Current trends in RNA-based therapeutic development

Cellular RNAs play crucial roles during disease progression and represent a diverse and largely untapped class of biomolecules that can be exploited for drug development.

By Dr Xiaoqiu Wu and Dr Andrew P. Turnbull

RNA species include messenger RNAs (mRNAs) that are translated into proteins, long non-coding RNAs including transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs), and small non-coding RNAs such as micro RNAs (miRNAs) and small interfering RNAs (siRNAs). Exploiting RNA species as therapeutic agents offers new opportunities for drug developers, and the possibility to develop agents against 'undruggable' genes and gene products (for a comprehensive review on RNA-targeted therapeutics, please refer to reference 1). Furthermore, new screening tools now make it easier to target disease-associated RNA sequences. However, developing RNA-based therapeutics is not without its challenges since RNA is inherently unstable and prone to degradation by active and abundant ribonucleases (RNases), is potentially immunogenic and may require a delivery vehicle for efficient and specific transport to target cells and across the lipid bilayer. These development hurdles have largely been overcome by chemically modifying RNA to enhance its stability, and by employing synthetic carriers such as lipid nanoparticle (LNP) or polymer-based nanoparticle (PNP) systems for RNA drug delivery. RNA drug development efforts have primarily focused on four modalities:

● mRNA vaccines for cancer and infectious disease.
● *In vitro* transcribed (IVT) mRNAs to replace or supplement proteins.
● Antisense RNAs, or RNA interference (RNAi) via miRNAs and siRNAs, to partially or completely turn off gene expression.
● RNA aptamers, or 'chemical antibodies', which bind to specific molecular targets and can act as drug carriers to deliver small-molecule chemotherapeutics, siRNAs, miRNAs or nanoparticles into targeted tissues.

These efforts have led to the therapeutic potential of RNA drugs being realised[2], with the RNA aptamer – pegaptanib (brand name Macugen) – representing the first FDA approval for an RNA-based drug in 2004. Since then, two antisense RNAs – nusinersen (Spinraza) and eteplirsen (Exondys 51) – and one siRNA drug – patisiran (Onpattro) – have gained FDA approval (**Table 1**). As of July 2018, 69 companies have mRNA, antisense RNA, RNAi or RNA aptamer therapeutics in clinical development with 315 ongoing clinical trials (data provided by GlobalData Plc; https://www.globaldata.com/). Furthermore, several strategic collaborations and partnerships have been forged between big Pharma and Biotech companies to leverage proprietary technology platforms. For example, Arbutus Biopharma Corporation, which has proprietary LNP and ligand-conjugate delivery technologies, recently entered into an agreement with Roivant Sciences to launch Genevant Sciences. New

Table 1: RNA-based therapeutics in clinical development. RNA drugs in five or more clinical trials as of July 2018 are tabulated. Data provided by GlobalData Plc

