

## TARGETING MESENCHYMAL STEM CELLS TO TREAT INFLAMMATORY BOWEL DISEASE VIA CELL SURFACE COATING

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**Introduction:** Inflammatory bowel disease (IBD) is an autoimmune disease characterized by T cell infiltration to colon, which is the cause of Crohn's disease and ulcerative colitis. Mesenchymal stem cells (MSCs) have been used to rescue IBD owing to their immunosuppressive capability. However, the delivery of MSCs to inflamed sites in IBD is quite low. This study tested a method to enhance the efficiency of MSCs delivery to IBD by coating MSCs surface with antibodies against addressins.

**Methods:** Antibodies (Abs) against addressins (VCAM-1, MAdCAM and ICAM-1) were coated on BMC9 cells (a murine MSC cell line). *In vitro* immunosuppressive capacity of BMC9 cells was evaluated by co-culturing mouse splenocytes stimulated by CD3 antibody (T cell receptor) with MSCs. For *in vivo* bioluminescent imaging (BLI),  $10^6$  BMC9 cells transduced to express luciferase were tail vein injected into C57BL6 mice (females, 7 weeks) at day 2 post-treatment with 5% dextran sulfate sodium (DSS), and then Xenogen imaged at 2 hr post-injection. To determine therapeutic effects of Ab-coated MSCs in DSS treated mice, body weight change and survival percentage was determined. At 16 days, mice were sacrificed and then colon length and weight were measured, followed by determination of histological scores based on H and E-stained images of colon (H & E-stained tissues of colon) and immunostaining against Foxp3 was used to quantify regulatory T cells (Tregs) numbers in the colon.

**Results and Discussion:** *In vitro* studies confirmed the immunosuppressive capabilities of murine BMC9 cells and showed that Ab<sub>VCAM-1</sub>-MSCs have greater T cell suppressive ability than MSC only, indicating the possibility that the antibodies themselves, along with the MSCs, may contribute to this suppressive effect. In the BLI study, Ab<sub>VCAM-1</sub>-MSCs showed highest delivery efficiency to inflamed mesenteric lymph node and colon compared to MSCs only, Ab<sub>MAdCAM</sub>-MSCs, Ab<sub>isotype</sub>-MSCs. For therapeutic effects, mice injected with MSCs showed faster weight recovery and significantly improved viability than PBS-injected mice. Moreover, Abs coated MSCs, especially Ab<sub>VCAM-1</sub>-MSCs, resulted in higher therapeutic score than MSCs only, strongly suggesting dual effects by MSCs and Abs coated on MSC surfaces.

**Conclusion:** In this study, MSC coating with addressin antibodies was shown to increase MSC delivery to the colon by BLI and that targeted MSCs enhanced IBD therapeutic scores (colon length & weight/length, histological scores), increased survival, accelerated body weight recovery, and showed increased numbers of Tregs in the colon. Targeted delivery of MSCs may provide a means of increasing the efficiency of cell delivery to augment therapeutic effects.