

METABASIS THERAPEUTICS INC
Form 424B2
March 27, 2006

PROSPECTUS SUPPLEMENT
(To Prospectus dated February 22, 2006)

Filed Pursuant to Rule 424(b)(2)
Registration No. 333-131518

4,938,272 Shares

Metabasis Therapeutics, Inc.

Common Stock

We are offering up to 4,938,272 shares of our common stock in this offering.

Our common stock is quoted on the Nasdaq National Market under the symbol MBRX. On March 24, 2006, the closing price of our common stock on the Nasdaq National Market was \$8.96 per share.

Our business and an investment in our common stock involve significant risks. See Risk Factors on page S-2 of this prospectus supplement.

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.

We are offering these shares of common stock on a best efforts basis primarily to institutional investors. We have retained Cowen & Co., LLC and Piper Jaffray & Co. to act as co-placement agents in connection with this offering.

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	Per Share		Maximum Offering Amount	
Public offering price	\$	8.100	\$	40,000,003
Placement agents' fees	\$	0.486	\$	2,400,000
Proceeds, before expenses, to us	\$	7.614	\$	37,600,003

We estimate the total expenses of this offering, excluding the placement agents' fees, will be approximately \$340,000. Because there is no minimum offering amount required as a condition to closing in this offering, the actual public offering amount, placement agents' fees and net proceeds to us, if any, in this offering are not presently determinable and may be substantially less than the total maximum offering amounts set forth above. The placement agents are not required to sell any specific number or dollar amount of the shares of common stock offered in this offering, but will use their best efforts to sell the shares of common stock offered. Pursuant to an escrow agreement among us, the placement agents and an escrow agent, a portion of the funds received in payment for the shares sold in this offering will be wired to an interest bearing escrow account and held until we and the placement agents notify the escrow agent that the offering has closed, indicating the date on which the shares are to be delivered to the purchasers and the proceeds are to be delivered to us.

Cowen & Company

Piper Jaffray & Co.

March 24, 2006

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ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement is a supplement to the accompanying prospectus that is also a part of this document. This prospectus supplement and the accompanying prospectus are part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, using a shelf registration process. Under the shelf registration process, we may offer from time to time shares of our common stock and warrants to purchase shares of our common stock in one or more offerings up to a total dollar amount of \$75,000,000. In the accompanying prospectus, we provide you with a general description of the securities we may offer from time to time under our shelf registration statement. In this prospectus supplement, we provide you with specific information about the shares of our common stock that we are selling in this offering. This prospectus supplement and the accompanying prospectus and the documents incorporated by reference herein and therein include important information about us, our common stock being offered and other information you should know before investing. This prospectus supplement also adds, updates and changes information contained in the accompanying prospectus. If information in this prospectus supplement is inconsistent with the accompanying prospectus, you should rely on this prospectus supplement. You should carefully read both this prospectus supplement and the accompanying prospectus as well as the additional information described under Where You Can Find More Information before investing in shares of our common stock.

You should rely only on the information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus. We have not authorized anyone to provide you with different or inconsistent information. If anyone provides you with different or inconsistent information, you should not rely on it. We are not making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should not assume that the information appearing in this prospectus supplement or the accompanying prospectus is accurate as of any date other than the date on the front cover of this prospectus supplement or the accompanying prospectus, or that the information contained in any document incorporated by reference is accurate as of any date other than the date of the document incorporated by reference, regardless of the time of delivery of this prospectus supplement or the accompanying prospectus. Our business, financial condition, results of operations and prospects may have subsequently changed.

In this prospectus supplement, unless the context otherwise indicates, the terms we, our, us, the company and Metabasis refer to Metabasis Therapeutics, Inc.

THE OFFERING

Common stock offered by us:	4,938,272 shares
Common stock outstanding before the offering:	25,312,935 shares
Common stock to be outstanding after the offering:	30,251,207 shares
Use of proceeds:	We currently anticipate that the net proceeds from the sale of the common stock will be used primarily for general corporate purposes. See Use of Proceeds.
Nasdaq National Market Symbol:	MBRX

The information above is based on 25,312,935 shares of our common stock outstanding as of December 31, 2005. It does not include:

1,405,670 shares of common stock issuable upon the exercise of outstanding stock options under our amended and restated 2001 equity incentive plan, or the 2001 Plan, and our 2004 non-employee directors stock option plan, or the 2004 Directors Plan, with a weighted average exercise price of \$3.18 per share,

1,978,599 shares of common stock available for future grant under the 2001 Plan, the 2004 Directors Plan and our 2004 employee stock purchase plan, or the 2004 ESPP, and

3,797,176 shares of common stock issuable upon the exercise of outstanding warrants with a weighted average exercise price of \$6.93 per share.

RISK FACTORS

Investment in our common stock involves risks. Before deciding whether to invest in our common stock, you should consider carefully the risk factors discussed in the section entitled "Risk Factors" contained in our Annual Report on Form 10-K for the year ended December 31, 2005, as filed with the SEC on March 23, 2006, which is incorporated herein by reference in its entirety, as well as any amendment or update thereto reflected in subsequent filings with the SEC. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could be seriously harmed. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment.