Class	Company	Drug (Brand Name)	Therapeutic Area	Indication	Clinical Trials (≥ 5)	Development Stage
mRNA	Argos Therapeutics Inc	Rocapuldencel-T	Oncology	Muscle Invasive Bladder Cancer (MIBC); Non-Small Cell Lung Cancer; Renal Cell Carcinoma	9	Phase II
		AGS-004	Infectious Disease	Human Immunodeficiency Virus (HIV) Infections (AIDS)	6	Phase II
	eTheRNA Immunotherapies NV	TriMix-based immunotherapy	Oncology	Melanoma; Multiple Myeloma (Kahler Disease)	6	Phase II
	Boehringer Ingelheim GmbH	BI-1361849	Oncology	Non-Small Cell Lung Cancer	5	Phase II
Antisense RNA	Biogen Inc	Nusinersen (Spinraza)	Central Nervous System	Spinal Muscular Atrophy (SMA)	13	Marketed
	Akcea Therapeutics Inc	Volanesorsen sodium	Metabolic Disorders	Familial Chylomicronemia (Type I Hyperlipoproteinemia)	13	Pre-registration
	Sarepta Therapeutics Inc	Eteplirsen (Exondys 51)	Genetic Disorders	Duchenne Muscular Dystrophy	12	Marketed
	Antisense Therapeutics Ltd	ATL1102	Central Nervous System	Relapsing Remitting Multiple Sclerosis (RRMS); Secondary Progressive Multiple Sclerosis (SPMS)	8	Phase II
	Pharmaxis Ltd	ASM-8	Respiratory	Allergic Asthma	6	Phase II
siRNA	The Medicines Company	Inclisiran	Cardiovascular	Atherosclerosis; Cardiovascular Disease	11	Phase III
			Metabolic Disorders	Homozygous Familial		
	Alnylam Pharmaceuticals Inc	Patisiran (Onpattro)	Metabolic Disorders	Hereditary transthyretin-mediated amyloidosis (hATTR)	8	Marketed
	RXi Pharmaceuticals Corp	RXI-109	Dermatology	Hypertrophic Scars	8	Phase II
			Ophthalmology	Wet (Neovascular/Exudative) Macular Degeneration		
	Alnylam Pharmaceuticals Inc	Fitusiran	Haematological Disorders	Hemophilia A; Hemophilia B	7	Phase III
		Cemdisiran	Gastrointestina	Atypical Hemolytic Uremic Syndrome (Nondiarrhea- Associated Hemolytic Uremic Syndrome)	7	Phase II
			Haematological Disorders	Paroxysmal Nocturnal Haemoglobinuria		
	Quark Pharmaceuticals Inc	QPI-1002	Genito Urinary System And Sex Hormones	Acute Renal Failure (ARF) (Acute Kidney Injury)	6	Phase III
			Immunology	Kidney Transplant Rejection		
	Bristol-Myers Squibb Co	BMS-986263	Gastrointestinal	Liver Fibrosis	6	Phase II
	Pfizer Inc	PF-655	Metabolic Disorders	Diabetic Macular Edema	5	Phase II
			Ophthalmology	Wet (Neovascular/Exudative) Macular Degeneration		
RNA Aptamer	Pfizer/Valeant Pharmaceuticals International Inc	Pegaptanib (Macugen)	Ophthalmology	Age-Related Macular Degeneration (AMD)	38	Marketed
	Ophthotech Corp	Avacincaptad pegol sodium (Zimura)	Ophthalmology	Dry (Atrophic) Macular Degeneration	11	Phase III
	Noxxon Pharma AG	Olaptesed pegol	Oncology	B-Cell Chronic Lymphocytic Leukemia	11	Phase II
		Emapticap pegol	Oncology	Sold Tumour	5	Phase II
			Metabolic Disorders	Diabetic Nephropathy		

modalities to target RNA are also being developed including the application of CRISPR-Cas9 genome editing technology and the development of selective small-molecule modulators of RNA or RNA-modifying enzymes. The global RNA drugs market is forecast to exceed $10 billion by 2024 (based on an analysis carried out using the GlobalData Plc database), highlighting the significant commercial potential of this emerging class of therapeutics.

Development hurdles

Despite the potential of RNA therapeutics, efficient and safe delivery remains a significant challenge. There are a number of significant issues that need to be overcome in their development: instability and immunogenicity; rapid clearance from the blood by the kidneys and liver scavenger receptors; cellular uptake and endosomal escape[3]. These hurdles can be overcome by chemically modifying RNA and by using improved synthetic delivery carriers[4].

Therapeutics

Chemical modification

mRNAs can be stabilised by incorporating naturally-occurring modified nucleosides including pseudouridine, which represents one of the most abundant post-transcriptional RNA modifications, and the more recently identified 5'-methyl-cytidine triphosphate (m^{5}CTP), N^6-methyl-adenosine-5'-triphosphate (m^{6}ATP), 2-thio-uridine triphosphate (s2UTP), N^6-methyladenosine (m^{6}A), and N^6,2-O-dimethyladenosine (m^{6}A$_m$)[5,6]. In addition, a 5'cap, optimised 3' poly(A) tail, and 5'- or 3'- untranslated regions can be added or the mRNA can be codon optimised to improve translational efficiency. Modified mRNAs can reduce immunogenicity and increase protein expression levels compared with unmodified mRNA. The most common chemical modifications that have been incorporated to enhance the stability of RNAi and antisense RNA drugs are phosphorothioate RNA backbone modifications and ribose modifications including 2'-O-methyl, 2'-fluoro and 2'-O-methylethyl substitutions[7]. These modifications enhance the stability of the RNA drug and provide protection from nuclease degradation. Furthermore, the new chemistries confer drug-like properties to RNA, reduce immune stimulation, maximise on-target potency and prolong the duration of the drug.

