Drug delivery

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Designer lipids for delivering mRNA to the brain

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Lipid nanoparticles formulated with ionizable lipids inspired by brain-targeting small molecules facilitate the delivery of mRNA past the blood–brain barrier and into the brain.

Neurological disorders, such as Alzheimer's disease, Parkinson's disease, brain cancer, stroke and traumatic brain injury, are a leading cause of death worldwide[1]. Recently, nucleic acids have emerged as a highly promising class of therapeutics to treat neurological disorders, including messenger RNA (mRNA), which can be used for protein replacement or gene editing therapies[2]. However, systemic delivery of mRNA to the brain remains a great challenge, in part due to its susceptibility to enzymatic degradation in circulation, as well as the blood–brain barrier (BBB), a highly selective cellular barrier composed of endothelial cells, basement membrane, astrocytes and pericytes, which prevents almost all large molecule drugs in circulation from entering the brain[3].

One strategy to facilitate the systemic delivery of mRNA past the BBB and into brain tissue is by loading mRNA into ionizable lipid nanoparticles (LNPs)[4]. LNPs are the most clinically advanced non-viral delivery vehicle for nucleic acids, as demonstrated by their recent US Food and Drug Administration (FDA) approval as mRNA LNP COVID-19 vaccines[5]. LNPs can protect mRNA cargo from nucleases and their individual lipid components, especially the ionizable lipid, can be designed to enable delivery to specific tissues and cell types[6,7]. Now, writing in *Nature Materials*, Wang et al.[8] report the design of a large library of ionizable lipids inspired by BBB-targeting small molecules that are used to formulate mRNA LNPs capable of crossing the BBB (Fig. 1). Following in vitro and in vivo screening-based optimizations, the authors identify a BBB-crossing LNP (BLNP) formulation that transfects neurons and astrocytes after systemic administration (Fig. 1), which they evaluate in a cocaine addiction mouse model and a glioblastoma mouse model.

Several classes of small molecules have been shown to cross the BBB through different pathways. Wang et al. began by selecting six of these small molecules, namely levodopa (L-DOPA), D-serine, temozolomide, tryptamine, cinnamic acid and the γ-secretase inhibitor MK-0752, and conjugated them to various lipid tails to generate a library of 72 unique ionizable lipids. For preliminary screening, each lipid was formulated into a BLNP encapsulating reporter luciferase mRNA cargo to quantify mRNA transfection using a bioluminescent readout. After testing each BLNP in vitro in neuroblastoma and brain endothelial cell lines, and subsequent in vivo screening after systemic BLNP injection, a lead candidate for brain mRNA delivery, the MK6 BLNP formulation was selected given that it outperforms the FDA-approved formulation containing the ionizable cationic lipid DLin-MC3-DMA (MC3).

Wang et al. further optimized the MK6 BLNP formulation by increasing the molar ratios of the ionizable lipid, tuning the weight ratio of mRNA to ionizable lipid and chemically modifying the MK6 lipid tail. From these optimized BLNP formulations, MK16 BLNP encapsulating luciferase mRNA exhibited the highest brain luminescence following

