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SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM S-3

REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

RXi PHARMACEUTICALS CORPORATION

(Exact name of registrant as specified in its charter)

Delaware

*(State or other jurisdiction
of incorporation or organization)*

20-8099512

*(I.R.S. Employer
Identification Number)*

60 Prescott Street
Worcester, MA 01605
(508) 767-3861

(Address, including zip code, and telephone number, including area code, of principal executive offices)

Noah D. Beerman
President and Chief Executive Officer
RXi Pharmaceuticals Corporation
60 Prescott Street
Worcester, MA 01605
(508) 767-3861

*(Name, address, including zip code, and telephone
number, including area code, of agent for service)*

Please send copies of all communications to:

Marc A. Rubenstein, Esq.
Ropes & Gray LLP
One International Place
Boston, Massachusetts 02110
(617) 951-7000

Approximate date of commencement of proposed sale to the public: From time to time after the effectiveness of the Registration Statement.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box:

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box:

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of “large accelerated filer,” “accelerated filer” and “smaller reporting company” in Rule 12b-2 of the Exchange Act.

Large accelerated filer Accelerated filer Non-accelerated filer Smaller reporting company
 (Do not check if a smaller reporting company)

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Amount to be Registered	Proposed Maximum Offering Price Per Share	Proposed Maximum Aggregate Offering Price	Amount of Registration Fee
Common Stock, \$.0001 par value per share (3)				
Preferred Stock (4)				
Warrants (5)				
Debt securities (6)	N/A	N/A	\$75,000,000(1)	\$5,347.50(2)

- (1) In no event will the aggregate offering price of all securities issued from time to time by the registrant under this registration statement exceed \$75,000,000 or its equivalent in any other currency, currency units, or composite currency or currencies. The securities covered by this registration statement may be sold separately, together, or as units with other securities registered under this registration statement.
- (2) The proposed maximum aggregate price of the securities has been estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(o) under the Securities Act.
- (3) Subject to note (1), the securities being registered in this registration statement consist of such an indeterminate amount of common stock (with accompanying purchase rights, if any), as may be sold, from time to time, at indeterminate prices, by the registrant.
- (4) Subject to note (1), the securities being registered in this registration statement consist of such an indeterminate number of shares of preferred stock (with accompanying purchase rights, if any) as may be sold from time to time at indeterminate prices by the registrant. In addition, the securities being registered in this registration statement also consist of such an indeterminate amount of common stock (with accompanying purchase rights, if any,) (i) as may be issuable or deliverable upon conversion of shares of preferred stock, and (ii) as may be required for delivery upon conversion of shares of preferred stock as a result of anti-dilution provisions.
- (5) Subject to note (1), the securities being registered in this registration statement consist of such an indeterminate amount and number of warrants, representing rights to purchase common stock, preferred stock and debt securities registered under this registration statement as may be sold from time to time at indeterminate prices by the registrant. In addition, the securities being registered in this registration statement also consist of such an indeterminate amount of common stock and preferred stock (in each case, with accompanying purchase rights, if any) and debt securities (i) as may be issuable or deliverable upon exercise of warrants and (ii) as may be required for delivery upon exercise of any warrants as a result of anti-dilution provisions.
- (6) Subject to note (1), the securities being registered in this registration statement consist of such an indeterminate amount of debt securities as may be sold from time to time at indeterminate prices by the registrant. If any debt securities are issued at an original issue discount, then the offering price shall be in such greater principal amount as shall result in an aggregate initial offering price not to exceed \$75,000,000. In addition, the securities being registered in this registration statement also consist of such an indeterminate amount of common stock and preferred stock (in each case, with accompanying purchase rights, if any) (i) as may be issuable or deliverable upon the exercise or conversion of debt securities and (ii) as may be required for delivery upon exercise or conversion of debt securities as a result of anti-dilution.

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with section 8(a) of the Securities Act of 1933 or until the registration statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said section 8(a) , may determine.

The information contained in this prospectus is not complete and may be changed. These securities may not be sold until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and is not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

PROSPECTUS

SUBJECT TO COMPLETION
Dated May 21, 2010

RXI PHARMACEUTICALS CORPORATION



\$75,000,000
Common Stock
Preferred Stock
Warrants
Debt Securities

We may offer to the public from time to time in one or more series or issuances:

- shares of our common stock;
- shares of preferred stock;
- warrants to purchase shares of our common stock, preferred stock and/or debt securities; or
- debt securities consisting of debentures, notes or other evidences of indebtedness.

This prospectus provides a general description of the securities we may offer. Each time we sell securities, we will provide specific terms of the securities offered in a supplement to this prospectus. Such a prospectus supplement may also add, update or change information contained in this prospectus. This prospectus may not be used to consummate a sale of securities unless accompanied by the applicable prospectus supplement. You should read both this prospectus and the applicable prospectus supplement together with additional information described under the heading “Where You Can Find More Information” before you make your investment decision.

We will sell the securities directly to our stockholders or to purchasers or through agents on our behalf or through underwriters or dealers as designated from time to time. If any agents or underwriters are involved in the sale of any of the securities, the applicable prospectus supplement will provide the names of the agents or underwriters and any applicable fees, commissions or discounts.

General Information

Our common stock is traded on the Nasdaq Capital Market under the symbol “RXII.” On May 19, 2010, the closing price of our common stock was \$4.17.

As of March 22, 2010, the aggregate market value of our outstanding common stock held by non-affiliates was approximately \$84,447,354 based on 16,241,125 shares of outstanding common stock, of which approximately 10,412,744 shares are held by non-affiliates, and a per share price of \$8.11 based on the closing sale price of our common stock on March 22, 2010.

Investing in our securities involves risks. Please see “Risk Factors” on page 5 and other information included and incorporated by reference in this prospectus, and in any applicable prospectus supplement, for a discussion of the factors you should consider carefully before deciding to purchase our securities .

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 May , 2010

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ABOUT THIS PROSPECTUS

The securities described in this prospectus are part of a registration statement that we filed with the Securities and Exchange Commission (the “SEC”) using a “shelf” registration process. Under this shelf registration process, we may offer to sell any combination of the securities described in this prospectus in one or more offerings up to a total dollar amount of \$75,000,000. This prospectus provides you with a general description of the securities we may offer. Each time we sell securities under this shelf registration, we will provide a prospectus supplement that will contain specific information about the terms of such offering. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and any applicable prospectus supplement, including all documents incorporated herein by reference, together with additional information described under “Where You Can Find More Information” below.

We have not authorized any dealer, agent or other person to give any information or to make any representation other than those contained or incorporated by reference in this prospectus and any accompanying prospectus supplement. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus or an accompanying prospectus supplement. This prospectus and the accompanying prospectus supplement, if any, do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor do this prospectus and any accompanying prospectus supplement constitute an offer to sell or the solicitation of an offer to buy securities 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 and any accompanying prospectus supplement 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 and any accompanying prospectus supplement is delivered or securities are sold on a later date.

Unless the context otherwise requires, “RXi,” the “Company,” “we,” “us,” “our” and similar names refer to RXi Pharmaceuticals Corporation.

THE COMPANY

Our Business

We were incorporated as Argonaut Pharmaceuticals, Inc. in Delaware on April 3, 2006, changed our name to RXi Pharmaceuticals Corporation on November 28, 2006, and began operations in January 2007. We are a discovery-stage biopharmaceutical company pursuing proprietary therapeutics based on RNA interference, or “RNAi”, a naturally occurring cellular mechanism that has the potential to effectively and selectively interfere with, or “silence”, expression of targeted disease-associated genes. It is believed that this specific silencing can be used to potentially treat human diseases by “turning off” genes that lead to disease. While no therapeutic RNAi products have yet been approved, there has been significant growth in the field of RNAi development and potential therapeutic applications in this field. This growth is driven by the potential ability to use RNAi to rapidly develop lead compounds that specifically and selectively inhibit a target gene, many of which are undruggable by other modalities.

By utilizing our expertise in RNAi and the comprehensive RNAi therapeutic platform that we have established, we believe we will be able to discover and develop lead compounds and progress them into and through clinical development for potential commercialization more efficiently than traditional drug development approaches.

