patients respond to treatment and others do not, we can then work to match the drug to the responsive patient population.

G. John Mohr
Topigen Pharmaceuticals

Our therapeutic focus is respiratory, a disease area that has largely seen incremental innovation in terms of successful new therapies reaching the market. We define category innovation as moving respiratory care beyond today's corticosteroid-driven market.

Our discovery innovation efforts center on local lung inflammation in respiratory disease models, i.e., understanding the cellular mechanisms that turn on lung inflammation and cellular processes responsible for complications of asthma and chronic obstructive pulmonary disease (COPD).

What we are finding in our models is that knocking down inflammatory mediators requires a multitargeted approach to maximize inhibition and efficacy. It's often a select combination of targets that show very dramatic and synergistic effects on efficacy in models of lung disease.

Robert J. Mulroy
Merrimack Pharmaceuticals

Merrimack's core technology is the Network Biology drug discovery and development platform, which is an integrated, multidisciplinary approach based on the principals of chemical engineering, computational modeling, and high-throughput biology. Network Biology has the potential to increase efficiency by using the same computational models and profiling tools for more accurate drug-target selection, research and development, and patient stratification in clinical development.

By applying network models from the preclinical to clinical phases of drug development, we aim to achieve early and effective decision making so that only the best possible therapeutics advance into the later stages of development.