

5,000,000 SHARES

(LEXICON GENETICS INCORPORATED LOGO)

LEXICON GENETICS INCORPORATED

COMMON STOCK

This prospectus relates to the offer and sale of previously issued shares of our common stock by selling stockholders. The selling stockholders are offering up to 5,000,000 shares of our common stock. See "Selling Stockholders" beginning on page 16.

We will not receive any proceeds from the sale of the shares offered by the selling stockholders.

The selling stockholders may offer the shares from time to time through public or private transactions at prevailing market prices, at prices related to prevailing market prices or at privately negotiated prices.

Our common stock is listed on The Nasdaq National Market under the symbol "LEXG". The last reported sale price on October 24, 2003 was \$5.31 per share.

INVESTING IN THE COMMON STOCK INVOLVES RISKS.
SEE "RISK FACTORS" BEGINNING ON PAGE 4.

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 October 27, 2003.

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This prospectus is part of a registration statement that we have filed on Form S-3 with the Securities and Exchange Commission using a "shelf" registration process. This means that the securities described in this prospectus may be offered and sold using this prospectus from time to time as described in the "Plan of Distribution." 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 19.

YOU SHOULD RELY ONLY ON THE INFORMATION CONTAINED IN THIS PROSPECTUS AND DOCUMENTS INCORPORATED INTO THIS PROSPECTUS BY REFERENCE. WE HAVE NOT AUTHORIZED ANYONE TO PROVIDE YOU WITH INFORMATION DIFFERENT FROM THAT CONTAINED IN THIS PROSPECTUS OR THE DOCUMENTS INCORPORATED BY REFERENCE HEREIN. THIS PROSPECTUS MAY ONLY BE USED WHERE IT IS LEGAL TO SELL THESE SECURITIES. THE INFORMATION CONTAINED IN THIS PROSPECTUS, THE DOCUMENTS INCORPORATED BY REFERENCE HEREIN 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.

The Lexicon name and logo, LexVision(R) and OmniBank(R) are registered trademarks and Genome5000(TM) and e-Biology(TM) are trademarks of Lexicon Genetics Incorporated.

LEXICON GENETICS INCORPORATED

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.

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, Inc. 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.

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 annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934 are made available free of charge on our corporate website located at www.lexicon-genetics.com as soon as reasonably practicable after the filing of those reports with the Securities and Exchange Commission. Information found on our website should not be considered part of this prospectus.

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 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 \$34.8 million for the six months ended June 30, 2003. As of June 30, 2003, we had an accumulated deficit of \$184.5 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:

- o our ability to obtain alliance, database subscription, collaboration and technology license agreements;
- o the amount and timing of payments under such agreements;
- o the level and timing of our research and development expenditures;
- o market acceptance of products that we successfully develop and commercially launch; and
- o 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 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 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 two quarters 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 six months ended June 30, 2003, Incyte accounted for approximately 30% of our revenues and Bristol-Myers Squibb accounted for approximately 15% 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:

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

OUR STOCK PRICE COULD BE EXTREMELY VOLATILE, AND YOU MAY NOT BE ABLE TO RESELL YOUR SHARES AT OR ABOVE YOUR PURCHASE 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 your purchase price.

CONCENTRATION OF OWNERSHIP AMONG OUR DIRECTORS AND EXECUTIVE OFFICERS
ENABLES THEM TO SIGNIFICANTLY INFLUENCE IMPORTANT CORPORATE DECISIONS.

Our directors and executive officers 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.

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:

- o a classified board of directors;
- o limitations on the removal of directors;
- o limitations on stockholder proposals at meetings of stockholders;
- o the inability of stockholders to act by written consent or to call special meetings; and
- o 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.

We have outstanding an aggregate of 62,781,270 shares of common stock, assuming no exercise of outstanding options or warrants. Of these shares, 52,717,879 shares are freely tradable or may be sold under this prospectus. The holders of the remaining 10,063,391 shares have demand and piggyback registration rights with respect to such shares.

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 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. 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. 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 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 and the documents incorporated by reference into this 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.

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 and other sections of the documents incorporated by reference into this 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.

USE OF PROCEEDS

All of the shares offered by this prospectus are being offered and sold by the selling stockholders. We will not receive any proceeds from the sale of the shares of common stock offered by the selling stockholders.

We will pay all expenses for the registration of the selling stockholders' offer and sale of the shares of common stock covered by this prospectus, including registration fees, the costs and expenses of our counsel and independent public accountants and the reasonable fees of one counsel for the selling stockholders. The selling stockholders will pay any underwriting discounts and commissions, brokerage fees and other similar expenses which they incur in selling shares of our common stock.

