



Weill Cornell Medicine

Switchable mRNAs with Enhanced Translational Efficiency for Tissue-Specific Expression

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Background & Unmet Need

- mRNA-based drugs provide a promising alternative for gene replacement in a broad range of diseases
- However, prolonged protein abundance following mRNA translation remains a major challenge for mRNA therapeutics, especially in highly metabolic tissues such as the liver
- The 5'-untranslated region (5'-UTR), located upstream of the coding region of a messenger RNA, plays a pivotal role in gene expression
- Large secondary structures, such as stem-loops, located upstream of the initiation codon may inhibit translation initiation by blocking cap-dependent ribosome entry
- MicroRNAs are regulatory small RNAs that bind to target mRNAs, some of which are expressed in a cell or tissue-dependent manner
- **Unmet Need:** Methods of enhancing mRNA expression in a tissue-specific manner, especially in metabolic tissues

Technology Overview

- **The Technology:** A novel design strategy for functionally switchable mRNAs that allow for tissue and cell-specific expression
- MicroRNA binding elements are incorporated in the 5'-UTR, which respond to endogenous microRNAs
- Upon binding to microRNAs, the secondary structure of the mRNA unwinds into to a linear conformation, switching mRNAs from an 'off' to an 'on' state
- The linearized conformation of the mRNA promotes translation initiation only in cells and tissues which contains the endogenous microRNA
- **PoC Data:** A miR-148-dependent LDLR-coding mRNA was constructed (miR-148 is a liver enriched microRNA)
- Treatment with switchable LDLR mRNA significantly reduced non-HDL cholesterol levels compared to generic LDLR mRNAs in severely hypercholesteremic male LDLR knockout mice

Inventors:

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Patents:

[PCT Application Filed](#)

US Application Filed

Publications:

N/A

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Technology Applications

- Targeted mRNA gene therapy for treatment of familial hypercholesterolemia or dyslipidemia
- Targeted mRNA gene therapy for other diseases caused by loss of function gene variants or which may be improved by tissue-specific gene expression
- Improved targeting of existing mRNA gene therapies

Technology Advantages

- Allows for tissue-specific translation of mRNAs
- Improves mRNA stability and translation in cells
- mRNA regulatory elements are easily incorporated into mRNA design

Supporting Data / Figures

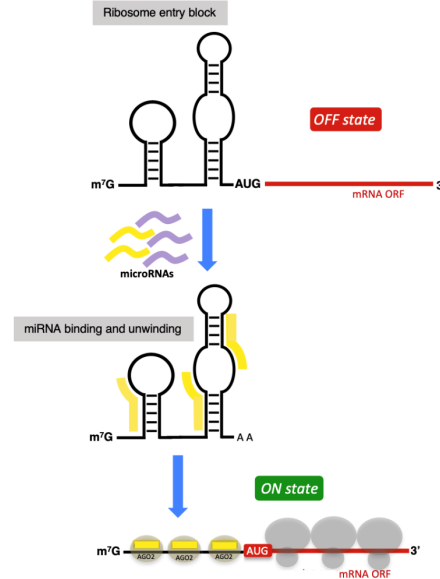


Figure 1: Schematic representation of proposed mechanism of microRNA-mediated regulation of mRNA constructs.

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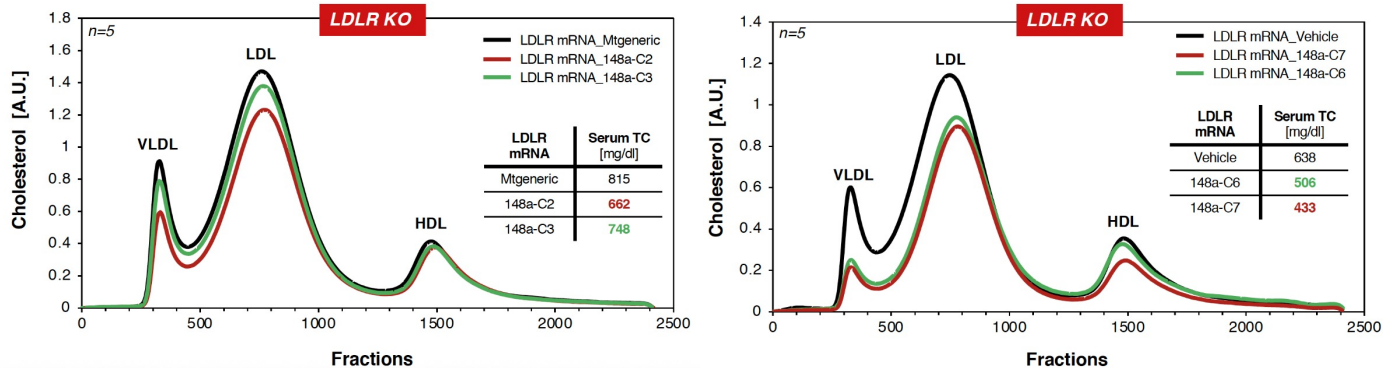


Figure 2: Injection of mRNA constructs incorporating miR-148 binding sites reduced non-HDL cholesterol levels in male (Left) and female (Right) LDLR knockout mice.

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