FORWARD-LOOKING INFORMATION

This prospectus supplement, the accompanying prospectus and the documents incorporated herein by reference contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, regarding, among other things, our business, our financial position and the research and development of biopharmaceutical products. Forward-looking statements include all statements that are not historical facts and can be identified by terms such as "anticipates," "believes," "could," "estimates," "expects," "intends," "may," "plans," "potential," "predicts," "projects," or similar expressions. Such statements are based largely upon our expectations and projections about future events, and so are subject to certain risks and uncertainties, particularly those inherent in the process of developing and commercializing biopharmaceutical products, that could cause actual results to differ materially from those expressed in or implied by the forward-looking statements. Among the factors that could cause actual results to differ materially from those expressed in or implied by the forward-looking statements are risks and uncertainties incorporated by reference under "Risk Factors" in this prospectus supplement, the accompanying prospectus and in our other filings with the SEC.

Although our forward-looking statements reflect good faith beliefs of our management, these statements are based only on facts and circumstances currently known to us. As a result, we cannot guarantee future results, events, levels of activity, performance or achievement as expressed in or implied by our forward-looking statements. We undertake no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, unless required by law.

USE OF PROCEEDS

We expect the net proceeds from this offering to be up to approximately \$37.3 million after deducting certain fees due to the placement agents and our estimated offering expenses, as described in Plan of Distribution. The net proceeds from this offering will be used for general corporate purposes, including clinical trials, research and development expenses, general and administrative expenses, manufacturing expenses, and potential acquisitions of companies and technologies that complement our business, although we are not currently a party to any binding agreements or commitments with respect to the acquisition of any companies or technologies. Pending these uses, we expect to invest the net proceeds in short- and intermediate-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government.

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DILUTION

Our net tangible book value on December 31, 2005 was approximately \$59.6 million, or approximately \$2.35 per share of common stock. Net tangible book value per share is determined by dividing our net tangible book value, which consists of tangible assets less total liabilities, by the number of shares of common stock outstanding on that date. Without taking into account any other changes in our net tangible book value after December 31, 2005, other than to give effect to our receipt of the estimated net proceeds from the sale of the maximum number of shares issuable in this offering (4,938,272 shares) at an offering price of \$8.10 per share, less the fees due to the placement agents and our estimated offering expenses, our net tangible book value as of December 31, 2005, after giving effect to the items above, would have been approximately \$96.8 million, or \$3.20 per share. This represents an immediate increase in the net tangible book value of \$0.85 per share to existing stockholders and an immediate dilution of \$4.90 per share to new investors. The following table illustrates this per share dilution:

Public offering price per share	\$	8.10
Net tangible book value per share as of December 31, 2005	\$	2.35
Increase in net tangible book value per share attributable to the offering	\$	0.85
Pro forma net tangible book value per share as of December 31, 2005, after giving effect to the offering	\$	3.20
Dilution per share to new investors in the offering	\$	4.90

The above table is based on 30,251,207 shares of common stock outstanding as of December 31, 2005 (as adjusted for 4,938,272 shares to be issued in this offering) and excludes, as of December 31, 2005:

1,405,670 shares of common stock issuable upon the exercise of outstanding stock options under the 2001 Plan and the 2004 Directors' Plan with a weighted average exercise price of \$3.18 per share,

1,978,599 shares of common stock available for future grant under the 2001 Plan, the 2004 Directors' Plan and the 2004 ESPP, and

3,797,176 shares of common stock issuable upon the exercise of outstanding warrants with a weighted average exercise price of \$6.93 per share.

To the extent that any of these options or warrants are exercised, new options are issued under the 2001 Plan or the 2004 Directors' Plan, additional shares of common stock are issued under the 2004 ESPP or we otherwise issue additional shares of common stock in the future, there will be further dilution to new investors.

PLAN OF DISTRIBUTION

We are offering our common stock through placement agents. Subject to the terms and conditions contained in the placement agent agreement, dated March 24, 2006, Cowen & Co., LLC and Piper Jaffray & Co. have agreed to act as the placement agents for the sale of up to 4,938,272 shares of common stock. The placement agents are not purchasing or selling any shares by this prospectus supplement or accompanying base prospectus, nor are they required to arrange for the purchase or sale of any specific number or dollar amount of shares, but have agreed to use best efforts to arrange for the sale of all 4,938,272 shares.

The placement agent agreement provides that the obligations of the placement agents and the investors are subject to certain conditions precedent, including the absence of any material adverse change in our business and the receipt of certain opinions, letters and certificates from our counsel, our independent auditors and us.

Confirmations and definitive prospectuses will be distributed to all investors who agree to purchase the common stock, informing investors of the closing date as to such shares. We currently anticipate that closing of the sale of 4,938,272 shares of common stock will take place on or about March 30, 2006. Investors will also be informed of the date and manner in which they must transmit the purchase price for their shares.

