



## UPDATE NOTE

Biotechnology Industry • May 14, 2010

### RXI PHARMACEUTICALS CORP. (NASDAQCM: RXII)

- Positive proof-of-concept results show self-delivering rxRNA useful for ocular applications.
- Partnering begins to heat up as three deals were completed recently.
- Updated therapeutic strategy will be unveiled in June – 2010 shaping up as a transformational year for RXi.
- We reiterate our BUY recommendation and our target price of \$22.00.

#### RXi Pharmaceuticals Corp. (NasdaqCM: RXII)

is a leader in the development of drugs that inhibit gene expression through an RNA interference (RNAi) pathway. The Company, which was co-founded in 2006 by Nobel Laureate Craig Mello, Ph.D., has created the smallest RNAi-based inhibitors. The most advanced molecular design for RXi's compounds includes a self-delivering capability that facilitates the drug's uptake into cells where it blocks gene expression at the level of messenger RNA (mRNA) translation.

The latest news from the R&D front shows that intraocular administration of the Company's self-delivering rxRNAs (sd-rxRNAs) results in uptake of these compounds in retinal cells where they then inhibit specific gene expression. These data complement RXi's earlier results obtained with both systemic administration and localized skin application. Thus, the Company has demonstrated the utility of its most advanced drug construct for treating localized diseases and for systemic maladies.

The research has helped to advance a variety of programs at a preclinical level, and it has set the stage for more extensive collaborations. Indeed, one of the RXi's goals for 2010 is to enter into a partnering agreement with a major drug corporation. The updated strategic plan, which is scheduled for completion in June, will outline

Share Price (5/13/10)	\$4.42
52-Week Price Low / High	\$1.51-\$8.99
Mkt. Capitalization (issued)	\$80.8 million
Shares Outstanding (issued)	18.28 million
12-month Target Price	\$22.00
Website	<a href="http://www.rxipharma.com">www.rxipharma.com</a>



key areas of interest for in-house development projects and set the stage for more partnering or outlicensing agreements.

We believe RXi is an undiscovered gem that's been overlooked by the investment community. But 2010 has the makings of a transformational year, as the Company further defines its internal R&D program, signs a major partnering deal, identifies a lead drug candidate, and continues to add to its extensive patent portfolio. With ample cash after a recent equity financing, RXi continues to merit our BUY recommendation and our \$22-a-share price target.

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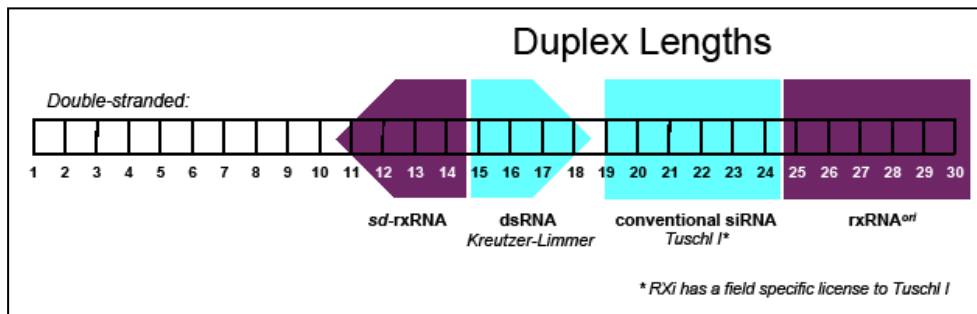
## RXi – AN UNDERVALUED COMPANY

RXi is a pioneer in the development of drugs based on a recently discovered pathway that cells use to regulate gene expression. This field of pharmacology is only in its infancy, even though corporate valuations might suggest otherwise. (Merck & Company paid more than \$1 billion for Sirna in 2006 and Alnylam has a market capitalization of \$700 million, based largely on some partnering agreements over the past few years.) These valuations contrast with RXi’s market cap of \$80 million. Yet as discussed below, RXi has proprietary, cutting-edge technology in the design of drugs capable of altering gene expression and it has a number important milestones approaching over the next six to nine months.

