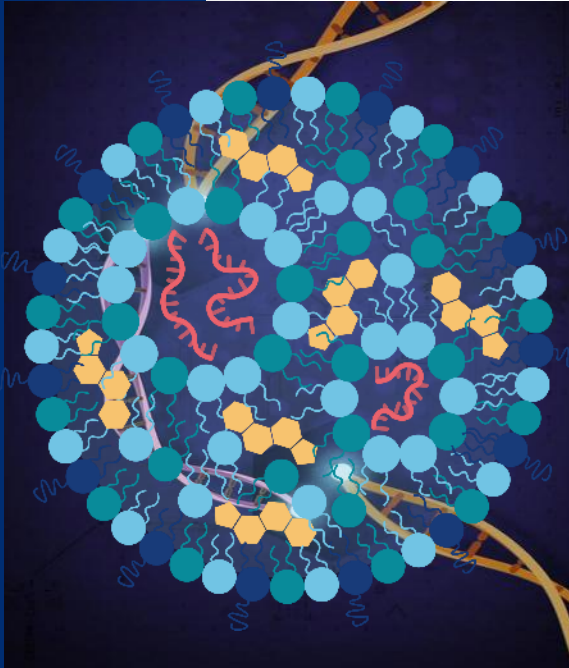




A CNS-Tropic Lipid Nanoparticle Platform Inspired by Natural Brain Chemistry

Speaker: Menggui Huang, Ph.D.
Principal Scientist

ASGCT 28TH ANNUAL MEETING
New Orleans
May 16th, 2025



Gene Therapy for Neurological Disorders : Why has success been limited?

Problem : Delivery of Genetic Medicines (e.g. mRNA, RNAi) to the CNS is a Major Bottleneck

