FROM THE ANALYST'S COUCH

Evolution of the market for mRNA technology

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2020 was a breakout year for mRNA technology platforms with the launch and widespread use of mRNA vaccines for COVID-19. At the end of 2019, the combined market capitalization of the five publicly listed companies focusing on mRNA platforms was ~US$15 billion. As of August 2021, that capitalization was more than $300 billion. This boost in valuation reflects optimism that mRNA technology can deliver much more than the current prophylactic COVID-19 vaccines, and perhaps also expectation that COVID-19 is here to stay.

Current mRNA-based agents in development can be classified into three major applications based on their underlying mechanisms of action: prophylactic vaccines, therapeutic vaccines and therapeutic drugs. Here, we present highlights of a holistic review we conducted of global mRNA R&D activities, including amount and stage of company pipelines, disease focus, clinical strategy and preliminary published data in comparison to other modalities. We analysed 180 pipeline assets from 31 mRNA companies as of July 2021 (FIG. 1), which represents all publicly available pipelines and products that we could source. We estimate the overall market size by a combination of top-down and bottom-up approaches for the three major applications of mRNA. Our focus was on the emerging applications beyond COVID-19, but we did include estimates for COVID-19 vaccines. The top-down approach looked at the total size of the market for a certain disease and mRNA product share against competing modalities. The bottom-up approach looked at all 180 pipeline assets/marketed product sales based on representative pipelines, adjusted for probability of success, likely launch timeline, and potential demand and uptake (see Supplementary information for details).

Trends in the mRNA product market

Prophylactic vaccines. We expect prophylactic vaccines to dominate the mRNA field in the next 15 years because of the large number of pipeline assets, higher probability of success (POS) and mRNA's advantages over other vaccine modalities.

Current R&D activities are concentrated in prophylactic vaccines (FIG. 1), with 77% of mRNA companies having at least one prophylactic vaccine in their pipeline. We expect that, in the near term, the majority of prophylactic vaccine revenues will still come from COVID-19 products, while in the mid-to-long term, other vaccines for diseases such as respiratory syncytial virus and influenza will probably reach a wider population overall, but with limited pricing upside. Despite many indications having established products, and competition likely to be fierce across vaccine modalities, mRNA appears to have clear advantages of speed of R&D over other modalities and in protection rates for COVID-19 at least. We therefore projected that prophylactic mRNA vaccines would win a good share against other vaccine modalities. We assumed an average POS for prophylactic mRNA vaccines given the proof of the technology by COVID-19 vaccines. Accounting for target population penetration, pricing and competition within major indications, we estimate the average peak sales per pipeline asset for prophylactic mRNA vaccines to be ~$800 million globally (for products other than COVID-19 vaccines), with a total risk-adjusted market size in 2035 of $7–10 billion (not including COVID-19 vaccines) and $12–15 billion (including COVID-19 vaccines) (FIG. 2).

Therapeutic vaccines. Therapeutic vaccines are likely to be a niche space for mRNA products, but with significant commercial potential owing to the size of the patient

