Mesenchymal Stem/Stromal Cells

**MesenCure: A Professionalized Cell Therapy for ARDS Reduced the Mortality of Severe Covid-19 Patients by 68% According to a Recently Concluded Multi-Center, Controlled Phase II Study**


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**Keywords:** COVID-19, ARDS, Mesenchymal Cells.

**Background & Aim:** The wide gap in severe Covid-19 management is increasingly addressed by mesenchymal cell (MSC) therapies, despite studies that failed to show significant efficacy in ARDS. To improve the therapeutic utility of MSCs in ARDS, Bonus BioGroup developed MesenCure: An allogeneic adipose-derived MSC product professionalized by a combination of culture conditions enhancing the cells’ potency and stability, producing unique transcriptomic, proteomic, and morphological signatures. Up to 100k fresh MesenCure doses with a shelf life sufficient for global supply can be produced from a single donor under 20 PDLs, further preventing potency loss due to cryopreservation and culture aging. Based on preclinical data presented during ISCT2021, demonstrating MesenCure’s advantages over non-professionalized MSCs, and its safety in a Phase I study, Bonus BioGroup initiated a multi-center Phase II trial in severe Covid-19 patients that was recently concluded.

**Methods, Results & Conclusion:** By defining rapid/slow proliferation cell populations based on CFSE intensity (low 30% population as rapid cells and high 70% population as slow cells), we built a LF-GC classifier based on support vector machine (SVM) with the area under the receiver operating characteristic curve (AUC) of 0.86. With the LF-GC classifier, we enriched the rapid proliferation cell population from 33.6% to 76.8%. After three weeks of culturing the cells as pellets, we measured glycosaminoglycans (GAGs) accumulations to evaluate the extracellular matrix production. The sorted samples accumulated more GAGs compared to the control samples with statistical significance. Here, we demonstrated LF-GC’s potential to purify the desired cells without any staining, which suggests that it could be a new effective tool for label-free and selective cell isolation and purification in regenerative medicine.

**Fig. 1** (abstract 25). (A) Mortality rates among test and control patients at Visit 8 (one month after the first MesenCure dose or the equivalent time points for the control). (B) Test and control patients’ risk of deteriorating to mechanical ventilation. (C) Average hospital length of stay (LoS) of patients having LoS > 7 days. Two-sided p values were calculated using the Fisher Exact test (A and B) or t-test (C).

**Fig. 2** (abstract 25). (A) CRP and (B) CK levels measured at Visit 6, the earliest of two weeks after the first MesenCure dose (Visit 2) or upon hospital release, or the equivalent time points for the control. The test and control groups started from similar median CRP and CK levels. (C) Changes in control and test patients’ LDH levels from Visit 1 (screening) to Visit 6. (D) Area of test patients’ diffuse pneumonia during Visits 1, 6, and 8 (one month after the first MesenCure dose or the equivalent time points for the control). (E) Blood oxygen saturation measured during test patients visits 1, 2-4 (upon or before receiving the first to third MesenCure dose), Visit 5 (the earliest of one week after Visit 2 or upon hospital release), and Visit 6. (F) Test patients’ blood lymphocytes levels (absolute) across Visits 1 and 6. Charts are presented as box-and-whiskers (according to the Tukey method). p values were calculated using the Mann-Whitney test (A, B, and C), Dunn’s multiple comparisons (D and E), or the Wilcoxon test (F).

patients having LoS>7 days (Fig. 1C, p<0.01). Starting from a similar baseline as the control, the median CRP and CK levels of the test patients, after MesenCure treatment, ended 52% (p<0.0001) and 33% (p<0.01) lower than their respective control levels. As shown in Fig. 2,
the more profound improvements in inflammatory and tissue damage markers observed in test patients were accompanied by a rapid recovery in pneumonia, respiratory functions, and lymphopenia, emphasizing MesenCure’s powerful effect. In conclusion, we show that MesenCure saves patients’ lives and accelerates their healing, possibly reducing the risk of long-term damages while freeing ICU beds allowing better care for other patients, and reducing the burden associated with hospitalization and additional long-term healthcare costs.

