

Prospectus Supplement
(To prospectus dated July 20, 2007)



3,800,000 Shares Common Stock

Targacept, Inc. is offering 3,800,000 shares of its common stock.

Our common stock is listed on the Nasdaq Global Market under the symbol "TRGT." The closing bid price of our common stock on the Nasdaq Global Market on January 16, 2008 was \$7.07 per share.

Investing in our common stock involves risks and uncertainties. See "[Risk Factors](#)" on page 4 of the accompanying prospectus. You should read this prospectus supplement, the accompanying prospectus and the documents incorporated by reference into the accompanying prospectus carefully before you make your investment decision.

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.

	<u>Per Share</u>	<u>Total</u>
Public offering price	\$ 7.07	\$26,866,000
Underwriting discount	\$ 0.37	\$ 1,406,000
Proceeds, before expenses, to Targacept	\$ 6.70	\$25,460,000

We have granted the underwriters the right to purchase up to an additional 570,000 shares of our common stock at the public offering price per share, less the underwriting discount, on the day of pricing.

The underwriters expect to deliver the shares against payment in New York, New York on January 23, 2008.

Deutsche Bank Securities

Lazard Capital Markets Oppenheimer & Co. Pacific Growth Equities, LLC

January 17, 2008

ABOUT THIS PROSPECTUS SUPPLEMENT

Unless otherwise mentioned or unless the context requires otherwise, all references in this prospectus supplement and the accompanying prospectus to “the company,” “Targacept,” “we,” “us,” “our,” or similar references mean Targacept, Inc. Our principal executive offices are located at 200 East First Street, Suite 300, Winston-Salem, North Carolina 27101 and our telephone number is (336) 480-2100.

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering of our common stock and supplements information contained in the accompanying prospectus and the documents incorporated by reference into the accompanying prospectus. The second part is the accompanying prospectus, which gives more general information about us and the shares of common stock we may offer from time to time under our shelf registration statement. To the extent there is a conflict between the information contained in this prospectus supplement, on the one hand, and the information contained in the accompanying prospectus or any document incorporated by reference therein, on the other hand, you should rely on the information in this prospectus supplement.

We have not authorized any dealer, salesman or other person to give any information or to make any representation other than those contained or incorporated by reference in this prospectus supplement and the accompanying prospectus. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus supplement or the accompanying prospectus. This prospectus supplement and the accompanying prospectus do not constitute an offer to sell or the solicitation of an offer to buy common stock, nor do this prospectus supplement and the accompanying prospectus constitute an offer to sell or the solicitation of an offer to buy common stock in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction. You should not assume that the information contained in this prospectus supplement and the accompanying prospectus is accurate on any date subsequent to the date set forth on the front of the document or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus supplement and any accompanying prospectus is delivered or common stock is sold on a later date.

THE OFFERING

Common stock offered by us 3,800,000 shares

Common stock to be outstanding after this offering 24,303,419 shares

Use of Proceeds We intend to use the proceeds of this offering to fund our operations and for other general corporate purposes, such as working capital, development of our clinical and preclinical product candidates, intellectual property protection and enforcement, capital expenditures, investments and acquisitions. See Use of Proceeds on page S-3 of this prospectus supplement.

Nasdaq Global Market Symbol TRGT

The information above and elsewhere in this prospectus supplement regarding outstanding shares of our common stock is based on 20,503,419 shares of common stock outstanding as of December 31, 2007 and excludes 3,125,161 shares of common stock issuable upon the exercise of options outstanding as of December 31, 2007, at a weighted average exercise price of \$5.11 per share.

Unless otherwise indicated, all information in this prospectus supplement assumes no exercise of the underwriters' over-allotment option to purchase up to 570,000 shares of common stock.

USE OF PROCEEDS

We estimate that the net proceeds from this offering will be approximately \$25.3 million, or approximately \$29.1 million if the underwriters exercise their over-allotment option in full, after deducting the underwriters' discounts and commissions and our estimated offering expenses. We intend to use any net proceeds from the sale of our common stock to fund our operations and for other general corporate purposes, such as working capital, development of our clinical and preclinical product candidates, intellectual property protection and enforcement, capital expenditures, investments and acquisitions. Pending use of the net proceeds as described above, we intend to invest the net proceeds in short-term, interest-bearing, investment grade securities.

