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PROSPECTUS SUPPLEMENT
(To Prospectus dated May 22, 2009)

Filed pursuant to Rule 424(b)(5)
Registration No. 333-158968

2,385,715 Shares of Common Stock
Warrants to Purchase 954,286 Shares of Common Stock

RXI PHARMACEUTICALS CORPORATION

We are offering up to 2,385,715 shares of our common stock and warrants to purchase up to 954,286 shares of our common stock in this offering (and the shares of common stock issuable from time to time upon exercise of these warrants). The common stock and warrants will be sold in units, with each unit consisting of one share of common stock and a warrant to purchase 0.40 shares of common stock at an exercise price of $4.50 per share of common stock. Each unit will be sold at a negotiated price of $3.50 per unit. The shares of common stock and warrants will be issued separately but can only be purchased together in this offering.

Units will not be issued or certificated. Our common stock is traded on the Nasdaq Capital Market under the symbol "RXII." On July 28, 2009, the closing price of our common stock was $4.79 per share.

Investing in our securities involves a high degree of risk. Before buying any securities, you should read the discussion of material risks of investing in our common stock under the heading "Risk factors" beginning on page S-4 of this prospectus supplement.

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

We have retained Rodman & Renshaw, LLC to act as our exclusive placement agent in connection with the arrangement of this transaction. We have agreed to pay the placement agent the placement agent fees set forth in the table below, which assumes that we sell all of the units we are offering. We have also agreed to issue the placement agent or its designees warrants to purchase common stock and to reimburse the placement agent for certain of its expenses as described under "Plan of distribution" in this prospectus supplement. The placement agent is not required to arrange for the sale of any specific number of units or dollar amount but will use best efforts to arrange for the sale of all of the units.

	Per Unit	Maximum Offering Amount
Offering price	$ 3.50	8,350,002.50
Placement agent fees	$ 0.21	$ 501,000.15
Proceeds, before expenses, to us	$ 3.29	7,849,002.30

We estimate the total expenses of this offering, excluding the placement agent fees, will be approximately $82,500. Because there is no minimum offering amount required as a condition to closing in this offering, the actual offering amount, the placement agent fees and net proceeds to us, if any, in this offering may be substantially less than the maximum offering amounts set forth above.

Rodman & Renshaw, LLC

The date of this prospectus supplement is July 30, 2009.

This prospectus supplement is not complete without, and may not be utilized except in connection with, the accompanying prospectus dated May 22, 2009 and any amendments to such prospectus. This prospectus supplement provides supplemental information regarding us, updates certain information contained in the accompanying prospectus and describes the specific terms of this offering. The accompanying prospectus gives more general information, some of which may not apply to this offering. We incorporate important information into this prospectus supplement and the accompanying prospectus by reference. You may obtain the information incorporated by reference into this prospectus supplement and the accompanying prospectus without charge by following the instructions under "Where you can find more information." You should carefully read both this prospectus supplement and the accompanying prospectus, as well as the additional information described under "Incorporation of certain documents by reference," before deciding to invest in the units.

You should rely only on the information contained and incorporated by reference in this prospectus supplement and the accompanying prospectus. We have not, and the placement agent has not, authorized anyone to give you different or additional information. You should not assume that the information included or incorporated by reference in this prospectus supplement and accompanying prospectus is accurate as of any date after the respective dates of the documents containing the information.

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Prospectus supplement

Prospectus

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

Prospectus supplement summary

This summary highlights selected information appearing elsewhere or incorporated by reference in this prospectus supplement and accompanying prospectus and may not contain all of the information that is important to you. This prospectus supplement and the accompanying prospectus include or incorporate by reference information about the shares we are offering as well as information regarding our business and detailed financial data. You should read this prospectus supplement and the accompanying prospectus in their entirety, including the information incorporated by reference.

BUSINESS OVERVIEW

We are a discovery-stage biopharmaceutical company pursuing proprietary therapeutics based on RNA interference, or RNAi, a naturally occurring cellular mechanism for the regulation of gene expression that has the potential to be harnessed to selectively inhibit the activity of any human gene. As described in Kim and Rossi's review published in March 2007 in Nature Reviews Genetics, it is believed that this inhibition may 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. This growth is driven by the potential ability to use RNAi to rapidly develop lead compounds that specifically and selectively inhibit a target gene.

We intend to focus our internal research and development programs on certain inflammatory and metabolic diseases, and to pursue other therapeutic areas with potential partners. By utilizing our expertise in RNAi and the RNAi technology platform we have built, we believe we will be able to discover lead compounds and move them into clinical development more efficiently than traditional drug discovery approaches.

Our proprietary technology 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 unique forms of rxRNA compounds, which have been shown to be highly potent.
- Multiple technologies to potentially enable the delivery of our rxRNA compounds via local, systemic and oral administration. For example, we believe our delivery technologies may enable the delivery of rxRNA compounds to macrophages, which are key inflammatory cells involved in the progression of various inflammatory diseases, resulting in efficient delivery of our rxRNA compounds to sites of inflammation. We believe this technology provides us with a potential competitive advantage in the delivery of RNAi therapeutics, and is a major focus of our R&D activities. We are also pursuing other potential approaches for the local and systemic delivery of rxRNA compounds to other targets of interest, such as certain targets involved in metabolic disease.

We intend to use our RNAi technology platform and our expertise in RNAi to identify lead compounds and advance towards pre-clinical and clinical development programs in the following therapeutic areas:

- *Inflammatory disease.* Inflammation is responsible for a variety of diseases representing significant unmet medical need and large market opportunities. Our initial targets include validated gene targets related to the TNFa pathway, which is involved in many diseases, including, for example, rheumatoid arthritis, Crohn's disease and psoriasis, and our follow-on programs involve other novel gene targets that are implicated in atherosclerosis, type 2 diabetes and other inflammatory diseases.
- *Metabolic disease.* We have two primary efforts in metabolic disease. First, we are 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. Studies conducted in Dr. Czech's laboratory at the University of Massachusetts Medical School (UMMS) and by others at Imperial College of London have demonstrated that inactivation of one of these genes, called RIP140, can cause fat cells to metabolize rather than store fat. Mice in these studies that did not express RIP140 remained lean and non-diabetic even when maintained on a high-fat diet. We are currently designing RNAi compounds targeting RIP140 as a potential treatment for obesity and obesity-related type 2 diabetes.

- *Additional indications.* There are many well-studied genes that have been associated with numerous diseases but have been difficult to target with conventional medicinal chemistry. We believe RNAi technology may play an important role in targeting these genes and potentially treating the related diseases. With that in mind, we may also pursue additional disease areas with the goal of creating multiple clinical development programs, either by our company alone or in partnership with pharmaceutical or larger biotechnology companies.

We believe that we possess a strong intellectual property portfolio. We have secured exclusive, co-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) 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.

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

The offering

Common stock we are offering	2,385,715 shares
Common stock to be outstanding after this offering	16,207,625 shares
Warrants we are offering	Warrants to purchase 954,286 shares of common stock will be offered in this offering. The warrants will be exercisable during the period commencing six months after the date of original issuance and ending five years from the date the warrants become exercisable at an exercise price of $4.50 per share of common stock. This prospectus supplement also relates to the offering of the shares of common stock issuable upon exercise of the warrants.
Use of proceeds	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. See “Use of proceeds.”
Nasdaq Capital Market symbol	RXII

The number of shares of common stock shown above to be outstanding after this offering is based on the 13,821,910 shares outstanding as of July 28, 2009 and excludes:

- 3,382,342 shares of our common stock subject to options outstanding as of July 28, 2009 having a weighted average exercise price of $5.53 per share;
- 1,295,832 shares of our common stock that have been reserved for issuance in connection with future grants under our stock option plans as of July 28, 2009;
- 332,500 shares of our common stock that have been reserved for issuance upon exercise of outstanding warrants as of July 28, 2009 having a weighted average exercise price of $5.85 per share; and
- shares of common stock issuable upon the exercise of warrants offered hereby.

Risk factors

Investing in our common stock and warrants involves a high degree of risk. In addition to the risks related to our business set forth in the accompanying prospectus and the other information included and incorporated by reference in this prospectus supplement and accompanying prospectus, you should carefully consider the risks described below before purchasing our common stock. If any of the following risks actually occurs, our business, results of operations and financial condition will likely suffer. As a result, the trading price of our common stock may decline, and you might lose part or all of your investment.

Risks Relating to RXi's Business and Industry

The approach we are taking to discover and develop novel therapeutics using RNAi is unproven and may never lead to marketable products.

The scientific discoveries that form the basis for our efforts to discover and develop new drugs are relatively new. The RNAi technologies that we have licensed or have created internally and that we intend to develop have not yet been clinically tested by us, nor are we aware of any clinical trials for efficacy having been completed by third parties involving these technologies. To date, neither we nor any other company has received regulatory approval to market therapeutics utilizing RNAi. The scientific evidence to support the feasibility of developing drugs based on these discoveries is both preliminary and limited. Successful development of RNAi-based products by us will require solving a number of issues, including providing suitable methods of stabilizing the RNAi material and delivering it into target cells in the human body. We may spend large amounts of money trying to solve these issues and never succeed in doing so. In addition, any compounds that we develop may not demonstrate in patients the chemical and pharmacological properties ascribed to them in laboratory studies, and they may interact with human biological systems in unforeseen, ineffective or even harmful ways.

Further, our exclusive focus on RNAi technology for developing products as opposed to multiple, more proven technologies for drug development increases the risk associated with our business. If we are not successful in developing a product candidate using RNAi technology, we may not be able to identify and successfully implement an alternative product development strategy.

We will be subject to competition and may not be able to compete successfully.

A number of medical institutions and pharmaceutical companies are seeking to develop therapeutic products. Companies working in this area include: Alnylam Pharmaceuticals, MDRNA Inc., Cequent Pharmaceuticals, Tacere Therapeutics, Benitec Ltd., OPKO Health, Silence Therapeutics, Dicerna Pharmaceuticals, Quark Pharmaceuticals, Rosetta Genomics, Lorus Therapeutics and Calando Pharmaceuticals, as well as a number of the multinational pharmaceutical companies. In addition, a number of companies are developing therapeutics for the same diseases we are targeting using technologies other than RNA interference. Most of these competitors have substantially greater research and development capabilities and financial, scientific, technical, manufacturing, marketing, distribution, and other resources than us, and we may not be able to successfully compete with them. In addition, even if we are successful in developing our product candidates, in order to compete successfully we may need to be first to market or to demonstrate that our RNAi based products are superior to therapies based on different technologies. If we are not first to market or are unable to demonstrate such superiority, any products for which we are able to obtain approval may not be successful.