## RXi’s PROPRIETARY TECHNOLOGY

RXi holds key patents in the field of inhibitory RNAi-based molecules, as shown in Figure 1. The initial patents describe constructs that have 25 or more base pairs and were the basis of RXi’s early efforts to develop therapeutic agents. More recently, the Company secured intellectual property around RNAi constructs that contain 14 or fewer nucleotide base pairs. This proprietary technology may well turn out to be of tremendous value, since experiments indicate that only 11 to 14 base pairs are needed to engage the RNAi machinery with high specificity to a particular messenger RNA (mRNA). (mRNA are the intermediate between genes and gene products.)

**Figure 1. RXi’s Patents Cover a Broad Range of Molecular Sizes**



The Company has gone well beyond creating conventional RNAi molecules (sometimes referred as small interfering RNAs, or siRNAs) – it has added modifications that protect against degradation and immunological recognition, and reduce renal clearance (designated rxRNA). It created single-oligonucleotide versions (rxRNAsolo), and self-delivering constructs that demonstrate unassisted uptake into cells (sd-rxRNA). As a result, RXi can operate free of others’ patents in any area of medicine that it chooses and with drug designs that have competitive advantages.

## UPCOMING MILESTONES

- Q2’10            Complete therapeutic strategy plan
- H2’10            Select lead drug candidate for in-house development
- H2’10            Enter into a significant partnership
- H2’10            Continue to expand the patent portfolio

We believe that achieving these milestones will accentuate RXi’s competitive advantages and help to clarify the commercial value of its technologies in the eye of the investment community.

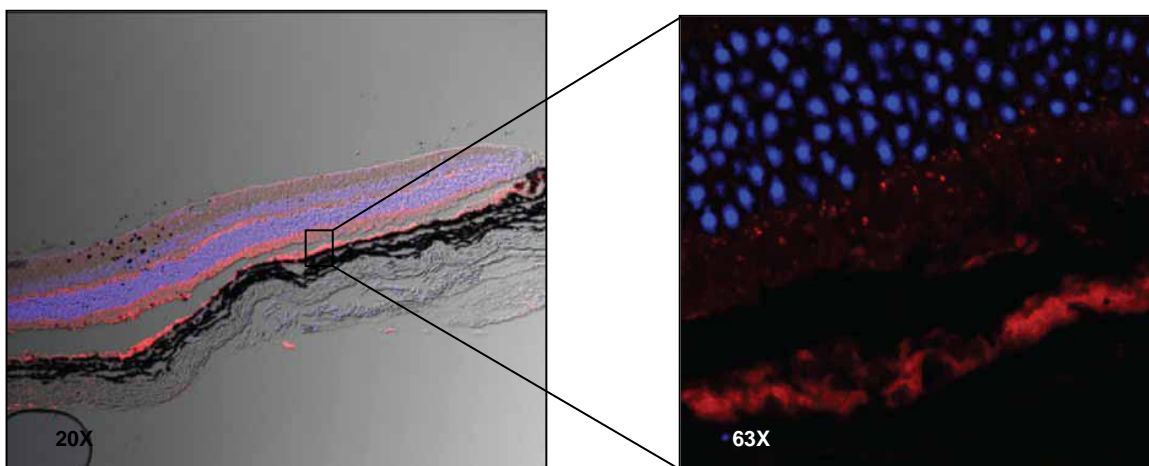
## SELF-DELIVERING RXRNA CONSTRUCT PROVEN CAPABLE ONCE AGAIN

RXi has performed a number of experiments to provide proof-of-concept data demonstrating the utility of its sd-rxRNA for a variety of indications, including systemic, dermatological, and ophthalmic maladies. We believe the goal of this work was to help define areas for further internal development and to show potential partners how its technology may be used in a therapeutic setting.

