

PROSPECTUS SUPPLEMENT NO. 1
(TO PROSPECTUS DATED JUNE 13, 2006)

1,000,000 SHARES

[LEXICON LOGO]

LEXICON GENETICS INCORPORATED

COMMON STOCK

You should carefully read this prospectus supplement and the accompanying prospectus before you invest. Both documents contain information you should carefully consider before making your investment decision.

Pursuant to this prospectus supplement and the accompanying prospectus, we are offering 1,000,000 shares of our common stock to Azimuth Opportunity Ltd. pursuant to our Common Stock Purchase Agreement with Azimuth dated June 12, 2006, at a price of approximately \$3.67 per share. The total purchase price for the shares is \$3,674,900. We will receive net proceeds from the sale of these shares of approximately \$3,634,900 after deducting our estimated offering expenses of approximately \$40,000, including a placement agent fee of \$36,749 payable to Reedland Capital Partners, an institutional division of Financial West Group, in connection with this offering. As permitted by the Common Stock Purchase Agreement, we agreed with Azimuth to shorten the draw down period for this offering.

In addition to our issuance of shares of common stock to Azimuth pursuant to the Common Stock Purchase Agreement, this prospectus supplement and the accompanying prospectus also cover the sale of those shares by Azimuth to the public. Azimuth is an "underwriter" within the meaning of Section 2(a)(11) of the Securities Act of 1933, as amended.

Our common stock is quoted on the Nasdaq National Market under the symbol "LEXG." The offering price of these shares was established with reference to the daily volume weighted average prices of our common stock on the Nasdaq National Market for the period beginning September 7, 2006 and ending September 13, 2006, averaging \$3.8888 per share over such period, less a discount of 5.5%.

We expect to issue the shares to Azimuth on or about September 15, 2006. On September 13, 2006, the last reported sale price of our common stock on the Nasdaq National Market was \$3.84 per share. As of September 12, 2006, we had 64,682,627 shares of common stock outstanding.

INVESTING IN OUR COMMON STOCK INVOLVES RISKS. SEE "RISK FACTORS" ON PAGE 4 OF THE ACCOMPANYING PROSPECTUS.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of 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 DATE OF THIS PROSPECTUS SUPPLEMENT IS SEPTEMBER 14, 2006.

\$150,000,000

[LEXICON LOGO]

LEXICON GENETICS INCORPORATED

COMMON STOCK
PREFERRED STOCK
DEBT SECURITIES
WARRANTS
UNITS

We may offer common stock, preferred stock, debt securities and/or warrants, either individually or in units, 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. We may also offer common stock or preferred stock upon conversion of debt securities, common stock upon conversion of preferred stock or common stock, preferred stock or debt securities upon the exercise of warrants.

Each time we sell these securities, 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 prospectus supplement will contain information, where applicable, regarding any other listing on The Nasdaq National Market or any securities exchange of the securities covered by the prospectus supplement. The last reported sale price of our common stock on June 9, 2006 was \$4.78 per share.

INVESTING IN OUR SECURITIES INVOLVES RISKS. SEE "RISK FACTORS" 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 June 13, 2006.

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LEXICON GENETICS INCORPORATED

Lexicon Genetics is a biopharmaceutical company focused on the discovery and development of breakthrough treatments for human disease. We are systematically discovering the physiological and behavioral functions of genes to identify those that encode potential targets for therapeutic intervention, or drug targets. We make these discoveries using our proprietary technology to knock out, or disrupt, the function of genes in mice to model the effects on physiology that could be expected from prospective drugs directed against those targets. For targets that we believe have high pharmaceutical value, we engage in programs for the discovery and development of potential small molecule, antibody and protein drugs. We focus our discovery efforts in six therapeutic areas - diabetes and obesity, cardiovascular disease, psychiatric and neurological disorders, cancer, immune system disorders and ophthalmic disease - and we have advanced targets into drug discovery programs in each of these areas with potential for addressing large medical markets.

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 are using these technologies in our Genome5000 program to discover the physiological and behavioral functions of 5,000 genes from the human genome that belong to gene families that we consider to be pharmaceutically important. We have completed our analysis of more than 60% of these genes, and we expect to complete the analysis of the remaining genes by the end of 2008. Through the end of 2005, we had identified and validated in living mammals, or in vivo, more than 90 targets with promising profiles for drug discovery. As of the date of this prospectus, we had advanced compounds for two of these targets into preclinical development and had advanced compounds from drug discovery programs for a number of additional targets into preclinical research. To date, none of our programs has yet advanced into clinical development.

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 Bristol-Myers Squibb Company to discover and develop novel small molecule drugs in the neuroscience field. 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, and to develop new biotherapeutic drugs based on certain targets selected from the alliance. We are working with N.V. Organon to discover, develop and commercialize new biotherapeutic drugs based on another group of secreted proteins and potential antibody targets. We are working with Takeda Pharmaceutical Company Limited for the discovery of new drugs for the treatment of high blood pressure. In addition, we have established collaborations and license agreements with many other leading pharmaceutical and biotechnology companies under which we receive fees and, in some 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

You should carefully consider the risk factors and all other information contained in this prospectus and any prospectus supplement and incorporated herein by reference before purchasing our securities. Investing in our securities 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 filings with the Securities and Exchange Commission 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 22 of this prospectus. See also "Special Note Regarding Forward-Looking Statements" on page 17 of this prospectus.

DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of 120 million shares of common stock, \$0.001 par value, and five million shares of preferred stock, \$0.01 par value. As of June 9, 2006, there were 64,633,608 shares of our common stock outstanding and no shares of preferred stock outstanding.

The following summary description of our capital stock is based on the provisions of our restated certificate of incorporation, restated bylaws and the applicable provisions of the Delaware General Corporation Law. This information may not be complete in all respects and is qualified entirely by reference to the provisions of our restated certificate of incorporation, restated bylaws and the Delaware General Corporation Law. For information on how to obtain copies of our restated certificate of incorporation and restated bylaws, see "Where You Can Find More Information" on page 22 of this prospectus.

COMMON STOCK

The holders of common stock are entitled to one vote for each share held of record on all matters submitted to a vote of the stockholders and do not have cumulative voting rights. Accordingly, holders of a majority of the shares of common stock entitled to vote in any election of directors may elect all of the directors standing for election. Subject to preferences that may be applicable to any outstanding shares of preferred stock, the holders of common stock are entitled to receive ratably such dividends as may be declared by the board of directors out of funds legally available therefor. Upon the liquidation, dissolution or winding up of Lexicon, holders of our common stock are entitled to share ratably in all assets remaining after payment of liabilities and the liquidation preferences of any outstanding shares of preferred stock. Holders of common stock have no preemptive rights and no right to convert their common stock into any other securities. There are no redemption or sinking fund provisions applicable to our common stock. All outstanding shares of our common stock are, and all shares of common stock that may be issued under this prospectus will be, fully paid and non-assessable.

