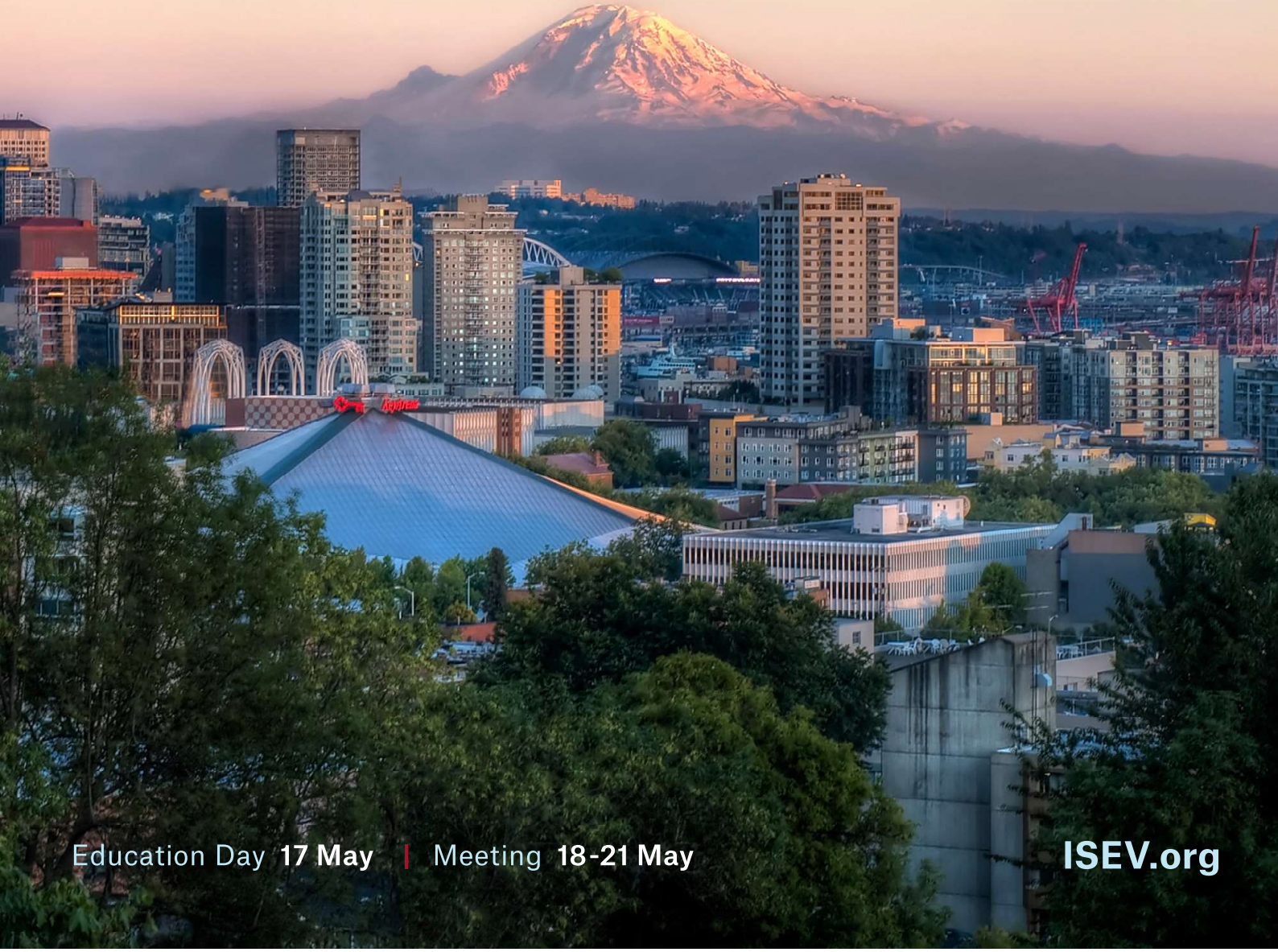
INTERNATIONAL SOCIETY FOR EXTRACELLULAR VESICLES

ISEV 2023 ANNUAL MEETING

SEATTLE CONVENTION CENTER • 17- 21 MAY 2023

PROGRAM AT-A-GLANCE



Education Day **17 May** | Meeting **18-21 May**

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Introduction: Many studies have now documented the safety and molecular profile of bone marrow-mesenchymal stem cells and their secretome. Still, safety and molecular content of each therapeutic is unique and must be characterized to support their clinical use. Herein are the results of murine preclinical safety, proteomic and extracellular vesicle (EV) identity studies of a BM-MSC EV enriched biologic currently being evaluated for its clinical safety and efficacy.
Methods: Safety was evaluated in murine models to assess acute tolerability, toxicity, and long term tumorigenicity. IgE levels were measured to assess acute allergic response after either subcutaneous or IV injection. Renal and liver histopathology was performed to assess acute toxicity (7 days). Long term (3 Month) tumorigenicity was determined in NOD.Cg-PrkdcscidIl2rgtm1Wjl/SzJ(NSG) mice using up to 20x human dose equivalent concentration. Animal studies were performed in ALAAS approved facilities. In molecular characterization studies, the EV content was evaluated using electron microscopy, STED Microscopy, SP-IRIS, and NTA. Proteomic analysis was performed using standard mass spectrophotometric (MS) protein sequencing.
Results: Safety: The therapeutic was deemed safe. No evidence of acute immune response, toxicity, or of tumor induction was observed within the tested time and dose ranges. Blood analyses were within normal ranges after 7 days and after 90 days. Identity: EVs were enriched for CD63+ EVs versus CD9+ or CD81+ EVs. At least 1173 different proteins were identified by MS sequencing of 5 different lots. Protein content was consistent with previously published data sets for MSC EVs.