We may not be able to maintain the third party relationships that are necessary to develop or potentially commercialize some or all of our product candidates.

We expect to depend on collaborators, partners, licensees, clinical research organizations and other third parties to support our discovery efforts, to formulate product candidates, and to conduct clinical trials for some or all of our product candidates. We cannot guarantee that we will be able to successfully negotiate agreements for or maintain relationships with collaborators, partners, licensees, clinical investigators and other third parties on favorable terms, if at all. If we are unable to obtain or maintain these agreements, we may not be able to clinically develop, formulate, obtain regulatory approvals for or commercialize our product candidates. Under certain license agreements that we have already entered into, we have minimum dollar amounts per calendar year that we are obligated to spend on the development of the technology we have licensed from our contract partners. If we fail to

meet this requirement under any of our licenses, we may be in breach of our obligations under such agreement which may result in the loss of the technology licensed. We cannot necessarily control the amount or timing of resources that our contract partners will devote to our research and development programs, product candidates or potential product candidates, and we cannot guarantee that these parties will fulfill their obligations to us under these arrangements in a timely fashion.

We will rely upon third parties for the manufacture of our clinical product candidates.

We do not have the facilities or expertise to manufacture supplies of any of our potential product candidates. Accordingly, we will be dependent upon contract manufacturers for these supplies. We have no manufacturing supply arrangements for any of our product candidates, and there can be no assurance that we will be able to secure needed supply arrangements on attractive terms, or at all. Our failure to secure these arrangements as needed could have a materially adverse effect on our ability to complete the development of our product candidates or, if we obtain regulatory approval for our product candidates, to commercialize them.

Our current plans call for the manufacture of our rxRNA compounds and, as necessary, any delivery vehicles that may be used to deliver our rxRNA compounds in vitro such as the particles used to delivery our rxRNA compounds to macrophages by contract manufacturers offering research grade, Good Laboratory grade and Good Manufacturing Practices grade materials for preclinical studies (e.g. toxicology studies) and for clinical use. The chemistry, manufacturing and controls for RNAi active pharmaceutical ingredient will be addressed by our clinical development team in close collaboration with a contract manufacturer with extensive experience in RNA drug synthesis. RNA is a complex molecule requiring many synthesis steps, which may lead to challenges with purification and scale-up. These challenges could result in increased costs and delays in manufacturing. Additionally, although we are not currently aware of any such litigation or threatened litigation or challenge, if we have litigation or threatened litigation for or challenge to the composition of our products candidates in the future, manufacturers may refuse to manufacture such compounds.

Any drug candidates we develop may fail in development or be delayed or may not be commercially viable.

All of our products in development must be approved by the FDA or similar foreign governmental agencies before they can be marketed. The process for obtaining FDA approval is both time-consuming and costly, with no certainty of a successful outcome. This process typically includes the conduct of extensive preclinical and clinical testing, which may take longer or cost more than we anticipate, and may prove unsuccessful due to numerous factors. Product candidates that may appear to be promising at early stages of development may not successfully reach the market for a number of reasons. The results of pre-clinical and initial clinical testing of these products may not necessarily indicate the results that will be obtained from later or more extensive testing. Companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in advanced clinical trials, even after obtaining promising results in earlier trials.

We, the FDA or other applicable regulatory authorities, or an institutional review board (“IRB”), an independent committee under the oversight of the United States Department of Health and Human Services (“HHS”), which has been formally registered with HHS and functions to approve, monitor and review biomedical and behavioral research involving humans, may suspend clinical trials of a drug candidate at any time for various reasons, including if we or they believe the subjects or patients participating in such trials are being exposed to unacceptable health risks. Among other reasons, adverse side effects of a drug candidate on subjects or patients in a clinical trial could result in the FDA or other regulatory authorities suspending or terminating the trial and refusing to approve a particular drug candidate for any or all indications of use.

Clinical trials of a new drug candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the drug candidate is intended to treat and who meet other eligibility criteria. Rates of patient enrollment are affected by many factors, and delays in patient enrollment can result in increased costs and longer development times.

Clinical trials also require the review and oversight of IRBs, which approve and continually review clinical investigations and protect the rights and welfare of human subjects. An inability or delay in obtaining IRB approval could prevent or delay the initiation and completion of clinical trials and the FDA may decide not to consider any data or information derived from a clinical investigation not subject to initial and continuing IRB review and approval.

Numerous factors could affect the timing, cost or outcome of our drug development efforts, including the following:

- Delays in filing initial drug applications,
- Difficulty in securing centers to conduct trials,
- Conditions imposed on us by the FDA or comparable foreign authorities regarding the scope or design of our clinical trials,
- Problems in engaging IRBs to oversee trials or problems in obtaining or maintaining IRB approval of studies,
- Difficulty in enrolling patients in conformity with required protocols or projected timelines,
- Unexpected adverse reactions by patients in trials,
- Difficulty in obtaining clinical supplies of the product,
- Negative or inconclusive results from our clinical trials or the clinical trials of others for drug candidates similar to our own or inability to generate statistically significant data confirming the efficacy of the product being tested,
- Changes in the FDA's requirements for our testing during the course of that testing,
- Modification of the drug during testing,
- Reallocation of our limited financial and other resources to other clinical programs, and
- Adverse results obtained by other companies developing RNAi drugs.

The substances we are intending to develop may represent a new class of drug, and the FDA has not yet established any definitive policies, practices or guidelines in relation to these drugs. While we expect any product candidates that we develop will be regulated as a new drug under the Federal Food, Drug, and Cosmetic Act, the FDA could decide to regulate them or other products we may develop as biologics under the Public Health Service Act. The lack of policies, practices or guidelines may hinder or slow review by the FDA of any regulatory filings that we may submit. Moreover, the FDA may respond to these submissions by defining requirements that we may not have anticipated.

It is possible that none of the product candidates that we develop will obtain the appropriate regulatory approvals necessary for us to begin selling them or that any regulatory approval to market a product may be subject to limitations on the indicated uses for which we may market the product. The time required to obtain FDA and other approvals is unpredictable but often can take years following the commencement of clinical trials, depending upon the complexity of the drug candidate. Any analysis we perform of data from clinical activities is subject to confirmation and interpretation by regulatory authorities, which could delay, limit or prevent regulatory approval. Any delay or failure in obtaining required approvals could have a material adverse effect on our ability to generate revenue from the particular drug candidate.

We are also subject to numerous foreign regulatory requirements governing the conduct of clinical trials, manufacturing and marketing authorization, pricing and third-party reimbursement. The foreign regulatory approval process includes all of the risks associated with FDA approval described above as well as risks attributable to the satisfaction of local regulations in foreign jurisdictions. Approval by the FDA does not assure approval by regulatory authorities outside of the United States.

The FDA approval process may be delayed for any drugs we develop that require the use of specialized drug delivery devices or vehicles.

Some drug candidates that we develop may need to be administered using specialized vehicles that deliver RNAi therapeutics directly to diseased parts of the body. For example, we anticipate using an implantable pump to deliver drug candidates to the nervous system. While we expect to rely on drug delivery vehicles that have been approved by the FDA or other regulatory agencies to deliver our drug candidates, we may need to modify the design or labeling of these delivery vehicles for some products we may develop. In such an event, the FDA may regulate the product as a combination product of a drug and a device or require additional approvals or clearances for the

modified delivery. Additionally, it has been observed in at least one previous clinical trial, conducted by another company, that delivery vehicles similar to the delivery vehicle in-licensed from UMMS may cause toxicity, which could delay or prevent approval of this delivery vehicle.

Further, to the extent the specialized delivery vehicle is owned by another company, we would need that company's cooperation to implement the necessary changes to the vehicle, or its labeling, and to obtain any additional approvals or clearances. Any delays in finding suitable drug delivery vehicles to administer RNAi therapeutics directly to diseased parts of the body could negatively affect our ability to successfully develop our RNAi therapeutics.

If we are not successful in developing pre-clinical product candidates, we will not be able to commence clinical trials in humans or obtain approval for our product candidates.

We are in the new drug discovery phase and we have not yet identified any lead compounds for therapeutic development in our initial areas of focus. RNA interference is a relatively new scientific field, and the technologies are still in the early stage of development. We have no compounds in pre-clinical toxicology studies, and we may not be able to advance any product candidate through the pre-clinical stage into clinical trials. Additionally, our development efforts may never result in the identification of a pre-clinical candidate which we are able to successfully develop into a drug. Even if we are able to designate a lead candidate, we may not be able to identify data that would support entering such a candidate into clinical trials. Furthermore, even if we successfully enter into clinical studies, the results from pre-clinical testing of a drug candidate may not predict the results that will be obtained on human clinical trials.

If our pre-clinical testing does not produce successful results or our clinical trials do not demonstrate safety and efficacy in humans, we will not be able to commercialize our drug candidates.

Before obtaining regulatory approval for the sale of our drug candidates, we must conduct, at our own expense, extensive pre-clinical tests and clinical trials to demonstrate the safety and efficacy in humans of our drug candidates. However, we are required to do extensive testing in animal models with our product candidates before we can be approved by the FDA to initiate clinical trials in humans. Furthermore, we cannot be sure that our product candidates will be safely tolerated by humans or be efficacious. Pre-clinical and clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. Success in pre-clinical testing and early clinical trials does not ensure that later clinical trials will be successful, and interim results of a clinical trial do not necessarily predict final results.