PREFERRED STOCK

Pursuant to our restated certificate of incorporation, our board of directors has the authority, without further action by the stockholders, to issue up to five million shares of preferred stock, in one or more series. Our board of directors is authorized to fix or alter from time to time the designation, powers, preferences and rights of the shares of each series of preferred stock, including dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences and sinking fund terms. Our board of directors may also establish from time to time the number of shares constituting any series of preferred stock, and to increase or decrease the number of shares of any series subsequent to the issuance of shares of that series, but not below the number of shares of any series then outstanding.

We will fix the rights, preferences, privileges and restrictions of the preferred stock of each series in the certificate of designation relating to that series. We will incorporate by reference as an exhibit to the registration statement that includes this prospectus or as an exhibit to a report filed under the Securities Exchange Act of 1934, the form of any certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of the related series of preferred stock. This description will include:

- the title and stated value;
- the number of shares we are offering;
- the liquidation preference per share;
- the purchase price;
- the dividend rate, period and payment date and method of calculation for dividends;
- whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;
- the provisions for a sinking fund, if any;
- the provisions for redemption or repurchase, if applicable, and any restrictions on our ability to exercise those redemption and repurchase rights;
- whether the preferred stock will be convertible into our common stock, and, if applicable, the conversion price, or how it will be calculated, and the conversion period;
- whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange price, or how it will be calculated, and the exchange period;
- voting rights, if any, of the preferred stock;
- preemption rights, if any;
- restrictions on transfer, sale or other assignment, if any;
- the relative ranking and preferences of the preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs;
- any limitations on issuance of any class or series of preferred stock ranking senior to or on a parity with the series of preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs; and
- any other specific terms, preferences, rights or limitations of, or restrictions on, the preferred stock.

If we issue shares of preferred stock under this prospectus, the shares will be fully paid and non-assessable and will not have, or be subject to, any preemptive or similar rights.

The Delaware General Corporation Law of the State of Delaware provides that the holders of preferred stock will have the right to vote separately as a class on any proposal involving fundamental changes in the rights of holders of that preferred stock. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

The issuance of preferred stock could adversely affect the voting power, conversion or other rights of holders of common stock. Preferred stock could be issued quickly with terms designed to delay or prevent a change in control of our company or make removal of management more difficult. Additionally, the issuance of preferred stock may have the effect of decreasing the market price of our common stock.

ANTI-TAKEOVER EFFECTS OF PROVISIONS OF DELAWARE LAW AND OUR CHARTER DOCUMENTS

Delaware Takeover Statute. We are subject to the provisions of Section 203 of the Delaware General Corporation Law. In general, the statute prohibits a publicly-held Delaware corporation such as Lexicon from engaging in a business combination with an interested stockholder for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the business combination is approved in a prescribed manner. For purposes of Section 203, a business combination includes a merger, asset sale or other transaction resulting in a financial benefit to the interested stockholder. An interested stockholder is a person who, together with affiliates and associates, owns (or within three years prior, did own) 15% or more of our voting stock.

Charter Documents. Our restated certificate of incorporation requires that any action required or permitted to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and may not be effected by a consent in writing. Additionally, our restated certificate of incorporation:

- does not provide for the use of cumulative voting in the election of directors;
- provides for a board of directors, classified into three classes of directors;
- provides that the authorized number of directors may be changed only by resolution of our board of directors; and
- provides for the authority of our board of directors to issue up to five million shares of "blank check" preferred stock and to determine the price, powers, preferences and rights of these shares, without stockholder approval.

Our restated bylaws provide that candidates for director may be nominated only by our board of directors or by a stockholder who gives written notice to us not less than 120 days nor more than 150 days in advance of the first anniversary of the date of our proxy statement relating to the previous year's annual meeting of stockholders. The authorized number of directors is fixed in accordance with our restated certificate of incorporation. Our board of directors currently consists of eight members, divided into three classes. As a result, a portion of the board of directors will be elected each year. The board of directors may appoint new directors to fill vacancies or newly created directorships. Our restated bylaws also limit who may call a special meeting of stockholders.

Delaware law and these charter provisions may have the effect of deterring hostile takeovers or delaying changes in control of our management, which could depress the market price of our common stock.

TRANSFER AGENT AND REGISTRAR

The transfer agent and registrar for our common stock is Mellon Investor Services L.L.C. The transfer agent for any series of preferred stock will be named and described in the prospectus supplement for that series.

DESCRIPTION OF DEBT SECURITIES

The following description, together with the additional information we may include in any applicable prospectus supplements, summarizes the material terms and provisions of the debt securities that we may offer under this prospectus and the related indenture. While the terms summarized below will apply generally to any debt securities we may offer under this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. If we indicate in the prospectus supplement, the terms of any debt securities offered under that prospectus supplement may differ from the terms described below. However, no prospectus supplement shall fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness.

We may offer debt securities in the form of either senior debt securities or subordinated debt securities. Unless otherwise specified in a supplement to this prospectus, the debt securities will be our direct, unsecured obligations and will rank equally with all of our other unsecured and unsubordinated indebtedness.

The debt securities will be issued under an indenture between us and a trustee. The following summary of the general features of the debt securities to be governed by the indenture is subject to, and qualified in its entirety by reference to, the provisions of the indenture applicable to a particular series of debt securities. We have filed a form of indenture as an exhibit to the registration statement which includes this prospectus. Capitalized terms used in the summary have the meanings specified in the indenture.

GENERAL

The terms of each series of debt securities will be established by or pursuant to a resolution of our board of directors, or a committee thereof, and set forth or determined in the manner provided in an officer's certificate or by a supplemental indenture. The particular terms of each series of debt securities will be described in a prospectus supplement relating to such series, including any pricing supplement.

