INDUCED PLURIPOTENT STEM CELLS FOR CANDIDATE CELL LINE SELECTION OF OFF-THE-SHELF NATURAL KILLER CELL THERAPY

Jason A. Mills, Process Development, Century Therapeutics, USA
jmills@centurytx.com
Chen-Yuan Kao, Process Development, Century Therapeutics, USA
Matthew O'Rourke, Process Development, Century Therapeutics, USA
Barry Morse, iPSC Biology, Century Therapeutics, USA
Bruno Marques, Process and Product Development, Century Therapeutics, USA
Greg Russotti, Technical Development and Manufacturing, Century Therapeutics, USA

Key words: Cell therapy; induced pluripotent stem cell; reprogramming; hematopoietic progenitor cells; natural killer cells

Cell therapies provide a new strategy for the treatment and cure of debilitating diseases such as many forms of cancer, in which the standard lines of care have been unsuccessful. Although autologous CAR-T immunotherapy has shown resounding clinical efficacy, introduction of new treatments is hampered by regulatory, financial, technical, and resource constraints. Allogeneic cell therapies provide an alternative to autologous treatments for making CAR-immunotherapies more available to a broader patient demographic, with the ability to address many of the constraints of autologous cell therapies. Induced pluripotent stem cells (iPSCs) can serve as a self-renewable source of allogeneic starting material for long-term material supply for cell therapies. Creating clinically relevant iPSC master cell banks requires critical sourcing of starting material, somatic cells type selection, vendor qualification, and application of appropriate controls and analytical methods for screening donor material in compliance with FDA requirements. The establishment of good manufacturing practices is essential to create a reproducible and reliable procedure for generation of clinical iPSC master cell banks and subsequent differentiated cell types. These criteria for principles of GMP include raw material sourcing, reprogramming strategy determination, establishment of critical process parameters, critical quality attributes with essential quality control testing, and analytical methods consistent with FDA recommendations. With the benefit of the iPSCs capacity for self-renewal, there is the opportunity for expansive manufacturing capacity to meet clinical and commercialization demands; however, the ability to generate large numbers of differentiated intermediates and immune effector cells (e.g.., natural killer and T cells) from iPSCs can lead to bottlenecks in supply chain requirements.

To address these process challenges, we assessed the hematopoietic differentiation capacity of gene edited iPSCs to various bioprocessing formats from 2D static cultures to 3D aggregate suspension cultures. We applied single-use scalable cell culture vessels, operational and analytical controls, and xeno-free, chemically-defined, culture conditions to generate hematopoietic progenitor cells (HPCs) during candidate cell line selection studies. This has resulted in robust differentiations to HPCs from many gene-edited IPSCs, which were further lineage committed to homogenous allogeneic iPSC-derived natural killer cells (iNKs) targeting CD19-positive cancer cells. The manufacturing process for iPSC-derived NK cells enabled comparability assessment of all gene edited iPSC candidate cell lines for feasibility of GMP facility fit, scale-out capacities, reduced cost-of-goods, xeno-free chemically defined media formulations, minimal batch-to-batch variability, operational controls for quality control (QC) and quality assurance (QA) methodologies essential for creating our "off-the-shelf" CAR-iNK therapies. These results use the critical principles of GMP applied during candidate cell line selection of Century's CNTY-101 program. Our results highlight the technologies and controls needed to enable clinically-relevant production of Century's iPSC-derived natural killer cell therapies.