Translation Regulated (TR)-Mediated Gene Expression: Novel Expression and Reporter Vectors

Published date: Aug. 14, 2013

Technology description

Background:
Often referred to as the crucial "drug discovery tool", cell based technology is one of the most significant sectors of pharmaceutical research and development. Of particular importance has been the development of information-rich cellular assays that determine drug candidate efficacy and safety (target identification, validation & predictive toxicity). Since longterm toxicity is the major cause of late-stage clinical trial failures and post-market withdrawals, the use of drug safety assays to model toxicity is increasing during early drug development efforts. However, existing technology is incapable of defining minor nontherapeutic activities that produce tolerable short-term side-effects but evolve into long-term toxic responses. Accepting that improved lead selection and optimization decisions will require new technology that can predict all cell toxicity, a novel cell based assay was developed that quantifies a universal cell Recovery process exhibited by all cells. Blinded studies show that the molecular target of this validated assay can predict acute and chronic toxicity produced by mono- and combinatorial drug formulations. Subsequent efforts defined biologically active compounds and formulations capable of enhancing or blocking this cell Recovery process. Furthermore, in vivo investigations verified that the cell Recovery response is a therapeutic target for treating metastatic cancer.
Technology
When exposed to acute, reversible stress (such as transient hypoxia, heat shock or nutrient depletion), cells immediately respond by blocking the synthesis of non-essential steady state proteins. In the vast majority of situations, normal or differentiated cells recover by transitioning to the synthesis of stress-specific Recovery proteins (such as anti-apoptotic growth factors, cytokines, heat shock proteins, and hypoxia regulatory proteins) that prevent cell death. This novel synthetic process has been termed Selective Translation or (SET). The Translation Regulated (TR) technology is based upon a human gene sequence that is only translated by stressed cells during Recovery protein synthesis. Changes in TR SET expression provides a particularly powerful metric for measuring the onset and magnitude of the cell Recovery process. During development of the TR cell library, it has been observed that SET affective treatments (drugs and cell culture conditions) induced cell-specific SET responses that were subsequently shown to correlate with pathologically defined Tumor cell Grades. In particular, these SET responses provide a simple tool for identifying and purifying highly desirable metastatic cancer cells, in

which a maximal SET Recovery response correlates with elevated drug resistance. Subsequent compound library screening identified bioactive compounds capable of activating or blocking SET protein synthesis. Using the known toxicity profile for each drug, a strong correlation was found between specific translational responses and increased levels of in vitro/in vivo toxicity. Of particular interest is the ability of the rapid TR SET assays to detect the onset of cell death much earlier than standard toxicology markers.

Application area

Translation-based assays exemplified by the TR SET technology provide significant advantage for predicting graded toxicity, as well as defining previously unknown correlations between drug action and protein synthesis. The power of this simple, rapid, cheap assay and the associated novel cancer cell models for improving the drug development process is obvious.

Advantages

Strong cost and time savings

Institution

Wayne State University

Inventors

Leon Carlock
Associate Professor
Center for Molecular Medicine & Genetics
Maria Cypher
Part-time Faculty
Center for Molecular Medicine & Genetics

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com