Additionally, we show that MIF is able to upregulate the expression of cytokines described as chemoattractants for MSC (IL8, IL6 and CCL2), reinforcing the role of this molecule as the first trigger for several downstream signalling pathways. Importantly we show that knock down (using lentiviral shRNAs) of either CXCR4 (in MSCs) or MIF (in cancer cells) decreases significantly MSC homing to tumors in an in vivo pulmonary metastasis model. Interestingly, MIF has been shown by others to be over-expressed in a large variety of human cancers and closely correlates with tumor aggressiveness and metastatic potential. Therefore, MSC homing to tumors triggered by MIF could be a general mechanism for a variety of cancers. This improved understanding of MSC tumor tropism will further enable development of novel cellular therapies for cancers by increasing the homing potential of these cells.

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NOD2 ACTIVATION PROMOTES ANTI-INFLAMMATORY ACTIVITY OF HUMAN MESENCHYMAL STEM CELLS AGAINST INFLAMMATORY BOWEL DISEASE

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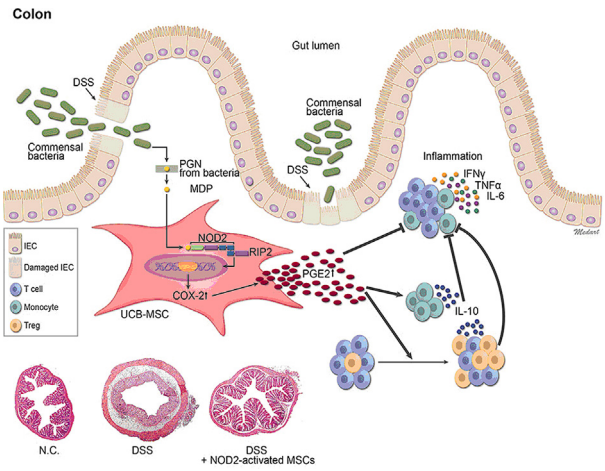
Decreased levels or function of nucleotide-binding oligomerization domain 2 (NOD2) are associated with Crohn's disease. NOD2 regulates intestinal inflammation, and is also expressed by human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs), to regulate their differentiation. We investigated whether NOD2 is required for the anti-inflammatory activities of MSCs in mice with colitis. Colitis was induced in mice by administration of dextran sulfate sodium or trinitrobenzene sulfonic acid. Mice were then given intraperitoneal injections of NOD2-activated hUCB-MSCs; colon tissues and mesenteric lymph nodes were collected for histologic analyses. Administration of hUCB-MSCs reduced the severity of colitis in mice. The anti-inflammatory effects of hUCB-MSCs were greatly increased by activation of NOD2 by its ligand, muramyl dipeptide (MDP). Administration of NOD2-activated hUCB-MSCs increased anti-inflammatory responses in colons of mice, such as production of interleukin (IL)10 and infiltration by T regulatory (Treg) cells, and reduced production of inflammatory cytokines. Proliferation of mononuclear cells was significantly inhibited by co-culture with hUCB-MSCs that had been stimulated with MDP. MDP induced prolonged production of prostaglandin (PG)E2 in hUCB-MSCs via the NOD2−RIP2 pathway, which suppressed proliferation of mononuclear cells derived from hUCB. PGE2 produced by hUCB-MSCs in response to MDP increased production of IL10 and Treg cells. In mice, production of PGE2 by MSCs and subsequent production of IL10 were required to reduce the severity of colitis. Taken together, these results indicate that activation of NOD2 is required for the ability of hUCB-MSCs to reduce the severity of colitis in mice and that NOD2 signaling increases the ability of these cells to suppress mononuclear cell proliferation by inducing production of PGE2.



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TREATMENT OF STEROID RESISTANT GRADE II TO IV ACUTE GVHD BY INFUSION OF MESENCHYMAL STROMAL CELLS EXPANDED WITH PLATELET LYSATE - A PHASE I/II STUDY

