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## Preparation of a standardized bank of iPSC-derived mesenchymalstem cells (MSC) engineered to deliver suicide genes into tumors

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ne appealing approach to cancer therapy involves targeted delivery of exogenous genes encoding an enzyme that converts a specific inert prodrug into cytotoxic derivatives. This strategy, often referred to as targeted suicide gene therapy, has recently been improved by exploiting the high transduction potential and tumor-tracking properties of mesenchymal stem/stromal cells or MSCs. However, clinical applications of tissue-derived MSCs are hindered by donor cell variability and inability to obtain the excessive cell numbers necessary for patient therapies. To overcome these limitations, here we employed induced pluripotent stem cells (iPSCs) as a feeder stock to generate an expandable and uniform source of MSCs. The standardized iPSC-MSCs were engineered to express the suicide gene that codes for cytosine deaminase (CD), an enzyme that converts the non-toxic prodrug 5-fluorocytosine (5-FC) locally into the chemotherapeutic agent 5-fluorouracil (5-FU). These genetically modified iPSC-MSCs constitutively expressed high levels of CD through numerous passages and following cryopreservation, and maintained features characteristic of tissue-derived MSCs. Moreover, the cells showed remarkable ability to kill all cancer cell lines tested (breast, prostate, and ovarian carcinoma, and melanoma) in vitro through bystander effects after addition of 5-FC to the cultures. Level of killing was dependent on time, concentration of 5-FC, and numbers of MSCs used. In mice, both local and systemic injections of iPSC-MSCs expressing CD not only limited formation of human breast tumors following administration of 5-FC, but also triggered regression of established tumors and reduced development of metastatic disease. Interestingly, the anti-tumor effects of iPSC-MSCs were more profound when the cells were primed in culture by addition of 5-FC prior to cell delivery, or suspended in 3-D cultures under conditions that reduced their physical size while increasing uptake by the cancer cells. Importantly, activation of the prodrug also resulted in elimination of the modified iPSC-MSCs thus providing a safeguard against wayward stem cell progeny. Taken together, the results here provide evidence that iPSC-MSCs have immense potential as cellular carriers of therapeutic transgenes and in precision medicine.

## **Biography**

Thomas Bartoshcompleted his PhD degreein Cell Biology and Genetics from The University of North Texas HSC. He joined the Institute for Regenerative Medicine (IRM) at Texas A&M Universityin 2008 to develop therapies with mesenchymal stem cells (MSCs). Currently, he an Assistant Professor of Internal Medicine and Director of flow cytometry and microscopy at the IRM. He studies the advantages of using three-dimensional (3-D) culture methods to activate MSCs and exploit their inherenttherapeutic potential. This approach was pioneered by Dr. Bartoshat theIRM and has been highlighted in numerous publications.

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