Quo vadis, biotech? (Part 1)

Jurgen Drews

The recent increase in the capitalization value of the biotechnology industry appears to be sustainable. The phenomenon is interpreted as an acknowledgement by the markets that this industry has become the main source of innovation for the pharmaceutical industry. In addition, biotechnology is beginning to impact on other industries. However, from a methodological and strategic point of view, the biotechnology industry is still too fragmented. Consolidation along the lines of value generation in drug research and development, however, will occur. Over the next 5 to 10 years, the biotechnology industry will remain the fastest growing industry in the health care arena.

Genomics, as represented by several tiers of companies, will make three major contributions to drug therapy. In the first place, new genes, which code for secreted proteins, will continue to be identified. Already several such agents have made their way to the market. Second, genomic sciences are about to identify the most suitable targets for drug intervention. Although current drug therapy rests on approximately 500 such targets, the emerging number is estimated to be in the range of 5000 to 10,000 target molecules. Third, we are learning why patients respond differently to drugs. The genetic patterns that define these responses are being identified and used to target drugs more effectively during their development. This approach will also allow for individualized drug therapy. To date, the utilization of combinatorial chemistry and poorly validated targets in high-throughput configurations has led to disappointing results. The 'innovation deficit' described several years ago still exists. However, target validation and target-oriented chemical approaches are now the focus of attention.

Anyone who has followed the financial markets and, in particular, the valuation of biotechnology companies over the past 12 months might find themselves in a state of confusion. Towards the end of a rather frugal 1999, during which the availability of capital for biotechnology initial public offerings (IPOs) and for private investment rounds appeared to be dried up, the markets suddenly turned around and gave the biotechnology industry their biggest bonanza ever.

The initiating signal might have been the rather spectacular IPO of Tularik (South San Francisco, CA, USA) followed by an equally friendly reception of Sequenom's (San Diego, CA, USA) public offering. Suddenly the doors seemed wide open. Many relatively mature biotechnology companies that had been waiting for a receptive market commenced their own IPO process. As the months went by without a sign of weakening or even so much as reluctance on the side of the financial market, these firms were joined by a growing number of younger and weaker companies.

In parallel to an increasing number of private equity rounds and IPOs, the valuation of the biotechnology sector reached an all-time high. Led by companies representing either genomic or antibody technologies, biotechnology stocks soared first at the Nasdaq, followed almost instantly by high valuations at other high-tech markets, such as the 'Neuer Markt' in Germany.

As seen from today's perspective, a biotechnology valuations showed a characteristic, almost symmetrical pattern. They started to increase steeply during the last 6–8 weeks of 1999, reached a peak in February and early March 2000 and declined until May. Since that date they have increased moderately but steadily. The majority of biotechnology companies still benefit from a higher valuation currently

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than they did in the middle of 1999, but in some cases, stock prices are back to where they were before the boom started.

In spite of these changes, the window for private equity financing and for IPOs continues to remain reasonably active. The valuation of biotechnology stocks, however, went from moderate to high, to extremely high and back to moderate in only a few months.

What does it all mean?

Of course, we can ask whether or not any conclusions can be drawn from this 'full circle' movement. Has this only been a caprice of the markets that are influenced more and more by private investors who buy and sell on-line with, at best, a superficial knowledge of the underlying technical and business realities? Such mechanisms might well have played a role in the recent roller coaster. I would argue, however, that something more fundamental might have occurred.

Companies with an obvious strength in genomics, such as Human Genome Sciences (Rockville, MD, USA), Millennium (Cambridge, MA, USA), Celera (Rockville, MD, USA) and Incyte (Palo Alto, CA, USA), and antibody firms such as Protein Design Labs (Fremont, CA, USA), Medarex (Princeton, NJ, USA), Abgenix (Fremont, CA, USA) and Morphosys (Munich, Germany), appeared to be the focus of investors' interest during the recent run on biotechnology stocks. Companies representing other segments of the biotechnology spectrum, such as combinatorial chemistry, HTS and cell biology appeared to benefit secondarily. It is also noteworthy that within the broad sectors of genomics and antibodies, technology platform companies and product-oriented companies seemed to benefit to similar degrees. Morphosys, for instance, a company that uses phage display technology to produce human antibodies of almost unlimited specificity went public in March 1999. During the months following the listing, the price lingered at or below the IPO level. Then during October 1999, the stock took off and culminated at US$ 330.6 in early March 2000. Thereafter it gradually lost some of its value but at the time of this writing, October 2000, it is still two times the IPO level. The antibody companies in the USA did similarly well, although their fall was much faster. It is likely that this difference reflects the more conservative attitude of some institutional investors in Europe who are supporting Morphosys.