A failure of one or more of our pre-clinical studies or clinical trials can occur at any stage of testing. We may experience numerous unforeseen events during, or as a result of, the pre-clinical testing and the clinical trial process that could delay or prevent our ability to receive regulatory approval or potentially commercialize our drug candidates, including:

- Regulators or IRBs may not authorize us to commence a clinical trial or conduct a clinical trial at a prospective trial site,
- Our pre-clinical tests or clinical trials may produce negative or inconclusive results, and we may decide, or regulator may require us, to conduct additional pre-clinical testing or clinical trials, or we may abandon projects that we previously expected to be promising,
- Enrollment in our clinical trials may be slower than we anticipate or participants may drop out of our clinical trials at a higher rate than we anticipate, resulting in significant delays,
- Our third party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner,
- Our drug candidates may have very different chemical and pharmacological properties in humans than in laboratory testing and it may interact with human biological systems in unforeseen, ineffective or harmful ways,
- We might have to suspend or terminate our clinical trials if the participants are being exposed to unacceptable health risks,

- IRBs or regulators, including the FDA, may require that we hold, suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements,
- the cost of our clinical trials may be greater than we anticipate,
- the supply or quality of our drug candidates or other necessary materials necessary to conduct our clinical trials may be insufficient or inadequate, and
- effects of our drug candidates may not be the desired effects or may include undesirable side effects or the drug candidates may have other unexpected characteristics.

Even if we obtain regulatory approvals, our marketed drugs will be subject to ongoing regulatory review. If we fail to comply with continuing U.S. and foreign regulations, we could lose our approvals to market drugs and our business would be materially adversely affected.

Following any initial regulatory approval of any drugs we may develop, we will also be subject to continuing regulatory review, including the review of adverse drug experiences and clinical results that are reported after our drug products are made available to patients. This would include results from any post marketing tests or vigilance required as a condition of approval. The manufacturer and manufacturing facilities we use to make any of our drug candidates will also be subject to periodic review and inspection by the FDA. The discovery of any new or previously unknown problems with the product, manufacturer or facility may result in restrictions on the drug or manufacturer or facility, including withdrawal of the drug from the market. Our product promotion and advertising also will be subject to regulatory requirements and continuing regulatory review. If we fail to comply with applicable continuing regulatory requirements, we may be subject to fines, suspension or withdrawal of regulatory approval, product recalls and seizures, operating restrictions and other adverse consequences.

Even if we receive regulatory approval to market our product candidates, our product candidates may not be accepted commercially, which may prevent us from becoming profitable.

The product candidates that we are developing are based on new technologies and therapeutic approaches. RNAi products are expected to be substantially more expensive to manufacture than traditional small molecule drugs, which may make them more costly than competing small molecule drugs. Additionally, RNAi products are likely to require injection or implantation, and do not readily cross the so-called blood brain barrier, which will make them less convenient to administer than drugs administered orally. Key participants in the pharmaceutical marketplace, such as physicians, medical professionals working in large reference laboratories, public health laboratories and hospitals, third-party payors and consumers, may not accept products intended to improve therapeutic results based on RNAi technology. As a result, it may be more difficult for us to convince the medical community and third-party payors to accept and use our product, or to provide favorable reimbursement. And if medical professionals working with large reference laboratories, public health laboratories and hospitals choose not to adopt and use our RNAi technology, our products may not achieve broader market acceptance.

Other factors that we believe will materially affect market acceptance of our product candidates include:

- The timing of our receipt of any marketing approvals, the terms of any approvals and the countries in which approvals are obtained,
- The safety, efficacy and ease of administration of our product candidates,
- The advantages of our product candidates over those of our competitors,
- The willingness of patients to accept relatively new therapies,
- The success of our physician education programs,
- The availability of government and third-party payor reimbursement,
- The pricing of our products, particularly as compared to alternative treatments, and
- The availability of effective alternative treatments and the relative risks and/or benefits of the treatments.

We may be unable to protect our intellectual property rights licensed from UMMS or others, our intellectual property rights may be inadequate to prevent third parties from using our technologies or developing competing products, and we may need to license additional intellectual property from others.

We have a non-exclusive license to the Mello and Fire foundational RNAi patent owned by UMMS and the Carnegie Institution of Washington, which claims various aspects of RNAi or genetic inhibition by double stranded RNA. This license continues to be available to third parties, and as such it does not provide us with the ability to exclude others from its use or protect us from competition. Therapeutic applications of gene silencing technologies, delivery methods, and other technologies that we license from UMMS are also claimed in a number of UMMS pending patent applications, but there can be no assurance that these applications will result in any issued patents or that those patents would withstand possible legal challenges or protect our technologies from competition. United States Patent and Trademark Office and patent granting authorities in other countries have upheld stringent standards for the RNAi patents that have been prosecuted so far. Consequently, pending patents that we have licensed may continue to experience long and difficult prosecution challenges and may ultimately issue with much narrower claims than those in the pending applications. We are aware of a number of issued patents covering various particular forms and compositions of RNAi-mediating molecules and therapeutic methods that we do not currently expect to use. Third parties may, however, hold or seek to obtain additional patents that could make it more difficult or impossible for us to develop products based on the gene silencing technology that we have licensed.

In addition, others may challenge the patent owned by UMMS and the Carnegie Institution of Washington or other patents that we currently license or may license in the future and, as a result, these patents could be narrowed, invalidated or rendered unenforceable, which would negatively affect our ability to exclude others from use of RNAi technologies described in these patents. There can be no assurance that these patent or other pending applications or issued patents we licensed in will withstand possible legal challenges. Moreover, the laws of some foreign countries may not protect our proprietary rights to the same extent as do the laws of the United States. Any patents issued to us or our licensors may not provide us with any competitive advantages, and there can be no assurance that the patents of others will not have an adverse effect on our ability to do business or to continue to use our technologies freely. Our efforts to enforce and maintain our intellectual property rights may not be successful and may result in substantial costs and diversion of management time. Even if our rights are valid, enforceable and broad in scope, competitors may develop products based on technology that is not covered by our licenses.

We may need to license additional intellectual property rights from third parties in order to be able to complete the development or enhance the efficacy of our product candidates or avoid possible infringement of the rights of others. Additionally, many of our UMMS licenses are limited to ALS, obesity, diabetes and cancer, and in order to pursue other diseases against proprietary gene targets, we may need licenses from other third parties that may be unavailable. To the extent that we are required to obtain multiple licenses from third parties to develop or commercialize a product candidate, the aggregate licensing fees and milestones and royalty payments made to these parties may materially reduce our economic returns or even cause us to abandon development or commercialization of a product candidate. Accordingly, there is no assurance that we will be able to acquire any additional intellectual property rights on satisfactory terms, or at all.

In addition to our licenses, we also rely on copyright and trademark protection, trade secrets, know-how, continuing technological innovation and licensing opportunities. In an effort to maintain the confidentiality and ownership of our trade secrets and proprietary information, we require our employees, consultants, advisors and others to whom we disclose confidential information to execute confidentiality and proprietary information agreements. However, it is possible that these agreements may be breached, invalidated or rendered unenforceable, and if so, there may not be an adequate corrective remedy available. Furthermore, like many companies in our industry, we may from time to time hire scientific personnel formerly employed by other companies involved in one or more areas similar to the activities we conduct. In some situations, our confidentiality and proprietary information agreements may conflict with, or be subject to, the rights of third parties with whom our employees, consultants or advisors have prior employment or consulting relationships. Although we require our employees and consultants to maintain the confidentiality of all confidential information of previous employers, we or these individuals may be subject to allegations of trade secret misappropriation or other similar claims as a result of their prior affiliations. Finally, others may independently develop substantially equivalent proprietary information and techniques, or otherwise gain access to our trade secrets. Our failure to protect our proprietary information and techniques may inhibit or limit our ability to exclude certain competitors from the market and execute our business strategies.

Our success depends upon our ability to obtain and maintain intellectual property protection for our products and technologies.

Our success will depend on our ability to obtain and maintain adequate protection of our intellectual property covering our product candidates and technologies. The ultimate degree of patent protection that will be afforded to biotechnology products and processes, including ours, in the United States and in other important markets remains uncertain and is dependent upon the scope of protection decided upon by the patent offices, courts and lawmakers in these countries. There is no certainty that our existing patents, or patent applications if obtained, will afford us substantial protection or commercial benefit. Similarly, there is no assurance that our pending patent applications or patent applications licensed from third parties will ultimately be granted as patents or that those patents that have been issued or are issued in the future will stand if they are challenged in court.

There may be patent or other intellectual property rights belonging to others that require us to alter our products, pay licensing fees or cease certain activities. If our products infringe patent or other intellectual property rights of others, the owners of those rights could bring legal actions against us claiming damages and seeking to enjoin manufacturing and marketing of the affected products. If these legal actions are successful, in addition to any potential liability for damages, we could be required to obtain a license in order to continue to manufacture or market the affected products. We may not prevail in any action brought against us, and any license required under any rights that we infringe may not be available on acceptable terms or at all.

Other companies or organizations may assert patent rights that prevent us from developing our products.

RNA interference is a relatively new scientific field that has generated many different patent applications from organizations and individuals seeking to obtain important patents in the field. These applications claim many different methods, compositions and processes relating to the discovery, development, delivery and commercialization of RNAi therapeutics. Because the field is so new, very few of these patent applications have been fully processed by government patent offices around the world, and there is a great deal of uncertainty about which patents will issue, when, to whom, and with what claims. While we are not aware of any litigation, threatened litigation or challenge to our intellectual property rights, it is likely that there will be significant litigation and other proceedings, such as interference and opposition proceedings in various patent offices, relating to patent rights in the RNAi field. Others may attempt to invalidate our intellectual property rights or those of our licensors. Even if our rights, or those of our licensors, are not directly challenged, disputes among third parties could lead to the weakening or invalidation of our intellectual property rights. Any attempt by third parties to circumvent or invalidate our intellectual property rights could be costly to defend, require significant time and attention of our management and have a material adverse effect on our business.

We are dependent on technologies we license, and if we lose the right to license such technologies or we fail to license new technologies in the future, our ability to develop new products would be harmed.

We currently are dependent on licenses from third parties for our key technologies relating to fundamental RNAi technologies. Our current licenses impose, and any future licenses we enter are likely to impose, various development, funding, royalty, diligence, sublicensing, insurance and other obligations on us. If our license with respect to any of these technologies is terminated for any reason, the development of the products contemplated by the licenses would be delayed, or suspended altogether, while we seek to license similar technology or develop new non-infringing technology. The costs of obtaining new licenses are high, and many patents in the RNAi field have already been exclusively licensed to third parties, including our competitors. If any of our existing licenses is terminated, the development of the products contemplated by the licenses could be delayed or terminated and we may not be able to negotiate additional licenses on acceptable terms, if at all, which would have a material adverse effect on our business.

