BY DENISE MYSHKO

BASIC RESEARCH

Going Back to Basics Could Yield Big Results

Opportunities exist for pharma and biotech companies to use new tools and technologies to provide new ways of looking at disease, **WHICH COULD LEAD TO BUILDING A PIPELINE FULL OF NEW DISCOVERIES**.

Start with the end in mind: patients. Leaders in drug discovery and research say this should guide how the biopharmaceutical industry approaches new medicines now and in the future.

The challenge is to align the understanding of disease biology and drug-discovery science with patient needs, says Alan Cross, Ph.D., executive director, disease area leader psychiatry, at AstraZeneca Pharmaceuticals LP.

"This requires a science-driven approach, strong cross-functional teams, and a breakdown of the traditional barriers that can exist in R&D organizations," he says.

It will also require a willingness on the part of companies to be more open minded to earlier-stage programs, says Nicholas Landekic, president and CEO of PolyMedix Inc.

"Every big pharma company employs legions of people to look for the elusive late-stage opportunities, but the reality is these do not grow on trees, and the world has been picked clean of most of the attractive clinical products for licensing," he says. "Unless the industry invests in early-stage discovery efforts, ultimately there will be no late-stage products."

DR. JACK SECRIST
Southern Research Institute

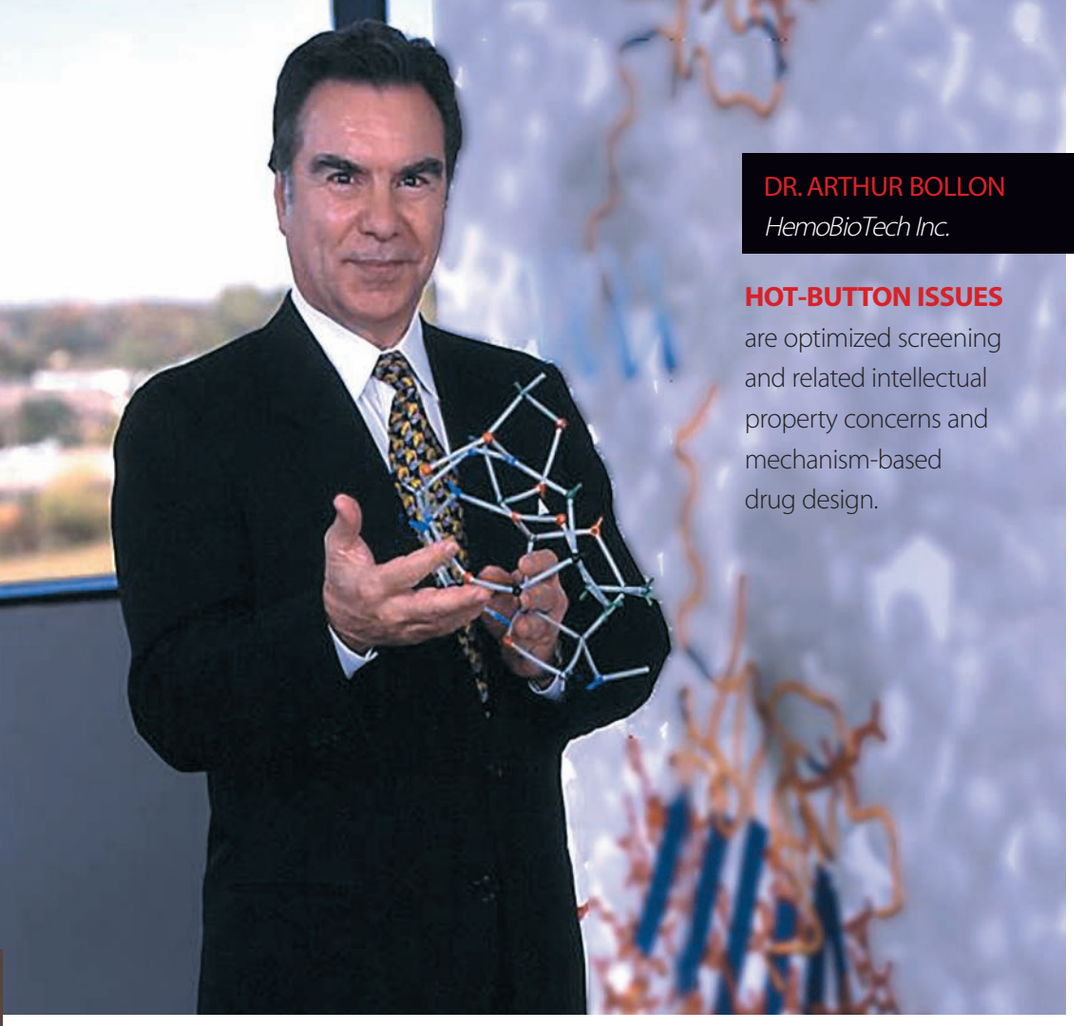
Pharma companies also have to bring translational research to the forefront of research, according to Trevor Mundel, global head of exploratory clinical development at Novartis Pharmaceuticals Corp.

