Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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.

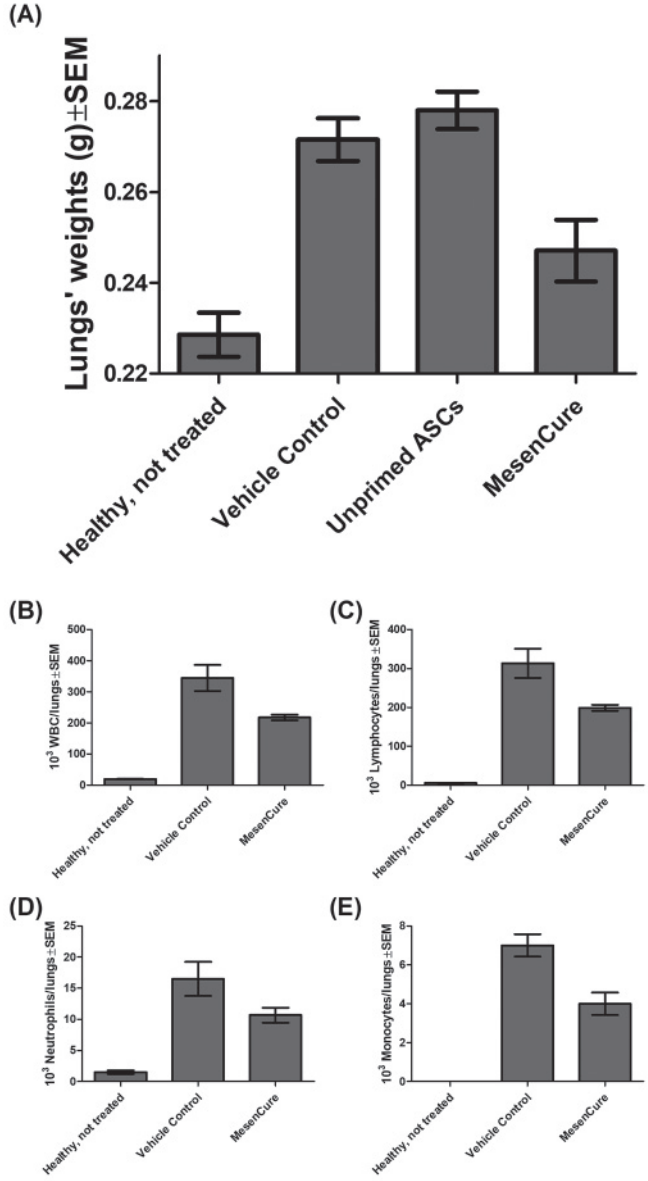

Fig. 1 (abstract 10). MesenCure effect in ALI model animals. MesenCure was injected 6 hours post-induction of an ALI model in C57BL mice by IT injection of LPS. Animals were sacrificed 18 hours post-treatment. (A) The effect of MesenCure on the lungs' weights was measured following lung harvesting from treated model animals compared to lungs harvested from healthy non-treated animals and model animals injected with Vehicle Control or unprimed ASCs. (B–E) The effect of MesenCure on the leukocytes' counts in the lung fluids was measured on bronchoalveolar lavage fluids (BALF) harvested from treated model animals and subjected to complete blood count protocol in comparison to BALF harvested from healthy non-treated animals, as well as model animals injected with the Vehicle Control item. Results are presented for (B) total white blood cells (WBC), (C) lymphocytes, (D) neutrophils, and (E) monocytes.

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Somatic Stem Cells: Mesenchymal Stem/Stromal Cells

MESENCURE—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.

