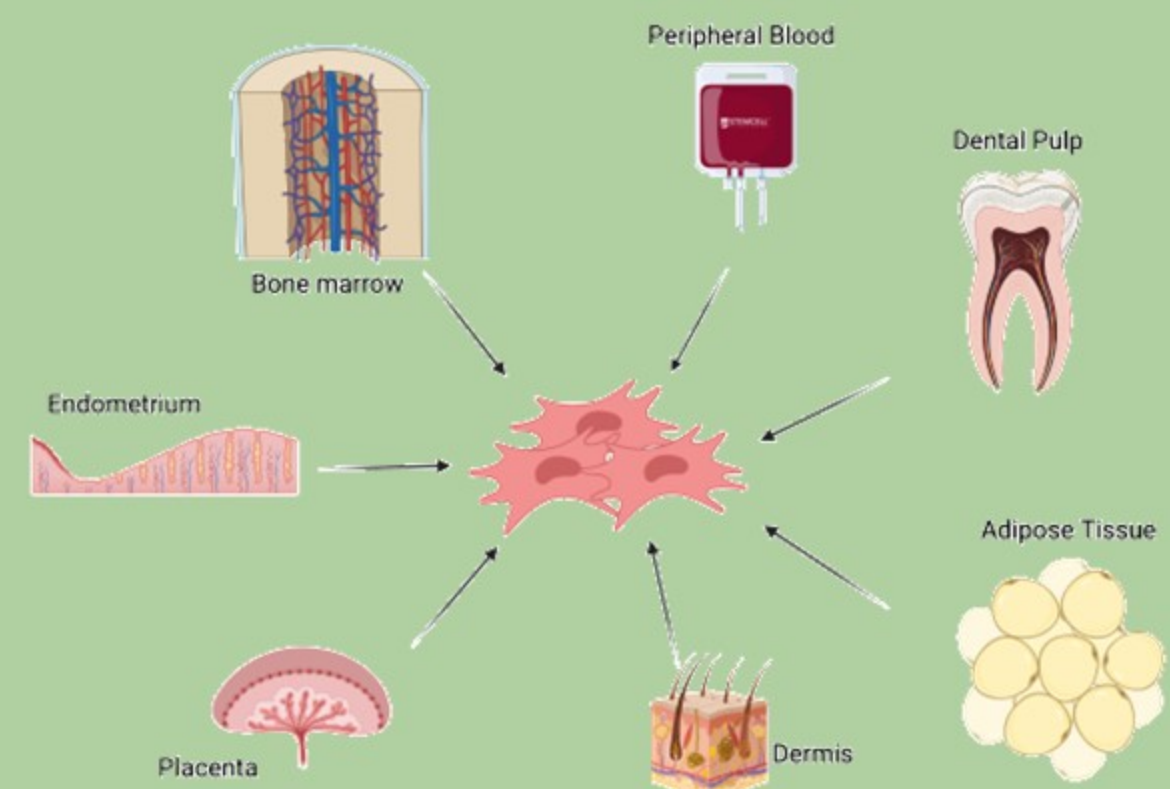


# Effects of Autoimmune Disease on Mesenchymal Stem Cells

Maya S. Washington; Hailey Swain; Parker Boyce; Jennifer Harrell; Lindsey Meeks; Grace Echele; Julie A. Semon, PhD  
Department of Biological Sciences, Missouri University of Science and Technology

