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COMMENTARY

From serendipity to rational design: Accelerating ionizable lipid discovery with LipidAI

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The rapid clinical success of messenger RNA (mRNA) therapeutics has established lipid nanoparticles (LNPs) as a cornerstone of nucleic acid delivery. At the heart of every LNP lies the ionizable lipid, which largely determines delivery efficiency and safety[1]. Yet discovering high-performing ionizable lipids remains a formidable challenge. Researchers can readily synthesize numerous chemically plausible candidates, but only a few demonstrate robust *in vivo* performance[2]. As chemical diversity continues to expand, the major bottleneck is no longer molecular synthesis but understanding the complex relationship between lipid structure and biological function. In this issue of Acta Pharmaceutica Sinica B, Song's group[3] present LipidAI, an interpretable machine-learning framework that represents a step toward data-driven ionizable lipid discovery.

A major obstacle to applying artificial intelligence in this field is the limited availability of high-quality *in vivo* datasets. To address this challenge, the authors established a curated lipid database and introduced a chemically informed Methyl Tail Augmentation (MTA) strategy that expands the training space while preserving structural plausibility. Rather than relying solely on computational techniques, this approach integrates chemical knowledge into data augmentation, illustrating how domain expertise can strengthen machine-learning performance[2,4]. Combined with Ensemble Stacking Learning (ESL), LipidAI achieves robust prediction of *in vivo* mRNA expression, an endpoint that remains difficult to infer from conventional *in vitro* assays. In our recent studies, we have demonstrated how artificial intelligence can transform ionizable lipid discovery from empirical screening toward rational and autonomous design. By integrating foundation models with active learning and automated experimentation, we established LUMI-lab, a closed-loop platform capable of efficiently navigating the vast chemical space of ionizable lipids[5].

Perhaps the most compelling aspect of this study is the story behind its development. LipidAI emerged not from advances in artificial intelligence alone, but from a practical challenge encountered during experimental research. After synthesizing and evaluating numerous ionizable lipids, the investigators found that only a small fraction achieved efficient *in vivo* delivery, while the underlying structure−activity relationships remained elusive. This prompted an interdisciplinary collaboration between pharmaceutical scientists and computer scientists, demonstrating how experimental questions can drive computational innovation. Importantly, the incorporation of SHAP analysis allows the model not only to predict promising candidates but also to identify molecular descriptors associated with delivery efficiency, providing mechanistic clues for future lipid design[6].

Beyond a single predictive model, LipidAI reflects a broader transition in biomaterial discovery—from empirical screening toward rational, data-driven design. Artificial intelligence is unlikely to replace experimental science, but it can become a powerful partner in navigating the enormous chemical space of ionizable lipids. As larger datasets and more sophisticated algorithms emerge, integrating AI with molecular design, automated experimentation, and biological validation may fundamentally reshape how RNA delivery materials are discovered[7,8]. Beyond

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improving predictive accuracy, AI-driven lipid engineering is increasingly moving toward the simultaneous optimization of multiple biological objectives. In our recent study, we developed MOLEA, a multiobjective AI framework that integrates lipid structural representations with context-specific delivery data to design LNPs with enhanced potency and tissue selectivity[9]. The work by Song's group therefore represents not only an advance in machine learning, but also an early example of how interdisciplinary collaboration is redefining the future of nanomedicine.

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