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Despite major improvements in the last decade in the field of HSCT, steroid-resistent acute graft versus host disease (aGVHD) remains a life-threatening complication. In an open-label, non-randomized prospective phase I/II study 50 patients with steroid-refractory GVHD grade II-IV were treated with MSC. Response rates, TRM and other adverse events were assessed for up to 12 months. Immunological changes after infusion of MSC were characterized in vitro. Anti-viral and antileukemia responses of reactive T-cells were tested and phenotypical changes in immune cells were followed up as were cytokines implicated in GVHD. MSC production takes ±22 days to expand from bone marrow to P3, resulting in ± 59x10e6 MSC per 2-layer CellStack. Between January 2009 and July 2012, 48 out of 50 patients included were eligible for analysis (7 children,41 adults). Mean age was 44.9 years (1.3-68.9). Organs involved were skin (52%), GI tract (88%) and liver (35%). Overall GVHD grade was II for 12 (25%), III for 33 (69%), and IV for 3 (6%) patients. Mean number of infusions were 3 (1−4). No severe side effects were observed upon infusions. Median follow up was 5,0 months (0.3-46.5). Complete overall response of aGVHD was observed in 24 patients (50%) after a median of 53 days (3−116 days). Overall survival was significantly improved in responders when compared to non-responders ($p < 0.001$). Patients who relapsed with GVHD of the gut were again sensitive to steroids, or a second cycle of MSC (one patient). Immunological monitoring shows that anti-viral and anti-leukemia reactive T-cells are well preserved in all patients who responded to MSC treatment. In addition we identified a combination of biomarkers that 2 weeks after initiation of treatment predicts a complete resolution of GVHD, whilst this usually becomes clinically apparent after months. Identified biomarkers predict early an usually late clinical resolution of GVHD and thus might be useful to early guide clinical decision making.

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UMBILICAL CORD-DERIVED MESENCHYMAL STROMAL CELL INFUSION IMPROVES BLOOD SUGAR CONTROL IN PATIENTS WITH TYPE II DIABETES

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Background: Diabetes is a systemic disease with end-organ complications secondary to hyperglycaemia and tissue ischaemia. In Type II Diabetes Mellitus (T2DM), there is initially insulin resistance followed by insulin depletion due to beta-islet cell dysfunction. We have previously demonstrated that mesenchymal stromal cell (MSC) may be induced to become insulin-producing cells in-vitro. MSC may also alleviate beta-islet cell dysfunction and improve skeletal muscle responsiveness to insulin. Therefore we postulate that MSC could further improve glycaemic control when added to conventional medical therapy.

Methods: We recruited 10 patients (mean age 63 years; 8 males) with T2DM who have been taking three or more oral hypoglycaemic medications at maximal dosage for at least 6 months. Co-morbidities include serious coronary artery disease (n=5), chronic renal disease (n=4) and previous stroke (n=2). Patients with proliferative retinopathy were excluded. Blood samples were collected at baseline, 3 months and 6 months after treatment. Patients received umbilical cord-derived MSC intravenously.

Results: All patients showed improvement in blood sugar control as evidenced by fall of HbA1c at 3 months and 6 months compared to baseline (Mean HbA1c 8.2% vs. 7.5% vs. 7.0%; ANOVA $p<0.05$). Five patients had at least one diabetic medicine reduced or stopped at three months. Two patients with renal disease showed significant improvement in serum creatinine level. There were no adverse events.

Conclusions: MSC could potentially further improve glycaemic control in patients on maximum oral hypoglycaemic medications. Several mechanisms are possible including closer patient surveillance.

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COMPLETION OF THE FIRST FDA PHASE 3 MULTICENTER TRIAL OF ISLET TRANSPLANTATION IN TYPE 1 DIABETES BY THE NIH CIT CONSORTIUM