### OPHTHALMIC CONDITIONS

The latest results from RXi's labs demonstrate once again the utility of its sd-rxRNA construct, this time in treating ophthalmic conditions including such back-of-the-eye diseases as macular degeneration.<sup>1</sup> Cultured human retinal pigment cells (ARPE 19 cell line), as well as HeLa cells, neuroblastoma, and macrophages, rapidly took up a fluorescently labeled sd-rxRNAs targeting the messenger RNA for MAP4K4, an enzyme that is implicated in down-regulating the inflammatory pathway mediated by tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Confocal microscopy pictures showed the presence of the sd-rxRNA in the cell cytoplasm where mRNA are translated during protein synthesis. Moreover, uptake of RXi's inhibitory molecule reduced the relative amount of MAP4K4 mRNA in a dose-dependent manner, with an EC50 of approximately 30 nM. These results have extended the number of cell types that sd-rxRNA is able to penetrate to 15 – in other words, all cells tested to date take up sd-rxRNA.

The cell culture experiments were extended with an *in vivo* study in which 10  $\mu$ g of the same fluorescently labeled sd-rxRNA was administered in 1  $\mu$ l either intravitreally or subretinally into the mouse eye. Confocal microscopy revealed uptake of the inhibitory molecule into ganglion and retinal pigment epithelial cells, as shown in Figure 2.

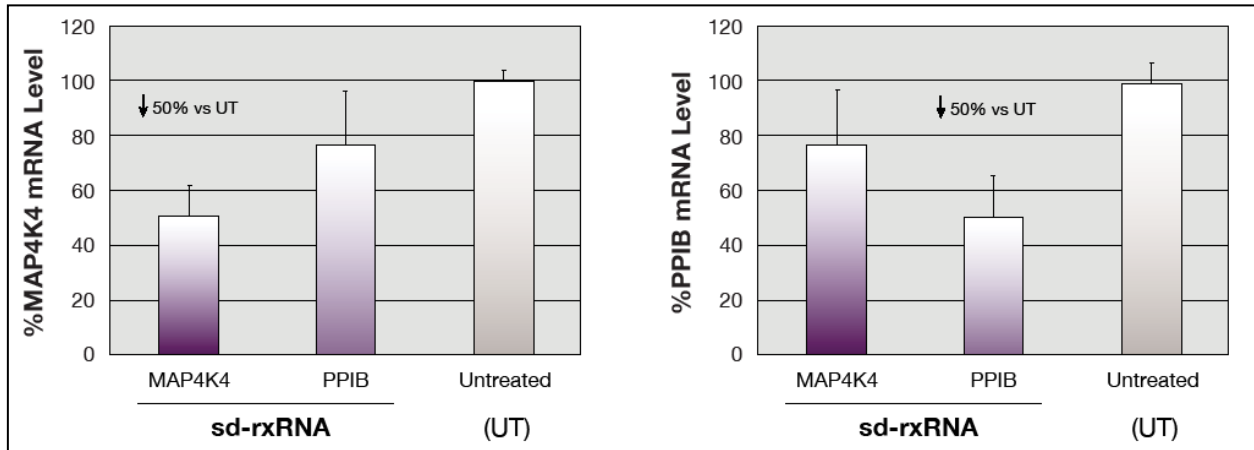


**Figure 2.** Intravitreal and subretinal administration of 10  $\mu$ g sd-rxRNA against the MAP4K4 mRNA and tagged with a red fluorescent marker shows that the sd-rxRNA entered cells of the ganglion layer and the retina. The sd-rxRNA was administered in 1  $\mu$ L and 24 hours later the tissue was cut transversely and nuclei were counterstained with Hoechst dye (blue). The left panel displays a section showing the different layers of the retina at 20x magnification. The right panel is a 63x magnification providing greater detail of the nuclear and cytoplasmic staining.

Source: Libertine, L, et al.<sup>1</sup>

The *in vivo* effect of sd-rxRNA was then evaluated using two mRNA targeting constructs – one was designed against the MAP4K4 mRNA and the other, against an enzyme involved in protein folding called peptidyl-prolyl *cis-trans* isomerase or PPIB. These sd-rxRNAs were administered into the vitreous humor (3  $\mu$ g sd-rxRNA in 1  $\mu$ l solution), with one type of inhibitory molecule per eye. The results (see Figure 3) show that the sd-rxRNA acts *in vivo* in a highly specific manner to reduce levels of its target mRNA.