DIVIDEND POLICY

We have never declared or paid cash dividends on any of our shares of capital stock. We currently intend to retain future earnings, if any, to finance the expansion and growth of our business and do not anticipate paying any cash dividends in the foreseeable future. Any future determination to pay dividends will be at the discretion of our board of directors and will depend on our financial condition, results of operations, capital requirements and other factors that our board of directors deems relevant. In addition, the terms of any future debt or credit facility may preclude us from paying dividends.

UNDERWRITING

Subject to the terms and conditions of the underwriting agreement, the underwriters named below, through their representative Deutsche Bank Securities Inc., have severally agreed to purchase from us the following respective numbers of shares of common stock at a public offering price less the underwriting discounts and commissions set forth on the cover page of this prospectus supplement:

<u>Underwriters</u>	<u>Number of Shares</u>
Deutsche Bank Securities Inc.	2,945,000
Lazard Capital Markets	285,000
Oppenheimer & Co.	285,000
Pacific Growth Equities, LLC	285,000
Total	<u>3,800,000</u>

The underwriting agreement provides that the obligations of the several underwriters to purchase the shares of common stock offered hereby are subject to certain conditions precedent and that the underwriters will purchase all of the shares of common stock offered by this prospectus supplement, other than those covered by the over-allotment option described below, if any of these shares are purchased.

We have been advised by the representatives of the underwriters that the underwriters propose to offer the shares of common stock to the public at the public offering price set forth on the cover of this prospectus supplement and to dealers at a price that represents a concession not in excess of \$0.22 per share under the public offering price. The underwriters may allow, and these dealers may re-allow, a concession of not more than \$0.10 per share to other dealers. After the public offering, representatives of the underwriters may change the offering price and other selling terms.

We have granted to the underwriters an option, exercisable not later than 30 days after the date of this prospectus supplement, to purchase up to 570,000 additional shares of common stock at the public offering price less the underwriting discounts and commissions set forth on the cover page of this prospectus supplement. The underwriters may exercise this option only to cover over-allotments made in connection with the sale of the common stock offered by this prospectus supplement. To the extent that the underwriters exercise this option, each of the underwriters will become obligated, subject to conditions, to purchase approximately the same percentage of these additional shares of common stock as the number of shares of common stock to be purchased by it in the above table bears to the total number of shares of common stock offered by this prospectus supplement. We will be obligated, pursuant to the option, to sell these additional shares of common stock to the underwriters to the extent the option is exercised. If any additional shares of common stock are purchased, the underwriters will offer the additional shares on the same terms as those on which the 3,800,000 shares are being offered.

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The underwriting discounts and commissions per share are equal to the public offering price per share of common stock less the amount paid by the underwriters to us per share of common stock. The underwriting discounts and commissions are 5.25% of the public offering price. We have agreed to pay the underwriters the following discounts and commissions, assuming either no exercise or full exercise by the underwriters of the underwriters' over-allotment option:

	Fee per Share	Total Fees	
		Without Exercise of Over-Allotment Option	With Full Exercise of Over-Allotment Option
Discounts and commissions paid by us	\$ 0.37	\$1,406,000	\$1,616,900

In addition, we estimate that the total expenses of this offering, excluding underwriting discounts and commissions, will be approximately \$135,000.

We have agreed to indemnify the underwriters against specified types of liabilities, including liabilities under the Securities Act, and to contribute to payments the underwriters may be required to make in respect of any of these liabilities.

Each of our directors and officers has agreed that, without the prior written consent of Deutsche Bank Securities on behalf of the underwriters, they will not, during the period ending 60 days after the date of this prospectus:

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock or any securities convertible into or exercisable or exchangeable for shares of our common stock; or
- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of shares of our common stock, whether any transaction described above is to be settled by delivery of shares of our common stock or such other securities, in cash or otherwise.

The 60-day restricted period described in the preceding paragraph will be extended if:

- during the last 17 days of the 60-day restricted period we issue an earnings release or material news or a material event relating to our company occurs; or
- prior to the expiration of the 60-day restricted period, we announce that we will release earnings results during the 16-day period beginning on the last day of the 60-day period,

in which case the restrictions described in the preceding paragraph will continue to apply until the expiration of the 18-day period beginning on the issuance of the earnings release or the occurrence of the material news or material event.