We are subject to potential liabilities from clinical testing and future product liability claims.

If any of our future products are alleged to be defective, they may expose us to claims for personal injury by patients in clinical trials of our products or by patients using our commercially marketed products. Even if the marketing of one or more of our products is approved by the FDA, users may claim that such products caused unintended adverse effects. We will seek to obtain clinical trial insurance for clinical trials that we conduct, as well as liability insurance for any products that we market. There can be no assurance that we will be able to obtain

insurance in the amounts we seek, or at all. We anticipate that licensees who develop our products will carry liability insurance covering the clinical testing and marketing of those products. There is no assurance, however, that any insurance maintained by us or our licensees will prove adequate in the event of a claim against us. Even if claims asserted against us are unsuccessful, they may divert management's attention from our operations and we may have to incur substantial costs to defend such claims.

Any drugs we develop may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which could have a material adverse effect on our business.

We intend to sell our products primarily to hospitals which receive reimbursement for the health care services they provide to their patients from third-party payors, such as Medicare, Medicaid and other domestic and international government programs, private insurance plans and managed care programs. Most third-party payors may deny reimbursement if they determine that a medical product was not used in accordance with cost-effective treatment methods, as determined by the third-party payor, or was used for an unapproved indication. Third-party payors also may refuse to reimburse for experimental procedures and devices. Furthermore, because our programs are in the early stages of development, we are unable at this time to determine their cost-effectiveness and the level or method of reimbursement. Increasingly, the third-party payors who reimburse patients are requiring that drug companies provide them with predetermined discounts from list prices, and are challenging the prices charged for medical products. If the price we are able to charge for any products we develop is inadequate in light of our development and other costs, our profitability could be adversely effected.

We currently expect that any drugs we develop may need to be administered under the supervision of a physician. Under currently applicable law, drugs that are not usually self-administered may be eligible for coverage by the Medicare program if:

- They are "incidental" to a physician's services,
- They are "reasonable and necessary" for the diagnosis or treatment of the illness or injury for which they are administered according to accepted standard of medical practice,
- They are not excluded as immunizations, and
- They have been approved by the FDA.

There may be significant delays in obtaining insurance coverage for newly-approved drugs, and insurance coverage may be more limited than the purpose for which the drug is approved by the FDA. Moreover, eligibility for insurance coverage does not imply that any drug will be reimbursed in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim payments for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement may be based on payments for other services and may reflect budgetary constraints or imperfections in Medicare data. Net prices for drugs may be reduced by mandatory discounts or rebates required by government health care programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates. Our inability to promptly obtain coverage and profitable reimbursement rates from both government-funded and private payors for new drugs that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to develop products, and our overall financial condition.

Additionally, third-party payors are increasingly attempting to contain health care costs by limiting both coverage and the level of reimbursement for medical products and services. A number of legislative and regulatory proposals to change the healthcare system in the United States and other major healthcare markets have been proposed in recent years and currently are under consideration in Congress. These proposals have included prescription drug benefit legislation recently enacted in the United States and healthcare reform legislation enacted by certain states. Levels of reimbursement may decrease in the future, and future legislation, regulation or reimbursement policies of third-party payors may adversely affect the demand for and price levels of our products. If our customers are not reimbursed for our products, they may reduce or discontinue purchases of our products, which could have a material adverse effect on our business, financial condition and results of operations.

Some states and localities have established drug importation programs for their citizens, and federal drug import legislation has been introduced in Congress. The Medicare Prescription Drug Plan legislation, which became law in December 2003, required the Secretary of Health and Human Services to promulgate regulations for drug reimportation from Canada into the United States under some circumstances, including when the drugs are sold at a lower price than in the United States. The Secretary, however, retained the discretion not to implement a drug reimportation plan if he finds that the benefits do not outweigh the costs, and has so far declined to approve a reimportation plan. Proponents of drug reimportation may attempt to pass legislation that would directly allow reimportation under certain circumstances. Legislation or regulations allowing the reimportation of drugs, if enacted, could decrease the price we receive for any products that we may develop and adversely affect our future revenues and prospects for profitability.

If we fail to attract, hire and retain qualified personnel, we may not be able to design, develop, market or sell our products or successfully manage our business.

We are highly dependent on our named executive officers and Scientific Advisory Board ("SAB") members. The continued service of our named executive officers and SAB members is critical to our success. We have entered into employment agreements with our named executive officers, all of which can be terminated by such persons on short or no notice. The loss of any of our named executive officers or SAB members, or our inability to identify, attract, retain and integrate additional qualified key personnel, could make it difficult for us to manage our business successfully and achieve our business objectives.

Competition for skilled research, product development, regulatory and technical personnel also is intense, and we may not be able to recruit and retain the personnel we need. The loss of the services of any key research, product development, regulatory, and technical personnel, or our inability to hire new personnel with the requisite skills, could restrict our ability to develop our product candidates.

We use biological and hazardous materials and if we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our research and development activities involve the controlled use of potentially harmful biological materials as well as hazardous materials, chemicals and various radioactive compounds. We cannot completely eliminate the risk of accidental contamination or injury; we could be held liable for any damages that result, and any liability could exceed our resources. We are subject to federal, state and local laws and regulations governing the use, storage, handling and disposal of these materials and specific waste products. We are also subject to numerous environmental, health and workplace safety laws and regulations, including those governing laboratory procedures, exposure to blood-borne pathogens and the handling of biohazardous materials. The cost of compliance with these laws and regulations could be significant and may adversely affect capital expenditures to the extent we are required to procure expensive capital equipment to meet regulatory requirements.

We are also subject to numerous environmental, health and workplace safety laws and regulations, including those governing laboratory procedures, exposure to blood-borne pathogens and the handling of biohazardous materials. We maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of these materials. The limits of our workers' compensation insurance are mandated by state law, and our workers' compensation liability is capped at these state-mandated limits. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials. Additional federal, state and local laws and regulations affecting our operations may be adopted in the future. We may incur substantial costs to comply with, and substantial fines or penalties if we violate any of these laws or regulations.

Risks Relating to a Publicly Traded Company and Future Financing Needs

You may have difficulty evaluating our business, because we have limited history and our historical financial information may not be representative of our future results.

The historical financial information included in our Annual Report on Form 10-K for the year ended December 31, 2008 does not necessarily reflect the financial condition, results of operations or cash flows that we would have achieved as a separate company during the periods presented or those that we will achieve in the future. Prior to the contribution of our RNAi assets from CytRx Corporation ("CytRx"), our RNAi research and

development activities were conducted by CytRx as part of its broader operations, rather than as an independent division or subsidiary, and were primarily conducted through sponsored research arrangements rather than through internal activities. CytRx also performed various corporate functions relating to our business, as discussed above. Our historical financial information reflects allocations of indirect expenses from CytRx for these and similar functions. We believe that these allocations are comparable to the expenses we would have incurred had we operated as a separate company, although we may incur higher expenses as a separate company.

We have limited operating experience and may not be able to effectively operate.

We are a discovery-stage company with limited operating history. We will focus solely on developing and, if we obtain regulatory approval for our product candidates, commercializing therapeutic products based upon RNAi technologies, and there is no assurance that we will be able to successfully implement our business plan. While our management collectively possesses substantial business experience, there is no assurance that we will be able to manage our business effectively, or that we will be able to identify, hire and retain any needed additional management or scientific personnel to develop and implement our product development plans, obtain third-party contracts or any needed financing, or achieve the other components of our business plan.

The obligations associated with being an independent public company require significant resources and management attention.

As a publicly traded company, we are subject to the reporting requirements of the U.S. Securities Exchange Act of 1934, as amended (the "Exchange Act"), and the Sarbanes-Oxley Act of 2002. In addition, the Exchange Act requires that we file annual, quarterly and current reports. Our failure to prepare and disclose this information in a timely manner could subject us to penalties under federal securities laws, expose us to lawsuits and restrict our ability to access financing. The Sarbanes-Oxley Act requires that we, among other things, establish and maintain effective internal controls and procedures for financial reporting and we are presently evaluating our existing internal controls in light of the standards adopted by the Public Company Accounting Oversight Board. It is possible that we or our independent registered public accounting firm may identify significant deficiencies or material weaknesses in our internal control over financial reporting in the future. Any failure or difficulties in implementing and maintaining these controls could cause us to fail to meet the periodic reporting obligations or result in material misstatements in our financial statements.

Section 404 of the Sarbanes-Oxley Act requires annual management assessments of the effectiveness of our internal control over financial reporting. Our failure to satisfy the requirements of Section 404 on a timely basis could result in the loss of investor confidence in the reliability of our financial statements, which in turn could have a material adverse effect on our business and our common stock.

We may not be able to obtain sufficient financing, and may not be able to develop our product candidates.

We believe that our existing cash, cash equivalents, and potential proceeds from this offering and the Standby Equity Distribution Agreement, or SEDA, we entered into on January 30, 2009 with YA Global Master SPV Ltd., or YA Global, should be sufficient to fund our operations through 2010. In the future, we will be dependent on obtaining further financing from third parties in order to maintain our operations and to meet our financial obligations. Before we are able to access additional capital from the SEDA, we must satisfy certain conditions, including the requirement that shares of our stock to be sold to YA Global be registered with the U.S. Securities and Exchange Commission ("SEC"), and there is risk of delays in our satisfying these conditions. In addition, pursuant to the terms of the securities purchase agreement related to this offering, we are prohibited from issuing shares under the SEDA for a period of 30 days. We cannot assure that additional debt or equity or other funding to maintain our operations and to meet our obligations to our licensors will be available to us in the future on acceptable terms, or at all. If we fail to obtain additional funding when needed, we would be forced to scale back, or terminate, our operations, or to seek to merge with or to be acquired by another company.