"This involves recruiting top-tier physician scientists who have the right background to think through the issues — safety, biomarkers, etc. — involved in selecting new targets, generating patient data to improve validation, and efficiently executing the final proof-of-concept clinical study," Mr. Mundel says. "This early focus on patients represents a major paradigm shift for most pharma research organizations. Sorting through competing new therapies with ever more extensive and sophisticated *in vitro* and *in vivo* animal modeling continues to be a focus."

BETTER PREDICTIONS OF TOXICITY AND EFFICACY EARLIER IN THE PROCESS will continue to be near the top of everyone's list of issues.

Richard DeSimone, cofounder, director, and chief financial officer at EKR Therapeutics Inc., says the knowledge gained from genomic research will make it even more clear that the disease states being addressed by the industry are not as predictable and as easily defined as scientists and companies would like them to be.

"The main element of discovery in this area will bear out that diseases are really families of similar complex conditions without silver-bullet solutions," he says. "The continuing efforts in genomic research will generate



DR. ARTHUR BOLLON
HemoBioTech Inc.

HOT-BUTTON ISSUES are optimized screening and related intellectual property concerns and mechanism-based drug design.

new ideas as we continue to move to personalized medicine with complex patient health and disease management approaches tailored to the individual needs of the patient."

THE TECHNOLOGIES
LEADING CHANGE

The increasing number of emerging companies in all areas of the life-sciences sector will generate new and interesting platforms from which new products will be spawned, Mr. DeSimone predicts.

"These will create opportunities for joint-development partnerships that will continue to feed the stream of new products," he adds.

Mr. Mundel says one area that is generating a great deal of interest is the use of biomarkers to stratify patients with related but distinct conditions. Biomarkers will allow pharma companies to make different treatments for different patient subpopulations and test them only in patients who suffer from those conditions, thereby reducing both the number and size of the trials to prove efficacy.

Experts

ARTHUR P. BOLLON, PH.D. Chairman, President, and CEO, HemoBioTech Inc., Dallas; HemoBioTech is engaged in the development of HemoTech, a novel human blood substitute technology. For more information, visit hemobiotech.com.

ALAN CROSS, PH.D. Executive Director, Disease Area Leader Psychiatry, AstraZeneca Pharmaceuticals LP, Wilmington, Del.; AstraZeneca is an international healthcare business engaged in the research, development, manufacture, and marketing of prescription pharmaceuticals and the supply of healthcare services. For more information, visit astrazeneca-us.com.

CRAIG DEES, PH.D. CEO, Provectus Pharmaceuticals Inc., Knoxville, Tenn.; Provectus specializes in developing oncology and dermatology therapies that are safer, more effective, less invasive, and more economical than conventional therapies. For more information, visit pvct.com.

RICHARD DESIMONE. Cofounder, Director, and Chief Financial Officer, EKR Therapeutics Inc., Cedar Knolls, N.J.; EKR Therapeutics is a privately held specialty pharmaceutical company that provides acute-care specialty products. For more information, visit ekrtx.com.

NICHOLAS LANDEKIC. President and CEO, PolyMedix Inc., Radnor, Pa.; PolyMedix is an emerging biotech company developing acute-care products for infectious diseases and acute cardiovascular disorders based on biomimetics. For more information, visit polymedix.com.

WARREN LEVY, PH.D. CEO, Unigene Laboratories, Fairfield, N.J.; Unigene is a biopharmaceutical company focusing on the oral and nasal delivery of large-market peptide drugs. For more information, visit unigene.com.

JEFF MORHET. CEO, InNexus Biotechnology Inc., New York; InNexus is a drug-development company commercializing the next generation of monoclonal antibodies based on its Dynamic Cross Linking technology. For more information, visit ixsbio.com.

