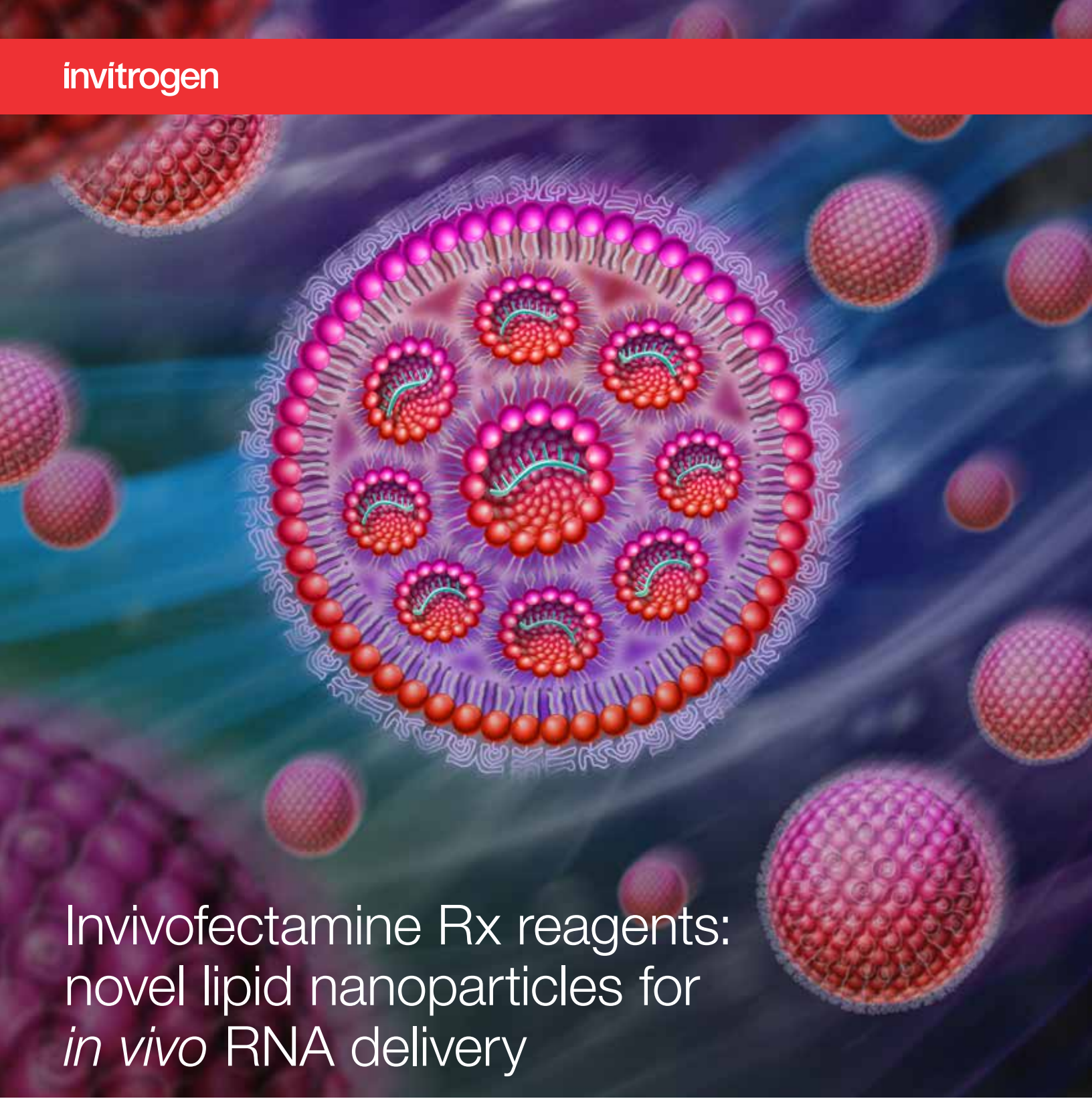
invitrogen



Invivofectamine Rx reagents: novel lipid nanoparticles for *in vivo* RNA delivery

Your total solution for mRNA and RNAi nanomedicine delivery research and development programs

ThermoFisher SCIENTIFIC

Dedicated to your commercial success

We have an active discovery and development program focused on next-generation lipid nanoparticle (LNP) technology. Our Invitrogen™ Invivofectamine™ Rx portfolio offers the most advanced *in vivo* mRNA and RNAi delivery platforms, designed to meet the highest performance and safety criteria required for translational research.