In principle, the companies with an original technological platform, with products in clinical development or with both, are still valued at higher prices at the time of this writing (October 2000) than they were a year ago. Financial dynamics, such as the flux of capital from internet companies into biotechnology firms, might have contributed to the sudden appreciation of biotechnology companies. There might, however, be something more fundamental behind the figures we have been following. The more sophisticated investors might have understood that genomic and antibody companies, and right behind them the companies that specialize in crucial steps of the drug discovery process (e.g. target validation), hold the essential keys to technical progress and to value generation in several other, more established industries. The pharmaceutical industry, for instance, is completely dependent on the achievements of the biotechnology sector, especially on contributions from genomic sciences.

There are approximately 12,000 human genes that specify the synthesis of secreted proteins. If only a small percentage of these proteins, such as 3%, qualified as drugs, there would be more than 300 protein drugs still awaiting discovery and development. Of course, antibodies, which are capable of neutralizing the physiological or patho-physiological effects of these proteins, might also qualify as drugs. Gamma-interferon, to mention a well-known example, is a mediator of cellular immunity[1]. Therapeutically, the protein can be used to enhance cellular immune responses. Conversely, an antibody to γ-interferon could be an effective immunosuppressive agent. It could be used in autoimmune diseases, such as inflammatory bowel disease. In summary, the majority of protein drugs and antibodies that can be used as their therapeutic antagonists still remain to be discovered. The key to these discoveries is held by companies that hold strong proprietary positions in genomics, covering many full-length gene sequences, and by antibody companies that can create and patent effective and well-tolerated human antibodies to these novel proteins.

The power of genomics

Small molecules such as drugs, insecticides or herbicides usually exert their effects by modifying biological targets. In the past, many of these molecules were found empirically with little or no knowledge of the mechanism of action involved. In many cases, the targets that are modified by these substances were identified in retrospect. Interestingly, the majority of drugs currently in use modulate either receptors, most of them G-protein-coupled receptors, or enzymes. With the progress of biochemistry and pathophysiology, scientists became increasingly capable of selecting potential biochemical targets on the basis of mechanistic information. Several modern drugs were found in the pursuit of a particular mechanism of action. For example, the inhibitors of the angiotensin converting enzyme or of renin, which are used clinically for lowering increased blood pressure.

Genomics, however, will lend a new dimension to this rational approach. The number of molecular targets that are modified by the complete armamentarium of modern drugs is not greater than 500. This is a surprisingly small

number, which we arrived at by examining all the drugs that are currently in use in the USA and by counting the targets that these drugs modify[2]. From early experiments and mathematical approaches[3,4], it is known that the number of genes that contribute to multifactorial diseases might not be very high. In fact, the numbers reported for different forms of diabetes and hypertension are 5–10 genes per disease[5]. There are 100–150 nosological entities (disease entities) that present an epidemiological and economical problem to industrialized societies. If one assumes 10 contributing genes for 100 multifactorial diseases (including different forms of cancer, asthma, diabetes, hypertension, atherosclerosis and osteoporosis), one arrives at 1000 'disease genes' that dispose patients to the most important multigenetic conditions.

The existence of these genes does, of course, not detract from the importance of environmental influences. These 1000 'disease genes' might not always guide the synthesis of proteins that are good drug targets. However, it appears reasonable to assume that each of these disease genes, or rather proteins that are specified by the disease genes, connects with at least 5–10 proteins that represent feasible levels for drug intervention. On the basis of these calculations, one can assume that there are 1000×5 or 1000×10 (i.e. 5000–10,000) gene products that can be used as targets for drug interventions. Even if the lower number would turn out to be the proper approximation, the utilization of information stemming from the Human Genome Project and from other related programs would allow for a tenfold increase in the number of drug targets, compared with the current situation. Undoubtedly, such an expansion of the operational possibilities of drug therapy would translate into more specific therapies and into therapeutic methods that are much closer to the molecular causes of diseases than current therapies. In addition, we should keep in mind that the estimates outlined above are on the conservative side. It is by no means unreasonable to postulate the existence of 10,000 or even 15,000 molecular drug targets.

