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From the Analyst's Couch

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The landscape for lipid-nanoparticle-based genomic medicines

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Lipid nanoparticles (LNPs) have recently risen to prominence as the technology platform that enables the delivery of mRNA, the key component of the Moderna and BioNTech/Pfizer COVID-19 vaccines. We estimate that by the end of 2021, more than two billion people had received a COVID-19 mRNA vaccine or booster that was facilitated by an LNP delivery system, with total sales worth more than US$50 billion. Although this is by far the most widespread application of LNP technology by the biopharmaceutical industry to date, LNPs have been investigated for decades as delivery vehicles. The first FDA approval for an LNP-based genomic medicine — the siRNA patisiran (Onpattro; Alnylam) to treat polyneuropathy caused by hereditary transthyretin-mediated amyloidosis — came in 2018.

LNPs typically have four components: a cationic or ionizable lipid, cholesterol, a helper lipid and a PEGylated lipid (*Nat. Rev. Drug Discov.* **20**, 817–838; 2021). They can encapsulate a wide range of pharmaceutical cargoes — including small molecules, peptides and nucleic acids — shielding the cargo from destructive enzymes, as well as enabling transport across cellular membranes. LNPs also support redosing and transient dosing, and their safety has been verified by the widespread use of the COVID-19 vaccines. Furthermore, the LNP manufacturing capacity built by contract development and manufacturing organizations and pharmaceutical companies during the pandemic means that scaling up production of an LNP-based medicine is now much less of a concern than a few years ago.

As a result, LNPs are well-positioned to play a key role in the progress of the emerging field of genomic medicines, for which safety and efficient in vivo delivery has been a key challenge. Furthermore, in some cases, LNPs may address limitations of other delivery approaches. For example, viral vectors are typically highly efficient for delivery of genes to the nucleus, but they have payload size constraints and a limited potential for redosing.

In vivo genomic medicines can be classified into four major segments based on the underlying mechanisms of action:

- Gene addition or replacement; for example, a viral vector incorporating the gene, or an mRNA encoding the gene encapsulated in an LNP.
- Gene expression control; for example, an siRNA encapsulated in an LNP, or an siRNA conjugated to the hepatocyte-targeted ligand GalNac (*N*-acetylgalactosamine).
- Gene editing; for example, viral vectors or LNPs to deliver components of CRISPR–Cas9 gene editing systems.
- DNA or RNA vaccines; for example, an mRNA vaccine encapsulated in an LNP or a polymeric nanoparticle.

With the aim of understanding the current and future importance of LNPs to the development of in vivo genomic medicines, we analysed all publicly available information on global clinical and approved pipelines for in vivo genomic medicines. This analysis identified 538 assets from 273 companies as of December 2021, which we segmented into the four mechanistic categories (Fig. 1a). We then assessed the extent of LNP penetration for each segment across the development pipeline to understand the application of this delivery technology so far. Based on these findings and

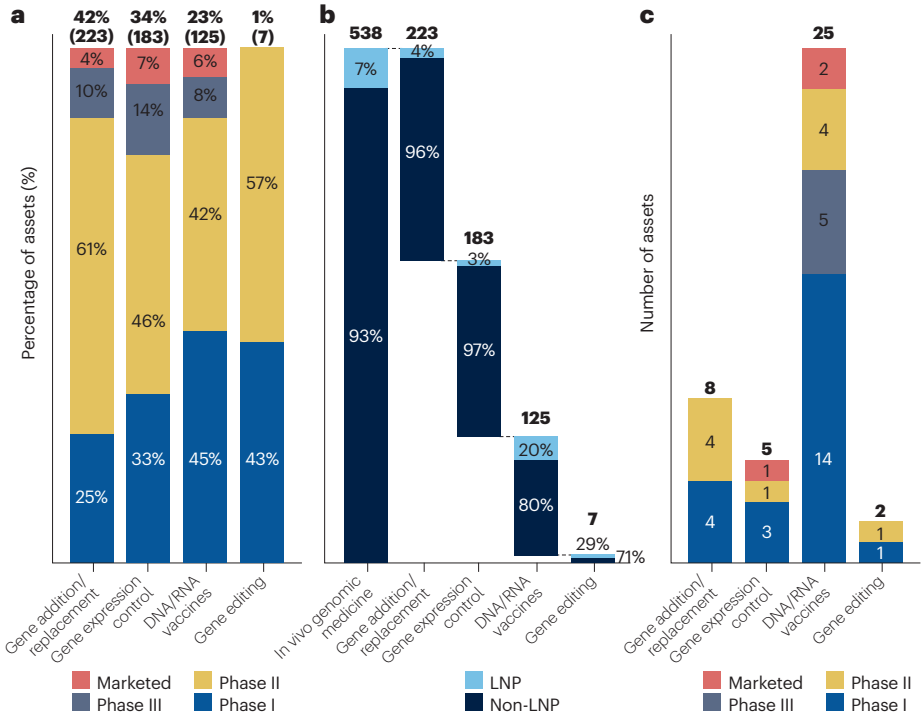

Fig. 1 | Landscape for lipid-nanoparticle-enabled in vivo genomic medicines. a, Percentages of in vivo genomic medicines overall at each stage in the clinical pipeline, segmented into four categories based on the underlying mechanism, with the total number of assets shown at the top of each bar. **b**, Level of penetration of lipid nanoparticle (LNP)-enabled medicines in the group of in vivo genomic medicines overall, and in each category. **c**, Number of LNP-enabled assets in each category by development stage. Information is as of December 2021. See Supplementary information for details.

