RIGEL PHARMACEUTICALS INC
Form 424B5
May 25, 2011

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Filed Pursuant to Rule 424(b)(5)
Registration Nos. 333-171159 and 333-174480

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities is effective. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities, and we are not soliciting offers to buy these securities, in any state or other jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED MAY 25, 2011

PROSPECTUS SUPPLEMENT
(to Prospectus dated January 7, 2011)

Shares

Common Stock

We are offering shares of our common stock. Our common stock is listed on The NASDAQ Global Select Market under the symbol "RIGL." On May 24, 2011, the last reported sales price of our common stock on The NASDAQ Global Select Market was $7.95 per share.

Investing in our common stock involves a high degree of risk. Please read "Risk Factors" beginning on page S-6 of this prospectus supplement and in our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2011, which has been filed with the Securities and Exchange Commission and is incorporated by reference in this prospectus supplement and the accompanying prospectus.

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

	PER SHARE	TOTAL
Public Offering Price	$	$
Underwriting Discounts and Commissions		
Proceeds to Rigel Pharmaceuticals before expenses		

Delivery of the shares of common stock is expected to be made on or about May , 2011. We have granted the underwriters an option for a period of 30 days to purchase up to an additional shares of our common stock solely to cover overallotments. If the underwriters exercise the option in full, the underwriting discounts and commissions payable by us will be $, and the proceeds to us, before expenses, will be $.

Joint Book-Running Managers

Jefferies **J.P. Morgan**

Co-Manager

Piper Jaffray

Prospectus Supplement dated May , 2011

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You should rely only on the information contained in or incorporated by reference in this prospectus supplement, the accompanying prospectus and in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We have not, and the underwriters have not, authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus supplement or the accompanying prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We are not, and the underwriters are not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and in any free writing prospectus prepared by or on behalf of us or to which we have referred you, is accurate only as of

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the date of those respective documents, regardless of the time of delivery of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and any free writing prospectus prepared by or on behalf of us or to which we have referred you, in their entirety before making an investment decision. You should also read and consider the information in the documents we have referred you to in the sections of this prospectus supplement entitled "Where You Can Find More Information" and "Information Incorporated by Reference."

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About this Prospectus Supplement

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering of common stock and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The second part, the accompanying prospectus dated January 7, 2011, including the documents incorporated by reference therein, provides more general information, some of which may not apply to this offering. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. In this prospectus supplement, as permitted by law, we "incorporate by reference" information from other documents that we file with the Securities and Exchange Commission, or the SEC. This means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be a part of this prospectus supplement and the accompanying prospectus and should be read with the same care. When we update the information contained in documents that have been incorporated by reference by making future filings with the SEC, the information included or incorporated by reference in this prospectus supplement is considered to be automatically updated and superseded. In other words, in case of a conflict or inconsistency between information contained in this prospectus supplement and information in the accompanying prospectus or incorporated by reference into this prospectus supplement, you should rely on the information contained in the document that was filed later.

Unless otherwise indicated or the context requires otherwise, references in this prospectus supplement and the accompanying prospectus to "Rigel," "the company," "we," "us" and "our" refer to Rigel Pharmaceuticals, Inc. The name Rigel Pharmaceuticals and our logo are our trademarks. All other trademarks, trade names or service marks included or incorporated by reference in this prospectus supplement and the accompanying prospectus are the property of their respective owners.

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Prospectus Supplement Summary

This summary highlights certain information about us, this offering and selected information contained elsewhere in or incorporated by reference into this prospectus supplement. This summary is not complete and does not contain all of the information that you should consider before deciding whether to invest in our common stock. For a more complete understanding of our company and this offering, you should read and consider carefully the more detailed information in this prospectus supplement and the accompanying prospectus, including the information incorporated by reference in this prospectus supplement and the accompanying prospectus, and the information included in any free writing prospectus prepared by or on behalf of us or to which we have referred you. If you invest in our common stock, you are assuming a high degree of risk. See "Risk Factors" beginning on page S-6 and in our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2011, which is incorporated by reference in this prospectus supplement and the accompanying prospectus.

Company Overview

We are a clinical-stage drug development company that discovers and develops novel, small-molecule drugs for the treatment of inflammatory and autoimmune diseases, as well as for muscle disorders. Our pioneering research focuses on intracellular signaling pathways and related targets that are critical to disease mechanisms. Our productivity has resulted in strategic collaborations with large pharmaceutical partners to develop and market our product candidates. Current product development programs include fostamatinib, an oral syk inhibitor that has started its Phase 3 clinical trial program for rheumatoid arthritis, or RA (partnered with AstraZeneca AB, or AZ), and R343, an inhaled syk inhibitor that has competed Phase 1 clinical trials for asthma.

Product Development Programs

Our product development portfolio features multiple novel, small-molecule drug candidates whose specialized mechanisms of action are intended to provide therapeutic benefit for a range of inflammatory and autoimmune diseases, as well as for muscle disorders.

Clinical Programs

Fostamatinib (previously referred to as R788) Rheumatoid Arthritis

Disease background. RA is a systemic autoimmune inflammatory disease that causes damage to the joints and other organs, affecting approximately 1 in 100 people in the U.S. It is a major cause of disability and is also associated with reduced life expectancy, especially if it is not adequately treated. Despite current treatment options, many patients still experience significant disease activity, including continued joint destruction leading to pain and disability, therefore new treatment options are needed.