<sup>1</sup> Libertine, L, et al. Novel self-delivering RNAi compounds (sd-rxRNA) demonstrate robust ocular cell uptake *in vitro* and *in vivo*. Presented at the annual meeting of the Association for Research in Vision and Ophthalmology, May 2010.

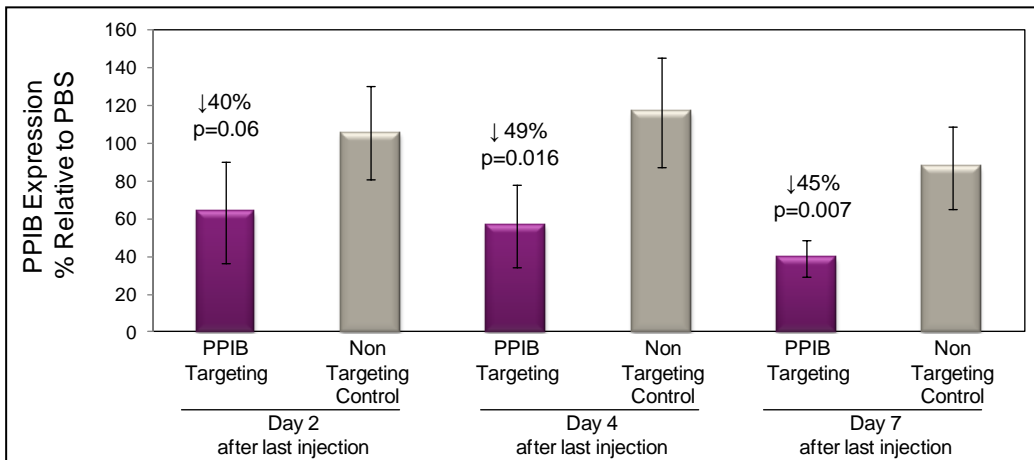


**Figure 3.** Intravitreal administration of an sd-rxRNA against MAP4K4 into one eye and another sd-rxRNA against PPIB in the contralateral eye resulted in a significant **local** reduction in the mRNA for these enzymes. The quantity of each sd-rxRNA administered was 3 µg in a 1 µl solution. The retinas were harvested 48 hours later and mRNA levels were quantified with qPCR. Levels of mRNA for MAP4K4 and PPIB were normalized to a housekeeping gene (β-actin) for comparative purposes. As shown in the left panel, the sd-rxRNA against MAP4K4 caused a significant reduction of the mRNA for that enzyme without significantly altering the mRNA for PPIB. The right panel shows the opposite eye, in which sd-rxRNA against PPIB markedly reduced that enzyme's mRNA without affecting the MAP4K4 mRNA.

Source: *Libertine, L, et al.*<sup>1</sup>

**DERMATOLOGICAL APPLICATIONS**

The results from the eye studies complement work done earlier with local injection of RXi's compounds into skin.<sup>2</sup> These *in vivo* preclinical studies showed that expression of multiple gene targets could be reduced in a dose dependent manner. Fluorescent sd-rxRNA molecules were taken up effectively by cells comprising the skin after local injection, and once inside a cell, the sd-rxRNA exerted its effect for at least seven days.<sup>3</sup>



**Figure 4.** The duration of gene silencing was determined with an sd-rxRNA against PPIB mRNA. The RNAi inhibitor or phosphate buffered saline (PBS) was administered on two consecutive days and then mRNA of PPIB was measured using qPCR at 2, 4, and 7 days after the last injection. Results were normalized against the β-actin gene. (Similar results were also obtained with a MAP4K4 sd-rxRNA.)

