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.

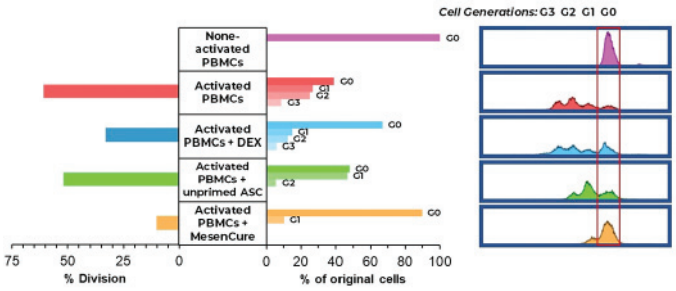

Fig. 3 (abstract 10). MesenCure effect on activated PBMCs. PBMCs stained with CFSE were added to reaction wells pre- seeded with MesenCure cells or unprimed ASCs and the following control wells: non-activated PBMCs (only), activated PBMCs (only), and activated PBMCs with 10 µM dexamethasone (DEX). The 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.

11

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.

12

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.

13

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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