Partner with us to leverage our innovative technologies, technical expertise, and global support infrastructure. Our team works with you every step of the way, forming strategic alliances to help ensure your commercial success.

World leader in delivery technologies—garnering from over 25 years of experience

We have a complete offering for all of your RNA therapeutics needs, from *in vitro* transcription through *in vivo* delivery.

- Scalable systems support early-stage research through clinical development and commercialization
- Leading innovation driven by continual process optimization
- Extensive library of proprietary delivery reagents
- Dedicated team of technical experts
- Superior quality management system
- Flexible licensing options

Advancing *in vivo* RNA delivery through high-performance technologies

As a world leader in providing *in vitro* transfection reagents, our committed team of scientists continually develops evolving technologies to meet the growing demands for the latest RNA delivery formulations, especially for therapeutic applications. Our *in vivo* RNA delivery platform provides optimal organ delivery with minimal toxicity in small animal models (Table 1).

Table 1. Comprehensive solution for *in vivo* RNA delivery.

Technology	Invivofectamine Rx mRNA	Invivofectamine Rx RNAi
Potency	*In vivo* luminescence (1 x 10^{10} photons/sec) at 1 mg/kg mRNA dose	ED_{50} <0.02 mg
Toxicity	Low toxicity	Low toxicity
Specificity*	Liver, spleen, lung, intramuscular	Liver, intramuscular
Scalable	Yes	Yes
GMP	Under development. Please inquire.	Under development. Please inquire.

* Inquire for interest in delivery to other tissues.

Optimized proprietary delivery

We utilize a combinatorial method to identify novel compounds and optimize formulations specific for different RNA payloads through proven design of experiment (DoE) and extensive proprietary know-how in the field of transfection (Figure 1).

- Extensive screening of potential candidates to select the optimal LNP formulations
- DoE for optimizing LNP formulation process parameters

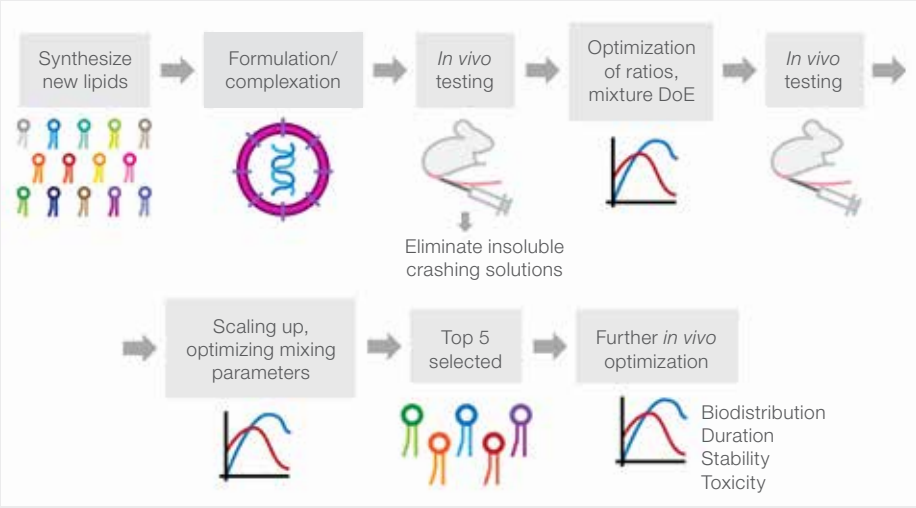


Figure 1. Schematic of DoE and formulation screening.

High-efficiency mRNA delivery

There is an immediate and growing demand for the potential use of mRNA in many therapeutic areas, including cancer immunotherapies, prophylactic vaccination, protein replacement, and gene editing. The Invivofectamine Rx platform provides a novel technology for *in vivo* mRNA delivery (Figure 2), enabling our partners to accelerate their research and development of new therapeutic modalities.