On the scheduled closing date, the following will occur:

we will receive funds in the amount of the aggregate purchase price; and

Cowen & Co., LLC will receive the placement agents' fee on behalf of the placement agents in accordance with the terms of the placement agent agreement.

We will pay the placement agents an aggregate commission equal to 6.0% of the gross proceeds of the sale of common stock in the offering. We may also reimburse the placement agents for certain legal expenses incurred by them. In no event will the total amount of compensation paid to the placement agents and other securities brokers and dealers upon completion of this offering exceed 8.0% of the maximum gross proceeds of the offering. The estimated offering expenses payable by us, in addition to the placement agents' fee of approximately \$2.4 million, are approximately \$340,000, which includes legal, accounting and printing costs and various other fees associated with registering and listing the common stock. After deducting certain fees due to the placement agents and our estimated offering expenses, we expect the net proceeds from this offering to be up to approximately \$37.3 million.

We have agreed to indemnify the placement agents against certain liabilities, including liabilities under the Securities Act. We have also agreed to contribute to payments the placement agents may be required to make in respect of such liabilities.

We, along with our executive officers and directors, have agreed to certain lock-up provisions with regard to future sales of our common stock for a period of 90 days after the offering as set forth in the placement agent agreement. These lock-up provisions are subject to limited extension

in certain circumstances.

The placement agent agreement is included as an exhibit to our Current Report on Form 8-K that will be filed with the SEC in connection with the consummation of this offering.

The transfer agent for our common stock is American Stock Transfer & Trust Company.

Our common stock is quoted on the Nasdaq National Market under the symbol MBRX.

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LEGAL MATTERS

The validity of the issuance of the shares of common stock offered hereby will be passed upon by our counsel, Cooley Godward LLP in San Diego, California. As of the date of this prospectus supplement, investment funds affiliated with Cooley Godward LLP owned 22,371 shares of common stock and warrants to purchase 5,940 shares of common stock having a weighted average exercise price of \$7.44 per share. Brown Raysman Millstein Felder & Steiner LLP in New York, New York is acting as counsel for the placement agents in connection with various legal matters relating to the shares of common stock offered hereby.

EXPERTS

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

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and special reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's web site at <http://www.sec.gov>. You may also read and copy any document we file at the SEC's public reference room at 100 F Street, N.E., Room 1580, Washington, D.C. 20549. You may obtain information on the operation of the SEC's public reference room in Washington, D.C. by calling the SEC at 1-800-SEC-0330.

The SEC allows us to incorporate by reference into this prospectus supplement the information in documents we file with it, which means that we can disclose important information to you by referring you to those documents. Any statement contained in any document incorporated or deemed to be incorporated by reference herein shall be deemed to be modified or superseded, for purposes of this prospectus, to the extent that a statement contained in or omitted from this prospectus supplement, or in any other subsequently filed document which also is or is deemed to be incorporated by reference herein, modifies or supersedes such statement. Any such statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus supplement. We incorporate by reference the documents listed below and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act until the offering is completed:

Our Annual Report on Form 10-K for the year ended December 31, 2005 which was filed on March 23, 2006, including all material incorporated by reference therein;

Our Definitive Proxy Statement for our 2006 Annual Meeting of Stockholders which was filed on March 23, 2006; and

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The description of our common stock contained in our Registration Statement on Form 8-A filed on May 28, 2004.

We will provide without charge to each person, including any beneficial owner, to whom this prospectus supplement is delivered, upon written or oral request of such person, a copy of any and all of the documents that have been incorporated by reference in this prospectus supplement (not including exhibits to such documents, unless such exhibits are specifically incorporated by reference in this prospectus supplement or into such documents). Such request may be directed to Metabasis Therapeutics, Inc., 11119 North Torrey Pines Road, La Jolla, California 92037, (858) 587-2770.

All documents that we file with the SEC pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus supplement and before the termination of the offering of the securities offered in this prospectus supplement shall be deemed incorporated by reference into this prospectus supplement and to be a part of this prospectus supplement from the respective date of filing such documents.

We have filed with the SEC a registration statement on Form S-3 under the Securities Act covering the securities described in this prospectus supplement. This prospectus supplement does not contain or incorporate by

reference all of the information included in the registration statement, some of which is contained in exhibits included with or incorporated by reference into the registration statement. The registration statement, including the exhibits contained or incorporated by reference therein, can be read at the SEC web site or at the SEC office referred to above. Any statement made or incorporated by reference in this prospectus supplement concerning the contents of any contract, agreement or other document is only a summary of the actual contract, agreement or other document. If we have filed or incorporated by reference any contract, agreement or other document as an exhibit to the registration statement, you should read the exhibit for a more complete understanding of the document or matter involved. Each statement regarding a contract, agreement or other document is qualified in its entirety by reference to the actual document.

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PROSPECTUS

\$75,000,000

**Common Stock
Warrants**

From time to time, we may sell any of the securities listed above in one or more offerings in amounts, at prices and on the terms that we will determine at the time of the offering, with an aggregate initial offering price of up to \$75,000,000.