The power of pharmacogenomics

An additional aspect deserves consideration in this context. Every physician knows from the medical literature, as well as from his or her own experience, that individual patients respond very differently to one and the same drug. A particular antihypertensive drug, such as propanolol or nifedipine, usually works well in 60–70% of a relevant patient population. The remaining 30–40% will not respond and will therefore require treatment with different drugs. The reason for this differential response to drug therapy is not always clear; sometimes it is caused by the ways in which drugs are metabolized. The cytochrome P450 monooxygenases are a large and ancient superfamily of proteins that carry out multiple reactions designed to eliminate foreign compounds from multicellular organisms. In *Drosophila melanogaster*, the fruit fly whose genome was recently sequenced, 90 such genes were found[6]. In humans, CYP2D6, one of the P450 enzymes, is involved in the degradation of β-blockers, antidepressants, anti-psychotics and codeine. Small changes in the sequence of these proteins can affect the metabolism of important drugs and lead to diverse drug responses.

Many examples of adverse drug reactions resulting from individual variations in P450 enzymes have been described. Varying drug responses, however, can also be caused by single nucleotide polymorphisms (SNPs) in target molecules or in genes (proteins) related to drug targets. For example, Pravastatin®, a cholesterol-lowering agent, slows down the progression of coronary heart disease in some patients but not in others. A single polymorphism in the first intron of the cholesteryl ester transfer protein (CETP) gene appears to be responsible for this difference[7]. Similarly, it has been shown that Albuterol®, a β-adrenoceptor drug, works well in some cases of bronchial asthma but not in others. Again, the individual response seems to depend on a single SNP in the β_2-adrenoceptor receptor gene[8]. As the search for correlations between specific genetic configurations and drug responses continues, many additional examples might be found in which a particular genotype determines the response to drugs. The most logical approach to this problem might not reside in the unselective comparison of SNP patterns with drug responses but rather in the identification of gene haplotypes or combination of haplotypes and their correlation to phenotypes or phenotypic responses[9].

Biotechnology and pharmaceutical industries: a changing relationship

Seen over the time span of a century, the pharmaceutical industry has been very successful. In 1900, drug therapy was an underdeveloped area. Physicians had only a limited number of drugs at their disposal. They could treat severe pain by the administration of morphine, and for moderate pain and fever there were the first drugs coming from plants and coal tar chemistry [e.g. sodium salicylate, acetylsalicylate (aspirin) and acetaminophen], heart failure could be treated with digitalis extracts, and the first inhalational anesthetics were available. Compared with the plentitude of effective and safe drugs that are currently available to the medical profession, the situation was rather bleak. Within one century, for example, medicine found ways to treat bacterial, fungal and even viral infections, manage hypertension and other cardiovascular conditions, improve

vastly the conditions for surgery by the use of muscle relaxants and sedatives, find drugs that are effective in the therapy of psychic disorders and replace hormone and vitamin deficiencies.

The innovation deficit

However, all is not well with the current status of the pharmaceutical industry. For the past 10 years, the quantitative output of the pharmaceutical industry has been on the decline. In 1995, S. Ryser and J. Drews published an analysis that was based on the quantitative assessment of all discovery projects in the top 50 pharmaceutical companies, as they existed in 1993 (Ref. 10). By applying historical success rates for the emergence of development compounds from discovery projects and for the progression of development compounds to launch, the number of new chemical entities to be introduced annually by the industry starting in 1999 could be estimated[10]. At the time the study was conducted, a total output of 51 new chemical entities was predicted to result from the collective 1993 portfolios. These 51 compounds were not expected to reach the markets in one year, but rather to make their appearance within a time frame of 3–4 years. We assumed a turnover time of four years for the pre-clinical portfolio and a constant development time of six years. Therefore, we arrived at an estimate of 13 compounds for the top 50 companies in 1999. The actual figure was 29. This figure, however, included three vaccines, one immunotherapeutic and four recombinant proteins. Also, four compounds received regulatory approval in 1999 but were not actually launched. The resulting figure of 17 new chemical entities (small molecules) is not far away from our estimate, although 15 major mergers and acquisitions over the past 10 years have brought about a considerable concentration within the top group of pharmaceutical companies.