TREVOR MUNDEL. Global Head of Exploratory Clinical Development, Novartis Pharmaceuticals Corp., East Hanover, N.J.; Novartis Pharmaceuticals develops, manufactures, markets, and sells innovative prescription drugs used to treat a number of diseases and conditions, including those in the cardiovascular, metabolic, cancer, organ transplantation, central nervous system, dermatological, gastrointestinal, and respiratory areas. For more information, visit pharma.us.novartis.com.

JOHN A. "JACK" SECRIST, III, PH.D. CEO, Southern Research Institute, Birmingham, Ala.; Southern Research Institute is a diversified network of collaborative centers for scientific discovery and technology development. For more information, visit southernresearch.org.

NICHOLAS LANDEKIC
PolyMedix

GENOMICS AND PROTEOMICS HAVE TREMENDOUS FUNDAMENTAL POTENTIAL, but several years of basic academic research are still needed before they are ready for prime-time drug discovery.

A VERY EARLY FOCUS ON PATIENTS represents a major paradigm shift for most pharma research organizations.

TREVOR MUNDEL
Novartis Pharmaceuticals

The level of activity in discovery and development of new disease-related biomarkers has increased dramatically over the last five years, according to a report by Insight Pharma Reports, a division of Cambridge Healthtech Institute. (For more information, see box on page 52 and related article on page 56.)

Disease-related biomarkers in pharma can be used initially for internal decision making, to qualify patients for clinical trials, or as surrogate endpoints. As programs move farther down the pipeline, biomarkers require increasingly more rigorous validation.

Recent deal activity, which has been fairly brisk in the disease-related biomarkers area, reflects this growing interest. Of 21 deals, the Insight Pharma Report found that 13 agreements involve a small biomarker content company and an *in vitro* diagnostics manufacturer.

"SNP densities and haplotype mapping have reached a point of maturity that allows for meaningful determination of the genetic underpinnings of some complex diseases as opposed to the many hit-or-miss failures in this realm in the past," Mr. Mundel says. "As most of these discoveries will be in the public domain, the key will be how fast and effectively companies can functionalize the discoveries."

Mr. Landekic says genomics and proteomics have tremendous fundamental potential, but realistically probably still need several years of basic academic research before they are ready for prime-time drug discovery.

"Structure-based, computational, drug-design approaches probably offer better odds for nearer-term value," he says. "The old-fashioned, brute-force approach of random screening of combinatorial libraries has not worked. In reality, it is often difficult to optimize a micromolar hit into a true nanomolar drug. All companies, big and small, will need to embrace multicomponent computational design approaches and take advantage of the capabilities of each tool to bring to bear a multipronged computational approach to drug design."

Functional Proteomics Can Speed Discovery

Proteomics research is undergoing excessive growth. Almost every major biotech and pharmaceutical firm has implemented a proteomics program. Functional proteomics, the study of protein function and identification of protein interactions, is playing a major role in drug discovery, biomarkers, molecular diagnostics, and antibody therapies.

Frost & Sullivan finds that the study of functional proteomics provides market drivers, technical challenges, and emerging enabling technologies in this space.

Functional proteomic technologies enable identification of functions for uncharacterized human proteins, the discovery of other proteins with which they interact, and an understanding of their involvement in important disease pathways. Understanding cell-signaling pathways and the manner in which cells communicate will provide greater understanding of disease mechanisms, revealing potential drug targets that are more likely to succeed. After the development of drugs, pathway knowledge is critical in understanding the downstream effects of drug treatment. Enhanced knowledge of pathways will reduce side effects.

Unfortunately, proteins are far more complicated than DNA. Technical problems have plagued functional proteomic R&D on every front. Problems associated with functional proteomic technologies, such as protein arrays, are also numerous.

Before accepting functional proteomics as a standard, high-throughput approach, technology developers need to address a number of challenges.

There is a need for new tools and research strategies on all fronts, for protein expression, purification, screening, and measuring protein interactions. In addition, assays sensitivity — the ability to detect low-abundance proteins — needs to follow standard techniques that provide reliable and acceptable results for pharmaceuticals applications.

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

DR. ALAN CROSS
AstraZeneca Pharmaceuticals

WE SHOULD BE OPEN TO WORKING WITH ACADEMIC INSTITUTES and using our tools and expertise to advance understanding in key areas.

The progress and rapid maturation of several next-generation sequencing technologies are driving down the cost of genome sequencing and resequencing at a precipitous rate, opening up a host of new scientific possibilities in the process, according to another report by Insight Pharma Reports.

