FROM THE ANALYST'S COUCH

RNA therapeutics on the rise

Feng Wang, Travis Zuroske and Jonathan K. Watts

Digifoto Bronze/ Alamy Stock Photo

The broad spectrum of options for therapeutic targeting of RNA has attracted substantial interest from both academic research institutes and pharmaceutical companies. With a growing number of approved RNA therapeutics now generating significant profits, the level of investment in the field has grown. In this article, we analyse investment data for companies developing RNA therapeutics and their pipelines.

Investment focus for RNA therapeutics

To understand where this investment is focused, we categorized RNA therapeutics into three groups (oligonucleotides, mRNA, and RNA-related small molecules) and analysed venture investment and market capitalization in representative private and public companies, respectively (FIG. 1a,b). The market capitalization of public oligonucleotide companies increased 94.2% from 2015 to 2020. Three representative mRNA therapeutic companies (Moderna Therapeutics, BioNtech, and CureVac) attracted US$2.8 billion of private investment since 2015. Notably, Moderna set a record for the biggest biotech IPO with its value at roughly $7.6 billion in 2018. Since 2017, RNA-related small molecule companies have raised significant investment, including those targeting RNA directly ($262 million to Arrakis, Expansion, Skyhawk and Ribometrix) and those targeting epitranscriptomics-related proteins ($194 million to Accent, Storm, Gotham and Twentyeight-Seven Therapeutics).

RNA therapeutics pipeline

These investments have translated into robust pipelines globally (FIG. 1c,d). We analysed 431 RNA-targeting drug development programmes (including mRNA vaccines) from Informa Pharma Intelligence's Biomedtracker. Of these drug candidates, 63% are in the pre-IND stage, 32% are in early-stage clinical trials (phase I or II), 3% are in phase III and 5 drugs are awaiting regulatory decisions.

The largest focus for all three modalities is oncology, encompassing 22% of oligonucleotide candidates and 45% of mRNA candidates. Beyond oncology, oligonucleotide biodistribution has shaped pipeline priorities. *N*-acetylgalactosamine (GalNAc) conjugation and lipid nanoparticle approaches enable robust delivery of oligonucleotides into hepatocytes, which has spurred the development of over 60 drug candidates for the treatment of hepatic viruses, liver-centric genetic diseases and cardiometabolic disorders. In addition, intrathecal delivery of oligonucleotides results in broad distribution in the central nervous system.

