Phenotypic and functional characterization of gene-circuit modified allogeneic mesenchymal stromal cells (MSCs) for solid tumor immunotherapy


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SENTO-101: Human allogeneic MSCs engineered with a genetic circuit to express IL12 and IL21

An optimized protocol enables highly efficient gene-modification of SENTI-101 in hBM-MSCs

Initial optimization and characterization of SENTI-101

Figure 1A. SENTI-101 is an allogeneic preparation of human Bone Marrow Mesenchymal Stromal Cells (BM-MSCs) engineered to express IL12 and IL21 for the treatment of a broad range of solid tumors including ovarian cancer [1-4]. (IP-Intraperitoneal)

Figure 1B. The SENTI-101 engineering process is represented in three key stages: 1) Production of lentiviral vectors expressing the genetic circuit, 2) Delivery of lentiviral vectors into hBM-MSCs for stable integration and protein expression and 3) Expansion of engineered hBM-MSCs for pre-clinical testing and clinical manufacturing.

SENTO-101 effector expression is consistent across donor BM-MSCs

GENE MODIFICATION OF HUMAN MSCs (SENTI-101)

SENTO-101 localizes into ovarian cancer tumors and expresses IL12 and IL21

Figure 2. The addition of transduction enhancers like polybrene (PB) and protamine sulfate (PS) in combination with SENTI-101 lentiviral vector during transduction improves transduction efficiency and protein secretion [5]. Desired transduction potential for SENTI-101 was achieved at higher MOI with transduction enhancer PS. Strong correlation was observed between transduction efficiency and protein secretion in hMSCs transduced at lower (0.5X) and higher (1X) MOI.

Figure 3. hBM-MSCs transduced with SENTI-101 lentivector exhibit similar growth rate, transduction potential and protein secretion across multiple donors. While SENTI-101 hMSCs generated from P0 and P2 exhibited comparable transduction efficiencies and protein secretion, gene-modified MSCs derived from P0 exhibited increased growth rate and higher cell yield compared to gene-modified MSCs derived from P2, making them an ideal choice for clinical grade production.

Figure 4. hBM-MSCs transduced with SENTI-101 lentivector exhibited stable effector expression, growth characteristics and in vivo biodistribution and freeze/thaw cycles. PBS are hMSCs isolated from bone marrow of healthy donors, transduced and expanded to a SENTI-101. P0 are PB hMSCs expanded for 2 additional passages prior to transduction and expansion.

Figure 5. SENTI-101 hMSCs administered intraperitoneally (IP) into OVCARB (human ovarian cancer cells) tumors selectively homed to tumor sites, leading to >10 fold increase in cytokine production in the peritoneal space compared to systemic fluid. PP: Peritoneal fluid.

Summary

Genetically engineered cell therapy
Highly efficient lentiviral vector mediated-transduction

Functional Stability
Stable growth rate and transgene expression over several passages
Consistent growth kinetics and product attributes across multiple donors

Scalable expansion for cell therapy
Robust and scalable GMP compliant process
Ongoing GMP manufacturing and IND-enabling studies

Tumor-localized cell therapy
Homing to peritoneal tumors
Local secretion of immune effectors

References


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