KPMG

RNA therapies: entering a new age

Rapid advances shaping a lucrative investment landscape

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Content

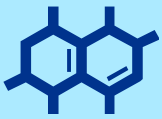
Executive summary

Big Pharma and financial institutions are actively investing in RNA therapies as the next big driver of advanced therapies. Clinical breakthroughs have already been achieved in technology domains such as RNA interference (RNAi), antisense oligonucleotides (ASO) and mRNA vaccines (e.g. Leqvio, Spinraza, Comirnaty, Spikevax). Yet only a handful of products have achieved commercial success, surpassing $1b in sales. Are these single-use cases or paving the way for a greater opportunity lying ahead? It remains to be seen whether RNA therapies will spark a therapeutic revolution similar to the one observed with monoclonal antibodies in the 90s. The next catalysts and milestones that could accelerate the success of RNA therapies include:

- mRNA to demonstrate further clinical benefit in oncology and rare diseases as well as vaccines beyond COVID-19 (e.g. MRNA-4157/V940, mRNA-3705 and potential anti-malaria vaccines)
- RNAi therapies to reach a blockbuster status in prevalent conditions (e.g. Leqvio for high cholesterol, Zilebesiran for hypertension)
- ASOs to confirm clinical benefit in rare diseases (e.g. DMD therapies)

In exploring promising RNA therapies, Pharma, Biotech and investment funds face the following pressing areas:

Big Pharma needs to carefully select assets and therapeutic areas that align with and complement their portfolio strategy. They also need to find synergies with existing business and operations when preparing for commercialization



Biotech needs to select areas with high unmet medical need, streamline portfolios and attract investment. Additionally, they also need to mobilize internal and external capabilities to solve development challenges and prepare for commercialization

Investment funds need to carefully select assets to invest in by tailoring due diligence and valuation with industry experts

This article is the continuation of the series of articles about advanced therapies (See ""One-and-done" gene therapies" 2022, "The precision medicine future in neurodegenerative diseases" and "Harnessing the power of the human microbiome" 2022 articles)

RNA therapies

The year 2023 has brought great recognition to the field of RNA therapies, as evidenced by a Nobel Prize in Physiology. RNA therapies, which involve the use of RNA molecules to treat diseases, represent a promising and evolving frontier in medicine. Over the past few decades, researchers have made significant progress in developing RNA-based treatments for a wide range of conditions, from rare genetic disorders to cancer and viral infections. RNA therapies offer several advantages over traditional small molecule drugs and protein-based therapies, including greater specificity and lower toxicity. In this article, we will explore the mechanisms of action of RNA therapies and their potential applications in the clinic as well as the challenges companies are facing.

RNA therapy mechanism of action (MoA) and types: RNA therapies employ RNA molecules to treat diseases employing two major approaches: a) manipulation of the expression of a disease-associated RNA b) gain of function by introducing an mRNA

- **RNA-mediated gene expression (RNAi, ASO)** involves the use of small RNA molecules (e.g. siRNA, miRNA) to silence specific genes that are responsible for disease. This can be used to treat a wide range of diseases, including viral infections, cancer and genetic disorders. By blocking the production of harmful proteins, RNAi can help prevent disease progression and improve patient outcomes
- **mRNA (messenger RNA)** therapy involves the use of synthetic mRNA molecules to produce therapeutic proteins within the patient's body. This approach can be used to treat genetic disorders as well as diseases such as cancer and infectious diseases. The synthetic mRNA is delivered to cells using lipid nanoparticles or other delivery methods, and is designed to enable the production of the therapeutic protein in target cells

RNAi, mRNA and ASO-based drugs have already been clinically validated and in some cases have achieved sales in the billions of US Dollars ($b).

Segmentation*

	MoA	Technology	Mechanisms	Example companies
More mature technologies	RNA-mediated gene expression control	RNAi	siRNA / miRNA / shRNA (translational repression, cleavage, degradation of multiple mRNA targets)	Novartis, Novo Nordisk, Alnylam, Arrowhead, Arbutus
		ASO	Targeted degradation, targeted augmentation, exon skipping, exon inclusion, translation blocking	Biogen, Ionis, Sarepta, PTC Tx **, NS Pharma
	Gain of function by exogenous mRNA	mRNA	Protein expression driven by the therapeutic mRNA, including vaccine	Moderna, BioNTech, Arcturus, CureVac, Sanofi
More novel technologies	RNA editing	ADAR, Cytidline Deaminase, Cas variants	Editing RNA (does not cause permanent DNA edits, potentially a safer approach than DNA editing)	Locana, Shape, Korro, ADARx, Ascidian
	Emerging RNA technologies		3 major types: • transfer RNA (tRNA) – using tRNA to modify translation • long non-coding RNA (lncRNA), including linear lncRNA • circular RNA (circRNA) act in a similar way as mRNA, but allow for improved durability	Alltrna, ReCode, Tevard, Orna, Orbital