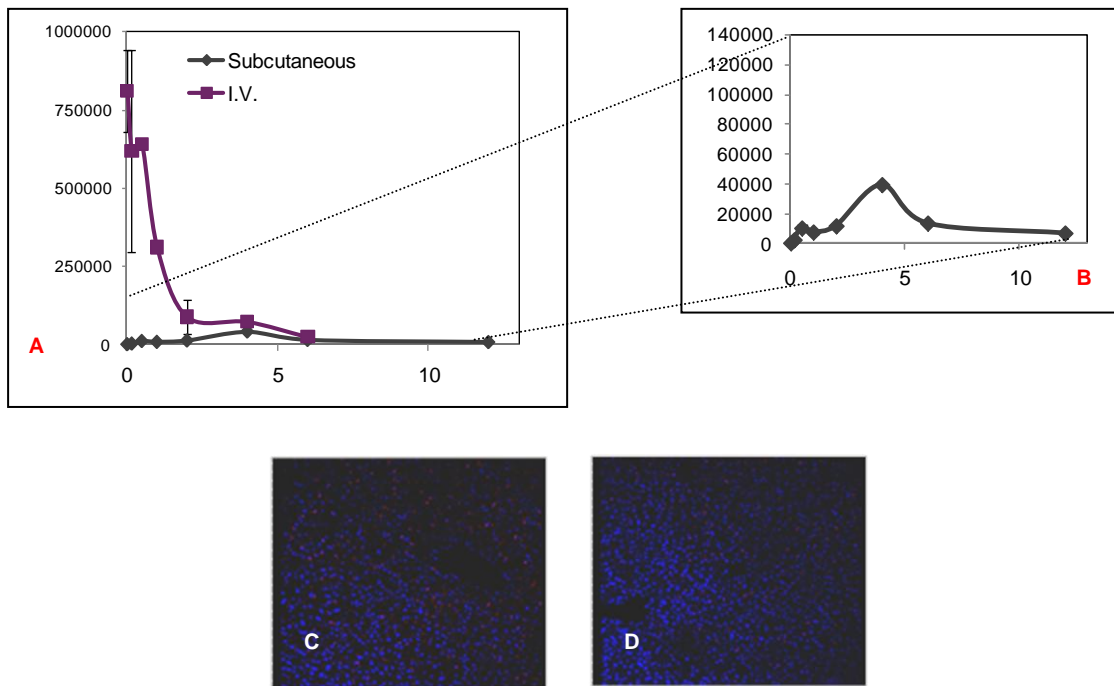
Source: *Varanasi, R.*<sup>3</sup>

<sup>2</sup> RXi Analyst Day presentation, October 5, 2009.

<sup>3</sup> Varanasi, R. RXi: A partner in RNAi technology. Presented at the BIO Conference – Chicago, May 2010.

**SYSTEMIC APPLICATIONS**

In preliminary experiments with intravenous and subcutaneous delivery, the Company showed that its sd-rxRNA molecules have a half-life of approximately one hour in circulation, versus minutes for legacy RNAi drug candidates. As presented in Figure 5, intravenous and subcutaneous routes of administration resulted in different pharmacokinetic profiles for sd-rxRNAs, but regardless of the route, the RNAi molecules were effective in reducing gene expression. Accordingly, RXi's proprietary self-delivering construct may be used to target a wide range of systemic and local diseases.



**Figure 5.** Pharmacokinetic profiles of sd-rxRNAs administered intravenously (IV) and subcutaneously (SC) differ. The IV route (Panel A only) was characterized by a sudden peak of sd-rxRNA in blood followed by a decline over about an hour. In contrast, subcutaneous administration (Panels A and B) was associated with a slower rate of absorption and a lower peak level that spanned roughly 60 minutes approximately four hours post injection. Both routes of administration resulted in marked uptake of the sd-rxRNA into liver cells at 12 hours post-injection (SC in panel D) and at 24 hours (images not shown).  
 Source: Varanasi, R.<sup>3</sup>

**THREE PARTNERING AGREEMENTS SIGNED RECENTLY**

RXi entered into partnerships with three small companies since early April. These deals have the potential to broaden the therapeutic applications of its technologies over time at little cost.

**TRANSDERM**

This biopharmaceutical company is developing nucleic acid skin delivery technologies and therapeutics for skin disorders, and it is working with RXi to assess the utility of rxRNA to treat dermatological conditions. Of particular interest is an orphan drug indication, Pachyonychia congenita, which is a rare genetic disorder associated with abnormal keratin formation. (Keratin is a structural protein of cells that is required for dermal integrity.) TransDerm has already tested an siRNA targeting one of the mutations associated with the disease in a single patient, but the therapy failed. With RXi's help, an effective molecule may be achievable. The partners have not disclosed the financial terms of the deal, but both are providing technologies and resources.