## Background

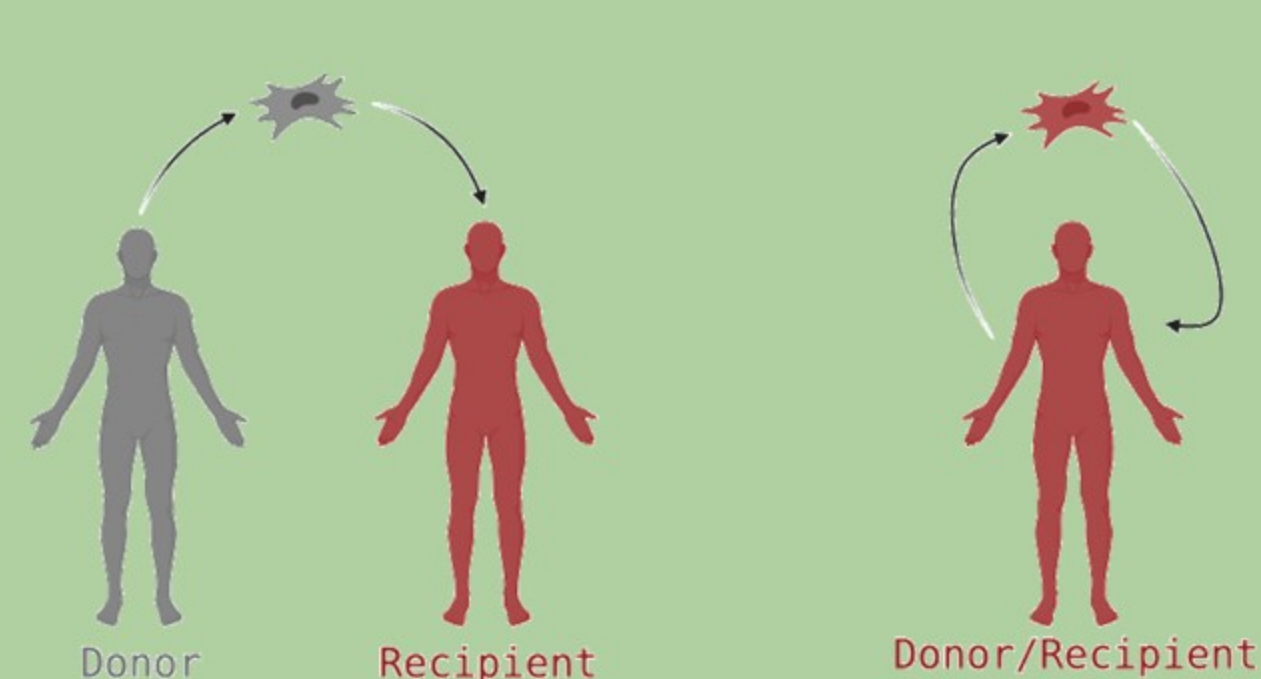
- Mesenchymal stem cells (MSCs) have a broad-ranging clinical potential and are a central building block in tissue engineering
- There are over 950 registered MSC clinical trials with the FDA, with over 10,000 patients
- The most common and longest utilized source for MSCs are bone marrow and adipose tissue
- Currently, it is believed MSCs therapeutic ability comes from their ability to produce factors and cytokines that stimulate tissue repair, modulate inflammation, and direct immune responses.



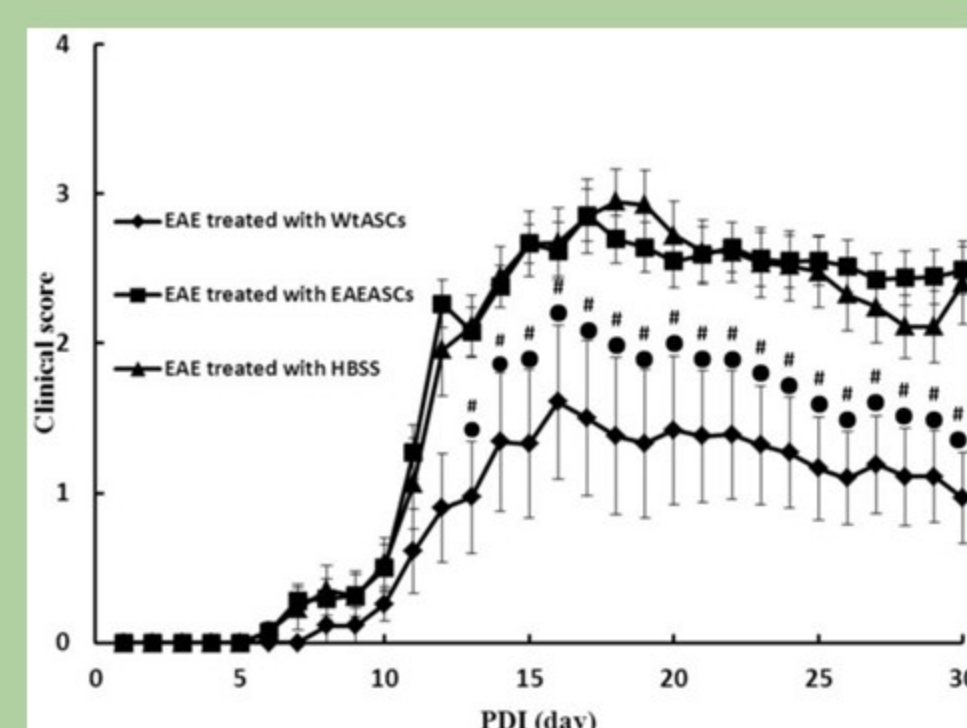
**Figure 1. Sources of MSCs.** MSCs can be obtained from many different tissues. Many studies collected for this analysis observe MSCs obtained from bone marrow and adipose tissue.

