



UPDATE REPORT

Biotechnology Industry • July 30, 2009

Keith A. Markey, Ph.D.
Chrystyna Bedrij

RXI PHARMACEUTICALS (NASDAQCM: RXII)

RXI TAKES THE LEAD IN RNAI MEDICINE

- **The latest breakthroughs in siRNA design and delivery yield:**
 - **Proprietary tripartite siRNA constructs that underpin self-delivering therapies for local and systemic administration,**
 - **Nano-siRNA platform that enables the creation of elegant therapeutic molecules with high target specificity and low production costs, and**
 - **Oral delivery of siRNA therapies for systemic inflammatory diseases.**

- **We are updating our coverage on RXi Pharmaceuticals (NasdaqCM: RXII) with a BUY rating and a target price of \$22.00 per share.**

RXi Pharmaceuticals Corporation is delivering on the promise of its extraordinary scientific foundation with the recent development of novel gene-silencing siRNA constructs and the creation of the first oral delivery system for this type of therapeutic agent. The new, proprietary siRNA molecules are much smaller than typical designs, with fewer than 15 base pairs, and a separate invention that enables siRNA molecules to self-deliver to targeted cells. Moreover, a single-sequence siRNA has been created that offers even greater flexibility in designing gene-silencing molecules for research purposes. The oral delivery system is equally important, as it provides the first simple approach to administering siRNA medicines for systemic inflammatory diseases. Indeed, the Company working to identify a lead drug candidate, while concurrently investigating the medically important inflammatory pathways behind such diseases as rheumatoid arthritis. In



Share Price (07/29/09)	\$4.59
52-Week Price Low/High	\$2.71 - \$12.25
Mkt. Capitalization (issued)	\$63.4 MM
Shares Outstanding (issued)	13.82 MM
12-month Target Price	\$22.00
Website	www.rxipharma.com

the meantime, the Company is engaged in serious discussions with several potential partners interested in employing its novel technology for other indications.

INVESTMENT HIGHLIGHTS/KEY POINTS:

- **SELF-DELIVERING siRNA CONSTRUCT OPENS MANY DOORS FOR COMMERCIALIZATION.** RXi has created an entirely new and proprietary drug platform that takes advantage of an endogenous regulatory pathway governing gene expression to create novel medicines. The construct has several desirable features that give it an advantage over prior designs, including high potency, low off-target effects, non-immunogenicity, and nuclease stability. Moreover, it is spontaneously taken up by cells and may be targeted to specific tissues. As a result, the self-delivering siRNA may be administered via different routes, including intravenous, subcutaneous, and inhaled. The new siRNA are also much smaller than prior designs, in that they have fewer than 15 base pairs, which simplifies their manufacture. Such characteristics of this drug development platform set RXi apart in the emerging field of siRNA medicine, in our view.
- **ORAL DELIVERY PROVIDES A NEW APPROACH TO TREATING INFLAMMATORY DISEASES WITH siRNA.** Successful commercialization of siRNA medicines will depend as much on the delivery of the drug to the proper cells as it will on the active molecule itself. RXi has employed a well known particle, derived from yeast, as an oral delivery vehicle for siRNA targeting a key component of the immune system, macrophages. This unique delivery platform takes advantage of the β 1,3-D-glucan particle to protect its siRNA in the gut and deliver it via Peyer's patches in the small intestine to macrophages. These sentinels of the immune system, which are targeted by the siRNA delivered in the particle, then travel throughout the body in a quiescent state. RXi has already created an siRNA against an important enzyme in the inflammatory pathway and delivered it orally with the β 1,3-D-glucan particle. The preclinical results have provided the proof of concept for this technology by specifically reducing the expression of the enzyme MAP4k4 and demonstrating that doing so reduced production of the inflammatory cytokine tumor necrosis factor α (TNF α). More impressive still, oral administration of the siRNA protected mice against an otherwise lethal inflammatory stimulus.
- **THE RECENT TECHNOLOGICAL ADVANCES SET THE STAGE FOR THE INTERNAL DRUG DEVELOPMENT PROGRAM AND FOR PARTNERING.** The availability of both the self-delivering siRNA construct and the oral delivery system for inflammatory diseases give RXi considerable flexibility in setting its clinical development priorities. The Company has stated a desire to target rheumatoid arthritis, but whether that will be the first clinical program will be determined in the months ahead, as one goal for this year is to identify its lead drug candidate, regardless of indication. The other important aspect of the latest technologies is the partnering opportunities that they create. Again, the ability to deliver an siRNA medicine via different routes places a broad range of diseases within the sphere of influence. Having perfected these technologies and having hired an experienced business development executive, the Company is well positioned to leverage its capabilities via corporate collaborations. We believe the first deal will be announced in the months ahead.
- **RXII SHARES MERIT A HIGHER VALUATION.** We believe the recent developments place RXi at the forefront of the siRNA industry. The Company has a scientific foundation and proven technologies that are unequalled, and an experienced management team. Moreover, it is working to select its lead drug candidate for clinical development, while several additional compounds with validated therapeutic potential are at earlier stages in the R&D pipeline. Our financial model takes into consideration the three types of drug development programs that we believe are likely to emerge: a therapy that is developed internally; another compound that is validated preclinically, but partnered for clinical development and marketing support; and a third project that a corporate client initiates and brings into a collaboration to gain RXi's expertise. Based on indications that we believe are representative of each of these programs, our financial model yields a per-share valuation of \$22.00. Accordingly, we are reiterating our BUY recommendation with a target price of \$22 per RXII share.

TABLE OF CONTENTS

RXi Takes the Lead in siRNA Drug Designs	4
Orally active siRNA construct for systemic inflammatory diseases.....	4
Self-delivering siRNA opens the door to multiple applications.....	7
RXi's Partnering potential.....	10
Business Development Makes Headway	13
Update on the Initial Therapeutic Programs	13
Financial Review – Historical Perspective	13
Investment Concerns and Risks	14
Financial Forecasts & Valuation	15
Revenue Sources.....	15
Income Statement	18
Balance Sheet	19
Discounted cash flow analysis	20
Disclosures	21

RXi TAKES THE LEAD IN siRNA DRUG DESIGNS.

The company has surpassed the industry's early leaders, **Alnylam (NasdaqGS: ALNY)** and **Sirna** (a subsidiary of **Merck & Company [NYSE: MRK]**), in devising new structures and delivery systems for drugs based on RNAi. (Naturally occurring interfering RNA serve important regulatory functions in controlling the translation of messenger RNA into proteins.) Typically, siRNA have been double-stranded structures, ranging in length from about 19 base pairs up to about 30 base pairs. Chemical modifications have been incorporated into the structures to protect against enzymatic degradation, and special delivery constructs, including liposomes and nanoparticles, have been devised to deliver siRNA to cellular targets. RXi initially focused on blunt-ended siRNA molecules, which it dubbed rxRNA, with 25 or more base pairs. This molecular structure, which does not infringe on others' intellectual property, is still a viable drug design, but recent advances provide even greater flexibility to create new pharmaceutical agents.

ORALLY ACTIVE siRNA CONSTRUCT FOR SYSTEMIC INFLAMMATORY DISEASES

RXi has created a β 1,3-D-glucan-encapsulated siRNA particle (GeRP) that protects the active molecule from digestion in the gastrointestinal tract, enabling oral administration.¹ Just as important, the new structure is readily absorbed by M cells in Peyer's patches of the intestine, where GeRPs are transferred intact from the M cells to macrophages. (See Figure 1.) Thus, a biologically active siRNA may be delivered to an early sentinel cell of the immune system, which is known to travel throughout the body.