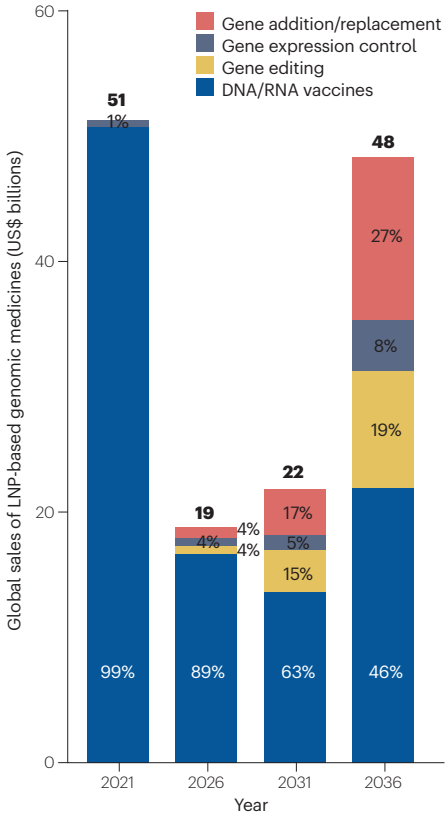

Fig. 2 | Market forecast for lipid-nanoparticle-enabled in vivo genomic medicines. In 2021, three assets based on lipid nanoparticles (LNPs) were on the market: the COVID-19 vaccines Comirnaty and Spikevax, and the siRNA therapy Onpattro. For pipeline assets in each of the four mechanistic categories shown, we applied a growth rate based on expected changes in addressable populations and insights into market dynamics and LNP penetration over time to forecast the development of the market. See Supplementary information for details.

trends within each segment, we estimate the worldwide market attributable to LNP-enabled in vivo genomic medicines from 2021 to 2036.

Landscape for LNP-enabled medicines

Across the four mechanistic segments, the average LNP penetration rate (the percentage of assets that use this modality) is 7% (Fig. 1b). It is highest for nucleic-acid-based vaccines and gene editing, which reflects that the nucleic acids to be delivered in these segments are generally too large to be suitable for GalNAc conjugation. LNP penetration for gene addition or replacement is lower because adeno-associated virus (AAV)-based delivery offers greater utility. Penetration is the lowest for gene expression control because of competition from GalNAc conjugation. Overall, the LNP-enabled genomic medicine pipeline is largely concentrated in the DNA and RNA vaccine segment, mostly in phase I trials (Fig. 1c).

By our estimate, the current market size for LNP-enabled in vivo genomic medicines is approximately $51 billion, dominated by the two COVID-19 mRNA vaccines, as there is only one other marketed product, Onpattro (Fig. 2). In the short term, the size of the market will probably shrink as COVID-19 mRNA vaccine revenues decline. We project that the market will then start growing again as the genomic medicine pipeline starts to mature and companies invest further in LNP innovations. By 2036, the LNP-enabled genetic medicine market is estimated to rebound to $48 billion.

COVID-19 mRNA vaccines and booster sales are expected to make up the majority of the LNP market for the next ten years. In vivo genome editing applications, some of which also involve LNP delivery, are then anticipated to gain market share as products from companies such as Intellia Therapeutics and Beam Therapeutics progress to approval.

Outlook

We believe LNPs will remain a core tool in the delivery of in vivo genomic medicines, especially for mRNA vaccines. Increased application of LNPs beyond vaccines will depend on companies' ability to tune lipids to reach specific organs beyond the liver. Other factors that could fuel wider application of LNPs in the development of in vivo genomic medicines include the ability to encapsulate larger genetic cargo, especially cargo greater than 5 kB long, the packaging limit of many AAV vectors.

Although current-generation LNPs are now clinically validated and broadly used with the mRNA vaccines, they are limited in their delivery efficiency, immunogenicity, shelf-life and cost for other applications. Next-generation LNPs leverage novel, non-lipid components (for example, fusogenic proteins and polymers) to address these limitations. Although next-generation LNPs are not yet clinically proven, they have the potential to increase delivery efficiency, thus enabling lower doses and decreasing immunogenicity. These innovations can be applied across all genomic medicine segments, especially in gene addition/replacement applications.

Some companies and academic research institutions are focused on leveraging LNPs for a variety of therapeutic indications. However, the barriers to entry for LNP development and manufacturing are high: discovering new ionizable lipids and producing them at scale is a very expensive, time-consuming proposition, engulfed in a murky intellectual property landscape.

Given the high barriers, genomic medicine companies may ask whether it makes sense to develop and manufacture LNPs in-house. If the goal is simply de-risking a new modality, a company can acquire LNP capability through licensing or partnering with leading LNP providers such as Acuitas. If, however, a company is building a platform therapeutic modality across different indications and needs the flexibility to make changes, the ability to tune LNPs in-house is critical for speedy drug development. For example, Beam Therapeutics acquired Guide Therapeutics to further expand the reach of their genomic medicines to new target tissues and diseases. We expect to see more genomic medicine companies build LNP capabilities internally as there are many opportunities to improve upon the LNPs used in previously approved products. Specifically, delivery efficiency, immunogenicity, storage and shelf-life conditions, and cost-effectiveness can all be improved.

To successfully build an LNP platform, genetic medicine companies will need automated processes and sufficient expertise to do high-throughput screening and testing, ideally in vivo. They will also need robust analytical methods to characterize what a good LNP is. Lastly, they will need to acquire the 'know-how' and trade secrets upon which a lot of LNP manufacturing is based.

Overall, we believe that LNPs have the potential to become an essential drug delivery system in the long term, fuelled by their widespread adoption of the COVID-19 mRNA vaccines and increased investment in improving their applicability across other genomic medicine segments.

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Competing interests

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Additional information

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