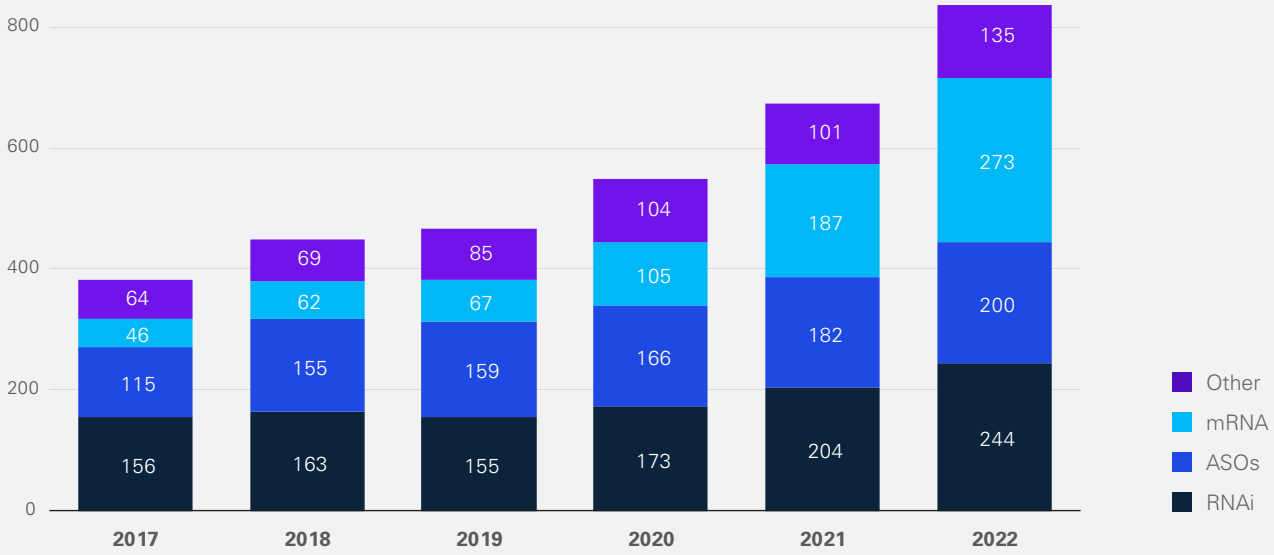
* Small molecule RNA modulators excluded from the analysis

** Tx = Therapeutics

Clinical landscape

The RNA therapy pipeline has more than doubled over the last five years largely driven by the mRNA-based vaccines; however, other segments have also experienced significant growth

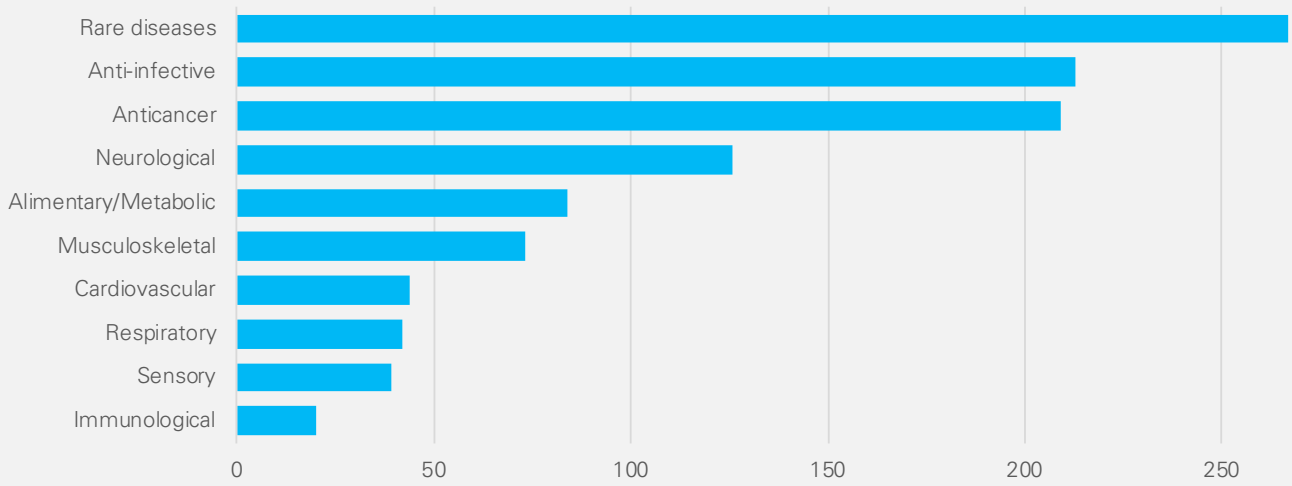
Figure 1: **RNA therapy pipeline by segment** (number of candidates incl. pre-clinical)



