Genetic Mismatch of Mesenchymal Stem Cells can affect their Immunosuppressive Properties both In Vitro and In Vivo
Catherine Malone Sullivan¹, J Mary Murphy¹, Cathal O’Flatharta¹, Mark Curtin¹, Matt Griffin¹, Ryan Porter², Chris Evans², Robert Coughlan³, and Frank P Barry¹
Corresponding Author: frank.barry@nuigalway.ie
¹Regenerative Medicine Institute, National University of Ireland Galway, Ireland, ²Harvard Medical School, Boston, MA, USA and ³Merlin Park Hospital, Galway, Ireland

Introduction
We previously noted a therapeutic effect of murine mesenchymal stem cells (MSCs) expressing CTLA4Ig on collagen induced arthritis (CIA). BalbC MSCs exacerbated disease progression in mismatched DBA/1 mice in this model. We sought to determine if MSCs were migrating to the site of inflammation and if the inflammatory environment exerted any effect on the cells. We also hypothesised that genetic mismatch alters the immunomodulatory effects of MSCs in inflammatory disease.

Materials and Methods
MSCs were isolated from DBA/1 (syngeneic), FVB (partial genetic mismatch), and BalbC (full mismatch) mice. Their migration and ability to undergo differentiation to the osteo-, adipo- and chondrogenic lineages was assessed in the presence of IL1-β and TNFα. Mixed lymphocyte reactions were used to determine immunosuppressive properties. Systemic injection of MSCs was performed in the CIA model with the outcome measurements of disease scores, joint histology and serum cytokine levels. To assess MSC migration to the joint qPCR was used.

Results
IL-1β and TNFα suppressed adipogenesis and osteogenesis. In BalbC and FVB MSCs osteogenesis (as demonstrated by the deposition of calcium) was significantly suppressed by both pro-inflammatory cytokines in a dose dependent manner (p ≤0.008; Fig. 1A). This was also demonstrated with Alizarin Red staining. In DBA/1 MSCs suppression of osteogenesis by pro-inflammatory cytokines was not demonstrated (Fig. 1B). There was no increased migration towards cytokines. Pre-stimulation with cytokines resulted in increased migratory capacity. All MSCs had a significant immunosuppressive effect on DBA CD4+T cells with a decrease in the Th1/Th2 cytokine ratio. The presence of FVB MSC in CIA affected joints was detected by qPCR at 5 and 14 days post-injection. BalbC MSCs resulted in a worsening of disease in the CIA model; the less mismatched FVB MSCs and syngeneic DBA MSCs had an effect equal to vehicle alone.

Discussion and Conclusions
We have demonstrated that MSCs migrate to inflamed joints and this inflammation affects MSC characteristics. Further, the genetic mismatch of MSCs can affect their immunosuppressive properties and the ability of MSCs to exert a therapeutic effect in an inflammatory environment. These results highlight significant implications for the use of MSCs in inflammatory disease.

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Disclosures
Authors have nothing to disclose.