SELLING STOCKHOLDERS

We issued the shares of common stock covered by this prospectus in private placements to Gordon A. Cain completed in the period from September 1995 to July 1997. Mr. Cain, who served as a member of our board of directors until his death in October 2002, subsequently transferred some of the shares by gift to The Gordon and Mary Cain Foundation. On July 10, 2003, RCM Financial Services, L.P. and Cogene Biotech Ventures, L.P. purchased the shares offered by this prospectus from the Estate of Gordon A. Cain and The Gordon and Mary Cain Foundation in private placements that were exempt from registration under the Securities Act of 1933.

The selling stockholders exercised their rights to cause us to register the offer and sale of the shares of common stock described in this prospectus under a registration rights agreement and letter agreement in which we agreed to use commercially reasonable best efforts to keep the registration statement effective for five years or until the distribution contemplated by the registration statement is complete. All of the shares to be offered by the selling stockholders using this prospectus were originally issued by us in transactions exempt from the registration requirements of the Securities Act of 1933.

The selling stockholders, or their donees of 500 or fewer shares, may offer the shares of common stock covered by this prospectus from time to time. Our registration of the selling stockholders' offer and sale of such shares does not necessarily mean that the selling stockholders will sell any or all of their shares. We do not know when or in what amounts a selling stockholder may offer shares for sale. Because the selling stockholders may offer all or some of the shares pursuant to this offering, and because there are currently no agreements, arrangements or understandings with respect to the sale of any of the shares, we cannot estimate the number of the shares that will be held by the selling stockholders after completion of the offering.

If a selling stockholder transfers more than 500 shares of common stock by gift, pledge or other non-sale transfer after the effective date of the registration statement of which this prospectus is a part, the donee, pledgee or transferee may make no offer or sale under this prospectus unless and until a supplement to this prospectus has been filed or an amendment to the related registration statement has become effective.

The table below sets forth the beneficial ownership of all common stock of each selling stockholder as of October 27, 2003, the number of such shares of common stock offered by this prospectus and the beneficial ownership of all common stock of each selling stockholder after completion of this offering, assuming that all shares offered hereby are sold. Percentage of ownership is based on 62,781,270 shares of common stock outstanding on October 27, 2003.

We prepared this table based on information supplied to us by the selling stockholders named in the table, and we have not sought to independently verify such information.

BENEFICIAL
 OWNERSHIP
 BENEFICIAL
 OWNERSHIP PRIOR
 TO OFFERING AFTER
 OFFERING -----

 ----- NUMBER
 OF NUMBER OF
 SHARES SHARES
 SHARES
 BENEFICIALLY
 PERCENTAGE
 OFFERED
 BENEFICIALLY
 PERCENTAGE NAME
 OF SELLING
 STOCKHOLDER OWNED
 OWNERSHIP HEREBY
 OWNED OWNERSHIP -

----- RCM
 Financial
 Services, L.P.
 4,250,000 6.8%
 4,000,000 250,000
 * Cogene Biotech
 Ventures, L.P.
 (1) 1,679,400
 2.7% 1,000,000
 679,400 1.1% - --
 ----- *

Represents
 beneficial
 ownership of less
 than 1%. (1) The
 Chairman of our
 Board of
 Directors, C.
 Thomas Caskey,
 M.D., is
 President and
 Chief Executive
 Officer of Cogene
 Biotech Ventures,
 L.P. and is
 deemed to have
 beneficial
 ownership of the
 shares held by
 Cogene Biotech
 Ventures, L.P.
 Dr. Caskey
 disclaims
 beneficial
 ownership of such

shares. PLAN OF DISTRIBUTION The shares covered by this prospectus may be offered and sold from time to time by the selling stockholders. The term "selling stockholder" includes donees selling 500 or fewer shares received from a selling stockholder as a gift after the effective date of the registration statement of which this prospectus is a part. The selling stockholders will act independently of us in making decisions with respect to the timing, manner and size of each sale. Such sales may be made on one or more exchanges or in the over-the-counter market or otherwise, at prices and under terms then prevailing or at prices related to the then current market price or in negotiated transactions. The selling stockholders have advised us that they may offer and sell the shares of common stock offered by this prospectus in one or more of, or a combination of, the following methods: o purchases by a broker-dealer as principal and resale by such broker-dealer for its own account pursuant to this prospectus; o ordinary brokerage transactions and transactions in which the broker solicits purchasers; o block trades in which the broker-dealer so engaged will attempt to sell the shares as agent but may position and

resell a portion of the block as principal to facilitate the transaction; o an over-the-counter distribution in accordance with the rules of the Nasdaq National Market; o through the Nasdaq National Market or any other securities exchange or association that quotes the common stock; o in privately negotiated transactions; and o in options transactions. 17