The current treatment options for RA have significant potential side effects and other shortfalls, including gastrointestinal complications and kidney damage. RA patients may receive multiple drugs depending on the extent and aggressiveness of their disease. Most RA patients eventually require some form of disease modifying anti-rheumatic drugs, or DMARDs. This category of drugs includes methotrexate and a variety of intravenously-delivered immunomodulatory agents (anti-tumor necrosis factor, or TNF, inhibitors and co-stimulation inhibitors).

Orally-available syk inhibitor program. Fostamatinib is an orally bio-available syk inhibitor. It has a novel mechanism of action for the treatment of RA in which it reversibly blocks signaling in multiple cell types involved in inflammation and tissue degradation (e.g., macrophages, osteoclasts, mast cells and B cells). RA is an autoimmune disease characterized by chronic inflammation that affects multiple tissues, but typically produces its most pronounced symptoms in the joints.

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TASKi2

In July 2009, we announced that fostamatinib produced significant clinical improvement in RA patients in the *TASKi2* Phase 2b clinical trial, which evaluated 457 RA patients for up to six months. *TASKi2* was a multi-center, randomized, double-blind, placebo-controlled, parallel-dose clinical trial involving RA patients in the U.S., Latin America and Europe who had failed to respond to methotrexate alone. Patients received either 100 mg of fostamatinib b.i.d. (twice a day), 150 mg q.d. (once a day) or placebo. The groups treated with 100 mg of fostamatinib b.i.d. and 150 mg q.d. reported higher response rates than the placebo group in all aforementioned criteria levels. The efficacy results for the two dosing groups were comparable, although the response rates for the 100 mg b.i.d. group were uniformly greater. Consistent with the previous Phase 2a clinical trial *(TASKi1)*, the onset effect of fostamatinib occurred within one week after the initiation of therapy and was maintained. The most common clinically meaningful drug-related adverse events noted in *TASKi2* were diarrhea and hypertension. Dose reduction options were pre-specified in the trial protocol and, in cases where doses were reduced, patients generally completed the clinical trial with minimal safety issues. The most common adverse events in the trial overall were related to infections, though these were generally evenly distributed among the placebo and fostamatinib groups.

Data for *TASKi2* was published in the *New England Journal of Medicine* in September 2010.

TASKi3

In July 2009, we also announced results for the *TASKi3* Phase 2b clinical trial involving 219 RA patients who had failed to respond to at least one biologic treatment. In the *TASKi3* clinical trial, patients received either 100 mg of fostamatinib b.i.d. or placebo b.i.d. for up to three months. The group treated with fostamatinib did not report significantly higher American College of Rheumatology (ACR) 20, ACR 50, ACR 70 and Disease Activity Score (DAS) 28 response rates than the placebo group at three months, and therefore, the trial failed to meet its efficacy endpoints. The objective components (C-Reactive Protein and Erythrocyte Sedimentation Rate) of these ACR scores did show a statistically significant difference; however, the subjective reported response rate components did not show a statistically significant difference as compared to placebo. Similar to *TASKi2*, the most common clinically meaningful drug-related adverse events noted in *TASKi3* were diarrhea and hypertension. Dose reduction options were pre-specified in the trial protocol and, in cases where doses were reduced, patients generally completed the clinical trial with minimal safety issues. The most common adverse events in the trial overall were related to infections, though these were generally evenly distributed among the placebo and fostamatinib groups.

OSKIRA

The OSKIRA (Oral Syk Inhibition in Rheumatoid Arthritis) Phase 3 clinical trial program is designed to investigate fostamatinib as a treatment for RA in patients with an inadequate response to DMARDs, including methotrexate, or MTX. AZ announced that the OSKIRA clinical trial program will include three pivotal Phase 3 studies assessing the efficacy and tolerability of fostamatinib: two 12-month studies examining the effect of fostamatinib on patients responding inadequately to DMARDs (including MTX), and a six-month study assessing the effect of fostamatinib on patients who have previously responded inadequately to anti-TNF therapy. In September 2010, the first patient was enrolled in the OSKIRA clinical trial program. The OSKIRA clinical trial program also includes a fourth clinical trial, which is a six-month study for the evaluation of efficacy and safety of fostamatinib monotherapy in patients who are DMARD naïve, DMARD intolerant or have inadequate response to DMARDs. The fostamatinib clinical trial program is also expected to include long-term safety extension studies involving more than 2,000 of the patients recruited during the course of the Phase 2 and 3 clinical trial programs. The first anticipated filings of new drug applications with the U.S. Food and Drug Administration, or FDA, and the European Medicines Agency, or EMA, based on the OSKIRA clinical trial program are planned for 2013.

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Fostamatinib Other Indications

In addition to RA, fostamatinib has been studied in patients with other immune disorders and some cancers. Our collaboration with AZ gives AZ sole responsibility for all development decisions for all indications except for one solid tumor oncology study, which was announced in June 2009 and is funded, designed and implemented by the National Cancer Institute, or NCI. Any decisions regarding the solid tumor oncology study are the responsibility of the NCI.