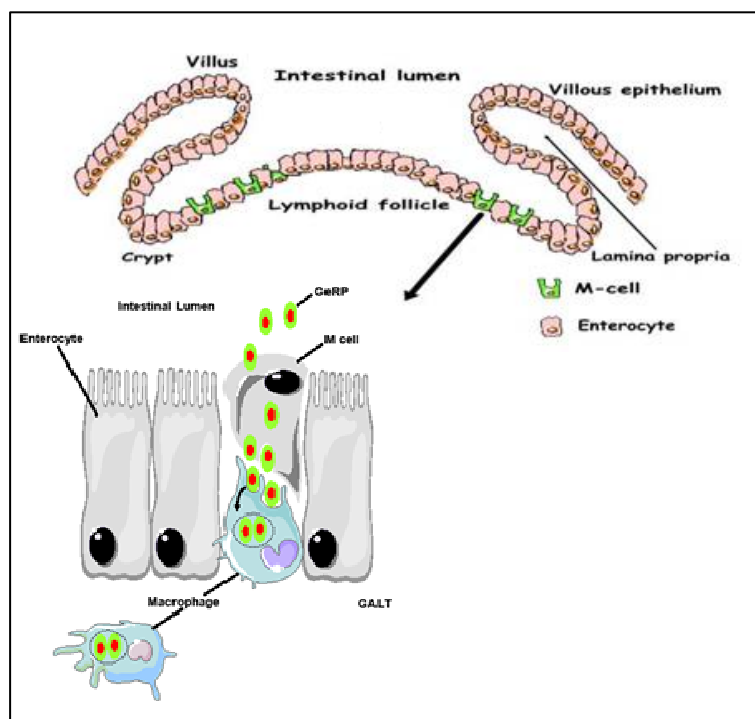


Figure 1. Peyer's patches, which are gut associated lymphatic tissue (GALT), are oval, raised areas of closely packed lymphoid follicles, measuring approximately 1 cm by 4 cm. Overlaying the lymphoid follicles are enterocytes or intraepithelial cells and specialized antigen-sampling cells, called M cells. M cells take up antigens, including GeRPs into pinocytotic vesicles, but do not degrade them. Instead, they present the antigens/GeRPs to macrophages and dendritic cells (not shown) to stimulate an appropriate immune response.

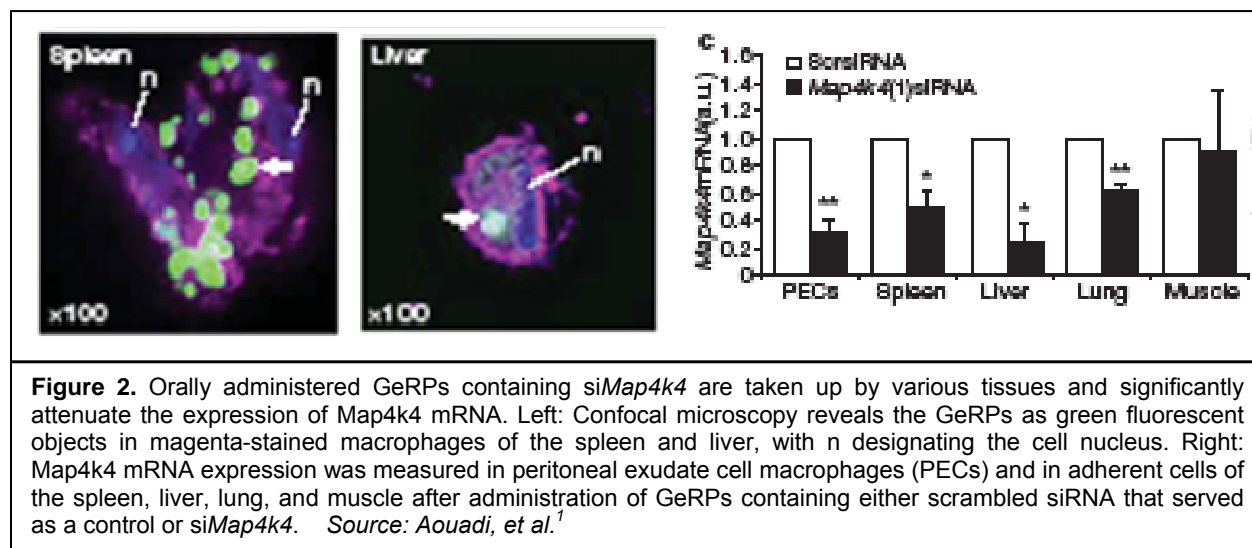
Sources: *Pharmainfo.net* (accessed 07/2009) and Aouadi, M, et al.¹

Preparation of GeRPs involves several steps: First, Baker's yeast is treated to remove the cytoplasm and cell wall polysaccharides, other than β 1,3-D-glucan. A core, consisting of tRNA coated with cationic polyethylenimine, is then introduced, followed by the anionic siRNA and then another layer of polyethylenimine. The resultant structure releases the siRNA upon exposure to the acidic environment of specialized compartments (phagosomes) inside macrophages. Subsequently, the siRNA molecule

¹ Aouadi, M, et al. Orally delivered siRNA targeting macrophage Map4k4 suppresses systemic inflammation. *Nature* 2009; 458(7242): 1180.

reaches the cytoplasm of the macrophage where it inhibits the translation of its targeted mRNA, thereby altering a cellular pathway(s).

Preclinical research of GeRPs has demonstrated their utility as a delivery system for down-regulating the immune system, and it has uncovered a new proinflammatory pathway.¹ Specifically, GeRP-delivery of an siRNA against tumor necrosis factor α (TNF α) mRNA² was found to block expression of the cytokine in macrophages *in vitro*. Subsequent work to characterize intracellular signals involved in controlling its expression led to the discovery that the regulatory enzyme Map4k4 (a mitogen-activated kinase that participates in the TNF α signaling pathway) is directly involved. An *siMap4k4*² that was delivered via GeRPs showed good activity in an experimental model of inflammation by inhibiting lipopolysaccharide-induced expression of TNF α from cultured macrophage in a dose-dependent manner. Moreover, it had no effect on the expression of participants in other pathways (cJun N-terminal kinases 1 and 2, extracellular signal-related kinase 1 and 2, and nuclear factor κ B) that are known to influence TNF α . When *siMap4k4* was administered orally, similar results were obtained. As shown in Figure 2, fluorescently labeled GeRPs were found in the spleen and liver, and the *siMap4k4* significantly reduced the mRNA of this enzyme in all tissues examined, except for skeletal muscle.



The effect of *siMap4k4* was also tested in cultured peritoneal exudate cell macrophages for its ability to attenuate the expression of both TNF α and another inflammatory cytokine, interleukin-1 β , which are known to act synergistically. The *siMap4k4* knocked down both cytokines by 80%, while an *siTNF α* had no effect on interleukin-1 β expression. This is important because *siMap4k4* significantly reduces two cytokines, TNF α and interleukin-1 β , that have been implicated in a serious inflammatory disease, rheumatoid arthritis (RA). (RA is discussed in detail in the blue area below.)

The scientists then examined the protective properties of *siMap4k4* on the lethality of a combination of lipopolysaccharide and d-galactosamine *in vivo*. (This combination typically elicits a lethal inflammatory response.) The results showed that the anti-inflammatory siRNA enabled 50% of the mice to survive for at least 8 hours and 40%, for the long term, while 90% of the unprotected (control) animals died within 4 to 8 hours of the injection. Hence, siRNA therapy is effective *in vivo* against a highly inflammatory condition.

² All references to an siRNA targeting the mRNA of a specific protein will be presented as "si" followed by the mRNA in italics – e.g., *siTNF α* for the siRNA targeting the mRNA of TNF α .

In all, orally administered GeRPs successfully delivered five different siRNA to macrophages, resulting in the silencing of three distinct genes for about eight days. The length of the therapeutic effect is noteworthy, as the siRNA tested were not chemically modified to optimize their stability, which means that GeRPs not only serve as an oral delivery system, but also effectively protect the siRNA until they are internalized and processed by the macrophage.

GeRP technology has multiple potential therapeutic applications, based on its ability to deliver siRNA that quell inflammatory pathways. Accordingly, potential clinical applications include rheumatoid arthritis, inflammatory bowel disease, psoriasis, atherosclerosis, and obesity-associated insulin resistance.

