Ramasamy Paulmurugan, J Stem Cell Res Ther 2017, 7:3(Suppl)
http://dx.doi.org/10.4172/2157-7633.C1.023

Novel combinatorial approach with multiple therapeutic genes and clinically feasible gene delivery method improves cancer gene therapy in pre-clinical animal model

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Triple Negative Breast Cancer (TNBC) is highly metastatic, and an obdurate cancer subtype that is not amenable to current chemotherapy regimens used in the clinic. Palliative chemotherapy with a combination of cyclophosphamide, paclitaxel, and cisplatin or carboplatin and doxorubicin is the only option currently available for treating patients with advanced stage metastatic TNBC. The use of high doses of chemotherapeutics often leads to the development of drug resistant cancer, and also can result in severe systemic toxicity. Gene-Directed Enzyme Prodrug Therapy (GDEPT) is a superior gene therapy method for treating cancers, proven to be effective against many sub-types of cancers, and is currently in various stages of clinical trials. Gene therapy utilizing a single enzyme/prodrug combination targeting a single cellular mechanism requires a significant level of overexpression of delivered therapeutic transgene in order to accomplish therapeutic response. Hence, to overcome this obstacle, we developed molecularly targeted multi-gene therapeutic system in combination with a clinically feasible delivery mechanism, which, when delivered targets several cellular mechanisms to kill cancer cells while simultaneously reprogramming cancer cells to evade from treatment response and in developing drug-resistant phenotypes. In addition, the genes that we use are holding the property of monitoring by noninvasive molecular imaging, which facilitates the monitoring the expression level of therapeutic genes in living animals to correlate with the therapeutic outcome. Moreover, target specific delivery and expression of therapeutic genes to cancer cells is another challenging task, which limits the efficiency of gene therapy. Hence, we are currently combining cancer specific expression of molecularly targeted multilevel therapeutic genes delivered by a minimally toxic nanoformulation, which efficiently deliver DNA for cancer gene therapy *in vivo*. This strategy will lead to a new generation of gene therapy system in combination with an efficient gene delivery system, which would change current treatment strategy for triple negative breast cancer, and can lead to a paradigm shift in cancer gene therapy.

Biography

Ramasamy Paulmurugan is an Associate Professor in the Department of Radiology, Stanford University School of Medicine, Stanford, California, USA. He finished his Master's in Biomedical Genetics from University of Madras, Chennai, India in 1991. In 1997, he earned his PhD degree in Molecular Virology from National Environmental Engineering Research Institute (under University of Madras, Chennai, India). After serving as Scientist for four years in Rajiv Gandhi Center for Biotechnology, Trivandrum, India, he joined University of California at Los Angeles as Visiting Scientist in 2001. In 2003, he joined Stanford University as Senior Research Scientist to work under Molecular Imaging Program at Stanford University. Since 2009, he is an Academic Faculty in the Department of Radiology at Stanford University. Currently his lab is working on developing *in vivo* molecular imaging assays to noninvasively monitor different epigenetic process in live animals. His lab is also working on developing novel molecularly targeted therapies (microRNA and gene therapy) for various cancers, such as breast, hepatocellular carcinoma and glioma.

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