R343 Asthma

Disease background. Allergic asthma is a chronic inflammatory disorder of the airways. Asthma affects the lower respiratory tract and is marked by episodic flare-ups, or attacks, that can be life threatening. In some patients, allergens, such as pollen, trigger the production of immunoglobulin E, or IgE, antibodies, which then bind to mast cells and cause an intracellular signal that results in the release of various chemical mediators. When this process occurs repeatedly over time, it creates persistent inflammation of the airway passages, resulting in the chronic congestion and airway obstruction associated with allergic rhinitis and asthma, respectively.

Inhaled syk inhibitor program. R343 is a potent syk inhibitor that blocks IgE receptor signaling. Mast cells play important roles in both early and late phase allergic reactions, and syk inhibitors could potentially prevent both phases.

In 2005, we announced a collaborative research and license agreement with Pfizer Inc. for the development of inhaled products for the treatment of allergic asthma and other respiratory diseases, such as chronic obstructive pulmonary disease. The collaboration was focused on our pre-clinical small molecule compounds, which inhibit syk. R343 was the oral syk inhibitor small molecule at the center of this collaboration. Pfizer completed the Phase 1a clinical trial of an inhaled formulation of R343, which commenced in December 2007 and resulted in a payment of $5.0 million to us. Pfizer also completed an initial Phase 1b allergen challenge clinical trial. We recently assumed development of R343 after Pfizer returned full rights to the R343 program as a result of its decision to exit research and development in the allergy and respiratory therapeutic area, and the collaborative research and license agreement was terminated. We are evaluating the details of R343's development to date and expect to design a Phase 2 clinical trial of R343 later this year that we anticipate would be initiated in the first half of 2012.

Preclinical Programs

We have a lead candidate in our oral janus kinase 3, or Jak3, inhibitor program and expect to begin clinical studies by the end of 2011. This program is focused on the treatment of transplant rejection, but could also extend to indications including RA and psoriasis. We also have a lead candidate in our topical Jak3 program and expect to begin clinical studies for this program in 2011. This program is expected to focus on cutaneous lupus.

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Research Programs

We are conducting proprietary research in the broad disease areas of inflammation/immunology and muscle wasting/muscle endurance. Within each disease area, our researchers are investigating mechanisms of action as well as screening compounds against potential novel targets and optimizing those leads that appear to have the greatest potential.

Corporate Collaborations

We conduct research and development programs independently and in connection with our corporate collaborators. We currently have active collaborations with two major pharmaceutical/biotechnology companies: AZ, relating to fostamatinib for the treatment of RA and other indications, and Daiichi Sankyo Co., Ltd., relating to oncology. Neither of these collaborations currently provide us with regular research reimbursement. In each of these collaborations, if certain conditions are met, we are entitled to receive future payments and royalties. We cannot guarantee that these conditions will be met or that research and development efforts will be successful. As a result, we may not receive any further payments or royalties under these agreements.

Corporate Information

We were incorporated in Delaware in June 1996. Our principal executive office is located at 1180 Veterans Boulevard, South San Francisco, California 94080. Our telephone number is (650) 624-1100. Our website address is *www.rigel.com*. The information contained in, or that can be accessed through, our website is not part of, and is not incorporated into, this prospectus supplement or the accompanying prospectus and should not be considered part of this prospectus supplement or the accompanying prospectus.

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The Offering

Common stock offered by us	**shares**
Common stock to be outstanding immediately after this offering	**shares**
Overallotment Option	

We have granted the underwriters an option to purchase up to additional shares of our common stock to cover overallotments, if any. This option is exercisable, in whole or in part, for a period of 30 days from the date of this prospectus supplement.

Use of Proceeds

We intend to use the net proceeds from this offering for research and development and general corporate purposes. We may also use a portion of the net proceeds to acquire or invest in businesses, products and technologies that are complementary to our own, although we currently are not planning or negotiating any such transactions. See "Use of Proceeds" on page S-11 of this prospectus supplement.

NASDAQ Global Select Market Listing

Our common stock is listed on The NASDAQ Global Select Market under the symbol "RIGL."

Risk Factors

An investment in our common stock involves a high degree of risk. See "Risk Factors" beginning on page S-6 and in our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2011, which is incorporated by reference in this prospectus supplement and the accompanying prospectus.

Outstanding Shares

The number of shares of our common stock to be outstanding immediately after this offering is based on 52,279,117 shares outstanding as of March 31, 2011 and excludes:

- 11,798,487 shares of our common stock issuable upon the exercise of stock options outstanding as of March 31, 2011, having a weighted-average exercise price of approximately $12.06 per share;
- 200,000 shares of our common stock issuable upon the exercise of a warrant outstanding as of March 31, 2011, having an exercise price of $6.61 per share; and
- an aggregate of 1,400,988 shares of our common stock available for issuance or future grant as of March 31, 2011 under our 2000 Equity Incentive Plan, or the 2000 Plan, our 2000 Employee Stock Purchase Plan, or the ESPP, and our 2000 Non-Employee Directors' Stock Option Plan, or the Directors' Plan.

On May 19, 2011, our stockholders approved the 2011 Equity Incentive Plan, or the 2011 Plan, under which 3,500,000 shares of our common stock were reserved for issuance as of such date, and also approved amendments to each of the 2000 Plan and the Directors' Plan to increase the number of shares authorized for issuance under such plans by 600,000 shares and 250,000 shares, respectively.