Delivery

RNA-based therapeutics must be delivered to the target cell and enter the cell to be active[8] (**Figure 1**). Overcoming delivery of RNAs across the lipid bilayer and into cells remains a major challenge[3]. Furthermore, once internalised, the endocytic pathway – a major cellular active uptake mechanism for agents too large to permeate passively – leads to entrapment in the endosome and subsequent degradation in the lysosome. For example, only 0.1% to 2% of siRNAs evade degradation and reach the RNAi machinery in the cytosol. New *in vivo* RNA delivery technologies including LNP or PNP systems and the use of aptamer or antibody conjugation have overcome some of the challenges associated with delivery of RNA-based therapeutics, with the selection of the delivery system depending on the therapeutics properties, type of target cell and desired delivery route. For example, LNPs tend to end up in the liver, which has been exploited at Alnylam Pharmaceuticals, Dicerna Pharmaceuticals and Arrowhead Pharmaceuticals Inc by attaching N-acetylgalactosamine (GalNAc) to siRNAs to specifically target the hepatic asialoglycoprotein receptor on liver cells and trigger internalisation. Improving endosome escape is another key step. The most common approaches are to use endosomolytic agents such as fusogenic peptides and polymers to enhance endosomal escape of siRNAs[7].

Classes of RNA-based therapeutics

RNA-based therapies can be classified according to their mechanism of action and include single-stranded mRNAs and antisense RNAs, double-stranded miRNAs and siRNAs, and RNA aptamers (**Figure 1**). RNA-based therapeutics range in size from thousands of bases for mRNAs down to 8-50 nucleotides for antisense RNAs and 20-25 base pairs for miRNAs and siRNAs.

mRNA

IVT mRNA is single-stranded and comprises structural features in common with native mRNA, with its bioavailability being determined by RNase degradation, delivery and cytosolic translocation. IVT mRNAs usually incorporate chemically modified nucleosides such as pseudouridine, which reduce immunogenicity and increase its translational efficiency[9]. Furthermore, the development of improved formulations, for example the use of LNPs and PNPs, protect IVT mRNAs from RNases and facilitate cellular uptake (**Figure 1**).
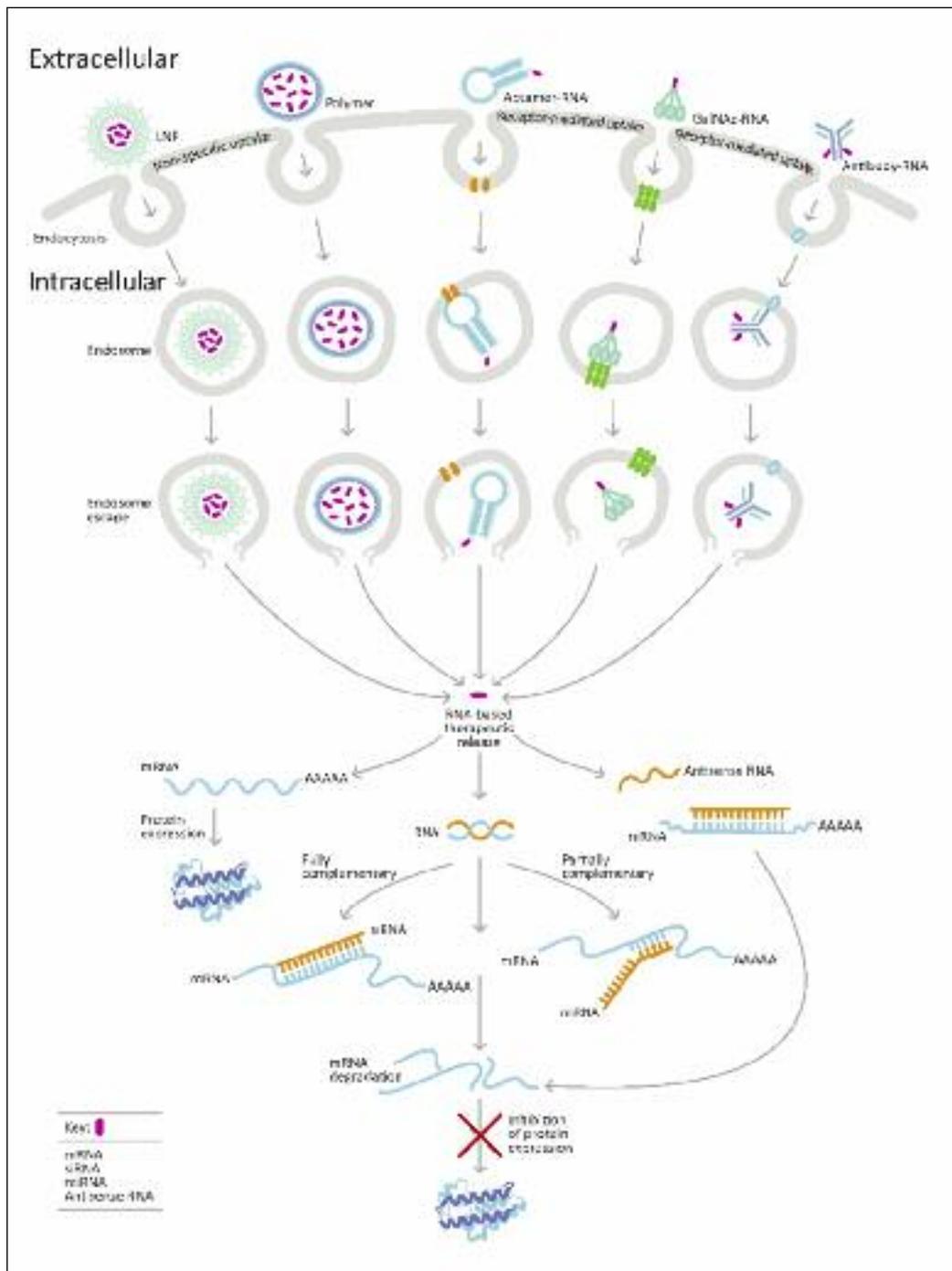
IVT mRNA can potentially be used to transiently express proteins to prevent or alter a disease state, with mRNA drugs being developed for cancer immunotherapies and infectious disease, protein-replacement and regenerative medicine[9]. mRNA-based protein replacement therapies are used to replace proteins *in vivo* that are not expressed/expressed at a low level or are non-functional using IVT mRNA. mRNA cancer immunotherapy agents are at advanced stages of development (**Table 1**), with first in man trials under way for mRNA vaccines including Rocapuldencel-T (Argos Therapeutics Inc) and BI-1361849 (Boehringer Ingelheim GmbH).