Rheumatoid arthritis is a complex inflammatory disease with genetic and environmental risk factors that afflicts between 0.5% and 1% of the developed world's population.³ Early research divided patients into two groups based upon the presence or absence of antibodies to rheumatoid factor. But more recent research has demonstrated that antibodies recognizing cyclic citrullinated peptide (ccp) antigens are more strongly correlated with the disease, and tests, based on this association, are now available to diagnose the disease at an early stage and to monitor progression.^{4,5} (Citrullinated peptides are formed when an enzyme converts arginine into the α -amino acid citrulline. The two peptide ends may be joined forming a cyclic peptide that is extremely resistant to enzymatic digestion. This probably contributes to their ability to elicit an immune response, autoantibodies.) More recent studies of the genetic basis of RA have found that there are at least two subpopulations, based on the presence or absence of ccp antibodies and certain susceptibility genes. For instance, certain alleles in the HLA-DRB1 locus are found in all patients who test positive and in some patients who test negative, while variants of another gene, for a tyrosine phosphatase, are only found associated with a lack of ccp antibodies.^{6,7} Genetic variants also influence susceptibility to the most common environmental risk factor, smoking, the age of onset, and disease severity.^{8,9}

Identifying RA early is important to minimizing joint damage and thereby preserving the patient's quality of life, since disease progression results in chronic pain, fatigue, and loss of function. Clinical studies have shown that swift intervention with multiple anti-inflammatory agents is able to prevent radiographic disease progression, even in patients at risk of severe tissue damage.¹⁰ Yet, a survey of physicians and patients suggests that, in clinical practice, remission is typically reached in about 30% of all patients, as both doctor and patient assessments characterize a low level of disease activity as "remission."¹¹ Thus, a better definition of clinical remission and/or routine detection methods is needed. There is another reason for intervening as quickly as possible, and that is an economic one. Studies have found that treatment costs increase as RA progresses, with one report showing that patients in the worst quartile of functional status incurred direct medical costs in the next year that were about \$5,000 more than those of patients

³ Gabriel, SE, and Michaud, K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009; 11: 229.

⁴ Schellekens, GA, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. *Arthritis Rheum* 2000; 43(1): 155.

⁵ van Venrooij, WJ and Zendman, AJ. Anti-CCP2 antibodies: an overview and perspective of the diagnostic abilities of this serological marker for early rheumatic arthritis. *Clin Rev Allerg Immunol* 2008; 34: 36.

⁶ Klareskog, L, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum* 2006; 54(1): 38.

⁷ Plenge, RM, et al. Replication of putative candidate-gene associations with rheumatoid arthritis in >4,000 samples from North America and Sweden: association of susceptibility with PTPN22, CTLA4, and PADI4. *Am J Hum Genet* 2005; 77(6): 1044.

⁸ Karlson, EW, et al. Associations between human leukocyte antigen, PTPN22, CTLA4 genotypes and rheumatoid arthritis phenotypes of autoantibody status, age at diagnosis and erosions in a large cohort study. *Ann Rheum Dis* 2008; 67(3): 358.

⁹ van Mil, AH, et al. The HLA_DRB1 shared epitope alleles differ in the interaction with smoking and predisposition to antibodies to cyclic citrullinated peptide. *Arthritis Rheum* 2007; 56(2): 425.

¹⁰ de Vries-Bouwstra, JK, et al. Progression of joint damage in early rheumatoid arthritis. *Arthritis Rheum* 2008; 58(5): 1293.

¹¹ Wolfe, F, et al. Remission in rheumatoid arthritis: physician and patient perspectives. *J Rheumatol* 2009; 36: 930.

in the best quartile.^{12,13} Presently, there is no evidence that early and swift intervention reduces direct medical costs over the long term, but thought-leaders are working under this hypothesis. Indeed, biological disease-modifying agents (notably, the anti-TNF α drugs etanercept, infliximab, and adalimumab; the interleukin-1 antagonist anakinra; the inhibitor of T cell stimulation, abatacept; and the B-cell targeting drug rituximab) that cost \$15,000 to \$25,000 per year (except for adalimumab, which costs \$47,000) are recommended for patients who fail to respond within a few months to less costly drug therapies.^{14,15} This has led to adverse events, such as an increased susceptibility to infection when the anti-TNF α drugs are used in combination with other disease-modifying agents. It has also led to difficult choices, given the financial constraints on health care budgets, and prompted research to identify patients who are most likely to require this type of drug and who are most likely to respond. (One third of RA patients have a minimal or no response to anti-TNF α therapy within 3 to 6 months, and many others lose response over time.) Data is beginning to be compiled, with one study identifying several genetic variations with predictive value in determining TNF α responders.¹⁶ Alternative therapies consist of older drugs, including methotrexate, sulfasalazine, and immunosuppressant glucocorticoid hormones, all of which come with serious toxicities.

We like RXi's decision to investigate the use of siRNA to target systemic inflammatory disease. The patient populations are huge and today's treatment options are far from ideal. The fact that *siMap4k4* affords an opportunity to intervene in two, synergistic inflammatory pathways may enable it to be more beneficial than current drugs. Given its success to date in the anti-inflammatory field, RXi should be able to garner a lucrative partnership agreement with an experienced global pharmaceutical corporation.

SELF-DELIVERING siRNA OPENS THE DOOR TO MULTIPLE APPLICATIONS.

RXi has advanced well beyond traditional siRNA designs in creating a patented molecule capable of self-delivery to targeted cells. The new, tripartite construct consists of two or three distinct portions: (1) an siRNA that inhibits translation of a specific mRNA for therapeutic applications, (2) a targeting agent that delivers the siRNA to a certain cell(s), and (3) an optional linker between the other two portions.¹⁷ As with any siRNA drug, the oligonucleotide portion of the self-delivering construct is designed to recognize a specific mRNA, and the targeting agent is chosen for its ability to facilitate uptake by a particular cell and, possibly, for localization of the siRNA within a region of the cell. In some circumstances, the company intends to use a linker that covalently joins the targeting agent and the siRNA. Its function is to provide the proper attachment between the other two portions of the molecule and, possibly, to permit the detachment (activation) of the siRNA once the cellular target has been reached. (Note that more recent patent applications have been filed for more advanced molecular structures, though the patent we cite provides a reasonable glimpse of the technological breakthroughs.)

The tripartite structure is only one aspect of the new siRNA construct, for RXi has also discovered ways to reduce the size of the siRNA to fewer than 15 base pairs, while retaining activity and specificity.¹⁸ As shown in Figure 3, the number of nucleotides in a self-delivering siRNA has a marked effect on the molecule to penetrate cell membranes. Self-delivering *siMap4k4* constructs with 25 and 21 nucleotides reduced the expression of Map4k4 in immortalized cervical cancer cells (Hela cell line) in culture by about 35% and 55%, respectively, at a concentration of 500 nM, while an siRNA with only 12 base pairs

¹² Michaud, K, et al. Direct medical costs and their predictors in patients with rheumatoid arthritis: a three-year study of 7,527 patients. *Arthritis Rheum* 2003; 48(10): 2750.

¹³ Bansback, N, et al. The economics of treatment in early rheumatoid arthritis. *Best Prac Res Clin Rheumatol* 2009; 23: 83.

¹⁴ Annual costs were calculated using retail prices quoted on Medscape Drug website as of June, 2009 and using an average adult's weight of 80 kg.

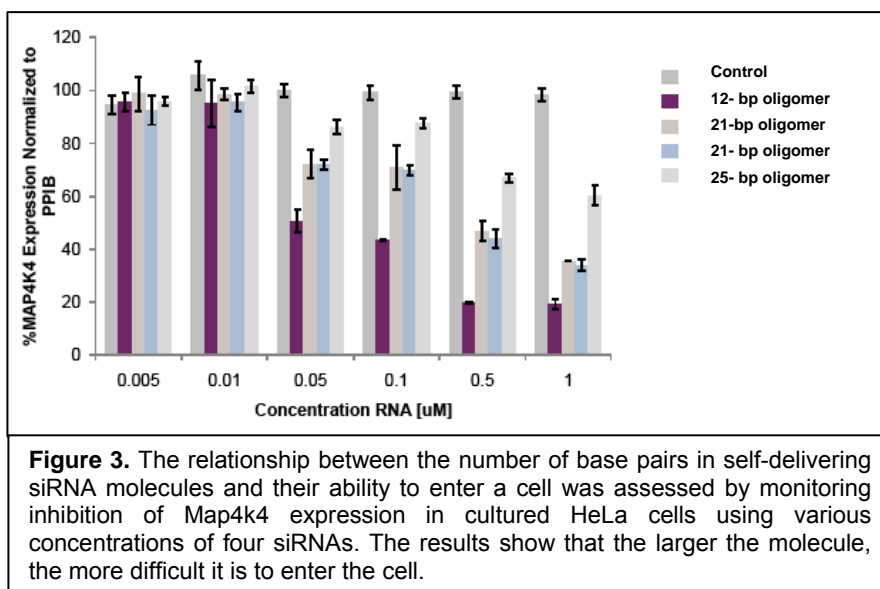
¹⁵ Combe, B, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (SCISIT). *Ann Rheum Dis* 2007; 66(1): 34.