Summary/Conclusion: These data demonstrate a superior safety profile relative to many traditional small molecule and single protein biologics, consistent with prior BM-MSC therapeutics studies. The complex protein composition indicates a potential multi-molecular, multi-modal mechanism of action for efficacy of this BM-MSC therapeutic.
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Keywords: GLP preclinical safety, In vivo, proteomics, EV therapeutic identity

PS10.04 | The pro-inflammatory role of EVs in chronic lung rejection

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Introduction: At present, lung transplantation (LT) is the treatment of choice for most end-stage lung diseases. Unfortunately, the prognosis is still relatively poor mainly due to chronic lung allograft disease (CLAD). Moreover, no early accurate biomarkers of graft rejection are known, thus we assessed CLAD lung microenvironment by profiling extracellular vesicles (EVs) from bronchoalveolar lavage (BAL) of LT patients.
Methods: We extracted EVs from BAL, then we analysed them for quantity and size by Nanoparticle Tracking Analysis (NTA). After purification by ultracentrifugation with saccharose gradient, we characterized the fractions by western blotting for characteristic markers (ARF6, TSG101, CD63) and electron microscopy. After EV coculture with normal bronchial epithelial cells (HBEpC), we analysed the culture supernatants for cytokines expression.
Results: After co-culture with EV-CLAD, we found up-regulation of secreted GM-CSF, while TNF-alpha, TREM-1, MIP-1, and IL-10/27 were down-expressed together with IL-17a. In cell lysates from EV-CLAD co-cultures, MIF, IL-1-ra and SERPIN were up-regulated, whereas MIP-1, CCL5 and TREM-1 were downregulated.
Summary/Conclusion: Overall, these results suggest a role for EVs in the axis CCL5-CCR-1, which regulates leukocyte migration and monocyte migration. Moreover, the up-regulation of MIF suggests that EVs may be involved in macrophage infiltration, and possibly in tissue repair during CLAD.
Keywords: lung graft rejection, cytokines