Merck's Alan Sachs, on RNAi's Big Challenge: Delivery, Delivery, Delivery

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Xconomy National — Merck hasn't said much in public about what it's doing in the field of RNA-based therapies, since it paid the jaw-dropping sum of **$1.1 billion** to acquire Sirna Therapeutics back in October 2006. So when I had the chance last week to sit down for an exclusive interview in San Francisco with Merck's RNA therapeutics leader, **Alan Sachs**, I jumped at it.

What's the big idea? RNA-based therapies hold the promise of silencing specific disease-related genes in ways conventional drugs don't. They can potentially reach targets inside cells that have previously been inaccessible for a whole array of diseases.

This promise of a new wave of pharmaceuticals has enticed a generation of RNA-based drug companies to exploit this emerging science, including Cambridge, MA-based **Alnylam Pharmaceuticals** (NASDAQ: **ALNY**), Vancouver, BC-based **Tekmira Pharmaceuticals**, and microRNA drug startups like Carlsbad, CA-based Regulus Therapeutics. So whatever Merck does has a big impact not just on its shareholders, but ripples through an emerging technology sector.

"This is a big story as it relates to RNA therapeutics in general," says Regulus CEO Kleanthis Xanthopoulos.

There was a lot of ground to cover during my 45-minute interview with Sachs. Before diving in, I should provide a little background on him. He's a former professor of molecular and cell biology at the University of California Berkeley. He joined Merck in July 2001, and has been given a lot of managerial experience running a couple of leading edge operations inside Merck, including Sirna and Rosetta Inpharmatics.

Xconomy: How did you first get exposed to RNAi?

Alan Sachs: At Berkeley, I worked on RNA post-transcriptional control. I joined Merck in 2001 to help start a clinical genomics group. At that time, we had just acquired [Seattle-based] Rosetta Inpharmatics, and so that first year I worked with [Stephen Friend, Rosetta's founder] to build up a molecular profiling unit which included gene expression genetics, proteomics, [and] informatics of course.

Alan Sachs

Molecular profiling at Merck was broad. It extended beyond Seattle to research sites in Boston, West Point, PA, just outside of Philadelphia, and Rahway, NJ. Then as part of the work in Seattle, we were developing siRNA as a tool for [drug] target discovery using cell-based screens. Thanks to Stephen, we really

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Somewhere around the middle of 2006, we realized that Alnylam did a big deal with Roche, and we realized the area was heating up. We needed to do more than a collaboration per se. It ultimately led to the decision to acquire Sirna Therapeutics, which closed at the end of 2006.

So I was asked at that time to lead a new department at Merck called RNA Therapeutics. The Sirna site which you're sitting in now is a geographic identifier. The department at Merck is called RNA Therapeutics. Sirna San Francisco is responsible for lead discovery and optimization. On the East Coast, we have a very large effort in RNAi delivery in West Point, PA. In Rahway, NJ, all of our manufacturing of oligonucleotides and delivery vehicles occurs. So RNA Therapeutics is split over three research sites within the company.

What you often read about, but many people don't understand, is how hard it is to make a drug. Our approach to RNA Therapeutics is made with a recognition of the full package it takes to launch a successful commercial product. We work based on that strategy. That's versus another strategy you see from smaller companies, which is to get an interesting experimental result, and publicly disclose it in an attempt to increase the value of your investment or a VC's investment, without a real [awareness] of what it will take to make a therapeutic eight years later. Timelines are very abbreviated for biotech. They can't do the 5-10 year plan. Nobody has that kind of runway, except maybe Alnylam and Isis. There are very few companies with the infrastructure to do long-term planning.

We immediately, after the acquisition, invested not just heavily in the RNA piece that is here in San Francisco, but we built an entire delivery group in West Point, PA. The thing that continues to differentiate Merck is that we have people with decades of experience in pharma R&D, drug safety, metabolism, pharmacokinetics. To us, the delivery vehicle is a really big medicinal chemistry program. It really is the blend of pharmaceutical and medicinal chemistry that's allowing us to make the advances we're making. Then with the appreciation of issues on safety, and input we can get from our regulatory and clinical colleagues, we feel we have a very strong engine here for developing RNA therapies.

X: You said there are three key components from around the company. The discovery group and optimization is here in San Francisco, delivery, and a third. What does the third group really do?

AS: Manufacturing. It's the synthesis of the oligos, not just in a standard way, but modified. And the delivery vehicles, whether it's a polymer or lipid, or an RNA conjugate. All of that is a specialized set of chemistries. They do all our small scale synthesis, and large scale synthesis that's need for large clinical trials and preclinical studies.

X: How many people across the company are working on RNAi?

AS: A lot.

X: How many?