Source: Citeline, KPMG analysis

RNAi has a proven application potential in rare diseases, mRNA in anti-infectives. New developments allow targeting cancer and other therapeutic areas (TA)

Figure 2: **Top 10 TAs in clinic for RNA therapies** (number of therapies)



Source: Citeline, KPMG analysis

RNA therapies have demonstrated both clinical and commercial proof-of-concept

FDA-approved marketed therapies *

N	Product (INN)	Company	Segment	Indication	Approved	Sales 2022, $m	Sales 2021, $m	Trend YoY
1	Amvuttra (vutrisiran)	Alnylam	siRNA	hATTR amyloidosis	2022	94	-	
2	Leqvio (inclisiran)	Alnylam / Novartis	siRNA	Hypercholesterolemia	2021	112	12	833%
3	Amondys 45 (casimersen)	Sarepta	ASO	DMD	2021	215	69	212%
4	Comirnaty (tozinameran)	Pfizer / BioNTech	mRNA	COVID-19	2020	37,806	36,781	3%
5	Spikevax (elasomeran)	Moderna	mRNA	COVID-19	2020	18,400	17,700	4%
6	Oxlumo (lumasiran)	Alnylam	siRNA	Primary hyperoxaluria type 1	2020	70	60	17%
7	Viltepso (viltolarsen)	NS Pharma	ASO	DMD	2020	110	70	57%
8	Vyondys 53 (golodirsen)	Sarepta	ASO	DMD	2019	117	90	30%
9	Givlaari (givosiran)	Alnylam	siRNA	Acute hepatic porphyria	2019	173	128	35%
10	Onpattro (patisiran)	Alnylam	siRNA	hATTR amyloidosis	2018	558	475	17%
11	Tegsedi (inotersen sodium)	Ionis	ASO	hATTR amyloidosis	2018	30 **	56 **	-46%
12	Spinraza (nusinersen)	Ionis / Biogen	ASO	SMA	2016	1,794	1,905	-6%
13	Exondys 51 (eteplirsen)	Sarepta	ASO	DMD	2016	512	454	13%
	Total without vaccines					**3,785**	**3,319**	**14%**
	Total					**59,991**	**57,800**	**4%**

Potentially over $1b products in late-stage pipeline: Evrysdi (Roche) – RNA modulator *, Amvuttara (Alnylam) – siRNA, Zilebesiran (Alnylam) – siRNA

* Small molecule RNA modulators excluded from the analysis

** Tegsedi sales are reported including Waylivra sales. Waylivra has not yet received an FDA approval

Source: "RNA-based therapeutics: an overview and prospectus" 2022 Zhu et al, Company reports, KPMG analysis

Why invest now?

One of the primary drivers of the increasing attention to RNA therapy are the advances in the delivery vehicle technologies that take therapeutic cargo, e.g. siRNA or mRNA, to its destination (also RNA cargo design itself can be helpful in tissue-targeting). Early attempts to use synthetic lipid nanoparticles (LNPs) as carriers of therapeutics posed toxicity problems because of the high doses required. Early vehicles were insufficiently tissue-specific and primarily ended up in the liver, which limited therapeutic application of RNA therapies reliant on such delivery. Discoveries in delivery vehicle design now allow it to be:

- precise, thereby reducing dosage, improving safety profile and reducing cost
- stable, thereby improving manufacturing/supply chain requirements
- tissue-specific, targeting tissues beyond the liver, allowing to address a myriad of diseases

Another groundbreaking development is optimizing the payload itself. mRNA cargo production is typically done through in-vitro transcription, an efficient method used since the 1980s. Such mRNA, however, is unstable, requiring sophisticated LNP carriers, and is immunogenic, as immune cells recognize in vitro transcribed mRNA as foreign. Through the 1990s-2010s, scientists discovered that certain chemical modifications (similar to those happening to in vivo transcribed mRNA) to the bases of the in vitro transcribed mRNA can make them seem "normal" to the immune system, hence triggering almost no inflammatory response and significantly increasing protein production. These discoveries in particular enabled the development of effective mRNA vaccines against COVID-19, for which the Noble Prize in Medicine was awarded in October 2023. In addition to the above, new technologies allow for mRNA payload programming, potentially enabling the control of duration and magnitude of protein expression as well as tissue-specificity.