- Although therapeutic efficacy of these cells has been clearly demonstrated in different disease animal models and in numerous human phase I/II clinical trials, only very few phase III trials using MSCs have demonstrated the expected potential for therapeutic benefit.
- A major controversy is to use allogeneic or autologous MSCs

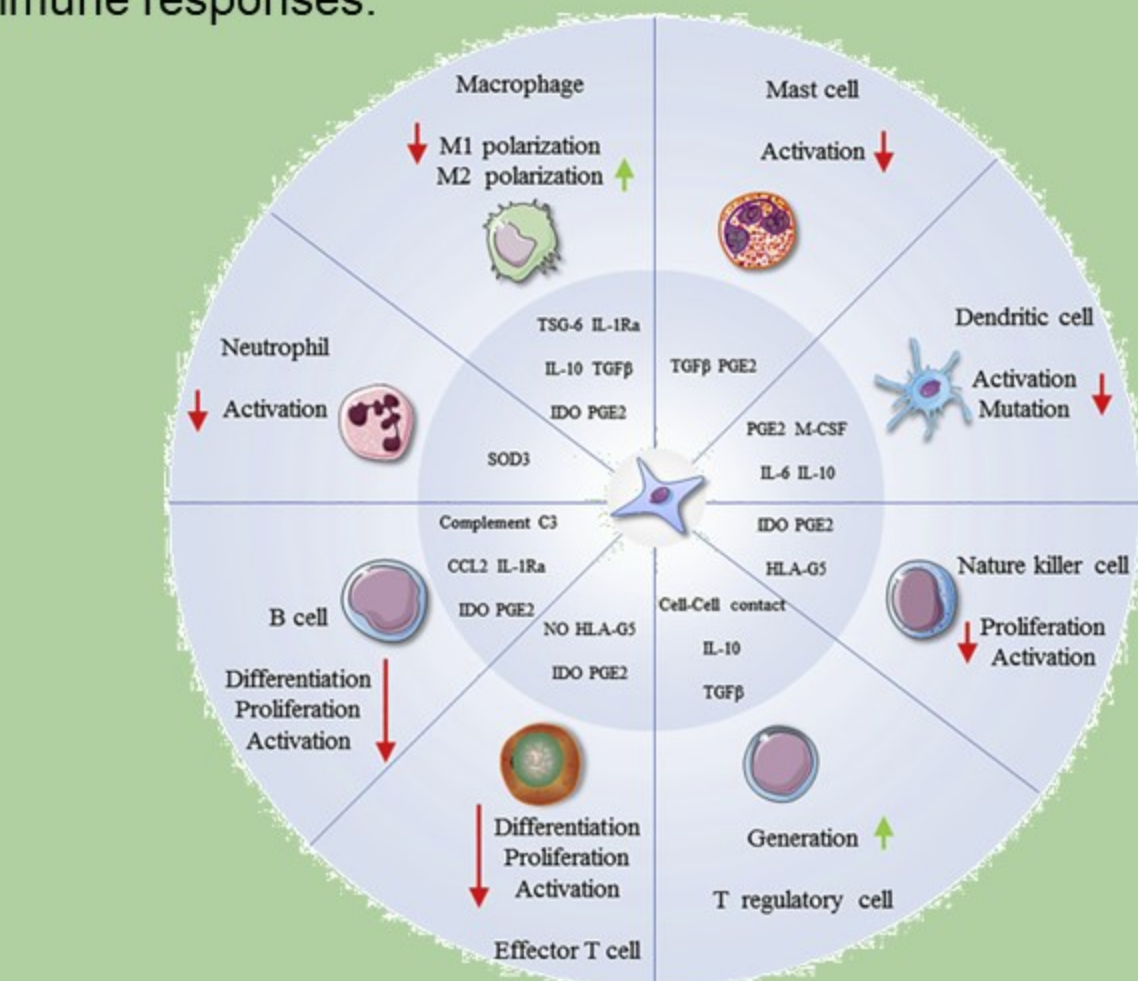
### Allogeneic VS. Autologous



**Figure 3. Autologous source vs Allogeneic source.** This demonstrates where autologous MSCs are obtained in comparison to allogeneic MSCs.

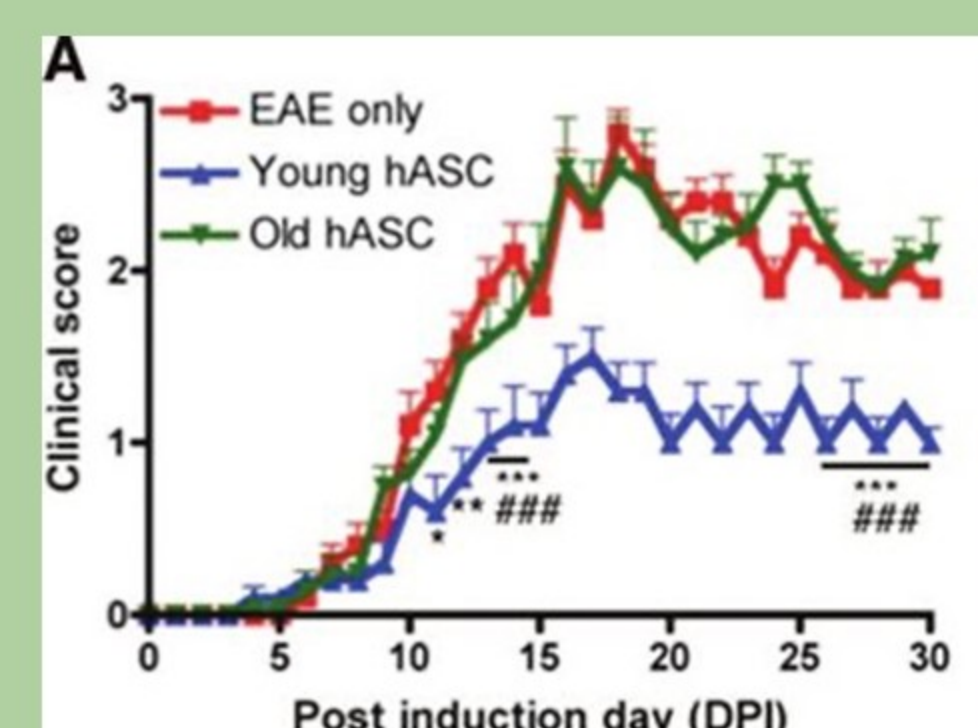


**Figure 5. MSCs from MS mouse are not therapeutic.** MS mice treated with MS-MSCs were ineffective, while MS mice treated with healthy MSCs had delayed onset and reduced disease severity. (Zhang et al.)



**Figure 2. MSCs regulate immune cells.** MSCs have the ability to exert effects on immune cells.

**Figure 4. Autologous vs. Allogeneic Therapy.** There are advantages and disadvantages of both therapies. However, autologous therapy remains the desired practice to avoid increased risks



**Figure 6. MSCs from 60+ yo humans are not therapeutic in mouse model of MS.** MSCs from persons under the age of 35, but not over the age of 60, were effective in treating a mouse model of MS. (Scruggs et al.)

## Current Study

- Our hypothesis: There is a common biomarker / panel of biomarkers that indicate a healthy MSC donor.
- Aim 1: Meta-Analysis to determine potential candidates
- Aim 2: Verify in presence of donors
- Aim 3: Evaluate pre-clinical effects of selected markers *in vitro* and *in vivo*

## Materials & Methods

### IDENTIFICATION OF RELEVANT RECORDS

Searches were conducted by three independent investigators using two different search engines: PubMed, Scopus, and OMIM Database. Four search terms were used on both search engines, and then duplicates were removed. Pathologies searched include Multiple sclerosis, Lupus, Rheumatoid Arthritis, Diabetes, and Systemic Sclerosis.