Except as otherwise indicated, all information in the prospectus supplement assumes no exercise by the underwriters of their overallotment option.

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Risk Factors

An investment 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 described below and discussed under the section captioned "Risk Factors" contained in our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2011, which are incorporated by reference in this prospectus supplement and the accompanying prospectus in their entirety, together with the other information in this prospectus supplement, the accompanying prospectus, the information and documents incorporated by reference, and in any free writing prospectus prepared by or on behalf of us or to which we have referred you. If any of these risks actually occur, our business, financial condition, results of operations or cash flows 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.

Risks Related to this Offering and our Common Stock

Our stock price may be volatile, and your investment in our common stock could decline in value.

The market prices for our common stock and the securities of other biotechnology companies have been highly volatile and may continue to be highly volatile in the future. If the market price of our common stock declines, the per share value of the common stock you purchase will decline. The following factors, in addition to other risk factors described in this section, may have a significant impact on the market price of our common stock:

- the progress and success of clinical trials and preclinical activities (including studies and manufacture of materials) of our product candidates conducted by us or our collaborative partners or licensees;
- the receipt or failure to receive the additional funding necessary to conduct our business;
- selling by large stockholders;
- presentations of detailed clinical trial data at medical and scientific conferences and investor perception thereof;
- changes in analysts' recommendations or projections;
- announcements of technological innovations or new commercial products by our competitors or us;
- developments concerning proprietary rights, including patents;
- developments concerning our collaborations;
- publicity regarding actual or potential medical results relating to products under development by our competitors or us;
- regulatory developments in the United States and foreign countries;
- litigation;

economic and other external factors or other disaster or crisis; and

period-to-period fluctuations in financial results.

The market price of our common stock may fluctuate significantly in the future and these fluctuations may be unrelated to our performance. General market price declines or market volatility in the future could adversely affect the price of our common stock, and the current market price of our common stock may not be indicative of future market prices.

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We will continue to need additional capital following this offering to sufficiently fund our operations and research.

We have consumed substantial amounts of capital to date as we continue our research and development activities, including preclinical studies and clinical trials. In February 2010, we entered into an exclusive worldwide license agreement with AZ for the global development and commercialization of our oral syk inhibitors for the treatment of human diseases other than those primarily involving respiratory or pulmonary dysfunction. The agreement includes a license of rights to fostamatinib, our late-stage investigational product candidate for the treatment of RA and other indications. The agreement became effective on March 26, 2010 and, in connection with the effectiveness of the agreement, we received an upfront payment of $100.0 million in April 2010 from AZ. In October 2010, we received $25.0 million from AZ for completing the transfer of the fostamatinib long-term open label extension study to AZ and for the initiation of Phase 3 in the fostamatinib program by AZ. AZ is required to pay us up to an additional $320.0 million if specified development, regulatory and launch events are achieved for fostamatinib. We are also eligible to receive up to an additional $800.0 million if specified sales levels are achieved for fostamatinib, as well as significant stepped double-digit royalties on net sales worldwide. Our collaborative research and license agreement with Pfizer recently terminated, and we are no longer entitled to any milestone or royalty payments from Pfizer. We believe that the net proceeds from this offering, together with our existing capital resources and the anticipated proceeds from our current collaborations, will be sufficient to support our current and projected funding requirements into 2014. We may need additional funds in the future and the amount of future funds needed will depend largely on the success of our internally developed programs as they proceed in later and more expensive clinical trials. Unless and until we are able to generate a sufficient amount of product and royalty revenue, we expect to finance future cash needs through public and/or private offerings of equity securities, debt financings or collaboration and licensing arrangements, as well as through interest income earned on the investment of our cash balances and short-term investments. With the exception of contingent and royalty payments that we may receive under our existing collaborations, we do not currently have any commitments for future funding. We do not know whether additional financing will be available when needed, or that, if available, we will obtain financing on reasonable terms.

To the extent we raise additional capital by issuing equity securities in the future, you could at that time experience substantial dilution. Any debt financing that we are able to obtain may involve operating covenants that restrict our business. To the extent that we raise additional funds through any new collaboration and licensing arrangements, we may be required to relinquish some rights to our technologies or product candidates, or grant licenses on terms that are not favorable to us.

Future equity issuances or a sale of a substantial number of shares of our common stock may cause the price of our common stock to decline.

Because we will continue to need additional capital following this offering to continue to expand our business and our research and development activities, among other things, we may conduct additional equity offerings. If we or our stockholders sell substantial amounts of our common stock (including shares issued upon the exercise of options and warrants) in the public market, the market price of our common stock could fall. A decline in the market price of our common stock could make it more difficult for us to sell equity or equity-related securities in the future at a time and price that we deem appropriate. Furthermore, if we obtain funds through a credit facility or through the issuance of debt or preferred securities, these securities would likely have rights senior to your rights as a common stockholder, which could impair the value of our common stock.

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Management will have broad discretion as to the use of the proceeds from this offering, and we may not use the proceeds effectively.

We have not designated any portion of the net proceeds from this offering to be used for any particular purposes. Our management will have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. Accordingly, you will be relying on the judgment of our management with regard to the use of these net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. Our failure to apply these funds effectively could have a material adverse effect on our business, delay the development of our product candidates and cause the price of our common stock to decline.

