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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.

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 nucleicacid-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-acidbased 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.

Date – January 2014 Date – January 2014 technology platform **Date** – January 2014 Value – \$125 million upfront and Value – undisclosed Regulus Therapeutics renews its partnership with Sanofi-Aventis to develop microRNA-based Date – January 2014 diseases and dystrophies Date – April 2014 Date – February 2014 Value – \$700 million stock Value – undisclosed Value – undisclosed Celgene acquires Nogra Pharma's late-stage oral undisclosed target Date – July 2014 Value –Undisclosed upfront payment and Date – April 2014 Value – \$710 million upfront and up to \$1.9 billion in Date – August 2014 Value – \$250 million upfront and up to \$200 million in Date – February 2015 Value – undisclosed Date – March 2015 Value – \$35 million Pharmaceuticals to develop antisense drugs for cardiovascular, metabolic **Date** – August 2014 **Value** – \$2 million upfront plus undisclosed milestones Date – August 2015 Value – \$65 million upfront and up to ~\$4 billion in milestone payments diseases **Date** – October 2015 Autotelic buys the rights to the GlaxoSmithKline collaborates with TGFβ2-specific antisense oligonucleotide trabedersen Value – \$10 million upfront and up to Date - October 2015 Date – November 2015 Value – undisclosed Value – \$2.5 million upfront and up Wave Life Sciences and Pfizer acid-based therapeutics for treatments for Alzheimer disease Date – February 2016 Value – undisclosed **Date** – May 2016 Value – \$40 million upfront Date – June 2016 Value – undisclosed agreement with Janssen Biotech for an oral Therapeutics for cystic fibrosis Date – July 2016 Value – \$40 million upfront and up to \$275 million in milestone and royalty payments antisense drug indicated for gastrointestinal disorders (original deal in January 2015) Date – July 2016 Value – \$10 million and up to \$800 million in milestone payments that covers three mRNA-based agents Antisense oligonucleotides Date – September 2016 Value – \$57 million upfront and up to Date – September 2016 Value – up to \$310 million in upfront and near-term milestone payments siRNA-based agents microRNA-based agents

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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; TGF β 2, transforming growth factor β 2.