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No adverse events were reported in mice receiving genetically modified cells. We expect our genome-edited therapeutic cells will advance novel and improved therapies for AMD and beyond.

6 Embryonic stem cells, iPSC and Related

GENERATION OF HIGH DENSITIES OF UNIVERSAL O-VE RED BLOOD CELLS FROM HUMAN INDUCED PLURIPOTENT STEM CELLS IN BIOREACTORS

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Keywords: red blood cells, hiPSC, microcarrier.

Background & Aim: Globally an estimated 112.5 million units of blood are collected for transfusion applications from blood donors. Continual advancements in the fields of lineage differentiation, bioprocessing and scale-up culture have brought closer the reality of using hiPSCs-differentiated cells for therapeutic applications and regenerative medicine. One such potential is the use of hiPSCs to generate O–ve universal RBCs for transfusion applications. However, unlike most cell therapies, generating RBCs for clinical application poses unique bioprocessing and manufacturing challenges. The need to generate 2 trillion RBCs for each transfusion unit of blood (equivalent to 300 ml of donated blood) requires the development of ultra-high density cultures of cells.

Methods, Results & Conclusion: We demonstrate significant progress in solving the manufacturing challenge by:

1) Implementing efficient reprogramming of 8 hiPSC lines in suspension microcarrier cultures at the start of the process. Screening hundreds of clones and selecting dozens with both features of high expansion capability (greater than 10-fold) and differentiation to early hematopoietic lineage, positive for CD34 and CD43 markers (above 70%).

2) Initiating of the mesoderm differentiation in suspension culture and selection of clones with at least 20-fold expansion and production of T-bra and KDR +ve cells (>20% expression).

3) Simplifying differentiation with implementation of designs of experiments to use small molecules and reduced cytokine cocktails towards the erythroblast lineage. Screening a second stage for high expandability to erythroblasts, > 20,000 fold or more; while decreasing cost of goods by 10 fold.

4) Applying high intensity culture methods using ultrasound to concentrate erythroblast expansion to achieve greater than 25 million cells/ml in controlled bioreactor cultures.

5) Applying shortened, simplified enucleation protocol with inactivated OP9 co-cultures and screened plasma sources to drive enucleations rates up by 10 fold or more from 6% to 65%.

6) Characterisation of oxygen binding curves, haemoglobin expression, membrane fluidity and SEM images.

We present solutions to developing a bioreactor scalable-process for generating high-density cultures of functional RBCS from hiPSCs.

We present solutions to developing a bioreactor, scalable-process for generating high-density cultures of functional universal O negative RBCs from hiPSCs.

9 Somatic Stem Cells: Mesenchymal Stem/Stromal Cells

EXTRACORPOREAL MESENCHYMAL STROMAL CELL THERAPY (SBI-101) IN SEVERE COVID-19 COMPlicated BY Acute Kidney Injury

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Keywords: COVID–19, AKI, inflammation.

Background & Aim: Severe cases of COVID–19 are characterized by development of an overactive host inflammatory response associated with multiorgan dysfunction and high morbidity and mortality. The complex pathophysiology and systemic nature of this inflammatory response supports the rationale for an advanced therapeutic agent, like a cell therapy, to provide a multifaceted immunomodulatory treatment. SBI-101 is an ex vivo cell product, engineered to control the dosing of human mesenchymal stromal cells (MSCs) in normalizing a dysregulated inflammatory response by reprogramming the peripheral blood with MSC-secreted factors including exosomes. This combination product immobilizes allogeneic human MSCs on a hollow-fiber hemofilter with a semi-permeable membrane, which maintains adherent MSC viability and is readily integrated into a continuous renal replacement circuit (CRRT) circuit, thereby exposing patient blood to MSC therapy in a controlled, measurable manner. A FIH study of low-dose SBI-101 treatment in severely inflamed acute kidney injury (AKI) patients showed pharmacodynamic trends consistent with a reduction in systemic inflammation. These results motivated a new trial in severe COVID–19 patients.

Methods, Results & Conclusion: A multi-center, ascending dose study of extracorporeal MSC therapy (SBI-101) was initiated in COVID–19 subjects with AKI requiring renal replacement therapy (NCT04445220). The initial cohort of analyzed patients received SBI-101 (250×10^6 cells) for up to 24 hours of treatment. The mean mSOFA score was 11, consistent with a high severity of illness typical of patients with septic shock. Six patients were enrolled to date, including one failed initiation of therapy due to technical error. Four out of six patients survived, 3 no longer required RRT and one no longer required mechanical ventilation immediately after treatment and 2 were ultimately discharged home. COVID-19-related inflammatory complications were observed in all patients, but no adverse events were reported in mice receiving genetically modified cells. We expect our genome-edited therapeutic cells will advance novel and improved therapies for AMD and beyond.
markers, including CRP, ferritin, D-dimer, IL-6, LDH, platelet count, and lymphocyte count, all showed various levels of improvement at day 7 after SBI-101. A comprehensive profiling of 200 exploratory biomarkers and immune cell subsets over timepoints pre- and post-treatment will be presented to characterize the pharmacokinetic and pharmacodynamic effects of SBI-101 on the immune system. Overall, these preliminary results suggest ex vivo MSC therapy carries significant promise and warrants further study in the treatment of patients with severe COVID-19 requiring CRRT.

10 Somatic Stem Cells: Mesenchymal Stem/Stromal Cells
MESENOCURE—AN ENHANCED CELL THERAPY EXPLICITLY DEVELOPED FOR TREATING ACUTE RESPIRATORY DISTRESS IN COVID-19: FROM BENCHTOP TO BEDSIDE
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Keywords: COVID-19, ARDS, Mesenchymal stromal cells.

Background & Aim: Mesenchymal stromal cells (MSC) have attracted much attention for treating pulmonary manifestations of Covid-19, for which they are already tested in clinical studies. These efforts are, nonetheless, overshadowed by studies predating the pandemic that failed to show MSC efficacy in treating acute respiratory distress syndrome (ARDS). Also, concerns regarding the hemocompatibility of MSCs were raised vis-à-vis their source tissue and administration route, especially in coagulopathic Covid-19 patients. With this in mind, and relying on years of MSC-related experience and manufacturing capacity of clinical-grade material, and technologies developed for the efficient and standardized isolation and cultivation of MSCs, Bonus BioGroup has developed MesenCure—an enhanced allogeneic MSC product for intravenous (IV) injection designed to treat ARDS in Covid-19 patients.

Methods, Results & Conclusion: MesenCure is based on adipose stromal cells (ASC) primed by a combination of biological and physical conditions to improve their potency, stability, and safety. Our data shows that MesenCure, but not unprimed ASCs, have alleviated edema in an acute lung injury (ALI) model by 60% (Fig. 1A) and reduced the leukocytes’ counts in the lung fluids by 40% (Fig. 1B-1E). Three IV administrations of MesenCure were shown to rescue animals from a lethal ALI (Fig. 2). In vitro, MesenCure inhibited the proliferation of activated T cells by >83% compared to <15% inhibition by unprimed ASCs (Fig. 3). Under refrigeration, MesenCure cells retained their immunomodulatory capacity longer than unprimed ASCs representing a more stable product for transplantation with a longer shelf-life. MesenCure cells’ hemocompatibility was found to resemble that of bone marrow MSCs, regarded as safe for IV injection. This was evidenced by 50% lower levels of coagulation factor 3 at the mRNA, protein, and activity levels, as well as a >2-fold higher level of tissue factor pathway inhibitor, expressed on MesenCure cells compared to unprimed ASCs. A GLP toxicity study found MesenCure to be well-tolerated.