PROSPECTUS SUPPLEMENT
(To Prospectus dated December 6, 2002)

10,000,000 Shares

Lexicon Genetics Incorporated

COMMON STOCK

We are offering 10,000,000 shares of our common stock.

Our common stock is quoted on the Nasdaq National Market under the symbol "LEXG." On July 23, 2003, the reported last sale price of our common stock on the Nasdaq National Market was $5.50 per share.

Investing in our common stock involves risks. See "Risk Factors" beginning on page S-7 of this prospectus supplement.

PRICE $5.25 A SHARE

	Price to Public	Underwriting Discounts and Commissions	Proceeds to Lexicon Genetics
Per Share	*$5.250*	*$.315*	*$4.935*
Total	*$52,500,000*	*$3,150,000*	*$49,350,000*

We have granted the underwriters the right to purchase up to an additional 1,500,000 shares to cover over-allotments.

The Securities and Exchange Commission and state securities regulators have not approved or disapproved these securities, or determined if this prospectus supplement or the accompanying prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares to purchasers on July 29, 2003.

MORGAN STANLEY ***UBS INVESTMENT BANK***

CIBC WORLD MARKETS ***PUNK, ZIEGEL & COMPANY***

July 23, 2003

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This prospectus supplement and the accompanying prospectus relate to the offer and sale by us of up to 10,000,000 shares of our common stock, and up to an additional 1,500,000 shares if the underwriters exercise their over-allotment option. You should rely only on the information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus. Neither we nor the underwriters have authorized anyone to provide you with information different from that contained or incorporated by reference in this prospectus supplement and the accompanying prospectus. We are offering to sell the shares of common stock, and are seeking offers to buy the shares of common stock, only in jurisdictions where offers and sales are permitted. The information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus is accurate only as of the date of this prospectus supplement, or the documents incorporated by reference, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or any sales of the shares of common stock.

In this prospectus supplement and the accompanying prospectus, unless otherwise indicated, "Lexicon," "Lexicon Genetics," "we," "us" and "our" refer to Lexicon Genetics Incorporated and its subsidiary, Lexicon Pharmaceuticals (New Jersey), Inc. We own or have rights to trademarks or trade names that we use in connection with the operation of our business. The Lexicon name and logo, LexVision® and OmniBank® are registered trademarks and Genome5000™ is a trademark of Lexicon Genetics Incorporated. This prospectus supplement and the accompanying prospectus also include trademarks owned by other persons.

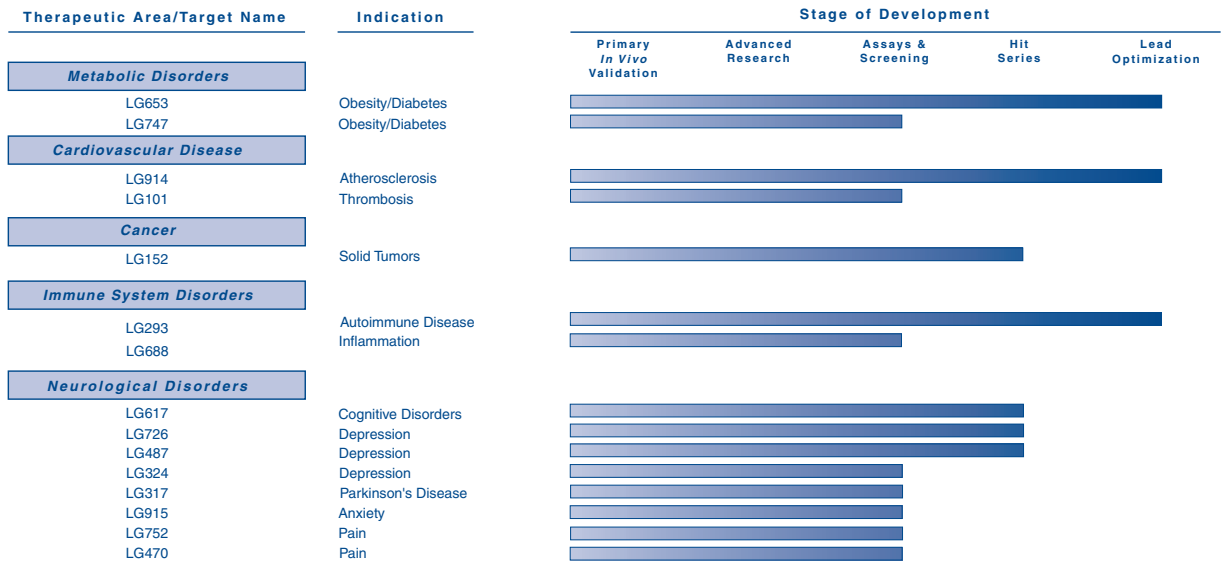
PROSPECTUS SUPPLEMENT SUMMARY

This summary does not contain all of the information that you should consider before investing in our common stock. You should read this entire prospectus supplement and the accompanying prospectus carefully, including "Risk Factors," the financial statements and other information incorporated by reference in this prospectus supplement and the accompanying prospectus, before making an investment decision.

LEXICON GENETICS

Lexicon Genetics is a biopharmaceutical company focused on the discovery of breakthrough treatments for human disease. We use proprietary gene knockout technology to systematically discover the physiological functions of genes in mice and to identify which corresponding human genes encode potential targets for therapeutic intervention, or drug targets. For those targets that we consider to have high pharmaceutical value, we engage in programs for the discovery and development of potential small molecule drugs, therapeutic antibodies and therapeutic proteins. Our physiology-based approach to understanding gene function and our use of mouse models in our drug discovery efforts allow us to make highly-informed decisions throughout the drug discovery and development process, which we believe will increase our likelihood of success in discovering breakthrough therapeutics.

The scope of our gene knockout technology, combined with the size and sophistication of our facilities and our evaluative technologies, provides us with what we believe to be a significant competitive advantage. We have completed our analysis of over 20% of the 5,000 genes in our Genome5000 program, and we expect to complete the analysis of the remaining genes by the end of 2007. We focus our discovery efforts in five therapeutic areas—metabolic disorders, cardiovascular disease, cancer, immune system disorders and neurological disorders—and we have established significant internal expertise in each of these areas. To date, we have advanced into drug discovery programs more than 20 targets, each of which we have validated in living mammals, or *in vivo*. We have highlighted 15 of our most advanced programs below.



The most advanced drug discovery programs in each of our therapeutic areas include:

Lead Metabolic Program—LG653. Our physiological analysis of LG653 in knockout mice suggests that LG653 plays a role in the regulation of metabolism. LG653 knockout mice displayed a 30% to 44% reduction in body fat, exhibited an increased metabolic rate and on average consumed 19% more food than normal mice. We have completed high-throughput screening against LG653 and have identified two series of potential lead compounds, which we are currently optimizing.

Lead Cardiovascular Program—LG914. Our physiological analysis of LG914 in knockout mice suggests that LG914 is involved in the regulation of certain cellular events associated with atherosclerosis and other coronary artery diseases. LG914 knockout mice exhibited reduced arterial thickening in response to an inflammatory stimulus compared to normal mice, and the inhibition of LG914 in mice with a genetic predisposition to atherosclerotic plaque resulted in a significant decrease in plaque formation. We are working in collaboration with Abgenix, Inc. to develop monoclonal antibodies to inhibit LG914.

Lead Cancer Program—LG152. Our physiological analysis of LG152 in knockout mice suggests that LG152 plays a significant role in the regulation of cell growth. LG152 knockout mice displayed a reduction in cell growth and proliferation, while over-expression of LG152 in mouse cell lines resulted in tumor formation. We have also observed over-expression of LG152 in human tumor cells isolated from melanomas and breast, colon, bladder and ovarian tumors. We have completed high-throughput screening against LG152 and have identified five series of hits, which we are currently analyzing.

Lead Immunology Program—LG293. Our physiological analysis of LG293 in knockout mice suggests that LG293 is involved in the regulation of immune system function and the maturation and proliferation of T and B cells, which are vital components of the immune system. LG293 knockout mice exhibited lower levels of circulating T and B cells, resulting in a reduction in the inflammatory response. Furthermore, LG293 knockout mice accepted transplanted tissues and mounted a significantly reduced inflammatory response when challenged. We have completed high-throughput screening against LG293 and have identified three series of potential lead compounds, which we are currently optimizing.

Lead Neurology Program—LG617. Our physiological analysis of LG617 in knockout mice suggests that LG617 plays a role in learning, attention and memory. LG617 knockout mice exhibited an increased amount of learned responses when challenged with a conditioned stimulus and demonstrated a significant increase in olfactory discrimination and exploratory behavior, each of which are widely accepted tests of learning and memory. We have completed high-throughput screening against LG617 and have identified six series of hits, which we are currently analyzing.

We are working both independently and through strategic collaborations and alliances to commercialize our technology and turn our discoveries into drugs. We have established multiple collaborations with leading pharmaceutical and biotechnology companies, as well as research institutes and academic institutions. We are working with Genentech, Inc. to discover the functions of secreted proteins and potential antibody targets identified through Genentech's internal drug discovery research. We are working with Abgenix to discover and develop therapeutic antibodies for *in vivo*-validated drug targets identified in our own research. We are also working with Incyte Corporation to discover and develop therapeutic proteins. In addition, we have established collaborations and license agreements with many other leading pharmaceutical and biotechnology companies under which we receive fees and, in many cases, are eligible to receive milestone and royalty payments, in return for granting access to some of our technologies and discoveries for use in such companies' own drug discovery efforts.

We were incorporated in Delaware in July 1995, and we commenced operations in September 1995. Our principal executive offices are located at 8800 Technology Forest Place, The Woodlands, Texas 77381, and our telephone number is (281) 863-3000. Our corporate website is located at www.lexicon-genetics.com. The information found on our website is not incorporated by reference into this prospectus supplement or the accompanying prospectus, and you should not consider it to be a part of this document.

THE OFFERING

Common stock offered	10,000,000 shares
Common stock to be outstanding after this offering	62,537,748 shares
Use of proceeds	The net proceeds of this offering are estimated to be approximately $49.0 million. We currently intend to use the net proceeds for research and development. We may also use a portion of the net proceeds to acquire or invest in complementary products and technologies or for general corporate purposes. See "Use of Proceeds."
Nasdaq National Market symbol	LEXG

The foregoing information is based on 52,537,748 shares of our common stock outstanding as of July 23, 2003 and excludes:

- 12,840,699 shares of common stock issuable upon the exercise of outstanding options at a weighted average exercise price per share of $6.14;
- 16,483 shares of common stock issuable upon the exercise of outstanding warrants at a weighted average exercise price per share of $11.93; and
- 1,102,832 shares of common stock available for future grant or issuance under our stock option plans, which will automatically be increased annually in accordance with the provisions of our stock option plans, except as may be limited by our board of directors.

Except as otherwise indicated, all information in this prospectus supplement assumes no exercise of the underwriters' over-allotment option in this offering.

SUMMARY FINANCIAL DATA

The statement of operations data for the year ended December 31, 2002 has been derived from our financial statements that have been audited by Ernst & Young LLP, independent auditors. The statements of operations data for each of the four years in the period ended December 31, 2001 have been derived from our audited financial statements that have been audited by Arthur Andersen LLP, independent public accountants who have ceased operations. The statements of operations data for the three months ended March 31, 2002 and 2003, and the balance sheet data as of March 31, 2003, are unaudited but include, in the opinion of management, all adjustments, consisting of only normal recurring adjustments, necessary for a fair presentation of such data. Our historical results for any prior or interim periods are not necessarily indicative of results to be expected for any future period.

The data presented below has been prepared in accordance with accounting principles generally accepted in the United States and should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations" included elsewhere in this prospectus supplement and with our financial statements and related notes incorporated by reference in this prospectus supplement and the accompanying prospectus.

	Year Ended December 31,					Three Months Ended March 31,	
	1998	1999	2000	2001	2002	2002	2003
						(unaudited)	
	(in thousands, except per share data)						
Statements of Operations Data:							
Revenues	$ 2,242	$ 4,738	$ 14,459	$ 30,577	$ 35,200	$ 7,656	$ 8,106
Operating expenses:							
Research and development[1]	8,410	14,646	31,647	53,355	74,859	16,864	19,834
General and administrative[2]	2,024	2,913	18,289	20,861	23,234	5,969	5,804
Total operating expenses	10,434	17,559	49,936	74,216	98,093	22,833	25,638
Loss from operations	(8,192)	(12,821)	(35,477)	(43,639)	(62,893)	(15,177)	(17,532)
Interest and other income, net	711	346	9,483	8,467	3,223	1,118	387
Net loss	(7,481)	(12,475)	(25,994)	(35,172)	(59,670)	(14,059)	(17,145)
Accretion on redeemable convertible preferred stock	(357)	(536)	(134)	—	—	—	—
Net loss attributable to common stockholders	$(7,838)	$(13,011)	$(26,128)	$(35,172)	$(59,670)	$(14,059)	$(17,145)
Net loss per common share, basic and diluted	$ (0.32)	$ (0.53)	$ (0.63)	$ (0.70)	$ (1.14)	$ (0.27)	$ (0.33)
Shares used in computing net loss per common share, basic and diluted	24,445	24,530	41,618	50,213	52,263	52,126	52,371

	As of March 31, 2003	
	Actual	As Adjusted[4]
	(unaudited) (in thousands)	
Balance Sheet Data:		
Cash, cash equivalents, restricted cash and investments[3]	$ 107,587	$ 156,537
Working capital[3]	99,197	148,147
Total assets	181,967	230,917
Long-term debt, net of current portion	4,000	4,000
Accumulated deficit	(166,890)	(166,890)
Stockholders' equity	155,321	204,271

(1) Includes stock-based compensation of $10,883 in 2000, $5,539 in 2001, $5,155 in 2002, $1,307 for the three months ended March 31, 2002 and $1,270 for the three months ended March 31, 2003.

(2) Includes stock-based compensation of $9,958 in 2000, $5,231 in 2001, $5,113 in 2002, $1,282 for the three months ended March 31, 2002 and $1,276 for the three months ended March 31, 2003.

(3) Includes restricted cash and investments of $57,710 as of March 31, 2003.

(4) Reflects the net proceeds from the sale of 10,000,000 shares of common stock in this offering at the public offering price of $5.25 per share after deducting underwriting discounts and commissions and estimated offering expenses.

RISK FACTORS

An investment in our common stock involves risks. You should carefully consider the following risk factors, together with all of the other information included in, or incorporated by reference into, this prospectus supplement and the accompanying prospectus in evaluating an investment in our common stock. If any of the following risks were to occur, our business, financial condition or results of operations could be materially adversely affected. In that case, the trading price of our common stock could decline and you could lose all or part of your investment.

Risks Related to Our Company and Business

We have a history of net losses, and we expect to continue to incur net losses and may not achieve or maintain profitability.

We have incurred net losses since our inception, including net losses of $59.7 million for the year ended December 31, 2002 and $17.1 million for the three months ended March 31, 2003. As of March 31, 2003, we had an accumulated deficit of $166.9 million. We are unsure when we will become profitable, if ever. The size of our net losses will depend, in part, on the rate of growth, if any, in our revenues and on the level of our expenses.

We derive substantially all of our revenues from subscriptions to our LexVision database and our OmniBank library, drug discovery alliances, target validation collaborations for the development and, in some cases, analysis of the physiological effects of genes altered in knockout mice and technology licenses, and will continue to do so for the foreseeable future. Our future revenues from database subscriptions, alliances and collaborations are uncertain because our existing agreements have fixed terms or relate to specific projects of limited duration. Our future revenues from technology licenses are uncertain because they depend, in part, on securing new agreements. Our ability to secure future revenue-generating agreements will depend upon our ability to address the needs of our potential future subscribers, collaborators and licensees, and to negotiate agreements that we believe are in our long-term best interests. We may determine that our interests are better served by retaining rights to our discoveries and advancing our therapeutic programs to a later stage, which could limit our near-term revenues. Given the early-stage nature of our operations, we do not currently derive any revenues from sales of pharmaceuticals.

A large portion of our expenses is fixed, including expenses related to facilities, equipment and personnel. In addition, we expect to spend significant amounts to fund research and development and to enhance our core technologies. As a result, we expect that our operating expenses will continue to increase significantly in the near term and, consequently, we will need to generate significant additional revenues to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis.

We will need additional capital in the future and, if it is not available, we will have to curtail or cease operations.

Our future capital requirements will be substantial and will depend on many factors, including:

- our ability to obtain alliance, database subscription, collaboration and technology license agreements;
- the amount and timing of payments under such agreements;
- the level and timing of our research and development expenditures;
- market acceptance of products that we successfully develop and commercially launch; and
- the resources we devote to developing and supporting such products.

Our capital requirements will increase substantially to the extent we advance potential therapeutics into preclinical and clinical development. Our capital requirements will also be affected by any expenditures we make in connection with license agreements and acquisitions of and investments in complementary products and technologies.

We anticipate that the net proceeds of this offering, our existing capital resources and the revenues we expect to derive from drug discovery alliances, subscriptions to our databases, target validation collaborations and technology licenses will enable us to fund our currently planned operations for approximately the next 24 months. However, we may generate less revenues than we expect, and changes may occur that would consume available capital resources more rapidly than we expect. If our capital resources are insufficient to meet future capital requirements, we will have to raise additional funds to continue the development of our technologies and complete the commercialization of products, if any, resulting from our technologies. Any sale of additional equity securities may result in additional dilution to our stockholders, and we cannot be certain that additional financing, whether debt or equity, will be available in amounts or on terms acceptable to us, if at all. In addition, any of such additional equity securities may be senior to our common stock. We may be unable to raise sufficient additional capital; if so, we will have to curtail or cease operations.

We are an early-stage company, and we have not successfully developed or commercialized any therapeutics or drug targets that we have identified.

Our business strategy of using our technology platform and, specifically, the discovery of the functions of genes using knockout mice to select promising drug targets and developing and commercializing drugs based on our discoveries, in significant part through collaborations and alliances, is unproven. Our success will depend upon our ability to successfully develop potential therapeutics for drug targets we consider to have pharmaceutical value, whether on our own or through collaborations, and to select an appropriate commercialization strategy for each potential therapeutic we choose to pursue.

Biotechnology and pharmaceutical companies have successfully developed and commercialized only a limited number of genomics-derived pharmaceutical products to date. We have not proven our ability to develop or commercialize therapeutics or drug targets that we identify, nor have we advanced any drug candidates to preclinical or clinical trials. We do not know that any pharmaceutical products based on our drug target discoveries can be successfully commercialized. In addition, we may experience unforeseen technical complications in the processes we use to generate gene knockout mice, conduct *in vivo* analyses, generate compound libraries, develop screening assays for drug targets or conduct screening of compounds against those drug targets. These complications could materially delay or limit the use of those resources, substantially increase the anticipated cost of generating them or prevent us from implementing our processes at appropriate quality and throughput levels. Finally, the information that we learn from knockout mice may prove not to be useful in identifying pharmaceutically-important drug targets or safe and effective therapies.

We face substantial competition in the discovery of the DNA sequences of genes and their functions and in our drug discovery and product development efforts.

There are a finite number of genes in the human genome, and we believe that the majority of such genes have been identified and that virtually all will be identified within the next few years. We face substantial competition in our efforts to discover and patent the sequence and other information derived from such genes from entities using alternative, and in some cases higher volume and larger scale, approaches for the same purpose.

We also face competition from other companies in our efforts to discover the functions of genes. A large number of universities and other not-for-profit institutions, many of which are funded by the United States and foreign governments, are also conducting research to discover the functions of genes. Competitors could discover and establish patents on genes or gene products that we identify as promising drug targets, which might hinder or prevent our ability to capitalize on such targets.

We may not be able to use our patent rights to prevent competition in the creation and use of knockout mice to discover the function of genes. Patent litigation is very expensive and time-consuming, and, therefore, it may not be cost-effective or otherwise expedient to pursue litigation if another entity infringes our patent rights relating to the creation and use of knockout mice. Our patent rights generally do not extend outside of the United States. We therefore are generally unable to prevent entities outside of the United States from using our knockout mouse technology or, in certain circumstances, from importing into the United States

products developed using this technology. Furthermore, other methods for conducting target validation research may ultimately prove superior, in some or all respects, to the use of knockout mice. In addition, technologies more advanced than or superior to our gene targeting and gene trapping technologies may be developed, thereby rendering those technologies obsolete.

We face significant competition from other companies, as well as from universities and other not-for-profit institutions, in our drug discovery and product development efforts. Many of our competitors have substantially greater financial, scientific and human resources than we do. As a result, our competitors may succeed in developing products earlier than we do, obtaining regulatory approvals faster than we do and developing products that are more effective or safer than any that we may develop.

We rely heavily on our collaborators to develop and commercialize pharmaceutical products based on genes that we identify as promising candidates for development as drug targets.

Since we do not currently possess the resources necessary to develop, obtain approvals for or commercialize potential pharmaceutical products based on all of the genes that we identify as promising candidates for development as drug targets or therapeutic proteins, we must enter into collaborative arrangements to develop and commercialize some of these products. We have limited or no control over the resources that any collaborator may devote to this effort. Any of our present or future collaborators may not perform their obligations as expected. These collaborators may breach or terminate their agreements with us or otherwise fail to conduct product discovery, development or commercialization activities successfully or in a timely manner. Further, our collaborators may elect not to develop pharmaceutical products arising out of our collaborative arrangements or may not devote sufficient resources to the development, approval, manufacture, marketing or sale of these products. If any of these events occurs, we may not be able to develop or commercialize potential pharmaceutical products.

Some of our existing collaboration agreements contain, and collaborations that we enter into in the future may contain, exclusivity agreements by us or other limitations on our activities. These agreements may have the effect of limiting our flexibility and may cause us to forego attractive business opportunities.

We rely on several key collaborators for a significant portion of our revenues.

