Unravelling the potential of nucleic-acid-based drugs

The potential of nucleic-acid-based drugs to halt the production of disease-associated proteins or to promote the production of therapeutic proteins has spurred a string of recent deals.

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BioPharma Dealmakers

For more than two decades, pharmaceutical and biotech companies have been pursuing the development of nucleic-acid-based technologies to modulate gene expression and create new therapies for rare genetic disorders, as well as for more common diseases in areas such as oncology and metabolism.

Building on pioneering approaches using antisense oligonucleotides, companies are now also exploring other types of nucleic-acid-based drugs including small interfering RNAs (siRNAs), microRNA-based agents and messenger RNA (mRNA)-based agents (see below).

Although a few antisense oligonucleotides have made it to the market, many of the other platforms in the field are still relatively new—only a small number of therapies are in late-stage trials—and major challenges remain, such as the efficient and targeted delivery of therapies. Nevertheless, a new crop of nucleic-acid-based drugs seems to be on the horizon, and there has been substantial deal activity in the field within the past few years, as summarized in **Figure 1**.

mRNAs

- mRNAs are a large family of RNAs that convey information encoded in genes to guide the synthesis of proteins in a process called translation.
- Through *ex vivo* transfection or vaccination, synthetic mRNAs can be used to generate therapeutic proteins of interest or function as vaccines that trigger an immune response to the encoded antigens.
- mRNAs have reached phase 3 trials as cancer immunotherapies, and mRNA vaccines for infectious diseases have also been clinically tested. A range of other applications, including protein replacement therapies, are at early stages of development.

Antisense oligonucleotides

- Synthetic antisense oligonucleotides can be designed to be complementary to the sequence of the mRNA that encodes a particular disease-associated protein. The antisense oligonucleotide then binds to the mRNA, leading to its degradation and thereby inhibiting the production of the encoded protein.
- Two antisense oligonucleotides that inhibit the expression of disease-associated proteins have reached the market: Vitravene (fomivirsen) was approved by the US Food and Drug Administration (FDA) in 1998 to treat cytomegalovirus retinitis in immunocompromised patients (although it is now discontinued) and Kynamro (mipomersen) was approved by the FDA for homozygous familial hypercholesterolemia in 2013. Both therapies were developed by Ionis Pharmaceuticals, in partnerships with CIBA Vision (a unit of Novartis) and Genzyme (a Sanofi company), respectively.
- Another class of antisense oligonucleotide functions by binding to target RNA sequences and blocking access of proteins involved in gene splicing, thereby leading to 'exon skipping'. One exon-skipping agent, Exondys 51 (eteplirsen; developed by Sarepta Therapeutics), has recently been granted accelerated approval by the FDA for the treatment of a subset of patients with Duchenne muscular dystrophy, and other exon-skipping agents are in clinical development.

siRNAs

- RNA-mediated interference (RNAi) is a natural process that regulates gene expression. The process involves the production of small double-stranded RNAs known as siRNAs and leads to the degradation of complementary mRNAs, thus reducing protein expression.
- Chemically synthesized siRNAs, or expression of siRNAs from viral vectors, can be used to harness the RNAi process to silence specific genes of interest, and siRNA technologies are widely employed in studies of gene function, including the identification of potential drug targets.
- siRNAs are also being investigated as therapeutics for diseases in which silencing of a particular gene is desirable, such as rare monogenic disorders and various cancers. Multiple siRNA-based therapies have reached clinical development, but none has yet been approved.

MicroRNAs

- MicroRNAs are small non-coding RNAs that have a central role in the regulation of gene expression through RNAi.
- Similar to siRNAs, microRNAs inhibit the translation of mRNAs into proteins. However, whereas siRNAs target a specific gene, microRNAs are not completely complementary to their target mRNAs, and so a single microRNA can regulate the expression of multiple genes.
- MicroRNA-based therapeutics, including microRNA inhibitors and microRNA mimics, are being explored to target diseases including cancer and viral infections, and a few of these therapeutics have reached phase 2 trials. MicroRNAs are also being investigated as biomarkers in oncology and other disease areas.