We anticipate that we will need to raise substantial amounts of money to fund a variety of future activities integral to the development of our business, which may include but are not limited to the following:

- to conduct research and development to successfully develop our RNAi technologies,
- to obtain regulatory approval for our products,

- to file and prosecute patent applications and to defend and assess patents to protect our technologies,
- to retain qualified employees, particularly in light of intense competition for qualified scientists,
- to manufacture products ourselves or through third parties,
- to market our products, either through building our own sales and distribution capabilities or relying on third parties, and
- to acquire new technologies, licenses, products or companies.

We cannot assure you that any financing needed for the development of our business will be available to us on acceptable terms or at all. If we cannot obtain additional financing in the future, our operations may be restricted and we may ultimately be unable to continue to develop and potentially commercialize our product candidates.

Future financing may be obtained through, and future development efforts may be paid for by, the issuance of debt or equity, which may have an adverse effect on our stockholders or may otherwise adversely affect our business.

If we raise funds through the issuance of debt or equity, any debt securities or preferred stock issued will have rights, preferences and privileges senior to those of holders of our common stock in the event of a liquidation. In such event, there is a possibility that once all senior claims are settled, there may be no assets remaining to pay out to the holders of common stock. In addition, if we raise funds through the issuance of additional equity, whether through private placements or additional public offerings, such an issuance would dilute your ownership in us.

The terms of debt securities may also impose restrictions on our operations, which may include limiting our ability to incur additional indebtedness, to pay dividends on or repurchase our capital stock, or to make certain acquisitions or investments. In addition, we may be subject to covenants requiring us to satisfy certain financial tests and ratios, and our ability to satisfy such covenants may be affected by events outside of our control.

We expect to continue to incur significant research and development expenses, which may make it difficult for us to attain profitability, and may lead to uncertainty about or as to our ability to continue as a going concern.

Substantial funds were expended to develop our RNAi technologies, and additional substantial funds will be required for further research and development, including pre-clinical testing and clinical trials of any product candidates, and to manufacture and market any products that are approved for commercial sale. Because the successful development of our products is uncertain, we are unable to precisely estimate the actual funds we will require to develop and potentially commercialize them. In addition, we may not be able to generate enough revenue, even if we are able to commercialize any of our product candidates, to become profitable.

In the event that we are unable to achieve or sustain profitability or to secure additional financing, we may not be able to meet our obligations as they come due, raising substantial doubts as to our ability to continue as a going concern. Any such inability to continue as a going concern may result in our common stock holders losing their entire investment. There is no guaranty that we will become profitable or secure additional financing. Our financial statements contemplate that we will continue as a going concern and do not contain any adjustments that might result if we were unable to continue as a going concern. Changes in our operating plans, our existing and anticipated working capital needs, the acceleration or modification of our expansion plans, increased expenses, potential acquisitions or other events will all affect our ability to continue as a going concern.

Risks Related to Ownership of Our Common Stock

The market price and trading volume of our common stock may be volatile

The market price of our common stock could fluctuate significantly for many reasons, including the following factors:

- announcements of regulatory developments or technological innovations by us or our competitors,
- changes in our relationship with our licensors and other strategic partners,
- changes in our ownership or other relationships with CytRx,

- our quarterly operating results,
- developments in patent or other technology ownership rights,
- public concern regarding the safety of our products,
- government regulation of drug pricing, and
- general changes in the economy, the financial markets or the pharmaceutical or biotechnology industries.

In addition, factors beyond our control may also have an impact on the price of our stock. For example, to the extent that other large companies within our industry experience declines in their stock price, our stock price may decline as well. In addition, when the market price of a company's common stock drops significantly, stockholders often institute securities class action lawsuits against the company. A lawsuit against us could cause us to incur substantial costs and could divert the time and attention of our management and other resources.

Future sales of our shares by CytRx, or the possibility of such sales, could adversely affect our stock price.

CytRx owns 6,268,881 shares of our common stock, or approximately 46% of our outstanding shares. We have agreed that, upon request by CytRx, we will use our best efforts to cause all of our shares issued to CytRx pursuant to the two contribution agreements we entered into in relation to our initial capitalization to be registered under the Securities Act, with certain exceptions, with all expenses incurred in connection with any such registration will be borne by us.

We also have granted CytRx what are commonly known as "piggyback" registration rights to include our shares currently owned by CytRx, or owned by CytRx in the future as a result of a dividend or distribution with respect to shares currently owned by CytRx, in other registration statements that we may file with the SEC on behalf of our company or our security holders. CytRx exercised this "piggyback" registration right in relation to our recent registration statement on Form S-3, to which this prospectus supplement relates, in which 500,000 shares owned by CytRx were registered for resale on an on-going basis. The availability of our shares held by CytRx for resale publicly, as well as any actual sales of these shares, could adversely affect the market price of our shares.

If the value of our shares owned by CytRx from time to time were to exceed 40% of the value of CytRx's total assets, CytRx may be deemed an "investment company" within the meaning of the Investment Company Act of 1940 and become subject to the stringent regulations applicable to investment companies. In this event, CytRx would likely seek to promptly sell or otherwise dispose of shares of our common stock in order to avoid becoming an inadvertent investment company. Any such sales or other disposition by CytRx of our shares, or the possibility of such sales or disposition, could adversely affect the market price of our shares.

We have granted CytRx preemptive rights to acquire shares that we may sell in the future, which may impair our ability to raise funds.

Under an agreement between us, CytRx and our founding stockholders, with some exceptions, CytRx has preemptive rights to acquire a portion of any new securities sold or issued by us so as to maintain its percentage ownership of us at the time of any such sale and issuance, which is currently approximately 46% of our outstanding shares. The exercise by CytRx of its preemptive rights may impair our ability to raise funds, or adversely affect the terms on which we are able to raise funds, as we may not be able to offer to new investors the quantity of our stock that they may desire to purchase.

CytRx's ownership of our common stock could delay or prevent a change in corporate control.

CytRx owns approximately 46% of our common stock, and has preemptive rights, as described above, to maintain its percentage ownership. CytRx has agreed with UMMS, us and our other founding stockholders to vote its shares of our common stock so that a majority of the members of our board of directors are not affiliated with CytRx. However, by virtue of its stock ownership, CytRx may be able to significantly influence the outcome of matters required to be submitted to a vote of our stockholders, including any proposed amendments to our certificate

of incorporation and approval of mergers and other significant corporate transactions. This concentration of ownership may adversely affect the market price of our common stock by:

- delaying, deferring or preventing a change in control of our company,
- impeding a merger, consolidation, takeover or other business combination involving our company, or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of our company.

CytRx could unilaterally effect a change of control of our company by selling or disposing of our shares owned by it.

If CytRx were to sell or otherwise dispose of all or a significant portion of our shares owned by it to a single buyer or group of affiliated buyers, it could effect a change of control of our company without the advice or participation by our board of directors or other stockholders, since transferees of the shares owned by CytRx will not be bound by CytRx's agreements with UMMS, us and our other founding stockholders not to vote our shares owned by it for the election of a majority of our board of directors who are affiliated with CytRx.

Anti-takeover provisions of our certificate of incorporation and by-laws and provisions of Delaware law could delay or prevent a change of control that you may favor.

Anti-takeover provisions of our certificate of incorporation and by-laws and provisions of Delaware law may discourage, delay or prevent a merger or other change of control that stockholders may consider favorable, or may impede the ability of the holders of our common stock to change our management. These provisions of our certificate of incorporation and by-laws, among other things:

- divide our board of directors into three classes, with members of each class to be elected for staggered three-year terms,
- limit the right of stockholders to remove directors,
- regulate how stockholders may present proposals or nominate directors for election at annual meetings of stockholders, and
- authorize our board of directors to issue preferred stock in one or more series, without stockholder approval.

In addition, Section 203 of the Delaware General Corporation Law provides that, subject to limited exceptions, persons that acquire, or are affiliated with a person that acquires, more than 15% of the outstanding voting stock of a Delaware corporation such as our company shall not engage in any business combination with that corporation, including by merger, consolidation or acquisitions of additional shares for a three-year period following the date on which that person or its affiliate crosses the 15% stock ownership threshold. Section 203 could operate to delay or prevent a change of control of our company.

We may acquire other businesses or form joint ventures that may be unsuccessful and could adversely dilute your ownership of our company.

As part of our business strategy, we may pursue future acquisitions of other complementary businesses and technology licensing arrangements. We also may pursue strategic alliances. We have no experience with respect to acquiring other companies and limited experience with respect to the formation of collaborations, strategic alliances and joint ventures. If we were to make any acquisitions, we may not be able to integrate these acquisitions successfully into our existing business and we could assume unknown or contingent liabilities. We also could experience adverse effects on our reported results of operations from acquisition related charges, amortization of acquired technology and other intangibles and impairment charges relating to write-offs of goodwill and other intangible assets from time to time following the acquisition. Integration of an acquired company also may require management resources that otherwise would be available for ongoing development of our existing business. We

may not identify or complete these transactions in a timely manner, on a cost-effective basis, or at all, and we may not realize the anticipated benefits of any acquisition, technology license or strategic alliance.

To finance acquisitions, we may choose to issue shares of our common stock as consideration, which would dilute your ownership interest in us. Alternatively, it may be necessary for us to raise additional funds through public or private financings. Additional funds may not be available on terms that are favorable to us and, in the case of equity financings, may result in dilution to our stockholders. Any future acquisitions by us also could result in large and immediate write-offs, the incurrence of contingent liabilities or amortization of expenses related to acquired intangible assets, any of which could harm our operating results.

Note regarding forward-looking statements

This prospectus supplement, the accompanying prospectus, any free writing prospectus used in connection with this offering 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 our results 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. All forward-looking statements attributable to us or to persons acting on our behalf are expressly qualified in their entirety by the cautionary statements and risk factors set forth in Risk factors and elsewhere in this prospectus supplement, our Form 10-K for the year ended December 31, 2008 and our Form 10-Q for the fiscal quarter ended March 30, 2009. 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 supplement, the accompanying 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

We estimate that the net proceeds from the sale of the 2,385,715 units will be approximately $7,766,500, assuming that we sell the maximum number of units we are offering pursuant to this prospectus supplement. Because there is no minimum offering amount required as a condition to the closing of this offering, the actual number of units sold, placement agent fees and proceeds to us are not presently determinable and may be substantially less than the maximum amount set forth above.

We intend to use the net proceeds of this offering 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.

