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time and sorted at high throughput. Cartilage regenerati
of the targets for regenerative therapy because of poor regenerative po-
tential. A previous study showed that the human chondrocytes flu-
orescently labeled with CFSE exhibited a wide variety in fluorescent
intensities, indicating heterogeneity in their proliferation rates. The
rapid proliferation cell population (low CFSE intensity) showed more
matrix production potential than the other cells (high CFSE intensity).
To evaluate if LF-GC is applicable to the enrichment of high matrix
producing chondrocytes, we analyzed CFSE-stained human chon-
drocytes on LF-GC.

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 clas-

ifier 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 signifi-
cance. Here, we demonstrated LF-GC's potential to purify the desired
cells without any staining, which suggests that it could be a new ef-
effective tool for label-free and selective cell isolation and purification
in regenerative medicine.

25
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 professional-
ized 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 pre-
dented 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 pa-

tients that was recently concluded.

Methods, Results & Conclusion: The Phase II trial included 50 severe
Covid-19 patients suffering from diffuse pneumonia and oxygen de-
saturation treated with up to 3 MesenCure doses (1.5x10\textsuperscript{6} cells/kg on
days 1, 3, and 5), on top of the Standard of Care (SoC), and 150 similar
severe control patients treated by the SoC only and stratified accord-
ing to gender, age, and comorbidities. A substantial 68% reduction in
the mortality rate of the test patients was measured (Fig. 1A, p<0.05),
along with a 57% drop in their risk of intubation relative to the control
(Fig. 2A, p<0.05). Over 50% of the patients treated with MesenCure
were released from the hospital within two days after treatment, and
a 38% reduction was measured in the hospital length of stay (LoS) of

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 pa-

tients, 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-immunflammatory 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 1 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.