¹⁶ Liu, C, et al. Genome-wide association scan identifies candidate polymorphisms associated with differential response to anti-TNF treatment in rheumatoid arthritis. *Mol Med* 2009; 14(9): 575.

¹⁷ Woolf, TM, et al. Tripartite RNAi Constructs. World Intellectual Property Organization Patent no. WO 2009/045457 A2.

¹⁸ Personal communication from RXi Pharmaceuticals, May 2009.

lowered expression by 80% at the same concentration. Further characterization of the self-delivering molecule has found that it causes little/no immune induction and has high specificity for the targeted mRNA. This novel design platform incorporates four different chemistries and six unique inventions.



As presented in Table 1, the self-delivering siRNA construct (designated sd-rxRNA™) has many potential applications. Local administration requires no special formulation to target such tissues as open wounds, mucosa, lung, the central nervous system, and the eye. Of course, suitable delivery technology, such as inhalation or infusion systems, will be needed to administer the drug to the lung or central nervous system, respectively. Systemic administration of self-delivering siRNA should be possible, given the low toxicity associated with highly-specific siRNA. This type of drug may also prove useful in targeting organs such as the liver and lung; cells comprising fat, heart, and bone marrow; and diseases characterized by aberrant cell behavior, including arthritis and cancer.

Table 1. Potential clinical applications of self-delivering siRNA.

Administration	Technologies	Properties	Targeted tissues
Local	sd-rxRNA™	Direct application, no formulation	<ul style="list-style-type: none"> ▪ Compromised skin ▪ Mucosal tissues ▪ Lung ▪ CNS ▪ Eye
Systemic (IV and SC)	sd-rxRNA™ Neutral Nanotransporters	Low toxicity	<ul style="list-style-type: none"> ▪ Liver ▪ Lung ▪ Adipocytes ▪ Cardiomyocytes ▪ Bone marrow ▪ Inflammation sites ▪ Tumors

RXi has not determined the first clinical application for its self-delivering siRNA, though it probably will involve local administration. For our financial modeling purposes, we have chosen idiopathic pulmonary fibrosis as representative of this R&D program. This disease is discussed in the blue area below.

Idiopathic pulmonary fibrosis is a progressive interstitial lung disease characterized by fibrotic foci that restrict lung flexibility and eventually prevent breathing. Patients often present with a feeling of breathlessness and a dry cough, typically in late stages of the disease, as the life expectancy of the average patient is only 3 to 5 years after diagnosis. The pathogenesis of IPF is poorly understood, although myofibroblast activation, extracellular matrix deposition, and alveolar epithelial type II cell dysfunction play important roles. Part of the problem is that there are several risk factors for interstitial lung diseases, including genetic and environmental (e.g., smoking, radiation therapy, and infection) that exert their influence via distinct paths.¹⁹ The most well documented contributor is transforming growth factor β 1 (TGF- β 1). This cytokine is important because it drives the transformation of epithelial cells into mesenchymal cells (i.e., fibroblasts) and the differentiation of fibroblasts to myofibroblasts.²⁰ These changes underlie a remodeling of the lung that includes the release of matrix metalloproteinases, a deposition of collagen, and an increase in myofibroblasts that express smooth muscle actin, which restricts lung flexibility. Several steps along the pathway lend themselves to intervention. An antibody against α v β 6 integrin, which converts secreted TGF- β 1 to an active state, has been shown to prevent lung fibrosis after exposure to radiation in an animal model.²¹ However, other genes may also play a role in development of IPF, as two studies of differences between patients characterized as rapid progressors and slow progressors found that the former overexpressed genes related to DNA replication, cell cycle regulation, morphogenesis, oxidative stress, and migration/proliferation.^{22,23} An analysis identified the following canonical pathways as significantly affected in IPF patients: insulin growth factor 1, which, like TGF- β 1, stimulates fibronectin synthesis in fibroblasts from IPF patients, but not normal individuals²⁴, and PI3K/AKT, inhibition of which reduces collagen deposition and TGF- β 1 induced fibrosis. Two individual genes that were upregulated were for the adenosine A_{2b} receptor, which is involved in the differentiation of fibroblasts to myofibroblasts, and for prominin-1/CD133, which is found in the embryonic epithelium and in alveolar epithelial cells of the lung, suggesting that this protein plays a role in the transformation of epithelial cells to fibroblasts. Another gene that was overexpressed was the gene for matrix metalloproteinase 9, which is known to damage basement membranes and activate TGF- β 1 under pathogenic conditions.²⁵ Yet other potential targets for drug development include several cytokines that bind to the CCR2 receptor and are involved in recruiting fibrocytes from circulation.²⁶ Indeed, expression of one ligand, CCL2, was required for fibrosis in a preclinical model.²⁷ Finally, we note that a recent study of alveolar epithelial type II cells identified the WNT/ β -catenin signaling pathway as upregulated during lung fibrosis.²⁸ Specifically, WNT1-inducible signaling protein was overexpressed in hyperplastic alveolar epithelial cells from patients with IPF and from an experimental model of the disease. It is believed that chronic stimulation and injury of these cells

¹⁹ Selman, M, et al. Accelerated variant of idiopathic pulmonary fibrosis: clinical behavior and gene expression pattern. PLoS ONE 2007; 2: e 482.

²⁰ Kasai, H, et al. TGF- β 1 induces human alveolar epithelial to mesenchymal cell transition (EMT). Respirat Res 2005; 6: 56.

²¹ Puthawala, K, et al. Inhibition of integrin α v β 6, an activator of latent transforming growth factor- β , prevents radiation-induced lung fibrosis. Am J Respir Crit Care Med 2008; 177: 82.

²² Selman, M, et al. Accelerated variant of idiopathic pulmonary fibrosis: clinical behavior and gene expression pattern. PLoS ONE 2007; 5: e482.

²³ Boon, K, et al. Molecular phenotypes distinguish patients with relatively stable from progressive idiopathic pulmonary fibrosis (IPF). PLoS ONE 2009; 4(4): e5134.

²⁴ Hetzel, M, et al. Different effects of growth factors on proliferation and matrix production of normal and fibrotic human lung fibroblasts. Lung 2005; 183(4): 225.

²⁵ Yu, Q, and Stamenkovic, I. Cell surface-localized matrix metalloproteinase-9 proteolytically activates TGF-beta and promotes tumor invasion and angiogenesis. Genes Dev 2000; 14(2): 163.

²⁶ Moore, BB, et al. The role of CCL12 in the recruitment of fibrocytes and lung fibrosis. Am J Respir Cell Mol Biol 2006; 35(2): 175.

²⁷ Gharaee-Kermani, M, et al. CC-chemokine receptor 2 required for bleomycin-induced pulmonary fibrosis. Cytokine 2003; 24(6): 266.

²⁸ Konigshoff, M, et al. WNT1-inducible signaling protein-1 mediates pulmonary fibrosis in mice and is upregulated in humans with idiopathic pulmonary fibrosis. J Clin Invest 2009; 119(4): 772.

plays a pivotal role in the activation of fibroblasts and IPF pathogenesis.²⁹ In sum, there are a number of gene silencing strategies that may be pursued to treat IPF.

No medicines available today reverse or slow the progression of IPF. Instead, patients receive palliative care that may include corticosteroids (e.g., prednisolone), cytotoxic drugs (e.g., azathioprine), anti-fibrotic agents (e.g., bosentan and penicillamine), antioxidants, and oxygen therapy. Ultimately, lung transplantation is an option for some. Developing effective therapies is important for the patient population is expected to increase significantly as baby boomers grow older, since disease prevalence rises with age, from 4 cases per 100,000 persons aged 18 to 34 years to more than 200 cases per 100,000 persons aged 75 years and older.³⁰ Overall prevalence is estimated to be 42.7 cases per 100,000 individuals in the United States today.