We can issue an unlimited amount of debt securities under the indenture that may be in one or more series with the same or various maturities, at par, at a premium or at a discount. We will set forth in a prospectus supplement, including any pricing supplement, relating to any series of debt securities being offered, the aggregate principal amount and the following terms of the debt securities:

- the title of the debt securities;

- the price or prices (expressed as a percentage of the principal amount) at which we will sell the debt securities;
- any limit on the aggregate principal amount of the debt securities;
- the date or dates on which we will pay the principal on the debt securities;
- the rate or rates (which may be fixed or variable) per annum or the method used to determine the rate or rates (including any commodity, commodity index, stock exchange index or financial index) at which the debt securities will bear interest, the date or dates from which interest will accrue, the date or dates on which interest will commence and be payable and any regular record date for the interest payable on any interest payment date;
- the place or places where principal of, and premium and interest on, the debt securities will be payable;
- the terms and conditions upon which we may redeem the debt securities;
- any obligation we have to redeem or purchase the debt securities pursuant to any sinking fund or analogous provisions or at the option of a holder of debt securities;
- the dates on which and the price or prices at which we will repurchase debt securities at the option of the holders of debt securities and other detailed terms and provisions of these repurchase obligations;
- the denominations in which the debt securities will be issued, if other than denominations of \$1,000 and any integral multiple thereof;
- whether the debt securities will be issued in the form of certificated debt securities or global debt securities;
- the portion of principal amount of the debt securities payable upon declaration of acceleration of the maturity date, if other than the principal amount;
- the currency of denomination of the debt securities;
- the designation of the currency, currencies or currency units in which payment of principal of, and premium and interest on, the debt securities will be made;
- if payments of principal of, or premium or interest on, the debt securities will be made in one or more currencies or currency units other than that or those in which the debt securities are denominated, the manner in which the exchange rate with respect to these payments will be determined;
- the manner in which the amounts of payment of principal of, or premium or interest on, the debt securities will be determined, if these amounts may be determined by reference to an index based on a currency or currencies other than that in which the debt securities are denominated or designated to be payable or by reference to a commodity, commodity index, stock exchange index or financial index;
- any provisions relating to any security provided for the debt securities;
- any addition to or change in the events of default described in this prospectus or in the indenture with respect to the debt securities and any change in the acceleration provisions described in this prospectus or in the indenture with respect to the debt securities;
- any addition to or change in the covenants described in this prospectus or in the indenture with respect to the debt securities;
- any conversion provisions, including the conversion price, the conversion period, provisions as to whether conversion will be mandatory, at the option of the holder or at our option, the events requiring an adjustment of the conversion price and provisions affecting conversion if such series of debt securities are redeemed;
- whether the debt securities will be senior debt securities or subordinated debt securities and, if applicable, a description of the subordination terms thereof;

- any depositaries, interest rate calculation agents, exchange rate calculation agents or other agents with respect to the debt securities; and

- any other terms of the debt securities, which may modify, delete, supplement or add to any provision of the indenture as it applies to that series.

We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with information on the federal income tax considerations and other special considerations applicable to any of these debt securities in the applicable prospectus supplement.

If we denominate the purchase price of any of the debt securities in a foreign currency or currencies or a foreign currency unit or units, or if the principal of, and premium and interest on, any series of debt securities is payable in a foreign currency or currencies or a foreign currency unit or units, we will provide you with information on the restrictions, elections, general tax considerations, specific terms and other information with respect to that issue of debt securities and such foreign currency or currencies or foreign currency unit or units in the applicable prospectus supplement.

TRANSFER AND EXCHANGE

Each debt security will be represented by either one or more global securities registered in the name of The Depository Trust Company, as Depository, or a nominee (we will refer to any debt security represented by a global debt security as a "book-entry debt security"), or a certificate issued in definitive registered form (we will refer to any debt security represented by a certificated security as a "certificated debt security") as set forth in the applicable prospectus supplement. Except as set forth under the heading "Legal Ownership of Securities" below, book-entry securities will not be issuable in certificated form.

You may transfer or exchange certificated debt securities at any office we maintain for this purpose in accordance with the terms of the indenture. No service charge will be made for any transfer or exchange of certificated debt securities, but we may require payment of a sum sufficient to cover any tax or other governmental charge payable in connection with a transfer or exchange.

You may effect the transfer of certificated debt securities and the right to receive the principal of, and any premium and interest on, certificated debt securities only by surrendering the certificate representing those certificated debt securities and either reissuance by us or the trustee of the certificate to the new holder or the issuance by us or the trustee of a new certificate to the new holder.

NO PROTECTION IN THE EVENT OF A CHANGE OF CONTROL

Unless we state otherwise in the applicable prospectus supplement, the debt securities will not contain any provisions which may afford holders of the debt securities protection in the event we have a change in control or in the event of a highly leveraged transaction (whether or not such transaction results in a change in control) which could adversely affect holders of debt securities.

COVENANTS

We will set forth in the applicable prospectus supplement any restrictive covenants applicable to any issue of debt securities.

CONSOLIDATION, MERGER AND SALE OF ASSETS

We may not consolidate with or merge with or into, or convey, transfer or lease all or substantially all of our properties and assets to, any person, which we refer to as a successor person, unless:

- we are the surviving corporation or the successor person (if other than Lexicon) is organized and validly existing under the laws of any U.S. domestic jurisdiction and expressly assumes our obligations on the debt securities and under the indenture;
- immediately after giving effect to the transaction, no event of default, and no event which, after notice or lapse of time, or both, would become an event of default, shall have occurred and be continuing under the indenture; and
- certain other conditions are met.

EVENTS OF DEFAULT

Event of default means, with respect to any series of debt securities, any of the following:

- default in the payment of any interest upon any debt security of that series when it becomes due and payable, and continuance of that default for a period of 30 days (unless the entire amount of the payment is deposited by us with the trustee or with a paying agent prior to the expiration of the 30-day period);
- default in the payment of principal of or premium on any debt security of that series when due and payable;
- default in the deposit of any sinking fund payment, when and as due in respect of any debt security of that series;
- default in the performance or breach of any other covenant or warranty by us in the indenture (other than a covenant or warranty that has been included in the indenture solely for the benefit of a series of debt securities other than that series), which default continues uncured for a period of 90 days after we receive written notice from the trustee or we and the trustee receive written notice from the holders of not less than a majority in principal amount of the outstanding debt securities of that series as provided in the indenture;
- certain events of bankruptcy, insolvency or reorganization of our company; and
- any other event of default provided with respect to debt securities of that series that is described in the applicable prospectus supplement accompanying this prospectus.

No event of default with respect to a particular series of debt securities (except as to certain events of bankruptcy, insolvency or reorganization) necessarily constitutes an event of default with respect to any other series of debt securities. The occurrence of an event of default may constitute an event of default under our bank credit agreements in existence from time to time. In addition, the occurrence of certain events of default or an acceleration under the indenture may constitute an event of default under certain of our other indebtedness outstanding from time to time.

If an event of default with respect to debt securities of any series at the time outstanding occurs and is continuing, then the trustee or the holders of not less than a majority in principal amount of the outstanding debt securities of that series may, by a notice in writing to us (and to the trustee if given by the holders), declare to be due and payable immediately the principal (or, if the debt securities of that series are discount securities, that portion of the principal amount as may be specified in the terms of that series) of, and accrued and unpaid interest, if any, on all debt securities of that series. In the case of an event of default resulting from certain events of bankruptcy, insolvency or reorganization, the principal (or such specified amount) of and accrued and unpaid interest, if any, on all outstanding debt securities will become and be immediately due and payable without any declaration or other act on the part of the trustee or any holder of outstanding debt securities. At any time after a declaration of acceleration with respect to debt securities of any series has been made, but before a judgment or decree for payment of the money due has been obtained by the trustee, the holders of a majority in principal amount of the outstanding debt securities of that series may rescind and annul the acceleration if all events of default, other than the non-payment of accelerated principal and interest, if any, with respect to debt securities of that series, have been cured or waived as provided in the indenture. We refer you to the prospectus supplement relating to any series of debt securities that are discount securities for the particular provisions relating to acceleration of a portion of the principal amount of such discount securities upon the occurrence of an event of default.