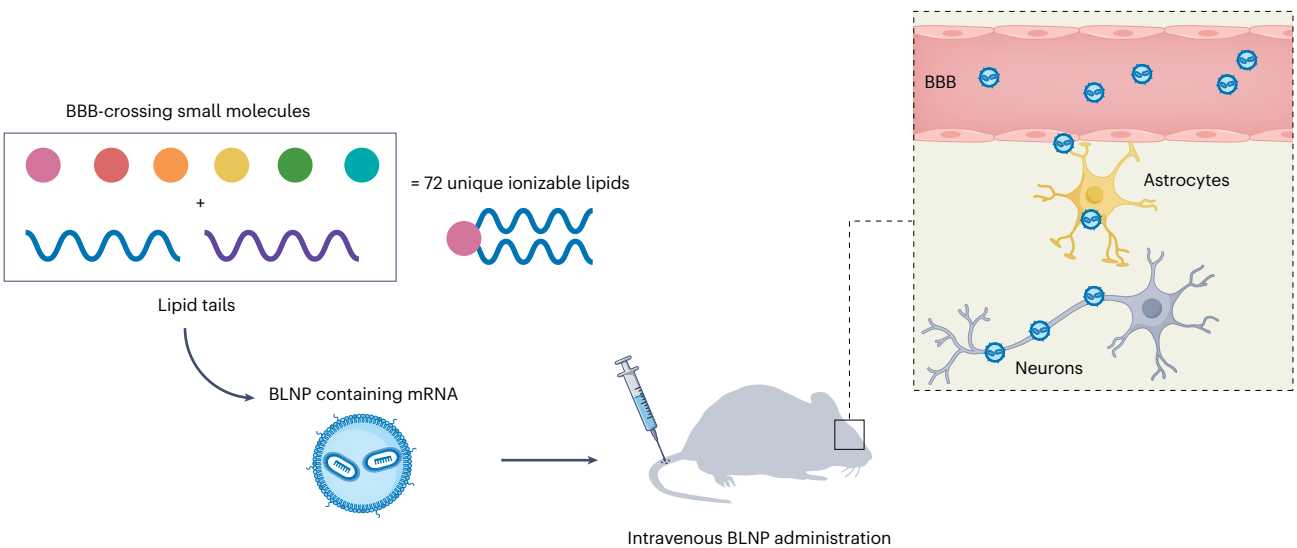

Fig. 1 | LNPs that cross the BBB to deliver mRNA into the brain. BBB-crossing small molecules are combined with lipid tails to form a library of 72 ionizable lipids. These lipids are then used to generate mRNA LNPs, which after several optimization steps result in an LNP formulation that can cross the BBB to transfect neurons and astrocytes after systemic administration. These LNPs hold the potential to deliver various therapeutic mRNAs to treat neurological disorders. Figure adapted from ref. 8, Springer Nature Limited.

systemic BLNP injection and again outperformed the MC3 formulation. To identify which regions of the brain and cell types the MK16 BLNP was reaching, the authors administered the MK16 BLNP encapsulating Cre mRNA into genetically engineered Ai14 reporter mice, where Cre-mediated recombination leads to expression of fluorescent tdTomato in cells. Systemic administration of the MK16 BLNP mediated potent Cre expression and thus tdTomato signal in both neurons and astrocytes in the hippocampus, thalamus and cerebral cortex regions of the brain in comparison to the MC3 LNP, highlighting the potential of the MK16 BLNP to transfect key cell types of interest in the brain.

Finally, the authors demonstrate the therapeutic potential of the MK16 BLNP in vivo in both a cocaine exposure model and a glioblastoma model. In the cocaine conditioned place preference model, the MK16 BLNP delivered mRNA for the transcription factor ΔFOSB, which is upregulated in the brains of patients with drug addiction, to the nucleus accumbens, a deep region of the brain involved in reward pathways. They find that mice treated with these LNPs were able to form drug-context associations at the subthreshold dose of cocaine. These LNPs could have therapeutic applications in treating addiction, as they could allow patients treated with subthreshold, non-reinforcing doses of cocaine to feel relatively reinforcing effects. Furthermore, in a mouse model of human glioblastoma, MK16 BLNPs delivering mRNA encoding for phosphatase and tensin homologue (PTEN), a mediator of tumour suppression, led to reduced tumour burden and extended survival compared with mice treated with MC3 LNPs encapsulating *Pten* mRNA.

This work takes a similar approach to an earlier study[9] that demonstrated the ability of LNPs containing lipids inspired by BBB-crossing neurotransmitters including tryptamine to deliver antisense oligonucleotides, small molecule drugs and proteins to the brain. Similarly, another study[10] reported using BBB-penetrant amphetamine to design cationic lipids for LNP-mediated delivery of small interfering RNA and small molecule drugs to the brain. However, the delivery of mRNA poses a unique challenge due to its large size, structural complexity and susceptibility to degradation, requiring advanced LNP designs for efficient transport across the BBB. To address this challenge, Wang et al. developed a library of lipids with high structural variance, and through rounds of in vitro and in vivo screening were able to find LNP formulations capable of delivering a large therapeutic cargo, mRNA, to the brain.

These BLNPs could potentially deliver any kind of therapeutic mRNA to the brain to treat a range of neurological disorders. However, translation of these BLNPs into the clinic would require comprehensive safety profiling. While the authors conducted several preliminary safety studies, such as analysis of pro-inflammatory cytokines and chemokines as well as liver and kidney function markers, further studies incorporating dose escalation and repeated administration, especially over an extended period of time, would be essential.

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Competing interests

The authors declare no competing interests.