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The untapped potential of mRNA–lipid nanoparticles

mRNA–lipid nanoparticles have transformed vaccines and are beginning to have an effect in cancer therapy, yet remain absent in therapies for acute critical illnesses, such as stroke, infarction or other traumatic injuries. Economic disincentives and historical reputation might be behind this gap.

In less than a decade, lipid nanoparticle (LNP) technology for RNA delivery has progressed from proof-of-concept to global-scale deployment. The approval of Onpattro in 2018 demonstrated that LNPs could safely and effectively deliver nucleic acids to specific tissues. The rapid development and mass administration of mRNA–LNP vaccines during the COVID-19 pandemic established their scalability, adaptability and transformative potential. Today, more than 150 RNA–LNP formulations are in clinical trials.

Yet, the vast majority (over 80%) target cancer and infectious diseases. Applications in acute critical illnesses (ACIs), such as myocardial infarction, stroke, acute respiratory diseases and other traumatic injuries — conditions that rank among the top global causes of death — are rare. This gap is surprising given that many ACIs present features that could make them particularly amenable to mRNA–LNP interventions. ACIs often occur in hospital settings where intravenous administration is straightforward. Moreover, their time course of hours to days aligns with the transient protein expression kinetics of mRNA therapeutics, as outlined in a Review by Jacob Brenner and colleagues in this issue.

mRNA–LNPs are particularly suitable for these settings; they can be engineered to deliver multiple RNA cargos, enabling simultaneous modulation of several disease pathways. They can produce intracellular proteins (or peptides), including those that are otherwise inaccessible to traditional biologics or small molecules. Organ-specific targeting strategies may reduce systemic exposure and toxicity in patients experiencing multi-system organ dysfunction. Moreover, there is minimal competition among platform technologies for ACIs, as most drug innovations are recombinant proteins that are over 20 years old, such as tissue plasminogen activator. The closest approved competitors are peptides[1], which offer simplicity but face limitations in pharmacokinetics and intracellular delivery.

Despite these advantages, development activity in ACIs is minimal compared with oncology or infectious diseases, for reasons that are largely structural rather than scientific. From a biopharma perspective, chronic diseases are more commercially attractive; each patient represents a long-term revenue stream, spreading costs over years of treatment. By contrast, ACIs are typically one-time events, limiting per-patient revenue potential. Moreover, in hospital-based care systems, some reimbursement models may further dampen incentives. In many countries, hospitals receive a fixed payment per diagnosis (for example, through diagnosis-related groups[2]). This sets a limit on how much they can spend on drugs for hospital treatments, because the payment must also cover other costs. If a drug is too expensive, hospitals may either avoid using it or reduce the number of accepted patients for that particular disease. By contrast, drugs for outpatient conditions (such as diabetes or hypertension) are not bound by this system, so their prices can be as high as the market can bear.

Last but not least, the historical reputation of ACIs as 'therapeutic graveyards' owing to historical failures in sepsis and stroke trials[3] — driven by incomplete understanding of disease biology, inadequate delivery systems and poorly timed interventions — might have further discouraged investment. Although modern platforms, such as mRNA–LNPs, overcome many of these historical limitations, the perception of high risk and low return remains a substantial barrier.

The first generation of mRNA–LNP therapeutics proved the platform's scalability and clinical impact in areas aligned with current market incentives. The next challenge is to extend those advances into other areas with unmet clinical needs, where the science is promising but the economic model has yet to catch up. For example, regulatory incentives, similar to those used for orphan diseases, could further de-risk investment in this space. A similar mindset may be needed in other areas (such as antibiotic discovery), in which economic disincentives have long stalled innovation.

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