DEVELOPMENT OF GENETIC MEDICINES FOR NEUROLOGICAL DISEASES

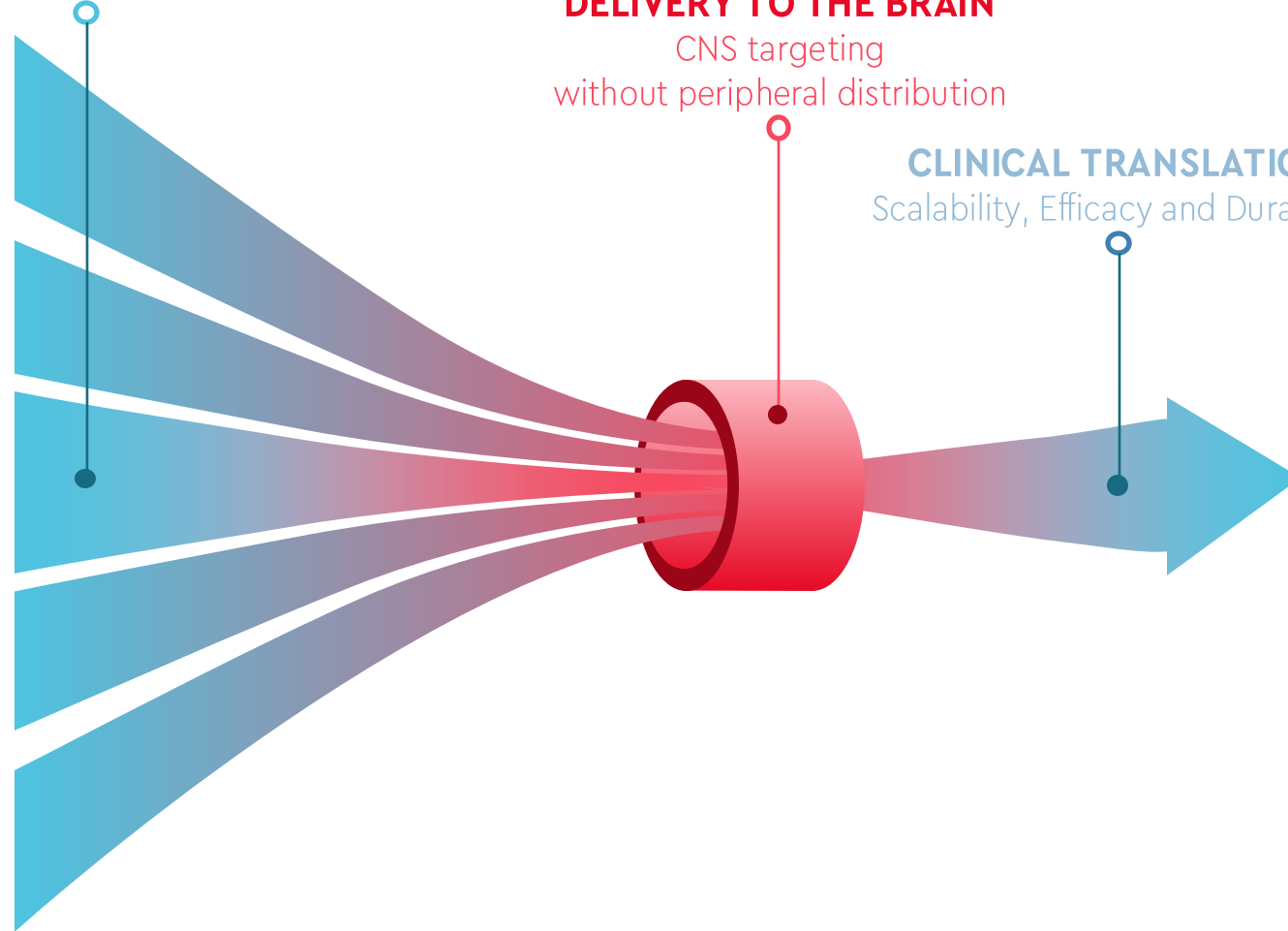
Selectivity, Efficiency and Durability

DELIVERY TO THE BRAIN

CNS targeting
without peripheral distribution

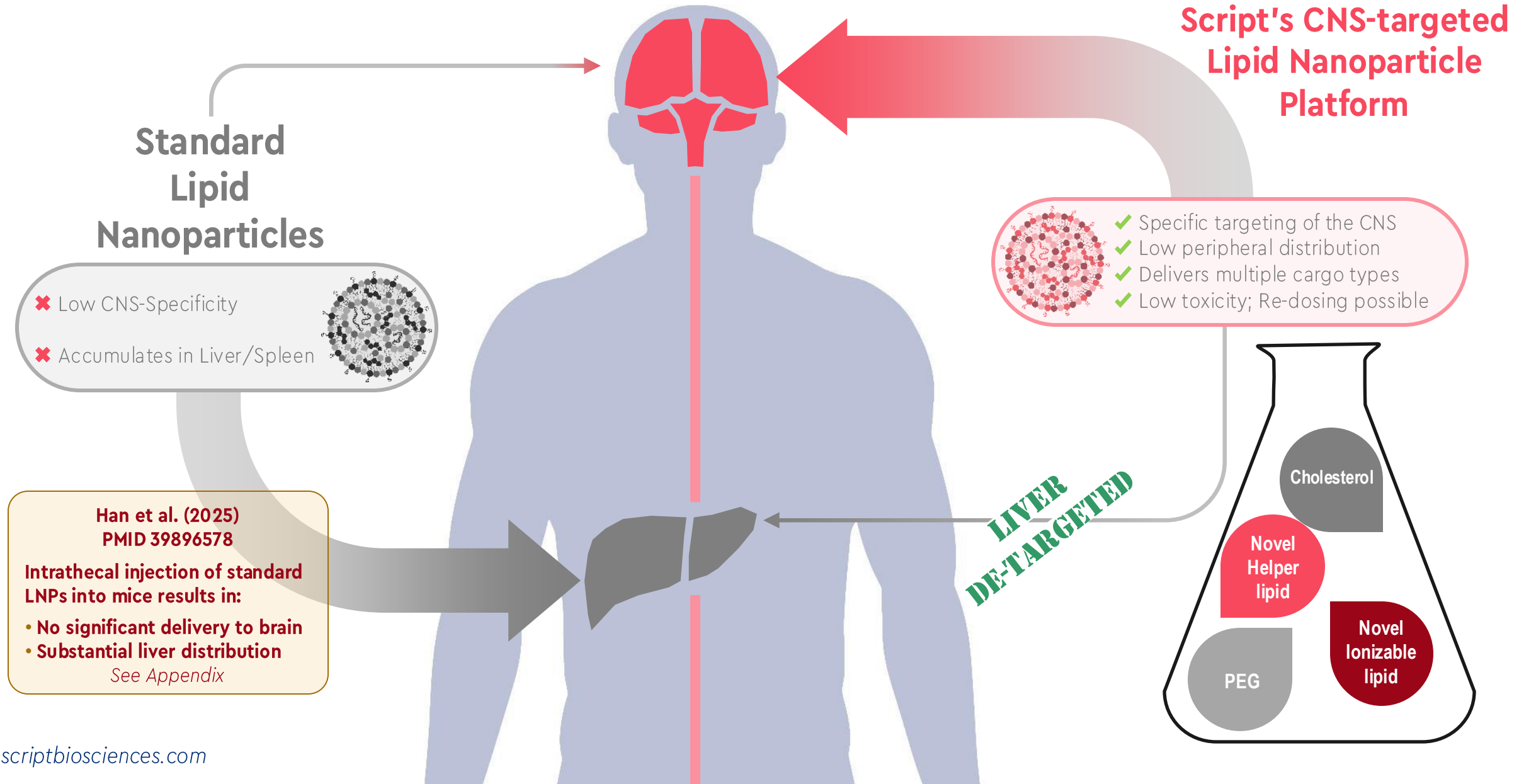
CLINICAL TRANSLATION

Scalability, Efficacy and Durability



Solution : A CNS-targeted Lipid Nanoparticle Inspired by Brain Chemistry

Re-engineering of lipid nanoparticle constituents



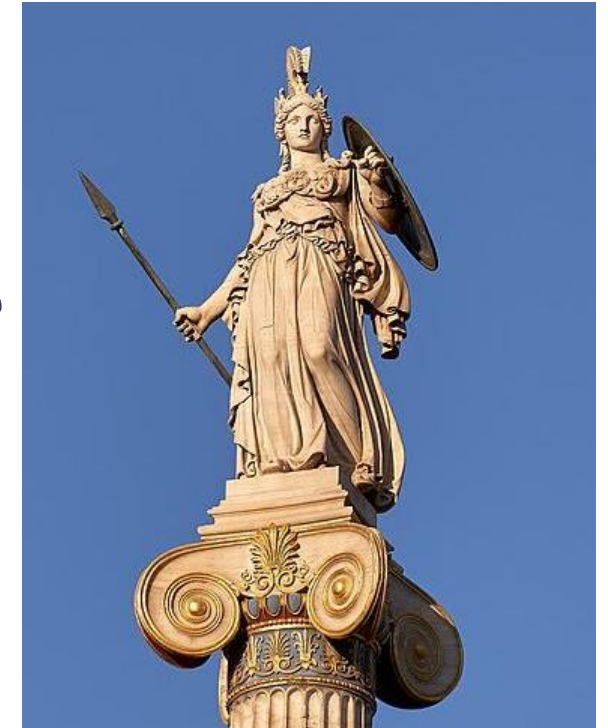
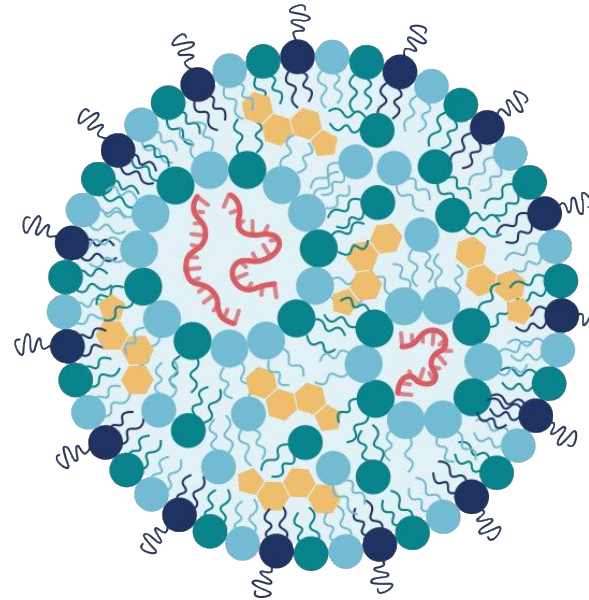
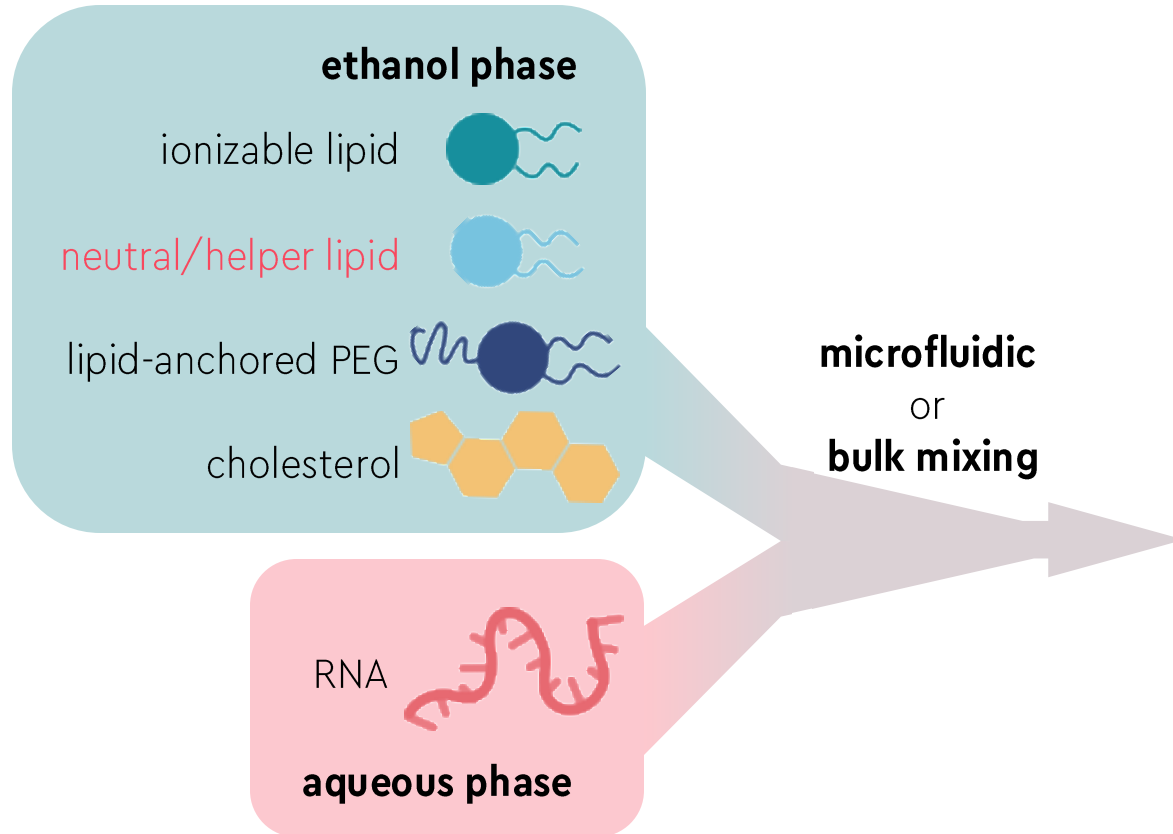
ATHENA™ : A CNS-Tropic Lipid Nanoparticle Platform

