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A Historical Perspective for the Development of Mechanistic-Based 3D Models of Toxicology Using Human Adult Stem Cells

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Abstract

THREE-DIMENSIONAL HUMAN STEM CELL "ORGANOIDS" IN VITRO AND IN VIVO AS A FUTURE GOAL FOR PREDICTIVE TOXICOLOGY Given the classical approach to use animals as sentinels for human toxicities and their related pathologies, as well as for drug discovery, and epidemiology to identify potential population causes of various diseases, both have served under the circumstances of many limitations (Trosko and Upham, 2005,2010) to provide toxicologists with valuable insights. However, given well-known limitations (eg, costs, time, lack of mechanistic insights, etc.) the report on "Toxicity Testing in the 21st Century: A Vision and a Strategy National Research Council" (National Research Council, 2007) suggested newer approaches will be necessary. Concurrent with those classical bapproaches, in vitro use of normal primary, immortal or cancer cells, (microbial, animal, plant), grown in suspension or 2D has, in turn, been used to provide some useful scientific information, but, again, without the type of "precision" required for individual prediction of pathological outcomes in human beings (developmental stage; gender, organ-specificity, unique genetic predispositions, or the unique pathogenesis outcome), there will continue to be misleading or incomplete information derived from these approached.

Biography

The Trosko lab focused on the mechanisms of carcinogenesis and mutagenesis. His initial research involved the study of radiation-induced mammalian mutagenesis. This led to the discovery of deoxyribonucleic acid (DNA) repair in normal human cells and the lack of DNA repair and increased mutagenesis in the cancer-prone xeroderma pigmentosum syndrome. Later work with the tumor promoter, phorbolester, he discovered that the inhibition by tumor-promoting chemicals, oncogenes and growth factors were related to the mechanism of tumor promotion by their shared ability to modulate gap junction function. Most recently, his group demonstrated that normal human epithelial stem cells could be isolated from kidney tissues and breast tissues. In addition, anti-tumor chemicals, as well as tumor suppressor genes appear to up-regulate GJIC in a manner opposite to tumor promoters and oncogenes. He has recently discovered biomarkers for adult human stem cells that has provided strong evidence for the "stem cell theory" of cancer.

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