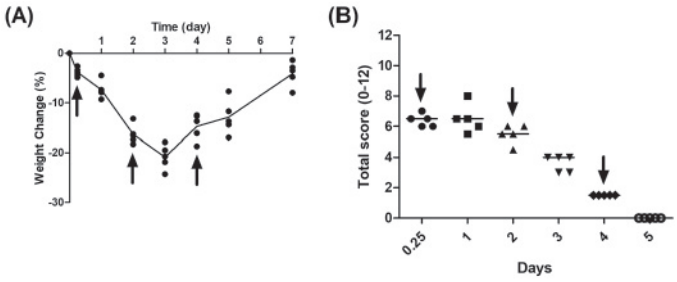

Fig. 2 (abstract 10). The effect of repeated MesenCure administrations in a lethal ALI model. MesenCure was injected thrice in 48 hours' intervals starting 6 hours (0.25 days) post model induction and two and four days after that (arrows designate administrations). Animals' survival, weights, and clinical scores were recorded until complete recovery was measured on Day 7, three days after the final injection. Results are presented as (A) individual and averaged weight changes (%) in respect to Day 0, as well as (B) individual and median clinical scores reflecting the animals' overall health as a combination of their appearance, activity, response, and respiratory quality.

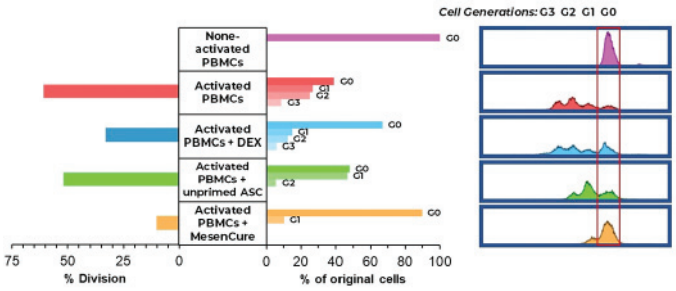

Fig. 3 (abstract 10). MesenCure effect on activated PBMCs. PBMCs stained with CFSE were added to reaction wells pre- seeded with MesenCure cells or unprimed ASCs and the following control wells: non-activated PBMCs (only), activated PBMCs (only), and activated PBMCs with 10 µM dexamethasone (DEX). The PBMCs were then activated by adding beads conjugated with anti-CD3 and anti-CD28 antibodies to all cultures except for the non-activated control. Seventy-two hours later, the PBMCs were removed, co-stained with anti-CD4 antibodies, and analyzed by flow cytometry for CD4+ and CFSE labeling. % Division of the PBMCs refers to the percent of cells, out of the original cells, that have undergone division. % of original cells refers to the proportion of original cells' progeny found in every generation. The FACS histograms on the panel's righthand side present the CFSE labeling data. Results are representative of at least three independent tests.

Based on our promising preclinical results, Bonus BioGroup has initiated a Phase I/II clinical study to assess the safety and efficacy of MesenCure for treating pulmonary manifestations of Covid-19 in up to 35 severe patients hospitalized at the Rambam Health Care Campus (Haifa, Israel). Encouraging preliminary results have already been obtained and will be presented, emphasizing MesenCure's potential in Covid-19 and ARDS management.

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Gene Therapies

RESULTS OF THE CELLULAR IMMUNO-THERAPY FOR COVID-19 RELATED ACUTE RESPIRATORY DISTRESS SYNDROME (CIRCA-PHASE I TRIAL

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Keywords: Mesenchymal stromal cells , COVID-19, Phase I trial.

Background & Aim: Approximately 20% of Ontario hospitalized patients require ICU admission for management of acute respiratory distress syndrome (ARDS) and mortality rates remain high. To date few studies evaluating different treatment options for COVID-19 associated ARDS have shown meaningful clinical impact. Mesenchymal stromal cells (MSCs) are rapidly emerging as promising therapeutics for COVID-19 due to their immunomodulatory effects, including selective downregulation of major pro-inflammatory cytokine pathways, and enhanced pathogen clearance in septic and ARDS animal models. We conducted a Phase I dose escalation trial of IV infusion of freshly cultured umbilical cord (UC) derived MSCs in adults with COVID-19 induced ARDS to assess its safety and tolerability.