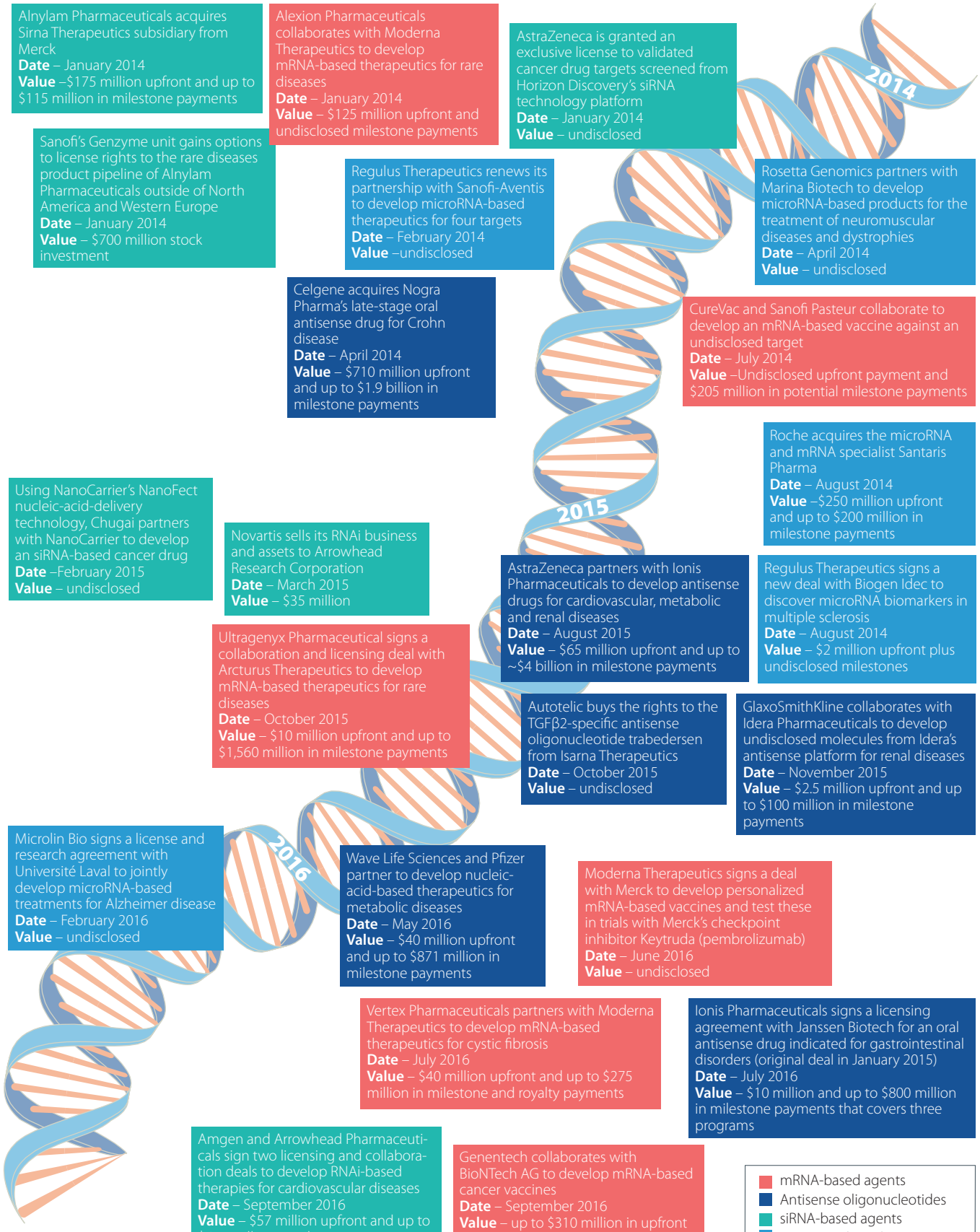

Figure 1: Selected recent deals since 2014 involving nucleic-acid-based agents. Deals are colour-coded according to the platform involved. mRNA, messenger RNA; RNAi, RNA-mediated interference; siRNA, small interfering RNA; TGFβ2, transforming growth factor β2.