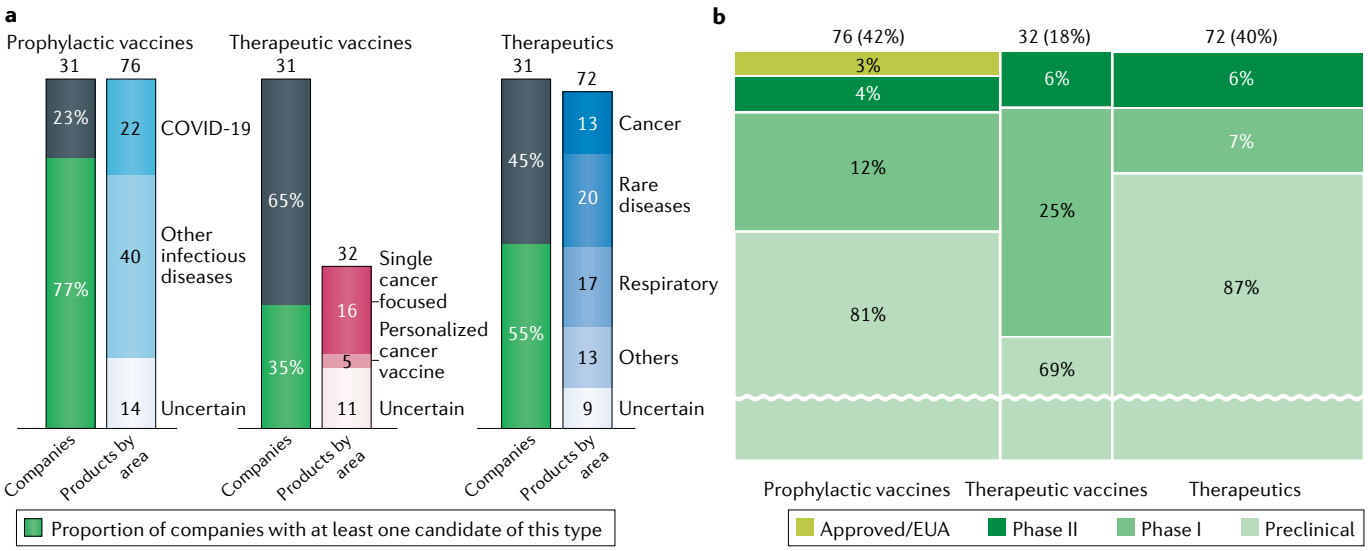

Fig. 1 | **Current profile of the mRNA technology pipeline. a** | Proportion of companies among the 31 mRNA companies analysed that have at least one candidate in the three main application areas, with the distribution of the 180 pipeline agents based on the therapeutic area shown to the right. **b** | Pipeline segmented based on application area and the phase of development. EUA, emergency use authorization. All pipeline information up to July 2021. See Supplementary information for details.

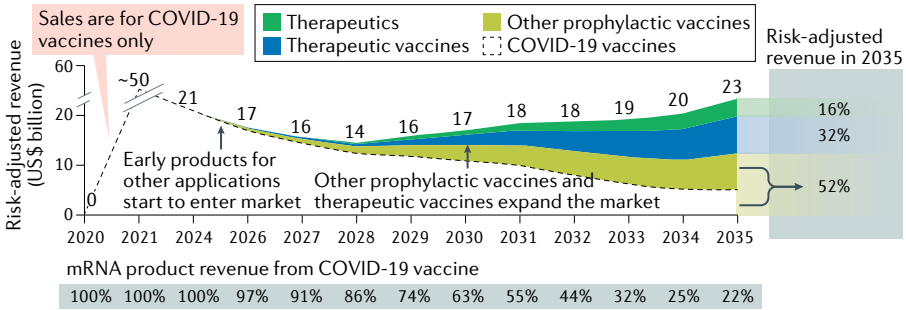

Fig. 2 | **A forecast for the evolution of the market for mRNA technology.** Until 2025, the forecast is based only on mRNA vaccines for COVID-19. Prophylactic vaccines in general are expected to remain the cornerstone of the market up to 2035, with therapeutic vaccines for cancer and mRNA therapeutics making increasing contributions towards the end of the forecast period. See Supplementary information for details.

populations and likely dominant share among other modalities targeting multiple tumour-associated antigens. However, clinical, regulatory and manufacturing risks remain high.

Therapeutic vaccine mRNA R&D is currently focused on immuno-oncology (IO), and candidates can be categorized based on whether they target single or multiple antigens. Single-antigen vaccines provide a path for targeting difficult-to-drug targets, which, if they succeed, could potentially justify high price premiums in relatively small populations of patients. Two examples of this kind of development are mRNA-5671 developed by Moderna/Merck & Co. for KRAS-mutated cancers and BNT113 developed by BioNTech for HPV-16^{+} cancers, both of which are in phase I. However, peptide-based vaccines could put competitive pressure on mRNA vaccines despite being at an earlier stage of development.