Advanced Technology for Highly Efficient Neural Administration

Αθηνά
Athena

Greek Goddess of Wisdom
Governing Principle of the Mind

(Athena) Wisdom → Mind → Brain → Neurons (LNP)

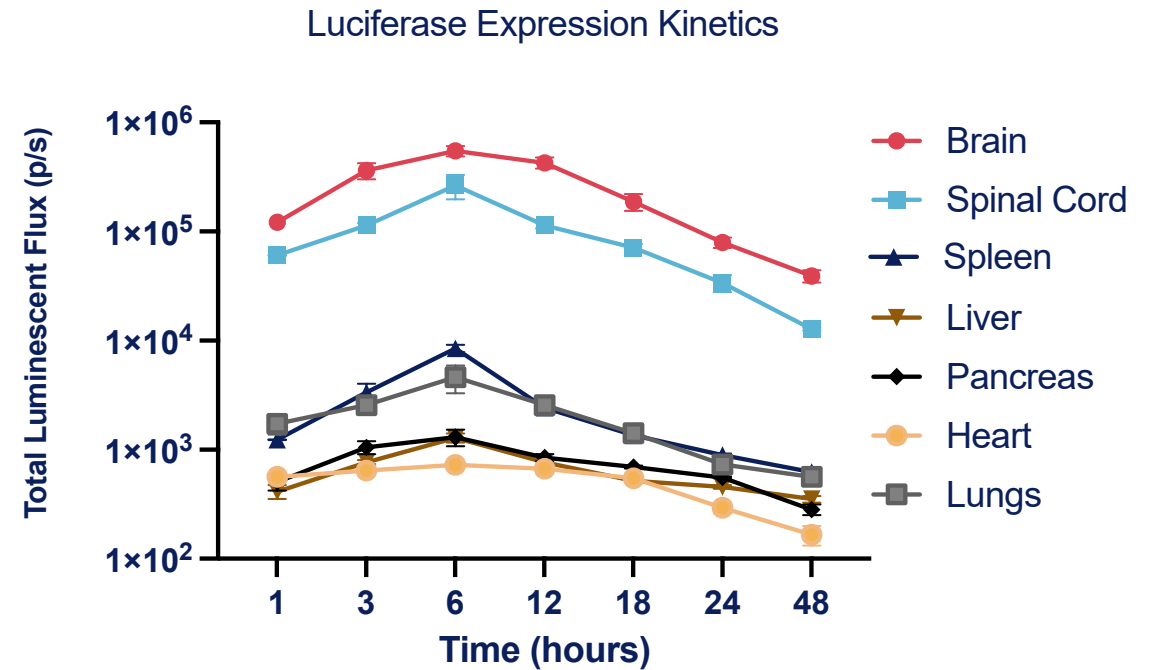
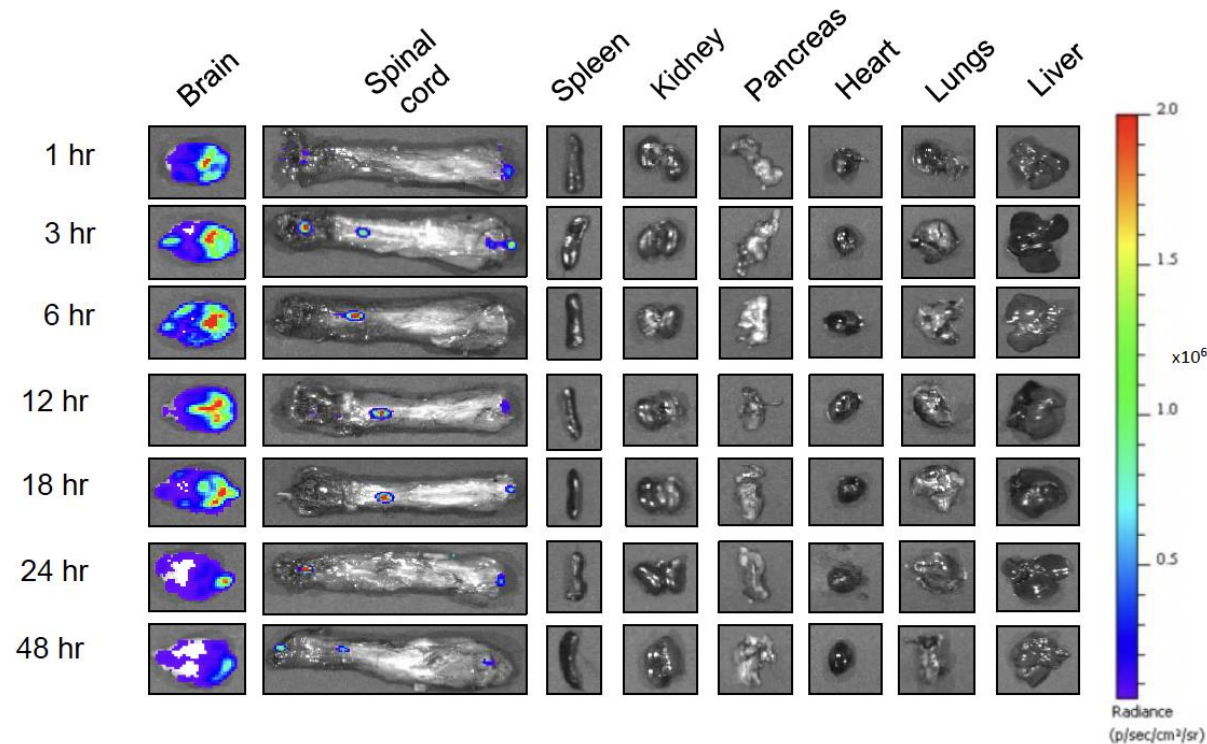