Sequential improvement in performance through DoE

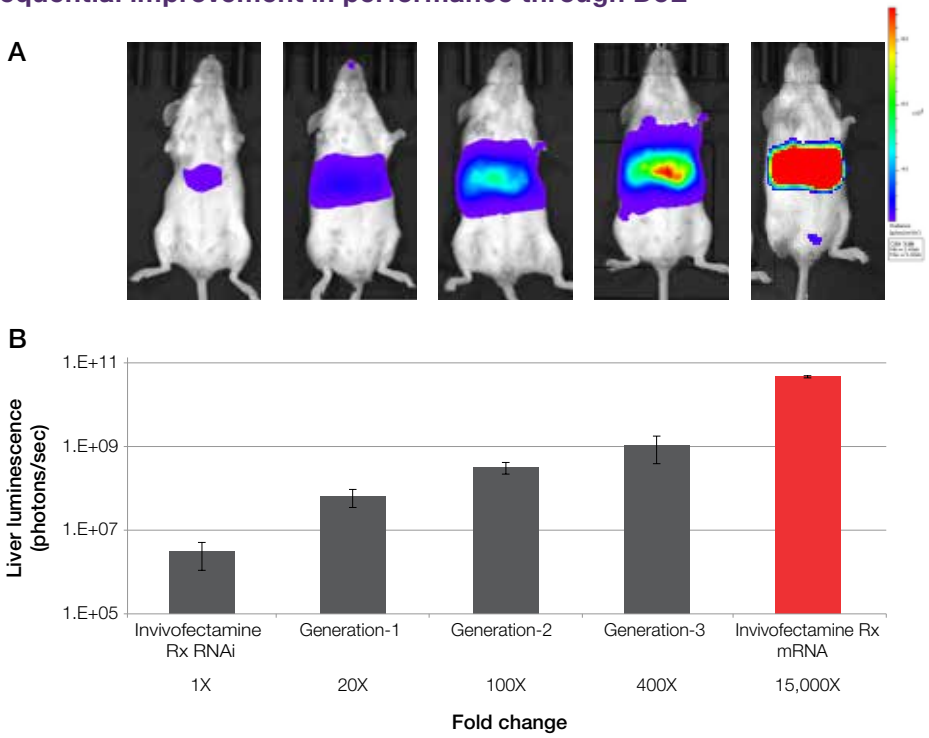


Figure 2. *In vivo* delivery of luciferase mRNA (FLuc) using Invitrogen™ Invivofectamine™ Rx mRNA demonstrating continuous improvement in Invivofectamine Rx mRNA delivery performance as shown in (A) visual and (B) quantitative assessment of luciferase expression 4 hours post–IV injection in mice.

Positive dose-response relationship

Invivofectamine Rx mRNA can effectively deliver a wide range of mRNA doses (Figure 3), thus offering the flexibility to modulate mRNA concentration based on the application.

Extended activity level

Invivofectamine Rx mRNA maintains luciferase expression in mice for up to 5 days post–intravenous (IV) administration (Figure 4). This suggests the need for less frequent dosing, which could potentially reduce treatment-associated toxicity.