The indenture provides that the trustee will be under no obligation to exercise any of its rights or powers under the indenture at the request of any holder of outstanding debt securities, unless the trustee receives indemnity satisfactory to it against any loss, liability or expense. Subject to certain rights of the trustee, the holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee or exercising any trust or power conferred on the trustee with respect to the debt securities of that series.

No holder of any debt security of any series will have any right to institute any proceeding, judicial or otherwise, with respect to the indenture or for the appointment of a receiver or trustee, or for any remedy under the

indenture, unless:

- that holder has previously given to the trustee written notice of a continuing event of default with respect to debt securities of that series; and

- the holders of at least a majority in principal amount of the outstanding debt securities of that series have made written request, and offered reasonable indemnity, to the trustee to institute the proceeding as trustee, and the trustee has not received from the holders of a majority in principal amount of the outstanding debt securities of that series a direction inconsistent with that request and has failed to institute the proceeding within 60 days.

Notwithstanding the foregoing, the holder of any debt security will have an absolute and unconditional right to receive payment of the principal of, and any premium and interest on, that debt security on or after the due dates expressed in that debt security and to institute suit for the enforcement of payment.

If any securities are outstanding under the indenture, the indenture requires us, within 120 days after the end of our fiscal year, to furnish to the trustee a statement as to compliance with the indenture. The indenture provides that the trustee may withhold notice to the holders of debt securities of any series of any default or event of default (except in payment on any debt securities of that series) with respect to debt securities of that series if it in good faith determines that withholding notice is in the interest of the holders of those debt securities.

MODIFICATION AND WAIVER

We may modify and amend the indenture with the consent of the holders of at least a majority in principal amount of the outstanding debt securities of each series affected by the modifications or amendments. We may not make any modification or amendment without the consent of the holders of each affected debt security then outstanding if that amendment will:

- reduce the amount of debt securities whose holders must consent to an amendment or waiver;
- reduce the rate of or extend the time for payment of interest (including default interest) on any debt security;
- reduce the principal of or premium on or change the fixed maturity of any debt security or reduce the amount of, or postpone the date fixed for, the payment of any sinking fund or analogous obligation with respect to any series of debt securities;
- reduce the principal amount of discount securities payable upon acceleration of maturity;
- waive a default in the payment of the principal of, or premium or interest on, any debt security (except a rescission of acceleration of the debt securities of any series by the holders of at least a majority in aggregate principal amount of the then outstanding debt securities of that series and a waiver of the payment default that resulted from such acceleration);
- make the principal of, or premium or interest on, any debt security payable in currency other than that stated in the debt security;
- make any change to certain provisions of the indenture relating to, among other things, the right of holders of debt securities to receive payment of the principal of, and premium and interest on, those debt securities and to institute suit for the enforcement of any such payment and to waivers or amendments; or
- waive a redemption payment with respect to any debt security.

Except for certain specified provisions, the holders of at least a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all debt securities of that series waive our compliance with provisions of the indenture. The holders of a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all the debt securities of such series waive any past default under the indenture with respect to that series and its consequences, except a default in the payment of the principal of, or any premium or interest on, any debt security of that series or in respect of a covenant or provision, which cannot be modified or amended without the consent of the holder of each outstanding debt security of the series affected; provided, however, that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration.

DEFEASANCE OF DEBT SECURITIES AND CERTAIN COVENANTS IN CERTAIN CIRCUMSTANCES

Legal Defeasance. The indenture provides that, unless otherwise provided by the terms of the applicable series of debt securities, we may be discharged from any and all obligations in respect of the debt securities of any series (except for certain obligations to register the transfer or exchange of debt securities of such series, to replace stolen, lost or mutilated debt securities of such series, and to maintain paying agencies and certain provisions relating to the treatment of funds held by paying agents). We will be so discharged upon the deposit with the trustee, in trust, of money and/or U.S. government obligations or, in the case of debt securities denominated in a single currency other than U.S. dollars, foreign government obligations, that, through the payment of interest and principal in accordance with their terms, will provide money in an amount sufficient in the opinion of a nationally recognized firm of independent public accountants to pay and discharge each installment of principal of, premium and interest on and any mandatory sinking fund payments in respect of the debt securities of that series on the stated maturity of those payments in accordance with the terms of the indenture and those debt securities.

This discharge may occur only if, among other things, we have delivered to the trustee an opinion of counsel stating that we have received from, or there has been published by, the United States Internal Revenue Service a ruling or, since the date of execution of the indenture, there has been a change in the applicable United States federal income tax law, in either case to the effect that, and based thereon such opinion shall confirm that, the holders of the debt securities of that series will not recognize income, gain or loss for United States federal income tax purposes as a result of the deposit, defeasance and discharge and will be subject to United States federal income tax on the same amounts and in the same manner and at the same times as would have been the case if the deposit, defeasance and discharge had not occurred.

Defeasance of Certain Covenants. The indenture provides that, unless otherwise provided by the terms of the applicable series of debt securities, upon compliance with certain conditions:

- we may omit to comply with the covenant described under the heading "Consolidation, Merger and Sale of Assets" and certain other covenants set forth in the indenture, as well as any additional covenants which may be set forth in the applicable prospectus supplement; and
- any omission to comply with those covenants will not constitute a default or an event of default with respect to the debt securities of that series, or covenant defeasance.

The conditions include:

- depositing with the trustee money and/or U.S. government obligations or, in the case of debt securities denominated in a single currency other than U.S. dollars, foreign government obligations, that, through the payment of interest and principal in accordance with their terms, will provide money in an amount sufficient in the opinion of a nationally recognized firm of independent public accountants to pay and discharge each installment of principal of, premium and interest on and any mandatory sinking fund payments in respect of the debt securities of that series on the stated maturity of those payments in accordance with the terms of the indenture and those debt securities; and
- delivering to the trustee an opinion of counsel to the effect that the holders of the debt securities of that series will not recognize income, gain or loss for United States federal income tax purposes as a result of the deposit and related covenant defeasance and will be subject to United States federal income tax on the same amounts and in the same manner and at the same times as would have been the case if the deposit and related covenant defeasance had not occurred.