Biodistribution of LNPs in Mouse Brain

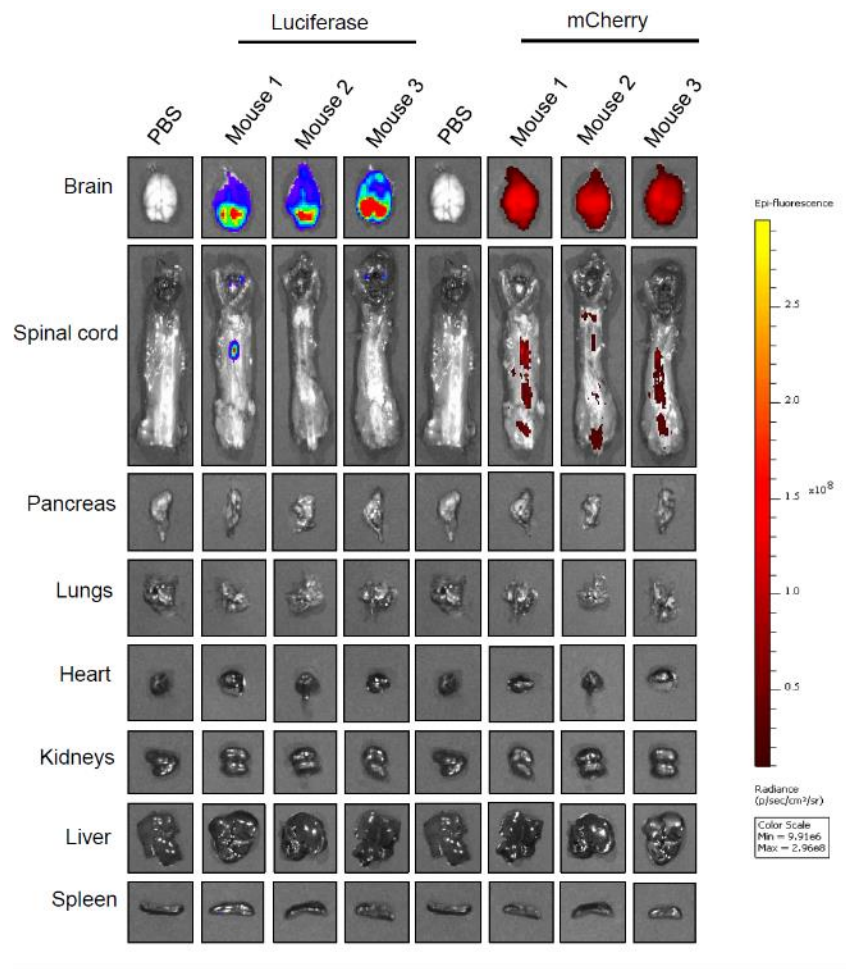
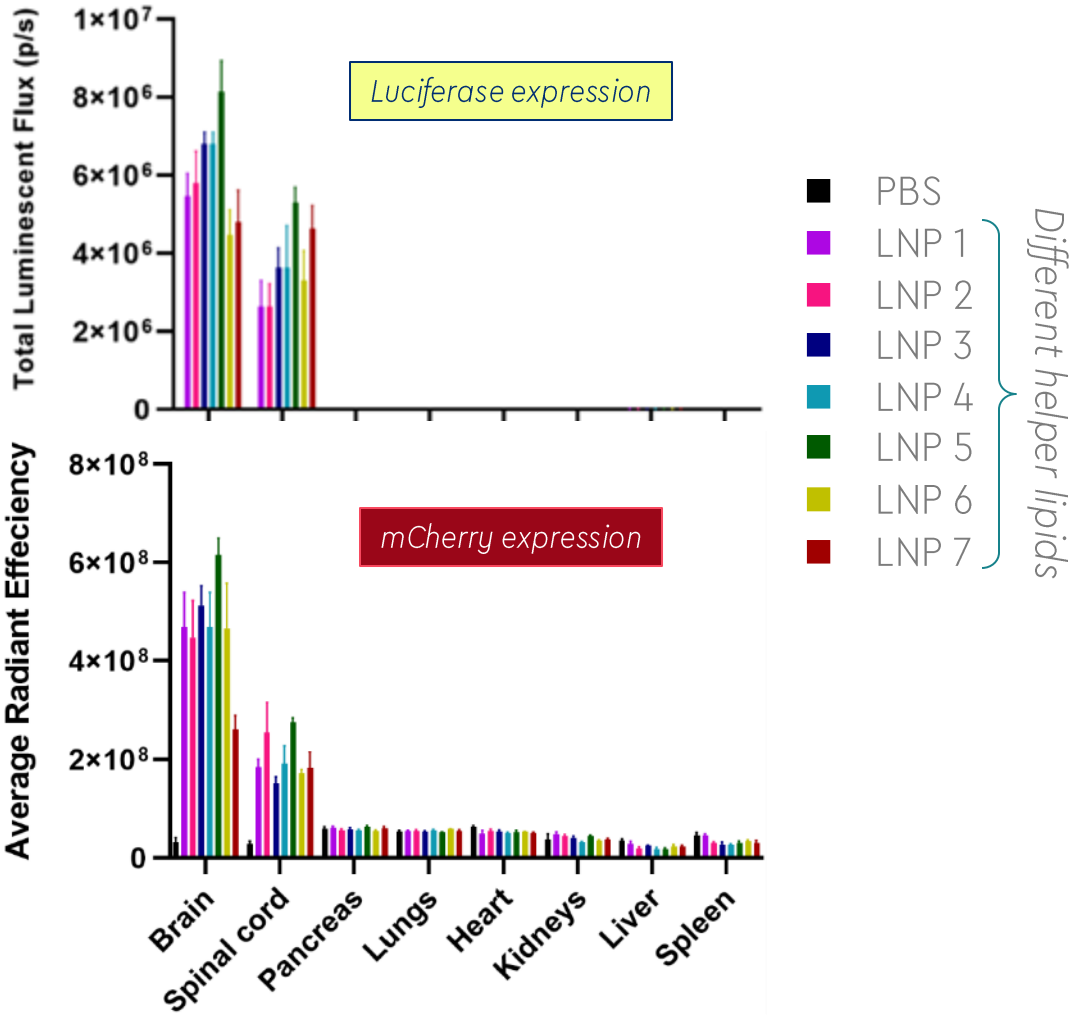
Script's LNPs Enable Highly Specific Delivery of mRNA to the CNS

Expression of LNP-encapsulated luciferase mRNA delivered intrathecally to mice



- Sustained (>48 hr) reporter gene expression in the CNS
- Low distribution to liver, spleen, and other peripheral organs

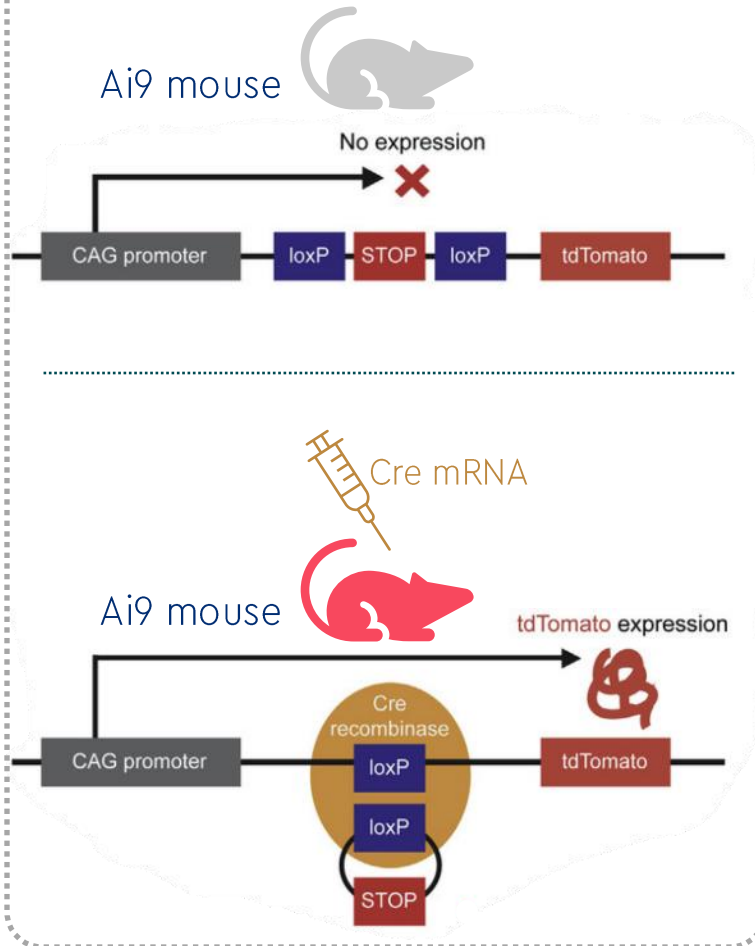
Helper lipid enables concurrent and localized expression of luciferase and mCherry in CNS of intrathecally injected mice



