RNA interference-based therapeutics and diagnostics

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It is an exciting time in the RNA interference (RNAi) field. We are in the midst of a rich period of clinical translation made possible by advances in delivery science and technology. Over the past few years alone, human of proof of concept for RNAi has been demonstrated using systemically administered small interfering RNA (siRNA) therapeutics. Also, siRNA and microRNA (miRNA)-based therapeutics have advanced to the clinic for a variety of important diseases including rare diseases like transthyretin (TTR) amyloidosis, infectious diseases such as hepatitis B, and cancer resulting in a growing pipeline of RNAi-based medicines. In addition, it is increasingly apparent that circulating RNAs in vivo may serve as biomarkers for use in clinical development and disease treatment. Techniques developed to capture and quantitate these RNA markers from serum and other body fluids will facilitate the development of RNAi-based and other medicines.

The RNAi field has come a long way in the decade or so since the fundamental discoveries by Fire and Mello, Tuschl, and others during the period from 1998 to 2001 launched hope and high expectations for a new class of therapeutics based on RNAi. The ability to harness the potential of this biological discovery and achieve clinical translation is being made possible by progress in delivery science and technology. Transporting a highly negatively charged RNA macromolecule susceptible to enzymatic degradation and rapid clearance systemically to a specific cell type in the body and then intracellularly into the cell's cytoplasm to engage the natural RNAi machinery is a tremendous challenge in drug delivery. This must be done with a delivery system that is both potent and safe in humans at a therapeutically relevant dose. The

RNAi delivery field has now accomplished this feat, however, for specific cell types mostly in the liver. This issue of *Drug Delivery and Translational Research* (DDTR) provides an excellent overview of the state of the progress RNAi field with respect to delivery and clinical translation as well as a window on future directions in RNAi delivery from leading scientists in the field.

While we have a considerable way to go to match the early expectations for RNAi, namely developing therapeutics to silence any gene in the genome, an increasing number of important new RNAi-based medicines enabled by the latest advances in delivery technology are now in the clinic to address significant unmet medical needs. As we consider where we stand today in the overall development of RNAi technology for new medicines, a historical perspective is helpful. Recombinant DNA technology for producing protein therapeutics was discovered in the 1970s. The first products emerged in the 1980s, and the technology was considered a platform in the pharmaceutical and emerging biotechnology industries with multiple commercialized products by the 1990s. This was a 20-year cycle. Similarly for monoclonal antibodies: discovery in the 1980s, first products in the 1990s, and platform in the 2000s. If RNAi technology follows this pattern, we are on track to see the first RNAi-based medicines commercialized in the next few years with the potential for RNAi technology to grow into a platform technology for new medicines over the next decade. Progress in delivery science and technology will continue to play a central role in determining this trajectory. This issue of DDTR provides an invaluable resource and reference for research and clinical translation in this exciting emerging field.

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Conflicts of interest MAT serves as a paid consultant for biotech/pharma companies including companies developing RNA-based therapeutics. He owns stock in Alnylam Pharmaceuticals, Inc.