### MIRNA THERAPEUTICS

RXi entered into a collaboration with Mirna to determine the utility of combining its proprietary rxRNA technology with Mirna's microRNA expertise to develop microRNA therapeutics for cancer. (microRNA comprise a relatively small group of regulatory molecules akin to siRNA, but governing post-transcriptional gene expression of hundreds of genes, rather than specific genes.) Mirna entered the partnership with a patent portfolio containing more than 300 miRNAs that may have potential applications in oncology and other diseases. We note that two of the company's miRNAs, miR-34 and *let-7*, have been shown to block tumor growth in preclinical models and are being developed initially to treat prostate cancer and non-small cell lung cancer, respectively. Drugs based on these molecules may have other applications, as *let-7*, which represses the RAS and Myc oncogenes, and miR-34, which plays a role in the p53 tumor suppressor network, are found at abnormally low levels in a wide range of cancers. The partners aim to apply RXi's rxRNA technology to develop replacement therapies based on Mirna's intellectual property.

### MIRAGEN THERAPEUTICS

miRagen is another company working to develop microRNA therapies, particularly for cardiovascular and muscular diseases. The company has nine compounds in early stages of development for such indications as post-myocardial infarction remodeling and amyotrophic lateral sclerosis, based on discoveries that miR-29 and miR-206 are implicated in these respective conditions. RXi will apply its drug design expertise to assist miRagen in developing therapies for cardiac and neuromuscular disorders.

### UPDATED THERAPEUTIC STRATEGY TO ADVANCE RXI TO NEXT LEVEL

RXi is faced with the unusual dilemma of having too many opportunities to pursue with its novel platform technology. As a result, it is working with a consulting firm to prepare a strategic plan that will clearly segregate projects into one of three categories: (i) those for in-house development; (ii) therapeutic areas of strategic interest to the Company that it will pursue via collaborations with other corporations, and (iii) areas of less strategic imperative for the Company that are suitable for out-licensing of its technology. The plan is scheduled for completion in June, and an announcement of the updated strategy will likely follow soon afterwards. Table 1 summarizes the current R&D programs:

**Table 1. Current Status of RXi's R&D Pipeline**

	Program	Target Selection	Compound Design	In vitro	In vivo	Disease Models	Current Status
Local	Compromised Skin						Ongoing animal studies
	Dermatology						Pharmaceutical collaboration
	Dermatology						
	Respiratory						Pharmaceutical collaboration
	Respiratory						Pharmaceutical collaboration
	CNS						
	Ocular Disease						UMass collaboration
Systemic	Oncology						
	Inflammatory Diseases						
	Metabolic						Ongoing animal studies
	Obesity						Assessing sd-rxRNA delivery to fat
	Cardiovascular						

As presented in Table 1, RXi has several collaborations under way. It is difficult to know the terms that a sizable partnering agreement could bring, but it may include an upfront payment that would strengthen the balance sheet further. The Company raised \$16.2 million in the first quarter via a 2.7 million share offering. A portion of those funds were used to repurchase stock from its largest shareholder, CytRx Corporation. We believe RXi has sufficient funds to support planned operations into the second quarter of 2011, even without taking into consideration any upfront support from a partner.

Overall, the updated therapeutic strategy should give investors a better understanding of where the Company intends to invest its resources and thus provide a better sense of its technologies' commercial value. The blueprint should also help management set the path and timeline for each project. We believe the plan will do one more thing, help RXi to undertake serious negotiations with larger companies that could provide non-dilutive financing. In sum, the new strategy should provide direction in the Company's transformation from a research-oriented enterprise to a business with an exceptional drug development platform, well defined therapeutic focus, and validating collaborations with multinational pharmaceutical corporations.

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## TWO-YEAR PRICE CHART



**9/03/08** – Initiating Coverage: share price: \$6.89; rating: BUY; 12-month price target: \$23.00; **7/30/2009** – Update Report: share price: \$4.59; 12-month price target: \$22.00; **5/13/2010** – Update Report: share price: \$4.42; 12-month price target: \$22.00.

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