Most of our revenues in 2002 and the first quarter of 2003 were derived from a limited number of collaborators. For the fiscal year ended December 31, 2002, Incyte accounted for approximately 28% of our revenues, Bristol-Myers Squibb Company accounted for approximately 14% of our revenues and Millennium Pharmaceuticals, Inc. accounted for approximately 11% of our revenues. For the three months ended March 31, 2003, Incyte accounted for approximately 31% of our revenues, Bristol-Myers Squibb accounted for approximately 16% of our revenues and Genentech accounted for approximately 9% of our revenues. In general, we cannot predict with certainty which, if any, of our major collaborators will continue to generate revenues for us. The loss of any of these large collaborators would likely significantly decrease our revenues and future prospects, which could materially and adversely affect our business, financial condition and results of operations.

Cancellations by or conflicts with our collaborators could harm our business.

Our alliance and collaboration agreements may not be renewed and may be terminated in the event either party fails to fulfill its obligations under these agreements. Failures to renew or cancellations by collaborators could mean a significant loss of revenues and could adversely affect our reputation in the business and scientific communities.

In addition, we may pursue opportunities in fields that could conflict with those of our collaborators. Moreover, disagreements could arise with our collaborators over rights to our intellectual property or our rights to share in any of the future revenues of compounds or therapeutic approaches developed by our collaborators. These kinds of disagreements could result in costly and time-consuming litigation. Conflicts with our collaborators could reduce our ability to obtain future collaboration agreements and could have a negative impact on our relationship with existing collaborators, adversely affecting our business and revenues. Some of

our collaborators are also potential competitors or may become competitors in the future. Our collaborators could develop competing products, preclude us from entering into collaborations with their competitors or terminate their agreements with us prematurely. Any of these events could harm our product development efforts.

We have no experience in developing and commercializing pharmaceutical products on our own.

Our ability to develop and commercialize pharmaceutical products on our own will depend on our ability to internally develop preclinical, clinical, regulatory and sales and marketing capabilities, or enter into arrangements with third parties to provide these functions. It will be expensive and will require significant time for us to develop these capabilities internally. We may not be successful in developing these capabilities or entering into agreements with third parties on favorable terms, or at all. Further, our reliance upon third parties for these capabilities could reduce our control over such activities and could make us dependent upon these parties. Our inability to develop or contract for these capabilities would significantly impair our ability to develop and commercialize pharmaceutical products.

We lack the capability to manufacture compounds for preclinical studies, clinical trials or commercial sales and will rely on third parties to manufacture our potential products.

We currently do not have the manufacturing capabilities or experience necessary to produce materials for preclinical studies, clinical trials or commercial sales and intend to rely on collaborators and third-party contractors to produce such materials. We will rely on selected manufacturers to deliver materials on a timely basis and to comply with applicable regulatory requirements, including the current Good Manufacturing Practices of the United States Food and Drug Administration, or FDA, which relate to manufacturing and quality control activities. These manufacturers may not be able to produce material on a timely basis or manufacture material at the quality level or in the quantity required to meet our development timelines and applicable regulatory requirements. In addition, there are a limited number of manufacturers that operate under the FDA's current Good Manufacturing Practices and that are capable of producing such materials, and we may experience difficulty finding manufacturers with adequate capacity for our needs. If we are unable to contract for the production of sufficient quantity and quality of materials on acceptable terms, our product development and commercialization efforts may be delayed. Moreover, noncompliance with the FDA's current Good Manufacturing Practices can result in, among other things, fines, injunctions, civil and criminal penalties, product recalls or seizures, suspension of production, failure to obtain marketing approval and withdrawal, suspension or revocation of marketing approvals.

We may engage in future acquisitions, which may be expensive and time consuming and from which we may not realize anticipated benefits.

We may acquire additional businesses, technologies and products if we determine that these businesses, technologies and products complement our existing technology or otherwise serve our strategic goals. We currently have no commitments or agreements with respect to any acquisitions. If we do undertake any transactions of this sort, the process of integrating an acquired business, technology or product may result in operating difficulties and expenditures and may absorb significant management attention that would otherwise be available for ongoing development of our business. Moreover, we may never realize the anticipated benefits of any acquisition. Future acquisitions could result in potentially dilutive issuances of our equity securities, the incurrence of debt and contingent liabilities and amortization expenses related to intangible assets, which could adversely affect our results of operations and financial condition.

If we lose our key personnel or are unable to attract and retain additional personnel, we may be unable to pursue collaborations or develop our own products.

We are highly dependent on Arthur T. Sands, M.D., Ph.D., our president and chief executive officer, as well as other principal members of our management and scientific staff. The loss of any of these personnel could have a material adverse effect on our business, financial condition or results of operations and could inhibit our product development and commercialization efforts. Although we have entered into employment

agreements with some of our key personnel, including Dr. Sands, these employment agreements are all at-will. In addition, not all key personnel have employment agreements.

Recruiting and retaining qualified scientific personnel to perform future research and development work will be critical to our success. Competition for experienced scientists is intense. Failure to recruit and retain scientific personnel on acceptable terms could prevent us from achieving our business objectives.

Because all of our target validation operations are located at a single facility, the occurrence of a disaster could significantly disrupt our business.

Our OmniBank mouse clone library and its backup are stored in liquid nitrogen freezers located at our facility in The Woodlands, Texas, and our knockout mouse research operations are carried out entirely at the same facility. While we have developed redundant and emergency backup systems to protect these resources and the facilities in which they are stored, they may be insufficient in the event of a severe fire, flood, hurricane, tornado, mechanical failure or similar disaster. If such a disaster significantly damages or destroys the facility in which these resources are maintained, our business could be disrupted until we could regenerate the affected resources and, as a result, our stock price could decline. Our business interruption insurance may not be sufficient to compensate us in the event of a major interruption due to such a disaster.

Our quarterly operating results have been and likely will continue to fluctuate, and we believe that quarter-to-quarter comparisons of our operating results are not a good indication of our future performance.

Our operating results and, in particular, our ability to generate additional revenues are dependent on many factors, including:

- our ability to establish new database subscriptions, research collaborations and technology licenses, and the timing of such arrangements;
- the expiration or other termination of database subscriptions and research collaborations with our collaborators, which may not be renewed or replaced;
- the success rate of our discovery efforts leading to opportunities for new research collaborations and licenses, as well as milestone payments and royalties;
- the timing and willingness of our collaborators to commercialize pharmaceutical products that would result in milestone payments and royalties; and
- general and industry-specific economic conditions, which may affect our and our collaborators' research and development expenditures.

Because of these and other factors, including the risks and uncertainties described in this section, our quarterly operating results have fluctuated in the past and are likely to do so in the future. Due to the likelihood of fluctuations in our revenues and expenses, we believe that quarter-to-quarter comparisons of our operating results are not a good indication of our future performance.

Risks Related to Our Industry

Our ability to patent our inventions is uncertain because patent laws and their interpretation are highly uncertain and subject to change.

The patent positions of biotechnology firms generally are highly uncertain and involve complex legal and factual questions that will determine who has the right to develop or use a particular technology or product. No clear policy has emerged regarding the scope of protection provided in biotechnology patents. The biotechnology patent situation outside the United States is similarly uncertain. Changes in, or different interpretations of, patent laws in the United States or other countries might allow others to use our inventions or to develop and commercialize any technologies or products that we may develop without any compensation to us. We anticipate that these uncertainties will continue for a significant period of time.

Our patent applications may not result in patent rights.

Our disclosures in our patent applications may not be sufficient to meet the statutory requirements for patentability. Our ability to obtain patent protection based on genes or gene sequences will depend, in part, upon identification of a use for the gene or gene sequences sufficient to meet the statutory requirements that an invention have utility and that a patent application enable one to make and use the invention. While the United States Patent and Trademark Office has issued guidelines for the examination of patent applications claiming gene sequences, their therapeutic uses and novel proteins encoded by such genes, the impact of these guidelines is uncertain and may delay or negatively affect our patent position. Furthermore, biologic data in addition to that obtained by our current technologies may be required for issuance of patents covering any potential human therapeutic products that we may develop. If required, obtaining such biologic data could delay, add substantial costs to, or affect our ability to obtain patent protection for such products. There can be no assurance that the disclosures in our current or future patent applications, including those we may file with our collaborators, will be sufficient to meet these requirements. Even if patents are issued, there may be current or future uncertainty as to the scope of the coverage or protection provided by any such patents.

Some court decisions indicate that disclosure of a partial sequence may not be sufficient to support the patentability of a full-length sequence. These decisions have been confirmed by recent pronouncements of the United States Patent and Trademark Office. We believe that these court decisions and the uncertain position of the United States Patent and Trademark Office present a significant risk that the United States Patent and Trademark Office will not issue patents based on patent disclosures limited to partial gene sequences. In addition, we are uncertain about the scope of the coverage, enforceability and commercial protection provided by any patents issued primarily on the basis of gene sequence information.

If other companies and institutions obtain patents relating to our drug target or product candidate discoveries, we may be unable to obtain patents for our inventions based upon those discoveries and may be blocked from using or developing some of our technologies and products.

Many other entities have filed or may file patent applications on genes or gene sequences, uses of those genes or genes sequences, gene products and drug targets, assays for identifying potential therapeutic products, potential therapeutic products and methods of treatment which are identical or similar to some of our filings. Some of these applications attempt to assign biologic function to the genes and proteins based on predictions of function based upon similarity to other genes and proteins or patterns of gene expression. There is the significant possibility that patents claiming the functional uses of such genes and gene products will be issued to our competitors based on such information. If any such patents are issued to other entities, we will be unable to obtain patent protection for the same or similar discoveries that we make. Moreover, we may be blocked from using or developing some of our existing or proposed technologies and products, or may be required to obtain a license that may not be available on reasonable terms, if at all.

Alternatively, the United States Patent and Trademark Office could decide competing patent claims in an interference proceeding. Any such proceeding would be costly, and we may not prevail. In this event, the prevailing party may require us or our collaborators to stop using a particular technology or pursuing a potential product or may require us to negotiate a license arrangement to do so. We may not be able to obtain a license from the prevailing party on acceptable terms, or at all.

The Human Genome Project, as well as many companies and institutions, have identified genes and deposited partial gene sequences in public databases and are continuing to do so. The entire human genome and the entire mouse genome are now publicly known. These public disclosures might limit the scope of our claims or make unpatentable subsequent patent applications on partial or full-length genes or their uses.

Issued or pending patents may not fully protect our discoveries, and our competitors may be able to commercialize technologies or products similar to those covered by our issued or pending patents.

Pending patent applications do not provide protection against competitors because they are not enforceable until they issue as patents. Issued patents may not provide commercially meaningful protection. If anyone infringes upon our or our collaborators' patent rights, enforcing these rights may be difficult, costly and

time-consuming. Others may be able to design around these patents or develop unique products providing effects similar to any products that we may develop. Other companies or institutions may challenge our or our collaborators' patents or independently develop similar products that could result in an interference proceeding in the United States Patent and Trademark Office or a legal action.

In addition, others may discover uses for genes, drug targets or therapeutic products other than those covered in our issued or pending patents, and these other uses may be separately patentable. Even if we have a patent claim on a particular gene, drug target or therapeutic product, the holder of a patent covering the use of that gene, drug target or therapeutic product could exclude us from selling a product that is based on the same use of that product.

We may be involved in patent litigation and other disputes regarding intellectual property rights and may require licenses from third parties for our discovery and development and planned commercialization activities. We may not prevail in any such litigation or other dispute or be able to obtain required licenses.

Our discovery and development efforts as well as our potential products and those of our collaborators may give rise to claims that they infringe the patents of others. This risk will increase as the biotechnology industry expands and as other companies and institutions obtain more patents covering the sequences, functions and uses of genes and the drug targets they encode. We are aware that other companies and institutions have conducted research on many of the same targets that we have identified. These other companies and institutions have filed and may in the future file patent applications potentially covering many of the genes and encoded drug targets that are the focus of our drug discovery programs, including each of the targets of our most advanced drug discovery programs. In some cases, patents have issued from these applications. In addition, many companies and institutions have well-established patent portfolios directed to common techniques, methods and means of developing, producing and manufacturing pharmaceutical products. Other companies or institutions could bring legal actions against us or our collaborators for damages or to stop us or our collaborators from engaging in certain discovery or development activities or from manufacturing and marketing any resulting therapeutic products. If any of these actions are successful, in addition to our potential liability for damages, these entities would likely require us or our collaborators to obtain a license in order to continue engaging in the infringing activities or to manufacture or market the resulting therapeutic products or may force us to terminate such activities or manufacturing and marketing efforts. We may also determine to seek licenses from these entities in order to avoid the cost and expense of litigation.

We may need to pursue litigation against others to enforce our patents and intellectual property rights and may be the subject of litigation brought by third parties to enforce their patent and intellectual property rights. In addition, we may become involved in litigation based on intellectual property indemnification undertakings that we have given to certain of our collaborators. Patent litigation is expensive and requires substantial amounts of management attention. The eventual outcome of any such litigation is uncertain and involves substantial risks. For example, each time we sue for patent infringement we face the risk that the patent will be held invalid or unenforceable. Such a determination is binding on us for all future litigation involving that patent.

We believe that there will continue to be significant litigation in our industry regarding patent and other intellectual property rights. We have expended and many of our competitors have expended and are continuing to expend significant amounts of time, money and management resources on intellectual property litigation. If we become involved in future intellectual property litigation, it could consume a substantial portion of our resources and could negatively affect our results of operations.

In 2000, we filed lawsuits against Deltagen, Inc. relating to infringement of a number of United States patents licensed to us. In September 2001, we and Deltagen settled the litigation. Under the terms of the settlement, Deltagen obtained a sublicense under the patents and we obtained a subscription to Deltagen's DeltaBase product, including perpetual licenses to approximately 1,250 drug targets in DeltaBase at the time or expected to be added to DeltaBase over the subsequent four years. In October 2002, we notified Deltagen of its failure to perform under our agreements related to the settlement, and in April 2003, we asserted certain

claims against Deltagen under those agreements. In accordance with the dispute resolution provisions of those agreements, arbitration proceedings have been initiated to resolve these matters.

In June 2003, Deltagen publicly asserted that we made our claims for competitive reasons in an attempt to interfere with Deltagen's financing efforts and with Deltagen's negotiations with current and prospective customers. Deltagen has also stated that it will hold us fully responsible for the damage allegedly done to Deltagen by our actions. On June 27, 2003, Deltagen filed for Chapter 11 bankruptcy protection, and the arbitration proceedings were automatically stayed. We believe that Deltagen's assertion regarding the reason for our claims and Deltagen's statements of purported illegal conduct on our part are without merit.

Furthermore, in light of recent United States Supreme Court precedent, our ability to enforce our patents against state agencies, including state sponsored universities and research laboratories, is limited by the Eleventh Amendment to the United States Constitution. In addition, opposition by academicians and the government may hamper our ability to enforce our patents against academic or government research laboratories. Finally, enforcement of our patents may cause our reputation in the academic community to be injured.

We use intellectual property that we license from third parties. If we do not comply with these licenses, we could lose our rights under them.

We rely, in part, on licenses to use certain technologies that are important to our business. We do not own the patents that underlie these licenses. Our rights to use these technologies and practice the inventions claimed in the licensed patents are subject to our abiding by the terms of those licenses and the licensors not terminating them. In many cases, we do not control the filing, prosecution or maintenance of the patent rights to which we hold licenses and rely upon our licensors to prosecute infringement of those rights. The scope of our rights under our licenses may be subject to dispute by our licensors or third parties.

We have not sought patent protection outside of the United States for some of our inventions, and some of our licensed patents only provide coverage in the United States.

We have decided not to pursue patent protection with respect to some of our inventions outside the United States, both because we do not believe it is cost-effective and because of confidentiality concerns. Accordingly, our international competitors could develop, and receive foreign patent protection for, genes or gene sequences, uses of those genes or gene sequences, gene products and drug targets, assays for identifying potential therapeutic products, potential therapeutic products and methods of treatment for which we are seeking United States patent protection. In addition, most of our gene trapping patents and our licensed gene targeting patents cover only the United States and do not apply to discovery activities conducted outside of the United States or, in some circumstances, to importing into the United States products developed using this technology.

We may be unable to protect our trade secrets.

Significant aspects of our intellectual property are not protected by patents. As a result, we seek to protect the proprietary nature of this intellectual property as trade secrets through proprietary information agreements and other measures. While we have entered into proprietary information agreements with all of our employees, consultants, advisers and collaborators, we may not be able to prevent the disclosure of our trade secrets. In addition, other companies or institutions may independently develop substantially equivalent information and techniques.

Our efforts to discover, evaluate and validate potential targets for therapeutic intervention and our drug discovery programs are subject to evolving data and other risks inherent in the drug discovery process.

We are employing our knockout technology and integrated drug discovery platform to systematically discover, evaluate and validate potential targets for therapeutic intervention and to develop drugs to address those targets. The drug discovery and development process involves significant risks of delay or failure due, in

part, to evolving data and the uncertainties involved with the applications of new technologies. As we refine and advance our efforts, it is likely that the resulting data will cause us to change our targets from time to time and, therefore, that the targets that we believe at any time to be promising may prove not to be so. These developments can occur at any stage of the drug discovery and development process.

We are subject to extensive and uncertain government regulatory requirements, which could adversely affect our ability to obtain, in a timely manner or at all, government approval of products based on genes that we identify, or to commercialize such products.

We must obtain approval from the FDA in order to conduct clinical trials and sell our future product candidates in the United States and from foreign regulatory authorities in order to conduct clinical trials and sell our future product candidates in other countries. In order to obtain regulatory approvals for the commercial sale of any products that we may develop, we will be required to complete extensive clinical trials in humans to demonstrate the safety and efficacy of our drug candidates. We may not be able to obtain authority from the FDA or other equivalent foreign regulatory agencies to initiate or complete any clinical trials. In addition, we have limited internal resources for making regulatory filings and dealing with regulatory authorities.

The results from preclinical testing of a drug candidate that is under development may not be predictive of results that will be obtained in human clinical trials. In addition, the results of early human clinical trials may not be predictive of results that will be obtained in larger scale, advanced stage clinical trials. A number of companies in the pharmaceutical industry have suffered significant setbacks in advanced clinical trials, even after achieving positive results in earlier trials. Negative or inconclusive results from a preclinical study or a clinical trial could cause us, one of our collaborators or the FDA to terminate a preclinical study or clinical trial or require that we repeat it. Furthermore, we, one of our collaborators or a regulatory agency with jurisdiction over the trials may suspend clinical trials at any time if the subjects or patients participating in such trials are being exposed to unacceptable health risks or for other reasons.

Any preclinical or clinical test may fail to produce results satisfactory to the FDA or foreign regulatory authorities. Preclinical and clinical data can be interpreted in different ways, which could delay, limit or prevent regulatory approval. The FDA or institutional review boards at the medical institutions and healthcare facilities where we sponsor clinical trials may suspend any trial indefinitely if they find deficiencies in the conduct of these trials. We must conduct clinical trials in accordance with the FDA's current Good Clinical Practices. The FDA and these institutional review boards have authority to oversee our clinical trials, and the FDA may require large numbers of test subjects. In addition, we must manufacture, or contract for the manufacture of, the product candidates that we use in our clinical trials under the FDA's current Good Manufacturing Practices.

The rate of completion of clinical trials is dependent, in part, upon the rate of enrollment of patients. Patient accrual is a function of many factors, including the size of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the study, the nature of the study, the existence of competitive clinical trials and the availability of alternative treatments. Delays in planned patient enrollment may result in increased costs and prolonged clinical development, which in turn could allow our competitors to bring products to market before we do and impair our ability to commercialize our products or potential products.

We may not be able to successfully complete any clinical trial of a potential product that we may initiate within any specified time period. In some cases, we may not be able to complete the trial at all. Moreover, clinical trials may not show our potential products to be both safe and effective. Thus, the FDA and other regulatory authorities may not approve any products that we develop for any indication or may limit the approved indications or impose other conditions.

If we obtain regulatory approval for our potential products, we will remain subject to extensive and rigorous ongoing regulation.

If we obtain initial regulatory approvals from the FDA or foreign regulatory authorities for any products that we may develop, we will be subject to extensive and rigorous ongoing domestic and foreign government regulation of, among other things, the research, development, testing, manufacture, labeling, promotion, advertising, distribution and marketing of our products and product candidates. Our failure to comply with these requirements or the identification of safety problems during commercial marketing could lead to the need for product marketing restrictions, product withdrawal or recall or other voluntary or regulatory action, which could delay further marketing until the product is brought into compliance. Our failure to comply with these requirements may also subject us to stringent penalties.

Moreover, several of our product development areas involve relatively new technology and have not been the subject of extensive product testing in humans. The regulatory requirements governing these products and related clinical procedures remain uncertain and the products themselves may be subject to substantial review by foreign governmental regulatory authorities that could prevent or delay approval in those countries. Regulatory requirements ultimately imposed on any products that we may develop could limit our ability to test, manufacture and, ultimately, commercialize such products.

The uncertainty of pharmaceutical pricing and reimbursement may decrease the commercial potential of any products that we or our collaborators may develop and affect our ability to raise capital.

Our ability and the ability of our collaborators to successfully commercialize pharmaceutical products will depend, in part, on the extent to which reimbursement for the cost of such products and related treatment will be available from government health administration authorities, private health coverage insurers and other organizations. The pricing, availability of distribution channels and reimbursement status of newly approved pharmaceutical products is highly uncertain. As a result, adequate third-party coverage may not be available for us to maintain price levels sufficient for realization of an appropriate return on our investment in product discovery and development.