You will experience immediate and substantial dilution in the net tangible book value per share of the common stock you purchase.

Since the price per share of our common stock being offered will be substantially higher than the net tangible book value per share of our common stock, you will suffer substantial dilution in the net tangible book value of the common stock you purchase in this offering. Our net tangible book value as of March 31, 2011 was approximately $149.3 million, or $2.86 per share. Assuming we sell 13,672,000 shares of our common stock in this offering at an assumed public offering of $7.95 per share (which was the last reported sale price of our common stock as reported on The NASDAQ Global Select Market on May 24, 2011) and based on our net tangible book value as of March 31, 2011, if you purchase shares of common stock in this offering, you would suffer immediate and substantial dilution of $4.14 per share in the net tangible book value of the common stock. See the section entitled "Dilution" below for a more detailed discussion of the dilution you would incur if you purchase common stock in this offering.

In addition, we have a significant number of stock options and warrants outstanding. To the extent that outstanding stock options or warrants have been or may be exercised or other shares issued, you may experience further dilution. Further, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. If additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to investors purchasing our common stock in this offering or result in downward pressure on the price of our common stock.

We do not intend to pay dividends in the foreseeable future.

We have never paid cash dividends on our common stock and currently do not plan to pay any cash dividends in the foreseeable future.

Anti-takeover provisions in our charter documents and under Delaware law may make an acquisition of us, which may be beneficial to our stockholders, more difficult.

Provisions of our amended and restated certificate of incorporation and bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us, even if doing so would benefit our stockholders. These provisions:

- establish that members of the board of directors may be removed only for cause upon the affirmative vote of stockholders owning a majority of our capital stock;
- authorize the issuance of "blank check" preferred stock that could be issued by our board of directors to increase the number of outstanding shares and thwart a takeover attempt;
- limit who may call a special meeting of stockholders;
- prohibit stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders;

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establish advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted upon at stockholder meetings;

provide for a board of directors with staggered terms; and

provide that the authorized number of directors may be changed only by a resolution of our board of directors.

In addition, Section 203 of the Delaware General Corporation Law, which imposes certain restrictions relating to transactions with major stockholders, may discourage, delay or prevent a third party from acquiring us.

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Disclosure Regarding Forward-Looking Statements

This prospectus supplement, the accompanying prospectus, the documents we have filed with the SEC that are incorporated herein by reference and any free writing prospectus prepared by or on behalf of us or to which we have referred you 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. These statements relate to future events or to our future operating or financial performance and are based on our current expectations, assumptions, estimates and projections about our business and our industry, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievement to be materially different from any future results, levels of activity, performance or achievements expressed or implied by the forward-looking statements. Forward-looking statements include, but are not limited to, statements about:

- our business and scientific strategies;
- the progress of our product development programs, including clinical testing, and the timing of results thereof;
- our corporate collaborations and revenues that may be received from our collaborations;
- our drug discovery technologies;
- our research and development expenses;
- protection of our intellectual property;
- sufficiency of our cash resources; and
- our operations and legal risks.

In some cases, you can identify forward-looking statements by terms such as "anticipate," "believe," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "should," "will," "would" and similar expressions intended to identify forward-looking statements. While we believe that we have a reasonable basis for each forward-looking statement, we caution you that these statements are based on a combination of facts and factors currently known by us and our projections of the future, about which we cannot be certain. We discuss many of these risks, uncertainties and other factors in greater detail under the sections captioned "Risk Factors" beginning on page S-6 of this prospectus supplement and in our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2011, which is incorporated herein by reference. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement. New factors emerge from time to time, and it is not possible for us to predict which factors will arise. In addition, we cannot assess the impact of each factor on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements.

You should read carefully this prospectus supplement, the accompanying prospectus, together with the information incorporated herein by reference as described under the heading "Information Incorporated by Reference" in this prospectus supplement, and any free writing prospectus prepared by or on behalf of us or to which we have referred you completely and with the understanding that our actual future results may be materially different from what we expect. We hereby qualify all of our forward-looking statements by these cautionary statements.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in these forward-looking statements, even if new information becomes available in the future.

Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements.

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Use of Proceeds

We estimate that the net proceeds from the sale of the shares of common stock that we are offering will be approximately $ million, or approximately $ million if the underwriters exercise in full their option to purchase additional shares of common stock, based on the public offering price of $ per share and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from this offering for research and development and general corporate purposes. We may also use a portion of the net proceeds to acquire or invest in businesses, products and technologies that are complementary to our own, although we currently are not planning or negotiating any such transactions. Pending these uses, we intend to invest our net proceeds from this offering primarily in investment grade, interest-bearing instruments. As of the date of this prospectus supplement, we cannot specify with certainty all of the particular uses for the net proceeds we will have upon completion of the offering. Accordingly, we will retain broad discretion over the use of these proceeds.

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Dilution

Our net tangible book value as of March 31, 2011 was approximately $149.3 million, or $2.86 per share. Net tangible book value per share is determined by dividing our total tangible assets, less total liabilities, by the number of shares of our common stock outstanding as of March 31, 2011. Dilution in net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the net tangible book value per share of our common stock immediately after this offering.