Mr. Mundel says there are likely to be multiple sources of new targets, or modalities, for research to deploy against old targets.

"With significant new robust polymorphism associations identified in 2007, it appears that SNP densities and study protocol methods may have finally reached sufficient maturity to be useful for drug discovery," he says. "Several companies have released data — for example Cytos and nicotine addiction — indicating that they have been able to break immune tolerance to endogenous targets and make a vaccine approach viable. This could lead to therapies that replace expensive antibodies/recombinant protein therapies with vaccinations for example, the anti-TNF-alpha blockers, and

The Genome Sequencing Market

The progress and rapid maturation of several next-generation sequencing technologies are driving down the cost of genome sequencing and resequencing at a precipitous rate, opening up a host of new scientific possibilities in the process, according to a report by Insight Pharma Reports, a division of Cambridge Healthtech Institute.

The field is dominated by four companies — 454, Illumina, Applied Biosystems, and Helicos — by virtue of their technological prowess, experience, and funding. By the end of 2007, all four will have commercial instruments on the market, offering scientists unprecedented choice and flexibility in addressing high-throughput sequencing questions. In addition, several other companies and academic groups are developing rival technologies that could well find a niche in this burgeoning space.

The report predicts that within two to three years, the era of the $1,000 genome will have arrived. This is when experts believe that human genome sequencing will reach the global middle class. At that point, having one's complete genome sequenced will cost no more than many other medical procedures that are taken for granted. The results will be a full genetic readout of one's DNA (or at least the coding portions of DNA), which could yield unimagined consequences in terms of revealing predispositions to a host of rare and common diseases.

Source: Insight Pharma Reports, Needham, Mass. For more information, visit insightpharmareports.com.

MORE FUNCTIONS WILL BE OUTSOURCED, perhaps to a level that R&D functions in the larger companies may be phased out in the future.

DR. CRAIG DEES
Provectus Pharmaceuticals

Biomarker Technologies Lead to New Advances

The level of activity in discovery and development of new disease-related biomarkers has increased dramatically over the last five years, according to a report by Insight Pharma Reports, a division of Cambridge Healthtech Institute. Much of the activity has centered in pharma as companies seek dramatic improvements in R&D productivity. The *in vitro* diagnostics industry has been slower to take advantage of new technologies for biomarker discovery, but it is starting to show signs of accelerated activity.

Biomarker discovery growth is being driven by the availability of powerful new "omic" technologies, the increasing utilization of new and untested targets in pharma, and the opportunity to replace suboptimal *in vitro* diagnostic assays with improved biomarkers.

The postgenomic era for biomarker discovery began with the introduction of DNA microarrays in the mid-1990s, which enabled a revolution in transcriptomics and triggered a major paradigm shift in the way life scientists approached research.

Although considerable progress has been made in disease-related protein biomarker discovery, this has yet to translate into major advances in their utilization. Metabolomics and metabonomics originally were applied mainly to safety-related biomarker work, but more recently attention is starting to turn to the disease-related variety.

Source: Insight Pharma Reports, Needham, Mass. For more information, visit insightpharmareports.com.

THE CONTINUING EFFORT IN GENOMIC RESEARCH WILL GENERATE NEW IDEAS as we continue to move to personalized medicine.

RICHARD DESIMONE
EKR Therapeutics

the improved ability to re-engineer protein therapies, antibodies, or recombinant proteins to impact half-life, which will lead to improved protein therapeutics. Additionally, RNA-interference may achieve clinical proof of concept in 2008, which will set off increased investment in this methodology."

BIOTECH PARTNERING

Experts agree that biotech and pharma companies should work together in their endeavors to improve early research efforts in the pursuit of pipeline developments.

John A. "Jack" Secrist, III, Ph.D., CEO, Southern Research Institute, believes that pharma companies will have to turn their focus to earlier in the discovery and development process and really evaluate the preclinical research that is being done effectively in universities and biotech companies and at hybrid institutions such as Southern Research.

"Institutions like ours, which conduct basic research with an eye toward developing drugs and fee-for-service work, could play an important role in the process," he says. "The challenge is to find organizations that can team with pharma companies in a time- and cost-efficient manner to achieve the goals they have in mind."

"Early-stage companies that have partnerships with universities and virtual biotech companies are a good resource for this type of research," says Arthur P. Bollon, Ph.D., chairman, president, and CEO of HemoBioTech.

Craig Dees, Ph.D., CEO of Provectus Pharmaceuticals Inc., believes the best resource pool for early-stage success is the same as it has always been: innovative and flexible small biotech or pharma companies.