Additional developments promote further interest towards RNA therapies:

- RNA-based therapies are expanding beyond the rare disease space into the ultra-prevalent diseases, a validation of the technology maturity: Inclisiran, an RNAi treatment, was launched in 2021 for use in adults with primary hypercholesterolaemia (high cholesterol). Another drug in development for a prevalent condition, namely hypertension, is Zilebesiran by Alnylam/Roche, which is currently in clinical Phase 2
- RNA-based therapies for cancer have shown promise in the treatment of cancer, including:
  - mRNA-based cancer immunotherapies (e.g. those developed by Moderna/Merck and BioNTech)
  - RNA interference and ASO therapies (e.g. those developed by Sirnaomics and Ionis/Flamingo Tx)
- New RNA therapy sub-modalities:
  - Self-replicating (e.g. Arcturus Tx, Strand Tx) and Circular RNA (e.g. Orna and Chimerna) to improve mRNA stability
  - RNA editing through technologies such as Adenosine Deaminases Acting on RNA (e.g. Shape Tx and Korro Bio) and RNA protein editors such as PUF and Cas-based systems (e.g. Locana and Carver Bio)

These breakthroughs have paved the way for the development of new RNA-based therapies and have the potential to transform the treatment of many diseases.

Source: nobelprize.org, Company reports, KPMG analysis

Challenges and developments

Current challenges: RNA therapies offer exciting new avenues for the treatment of a wide range of diseases. However, there are several challenges to solve before RNA therapies become mainstream commercial drugs. These challenges span from the development stage all the way to operations and commercial:

Development

- **Delivery:** transporting RNA molecules to target cells and tissues can be difficult, as RNA is prone to degradation by enzymes in the body (RNAses)
- **Off-target effects:** RNA molecules can interact with unintended targets in the body, leading to unwanted side effects
- **Immunogenicity:** RNA molecules can trigger an immune response in the body, which can limit their effectiveness and lead to adverse reactions
- **Stability:** RNA molecules are inherently unstable compared to other biologic molecules such as DNA or proteins. In addition to the implication reflected in the "delivery" point, this limits their shelf life and makes their storage and transportation challenging. Approaches such as self-replicating RNA (e.g. Arcturus Tx, Strand Tx) and circular RNA (e.g. Orna, Orbital Tx) may allow to overcome this challenge
- **Supply chain setup:** "inbound" and "outbound" supply chain challenges may arise as companies prepare for large scale manufacturing (that may even be required for later-stage clinical batches)
  - "Inbound" SC challenges: robust supply of high-quality raw materials may be challenging to secure, as it includes specialty components such as plasmid DNA, enzymes, nucleotides and LNPs. Only a few suppliers with limited volumes might be available, resulting in long wait times, competition for suppliers and high raw material costs
  - "Outbound" SC challenges: depending on the therapeutic indication, such details may not matter, or they could have a significant limitation. Remarkable are the cold chain solutions that Moderna and Pfizer tackled for Covid vaccines in 2020-2021: Moderna's vaccine required long-term storage at -20°C, and Pfizer/BioNTech's vaccine needed a -70°C or lower transportation which presented great challenges at rollout
- **Talent availability:** already facing a talent shortage, the life sciences workforce will face a growing shortage of advanced degrees to fill specialized roles going forward, especially in fast-growing areas such as RNA therapy

Where KPMG can help

Operations: Manufacturing (MSAT) & Supply Chain

- **Manufacturing:** RNA manufacturing as well as vehicle synthesis (e.g. LNP formulation screening and optimization, LNP analysis and characterization, functional verification, scale-up and process optimization) and final assembly and control require new capabilities. Only a few companies can perform this complex process development in-house. MSAT function plays a central role in ensuring that pipeline products are manufactured following a scalable and robust process. Adopting RNA therapies necessitates a capability review of MSAT function and a potential refresh of the operating model to accommodate for these new, complex modalities