RXi's PARTNERING POTENTIAL

The Company's multiple siRNA technologies, which have no equal, are attracting considerable attention among pharmaceutical companies seeking novel approaches, especially for drugging disease-related targets that cannot be approached via traditional medicinal chemistry. Huge sums have already been invested in the siRNA field, as evidenced by Merck's \$1.2 billion purchase of Sirna in 2006. Yet, the number of compounds that have reached clinical trials is still very small. (According to a search of the website ClinicalTrials.gov, only seven siRNA therapies are currently undergoing human testing.³¹) We believe RXi's unique technologies will enable it to enter into multiple partnering agreements in time. Accordingly, our financial model includes one early-stage partnering agreement that is representative of the possibilities. Our assumption is that RXi is engaged by another corporation to create an siRNA therapy to treat cancer, an area in which the Company has expressed little direct interest. The indication that we have chosen for modeling purposes is colorectal cancer, which is discussed in detail in the blue area below.

Colorectal cancer has constituted a large and fairly homogeneous market for drug therapies, with sales of monoclonal antibody-based drugs alone totaling \$3.6 billion (all indications) last year. That is changing, though, with improved diagnostic techniques, including the use of biomarkers, that identify patients who are most likely to respond to a particular treatment. This is being driven by both medical and economic reasons, since high-priced biotech drugs are not effective for all patients (and have toxicity issues) and health care budget constraints are forcing tough decisions by payers. In addition, evidence that the etiology of colorectal cancer includes multiple molecular paths is supporting a trend toward the use of combination therapies.

Based on the genetic heterogeneity of colorectal cancer, a number of proteins involved in various pathways have already been targeted with siRNA or gene antisense technology. Table 2 provides a summary of the targets and genetic knockdown results identified through a brief (non-exhaustive) search of the scientific literature:

²⁹ Selman, M, and Pardo, A. Role of epithelial cells in idiopathic pulmonary fibrosis. Proc Am Thorac Soc 2006; 3: 364.

³⁰ Raghu, G, et al. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care 2006; 174(7): 810.

³¹ Accessed the website www.clinicaltrials.gov on July 27, 2009.

Table 2. Molecules Successfully Targeted via siRNA

Target	Normal Function	Effect of Genetic Knockdown
FLIP/XIAP	Both proteins are inhibitors of caspase signaling apoptosis pathways	Induces Bax-independent apoptosis ³²
IGF1R/EGFR	Insulin-like growth factor-1 receptor and epidermal growth factor receptor use tyrosine kinase to effect cell growth and proliferation	Reduced proliferation and increased apoptosis ³³ ; IGF1R found in 90% of colorectal carcinomas
mTOR kinase	Helps to mediate cell responses to such stress as DNA damage and nutrient deprivation	Decreased <i>in vitro</i> and <i>in vivo</i> cell growth ³⁴
TLR4	A member of the toll-like receptor family; plays a role in pathogen recognition and activation of innate immunity	Decreases liver tumor burden of colorectal metastases ³⁵
VEGF-C	A vascular endothelial growth factor that promotes formation & maintenance of lymphatic endothelium	Inhibits tumor lymphangiogenesis and growth ³⁶

Undoubtedly, additional molecules that are overexpressed and/or play key roles in colorectal cancer genesis or metastasis will be targeted, at least experimentally, via siRNA. Our literature search turned up a short list we believe are bona fide targets, which are presented in Table 3:

Table 3. Potential Molecular Targets for siRNA Therapies

Target	Rationale
14-3-3 sigma	A cell cycle regulatory protein whose expression in colorectal cancer is an indicator of poor prognosis; also protects breast cancer cells from chemotherapy ^{37,38}
AURKA	A regulator of mitosis that is overexpressed in colorectal cancer and is associated with chromosomal instability ³⁹
Hsp 27	A molecular chaperone whose overexpression is directly related to metastatic capacity of colorectal cancer cells and has been impli-

³² Wilson, TR, et al. Combined inhibition of FLIP and XIAP induces Bax-independent apoptosis in type II colorectal cancer cells. *Oncogene* 2009; 28(1): 63.

³³ Kaufub, S, et al. Dual silencing of insulin-like growth factor-1 receptor and epidermal growth factor receptor in colorectal cancer cells is associated with decreased proliferation and enhanced apoptosis. *Mol Cancer Ther* 2009; 8(4): 821.

³⁴ Zhang, YJ, et al. mTOR Signaling pathway is a target for the treatment of colorectal cancer. *Ann Surg Oncol* 2009; June 11: epub ahead of print.

³⁵ Earl, TM, et al. Silencing of TLR4 decreases liver tumor burden in a murine model of colorectal metastasis and hepatic steatosis. *Ann Surg Oncol* 2009; 16(4): 1043.

³⁶ He, XW, et al. Vector-based RNA interference against VEGF-C inhibits tumor lymphangiogenesis and growth of colorectal cancer in vivo and in mice. *Chin Med J (Engl)* 2008; 121(5): 439.

³⁷ Perathoner, A, et al. 14-3-3sigma expression is an independent prognostic parameter for poor survival in colorectal carcinoma patients. *Clin Cancer Res* 2005; 11(9): 3274.

³⁸ Liu, Y, et al. Identification of 14-3-3sigma as a contributor to drug resistance in human breast cancer cells using functional proteomic analysis. *Cancer Res* 2006; 66(6): 3248.

³⁹ Baba, Y, et al. Aurora-A expression is independently associated with chromosomal instability in colorectal cancer. *Neoplasia* 2009; 11(5): 418.

	cated in irinotecan resistance; has been targeted via antisense gene therapy in bladder cancer ^{40,41,42}
MUC1	A highly glycosylated transmembrane protein that plays a role in protecting cells lining various tissues; overexpressed in colorectal cancer, enabling anchorage-independent growth and tumorigenicity; blocks apoptosis and protects against chemotherapy in multiple myeloma cells, as demonstrated via siRNA targeting ^{43,44}
Osteopontin	A secreted glycoprotein normally involved in various physiological processes, but also a highly upregulated target of the Wnt signalling pathway that's been linked to tumorigenesis, cell motility, and metastasis formation; found predominantly in established primary tumors and metastases, but not early tumors ⁴⁵
PTMA	Expression is markedly higher in radioresistant rectal cancer ⁴⁶
VICKZ	Three regulatory RNA-binding proteins used during embryogenesis for cell migration; overexpressed in 97% of colorectal cancer cells in lymph node metastases and found in early-stage disease ⁴⁷

Even with the additional targets that we've identified, the list could be significantly longer, as gene expression profiles of microsatellite stable and highly unstable colorectal cancers identified 72 genes that were differentially expressed between the two forms of the disease under stringent prognostic screening criteria and 451 mRNAs under less restrictive selection criteria.⁴⁸ (The two types of colorectal cancer could actually be distinguished based on the expression profiles of just 27 mRNA and miRNA, indicating that these tumors have different molecular origins.) Thus, RXi will have ample opportunities to develop anticancer drugs with partners.

Another important observation that comes from Tables 2 and 3 is that siRNA intervention is consistent with the trend toward combination drug regimens. Indeed, several of the targets were noted for their ability to protect a cell from radiation and/or chemotherapy, and siRNA rendered the cells sensitive. A couple of the regimens listed have even involved combinations of siRNA against two different cell pathways. In such cases, the individual siRNA were not as effective as the combinations.

⁴⁰ Garrido, C, et al. Heat shock protein 27 enhances the tumorigenicity of immunogenic rat colon carcinoma cell clones. *Cancer Res* 1998; 58(23): 5495.

⁴¹ Choi, DH, et al. Heat shock protein 27 is associated with irinotecan resistance in human colorectal cancer cells. *FEBS Lett* 2007; 581(8): 1649.

⁴² Kamada, M, et al. Hsp27 knockdown using nucleotide-based therapies inhibit tumor growth and enhance chemotherapy in human bladder cancer cells. *Mol Cancer Ther* 2007; 6(1): 299.

⁴³ Byrd, JC and Bresalier, RS. Mucins and mucin binding proteins in colorectal cancer. *Cancer Metastasis Rev* 2004; 23: 77.

⁴⁴ Kawano, T, et al. MUC1 oncoprotein promotes growth and survival of human multiple myeloma cells. *Int J Oncol* 2008; 33: 153.

⁴⁵ Rohde, F, et al. Expression of osteopontin, a target gene of de-regulated Wnt signaling, predicts survival in colon cancer. *Int J Cancer* 2007; 121: 1717.

⁴⁶ Ojima, E, et al. Effectiveness of gene expression profiling for response prediction of rectal cancer to preoperative radiotherapy. *J Gastroenterol* 2007; 42(9): 730.

