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Molecular Therapy

Is RNAi Dead?

A recurring theme in the way that many pharmaceutical companies approach new technologies is that they are initially extremely enthusiastic, perhaps excessively so, but then subsequently overreact in the opposite direction, abandoning them when the first bumps in the road come along. Only a few years ago, the affection of big pharma for RNA interference (RNAi) seemed unlimited. Merck had acquired Sirna Therapeutics for $1.1 billion, and Novartis was collaborating with Alnylam, another leading developer of RNAi-based therapeutics. In 2007, Alnylam received a whopping $431 million up front from Roche and Takeda for certain rights to their RNAi technology. However, within the last year this momentum has reversed. Novartis effectively terminated its partnership with Alnylam last September by declining a $100 million option to broadly license their RNAi intellectual property. Then, in November, Roche announced its decision to exit the RNAi field, and in February of this year Pfizer announced the elimination of its Oligonucleotide Therapeutics Unit. Some observers have speculated that these moves herald the failure of RNAi as a therapeutic platform. As the former chief scientific officer of Pfizer's oligonucleotide unit and a longtime investigator in the field of oligonucleotide therapeutics, I would like to share an alternative view of the significance of these steps and of the perceptions that have led us here.

Conventional development of small-molecule drugs is difficult—it takes a team of medicinal chemists an average of 5–7 years to develop a drug candidate to the point where it is ready to enter human clinical trials, and only about a third of disease-associated genes are "druggable" by small molecules. Furthermore, fewer than 10% of the molecules that start human testing will ever reach the marketplace. The number of blockbuster drugs that will lose their patent exclusivity this year alone is far greater than the number of new drugs being approved, and this trend will continue for at least the next few years. A quick fix to the internal R&D drought has been to acquire drugs from other companies. Recognizing that acquisitions only buy time, pharmaceutical firms have tried a variety of strategies to improve internal R&D productivity, but none of these has shown the hoped-for benefits.

Enter RNAi. RNAi promised rational drug design with unparalleled specificity and rapidity of development, and it obviated the issue of undruggable targets. In theory, a research team could pick a new drug target and have a lead RNAi drug specific for its gene ready for human clinical trials within 15 months. A good deal of early pharma interest in RNAi development was founded on very optimistic projections for this platform. In more than one case, companies jumped onto the RNAi bandwagon not because they were interested in a long-term investment in building a new platform but rather in the hope that it would be a quick way to bulk up their clinical pipelines.

So what went wrong? First and foremost is probably the challenge of delivery—a hurdle common to the development of all "molecular therapies." Certain early, high-profile publications created expectations that this challenge would be easily overcome for RNAi. Alas, such was not to be the case to the extent that had been hoped for. Although I may be considered partial, I think the progress in RNAi delivery over the past few years has been nothing short of spectacular. In 2008, a very potent RNAi delivery system might have an IC_{50} for a liver target of 1–3 mg/kg, but in the past year the RNAi dose required for 50% inhibition of target expression has been reduced to about 1% of this value, an improvement of two logs! There have also been many advances in reducing off-target and other undesired systemic effects of RNAi therapeutics in animal models, and further improvements seem likely. Unfortunately, however, the current delivery solutions do not meet companies' needs as quickly as they want. If they are unable to take the platform into clinical development this year, then the next time there is an R&D portfolio review and prioritization, investments in "high-risk" (i.e., unvalidated) platforms are likely to be cut—and every pharmaceutical firm is cutting projects. In the past two years in the United States alone, drug companies laid off more than 100,000 employees. The focus at many firms is on quick, sure returns, and RNAi is not thought likely to offer these.

Since the establishment of the first antisense companies in the late 1980s, only two oligonucleotide drugs have been approved: fomivirsen (Vitravene, an antisense phosphorothioate developed by Isis) and pegaptanib (Macugen, an aptamer developed by Eyetech and now marketed by Pfizer). Both products are administered intraocularly, and neither has achieved substantial commercial success. However, those of us working on therapeutic oligonucleotides take heart in recalling that the early monoclonal antibody programs failed repeatedly—successive waves of innovation were required to advance from mouse monoclonals to fully humanized libraries and the myriad antibody platforms available today. These innovations were spearheaded by the biotechs on the cutting edge, not by pharma.

Pharmaceutical firms have not abandoned RNAi altogether. Novartis is rumored to have approximately 100 scientists working on RNAi therapeutic development. The Alnylam collaboration left Novartis with rights to develop RNAi therapeutics against 31 targets, which is enough to keep any company busy for a while. Alnylam's other partnerships continue, and Merck, too, retains a major internal effort on RNAi development. Silence Therapeutics, RXi, and other biotech companies also continue active clinical development. In the long run, I have no doubt that drug development using RNAi and other oligonucleotide platforms will turn out to be faster than those based on conventional drugs or protein therapeutics. Innovative and exciting work is ongoing in the wide range of biotechs leading this field. As progress continues, I believe that we will see pharma reinvesting in the field. The move away from RNAi has been quick, but I think the move back into the field will be just as fast once better delivery modalities are validated in animal models and the pathway to clinical development becomes clearer.

Arthur M Krieg
Editorial Board Member