"These entities have the innovative power to make the biggest and newest strides, whereas large companies are weighed down by corporate regulations and rules," Dr. Dees says. "And academic institutions don't generally have the requisite skills and knowledge of markets, regulatory guidelines, or proprietary properties to design products."

In addition to early-stage companies, biotechnology and biopharmaceutical companies are developing ideas and taking them to a more advanced stage, which will help to pro-

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BIOTECHNOLOGY COMPANIES ARE INCREDIBLY FOCUSED AND RESPONSIVE TO PHARMA COMPANY NEEDS so that they are often evolving their work in a package format.

vide concept validation and eliminate considerable early stage risk, says Warren Levy, Ph.D., CEO of Unigene Laboratories.

"These companies are in a position to provide the leads that big pharma is looking for on terms that are mutually beneficial," he says. "It's a win-win situation."

The basic research continued by biotechnology companies is often confirmatory rather than exploratory, says Jeff Morhet, CEO of InNexus Biotechnology Inc.

"Confirmatory means that the research has a starting point and intended goal, unlike basic research done in an educational forum where the goal is to expand or explore a concept," he says. "Biotechnology companies are also incredibly focused and responsive to pharma company needs and they are often evolving their work in a package format."

Mr. Morhet points out that many large pharma companies have launched entire divisions dedicated to the utilization of biologics as a drug-development platform.

"This trend has only begun and should other technologies provide the same opportunity, they too will be leveraged as product-development platforms," he says.

But Dr. Cross says basic research in academic institutes will always be the foundation from which pharma builds and contributes to advances in biomedical research.

"What will change is the way that pharma interacts with academic institutes," he says. "There is an increasing trend toward true research collaborations and a sharing of research goals that may extend beyond short-term returns. We should be open to working with academic institutes and using our tools and expertise to advance understanding in key areas, in particular disease pathophysiology, disease and treatment genetics, and translational medicine."

OUTSOURCING TRENDS

Experts agree that outsourcing in the discovery phase will continue to increase as more functions are needed as part of the drug-development process.

"Outsourcing has continued to grow in so many areas: manufacturing, process chemistry, biological screening," Mr. Landekic says. "One wonders if actual drug design and target validation may become outsourced, particularly as the biopharmaceutical industries in China and India continue to become more sophisticated."

Dr. Secrist says outsourcing partners will play an ever increasing role in helping to bring new drugs to market.

"These relationships will include a mixture of routine task outsourcing, conducted on an efficient fee-for-service basis, and value-added collaborations that will allow the sharing of intellectual property," he says. "Having access to trusted partners who can provide this type of relationship will be highly desirable for a pharmaceutical company that wants to be the most successful at driving new drugs to market."

Dr. Levy says given the small percentage of early-stage product candidates that become successful products, even the largest pharmaceutical companies will rely on outsourcing.

"History has shown that multibillion-dollar research budgets cannot provide sufficient leads for big pharma," he says. "There will continue to be an increasing reliance on smaller companies that take the initial risks in product development."

DR. WARREN LEVY
Unigene Laboratories

THE MOST IMPORTANT ISSUE TODAY is coming up with product candidates that have acceptable safety profiles.

BEST PRACTICES FOR DISCOVERY

To be cost-effective, Mr. Mundel says pharma needs to focus on a couple of key technologies and supportive activities.

"For example, high-throughput screens are expensive so a system for validating and prioritizing targets, as well as defining secondary screens is critical," he says. "Toxicology and drug metabolism give essential feedback to discovery programs, but if extensive expensive profiling is done very early on, cost-benefit may not be high. Drug supply contributes to the bulk of costs of the preclinical/proof-of-concept phase so it is necessary to minimize the amount of drug at risk at any time."

Mr. Landekic suggests focusing solely on what is needed.

"It's vital to not waste sometimes infinite resources and indefinite time to make countless molecules that are not needed in the hope that the one that is left will be the one that is needed," he says. "Chemistry space is too vast to make all the unnecessary molecules in hopes that what will be left will be the drug."

Dr. Secrist says the key is to use and promote technologies that will increase the percentage of drug candidates that succeed compared with those that start clinical trials.

"Focusing on new, relevant efficacy models, and continuing to improve toxicity prediction are two of the keys to increasing this percentage," he says. "The more we can improve in these areas, the more compounds we can weed out earlier in the process before they go into the clinic." ✦

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