Where KPMG can help

Commercial and Corporate strategy

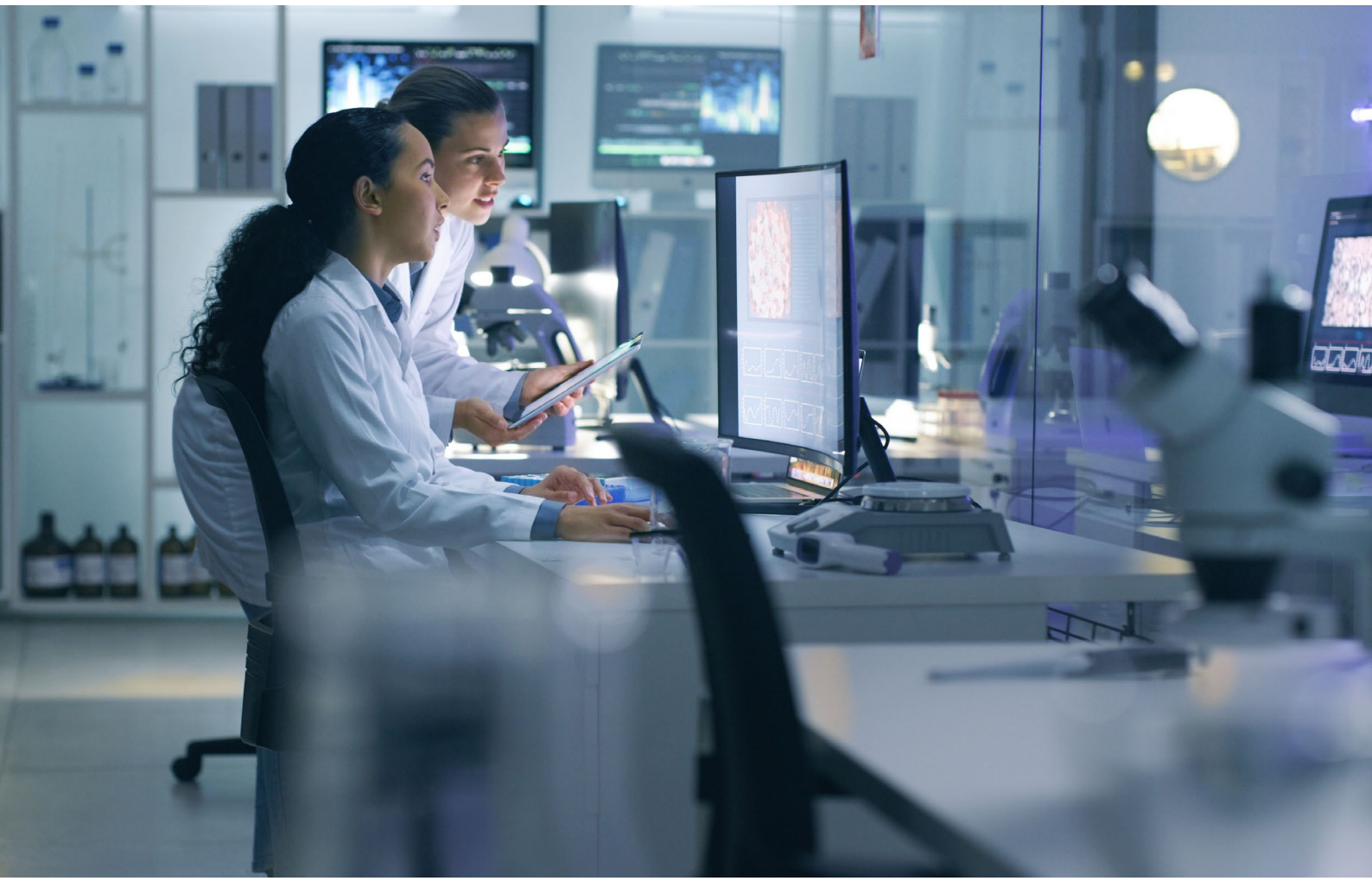
- **Choice of indication:** it's not uncommon for new entrants in the space to select "low hanging fruit", i.e. indications that may be less risky from both a scientific and a clinical perspective. However, this leads to increasing competition in certain indications such as duchenne muscular dystrophy (for ASOs) and influenza vaccines (for mRNA). In-depth therapeutic potential analysis and market assessment early in the development phase may help companies identify indications with the highest unmet need while minimizing clinical and competitive risk

- **Regulatory and market access** ensuring a successful launch: in-depth assessment of regulatory framework as well as market access specifics across key geographies may improve the chances of a successful product launch. Developing doctor and patient acceptance strategies programs may also help succeed with future launches

- **Challenges from other modalities:** new entrants may always challenge the incumbents, regardless of the modality. An example of this: a chain of launches for Spinal Muscular Atrophy, a devastating rare pediatric disorder. Zolgensma's (a gene therapy) launch in 2019 impacted Spinraza (ASO) sales, and the launch of Evrysdi (RNA-targeting small molecule) is expected to affect both. A competitive environment assessment and risk mitigation strategy is needed to fully realize product potential

- **Asset / company due diligence:** in-depth assessment of product potential and company valuation may help reduce the risk of asset mispricing when it comes to in/out-licensing or M&A. This is applicable for both buy- and sell-side