Antisense RNA

Most current antisense RNAs have been developed from sequences complementary to the target mRNA, and are introduced into cells to reduce or modify expression of the protein upon binding to mRNA to alleviate the symptoms of the disease. Sequence-specific antisense RNAs inhibit gene expression by altering mRNA splicing, arresting mRNA translation and inducing mRNA degradation by ribonucleases (RNase H). Previously, natural antisense RNAs were evaluated for gene silencing, however, their inherent instability led to the development of modified antisense RNAs that are either more nuclease resistant but still activate RNase H or

bind to RNA without activating RNase H. Modified antisense RNAs exhibit significantly-improved tissue half-life and prolonged inhibitory activity. To date, two antisense RNA drugs have gained FDA approval: Spinraza (Biogen Inc) and Exondys 51 (Sarepta Therapeutics Inc) (**Table 1**).

RNAi: miRNA and siRNA
The cellular process of RNAi utilises miRNAs and siRNAs to silence gene expression through post-translational gene silencing or transcriptional silencing. Double-stranded miRNAs and siRNAs bind to mRNA and inhibit protein translation. Endogenous miRNAs induce translational repression and mRNA degradation when the antisense strand displays limited complementarity to the target mRNA, whereas sequence-specific cleavage is exploited by exogenous siRNAs that display perfect

or near-perfect base pairing with the mRNA target (**Figure 1**).

miRNA

miRNAs are small non-coding RNAs that play key roles in cell differentiation, proliferation and survival. The dysregulation of endogenous miRNAs occurs in multiple diseases including hepatitis, cardiovascular diseases and cancer (where miRNAs act as tumour suppressors or oncogenes). miRNAs are loaded on to the RNA-induced silencing complex (RISC) and interact with partially complementary targets on mRNA to suppress protein expression (**Figure 1**). Antisense RNAs complementary to miRNA can block activity, whereas double- or single-stranded RNAs that mimic miRNA can enhance activity. Both miRNA inhibitors and mimics are currently being developed and have shown encouraging results[10]. For example, RG-012 (Regulus Therapeutics Inc) is a miRNA drug currently being evaluated in Phase I trials for the treatment of Alport syndrome[11].