We will provide the specific terms of these securities in one or more supplements to this prospectus. You should read this prospectus, the information incorporated by reference in this prospectus and any prospectus supplement carefully before you invest.

Our common stock is traded on the Nasdaq National Market under the symbol MBRX. On February 2, 2006, the last reported sales price for our common stock was \$9.00 per share. The applicable prospectus supplement will contain information, where applicable, as to any other listing on the Nasdaq National Market or any securities market or exchange of the securities covered by the prospectus supplement.

INVESTING IN OUR SECURITIES INVOLVES RISKS. SEE RISK FACTORS BEGINNING ON PAGE 3.

THIS PROSPECTUS MAY NOT BE USED TO OFFER OR SELL ANY SECURITIES UNLESS ACCOMPANIED BY A PROSPECTUS SUPPLEMENT.

The securities may be sold by us to or through underwriters or dealers, directly to purchasers or through agents designated from time to time. For additional information on the methods of sale, you should refer to the section entitled Plan of Distribution in this prospectus. If any underwriters are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such underwriters and any applicable discounts or commissions and over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds we expect to receive from such sale will also be set forth in a prospectus supplement.

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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 February 22, 2006

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You should rely only on the information contained in or incorporated by reference into this prospectus or any applicable prospectus supplement. We have not authorized anyone to provide you with different information. We are not making an offer of the securities to be sold under this prospectus in any jurisdiction where the offer or sale is not permitted. You should not assume that the information contained in this prospectus or any applicable prospectus supplement is accurate as of any date other than the date on the front cover of this prospectus or the prospectus supplement, or that the information contained in any document incorporated by reference is accurate as of any date other than the date of the document incorporated by reference, regardless of the time of delivery of this prospectus or any sale of a security.

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, using a shelf registration process. Under this shelf registration process, we may sell common stock and warrants in one or more offerings up to a total dollar amount of \$75,000,000. This prospectus provides you with a general description of the securities we may offer. Each time we sell any securities under this prospectus, we will provide a prospectus supplement that will contain more specific information about the terms of those securities. We may also add, update or change in a prospectus supplement any of the information contained in this prospectus or in documents we have incorporated by reference into this prospectus. This prospectus, together with the applicable prospectus supplements and the documents incorporated by reference into this prospectus, includes all material information relating to this offering. You should carefully read both this prospectus and the applicable prospectus supplement together with the additional information described under Where You Can Find More Information before buying securities in this offering.

SUMMARY

This prospectus contains forward-looking statements which involve risks and uncertainties. Our actual results could differ materially from those anticipated in these forward-looking statements as a result of certain factors referred to in Risk Factors and elsewhere in this prospectus.

The following summary does not contain all the information that may be important to you. You should read the entire prospectus, including the financial statements and other information incorporated by reference in this prospectus, before making an investment decision.

Metabasis Therapeutics, Inc.

We are a biopharmaceutical company focused on the discovery, development and commercialization of novel drugs to address some of the world's most widespread and costly chronic diseases involving pathways in the liver. These diseases include metabolic diseases such as diabetes, hyperlipidemia, a disease involving elevated levels of lipids such as cholesterol, and obesity, among others, and liver diseases such as hepatitis and primary liver cancer. We have established a broad and growing product pipeline targeting large markets with significant unmet medical needs.

We currently have three product candidates in clinical development, CS-917, pradeфовir and MB07133, which are being developed for the treatment of type 2 diabetes, hepatitis B and primary liver cancer, respectively. In addition to these product candidates, we have two clinical development candidates, MB07803 and MB07811, which have been recommended for clinical development. MB07803 is a clinical development candidate for the treatment of type 2 diabetes that works by the same mechanism as CS-917. MB07811 is a clinical development candidate for the treatment of high cholesterol and possibly obesity that acts through a liver mechanism. We filed an Investigational New Drug Application, or IND, for MB07803 in December 2005. We plan to file an IND for MB07811 in 2006, and expect to commence clinical trials of both MB07803 and MB07811 in 2006 as well.

All our product candidates and clinical development candidates have been discovered at Metabasis and our discovery efforts are continuing. In addition to our product candidates and clinical development candidates, we have research programs focused on metabolic diseases linked to pathways in the liver such as type 2 diabetes, hyperlipidemia and obesity, as well as liver diseases such as hepatitis C and liver fibrosis. We are developing CS-917 and pradeфовir in collaboration with Sankyo Co., Ltd. and Valeant Pharmaceuticals International, respectively. We are independently developing and currently retain all rights to MB07133, MB07803 and MB07811 and all the compounds generated from our research programs, with the exception of the compounds covered by our two collaborations with Merck & Co., Inc.

We were incorporated in Delaware in April 1997 as a wholly owned subsidiary of Gensia Sicor Inc., now Sicor Inc., which became an indirect wholly owned subsidiary of Teva Pharmaceutical Industries Limited in January 2004. In December 1997, Sicor assigned to us specified assets and liabilities relating to its then existing business of discovering and developing proprietary pharmaceutical products. Although we established a new business plan, pursued new opportunities and discovered new products and technologies following our inception, many of the assets we obtained in the transfer served as a foundation upon which we built our technologies and know-how. In June 1999, we completed a corporate restructuring and management stock purchase in which we became an independent company. We have a wholly owned subsidiary, Aramed, Inc., which was transferred to us by Sicor and does not conduct an active business.