Price range of common stock

Our common stock trades on the Nasdaq Capital Market under the symbol “RXII.” The following table sets forth, for the periods indicated, the high and low intraday sales prices per share of our common stock as reported by the Nasdaq Capital Market. These prices do not include retail markups, markdowns or commissions.

	High	Low
Fiscal year ending December 31, 2008		
First quarter	$23.95	$6.01
Second quarter	10.12	5.22
Third quarter	9.05	6.42
Fourth quarter	12.25	5.41
Fiscal year ending December 31, 2009		
First quarter	$ 7.19	$3.90
Second quarter	7.57	4.00
Third quarter (through July 28, 2009)	4.93	3.15

The last reported sales price of our common stock on the Nasdaq Capital Market on July 28, 2009 was $4.79 per share. As of July 28, 2009, there were outstanding 13,821,910 shares of our common stock outstanding.

Dividend policy

We have never paid any dividends and do not anticipate paying any dividends on our common stock in the foreseeable future. We expect to retain future earnings, if any, for use in our development activities and the operation of our business.

Dilution

If you invest in our common stock and warrants, you will experience dilution to the extent of the difference between the price per share you pay in this offering and the net tangible book value per share of our common stock immediately after this offering.

Our net tangible book value as of June 30, 2009 was approximately $3.2 million, or $0.23 per share of common stock. Net tangible book value per share is equal to our total tangible assets minus total liabilities, all divided by the number of shares of common stock outstanding as of July 28, 2009. After giving effect to the sale of 2,385,715 shares of common stock, at an offering price of $3.50 per share, and after deducting our estimated placement agent fees and offering expenses payable by us, our as adjusted net tangible book value would have been approximately $10,989,500, or approximately $0.68 per share of common stock, as of July 30, 2009. This represents an immediate increase in net tangible book value of approximately $0.45 per share to existing stockholders and an immediate dilution of approximately $2.82 per share to new investors. The following table illustrates this calculation on a per share basis:

Offering price for one share of common stock and one warrant to purchase 0.40 shares of common stock		$3.50
Net tangible book value per share as of June 30, 2009	$0.23	
Increase per share attributable to the offering	$0.45	
As adjusted net tangible book value per share after this offering		0.68
Dilution per share to new investors		2.82

Because there is no minimum offering amount required as a condition to the closing of this offering, the dilution per share to new investors may be more than that indicated above in the event that the actual number of units sold, if any, is less than the maximum number of units we are offering.

The above illustration of dilution per share to investors participating in this offering assumes (i) no exercise of outstanding options to purchase our common stock or outstanding warrants to purchase shares of our common stock; and (ii) no exercise of the warrants offered hereby. The exercise of outstanding options and warrants having an exercise price less than the offering price will increase dilution to new investors.

Investors that purchase common stock upon the exercise of the warrants offered hereby may experience dilution depending on our net tangible book value (deficit) at the time of exercise.

The number of shares of common stock shown above to be outstanding after this offering is based on the 13,821,910 shares outstanding as of July 28, 2009 and excludes:

- 3,382,342 shares of our common stock subject to options outstanding as of July 28, 2009 having a weighted average exercise price of $5.53 per share;
- 1,295,832 shares of our common stock that have been reserved for issuance in connection with future grants under our stock option plans as of July 28, 2009;
- 332,500 shares of our common stock that have been reserved for issuance upon exercise of outstanding warrants as of July 28, 2009 having a weighted average exercise price of $5.85 per share; and
- shares of common stock issuable upon the exercise of warrants offered hereby.

Description of securities

In this offering, we are offering a maximum of 2,385,715 units, each consisting of (i) one share of our common stock and (ii) a warrant to purchase up to 0.40 shares of our common stock at an exercise price of $4.50 per share.

Units will not be issued or certificated. The shares of common stock and warrants are immediately separable and will be issued separately. This prospectus supplement also relates to the offering of shares of our common stock issuable upon exercise, if any, of the warrants.

Common Stock

The material terms and provisions of our common stock are described under the caption “Description of Common Stock” starting on page 7 of the accompanying prospectus.

Warrants

The warrants offered in this offering will be issued pursuant to a securities purchase agreement between each of the purchasers and us. The following is a brief summary of the material terms of the warrants and is subject in all respects to the provisions contained in the warrants. A form of the warrants is being filed as an exhibit to our Current Report on Form 8-K that we will file with the SEC in connection with this offering and reference is made thereto for a complete description of the warrants.

Exercise Price. The exercise price per share of common stock purchasable upon exercise of the warrants is $4.50 per share of common stock being purchased. If we, at any time while the warrants are outstanding, (i) pay a stock dividend or otherwise make a distribution or distributions on shares of common stock or any other equity or equity equivalent securities payable in shares of common stock, (ii) subdivides outstanding shares of common stock into a larger number of shares, (iii) combines (including by way of reverse stock split) outstanding shares of common stock into a smaller number of shares, or (iv) issues by reclassification of shares of the common stock any shares of capital stock, then in each case the exercise price shall be multiplied by a fraction of which the numerator shall be the number of shares of common stock (excluding treasury shares, if any) outstanding immediately before such event and of which the denominator shall be the number of shares of common stock outstanding immediately after such event, and the number of shares issuable upon exercise of the warrants shall be proportionately adjusted such that the aggregate exercise price of the warrants shall remain unchanged.

Exercisability. Holders may exercise the warrants beginning on the date that is six months after the date of original issuance and at any time up to the date that is five years after the closing of the offering.

Cashless Exercise. If at any time during the warrant exercisability period the issuance of shares of our common stock upon exercise of the warrant is not covered by an effective registration statement, or the prospectus contained therein is not available for the issuance of the common stock to the holder, the holders are permitted to effect a cashless exercise of the warrants (in whole or in part) by surrendering the warrants to us, together with delivery to us of a duly executed exercise notice, canceling a portion of the warrant in payment of the purchase price payable in respect of the number of shares of our common stock purchased upon such exercise.

Transferability. The warrants may be transferred at the option of the warrant holder upon surrender of the warrants with the appropriate instruments of transfer.

Exchange Listing. We do not plan on making an application to list the warrants on the Nasdaq Capital Market, any national securities exchange or other nationally recognized trading system.

Rights as a Stockholder. Except as otherwise provided in the warrants or by virtue of such holder’s ownership of shares of our common stock, the holders of the warrants do not have the rights or privileges of holders of our common stock, including any voting rights, until they exercise their warrants.

Fundamental Transactions. In the event of any fundamental transaction, as described in the warrants and generally including any merger with another entity, the sale, transfer or other disposition of all or substantially all of our assets to another entity, or the acquisition by a person of more than 50% of our common stock, then the holders of the warrants will thereafter have the right to receive upon exercise of the warrants such shares of stock, securities or assets as would have been issuable or payable with respect to or in exchange for a number of shares of our common stock equal to the number of shares of our common stock issuable upon exercise of the warrants immediately prior

to the fundamental transaction, had the fundamental transaction not taken place, and appropriate provision will be made so that the provisions of the warrants (including, for example, provisions relating to the adjustment of the exercise price) will thereafter be applicable, as nearly equivalent as may be practicable in relation to any share of stock, securities or assets deliverable upon the exercise of the warrants after the fundamental transaction.

In the event of a fundamental transaction that is (1) an all cash transaction, (2) a "Rule 13e-3 transaction" as defined in Rule 13e-3 under the Exchange Act, or (3) a fundamental transaction involving a person or entity not traded on a national securities exchange, the holders of the warrants may require us to redeem the warrant for a purchase price payable in case of the Black-Scholes value of the warrant, as calculated pursuant to the terms of the warrant.

Limits on Exercise of Warrants. Except upon at least 61 days' prior notice from the holder to us, the holder will not have the right to exercise any portion of the warrant if the holder, together with its affiliates, would beneficially own in excess of 4.99% of the number of shares of our common stock (including securities convertible into common stock) outstanding immediately after the exercise.

Plan of distribution

Pursuant to a placement agency agreement between us and Rodman & Renshaw, LLC, we have engaged Rodman & Renshaw, LLC as our exclusive placement agent to solicit offers to purchase the units in this offering. The placement agent is not purchasing or selling any of the units we are offering, and they are not required to arrange the purchase or sale of any specific number of units or dollar amount, but they have agreed to use best efforts to arrange for the sale of the units.

The placement agent proposes to arrange for the sale of the units we are offering pursuant to this prospectus supplement to one or more investors through securities purchase agreement directly between the purchasers and us. All of the units will be sold at the same price and, we expect, at a single closing. We established the price following negotiations with prospective investors and with reference to the prevailing market price of our common stock, recent trends in such price and other factors. It is possible that not all of the units we are offering pursuant to this prospectus supplement will be sold at the closing, in which case our net proceeds would be reduced. We expect that the sale of the units will be completed on the date indicated on the cover page of this prospectus supplement.

In connection with this offering, the placement agent may distribute this prospectus supplement and the accompanying prospectus electronically.

We will pay the placement agent a placement agent fee equal to 6% of the gross proceeds of this offering. The following table shows the per share and total placement agent fees we will pay to the placement agent in connection with the sale of the units, assuming the purchase of all of the units we are offering.

Per unit	$ 0.21
Total	$ 501,000.15

As additional compensation, we will issue the placement agent, or it designee, warrants to purchase shares of common stock equal to (i) 1% of the aggregate number of securities placed in the offering if the gross proceeds of the offering are less than 10,000,000, and 2% of the aggregate number of securities placed in the offering if the gross proceeds of the offering are 10,000,000 or more. These warrants shall have an exercise price equal to $4.50, and shall be exercisable for a term of five years from the effective date of the registration statement to which this prospectus supplement is a part of, have no price-based dilution protection, have no registration rights and shall be restricted from transfer for a period of six months from the closing date except as expressly permitted by FINRA Rule 5110(g).

We estimate the total expenses of this offering which will be payable by us, excluding the placement agent fees, will be approximately $82,500. We may also reimburse the placement agent for certain fees and legal expenses reasonably incurred by them. Under no circumstances will any fees, discounts, commissions or concessions received by the placement agent and any FINRA member or independent broker-dealer exceed 8% of the gross proceeds of the offering. The estimated offering expenses payable by us, in addition to the placement agent fees of $501,000, are approximately $583,500, which includes legal, accounting and printing costs and various other fees associated with registering and listing the common stock. After deducting certain fees due to the placement agent and our estimated offering expenses, we expect the net proceeds from this offering to be approximately $7,766,500.

