Read-Through Compound Prodrugs Suppressing Premature Nonsense Mutations

Tech ID: 24094 / UC Case 2013-576-0

SUMMARY

UCLA researchers in the Department of Neurology have identified a novel prodrug to enhance the aqueous solubility of RTC13 for the treatment of Duchenne Muscular Dystrophy and other genetic disorders caused by nonsense mutations.

BACKGROUND

Nearly 30% of genetic disorders including Duchenne Muscular Dystrophy (DMD) are caused by nonsense mutations that result in nonfunctional proteins. Compounds that override the premature termination signal to promote the synthesis of full-length proteins provide great therapeutic potential for the treatment of many genetic disorders. Recent advances have been made with the newly identified read through compound (RTC13), which has demonstrated therapeutic function in the mdx mouse model of DMD. However, the poor water solubility and low absorption rate of RTC13 greatly limits its clinical application. The identification of a prodrug capable of enhancing RTC13 solubility for oral, subcutaneous or intravenous administration, would greatly improve therapeutic outcomes for genetic diseases caused by nonsense mutations.

INNOVATION

UCLA researchers in the Department of Neurology have identified a novel prodrug that increases aqueous solubility to promote full-length protein synthesis in mdx. Luciferase-independent high throughput screens of approximately 34,000 compounds were utilized to identify RTC13. Systemic administration of RTC13 conferred increased muscle strength paralleled by a reduction in expression levels of a marker for muscle degeneration, creatine kinase. The newly generated prodrug is suitable for administration in mammals and provides a platform to support *in vivo*, toxicology and safety studies required to advance RTC13 toward clinical evaluation.

APPLICATIONS

Therapeutic treatment for Duchenne Muscular Dystrophy and other genetic diseases caused by

nonsense mutations.

ADVANTAGES

- The present technology has been shown to regenerate RTC13 under *in vitro* and *in vivo* biological environments, conferring prodrug properties.
- The present technology can be administered orally (preferred route), or by other means including, but not limited to, intravenous, intraperitoneal and subcutaneous.

STATE OF DEVELOPMENT

- Dystrophin protein was detected in all muscle groups analyzed, including the diaphragm and heart – two of the muscles most difficult to target by current therapeutic approaches.
- Intramuscular injection of the prodrug resulted in widespread expression of dystrophin into muscle, demonstrating its biological activity in vivo.
- Several prodrug structures have been generated – four of which were tested in vitro in the presence of total liver protein extract to determine the rate of conversion of the prodrug into its parent compound (RTC13).
- A preferred prodrug derivative has been identified and dosed to mice for determination of pharmacokinetic and tissue exposure data.

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OTHER INFORMATION

KEYWORDS

Nonsense mutation, prodrug, Duchenne Muscular Dystrophy, mdx, genetic diseases

CATEGORIZED AS

- **Materials & Chemicals**
  - Biological
- **Medical**
  - Disease: Central Nervous System
  - Gene Therapy
  - Other
  - Research Tools

RELATED CASES

2013-576-0

▶ Dosing for demonstration of efficacy in the mdx mice is currently underway.

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	10,287,283	05/14/2019	2013-576
United States Of America	Issued Patent	10,077,260	09/18/2018	2013-576

RELATED MATERIALS

▶ Kayali R1, Ku JM, Khitrov G, Jung ME, Prikhodko O, Bertoni C. Read-through compound 13 restores dystrophin expression and improves muscle function in the mdx mouse model for Duchenne muscular dystrophy. Hum Mol Genet. 2012 Sep 15;21(18):4007-20.

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