In certain foreign markets, pricing or profitability of healthcare products is subject to government control. In the United States, there have been, and we expect that there will continue to be, a number of federal and state proposals to implement similar governmental control. In addition, an increasing emphasis on managed care in the United States has increased and will continue to increase the pressure on pharmaceutical pricing. While we cannot predict the adoption of any such legislative or regulatory proposals or the effect such proposals or managed care efforts may have on our business, the announcement of such proposals or efforts could harm our ability to raise capital, and the adoption of such proposals or efforts could harm our results of operations. Further, to the extent that such proposals or efforts harm other pharmaceutical companies that are our prospective collaborators, our ability to establish corporate collaborations would be impaired. In addition, third-party payers are increasingly challenging the prices charged for medical products and services. We do not know whether consumers, third-party payers and others will consider any products that we or our collaborators develop to be cost-effective or that reimbursement to the consumer will be available or will be sufficient to allow us or our collaborators to sell such products on a profitable basis.

We use hazardous chemicals and radioactive and biological materials in our business; any disputes relating to improper handling, storage or disposal of these materials could be time consuming and costly.

Our research and development processes involve the use of hazardous materials, including chemicals and radioactive and biological materials. Our operations also produce hazardous waste products. We cannot eliminate the risk of accidental contamination or discharge or any resultant injury from these materials. Federal, state and local laws and regulations govern the use, manufacture, storage, handling and disposal of these materials. We could be subject to civil damages in the event of an improper or unauthorized release of, or exposure of individuals to, these hazardous materials. In addition, claimants may sue us for injury or contamination that results from our use or the use by third parties of these materials, and our liability may

exceed our total assets. Compliance with environmental laws and regulations may be expensive, and current or future environmental regulations may impair our research, development or production efforts.

We may be sued for product liability.

We or our collaborators may be held liable if any product that we or our collaborators develop, or any product that is made with the use or incorporation of any of our technologies, causes injury or is found otherwise unsuitable during product testing, manufacturing, marketing or sale. Although we currently have and intend to maintain product liability insurance, this insurance may become prohibitively expensive or may not fully cover our potential liabilities. Our inability to obtain sufficient insurance coverage at an acceptable cost or otherwise to protect against potential product liability claims could prevent or inhibit the commercialization of products developed by us or our collaborators. If we are sued for any injury caused by our or our collaborators' products, our liability could exceed our total assets.

Public perception of ethical and social issues may limit or discourage the use of our technologies, which could reduce our revenues.

Our success will depend, in part, upon our ability to develop products discovered through our knockout mouse technologies. Governmental authorities could, for ethical, social or other purposes, limit the use of genetic processes or prohibit the practice of our knockout mouse technologies. Claims that genetically engineered products are unsafe for consumption or pose a danger to the environment may influence public perceptions. The subject of genetically modified organisms, like knockout mice, has received negative publicity and aroused public debate in some countries. Ethical and other concerns about our technologies, particularly the use of genes from nature for commercial purposes and the products resulting from this use, could adversely affect the market acceptance of our technologies.

Risks Related to this Offering

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

As of the date of this prospectus supplement, we cannot specify with certainty the particular uses for the net proceeds we will receive from this offering. Management will have broad discretion in the application of the net proceeds, including any of the purposes described in "Use of Proceeds." The failure by our management to apply these funds effectively could have a material adverse effect on our business.

Our stock price could be extremely volatile, and you may not be able to resell your shares at or above the public offering price.

The stock market has experienced significant price and volume fluctuations, and the market prices of technology companies, particularly life science companies such as ours, have been highly volatile. Since January 1, 2001, the market price of our common stock has ranged from a high of $17.25 on January 2, 2001 to a low of $2.97 on October 7, 2002. In addition, broad market and industry fluctuations that are not within our control may adversely affect the trading price of our common stock. As a result, you may not be able to resell your shares at or above the public offering price.

Concentration of ownership among our directors and executive officers enables them to significantly influence important corporate decisions.

Following this offering, our directors and executive officers will beneficially own, or have voting rights with respect to, approximately 24.7% of our outstanding common stock. These stockholders as a group will be able to exert significant influence on the election of our directors and officers, the management and affairs of our company and the outcome of most matters requiring the approval of our stockholders, including any merger, consolidation or sale of all or substantially all of our assets and any other significant corporate transaction. This concentration of ownership may also prevent a change of control of our company at a

premium price if these stockholders oppose it. Please read "Principal Stockholders" for details on our stock ownership.

Provisions contained in our charter documents and Delaware law may inhibit a takeover attempt, which could reduce or eliminate the likelihood of a change of control transaction and, therefore, the ability of our stockholders to sell their shares for a premium.

Provisions in our corporate charter and bylaws and applicable provisions of the Delaware General Corporation Law may make it more difficult for a third party to acquire control of us without the approval of our board of directors. These provisions include:

- a classified board of directors;
- limitations on the removal of directors;
- limitations on stockholder proposals at meetings of stockholders;
- the inability of stockholders to act by written consent or to call special meetings; and
- the ability of our board of directors to designate the terms of and issue new series of preferred stock without stockholder approval.

These provisions may discourage transactions that otherwise could involve the payment of a premium over prevailing market prices of our common stock.

The availability of shares of our common stock for future sale could depress our stock price.

Upon completion of this offering, we will have outstanding an aggregate of 62,537,748 shares of common stock, assuming no exercise of outstanding options or warrants. Of these shares, 47,474,357 shares are freely tradable. The holders of the remaining 15,063,391 shares have demand and piggyback registration rights with respect to such shares. We have received a request for the registration of an aggregate of 5,000,000 shares, which we will include in a registration statement to be filed after the expiration of the 90-day lock-up period described below.

Sales of a substantial number of shares of our common stock in the public markets following this offering, or the perception that such sales might occur, could have a material adverse effect on the price of our common stock or could impair our future ability to obtain capital through offerings of our equity securities.

Our executive officers, directors and certain of our stockholders have agreed pursuant to "lock-up" agreements that, for a period of 90 days from the date of this prospectus supplement, they will not sell any shares of common stock without the prior written consent of Morgan Stanley & Co. Incorporated. See "Underwriting."

Our former independent public accountant, Arthur Andersen LLP, has been found guilty of a federal obstruction of justice charge, and you may be unable to exercise effective remedies against it in any legal action.

Our former independent public accountant, Arthur Andersen LLP, provided us with auditing services for prior fiscal periods through December 31, 2001, including issuing an audit report with respect to our audited consolidated financial statements as of and for the years ended December 31, 2000 and 2001 included in our Annual Report on Form 10-K for the year ended December 31, 2002 and incorporated by reference in this prospectus supplement and the accompanying prospectus. On June 15, 2002, a jury in Houston, Texas found Arthur Andersen LLP guilty of a federal obstruction of justice charge arising from the federal government's investigation of Enron Corp. On August 31, 2002, Arthur Andersen LLP ceased practicing before the Securities and Exchange Commission, or the SEC.

We were unable to obtain Arthur Andersen LLP's consent to include its report with respect to our audited consolidated financial statements as of and for the years ended December 31, 2000 and 2001 in our Annual Report on Form 10-K for the year ended December 31, 2002 or to incorporate by reference such report in this prospectus supplement and the accompanying prospectus. Rule 437a under the Securities Act of

1933, or the Securities Act, permits us to dispense with the requirement to file their consent. As a result, you may not have an effective remedy against Arthur Andersen LLP in connection with a material misstatement or omission with respect to our audited consolidated financial statements that are incorporated by reference in this prospectus supplement or any other filing we may make with the SEC, including, with respect to this offering or any other offering registered under the Securities Act, any claim under Section 11 of the Securities Act. In addition, even if you were able to assert such a claim, as a result of its conviction and other lawsuits, Arthur Andersen LLP may fail or otherwise have insufficient assets to satisfy claims made by investors or by us that might arise under federal securities laws or otherwise relating to any alleged material misstatement or omission with respect to our audited consolidated financial statements.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus contain certain information regarding our financial projections, plans and strategies that are forward-looking statements within the meaning of Section 27A of the Securities Act and 21E of the Securities Exchange Act of 1934. We have attempted to identify forward-looking statements by terminology including "anticipate," "believe," "can," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "should" or "will" or the negative of these terms or other comparable terminology. These statements, which are only predictions and involve known and unknown risks, uncertainties and other important factors may include, among other things, statements which address our strategy and operating performance, events or developments that we expect or anticipate will occur in the future, such as projections of our future results of operations or of our financial condition, the status of any collaborative agreements, our research and development efforts and anticipated trends in our business. Discussions containing forward-looking statements may be found, among other places, in "Business" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" in this prospectus supplement.

We have based these forward-looking statements on our current expectations and projections about future events. However, there may be events in the future that we are not able to predict accurately or which we do not fully control that could cause actual results to differ materially from those expressed or implied in our forward-looking statements. Many important factors could cause actual results to differ materially from those expressed or implied by these forward-looking statements, including those discussed under "Risk Factors" in this prospectus supplement and other sections of the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. We undertake no obligation to publicly release any revisions to the forward-looking statements or reflect events or circumstances after the date of this prospectus supplement.

USE OF PROCEEDS

We estimate that the net proceeds from the sale of the 10,000,000 shares of common stock that we are offering will be approximately $49.0 million, based on the public offering price of $5.25 per share, after deducting underwriting discounts and commissions and estimated offering expenses. If the underwriters exercise their option to purchase 1,500,000 additional shares in this offering, we estimate the aggregate net proceeds to us will be approximately $56.4 million. We currently intend to use the net proceeds from this offering for research and development, particularly to continue to discover what we believe to be pharmaceutically attractive drug targets, to screen compounds against these targets to identify potential therapeutic products and to advance the most promising of these potential products into preclinical testing and clinical trials. We may also use a portion of the net proceeds to acquire or invest in complementary products and technologies or for general corporate purposes. We have no current plans or commitments as to any such acquisition or investment.

The amounts that we actually expend for research and development, acquisitions, investments or general corporate purposes will vary significantly depending on a number of factors, including our future revenues, the amount of cash we generate from operations and the progress of our product development efforts. Accordingly, our management will retain broad discretion in the allocation of the net proceeds from this offering.

Pending such uses, we intend to invest the net proceeds from this offering in interest-bearing, investment-grade securities.

PRICE RANGE OF COMMON STOCK

Our common stock is quoted on the Nasdaq National Market under the symbol "LEXG." The following table sets forth, for the periods indicated, the range of the high and low sales prices per share for our common stock as reported on the Nasdaq National Market.

	High	Low
Year ended December 31, 2001		
First Quarter	$17.25	$5.63
Second Quarter	13.25	5.41
Third Quarter	12.80	5.45
Fourth Quarter	12.14	6.96
Year ended December 31, 2002		
First Quarter	13.00	7.94
Second Quarter	9.10	4.12
Third Quarter	6.44	3.45
Fourth Quarter	5.30	2.97
Year ended December 31, 2003		
First Quarter	5.29	3.00
Second Quarter	7.00	3.98
Third Quarter (through July 23)	7.45	5.38

As of June 30, 2003, there were approximately 253 holders of record of our common stock. On July 23, 2003, the reported last sale price of our common stock on the Nasdaq National Market was $5.50 per share.

DIVIDEND POLICY

We have never paid cash dividends on our common stock. We anticipate that we will retain all of our future earnings, if any, for use in the expansion and operation of our business and do not anticipate paying cash dividends in the foreseeable future. In addition, our synthetic lease agreement contains restrictions that may limit our ability to pay dividends.

CAPITALIZATION

The following table presents our unaudited capitalization and other data as of March 31, 2003 on an actual basis and as adjusted to give effect to the sale by us of 10,000,000 shares of common stock in this offering at the public offering price of $5.25 per share, after deducting underwriting discounts and commissions and estimated offering expenses. You should read the following table in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations" included elsewhere in this prospectus supplement and the consolidated financial statements and the related notes incorporated by reference into this prospectus supplement and the accompanying prospectus.

	As of March 31, 2003	
	Actual	As Adjusted
	(in thousands, except share data)	
Cash, cash equivalents, restricted cash and investments	$ 107,587	$ 156,537
Long-term debt, net of current portion	$ 4,000	$ 4,000
Stockholders' equity:		
Preferred stock, $0.01 par value; 5,000,000 shares authorized, no shares issued and outstanding	—	—
Common stock, $0.001 par value; 120,000,000 shares authorized, 52,374,095 shares issued and outstanding, actual; 62,374,095 shares issued and outstanding, as adjusted	52	62
Additional paid-in capital	330,666	379,606
Deferred stock compensation	(8,507)	(8,507)
Accumulated deficit	(166,890)	(166,890)
Total stockholders' equity	155,321	204,271
Total capitalization	$ 159,321	$ 208,271

DILUTION

As of March 31, 2003, our net tangible book value was approximately $125.6 million, or approximately $2.40 per share. Net tangible book value per share represents the amount of our total tangible assets, excluding goodwill and other intangible assets, less total liabilities divided by the 52,374,095 shares of our common stock outstanding as of March 31, 2003. After giving effect to our sale of 10,000,000 shares of common stock in this offering at the public offering price of $5.25 per share, after deducting underwriting discounts and commissions and estimated offering expenses, the net tangible book value as of March 31, 2003 would have been approximately $174.5 million, or approximately $2.80 per share. This represents an immediate increase in net tangible book value of $.40 per share to existing stockholders and an immediate dilution in net tangible book value of $2.45 per share to new investors purchasing shares of common stock at the public offering price.

The following table illustrates this dilution on a per share basis:

Public offering price per share		$5.25
Net tangible book value per share as of March 31, 2003	$2.40	
Increase in net tangible book value per share attributable to new investors	.40	
Net tangible book value per share as of March 31, 2003 after giving effect to this offering		2.80
Dilution in net tangible book value per share to new investors		$2.45

As of March 31, 2003, there were outstanding options to purchase a total of 12,740,214 shares of common stock at a weighted average exercise price of $6.14 per share and outstanding warrants to purchase a total of 266,482 shares of common stock at a weighted average exercise price of $3.08 per share. To the extent that any of these options or warrants are exercised, there will be further dilution to new public investors.

SELECTED FINANCIAL DATA

The statement of operations data for the year ended December 31, 2002 and the balance sheet data as of December 31, 2002 have been derived from our financial statements that have been audited by Ernst & Young LLP, independent auditors. The statements of operations data for each of the four years in the period ended December 31, 2001 and the balance sheet data as of December 31, 1998 through 2001 have been derived from our audited financial statements that have been audited by Arthur Andersen LLP, independent public accountants who have ceased operations. The statements of operations data for the three months ended March 31, 2002 and 2003, and the balance sheet data as of March 31, 2003, are unaudited but include, in the opinion of management, all adjustments, consisting of only normal recurring adjustments, necessary for a fair presentation of such data. Our historical results for any prior or interim period are not necessarily indicative of results to be expected for any future period.

The data presented below has been prepared in accordance with accounting principles generally accepted in the United States and should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations" included elsewhere in this prospectus supplement and with our financial statements and related notes incorporated by reference in this prospectus supplement and the accompanying prospectus.

	Year Ended December 31,					Three Months Ended March 31,	
	1998	1999	2000	2001	2002	2002	2003
						(unaudited)	
	(in thousands, except per share data)						
Statements of Operations Data:							
Revenues	$ 2,242	$ 4,738	$ 14,459	$ 30,577	$ 35,200	$ 7,656	$ 8,106
Operating expenses:							
Research and development[1]	8,410	14,646	31,647	53,355	74,859	16,864	19,834
General and administrative[2]	2,024	2,913	18,289	20,861	23,234	5,969	5,804
Total operating expenses	10,434	17,559	49,936	74,216	98,093	22,833	25,638
Loss from operations	(8,192)	(12,821)	(35,477)	(43,639)	(62,893)	(15,177)	(17,532)
Interest and other income, net	711	346	9,483	8,467	3,223	1,118	387
Net loss	(7,481)	(12,475)	(25,994)	(35,172)	(59,670)	(14,059)	(17,145)
Accretion on redeemable convertible preferred stock	(357)	(536)	(134)	—	—	—	—
Net loss attributable to common stockholders	$(7,838)	$(13,011)	$(26,128)	$(35,172)	$(59,670)	$(14,059)	$(17,145)
Net loss per common share, basic and diluted	$ (0.32)	$ (0.53)	$ (0.63)	$ (0.70)	$ (1.14)	$ (0.27)	$ (0.33)
Shares used in computing net loss per common share, basic and diluted	24,445	24,530	41,618	50,213	52,263	52,126	52,371

	As of December 31,					As of March 31,
	1998	1999	2000	2001	2002	2003
	(in thousands)					
Balance Sheet Data:						
Cash, cash equivalents, restricted cash and investments[3]	$ 19,422	$ 9,156	$202,680	$166,840	$123,096	$107,587
Working capital[3]	18,102	2,021	194,801	147,663	111,833	99,197
Total assets	28,516	22,295	220,693	239,990	201,772	181,967
Long-term debt, net of current portion	5,024	3,577	1,834	—	4,000	4,000
Redeemable convertible preferred stock	29,515	30,050	—	—	—	—
Accumulated deficit	(16,434)	(28,909)	(54,903)	(90,075)	(149,745)	(166,890)
Stockholders' equity (deficit)	(9,035)	(21,937)	207,628	218,372	169,902	155,321

(1) Includes stock-based compensation of $10,883 in 2000, $5,539 in 2001, $5,155 in 2002, $1,307 for the three months ended March 31, 2002 and $1,270 for the three months ended March 31, 2003.

(2) Includes stock-based compensation of $9,958 in 2000, $5,231 in 2001, $5,113 in 2002, $1,282 for the three months ended March 31, 2002 and $1,276 for the three months ended March 31, 2003.

(3) Includes restricted cash and investments of $13,879 as of December 31, 2000, $43,338 as of December 31, 2001, $57,710 as of December 31, 2002 and $57,710 as of March 31, 2003.

MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis together with our consolidated financial statements, related notes and other financial information incorporated by reference in this prospectus supplement and the accompanying prospectus. In addition to historical information, the following discussion and analysis and other parts of this prospectus supplement and the accompanying prospectus contain forward-looking information that involves risks and uncertainties. Our actual results could differ materially from those anticipated by such forward-looking information due to competitive factors and other factors discussed under "Special Note Regarding Forward-Looking Statements," "Risk Factors" and elsewhere in this prospectus supplement and the accompanying prospectus.

Overview

We are a biopharmaceutical company focused on the discovery of breakthrough treatments for human disease. We use proprietary gene knockout technology to systematically discover the physiological functions of genes in mice and to identify which corresponding human genes encode potential targets for therapeutic intervention, or drug targets. The study of mice can be a very powerful tool for understanding human genetics because of the close similarity of gene function and physiology in mice and humans. Approximately 99% of all human genes have a counterpart in the mouse genome. Our patented gene trapping and gene targeting technologies enable us to rapidly generate these knockout mice by altering the DNA of genes in a special variety of mouse cells, called embryonic stem cells, which can be cloned and used to generate mice with the altered gene. We then employ an integrated platform of advanced medical technologies to systematically discover and validate, *in vivo,* the physiological functions and pharmaceutical utility of the genes we have knocked out and the drug targets they encode.

We are working both independently and with our drug discovery collaborators to discover potential small molecule drugs, therapeutic antibodies and therapeutic proteins for those *in vivo*-validated drug targets that we consider to have high pharmaceutical value. We are working with Genentech to discover the functions of secreted proteins and potential antibody targets identified through Genentech's internal drug discovery research. We are working with Abgenix to discover and develop therapeutic antibodies for *in vivo*-validated drug targets identified in our own research. We are also working with Incyte to discover and develop therapeutic proteins. In addition, we have established collaborations and license agreements with many other leading pharmaceutical and biotechnology companies under which we receive fees and, in many cases, are eligible to receive milestone and royalty payments, in return for granting access to some of our technologies and discoveries for use in such companies' own drug discovery efforts.

We derive substantially all of our revenues from drug discovery alliances, subscriptions to our databases, target validation collaborations for the development and, in some cases, analysis of the physiological effects of genes altered in knockout mice, and technology licenses. To date, we have generated a substantial portion of our revenues from a limited number of sources and have not generated any revenue from sales of pharmaceuticals.

Our operating results and, in particular, our ability to generate additional revenues are dependent on many factors, including:

- our ability to establish new database subscriptions, research collaborations and technology licenses, and the timing of such arrangements;
- the expiration or other termination of database subscriptions and research collaborations with our collaborators, which may not be renewed or replaced;
- the success rate of our discovery efforts leading to opportunities for new research collaborations and licenses, as well as milestone payments and royalties;
- the timing and willingness of our collaborators to commercialize pharmaceutical products that would result in milestone payments and royalties; and

- general and industry-specific economic conditions, which may affect our and our collaborators' research and development expenditures.

Our future revenues from database subscriptions, collaborations and alliances are uncertain because our existing agreements have fixed terms or relate to specific projects of limited duration. Our future revenues from technology licenses are uncertain because they depend, in part, on securing new agreements. Our ability to secure future revenue-generating agreements will depend upon our ability to address the needs of our potential future subscribers, collaborators and licensees, and to negotiate agreements that we believe are in our long-term best interests. We may determine that our interests are better served by retaining rights to our discoveries and advancing our therapeutic programs to a later stage, which could limit our near-term revenues. Because of these and other factors, our quarterly operating results have fluctuated in the past and are likely to do so in the future, and we do not believe that quarter-to-quarter comparisons of our operating results are a good indication of our future performance.

Since our inception, we have incurred significant losses and, as of March 31, 2003, we had an accumulated deficit of $166.9 million. Our losses have resulted principally from costs incurred in research and development, general and administrative costs associated with our operations, and non-cash stock-based compensation expenses associated with stock options granted to employees and consultants prior to our April 2000 initial public offering. Research and development expenses consist primarily of salaries and related personnel costs, material costs, facility costs, depreciation on property and equipment, legal expenses resulting from intellectual property prosecution, and other expenses related to our drug discovery and LexVision programs, the development and analysis of knockout mice and our other target validation research efforts, and the development of compound libraries. General and administrative expenses consist primarily of salaries and related expenses for executive, finance and other administrative personnel, professional fees and other corporate expenses, including business development and general legal activities. In connection with the expansion of our drug discovery programs and our target validation research efforts, we expect to incur increasing research and development and general and administrative costs. As a result, we will need to generate significantly higher revenues to achieve profitability.