We have agreed to indemnify the placement agent against certain liabilities, including liabilities under the Securities Act of 1933, as amended, and liabilities arising from breaches and representations and warranties contained in the placement agency agreement. We have also agreed to contribute to payments the placement agent may be required to make in respect of such liabilities.

The placement agency agreement is included as an exhibit to our Current Report on Form 8-K that we will file with the SEC in connection with this offering.

NASDAQ GLOBAL MARKET

Our common stock is quoted on the Nasdaq Capital Market under the symbol “RXII.”

PRICE STABILIZATION

The placement agent has informed us that it will not engage in over-allotment, stabilizing transactions or syndicate covering transactions in connection with this offering.

AFFILIATION

The placement agent and its affiliates may provide certain commercial banking, financial advisory or investment banking services for us for which they receive fees. The placement agent and its affiliates may from time to time in the future engage in transactions with us and perform services for us in the ordinary course of its business.

Where you can find more information

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at *http://www.sec.gov* . The SEC's website contains reports, proxy and information statements and other information regarding issuers, such as us, that file electronically with the SEC. You may also read and copy any document we file with the SEC at the SEC's Public Reference Room at 100 F Street, N.E., Room 1580, Washington, D.C. 20549. You may also obtain copies of these documents at prescribed rates by writing to the SEC. Please call the SEC at 1-800-SEC-0330 for further information on the operation of its Public Reference Room.

Incorporation of certain documents by reference

The SEC allows us to "incorporate by reference" into this prospectus supplement the information we have filed with the SEC. The information we incorporate by reference into this prospectus supplement is an important part of this prospectus supplement. Any statement in a document we incorporate by reference into this prospectus supplement or the accompanying prospectus will be considered to be modified or superseded to the extent a statement contained in this prospectus supplement or any other subsequently filed document that is incorporated by reference into this prospectus supplement modifies or supersedes that statement. The modified or superseded statement will not be considered to be a part of this prospectus supplement or accompanying prospectus, as applicable, except as modified or superseded.

We incorporate by reference into this prospectus supplement the information contained in the documents listed below, which is considered to be a part of this prospectus supplement:

- our Annual Report on Form 10-K for the year ended December 31, 2008, 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, 2009;
- Our Current Reports on Form 8-K filed with the SEC on January 7, 2009, January 22, 2009, January 29, 2009, February 5, 2009, April 28, 2009 and June 10, 2009;
- Our Proxy Statement of Schedule 14A filed with the SEC on April 23, 2009; and
- the description of our common stock and related rights contained in our registration statements on Form 8-A (file no. 001-33958) filed under the Exchange Act, including any amendment or report filed for the purpose of updating such description.

We also incorporate by reference all documents filed pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus supplement and prior to the termination of this offering; 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.

Statements made in this prospectus supplement or the accompanying prospectus or in any document incorporated by reference in this prospectus supplement or the accompanying prospectus as to the contents of any contract or other document referred to herein or therein are not necessarily complete, and in each instance reference is made to the copy of such contract or other document filed as an exhibit to the documents incorporated by reference, each such statement being qualified in all material respects by such reference.

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.

Legal matters

The validity of the issuance of the securities offered hereby will be passed upon for us by Ropes & Gray LLP. Weinstein Smith LLP is counsel for the placement agent in connection with this offering.

Experts

BDO Seidman, LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2008, as set forth in their report, which is incorporated by reference in the prospectus and elsewhere in this registration statement. Our consolidated financial statements are incorporated by reference in reliance on BDO Seidman, LLP's report, given on their authority as experts in accounting and auditing.

PROSPECTUS

RXI PHARMACEUTICALS CORPORATION

Primary Securities	**Secondary Securities**
$30,000,000	500,000 Shares
Common Stock	of Common Stock
Preferred Stock	
Warrants	
Debt Securities	

This prospectus relates to both (i) shares of our own securities which we may offer for sale from time to time, and which may take the form of equity, debt or warrants (the "Primary Securities"), and (ii) shares of our common stock being offered for resale by CytRx Corporation, or CytRx (the "Secondary Securities").

The Primary Securities Offering

We may offer the Primary Securities 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 Primary Securities we may offer. Each time we sell Primary 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 Primary 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 these Primary 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 these Primary Securities, the applicable prospectus supplement will provide the names of the agents or underwriters and any applicable fees, commissions or discounts.

The Secondary Securities Offering

CytRx is offering to sell up to 500,000 shares of our common stock, which we refer to in this Prospectus as Secondary Securities. You should read this prospectus together with additional information described under the heading "Where You Can Find More Information" before you make your investment decision.

The selling stockholder may offer the Secondary Securities from time to time to or through brokers, dealers or other agents, or directly to other purchasers, in one or more market transactions or private transactions at prevailing market or at negotiated prices. Brokers or dealers effecting transactions in Secondary Securities should confirm that the Secondary Securities are registered under applicable state law or that an exemption from registration is available.

We will not receive any proceeds from any sale of the Secondary Securities.

General Information

Our common stock is traded on the Nasdaq Capital Market under the symbol "RXII." On April 30, 2009, the closing price of our common stock was $4.55.

As of April 30, 2009, the aggregate market value of our outstanding common stock held by non-affiliates was approximately $33,791,371 based on 13,821,629 shares of outstanding common stock, of which approximately 7,426,675 shares are held by non-affiliates, and a per share price of $4.55 based on the closing sale price of our common stock on April 30, 2009. As of the date hereof, we have not offered any securities pursuant to General Instruction I.B.6 of Form S-3 during the prior 12 calendar month period that ends on and includes the date hereof.

Investing in our securities involves risks. See "Risk Factors" on page 2 .

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 22, 2009

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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, or the SEC, using a “shelf” registration process. Under this shelf registration process, we may offer to sell any combination of the Primary Securities described in this prospectus in one or more offerings up to a total dollar amount of $30,000,000.00. This prospectus provides you with a general description of the Primary Securities we may offer. Each time we sell Primary 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. Separate from the Primary Securities, we are also registering for resale up to 500,000 shares of the Secondary Securities owned by CytRx, which they may sell from time to time in accordance with 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, if any, 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.

OUR COMPANY

We are a discovery-stage biopharmaceutical company pursuing proprietary therapeutics based on RNA interference, or RNAi, a naturally occurring cellular mechanism for the regulation of gene expression that has the potential to be harnessed to selectively inhibit the activity of any human gene. As described in Kim and Rossi's review published in March 2007 in *Nature Reviews Genetics*, it is believed that this inhibition may 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. This growth is driven by the potential ability to use RNAi to rapidly develop lead compounds that specifically and selectively inhibit a target gene.

We intend to focus our internal research and development programs on certain inflammatory and metabolic diseases, and to pursue other therapeutic areas with potential partners. By utilizing our expertise in RNAi and the RNAi technology platform we have built, we believe we will be able to discover lead compounds and move them into clinical development more efficiently than traditional drug discovery approaches.

Our proprietary technology 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 several unique forms of rxRNA compounds, each of which has been shown to be highly potent and, we believe, unencumbered by the intellectual property rights of others.
- Multiple technologies to potentially enable the delivery of our rxRNA compounds via local, systemic and oral administration. In October 2008, we exclusively licensed intellectual property rights to novel technology that we believe should enable the oral delivery of rxRNA compounds to macrophages, which are key inflammatory cells involved in the progression of various inflammatory diseases, resulting in efficient delivery of our rxRNA compounds to sites of inflammation. Oral administration is preferred to injection, the route used to administer current drugs for inflammation, as a method of administering a drug. We believe this technology provides us with a potential competitive advantage in the delivery of RNAi therapeutics, and is a major focus of our R&D activities. We are also pursuing other potential approaches for the local and systemic delivery of rxRNA compounds to other targets of interest, such as certain targets involved in metabolic disease.

We intend to use our RNAi technology platform and our expertise in RNAi to identify lead compounds and advance towards pre-clinical and clinical development programs in the following therapeutic areas:

- *Inflammatory disease.* Our lead program targets genes involved in inflammation, which is responsible for a variety of diseases representing significant unmet medical needs and large market opportunities. Our initial targets include validated gene targets related to the TNFa pathway, which is involved in many diseases, including, for example, rheumatoid arthritis, Crohn's disease and psoriasis, and our follow-on programs involve other novel gene targets that are implicated in atherosclerosis, type 2 diabetes and other inflammatory diseases.
- *Metabolic disease.* We have two primary efforts in metabolic disease. First, we are 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. Studies conducted in Dr. Czech's laboratory at the University of Massachusetts Medical School (UMMS) and by others at Imperial College of London have demonstrated that inactivation of one of these genes, called RIP140, can cause fat cells to metabolize rather than store fat. Mice in these studies that did not express RIP140 remained lean and non-diabetic even when maintained on a high-fat diet. We are currently designing RNAi compounds targeting RIP140 as a potential treatment for obesity and obesity-related type 2 diabetes.

- *Additional indications.* There are many well-studied genes that have been associated with numerous diseases but have been difficult to target with conventional medicinal chemistry. We believe RNAi technology may play an important role in targeting these genes and potentially treating the related diseases. With that in mind, RXi may also pursue additional disease areas with the goal of creating multiple clinical development programs, either by our company alone or in partnership with pharmaceutical or larger biotechnology companies.

We believe that we possess 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) 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.

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, 2008 filed on March 18, 2009 with the Securities and Exchange Commission (“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 Primary Securities will contain a discussion of the risks applicable to such an investment in us. Prior to making a decision about investing in our Primary 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

Primary Securities

Except as otherwise provided in the applicable prospectus supplement, we intend to use the net proceeds from the sale of the Primary 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 Primary Securities covered by this prospectus may be set forth in any prospectus supplement relating to the specific offering.

Secondary Securities

The net proceeds from any disposition of the Secondary Securities covered by this prospectus will be received by CytRx. We will not receive any of the proceeds from any such sale of the Secondary Securities offered by this prospectus.