These restrictions do not apply to:

- the adoption by a director or officer of a plan pursuant to Rule 10b5-1 under the Securities Exchange Act of 1934, as amended, but not the disposition of shares under such plan;
- the sale of shares to the underwriters;

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- the issuance by us of shares of our common stock upon the exercise of an option or a warrant or the conversion of a security outstanding on the date of this prospectus of which the underwriters have been advised in writing;
- the issuance by us of shares or options to purchase shares of our common stock pursuant to our 2000 plan or our 2006 plan, provided that the recipient of the shares agrees to be subject to the restrictions described above;
- transactions by any person other than us relating to shares of common stock or other securities acquired in open market transactions after the completion of the offering of the shares;
- transfers of shares as a gift or charitable contribution, or by will or intestacy;
- transfers of shares to any trust the sole beneficiaries of which are the transferee or a member of the immediate family of the transferee; or
- transfers to certain entities or persons affiliated with the stockholder;

provided that in the case of each of the last three transactions, each donee, distributee, transferee and recipient agrees to be subject to the restrictions described in the immediately preceding paragraph, no filing under Section 16 of the Exchange Act is required in connection with these transactions, other than a filing on a Form 5 made after the expiration of the 60-day period, and no transaction includes a disposition for value.

In connection with the offering, the underwriters may purchase and sell shares of our common stock in the open market. These transactions may include short sales, purchases to cover positions created by short sales and stabilizing transactions.

Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in the offering. Covered short sales are sales made in an amount not greater than the underwriters' option to purchase additional shares of common stock from us in the offering. The underwriters may close out any covered short position by either exercising their option to purchase additional shares or purchasing shares in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the over-allotment option.

Naked short sales are any sales in excess of the over-allotment option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if underwriters are concerned that there may be downward pressure on the price of the shares in the open market prior to the completion of the offering.

Stabilizing transactions consist of various bids for or purchases of our common stock made by the underwriters in the open market prior to the completion of the offering.

The underwriters may impose a penalty bid. This occurs when a particular underwriter repays to the other underwriters a portion of the underwriting discount received by it because the representatives of the underwriters have repurchased shares sold by or for the account of that underwriter in stabilizing or short covering transactions.

Purchases to cover a short position and stabilizing transactions may have the effect of preventing or slowing a decline in the market price of our common stock. Additionally, these

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purchases, along with the imposition of a penalty bid, may stabilize, maintain or otherwise affect the market price of our common stock. As a result, the price of our common stock may be higher than the price that might otherwise exist in the open market. These transactions may be effected on The Nasdaq Global Market, in the over-the-counter market or otherwise.

In connection with this offering, the underwriters may engage in passive market making transactions in our common stock on the Nasdaq Global Market in accordance with Rule 103 of Regulation M under the Exchange Act during a period before the commencement of offers or sales of common stock and extending through the completion of distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker's bid, that bid must then be lowered when specified purchase limits are exceeded.

A prospectus supplement and the accompanying prospectus in electronic format are being made available on Internet web sites maintained by one or more of the lead underwriters of this offering and may be made available on web sites maintained by other underwriters. Other than the prospectus supplement and the accompanying prospectus in electronic format, the information on any underwriter's web site and any information contained in any other web site maintained by an underwriter is not part of the prospectus supplement and the accompanying prospectus or the registration statement of which the prospectus supplement and the accompanying prospectus form a part.

Lazard Frères & Co. LLC referred this transaction to Lazard Capital Markets and will receive a referral fee from Lazard Capital Markets LLC in connection therewith.

DESCRIPTION OF SECURITIES

Each holder of common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders, including the election of directors, and there are no cumulative voting rights. Subject to preferences that may be applicable to any shares of preferred stock that may become outstanding from time to time, holders of common stock are entitled to receive, ratably, dividends declared from time to time by our board of directors, if any, out of funds legally available for that purpose. In the event of our liquidation, dissolution or winding up, holders of common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities and the satisfaction of any liquidation preference granted to the holders of any shares of preferred stock then outstanding. Holders of common stock have no conversion, preemptive or other subscription rights, and there are no redemption or sinking fund provisions applicable to the common stock. The rights, preferences and privileges of the holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future. Please refer to "Description of Capital Stock" in our registration statement on Form S-1, as amended, initially filed with the Commission on January 17, 2006 (Reg. No. 333-131050), for additional information relating to the common stock offered hereby.