Covenant Defeasance and Events of Default. In the event we exercise our option to effect covenant defeasance with respect to any series of debt securities and the debt securities of that series are declared due and payable because of the occurrence of any event of default, the amount of money and/or U.S. government obligations or foreign government obligations on deposit with the trustee will be sufficient to pay amounts due on the debt securities of that series at the time of their stated maturity but may not be sufficient to pay amounts due on the debt securities of that series at the time of the acceleration resulting from the event of default. In such a case, we would remain liable for those payments.

"Foreign Government Obligations" means, with respect to debt securities of any series that are denominated in a currency other than U.S. dollars:

- direct obligations of the government that issued or caused to be issued such currency for the payment of which obligations its full faith and credit is pledged which are not callable or redeemable at the option of the issuer thereof; or
- obligations of a person controlled or supervised by or acting as an agency or instrumentality of that government the timely payment of which is unconditionally guaranteed as a full faith and credit obligation by that government which are not callable or redeemable at the option of the issuer thereof.

GOVERNING LAW

The indenture and the debt securities will be governed by and construed in accordance with the laws of the State of New York.

DESCRIPTION OF WARRANTS

The following description, together with the additional information we may include in any applicable prospectus supplements, summarizes the material terms and provisions of the warrants that we may offer under this prospectus and the related warrant agreements and warrant certificates. While the terms summarized below will apply generally to any warrants that we may offer under this prospectus, we will describe the particular terms of any series of warrants that we may offer in more detail in the applicable prospectus supplement. If we indicate in the prospectus supplement, the terms of any warrants offered under that prospectus supplement may differ from the terms described below. However, no prospectus supplement shall fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness. Specific warrant agreements will contain additional important terms and provisions and will be incorporated by reference as an exhibit to the registration statement that includes this prospectus or as an exhibit to a report filed under the Securities Exchange Act of 1934.

GENERAL

We will describe in the applicable prospectus supplement the terms of the series of warrants, including:

- the offering price and aggregate number of warrants offered;
- the currency for which the warrants may be purchased;
- if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each such security or each principal amount of such security;
- if applicable, the date on and after which the warrants and the related securities will be separately transferable;
- in the case of warrants to purchase common stock or preferred stock, the number of shares of common stock or preferred stock, as the case may be, purchasable upon the exercise of one warrant and the price at which these shares may be purchased upon such exercise;
- in the case of warrants to purchase debt securities, the principal amount of debt securities purchasable upon exercise of one warrant and the price at, and currency in which, this principal amount of debt securities may be purchased upon such exercise;
- the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreements and the warrants;
- the terms of any rights to redeem or call the warrants;
- any provisions for changes to or adjustments in the exercise price or number of securities issuable upon exercise of the warrants;
- the dates on which the right to exercise the warrants will commence and expire;
- the manner in which the warrant agreements and warrants may be modified;
- federal income tax consequences of holding or exercising the warrants;

- the terms of the securities issuable upon exercise of the warrants; and
- any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the securities purchasable upon such exercise, including:

- in the case of warrants to purchase common stock or preferred stock, the right to receive dividends, if any, or, payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any; or
- in the case of warrants to purchase debt securities, the right to receive payments of principal of, or premium, if any, or interest on, the debt securities purchasable upon exercise or to enforce covenants in the applicable indenture.

EXERCISE OF WARRANTS

Each warrant will entitle the holder to purchase the securities that we specify in the applicable prospectus supplement at the exercise price that we describe in the applicable prospectus supplement. Unless we otherwise specify in the applicable prospectus supplement, holders of the warrants may exercise the warrants at any time up to the specified time on the expiration date that we set forth in the applicable prospectus supplement. After the close of business on the expiration date, unexercised warrants will become void.

Holders of the warrants may exercise the warrants by delivering the warrant certificate representing the warrants to be exercised together with specified information, and paying the required amount to the warrant agent in immediately available funds, as provided in the applicable prospectus supplement. We will set forth on the reverse side of the warrant certificate and in the applicable prospectus supplement the information that the holder of the warrant will be required to deliver to the warrant agent.

Upon receipt of the required payment and the warrant certificate properly completed and duly executed at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement, we will issue and deliver the securities purchasable upon such exercise. If fewer than all of the warrants represented by the warrant certificate are exercised, then we will issue a new warrant certificate for the remaining amount of warrants. If we so indicate in the applicable prospectus supplement, holders of the warrants may surrender securities as all or part of the exercise price for warrants.

GOVERNING LAW

The warrants and warrant agreements will be governed by and construed in accordance with the laws of the State of New York.

ENFORCEABILITY OF RIGHTS BY HOLDERS OF WARRANTS

Each warrant agent will act solely as our agent under the applicable warrant agreement and will not assume any obligation or relationship of agency or trust with any holder of any warrant. A single bank or trust company may act as warrant agent for more than one issue of warrants. A warrant agent will have no duty or responsibility in case of any default by us under the applicable warrant agreement or warrant, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a warrant may, without the consent of the related warrant agent or the holder of any other warrant, enforce by appropriate legal action its right to exercise, and receive the securities purchasable upon exercise of, its warrants.

DESCRIPTION OF UNITS

The following description, together with the additional information we may include in any applicable prospectus supplements, summarizes the material terms and provisions of the units that we may offer under this prospectus and the related unit agreements. While the terms summarized below will apply generally to any units that we may offer under this prospectus, we will describe the particular terms of any series of units that we may offer in more detail in the applicable prospectus supplement. If we indicate in the prospectus supplement, the terms of any units offered under that prospectus supplement may differ from the terms described below. However, no prospectus supplement shall fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness. Specific unit agreements will contain

additional important terms and provisions and will be incorporated by reference as an exhibit to the registration statement that includes this prospectus or as an exhibit to a report filed under the Securities Exchange Act of 1934.

GENERAL

We may issue units comprised of one or more shares of common stock, shares of preferred stock, debt securities and warrants in any combination. Each unit will be issued so that the holder of the unit is also the holder of each security included in the unit. Thus, the holder of a unit will have the rights and obligations of a holder of each included security. The unit agreement under which a unit is issued may provide that the securities included in the unit may not be held or transferred separately, at any time or at any time before a specified date.

We will describe in the applicable prospectus supplement the terms of the series of units, including:

- the designation and terms of the units and of the securities comprising the units, including whether and under what circumstances those securities may be held or transferred separately;
- any provisions of the governing unit agreement that differ from those described below; and
- any provisions for the issuance, payment, settlement, transfer or exchange of the units or of the securities comprising the units.

The provisions described in this section, as well as those described under "Description of Capital Stock," "Description of Debt Securities" and "Description of Warrants" will apply to each unit and to any common stock, preferred stock, debt security or warrant included in each unit, respectively.

ISSUANCE IN SERIES

We may issue units in such amounts and in numerous distinct series as we determine.