This figure, in addition to signs of a declining productivity, appear to corroborate (at least in principle) the rather gloomy forecast made in 1995 (Ref. 10,11). The mergers and acquisitions that took place in the pharmaceutical arena during the 1990s, a total of 15 in only 10 years, might have mitigated temporarily the consequences of the innovation deficit. However, they have not changed anything in principle because the pharmaceutical industry has not been able to organize its R&D organizations in ways that would increase their productivity. Most pharmaceutical companies, large as they are, still direct their research in a centralistic way. Some firms, for example, Hoffmann La Roche, have tried to set up at least part of their international research organizations in the form of 'independent units' that resemble biotechnology companies. However, such initiatives have been sporadic and have not been sustained. The fundamental error held by pharmaceutical managers is the notion that research and research funding must be aligned with market needs as perceived by their respective marketing organizations. Because marketing organizations always extrapolate future developments in the markets from past events, this orientation virtually excludes the generation and appreciation of something novel, for which there is no precedent.

Cultural changes in the pharmaceutical industry

Today, most big pharmaceutical companies are not run by chemists or physicians but by marketing managers, lawyers or financial experts. Science and medicine have been relegated to functions that must serve corporate goals, as seen by non-scientists and medical laymen.

This cultural change within the pharmaceutical industry is set to have some fundamental consequences[12]. Most pharmaceutical companies emphasize their skills in development, marketing and sales. In discovery and in basic science preceding discovery, the industry has reacted rather than acted for the past 15 years. Virtually all the new discoveries and inventions, which are about to reshape drug discovery, came from the outside, from academia and from science-driven small companies. For example, the identification of new drug targets by genomics, the validation of such targets through the developmental biology of molecular genetics, new assay configurations, HTS or ultra-HTS (uHTS) methods, combinatorial chemistry, the concerted efforts to understand protein structure (structural genomics), bioinformatics and many other fields that are currently well established or just emerging. Although the pharmaceutical industry had difficulties assimilating these new technologies, it had no choice, for competitive reasons. However, cutting-edge research is rarely carried out and hardly ever enthusiastically supported by large pharmaceutical companies. More and more, the epicentre of research relating to drug discovery is drifting towards the biotechnology industry, which is now quickly emerging as a discovery industry.

To date, the role of the discovery industry has been largely viewed in relation to other industries: the pharmaceutical industry, diagnostic firms and the agricultural biotechnology industry. Eventually, the biotechnology industry would have to offer its goods and services to more established industries who could market them worldwide. The current assumption is that large pharmaceutical companies will eventually sell recombinant proteins such as erythropoietin, thrombolytic enzymes or G-CSF (granulocyte-colony stimulating factor). The same would be true for monoclonal antibodies and small molecules. Indeed, recent experience indicates that innovators such as Idec (Osaka, Japan), Tanox (Houston, TX, USA) or Gilead (Foster City, CA, USA) always needed a Genentech (San Francisco, CA, USA), a Novartis or a Roche

(both Basel, Switzerland) to effectively distribute their drugs (Rituximab®, Anti-IgE or the neuraminidase inhibitor Thera-Flu®) in order to benefit appropriately from their inventions.

Although this might remain to be the prevailing pattern for the foreseeable future, other arrangements might come into play. Encouraged by the recent increase in biotechnology valuations, and at the same time frustrated by the tardiness of the decision-making processes in many large pharmaceutical companies, a greater number of biotechnology companies are now seriously entertaining the concept of holding on to their products and bringing them to the market alone or with the help of other biotechnology companies. In fact, the frequency and attractiveness of biotechnology to biotechnology deals is increasing.

In summary, several developments can be highlighted:

(1) Owing to cultural changes within their organizations, large pharmaceutical companies are less enthusiastic about pre-discovery and discovery research. Many large pharmaceutical organizations are emphasizing their development, marketing and sales efforts, and are gradually withdrawing from early drug discovery.
(2) The biotechnology industry has assumed the role of the drug discovery industry. Until recently, biotechnology companies have played this role with a clear view towards eventually selling their products (and for that matter their technologies) to well established pharmaceutical companies.
(3) Increasingly, biotechnology companies are envisioning strategies that will allow them to become product-based health care companies in their own right. This new strategic orientation appears to be supported by the readiness of investors to take large risks in exchange for the prospect of exceptional returns.

Can the biotechnology industry reverse the innovation deficit?

It was already mentioned that, with respect to productivity, the reality of 1999 is only slightly better than the predictions given in 1995 on the basis of figures that described the industry's activities in 1993. This statement holds true for all pharmaceutical companies as well as for subgroups like the top 50. Without the contributions of recombinant proteins and monoclonal antibodies, which have already entered the market or will be launched within the next few years, the picture would be even gloomier.