L LEGAL MATTERS

Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts, will pass upon the validity of the issuance of the common stock offered by this prospectus. Wilmer Cutler Pickering Hale and Dorr LLP, New York, New York, has acted as counsel to the underwriters in connection with certain legal matters related to this offering.

PROSPECTUS

\$75,000,000


TARGACEPT, INC.
COMMON STOCK

This prospectus will allow us to issue up to \$75,000,000 of our common stock from time to time at prices and on terms to be determined at or prior to the time of the applicable offering. We will provide you with specific terms of any offering in one or more supplements to this prospectus. You should read this document and the applicable prospectus supplement carefully before you invest.

Our common stock is listed on The Nasdaq Global Market under the symbol "TRGT." On May 24, 2007, the last reported sale price of our common stock was \$9.49 per share. Prospective purchasers of common stock are urged to obtain current information as to the market prices of our common stock.

Investing in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risks that we have described on page 4 of this prospectus under the caption "[Risk Factors](#)." We may also include specific risk factors in supplements to this prospectus under the caption "Risk Factors." This prospectus may not be used to offer or sell our common stock unless accompanied by a prospectus supplement.

Our common stock may be sold directly by us to investors, through agents designated from time to time or to or through underwriters or dealers. 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 our common stock with respect to which this prospectus is being delivered, the names of such underwriters and any applicable commissions or discounts and over-allotment options will be set forth in a prospectus supplement. The price to the public of such common stock and the net proceeds that we expect to receive from such sale will also be set forth in a prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is July 20, 2007.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, utilizing a “shelf” registration process. Under the shelf registration process, we may sell shares of our common stock, with an aggregate initial offering price of up to \$75,000,000, in one or more offerings. Each time we sell shares subject to the shelf registration, we will provide a prospectus supplement that contains specific information about the terms of that offering.

This prospectus does not contain all of the information included in the registration statement. For a more complete understanding of the offering of the shares of our common stock, you should refer to the registration statement, including its exhibits. Each prospectus supplement may also add to, update or supersede information contained or incorporated by reference in this prospectus. However, no prospectus supplement will 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 the registration statement becomes effective. This prospectus, together with the documents incorporated by reference into this prospectus and as supplemented by the prospectus supplement applicable to an offering, includes all material information relating to that offering. You should carefully read this prospectus, the applicable prospectus supplement, the information and documents incorporated herein by reference and the additional information under the heading “Where You Can Find More Information” before making an investment decision.

You should rely only on the information contained or incorporated by reference in this prospectus, as supplemented by the applicable prospectus supplement. We have not authorized anyone to provide you with information different from that contained or incorporated by reference in this prospectus or a prospectus supplement. No dealer, salesperson or other person is authorized to give any information or to represent anything not contained or incorporated by reference in this prospectus or a prospectus supplement. You must not rely on any unauthorized information or representation. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. You should assume that the information in this prospectus or any prospectus supplement is accurate only as of the date on the front of the document and that any information we have incorporated herein by reference is accurate only as of the date of the document that is incorporated by reference, regardless of the time of delivery of this prospectus or a prospectus supplement or any sale of a security.

This prospectus may not be used to consummate sales of common stock, unless it is accompanied by a prospectus supplement. To the extent there are inconsistencies between any prospectus supplement, this prospectus and any documents incorporated by reference in this prospectus, the document with the most recent date will control.

Unless the context otherwise requires, “Targacept,” “the Company,” “we,” “us,” “our” and similar names refer to Targacept, Inc.

TARGACEPT, INC.

We are a biopharmaceutical company engaged in the design, discovery and development of NNR Therapeutics, a new class of drugs for the treatment of multiple diseases and disorders of the central nervous system. Our NNR Therapeutics selectively target neuronal nicotinic receptors, or NNRs. NNRs are found on nerve cells throughout the nervous system and serve as key regulators of nervous system activity.