- **Maximizing deal outcomes:** companies preparing for a new financing round, including crossover or an IPO, need to be particularly careful about their valuation as well as the targeted raise size. An environment assessment, investor sentiment analysis and clear company strategy going forward are some of the key prerequisites of success



Big Pharma collaborations

Big Pharma realizes the importance of key value drivers (and bottlenecks) in RNA therapies and invests accordingly: large indications, advanced payload delivery and new technologies

Selected RNA therapeutics collaborations in 2022 -2023 (not exhaustive)

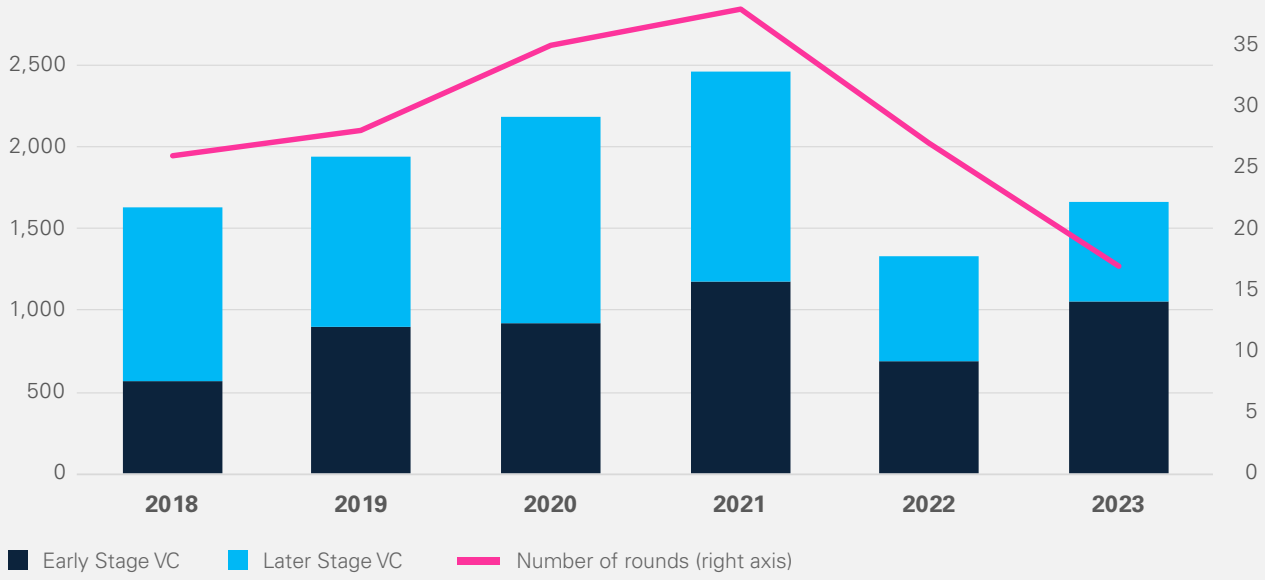
Companies	Description	Deal terms
Roche and Alnylam, Jul 2023	Alnylam announces partnership with Roche to co-develop and co-commercialize Zilebesiran, an investigational RNAi therapeutic for the treatment of hypertension in patients with high cardiovascular risk	$310m upfront, total potential deal value of up to $2.8b
Novo Nordisk and Eleven Therapeutics, Jul 2023	Eleven Therapeutics announces research collaboration with Novo Nordisk to discover cell-specific carriers of nucleic acid therapeutics	No data
Bayer and Acuitas Therapeutics, June 2023	Acuitas' LNP technology will support Bayer's in vivo gene editing and protein replacement programs by specifically delivering RNA payloads to the desired target organ, the liver	No data
Eli Lilly and ProQR, Dec 2022	Lilly and ProQR to expand RNA editing collaboration originally announced in Sep 2021, that applied ProQR's RNA editing platform to target disorders of the liver and nervous system	$75m upfront and equity, total potential deal value of ~ $3.75b
CSL Seqirus and Arcturus Tx, Nov 2022	Arcturus announces collaboration with CSL to develop and commercialize self-amplifying mRNA vaccines	$200m upfront, total potential deal value of over $4.0b

Source: Company press releases, KPMG analysis

Transactions and investments

VC financing: despite challenging market environment, private RNA therapy-focused companies still attract over $1b per year in VC investments