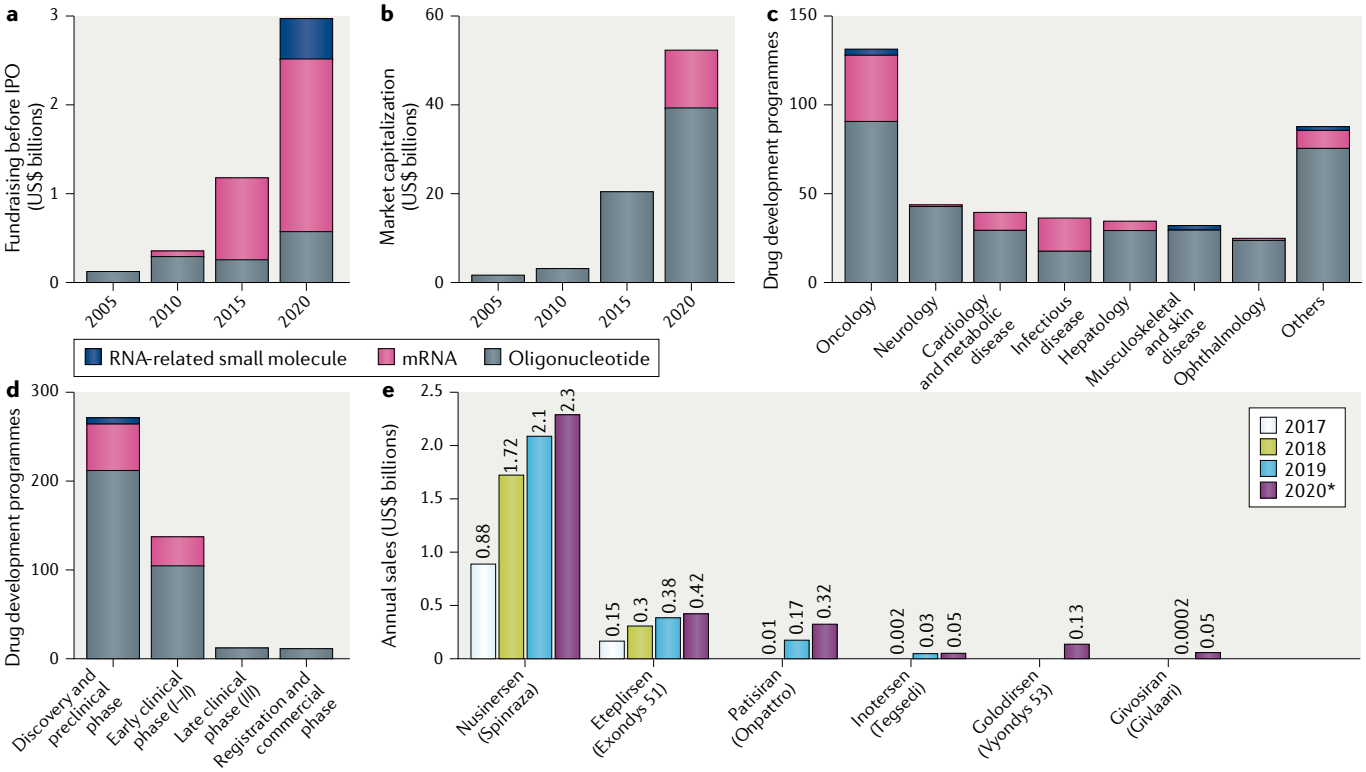

Fig. 1 | **Financial data and pipeline characteristics for RNA therapeutics. a** | Fundraising of private RNA therapeutics companies. Source: CrunchBase. **b** | Market capitalization of public RNA therapeutics companies. Source: Y-Charts. **c** | Targeted diseases by RNA therapeutics. **d** | Development stages of RNA therapeutics. Source: Biomedtracker, Informa, June 2019; updated January 2020. **e** | Revenue from approved RNA therapeutics. *Projected revenues for 2020. Source: companies' Form 10-K and Datamonitor Healthcare, Informa, January 2020.

Table 1 | **Selected RNA therapeutics approved and in development**

Drug	Company	Indication	Status
ASO			
Eteplirsen (Exondys 51)	Sarepta	DMD	Approved (2016)[a]
Nusinersen (Spinraza)	Ionis/Biogen	SMA	Approved (2016)[a]
Inotersen (Tegsedi)	Ionis/Akcea/PTC	hATTR	Approved (2018)[a]
Volanesorsen (Waylivra)	Ionis/Akcea/PTC	FCS	Approved (2019)[b]
Golodirsen (Vyondys 53)	Sarepta	DMD	Approved (2019)[a]
Viltolarsen	NS Pharma	DMD	NDA
Casimersen (SRP-4045)	Sarepta	DMD	NDA
TQJ230 (AKCEA-APO(a)-L_{Rx})	Ionis/Akcea/Novartis	Hyperlipoproteinaemia with cardiovascular risk	Phase III
Tofersen	Ionis/Biogen	SOD1-driven ALS	Phase III
IONIS-HTT_{Rx}	Ionis/Roche	Huntington disease	Phase III
Trabedersen (OT-101)	Mateon (Oncotelic)	Brain cancer	Phase III
Volanesorsen	Ionis/Akcea	FPL	Phase III
siRNA			
Patisiran (Onpattro)	Alnylam	hATTR	Approved (2018)[a]
Givosiran (Givlaari)	Alnylam	AHP	Approved (2019)[a]
Lumasiran	Alnylam	Hyperoxaluria	NDA
Inclisiran	Alnylam/Novartis (The Medicines Company)	Dyslipidaemia/ hypercholesterolaemia	NDA
QR-110	ProQR	Leber's congenital amaurosis	Phase III
Vutrisiran	Alnylam	ATTR/hATTR	Phase III
QP-1002	Quark	Renal disease/failure, delayed graft function	Phase III
Tivanisiran (SYL1001)	Sylentis	Dry eye	Phase III
Fitusiran	Alnylam/Sanofi Genzyme	Haemophilia A and B	Phase III

AHP, acute hepatic porphyria; ALS, amyotrophic lateral sclerosis; ASO, antisense oligonucleotide; DMD, Duchenne muscular dystrophy; FCS, familial chylomicronaemia syndrome; FPL, familial partial lipodystrophy; hATTR, hereditary transthyretin amyloidosis; NDA, new drug application; SMA, spinal muscular atrophy. [a]This refers to approval in the USA by the FDA, which was the first major market approval for all agents. [b]Volanesorsen (Waylivra) is approved in the EU, but is still at NDA stage in the USA. Source: Biomedtracker, Informa, June 2019; updated January 2020.