siRNA

In contrast to miRNAs, which attenuate protein production, when an siRNA recognises mRNA it causes cleavage and degradation of the mRNA and completely silences the gene, shutting down protein production (**Figure 1**). siRNAs arose as a natural defence mechanism against RNA viruses and are double-stranded RNAs acting as prodrugs: the antisense strand is pharmacologically active whereas the sense strand facilitates drug delivery, transporting the antisense strand to the intracellular Argonaute (Ago) loading complex. There are four Ago proteins that can be loaded with miRNAs or siRNAs and alter translation and/or RNA stability: siRNAs preferentially bind to Ago2. siRNAs can also compete with miRNAs loaded on to Ago2, thereby altering the half-lives of other cellular RNAs. Exogenous siRNAs operate via a sequence-specific mechanism with perfect complementarity to the target mRNA but can also have miRNA-like effects on some partially complementary mRNA sequences, leading to a lack of specificity. Therefore, a single siRNA sequence can potentially modulate expression of hundreds of off-target genes, which can impact on the efficacy of the RNA drug.

Following systemic injection, siRNAs encapsulated in LNPs often tend to accumulate in the liver and spleen[12]. For systematic delivery, synthetic carriers are usually decorated with cell-specific ligands or aptamers that facilitate receptor-mediated uptake (**Figure 1**). Furthermore, biodegradable nanoparticle carriers allow for slow drug release within the cell to regulate dose. Patisiran (brand name Onpattro; Alnylam Pharmaceuticals Inc) represents the first FDA approval of an RNAi therapeutic in an LNP formulation for hereditary transthyretin-mediated amyloidosis (hATTR) in adults (FDA approved in August 2018; **Table 1**).

RNA aptamers

RNA aptamers are short, single-stranded RNAs that are usually selected *in vivo* to bind to specific molecular targets using SELEX (systematic evolution of ligands by exponential enrichment). RNA aptamers have a propensity to form complementary base pairs, which drives the formation of aptamer-target complexes. Aptamers feature the high affinity of antibodies but also offer several distinct advantages: their relatively small size and flexibility allow engagement with binding sites inaccessible to larger antibodies; improved transport and tissue penetration; quick synthesis and comparatively lower manufacturing costs; and high stability and minimal immunogenicity. Many aptamers are internalised upon binding to cell-specific receptors, making them useful drug carriers to deliver small-molecule chemotherapeutics, siRNAs, miRNAs or antisense RNAs into targeted tissues (**Figure 1**). However, the inherent physiochemical characteristics of aptamers, which affect metabolic stability and limit *in vivo* potency, combined with a lack of available safety data, have hindered their development. As with other classes of RNA-based therapeutics, unmodified aptamers are susceptible to nuclease-mediated degradation leading to very short *in vivo* half-lives (typically less than 10 minutes). Therefore, most aptamers in clinical development feature chemical modifications to improve nuclease resistance and pharmacokinetic properties[13]. For example, Macugen is PEGylated and conjugated to polyethylene glycol (PEG) to extend its half-life *in vivo*.

Aptamers can act as antagonists to block protein-protein or receptor-ligand interactions; as agonists to activate receptors; or as cell-specific delivery systems. All aptamers currently in clinical development are inhibitors that disrupt the function of a target protein. In addition, aptamers can be designed to act as RNA decoys that compete with a natural RNA sequence that represents the target of an RNA-binding protein, sequestering its interaction. In December 2004, Macugen (Pfizer/Valeant Pharmaceuticals International Inc), a VEGF-specific modified RNA aptamer, gained FDA approval for the treatment of age-related macular degeneration (AMD) and several other