Critical Accounting Policies

Revenue Recognition

We recognize revenues when persuasive evidence of an arrangement exists, delivery has occurred or services have been rendered, the price is fixed and determinable, and collectability is reasonably assured. Payments received in advance under these arrangements are recorded as deferred revenue until earned.

Fees for access to our databases and other target validation resources are recognized ratably over the subscription or access period. Collaborative research payments are recognized as revenue as we perform our obligations related to such research to the extent such fees are non-refundable. Milestone-based fees are recognized upon completion of specified milestones according to contract terms. Non-refundable technology license fees are recognized as revenue upon the grant of the license to third parties, when performance is complete and there is no continuing involvement.

Revenues recognized from multiple element contracts are allocated to each element of the arrangement based on the relative fair value of the elements. The determination of fair value of each element is based on objective evidence. When revenues for an element are specifically tied to a separate earnings process, revenue is recognized when the specific performance obligation associated with the element is completed. When revenues for an element are not specifically tied to a separate earnings process, they are recognized ratably over the term of the agreement.

A change in our revenue recognition policy or changes in the terms of contracts under which we recognize revenues could have an impact on the amount and timing of our recognition of revenues.

Research and Development Expenses

Research and development expenses consist of costs incurred for company-sponsored as well as collaborative research and development activities. These costs include direct and research-related overhead expenses and are expensed as incurred. Patent costs and technology license fees for technologies that are utilized in research and development and have no alternative future use are expensed when incurred.

Stock-Based Compensation

Deferred stock-based compensation and related amortization represents the difference between the exercise price of stock options granted and the fair value of our common stock on the applicable date of grant. Stock-based compensation is amortized as research and development expense or general and administrative expense, as appropriate, over the vesting period of the individual stock options for which it was recorded, generally four years. If employees and consultants continue to vest in accordance with their individual stock option agreements subsequent to March 31, 2003, we expect to record amortization expense for deferred stock-based compensation of $7.6 million during the last nine months of 2003 and $.9 million during 2004. The amount of stock-based compensation expense to be recorded in future periods may decrease if unvested stock options for which deferred stock-based compensation has been recorded are subsequently canceled or forfeited or may increase if additional stock options are granted to individuals other than employees or directors.

Goodwill Impairment

Goodwill is not amortized, but is tested at least annually for impairment at the reporting unit level. Impairment is the condition that exists when the carrying amount of goodwill exceeds its implied fair value. The first step in the impairment process is to determine the fair value of the reporting unit and then compare it to the carrying value, including goodwill. If the fair value exceeds the carrying value, no further action is required and no impairment loss is recognized. Additional impairment assessments may be performed on an interim basis if we encounter events or changes in circumstances that would indicate that, more likely than not, the carrying value of goodwill has been impaired.

Recent Accounting Pronouncements

In November 2002, the Emerging Issues Task Force, or EITF, reached a consensus on EITF Issue No. 00-21, "Accounting for Revenue Arrangements with Multiple Deliverables." This consensus requires that revenue arrangements with multiple deliverables be divided into separate units of accounting if the delivered items have value to the customer on a standalone basis, there is objective and reliable evidence of fair value of the undelivered items and, if the arrangement includes a general right of return, performance of the undelivered item is considered probable and substantially in our control. The final consensus will be applicable to agreements entered into in fiscal periods beginning after June 15, 2003, with early adoption permitted.

In December 2002, the Financial Accounting Standards Board, or FASB, issued Statement of Financial Accounting Standards, or SFAS, No. 148, "Accounting for Stock-Based Compensation—Transition and Disclosure." This statement amends SFAS 123, "Accounting for Stock-Based Compensation," to provide alternative methods of transition for a voluntary change to the fair value based method of accounting for stock-based employee compensation. In addition, this statement amends the disclosure requirements of SFAS 123 to require prominent disclosures in both annual and interim financial statements about the method of accounting for stock-based accounting for employee compensation and the effect of the method used on reported results. We are currently evaluating whether to adopt the fair value based method.

In January 2003, the FASB issued Interpretation, or FIN, No. 46, "Consolidation of Variable Interest Entities." FIN 46 requires that unconsolidated variable interest entities be consolidated by their primary beneficiaries. A primary beneficiary is the party that absorbs a majority of the entity's expected losses or residual benefits. FIN 46 applies immediately to variable interest entities created after January 31, 2003 and to existing variable interest entities in the periods beginning after June 15, 2003. In October 2000, we entered into a synthetic lease agreement under which the lessor purchased our existing laboratory and office buildings

and animal facility in The Woodlands, Texas and agreed to fund the construction of an additional laboratory and office building and a second animal facility. The synthetic lease agreement was subsequently expanded to include funding for the construction of a central plant facility for the distribution of utilities and related services among our facilities. As adopted on July 1, 2003, FIN 46 will require us to consolidate the lessor under our synthetic lease. Accordingly, our balance sheet would reflect as assets additional property and equipment approximating the $55.0 million funded under the synthetic lease for property and improvements, less accumulated depreciation, and a similar amount as a liability. We would be required to depreciate such improvements over their useful lives. In addition, our income statement will reflect a charge of approximately $2.3 million for depreciation through June 30, 2003, as a cumulative effect of an accounting change. We believe that the consolidation of the lessor would not have a material adverse effect on our financial condition or results of operations. However, we are currently seeking to replace the synthetic lease. See "—Liquidity and Capital Resources."

Results of Operations

Three Months Ended March 31, 2003 and 2002

Revenues. Total revenues increased 6% to $8.1 million in the three months ended March 31, 2003 from $7.7 million in the corresponding period in 2002. The increase of $.4 million was primarily the result of revenues recognized under our drug discovery alliance with Genentech, entered in December 2002, offset, in part, by reduced revenues under technology license agreements.

During the three months ended March 31, 2003, Incyte, Bristol-Myers Squibb and Genentech represented 31%, 16% and 9% of revenues, respectively. During the three months ended March 31, 2002, Incyte, Bristol-Myers Squibb and Immunex Corporation represented 33%, 16% and 9% of revenues, respectively.

Research and Development Expenses. Research and development expenses increased 18% to $19.8 million in the three months ended March 31, 2003 from $16.9 million in the corresponding period in 2002. The increase of $2.9 million was primarily attributable to increased personnel costs and facilities costs to support the expansion of our drug discovery programs, the development and analysis of knockout mice and our other target validation research efforts. Research and development expenses for each of these three-month periods included $1.3 million of stock-based compensation primarily relating to option grants made prior to our April 2000 initial public offering.

General and Administrative Expenses. General and administrative expenses decreased 3% to $5.8 million in the three months ended March 31, 2003 from $6.0 million in the corresponding period in 2002. General and administrative expenses for each of these three-month periods included $1.3 million of stock-based compensation primarily relating to option grants made prior to our April 2000 initial public offering.

Interest and Other Income. Interest and other income decreased 58% to $.5 million in the three months ended March 31, 2003 from $1.1 million in the corresponding period in 2002. The decrease resulted from lower average cash and investment balances and lower average interest rates on our investments during the 2003 period.

Net Loss and Net Loss Per Common Share. Net loss increased 22% to $17.1 million in the three months ended March 31, 2003 from $14.1 million in the corresponding period in 2002. Net loss per common share increased to $.33 in the three months ended March 31, 2003 from $.27 in the corresponding period of 2002. As a complement to reporting net loss and net loss per common share in accordance with generally accepted accounting principles, or GAAP, we provide net loss and net loss per common share excluding non-cash, stock-based compensation. We use these results in establishing budgets and believe it is useful to investors in measuring the performance of our business. Excluding stock-based compensation expense of $2.5 million and $2.6 million in the three months ended March 31, 2003 and 2002, respectively, we would have had a net loss of $14.6 million and net loss per common share of $.28 in the three months ended March 31, 2003, as compared to a net loss of $11.5 million and net loss per common share of $.22 in the corresponding period in 2002.

Our quarterly operating results have fluctuated in the past and are likely to do so in the future, and we believe that quarter-to-quarter comparisons of our operating results are not a good indication of our future performance.

Years Ended December 31, 2002 and 2001

Revenues. Total revenues increased 15% to $35.2 million in 2002 from $30.6 million in 2001. The increase of $4.6 million was primarily attributable to a $5.9 million increase in revenues from target validation collaborations and our drug discovery alliance with Incyte and a $3.1 million increase in revenues from database subscription and technology license fees, offset in part by a $4.4 million decrease in compound libraries and other revenue. We did not make our compound libraries available for purchase in 2002 and, subject to limited exceptions, do not intend to make our compound libraries available for purchase in the future.

In 2002, Incyte, Bristol-Myers Squibb and Millennium Pharmaceuticals represented 28%, 14% and 11% of revenues, respectively. In 2001, Incyte, Bristol-Myers Squibb and Merck & Co., Inc. represented 16%, 13% and 12% of revenues, respectively.

Research and Development Expenses. Research and development expenses increased 40% to $74.9 million in 2002 from $53.4 million in 2001. The increase of $21.5 million was primarily attributable to increased personnel and facility costs to support the expansion of our drug discovery programs, including a full year of medicinal chemistry operations that we obtained in our July 2001 acquisition of Coelacanth Corporation, the development and analysis of knockout mice and our other target validation research efforts. Research and development expenses for 2002 and 2001 included $5.2 million and $5.5 million, respectively, of stock-based compensation primarily relating to option grants made prior to our April 2000 initial public offering.

General and Administrative Expenses. General and administrative expenses increased 11% to $23.2 million in 2002 from $20.9 million in 2001. The increase of $2.3 million was due primarily to additional personnel costs offset by a reduction in legal costs as a result of the September 2001 settlement of our patent infringement litigation against Deltagen, Inc. General and administrative expenses for 2002 and 2001 included $5.1 million and $5.2 million, respectively, of stock-based compensation primarily relating to option grants made prior to our April 2000 initial public offering.

Interest and Other Income. Interest and other income decreased 63% to $3.2 million in 2002 from $8.8 million in 2001. This decrease resulted from lower cash and investment balances and lower average interest rates on our investments during 2002.

Net Loss and Net Loss Per Common Share. Net loss attributable to common stockholders increased to $59.7 million in 2002 from $35.2 million in 2001. Net loss per common share increased to $1.14 in 2002 from $.70 in 2001. Excluding stock-based compensation expense of $10.3 million and $10.8 million in 2002 and 2001, respectively, we would have had a net loss of $49.4 million and net loss per common share of $.95 in 2002, as compared to a net loss of $24.4 million and net loss per common share of $.49 in 2001.

Years Ended December 31, 2001 and 2000

Revenues. Total revenues increased 111% to $30.6 million in 2001 from $14.5 million in 2000. The increase of $16.1 million was primarily attributable to a $10.2 million increase in revenues from database subscription and technology license fees, a $1.7 million increase in revenues from target validation collaborations and our drug discovery alliance with Incyte and revenues of $4.5 million from compound library sales, offset in part by a $.3 million decrease in other revenue.

In 2001, Incyte, Bristol-Myers Squibb and Merck represented 16%, 13% and 12% of revenues, respectively. In 2000, the Merck Genome Research Institute and Millennium Pharmaceuticals represented 35% and 14% of revenues, respectively.

Research and Development Expenses. Research and development expenses increased 69% to $53.4 million in 2001 from $31.6 million in 2000. The increase of $21.8 million was attributable to continued growth of

research and development activities, primarily related to increased personnel costs to support the expansion of our drug discovery programs, the development and analysis of knockout mice and our other target validation research efforts, offset in part by lower stock-based compensation in 2001. Research and development expenses for 2001 and 2000 included $5.5 million and $10.9 million, respectively, of stock-based compensation primarily relating to option grants made prior to our April 2000 initial public offering.

General and Administrative Expenses. General and administrative expenses increased 14% to $20.9 million in 2001 from $18.3 million in 2000. The increase of $2.6 million was due primarily to additional personnel costs for business development and finance and administration, as well as expenses associated with our patent infringement litigation against Deltagen, offset in part by lower stock-based compensation in 2001. General and administrative expenses for 2001 and 2000 included $5.2 million and $10.0 million, respectively, of stock-based compensation primarily relating to option grants made prior to our April 2000 initial public offering.

Interest and Other Income. Interest income decreased 11% to $8.8 million in 2001 from $9.9 million in 2000. This decrease resulted from lower cash and investment balances and lower average interest rates on our investments during 2001.

Net Loss and Net Loss Per Common Share. Net loss attributable to common stockholders increased to $35.2 million in 2001 from $26.1 million in 2000. Net loss per common share increased to $.70 in 2001 from $.63 in 2000.

Liquidity and Capital Resources

We have financed our operations from inception primarily through sales of common and preferred stock, contract and milestone payments to us under our drug discovery alliance, database subscription, collaboration and license agreements, equipment financing arrangements and leasing arrangements. From our inception through March 31, 2003, we had received net proceeds of $242.7 million from issuances of common and preferred stock, including $203.2 million of net proceeds from the initial public offering of our common stock in April 2000. In addition, from our inception through March 31, 2003, we received $108.1 million in cash payments from drug discovery alliances, database subscription and technology license fees, target validation collaborations, sales of compound libraries and reagents, and government grants, of which $96.6 million had been recognized as revenues through March 31, 2003.

As of March 31, 2003, we had $107.6 million in cash, cash equivalents and short-term investments, including $57.7 million of restricted cash and investments, as compared to $123.1 million as of December 31, 2002. We used cash of $14.8 million in operations during the three months ended March 31, 2003. This consisted primarily of the net loss for the period of $17.1 million offset by non-cash charges of $2.5 million related to stock-based compensation expense, $2.5 million related to depreciation expense and $300,000 related to amortization of intangible assets other than goodwill. Investing activities provided cash of $14.6 million in the three months ended March 31, 2003, principally as a result of net maturities of short-term investments, offset in part by an increase in restricted cash.

As of December 31, 2002, we had $123.1 million in cash, cash equivalents and short-term and long-term investments, including $57.7 million of restricted cash and investments, as compared to $166.8 million, including $43.3 million of restricted cash and investments, as of December 31, 2001. We used cash of $28.8 million in operations in 2002. This consisted primarily of the net loss for the year of $59.7 million offset by non-cash charges of $10.3 million related to stock-based compensation expense, $9.1 million related to depreciation expense and $1.2 million related to amortization of intangible assets other than goodwill, a $5.6 million increase in deferred revenue, and changes in other operating assets and liabilities of $4.5 million. Investing activities provided cash of $47.2 million in 2002, principally as a result of net maturities of short-term investments and the sale of long-term investments, offset by an increase in restricted cash and purchases of property and equipment. We received cash of $4.6 million in financing activities in 2002, consisting principally of proceeds from a $4.0 million loan and stock option exercises.

In October 2000, we entered into a synthetic lease agreement under which the lessor purchased our existing laboratory and office buildings and animal facility in The Woodlands, Texas and agreed to fund the construction of an additional laboratory and office building and a second animal facility. The synthetic lease agreement was subsequently expanded to include funding for the construction of a central plant facility for the distribution of utilities and related services among our facilities. Including the purchase price for our existing facilities, the synthetic lease, as amended, provided for funding of up to $55.0 million in property and improvements. The term of the agreement is six years, which includes the construction period and a lease period, and may be extended at our option for up to seven additional one-year terms. Alternatively, the lease may be terminated at an earlier date if we elect to (1) purchase the properties for a price equal to the $55.0 million funded under the synthetic lease for property and improvements plus the amount of any accrued but unpaid lease payments, (2) arrange for the sale of the properties to a third party or (3) surrender the properties to the lessor. If we elect to arrange for the sale of the properties or surrender the properties to the lessor, we have guaranteed approximately 86% of the total original cost as the residual fair value of the properties. Lease payments for the new facilities began upon completion of construction, which occurred at the end of the first quarter of 2002. Lease payments are subject to fluctuation based on LIBOR rates. Based on a LIBOR rate of 1.3% at March 31, 2003, our total lease payments would be approximately $.9 million per year. We are required to maintain restricted cash and investments to collateralize amounts funded under the synthetic lease agreement. In addition, we have agreed to maintain cash and investments of at least $12.0 million in excess of our restricted cash and investments. If our cash and investments fall below that level, we may be required to seek a waiver of that agreement or to purchase the properties or arrange for their sale to a third party. Because our cost to purchase the properties would not materially exceed the $55.0 million funded under the synthetic lease for property and improvements and would likely be less than the amount of restricted cash and investments we are required to maintain under the synthetic lease, we believe that any requirement that we do so would not have a material adverse effect on our financial condition. As of March 31, 2003 and December 31, 2002, we maintained restricted cash and investments of $57.2 million to collateralize funding for property and improvements under the synthetic lease of $55.0 million.

We intend to replace our synthetic lease agreement covering all of our facilities in The Woodlands, Texas, and we are currently engaged in discussions to do so. We expect that any such new arrangement would require us to maintain substantially lower amounts of restricted cash and investments while increasing our payments with respect to these facilities, as compared to our synthetic lease agreement.

In May 2002, our subsidiary, Lexicon Pharmaceuticals (New Jersey), Inc., signed a ten-year lease for a 76,000 square-foot laboratory and office facility in Hopewell, New Jersey. Our subsidiary has exercised its option under the lease to obtain $2.0 million in tenant improvement funds from the landlord. The lease provides that the expiration of the term of the lease will be extended to June 30, 2013, the tenth anniversary of the date on which the landlord provided the tenant improvement funds, and that such funds will be amortized over a ten-year period. Accordingly, we expect that the escalating yearly base rent payment under the lease will increase to a range of approximately $2.1 million in the first year following the funding of the tenant improvements on June 30, 2003 to approximately $2.4 million in the tenth year. We are the guarantor of the obligations of our subsidiary under the lease.

In December 2002, we borrowed $4.0 million under a convertible promissory note we issued to Genentech. The proceeds of the loan are to be used to fund research efforts under our alliance with Genentech for the discovery of therapeutic proteins and antibody targets. The note matures on or before December 31, 2005, but we may prepay it at any time. We may repay the note, at our option, in cash or in shares of our common stock valued at the then-current market value, or in a combination of cash and shares, subject to certain limitations. The note accrues interest at an annual rate of 8%, compounded quarterly.

Including the lease and debt obligations described above, we had incurred the following contractual obligations as of March 31, 2003:

	Payments Due By Period				
Contractual Obligations	**Total**	**Less than 1 Year**	**1–3 Years**	**3–5 Years**	**More than 5 Years**
			(in millions)		
Long-term debt	$ 4.0	—	$ 4.0	—	—
Capital lease obligations	—	—	—	—	—
Operating leases	27.3	$3.6	6.2	$5.0	$12.5
Other long-term liabilities reflected on our balance sheet under GAAP	0.3	—	—	0.3	—
Total	$31.6	$3.6	$10.2	$5.3	$12.5

Our future capital requirements will be substantial and will depend on many factors, including our ability to obtain alliance, database subscription, collaboration and technology license agreements, the amount and timing of payments under such agreements, the level and timing of our research and development expenditures, market acceptance of products that we may develop and the resources we devote to developing and supporting such products. Our capital requirements will also be affected by any expenditures we make in connection with license agreements and acquisitions of and investments in complementary products and technologies. We expect to devote substantial capital resources to continue our research and development efforts, to expand our support and product development activities, and for other general corporate activities. We anticipate that the net proceeds of this offering, our existing capital resources and the revenues we expect to derive from drug discovery alliances, subscriptions to our databases, target validation collaborations and technology licenses will enable us to fund our currently planned operations for approximately the next 24 months. During or after this period, if cash generated by operations is insufficient to satisfy our liquidity requirements, we will need to sell additional equity or debt securities or obtain additional credit arrangements. Additional financing may not be available on terms acceptable to us or at all. The sale of additional equity or convertible debt securities may result in additional dilution to our stockholders, and, in the case of debt securities, could subject us to restrictive covenants.

We currently estimate that our capital expenditures for 2003 will be approximately $5 million to $7 million and will relate primarily to the completion of our laboratory and office facilities in Hopewell, New Jersey, as well as to the purchase of high-throughput screening and other equipment for our development activities.

BUSINESS

Overview

Lexicon Genetics is a biopharmaceutical company focused on the discovery of breakthrough treatments for human disease. We use proprietary gene knockout technology to systematically discover the physiological functions of genes in mice and to identify which corresponding human genes encode potential targets for therapeutic intervention, or drug targets. For those targets that we consider to have high pharmaceutical value, we engage in programs for the discovery and development of potential small molecule drugs, therapeutic antibodies and therapeutic proteins. Our physiology-based approach to understanding gene function and our use of mouse models in our drug discovery efforts allow us to make highly-informed decisions throughout the drug discovery and development process, which we believe will increase our likelihood of success in discovering breakthrough therapeutics.

We are using our gene knockout technology to discover the physiological functions of 5,000 genes from the human genome that belong to gene families that we consider to be pharmaceutically important. Our state-of-the-art animal facilities enable us to capitalize on our gene knockout and physiological analysis technologies by generating knockout mice and analyzing the physiological function of genes on a large scale. Using this physiological information, we select targets for our drug discovery programs that, when knocked out, exhibit favorable therapeutic profiles with potential for addressing large medical markets. We focus our discovery efforts in five therapeutic areas—metabolic disorders, cardiovascular disease, cancer, immune system disorders and neurological disorders—and we have established significant internal expertise in each of these areas. Our experience suggests that from the 5,000 genes for which we are seeking to discover physiological function, a total of approximately 100 to 150 will prove to be targets with important pharmaceutical utility. To date, we have advanced into drug discovery programs more than 20 targets, each of which we have validated *in vivo*. Our most advanced drug discovery programs include LG653 for obesity and diabetes, LG914 for atherosclerosis, LG152 for cancer, LG293 for inflammation and LG617 for cognitive disorders.

