the Medicine Maker

Believe in RNAi

The gates for gene and cell therapies are open – and RNAi technology could be a serious contender for the therapy of the future.

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The discovery of RNA interference (RNAi) was regarded by the scientific community as a crucial advance – evidenced by the selection of RNAi as Science journal's 2002 "Breakthrough of the Year" and the fact that its co-discoverers, Andrew Fire and Craig Mello, were awarded the 2006 Nobel Prize in Medicine. RNAi has high specificity for targeted genes and high potency – and because of its ability to silence genes, RNAi is being investigated as a platform for the development of novel therapies by many researchers, including those in our company (co-founded by Mello).

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Much like antibodies transformed medicine, I truly believe that RNAi-based therapeutics will be the next generation of medicine. In fact, I believe that 20 years from now, RNAi-based therapeutics will be at the forefront of approved treatments over antibodies. The exciting aspect of RNAi compounds is that they can potentially be designed to target any one of the thousands of human genes – many of which, such as transcription factors and targets that act by protein-protein interactions, are undruggable by other modalities. The overexpression of certain proteins plays a role in many diseases, so the ability to inhibit gene expression with RNAi is a powerful tool. RNAi drugs also offer key safety advantages in that they can achieve their effects without the need for permanent, and potentially dangerous, gene modifications.

But what is needed to help the field flourish? RNAi is a complex and challenging field of research. Although there has been significant progress in the clinical development of RNAi products, none have yet reached the commercial stage. RNAi needs a "first" to convince the market that previously identified roadblocks for successful RNAi therapy can be resolved. One of the most significant challenges has been the appropriate delivery of RNAi compounds into the cell type of interest. Chemically stabilized small interfering RNAs have been well explored but have demonstrated limited clinical efficacy. Some companies have used encapsulation in a lipid-based particle, such as a liposome, to improve circulation time and cellular uptake, but there are also compounds being developed with built-in delivery properties that do not require a delivery vehicle for local therapeutic applications. Our company is exploring the latter approach as we seek to develop RNAi-based therapeutics.

RXi's first clinical candidate, RXI-109, targets connective tissue growth factor, a critical regulator of fibrosis. A phase II clinical trial is underway to evaluate RXI-109's ability to reduce the formation of hypertrophic scars after revision surgery. An additional clinical trial is evaluating treatment with the same compound in patients with subretinal fibrosis associated with advanced wet age-related macular degeneration.

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We have also initiated an immuno-oncology program that will initially focus on cell-based therapies for the treatment of cancer. This approach builds on well-established methodologies of adoptive cell transfer, in which immune cells are isolated, expanded and processed to optimize their anti-tumor activity. We have developed an approach for the ex vivo treatment of adoptively transferred cells to silence immune checkpoint genes, and make the cells more effective in the immunosuppressive tumor microenvironment. We can target multiple immune checkpoints in a single cell-based therapeutic treatment that will hopefully come with fewer of the side effects associated with combination antibody treatments, while potentially providing similar efficacy.

I eagerly await the day when the first company – whoever that may be – gets an RNAi therapeutic approved. Whoever reaches the finish line first will stand in the media spotlight but, more importantly, will signal to the rest of the biomedical community that a new era in drug development has arrived.

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