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Our principal offices are located at 11119 North Torrey Pines Road, La Jolla, California 92037, and our telephone number is (858) 587-2770. Our website address is <http://www.mbasis.com>. The information contained in, or that can be accessed through, our website is not part of this prospectus. Unless the context indicates otherwise, as used in this prospectus, the terms Metabasis, we, us and our refer to Metabasis Therapeutics, Inc., a Delaware corporation. We use Metabasis, NuMimetic and HepDirect as trademarks in the U.S. and other countries. This prospectus also contains trademarks and tradenames of other companies.

The Securities We May Offer

We may offer shares of our common stock and warrants to purchase shares of our common stock with a total offering price of up to \$75 million from time to time under this prospectus at prices and on terms to be determined by market conditions at the time of offering. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type of security, we will provide a prospectus supplement that will describe the specific amounts, prices and other important terms of the offering: The prospectus supplement also may add, update or change information contained in this prospectus or in documents we have incorporated by reference into this prospectus.

This prospectus may not be used to offer or sell any securities unless accompanied by a prospectus supplement.

We may sell the securities directly or through underwriters, dealers or agents. We, and our underwriters, dealers or agents, reserve the right to accept or reject all or part of any proposed purchase of securities. If we do offer securities through underwriters or agents, we will include in the applicable prospectus supplement:

the names of those underwriters or agents;

applicable fees, discounts and commissions to be paid to them;

details regarding over-allotment options, if any; and

the net proceeds to us.

Common Stock. We may issue shares of our common stock from time to time. Holders of our common stock are entitled to one vote per share for the election of directors and on all other matters that require stockholder approval. Subject to any preferential rights of any then outstanding preferred stock, in the event of our liquidation, dissolution or winding up, holders of our common stock are entitled to share ratably in the assets remaining after payment of liabilities and the liquidation preferences of any then outstanding preferred stock. Our common stock does not carry any preemptive rights enabling a holder to subscribe for, or receive shares of, any class of our common stock or any other securities convertible into shares of any class of our common stock, or any redemption rights.

Warrants. We may issue warrants for the purchase of common stock from time to time. We may issue warrants independently or together with common stock, and the warrants may be attached to or separate from the common stock.

The warrants will be evidenced by warrant certificates issued under one or more warrant agreements, which are contracts between us and an agent for the holders of the warrants. In this prospectus, we have summarized certain general features of the warrants. We urge you, however, to read the prospectus supplements related to the warrants being offered, as well as the complete forms of warrant agreement and warrant certificate that contain the terms of the warrants. Forms of the warrant agreements and warrant certificate relating to warrants for the purchase of common stock have been filed as exhibits to the registration statement of which this prospectus is a part, and complete forms of the warrant agreement and warrant certificate containing the terms of the warrants being offered will be incorporated by reference into the registration statement of which this prospectus is a part from reports we file with the SEC.

RISK FACTORS

Investing in our securities involves risks. Before deciding whether to invest in our securities, you should consider carefully the risk factors discussed in the section entitled "Risk Factors" contained in our Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2005, as filed with the SEC on November 14, 2005, which is incorporated herein by reference in its entirety, as well as any amendment or update thereto reflected in subsequent filings with the SEC. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could be seriously harmed. This could cause the trading price of our securities to decline, resulting in a loss of all or part of your investment.

FORWARD-LOOKING INFORMATION

This prospectus and the documents incorporated herein by reference contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, regarding, among other things, our business, our financial position and the research and development of biopharmaceutical products. Forward-looking statements include all statements that are not historical facts and can be identified by terms such as "anticipates," "believes," "could," "estimates," "expects," "intends," "may," "plans," "potential," "predicts," "projects," "should," "will," "would" or similar expressions. These statements are based largely upon our expectations and projections about future events, and so are subject to certain risks and uncertainties, particularly those inherent in the process of developing and commercializing biopharmaceutical products, that could cause actual results to differ materially from those expressed in or implied by the forward-looking statements. Among the factors that could cause actual results to differ materially from those expressed in or implied by the forward-looking statements are risks and uncertainties incorporated by reference under "Risk Factors" in this prospectus and in our other filings with the SEC.

Although our forward-looking statements reflect good faith beliefs of our management, these statements are based only on facts and circumstances currently known to us. As a result, we cannot guarantee future results, events, levels of activity, performance or achievement as expressed in or implied by our forward-looking statements. We undertake no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, unless required by law.

USE OF PROCEEDS

Except as described in any prospectus supplement, we currently intend to use the net proceeds from the sale of securities under this prospectus for general corporate purposes, including clinical trials, research and development expenses, general and administrative expenses, manufacturing expenses, and potential acquisitions of companies and technologies that complement our business, although we are not currently a party to any binding agreements or commitments with respect to the acquisition of any companies or technologies. Pending these uses, we expect to invest the net proceeds in investment-grade, interest-bearing instruments.