⁴⁷ Vainer, G, et al. A role for VICKZ proteins in the progression of colorectal carcinomas: regulating lamellipodia formation. *J Pathol* 2008; 215(4): 445.

⁴⁸ Lanza, G, et al. mRNA/microRNA gene expression profile in microsatellite unstable colorectal cancer. *Mol Cancer* 2007; 6: 54.

BUSINESS DEVELOPMENT MAKES HEADWAY

In April, Ramani Varanasi joined RXi as their Vice President of Business Development. She came with an excellent track record covering 15 years of experience in structuring, negotiating, and closing business alliances for Millennium Pharmaceuticals, Momenta Pharmaceuticals, and Archemix Corporation. As such, she has extensive contacts throughout the pharmaceutical and biotechnology industries. Given her background and the announcements of RXi's latest technological advances, we believe her efforts will begin to bear fruit in the closing months of this year.

The deals will serve multiple purposes, in our view. For one, they will provide external validation to the Company's technologies. For another, they will probably add clarity to the R&D pipeline and thereby provide a better understanding of the siRNA platforms' commercial potential. Any upfront fees will give the Company non-dilutive financing. Finally, we believe the deals will help to increase the investment community's awareness of RXi's competitive advantages in the field of siRNA therapeutics.

UPDATE ON THE INITIAL THERAPEUTIC PROGRAMS

RXi has adjusted its R&D pipeline to reflect the opportunities that its latest technologies afford and the areas of strategic interest. The following updates should be read in conjunction with our initiation report, dated September 3, 2008. The current status of the development pipeline is as follows:

- **Amyotrophic Lateral Sclerosis:** This project, founded on abnormal superoxide dismutase-1 in the familial form of the disease, was undertaken to validate the Company's early technology and was not intended to be developed internally. Dr. Robert Brown, who identified the genetic basis of this form of ALS and is an advisor to the Company, is working with the Amyotrophic Lateral Sclerosis Society to conduct clinical trials of the siRNA. Familial ALS is a rare disease with limited commercial value.
- **Metabolic disorder:** Discovery of the RIP140 gene by Dr. Michael Czech, a member of RXi's scientific advisory board, provided the foundation for the development of an siRNA therapy to combat obesity and obesity-related insulin resistance. This project is active, but it has been modified to utilize a self-delivering siRNA construct. Research is under way to optimize the molecule and ensure that it penetrates adipose cells.
- **Cholesterol-Lowering Therapy:** The siRNA project targeting apolipoprotein B is still active, but it is being modified to utilize the self-delivering construct. This is a therapy that RXi intends to outlicense for clinical development and commercialization.

FINANCIAL REVIEW – HISTORICAL PERSPECTIVE

RXi's progress with its technology platforms in early 2009 was reflected in a 30% increase in R&D expenditures, to \$1.4 million. The Company expanded the number of personnel engaged in its research by 50% and invested in patents to protect its discoveries. General & administrative costs also rose by 69%, to \$2.76 million, largely for business advisory services. Overall, operations generated a \$4.17 million loss, though the cash burn was held to \$2.67 million. Without the aforementioned one-time costs, we estimate that expenses will decline, resulting in a loss of about \$11 million for the year before factoring in any upfront fees from licensing agreements.

As shown on page 19, the Company recently had \$7.17 million of cash on hand and no debt. We believe that future financing needs will be determined partly by the terms of partnering agreements, since upfront licensing fees may well constitute a good source of funds. New partnering agreements and progress on the R&D front should set the stage for an equity financing.

INVESTMENT CONCERNS AND RISKS

For a complete description of risks and uncertainties related to RXi Pharmaceuticals' business, see the "Risk Factors" section in RXi's SEC filings, which can be accessed directly from the SEC Edgar filings at www.sec.gov. Potential risks include:

- **Stock risk and market risk:** There is a limited trading market for the Company's common stock. There can be no assurance that an active and liquid trading market will develop or, if developed, that it will be sustained, which could limit one's ability to buy or sell the Company's common stock at a desired price. Investors should also consider technical risks common to many small-cap or micro-cap stock investments, such as small float, risk of dilution, dependence upon key personnel, and the strength of competitors that may be larger and better capitalized.
- **Competitive risk:** The pharmaceutical and biotechnology markets are rapidly evolving, and research and development are expected to continue at an accelerated pace. Other companies are also actively engaged in the development of therapies to directly or indirectly treat those disorders being pursued by RXi. These companies may have substantially greater research and development capabilities, as well as significantly greater marketing, financial, and human resources than RXi.
- **Products still in development phases:** RXi's products are still in the discovery stage. Such products may appear to be promising, but may not reach commercialization for various reasons, including failure to achieve regulatory approvals, safety concerns, and/or the inability to be manufactured at a reasonable cost. And even if its products are commercialized, there can be no assurance that they will be accepted, which may prevent the Company from becoming profitable.
- **Funding requirements:** It is difficult to predict the Company's future capital requirements. The Company may need additional financing to continue funding the research and development of its products and to expand its business. There is no guarantee that it can secure the desired future capital or, if sufficient capital is secured, that current shareholders will not suffer significant dilution.
- **Regulatory risk:** There is no guarantee that RXi's products will be approved by the U.S. Food and Drug Administration (FDA) or international regulatory bodies for marketing in the U.S. or abroad.
- **Patent risk:** The field of RNAi pharmaceuticals is at an early stage of development, and although RXi Pharmaceuticals has licensed and/or filed for numerous patents to secure its right to commercialize its technology, not all of these patents have been challenged, and therefore some may not protect the Company's rights adequately in a competitive marketplace.

FINANCIAL FORECASTS & VALUATION

REVENUE SOURCES

Our financial model reflects the three basic versions of siRNA molecules that the Company has developed, as well as the three major types of commercialization schemes in the corporate plans. Rheumatoid arthritis, which is being targeted with the oral drug formulation, is the lead indication in RXi's R&D pipeline and one that probably will be outlicensed for final clinical development and commercialization. Idiopathic pulmonary fibrosis is a disease that we think typifies a condition RXi may pursue entirely on its own. And, oncology is a therapeutic area that the Company does not intend to pursue on its own, and as such, constitutes an opportunity that may be pursued via licensing agreements in which siRNA technology is used to develop a medicine against a partner's target.

Rheumatoid Arthritis – oral delivery, outlicensed after internal development

Inflammation - Rheumatoid Arthritis (oral)			
Year penetration starts	2017	Prevalence	7328200
Starting penetration rate	3%	Percent addressable	90%
Years between penetration start and peak	5	Market growth rate	2%
Peak penetration	9%	Price per patient	\$5,000
Duration of peak penetration in years	5	Treatment price growth	0%
Retention rate in decline years	90%	Royalty rate	12%
Stage of development	Preclinical	Probability of commercialization	10%

Assumptions regarding a rheumatoid arthritis drug:

- The Company develops its rheumatoid arthritis drug through a Phase I clinical trial before outlicensing it to a partner in exchange for \$50 million in upfront and milestone payments and a 12% royalty rate.
- Clinical studies demonstrate that the drug is effective against the inflammatory component of rheumatoid arthritis and that it has a better safety profile than the anti-TNF α therapies currently on the market.
- The drug is approved for treating adults with RA in 2017 and is launched at a significant price advantage to biological medicines currently used for this indication.
- The patient population consists of newly diagnosed patients (currently 316,780 patients in more developed countries of the world), who receive aggressive therapeutic intervention via a combination of drugs, and chronic RA patients whose disease relapses into an active form. In any given year, 10% of the chronic patient population has active RA.
- Despite evidence suggesting that the incidence of RA is declining, the overall patient population expands through 2024 because of the demographic influence of aging baby boomers.
- Each patient receiving siRNA therapy is treated for a period of two years, with a retention rate of 90% in the second year.
- Acceptance of the drug is propelled by its efficacy against the inflammatory process, a favorable safety profile, price advantage, and a philosophy within the medical community that favors swift intervention with the best possible drugs. As a result, the siRNA's penetration rate among newly diagnosed patients rises from 40% initially to 70% within four years. Likewise, the drug is used to treat chronic RA patients with active disease. Penetration of this population is estimated to rise from 16% initially to 60% over the ensuing seven years. Combined, these patients comprise 3%

and 9%, respectively, of the projected RA populations upon approval, in 2017, and at the terminal period of our financial model, in 2024.