We will pay the costs and expenses relating to the offering by CytRx of the Secondary Securities, except that CytRx will bear any discounts and commissions relating to any sale of the Secondary Securities.

SELLING STOCKHOLDER

The following table sets forth information with respect to the beneficial ownership of our common stock by CytRx as of April 30, 2009 after giving further effect to the offering of the Secondary Securities pursuant to this prospectus. The information shown does not give effect to the sale of any of the Primary Securities. Beneficial ownership is determined in accordance with SEC rules, and generally includes voting or investment power with respect to securities.

CytRx, if it desires, may dispose of the Secondary Securities covered by this prospectus from time to time at such prices as it may choose. Before any stockholder other than CytRx may use this prospectus in connection with an offering of Secondary Securities, this prospectus must be amended or supplemented to include the name and number of Secondary Securities beneficially owned by the selling stockholder and the number of Secondary Securities to be offered. Any amended or supplemented prospectus also will disclose whether any selling stockholder named in that amended or supplemented prospectus has held any position, office or other material relationship with us or any of our predecessors or affiliates during the three years prior to the date of the amended or supplemented prospectus.

	Beneficial Ownership of Selling Stockholder Before this Offering		Number of Shares Being Offered	Beneficial Ownership Upon Completion of this Offering (Assuming all Shares Offered are Sold)	
	Number of Shares	Percent		Number of Share	Percent
CytRx Corporation	6,268,881	45.4%	500,000	5,768,881	41.7%

Arrangements with CytRx

We were incorporated in April 2006 by CytRx and four founding members of our scientific advisory board for the purpose of pursuing the development or acquisition of RNAi-related technologies and assets. The President and Chief Executive Officer of CytRx, Steven A. Kriegsman, is a member of our Board of Directors. The Chairman of our Board of Directors, Sanford J. Hillsberg, is an attorney with TroyGould PC, which has represented CytRx since 2003.

We have entered into the following agreements with CytRx.

Contribution Agreements

On January 8, 2007, we entered into a contribution agreement with CytRx under which CytRx assigned and contributed to us substantially all of its RNAi-related technologies and assets. The assigned assets consisted primarily of CytRx's licenses from University of Massachusetts Medical School (UMMS) and from the Carnegie Institution of Washington relating to fundamental RNAi technologies, as well as equipment situated at CytRx's Worcester, Massachusetts, laboratory. In connection with the contribution, we issued to CytRx approximately 85% of our outstanding shares of common stock immediately following the issuance.

On April 30, 2007, we entered into another contribution agreement with CytRx under which CytRx contributed to us $17.0 million in exchange for an additional 3,273,292 shares of our common stock. We used $2.0 million of this amount to reimburse CytRx for the estimated amount of expenses that had been incurred by CytRx as of April 30, 2007 pursuant to the January 8, 2007 reimbursement agreement described below.

Registration Rights Agreement

On April 30, 2007, we also entered into a registration rights agreement with CytRx under which we agreed, upon CytRx's request, to use our best efforts to cause to be registered under the Securities Act the RXi shares originally issued to CytRx pursuant to our contribution agreements with CytRx. Pursuant to the registration rights agreement, we also granted to CytRx "piggyback" registration rights entitling CytRx to include its RXi shares in any registration statement filed by us with the SEC. The offer and sale of the Secondary Securities have been included in the registration statement of which this prospectus is a part pursuant to CytRx's exercise of its piggyback registration rights.

Reimbursement Agreements

On January 8, 2007, we also entered into a letter agreement with CytRx under which we agreed to reimburse CytRx, following our initial funding, for all organizational and operational expenses incurred by CytRx in connection with our formation and initial operations, and to bear or reimburse CytRx for an allocable share of any investment banking fees, placement agent fees and other offering expenses incurred by CytRx in connection with our fundraising activities. In connection with the April 30, 2007 contribution agreement with CytRx described above, we reimbursed CytRx in accordance with this letter agreement. There are no further payments or obligations owed in accordance with this letter agreement.

On December 27, 2007, we entered into a letter agreement with CytRx under which we and CytRx agreed to a "fee-sharing" arrangement for expenses arising from the preparation of the registration statement for our initial public offering, and our application for the listing of our common stock on the Nasdaq Capital Market. Pursuant to this agreement, we agreed to reimburse CytRx an amount equal to the sum of (i) $30,000 plus (ii) 50% of the total relevant fees and expenses paid by CytRx to certain financial services professionals. Also under this agreement CytRx agreed to reimburse us 50% of the total relevant fees and expenses paid by us to our financial printer, our transfer agent and our legal counsel. There are no further payments or obligations owed in accordance with this letter agreement.

Stockholder and Preemptive Rights Agreement

On February 15, 2007, we entered into a letter agreement with CytRx and certain of our current stockholders. Under this letter agreement, we agreed to grant to CytRx preemptive rights to acquire any new securities that we propose to sell or issue so that CytRx may maintain its percentage ownership of us. The preemptive rights will expire on January 8, 2012, or such earlier time at which CytRx owns less than 10% of our outstanding common stock. Under this letter agreement, CytRx also undertakes to vote its shares of our stock in the election of our directors and dispose of their shares of our stock in accordance with the terms of its letter agreement with UMMS. CytRx has further agreed in this letter agreement to approve of actions that may be adopted and recommended by our Board of Directors to facilitate any future financing. We amended this letter agreement on July 28, 2008 to adjust certain non-material terms.

PLAN OF DISTRIBUTION

Primary Securities

We may sell Primary 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 Primary 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 Primary Securities and any applicable restrictions.

The prospectus supplement with respect to the Primary Securities of a particular series will describe the terms of the offering of the Primary Securities, including the following:

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

Any offering price and any discounts or concessions allowed or reallowed 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 Primary Securities covered by the prospectus.

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

We may authorize underwriters, dealers or other persons acting as our agents to solicit offers by certain institutions to purchase Primary 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 Primary 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.

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 Primary 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 Primary Securities in accordance with the terms of the Primary 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 Primary 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 Primary 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 Primary Securities may be new issues of Primary Securities and may have no established trading market. The Primary Securities may or may not be listed on a securities exchange. Underwriters may make a market in these Primary 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 Primary 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 Primary 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 Primary 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 Primary Securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

Secondary Securities

CytRx may, from time to time, sell, transfer, or otherwise dispose of any or all of its Secondary Securities on any stock exchange, market, or trading facility on which the shares are traded or in private transactions. These dispositions may be at fixed prices, at prevailing market prices at the time of sale, at prices related to the prevailing market price, at varying prices determined at the time of sale, or at negotiated prices.

CytRx may use any one or more of the following methods when disposing of Secondary Securities:

- ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;
- block trades in which the broker-dealer will attempt to sell the shares as agent, but may position and resell a portion of the block as principal to facilitate the transaction;
- purchases by a broker-dealer as principal and resale by the broker-dealer for its account;
- an exchange distribution in accordance with the rules of the applicable exchange;
- privately negotiated transactions;
- broker-dealers may agree with CytRx to sell a specified number of such shares at a stipulated price per share; or
- a combination of any such methods of sale.

The aggregate proceeds to CytRx from any sale of the Secondary Securities offered by it will be the purchase price of the common stock less discounts or commissions, if any. CytRx reserves the right to accept and, together with its agents from time to time, to reject, in whole or in part, any proposed purchase of Secondary Securities to be made directly or through agents. We will not receive any of the proceeds from any such sale.

CytRx also may resell all or a portion of the Secondary Securities in open market transactions in reliance upon Rule 144 promulgated under the Securities Act, provided that it meets the criteria and conform to the requirements of that rule.

CytRx and any broker-dealers or agents that participate in the sale of the Secondary Securities may be deemed to be "underwriters" within the meaning of Section 2(11) of the Securities Act. Any discounts, commissions, concessions or profit they earn on any resale of the shares may be underwriting discounts and commissions under the Securities Act. CytRx is subject to the prospectus delivery requirements of the Securities Act.

We have agreed with CytRx to keep the registration statement, of which this prospectus constitutes a part, effective for one year, subject to certain extensions, or earlier if all of the Secondary Shares are sold prior to the end of such period.

We will pay the costs and expenses relating to the offering by CytRx of the Secondary Securities, except that CytRx will bear any discounts and commissions relating to any sale of the Secondary Securities.

Prior Proposed Offering

Prior to filing the registration statement of which this prospectus is a part, we explored the possibility of conducting a private placement of our common stock with certain prospective investors. The proposed private placement sought to raise up to approximately $14,000,000 in gross proceeds. We did not accept any offers to buy our securities and none of our securities were sold in the proposed private placement. We terminated all offering activity related to the proposed private placement on April 29, 2009. This prospectus supersedes any offering materials used in the proposed private placement.

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 April 30, 2009, we are authorized to issue 50,000,000 shares of common stock. As of April 30, 2009, we had 13,821,629 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. Our common stock is not redeemable. For a more complete discussion of our dividend policy, please see "Dividend Policy."

The holders of our common stock, other than 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. Additionally,

under our agreement with CytRx and our current stockholders, 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.

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:

- 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 April 30, 2009, we had 332,500 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;
- 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 filed a copy of the form of indenture as an exhibit to the registration statement in which this prospectus is included. The indenture will be subject to and governed by the terms of the Trust Indenture Act of 1939.

We may offer under this prospectus up to an aggregate principal amount of $30,000,000 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 $30,000,000. Unless otherwise specified in the applicable prospectus supplement, the debt securities will represent direct, unsecured obligations of the Company 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;
- 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.

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 depositary for the global securities or the nominee of the depositary, and the global securities will be delivered by the trustee to the depositary 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 depositary arrangement for debt securities of a series that are issued in global form. None of our Company, 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 the Company, 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;
- 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 of 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
- 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;
- 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.

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. We hereby incorporate by reference the following documents:

- Our Annual Report on Form 10-K for the year ended December 31, 2008;
- Our Current Reports on Form 8-K filed on March 20, 2009 and April 28, 2009 (excluding any information furnished in such reports under Item 2.02, Item 7.01 or Item 9.01);
- 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; and
- Our definitive Proxy Statement on Schedule 14A filed on April 23, 2009.

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.

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, 2008 and 2007 and for the years then ended and for the period from inception (January 1, 2003) through December 31, 2008 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.