Our proprietary therapeutic platform is comprised of two main components:

- **Novel RNAi Compounds**, referred to as rxRNA™ compounds, that are distinct from, and we believe convey significant advantages over classic siRNA (conventionally-designed “small interfering RNA” compounds), and offer many of the properties that we believe are important to the clinical development of RNAi-based drugs. We have developed a number of unique forms of rxRNA compounds, all of which have been shown to be highly potent both *in vitro* and *in vivo*. These RNAi compounds include rxRNA *ori*™, rxRNA *solo*™ and *sd*-rxRNA™, or “self delivering” RNA. Based on our research we believe that these different, novel siRNA configurations have various advantages for therapeutic use. These advantages include high potency, increased resistance to nucleases and off-target effects, and, in the case of the *sd*-rxRNA compounds, access to cells and tissues with no additional formulation required.
- **Advanced Delivery Technologies**, may enable the delivery of our rxRNA compounds to treat a variety of acute and chronic diseases using both local and systemic approaches, potentially providing a competitive advantage in the development of many RNAi therapeutic compounds. RXi’s suite of delivery technologies is comprised of delivery vehicles, which can be combined with various rxRNA compounds, as well as *sd*-rxRNA compounds, which are chemically modified and have the unique property of entering cells and tissues to effect silencing without the need for any additional delivery vehicle. This suite of delivery technologies has broad applications for multiple therapeutic areas targeting both local and systemic applications.
- **Local Applications.** An area of application of the RXi therapeutic platform which uses rxRNA compounds to target genes expressed in tissues that can be silenced by direct, local delivery. The numerous diseases common to tissues accessible by local delivery represent significant unmet medical needs and large market opportunities. Most of our initial targets are validated gene targets relevant in important biological pathways and are implicated in multiple diseases enabling us to leverage these targets and associated compounds across a broad array of therapeutic areas.
- **Systemic Applications.** RXi has active internal efforts to advance the therapeutic platform to optimize robust systemic delivery to various tissues and organs of the body. In some cases, such as in targeting a treatment to the liver, the optimal route of administration is by systemic delivery. Efforts to improve the systemic delivery of RNAi compounds are currently ongoing, and these efforts are supported by internal activities targeting an undisclosed gene thought to be responsible for elevated cholesterol. We have also in-licensed intellectual property developed by Dr. Michael Czech (one of our scientific co-founders and scientific advisory board members) on genes that appear to be important regulators of metabolism, and continue to develop and validate this approach with these other potential target genes.

We intend to use our RNAi therapeutic platform and our expertise in RNAi to identify lead compounds against multiple target genes, and advance them towards pre-clinical and clinical development in therapeutic areas that address broad unmet medical needs, in both acute and chronic settings. There are many well-studied genes that have been associated with numerous diseases but have been difficult to target with conventional medicinal chemistry or traditional modalities involving both large and small molecules. We believe RNAi technology may play an important role in targeting these genes and potentially treating the related diseases and disorders. We plan on pursuing disease areas with the goal of creating multiple clinical development program opportunities, either through independent internal efforts at the company or in conjunction with partners through various collaborations and partnerships with pharmaceutical or biotechnology companies.

We believe that we have created and established a strong intellectual property portfolio. We have secured exclusive and nonexclusive licenses from both academic institutions and commercial entities to certain issued and pending patents and patent applications covering RNAi technologies in the following three categories: (i) therapeutic targets, (ii) chemistry and configurations of RNAi compounds and (iii) formulation and delivery of RNAi compounds within the body. We have also filed patents based on our internal discoveries in the each of the areas mentioned above, which enables us to further strengthen our broad intellectual property portfolio.

Our founding scientists recognized that the key to therapeutic success with RNAi lies in delivering intact RNAi compounds to the target tissue and the interior of the target cells. To accomplish this, we are developing a comprehensive platform that includes local, systemic and oral delivery approaches that give rise to target silencing after RNAi compound administration. We work with chemically synthesized RNAi compounds that we believe are optimized for stability and efficacy. We endow these compounds with favorable delivery profiles and properties either by covalent chemical modification or combination with appropriate formulations to achieve optimal delivery to specific target tissues.

Local Delivery

The local delivery method may avoid some hurdles associated with systemic approaches such as rapid clearance from the bloodstream and inefficient extravasation (e.g. crossing the endothelial barrier from the blood stream). The *sd*-rxRNA molecules have unique properties which improve tissue uptake in local delivery models. We have studied *sd*-rxRNA molecules in a rat model of dermal delivery. Direct application of *sd*-rxRNA with no additional delivery vehicle to compromised skin (incision introduced) demonstrates that target gene silencing can be measured after topical delivery. We have also injected *sd*-rxRNA to the skin layers and observed efficient uptake and target gene silencing. The dose levels required for these direct injection methods are small and suitable for clinical development suggesting that local delivery indications will be very accessible with the *sd*-rxRNA technology platform. Target tissues that are potentially accessible for local delivery using rxRNA compounds include lung, eye, skin, CNS, mucosal tissues, sites of inflammation, and tumors (locally).

Systemic Delivery

Systemic delivery occurs when a drug accesses the tissue of interest through the circulatory system. In some cases, such as in targeting a treatment to the liver, the optimal route of delivery may be by a systemic route. We have a portfolio of systemic delivery solutions utilizing our RNAi therapeutic platforms. One novel approach involves the use of *sd*-rxRNA compounds. The self-delivering technology introduces properties required for *in vivo* efficacy such as cell and tissue penetration and improved blood clearance and distribution properties. Systemic delivery of these compounds to mice has resulted in gene specific inhibition at 50 mg/kg doses with no additional delivery vehicle required. In addition, we have developed novel nanotransporter formulations to aid in transport of RNAi compounds to both liver and various other target tissues in the body. These nanotransporters are chemically synthesized molecules that form nanometer-sized particles when mixed with RNAi compounds and alter the clearance, distribution and tissue penetration properties of the RNAi compounds. Delivery of RNAi compounds to the liver might be critical for the treatment of many diseases and using rxRNA in conjunction with such delivery vehicles has enabled us to demonstrate gene specific inhibition at low doses (1 mg/kg) in a mouse model after intravenous, systemic delivery. Target tissues that are potentially accessible using rxRNA compounds by systemic

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delivery approach include liver, lung, adipocytes, cardiomyocytes, bone marrow, sites of inflammation, tumors, vascular endothelium, and kidney.

Oral Delivery

Most RNAi therapeutic products being developed today require recurring intravenous injections or other forms of administration which are not patient friendly. To address the desire for RNAi therapeutics with improved modes of administration, we are testing a novel formulation technology, Glucan Encapsulated RNAi Particles (GeRPs) that may allow our rxRNA compounds to be incorporated into orally administered pills. In research to date, the GeRP delivery system appears to be 5 to 250 times more potent than previous methods used for systemic delivery of RNAi therapeutics by intravenous injection. The GeRP system is very flexible and can either be used to administer a single RNAi compound, multiple RNAi compounds, or could potentially allow co-delivery of RNAi, DNA, protein and small molecule combinations.

Therapeutic Programs and Markets

By utilizing our expertise in RNAi compound design and delivery, we intend to identify lead compounds to both tractable and intractable targets implicated in diseases that address broad unmet medical needs in both acute and chronic settings. The broad applicability of our RNAi therapeutic platform has the potential to enable delivery to various tissues in both a local setting as well as in a systemic setting. Target tissues that are potentially accessible using our rxRNA compounds in the context of a local delivery approach include lung, eye, skin, CNS, mucosal, sites of inflammation, and tumors (locally). Similarly, target tissues that are potentially accessible using our rxRNA compounds in the context of a systemic delivery approach include liver, lung, adipocytes, cardiomyocytes, bone marrow, sites of inflammation, tumors, vascular endothelium, and kidney. We will continue to focus our efforts selecting targets to prosecute internally, and as we identify relevant compounds, we intend to begin preclinical development in specific areas as appropriate.

Corporate Information

Our principal executive offices are located at 60 Prescott Street, Worcester, MA 01605, and our phone number is (508) 767-3861.

RISK FACTORS

Investing in our securities involves risk. You should consider the risks, uncertainties and assumptions discussed under the heading “Risk Factors” in our Annual Report on Form 10-K for the fiscal year ended December 31, 2009 filed on March 31, 2010 with the SEC, which is incorporated herein by reference, and may be amended, supplemented or superseded from time to time by other reports we file with the SEC in the future. 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. If any of these risks were to occur, our business, financial condition, and results of operations could be severely harmed. This could cause the trading price of our common stock to decline, and you could lose all or part of your investment.

In addition, any prospectus supplement applicable to each offering of our securities will contain a discussion of the risks applicable to such an investment in us. Prior to making a decision about investing in our securities, you should carefully consider the specific factors discussed under the heading “Risk Factors” in the applicable prospectus supplement, together with all of the other information contained or incorporated by reference in such prospectus supplement or appearing or incorporated by reference in this prospectus.