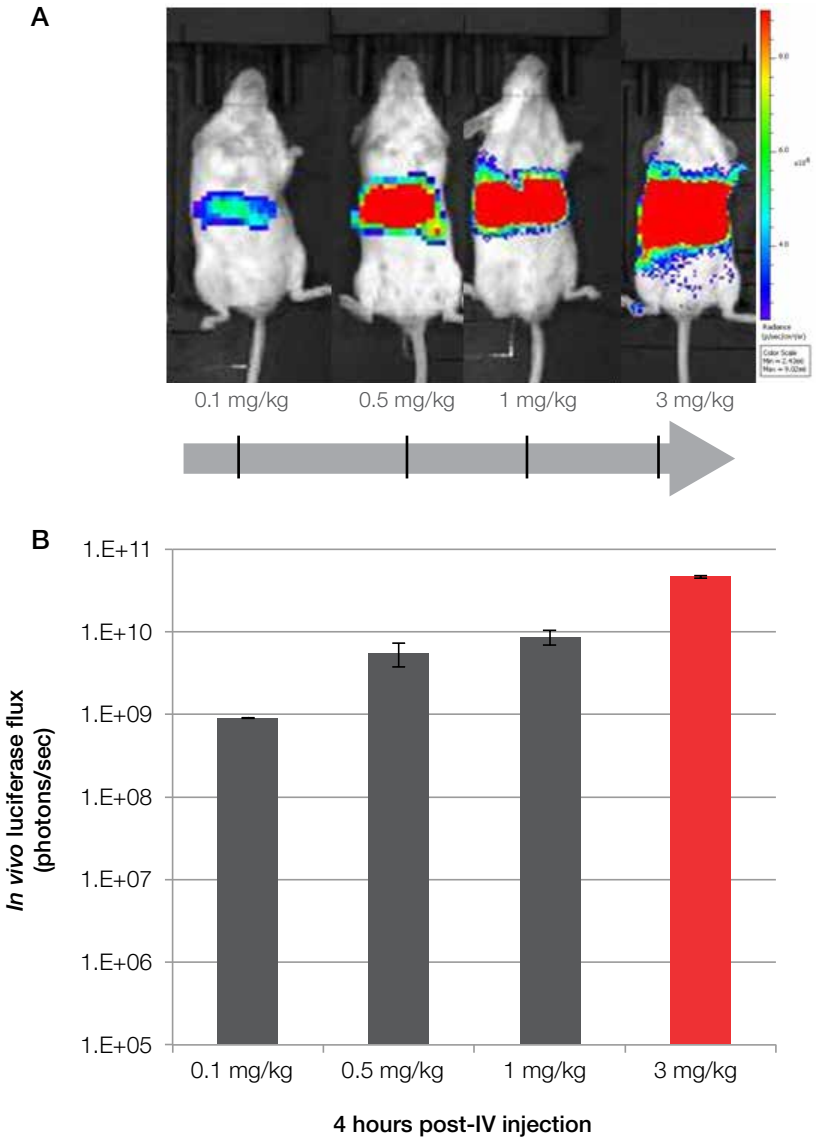


Figure 3. (A) Visual and (B) quantitative representation of dose titration study at 4 hours demonstrating effective payload delivery of luciferase (Fluc) mRNA in mice.

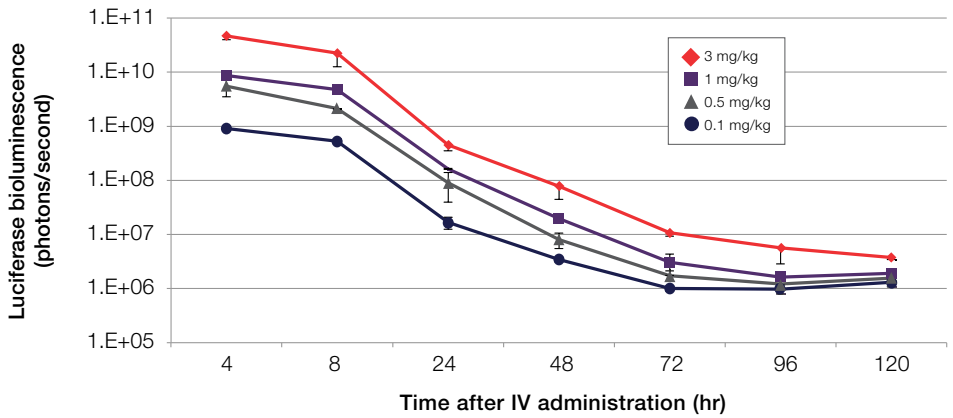


Figure 4. Time-course study showing up to 5 days post–IV administration of a single injection of Invivofectamine Rx mRNA with Fluc mRNA (non–codon-optimized) at different mRNA doses in mice.

Minimal cytotoxicity

Invivofectamine Rx mRNA provides a balance of efficient *in vivo* nucleic acid delivery combined with minimal systemic toxicity (Figure 5), making it an ideal delivery platform to support therapeutic research and development programs.

