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MMST THESIS ABSTRACT

Development of PET tracer-reporter gene system for non-invasive monitoring of gene therapy

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The therapy of human diseases utilizing the powerful tools of modern cellular and molecular biology and gene technology is one of the highly intellectual and technical challenges faced by modern medicine. It is believed that cellular and gene therapy will play a major role in treatment of many and very common diseases that are difficult to be treated by conventional medicine. Since 1990, when the first clinical trials for gene therapy was carried out to combat few previously untreatable disorders such as Cystic Fibrosis, Severe Combined Immuno deficiency syndrome, there is continuous and sustained efforts in making this novel therapy for the benefits of many genetic and non-genetic conditions. The vast potential of gene therapy as a therapeutic modality has been well recognized as addressed in Sixth Annual Meeting of American Society of Gene Therapy held in June 2003. These increments in applications of gene therapy has evoked the necessity of efficient monitoring and evaluation systems to aim successful and targeted treatment of various genetic and acquired disorders. There is remarkable progress over the last decade in non-invasive imaging of Gene expression and Gene therapy with the development of new reporter gene expressing vector constructs and appropriate PET imaging probes. This is heralded by few successful PET reporter gene/probe pairs such as HSV-tk/FIAU, D2 receptor/FESP, Sodium Iodide symporter/ Iodide and so on. Research is in continuum to identify new such successful reporter gene-imaging probe pairs. This study intends to present the development of a therapeutic and a new reporter gene co-expressing plasmid and an adenoviral vector constructs with their preliminary experimental data obtained from cell culture and animal models.
The therapeutic gene model used is Human Thymidine Phosphorylase (hTP), which is similar to VEGF that promotes Angiogenesis. The reporter gene is Human Estrogen receptor ligand binding domain (hERL). The PET imaging probe is ^{18}F-Fluoroestradiol, for which the safety profile for use in humans is confirmed. However, for initial studies in vitro, we tested the efficiency of vector expressed reporter protein specificity with ^{3}H-Estradiol as radioligand. Gene expression analysis from the viral construct for the reporter and therapeutic proteins in cell culture model were assessed and compared with that of the plasmid construct. Considering the positive results in cell model, transition to animal model is expected to yield promising results, the success of which can lead a step forward for evaluation in clinical trials.