This facilitated the development of the FDA-approved exon-skipping oligonucleotide nusinersen (Spinraza; Biogen) for spinal muscular atrophy (SMA), and more than 40 additional oligonucleotide drug candidates are in development for neurological disorders.

The potential of mRNA technology for rapid vaccine development is valuable in light of the COVID-19 pandemic: the first clinical batch of an mRNA vaccine (mRNA-1273, Moderna) was designed and synthesized within a month of the release of the genetic sequence of the novel coronavirus and is now in phase I trials. Additional COVID-19 vaccine candidates are also in development.

From rare to common diseases

RNA therapeutics have demonstrated most success in the treatment of rare diseases, especially neurological and hepatic diseases. Of the 21 late-stage RNA therapeutics, 18 have orphan status (TABLE 1). The most commercially successful drug to date has been nusinersen, which has $4.7 billion in sales up to the end of 2019 (FIG. 1e). The two currently approved siRNA drugs — patisiran (Onpattro; Alnylam) and givosiran (Givlaari; Alnylam) — target liver mRNAs for the treatment of hereditary transthyretin amyloidosis and acute hepatic porphyria, respectively. Patisiran achieved sales of more than $150 million in its first full year on the market in 2019, which are forecast to approximately double in 2020.

Current prospects are less clear for oligonucleotide therapeutics in muscle diseases. So far, the evidence for muscle function improvement from treatment with eteplirsen (Exondys 51; Sarepta) and golodirsen (Vyondys 53; Sarepta) in patients with Duchenne muscular dystrophy is marginal and could be surpassed by gene therapies in development. Nevertheless, eteplirsen is commercially successful, with $840 million in sales up to the end of 2019 (FIG. 1e), and there is extensive investment in oligonucleotide drugs to treat muscular diseases. In the future, oligonucleotides may show better muscle uptake as antibody conjugates (which are being developed by Avidity Biosciences and Dyne Therapeutics) or peptide conjugates (which are being developed by PepGen).

RNA therapeutics are also being pursued in cardiovascular diseases. The PCSK9-targeted siRNA inclisiran met all primary and secondary endpoints across three phase III trials, had a clean safety signature, and matched the LDL-lowering efficiency of antibody-based PCSK9 inhibitors alirocumab (Praluent; Regeneron/Sanofi) and evolocumab (Repatha; Amgen) after a twice-annual subcutaneous injection. In a recent phase II trial of TQJ230 (AKCEA-APO(a)-L_{Rx}), an antisense oligonucleotide targeting LPA mRNA, more than 90% of patients achieved lipoprotein(a) concentrations below 50 mg/dl (a threshold conferring an increased risk of heart disease), after either 20 mg weekly injection or 60 mg injection every 4 weeks. Notably, Novartis recently acquired the Medicines Company, the developer of inclisiran, for $9.7 billion and also initiated a large phase III trial for TQJ230 in 2019.

Conclusion

RNA therapeutics have at last reached the point of profitability. Multiple oligonucleotide drugs are approved and a dozen more are in phase III trials, primarily for genetically well-defined rare diseases. The current bolus of investment in RNA therapeutics is likely to lead to further clinical success across multiple modalities and disease areas.

Feng Wang[1], Travis Zuroske[2] and Jonathan K. Watts[1]✉

[1]University of Massachusetts Medical School, Worcester, MA, USA.

[2]University of San Diego, San Diego, CA, USA.

✉*e-mail: Jonathan.Watts@umassmed.edu*

https://doi.org/10.1038/d41573-020-00078-0

Competing interests

J.K.W. is an ad hoc consultant or has received seminar honoraria from Biogen, AstraZeneca, Flagship Pioneering, or The Medicines Company within the past 12 months.