ENFORCEABILITY OF RIGHTS BY HOLDERS OF UNITS

Each unit agent will act solely as our agent under the applicable unit agreement and will not assume any obligation or relationship of agency or trust with any holder of any unit. A single bank or trust company may act as unit agent for more than one series of units. A unit agent will have no duty or responsibility in case of any default by us under the applicable unit agreement or unit, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a unit may, without the consent of the related unit agent or the holder of any other unit, enforce by appropriate legal action its rights as holder under any security included in the unit.

TITLE

Lexicon, the unit agents and any of their agents may treat the registered holder of any unit certificate as an absolute owner of the units evidenced by that certificate for any purpose and as the person entitled to exercise the rights attaching to the units so requested, despite any notice to the contrary. See "Legal Ownership of Securities."

LEGAL OWNERSHIP OF SECURITIES

We can issue securities in registered form or in the form of one or more global securities. We describe global securities in greater detail below. We refer to those persons who have securities registered in their own names on the books that we or any applicable trustee maintain for this purpose as the "holders" of those securities. These persons are the legal holders of the securities. We refer to those persons who, indirectly through others, own beneficial interests in securities that are not registered in their own names, as "indirect holders" of those securities. As we discuss below, indirect holders are not legal holders, and investors in securities issued in book-entry form or in street name will be indirect holders.

BOOK-ENTRY HOLDERS

We may issue securities in book-entry form only, as we will specify in the applicable prospectus supplement. This means securities may be represented by one or more global securities registered in the name of a financial institution that holds them as depository on behalf of other financial institutions that participate in the depository's book-entry system. These participating institutions, which are referred to as participants, in turn, hold beneficial interests in the securities on behalf of themselves or their customers.

Only the person in whose name a security is registered is recognized as the holder of that security. Securities issued in global form will be registered in the name of the depositary or its nominee. Consequently, for securities issued in global form, we will recognize only the depositary as the holder of the securities, and we will make all payments on the securities to the depositary. The depositary passes along the payments it receives to its participants, which in turn pass the payments along to their customers who are the beneficial owners. The depositary and its participants do so under agreements they have made with one another or with their customers; they are not obligated to do so under the terms of the securities.

As a result, investors in a book-entry security will not own securities directly. Instead, they will own beneficial interests in a global security, through a bank, broker or other financial institution that participates in the depositary's book-entry system or holds an interest through a participant. As long as the securities are issued in global form, investors will be indirect holders, and not holders, of the securities.

STREET NAME HOLDERS

We may terminate a global security or issue securities in non-global form. In these cases, investors may choose to hold their securities in their own names or in "street name." Securities held by an investor in street name would be registered in the name of a bank, broker or other financial institution that the investor chooses, and the investor would hold only a beneficial interest in those securities through an account he or she maintains at that institution.

For securities held in street name, we will recognize only the intermediary banks, brokers and other financial institutions in whose names the securities are registered as the holders of those securities, and we will make all payments on those securities to them. These institutions pass along the payments they receive to their customers who are the beneficial owners, but only because they agree to do so in their customer agreements or because they are legally required to do so. Investors who hold securities in street name will be indirect holders, not holders, of those securities.

LEGAL HOLDERS

Our obligations, as well as the obligations of any applicable trustee and of any third parties employed by us or a trustee, run only to the legal holders of the securities. We do not have obligations to investors who hold beneficial interests in global securities, in street name or by any other indirect means. This will be the case whether an investor chooses to be an indirect holder of a security or has no choice because we are issuing the securities only in global form.

For example, once we make a payment or give a notice to the holder, we have no further responsibility for the payment or notice even if that holder is required, under agreements with depositary participants or customers or by law, to pass it along to the indirect holders but does not do so. Similarly, we may want to obtain the approval of the holders to amend an indenture, to relieve us of the consequences of a default or of our obligation to comply with a particular provision of the indenture or for other purposes. In such an event, we would seek approval only from the holders, and not the indirect holders, of the securities. Whether and how the holders contact the indirect holders is up to the holders.

SPECIAL CONSIDERATIONS FOR INDIRECT HOLDERS

If you hold securities through a bank, broker or other financial institution, either in book-entry form or in street name, you should check with your own institution to find out:

- how it handles securities payments and notices;
- whether it imposes fees or charges;
- how it would handle a request for the holders' consent, if ever required;
- whether and how you can instruct it to send you securities registered in your own name so you can be a holder, if that is permitted in the future;
- how it would exercise rights under the securities if there were a default or other event triggering the need for holders to act to protect their interests; and
- if the securities are in book-entry form, how the depositary's rules and procedures will affect these matters.

GLOBAL SECURITIES

A global security is a security that represents one or any other number of individual securities held by a depository. Generally, all securities represented by the same global securities will have the same terms.

Each security issued in book-entry form will be represented by a global security that we deposit with and register in the name of a financial institution or its nominee that we select. The financial institution that we select for this purpose is called the depository. Unless we specify otherwise in the applicable prospectus supplement, The Depository Trust Company, New York, New York, known as DTC, will be the depository for all securities issued in book-entry form.

A global security may not be transferred to or registered in the name of anyone other than the depository, its nominee or a successor depository, unless special termination situations arise. We describe those situations below under "Special Situations When a Global Security Will Be Terminated." As a result of these arrangements, the depository, or its nominee, will be the sole registered owner and holder of all securities represented by a global security, and investors will be permitted to own only beneficial interests in a global security. Beneficial interests must be held by means of an account with a broker, bank or other financial institution that in turn has an account with the depository or with another institution that does. Thus, an investor whose security is represented by a global security will not be a holder of the security, but only an indirect holder of a beneficial interest in the global security.

If the prospectus supplement for a particular security indicates that the security will be issued in global form only, then the security will be represented by a global security at all times unless and until the global security is terminated. If termination occurs, we may issue the securities through another book-entry clearing system or decide that the securities may no longer be held through any book-entry clearing system.

SPECIAL CONSIDERATIONS FOR GLOBAL SECURITIES

As an indirect holder, an investor's rights relating to a global security will be governed by the account rules of the investor's financial institution and of the depository, as well as general laws relating to securities transfers. We do not recognize an indirect holder as a holder of securities and instead deal only with the depository that holds the global security.

If securities are issued only in the form of a global security, an investor should be aware of the following:

- An investor cannot cause the securities to be registered in his or her name, and cannot obtain non-global certificates for his or her interest in the securities, except in the special situations we describe below;
- An investor will be an indirect holder and must look to his or her own bank or broker for payments on the securities and protection of his or her legal rights relating to the securities, as we describe above;
- An investor may not be able to sell interests in the securities to some insurance companies and to other institutions that are required by law to own their securities in non-book-entry form;
- An investor may not be able to pledge his or her interest in a global security in circumstances where certificates representing the securities must be delivered to the lender or other beneficiary of the pledge in order for the pledge to be effective;
- The depository's policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor's interest in a global security. We and any applicable trustee have no responsibility for any aspect of the depository's actions or for its records of ownership interests in a global security. We and the trustee also do not supervise the depository in any way;
- The depository may, and we understand that DTC will, require that those who purchase and sell interests in a global security within its book-entry system use immediately available funds, and your broker or bank may require you to do so as well; and
- Financial institutions that participate in the depository's book-entry system, and through which an investor holds its interest in a global security, may also have their own policies affecting payments, notices and other matters relating to the securities. There may be more than

one financial intermediary in the chain of ownership for an investor. We do not monitor and are not responsible for the actions of any of those intermediaries.