We are working both independently and through strategic collaborations and alliances to commercialize our technology and turn our discoveries into drugs. We have established multiple collaborations with leading pharmaceutical and biotechnology companies, as well as research institutes and academic institutions. We are working with Genentech to discover the functions of secreted proteins and potential antibody targets identified through Genentech's internal drug discovery research. We are working with Abgenix to discover and develop therapeutic antibodies for *in vivo*-validated drug targets identified in our own research. We are also working with Incyte to discover and develop therapeutic proteins. In addition, we have established collaborations and license agreements with many other leading pharmaceutical and biotechnology companies under which we receive fees and, in many cases, are eligible to receive milestone and royalty payments, in return for granting access to some of our technologies and discoveries for use in such companies' own drug discovery efforts.

Our Drug Discovery Process

Our drug discovery process begins with our Genome5000 program, in which we are using our gene knockout technology to discover the physiological functions of 5,000 human genes over five years. Our Genome5000 efforts are focused on the discovery of the functions in mammalian physiology of proteins encoded by gene families that we consider to be pharmaceutically important, such as G-protein coupled, or GPCRs, and other receptors, kinases, ion channels, other key enzymes and secreted proteins. We have already completed our physiology-based analysis of over 20% of these 5,000 genes, and we expect to complete the analysis of the remaining genes at a rate of approximately 1,000 genes per year.

We use knockout mice—mice whose DNA has been altered to disrupt, or "knock out," the function of the altered gene—to discover gene function. The study of mice can be a very powerful tool for understanding human genetics because of the close similarity of gene function and physiology in mice and humans. Approximately 99% of all human genes have a counterpart in the mouse genome. Our patented gene trapping and gene targeting technologies enable us to rapidly generate these knockout mice by altering the DNA of genes in a special variety of mouse cells, called embryonic stem cells, which can be cloned and used to generate mice with the altered gene.

We employ an integrated platform of advanced medical technologies to systematically discover and validate, *in vivo,* the physiological functions and pharmaceutical utility of the genes we have knocked out and the drug targets they encode. These technologies include many of the most sophisticated diagnostic technologies that might be found in a major medical center, including CAT-scans, magnetic resonance imaging, or MRI, complete blood cell analysis and other technologies, all adapted specifically for the analysis of mouse physiology. We conduct these activities in two state-of-the-art animal facilities occupying a total of approximately 100,000 square feet. These facilities, completed in 1999 and 2002, respectively, were custom designed for the generation and analysis of knockout mice and are accredited by AAALAC International, or Association for Assessment and Accreditation of Laboratory Animal Care. The scope of our gene knockout technology, combined with the size and sophistication of our facilities and our evaluative technologies, provides us with what we believe to be a significant competitive advantage.

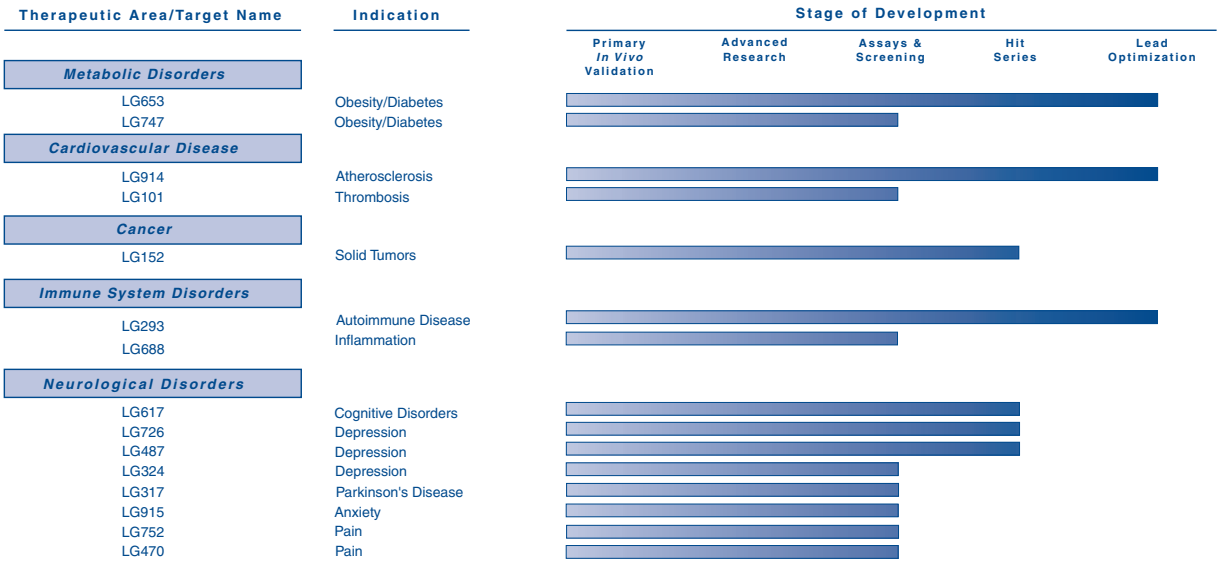
We believe that the power of our technology is demonstrated by a retrospective analysis that we performed of the 100 best selling drugs of 2001 as modeled by the physiological characteristics of knockout mice. This analysis was published in the January 2003 issue of *Nature Reviews Drug Discovery*, a peer-reviewed scientific journal. In this analysis we concluded that in most cases there was a direct correlation between the physiological characteristics, or phenotypes, of knockout mice and the therapeutic effect of the 100 best-selling drugs of 2001. These drugs targeted only 43 host proteins. Of those targets, 34 had been knocked out and 29, or 85 percent, of the resulting knockout mice were informative in describing the gene function and pharmaceutical utility of the target.

We are working to discover potential small molecule drugs, therapeutic antibodies and therapeutic proteins for those *in vivo*-validated drug targets that we consider to have high pharmaceutical value. We have established an internal small molecule drug discovery program, in which we use our own sophisticated libraries of drug-like chemical compounds in high-throughput screening assays to identify "hits," or chemical compounds demonstrating activity, against these targets. We then employ our industrialized medicinal chemistry platform to optimize the potency and selectivity of these hits and to identify lead compounds for potential development. Our compound libraries include chemical scaffolds and building blocks that we designed based on analyses of the characteristics of drugs that have proven safe and effective in the past. When we identify a hit, we can rapidly reassemble these building blocks to create hundreds or thousands of variations around the structure of the initial compound, enabling us to accelerate our medicinal chemistry efforts.

In all of our drug discovery programs, we use the same physiological analysis technology platform that we use in the discovery of gene function to analyze the *in vivo* efficacy and safety profiles of drug candidates in mice. We believe that our approach, by focusing on the physiological functions and pharmaceutical utility of genes at the outset of the drug discovery process, will increase our likelihood of success in discovering breakthrough treatments for human disease.

Our Drug Discovery Pipeline

We focus our drug discovery programs in five therapeutic areas—metabolic disorders, cardiovascular disease, cancer, immune system disorders and neurological disorders—and we have established significant internal expertise in each of these areas. To date, we have advanced more than 20 *in vivo*-validated targets into drug discovery programs. We have highlighted 15 of our most advanced programs below.



The status levels of these programs are described below:

- *Primary In Vivo Validation* means we have generated knockout mice for a drug target and preliminarily validated physiological gene function *in vivo* by systematically analyzing those knockout mice in our comprehensive series of diagnostic medical procedures.

- *Advanced Research* means we have applied a more focused and in-depth approach to our physiological analysis of those knockout mice generated for a drug target that we believe may have significant pharmaceutical importance.

- *Assays and Screening* means we are developing, or have developed and are continuing to develop, assays and are conducting high-throughput screening to identify hits against a drug target.

- *Hit Series* means we have identified one or more series of potential hits against a drug target and we are applying our advanced medicinal chemistry capabilities in our efforts to identify potential lead compounds.

- *Lead Optimization* means we have identified one or more series of potential lead compounds for a drug target and we are applying our advanced medicinal chemistry capabilities in our efforts to optimize those potential leads.

The prioritization and allocation of our internal resources among these programs are based on our expectations regarding their relative likelihood of success and the relevant medical market, as well as progress realized in our drug discovery efforts for the program. We revise our prioritization and resource allocation among programs as necessary in order to capitalize on new discoveries and opportunities. As a result, our priorities will continually shift as new information becomes available to us, and higher priority targets may replace targets that we had previously emphasized as we progress in the drug discovery process.

Metabolic Disorders

Metabolic disorders include the serious and growing problems of obesity and diabetes and the complications they cause. Obesity rates among American adults increased by 74% during the period from 1991 to 2001. According to the American Obesity Association, 60 million American adults are now considered obese. Obesity is also a contributing factor to over 30 diseases, including diabetes, heart disease and stroke. According to the International Diabetes Federation, at least 194 million people worldwide suffer from diabetes. Current pharmaceutical treatments for obesity have shown only limited effectiveness and have exhibited unfavorable side effects. Current treatments for diabetes also have significant limitations. We have identified and validated, *in vivo,* multiple novel targets for the development of potential therapeutics for certain metabolic disorders. To date, we have initiated drug discovery efforts for LG653 and LG747, each of which is a potential target for the treatment of obesity and diabetes. We are currently optimizing lead compounds for LG653 and conducting high-throughput screening of small molecule drug candidates for LG747.

Lead Metabolic Program—LG653. LG653 is an enzyme that we believe has utility as a target for the development of drugs for the treatment of obesity, diabetes, heart disease and stroke. Our physiological analysis of LG653 in knockout mice suggests that LG653 plays a role in the regulation of metabolism. LG653 knockout mice displayed a 30% to 44% reduction in body fat, exhibited an increased metabolic rate and on average consumed 19% more food than normal mice. LG653 knockout mice have normal muscle mass, lean body mass and bone mineral density. We have not observed in LG653 knockout mice any physiological effects that would limit the utility of LG653 as a drug target or that would be considered an undesirable side effect for a drug. We have completed high-throughput screening against LG653 and have identified two series of potential lead compounds, which we are currently optimizing.

Cardiovascular Disease

More than 60 million people in the United States have some form of cardiovascular disease. The American Heart Association estimates that 1.1 million Americans will suffer a heart attack this year and another 700,000 will suffer a stroke. We have identified and validated, *in vivo,* multiple novel targets for the development of potential therapeutics for certain cardiovascular diseases. To date, we have initiated drug discovery efforts for two of these targets: LG914 for atherosclerosis, which is the progressive blockage of arteries, and LG101 for thrombosis, which is the formation of blood clots within a vein. We are currently working with Abgenix to develop monoclonal antibodies for LG914 and conducting high-throughput screening of small molecule drug candidates for LG101.

Lead Cardiovascular Program—LG914. LG914 is a secreted protein that we believe has utility as a target for the treatment of atherosclerosis. Our physiological analysis of LG914 in knockout mice suggests that LG914 is involved in the regulation of certain cellular events associated with atherosclerosis and other coronary artery diseases. LG914 knockout mice exhibited reduced arterial thickening in response to an inflammatory stimulus compared to normal mice, and the inhibition of LG914 in mice with a genetic predisposition to atherosclerotic plaque resulted in a significant decrease in plaque formation. We have not observed in LG914 knockout mice any physiological effects that would limit the utility of LG914 as a drug target or that would be considered an undesirable side effect for a drug. We are working in collaboration with Abgenix to develop monoclonal antibodies to inhibit LG914.

Cancer

This year, according to the American Cancer Society, over 500,000 Americans are expected to die of cancer and approximately 1.3 million new cancer cases are expected to be diagnosed in the United States.

Cancer is the second leading cause of death in the United States, exceeded only by heart disease. We have identified and validated, *in vivo,* a novel target, LG152, for the development of potential cancer therapeutics.

Lead Cancer Program—LG152. LG152 is a kinase that we believe has utility as a target for the development of drugs for the treatment of solid tumor cancers. Our physiological analysis of LG152 in knockout mice suggests that LG152 plays a significant role in the regulation of cell growth. The breakdown or malfunction of such regulation is often a key cause of many cancers. LG152 knockout mice displayed a reduction in cell growth and proliferation, while over-expression of LG152 in mouse cell lines resulted in tumor formation. Additional analysis suggests that reduction of LG152 expression results in the blockage of human tumor cell growth *in vitro*. We have also observed over-expression of LG152 in human tumor cells isolated from melanomas and breast, colon, bladder and ovarian tumors. Additionally, although LG152 knockout mice are smaller than normal mice, we have not observed in LG152 knockout mice any physiological effects that would limit the utility of LG152 as a drug target or that would be considered an undesirable side effect for a drug. We have completed high-throughput screening against LG152 and have identified five series of hits, which we are currently analyzing.

Immune System Disorders

Rheumatoid arthritis, lupus and other disorders of the immune system, as well as inflammatory disease and organ transplant rejection, affect substantial numbers of people and represent multiple large medical markets. For example, according to the Arthritis Foundation, rheumatoid arthritis affects approximately 2.1 million Americans, and the Lupus Foundation of America, Inc. estimates that approximately 1.4 million Americans have a form of lupus. According to the National Institute of Arthritis and Musculoskeletal and Skin Diseases, an estimated 43 million Americans have arthritis or other rheumatic conditions. We have identified and validated, *in vivo,* multiple novel targets for the development of potential therapeutics for immune system disorders. To date, we have initiated drug discovery efforts for two of these targets: LG293 for autoimmune diseases and LG688 for inflammation. We are currently optimizing lead compounds for LG293 and working with Abgenix to develop monoclonal antibodies for LG688.

Lead Immunology Program—LG293. LG293 is an enzyme that we believe has utility as a target for the development of drugs for the treatment of immunosuppression, autoimmune disorders and inflammatory diseases. Our physiological analysis of LG293 in knockout mice suggests that LG293 is involved in the regulation of immune system function and the maturation and proliferation of T and B cells, which are vital components of the immune system. LG293 knockout mice exhibited lower levels of circulating T and B cells, resulting in a reduction in the inflammatory response. Our analysis suggests that inhibiting LG293 increases the retention of immune cells in the thymus and spleen and blocks the deployment of T and B cells into the peripheral blood supply. Furthermore, LG293 knockout mice accepted transplanted tissues and mounted a significantly reduced inflammatory response when challenged. These results lead us to believe that LG293 inhibition or drugs that target LG293 could be used to treat autoimmune disorders and chronic inflammatory conditions. We have completed high-throughput screening against LG293 and have identified three series of potential lead compounds, which we are currently optimizing.

Neurological Disorders

Central nervous system, or CNS, disorders encompass a broad array of disease areas, including depression, Alzheimer's disease, Attention Deficit Hyperactivity Disorder and Parkinson's disease. According to the National Institute of Mental Health, depression affects approximately 19 million American adults. The Alzheimer's Disease Education and Referral Center estimates that up to four million Americans suffer from Alzheimer's disease. The treatments currently available for neurological diseases are among the most frequently prescribed drugs in the United States, yet often have limited efficacy or significant side effects for

many patients. We have identified and validated, *in vivo,* multiple novel targets for the development of potential therapeutics for certain neurological disorders. To date, we have initiated drug discovery efforts for three of these targets: LG617 for Alzheimer's disease and other cognitive disorders and LG487 and LG726 for depression. We are currently analyzing hit series for LG617 and LG487. We are also working with Abgenix to develop monoclonal antibodies for LG726. We are currently working to develop high-throughput screening assays for five of our other targets in this therapeutic area: LG324 for depression, LG317 for Parkinson's disease, LG915 for anxiety and LG752 and LG470 for pain.

Lead Neurology Program—LG617. LG617 is a membrane protein that we believe has utility as a target for the treatment of certain cognitive disorders. Our physiological analysis of LG617 in knockout mice suggests that LG617 plays a role in learning, attention and memory. LG617 knockout mice exhibited an increased amount of learned responses when challenged with a conditioned stimulus and demonstrated a significant increase in olfactory discrimination and exploratory behavior, each of which are widely accepted tests of learning and memory. We have not observed in LG617 knockout mice any *physiological* effects that would limit the utility of LG617 as a drug target or that would be considered an undesirable side effect for a drug. We have completed high-throughput screening against LG617 and have identified six series of hits, which we are currently analyzing.

Our Technology

The scope of our gene knockout and evaluative technologies allows us to create and analyze knockout mice at a rate and on a scale that we believe is unmatched by our competitors. Combined with our state-of-the-art facilities, which are among the largest and most sophisticated of their kind in the world, these technologies provide us with what we believe to be a significant competitive advantage. We have already completed our analysis of over 20% of the 5,000 genes in our Genome5000 program, and we expect to complete the analysis of the remaining genes by the end of 2007. The core elements of our technology platform include our patented technologies for the generation of knockout mice, our integrated platform of advanced medical technologies for the systematic and comprehensive biological analysis of *in vivo* physiology and our industrialized approach to medicinal chemistry and the generation of high-quality, drug-like compound libraries.

Gene Knockout Technologies

Gene Targeting. Our gene targeting technology, which is covered by six issued patents that we have licensed, enables us to generate highly specific alterations in targeted genes. The technology uses a vector to replace DNA of a gene in a mouse embryonic stem cell through a process known as homologous recombination to disrupt the function of the targeted gene, permitting the generation of knockout mice. By using this technology in combination with one or more additional technologies, we are able to generate alterations that selectively disrupt, or conditionally regulate, the function of the targeted gene for the analysis of the gene's function in selected tissues, at selected stages in the animal's development or at selected times in the animal's life. We can also use this technology to replace the targeted gene with its corresponding human gene for use for preclinical research in our therapeutic discovery programs.

Gene Trapping. Our gene trapping technology, which is covered by six issued patents that we own, is a high-throughput method of generating knockout mouse clones that we invented. The technology uses genetically engineered retroviruses that infect mouse embryonic stem cells *in vitro,* integrate into the chromosome of the cell and disrupt the function of the gene into which it integrates, permitting the generation of knockout mice. This process also stimulates transcription of a portion of the trapped gene, using the cell's own splicing machinery to extract this transcript from the chromosome for automated DNA sequencing. This allows us to identify and catalogue each embryonic stem cell clone by DNA sequence from the trapped gene and to select embryonic stem cell clones by DNA sequence for the generation of knockout mice.

Physiological Analysis Technologies

We employ an integrated platform of advanced medical examinations to rapidly and systematically discover and catalogue the functions of the genes we have knocked out using our gene trapping and gene targeting technologies. These examinations include many of the most sophisticated diagnostic technologies and tests currently available, many of which might be found in a major medical center. These technologies and tests include:

- CAT-scans;
- magnetic resonance imaging, or MRI;
- complete blood cell analysis, including HDL counts and white blood cell counts;
- fluorescently activated cell sorting, or FACS, analysis;
- comprehensive automated behavior analysis; and
- nuclear magnetic resonance, or NMR, analysis.

Each of these technologies has been adapted specifically for the analysis of mouse physiology. This state-of-the-art technology platform enables us to assess the function of the knocked-out gene in a living mammal across a wide variety of parameters relevant to human disease.

We believe that our medical center approach and the technology platform that makes it possible provide us with substantial advantages over other approaches to determine gene function and drug target discovery. In particular, we believe that the comprehensive nature of this approach allows us to uncover functions within the context of mammalian physiology that might be missed by more narrowly focused efforts directed on the basis of hypotheses as to a gene's likely function, particularly when these hypotheses are based on expression analyses and other factors that our experience indicates are unreliable predictors of gene function. We also believe our approach is more likely to reveal those side effects that may be a direct result of inhibiting or otherwise modulating the drug target. Such target-related side effects might limit the utility of potential therapeutics directed at the drug target or prove to be unacceptable in light of the potential therapeutic benefit. We believe these advantages will contribute to better target selection and, therefore, to the success of our drug discovery and development efforts.

We employ the same physiological analysis technology platform that we use in the discovery of gene function to analyze the *in vivo* efficacy and safety profiles of therapeutic candidates in mice. We believe that this approach will allow us, at an early stage, to identify and optimize therapeutic candidates for further preclinical and clinical development that demonstrate *in vivo* efficacy and to distinguish side effects caused by a specific compound from the target-related side effects that we defined using the same comprehensive series of tests.

Production and Analysis Infrastructure

Our facilities, which are among the largest and most sophisticated of their kind in the world, enable us to capitalize on our gene knockout and physiological analysis technologies by generating knockout mice and analyzing the physiological function of genes on an expansive scale. We are able to generate knockout mice for the large number of genes that we believe may be pharmaceutically important and analyze the physiology of each of those knockout mice by utilizing our broad range of medical technologies. Our state-of-the-art animal facilities, occupying a total of approximately 100,000 square feet, allow us to generate and analyze over 1,000 knockout mice per year. These facilities also enable us to maintain in-house control over our entire *in vivo* validation process, from the generation of embryonic stem cell clones through the completion of *in vivo* analysis, in a specific pathogen-free environment. As part of our Genome5000 program, we have already examined the physiological functions of over 1,000 genes and expect to complete our analysis of an aggregate of 5,000 genes by the end of 2007. We are not aware of any study approaching either the magnitude or breadth of our Genome5000 program, and we believe that the investment of significant resources over a period of

several years would be required for any competitor to duplicate our gene knockout and physiological analysis capabilities.

Medicinal Chemistry Technology

We use solution-phase chemistry to generate diverse libraries of optically pure compounds that are targeted against the same pharmaceutically relevant gene families that we address in our Genome5000 program. These libraries are built using highly robust and scalable organic reactions that allow us to generate compound collections of great diversity and to specially tailor the compound collections to address various therapeutic target families. We design these libraries by analyzing the chemical structures of drugs that have been proven safe and effective against human disease and using that knowledge in the design of scaffolds and chemical building blocks for the generation of large numbers of new drug-like compounds. We can rapidly reassemble these building blocks to generate optimization libraries when we identify a hit against one of our *in vivo*-validated targets, enabling us to rapidly optimize those hits and accelerate our medicinal chemistry efforts.

