A novel gene design method boosts recombinant protein translation:

Efficient recombinant protein production in heterologous systems

Project Number: 1546	
Principal Investigator:	Prof. Tzahi Pilpel
Patent Status:Pending	

Overview

A novel gene design method to achieve optimal, jam-free heterologous protein translation, offering a cost-effective mechanism to significantly increase production yield.

Background and Unmet Need

Biomedical research and biotechnological production processes rely on successful heterologous gene expression for the development of recombinant proteins as key reagents and biomolecules. One of the primary challenges in heterologous gene expression is adaptation of the coding sequence to the optimal codon usage in the host organism. **Common strategies for "codon optimization" do not take into account the burden that is imposed on the cell as a result of protein over-expression.** Therefore, a tunable expression system is required, which would increase translation efficiency and thus productivity of expression, while minimizing the costs to the host system.

The innovative concepts of the outlined method rely on an evolutionary conserved translation profile, which increase recombinant protein expression while reducing burdens .that are associated with uncontrolled translation, ultimately boosting production

The Innovation

The team led by Prof. Pilpel have discovered an evolutionarily conserved mechanism that governs the efficiency of protein translation: an approximately 30 codon long region at the 5' end of the gene with about two-fold lower rate of translation compared to the rest of the gene. This feature is implemented into codon usage design enabling control of translation dynamics and is predicted to reduce the costs of translation, thus increasing protein production yields.

Technology Essence:

Prof. Pilpel's team have discovered a common feature in the sequence of highly expressed genes across evolution. The first 30-50 codons at the 5'-end of these genes are characterized by codons using relatively rare tRNA molecules, corresponding to reduced translation speed. This region was found to serve as a 'ramp' for ribosomal passage upon the translating transcript. By reducing the translation speed of the first 30-50 amino acids of the translated gene we can effectively control the amount of ribosomes on the gene attenuating the possibility of having the ribosomes too closely spaced causing them to jam and, potentially abort translation (Figure 1).

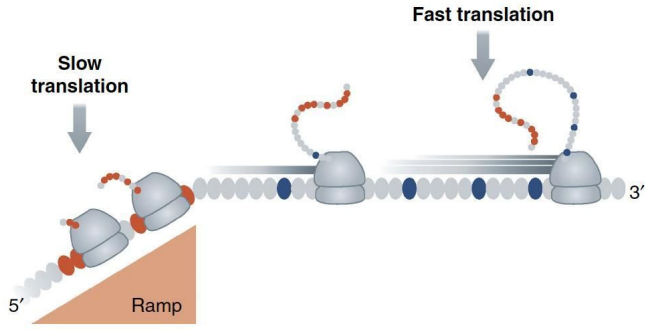

Figure1: A design of high (blue) and low (orange) efficiency codons to achieve an optimal schedule for ribosomal flow on transcripts.

By simply calculating the translation efficiency profile of a sequence of interest in a given host, an artificial ramp region can be designed to optimize translation dynamics and improve protein production yields.

Advantages and Applications

- Increased protein expression with **reduced cost** to the host cell, leading **to efficient production and high yield**.
- **Applicable with a variety of production systems**. Since the modification is at the level of the sequence, it is both cost effective, can be customized for each expression system, and can be used in a combination with any downstream processing step.
- Efficient heterologous protein production.

Development Status

A library of synthetic constructs in *E. coli* was analyzed and shown that the extent of variants obedience to the ramping design correlates significantly with protein abundance and growth rate, telltale of a cost-effective production. This research was published in the prestigious journal Cell[1]**.**

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[1] Tuller, Tamir, Asaf Carmi, Kalin Vestsigian, Sivan Navon, Yuval Dorfan, John Zaborske, Tao Pan, Orna Dahan, Itay Furman, and Yitzhak Pilpel. "An evolutionarily conserved mechanism for controlling the efficiency of protein translation." *Cell* 141, no. 2 (2010): 344-354.