Assuming we sell 13,672,000 shares of our common stock in this offering at an assumed public offering price of $7.95 per share (which was the last reported sale price of our common stock as reported on The NASDAQ Global Select Market on May 24, 2011) and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of March 31, 2011 would have been approximately $251.1 million, or $3.81 per share. Assuming we sell 13,672,000 shares of our common stock in this offering, this represents an immediate increase in net tangible book value of $0.95 per share to existing stockholders and immediate dilution in net tangible book value of $4.14 per share to investors purchasing our common stock in this offering at the assumed public offering price. The following table illustrates this dilution on a per share basis:

Assumed public offering price per share		$ 7.95
Net tangible book value per share as of March 31, 2011	$ 2.86	
Increase per share attributable to investors purchasing our common stock in this offering	0.95	
As adjusted net tangible book value per share after this offering		3.81
Dilution per share to investors purchasing our common stock in this offering		$ 4.14

Each $1.00 increase (decrease) in the assumed public offering price of $7.95 per share would increase (decrease) our as adjusted net tangible book value after this offering by approximately $12.9 million, or approximately $0.19 per share, and the dilution per share to new investors by approximately $0.81 per share, assuming that the number of shares offered by us, as set forth above, remains the same and after deducting underwriting discounts and commissions and estimated offering expenses payable by us. We may also increase or decrease the number of shares we are offering from the assumed number of shares set forth above. An increase of 2,700,000 shares in the number of shares offered by us from the assumed number of shares set forth above would increase our as adjusted net tangible book value after this offering by approximately $20.2 million, or $0.14 per share, and the dilution per share to new investors would be $4.00 per share, assuming that the assumed public offering price remains the same, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us. Similarly, a decrease of 2,700,000 shares in the number of shares offered by us from the assumed number of shares set forth above would decrease our as adjusted net tangible book value after this offering by approximately $20.2 million, or $0.16 per share, and the dilution per share to new investors would be $4.30 per share, assuming that the assumed public offering price remains the same, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us. The information discussed above is illustrative only and will adjust based on the actual public offering price, the actual number of shares that we offer in this offering, and other terms of this offering determined at pricing.

If the underwriters exercise in full their option to purchase additional shares of common stock at the assumed public offering price of $7.95 per share, assuming the number of shares subject to this option is 2,050,800 shares, the as adjusted net tangible book value after this offering would be $3.92 per share, representing an increase in net tangible book value of $1.06 per share to existing stockholders and immediate dilution in net tangible book value of $4.03 per share to investors purchasing our common stock in this offering at the assumed public offering price.

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The above discussion and table are based on 52,279,117 shares outstanding as of March 31, 2011 and exclude:

- 11,798,487 shares of our common stock issuable upon the exercise of stock options outstanding as of March 31, 2011, having a weighted-average exercise price of approximately $12.06 per share;

- 200,000 shares of our common stock issuable upon the exercise of a warrant outstanding as of March 31, 2011, having an exercise price of $6.61 per share; and

- an aggregate of 1,400,988 shares of our common stock available for issuance or future grant as of March 31, 2011 under our 2000 Equity Incentive Plan, or the 2000 Plan, our 2000 Employee Stock Purchase Plan, or the ESPP, and our 2000 Non-Employee Directors' Stock Option Plan, or the Directors' Plan.

On May 19, 2011, our stockholders approved the 2011 Plan under which 3,500,000 shares of our common stock were reserved for issuance as of such date, and also approved amendments to each of the 2000 Plan and the Directors' Plan to increase the number of shares authorized for issuance under such plans by 600,000 shares and 250,000 shares, respectively.

To the extent that outstanding options or warrants are exercised or new stock awards are issued under our equity compensation plans, you will experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

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Material U.S. Federal Income and Estate Tax Consequences to Non-U.S. Holders

The following summary describes the material U.S. federal income and estate tax consequences of the acquisition, ownership and disposition of our common stock acquired in this offering by a Non-U.S. Holder (as defined below). This discussion does not address all aspects of U.S. federal income and estate taxes and does not deal with foreign, state and local consequences that may be relevant to Non-U.S. Holders in light of their particular circumstances. Special rules may apply to certain Non-U.S. Holders that are subject to special treatment under the Internal Revenue Code of 1986, as amended, or the Code, such as financial institutions, insurance companies, tax-exempt organizations, broker-dealers and traders in securities, U.S. expatriates, "controlled foreign corporations," "passive foreign investment companies," corporations that accumulate earnings to avoid U.S. federal income tax, persons that hold our common stock as part of a "straddle," "hedge," "conversion transaction," "synthetic security" or integrated investment, partnerships and other pass-through entities, and investors in such pass-through entities. Such Non-U.S. Holders are urged to consult their own tax advisors to determine the U.S. federal, state, local and other tax consequences that may be relevant to them. Furthermore, the discussion below is based upon the provisions of the Code, and Treasury regulations, rulings and judicial decisions thereunder as of the date hereof, and such authorities may be repealed, revoked or modified, perhaps retroactively, so as to result in U.S. federal income and estate tax consequences different from those discussed below. No ruling has been or will be sought from the Internal Revenue Service, or IRS, with respect to the matters discussed below, and there can be no assurance that the IRS will not take a contrary position regarding the tax consequences of the acquisition, ownership or disposition of our common stock, or that any such contrary position would not be sustained by a court. This discussion is limited to Non-U.S. Holders that purchase our common stock pursuant to this offering and hold our common stock as a capital asset within the meaning of Code Section 1221 (generally, property held for investment).