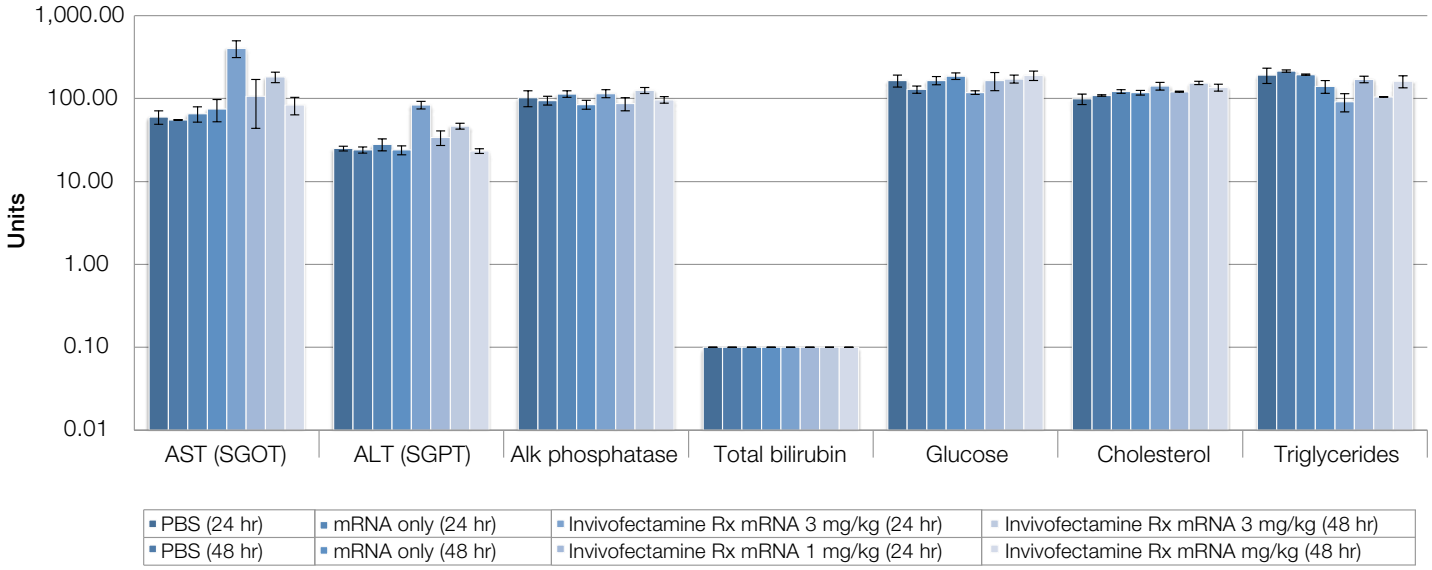


Figure 5. LNP toxicity data. Invivofectamine Rx mRNA demonstrated low cellular toxicity by serum chemistry analysis at 24 hr and 48 hr at doses of 1 mg/kg and 3 mg/kg in mice.

As shown in Figure 6, the average particle size of the LNPs was 91 nm, with a polydispersity index (PDI) of 0.203, indicating they are monodisperse particles.

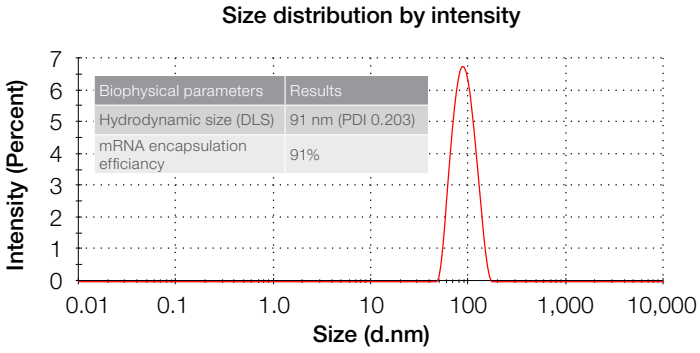


Figure 6. Biophysical characterization of LNP.

Organ-specific targeted delivery

Invivofectamine Rx mRNA can be tailored to deliver mRNA to specific organs, allowing for a wider range of clinical research options (Figure 7).