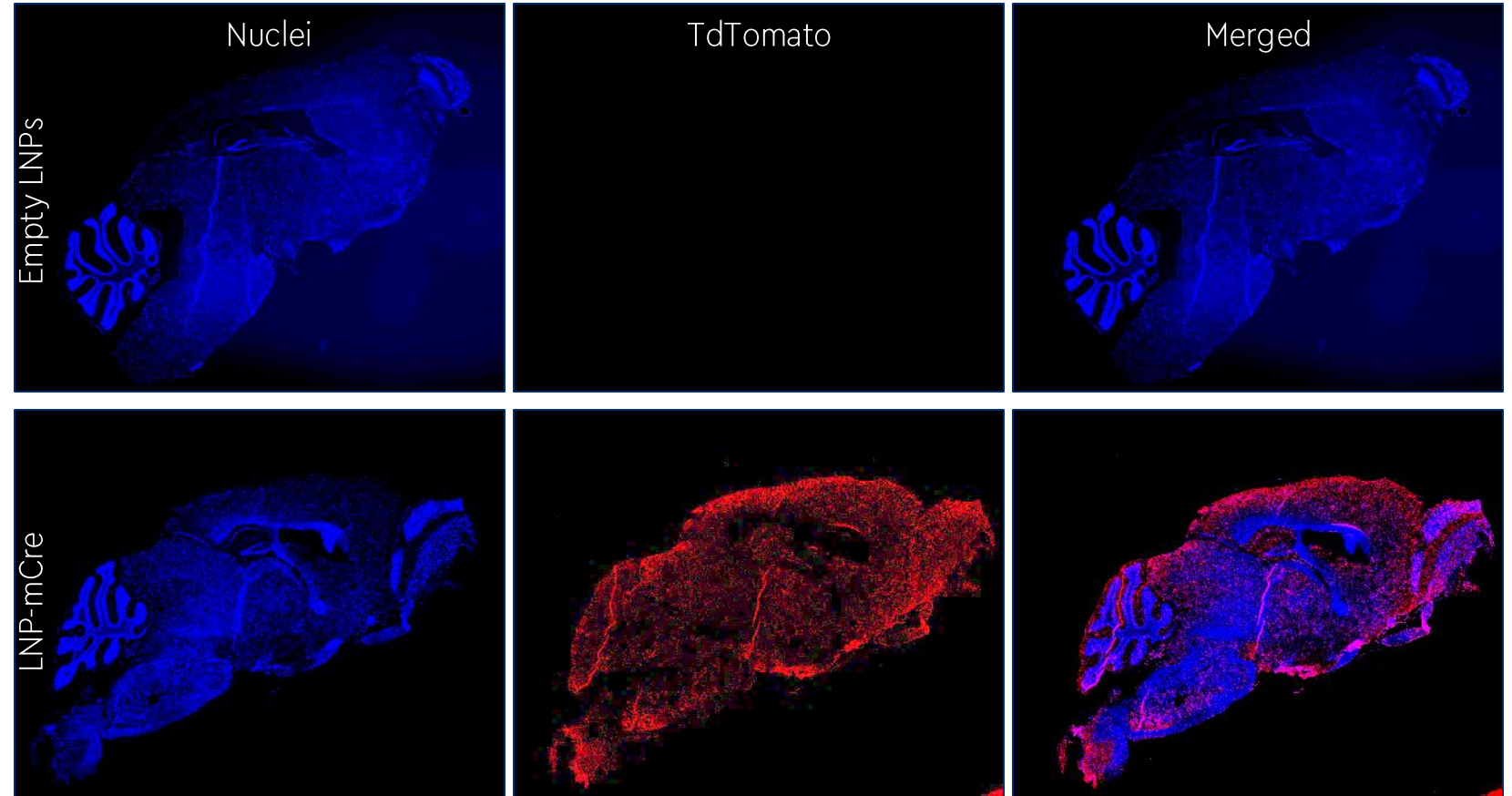
Efficient tissue-specific delivery of multiple mRNAs enables diverse therapeutic applications

Script's LNPs Deliver mRNAs Throughout the Brain

Restoration of reporter gene fluorescence upon IT delivery of Cre recombinase mRNA



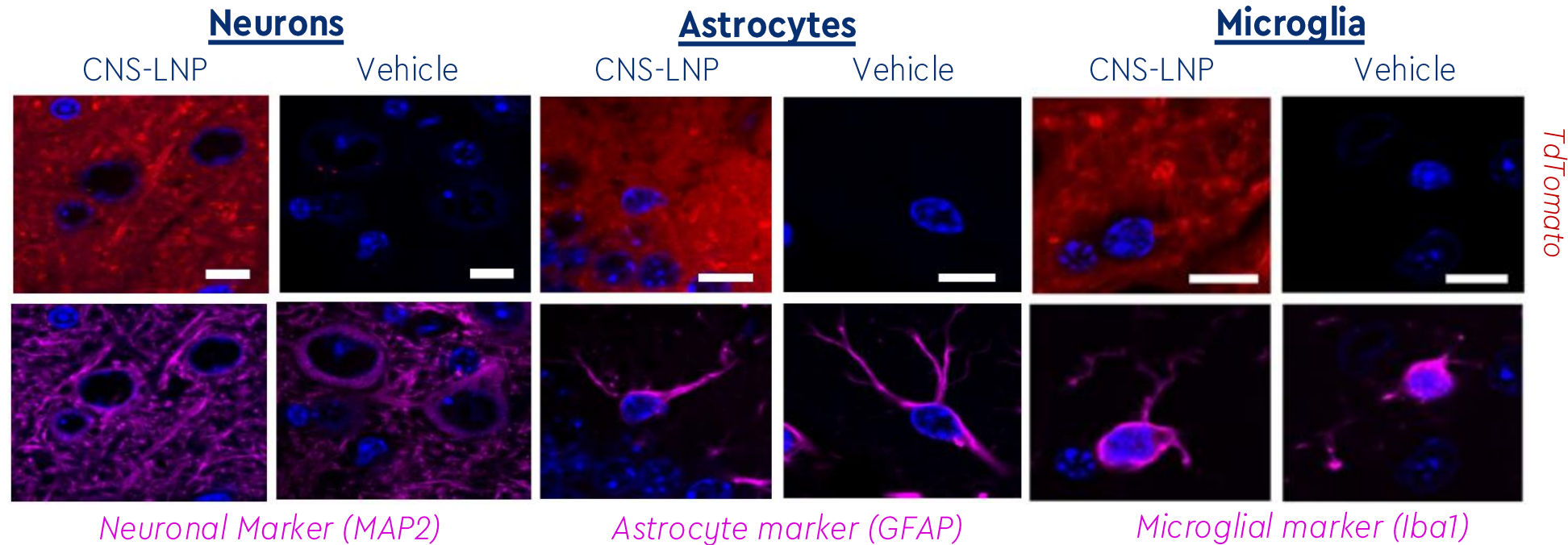
Ai9 mouse brain sagittal section showing widespread TdTomato expression