FORWARD-LOOKING STATEMENTS

This prospectus, any prospectus supplement and the other documents we have filed with the SEC that are incorporated herein by reference contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 that involve risks and uncertainties, as well as assumptions that, if they never materialize or prove incorrect, could cause the results of RXi to differ materially from those expressed or implied by such forward-looking statements. All statements other than statements of historical fact are statements that could be deemed forward-looking statements, including any projections of financing needs, revenue, expenses, earnings or losses from operations, or other financial items; any statements of the plans, strategies and objectives of management for future operations; any statements concerning product research, development and commercialization plans and timelines; any statements regarding safety and efficacy of product candidates; any statements of expectation or belief; and any statements of assumptions underlying any of the foregoing. In addition, forward-looking statements may contain the words “believe,” “anticipate,” “expect,” “estimate,” “intend,” “plan,” “project,” “will be,” “will continue,” “will result,” “seek,” “could,” “may,” “might,” or any variations of such words or other words with similar meanings.

Given these uncertainties, you should not place undue reliance on these forward-looking statements. You should read this prospectus, any supplements to this prospectus and the documents that we reference in this prospectus with the understanding that our actual future results may be materially different from what we expect. Except as required by law, we do not undertake any obligation to update or revise any forward-looking statements contained in this prospectus and any supplements to this prospectus, whether as a result of new information, future events or otherwise.

USE OF PROCEEDS

Except as otherwise provided in the applicable prospectus supplement, we intend to use the net proceeds from the sale of the securities covered by this prospectus for general corporate purposes, which may include working capital, capital expenditures, research and development expenditures, clinical trial expenditures, commercial expenditures, acquisitions of new technologies or businesses, and investments. Additional information on the use of net proceeds from the sale of securities covered by this prospectus may be set forth in any prospectus supplement relating to a specific offering.

PLAN OF DISTRIBUTION

We may sell the securities in any of the ways described below or in any combination:

- to or through underwriters or dealers;
- through one or more agents; or
- directly to purchasers or to a single purchaser.

The distribution of the securities may be effected from time to time in one or more transactions:

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

Each prospectus supplement will describe the method of distribution of the securities and any applicable restrictions.

Any prospectus supplement with respect to the securities of a particular series will describe the terms of the offering of the securities, including the following:

- the name or names of any underwriters, dealers or agents and the amounts of securities underwritten or purchased by each of them;
- the public offering price of the securities and the proceeds to us and any discounts, commissions or concessions allowed or reallocated or paid to dealers; and
- any securities exchanges on which the securities may be listed.

Any offering price and any discounts or concessions allowed or reallocated or paid to dealers may be changed from time to time. Under no circumstances will any fees, discounts, commissions or concessions received by any FINRA member or independent broker-dealer exceed eight percent of the gross proceeds to us in any offering in the United States of the securities covered by the prospectus.

Only the agents or underwriters named in each prospectus supplement are agents or underwriters in connection with the securities being offered thereby.

We may authorize underwriters, dealers or other persons acting as our agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in each applicable prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor more than, the respective amounts stated in each applicable prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutions, but shall in all cases be subject to our approval. Delayed delivery contracts will be subject only to those conditions set forth in each applicable prospectus supplement, and each prospectus supplement will set forth any commissions we pay for solicitation of these contracts.

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Agents, underwriters and other third parties described above may be entitled to indemnification by us against certain civil liabilities, including liabilities under the Securities Act of 1933, or to contribution from us with respect to payments which the agents, underwriters or other third parties may be required to make in respect thereof. Agents, underwriters and such other third parties may be customers of, engage in transactions with, or perform services for us in the ordinary course of business.

One or more firms, referred to as “remarketing firms,” may also offer or sell the securities, if a prospectus supplement so indicates, in connection with a remarketing arrangement upon their purchase. Remarketing firms will act as principals for their own accounts or as our agents. These remarketing firms will offer or sell the securities in accordance with the terms of the securities. Each prospectus supplement will identify and describe any remarketing firm and the terms of its agreement, if any, with us and will describe the remarketing firm’s compensation. Remarketing firms may be deemed to be underwriters in connection with the securities they remarket. Remarketing firms may be entitled under agreements that may be entered into with us to indemnification by us against certain civil liabilities, including liabilities under the Securities Act of 1933, and may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

Certain underwriters may use this prospectus and any accompanying prospectus supplement for offers and sales related to market-making transactions in the securities. These underwriters may act as principal or agent in these transactions, and the sales will be made at prices related to prevailing market prices at the time of sale.

The securities may be new issues of securities and may have no established trading market. The securities may or may not be listed on a securities exchange. Underwriters may make a market in these securities, but will not be obligated to do so and may discontinue any market making at any time without notice. We can make no assurance as to the liquidity of, or the existence of trading markets for, any of the securities.

Certain persons participating in an offering may engage in overallotment, stabilizing transactions, short covering transactions and penalty bids in accordance with rules and regulations under the Securities Exchange Act of 1934. Overallotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Short covering transactions involve purchases of the securities in the open market after the distribution is completed to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a short covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

DESCRIPTION OF COMMON STOCK

The following summary of the terms of our common stock is subject to and qualified in its entirety by reference to our charter and by-laws, copies of which are on file with the SEC as exhibits to previous SEC filings. Please refer to “Where You Can Find More Information” below for directions on obtaining these documents.

As of May 21, 2010, we are authorized to issue 50,000,000 shares of common stock. As of May 21, 2010, we had 18,372,759 shares of common stock outstanding.

General

The holders of our common stock are entitled to one vote for each share on all matters voted on by stockholders, including elections of directors, and, except as otherwise required by law or provided in any resolution adopted by our board with respect to any series of preferred stock, the holders of such shares possess all voting power. Our certificate of incorporation does not provide for cumulative voting in the election of directors. Subject to any preferential rights of any outstanding series of our preferred stock created by our board from time to time, the holders of common stock are entitled to such dividends as may be declared from time to time by our board from funds available therefore and upon liquidation are entitled to receive pro rata all assets available for distribution to such holders.

The holders of our common stock, other than CytRx Corporation (“CytRx”), have no preemptive rights. The rights, preferences and privileges of 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 which we may designate and issue in the future. Under our agreement with CytRx, with some exceptions, CytRx has preemptive rights to acquire a portion of any new securities sold or issued by us so as to maintain their percentage beneficial ownership of us at the time of such sale or issuance.

The holders of our common stock, other than CytRx, have no redemption rights. Pursuant to a stock redemption agreement dated March 22, 2010 between us and CytRx, we are required to use 25% of the proceeds from the exercise of certain warrants that we issued in a March 2010 registered direct offering to repurchase from CytRx a number of shares of common stock held by CytRx equal to 25% of shares issued upon the exercise of such warrants. We issued warrants to purchase an aggregate of 540,000 shares of our common stock in the March 2010 registered direct offering. We estimate that we will be required to redeem 135,000 shares of common stock from CytRx for an aggregate price of \$810,000 if all of the warrants issued in the March 2010 registered direct offering are exercised.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A.

Nasdaq Capital Market

Our common stock is listed for quotation on the Nasdaq Capital Market under the symbol “RXII.”

DESCRIPTION OF PREFERRED STOCK

We are authorized to issue up to 5,000,000 shares of preferred stock, par value \$0.0001 per share. Our board of directors, without further action by the holders of our common stock, may issue shares of our preferred stock. Our board is vested with the authority to fix by resolution the designations, preferences and relative, participating, optional or other special rights, and such qualifications, limitations or restrictions thereof, including, without limitation, redemption rights, dividend rights, liquidation preferences and conversion or exchange rights of any class or series of preferred stock, and to fix the number of classes or series of preferred stock, the number of shares constituting any such class or series and the voting powers for each class or series.

The authority possessed by our board to issue preferred stock could potentially be used to discourage attempts by third parties to obtain control of RXi through a merger, tender offer, proxy contest or otherwise by making such attempts more difficult or more costly. Our board may issue preferred stock with voting rights or conversion rights that, if exercised, could adversely affect the voting power of the holders of common stock. There are no current agreements or understandings with respect to the issuance of preferred stock.