Currently, most therapeutic mRNA vaccines (19 out of 26 known targets) are multi-antigen vaccines such as personalized cancer vaccines (PCVs), where mRNA has advantages over peptide-based vaccines. PCVs have provided initial positive safety and efficacy data, such as Moderna's mRNA-4157 as a monotherapy and in combination with pembrolizumab.

Companies are increasingly focused on combination strategies with IO agents such as PD1/PDL1 blockers in earlier-line treatments for patients with a lower disease burden and immune systems that are still competent. So, we believe that the market size for a single PCV can be substantial. We also anticipate an explosion of mRNA PCV pipelines for a wide range of cancer types after proof-of-concept data from field leaders. Part of the growth in activities is also driven by China as a rising hub of IO R&D, with multiple companies focusing on mRNA founded in the past 5 years, including Abogen, Stemirna and RNACure.

However, mRNA therapeutic vaccines face several challenges. First, targeting an earlier line of treatment for patients in combination with another IO agent will probably require a long follow-up time and a pivotal trial involving direct comparison with an IO monotherapy arm; both requirements represent high clinical and regulatory risks. We therefore used an average POS that is lower than the average for oncology (Supplementary information). Second, to unlock the PCV market potential, challenges in achieving an optimized manufacturing and commercial pathway need to be addressed. PCVs need long manufacturing lead times (usually 4 weeks to 3 months), which would be longer than CAR-T cell therapies (typically 2 weeks). One solution is to identify patient subgroups that share similar tumour-associated antigens to enable scale of production. We see mRNA companies partnering with genomics companies to develop companion diagnostics, which should help to address issues in identifying and segmenting potential patients.

Taking into account the above factors, as well as target population sizes, competition across and within modalities, pricing, market penetration and higher risk, we estimate the average PCV product's peak sales to be ~$5 billion, and single disease-focused products to be ~$1.3 billion. The total market (risk-adjusted) is estimated to be $7–10 billion in 2035 (FIG. 2).

Therapeutics. Therapeutics will be an opportunistic area for mRNA products, involving many indications, but whether they will have clinical advantages over other modalities is unclear and there are also high clinical risks. Long-term opportunities will depend on technological advances in areas such as delivery systems and gene editing.

For protein replacement therapy, in some cases mRNA platforms could have delivery advantages compared with standard recombinant protein strategies, but face technical challenges that do not yet have clear near-term solutions, including lack of organ selectivity, a potential need for frequent delivery and high immunogenicity. Initially, this might limit mRNA therapeutics to addressing a subset of oncology indications where treatment agents harness the immune system; for example, an mRNA encoding a bispecific antibody that binds to CD3 on T cells and a target antigen on tumour cells. For genetic disorders and rare diseases, mRNA therapeutics will probably need to compete with gene therapies. These are at a more advanced clinical stage in genetic disorders and could provide patients with a more sustained supply of therapeutic proteins.

Given the above, we applied a 10–30% share of mRNA among modalities for therapeutics and we lowered the mRNA therapeutic POS to below average in each therapeutic area. Based on this, we projected average global pipeline asset peak sales in oncology, respiratory diseases (primarily cystic fibrosis) and rare diseases to be around $1.1 billion, $1.8 billion and $500 million, respectively. We estimate the overall risk-adjusted 2035 market size to be $4–5 billion (FIG. 2).

Outlook

In the short term, the mRNA product market is based only on COVID-19 vaccine sales, and we estimate it will be worth more than $50 billion in 2021 (FIG. 2). Between 2023 and 2025, we anticipate a decline due to decreased need for COVID-19 vaccines in major markets and a lack of new product launches, while booster shots and wider global use may support sales of ~$20 billion. The market is then anticipated to grow from 2028 as other prophylactic vaccines and therapeutic vaccines enter, reaching $23 billion in 2035. Prophylactic vaccines are still expected to be the cornerstone, with more than 50% revenue up to 2035. Therapeutic vaccines for cancer are estimated to contribute ~30% of mRNA product sales, with therapeutics contributing less than 20%. Overall, we believe mRNA has the potential to become a competitive modality across broad applications, especially as further advances in improving delivery and stability are made.

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