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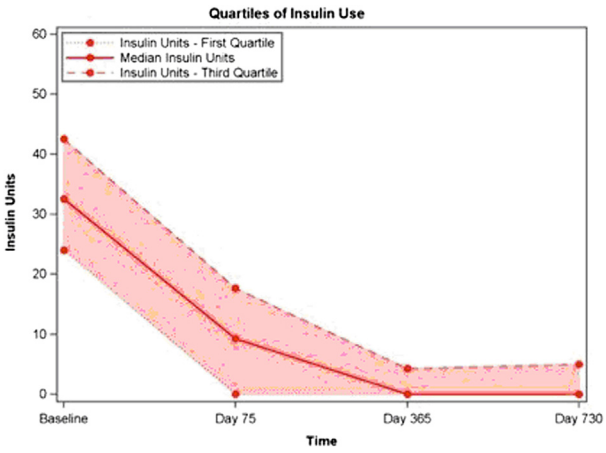
The Clinical Islet Transplantation (CIT) Consortium was established in 2005 by the NIH with the goals of advancing CIT through clinical trials, developing standard procedures for islet manufacturing and patient care, and generating the information needed for FDA licensure for islet products. In this FDA Phase 3 single-arm study (NCT #00434811), 8 centers and the CIT Data Coordinating Center evaluated the efficacy/safety of CIT for treatment of T1D in adults with hypoglycemia unawareness and a history of severe hypoglycemic episodes. The clinical study and islet manufacturing protocols were developed by the CIT consortium and are available online (http://www.isletstudy.org). Clinical protocols were approved by the NIH DSMB and local IRBs. Informed consent was obtained from all participants. All serious adverse events were reported to and reviewed regularly by the DSMB, the IRBs, and the FDA. 48 subjects received a total of 75 islet infusions, with 22 subjects (45.8%) receiving 1 infusion, 25 (52.1%) receiving 2 infusions, and 1 (2.0%) receiving 3 infusions.Total # IEQ transplanted per subject was 806,587±290,340 (mean±SD), corresponding to 11,476.4 ± 4,023.0 IEQ/kg. Induction immunosuppression (IS) was with rabbit antithymocyte globulin (rATG) and peri-transplant etanercept, anticoagulation and antimicrobial prophylaxis. In those who received a second islet infusion (>4000 IEQ/kg), basiliximab replaced rATG in the induction IS. Maintenance IS included sirolimus and reduced-dose tacrolimus. The primary endpoint was the proportion of subjects with an HbA1c <7.0% at day 365 and free of severe hypoglycemic events from day 28 to day 365 inclusive following the first islet transplant. Key secondary endpoints included also the proportion of insulin-independent subjects. Insulin usage dropped dramatically after transplantation (Figure). Islet graft function and insulin independence was achieved by 94% and 52.1% of subjects at day 365 after the first islet transplant.



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REPEATED INTRA ARTICULAR INJECTION OF BONE MARROW DERIVED MESENCHYMAL STEM CELL IN KNEE OSTEOARTHRITIS: DOUBLE BLIND RANDOMIZED CLINICAL TRIAL

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Recent non-randomized studies including our three previous phase I/II clinical trials have shown the safety of mesenchymal stem cells injection in the treatment of osteoarthritis. To investigate the effects of intra articular injection of autologous bone marrow derived mesenchymal stem cells (BM-MSC) on the symptoms of moderate to sever knee osteoarthritis we performed a double blind, placebo-controlled study in 46 patients.

Methods: Patients fulfill criteria for knee OA were randomly assigned into two groups: group one received BM-MSC (20 million cells, twice at day 0 and week 12th) and group two received carrier media as placebo. Primary end points were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and a visual analogue score (VAS) for pain at baseline and at the end of weeks 12, 24 and 36. Secondary end points were pain free walking distance, cartilage thickness, subchondral edema and tumor formation at 24 and 36 weeks.

Results: The results indicated that the intra articular injection of autologous BM-MSC is very well tolerated. Moreover BM-MSC treated group had significantly clinical improvement as compare to placebo group in all clinical end points. In particular, the WOMAC-Total score, WOMAC-Physical Function sub score, WOMAC-pain sub score and pain free walking distance in BM-MSC, were superior compared to the placebo group (P =0.03, p=0.02, p=0.03 and P =0.01, respectively). Primary radiologic data indicated that subchondral edema decreased in some patients also thickness of cartilage increased in MSC group.

Conclusion: Our short term follow up (9 months) have shown that repeated intra articular injection of BM-MSC is safe and effective in reducing functional impairment and relieving pain in patients with moderate to severe osteoarthritis of the knee. Clinical trial registration: NCT01504464.

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TARGETED MESENCHYMAL STEM CELL THERAPY FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Background: Chronic obstructive pulmonary disease is both an obstructive and inflammatory disease. Mesenchymal stem cell (MSC) therapy has shown early promise to modulate inflammation and improve lung function. The therapy has limitations resulting from cell loss and sub-optimal delivery. Our goal was to develop a MSC therapy that can use the inflammation in the lungs which results in SDF-1 expression as a target.

Methods: Patients with severe COPD were randomized to receive either saline, MSCs, or MSCs primed with CXCR4 protein (the natural ligand for SDF-1). All clinical events along with pulmonary functions tests (FEV!/FVC) and oxygen requirements were evaluated.

Results: Thirty patients successfully were enrolled in the study. All patients were prior or recent smokers. There were no acute adverse events. The MSC