SPECIAL SITUATIONS WHEN A GLOBAL SECURITY WILL BE TERMINATED

In a few special situations described below, the global security will terminate and interests in it will be exchanged for physical certificates representing those interests. After that exchange, the choice of whether to hold securities directly or in street name will be up to the investor. Investors must consult their own banks or brokers to find out how to have their interests in securities transferred to their own name, so that they will be direct holders. We have described the rights of holders and street name investors above.

The global security will terminate when the following special situations occur:

- if the depository notifies us that it is unwilling, unable or no longer qualified to continue as depository for that global security and we do not appoint another institution to act as depository within 90 days;
- if we notify any applicable trustee that we wish to terminate that global security; or
- if an event of default has occurred with regard to securities represented by that global security and has not been cured or waived.

The prospectus supplement may also list additional situations for terminating a global security that would apply only to the particular series of securities covered by the prospectus supplement. When a global security terminates, the depository, and not we or any applicable trustee, is responsible for deciding the names of the institutions that will be the initial direct holders.

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 of 1933 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 any prospectus supplement 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.

RATIO OF EARNINGS TO FIXED CHARGES

Our earnings were insufficient to cover fixed charges in each of the years in the five-year period ended December 31, 2005 and in the three-month period ended March 31, 2006. "Fixed charges" consist of (a) interest expensed and capitalized, (b) amortized premiums, discounts and capitalized expenses related to indebtedness, (c) an estimate of the interest within rental expense and (d) preference security dividend requirements of consolidated subsidiaries. The following table sets forth the computation of our ratio of earnings to fixed charges for the periods indicated:

	THREE MONTHS	FISCAL YEARS ENDED DECEMBER 31,				
	ENDED MARCH 31, 2006	2005	2004	2003	2002	2001
Ratio of earnings to fixed charges (1)	--	--	--	--	--	--

(1) For the three months ended March 31, 2006, and the fiscal years ended December 31, 2005, 2004, 2003, 2002 and 2001, our earnings were insufficient to cover fixed charges by \$10.8 million, \$36.3 million, \$47.2 million, \$61.1 million, \$59.7 million, and \$35.2 million, respectively.

For the periods indicated above, we had no outstanding shares of preferred stock with required dividend payments. Therefore, our ratios of earnings to combined fixed charges and preferred stock dividends for the periods indicated are identical to the ratios presented in the table above.

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 securities offered pursuant to this prospectus and any prospectus supplement for research and development and general corporate purposes, including the preclinical and clinical development of our lead programs, 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

GENERAL

We may sell securities 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 securities 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 securities will set forth the terms of the offering of such securities, including the name or names of any underwriters, brokers, dealers or agents we utilize in the sale of securities under this prospectus, the name or names of any managing underwriter or underwriters, the purchase price of the securities 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, any discounts or concessions allowed or reallowed or paid to dealers, any commissions paid to agents and any securities exchange or market on which the securities may be listed.

If we use underwriters in the sale of securities, the underwriters will acquire the securities for their own account. The underwriters may resell the securities 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 securities 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 securities will be subject to certain conditions, and the underwriters will be obligated to purchase all of the offered securities 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 reallocated or paid to dealers.

In connection with the sale of our securities, 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 securities 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 securities, we will sell the securities to such dealers or brokers as principals. The dealers or brokers acting as dealers may then resell such securities 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 we utilize in the sale of securities under this prospectus who act as dealers and the terms of the transaction will be set forth in the prospectus supplement relating to such securities. We may sell the securities directly or through agents designated by us from time to time. Any agent involved in the offer or sale of the securities will be named, and any commissions that we pay to such agent will be set forth, in the prospectus supplement relating to such securities. 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 securities directly, in which case no underwriters or agents would be involved. We may sell securities 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 securities.

All securities we offer, other than common stock and other securities issued upon a reopening of a previous series, will be new issues of securities with no established trading market. Any underwriters may make a market in these securities, but will not be obligated to do so and may discontinue any market making at any time without notice. We cannot guarantee the liquidity of the trading markets for any securities.

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 securities 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.

EQUITY LINE OF CREDIT

On June 12, 2006, we entered into a Common Stock Purchase Agreement with Azimuth Opportunity Ltd., pursuant to which we may offer and sell, and Azimuth is committed to purchase, up to \$75,000,000 of our common stock, or the number of shares which is one less than twenty percent (20%) of the issued and outstanding shares of our common stock as of June 12, 2006, whichever is fewer, over the approximately 18-month term of the Purchase Agreement. We will not be obligated to issue, and Azimuth will not be obligated to purchase, any shares which would result in Azimuth beneficially owning more than 9.9% of our then outstanding common stock.

From time to time until January 1, 2008, at our sole discretion, we may deliver to Azimuth up to 24 draw down notices constituting offers to purchase our common stock at the conclusion of a pricing period of 10 consecutive trading days or such other period mutually agreed upon by the parties. In each draw down notice, we will specify (a) the aggregate dollar amount of our common stock to be sold to Azimuth at the conclusion of the pricing period, which will not exceed \$6,000,000, and (b) the minimum threshold price at which we will sell such shares, which will not be less than \$3.00 per share. Upon delivery of a draw down notice, Azimuth will be required to purchase a pro rata portion of the shares for each trading day during the pricing period on which the daily volume weighted average price for our common stock exceeds the minimum threshold price. The per share purchase price for these shares will equal the daily volume weighted average price of our common stock on such date, less a discount ranging from 3.75% to 5.5%, based on the minimum threshold price. If the daily volume weighted average price of our common stock falls below the minimum threshold price on any trading day during the pricing period, Azimuth will not be required to purchase the pro rata portion of shares allocated for that day, but may, at its election, purchase such shares at the minimum threshold price less the discount described above.

The Purchase Agreement also provides that, from time to time and in our sole discretion, we may grant Azimuth the right to purchase additional shares of our common stock during each draw down pricing period for an aggregate dollar amount and at a minimum threshold price per share that we specify in the draw down notice. Upon Azimuth's exercise of such right, we will sell to Azimuth up to the optional number of shares specified in such draw down notice at a price equal to the greater of the daily volume weighted average price of our common stock on the day Azimuth notifies us of its election to exercise such right or the minimum threshold price for such optional shares specified by us in the draw down notice, less a discount ranging from 3.75% to 5.5%.