- The probability of commercialization is consistent with historical success rates of drugs at a preclinical stage of development.

Idiopathic Pulmonary Fibrosis – self-delivering siRNA, internally developed

Inflammation - Idiopathic Pulmonary Fibrosis			
Year penetration starts	2016	Prevalence	520000
Starting penetration rate	15%	Percent addressable	80%
Years between penetration start and peak	5	Market growth rate	1%
Peak penetration	45%	Price per patient	\$20,000
Duration of peak penetration in years	10	Treatment price growth	0%
Retention rate in decline years	90%	Royalty rate	30%
Stage of development	Preclinical	Probability of commercialization	10%

Assumptions regarding a drug for idiopathic pulmonary fibrosis:

- The estimated patient population reflects prevalence of the disease in the United States,⁴⁹ applied to the population of “developed countries” as defined by the U.S. Census Bureau.
- The patient population that is addressable is 80%, based on a finding that two-thirds of the patients succumb to the disease within five years of diagnosis. We assume that patients with an advanced stage of the disease are not suitable candidates for siRNA therapy.
- Commercialization begins in 2016 with an initial penetration rate of 15%. Penetration rises over the next five years to a peak of 45%, reflecting a good therapeutic index of the self-delivering siRNA and a paucity of alternative treatments.
- The price of chronic therapy for IPF is comparable to that of antibodies against other life-threatening diseases, such as cancer.
- RXi retains marketing rights to the idiopathic pulmonary fibrosis drug in the United States and much of Europe. In select countries, the company grants marketing rights in exchange for royalties at 30% of its partner’s sales.

⁴⁹ Facts about Idiopathic Pulmonary Fibrosis. Published by the Coalition for Pulmonary Fibrosis. (www.coalitionforfp.org)

Metastatic Colorectal Cancer – liposomal formulation, developed via partnership

Metastatic CRC cancer - via partner			
Year penetration starts	2016	Incidence	583,510
Starting penetration rate	7%	Percent addressable	90%
Years between penetration start and peak	6	Market growth rate	1%
Peak penetration	30%	Price per patient	\$30,000
Duration of peak penetration in years	5	Treatment price growth	0%
Retention rate in decline years	90%	Royalty rate	12%
Stage of development	Preclinical	Probability of commercialization	10%

Assumptions regarding a metastatic colorectal cancer drug:

- RXi collaborates to develop an rxRNA therapy that targets a molecule identified by its partner and utilizes liposomes to deliver the active molecule to the liver. The goal is to treat metastatic liver cancer, which afflicts roughly 50% of all patients with colorectal cancer.^{50,51} Terms of the partnership call for RXi to provide its technology in exchange for \$25 million in upfront and milestone payments, plus a 12% royalty.
- The overall patient population consists of 50% of newly diagnosed colorectal cancer patients in “more developed countries” (as defined by the US Census Bureau), while the addressable population is 90%, allowing for general health issues that may prevent treatment with an rxRNA drug. We’ve assumed that patients are treated only during the first year after diagnosis of metastatic disease.
- The price of the therapy is less than that of antibody-based drugs and some biological medicines, reflecting the relatively lower production costs associated with RNAi molecules.
- Commercialization begins in 2016, with an initial penetration rate of 7%. Six years later, the penetration rate reaches a maximum of 30%, due to good efficacy and safety profiles. Sales continue to trend upward with the market’s growth for five subsequent years, until competition intensifies.
- The probability of commercialization is 10%, which is consistent with historical rates observed for drugs at a preclinical stage of development.

⁵⁰ Steele, G and Ravikumar, TS. Resection of hepatic metastases from colorectal cancer. *Ann Surg* (1989); 210(2):127.

⁵¹ Alberts, SR, and Wagman, LD. Chemotherapy for colorectal cancer liver metastases. *Oncologist* (2008); 13: 1063.

INCOME STATEMENT (All data is in thousands, except per-share figures.)Fiscal year ends December 31st.

	2009	2010	2011	2012	2013
Total revenue	\$ 3,000	\$ 8,000	\$ 11,000	\$ 11,000	\$ 11,000
COGS	-	-	-	-	-
Gross profit	\$ 3,000	\$ 8,000	\$ 11,000	\$ 11,000	\$ 11,000
Operating expenses					
R&D	\$ 9,500	\$ 10,000	\$ 12,000	\$ 15,000	\$ 18,000
Selling & marketing					
General & administrative	5,000	5,250	5,750	6,000	6,500
Total expense	14,500	15,250	17,750	21,000	24,500
Operating profit	\$ (11,500)	\$ (7,250)	\$ (6,750)	\$ (10,000)	\$ (13,500)
Non-operating income/expense					
Interest expense					
Interest income	200	200	250	250	250
Other					
Total non-operating	200	200	250	250	250
Pretax profit	\$ (11,300)	\$ (7,050)	\$ (6,500)	\$ (9,750)	\$ (13,250)
Income tax					
Net income	\$ (11,300)	\$ (7,050)	\$ (6,500)	\$ (9,750)	\$ (13,250)
Earnings (loss) per share	\$ (0.73)	\$ (0.39)	\$ (0.35)	\$ (0.51)	\$ (0.66)
Diluted shares outstanding	15,500	18,000	18,750	19,250	20,000

Assumptions regarding the Income Statement:

- RXi books upfront and milestone payments, as well as royalties, on its RA and colorectal cancer drugs and incurs only minor administrative costs related to these sources of income.
- The company markets its drug for idiopathic pulmonary fibrosis directly in the United States and much of Europe, enabling it to book roughly two-thirds of all sales made in developed nations.
- The corporate infrastructure expands moderately through 2014, but increases more significantly starting in 2015 in preparation for the launch of the idiopathic pulmonary fibrosis drug. In 2016 and thereafter, general and administrative costs amount to 8% of revenues.
- R&D costs trend upward through 2015 as the company initiates clinical trials of its idiopathic pulmonary fibrosis drug and advances more compounds into preclinical and early clinical phases of development. Beginning in 2016, R&D expenses equate to 15% of revenues, as more drug candidates enter advanced clinical trials.
- Marketing and selling expenditures begin in 2015 to prepare for the introduction of the idiopathic pulmonary fibrosis drug. Thereafter, these costs amount to 20% of revenues.
- The company begins to book tax liabilities for financial reporting purposes in 2016 at an effective tax rate of 38%.
- Equity financings and grants of stock options increase the number of basic and fully diluted shares outstanding.

BALANCE SHEET (All data is in thousands.)
(Fiscal year ends December 31st.)

ASSETS	3/31/2009
Current Assets	
Cash & equivalents	7,172
Accounts Receivable	-
Other	391
Total Current Assets	<u>\$ 7,563</u>
Property & equipment	\$ 384
Intangible assets	-
Other	16
Total Assets	<u><u>\$ 7,963</u></u>
LIABILITIES	
Current Liabilities	
Accounts payable	\$ 409
Debt due	17
Other	1,066
Total Current Liabilities	<u>\$ 1,492</u>
Long-term debt	\$ -
Other	-
Total Long-Term Liabilities	<u>\$ -</u>
Shareholders Equity	
Common Stock, par value	\$ 1
Additional Paid-In Capital	36,004
Accumulated Deficit	(29,534)
Treasury Stock	-
Total Shareholders Equity	<u>\$ 6,471</u>
Total liabilities & equity	<u><u>\$ 7,963</u></u>

DISCOUNTED CASH FLOW ANALYSIS (All data is in thousands, except per-share figures.)