DESCRIPTION OF CAPITAL STOCK

As of the date of this prospectus, our certificate of incorporation authorizes us to issue 105,000,000 shares of common stock, par value \$0.001 per share, and 5,000,000 shares of preferred stock, par value \$0.001 per share. As of January 30, 2006, approximately 25,322,742 shares of common stock were outstanding and no shares of preferred stock were outstanding.

The following summary describes the material terms of our capital stock. The description of capital stock is qualified by reference to our amended and restated certificate of incorporation, as amended, and our bylaws, as amended, which are incorporated by reference as exhibits into the registration statement of which this prospectus is a part.

Common Stock

The description of our common stock contained in our Registration Statement on Form 8-A filed with the SEC on May 28, 2004 is incorporated herein by reference in its entirety, as well as any amendment or update thereto reflected in subsequent filings with the SEC. See [Where You Can Find More Information](#).

Delaware Anti-Takeover Law and Provisions of our Amended and Restated Certificate of Incorporation and Bylaws

Delaware Anti-Takeover Law. We are subject to Section 203 of the Delaware General Corporation Law. Section 203 generally prohibits a public Delaware corporation 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

prior to the date of the transaction, the board of directors of the corporation approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;

the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares outstanding (a) shares owned by persons who are directors and also officers and (b) shares owned by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

on or subsequent to the date of the transaction, the business combination is approved by the board and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at

least 66 2/3% of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a business combination to include:

any merger or consolidation involving the corporation and the interested stockholder;

any sale, transfer, pledge or other disposition involving the interested stockholder of 10% or more of the assets of the corporation;

subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder; and

the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an interested stockholder as any entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person affiliated with or controlling or controlled by the entity or person.

Amended and Restated Certificate of Incorporation and Bylaws. Provisions of our amended and restated certificate of incorporation and bylaws may delay or discourage transactions involving an actual or potential change in our control or change in our management, including transactions in which stockholders might otherwise receive a premium for their shares, or transactions that our stockholders might otherwise deem to be in their best interests. Therefore, these provisions could adversely affect the price of our common stock. Among other things, our amended and restated certificate of incorporation and bylaws:

permit our board of directors to issue up to 5,000,000 shares of preferred stock, with any rights, preferences and privileges as they may designate (including the right to approve an acquisition or other change in control);

provide that the authorized number of directors may be changed only by resolution of the board of directors;

provide that all vacancies, including newly created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum;

divide our board of directors into three classes;

require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and not be taken by written consent;

provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide notice in writing in a timely manner, and also specify requirements as to the form and content of a stockholder's notice;

do not provide for cumulative voting rights (therefore allowing the holders of a majority of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election, if they should so choose); and

provide that special meetings of our stockholders may be called only by the chairman of the board, our chief executive officer or by the board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors.

The amendment of any of these provisions generally would require approval by the holders of at least 66 2/3% of our then outstanding common stock.

Nasdaq National Market Listing

Our common stock is listed on the Nasdaq National Market under the symbol MBRX.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company. The transfer agent and registrar's address is 59 Maiden Lane, New York, New York 10038.

DESCRIPTION OF WARRANTS

The following description, together with the additional information we include in any applicable prospectus supplements, summarizes the material terms and provisions of the warrants to purchase common stock that we may offer under this prospectus. Warrants may be offered independently or together with common stock offered by any prospectus supplement, and may be attached to or separate from the common stock. While the terms we have summarized below will generally apply to any future warrants we may offer under this prospectus, we will describe the particular terms of any warrants that we may offer in more detail in the applicable prospectus supplement. The terms of any warrants we offer under a prospectus supplement may differ from the terms we describe below.

We will issue the warrants under a warrant agreement which we will enter into with a warrant agent to be selected by us. We have filed forms of the warrant agreement and the related warrant certificate for the warrants we may offer under this prospectus as exhibits to the registration statement of which this prospectus is a part. The warrant agent will act solely as an agent of ours in connection with the warrants and will not act as an agent for the holders or beneficial owners of the warrants.

The following summaries of material provisions of the warrants and the warrant agreement are subject to, and qualified in their entirety by reference to, all the provisions of the warrant agreement. We urge you to read the applicable prospectus supplements related to the warrants that we sell under this prospectus, as well as the complete warrant agreement that contains the terms of the warrants.

General

We will describe in the applicable prospectus supplement the following terms relating to the warrants, to the extent applicable:

the offering price and the aggregate number of warrants offered;

the total number of shares that can be purchased if a holder of the warrants exercises them;

the number of warrants being offered with each share of common stock;

the number of shares of common stock that can be purchased if a holder exercises the warrant and the price at which such common stock may be purchased upon exercise, including, if applicable, any provisions for changes to or adjustments in the exercise price and in the securities or other property receivable upon exercise;

the terms of any rights to redeem or call, or accelerate the expiration of, the warrants;

the date on which the right to exercise the warrants begins and the date on which that right expires;

the federal income tax consequences of holding or exercising the warrants; and

any other specific terms, preferences, rights or limitations of, or restrictions on, the warrants.

