Nanoparticle-loaded stem cells for MR imaging and hyperthermia

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Introduction: Injection of magnetic fluids into tumors and their subsequent heating in an alternating magnetic field has been developed as a cancer treatment, which either results in direct tumor cell killing or makes the cells more susceptible to radiation- or chemotherapy (1). Targeted hyperthermia has clinical potential because it is associated with fewer side effects, and can also be used in combination with conventional treatment modalities.

Despite promising results, hyperthermia has not yet been established in the clinic because technological limitations preclude selective deposition of heat to the tumor, especially to radioresistant hypoxic areas (2). Magnetic iron oxide nanoparticles are increasingly used for clinical applications, such as MRI, drug delivery, and hyperthermia. We propose cell-based delivery of bi-functional magnetic nanoparticles (designed to heat) to tumors for MR tracking and hyperthermia.

Methods and Results: The main goal of this study is to sensitize tumors to radiation therapy with heat generated by magnetic nanoparticles within stem cells that home to hypoxic areas in tumors. Previously, we demonstrated with MRI and immunohistology that in mouse models of prostate cancer intravenously injected mesenchymal stem cells (MSCs) migrate to tumors, home to the hypoxic areas, and presumably participate in neovasculogenesis in growing tumors (3). It was also demonstrated that heating of tumor-bearing mice injected with bionized nanoferrite (BNF) particles resulted in tumor size reduction and significantly delayed tumor growth (4). However, nonspecific distribution, dilution, and poor retention of naked particles in tumors remain a problem. Here, we aim to develop methods for stem cell-based delivery of magnetic nanoparticles to hypoxic areas in tumors to sensitize those areas with hyperthermia to subsequent irradiation.

We imaged with MRI mouse mesenchymal stem cells loaded with novel magnetic iron oxide BNF-nanoparticles that have unique heating characteristics (Fig. 1, 2). We demonstrated that mouse mesenchymal stem cells can be efficiently loaded with iron-oxide BNF-particles without disturbing their proliferation, migration, and differentiation potential (Fig 3).

Significance: BNF-loaded MSCs can be potentially used to track the tumor and tissue distribution of the labeled stem cells and to selectively heat targeted tumors with alternating magnetic field.

We hypothesize that stem cell-based delivery of magnetic particles to hypoxic areas in tumors for hyperthermic sensitization of those areas to subsequent irradiation and disruption of vasculature in those tumors will significantly improve the outcome of cancer radiotherapy.

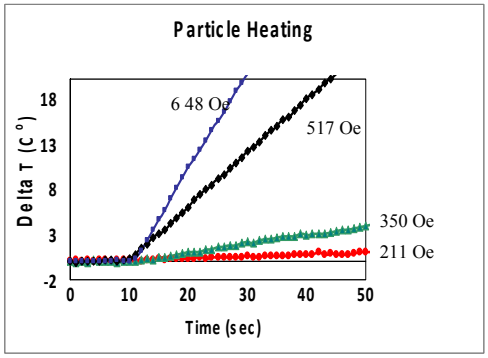

Fig.1. Heat output of the BNF particles as a function of magnetic field strength. (Oe-magnetic field amplitude in Oersteds).

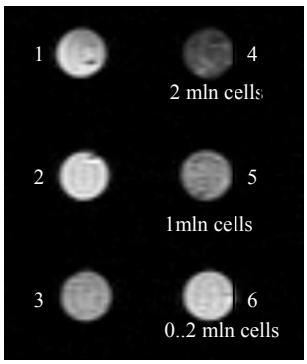

Fig.2. T2* images of BNF-loaded stem cells in 2% agarose. 1-unlabeled cells; 2-unlabeled cells with PLL; 3- BNF-labeled cells (2mln cells); 4-6-BNF(PLL)-labeled cells

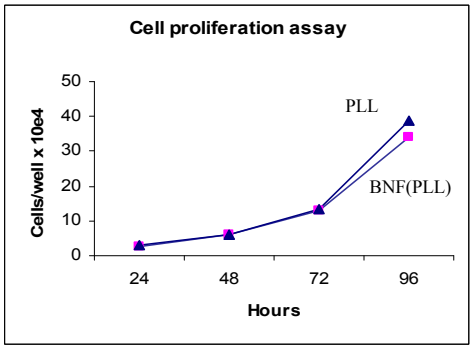

Fig.3. Proliferation assay for the BNF(PLL)-loaded mouse mesenchymal stem cells

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