Discovery of the Unique GMP-Grade iPSC Clones that Give Rise to Functional, High Purity, Matured CD8 αβT or γδT with Exponential Expansion Capacity

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Although autologous cell therapy has shown remarkable clinical success and brought forth a medicinal revolution, significant hurdles remain. These include, but not limited to cell supply scarcity, prohibitively high costs stemming from the source material and manufacturing variabilities, lengthened and complex patient journey before receiving treatment, and the restrictive sites of manufacturing and therapeutic administration, creating formidable accessibility and affordability challenges. Many of the aforementioned issues central to successfully democratizing cell therapy could be ameliorated by developing off-the-shelf cell products that are uniformed, universal, and massively scalable. While donor-based allogeneic cell therapy could tackle certain aspects of the issues, allogeneic induced pluripotent stem cell (iPSC)-derived cell therapy offers an unequalled solution to answer most of the challenges. iPSC-derived cell therapy will ride on a stable, unlimited cell supply, a uniformed manufacturing process, and a homogeneously edited cellular product manufactured at a low cost.

However, there are three conditions to fulfill before one can take the full advantage of the iPSC-derived cell therapy. First is the acquisition of the well-characterized GMP-grade iPSC lines that are free of pathogenic genetic alterations. The publicly or commercially available iPSC banks are usually populated with uncharacterized and sometimes dubious iPSC clones. It has been published that 20% of the publicly available iPSC lines harbor at least one cancer-related mutations. Therefore, obtaining iPSC clones with very high confidence of genomic integrity could not be underestimated. Second, not one iPSC clone is the same, and each will offer certain degree of differentiation and expansion efficiency into a given cell type due to the unknown donor genetics and epigenetics composition. Therefore, a survey of the most suitable iPSC clones will be required. Third, the tailored optimization of the differentiation and expansion methodologies is needed to exploit the maximum productivity of the selected iPSC clones. It is the perfect marriage between finding the right clone and establishing the most optimal differentiation and expansion approaches pertinent to a given iPSC clone that will ultimately realize the full potential of the iPSC-derived cell therapies and bring the next wave of cell therapy revolution.

To meet the aforementioned requisites, a stringent donor recruitment process compliant with the regulations of multiple key regions was implemented. Eligible donors' blood cells were reprogrammed to clinical-grade T cell-derived iPSC lines (αβT-derived iPSC and γδT-derived iPSC). Selected T-iPSC clones underwent rigorous characterization through various methodologies, including pluripotent marker

expression, in vitro and in vivo differentiation assays, karyotyping, and comprehensive genome integrity assessments. Ten clinical-grade T-iPSC lines successfully passed all tests and were found to be free of likely-pathogenic variants present in the OncoKB, ClinVar, and COSMIC databases.

Subsequently, unique protocols were created to maximize the differentiation and explosion potential of the selected GMP-grade T-iPSC clones. Here, we describe industry-leading feeder-free differentiation and expansion platforms using our GMP-grade iPSCs. Our platforms are capable of producing 95% CD8αβ+ mature T cells and over 99% γδ T cells without enrichment process. Remarkably, both iPSC-derived αβ T and γδ T cells can be expanded more than 10 million-fold from a single iPSC. These protocols represent the most competitive approach in the field, offering unparalleled scalability and efficiency for the iPSC-derived T cell production. Moreover, both iPSC-derived αβ T and γδ T cells demonstrated cytotoxic activity in functional assays. To achieve commercial-scale expansion, the differentiation and expansion process were reproduced in a closed system, enabling large-scale production of functional T cells in a single manufacturing batch. These advancements could significantly enhance the accessibility and affordability of iPSC-based therapies.

By leveraging iPSC-derived therapy platforms, BeiGene Cell Therapy represents a substantial advancement in the field, providing a powerful resource for developing allogeneic T cell therapies and paving the way for future innovations in cell therapy.