Warrants for the purchase of common stock will be in registered form only.

If the warrants are attached to common stock, the prospectus supplement will also describe the date on and after which the holder of the warrants can transfer them separately from the related common stock.

A holder of warrant certificates may exchange them for new certificates of different denominations, present them for registration of transfer and exercise them at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement. Until any warrants to purchase common stock are exercised, holders of the warrants will not have any rights of holders of the underlying common stock, including any

rights to receive dividends or to exercise any voting rights, except to the extent set forth under **Warrant Adjustments** below.

Exercise of Warrants

Each holder of a warrant is entitled to purchase the number of shares of common stock at the exercise price described in the applicable prospectus supplement. After the close of business on the day when the right to exercise terminates (or a later date if we extend the time for exercise), unexercised warrants will become void.

A holder of warrants may exercise them by following the general procedure outlined below:

delivering to the warrant agent the consideration required by the applicable prospectus supplement to purchase the underlying common stock;

properly completing and signing the reverse side of the warrant certificate representing the warrants; and

delivering the warrant certificate representing the warrants to the warrant agent within five business days of the warrant agent receiving payment of the exercise price.

If you comply with the procedures described above, your warrants will be considered to have been exercised when the warrant agent receives payment of the exercise price, subject to the transfer books for the securities issuable upon exercise of the warrant not being closed on such date. After you have completed those procedures and subject to the foregoing, we will, as soon as practicable, issue and deliver to you the common stock that you purchased upon exercise. If you exercise fewer than all of the warrants represented by a warrant certificate, a new warrant certificate will be issued to you for the unexercised amount of warrants. Holders of warrants will be required to pay any tax or governmental charge that may be imposed in connection with transferring the underlying common stock in connection with the exercise of the warrants.

Amendments and Supplements to the Warrant Agreements

We may amend or supplement a warrant agreement without the consent of the holders of the applicable warrants to cure ambiguities in the warrant agreement, to cure or correct a defective provision in the warrant agreement, or to provide for other matters under the warrant agreement that we and the warrant agent deem necessary or desirable, so long as, in each case, such amendments or supplements do not materially adversely affect the interests of the holders of the warrants.

Warrant Adjustments

Unless the applicable prospectus supplement states otherwise, the exercise price of, and the number of securities covered by a warrant will be adjusted proportionately if we subdivide or combine our common stock. In addition, unless the prospectus supplement states otherwise, if we, without payment for:

issue capital stock or other securities convertible into or exchangeable for common stock, or any rights to subscribe for, purchase or otherwise acquire any of the foregoing, as a dividend or distribution to holders of our common stock;

pay any cash to holders of our common stock other than a cash dividend paid out of our current or retained earnings;

issue any evidence of our indebtedness or rights to subscribe for or purchase our indebtedness to holders of our common stock; or

issue common stock or preferred stock or additional stock or other securities or property to holders of our common stock by way of spinoff, split-up, reclassification, combination of shares or similar corporate rearrangement,

then the holders of warrants will be entitled to receive upon exercise of the warrants, in addition to the common stock otherwise receivable upon exercise of the warrants and without paying any additional consideration, the amount of stock and other securities and property such holders would have been entitled to receive had they held the common stock issuable under the warrants on the dates on which holders of the common stock received or became entitled to receive such additional stock and other securities and property.

Except as stated above, the exercise price and number of securities covered by a warrant, and the amounts of other securities or property to be received, if any, upon exercise of those warrants, will not be adjusted or provided for if we issue those securities or any securities convertible into or exchangeable for those securities, or securities carrying the right to purchase those securities or securities convertible into or exchangeable for those securities.

Holders of warrants may have additional rights under the following circumstances:

certain reclassifications, capital reorganizations or changes of the common stock;

certain share exchanges, mergers, or similar transactions involving us and which result in changes of the common stock; or

certain sales or dispositions to another entity of all or substantially all of our property and assets.

If one of the above transactions occurs and holders of our common stock are entitled to receive stock, securities or other property with respect to or in exchange for their common stock, the holders of the warrants then outstanding will be entitled to receive upon exercise of their warrants the kind and amount of shares of stock and other securities or property that they would have received upon the applicable transaction if they had exercised their warrants immediately before the transaction.

PLAN OF DISTRIBUTION

We may sell the securities covered by this prospectus in any of three ways (or in any combination):

to or through underwriters or dealers;

directly to a limited number of purchasers or to a single purchaser; or

through agents.

The prospectus supplement will set forth the terms of the offering of the securities covered by this prospectus, including:

the name or names of any underwriters, dealers or agents and the amounts of securities underwritten or purchased by each of them;

any over-allotment options under which underwriters may purchase additional securities from us;

any underwriting discounts or commissions or agency fees and other items constituting underwriters' or agents' compensation;

the initial public offering price of the securities and the proceeds to us and any discounts, commissions or concessions allowed or reallocated or paid to dealers; and

any securities exchanges or markets on which the securities may be listed.