26 Mesenchymal Stem/Stromal Cells

TWIST1 AND TSG6 AS POTENCY BIOMARKERS OF HUMAN MSCS IN PRE-CLINICAL DISEASE MODELS

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Keywords: Biomarker, Potency, Pre-clinical.

Background & Aim: Mesenchymal stem/stromal cells (MSCs) have been evaluated in over 1000 clinical trials, but patient outcomes have been disappointing when compared to results in pre-clinical models. Variables including patient-based factors, MSC donor source, and manufacturing practices all impact trial outcomes. To better inform clinical studies, we previously identified TWIST1 as a biomarker that predicts inter-donor differences in the growth, multi-potency and pro-angiogenic activity of human MSC (hMSCs) populations, and independently identified TSG6 as a biomarker that predicts inter-donor differences in hMSC anti-inflammatory activity.

Methods, Results & Conclusion: Herein, we demonstrate that TWIST1 represses TSG6 expression via direct promoter binding, that TWIST1 and TSG6 expression are inversely correlated in multiple hMSC donor cohorts (r = 0.826, p = 0.0003), and that TWIST1 and TSG6 positively and negatively correlate, respectively, with the height and weight of human donors. To confirm this relationship, we show that TWIST1 positively correlates with growth/CFU-F activity and negatively correlates with in vitro immuno-suppressive activity of hMSC donors (N=8) while the opposite is true for TSG6. Additionally, we quantified TWIST1 levels in hMSC donors (N=7) whose potency in a sterile inflammation model was positively correlated with TSG6 levels and show that TWIST1 negatively correlates with donor potency (r = -0.777, p = 0.0395). Lastly, we evaluated hMSC donors (N=6) in a murine model of adoptive transfer of autoimmune Type I Diabetes and showed that TWIST1 (r = -0.8514, p = 0.0315) and TSG6 (r = 0.885, p = 0.002) negatively and positively correlated, respectively, with T cell-mediated immune responses in this model. These studies identify two functionally related biomarkers that reliably predict inter-donor differences in the potency of hMSCs in pre-clinical models of inflammatory and immune-mediated diseases. Therefore, these biomarkers may be used to pre-screen hMSC donors prior to patient administration to match their potency to the appropriate disease indication and inform how large-scale manufacturing practices impact the potency of clinical grade MSC products. By demonstrating intrinsic differences in donor potency in these pre-clinical models, our findings challenge the paradigm that interaction with the host microenvironment dictates MSC potency in vivo, and by doing so highlights the importance of donor selection and manufacturing processes in the design of clinical trials.

27 Mesenchymal Stem/Stromal Cells

ALLOGENEIC, OFF THE SHELF, POOLED, BM - MSCS (STEMPEUCEL®) – A POTENTIAL BREAK THROUGH THERAPY FOR GRADE II AND III OSTEOARTHRITIS KNEE

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Keywords: stempeucel®, Osteoarthritis, WOMAC.

Background & Aim: Osteoarthritis (OA) is the most prevalent joint disease and a common cause of disability. We had conducted a randomized, double blind, multi-centric, Phase 3 study (CTRI/2018/09/015785) to assess the efficacy and safety of intra-articular administration of stempeucel® in patients with Osteoarthritis of Knee.

Methods, Results & Conclusion: Methods 146 patients having Grade II & III OA based were randomized in the study. 73 patients each received either a single intra-articular injection of stempeucel® (25 million cells) or Placebo followed by 20mg hyaluronan and were followed up for 12 months. The primary end point was evaluation at one year follow up of WOMAC Composite Index score as compared to the pla-

Fig. 1 (abstract 27) Mean ± SD graph for WOMAC Composite Index score across visits (mITT cohort).

Fig. 2 (abstract 27) Percentage change for WOMAC Composite Index score across visits (mITT cohort).