Wide distribution of Cre mRNA in the mouse brain

Script's LNPs Deliver mRNAs to Multiple Cell Types in the Brain

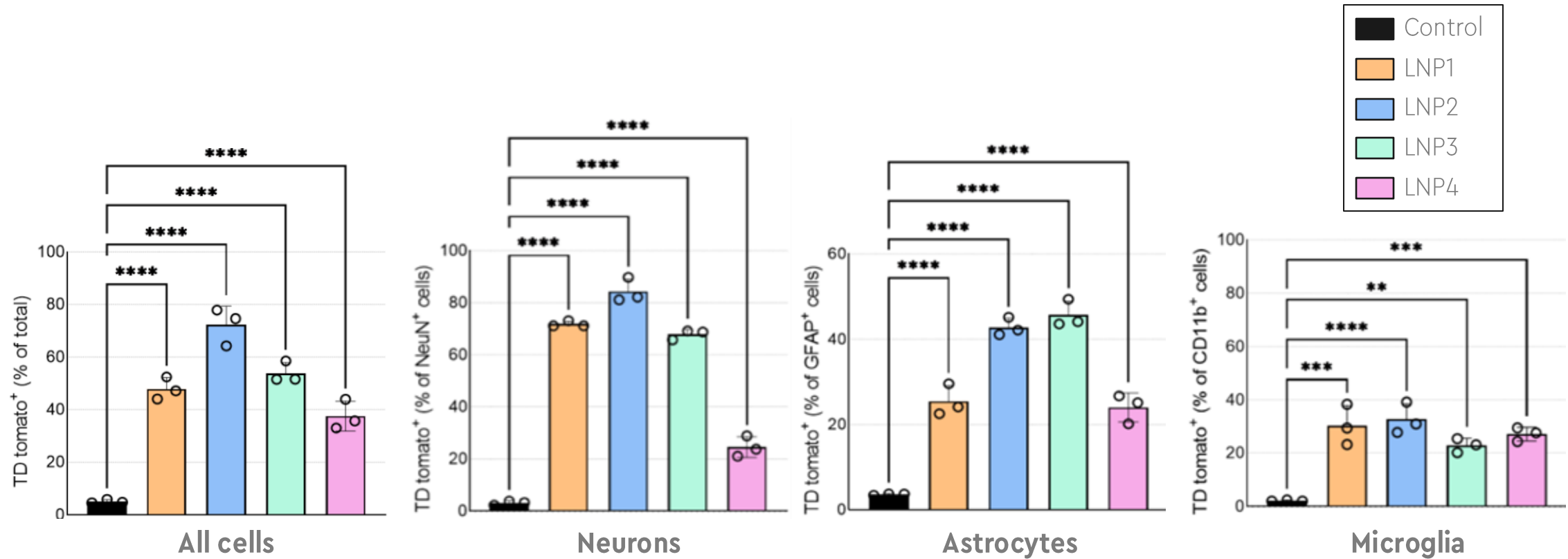
Cell type specificity of LNP-mediated delivery of Cre mRNA in Ai9 mouse brain



- **CNS-tropic LNPs deliver RNA cargo to neurons, astrocytes, microglia, and oligodendrocytes**
- **Opportunity to address a range of pathologies associated with diverse cell types**

Cell Type Specificity of CNS-optimized LNPs in Mouse Brain

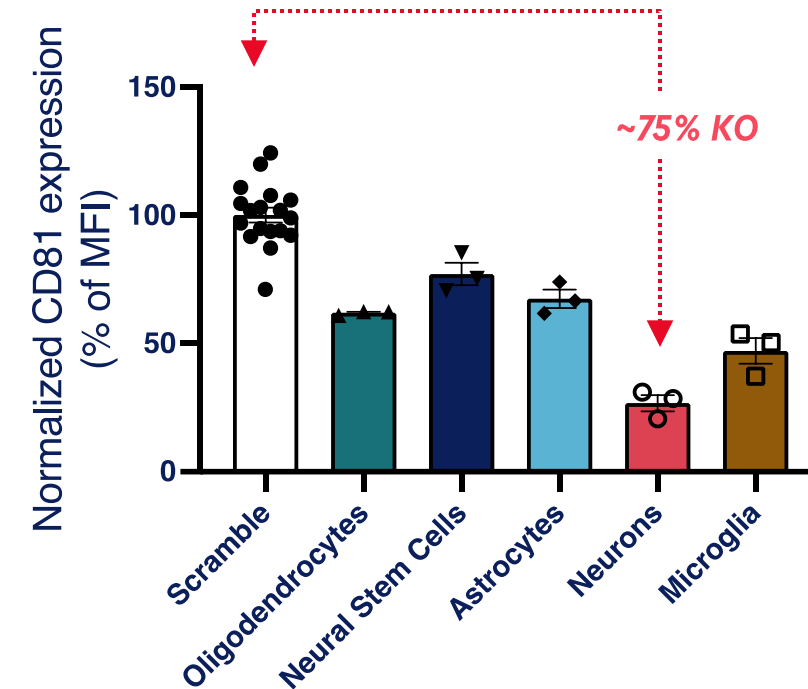
Restoration of TdTomato fluorescence upon IT delivery of Cre recombinase mRNA into Ai9 mice



Proprietary LNP formulations successfully target neurons upon intrathecal administration

- CD81 is ubiquitously expressed in the brain
- LNPs encapsulating Cas mRNA and CD81-targeted gRNA injected intrathecally
- Whole brain disaggregated and analyzed for CD81 expression by flow cytometry
- Cell-type specific markers used to determine CD81 expression in various cell types

PoC: Cas-mediated knockout of CD81 in vivo



Proprietary LNP formulations successfully target neurons upon intrathecal administration



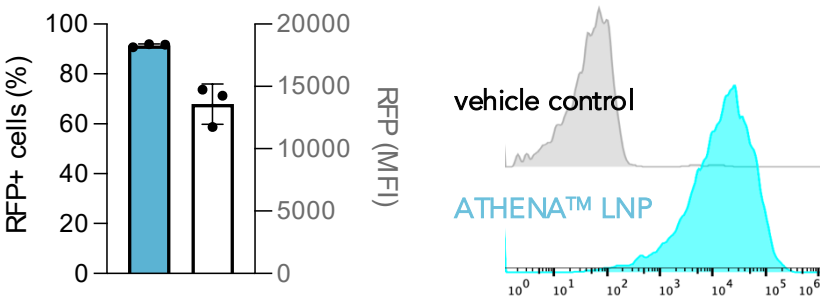
Biodistribution in Rat brain

PoC for translatability to larger (>10X) animals

LNP characterization and rat brain biodistribution

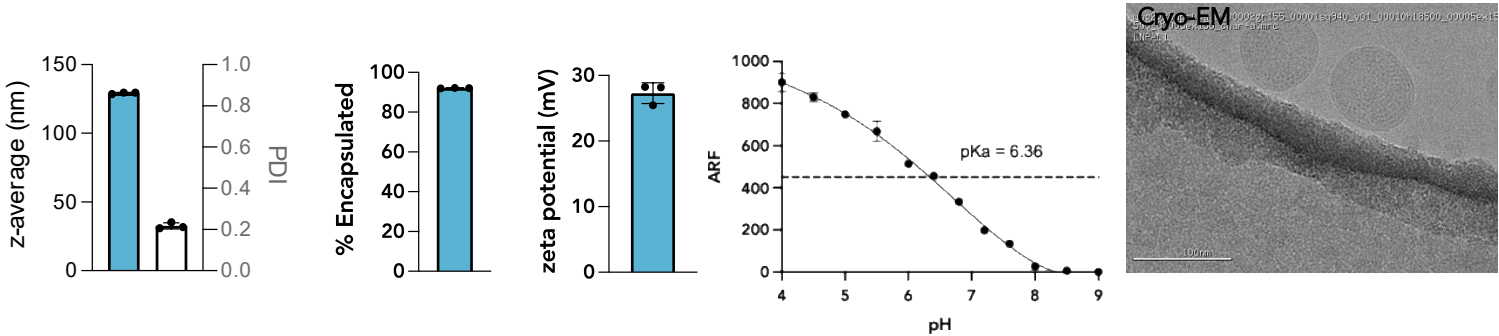
1. Functionality

High delivery efficiency *in vitro* (>90%)

