

RNA Therapeutics for Diseases Caused by Nonsense Mutations

A method to suppress premature translation termination and NMD to generate full-length protein using target-specific guide RNAs.

Problem Solved by This Technology

A disease-modifying therapy for conditions caused by nonsense mutations, such as Duchenne or Becker muscular dystrophies and cystic fibrosis has long been sought, but to date, none has been found. A few therapies at various clinical phases of development either address the already-mutated RNA, or simply ameliorate the symptoms of the diseases. This invention is aimed to generate functional full length mRNAs and subsequently proteins to provide a cure for the diseases.

Applications

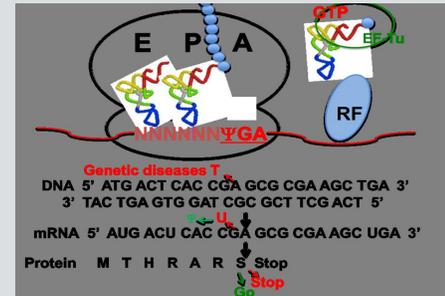
Researchers at the University of Rochester have developed a method for the site-specific conversion of a target uridine within an RNA chain into a pseudouridine through the introduction of a target-specific guide RNA into the cells. Guide RNAs can be conveniently designed and remain stable *in vivo* throughout the lifetime of the cells. Remarkably, uridine-to-pseudouridine conversion at a pre-mature stop codon of an mRNA results in NMD (nonsense-mediated mRNA decay) suppression and stop codon read-through (aka nonsense suppression), and consequently, synthesis of the full-length protein is restored. This approach can therefore be applied to diseases that are caused by nonsense mutations (e.g., some Duchenne muscular dystrophy patients bearing a nonsense mutation in the dystrophin gene, and some cystic fibrosis patients who have a nonsense mutation in the CFTR gene).

Publications

Chen, C., Zhao, X., Kierzek, R. and Yu, Y.-T. (2010) "A flexible RNA backbone within the polypyrimidine tract is required for U2AF65 binding and pre-mRNA splicing *in vivo*." *Mol Cell Biol.* 30, 4108-19. PMID: 20606010. Karijolich, J. and Yu, Y.-T. (2011) "Converting nonsense codons into sense codons by targeted pseudouridylation." *Nature*, 474, 395 - 398.

Fernandez, I. S., Ng, C. L., Kelley, A. C., Wu, G., Yu, Y.-T. and Ramakrishnan, V. (2013) "Unusual base pairing during the recoding of a stop codon containing pseudouridine." *Nature*, 500, 107-110.

URV Reference Number
6-1446



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Intellectual Property Status

U.S. Patent number **8,603,457**
Nonsense Suppression and Genetic Codon Alteration by Targeted Modification issued 10 December 2013.

U.S. Patent number **9,238,813**
Targeted Pre-mRNA/mRNA Modification and Gene Regulation issued 19 January 2016.

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