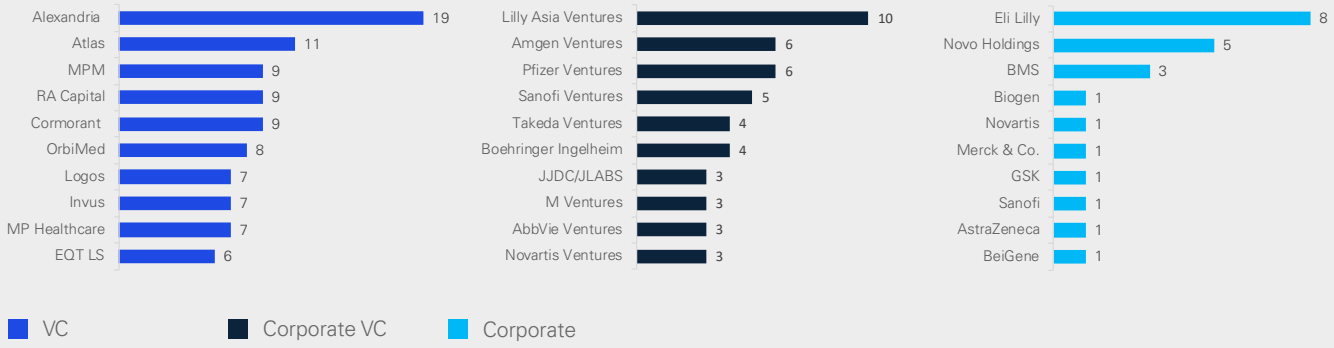
Figure 3: **VC investments in RNA Therapeutics ($m)**



Source: PitchBook, KPMG analysis

Biotech-focused venture funds are the most active investors, corporate venture funds are #2:

Figure 4: **Most active investors in VC rounds of RNA therapy companies (number of investments 2018-2023 YTD)**



Source: PitchBook, KPMG analysis

Recent VC deals

4 of the top 10 venture rounds for US companies in 2023 were RNA-focused players:

- $300m Series A by ReNAgade (RNA editing, led by MPM Capital)
- $270m Series A by Orbital (RNA delivery, led by ARCH)
- $260m Series B by ReCode (RNA tx and delivery, led by Pfizer Ventures)
- $200m Series C by ADARx (RNA editing, led by Bain Capital Life Sciences)

Despite lower number of deals in 2023, an average investment exceeded $100m, a record high for RNA therapy companies and 2.4x larger than in 2022

Average crossover to IPO valuation step-up for RNA therapy companies starting from 2021: 1.26x

Top 15 IPOs: mixed IPO performance with vaccine leaders at the top of the list

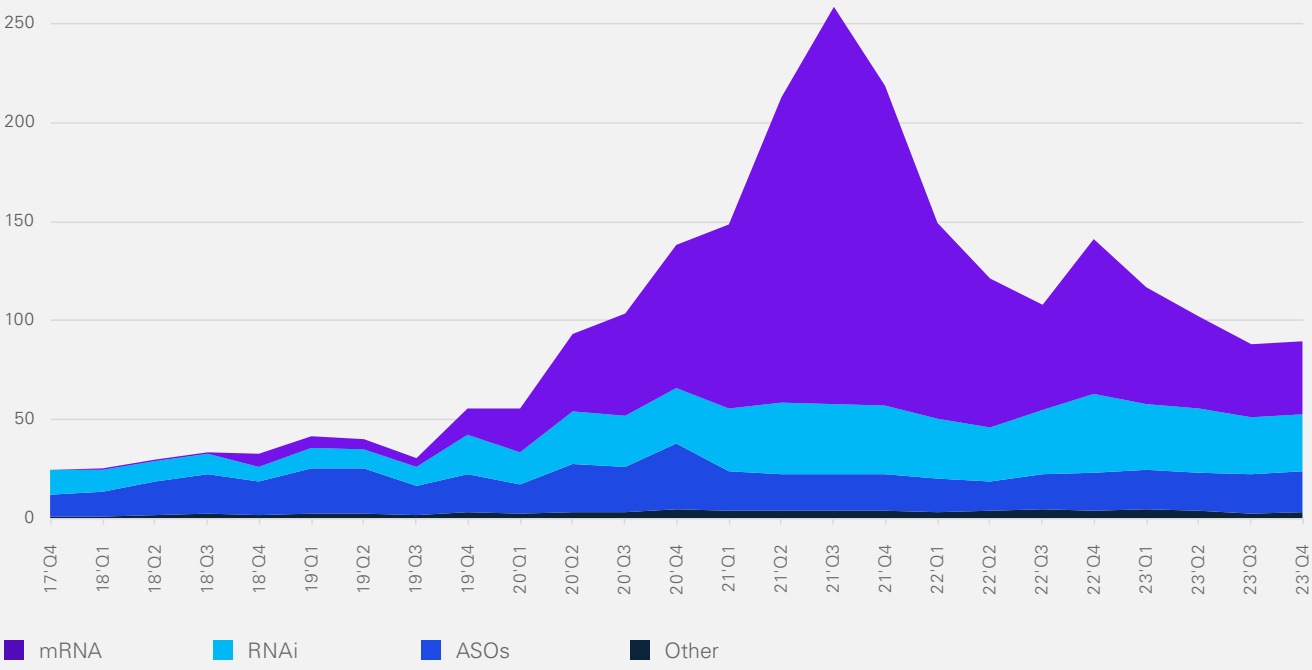
RNA therapy company IPOs since 2018, current valuation as of 29.12.2023 or acquisition value