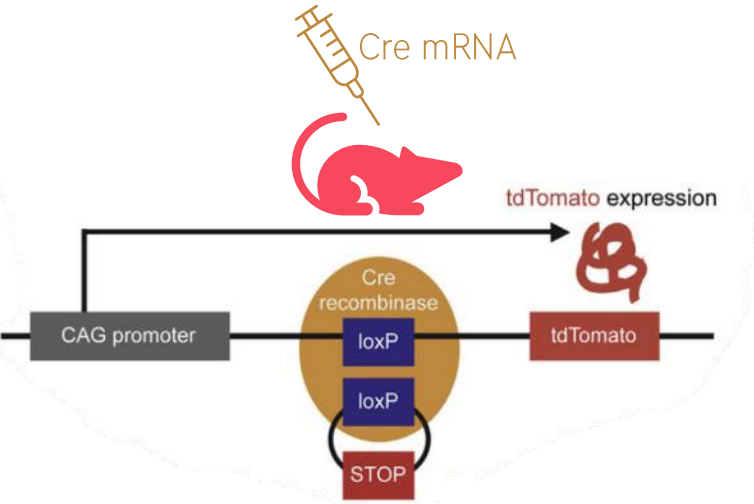


2. Physicochemical Characterization

Size, polydispersity, encapsulation, zeta potential, pKa, Cryo-EM



TdTomato reporter knockin rat

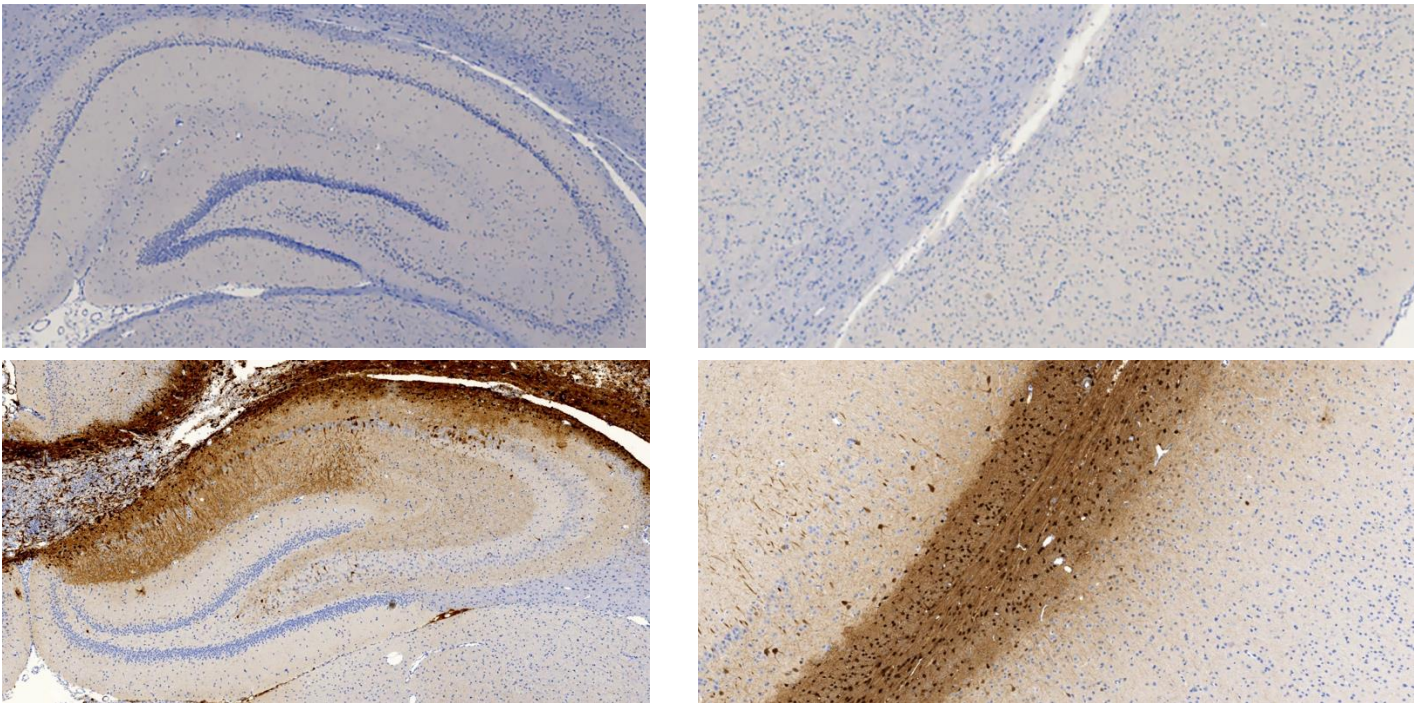


Hippocampus

Cortex

Vehicle

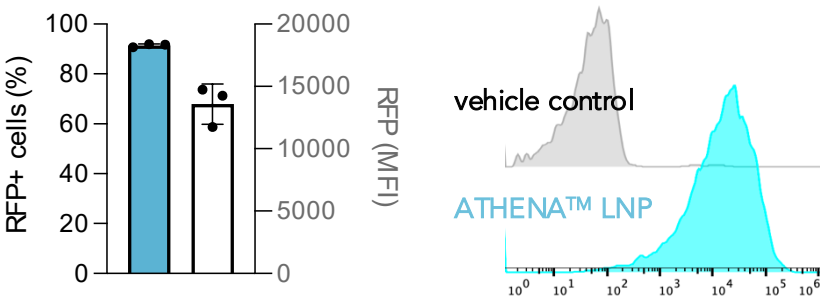
LNP-Cre mRNA



LNP characterization and rat brain biodistribution

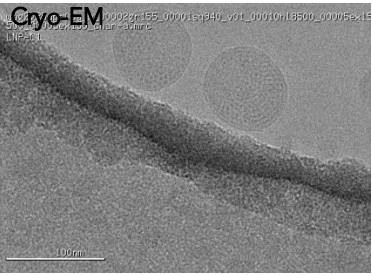
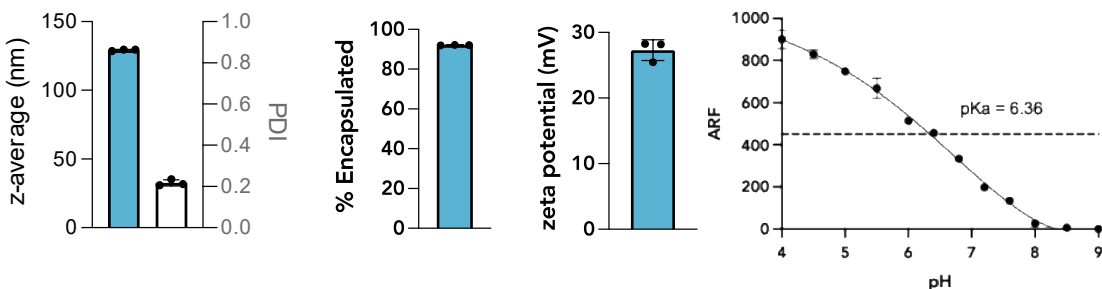
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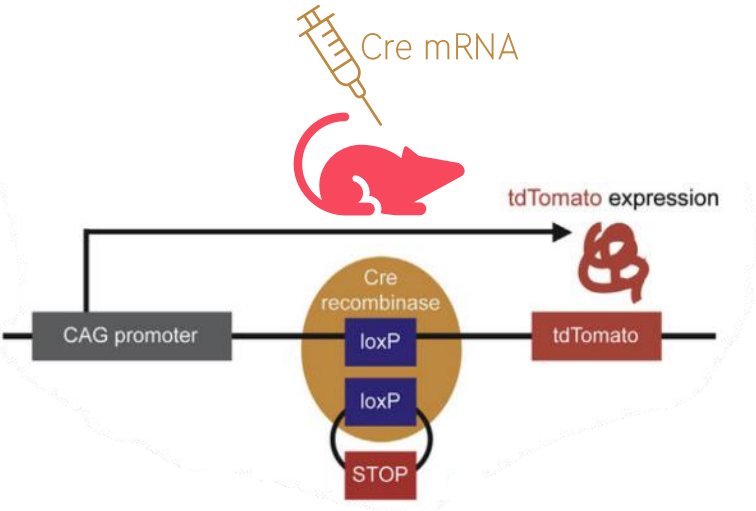