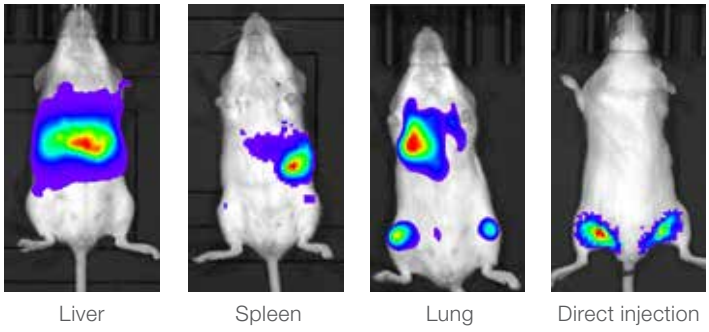


Figure 7. LNPs optimized for organ-specific delivery. From left to right, panels show successful proof-of-concept studies with LNPs that can be used for organ-specific delivery of Fluc mRNA to liver (intravenous), spleen (intraperitoneal), lungs (intravenous), and by direct injection in mice.

Optimized formulation for RNA interference (RNAi)

Superior gene knockdown using Invivofectamine Rx RNAi

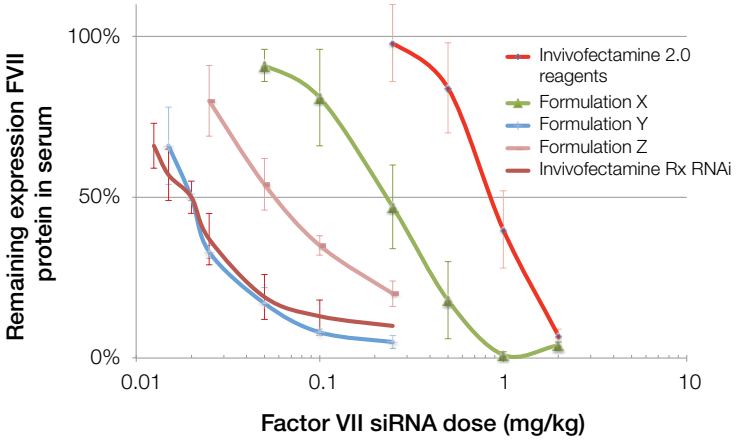


Figure 8. Dose titration of *in vivo* formulations for delivery of siRNA targeting factor VII (FVII) protein. The improvement with Invivofectamine Rx RNAi is a synergistic combination of new LNP technology and optimized formulation parameters.

Small interfering RNA (siRNA) has the ability to mediate RNAi by down-regulating gene expression and is currently being explored in a clinical setting for modulating a wide range of targets beyond the conventional cell surface molecules, enzymes, or nuclear hormone receptors. To address the current challenge of effective *in vivo* delivery of siRNA for therapeutic applications, we have developed the Invitrogen™ Invivofectamine™ Rx RNAi delivery platform—a potent nanoparticle formulation with minimal cytotoxicity (Figures 8–10).

