J Stem Cell Res Ther 2017, 7:3(Suppl)
http://dx.doi.org/10.4172/2157-7633.C1.024

6th International Conference and Exhibition on

Cell and Gene Therapy

March 27-28, 2017 Madrid, Spain

Clinical proof of the safety and efficacy of a new method delivering Ad5FGF-4 to patients with refractory angina

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One of the main hurdles of effective gene therapy is delivery of the product. We have developed a practical method of intracoronary artery infusion of Ad5 vector in pigs based on observations that both short term ischemia and nitric oxide augment Ad5 transfection in hearts. The new technique uses two consecutive transient (3 min) coronary artery occlusions by an inflatable balloon catheter combined with intracoronary infusion of nitroglycerin, which increased Ad5Luc expression in the pig heart by more than 100-fold. In order to prove the safety and efficacy of the new delivery method, we have initiated the ASPIRE clinical study. Eleven patients (7 who received a single intracoronary injection of 6x10e9 vp Ad5FGF-4 and 4 with standard of care) completed the study. None of treated patients showed any clinical signs of untoward effects due to the product delivery, and there was no elevation of blood troponin I levels. The treated patients showed a statistically significant ($p<0.01$) improvement in myocardial perfusion assessed by SPECT eight weeks after product administration. In conclusion, the new Ad5FGF-4 delivery method proved to be safe and well tolerated, and resulted in significant improvement in the primary efficacy endpoint in patients with refractory angina. This pilot study formed the basis for the start of a pivotal Phase III clinical trial in the US.

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Glioblastoma stem cells: Overcoming resistance using gene/cell therapy

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Glioblastomas (GBMs) comprises >50% of all primary brain tumors and are the most malignant type with a 5-year survival rate of only 3.3%, despite standard-of-care (surgery, radiation and temozolomide). Recently, it has been shown that the glioma stem-like cells (GSCs; or tumor initiating cells) subpopulation of the tumor are largely responsive for tumor resistance, recurrence and patient death, thus providing a clinically-relevant model to study GBM. GBMs are highly heterogeneous and there is a complex interaction among different subtypes of tumor cells and stromal cells associated with the tumor which can modify the tumor itself as well as its microenvironment to promote tumor growth, invasion, angiogenesis and immune suppression. The transcriptome profiles of GBMs has identified four major subtypes, two of which, proneural (PN) and mesenchymal (MES), predominate with multiple subtypes residing in the same tumor. GBM with enriched MES properties typically display more aggressive phenotype, both in *in vitro* and *in vivo* with pronounced radio/chemo resistance. Our goal is to understand GBM progression and therapeutic resistance to help us develop novel diagnostics/therapeutics aiming at eradicating this cancer type. Over the last several years, we have developed novel efficient gene/cell therapeutic strategies that bypass the blood-brain barrier to target and eradicate patient-derived GBM stem cells model.

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