We trace our scientific lineage to a research program initiated by R.J. Reynolds Tobacco Company in 1982 to study the activity and effects of nicotine, a compound that interacts non-selectively with all nicotinic receptors. Based on years of focused research in the NNR area, we believe that compounds that interact selectively with specific NNR subtypes have the potential to achieve positive medical effects by modulating their activity. We have built an extensive patent estate covering the structure or therapeutic use of small molecules designed to regulate the central nervous system by selectively affecting specific NNR subtypes.

We currently have four clinical-stage product candidates and three preclinical product candidates. Our lead product candidate is a novel small molecule that we have historically referred to as TC-1734 and that our strategic collaborator, AstraZeneca, refers to as AZD3480. AZD3480 (TC-1734) modulates the activity of the $\alpha 4\beta 2$ NNR. In December 2005, we entered into a collaborative research and license agreement with AstraZeneca AB for the development and worldwide commercialization of AZD3480 (TC-1734) as a treatment for Alzheimer's disease, cognitive deficits in schizophrenia and potentially other conditions characterized by cognitive impairment such as attention deficit hyperactivity disorder, commonly referred to as ADHD, age associated memory impairment, commonly referred to as AAMI, and mild cognitive impairment, commonly referred to as MCI. We currently expect that AstraZeneca will initiate two Phase II clinical trials of AZD3480 (TC-1734) in mid-2007, one in mild to moderate Alzheimer's disease and one in cognitive deficits in schizophrenia, and that both trials will be completed by the end of 2008.

Our most advanced product candidates, in addition to AZD3480 (TC-1734), are described below.

- *TC-2216.* TC-2216 is a product candidate that we are developing as a monotherapy for depression and anxiety disorders. TC-2216 modulates the activity of the $\alpha 4\beta 2$ NNR. We are currently conducting a Phase I single rising dose clinical trial of TC-2216 to evaluate its safety and tolerability and to assess its pharmacokinetic profile in healthy volunteers.
- *Mecamylamine hydrochloride and TC-5214.* In 2006, we completed a Phase II clinical trial of mecamylamine hydrochloride as an augmentation treatment to citalopram hydrobromide, a commonly prescribed treatment for depression marketed as Celexa in the United States, for major depression. We refer to this treatment combination as TRIDMAC. Mecamylamine hydrochloride is the active ingredient in Inversine, our only product approved by the U.S. Food and Drug Administration, or FDA, for marketing. TC-5214 is one of the molecular components, known as enantiomers, of mecamylamine hydrochloride. We have not yet conducted a clinical trial of TC-5214, but expect that we will elect to advance TC-5214 into clinical development as an augmentation treatment for major depression in lieu of further development of mecamylamine hydrochloride.
- *TC-2696.* TC-2696 is a product candidate that we are developing currently as a treatment for acute post-operative pain. Depending on clinical trial results, available resources and other considerations, we may pursue development of TC-2696 in the future for other classes of pain in addition to or instead of acute post-operative pain.

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TC-2696 modulates the activity of the $\alpha 4\beta 2$ NNR. We are currently conducting a Phase II clinical trial of TC-2696 to assess its pain relieving effects in third molar extraction patients.

- *TC-5619.* TC-5619 is a preclinical product candidate that modulates the $\alpha 7$ NNR. We believe compounds that selectively target the $\alpha 7$ NNR may have application in the treatment of conditions such as schizophrenia, cognitive impairment and inflammation. We currently plan to initiate clinical development of TC-5619 in the second quarter of 2007.
- *TC-6499.* TC-6499 is a preclinical product candidate that we plan to develop initially as a treatment for neuropathic pain. We are currently conducting manufacturing activities necessary to support the initiation of clinical development of this product candidate.

In addition, under our agreement with AstraZeneca, we and AstraZeneca are conducting a preclinical research collaboration designed to discover and develop additional compounds that, like AZD3480 (TC-1734), act on the $\alpha 4\beta 2$ NNR. AstraZeneca is responsible for funding the research collaboration, which began in January 2006 and has a planned term of four years.

In addition to our $\alpha 4\beta 2$ research collaboration with AstraZeneca, we have a preclinical program focused on identifying and developing compounds that selectively target the $\alpha 7$ NNR and other preclinical programs in areas in which we believe drugs that target specific NNR subtypes can be exploited for medical benefit, such as smoking cessation (and other addictions), obesity and Parkinson's disease.

