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Is this really the RNAissance?

Renewed investor interest in RNA interference (RNAi) is enabling pioneering companies to forge ahead in the clinic. Does this signify a renaissance in RNAi therapy?

Champagne corks have been popping at several RNAi drug developers in recent weeks. The New Year celebrations started when RNAi bellwether Alnylam announced it had brokered deals to acquire Merck's entire Sirna Therapeutics portfolio for just $175 million and to sell rights to several of its rare disease assets to Sanofi/Genzyme, the latter company taking a 12% stake in the Cambridge, Massachusetts–based biotech (p. 203). In February, fellow RNAi developer Dicerna staged a staggeringly successful initial public offering, raising $90 million (p. 204). Festivities continued over at Arrowhead Research, which raised $104.2 million in a follow-on financing. This influx of investment into the sector is enabling RNAi companies to push ahead with clinical testing of lead candidates. But even though some pundits have greeted these announcements as signs of an "RNAissance," is this really what we're witnessing?

The *Oxford English Dictionary* defines the word renaissance (ren·ais·sance) as "a revival of, or renewed interest in, something." Certainly, it has been sometime since the pharmaceutical industry showed interest in RNAi therapeutics. As boardrooms have become more concerned about the next quarter rather than the next breakthrough, Roche, Pfizer and Abbott have all exited the RNAi sector; now Alnylam's January deal signals Merck is also out of the game. The only large companies left with serious RNAi efforts are Novartis and Sanofi.

Conversely, one might view the flux of investors into the sector as something of a turnaround—particularly with pharma backing so scarce. Part of this renewed investor enthusiasm relates to positive clinical data. In July 2012, Alnylam's stock jumped 53% after it presented compelling phase 1 data for its short interfering (siRNA) therapy against transthyretin-mediated amyloidosis. Last August, results from a phase 2 trial showing that the same drug could knock down levels of transthyretin by 93%, together with data from a subcutaneously delivered version of the drug, again cheered investors—the market cap today is $5.7 billion (up from $1.5 billion 12 months ago).

Last year, Arrowhead announced that its hepatitis B siRNA therapy was well tolerated in a phase 1 trial and subsequently filed to begin phase 2a testing, all of which helped the company's market cap to reach $891 million (a 30-fold rise). Currently, Benitech Biopharma, CalImmune, Gradalis, Nitto Denko, Quark Pharmaceuticals, RXi Pharmaceuticals, Silence Therapeutics, Senesco Technologies, Silenseed, Sylentis and Tekmira Pharmaceuticals all have human safety testing of siRNA drugs under way.

Clinical progress could not have taken place without numerous research advances over the past decade. Serum stability has been improved through the introduction of new oligonucleotide chemistries, such as 2′-*O*-methyl (2′-*O*-Me) ribose groups, 2′ fluoro-β-D-arabinonucleotides or unlocked nucleic acids. Potency and off-target effects have been addressed through siRNA seed element design using algorithms (e.g., GC content, asymmetric thermostability, interaction scanning with 3′ UTRs across the genome) or novel architectures (e.g., blunt 2′-*O*-Me RNA duplexes that reduce passenger strand loading into RISC). Similarly, increased understanding of the role of oligonucleotide length and GU-rich content in siRNA interactions with toll-like receptors 3, 7 and 8, RIG-I and PKR has reduced immunogenicity concerns.

But it is perhaps delivery where the greatest strides have been made. Refinements in Tekmira's small nucleic acid lipid particles have allowed companies like Alnylam to achieve 100- to 1,000-fold improvements in therapeutic index. Other platforms, such as neutrally charged polyconjugates (e.g., Arrowhead's DPC technology) or simple conjugates (e.g., Alnylam's trivalent *N*-acetyl galactosamine conjugates) also show promise, particularly for delivery to hepatocytes. Last month's formation of Voyager Therapeutics also raises the possibility that novel adeno-associated viral vectors may be combined with DNA-directed RNAi drugs to achieve the same goal. Startup Solstice Biologics is pioneering an alternative approach in which the siRNA backbone is directly modified with amidite chemistry to facilitate delivery (p. 229).

Thus, the liver, which captures nanoparticle drugs by means of endothelial fenestrations and the reticuloendothelial system, has become a dominant focus for many advanced siRNA drug programs: Alnylam is focusing on hemophilia and dyslipidemia, Arrowhead on hepatitis B, Benitec on hepatitis C and Gradalis on liver metastases.

Unfortunately, this does not mean that the path to market is clear. As for any therapeutic modality, moving from proof-of-concept trials to large-scale human testing will bring drug attrition surprises related to target biology and unanticipated off-target effects. To some extent companies are aiming to improve their odds by focusing on rare diseases with monogenetic components or developing oligos against established targets (e.g., PCSK9 or hepatitis B) already drugged by small molecules or antibodies.

A big question surrounds the long-term toxicities of lipid nanoparticles. Thus far, these have mostly been used to enhance approved chemotherapies or fungicides, and these preparations have fairly toxic side effects, sometimes requiring administration of corticosteroids or antihistamines. Stringent oversight of the potential effects of these delivery agents on humans will likely be a major focus for regulators.

But there remains reason for optimism. Sanofi's option on Alnylam's siRNA clinical programs indicates that the era of investing in RNAi as a technology platform is coming to an end—the era of product-specific partnerships is beginning. The shift of many companies from a focus on heroic, last-ditch cancer treatments to drugs against potentially 'more tractable' rare diseases also indicates maturation. RNAi drugs represent an intriguing opportunity, enabling the modulation of targets undruggable by antibodies or small molecules, all with facile manufacture and short preclinical development times. So although this may not be a RNAissance, it certainly looks like a rally.

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Erratum: Is this really the RNAissance?

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In the version of this article initially published, Alnylam Pharmaceuticals was misspelled. The error has been corrected in the HTML and PDF versions of the article.