Polyrotaxane Nanoparticles for Delivery of Large Plasmid DNA in Duchenne Muscular Dystrophy

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SUMMARY

UCLA researchers have designed, synthesized, and validated a polyrotaxane nanocarrier for targeted delivery of large plasmids for gene therapy applications for treatment of Duchenne muscular dystrophy and cancer.

BACKGROUND

Rapid development of genome/epigenome approaches have the potential to correct disease related mutations and activate or suppress genes for therapy.However, achieving efficient and safe delivery of these genetic tools remains a key task. From the formulation perspective, large plasmid size is a major challenge that hinders for successful delivery in vivo.

This can be illustrated by the case of CRISPR/Cas9 technology, which is a groundbreaking tool for gene editing and holds potential for treatment of various diseases such as Duchenne muscular dystrophy and cancer. However, the technical challenges of applying the CRISPR/Cas9 therapy in vivo impede further development of this platform. Current gene editing therapies largely use viral-based delivery systems, which suffer from immunogenicity that prevents repetitive dosing, low uptake, poor bioavailability, and poor cell targeting and an inability to engineer them for cell specific targeting.

Custom design, synthesis, and characterization of a gene delivery system that facilitates targeted delivery of CRISPR gene therapy in vivo would allow for systemic treatment of these diseases. Moreover, availability of a carriercapable of large plasmid delivery would represent a platform discovery that is useful for a range of plasmid based therapeutic candidates.

INNOVATION

The inventors have designed and synthesized a nanoparticle delivery system whose properties can be modulated via controlled synthesis. This allows for a number of tunable properties, including particle size, loading capacity, release profile, interactions with nucleotides, and bioclevable linkers that are responsive to different external stimuli. This system allows for targeted gene delivery and controlled intracellular release of cargo.

The inventors have demonstrated the use of this system for effective delivery and transfection of targeted muscle cells and various cancer cells with various plasmids (e.g. reporter and CRISPR/Cas9 plasmid). The delivery system also leads to in vivo efficiency in various mouse models.

APPLICATIONS

- Delivery of large plasmids *in vivo*
- Targeted delivery of the CRISPR plasmid to skeletal muscles
- Cancer gene therapy

ADVANTAGES

- Highly bio-compatible materials
- Controllable intracellular release features
- Modulation of properties via synthesis
- Non-viral delivery method

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OTHER INFORMATION

KEYWORDS

gene editing, gene delivery, gene therapy, non-viral gene delivery, polyrotaxane nanoparticle, Duchenne muscular dystrophy, genetic disease, cancer gene therapy

CATEGORIZED AS

- **Materials & Chemicals**
  - Nanomaterials
  - Polymers
- **Medical**
  - Delivery Systems
  - Disease: Cancer
  - Disease: Genetic Diseases and Dysmorphic Syndromes
  - Disease: Musculoskeletal Disorders
  - Gene Therapy
- **Nanotechnology**
  - NanoBio

RELATED CASES

2017-701-0

STATE OF DEVELOPMENT

The inventors have demonstrated effective delivery and transfection of CRISPR plasmid DNA by the synthesized nanocarriers into muscle cells and cancer cells *in vitro*. The nanoparticle system has also been systemically delivered to mouse muscle cells *in vivo* by intravenous injection and showed some dystrophin protein restoration.

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	11,779,653	10/10/2023	2017-701

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