Methods, Results & Conclusion: Eligible ICU patients were enrolled within 96hrs of ARDS onset (P/F ratio <300 with PEEP ≥5cm H_0 or on high flow nasal cannula, minimum total flow rate of 40 lpm). There were 3 UC-MSC dose cohorts, with 3 participants per cohort. Participants received repeated doses of UC-MSCs over 3 consecutive days (24±4 hours) according to one of the following dose panels: Panel 1: 25 million MSCs/dose (cumulative dose: 75 million MSCs); Panel 2: 50 million MSCs/dose (cumulative dose: 150 million MSCs); Panel 3: 90 million MSCs/dose (cumulative dose: 270 million MSCs). Participants were monitored for pre-specified MSC transfusion associated adverse events (AEs) and serious unexpected AEs.

Nine participants were enrolled with median age of 68 yrs (range: 57 to 78); median APACHE II score of 15 (range: 12 to 17); and median P/F ratio 102 (range 57 to 163). Median time of UC-MSC infusion from ICU admission was 48h17 (range 21h27 to 91h57). The UC-MSCs had a viability of >95%, endotoxin levels of <0.2 EU/mL and were free of any bacterial contaminants. All 3 panels were well tolerated with 0 pre-specified MSC transfusion associated AEs or serious unexpected AEs considered related to the MSCs.

A cumulative dose of 270 million freshly cultured UC-MSCs infused into COVID-19 induced ARDS participants appears safe. These results support the feasibility of our multi-site, blinded, RCT to examine efficacy of UC-MSCs in COVID-19 associated ARDS.

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Somatic Stem Cells: Mesenchymal Stem/Stromal Cells

MODULAR BIOMIMETIC MATRICES ENABLE HIGHLY DEFINED CULTURE OF FUNCTIONAL STEM CELLS

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Keywords: cell culture, chemically defined biomatrix, serum-/xeno-free.

Background & Aim: Stem cells have the remarkable ability to self-renew as well as differentiate into more specialized cell types. This capacity is highly influenced by the cellular microenvironment, which is an organized combination of extracellular matrix (ECM), cells, and interstitial fluid that influence cellular phenotype through physical, mechanical, and biochemical mechanisms. Similar to the ecological niche of an organism, the cellular microenvironment is specific to each cell type. To recreate its complexity for ex vivo cell expansion we developed biomatrices that combine ECM components such as glycosaminoglycans (GAGs) with biofunctional peptides. The incorporation of GAGs is beneficial for adhesion-dependent and growth factor-sensitive stem cells and their derivatives. Their ability to bind and stabilize growth factors facilitates the maintenance of stemness and supports differentiation.

Methods, Results & Conclusion: With our modular technique, we established a library of 96 different microenvironments to screen for biologically relevant compositions. In a first approach, we identified a biomatrix that supports the long-term expansion of mesenchymal stromal cells (MSCs) in serum-free medium. We continued with the development of a biomatrix that enables xeno-/serum-free isolation of high-quality MSCs from human bone marrow.

We also established specific biomatrices for the long-term culture of induced pluripotent stem cells (iPSCs), for their reprogramming as well as for differentiated derivatives of iPSCs such as neurons. Each of these biomatrices has a unique design tailored to the needs for a molecular composition mimicking the cell type-specific microenvironment. Moreover, even the same type of cell may require different support during different stages of in vitro culture as exemplify by the two MSC-specific biomatrices. Our modular, chemically defined and scalable technology enables the development of animal-source-free, high performance and reproducible cell culture protocols for stem cell research, drug development and cell therapy applications.

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Somatic Stem Cells: Mesenchymal Stem/Stromal Cells

SECURITY AND EFFICACY OF INTRADERMAL INJECTION OF MESENCHYMAL STEM CELLS DERIVATIVES ON CHRONIC DIABETIC FOOT ULCERS: A RANDOMIZED CONTROLLED CLINICAL TRIAL

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