533 siRNA Delivery using Bioreducible Lipid-Like Nanoparticles

Asset Overview

Product Type	Gene therapy
Indication	Oncology
Current Stage	Discovery
Target(MoA)	Bioreducible lipid-like materials and negatively supercharged protein for effective protein delivery and genome editing
Brief Description	The therapeutic potential of protein-based genome editing is dependent on the delivery of proteins to appropriate intracellular targets. Here we report that combining bioreducible lipid nanoparticles and negatively supercharged Cre recombinase or anionic Cas9:single-guide (sg)RNA complexes drives the self-assembly of nanoparticles for potent protein delivery and genome editing. The design of bioreducible lipids facilitates the degradation of nanoparticles inside cells in response to the reductive intracellular environment, enhancing the endosome escape of protein.
Organization	Hopewell Therapeutics, Inc.

Differentiation

□ **A central challenge to the development of protein-based therapeutics**

- The inefficiency of delivery of protein cargo across the mammalian cell membrane, including escape from endosomes
- Toxicity and immunogenicity still represent a great hindrance for these novel class of therapeutics

□ **Bioreducible lipid nanoparticles**

- These complexes act as biodegradable gene nanocarriers by taking advantage of the acidic or strongly reductive environment that can be found within cells
- The integration of a bioreducible disulfide bond into lipids facilitates endosomal escape of nanoparticles containing protein cargo, enabling delivery into the nucleus for protein-based genome editing
- The leading bioreducible lipid can deliver mRNA and sgRNA while efficiently release them in response to the reductive intracellular environment

□ **Advantages of bioreducible lipids**

- Bioreducible lipids could efficiently reduce the toxicity and immunogenicity which still represent a great hindrance for these novel class of therapeutics
- They developed several Bioreducible lipid formulations that are efficient for *in vitro* and *in vivo* protein delivery

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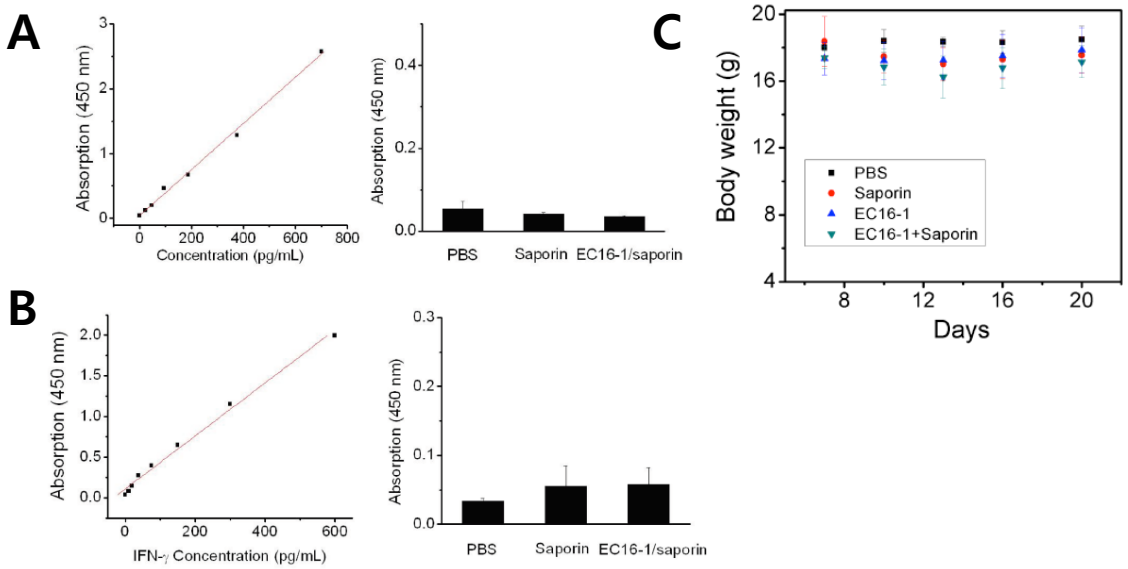
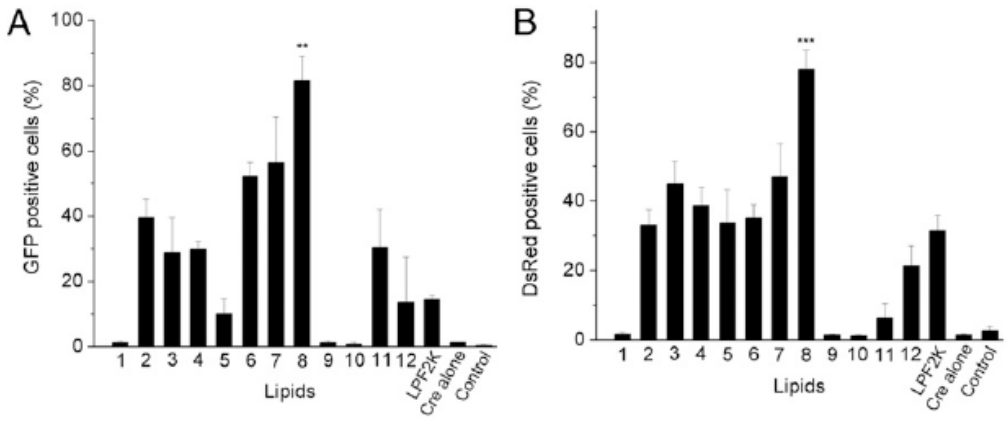
Key Data