	2009	2010	2011	2012	2013			
Revenue	\$ 3,000	\$ 8,000	\$ 11,000	\$ 11,000	\$ 11,000			
Operating income	-11500	-7250	-6750	-10000	-13500			
Net income	-11300	-7050	-6500	-9750	-13250			
Depreciation/amortization	1	1	1	1000	1000			
Stock-based compensation	5000	5000	5000	5000	5000			
Tax loss carryforwards	0	0	0	0	0			
Capital expenditures	0	0	0	-20000	-500			
Asset purchases								
Other								
Total cash flow adjustments	5,001	5,001	5,001	(14,000)	5,500			
Free cash flow	\$ (6,299)	\$ (2,049)	\$ (1,499)	\$ (23,750)	\$ (7,750)			
Risk-adjusted free cash flow	\$ (6,299)	\$ (2,049)	\$ (1,499)	\$ (23,750)	\$ (7,750)			
PV of Terminal Value at a								
Discount Rate	Discounted Cash Flows (2009 - 2024)	Perpetual growth rate of rFCF			Enterprise Value			
		2.0%	3.0%	4.0%	2.0%	3.0%	4.0%	
7.5%	\$310,617.29	\$ 937,332	\$ 1,156,860	\$ 1,501,832	\$1,247,949	\$1,467,477	\$1,812,449	
10.0%	\$223,539.67	\$ 456,460	\$ 526,783	\$ 620,547	\$680,000	\$750,323	\$844,087	
12.5%	\$161,034.35	\$ 248,260	\$ 277,082	\$ 312,687	\$409,294	\$438,117	\$473,721	
15.0%	\$115,838.53	\$ 144,202	\$ 157,751	\$ 173,762	\$260,041	\$273,589	\$289,601	
17.5%	\$82,944.07	\$ 87,596	\$ 94,555	\$ 102,545	\$170,540	\$177,499	\$185,489	
Total Equity Value						Value per Diluted Share		
Discount Rate	Net Debt	2.0%	3.0%	4.0%	2.0%	3.0%	4.0%	
7.5%	\$ (7,155)	\$1,255,104	\$1,467,477	\$1,819,604	\$ 62.76	\$ 73.37	\$ 90.98	
10.0%	(7,155)	\$687,155	\$757,478	\$851,242	\$ 34.36	\$ 37.87	\$ 42.56	
12.5%	(7,155)	\$416,449	\$445,272	\$480,876	\$ 20.82	\$ 22.26	\$ 24.04	
15.0%	(7,155)	\$267,196	\$280,744	\$296,756	\$ 13.36	\$ 14.04	\$ 14.84	
17.5%	(7,155)	\$177,695	\$184,654	\$192,644	\$ 8.88	\$ 9.23	\$ 9.63	
Terminal Value as % Enterprise Value						Implied EBITDA Multiple		
Discount Rate		2.0%	3.0%	4.0%	2.0%	3.0%	4.0%	
7.5%		75.1%	78.8%	82.9%	11.53	14.23	18.48	
10.0%		67.1%	70.2%	73.5%	7.93	9.15	10.78	
12.5%		60.7%	63.2%	66.0%	6.04	6.74	7.61	
15.0%		55.5%	57.7%	60.0%	4.88	5.34	5.88	
17.5%		51.4%	53.3%	55.3%	4.09	4.42	4.79	

Assumptions related to the Discounted Cash Flow Analysis:

- The DCF model projects cash flow through 2024, discounted back at multiple annual rates (7.5%, 10.0%, 12.5%, 15.0%, and 17.5%) to demonstrate the potential variability related to this assumption. It also includes three perpetual growth rates (2%, 3%, and 4%) to show the impact on the present value of the company's terminal value. The rates used in calculating the per-share value for RXi Pharmaceuticals are a 12.5% annual discount rate and a perpetual growth rate of 3%. The number of shares estimated to be outstanding in 2013, 20 million, is used in the per-share calculation.
- The cash flows are risk adjusted, based on the proportional gross profit contribution by each drug/indication on an annual basis and the probability of that drug/indication being commercialized. For any years in which we are projecting losses, the probability is conservatively set at 100%.

DISCLOSURES

ANALYST(S) CERTIFICATION: The analyst(s) responsible for covering the securities in this report certify that the views expressed in this research report accurately reflect their personal views about RXi Pharmaceuticals (the “Company”) and its securities. The analyst(s) responsible for covering the securities in this report certify that no part of their compensation was, is, or will be directly or indirectly related to the specific recommendation or view contained in this research report.

MEANINGS OF RATINGS: Our rating system is based upon 12 to 36 month price targets. **BUY** describes stocks that we expect to appreciate by more than 20%. **HOLD** describes stocks that we expect to change plus or minus 20%. **SELL** describes stocks that we expect to decline by more than 20%. **SC** describes stocks that Griffin Securities has **Suspended Coverage** of this Company and price target, if any, for this stock, because it does not currently have a sufficient basis for determining a rating or target and/or Griffin Securities is redirecting its research resources. The previous investment rating and price target, if any, are no longer in effect for this stock and should not be relied upon. **NR** describes stocks that are **Not Rated**, indicating that Griffin Securities does not cover or rate this Company.

DISTRIBUTION OF RATINGS: Currently Griffin Securities has assigned BUY ratings or NO RATINGS on all of the companies it covers. The Company has provided investment-banking services for 11% of companies in which it has had BUY ratings in the past 12 months, 0% for companies in which it has had NR or no coverage in the past 12 months or has suspended coverage (SC) in the past 12 months.

MARKET MAKING: Griffin Securities does not maintain a market in the shares of this Company or any other Company mentioned in the report.

COMPENSATION OR SECURITIES OWNERSHIP: The analyst(s) responsible for covering the securities in this report receive compensation based upon, among other factors, the overall profitability of Griffin Securities, including profits derived from investment banking revenue. The analyst(s) that prepared the research report did not receive any compensation from the Company or any other companies mentioned in this report in connection with the preparation of this report. The analysts responsible for covering the securities in this report do not currently own common stock in the Company, but in the future may from time to time engage in transactions with respect to the Company or other companies mentioned in the report. Griffin Securities from time to time in the future may request expenses to be paid for copying, printing, mailing and distribution of the report by the Company and other companies mentioned in this report. Griffin Securities expects to receive, or intends to seek, compensation for investment banking services from the Company in the next three months.

TWO-YEAR PRICE CHART

FORWARD-LOOKING STATEMENTS: This Report contains forward-looking statements, which involve risks and uncertainties. Actual results may differ significantly from such forward-looking statements. Factors that might cause such a difference include, but are not limited to, those discussed in the “Risk Factors” section in the SEC filings available in electronic format through SEC Edgar filings at www.SEC.gov on the Internet.

GENERAL: Griffin Securities, Inc. (“Griffin Securities”) a FINRA (formerly known as the NASD) member firm with its principal office in New York, New York, USA is an investment banking firm providing corporate finance, merger and acquisitions, brokerage, and investment opportunities for institutional, corporate, and private clients. The analyst(s) are employed by Griffin Securities. Our research professionals provide important input into our investment banking and other business selection processes. Our salespeople, traders, and other professionals may provide oral or written market commentary or trading strategies to our clients that reflect opinions that are contrary to the opinions expressed herein, and our proprietary trading and investing businesses may make investment decisions that are inconsistent with the recommendations expressed herein.

Griffin Securities may from time to time perform corporate finance or other services for some companies described herein and may occasionally possess material, nonpublic information regarding such companies. This information is not used in preparation of the opinions and estimates herein. While the information contained in this report and the opinions contained herein are based on sources believed to be reliable, Griffin Securities has not independently verified the facts, assumptions and estimates contained in this report. Accordingly, no representation or warranty, express or implied, is made as to, and no reliance should be placed on, the fairness, accuracy, completeness or correctness of the information and opinions contained in this report.

The information contained herein is not a complete analysis of every material fact in respect to any company, industry or security. This material should not be construed as an offer to sell or the solicitation of an offer to buy any security in any jurisdiction where such an offer or solicitation would be illegal. We are not soliciting any action based on this material. It is for the general information of clients of Griffin Securities. It does not take into account the particular investment objectives, financial situations, or needs of individual clients. Before acting on any advice or recommendation in this material, clients should consider whether it is suitable for their particular circumstances and, if necessary, seek professional advice. Certain transactions - including those involving futures, options, and other derivatives as well as non-investment-grade securities - give rise to substantial risk and are not suitable for all investors. The material is based on information that we consider reliable, but we do not represent that it is accurate or complete, and it should not be relied on as such. The information contained in this report is subject to change without notice and Griffin Securities assumes no responsibility to update the report. In addition, regulatory, compliance, or other reasons may prevent us from providing updates.

DISCLOSURES FOR OTHER COMPANIES MENTIONED IN THIS REPORT: To obtain applicable current disclosures in electronic format for the subject companies in this report, please refer to SEC Edgar filings at www.SEC.gov. In particular, for a description of risks and uncertainties related to subject companies’ businesses in this report, see the “Risk Factors” section in the SEC filings.