Our drug discovery activities utilize sophisticated proprietary computer-based molecular design methodologies and extensive biological data for a library of diverse compounds developed and collected over more than 20 years. We refer to these technologies collectively as Pentad. We used Pentad to design or optimize AZD3480 (TC-1734), TC-2696, TC-2216, TC-5619 and TC-6499.

We were incorporated in Delaware in 1997 as a wholly owned subsidiary of R.J. Reynolds Tobacco Company. In August 2000, we became an independent company when we issued and sold stock to venture capital investors. Our principal executive offices are located at 200 East First Street, Suite 300, Winston-Salem, North Carolina 27101 and our telephone number is (336) 480-2100.

Our internet address is www.targacept.com. The information contained on, or that can be accessed through, our website is not incorporated by reference into this prospectus or any prospectus supplement and does not constitute a part of this prospectus or any prospectus supplement. We have included our website address as a factual reference and do not intend it as an active link to our website.

Our trademarks include Targacept®, Inversine®, Pentad™, NNR Therapeutics™, TRIDMAC™ and AMPLIXA™. Other service marks, trademarks and trade names appearing in this prospectus or any prospectus supplement are the property of their respective owners.

RISK FACTORS

Investing in our common stock involves risk. Prior to making a decision about investing in our common stock, you should carefully consider all of the information contained or incorporated by reference in this prospectus or the applicable prospectus supplement. In particular, you should carefully consider the risks, uncertainties and assumptions discussed under the heading "Risk Factors" in our most recent annual report on Form 10-K, which is on file with the SEC and incorporated herein by reference, and in subsequent filings that we make with the SEC, as well as any discussion of risks contained in the applicable prospectus supplement. The risks and uncertainties we have described are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our operations.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus, each prospectus supplement and the documents we file or have filed with the SEC that are incorporated herein by reference include forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, which we refer to as the Securities Act, or Section 21E of the Securities Exchange Act of 1934, as amended, which we refer to as the Exchange Act. For this purpose, any statements contained in this prospectus, any prospectus supplement or any of the documents we file or have filed with the SEC that are incorporated herein by reference regarding the progress, timing and scope of the research and development of our product candidates or related regulatory filings or clinical trials, our development plans for the treatment combination that we refer to as TRIDMAC, our future operations, financial position, revenues or costs, or our strategies, prospects, plans, expectations or objectives, other than statements of historical fact, are forward-looking statements made under the provisions of The Private Securities Litigation Reform Act of 1995. In some cases, words such as "may," "will," "could," "would," "should," "expect," "intend," "plan," "anticipate," "believe," "estimate," "predict," "project," "potential," "continue," "ongoing" or other comparable words identify forward-looking statements. Actual results, performance or experience may differ materially from those expressed or implied by forward-looking statements as a result of various important factors, including our critical accounting policies and risks and uncertainties relating to:

- our dependence on the success of our collaboration with AstraZeneca;
- the amount and timing of resources that AstraZeneca devotes to the development of AZD3480 (TC-1734);
- AstraZeneca's right in the future to terminate the preclinical research collaboration that we and AstraZeneca are currently conducting prior to the end of the planned four-year term;
- the position of applicable regulatory authorities with regard to a treatment combination that includes mecamlamine hydrochloride, which is a mixture of two different enantiomers that are mirror images of each other and have the same chemical but potentially different biological properties, known as a racemate, as compared to one of its constituent enantiomers such as TC-5214;
- the results of clinical trials and non-clinical studies and assessments with respect to our current and future product candidates in development;
- the conduct of such trials, studies and assessments, including the performance of third parties that we engage to execute them and difficulties or delays in the completion of patient enrollment or data analysis;

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- the timing and success of submission, acceptance and approval of regulatory filings;
- our ability to obtain substantial additional funding;
- our ability to establish additional strategic collaborations;
- our ability to obtain, maintain and enforce patent and other intellectual property protection for our product candidates and discoveries; and
- the performance of third-party manufacturers with which we contract to provide a supply of our product candidates.

These and other risks and uncertainties are described in more detail under the caption “Risk Factors” in our most recent annual report on Form 10-K and in subsequent filings that we make with the SEC, and may also be described in the applicable prospectus supplement. As a result of the risks and uncertainties, the results or events indicated by the forward-looking statements may not occur. We caution you not to place undue reliance on any forward-looking statement.

