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Mini Review **Open Access**

Genetic Approach To The Construction of A Controllable Phage Display Platform For Use In Optimized Therapeutic Development

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Bacteriophage Lambda (λ) has played an historical role as an essential tool in our current understanding of molecular genetics. It's major capsid protein gpD occurs on each capid at 405 to 420 copies per phage in homotrimeric form and functions to stabilize the head and likely to compact the genomic DNA. Th e interesting conformation of this protein allows for its exploitation through the genetic fusion of peptides or proteins to either the amino or carboxy terminal end, while retaining phage assembly and viability. We endeavoured to design and construct a highly controllable head decoration system governed by two genetic conditional regulation systems; temperature sensitive repressor expression and bacterial conditional amber mutation suppression. We have sequenced an historical amber mutant of D identifying the position of the stop codon, and employing this mutant in combination with our cellular and plasmid constructs, we will endeavour to measure the decoration of the capsid by a D::gfp fusion under varying conditions. Th is controllable system has the ability to establish a variable number of fusions per phage based on genetic and physical environment without compromising viability.This approach has important implications in the design of new therapeutics in which steric hindrance and avidity are important concerns. To this end we have applied this process innovation and are in the process of testing, toward the development and optimization of new Alzheimer's Disease therapeutic vaccines, S. aureus, M. tuberculosis and P. acnes antibacterials.

A high Therapeutic Index (TI) is preferable for a drug to have a favorable safety profile. At early discovery / development stage, the clinical TI of a drug candidate is not known. However, understanding the preliminary TI of a drug candidate is of utmost importance as early as possible since TI is an important indicator of the probability of the successful development of a drug. Recognizing drug candidates with potentially suboptimal TI at earliest possible stage helps to initiate mitigation or potentially re-deploy resources.

In a drug development setting, TI is the quantitative relationship between efficacy (pharmacology) and safety (toxicology), without considering the nature of pharmacological or toxicological endpoints themselves. However, to convert a calculated TI to something that is more than just a number, the nature and limitations of pharmacological and/or toxicological endpoints must be considered. Depending on the intended clinical indication, the associated unmet medical need and/or the competitive situation, more or less weight can be given to either the safety or efficacy of a drug candidate with the aim to create a well balanced indication-specific safety vs efficacy profile.

In general, it is the exposure of a given tissue to drug (i.e. drug concentration over time), rather than dose, that drives the pharmacological and toxicological effects. For example, at the same dose there may be marked inter-individual variability in exposure due to polymorphisms in metabolism, DDIs or differences in body weight or environmental factors. These considerations emphasize the importance of using exposure rather than dose for calculating TI. To account for delays between exposure and toxicity, the TI for toxicities that occur after multiple dose administrations should be calculated using the exposure to drug at steady state rather than after administration of a single dose.

A review published by Muller and Milton in Nature Reviews Drug Discovery critically discusses the various aspects of TI determination and interpretation in a translational drug development setting for both small molecules and biotherapeutics