



An *in Vivo* Method to Measure Protein Stability

Improving drug efficacy and half-lives through stability

Significant growth in the field of protein-based therapeutics is best exemplified by the billion dollar protein-based drugs that biotechnology companies Amgen and Genentech have produced and sold in the past 10 years. Both companies are profitable due to sales of protein growth factors [e.g., **EPOGEN®** (Epoetin alfa) and **NEUPOGEN®** (Filgrastim)] and monoclonal antibodies directed against various forms of human cancers [e.g., **HERCEPTIN®** (Trastuzumab) and **RITUXAN®** (Rituximab)]. An

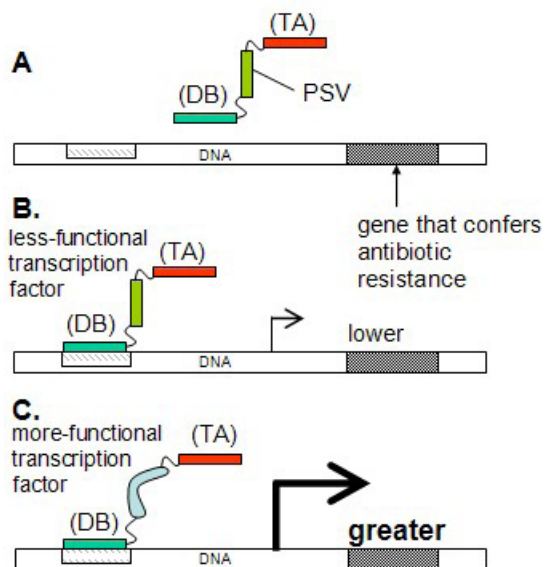
important biophysical parameter that is directly correlated to the efficacy of these protein-based drugs is protein stability.

It is possible to mutate protein-based drugs such that they retain their functional structure and also possess a higher degree of stability. A protein-based drug of higher stability would be less prone to aggregation and therefore would be handled more easily and have a longer shelf life. In addition, a more

stable protein-based drug would potentially be cleared from the body less readily and therefore a lower dose may be administered less frequently. This would save biotechnology companies money in production costs and, because fewer injections would be needed, the risk of infection would also be significantly reduced.

are directly correlated to the expression of a reporter gene expressed in host bacteria (e.g., *E. coli*). This allows for the measurement of the variant's stability based on the differential ability of the bacteria to survive on plates that contain antibiotic.

This technology has applications in both drug development and basic research because it allows scientists to select for *in vivo* stability of a focus protein while maintaining the functional structure.



Advantages

- Selects for *in vivo* protein stability
- Simple to use, with an established base technology
- Low-cost method of evaluating protein stability

Applications

- Improved half-lives of protein-based drugs
- Less frequent drug dosing
- Longer shelf-lives for drug stockpiles

Dr. John Love has successfully engineered an *in vivo* method in which physical parameters of a test protein (thermal stability and conformational specificity)

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