Force-Profile Analysis to study the co-translational folding of Firefly Luciferase

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Proper protein folding is crucial to the function of proteins. On the other hand, protein misfolding can lead to various serious diseases such as Alzheimer's and Parkinson's. However, our understanding of protein folding primarily comes from research on small, single-domain proteins, and much less work has been done on larger, multidomain proteins.

Multidomain proteins can undergo co-translational folding, a process where different domains start to fold into their native conformations as soon as they emerge from the peptide exit tunnel of the ribosome during translation. The co-translational folding of multidomain proteins adds another layer of complexity to the folding process, as it involves the simultaneous synthesis and folding of multiple structural units with a single polypeptide chain. Firefly Luciferase (Fluc), a widely studied bioluminescent protein, serves as a prominent illustration for the class of large proteins and is an ideal model system for investigating the co-translational folding of multidomain proteins. From previous studies, it is known that Firefly luciferase N-terminal subdomain folds co-translationally [1], [2]. Here, we aim to elucidate the co-translational folding of firefly luciferase using force-profile analysis, an experimental approach used to explore the folding pathways of proteins by following oscillations in the mechanical force that co-translational folding exerts on the nascent chain. The project aims to enlighten our knowledge about the folding patterns that large and multidomain proteins, like Fluc, follow during translation.

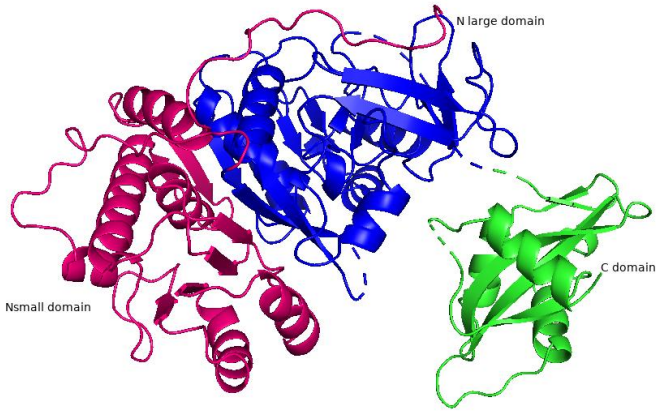

Figure 1. Representation of the domains of FLuc. In magenta colour is the N-small subdomain, in blue colour is the N-large subdomain, and in green is the C-terminal domain. (Generated using the program PyMol).

References:

1. Frydman J., Erdjument-Bromage H. , Tempst P. , Hartl, F. Ulrich. 1999. Co-translational domain folding as the structural basis for the rapid de novo folding of firefly luciferase. *Nature Structural Biology*. **6**:697-705.
2. Svetlov MS, Kommer A, Kolb VA, Spirin AS. 2006. Effective cotranslational folding of firefly luciferase without chaperones of the Hsp70 family. *Protein Sci.* **15**:242-247.