AS: We don't disclose how many. It's viewed as, in the pharmaceutical industry

player. The decision to acquire Sirna for $1.15 billion was for us to be a leader in a modality that could differentiate our company. While we don't talk about the size of the investment, the size of the original investment is an indication of the seriousness with which Peter Kim has toward making sure we are successful.

X: I won't belabor this, but can you say how many people you have here in San Francisco?

AS: We have two floors here, and it's about 60,000 square feet. We're effectively fully staffed. But we don't disclose headcount.

X: Obviously the Sirna acquisition was a high-profile public event. But has Merck formed any other less visible partnerships with small biotech companies or academic groups to work on key parts of the problem, like delivery? Or is everything in-house?

AS: At the time of the acquisition of Sirna, we had two existing agreements. One was with GlaxoSmithKline, the other was with Allergan. GSK was for respiratory diseases, and Allergan was for the eye. We successfully completed both of those collaborations, per the terms of the agreement. The GSK collaboration ended about a year ago, or a year and half. Those are pretty good sized-collaborations in which both of those companies have the rights to RNAs we've discovered. They can develop them for indications they've specified. We have an enormous external licensing evaluation effort.

We have a graph we've disclosed which represents the number of opportunities we have looked at to do exactly what you describe, which is collaborate, particularly in the delivery space to advance this field. We are fully funded to do that, not just the evaluation, but the actual work. And what's really disappointing is that when you look at that graph, which is current as of mid-2009, there were 250-260 interesting opportunities, and there are really only two or three which have data that's valuable—meaning they have data from non-human primates.

Our approach to external licensing has been very much an evaluation prior to the collaboration. We have done a number of evaluations, and I'm sorry to report that the number that has progressed to a true collaboration has been only a handful.

So the yield here is reasonably low. Less than 2-3 percent of the things we are told are true are things we can confirm to be true enough to have value.

X: So I guess that means there's a lot of hype here, right?

AS: There's a lot of hype, and there's a lot of ideas. But it's not a straightforward problem. Injecting something in the bloodstream, leading to something appearing in the cytoplasm in the RNA-silencing complex, there are a lot of black boxes between those two steps. People who are entering the field start with a white paper. It's much like people who started on targeted therapeutics years ago started with a white paper. If it were so easy, one would have to describe why so few examples exist. The same is true in the RNAi delivery process. You can write down the steps. You can write down what you think will happen. But then you have to put it in a 50-nanometer particle that's safe and potent to deliver.

collaborations? Have they been announced?

AS: No. But we've done a lot of evaluations in anticipation of collaborations. A few have proceeded to collaborations, and we don't disclose those. We generally don't unless it's something unusual. There's a lot of activity we've done that we can't or choose not to disclose.

X: Why? Because of the competition?

AS: It's a combination of the competition, and from our seat, a misunderstanding of the intent of the collaboration. That is, the field is so ready to put money in, we don't want a Merck collaboration to be read as a sign of approval. The goals of our collaboration, after an initial period, are to develop something that is usable in the non-human primate.

Ian McConnell: It's fundamentally about managing expectations.

X: On a different train of thought, what kind of delivery technologies do you like or think have promise at the moment?

AS: There are three main areas of delivery. First are lipid-based delivery systems. At the time of our acquisition of Sirna, they had successfully shown lipid-based delivery to the liver. Initially, it was through a collaboration with what is now called [Vancouver, BC-based] Tekmira. That was really the leading standard for the area. Several [applications to begin clinical trials] have been filed with the FDA. We spent a lot of internal research money and time on novel lipids. The liability of that platform is absolutely its safety. As you know from writing about the area, the biodistribution of lipid is focused toward the liver. Which has some indications that are useful for IV therapy, but it's restrictive with respect to cancers and diseases of other organs.

We've also moved into two other delivery areas. One is polymer-based delivery. It's exemplified by the Mirus delivery system that Roche fully acquired in 2008 for $125 million. That's a really nice delivery system because it's a targeted delivery system. But, it too, has liabilities as does every delivery system.

The last one is a conjugation to RNA system. You directly attach to the RNA molecule a targeting agent. It's a defined complex, which for local delivery, works well. It can work well for systemic delivery as well. By local I mean something like injection into the joint.

X: What kind of data do you have in hand at this point to support your programs? What's the best thing that happened in this department in 2009?

AS: There have been a lot of breakthroughs in the department. I think one thing I emphasize, and is good to capture, is that the value for this space is in the commercial product. That's the long-term goal. The short to mid-term goal may be somewhat opaque to a biotech company, because they don't have the same pipeline needs as someone like Merck or another large company. It's about increasing the probability of success of this pipeline. In order to do that, we need to validate targets, and de-risk targets. Before we inject three years and, Lord only knows how many chemists and support people, to make a small

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