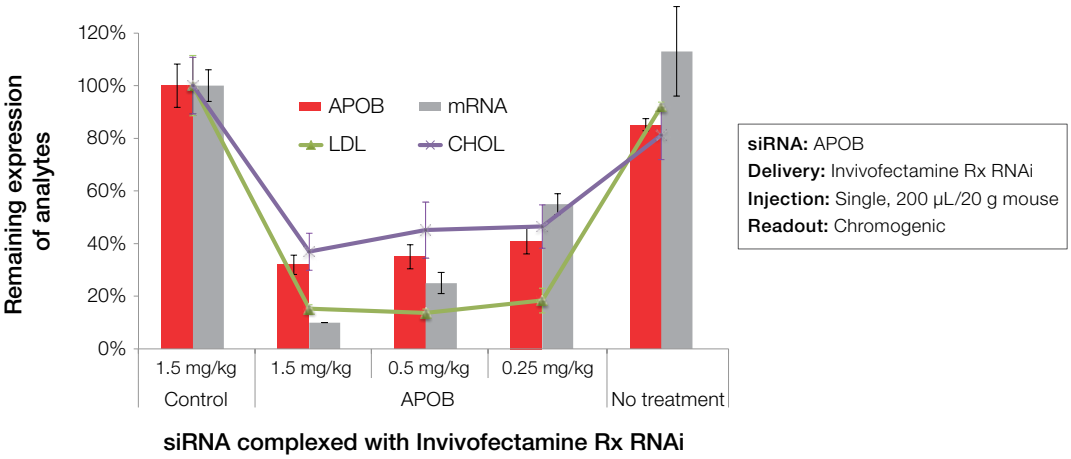


Figure 9. Dose titration and pharmacological effect of silencing ApoB-100. Invivofectamine Rx RNAi was complexed with ApoB siRNA and injected at doses of 0.25, 0.5, and 1.5 mg/kg. Liver tissue and plasma from mice were collected 48 hours post-injection and were analyzed for ApoB mRNA, APOB protein, and various lipid analytes.

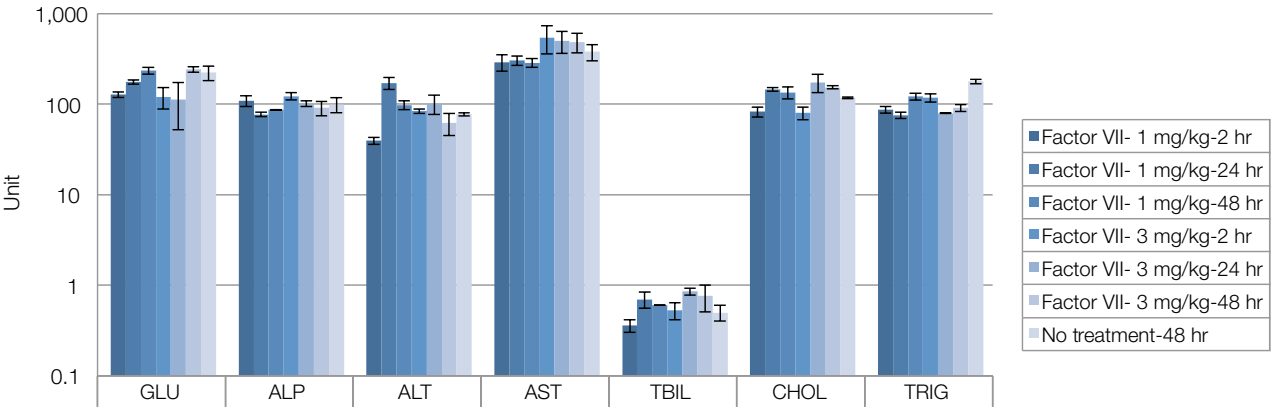


Figure 10. Toxicity profile of Invivofectamine Rx RNAi by serum chemistry analysis at 2 hr, 24 hr, and 48 hr at doses of 1 mg/kg and 3 mg/kg in mice.

A premier brand with Thermo Fisher Scientific

We can help you accelerate innovation and enhance productivity in discovering novel RNA-based therapies. We offer flexible licensing options to meet your business needs. You can be confident that we will provide ongoing technical support, optimal product performance, proprietary formulation protocols, reagent supply and, most importantly, our continual dedication to your success.

Invivofectamine Rx platform

- We have an active discovery and development program focused on the next-generation lipid nanoparticle technology: Invivofectamine Rx reagents.
- Invivofectamine Rx reagents are a family of LNP carriers designed to deliver RNAi or mRNA *in vivo* to the liver and other tissues with high specificity and minimal toxicity.

Intellectual property

- We have broad intellectual property covering the Invivofectamine Rx platform for the delivery of the next generation of RNAi and mRNA therapeutics.

Partnership goals

- We offer access to our proprietary lipid nanoparticle evaluation materials and technical guidance through our Invitrogen™ Invivofectamine™ Rx Early Access Program. Under this program, partners have the opportunity to:
  - Preview new and novel organ-specific lipid nanoparticles
  - Access materials and technical guidance to evaluate specific Invivofectamine Rx lipids for preclinical and clinical research
  - Receive commercial support to help meet your business objectives
- Upon completion of evaluation, we enable our partners' delivery needs through a long-term and mutually committed product supply, and licensing business framework.

invitrogen

Contact us at **outlicensing@thermofisher.com** to learn more and to discuss how we can address your delivery needs.

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