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A billion dollar punt

Merck's acquisition of Sirna Therapeutics is a gamble, but gambling may not always be such a bad thing.

At the end of October, Merck & Co. announced its intentions to acquire the RNA interference (RNAi) developer, Sirna Therapeutics. Merck will pay $1.1 billion for Sirna, or $13 a share—a 102% premium over Sirna's prevailing share price. This is good news for Sirna shareholders and a positive sign for other firms developing RNAi approaches. But perhaps the most significant aspect of the Merck-Sirna acquisition is the signal it sends about risk-taking in the pharmaceutical industry.

In April of 2003, Sirna emerged, phoenix-like, from the ashes of Ribozyme Pharmaceuticals, a firm focusing on ribozymes with less than $15 million in the bank and a lead compound that looked dead in the clinical water. With a $53 million cash injection and an opportunistic shift in strategic focus from one nucleic acid approach (ribozymes) to another (RNAi), Sirna set out to exploit its expertise in RNA chemistry to turn raw small-interfering RNA (siRNA) into something resembling a therapeutic. In March, together with Allergan, the company reported its lead compound Sirna-027 had successfully completed a phase 1 trial in age-related macular degeneration (AMD).

Sirna's acquisition by Merck is not surprising given the pharma firm's deep-seated interest in RNAi technology. In July this year, for instance, it shelled out $120 million in milestone payments for the development of siRNAs against three undisclosed targets to another dominant player in RNAi, Alnylam, under a deal originally made in 2003. But why did it decide to acquire Sirna rather than partner with it, as with Alnylam?

The answer certainly doesn't lie with Sirna's clinical pipeline. Sirna has one compound in the clinic, in AMD—not an indication traditionally thought of as having blockbuster potential. And, according to insiders, the initial negotiations with Sirna were for research collaborations in other areas: oncology and metabolic disease.

One key factor was Sirna's intellectual property (IP) base in RNAi. Sirna is the only other licensee of the key Tuschl patents on RNAi technology that form the foundation for Alnylam. In addition, Sirna has over 40 issued patents covering RNA chemistry and biology, ~150 pending patents filed worldwide on everything from siRNAs that target multiple transcripts to oligonucleotide chemistry, delivery and manufacture, and >100 patents pending for siRNAs targeting specific "disease-causing genes and viruses." Whether or not Sirna's IP blocks others, the acquisition of Sirna clears Merck's routes to market (for the compounds developed with Alnylam, for instance) and muddies the water for competitors (including other pharma collaborators of Alnylam's). And, of course, Sirna's IP is bolstered by Merck's legal and financial muscle.

In addition, Sirna's technology will contribute to Merck's internal research programs. Merck and its subsidiary Rosetta Inpharmatics have been using RNAi to interrogate biochemical pathways and disease mechanisms. Intriguingly, Rosetta's systematic, genome-wide screens of off-target effects of siRNAs on gene expression are likely to facilitate the refinement of heuristics and algorithms to design siRNA compounds with greater specificity and activity. Targets from Rosetta's internal research that appear 'undruggable' using traditional small molecules may now also be exploited by Merck—RNAi is not constrained by the conformation of protein targets.

But perhaps the most important factor for Merck was that the Sirna acquisition places it front and center in RNAi. The first siRNA clinic therapeutics have targeted the eye—a location that is immune-privileged, easy to access and where drug effects are local. This is because, as with antisense and other nucleic acid therapeutics, delivery, immunogenicity and stability pose problems. For RNAi therapeutics to ever be useful in oncology, metabolic or cardiovascular disease, efficient systemic delivery will be needed. Lots of companies are developing delivery technologies for RNAi. Sirna will act as a magnet, bringing those potential companies to Merck.

Those making the case for acquisition of Sirna can, therefore, point to at least three good reasons justifying the purchase: internal R&D, IP clarity for Merck, and the attractant value for potential collaborators. However, the value of the latter two is highly dependent on siRNA proving itself in the clinic, and not just in niche indications.

siRNA still faces many of the same clinical hurdles as its older relatives (antisense oligonucleotides, ribozymes and gene therapy). There is an awful lot still to learn, for instance, about siRNA's toxicity and off-target effects. High dosages of siRNA may saturate the endogenous microRNA regulatory machinery causing toxicity. And in certain cases double-stranded RNAs have been claimed to upregulate, rather than downregulate, expression (*Proc. Natl. Acad. Sci. USA* **103**, 17337–17342, 2006).

Many of the first-generation siRNAs also activate protein kinase PKR and 2′,5′-oligoadenylate synthetase, leading to nonspecific cleavage of mRNA by ribonuclease L and induction of the interferon pathway, not to mention the triggering of Toll-like receptors on immune cells via CpG nucleotides. In addition, unmodified siRNAs bind nonspecifically with blood proteins and are rapidly degraded by nucleases. Merck hopes that Sirna's battery of chemical modifications can overcome these class-specific problems without significantly affecting the RNAi catalytic mechanism, but little of this has been published as yet.

On the one hand, therefore, siRNA could turn out to be restricted to a range of niche indications, with the only value to Merck arising from the undoubted R&D value of siRNA, which would make this an extremely expensive technology deal. On the other hand, siRNA may create new therapeutic entities that address completely novel and previously undruggable targets across a broad set of indications. In which case, this will be one of the best $1.1 billion ever spent in pharmaceutical history.

In the end, it is this very dichotomy that may be the most heartening aspect of this acquisition. siRNA is not a safe, me-too approach. It is not going to lead to refinements of existing drugs and extension of existing commercial franchises. It is either a passport to a set of huge and varied drug franchises, or it is a ticket to nothing of particular value. But the deal shows that at least one large pharmaceutical firm is willing to underwrite quite a large risk.