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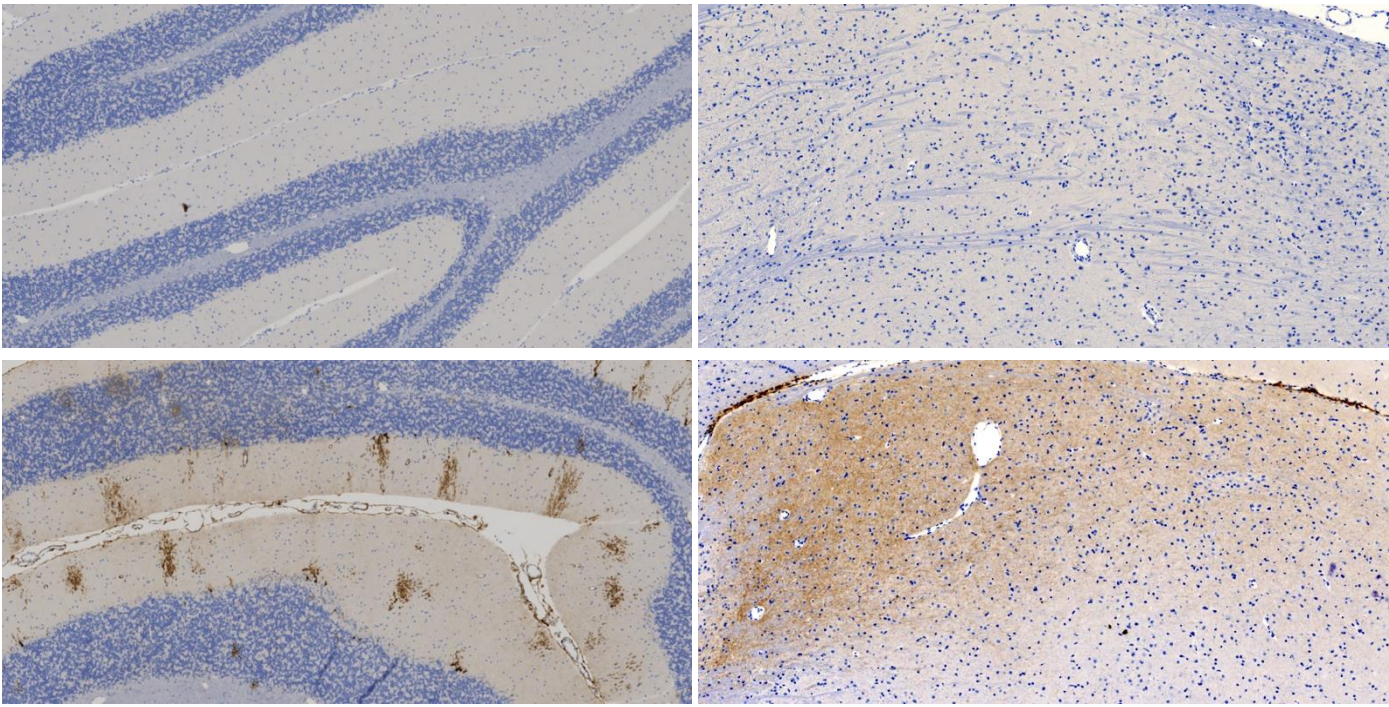


Cerebellum

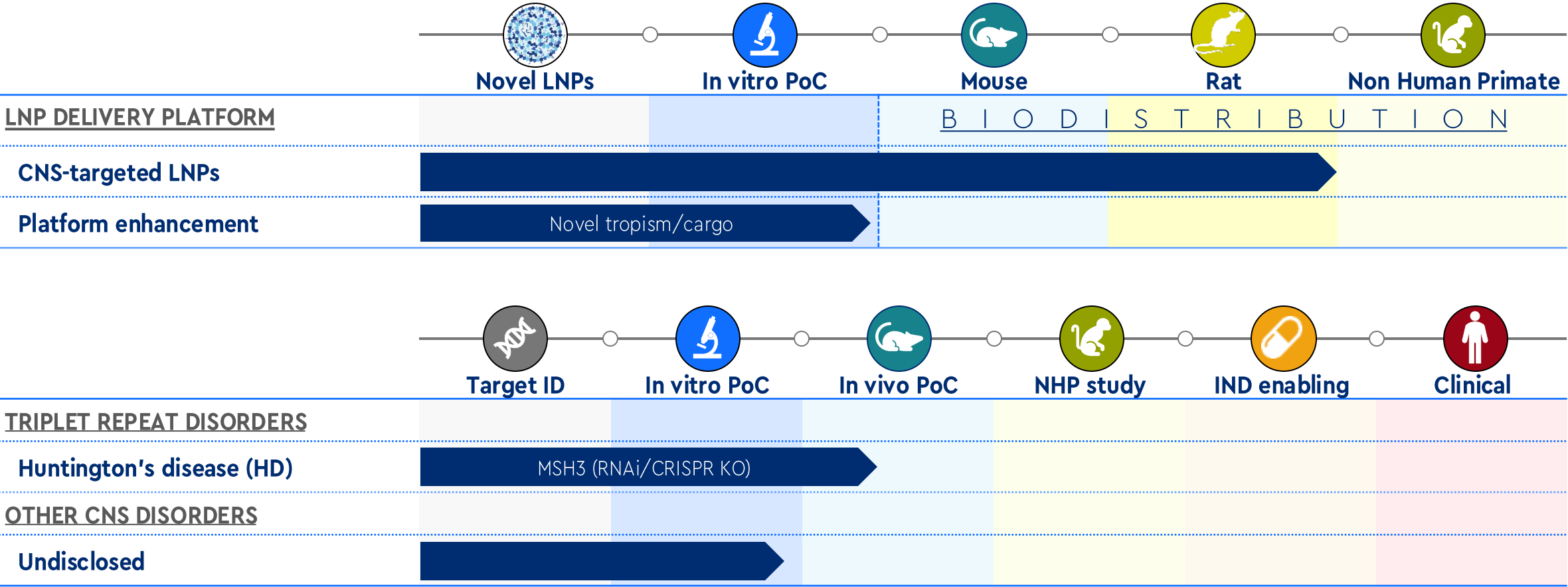
Thalamus

Vehicle

LNP-Cre mRNA



Script's Platform Development and Therapeutic Pipeline



- Platform enables development of a wide range of brain-targeted therapeutic modalities
- Pipeline represents diseases with high unmet needs and few therapeutic options

Summary

- **Script's ATHENA™ LNP platform:**
 - Delivers to CNS specifically without peripheral exposure.
 - Can encapsulate mRNA, siRNA, ASO, or CRISPR.
 - Shows distribution in multiple rat brain regions including hippocampus, thalamus, cortex, and cerebellum.
 - Is modular and can be expanded for alternative tissue- and cell- type tropism.
- **Rat biodistribution suggests translation and scalability to larger animal models.**

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