If we offer a specific class or series of preferred stock under this prospectus, we will describe the terms of the preferred stock in the prospectus supplement for such offering and will file a copy of the certificate establishing the terms of the preferred stock with the SEC. To the extent required, this description will include:

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- the title and stated value;
- the number of shares offered, the liquidation preference per share and the purchase price;
- the dividend rate(s), period(s) and/or payment date(s), or method(s) of calculation for such dividends;
- whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;
- the procedures for any auction and remarketing, if any;
- the provisions for a sinking fund, if any;
- the provisions for redemption, if applicable;
- any listing of the preferred stock on any securities exchange or market;
- whether the preferred stock will be convertible into our common stock, and, if applicable, the conversion price (or how it will be calculated) and conversion period;
- whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange price (or how it will be calculated) and exchange period;
- voting rights, if any, of the preferred stock;
- a discussion of any material U.S. federal income tax considerations applicable to the preferred stock;
- the relative ranking and preferences of the preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of the affairs of the Company; and
- any material limitations on issuance of any class or series of preferred stock ranking senior to or on a parity with the series of preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of the Company.

The preferred stock offered by this prospectus, when issued, will not have, or be subject to, any preemptive or similar rights.

Transfer Agent and Registrar

The transfer agent and registrar for any series or class of preferred stock will be set forth in each applicable prospectus supplement.

DESCRIPTION OF WARRANTS

As of May 21, 2010, we had 2,100,642 warrants outstanding to purchase shares of our common stock. We may issue warrants to purchase shares of our common stock, preferred stock and/or debt securities in one or more series together with other securities or separately, as described in each applicable prospectus supplement. Below is a description of certain general terms and provisions of the warrants that we may offer. Particular terms of the warrants will be described in the applicable warrant agreements and the applicable prospectus supplement for the warrants.

The applicable prospectus supplement will contain, where applicable, the following terms of and other information relating to the warrants:

- the specific designation and aggregate number of, and the price at which we will issue, the warrants;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;

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- the designation, amount and terms of the securities purchasable upon exercise of the warrants;
- if applicable, the exercise price for shares of our common stock and the number of shares of common stock to be received upon exercise of the warrants;
- if applicable, the exercise price for shares of our preferred stock, the number of shares of preferred stock to be received upon exercise, and a description of that class or series of our preferred stock;
- if applicable, the exercise price for our debt securities, the amount of our debt securities to be received upon exercise, and a description of that series of debt securities;
- the date on which the right to exercise the warrants will begin and the date on which that right will expire or, if the warrants may not be continuously exercised throughout that period, the specific date or dates on which the warrants may be exercised;
- whether the warrants will be issued in fully registered form or bearer form, in definitive or global form or in any combination of these forms, although, in any case, the form of a warrant included in a unit will correspond to the form of the unit and of any security included in that unit;
- any applicable material U.S. federal income tax consequences;
- the identity of the warrant agent for the warrants and of any other depositaries, execution or paying agents, transfer agents, registrars or other agents;
- the proposed listing, if any, of the warrants or any securities purchasable upon exercise of the warrants on any securities exchange;
- if applicable, the date from and after which the warrants and the common stock, preferred stock and/or debt securities will be separately transferable;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- information with respect to book-entry procedures, if any;
- the anti-dilution provisions of the warrants, if any;
- any redemption or call provisions;
- whether the warrants are to be sold separately or with other securities as parts of units; and
- any additional terms of the warrants, including terms, procedures and limitations relating to the exchange and exercise of the warrants.

Transfer Agent and Registrar

The transfer agent and registrar for any warrants will be set forth in the applicable prospectus supplement.

DESCRIPTION OF DEBT SECURITIES

We will issue the debt securities offered by this prospectus and any accompanying prospectus supplement under an indenture to be entered into between us and the trustee identified in the applicable prospectus supplement. The terms of the debt securities will include those stated in the indenture and those made part of the indenture by reference to the Trust Indenture Act of 1939, as in effect on the date of the indenture. We have previously filed a copy of the form of indenture as an exhibit to a previous SEC filing. Please refer to “Where You Can Find More Information” below for directions on obtaining this document. The indenture will be subject to and governed by the terms of the Trust Indenture Act of 1939.

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We may offer under this prospectus up to an aggregate principal amount of \$75,000,000 in debt securities, or if debt securities are issued at a discount, or in a foreign currency, foreign currency units or composite currency, the principal amount as may be sold for an initial public offering price of up to \$75,000,000. Unless otherwise specified in the applicable prospectus supplement, the debt securities will represent direct, unsecured obligations of RXi and will rank equally with all of our other unsecured indebtedness.

The following statements relating to the debt securities and the indenture are summaries, qualified in their entirety by reference to the detailed provisions of the indenture.

General

We may issue the debt securities in one or more series with the same or various maturities, at par, at a premium, or at a discount. We will describe the particular terms of each series of debt securities in a prospectus supplement relating to that series, which we will file with the SEC.

The prospectus supplement will set forth, to the extent required, the following terms of the debt securities in respect of which the prospectus supplement is delivered:

- the title of the series;
- the aggregate principal amount;
- the issue price or prices, expressed as a percentage of the aggregate principal amount of the debt securities;
- any limit on the aggregate principal amount;
- the date or dates on which principal is payable;
- the interest rate or rates (which may be fixed or variable) or, if applicable, the method used to determine such rate or rates;
- the date or dates from which interest, if any, will be payable and any regular record date for the interest payable;
- the place or places where principal and, if applicable, premium and interest, is payable;
- the terms and conditions upon which we may, or the holders may require us to, redeem or repurchase the debt securities;
- the denominations in which such debt securities may be issuable, if other than denominations of \$1,000 or any integral multiple of that number;
- whether the debt securities are to be issuable in the form of certificated securities (as described below) or global securities (as described below);
- the portion of principal amount that will be payable upon declaration of acceleration of the maturity date if other than the principal amount of the debt securities;
- the currency of denomination;
- the designation of the currency, currencies or currency units in which payment of principal and, if applicable, premium and interest, will be made;
- if payments of principal and, if applicable, premium or interest, on the debt securities are to be made in one or more currencies or currency units other than the currency of denomination, the manner in which the exchange rate with respect to such payments will be determined;

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- if amounts of principal and, if applicable, premium and interest may be determined by reference to an index based on a currency or currencies or by reference to a commodity, commodity index, stock exchange index or financial index, then the manner in which such amounts will be determined;
- the provisions, if any, relating to any collateral provided for such debt securities;
- any addition to or change in the covenants and/or the acceleration provisions described in this prospectus or in the indenture;
- any events of default, if not otherwise described below under “Events of Default”;
- the terms and conditions, if any, for conversion into or exchange for shares of our common stock or preferred stock;
- any depositaries, interest rate calculation agents, exchange rate calculation agents or other agents; and
- the terms and conditions, if any, upon which the debt securities shall be subordinated in right of payment to other indebtedness of the Company.

We may issue discount debt securities that provide for an amount less than the stated principal amount to be due and payable upon acceleration of the maturity of such debt securities in accordance with the terms of the indenture. We may also issue debt securities in bearer form, with or without coupons. If we issue discount debt securities or debt securities in bearer form, we will describe material U.S. federal income tax considerations and other material special considerations which apply to these debt securities in the applicable prospectus supplement.

We may issue debt securities denominated in or payable in a foreign currency or currencies or a foreign currency unit or units. If we do, we will describe the restrictions, elections, and general tax considerations relating to the debt securities and the foreign currency or currencies or foreign currency unit or units in the applicable prospectus supplement.

Exchange and/or Conversion Rights

We may issue debt securities which can be exchanged for or converted into shares of our common stock or preferred stock. If we do, we will describe the terms of exchange or conversion in the prospectus supplement relating to these debt securities.

Transfer and Exchange

We may issue debt securities that will be represented by either:

- “book-entry securities,” which means that there will be one or more global securities registered in the name of a depositary or a nominee of a depositary; or
- “certificated securities,” which means that they will be represented by a certificate issued in definitive registered form.

We will specify in the prospectus supplement applicable to a particular offering whether the debt securities offered will be book-entry or certificated securities.

Certificated Debt Securities

If you hold certificated debt securities, you may transfer or exchange such debt securities at the trustee’s office or at the paying agent’s office or agency in accordance with the terms of the indenture. You will not be charged a service charge for any transfer or exchange of certificated debt securities but may be required to pay an amount sufficient to cover any tax or other governmental charge payable in connection with such transfer or exchange.

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You may effect the transfer of certificated debt securities and of the right to receive the principal of, premium, and/or interest, if any, on the certificated debt securities only by surrendering the certificate representing the certificated debt securities and having us or the trustee issue a new certificate to the new holder.