### INCLUSION/EXCLUSION CRITERIA

- Inclusion Criteria:**
- Any tissue source of MSCs
  - In English
- Exclusion Criteria:**
- Non-Human MSCs
  - Cells treated with pharmaceuticals, biomaterials, or any other agent
  - Reviews, conference proceedings, and retracted papers

### DATA COLLECTION

Full text articles were assessed further for eligibility. Articles that were determined eligible were recorded and appropriate data was included in the current study.

### ANALYSIS

- Studies compared:
- Between healthy donors of all studies
  - Between studies of the same MSC source and same pathology
  - Within the same pathology, for all MSCs
  - Within the same source of MSCs, for all pathologies
  - Between healthy donors and all sources of MSCs for all pathologies

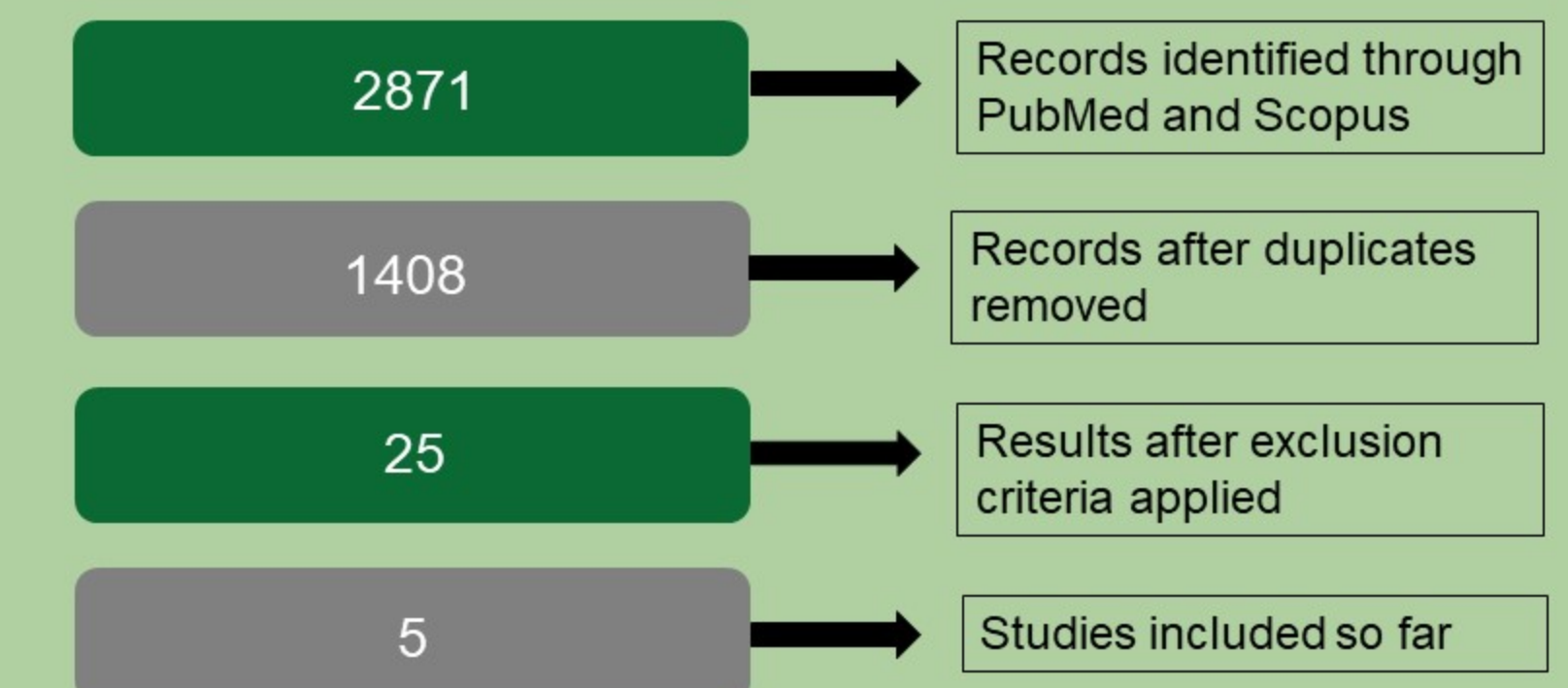
**Figure 7. Methods for collecting relevant records.** This is the direction of which the literature searches are being conducted to collect data for the meta-analysis.