The following discussion is for general information only and is not tax advice. Persons considering the purchase of our common stock should consult their own tax advisors concerning the U.S. federal income and estate tax consequences in light of their particular situations as well as any consequences arising under the laws of any other taxing jurisdiction, including any state, local or foreign tax consequences, and those arising under any applicable tax treaty.

Except as otherwise described in the discussion of estate tax below, a "Non-U.S. Holder" is a beneficial owner of our common stock that is not a U.S. Holder or an entity treated as a partnership for U.S. tax purposes. A "U.S. Holder" means a beneficial owner of our common stock that is for U.S. federal income tax purposes (i) an individual who is a citizen or resident of the United States, (ii) a corporation or other entity treated as a corporation created or organized in or under the laws of the United States or any political subdivision thereof, (iii) an estate the income of which is subject to U.S. federal income taxation regardless of its source or (iv) a trust if it (x) is subject to the primary supervision of a court within the United States and one or more U.S. persons have the authority to control all substantial decisions of the trust or (y) has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person.

If a partnership (including any entity or arrangement treated as a partnership for U.S. federal income tax purposes) acquires our common stock, the tax treatment of a partner in the partnership will generally depend upon the status of the partner and the activities of the partnership. Persons who are partners of partnerships holding our common stock are urged to consult their tax advisors.

Distributions

Subject to the discussion below, distributions, if any, made to a Non-U.S. Holder of our common stock out of our current or accumulated earnings and profits generally will constitute dividends for U.S. tax purposes and will be subject to withholding tax at a thirty percent rate or such lower rate as may be specified by an applicable income tax treaty. To obtain a reduced rate of withholding under a treaty, a Non-U.S. Holder generally will be required to provide us with a properly-executed IRS Form W-8BEN, or other appropriate

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form, certifying the Non-U.S. Holder's entitlement to benefits under that treaty. Treasury regulations provide special rules to determine whether, for purposes of determining the applicability of a tax treaty, dividends paid to a Non-U.S. Holder that is an entity should be treated as paid to the entity or to those holding an interest in that entity. If a Non-U.S. Holder holds our common stock through a financial institution or other agent acting on the holder's behalf, the holder will be required to provide appropriate documentation to such agent. The holder's agent will then be required to provide certification to us or our paying agent, either directly or through other intermediaries.

We generally are not required to withhold tax on dividends paid to a Non-U.S. Holder that are effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States if a properly-executed IRS Form W-8ECI, stating that the dividends are so connected (and are not exempt from U.S. federal income tax on net income under a treaty as described below), is filed with us. Effectively connected dividends will be subject to U.S. federal income tax on net income, generally in the same manner and at the regular rate as if the Non-U.S. Holder were a U.S. citizen or resident alien or a domestic corporation, as the case may be, unless a specific treaty exemption applies. If the Non-U.S. Holder is eligible for the benefits of a tax treaty between the United States and the holder's country of residence, any effectively connected dividends would generally be subject to net U.S. federal income tax only if they are also attributable to a permanent establishment maintained by the holder in the United States. A corporate Non-U.S. Holder receiving effectively connected dividends may also be subject to an additional "branch profits tax", which is imposed, under certain circumstances, at a rate of thirty percent (or such lower rate as may be specified by an applicable treaty) of the corporate Non-U.S. Holder's effectively connected earnings and profits, subject to certain adjustments.

If you are eligible for a reduced rate of withholding tax pursuant to a tax treaty, you may generally obtain a refund of any excess amounts currently withheld if you timely file an appropriate claim for refund with the IRS.

To the extent distributions on our common stock, if any, exceed our current and accumulated earnings and profits, they will constitute a return of capital and will first reduce your basis in our common stock, but not below zero, and then will be treated as gain from the sale of stock.

Gain on disposition of common stock

A Non-U.S. Holder generally will not be subject to U.S. federal income tax with respect to gain realized on a sale or other disposition of our common stock unless (i) the gain is effectively connected with a trade or business of such holder in the United States and, if required by an applicable income tax treaty, attributable to a permanent establishment maintained in the United States by the Non-U.S. Holder, (ii) the Non-U.S. Holder is a nonresident alien individual and is present in the United States for 183 or more days in the taxable year of the disposition and certain other conditions are met, or (iii) we are or have been a "United States real property holding corporation" within the meaning of Code Section 897(c)(2) at any time within the shorter of the five-year period preceding such disposition or such holder's holding period. In general, we would be a United States real property holding corporation if interests in U.S. real estate comprised at least half of our business assets. We believe that we are not, and do not anticipate becoming, a United States real property holding corporation. Even if we are treated as a United States real property holding corporation, gain realized by a Non-U.S. Holder on a disposition of our common stock will not be subject to U.S. federal income tax so long as (1) the Non-U.S. Holder owned directly, indirectly and constructively, no more than five percent of our common stock at all times within the shorter of (a) the five year period preceding the disposition or (b) the holder's holding period and (2) our common stock is regularly traded on an established securities market. There can be no assurance that our common stock will continue to qualify as regularly traded on an established securities market.