In addition to our issuance of shares of common stock to Azimuth pursuant to the Purchase Agreement, the registration statement of which this prospectus forms a part also covers the sale of those shares from time to time by Azimuth to the public. Azimuth is an "underwriter" within the meaning of Section 2(a)(11) of the Securities Act of 1933.

Azimuth has informed us that, unless it notifies us that it will use a different broker-dealer and we have filed a prospectus supplement, it will use an unaffiliated broker-dealer to effectuate all sales, if any, of our common stock that it may purchase from us pursuant to the Purchase Agreement. Such sales will be made on the Nasdaq National Market at prices and at terms then prevailing or at prices related to the then current market price. Each such unaffiliated broker-dealer will be an underwriter within the meaning of Section 2(a)(11) of the Securities Act of 1933. Azimuth has informed us that each such broker-dealer will receive commissions from Azimuth which will not exceed customary brokerage commissions. Azimuth also will pay other expenses associated with the sale of shares of our common stock it acquires pursuant to the Purchase Agreement.

The shares of common stock may be sold in one or more of the following manners:

- ordinary brokerage transactions and transactions in which the broker solicits purchasers; or
- a block trade in which the broker or 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.

Azimuth has agreed that prior to, during the term of and for a period of ninety (90) days after the termination of the Purchase Agreement, neither Azimuth nor any of its affiliates will, directly or indirectly, sell any of our securities except the shares that it owns or has the right to purchase pursuant to the provisions of a draw down notice. Azimuth has agreed that during the periods listed above it will not enter into a short position with respect to shares of our common stock, except that Azimuth may sell shares that it is obligated to purchase under a pending draw down notice but has not yet taken possession of so long as Azimuth covers any such sales with the shares purchased

pursuant to such draw down notice. Azimuth has further agreed that during the periods listed above it will not grant any option to purchase or acquire any right to dispose or otherwise dispose for value of any shares of our

common stock or any securities convertible into, or exchangeable for, or warrants to purchase, any shares of our common stock, or enter into any swap, hedge or other agreement that transfers, in whole or in part, the economic risk of ownership of our common stock, except for the sales permitted by the prior two sentences.

In addition, Azimuth and any unaffiliated broker-dealer will be subject to liability under the federal securities laws and must comply with the requirements of the Securities Act of 1933 and the Securities Exchange Act of 1934, including without limitation, Rule 10b-5 and Regulation M under the Securities Exchange Act of 1934. These rules and regulations may limit the timing of purchases and sales of shares of our common stock by Azimuth or any unaffiliated broker-dealer. Under these rules and regulations, Azimuth and any unaffiliated broker-dealer:

- may not engage in any stabilization activity in connection with our securities;
- must furnish each broker which offers shares of our common stock covered by this prospectus with the number of copies of such prospectus and any prospectus supplement which are required by each broker; and
- may not bid for or purchase any of our securities or attempt to induce any person to purchase any of our securities other than as permitted under the Securities Exchange Act of 1934.

These restrictions may affect the marketability of the shares of our common stock by Azimuth and any unaffiliated broker-dealer.

We have agreed to indemnify and hold harmless Azimuth, any unaffiliated broker-dealer and each person who controls Azimuth or any unaffiliated broker-dealer against certain liabilities, including liabilities under the Securities Act of 1933, which may be based upon, among other things, any untrue statement or alleged untrue statement of a material fact contained in or incorporated by reference in the registration statement of which this prospectus forms a part, or any omission or alleged omission to state in such registration statement or any document incorporated by reference in such registration statement, a material fact required to be stated therein or necessary to make the statements therein not misleading, unless made or omitted in reliance upon written information provided to us by Azimuth or any unaffiliated broker-dealer. We have agreed to pay up to thirty five thousand dollars (\$35,000) of Azimuth's reasonable attorneys' fees and expenses (exclusive of disbursements and out-of-pocket expenses) incurred by Azimuth in connection with the preparation, negotiation, execution and delivery of the Purchase Agreement. We have also agreed to make quarterly payments of twelve thousand five hundred dollars (\$12,500) covering the due diligence expenses incurred by Azimuth during the term of the Purchase Agreement and the attorneys' fees and expenses incurred by Azimuth in connection with ongoing legal due diligence, any amendments, modifications or waivers of the Purchase Agreement and review of any prospectus supplements and other related documents delivered in connection with any draw down. Further, we have agreed that if we issue a draw down notice and fail to deliver the shares to Azimuth on the applicable settlement date, and such failure continues for ten trading days, we will pay Azimuth liquidated damages in cash or restricted shares of our common stock, at the option of Azimuth.

Azimuth has agreed to indemnify and hold harmless us and each of our directors, officers and persons who control us against certain liabilities, including liabilities under the Securities Act of 1933, which may be based upon, among other things, an untrue statement, alleged untrue statement, omission or alleged omission, included in this prospectus or any prospectus supplement or any amendment or supplement to this prospectus or any prospectus supplement in reliance upon, and in conformity with, written information furnished by Azimuth to us for inclusion in such prospectus or prospectus supplement, or any omission or alleged omission to state in such prospectus or any prospectus supplement or any amendment or supplement to such prospectus or any prospectus supplement a material fact required to be stated therein or necessary to make the statements therein not misleading, to the extent, but only to the extent, the untrue statement, alleged untrue statement, omission or alleged omission was made in reliance upon, and in conformity with, written information provided to us by Azimuth.

Upon each sale of our common stock to Azimuth under the Purchase Agreement, we have also agreed to pay Reedland Capital Partners, an Institutional Division of Financial West Group, a placement fee equal to one percent of the aggregate dollar amount received by us from such sale. We have agreed to indemnify and hold harmless Reedland Capital Partners against certain liabilities, including liabilities under the Securities Act of 1933.

LEGAL MATTERS

The validity of the issuance of the securities offered by this prospectus has been passed upon for us by Vinson & Elkins L.L.P., Houston, Texas. Certain legal matters will be passed upon for any agents or underwriters by counsel for such agents or underwriters identified in the applicable prospectus supplement.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2005, and management's assessment of the effectiveness of our internal control over financial reporting as of December 31, 2005, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements and management's assessment are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

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 the offer and sale of securities under this prospectus. This prospectus, which constitutes a part of the 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 securities, 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, 100 F Street, N.E., 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 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.

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. 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, 2005;
- our quarterly report on Form 10-Q for the quarterly period ended March 31, 2006;
- our current reports on Form 8-K dated February 1, April 18, May 30, and June 13, 2006; 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. You may rely on any statement contained in this prospectus or in documents

incorporated or deemed to be incorporated in this

prospectus, unless that statement has been subsequently modified or superseded as described above prior to the time you make your investment decision.

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

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 SECURITIES.

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

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