Systemic Immune Modulation Alters Local Bone Regeneration in a Delayed Treatment Composite Model of Non-Union Extremity Trauma

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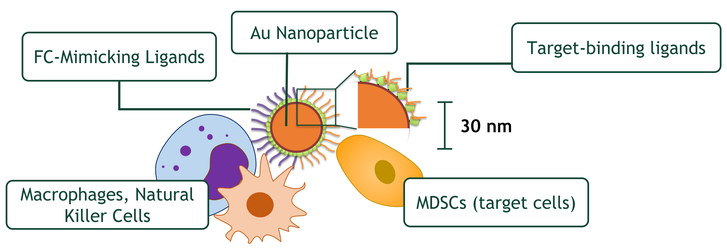
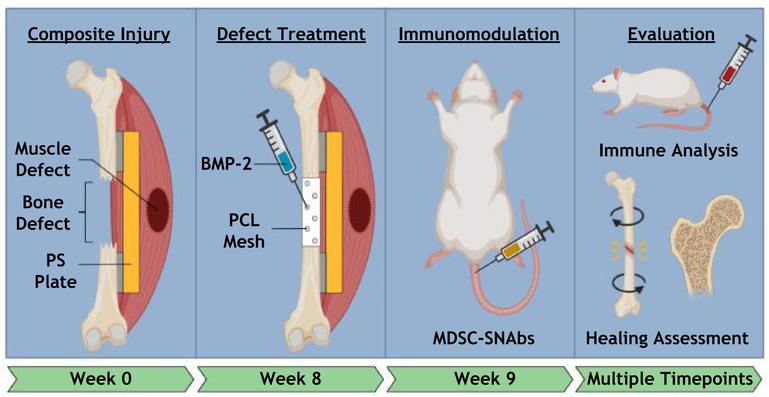
BACKGROUND AND APPROACH

Severe musculoskeletal trauma is exceedingly common and frequently presents challenging clinical scenarios such as bone non-unions and infections. Chronic immunosuppression after trauma has previously been linked to poor outcomes. Most notably, systemic myeloid-derived suppressor cells (MDSCs), which expand rapidly after trauma and suppress other immune cells, have been directly correlated to impaired bone regeneration.[1] In this study, we aimed to deplete MDSCs after trauma using Synthetic Nanoparticle Antibodies (SNAbs), a therapeutic platform consisting of gold janus nanospheres that mimic the structure and function of antibodies to deplete a cellular target.[2] Here, rats being treated for musculoskeletal trauma were arterially injected with SNAbs targeting S100A8/A9, a protein expressed by MDSCs. Blood immune cells were evaluated at multiple timepoints via flow cytometry, and healing was assessed by micro-CT imaging and torsional testing of regenerated bones. **We hypothesized that treatment with SNAbs would deplete blood MDSCs and improve bone healing.**

Synthetic Nanoparticles for MDSC Depletion

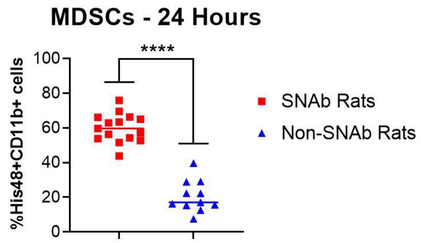


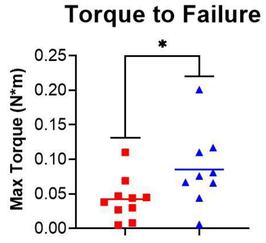
METHODS

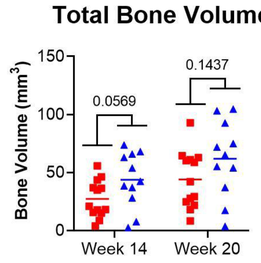


1. Unexpectedly, treatment with SNAbs resulted in an increase in total blood MDSCs and worse bone healing.
2. Closer examination revealed that a high sidescatter sub-population of MDSCs was depleted, while a low sidescatter sub-population expanded.
3. MDSC sub-populations exhibit differential expression of the target protein S100A8/A9, possibly explaining their variable depletion.

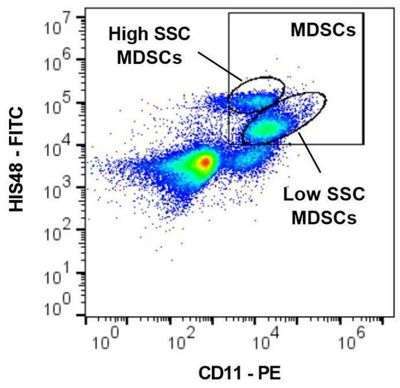
1 SNAb treatment led to an increase in total MDSCs and worse bone healing.

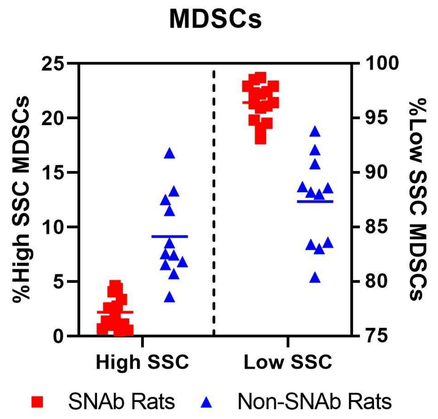




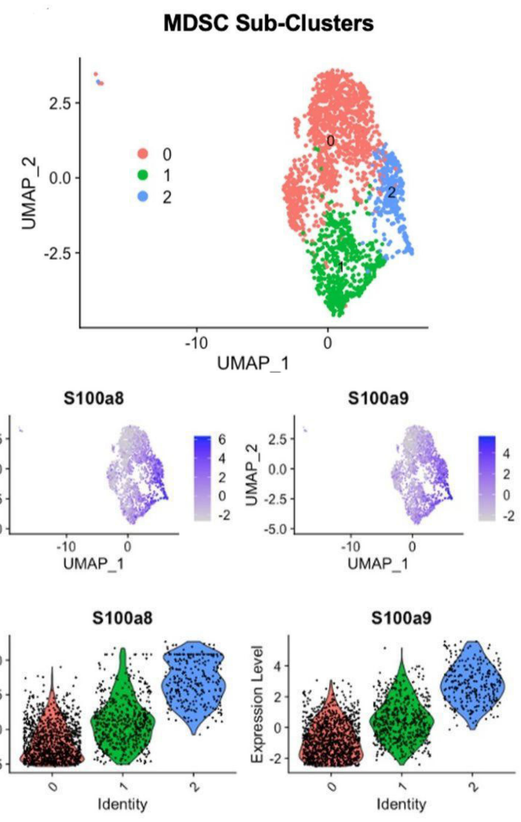


2 In SNAb rats, high sidescatter MDSCs were significantly depleted, while low sidescatter MDSCs significantly expanded.





3 MDSC sub-populations exhibit different expression of the S100A8/A9 protein.



References: [1] Cheng, A. and Vantucci, C. et al., PNAS, 2021, 118. [2] Vantucci, C. and Guyer, T. et al., Frontiers in Surgery, 2022, 9.