Company	Ticker	Country	Founded	IPO Year	IPO size, $m	IPO post-valuation, $m	Current valuation, $m
Moderna Tx	MRNA	US	2010	2018	604	7,570	37,979
BioNTech	BNTX	Germany	2008	2019	150	3,390	25,129
Translate Bio	ex-TBIO	US	2010	2018	107	452	3,200
Vir	VIR	US	2016	2019	143	2,190	1,355
CureVac	CVAC	Germany	2000	2020	213	2,820	944
Dyne Tx	DYN	US	2017	2020	233	828	818
Avidity Bio	RNA	US	2013	2020	259	636	672
Entrada Tx	TRDA	US	2016	2021	182	598	504
Sirnaomics	2257	US	2007	2021	70	820	402
Stoke Tx	STOK	US	2014	2019	142	566	235
Gritstone Bio	GRTS	US	2015	2018	100	432	195
Praxis	PRAX	US	2015	2020	190	698	191
Omega Tx	OMGA	US	2017	2021	126	794	166
PepGen	PEPG	US	1995	2022	108	269	162
Aligos Tx	ALGS	US	2018	2020	150	553	50

Source: PitchBook, CapitalIQ, KPMG analysis

Enterprise value of publicly traded RNA companies was driven by mRNA vaccine focused companies, namely Moderna and BioNTech

Figure 5: **Enterprise value of publicly traded RNA companies by segment ($b)**



Source: CapitalIQ, KPMG analysis

M&A: Big Pharma acquires 1-2 RNA therapy companies per year

Strategies vary from establishing a footprint in a new modality to acquiring a unique capability

M&A *

Companies	Country	Acquirer	Founded	Deal year	Deal size, $m
The Medicines Company	US	Novartis	1996	2020	9,700
IVERIC bio	US	Astellas	2007	2023	5,900
Dicerna	US	Novo Nordisk	2006	2021	3,300
Translate Bio	US	Sanofi	2010	2021	3,200
DTx Pharma	US	Novartis	2017	2023	1000
GeneTx	US	Ultragenyx	2017	2022	75
Trasir Tx	US	Auris	2014	2021	3.5

Source: Reuters, Company press releases, KPMG analysis
* Full acquisitions only, excludes partial stock acquisition

CDMOs

CDMO (Contract Development and Manufacturing Organizations) and raw material suppliers play a crucial role in the RNA therapy industry, that will be further increasing as the number of commercialized products grows. Most emerging biotech startups either do not have sufficient resources and expertise to build GMP-grade manufacturing capabilities or proprietary vehicles (even basic LNPs) and rely on a limited number of providers. Partnerships between biotech companies and CDMOs are generally sticky due to limited expertise, capacity, stringent regulatory requirements and terms of such agreements. With the recent 2020-2023 mRNA boom some biotech companies experienced delays in product shipments that led to delays in clinical trials and regulatory processes. In the current biotech funding environment, such delays could impact the very existence of biotech companies themselves as their cash runways are tight.

Big pharma and PE players recognize the bottlenecks and invest accordingly. For example, Astorg, a European PE, has locked up a deal with ICIG to take over CordenPharma. The company serves more than 250 blue-chip pharma and biotech customers across several technology platforms. Another recent transaction – the acquisition of Exelead by MilliporeSigma (the US and Canada Life Science business sector of Merck KGaA) to expand its capabilities in commercial manufacturing of LNP formulations including fill and finish. The business combination is expected to provide end-to-end CDMO services across the mRNA value chain.

However, despite the deals, the RNA therapy supply chain is still fragmented, and the field seems to be lacking a clear and unified solution or best-practice across each step in the value chain (sequence design, mRNA synthesis, purification, LNP design/assembly, etc). It is important for CDMOs to harness new developments in the RNA therapy field and recognize its bottlenecks. The further integration of drug development capabilities (such as RNA payload optimization) and LNP platforms allows for tissue-specificity and greater stability, playing an important role in the field going forward.

Source: Company press releases, KPMG analysis

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