Global Securities

If we decide to issue debt securities in the form of one or more global securities, then we will register the global securities in the name of the depository for the global securities or the nominee of the depository, and the global securities will be delivered by the trustee to the depository for credit to the accounts of the holders of beneficial interests in the debt securities.

The prospectus supplement will describe the specific terms of the depository arrangement for debt securities of a series that are issued in global form. None of RXi, the trustee, any payment agent or the security registrar will have any responsibility or liability for any aspect of the records relating to or payments made on account of beneficial ownership interests in a global debt security or for maintaining, supervising or reviewing any records relating to these beneficial ownership interests.

No Protection in the Event of Change of Control

The indenture does not have any covenants or other provisions providing for a put or increased interest or otherwise that would afford holders of our debt securities additional protection in the event of a recapitalization transaction, a change of control of RXi, or a highly leveraged transaction. If we offer any covenants or provisions of this type with respect to any debt securities covered by this prospectus, we will describe them in the applicable prospectus supplement.

Covenants

Unless otherwise indicated in this prospectus or the applicable prospectus supplement, our debt securities will not have the benefit of any covenants that limit or restrict our business or operations, the pledging of our assets or the incurrence by us of indebtedness. We will describe in the applicable prospectus supplement any material covenants in respect of a series of debt securities.

Consolidation, Merger and Sale of Assets

We have agreed in the indenture that we will not consolidate with or merge into any other person or convey, transfer, sell or lease our properties and assets substantially as an entirety to any person, unless:

- the person formed by the consolidation or into or with which we are merged or the person to which our properties and assets are conveyed, transferred, sold or leased, is a corporation organized and existing under the laws of the U.S., any state or the District of Columbia or a corporation or comparable legal entity organized under the laws of a foreign jurisdiction and, if we are not the surviving person, the surviving person has expressly assumed all of our obligations, including the payment of the principal of and, premium, if any, and interest on the debt securities and the performance of the other covenants under the indenture; and
- immediately before and immediately after giving effect to the transaction, no event of default, and no event which, after notice or lapse of time or both, would become an event of default, has occurred and is continuing under the indenture.

Events of Default

Unless otherwise specified in the applicable prospectus supplement, the following events will be events of default under the indenture with respect to debt securities of any series:

- we fail to pay any principal or premium, if any, when it becomes due;

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- we fail to pay any interest within 30 days after it becomes due;
- we fail to observe or perform any other covenant in the debt securities or the indenture for 60 days after written notice specifying the failure from the trustee or the holders of not less than 25% in aggregate principal amount of the outstanding debt securities of that series; and
- certain events involving bankruptcy, insolvency or reorganization of RXi or any of our significant subsidiaries.

The trustee may withhold notice to the holders of the debt securities of any series of any default, except in payment of principal or premium, if any, or interest on the debt securities of a series, if the trustee considers it to be in the best interest of the holders of the debt securities of that series to do so.

If an event of default (other than an event of default resulting from certain events of bankruptcy, insolvency or reorganization) occurs, and is continuing, then the trustee or the holders of not less than 25% in aggregate principal amount of the outstanding debt securities of any series may accelerate the maturity of the debt securities. If this happens, the entire principal amount, plus the premium, if any, of all the outstanding debt securities of the affected series plus accrued interest to the date of acceleration will be immediately due and payable. At any time after the acceleration, but before a judgment or decree based on such acceleration is obtained by the trustee, the holders of a majority in aggregate principal amount of outstanding debt securities of such series may rescind and annul such acceleration if:

- all events of default (other than nonpayment of accelerated principal, premium or interest) have been cured or waived;
- all lawful interest on overdue interest and overdue principal has been paid; and
- the rescission would not conflict with any judgment or decree.

In addition, if the acceleration occurs at any time when we have outstanding indebtedness which is senior to the debt securities, the payment of the principal amount of outstanding debt securities may be subordinated in right of payment to the prior payment of any amounts due under the senior indebtedness, in which case the holders of debt securities will be entitled to payment under the terms prescribed in the instruments evidencing the senior indebtedness and the indenture.

If an event of default resulting from certain events of bankruptcy, insolvency or reorganization occurs, the principal, premium and interest amount with respect to all of the debt securities of any series will be due and payable immediately without any declaration or other act on the part of the trustee or the holders of the debt securities of that series.

The holders of a majority in principal amount of the outstanding debt securities of a series will have the right to waive any existing default or compliance with any provision of the indenture or the debt securities of that series and to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, subject to certain limitations specified in the indenture.

No holder of any debt security of a series will have any right to institute any proceeding with respect to the indenture or for any remedy under the indenture, unless:

- the holder gives to the trustee written notice of a continuing event of default;
- the holders of at least 25% in aggregate principal amount of the outstanding debt securities of the affected series make a written request and offer reasonable indemnity to the trustee to institute a proceeding as trustee;
- the trustee fails to institute a proceeding within 60 days after such request; and

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- the holders of a majority in aggregate principal amount of the outstanding debt securities of the affected series do not give the trustee a direction inconsistent with such request during such 60-day period.

These limitations do not, however, apply to a suit instituted for payment on debt securities of any series on or after the due dates expressed in the debt securities.

We will periodically deliver certificates to the trustee regarding our compliance with our obligations under the indenture.

Modification and Waiver

From time to time, we and the trustee may, without the consent of holders of the debt securities of one or more series, amend the indenture or the debt securities of one or more series, or supplement the indenture, for certain specified purposes, including:

- to provide that the surviving entity following a change of control of RXi permitted under the indenture will assume all of our obligations under the indenture and debt securities;
- to provide for certificated debt securities in addition to uncertificated debt securities;
- to comply with any requirements of the SEC under the Trust Indenture Act of 1939;
- to provide for the issuance of and establish the form and terms and conditions of debt securities of any series as permitted by the indenture;
- to cure any ambiguity, defect or inconsistency, or make any other change that does not materially and adversely affect the rights of any holder; and
- to appoint a successor trustee under the indenture with respect to one or more series.

From time to time we and the trustee may, with the consent of holders of at least a majority in principal amount of an outstanding series of debt securities, amend or supplement the indenture or the debt securities series, or waive compliance in a particular instance by us with any provision of the indenture or the debt securities. We may not, however, without the consent of each holder affected by such action, modify or supplement the indenture or the debt securities or waive compliance with any provision of the indenture or the debt securities in order to:

- reduce the amount of debt securities whose holders must consent to an amendment, supplement, or waiver to the indenture or such debt security;
- reduce the rate of or change the time for payment of interest or reduce the amount of or postpone the date for payment of sinking fund or analogous obligations;
- reduce the principal of or change the stated maturity of the debt securities;
- make any debt security payable in money other than that stated in the debt security;
- change the amount or time of any payment required or reduce the premium payable upon any redemption, or change the time before which no such redemption may be made;
- waive a default in the payment of the principal of, premium, if any, or interest on the debt securities or a redemption payment;
- waive a redemption payment with respect to any debt securities or change any provision with respect to redemption of debt securities; or

- take any other action otherwise prohibited by the indenture to be taken without the consent of each holder affected by the action.

Defeasance of Debt Securities and Certain Covenants in Certain Circumstances

The indenture permits us, at any time, to elect to discharge our obligations with respect to one or more series of debt securities by following certain procedures described in the indenture. These procedures will allow us either:

- to defease and be discharged from any and all of our obligations with respect to any debt securities except for the following obligations (which discharge is referred to as “legal defeasance”):
 - (1) to register the transfer or exchange of such debt securities;
 - (2) to replace temporary or mutilated, destroyed, lost or stolen debt securities;
 - (3) to compensate and indemnify the trustee; or
 - (4) to maintain an office or agency in respect of the debt securities and to hold monies for payment in trust; or
- to be released from our obligations with respect to the debt securities under certain covenants contained in the indenture, as well as any additional covenants which may be contained in the applicable supplemental indenture (which release is referred to as “covenant defeasance”).

In order to exercise either defeasance option, we must deposit with the trustee or other qualifying trustee, in trust for that purpose:

- money;
- U.S. Government Obligations (as described below) or Foreign Government Obligations (as described below) which through the scheduled payment of principal and interest in accordance with their terms will provide money; or
- a combination of money and/or U.S. Government Obligations and/or Foreign Government Obligations sufficient in the written opinion of a nationally-recognized firm of independent accountants to provide money;

which in each case specified above, provides a sufficient amount to pay the principal of, premium, if any, and interest, if any, on the debt securities of the series, on the scheduled due dates or on a selected date of redemption in accordance with the terms of the indenture.