But what about the new technologies that were expected to boost the efficiency of drug discovery? What about the identification of new drug targets, target validation and combinatorial chemistry? Why have these technologies not yet influenced the productivity of drug discovery?

Several reasons have to be considered. First, the biotechnology industry, similar to other technology-driven industries, seems to be plagued by exaggerated expectations. In particular, this holds true for the time periods needed to assimilate new technologies and to make them effective within an already established process, for example, drug discovery or drug development. When gene sequencing became a systematic effort in 1996, many people expected a growing stream of new drug targets to emerge from this activity. In principle, this expectation was realistic. With respect to its manifestation in time, however, it was unrealistic. In many cases, genetic sequences that became available to drug researchers during the past four years described proteins already known. In other similarly frequent cases, such nucleotide sequences could not be classified. The function of the proteins encoded by these genes was completely unknown, and both classes of sequence information were therefore ineffective. Even when gene sequences were emerging at an ever-increasing rate that could somehow be associated with a particular disease or with a pathophysiological mechanism, the situation did not improve immediately. The hypothetical association of a gene (or the protein it encodes) with a disease phenotype is not a sufficiently firm basis for drug development. Before the target in question is incorporated into screening assays, it must be validated, that is; its biological role, especially its relationship to a particular phenotype, must be understood. It must be shown (by genetic or by biochemical experiments) that the manipulation of the potential target does indeed lead to a phenotypic change that is therapeutically desirable. Only then can a protein be regarded as a viable target. Of course, the ultimate validation lies in the predicted clinical response of a patient to a drug that interferes with the target.

Target validation is a time-consuming process. Genes can be sequenced very rapidly, as the accelerating pace of the Human Genome Project has shown[13]. The hypothetical association of a gene product with a disease phenotype takes at least as much time as the sequencing, probably more. The validation of such a hypothetical association can indeed be very demanding. Some companies do not consider a molecular target to be validated if its functionality has not been confirmed in several animal models. Such models must, of course, carry some mechanistic features of a human disease. Applying these strict criteria, the number of validated targets that a pharmaceutical company can generate per year can be in the range of 2 to 10. Lower validation hurdles, of course, allow for a greater number of so called 'validated' targets. The majority of targets that were used in HTS configurations were only poorly validated, and this might have been one reason for the modest yields of HTS or even uHTS programs in the past.

Undoubtedly, additional reasons for these disappointing results were the poor quality of chemical libraries that were used in HTS programs. The results can be summarized as follows: 'many hits, few leads and even fewer development compounds, none so far that have reached advanced stages of clinical trials'[14]. Is this going to change? It is likely that it will. The first signs of improvement would appear as an increase in the number of compounds that pharmaceutical companies commit to development. In order to launch 2–4 novel chemical entities per year, a company must send at least 20 new candidates into development annually. Most major firms are still far away from reaching this goal.

However, the techniques of target validation are improving. Consequently, the number of validated targets will increase rapidly. Also, the quality of chemical libraries that will be used to modify these targets are going to improve. There is every indication that essential steps, such as assay configuration, the precision of uHTS (300,000 data points per day and per machine) and the evaluation of data, are also going to improve.

The number of compounds entering development annually might indeed be on the rise. However, it is not clear who will benefit most from the recent methodological advances related to drug screening. Most certainly the biotechnology industry will benefit in two ways. First, the companies that raise the standards of uHTS will benefit through deals with larger, more integrated companies. Second, large biotechnology companies that have collected enough money during the recent biotechnology rally will be able to develop their own pipeline and bring compounds forward, if not always to the market then at least to later stages of development.

New technologies

When assessing future advances in the biotechnology and pharmaceutical industries, emerging technologies must be taken into consideration. The elucidation of the human genome, roughly completed in the year 2000, and of other important genomes (*Drosophila*, bacteria, yeast, *Caenorhabditis elegans*) represents a huge achievement. However, drugs are not to be modeled against genes but against proteins. The next significant step in creating a base for drug research would therefore reside in the structural elucidation of many or all medically relevant proteins. This might seem like an unreasonably difficult task. In fact, it is not. Improvements in structural biology, more specifically in NMR, spectroscopy, robotic crystallization, cryogenic crystal handling, X-ray crystallography and high-speed computing have greatly facilitated protein structure determination[15]. Indeed, technological advances have propelled structural biology to a position where the elucidation of the three-dimensional structure of medically relevant proteins on a large scale appears possible. The feasibility of this concept of structural genomics is supported by the fact that the universe of compact globular protein folds is relatively limited. Indeed, it might not exceed 5000 distinct spatial arrangements of peptide change[16].