In addition, the selling stockholders have advised us that they may sell shares of common stock in compliance with Rule 144, if available, or pursuant to other available exemptions from the registration requirements under the Securities Act, rather than pursuant to this prospectus. To the extent required, this prospectus may be amended or supplemented from time to time to describe a specific plan of distribution. In connection with distributions of the shares or otherwise, the selling stockholders have advised us that they may enter into hedging transactions with broker-dealers or other financial institutions. In connection with such transactions, broker-dealers or other financial institutions may engage in short sales of the common stock in the course of hedging the positions they assume with a selling

stockholder. The selling stockholders have advised us that they may also sell the common stock short and redeliver the shares to close out such short positions. The selling stockholders have advised us that they may also enter into option or other transactions with broker-dealers or other financial institutions which require the delivery to such broker-dealer or other financial institution of shares offered by this prospectus, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction). The selling stockholders have advised us that they may also pledge shares to a broker-dealer or other financial institution, and, upon a default, such broker-dealer or other financial institution may effect sales of the pledged shares pursuant to this prospectus (as supplemented or amended to reflect such transaction). In effecting sales, broker-dealers or agents engaged by a selling stockholder may arrange for other broker-dealers to participate. Broker-dealers or agents may receive commissions, discounts or concessions from the selling stockholder in amounts to be negotiated immediately prior

to the sale. In offering the shares covered by this prospectus, a selling stockholder and any broker-dealers who execute sales for such selling stockholder may be deemed to be "underwriters" within the meaning of the Securities Act in connection with such sales. Any profits realized by a selling stockholder and the compensation of any broker-dealer may be deemed to be underwriting discounts and commissions. In order to comply with the securities laws of certain states, if applicable, the shares must be sold in such jurisdictions only through registered or licensed brokers or dealers. In addition, in certain states the shares may not be sold unless they have been registered or qualified for sale in the applicable state or an exemption from the registration or qualification requirement is available and is complied with.

The selling stockholders have advised us that they may sell their shares at market prices prevailing at the time of sale, at prices related to such prevailing market prices, at negotiated prices or at fixed prices and that the transactions listed above may include cross or block transactions. We have advised the selling stockholders that the anti-manipulation

rules of Regulation M under the Securities Exchange Act of 1934 may apply to their sales of common stock and to the activities of the selling stockholders and their affiliates. In addition, we will make copies of this prospectus available to the selling stockholders for the purpose of satisfying the prospectus delivery requirements of the Securities Act of 1933. The selling stockholders have advised us that they may indemnify any broker-dealer that participates in transactions involving the sale of the shares against certain liabilities, including liabilities arising under the Securities Act. At the time a particular offer of shares is made, if required, a prospectus supplement will be distributed that will set forth the number of shares being offered and the terms of the offering, including the name of any underwriter, dealer or agent, the purchase price paid by any underwriter, any discount, commission and other item constituting compensation, any discount, commission or concession allowed or reallocated or paid to any dealer, and the proposed selling price to the public. We have agreed to indemnify the selling

stockholders
against certain
liabilities,
including certain
liabilities under
the Securities
Act. All shares
offered by this
prospectus by the
selling
stockholders will
be sold subject
to the terms and
conditions of the
registration
rights agreement
and letter
agreement
described in the
section entitled
"Selling
Stockholders." 18

LEGAL MATTERS The validity of the common stock offered by this prospectus has been passed upon for us by Vinson & Elkins L.L.P., Houston, Texas.

EXPERTS The consolidated financial statements of Lexicon Genetics Incorporated included in our annual report on Form 10-K for the year ended

December 31, 2002 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),

included therein and incorporated herein by reference. Such financial statements have been incorporated

herein by reference 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, 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, 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, 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. WHERE YOU CAN FIND MORE INFORMATION We have filed with the SEC a registration statement on Form S-3 under the Securities Act of 1933 regarding the offer and sale of shares of common stock by the selling stockholders.

This prospectus, which constitutes

a part of the registration statement, does not contain all of the information contained in the registration statement, some items of which are contained in 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 without charge 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 SEC 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. 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 19

13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934 (other than information furnished to the SEC under Items 9 or 12 of Form 8-K), prior to the termination of the offering of the securities covered by this prospectus: o our annual report on Form 10-K for the year ended December 31, 2002; o our quarterly reports on Form 10-Q for the quarters ended March 31 and June 30, 2003; o our current reports on Form 8-K dated July 10 and July 23, 2003; and o 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 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 Telephone:
(281) 863-3000 20