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Synthesis of RNAs Containing Methylated Adenosine Residues and Their Use in Enhancing Translation

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Background & Unmet Need

- Several diseases are associated with abnormalities in translation initiation or reduced protein production from specific mRNAs, including cancer and viral infection
- Gene therapies can also be limited by low levels of translation of therapeutic products
- Protein translation typically begins with the recruitment of the 43S ribosomal complex to the 5' cap of mRNAs by a cap-binding complex
- Some transcripts are translated in a cap-independent manner through poorly understood mechanisms
- **Unmet Need:** Methods to enhance mRNA translation and protein production for basic research and therapeutic applications

Technology Overview

- **The Technology:** A method for enhancing mRNA translation by incorporating N6-methyladenosine (m6A) in the 5' UTR
- **The Discovery:** m6A is a reversible base modification seen in the 5' UTR of many eukaryotic mRNAs which functions as an alternative to the 5' cap to stimulate mRNA translation
- m6A can be incorporated in this position by including an adenosine methylation motif in the 5' UTR
- m6A can then bind eukaryotic initiation factor 3 (eIF3), which is sufficient to recruit the 43S complex to initiate translation in the absence of the cap-binding factor eIF4E
- **PoC Data:** In the absence of eIF4E, m6A is sufficient to initiate translation in uncapped mRNA ($p<0.01$)
- Induction of cellular stress via heat shock increases cellular expression of mRNAs containing m6A in the 5'UTR

Inventors:
Samie Jaffrey
Kate Meyer

Patents:
US Patent 10,584,343

Publications:
Meyer et al. *Cell*. 2015.

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Technology Applications

- Kits to enhance protein yields in *in vitro* protein synthesis reactions
- Increased protein production for *in vivo* applications, such as gene therapy
- Enhanced mRNA translation for the treatment of diseases like cancer or viral infection

Technology Advantages

- Translation is independent of the 5’ cap or cap-binding proteins, allowing use in conditions wherein cap-dependent translation is suppressed
- Translation requires only a single m6A or other form of methyladenosine to be present within the 5’UTR, rather than multiple nucleotides throughout the transcript

Supporting Data / Figures

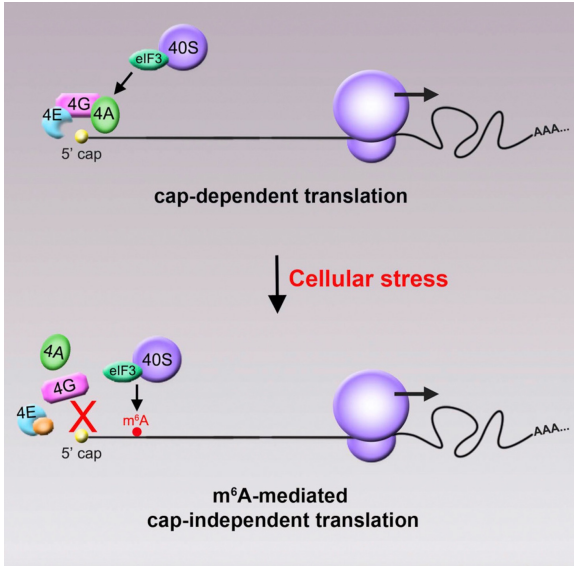

Figure 1: Graphical abstract depicting how m6a mediates cap-independent translation.

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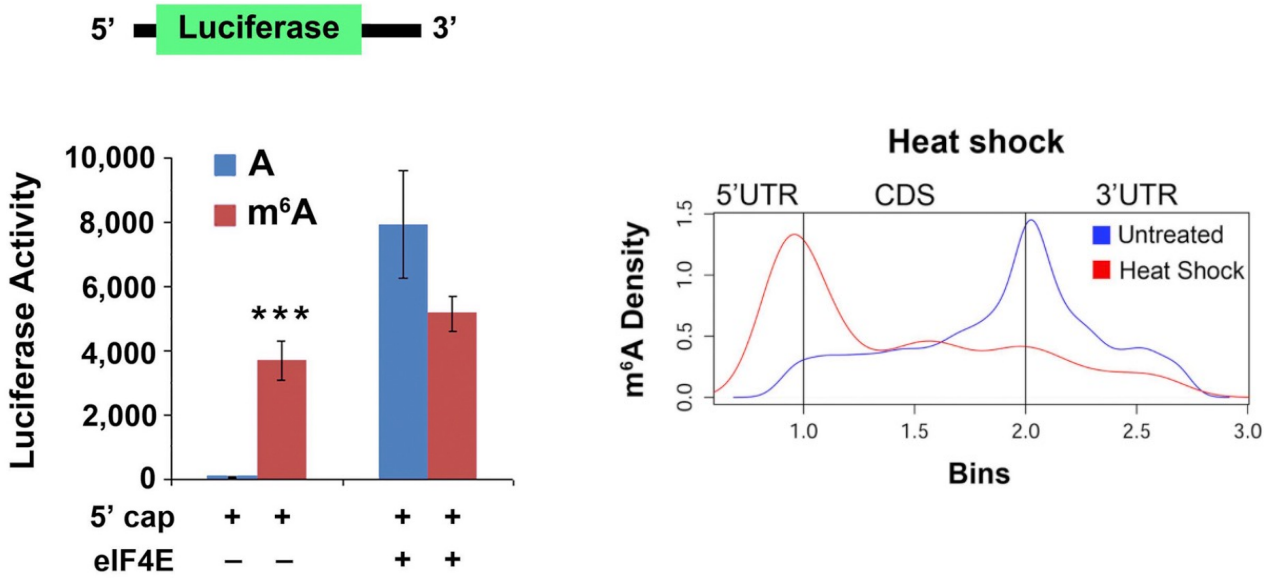

Figure 1: Left: m6A in the 5’ UTR is sufficient to induce translation in the absence of eIF4E **Right:** Heat shock increases cellular expression of mRNAs with 5’ UTR m6As.

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