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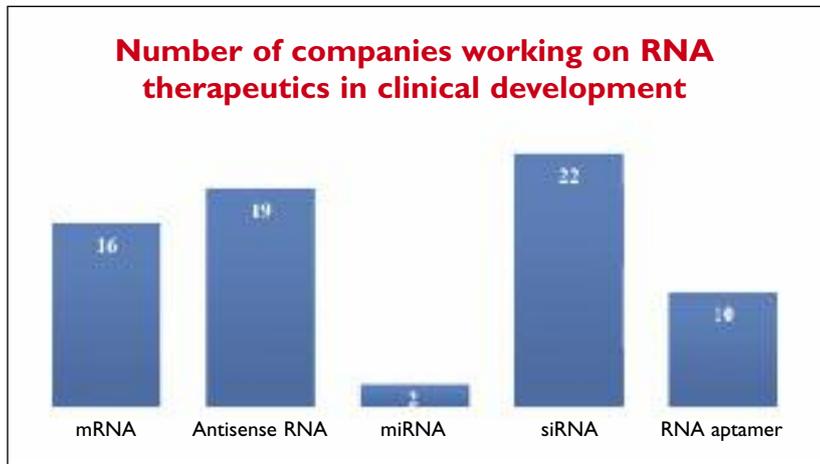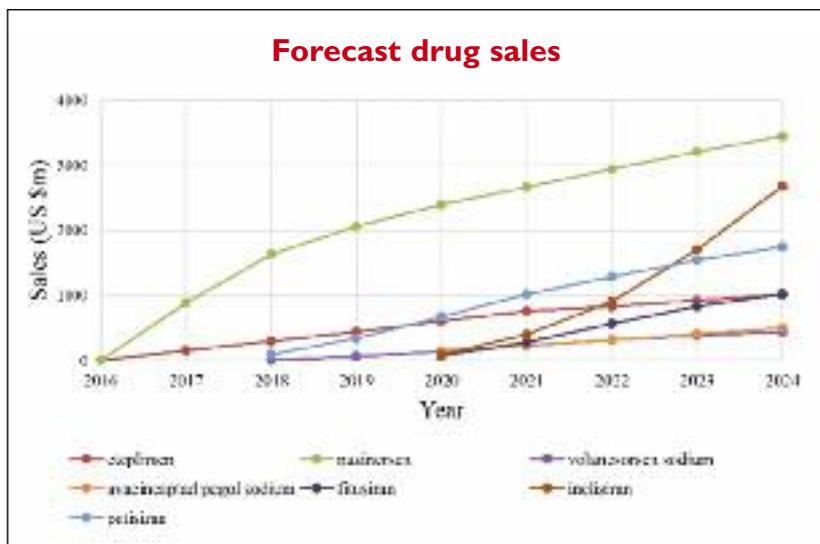
Graph 1: Companies developing RNA-based therapeutics in the clinic (as of July 2018). Data provided by GlobalData Plc
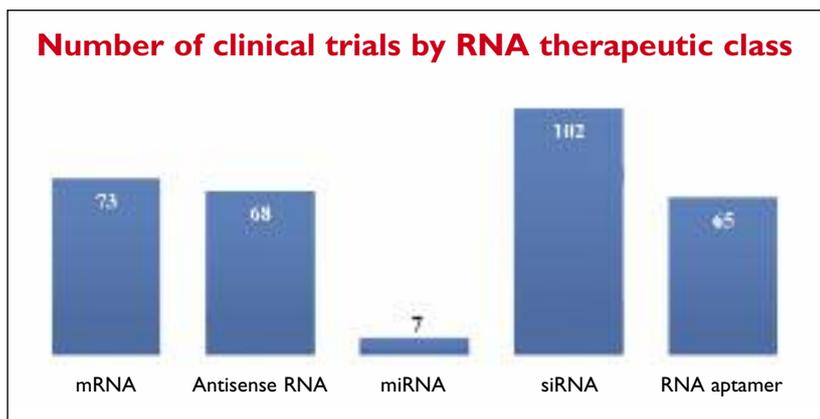
Graph 2: Number of RNA-based therapeutics in clinical trials (as of July 2018). Data provided by GlobalData Plc

Graph 3: Forecasted global sales for RNA-based therapeutics from 2016-24. Revenue is given in US$m. Data provided by GlobalData Plc

RNA-based aptamers or decoys have entered clinical development (**Table 1**).

Emerging technologies

New technologies and modalities to target RNA include the application of the CRISPR-Cas9 genome editing technology, DNA-directed RNA interference (ddRNAi) technology, and the development of selective small-molecule modulators of RNA or RNA-modifying enzymes[14]. For example, CAL-1, Calimmune's lead therapeutic candidate, represents an RNA-based gene therapy using ddRNAi to silence the CCR5 gene to control HIV infection and to protect individuals with HIV from developing AIDS. Several companies that focus on the development of small-molecule RNA modulators have been established in recent years. For example, Expansion Therapeutics Inc (San Diego, California, USA) has developed a platform to identify small molecules interacting with RNA (SMiRNA™), including mRNA and various non-coding RNAs, across multiple therapeutic areas. In addition, STORM Therapeutics (Cambridge, UK) specialises in RNA epigenetics, and the development of small-molecule inhibitors of RNA-modifying enzymes for the treatment of cancer.