If you are a Non-U.S. Holder described in (i) above, you will be required to pay tax on the net gain derived from the sale at generally applicable United States federal income tax rates, subject to an applicable

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income tax treaty providing otherwise, and corporate Non-U.S. Holders described in (i) above may be subject to the branch profits tax at a thirty percent rate or such lower rate as may be specified by an applicable income tax treaty. If you are an individual Non-U.S. Holder described in (ii) above, you will be required to pay a flat thirty percent tax (or a reduced rate under an applicable income tax treaty) on the gain derived from the sale, which gain may be offset by U.S. source capital losses if you have timely filed tax returns with respect to such losses (even though you are not considered a resident of the United States). If you are a Non-U.S. Holder described in (iii) above and an exception from U.S. federal income tax does not apply (e.g., because our common stock does not qualify as regularly traded on an established securities market or, if it does so qualify, you own more than five percent of our common stock during the relevant period), any gain derived from the sale may be treated as effectively connected with a trade or business in the United States, taxable in the manner described in (i) above.

Information reporting and backup withholding

Generally, we must report to the IRS the amount of dividends paid, the name and address of the recipient, and the amount, if any, of tax withheld. A similar report is sent to the holder. Pursuant to tax treaties or certain other agreements, the IRS may make its reports available to tax authorities in the recipient's country of residence. Backup withholding will generally not apply to payments of dividends made by us or our paying agents to a Non-U.S. Holder if the holder has provided its federal taxpayer identification number, if any, or the required certification that it is not a U.S. person (which is generally provided by furnishing a properly-executed IRS Form W-8BEN), unless the payer otherwise has knowledge or reason to know that the payee is a U.S. person, or the Non-U.S. Holder otherwise establishes an exemption. The backup withholding rate is currently twenty-eight percent.

Under current U.S. federal income tax law, information reporting and backup withholding will apply to the proceeds of a disposition of our common stock effected by or through a U.S. office of a broker unless the disposing holder certifies as to its non-U.S. status or otherwise establishes an exemption. The certification procedures for claiming benefits under a tax treaty described in " Distributions" above will satisfy the certification requirements to avoid information reporting and backup withholding as well. Generally, U.S. information reporting and backup withholding will not apply to a payment of disposition proceeds where the transaction is effected outside the United States through a non-U.S. office of a non-U.S. broker. However, information reporting and backup withholding will apply to a payment of disposition proceeds if the broker has actual knowledge or reason to know that the holder is a U.S. person.

Backup withholding is not an additional tax. Rather, the tax liability of persons subject to backup withholding will be reduced by the amount of tax withheld. If withholding results in an overpayment of taxes, a refund may be obtained, provided that the required information is timely furnished to the IRS.

Legislation relating to foreign accounts

Legislation enacted in 2010 may impose withholding taxes on certain types of payments made to "foreign financial institutions" (as specifically defined in this legislation) and certain other non-U.S. entities (including financial intermediaries). Under this legislation, the failure to comply with additional certification, information reporting and other specified requirements could result in withholding tax being imposed on payments of dividends and sales proceeds to foreign intermediaries and certain Non-U.S. Holders. The legislation imposes a thirty percent withholding tax on dividends, or gross proceeds from the sale or other disposition of, common stock paid to a foreign financial institution or to a foreign non-financial entity, unless (i) the foreign financial institution undertakes certain diligence and reporting obligations or (ii) the foreign non-financial entity either certifies it does not have any substantial United States owners or furnishes identifying information regarding each substantial United States owner. If the payee is a foreign financial institution, it must enter into an agreement with the United States Treasury requiring, among other things, that it undertake to identify accounts held by certain United States persons or United States-owned

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foreign entities, annually report certain information about such accounts, and withhold thirty percent on payments to account holders whose actions prevent it from complying with these reporting and other requirements. The legislation applies to payments made after December 31, 2012. Prospective investors should consult their tax advisors regarding this legislation.

Federal estate tax

An individual who at the time of death is not a citizen or resident of the United States and who is treated as the owner of, or has made certain lifetime transfers of, an interest in our common stock will be required to include the value thereof in his or her taxable estate for U.S. federal estate tax purposes, and may be subject to U.S. federal estate tax unless an applicable estate tax treaty provides otherwise. The test for whether an individual is a resident of the United States for federal estate tax purposes differs from the test used for U.S. federal income tax purposes. Some individuals, therefore, may be "Non-U.S. Holders" for U.S. federal income tax purposes, but not for U.S. federal estate tax purposes, and vice versa.

THE PRECEDING DISCUSSION OF U.S. FEDERAL INCOME AND ESTATE TAX CONSIDERATIONS IS FOR GENERAL INFORMATION ONLY. IT IS NOT TAX ADVICE. EACH PROSPECTIVE INVESTOR SHOULD CONSULT ITS OWN TAX ADVISOR REGARDING THE TAX CONSEQUENCES OF PURCHASING, HOLDING AND DISPOSING OF OUR COMMON STOCK, INCLUDING THE CONSEQUENCES OF ANY PROPOSED CHANGE IN APPLICABLE LAW.

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Underwriting

Subject to the terms and conditions set forth in the underwriting agreement dated May , 2011, among us and the underwriters named below, we have agreed to sell to the underwriters and the underwriters have severally agreed to purchase from us the number of shares of common stock indicated in the table below:

Underwriter	Number of Shares
Jefferies & Company, Inc.	
J.P. Morgan Securities LLC	
Piper Jaffray & Co.	