Section/topic	#	Checklist Item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria; participants; and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	

**Table 1. PRISMA Guidelines.** PRISMA guidelines that will be followed for the duration of this meta-analysis (PRISMA.org)

## Results

- Autoimmune disease alters the gene expression of MSCs
- In each disease family, there are still discrepancies if genes are unregulated / down regulated



**Figure 8. Multiple sclerosis results.** Results obtained from a single researcher by conducting literature search for all four search terms in PubMed and Scopus search engines.

	Increased	Decreased	Discrepancies	Analysis Results
Diabetes	P16, P27, P53, MAP-2, PIGF, HGF, THBS1, INCR, NCAM1, NCAM-5, Vimetin, Nestin, Smooth muscle actin, Fibronectin, E-Cadherin, PECAM1, ITAGV.	SOP, GSH, CAT-enzyme, FGF2, PFGF, tPA, PDGF- $\alpha$ , SDF-1, CXCR4, FGFR-2, PDGF-R $\alpha$ , SDF-1, IGFBP, MCP-1, vWF, CD31, MMP-2, MMP-9, Ang-1, Ang-2	Expression of CD34, VEGF and MDA (sometimes showed increase and sometimes decrease in expression)	2978 differentially expressed genes (1926 upregulated; 1052 downregulated)
Multiple Sclerosis	IP10, HLA-DP-DQ-DR, TLR2, FGF2	CD29, CD105, CD73, CD44, IGF, HGF, FGF3, FGF receptor 1, GAB1, AKT2, PTPN11, TGF- $\beta$	IL-10 and IL-6 (sometimes showed increased and sometimes showed no change)	618 differentially expressed genes (370 upregulated; 248 downregulated)
Rheumatoid Arthritis	Ink4a-d, Kip1,2, Smad2/3, TGF- $\beta$	Cyclin-D	-Further studies required-	4828 differentially expressed genes (3117 upregulated; 1711 downregulated)

**Table 2. Autoimmune diseases alters MSC gene expression.** There are differentially expressed genes when observing MSCs from pathology in comparison to healthy MSCs.

## Future Directions

- Evaluate miRNA and methylation biomarker using the same methods
- Identify biomarkers in older and obese populations

## Acknowledgements

Thank you to Dr. Gayla Olbricht for her committed assistance in the statistical analysis of the OMIM data. Thank you to Ellen Cline for Mendeley training and providing understanding on search engines. Thank you to Kaiden Barozinsky and Megan Eilerman for committing to assist in record collections. Thank you to Dr. Julie Semon for her amazing mentorship in the progression of this project.

## References

- de Oliveira GLV, de Lima KWA, Colombini AM, Pinheiro DG, Panepucci RA, Palma PVB, et al. Bone marrow mesenchymal stromal cells isolated from multiple sclerosis patients have distinct gene expression profile and decreased suppressive function compared with healthy counterparts. *Cell Transplant*. 2015;24(2):151-65.
- Zhang, X., Bowles, A. C., Semon, J. A., Scruggs, B. A., Zhang, S., Strong, A. L., Gimble, J. M., & Bunnell, B. A. (2014). Transplantation of Autologous Adipose Stem Cells Lacks Therapeutic Efficacy in the Experimental Autoimmune Encephalomyelitis Model. *PLoS ONE*, 9(1), e85007. <https://doi.org/10.1371/journal.pone.0085007>
- Scruggs, B. A., Semon, J. A., Zhang, X., Zhang, S., Bowles, A. C., Pandey, A. C., Imhof, K. M. P., Kalueff, A. V., Gimble, J. M., & Bunnell, B. A. (2013). Age of the Donor Reduces the Ability of Human Adipose-Derived Stem Cells to Alleviate Symptoms in the Experimental Autoimmune Encephalomyelitis Mouse Model. *Stem Cells Translational Medicine*, 2(10), 797-807. <https://doi.org/10.5966/sctm.2013-0026>
- <http://www.prisma-statement.org/>