In addition, defeasance may be effected only if, among other things:

- in the case of either legal or covenant defeasance, we deliver to the trustee an opinion of counsel, as specified in the indenture, stating that as a result of the defeasance neither the trust nor the trustee will be required to register as an investment company under the Investment Company Act of 1940;
- in the case of legal defeasance, we deliver to the trustee an opinion of counsel stating that we have received from, or there has been published by, the Internal Revenue Service a ruling to the effect that, or there has been a change in any applicable federal income tax law with the effect that (and the opinion shall confirm that), the holders of outstanding debt securities will not recognize income, gain or loss for U.S. federal income tax purposes solely as a result of such legal defeasance and will be subject to U.S. federal income tax on the same amounts, in the same manner, including as a result of prepayment, and at the same times as would have been the case if legal defeasance had not occurred;

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- in the case of covenant defeasance, we deliver to the trustee an opinion of counsel to the effect that the holders of the outstanding debt securities will not recognize income, gain or loss for U.S. federal income tax purposes as a result of covenant defeasance and will be subject to U.S. federal income tax on the same amounts, in the same manner and at the same times as would have been the case if covenant defeasance had not occurred; and
- certain other conditions described in the indenture are satisfied.

If we fail to comply with our remaining obligations under the indenture and applicable supplemental indenture after a covenant defeasance of the indenture and applicable supplemental indenture, and the debt securities are declared due and payable because of the occurrence of any undefeased event of default, the amount of money and/or U.S. Government Obligations and/or Foreign Government Obligations on deposit with the trustee could be insufficient to pay amounts due under the debt securities of the affected series at the time of acceleration. We will, however, remain liable in respect of these payments.

The term “U.S. Government Obligations” as used in the above discussion means securities which are direct obligations of or non-callable obligations guaranteed by the United States of America for the payment of which obligation or guarantee the full faith and credit of the United States of America is pledged.

The term “Foreign Government Obligations” as used in the above discussion means, with respect to debt securities of any series that are denominated in a currency other than U.S. dollars (1) direct obligations of the government that issued or caused to be issued such currency for the payment of which obligations its full faith and credit is pledged or (2) obligations of a person controlled or supervised by or acting as an agent or instrumentality of such government the timely payment of which is unconditionally guaranteed as a full faith and credit obligation by that government, which in either case under clauses (1) or (2), are not callable or redeemable at the option of the issuer.

Regarding the Trustee

We will identify the trustee with respect to any series of debt securities in the prospectus supplement relating to the applicable debt securities. You should note that if the trustee becomes a creditor of RXi, the indenture and the Trust Indenture Act of 1939 limit the rights of the trustee to obtain payment of claims in certain cases, or to realize on certain property received in respect of any such claim, as security or otherwise. The trustee and its affiliates may engage in, and will be permitted to continue to engage in, other transactions with us and our affiliates. If, however, the trustee acquires any “conflicting interest” within the meaning of the Trust Indenture Act of 1939, it must eliminate such conflict or resign.

The holders of a majority in principal amount of the then outstanding debt securities of any series may direct the time, method and place of conducting any proceeding for exercising any remedy available to the trustee. If an event of default occurs and is continuing, the trustee, in the exercise of its rights and powers, must use the degree of care and skill of a prudent person in the conduct of his or her own affairs. Subject to that provision, the trustee will be under no obligation to exercise any of its rights or powers under the indenture at the request of any of the holders of the debt securities, unless they have offered to the trustee reasonable indemnity or security.

LEGAL MATTERS

The validity of the issuance of the securities offered hereby will be passed upon for us by Ropes & Gray LLP, Boston, Massachusetts. The validity of any securities will be passed upon for any underwriters or agents by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The financial statements as of December 31, 2009 and 2008 and for the years then ended and for the cumulative period from inception (January 1, 2003) through December 31, 2009 incorporated by reference in this Prospectus have been so incorporated in reliance on the report of BDO Seidman, LLP, an independent registered public accounting firm, incorporated herein by reference, given on the authority of said firm as experts in auditing and accounting.

WHERE YOU CAN FIND MORE INFORMATION

We have filed a registration statement on Form S-3 with the SEC for the securities we are offering by this prospectus. This prospectus does not include all of the information contained in the registration statement. You should refer to the registration statement and its exhibits for additional information.

We are required to file annual and quarterly reports, special reports, proxy statements, and other information with the SEC. We make these documents publicly available, free of charge, on our website at www.rxipharma.com as soon as reasonably practicable after filing such documents with the SEC. You can read our SEC filings, including the registration statement, on the SEC's website at <http://www.sec.gov>. You also may read and copy any document we file with the SEC at its public reference facility at:

Public Reference Room
100 F Street N.E.
Washington, DC 20549.

Please call the SEC at 1-800-732-0330 for further information on the operation of the public reference facilities.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" into this prospectus the information we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus, and information in documents that we file later with the SEC will automatically update and supersede information in this prospectus. We incorporate by reference into this prospectus the documents listed below and any future filings made by us with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act until we close this offering, including all filings made after the date of the initial registration statement and prior to the effectiveness of the registration statement; provided, however, that we are not incorporating any information furnished under Item 2.02 or Item 7.01 of any current report on Form 8-K we may subsequently file. We hereby incorporate by reference the following documents:

- our Annual Report on Form 10-K for the year ended December 31, 2009 filed with the SEC on March 31, 2009, including any amendment filed for the purpose of updating such Annual Report;
- our Quarterly Report on Form 10-Q for the quarterly period ending March 31, 2010 filed with the SEC on May 17, 2010;
- our Current Report on Form 8-K filed with the SEC on March 23, 2010;
- our Proxy Statement on Schedule 14A filed with the SEC on April 23, 2010; and

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- the description of our common stock contained in our registration statement on Form 8-A filed February 8, 2008, under the Securities Act, including any amendment or report filed for the purpose of updating such description.

You may request a copy of these filings, at no cost, by writing or telephoning us at the following address:

RXi Pharmaceuticals Corporation
60 Prescott Street
Worcester, MA 01650
Attention: Investor Relations
Phone: (508) 767-3861

Copies of these filings are also available, without charge, through the “Investor Relations” section of our website (www.rxipharma.com) as soon as reasonably practicable after they are filed electronically with the SEC. The information contained on our website is not a part of this prospectus.

RXi Pharmaceuticals Corporation



\$75,000,000

Common Stock
Preferred Stock
Warrants
Debt Securities

PROSPECTUS

, 2010

We have not authorized any dealer, salesperson or other person to give any information or represent anything not contained in this prospectus. You must not rely on any unauthorized information. If anyone provides you with different or inconsistent information, you should not rely on it. This prospectus does not offer to sell any shares in any jurisdiction where it is unlawful. Neither the delivery of this prospectus, nor any sale made hereunder, shall create any implication that the information in this prospectus is correct after the date hereof.

PART II
INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. Other expenses of Issuance and Distribution.

The following table sets forth the various expenses in connection with the sale and distribution of the securities being registered. All amounts shown are estimates, except the SEC registration fee. The registrant has agreed to pay these costs and expenses.

Securities and Exchange Commission registration fee	\$ 5,347.50
Printing and engraving expenses	5,000*
Legal fees and expenses	20,000*
Accounting fees and expenses	20,000*
Transfer Agent and Registrar fees	2,500*
Miscellaneous	700*
Total	\$53,547.50*

* Estimated

Item 15. Indemnification of Directors and Officers.

Section 145 of the Delaware General Corporation Law provides that a corporation may indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative, other than an action by or in the right of the corporation, by reason of the fact that the person is or was a director, officer, employee or agent of the corporation or is or was serving at the corporation's request as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against expenses, including attorneys' fees, judgments, fines and amounts paid in settlement actually and reasonably incurred by the person in connection with the action, suit or proceeding if the person acted in good faith and in a manner the person reasonably believed to be in or not opposed to the best interests of the corporation, and, with respect to any criminal action or proceeding, had no reasonable cause to believe the person's conduct was unlawful. The power to indemnify applies to actions brought by or in the right of the corporation as well, but only to the extent of expenses, including attorneys' fees but excluding judgments, fines and amounts paid in settlement, actually and reasonably incurred by the person in connection with the defense or settlement of the action or suit if the person acted in good faith and in a manner the person reasonably believed to be in or not opposed to the best interests of the corporation and except that no indemnification shall be made in respect of any claim, issue or matter as to which such person shall have been adjudged to be liable to the corporation unless and only to the extent that a court of competent jurisdiction shall determine that such indemnity is proper.