Targeting splice-variant control sequences within introns (non-coding regions of an RNA transcript or DNA sequence within a gene) or exons (coding regions) offers further opportunities to develop therapeutics. For example, Skyhawk Therapeutics Inc (Waltham, Massachusetts, USA), was founded this year with a platform to identify selective small-molecule modulators of the RNA spliceosome complex that target RNA mis-splicing (exon skipping), which drives multiple diseases including neurological conditions and cancer. These emerging technologies offer great opportunities to develop alternative strategies to target RNA for drug development.

Marketplace

The first notable success for RNA-based therapeutics was the FDA approval of the RNA aptamer, Macugen (Pfizer/Valeant Pharmaceuticals International Inc), for the treatment of AMD in December 2004. Since then, two antisense RNAs and one siRNA have gained FDA approval: Exondys 51 (approved in September 2016; Sarepta Therapeutics Inc) is used to treat Duchenne muscular dystrophy; Spinraza (December 2016; Biogen Inc) represents the first approved drug for the treatment of spinal muscular atrophy in children and adults; Onpattro (August 2018; Alnylam Pharmaceuticals Inc) represents the first FDA

approval of an RNAi therapeutic for hATTR in adults. As of July 2018, 69 companies are actively developing mRNA, antisense RNA, RNAi or RNA aptamer therapeutics (**Graph 1**) with 315 ongoing clinical trials (**Graph 2**). **Table 1** highlights the major RNA drugs in five or more clinical trials and their current highest development stage. Furthermore, the forecast global sales for RNA-based therapeutics is expected to exceed US$10 billion by 2024 (based on an analysis carried out using the GlobalData Plc database (**Graph 3**).

The market has recently witnessed several strategic collaborations and partnerships between big Pharma and Biotech companies, which leverage proprietary technology platforms. For example, Moderna (Cambridge, USA) has established a number of strategic partnerships to advance mRNA medicines. In April 2018, Arbutus Biopharma Corporation, which has proprietary LNP and ligand-conjugate delivery technologies, and Roivant Sciences entered into an agreement to launch Genevant Sciences (Burnaby, Canada) – a jointly-owned company aiming to develop and commercialise a range of RNA therapeutics targeting genetic disorders with limited or no treatment options available. Genevant plans to develop products both in-house and in industrial partnerships across RNAi, mRNA and gene editing modalities with the goal of delivering between five and 10 RNA programmes to the clinic by 2020. Recently (in August 2018), BioNTech AG entered into a multi-year research and development collaboration with Pfizer to jointly develop mRNA-based influenza vaccines. These new and exciting strategic collaborations and partnerships will potentially lead to ground-breaking developments in the RNA-based therapeutics field.

Outlook

RNA-based therapeutics offer opportunities for Biotech and Pharma companies to go beyond their existing repertoire of small-molecule and antibody portfolios. However, the development of RNA-based therapeutics is challenging since RNA is inherently unstable and prone to degradation, is immunogenic and rapidly cleared and requires safe and effective delivery. The use of RNA modifications to enhance stability and improved synthetic delivery carriers, such as nanoparticle systems, have helped overcome some of these development hurdles. However, delivery across the lipid bilayer remains a significant challenge and approaches to enhance endosomal escape of RNA drugs are required. To date, four RNA-based drugs – Macugen, Exondys 51, Spinraza and Onpattro –

have successfully made it through to market and several other RNA agents are currently in clinical programmes. In addition, new screening tools are making it easier to identify disease-associated RNA sequences to target. To date, drug discovery efforts have primarily focused on mRNAs, silencing gene expression using antisense RNAs and siRNAs, or developing RNA aptamers that bind to specific molecular targets. Emerging technologies and modalities, including CRISPR-Cas9 genome editing and small-molecule modulators of RNA or RNA-modifying enzymes, offer further opportunities to target mRNA for drug discovery. Future advances in RNA therapeutic design and delivery technologies will help exploit the full commercial potential of RNA-based therapeutics.

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