Any forward-looking statements in this prospectus, any prospectus supplement or any of the documents we file or have filed with the SEC that are incorporated herein by reference represent our views only as of the respective dates of those documents and should not be relied upon as representing our views as of any subsequent date. We anticipate that subsequent events and developments may cause our views to change. Although we may elect to update these forward-looking statements publicly at some point in the future, whether as a result of new information, future events or otherwise, we specifically disclaim any obligation to do so, except as required by applicable law. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

USE OF PROCEEDS

Unless otherwise indicated in the prospectus supplement applicable to an offering, we intend to use any net proceeds from the sale of our common stock to fund our operations and for other general corporate purposes, such as working capital, development of our clinical and preclinical product candidates, intellectual property protection and enforcement, capital expenditures, investments and acquisitions. Pending use of the net proceeds as described above, we intend to invest the net proceeds in short-term, interest-bearing, investment grade securities.

PLAN OF DISTRIBUTION

We may offer the common stock from time to time pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods. We may sell the common stock (1) through underwriters or dealers, (2) through agents or (3) directly to one or more purchasers, or through a combination of such methods. We may distribute the common stock from time to time in one or more transactions at:

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

The applicable prospectus supplement will describe the terms of the offering of our common stock, including:

- the number of shares of common stock we are offering;
- the name or names of any underwriters;
- any securities exchange or market on which the common stock may be listed;
- the purchase price or other consideration to be paid in connection with the sale of our common stock being offered and the proceeds we will receive from the sale;
- any over-allotment options pursuant to which the underwriters may purchase additional shares of common stock from us;
- any underwriting discounts or agency fees and other items constituting underwriters' or agents' compensation; and
- any discounts or concessions allowed or reallocated or paid to dealers.

We may directly solicit offers to purchase the common stock. We may also designate agents to solicit offers to purchase the common stock from time to time. We will name in a prospectus supplement any agent involved in the offer or sale of our common stock.

If we utilize a dealer in the sale of the common stock being offered by this prospectus, we will sell the common stock to the dealer, as principal. The dealer may then resell the common stock to the public at varying prices to be determined by the dealer at the time of resale.

If we utilize an underwriter in the sale of the common stock being offered, we will execute an underwriting agreement with the underwriter at the time of sale. In connection with the sale of the common stock, we, or the purchasers of our common stock for whom the underwriter

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may act as agent, may compensate the underwriter in the form of underwriting discounts or commissions. The underwriter may sell the common stock to or through dealers, and the underwriter may compensate those dealers in the form of discounts, concessions or commissions. Subject to certain conditions, the underwriters will be obligated to purchase all of the shares of common stock offered by the prospectus supplement. We may change from time to time the public offering price and any discounts or concessions allowed or reallocated or paid to dealers.

Underwriters, dealers and agents participating in the distribution of the common stock may be deemed to be underwriters within the meaning of the Securities Act, and any discounts and commissions received by them and any profit realized by them on resale of the common stock may be deemed to be underwriting discounts and commissions. We may enter into agreements to indemnify underwriters, dealers and agents against civil liabilities, including liabilities under the Securities Act, or to contribute to payments they may be required to make in respect thereof.

Shares of our common stock sold pursuant to the registration statement of which this prospectus is a part will be authorized for quotation and trading on The Nasdaq Global Market. One or more underwriters may make a market in our common stock, but no underwriter will be obligated to do so and any underwriter may discontinue market making at any time without notice. We cannot give any assurance as to liquidity of the trading market for our common stock.

To facilitate an offering of the common stock, certain persons participating in the offering may engage in transactions that stabilize, maintain or otherwise affect the price of our common stock. This may include over-allotments or short sales of the common stock, which involve the sale by persons participating in the offering of more shares of common stock than we sell to them. In these circumstances, these persons would cover the over-allotments or short positions by making purchases in the open market or by exercising their over-allotment option. In addition, these persons may stabilize or maintain the price of the common stock by bidding for or purchasing the common stock in the open market or by imposing penalty bids, whereby selling concessions allowed to underwriters or dealers participating in the offering may be reclaimed if the shares of common stock sold by them are repurchased in connection with stabilization transactions. The effect of these transactions may be to stabilize or maintain the market price of our common stock at a level above that which might otherwise prevail in the open market. These transactions, if commenced, may be discontinued at any time.