Section 145(g) of the Delaware General Corporation Law provides that a corporation shall have the power to purchase and maintain insurance on behalf of its officers, directors, employees and agents, against any liability asserted against and incurred by such persons in any such capacity.

Section 102(b)(7) of the General Corporation Law of the State of Delaware provides that a corporation may eliminate or limit the personal liability of a director to the corporation or its stockholders for monetary damages for breach of fiduciary duty as a director, provided that such provision shall not eliminate or limit the liability of a director (i) for any breach of the director's duty of loyalty to the corporation or its stockholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) under Section 174 of the General Corporation Law of the State of Delaware, or (iv) for any transaction from which the director derived an improper personal benefit. No such provision shall eliminate or limit the liability of a director for any act or omission occurring prior to the date when such provision becomes effective.

Our Amended and Restated Certificate of Incorporation provides that our directors shall not be liable to the Registrant or its stockholders for monetary damages for breach of fiduciary duty as a director, except to the extent

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that the exculpation from liabilities is not permitted under the Delaware General Corporation Law as in effect at the time such liability is determined. In addition, our Amended and Restated Certificate of Incorporation provides that we shall indemnify our directors to the fullest extent permitted by the laws of the State of Delaware. We have entered into an indemnification agreement with Noah D. Beerman, our President and Chief Executive Officer, that provides for indemnification and expense advancement to the fullest extent permitted by the laws of the State of Delaware. We may enter into indemnification agreements with our other directors and officers in the future.

Our Amended and Restated Certificate of Incorporation provides that we may purchase and maintain insurance policies on behalf of our directors and officers against specified liabilities for actions taken in their

Item 16. Exhibits.

See Exhibit Index beginning on page II-7 of this registration statement.

Item 17. Undertakings.

(a) The undersigned registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;

(ii) To reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20 percent change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement;

(iii) To include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement.

Provided, however, that:

(A) Paragraphs (a)(1)(i) and (a)(1)(ii) of this section do not apply if the registration statement is on Form S-8, and the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the SEC by the registrant pursuant to section 13 or section 15(d) of the Exchange Act that are incorporated by reference in the registration statement; and

(B) Paragraphs (a)(1)(i), (a)(1)(ii) and (a)(1)(iii) of this section do not apply if the registration statement is on Form S-3 or Form F-3 and the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the SEC by the registrant pursuant to section 13 or section 15(d) of the Exchange Act that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of the registration statement.

(C) *Provided, further, however,* that paragraphs (a)(1)(i) and (a)(1)(ii) do not apply if the registration statement is for an offering of asset-backed securities on Form S-1 or Form S-3, and the information required to be included in a post-effective amendment is provided pursuant to Item 1100(c) of Regulation AB.

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(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

(i) If the registrant is relying on Rule 430B:

(A) Each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and

(B) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii), or (x) for the purpose of providing the information required by section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof. *Provided, however*, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

(ii) If the registrant is subject to Rule 430C, each prospectus filed pursuant to Rule 424(b) as part of a registration statement relating to an offering, other than registration statements relying on Rule 430B or other than prospectuses filed in reliance on Rule 430A, shall be deemed to be part of and included in the registration statement as of the date it is first used after effectiveness. *Provided, however*, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such first use, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such date of first use.

(5) That, for the purpose of determining liability of the registrant under the Securities Act of 1933 to any purchaser in the initial distribution of the securities,:

The undersigned registrant undertakes that in a primary offering of securities of the undersigned registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

(i) any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;

(ii) any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;

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(iii) the portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and

(iv) any other communication that is an offer in the offering made by the undersigned registrant to the purchaser.

(b) The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the registrant's annual report pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

(c) The undersigned registrant hereby undertakes that: (i) for purposes of determining any liability under the Securities Act of 1933, the information omitted from the form of prospectus filed as part of the registration statement in reliance upon Rule 430A and contained in the form of prospectus filed by the registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act shall be deemed to be part of the registration statement as of the time it was declared effective; and (ii) for the purpose of determining any liability under the Securities Act, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

(d) If and when applicable, the undersigned registrant, hereby undertakes to file an application for the purpose of determining the eligibility of the trustee to act under subsection (a) of Section 310 of the Trust Indenture Act in accordance with the rules and regulations prescribed by the Commission under Section 305(b)(2) of the Act.

(e) Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act of 1933 and is therefore unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act of 1933, and will be governed by the final adjudication of such issue.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this registration statement on Form S-3 to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Worcester, The Commonwealth of Massachusetts, on the 21st day of May, 2010.

RXI PHARMACEUTICALS CORPORATION

By: /s/ Noah D. Beerman
Name: Noah D Beerman
Title: President, Chief Executive Officer and
Director

POWER OF ATTORNEY

Each person whose signature appears below constitutes and appoints Noah D. Beerman, Amy Tata and Marc A. Rubenstein, and each of them singly, his or her true and lawful attorney-in-fact and agent with full power of substitution and resubstitution, for him or her and in his or her name, place, and stead, in any and all capacities, to sign any and all amendments and supplements (including post-effective amendments) to this Registration Statement on Form S-3, and any related Rule 462(b) registration statement or amendment thereto, to be filed by RXi Pharmaceuticals Corporation, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents full power and authority to be done in and about the premises, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or their substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, as amended, this Registration Statement has been signed by the following persons in the capacities indicated on May 21, 2010:

<u>Signature</u>	<u>Title</u>
<u>/s/ Noah D. Beerman</u> Noah D. Beerman	President, Chief Executive Officer and Director (Principal Executive Officer)
<u>/s/ Amy Tata</u> Amy Tata	Principal Accounting Officer (Principal Financial and Accounting Officer)
<u>Sanford J. Hillsberg</u>	Director
<u>/s/ Richard Chin</u> Richard Chin	Director
<u>/s/ Mark J. Ahn</u> Mark J. Ahn	Director
<u>/s/ Stephen S. Galliker</u> Stephen S. Galliker	Director
<u>/s/ Steven A. Kriegsman</u> Steven A. Kriegsman	Director
<u>/s/ Rudolph Nisi</u> Rudolph Nisi	Director

EXHIBIT INDEX

The following is a list of exhibits filed as part of this registration statement.

Exhibit	Description
4.1	Form of Underwriting Agreement*
4.2	Form of Amended and Restated Certificate of Incorporation of RXi Pharmaceuticals Corporation(1)
4.3	Form of Amended and Restated By-laws of RXi Pharmaceuticals Corporation(1)
4.4	Specimen common stock certificate(2)
4.5	Form of Common Stock Warrant Agreement and Warrant Certificate*
4.6	Form of Preferred Stock Warrant Agreement and Warrant Certificate*
4.7	Form of Debt Securities Warrant Agreement and Warrant Certificate*
4.8	Form of Indenture(3)
5.1	Opinion of Ropes & Gray LLP(4)
23.1	Consent of Ropes & Gray LLP (included in Exhibit 5.1)(4)
23.2	Consent of BDO Seidman, LLP(4)
24.1	Power of attorney (included on the signature page)
25.1	Statement of Eligibility of Trustee Under Debt Indenture (to be filed separately pursuant to Section 305(b)(2) of the Trust Indenture Act of 1939)

(1) Previously filed as an Exhibit to the Company's Registration Statement on Form S-1 filed with the Commission on October 30, 2007 (File No. 333-147009) and incorporated by reference herein.

(2) Previously filed as an Exhibit to Amendment No. 2 to the Company's Registration Statement on Form S-1 filed with the Commission on January 20, 2008 (File No. 333-147009) and incorporated by reference herein.

(3) Previously filed as an Exhibit to the Company's Registration Statement on Form S-3 filed with the Commission on May 4, 2009 (File No. 333-158968) and incorporated by reference herein.

(4) Filed herewith.

* To be filed if necessary subsequent to the effectiveness of this registration statement by an amendment to this registration statement or incorporated by reference pursuant to a Current Report on Form 8-K in connection with the offering of securities.



ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624
WWW.ROPESGRAY.COM

May 21, 2010

RXi Pharmaceuticals Corporation
60 Prescott Street
Worcester, MA 01605

Re: Registration of Securities by RXi Pharmaceuticals Corporation

Ladies and Gentlemen:

This opinion is being furnished to you in connection with the Registration Statement on Form S-3 (the "Registration Statement"), including the prospectus that is part of the Registration Statement (the "Prospectus"), filed by RXi Pharmaceuticals Corporation, a Delaware corporation (the "Company"), with the Securities and Exchange Commission (the "SEC") under the Securities Act of 1933, as amended (the "Securities Act") on or about the date hereof. The Prospectus provides that it will be supplemented in the future by one or more prospectus supplements (each, a "Prospectus Supplement"). The Prospectus, as supplemented by the various Prospectus Supplements, will provide for the issuance and sale by the Company from time to time of (i) shares of common stock, \$0.0001 par value per share (the "Common Stock"); (ii) shares of preferred stock (the "Preferred Stock"); (iii) one or more series of the debt securities of the Company, which may be either senior securities or subordinated securities and which may be convertible into or exchangeable for shares of Common Stock or Preferred Stock (the "Debt Securities"); or (iv) warrants to purchase shares of Common Stock, shares of Preferred Stock and/or Debt Securities (the "Warrants").

The Common Stock, the Preferred Stock, the Debt Securities and the Warrants are collectively referred to herein as the "Securities." The Securities are being registered for offering and sale from time to time pursuant to Rule 415 under the Securities Act. The maximum aggregate public offering price of the Securities being registered is \$75 million.

The Debt Securities will be issued pursuant to one or more indentures in the form filed as an exhibit to the Registration Statement, as amended or supplemented from time to time (each, an "Indenture"), between the Company, as obligor, and a trustee chosen by the Company and qualified to act as such under the Trust Indenture Act of 1939, as amended (the "Trustee").

We have examined and relied upon the information set forth in the Registration Statement and such other records, agreements, certificates and documents, and have made legal and factual inquiries, as we have deemed necessary as a basis for the opinions expressed herein. As to questions of fact not independently verified by us, we have relied upon certificates of public officials and officers of the Company.

The opinions expressed herein are limited to matters governed by the Delaware General Corporation Law, including the applicable provisions of the Delaware constitution and the reported cases interpreting those laws.

Based upon the foregoing and subject to the additional qualifications set forth below, we are of the opinion that:

1. When the issuance and the terms of the sale of the shares of Common Stock have been duly authorized by the board of directors of the Company in conformity with its certificate of incorporation, and such shares have been issued and delivered against payment of the purchase price therefor in an amount in excess of the par value thereof, in accordance with the applicable definitive purchase, underwriting or similar agreement, and as contemplated by the Registration Statement, the Prospectus and the related Prospectus Supplement, and, if issued upon the conversion, exchange or exercise of Debt Securities or Warrants, when such shares have been duly issued

and delivered as contemplated by the terms of the applicable Indenture or Warrant, the shares of Common Stock will be validly issued, fully paid and nonassessable.

2. When the issuance and the terms of the sale of the shares of Preferred Stock have been duly authorized by the board of directors of the Company in conformity with its certificate of incorporation; an appropriate certificate of designation relating to a series of the Preferred Stock to be sold under the Registration Statement has been duly authorized and adopted and filed with the Secretary of State of The State of Delaware; the terms of issuance and sale of shares of such series of Preferred Stock have been duly established in conformity with the Company's certificate of incorporation and by-laws so as to not violate any applicable law or result in a default under, or breach of, any agreement or instrument binding upon the Company and so as to comply with any requirement or restriction imposed by any court or governmental or regulatory body having jurisdiction over the Company or any of its property; and such shares have been issued and delivered against payment of the purchase price therefor in an amount in excess of the par value thereof, in accordance with the applicable definitive purchase, underwriting or similar agreement, and as contemplated by the Registration Statement, the Prospectus and the related Prospectus Supplement, and, if issued upon the conversion, exchange or exercise of any Debt Securities or Warrants, when such shares have been duly issued and delivered as contemplated by the terms of the applicable Indenture or Warrant, the shares of Preferred Stock will be validly issued, fully paid and nonassessable.

3. When the issuance and the terms of the sale of the Debt Securities have been duly authorized by the board of directors of the Company and duly established in conformity with the applicable Indenture so as not to violate any applicable law or result in a default under, or breach of, any agreement or instrument binding upon the Company and so as to comply with any requirement or restriction imposed by any court or governmental or regulatory body having jurisdiction over the Company or any of its property, and the Debt Securities have been duly executed, authenticated, issued, delivered and sold in accordance with the applicable definitive purchase, underwriting or similar agreement, as contemplated by the Registration Statement, the Prospectus and the related Prospectus Supplement, and in the manner provided for in the applicable Indenture against payment of the purchase price therefor, the Debt Securities will constitute valid and binding obligations of the Company enforceable against the Company in accordance with their respective terms.

4. When the issuance and the terms of the sale of the Warrants have been duly authorized by the board of directors of the Company; the terms of the Warrants and of their issuance and sale have been duly established so as to not violate any applicable law or result in a default under, or breach of, any agreement or instrument binding upon the Company and so as to comply with any requirement or restriction imposed by any court or governmental or regulatory body having jurisdiction over the Company or any of its property; and the Warrants have been duly executed and issued and sold in accordance with the applicable definitive purchase, underwriting or similar agreement, as contemplated by the Registration Statement, the Prospectus and the related Prospectus Supplement, the Warrants will constitute valid and binding obligations of the Company enforceable against the Company in accordance with their terms.

In rendering the opinions set forth above, we have assumed that: (i) the Registration Statement will have become effective under the Securities Act, a Prospectus Supplement will have been prepared and filed with the SEC describing the Securities offered thereby and such Securities will have been issued and sold in accordance with the terms of such Prospectus Supplement; (ii) a definitive purchase, underwriting or similar agreement with respect to such Securities (if applicable) will have been duly authorized, executed and delivered by the Company and the other parties thereto; (iii) the Securities will be duly authorized by all necessary corporate action by the Company and any Indenture, any applicable supplemental indenture thereto and any other agreement pursuant to which such Securities may be issued will be duly authorized, executed and delivered by the Company and the other parties thereto; (iv) the Company is, and will remain, duly organized, validly existing and in good standing under applicable state law; and (v) the Company will have reserved a sufficient number of shares of its duly authorized, but unissued, Common Stock and Preferred Stock as is necessary to provide for the issuance of the shares of Common Stock and Preferred Stock pursuant to the Registration Statement.

The opinions set forth above are subject to the following exceptions, limitations and qualifications: (i) the effect of bankruptcy, insolvency, reorganization, fraudulent conveyance, moratorium or other similar laws now or hereafter in effect relating to or affecting the rights and remedies of creditors; (ii) the effect of general principles of equity, including without limitation, concepts of materiality, reasonableness, good faith and fair dealing and the possible unavailability of specific performance or injunctive relief, regardless of whether enforcement is considered in a proceeding in equity or at law, and the discretion of the court before which any proceeding therefor may be brought; and (iii) the unenforceability under certain circumstances under law or court decisions of provision providing for the indemnification of, or contribution to, a party with respect to a liability where such indemnification or contribution is contrary to public policy. We express no opinion (i) concerning the enforceability of any waiver of rights or defenses with respect to stay, extension or usury laws or (ii) with respect to whether acceleration of Debt Securities may affect the collectibility of any portion of the stated principal amount thereof which might be determined to constitute unearned interest thereon. Our opinions expressed herein are also subject to the qualification that no term or provision shall be included in any Indenture, any Warrant or any other agreement or instrument pursuant to which any of the Securities are to be issued that would affect the validity of such opinions.

We hereby consent to the filing of this letter as an exhibit to the Registration Statement and to the reference to this firm under the caption "Legal Matters" in the Prospectus included therein. Our consent shall not be deemed an admission that we are experts whose consent is required under Section 7 of the Securities Act. This opinion may be used only in connection with the offer and sale of the Securities while the Registration Statement is effective.

Very truly yours,

/s/ Ropes & Gray LLP

Ropes & Gray LLP

Consent of Independent Registered Public Accounting Firm

RXi Pharmaceuticals Corporation

Worcester, MA

We hereby consent to the incorporation by reference in the Prospectus constituting a part of this Registration Statement on Form S-3 filed by RXi Pharmaceuticals Corporation (the “Company”) on May 21, 2010 of our report dated March 31, 2010, relating to the financial statements of the Company appearing in the Company’s Annual Report on Form 10-K for the year ended December 31, 2009.

We also consent to the reference to us under the caption “Experts” in the Prospectus.

/s/ BDO Seidman, LLP

Boston, MA

May 21, 2010