Our medicinal chemistry technology is housed in a state-of-the-art 76,000 square foot facility in Hopewell, New Jersey. Our lead optimization chemistry groups are organized around specific discovery targets and work closely with their pharmaceutical biology counterparts in our facilities in The Woodlands, Texas. The medicinal chemists optimize lead compounds in order to select clinical candidates with the desired absorption, distribution, metabolism, excretion and physicochemical characteristics. We have the capability to profile our compounds using the same battery of *in vivo* assays that we use to characterize our drug discovery targets. This provides us with valuable detailed information relevant to the selection of the highest quality compounds for clinical development.

OmniBank Library and LexVision Database

We have capitalized on these core elements of our technology platform by developing our OmniBank library of gene knockout clones and our LexVision database cataloging the functions of certain *in vivo*-validated drug targets.

OmniBank Library. We have used our gene trapping technology in an automated process to create our OmniBank library of more than 200,000 frozen gene knockout embryonic stem cell clones, each identified by DNA sequence in a relational database. Each OmniBank mouse clone contains a single genetic mutation that can model the action of future drugs. We estimate that our OmniBank library currently contains gene knockout clones for more than half of all genes in the mammalian genome and believe it is the largest library of its kind. We believe our OmniBank library permits us to generate knockout mice at a significantly higher rate than is possible using other methods and, therefore, provides us with a significant strategic advantage in the discovery of *in vivo* gene function.

LexVision Database. Our LexVision database is a comprehensive, relational database of *in vivo*-validated drug targets that catalogs the physiological functions of genes that we have knocked out using our gene targeting and gene trapping technologies. Our LexVision collaborators obtain non-exclusive access to the LexVision database for the discovery of small molecule drugs. We are committed to include 1,250 *in vivo*-validated drug targets in our LexVision database over a period of five years. We deposit such targets in our LexVision database on a quarterly basis. As of June 30, 2003, we had deposited a total of 631 targets.

Our Commercialization Strategy

We are working both independently and through strategic collaborations and alliances with leading pharmaceutical and biotechnology companies, research institutes and academic institutions to commercialize our technology and turn our discoveries into drugs. Consistent with this approach, we intend to develop and commercialize certain of our drug discovery programs internally and retain exclusive rights to the benefits of such programs and to collaborate with third parties with respect to the development and commercialization of other drug discovery programs.

We apply our internal resources to our drug discovery programs in order to commercialize our technology and turn our discoveries into drugs. As we advance targets into our drug discovery programs, we allocate our internal resources in a manner designed to maximize our ability to commercialize opportunities presented by these programs. Our prioritization and allocation of internal resources among these programs are based on our expectations regarding their relative likelihood of success and the relevant medical market, as well as progress realized in our drug discovery efforts for the program. We revise our prioritization and resource allocation among programs as necessary in order to capitalize on new discoveries and opportunities.

Our collaboration and alliance strategy involves drug discovery alliances to discover and develop therapeutics based on our drug target discoveries, particularly when the alliance enables us to obtain access to technology and expertise that we do not possess internally or is complementary to our own. These strategic collaborations, as well as our licenses with pharmaceutical and biotechnology companies, research institutes and academic institutions, enable us to generate near-term revenues in exchange for access to some of our technologies and discoveries for use by these third parties in their own drug discovery efforts. These collaborations and licenses also offer us the potential, in many cases, to receive milestone payments and royalties on products that our collaborators and licensees develop using our technology.

Alliances, Collaborations and Licenses

Drug Discovery Alliances

We have entered into the following alliances for the discovery and development of therapeutics based on our *in vivo* drug target discovery efforts:

Genentech, Inc. We established a drug discovery alliance with Genentech in December 2002 to discover novel therapeutic proteins and antibody targets. Under the alliance agreement, we are using our target validation technologies to discover the functions of secreted proteins and potential antibody targets identified through Genentech's internal drug discovery research. Genentech will have exclusive rights to the discoveries resulting from the collaboration for the research, development and commercialization of therapeutic proteins and antibodies. We will retain certain other rights to those discoveries, including non-exclusive rights, along with Genentech, for the development and commercialization of small molecule drugs. We received an up-front payment and are entitled to receive performance payments for our work in the collaboration as it is completed. We are also entitled to receive milestone payments and royalties on sales of therapeutic proteins and antibodies for which Genentech obtains exclusive rights. The agreement has an expected collaboration term of three years.

Abgenix, Inc. We established a drug discovery alliance with Abgenix in July 2000 to discover novel therapeutic antibodies using our target validation technologies and Abgenix's technology for generating fully human monoclonal antibodies. We and Abgenix expanded and extended the alliance in January 2002, with the intent of accelerating the selection of *in vivo*-validated antigens for antibody discovery and the development and commercialization of therapeutic antibodies based on those targets. Under the alliance agreement, we and Abgenix will each have the right to obtain exclusive commercialization rights, including sublicensing rights, for an equal number of qualifying therapeutic antibodies, and will each receive milestone payments and royalties on sales of therapeutic antibodies from the alliance that are commercialized by the other party or a third-party sublicensee. Each party bears its own expenses under the alliance. The expanded alliance also provides us with access to Abgenix's XenoMouse® technology for use in some of our own drug discovery programs. The collaboration period, as extended, expires in July 2004, subject to the right of the parties to extend the term by mutual agreement for up to three additional one-year periods.

Incyte Corporation. We established a drug discovery alliance with Incyte in June 2001 to discover novel therapeutic proteins using our target validation technologies in the discovery of the functions of secreted proteins identified in Incyte's LifeSeq® Gold database. The alliance agreement provides that up to 250 secreted proteins will be jointly selected for functional characterization, and we expect 150 to be selected in the first three years. Under the alliance agreement, we receive research funding from Incyte during the term of the collaboration. In addition, we and Incyte will each have the right to obtain exclusive commercialization rights, including sublicensing rights, for an equal number of qualifying therapeutic proteins, and will each receive

milestone payments and royalties on sales of therapeutic proteins from the alliance that are commercialized by the other party or a third-party sublicensee. The collaboration period has a term of five years, although either party may terminate the collaboration period on June 27, 2004.

LexVision Collaborations

We have entered into the following collaborations for access to our LexVision database of *in vivo*-validated drug targets:

Bristol-Myers Squibb Company. We established a LexVision collaboration with Bristol-Myers Squibb in September 2000, under which Bristol-Myers Squibb has non-exclusive access to our LexVision database and OmniBank library for the discovery of small molecule drugs. We receive annual access fees under this agreement and are entitled to receive milestone payments and royalties on products Bristol-Myers Squibb develops using our technology. The collaboration period extends through December 31, 2005, although either party may terminate the collaboration period on December 31, 2003.

Incyte Corporation. We established a LexVision collaboration with Incyte in June 2001, under which Incyte has non-exclusive access to our LexVision database and OmniBank library for the discovery of small molecule drugs. We receive annual access fees under this agreement, and are entitled to receive milestone payments and royalties on products Incyte develops using our technology. The collaboration period extends through December 31, 2005, although either party may terminate the collaboration period at the end of three years.

Target Validation Collaborations

We have established target validation collaboration agreements with a number of leading pharmaceutical and biotechnology companies. Under these collaboration agreements, we generate and, in some cases, analyze knockout mice for genes requested by the collaborator. In addition, we grant non-exclusive licenses to the collaborator for use of the knockout mice in its internal drug discovery programs and, if applicable, analysis data that we generate under the agreement. Some of these agreements also provide for non-exclusive access to our OmniBank library. We typically receive annual subscription fees and fees for knockout mice with annual minimum commitments and, under some of these agreements, may receive royalties on products that our collaborators discover or develop using our technology. Each of these agreements has a specified access period during which the collaborator may request new projects, although, in most cases, the agreement remains in effect as we continue to conduct work until the projects requested during the access period are completed, typically within 12 to 24 months following the end of the access period.

We have entered into target validation collaboration agreements with the following companies:

Company Name	Date of Agreement	End of Access Period
Amgen, Inc.	July 2001	July 2003
Abgenix, Inc.	January 2001	January 2004
Tularik, Inc.	October 2000	October 2003
Wyeth	March 2000	March 2003
Boehringer Ingelheim Pharmaceuticals, Inc.	February 2000	February 2004
Pharmacia Corp.	January 2000	January 2003
Johnson & Johnson Pharmaceutical Research and Development L.L.C.	December 1999	December 2003
N.V. Organon	December 1999	December 2002

We have also entered into target validation collaboration agreements with a number of additional companies and academic institutions under which we receive research fees for the generation of knockout mice and, with participating academic institutions, certain rights to license inventions or royalties on products discovered using such mice.

Technology Licenses

We have granted non-exclusive, internal research-use sublicenses under certain of our gene targeting patent rights to a total of 11 leading pharmaceutical and biotechnology companies. Many of these agreements have terms of one to three years, in some cases with provisions for subsequent renewals. Others extend for as long as the life of the patents. We typically receive up-front license fees and, in some cases, receive additional license fees or milestone payments on products that the sublicensee discovers or develops using our technology.

Research and Development Expenses

During the fiscal years ended December 31, 2002, 2001 and 2000, we spent approximately $74.9 million, $53.4 million and $31.6 million, respectively, on research and development activities, all of which was company-sponsored, including $5.2 million, $5.5 million and $10.9 million of stock-based compensation expenses.

Patents and Proprietary Rights

We will be able to protect our proprietary rights from unauthorized use by third parties only to the extent that those rights are covered by valid and enforceable patents or are effectively maintained as trade secrets. Accordingly, patents and other proprietary rights are an essential element of our business. Therefore, we have sought or plan to seek patent protection for:

- the sequences of genes that we believe to be novel, including full-length human genes and partial human and mouse gene sequences, the proteins they encode and their predicted utility as a drug target or therapeutic protein;
- the utility of genes and the drug targets or therapeutic proteins they encode based on our discoveries of their biological functions using knockout mice;
- drug discovery assays for our *in vivo*-validated targets;
- chemical compounds and their use in treating human diseases and conditions; and
- various enabling technologies in the fields of mutagenesis, embryonic stem cell manipulation and transgenic or knockout mice.

We own or have exclusive rights to six issued United States patents that are directed to our gene trapping technology, 23 issued United States patents that are directed to full-length sequences of potential drug targets identified in our gene discovery programs, and five issued United States patents that are directed to specific knockout mice and discoveries of the functions of genes made using knockout mice. We have licenses under 60 additional United States patents, and corresponding foreign patents and patent applications, directed to gene targeting, gene trapping and genetic manipulation of mouse embryonic stem cells. These include patents to which we hold exclusive rights in certain fields, including a total of six United States patents directed to the use of gene targeting technologies known as positive-negative selection and isogenic DNA targeting, as well as patents directed to the use of site specific genetic recombination technology known as Cre/lox technology.

We have filed or have exclusive rights to more than 500 pending patent applications in the United States Patent and Trademark Office, the European Patent Office, the national patent offices of other foreign countries or under the Patent Cooperation Treaty, directed to our gene trapping technology, the DNA sequences of genes, the uses of specific drug targets, drug discovery assays, and other products and processes. Collectively, these patent applications are directed to, among other things, approximately 200 full-length human gene sequences, more than 50,000 partial human gene sequences, and more than 45,000 knockout mouse clones and corresponding mouse gene sequence tags. Patents typically have a term of no longer than 20 years from the date of filing. The issued patents that we own or license have expiration dates ranging from 2009 to 2022.

As noted above, we hold rights to a number of these patents and patent applications under license agreements with third parties. In particular, we license our gene targeting technologies from GenPharm International, Inc. and our Cre/lox technology from DuPont Pharmaceuticals Company. Our patent licenses typically are royalty bearing or require some other form of payment to the licensor and impose diligence obligations on us. Many of these licenses are nonexclusive, although some are exclusive in specified fields. Most of the licenses have terms that extend for the life of the licensed patents. In the case of our license from GenPharm, the license generally is exclusive in specified fields, subject to specific rights held by third parties, and we are permitted to grant sublicenses.

All of our employees, consultants and advisors are required to execute a proprietary information agreement upon the commencement of employment or consultation. In general, the agreement provides that all inventions conceived by the employee or consultant, and all confidential information developed or made known to the individual during the term of the agreement, shall be our exclusive property and shall be kept confidential, with disclosure to third parties allowed only in specified circumstances. We cannot assure you, however, that these agreements will provide useful protection of our proprietary information in the event of unauthorized use or disclosure of such information.

Competition

The biotechnology and pharmaceutical industries are highly competitive and characterized by rapid technological change. We face significant competition in each of the aspects of our business from for-profit companies such as Human Genome Sciences, Inc., Millennium Pharmaceuticals and Exelixis, Inc., among others, many of which have substantially greater financial, scientific and human resources than we do. In addition, the Human Genome Project and a large number of universities and other not-for-profit institutions, many of which are funded by the United States and foreign governments, are also conducting research to discover genes and their functions.

While we are not aware of any other commercial entity that is using gene trapping technology on a large scale, we face significant competition from entities using gene targeting technology and other technologies. Several companies, including Regeneron Pharmaceuticals, Inc., Deltagen, Inc. and DNX, which is a subsidiary of Xenogen Corporation, and a large number of academic institutions create knockout mice for third parties using these more traditional methods, and a number of companies create knockout mice for use in their own research.

Many of our competitors in drug discovery and development have substantially greater research and product development capabilities and financial, scientific, marketing and human resources than we do. As a result, our competitors may succeed in developing products earlier than we do, obtaining approvals from the FDA or other regulatory agencies for those products more rapidly than we do, or developing products that are more effective than those we propose to develop. Similarly, our collaborators face similar competition from other competitors who may succeed in developing products more quickly, or developing products that are more effective, than those developed by our collaborators. We expect that competition in this field will intensify.

We believe that our OmniBank library of more than 200,000 frozen gene knockout embryonic stem cell clones and our gene knockout and evaluative technologies, combined with our facilities, which are among the largest and most sophisticated of their kind in the world, permit us to generate and analyze knockout mice at a significantly higher rate than our competitors. We believe that these factors provide us with a significant strategic advantage in the discovery of *in vivo* gene function.

Government Regulation

Regulation of Pharmaceutical Products

The development, manufacture and sale of any pharmaceutical or biological products developed by us or our collaborators will be subject to extensive regulation by United States and foreign governmental authorities, including federal, state and local authorities. In the United States, new drugs are subject to regulation under

the Federal Food, Drug and Cosmetic Act and the regulations promulgated thereunder, or the FDC Act, and biological products are subject to regulation both under certain provisions of the FDC Act and under the Public Health Services Act and the regulations promulgated thereunder, or the PHS Act. The FDA regulates, among other things, the development, preclinical and clinical testing, manufacture, safety, efficacy, record keeping, reporting, labeling, storage, approval, advertising, promotion, sale, distribution and export of drugs and biologics. The process of obtaining FDA approval has historically been costly and time-consuming.

The standard process required by the FDA before a pharmaceutical or biological product may be marketed in the United States includes:

- preclinical laboratory and animal tests performed under the FDA's current Good Laboratory Practices regulations;
- submission to the FDA of an Investigational New Drug application, or IND, which must become effective before human clinical trials may commence;
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the drug or biologic in our intended application;
- for drugs, submission of a New Drug Application, or NDA, and, for biologics, submission of a Biologic License Application, or BLA, with the FDA; and
- FDA approval of the NDA or BLA prior to any commercial sale or shipment of the product.

Among other things, the FDA reviews an NDA to determine whether a product is safe and effective for its intended use and a BLA to determine whether a product is safe, pure and potent and the facility in which it is manufactured, processed, packed, or held meets standards designed to assure the product's continued safety, purity and potency.

In addition to obtaining FDA approval for each product, each drug or biologic manufacturing establishment must be inspected and approved by the FDA. All manufacturing establishments are subject to inspections by the FDA and by other federal, state and local agencies and must comply with current Good Manufacturing Practices requirements. Non-compliance with these requirements can result in, among other things, total or partial suspension of production, failure of the government to grant approval for marketing and withdrawal, suspension or revocation of marketing approvals.

Preclinical studies can take several years to complete, and there is no guarantee that an IND based on those studies will become effective to even permit clinical testing to begin. Once clinical trials are initiated, they take years to complete. In addition, the FDA may place a clinical trial on hold or terminate it if, among other reasons, the agency concludes that clinical subjects are being exposed to an unacceptable health risk. After completion of clinical trials of a new drug or biologic product, FDA marketing approval of the NDA or BLA must be obtained. An NDA or BLA, depending on the submission, must contain, among other things, information on chemistry, manufacturing controls and potency and purity, non-clinical pharmacology and toxicology, human pharmacokinetics and bioavailability and clinical data. The process of obtaining approval requires substantial time and effort and there is no assurance that the FDA will accept the NDA or BLA for filing and, even if filed, that approval will be granted. The FDA's approval of an NDA or BLA can take years and can be delayed if questions arise. Limited indications for use or other conditions could also be placed on any approvals that could restrict the commercial applications of products.

Once the FDA approves a product, a manufacturer must provide certain updated safety and efficacy information. Product changes as well as certain changes in a manufacturing process or facility would necessitate additional FDA review and approval. Other post-approval changes may also necessitate further FDA review and approval. Additionally, a manufacturer must meet other requirements including those related to adverse event reporting and record keeping.

Violations of the FDC Act, the PHS Act or regulatory requirements may result in agency enforcement action, including voluntary or mandatory recall, license suspension or revocation, product seizure, fines, injunctions and civil criminal penalties.

In addition to regulatory approvals that must be obtained in the United States, a drug or biological product is also subject to regulatory approval in other countries in which it is marketed, although the requirements governing the conduct of clinical trials, product licensing, pricing, and reimbursement vary widely from country to country. No action can be taken to market any drug or biological product in a country until the regulatory authorities in that country have approved an appropriate application. FDA approval does not assure approval by other regulatory authorities. The current approval process varies from country to country, and the time spent in gaining approval varies from that required for FDA approval. In some countries, the sale price of a drug or biological product must also be approved. The pricing review period often begins after marketing approval is granted. Even if a foreign regulatory authority approves a drug or biological product, it may not approve satisfactory prices for the product.

Other Regulations

In addition to the foregoing, our business is and will be subject to regulation under various state and federal environmental laws, including the Occupational Safety and Health Act, the Resource Conservation and Recovery Act and the Toxic Substances Control Act. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in and wastes generated by our operations. We believe that we are in material compliance with applicable environmental laws and that our continued compliance with these laws will not have a material adverse effect on our business. We cannot predict, however, whether new regulatory restrictions on the production, handling and marketing of biotechnology products will be imposed by state or federal regulators and agencies or whether existing laws and regulations will not adversely affect us in the future.

Employees

We believe that our success will be based on, among other things, achieving and retaining scientific and technological superiority and identifying and retaining capable management. We have assembled a highly qualified team of scientists as well as executives with extensive experience in the biotechnology industry.

As of June 30, 2003, we employed 610 persons, of whom 130 hold M.D., Ph.D. or D.V.M. degrees and another 83 hold other advanced degrees. We believe that our relationship with our employees is good.

Properties

We currently lease approximately 300,000 square feet of space for our corporate offices and laboratories in buildings located in The Woodlands, Texas, a suburb of Houston, and approximately 118,000 square feet of space for offices and laboratories near Princeton, New Jersey.

Our facilities in The Woodlands, Texas include two state-of-the-art animal facilities totaling approximately 100,000 square feet. These facilities, completed in 1999 and 2002, respectively, were custom designed for the generation and analysis of knockout mice and are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care. These facilities enable us to maintain in-house control over our entire *in vivo* validation process, from the generation of embryonic stem cell clones through the completion of *in vivo* analysis, in a specific pathogen free environment. We believe these facilities, which are among the largest and most sophisticated of their kind in the world, provide us with significant strategic and operational advantages relative to our competitors. Because of the size and sophistication of our facilities, it would require the investment of significant resources over an extended period of time for any competitor to develop facilities with the scale, efficiency and productivity with respect to the analysis of the functionality of genes that our facilities provide.

In October 2000, we entered into a synthetic lease agreement under which the lessor purchased our existing laboratory and office buildings and animal facility in The Woodlands, Texas and agreed to fund the construction of an additional laboratory and office building and a second animal facility. The synthetic lease agreement was subsequently expanded to include funding for the construction of a central plant facility for the distribution of utilities and related services among our facilities. However, we intend to replace this synthetic lease agreement. For a description of the synthetic lease agreement and our plan to replace it, see

"Management's Discussion and Analysis of Financial Condition and Results of Operations—Liquidity and Capital Resources."

In May 2002, our subsidiary, Lexicon Pharmaceuticals (New Jersey), Inc., entered into a ten-year lease for a 76,000 square-foot laboratory and office facility in Hopewell, New Jersey. For a description of this lease agreement, see "Management's Discussion and Analysis of Financial Condition and Results of Operations—Liquidity and Capital Resources."

We believe that our facilities are well maintained, in good operating condition and acceptable for our current operations.