Any initial public offering price and any discounts or concessions allowed or reallocated or paid to dealers may be changed from time to time.

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Underwriters may offer and sell the offered 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. If underwriters are used in the sale of any securities, the securities will be acquired by the underwriters for their own account and may be resold from time to time in one or more transactions described above. The securities may be either offered to the public through underwriting syndicates represented by managing underwriters, or directly by underwriters. Generally, the underwriters' obligations to purchase the securities will be subject to certain conditions precedent. The underwriters will be obligated to purchase all of the securities if they purchase any of the securities. We may use underwriters with whom we have a material relationship. We will describe the nature of any such relationship in the prospectus supplement, naming the underwriter.

We may sell the securities through agents from time to time. The prospectus supplement will name any agent involved in the offer or sale of the securities and any commissions we pay to them. Generally, any agent will be acting on a best efforts basis for the period of its appointment.

We may authorize underwriters, dealers or agents to solicit offers by certain purchasers to purchase the securities from us 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. The contracts will be subject only to those conditions set forth in the prospectus supplement, and the prospectus supplement will set forth any commissions we pay for solicitation of these contracts.

Agents and underwriters may be entitled to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, or to contribution with respect to payments which the agents or underwriters may be required to make in respect thereof. Agents and underwriters may be customers of, engage in transactions with, or perform services for us in the ordinary course of business.

All warrants we offer 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.

Any underwriter may engage in over-allotment, stabilizing transactions, short covering transactions and penalty bids in accordance with Regulation M under the Exchange Act. Over-allotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying securities so long as the stabilizing bids do not exceed a specified maximum. Short covering transactions involve purchases of the securities in the open market after the distribution is completed to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

LEGAL MATTERS

The validity of the securities being offered by this prospectus will be passed upon by Cooley Godward LLP, San Diego, California. As of the date of this prospectus, investment funds affiliated with Cooley Godward LLP owned 22,371 shares of common stock and warrants to purchase 5,940 shares of common stock having a weighted average exercise price of \$7.44 per share.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2004, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and special reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's web site at <http://www.sec.gov>. You may also read and copy any document we file at the SEC's public reference room at 100 F Street, NE., Room 1580, Washington, D.C. 20549. You may obtain information on the operation of the SEC's public reference room in Washington, D.C. by calling the SEC at 1-800-SEC-0330.

The SEC allows us to incorporate by reference into this prospectus the information in documents we file with it, which means that we can disclose important information to you by referring you to those documents. Any statement contained in any document incorporated or deemed to be incorporated by reference herein shall be deemed to be modified or superseded, for purposes of this prospectus, to the extent that a statement contained in or omitted from this prospectus, or in any other subsequently filed document which also is or is deemed to be incorporated by reference herein, modifies or supersedes such statement. Any such statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus. We incorporate by reference the documents listed below and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act until the offering is completed:

Our Annual Report on Form 10-K for the year ended December 31, 2004 which was filed on March 31, 2005, including all material incorporated by reference therein;

Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2005, June 30, 2005 and September 30, 2005 which were filed on May 16, 2005, August 15, 2005 and November 14, 2005, respectively;

Our Current Reports on Form 8-K filed on January 25, 2005, March 17, 2005, June 27, 2005 and October 5, 2005; and

The description of our common stock contained in our Registration Statement on Form 8-A filed on May 28, 2004.

We will provide without charge to each person, including any beneficial owner, to whom this prospectus is delivered, upon written or oral request of such person, a copy of any and all of the documents that have been incorporated by reference in this prospectus (not including exhibits to such documents, unless such exhibits are specifically incorporated by reference in this prospectus or into such documents). Such request may be directed to Metabasis Therapeutics, Inc., 11119 North Torrey Pines Road, La Jolla, California 92037, (858) 587-2770.

All documents that we file with the SEC pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus and before the termination of the offering of the securities offered in this prospectus shall be deemed incorporated by reference into this prospectus and to be a part of this prospectus from the respective date of filing such documents.

We have filed with the SEC a registration statement on Form S-3 under the Securities Act covering the securities described in this prospectus. This prospectus does not contain or incorporate by reference all of the information included in the registration statement, some of which is contained in exhibits included with or incorporated by reference into the registration statement. The registration statement, including the exhibits contained or incorporated by reference therein, can be read at the SEC web site or at the SEC office referred to above. Any statement made or incorporated by reference in this prospectus concerning the contents of any contract, agreement or other document is only a summary of the actual contract, agreement or other document. If we have filed or incorporated by reference any contract, agreement or other document as an exhibit to the registration statement, you should read the exhibit for a more complete understanding of the document or matter involved. Each statement regarding a contract, agreement or other document is qualified in its entirety by reference to the actual document.

4,938,272 Shares

Common Stock

PROSPECTUS SUPPLEMENT

Cowen & Company

Piper Jaffray & Co.

March 24, 2006