Any underwriters who are qualified market makers on The Nasdaq Global Market may engage in passive market making transactions in the common stock on The Nasdaq Global Market in accordance with Rule 103 of Regulation M during the business day prior to the pricing of the offering, before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; however, if all independent bids are lowered below the passive market maker's bid, the passive market maker's bid must then be lowered when certain purchase limits are exceeded.

In compliance with guidelines of the National Association of Securities Dealers, or NASD, the maximum consideration or discount to be received by any NASD member or independent broker dealer may not exceed 8% of the aggregate amount of the securities offered pursuant to this prospectus and any applicable prospectus supplement.

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Underwriters, dealers and agents may engage in other transactions with us, or perform other services for us, in the ordinary course of their business. We will describe such relationships in the applicable prospectus supplement, naming the underwriter and the nature of any such relationship.

LEGAL MATTERS

Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts, will pass upon the validity of the issuance of the common stock offered by this prospectus.

EXPERTS

The financial statements of Targacept, Inc. appearing in Targacept, Inc.'s Annual Report (Form 10-K) for the year ended December 31, 2006 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon included therein, and incorporated herein by reference. Such financial statements are, and audited financial statements to be included in subsequently filed documents will be, incorporated herein in reliance upon the reports of Ernst & Young LLP pertaining to such financial statements (to the extent covered by consents filed with the SEC) given on the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We are subject to the reporting requirements of the Exchange Act and file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy these reports, proxy statements and other information at the SEC's public reference facilities at 100 F Street, N.E., Room 1580, Washington, D.C. 20549. You can request copies of these documents by writing to the SEC and paying a fee for the copying cost. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the public reference facilities. SEC filings are also available at the SEC's website at <http://www.sec.gov>. Our common stock is listed on The Nasdaq Global Market, and you can read and inspect our filings at the offices of the National Association of Securities Dealers, Inc. at 1735 K Street, Washington, D.C. 20006.

This prospectus is only part of a registration statement on Form S-3 that we have filed with the SEC under the Securities Act and therefore omits certain information contained in the registration statement. We have also filed exhibits with the registration statement that are excluded from this prospectus, and you should refer to the applicable exhibit for a complete description of any statement referring to any contract or other document. You may inspect a copy of the registration statement, including the exhibits, without charge, at the public reference room or obtain a copy from the SEC upon payment of the fees prescribed by the SEC.

The reports, proxy statements and other information that we file with the SEC are available to you free of charge through the Investor Relations page of our website, www.targacept.com, as soon as reasonably practicable after they have been electronically filed with, or furnished to, the SEC. We have included our website address as a factual reference and do not intend it as an active link to our website.

INCORPORATION OF DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" information from other documents that we file, which means that we can disclose important information in this prospectus by referring to those documents. The information incorporated by reference is considered to be part of this prospectus and will automatically add to, update and, if applicable, supersede the information in this prospectus. We incorporate by reference into this prospectus the documents listed below:

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2006, filed on March 22, 2007;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2007, filed on May 11, 2007;
- our Current Reports on Form 8-K filed on January 16, 2007 and January 26, 2007;

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- the description of our common stock contained in our Registration Statement on Form 8-A filed on April 6, 2006; and
- all filings that we make pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of the filing of the registration statement on Form S-3 of which this prospectus is a part and prior to the termination or completion of any offering of securities under this prospectus and all applicable prospectus supplements (except, in each case, for information contained in any such filing that is furnished and not "filed" under the Exchange Act), which filings will be deemed to be incorporated by reference in this prospectus, as supplemented by the applicable prospectus supplement, and to be a part hereof from the respective dates of such filings.

The SEC file number for each of the documents listed above is 000-51173.

We will provide without charge to each person, including any beneficial owner, to whom a copy of this prospectus is delivered, upon the request of any such person, a copy of any or all of the information incorporated herein by reference (exclusive of exhibits to such documents, unless such exhibits are specifically incorporated by reference herein). Requests, whether written or oral, for such copies should be directed to Targacept, Inc., 200 East First Street, Suite 300, Winston-Salem, North Carolina 27101, Attn: Chief Financial Officer, (336) 480-2100.

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