MANAGEMENT

The names, ages and positions of our executive officers and directors as of June 30, 2003 are as follows:

Name	Age	Position
Arthur T. Sands, M.D., Ph.D.	41	President and Chief Executive Officer and Director (Class III)
C. Thomas Caskey, M.D.	64	Chairman of the Board of Directors (Class III)
William A. McMinn	72	Director (Class III)
Sam L. Barker, Ph.D.	60	Director (Class II)
Patricia M. Cloherty	60	Director (Class II)
Robert J. Lefkowitz, M.D.	60	Director (Class I)
Julia P. Gregory	50	Executive Vice President and Chief Financial Officer
Jeffrey L. Wade, J.D.	38	Executive Vice President and General Counsel
Brian P. Zambrowicz, Ph.D.	41	Executive Vice President of Research
Walter F. Colbert	53	Senior Vice President of Human Resources and Corporate Services
Alan J. Main, Ph.D.	49	Senior Vice President, Lexicon Pharmaceuticals
James R. Piggott, Ph.D.	46	Senior Vice President of Pharmaceutical Biology
Randall B. Riggs	36	Senior Vice President of Business Development
David A. Boulton	45	Vice President of Technology Operations, Lexicon Pharmaceuticals
Philip M. Brown, M.D., J.D., FCLM	42	Vice President of Clinical Development
William E. Heydorn, Ph.D.	48	Vice President of Preclinical Development
Lance K. Ishimoto, Ph.D., J.D.	44	Vice President of Intellectual Property
S. David Kimball, Ph.D.	53	Vice President of Medicinal Chemistry
Stephen J. McAndrew, Ph.D.	49	Vice President of Pharmaceutical Business Development
Christophe Person	36	Vice President of Informatics

Arthur T. Sands, M.D., Ph.D. co-founded our company and has been our President and Chief Executive Officer and a director since September 1995. From 1992 to September 1995, Dr. Sands served as an American Cancer Society postdoctoral fellow in the Department of Human and Molecular Genetics at Baylor College of Medicine, where he studied the function of the p53 gene in cancer formation and created the XPC knockout mouse, a model for skin cancer. He received his B.A. in Economics and Political Science from Yale University and his M.D. and Ph.D. from Baylor College of Medicine.

C. Thomas Caskey, M.D. became Chairman of our Board of Directors in April 2000. Dr. Caskey has been President and Chief Executive Officer of Cogene Biotech Ventures, Ltd., a venture capital firm, since April 2000. He served as Senior Vice President, Research at Merck Research Laboratories, a division of Merck & Co., Inc., a pharmaceutical company, from 1995 to March 2000 and as President of the Merck Genome Research Institute from 1996 to March 2000. Before joining Merck, Dr. Caskey served 25 years at Baylor College of Medicine in a series of senior positions, including Chairman, Department of Human and Molecular Genetics and Director, Human Genome Center. He is a member of the National Academy of Sciences. Dr. Caskey serves as a director of Luminex Corporation and several private companies. He received his B.A. from the University of South Carolina and his M.D. from Duke University Medical School.

William A. McMinn has been a director since September 1997 and was the Chairman of our Board of Directors from July 1999 until April 2000. Mr. McMinn has served as Chairman of the Board of Texas Petrochemicals Corporation since 1996. He was Corporate Vice President and Manager of the Industrial Chemical Group of FMC Corporation, a manufacturer of machinery and chemical products, from 1973 through 1985. He became President and Chief Executive Officer of Cain Chemical Inc. in 1987, and served in that capacity until its acquisition by Occidental Petroleum in May 1988. He became Chairman of the board of

directors of Arcadian Corporation in August 1990 and served in that capacity until it was sold in April 1997. Mr. McMinn received his B.S. from Vanderbilt University.

Sam L. Barker, Ph.D. has been a director since March 2000. Since March 2001, Dr. Barker has served as a founder and principal of Clearview Projects, Inc., a company engaged in providing partnering and transaction services to biotechnology companies. Dr. Barker served in a series of senior domestic and international management positions at Bristol-Myers Squibb Company, a pharmaceuticals and healthcare products company, until his retirement in 1998. His positions at Bristol-Myers Squibb included service as Executive Vice President, Worldwide Franchise Management and Strategy during 1998, President, United States Pharmaceutical Group from 1995 to 1997 and President, United States Pharmaceuticals from 1992 to 1995. Dr. Barker received his B.S. from Henderson State College, his M.S. from the University of Arkansas and his Ph.D. from Purdue University.

Patricia M. Cloherty has been a director since May 1998. Ms. Cloherty has served as Chairman of the United States Russia Investment Fund, established by the United States government to invest in Russian companies, since President Clinton appointed her to that position in 1995. From 1973 through 1999, she was General Partner of Patricof & Co. Ventures, Inc., an international venture capital company, and successively served as Senior Vice President, President and Co-Chairman of that company. Ms. Cloherty served as deputy administrator of the United States Small Business Administration from 1977 to 1978. She is past president and chairman of the National Venture Capital Association. Ms. Cloherty serves as a director of several private companies and philanthropies. She holds a B.A. from the San Francisco College for Women and an M.A. and an M.I.A. from Columbia University.

Robert J. Lefkowitz, M.D. has been a director since February 2001 and a consultant to our company since March 2003. Dr. Lefkowitz is the James B. Duke Professor of Medicine, Professor of Biochemistry and a Howard Hughes Medical Institute investigator at Duke University Medical Center, where he has served on the faculty since 1973. He is a member of the National Academy of Sciences. Dr. Lefkowitz received his B.A. from Columbia University and his M.D. from Columbia University College of Physicians and Surgeons.

Julia P. Gregory has been our Executive Vice President and Chief Financial Officer since February 2000. From 1998 to February 2000, Ms. Gregory served as the Head of Investment Banking for Punk, Ziegel & Company, a specialty investment banking firm focusing on technology and healthcare and, from 1996 to February 2000, as the Head of the firm's Life Sciences practice. From 1980 to 1996, Ms. Gregory was an investment banker with Prime Charter Ltd. and then Dillon, Read & Co., Inc., where she represented life sciences companies beginning in 1986. Ms. Gregory is a member of the board of directors and the scientific advisory board of the Estee Lauder Foundation's Institute for the Study of Aging, Inc. and a member of The International Council for George Washington University's Elliott School of International Affairs. She received her B.A. in International Affairs from George Washington University and her M.B.A. from the Wharton School of the University of Pennsylvania.

Jeffrey L. Wade, J.D. has been our Executive Vice President and General Counsel since February 2000 and was our Senior Vice President and Chief Financial Officer from January 1999 to February 2000. From 1988 through December 1998, Mr. Wade was a corporate securities and finance attorney with the law firm of Andrews & Kurth L.L.P., for the last two years as a partner, where he represented companies in the biotechnology, information technology and energy industries. Mr. Wade is a member of the boards of directors of the Texas Healthcare and Bioscience Institute and the Texas Life Sciences Foundation. He received his B.A. and J.D. from The University of Texas.

Brian P. Zambrowicz, Ph.D. has been our Executive Vice President of Research since August 2002. Dr. Zambrowicz served as our Senior Vice President of Genomics from February 2000 to August 2002, Vice President of Research from January 1998 to February 2000 and Senior Scientist from April 1996 to January 1998. From 1993 to April 1996, Dr. Zambrowicz served as a National Institutes of Health, or NIH, postdoctoral fellow at The Fred Hutchinson Cancer Center in Seattle, Washington, where he studied gene trapping and gene targeting technology. Dr. Zambrowicz received his B.S. in Biochemistry from the University of Wisconsin. He received his Ph.D. from the University of Washington, where he studied tissue-specific gene regulation using transgenic mice.

Walter F. Colbert has been our Senior Vice President of Human Resources and Corporate Services since May 2002. Mr. Colbert served as our Vice President of Human Resources from December 2000 to May 2002. From September 1997 to December 2000, Mr. Colbert was Vice President, Human Resources and Public Affairs at the Sony Technology Center—San Diego of Sony Electronics Inc., a manufacturer of electronic equipment. From September 1995 to September 1997, Mr. Colbert served as Vice President, Human Resources for The NutraSweet Kelco Company, Monsanto Company's food ingredients business unit. From 1976 through September 1995, Mr. Colbert served in a variety of human resources positions in the United States and Europe with Ford Motor Company and Monsanto Company. He received his B.A. in Political Science from Stanford University and his M.A. in International Affairs from The Fletcher School of Law and Diplomacy at Tufts University.

Alan J. Main, Ph.D. has been our Senior Vice President, Lexicon Pharmaceuticals since July 2001. Dr. Main was President and Chief Executive Officer of Coelacanth Corporation, a leader in using proprietary chemistry technologies to rapidly discover new chemical entities for drug development, from January 2000 until our acquisition of Coelacanth in July 2001. Dr. Main was formerly Senior Vice President, United States Research at Novartis Pharmaceuticals Corporation, the United States affiliate of Swiss-based Novartis AG, a diversified healthcare company, where he worked for 20 years before joining Coelacanth. Dr. Main holds a B.Sc. from the University of Aberdeen, Scotland and a Ph.D. in Organic Chemistry from the University of Liverpool, England and completed postdoctoral studies at the Woodward Research Institute.

James R. Piggott, Ph.D. has been our Senior Vice President of Pharmaceutical Biology since January 2000. From 1990 through October 1999, Dr. Piggott worked for ZymoGenetics, Inc., a subsidiary of Novo Nordisk, a company focused on the discovery, development and commercialization of therapeutic proteins for the treatment of human disease, most recently as Senior Vice President-Research Biology from 1997 to October 1999. Dr. Piggott's pharmaceutical research experience also includes service at the Smith Kline & French Laboratories Ltd. unit of SmithKline Beecham plc and the G.D. Searle & Co. unit of Monsanto Company. Dr. Piggott received his B.A. and Ph.D. from Trinity College, Dublin.

Randall B. Riggs has been our Senior Vice President of Business Development since February 2000 and served as our Vice President of Business Development from December 1998 to February 2000. From January through November 1998, Mr. Riggs was director of Business Development for the Infectious Disease Business Unit of GeneMedicine, Inc., a genetics-based pharmaceuticals company. From 1992 to January 1998, Mr. Riggs was employed by Eli Lilly and Company, a pharmaceutical company, for the last two years as Manager, Corporate Business Development at Eli Lilly's Indianapolis, Indiana headquarters. Before joining Eli Lilly, Mr. Riggs' experience included service as a business analyst for the National Aeronautics and Space Administration and a subsidiary of Amoco Production Company. He received his B.B.A. from Texas A&M University and his M.B.A. from The University of Houston.

David A. Boulton has been our Vice President of Technology Operations, Lexicon Pharmaceuticals since July 2001. Mr. Boulton co-founded Coelacanth and served as its Vice President of Technology Operations from October 1996 until our acquisition of Coelacanth in July 2001. From April 1994 to October 1996, Mr. Boulton was Senior Director of Automated Synthesis at ArQule, Inc., where he was instrumental in developing ArQule's chemical automation platform. Before joining ArQule, he served for 15 years in chemistry research and development at Merck & Co., Inc. and was a founding member of Merck's automated synthesis group. He holds a B.S. in Chemistry from Lafayette College.

Philip M. Brown, M.D., J.D., FCLM has been our Vice President of Clinical Development since April 2003. Dr. Brown served as Vice President of Clinical Development for Encysive Pharmaceuticals Inc. (formerly Texas Biotechnology Corporation), a biopharmaceutical company, from June 2000 until April 2003, and was Senior Medical Director within the organization from December 1998 until June 2000. From July 1994 to December 1998, Dr. Brown served as Associate Vice President of Medical Affairs for Pharmaceutical Research Associates, a clinical research organization. He has conducted numerous clinical trials as an investigator in a variety of therapeutic areas, as well as managed programs from IND through NDA and product commercialization. He is a fellow of the American College of Legal Medicine and serves as an adjunct faculty member at the Massachusetts General Hospital, Institute of Health Professions in Boston. He

received his B.A. from Hendrix College, his M.D. from Texas Tech University School of Medicine, and his J.D. from the University of Texas School of Law.

William E. Heydorn, Ph.D. has been our Vice President of Preclinical Development since June 2003. Dr. Heydorn was employed by Forest Laboratories, Inc., a pharmaceutical company, from March 1999 until June 2003, for the last three years as Director. From 1993 through March 1999, Dr. Heydorn worked for Synaptic Pharmaceutical Corporation, a biopharmaceutical company, most recently as Director of Pharmaceutical Operations. Dr. Heydorn's experience also includes service at Marion Merrell Dow Pharmaceuticals, Inc., the FDA and the NIH. Dr. Heydorn received his B.S. in Pharmacy from the Philadelphia College of Pharmacy and Science and his Ph.D. in Pharmacology from the University of Pennsylvania.

Lance K. Ishimoto, J.D., Ph.D. has been our Vice President of Intellectual Property since July 1998. From 1994 to July 1998, Dr. Ishimoto was a biotechnology patent attorney at the Palo Alto, California office of the law firm of Pennie & Edmonds LLP. Dr. Ishimoto received his B.A. and Ph.D. from the University of California at Los Angeles, where he studied molecular mechanisms of virus assembly and the regulation of virus ultrastructure. After receiving his Ph.D., Dr. Ishimoto served as an NIH postdoctoral fellow at University of Washington School of Medicine. He received his J.D. from Stanford University.

S. David Kimball, Ph.D. has been our Vice President of Medicinal Chemistry since August 2002 and served as our Senior Director of Medicinal Chemistry from August 2001 to August 2002. Before joining Lexicon, Dr. Kimball spent 19 years at the Bristol-Myers Squibb Pharmaceutical Research Institute, a research organization dedicated to discovering and developing innovative, cost-effective medicines, most recently as Research Fellow in the Division of Medicinal Chemistry, Princeton, New Jersey, from June 2001 to August 2001 and as Associate Director from May 1998 to May 2001. During his tenure at the Institute, Dr. Kimball led several significant drug discovery and development research efforts involving molecular targets in oncology, serine protease inhibitors of blood coagulation and ion channel modulators for the treatment of hypertension and angina. Dr. Kimball has been an Associate Member of the Graduate Faculty at Rutgers University School of Pharmacy since 1989. Dr. Kimball earned a B.A. and a Ph.D. in Organic Chemistry/Chemical Biology from the State University of New York at Stony Brook.

Stephen J. McAndrew, Ph.D. has been our Vice President of Pharmaceutical Business Development since January 2002. From March 1990 to December 2001, he held increasing levels of responsibility at Bristol-Myers Squibb Company, leading to his final position of Executive Director of Biotechnology Licensing at the Bristol-Myers Squibb Pharmaceutical Research Institute from October 2001 to December 2001. In this position, he was primarily responsible for identifying, evaluating and negotiating numerous preclinical lead compound collaborations and platform technology alliances. Before his 11-year career at Bristol-Myers Squibb, Dr. McAndrew spent seven years conducting basic research at the Roche Institute of Molecular Biology at Hoffmann LaRoche. He received his B.S. from State University College at Oswego, New York and holds a Ph.D. in molecular and cellular biology from Ohio University.

Christophe Person has been our Vice President of Informatics since November 1999 and served as our Director of Informatics from May 1997 to November 1999. From 1994 to May 1997, Mr. Person was the Senior Scientific Programmer for the Center for Theoretical Neurosciences at Baylor College of Medicine. From 1990 to 1994, Mr. Person was the CEPH Database Manager at the Human Polymorphism Studies Center in Paris, France. Mr. Person received his degree in Electrical Engineering from Groupe ESTE/ESIEE (Ecole Superieure de Technologie Electronique/Ecole Superieure d'Ingenieurs en Electrotechnique et Electronique).

PRINCIPAL STOCKHOLDERS

The following table presents information regarding the beneficial ownership of our common stock as of July 23, 2003 by:

- our chief executive officer and each of our four other most highly compensated executive officers for the fiscal year ended December 31, 2002;
- each of our directors;
- each person, or group of affiliated persons, who is known by us to beneficially own more than five percent of our common stock; and
- all current directors and executive officers as a group.

Beneficial ownership is determined in accordance with the rules of the SEC computing the number of shares beneficially owned by a person and the percentage ownership of that person. Shares of common stock under options held by that person that are currently exercisable or exercisable within 60 days of July 23, 2003 are considered outstanding for purposes of calculating the percentage beneficially owned by the person holding such options, but are not considered outstanding for purposes of calculating the percentage beneficially owned by each other person. We issued options to purchase an aggregate of 2,169,873 shares of common stock to our employees in 2002.

Except as indicated in the footnotes to this table and pursuant to state community property laws, each stockholder named in the table has sole voting and investment power for the shares shown as beneficially owned by such stockholder. Percentage of ownership is based on 52,537,748 shares of common stock outstanding on July 23, 2003 and 62,537,748 shares of common stock to be outstanding upon completion of this offering. Unless otherwise indicated in the footnotes, the address of each of the individuals named below is: c/o Lexicon Genetics Incorporated, 8800 Technology Forest Place, The Woodlands, Texas 77381.

	Beneficial Ownership			
Name and Address of Beneficial Owner	Number of Shares Currently Owned	Shares Issuable Pursuant to Options Exercisable Within 60 Days of July 23, 2003	Percentage Beneficially Owned After Offering	Percentage Beneficially Owned Before Offering
Mary H. Cain and James D. Weaver[1]	8,002,000	8,500	12.8%	15.2%
Royce & Associates, LLC[2]	6,575,300	—	10.5	12.5
Robert C. McNair[3]	5,949,400	—	9.5	11.3
Baylor College of Medicine[4]	4,461,105	—	7.1	8.5
Arthur T. Sands, M.D., Ph.D.[5]	1,032,300	2,526,033	5.5	6.5
Julia P. Gregory[6]	75,047	501,564	*	1.1
Jeffrey L. Wade, J.D.	3,000	554,982	*	1.1
Alan J. Main, Ph.D.	—	282,944	*	*
Brian P. Zambrowicz, Ph.D.	—	920,582	1.5	1.7
C. Thomas Caskey, M.D.[7]	1,683,200	153,122	2.9	3.5
Sam L. Barker, Ph.D.	7,000	33,000	*	*
Patricia M. Cloherty	—	28,000	*	*
Robert J. Lefkowitz, M.D.	—	21,000	*	*
William A. McMinn[8]	7,746,091	20,500	12.4	14.8
All directors and executive officers as a group[5][6][7][8] (20 persons)	10,589,954	6,432,161	24.7	28.9

* Represents beneficial ownership of less than 1%.

(footnotes on next page)

(1) Based upon a Schedule 13D/A filed with the SEC on July 22, 2003, reflecting the beneficial ownership of our common stock by the Estate of Gordon A. Cain (6,687,000 shares), the Gordon and Mary Cain Foundation (1,300,000 shares) and Mr. Weaver (15,000 shares). Mrs. Cain and Mr. Weaver are co-executors of the Estate of Gordon A. Cain and share voting and investment power with respect to the shares held by it. Mrs. Cain is Chairman and Mr. Weaver is President of the Gordon and Mary Cain Foundation and share voting and investment power with respect to the shares held by it. The shares held by or issuable to the Estate of Gordon A. Cain are subject to a proxy held by William A. McMinn, as described in note 8 below. The address for Mrs. Cain and Mr. Weaver is c/o Gordon Cain and Associates, 8 Greenway Plaza, Suite 702, Houston, Texas 77046.

(2) Based upon a Schedule 13G filed with the SEC on February 3, 2003, reflecting the beneficial ownership of our common stock by Royce & Associates, LLC, an investment advisor. The address for Royce & Associates, LLC is 1414 Avenue of the Americas, New York, New York 10019.

(3) Based upon a Schedule 13D filed with the SEC on July 18, 2003, reflecting the beneficial ownership of our common stock by RCM Financial Services, L.P. (4,250,000 shares), Cogene Biotech Ventures, L.P. (1,679,400 shares) and Palmetto Partners, Ltd. (20,000 shares). Mr. McNair has sole voting and investment power with respect to all of such shares. The address for Mr. McNair is 4400 Post Oak Parkway, Suite 1400, Houston, Texas 77027. 949,400 of these shares have been pledged to a third party.

(4) Based upon a Schedule 13G filed with the SEC on January 15, 2003, reflecting the beneficial ownership of our common stock by Baylor College of Medicine and BCM Technologies, Inc., a wholly owned subsidiary of Baylor College of Medicine. The number of shares beneficially owned includes 222,280 shares held by BCM Technologies, Inc. The address of Baylor College of Medicine is One Baylor Plaza, T-128, Houston, Texas 77030-3498.

(5) The number of shares beneficially owned by Dr. Sands includes 60,000 shares held in the name of his minor children and 817,500 shares owned by Sands Associates LP. The general partners of Sands Associates LP are ATS Associates, L.L.C., owned by Dr. Sands, and MES Associates, L.L.C., owned by Dr. Sands' wife.

(6) The number of shares beneficially owned by Ms. Gregory includes 6,647 shares held in the name of her minor children and trusts for their benefit, of which she serves as a trustee.

(7) The number of shares beneficially held by Dr. Caskey includes 1,679,400 shares held by Cogene Biotech Ventures, L.P., of which Dr. Caskey is President and Chief Executive Officer. Dr. Caskey disclaims beneficial ownership of these shares.

(8) The number of shares beneficially owned by Mr. McMinn includes 6,687,000 shares owned by, and 8,500 shares issuable within 60 days of July 23, 2003 to, the Estate of Gordon A. Cain, which are subject to a proxy granted to Mr. McMinn by Mr. Cain to vote these shares in the event of Mr. Cain's incapacity or death. The proxy will terminate upon the distribution of the shares from Mr. Cain's estate. Mr. McMinn disclaims beneficial ownership of these shares.

UNDERWRITERS

Under the terms and subject to the conditions contained in an underwriting agreement dated the date of this prospectus supplement, the underwriters named below have severally agreed to purchase, and we have agreed to sell to them, severally, the number of shares indicated below:

Name	Number of Shares
Morgan Stanley & Co. Incorporated	5,000,000
UBS Securities LLC	2,500,000
CIBC World Markets Corp.	1,500,000
Punk, Ziegel & Company, L.P.	1,000,000
Total	10,000,000

The underwriters are offering the shares of common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the shares of common stock offered by this prospectus supplement and the accompanying prospectus are subject to the approval of various legal matters by their counsel and to other conditions. The underwriters are obligated to take and pay for all of the shares of common stock offered by this prospectus supplement and the accompanying prospectus if any such shares are taken. However, the underwriters are not required to take or pay for the shares covered by the underwriters' over-allotment option described below.