Several newly founded biotechnology companies are now addressing this new frontier; Structural Genomix (San Diego, CA, USA) and SyrRx (San Diego, CA, USA) are among the most prominent. Another company, Prospect Genomics (Belmont, CA, USA), is taking this idea one step further. The company plans to use the protein data emanating from a structural genomics project to model chemical compounds against medically important proteins, first by comparative modeling and, as the databases become richer, also by '*ab initio*' methods.

Protein–protein interactions, for example, the binding of immunoglobulin E, vascular endothelial growth factor, IL-2 or IL-5 to their respective receptors might represent attractive drug targets for the treatment of allergies, cancer, autoimmune diseases or asthma. Traditionally, small-molecule drug discovery has largely failed with these targets. However, protein–protein interfaces have 'hot spots', which are small regions that are crucial to binding and have the same size as small molecules. The targeting of these hot spots by small molecules might turn out to be capable of disrupting undesirable protein–protein interactions. Companies such as Sunesis (South San Francisco, CA, USA) and Therascope (Heidelberg, Germany) are addressing this possibility[17].

However, there are additional technologies, derived from a more holistic view of target validation. For a long time, computer simulations have helped to illustrate and to predict pharmacokinetic events such as the uptake, distribution and excretion of drugs[18]. In a similar way, metabolic pathways and/or regulatory cascades can be simulated in silicon. This would allow us to virtually manipulate single components of such pathways, receptors, kinases, phosphatases and other regulatory proteins and to assess the consequences of such interventions on important physiological parameters, for example, glucose levels, cholesterol concentrations, blood pressure, respiratory parameters such as FEV (forced expiratory volume), energy balance and so on.

Skills in both biology and informatics are required in order to solve the technical problems inherent in this approach. A new generation of companies, including Entelos (Menlo Park, CA, USA), have begun to integrate these disciplines in order to make more reliable predictions regarding the viability of drug targets.

To date, new technologies have led to an accumulation of data that is difficult to handle. The notion that scientists who are involved in interdisciplinary endeavors such as drug

research might 'drown' in the data flood has become very real. In order to be useful, data has to be ordered and linked in a logical and transparent manner. Also, it must be possible to connect heterogeneous databases in ways that allow the comprehensive evaluation of different classes of data, such as chemical, pharmacological, genetic and clinical data. This area has become a hunting ground for new biotechnology companies such as NetGenics (Cleveland, OH, USA).

Part 2 of this special report by Jurgen Drews will be continued in the January 2001 issue of *Drug Discovery Today*.

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End of collaboration…

Lexicon Genetics (The Woodlands, TX, USA) has announced the conclusion of its 1997 agreement with the **Merck Genome Research Institute** (MGRI, Whitehouse Station, NJ, USA). MGRI had provided an initial contribution of US$4 million, and additional funding over time, for the development of Lexicon's proprietary 'gene-trapping' process used in the generation of the Omnibank® library of knockout mouse clones for functional genomics research. After significant achievements, such as the widespread use of knockout mice from Omnibank, in both academic and industrial drug discovery processes, altering one-third of the mouse genome and the issuance of a patent to Lexicon for its 'gene-trapping' technology, MGRI and Lexicon have agreed to conclude their partnership. Lexicon regain exclusive rights to all lines of Omnibank mice produced for MGRI except those delivered before the end of the agreement. MGRI retain the rights to distribute Omnibank mice delivered before the conclusion of the agreement, but will allow Lexicon to include phenotypic information from such mice in their Lexicon LexVision™ database, which is designed to discover the function of thousands of genes that are putative drug targets.

Collaboration…

Bristol-Myers Squibb (BMS; New York, NY, USA) and **Lexicon Genetics** (The Woodlands, TX, USA) have announced a database access and license agreement aimed at high-throughput target validation. The agreement, which is for five years with an option for either party to terminate after three years, could result in Lexicon receiving between US$15 million and US$25 million in access and delivery fees, in addition to milestones and royalties on BMS products developed using Lexicon technology. BMS will have access to Lexicon's Lexvision™ database and Omnibank® knockout-mice library, which will provide crucial functional information for target validation and more efficient drug development.