Low immunogenicity and toxicity *in vivo*



TNF-α (A) and IFN-γ (B) concentration in the serum of Balb/c mice treated with PBS, free saporin and EC16-1(Bioreducible Lipid-Like Nanoparticles)/saporin nanoparticle formulation. The TNF-α and IFN-γ level was measured using the ELISA kits (R&D systems, MN). (C) Average mouse weight changes during the course of treatment with different saporin or EC16-1 nanoparticle formulation. 4T1-12B tumor bearing Balb/c mice were treated with EC16-1/saporin nanoparticle formulation, PBS, saporin, or EC16-1 controls.

Design of bioreducible lipid-like materials



Cellular uptake (A) and DsRed expression profile (B) of HeLa-DsRed cells treated with (–27)GFP-Cre alone or different lipid complexes. For the cellular uptake study, cells were treated with complexes of 25 nM protein and 2 μg/mL lipid for 6 h, and DsRed expression was quantified 24 h after delivery.

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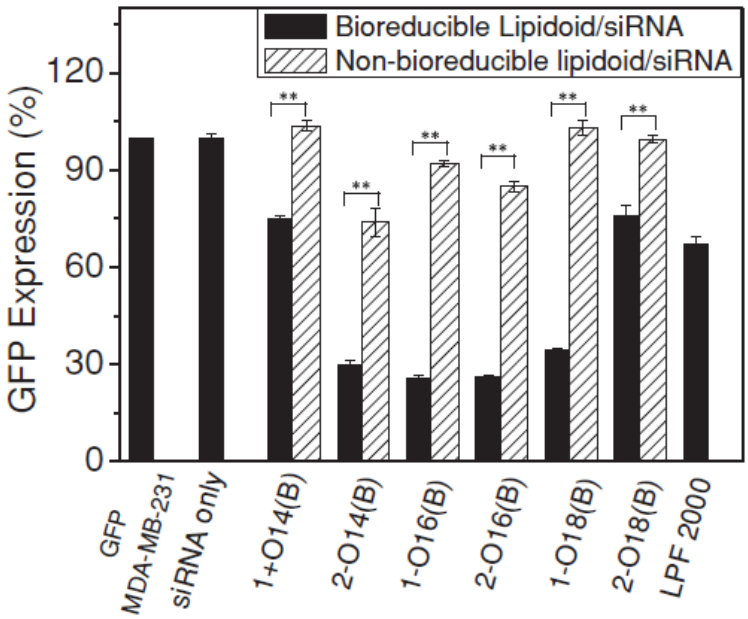
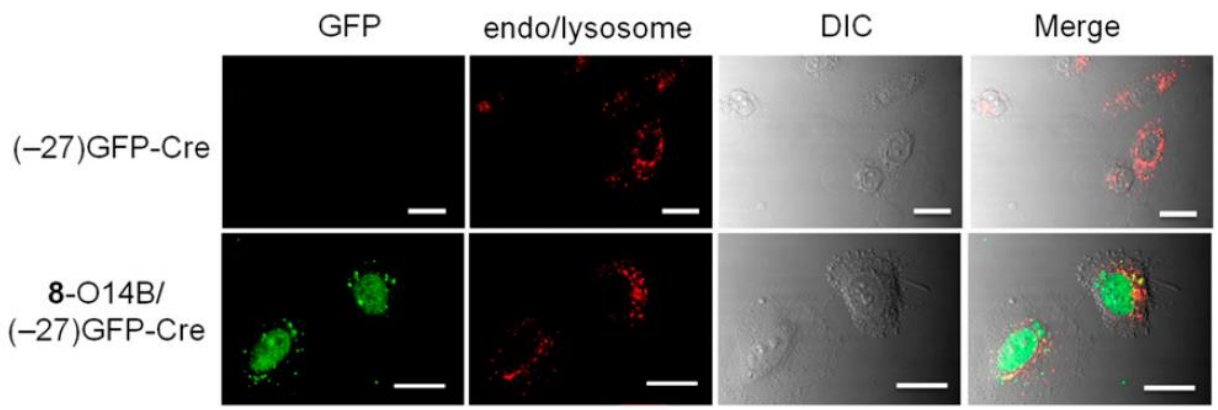
GFP expression of GFP-MDA-MB-231 cells



GFP expression of GFP-MDA-MB-231 cells treated with naked siGFP, lipidoid (Bioreducible Lipid-Like nanoparticles)/siGFP nanocomplexes, and Lipofectamine 2000 (LPF 2000)/siGFP complexes. The siRNA complexes were prepared by mixing siGFP (24 × 10−9 M) with lipidoids at N/P ratios of 5:1 or LPF2000 at weight/weight ratio of 6:1.

Endosome/Lysosome escape study



Treatment with 8-O14B(Bioreducible Lipid-Like nanoparticles)/(–27)GFP-Cre nanocomplexes (12.5 nM protein) showed significant accumulation of GFP fluorescence in the cytosol and nucleus, with a low level of colocalization with endosome/lysosome, indicating the efficient endosome escape of 8-O14B/(–27)GFP-Cre nanoparticles.

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

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