The underwriters initially propose to offer part of the shares of common stock directly to the public at the public offering price listed on the cover page of this prospectus supplement and part to certain dealers at a price that represents a concession not in excess of $.20 a share under the public offering price. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the underwriters.

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to an aggregate of 1,500,000 additional shares of common stock at the public offering price set forth on the cover page of this prospectus supplement, less underwriting discounts and commissions. The underwriters may exercise this option solely for the purpose of covering over-allotments, if any, made in connection with the offering of the shares of common stock offered by this prospectus supplement and the accompanying prospectus. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional shares of common stock as the number listed next to the underwriter's name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table. If the underwriters' option is not exercised, the total underwriters' discounts and commissions would be $3,150,000, or $.315 a share. If the underwriters' option is exercised in full, the total price to the public would be $60,375,000, or $5.25 a share, the total underwriters' discounts and commissions would be $3,622,500, or $.315 a share, and total proceeds to us would be $56,752,500, or $4.935 a share.

The estimated offering expenses payable by us, in addition to the underwriting discounts and commissions, are approximately $400,000, or $.04 a share, which includes legal, accounting and printing costs and various other fees associated with registering and listing the common stock.

We, our directors and executive officers and certain of our stockholders have agreed, without the prior written consent of Morgan Stanley & Co. Incorporated on behalf of the underwriters, during the period ending 90 days after the date of this prospectus supplement, not to:

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend, or otherwise transfer or dispose of directly or indirectly, any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock; or
- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of the common stock;

whether any such transaction described above is to be settled by delivery of common stock or such other securities, in cash or otherwise. The restrictions described in this paragraph do not apply:

- in our case, to (1) the sale of the common stock offered hereby; (2) the issuance by us of any shares of common stock upon the exercise of an option or warrant or the conversion of a security outstanding on the date of this prospectus supplement; and (3) the grant of options to purchase our common stock under our stock option plans; or
- in the case of our directors, executive officers and stockholders, to (1) the sale of any shares of common stock to the underwriters; (2) the transfer of shares of common stock or other securities to an immediate family member or any trust established for the benefit of the transferor or an immediate family member or a corporation, partnership, limited partnership or limited liability company wholly owned by the transferor or any combination of the transferor and members of his or her immediate family, provided that, in each case, the transferee agrees in writing to be bound by the restrictions set forth above and (3) transactions relating to shares of common stock or other securities acquired in open market transactions after the completion of this offering or, in certain cases, pledged to third parties as of the date of this prospectus supplement.

In order to facilitate the offering of the common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the common stock. Specifically, the underwriters may sell more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the over-allotment option. The underwriters can close out a covered short sale by exercising the over-allotment option or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the over-allotment option. The underwriters may also sell shares in excess of the over-allotment option, creating a naked short position. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in the offering. As an additional means of facilitating the offering, the underwriters may bid for, and purchase, shares of common stock in the open market to stabilize the price of the common stock. The underwriting syndicate may also reclaim selling concessions allowed to an underwriter or a dealer for distributing the common stock in the offering, if the syndicate repurchases previously distributed common stock to cover syndicate short positions or to stabilize the price of the common stock. These activities may raise or maintain the market price of the common stock above independent market levels or prevent or retard a decline in the market price of the common stock. These transactions may be effected on the Nasdaq National Market, in the over-the-counter market or otherwise. The underwriters are not required to engage in these activities, and may end any of these activities at any time.

The underwriters and dealers may engage in passive market making transactions in our common stock in accordance with Rule 103 of Regulation M promulgated by the SEC. In general, a passive market maker may not bid for, or purchase, our common stock at a price that exceeds the highest independent bid. In addition, the net daily purchases made by any passive market maker generally may not exceed 30% of its average daily

trading volume in our common stock during a specified two-month prior period, or 200 shares, whichever is greater. A passive market maker must identify passive market making bids as such on the Nasdaq electronic inter-dealer reporting system. Passive market making may stabilize or maintain the market price of our common stock above independent market levels. The underwriters and dealers are not required to engage in passive market making and may end passive market making activities at any time.

We and the underwriters have agreed to indemnify each other against certain liabilities, including liabilities under the Securities Act.

The maximum underwriting compensation payable in connection with this offering will not exceed 8% of the aggregate offering proceeds.

LEGAL MATTERS

Vinson & Elkins L.L.P., Houston, Texas, will pass upon the validity of the shares of common stock offered by this prospectus supplement and the accompanying prospectus for us. Certain legal matters in connection with this offering will be passed upon for the underwriters by Hale and Dorr LLP, Boston, Massachusetts.

EXPERTS

The consolidated financial statements of Lexicon Genetics Incorporated at December 31, 2002 and for the year ended December 31, 2002, incorporated by reference in this prospectus supplement and the accompanying prospectus, have been audited by Ernst & Young LLP, independent auditors, as set forth in their report thereon (which contains one explanatory paragraph describing the audit procedures relating to certain revisions to the 2001 and 2000 financial statements for reclassification adjustments and conforming disclosures that were applied to revise the 2001 and 2000 financial statements described in Note 4 to the consolidated financial statements; the 2001 and 2000 financial statements were audited by other auditors who have ceased operations and for which Ernst & Young LLP has expressed no opinion or other form of assurance on the 2001 and 2000 financial statements taken as a whole), and are included in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

The financial statements as of December 31, 2000 and 2001 and for each of the two years in the period ended December 31, 2001, incorporated by reference in this prospectus supplement and the accompanying prospectus, have been audited by Arthur Andersen LLP, independent public accountants, as indicated in their report with respect thereto, and are included herein in reliance upon the authority of said firm as experts in accounting and auditing. Arthur Andersen LLP has not consented to the inclusion of their report in this prospectus supplement and the accompanying prospectus, and we have not obtained their consent to do so in reliance upon Rule 437a of the Securities Act. Because Arthur Andersen LLP has not consented to the inclusion of their report in this prospectus supplement and the accompanying prospectus, you will not be able to recover against Arthur Andersen LLP under Section 11(a) of the Securities Act for any untrue statement of a material fact contained in the financial statements audited by Arthur Andersen LLP or any omission to state a material fact required to be stated therein.

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12,000,000 Shares

Lexicon Genetics Incorporated

COMMON STOCK

We may offer shares of our common stock from time to time in one or more offerings in amounts, at prices and on terms to be determined in light of market conditions at the time of sale. Each time we sell shares of our common stock, we will provide a supplement to this prospectus that contains specific information about the offering. The supplement may also add, update or change information contained in this prospectus. You should carefully read this prospectus and any supplement before you invest.

Our common stock is listed on the Nasdaq National Market under the symbol "LEXG". The last reported sale price on November 26, 2002 was $4.15 per share.

Investing in our common stock involves risks. See "Risk Factors" on page 2.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is December 6, 2002.

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We have filed a registration statement on Form S-3 to register with the Securities and Exchange Commission the offering of the shares described in this prospectus. This prospectus is part of that registration statement. As allowed by the SEC's rules, this prospectus does not contain all of the information you can find in the registration statement or the exhibits to the registration statement. Please see "Where You Can Find More Information" on page 5.

You should rely only on the information contained in this prospectus. We have not authorized anyone to provide you with information different from that contained in this prospectus. This prospectus may only be used where it is legal to sell these securities. The information contained in this prospectus and any supplements to this prospectus is accurate only as of the dates of their respective covers or earlier dates as specified therein, regardless of the time of delivery of this prospectus or any supplement to this prospectus or of any sale of our common stock.

In this prospectus, "Lexicon," "Lexicon Genetics," "we," "us" and "our" refer to Lexicon Genetics Incorporated and its subsidiary.

LEXICON GENETICS INCORPORATED

Lexicon Genetics is a biopharmaceutical company focused on the discovery of breakthrough treatments for human disease. We are using gene knockout technology to systematically discover the physiological functions of genes in living mammals, or *in vivo.* Our gene function discoveries fuel therapeutic discovery programs in cancer, cardiovascular disease, immune disorders, neurological disease, diabetes and obesity. We have established drug discovery alliances and functional genomics collaborations with leading pharmaceutical and biotechnology companies, research institutes and academic institutions throughout the world to commercialize our technology and further develop our discoveries.

We generate our gene function discoveries using knockout mice — mice whose DNA has been altered to disrupt, or "knock out," the function of the altered gene. Our patented gene trapping and gene targeting technologies enable us to rapidly generate these knockout mice by altering the DNA of genes in a special variety of mouse cells, called embryonic stem (ES) cells, which can be cloned and used to generate mice with the altered gene. We employ an integrated platform of advanced medical technologies to systematically discover and validate, *in vivo,* the functions and pharmaceutical utility of the genes we have knocked out and the potential targets for therapeutic intervention, or drug targets, they encode.

We employ internal resources and drug discovery alliances to discover potential small molecule drugs, therapeutic antibodies and therapeutic proteins for *in vivo*-validated drug targets that we consider to have high pharmaceutical value. We use our own sophisticated libraries of drug-like chemical compounds and an industrialized medicinal chemistry platform to identify small molecule drug candidates for our *in vivo*-validated drug targets. We have established alliances with Abgenix, Inc. for the discovery and development of therapeutic antibodies based on our drug target discoveries and with Incyte Genomics, Inc. for the discovery and development of therapeutic proteins. In addition, we have established collaborations and license agreements with many other leading pharmaceutical and biotechnology companies under which we receive fees and, in many cases, are eligible to receive milestone and royalty payments, for access to some of our technologies and discoveries for use in their own drug discovery efforts.

We believe that our industrialized approach of discovering and validating drug targets *in vivo,* together with our capabilities in small molecule drug discovery and the integration of our own capabilities with those of our alliance partners in therapeutic antibody and therapeutic protein discovery, will significantly increase our likelihood of success in discovering breakthrough treatments for human disease. We believe our system will reduce the risk, time and expense of discovering and developing therapeutics for new drug targets. Together, we believe that these factors will provide us with substantial strategic advantages in the competition to discover and develop genomics-based pharmaceutical products.

Lexicon Genetics was incorporated in Delaware in July 1995, and commenced operations in September 1995. Our corporate headquarters are located at 8800 Technology Forest Place, The Woodlands, Texas 77381, and our telephone number is (281) 863-3000. Our corporate website is located at *www.lexicon-genetics.com.* Information found on our website should not be considered part of this prospectus.

RISK FACTORS

You should carefully consider the following risk factors and all other information contained in this prospectus and incorporated into it by reference before purchasing our common stock. Investing in our common stock involves a high degree of risk. For a discussion of these risks, please see:

- *Our most recent Annual Report on Form 10-K, and*
- *Our other SEC filings that are incorporated by reference into this prospectus.*

For more information about our SEC filings, please see "Where You Can Find More Information" and "Documents Incorporated By Reference" on page 5 of this prospectus. See also "Special Note Regarding Forward-Looking Statements" below.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains forward-looking statements. These statements relate to future events or our future financial performance. We have attempted to identify forward-looking statements by terminology including "anticipate," "believe," "can," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "should" or "will" or the negative of these terms or other comparable terminology. These statements are only predictions and involve known and unknown risks, uncertainties and other factors, including the risks referred to under "Risk Factors," that may cause our or our industry's actual results, levels of activity, performance or achievements to be materially different from any future results, levels or activity, performance or achievements expressed or implied by these forward-looking statements.

Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. We are not under any duty to update any of the forward-looking statements after the date of this prospectus to conform these statements to actual results, unless required by law.

USE OF PROCEEDS

Except as otherwise described in the prospectus supplement relating to an offering, we intend to use the net proceeds from the sale(s) of shares of our common stock offered pursuant to this prospectus and any prospectus supplement for research and development and general corporate purposes, including capital expenditures and working capital needs. We may also use some or all of the net proceeds to acquire or invest in businesses, products and technologies that are complementary to our own.

The amounts that we actually expend for working capital purposes, investments or acquisitions will vary significantly depending on a number of factors, including future revenue growth, if any, the amount of cash we generate from operations and the progress of our product development efforts. Accordingly, our management will retain broad discretion in the allocation of the net proceeds from the sale(s) of the offered securities. If we elect at the time of the issuance of the securities to make different or more specific use of proceeds other than as described in this prospectus, the change in use of proceeds will be described in the applicable prospectus supplement.

PLAN OF DISTRIBUTION

We may sell shares of our common stock under this prospectus from time to time in any one or more of the following ways:

- to or through underwriters;
- through brokers or dealers;
- directly to other purchasers; or
- through agents.

We may sell shares of our common stock under this prospectus from time to time in one or more transactions:

- at a fixed price or prices, which may be changed;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

The prospectus supplement relating to the shares of common stock will set forth the terms of the offering of such shares, including the names or names of any underwriters, brokers, dealers or agents, the name or names of any managing underwriter or underwriters, the purchase price of the shares and the net proceeds to us from such sale, any delayed delivery arrangements, any underwriting discounts and commissions and other items constituting underwriters' compensation, any public offering price and any discounts or concessions allowed or reallowed or paid to dealers and any commissions paid to agents.

If we use underwriters in the sale of shares of common stock, the underwriters will acquire the shares for their own account. The underwriters may resell the shares from time to time in one or more transactions, including negotiated transactions, at a fixed public offering price or at varying prices determined at the time of sale. Underwriters may offer shares to the public either through underwriting syndicates represented by one or more managing underwriters or directly by one or more firms acting as underwriters. Unless we inform you otherwise in the prospectus supplement, the obligations of the underwriters to purchase the shares will be subject to certain conditions, and the underwriters will be obligated to purchase all of the offered shares if they purchase any of them. The underwriters may change from time to time any public offering price and any discounts or concessions allowed or reallowed or paid to dealers.

In connection with the sale of shares of our common stock, underwriters, brokers, dealers or agents may receive compensation from us or purchasers of securities for whom they may act as agents, in the form of discounts, concessions or commissions. Underwriters, dealers and agents that participate in the distribution of our common stock may be deemed to be underwriters, and any discounts or commissions received by them from us and any profit on the resale of securities by them may be deemed to be underwriting discounts and commissions under the Securities Act of 1933. Any person who may be deemed to be an underwriter will be identified, and the compensation received from us will be described, in the prospectus supplement.

During and after an offering through underwriters, the underwriters may purchase and sell the securities in the open market. These transactions may include over-allotment and stabilizing transactions and purchases to cover syndicate short positions created in connection with the offering. The underwriters may also impose a penalty bid, whereby selling concessions allowed to syndicate members or other broker-dealers for the securities sold for their account may be reclaimed by the syndicate if those securities are repurchased by the syndicate in stabilizing or covering transactions. These activities may stabilize, maintain or otherwise affect the market price of the securities, which may be higher than the price that might otherwise prevail in the open market, and, if commenced, may be discontinued at any time.

If dealers or brokers acting as dealers are used in the sale of the shares of common stock, we will sell the shares to such dealers or brokers as principals. The dealers or brokers acting as dealers may then resell such shares to the public at varying prices to be determined by such dealers or brokers at the time of resale. The names of dealers or brokers acting as dealers and the terms of the transaction will be set forth in the prospectus supplement relating to such shares. We may sell the shares of common stock directly or through agents designated by us from time to time. Any agent involved in the offer or sale of the shares will be named, and any commissions that we pay to such agent will be set forth, in the prospectus supplement relating to such shares. Unless otherwise indicated in the prospectus supplement, any such agent will be acting on a best efforts basis for the period of its appointment.

We may sell shares of common stock directly. In this case, no underwriters or agents would be involved. We may sell shares directly to institutional investors or others who may be deemed to be underwriters within the meaning of the Securities Act of 1933 with respect to any sale of those shares.

If so indicated in the prospectus supplement, we will authorize agents, underwriters, brokers or dealers to solicit offers from certain types of institutions to purchase shares of common stock at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. Such contracts will be subject only to those conditions set forth in the prospectus supplement, and the prospectus supplement will set forth also the commission payable for solicitation of such contracts.

We may have agreements with the underwriters, dealers and agents to indemnify them against specific civil liabilities, including liabilities under the Securities Act of 1933, or to contribute with respect to payments which the underwriters, dealers or agents may be required to make as a result of those specific civil liabilities.

Underwriters and agents and their affiliates may be customers of, engage in transactions with, or perform services for us or our subsidiaries in the ordinary course of their businesses.

LEGAL MATTERS

The validity of the issuance of the common stock offered by this prospectus will be passed upon for us by Vinson & Elkins L.L.P., Houston, Texas.

EXPERTS

The financial statements, as of December 31, 2000 and 2001, and for each of the three years in the period ended December 31, 2001, incorporated by reference in this prospectus have been audited by Arthur Andersen LLP, independent public accountants, as indicated in their report with respect thereto, and are included herein in reliance upon the authority of said firm as experts in giving said report. Arthur Andersen LLP has not consented to the inclusion of their report in this prospectus, and we have not obtained their consent to do so in reliance upon Rule 437a of the Securities Act of 1933. Because Arthur Andersen LLP has not consented to the inclusion of their report in this prospectus, you will not be able to recover against Arthur Andersen LLP under Section 11(a) of the Securities Act for any untrue statements of a material fact contained in the financial statements audited by Arthur Andersen LLP or any omissions to state a material fact required to be stated therein.

CHANGE IN INDEPENDENT PUBLIC ACCOUNTANTS

On March 26, 2002, our Board of Directors and Audit Committee dismissed Arthur Andersen LLP as our independent public accountants and engaged Ernst & Young LLP to serve as our independent public accountants for the year ending December 31, 2002. The appointment of Ernst & Young was ratified at our 2002 annual meeting of stockholders held on May 8, 2002.

Arthur Andersen LLP's reports on our consolidated financial statements for the years ended December 31, 2001 and 2000 did not contain an adverse opinion or disclaimer of opinion, nor were they qualified or modified as to uncertainty, audit scope or accounting principles.

During the years ended December 31, 2001 and 2000 and through March 26, 2002, there were no disagreements with Arthur Andersen LLP on any matter of accounting principles or practices, financial statement disclosure, or auditing scope or procedure which, if not resolved to Arthur Andersen LLP's satisfaction, would have caused them to make reference to the subject matter in connection with their report on our consolidated financial statements for such years; and there were no reportable events as defined in Item 304(a)(1)(v) of Regulation S-K.

We provided Arthur Andersen LLP with a copy of the foregoing disclosures. Attached as Exhibit 16.1 to our report on Form 8-K dated March 29, 2002, which is incorporated into this registration statement by reference, is a copy of Arthur Andersen LLP's letter, dated March 29, 2002, stating its agreement with such statements.

During the two-year period ended December 31, 2001 and through the date of the Board of Directors' decision, we did not consult Ernst & Young LLP with respect to the application of accounting principles to a specified transaction, either completed or proposed, or the type of audit opinion that might be rendered on our consolidated financial statements, or any other matters or reportable events as set forth in Items 304(a)(2)(i) and (ii) of Regulation S-K.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the Securities and Exchange Commission a registration statement on Form S-3 under the Securities Act of 1933 regarding our offering and sale of shares of our common stock by this prospectus. This prospectus, which constitutes a part of that registration statement, does not contain all of the information contained in the registration statement or the exhibits to the registration statement, as permitted by the rules and regulations of the SEC. For further information about us and our common stock, please review the registration statement and the exhibits filed as a part of it. Statements made in this prospectus that describe documents may not necessarily be complete. We recommend that you review the documents that we have filed with the registration statement to obtain a more complete understanding of these documents. A copy of the registration statement, including the exhibits filed as a part of it, may be inspected at the SEC's Public Reference Room, 450 Fifth Street, N.W., Washington, D.C. 20549, and copies of all or any part of the registration statement may be obtained from the SEC upon the payment of fees prescribed by it. You may obtain information on the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains a Web site at http://www.sec.gov that contains reports, proxy and information statements and other information regarding companies that file electronically with it.

We are subject to the information and reporting requirements of the Securities Exchange Act of 1934 and will file periodic reports, proxy statements and other information with the SEC. You may inspect any of these documents as described in the preceding paragraph. These reports, proxy statements and other information may also be inspected at the offices of Nasdaq Operations, 1735 K Street, N.W., Washington, D.C. 20006.

DOCUMENTS INCORPORATED BY REFERENCE

The Securities and Exchange Commission allows us to "incorporate by reference" into this prospectus information that we file with the SEC in other documents. This means that we can disclose important information to you by referring to other documents that contain that information. The information incorporated by reference is considered to be part of this prospectus, except for information superseded by information in this prospectus. Information that we file later with the SEC will automatically update and supercede the information incorporated by reference in this prospectus. We incorporate by reference the documents listed below that we have previously filed with the SEC and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, prior to the termination of the offering of the securities covered by this prospectus:

- our annual report on Form 10-K for the year ended December 31, 2001;
- our quarterly reports on Form 10-Q for the quarterly periods ended March 31, 2002, June 30, 2002 and September 30, 2002;
- our current report on Form 8-K dated March 29, 2002; and
- the description of our common stock contained in our registration statement on Form 8-A filed with the Commission on March 27, 2000 pursuant to Section 12 of the Securities Exchange Act of 1934, including any amendments and reports filed for the purpose of updating such description.

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus or in any other subsequently filed document which also is or is deemed to be incorporated by reference in this prospectus modifies or supersedes that statement. Any statement that is modified or superseded will not constitute a part of this prospectus, except as so modified or superseded.

Upon your written or oral request, we will provide you at no cost a copy of any or all of the documents incorporated by reference in this prospectus, other than the exhibits to those documents, unless the exhibits are specifically incorporated by reference into this prospectus. You may request a copy of these documents by contacting:

Investor Relations
Lexicon Genetics Incorporated
8800 Technology Forest Place
The Woodlands, Texas 77381-1160
Telephone: (281) 863-3000

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