

# The need for highly sensitive imaging as a rapid functional test of mesenchymal stem cell (MSC) therapeutics

Amelia Bartholomew, Erszebet Szilagyi, Rachana Patil, Kavitha Premand, and Jiangzhou Yu

Department of Surgery, University of Illinois

**Abstract—** Autologous mesenchymal stem cells have been developed for cellular therapeutics using a variety of culture conditions, cell surface markers, and source of origin. Unique conditions of the donating host, including age, comorbidities, and prior treatments such as radiation or chemotherapy may affect the quality of autologous mesenchymal stem cells isolated reducing therapeutic efficacy. Variable efficacy has been observed in clinical trials with these cells in conditions such as graft versus host disease 1, multiple sclerosis 2, and heart disease 3. With mesenchymal stem cells demonstrating significant heterogeneity in form and function, a means to select qualitatively better functioning cells has become a significant priority of the field.

Mesenchymal stem cell function can be enhanced following exposure to high doses of interferon gamma. In wound healing, interferon gamma activated mesenchymal stem cells can significantly improve wound tensile strength to that of young animals 4, demonstrating a role for enhanced regenerative capacity of these activated cells. Interferon gamma activation can also potentiate immunosuppression of T cells in the treatment and prevention of graft versus host disease 5. Increasing mesenchymal stem cell therapeutic capacity corresponds to morphologic changes; MSC become rounder and wider, with some cells relinquishing their characteristic spindle shape. Increased production of potent cytokines and growth factors such as pro-angiogenic hepatocyte growth factor, immunosuppressive IL-10, and chemotactic CXCL10. Correspondingly, growth kinetics and doubling times are reduced as the cells focus much of their efforts in producing increased amounts of desired therapeutic molecules.

Examination of the cells microscopically and by flow cytometry demonstrates heterogeneity. Light microscopy shows variability in cell shape with not all cells adopting a rounded configuration. The cell surface marker MHC class II increases in expression in a sub-population of cells; sorting of these cells demonstrates greater potency than MHC class II- expressing MSC in enhanced wound tensile strength. These findings underscore the presence of heterogeneous effects with MSC populations and the need for correlation between imaging and function.

Ideally, the MSC functional capacity of a therapeutic could be rapidly screened by highly sensitive morphologic criteria. Using the demonstrated superior efficacy of MHC Class II+ interferon

gamma-activated MSC as a standard, new imaging strategies could be developed to take into account nuanced changes of the cytoskeleton, nuclear volume, which are involved in enhanced efficacy.

**Index Terms—**stem cells, functional test

## References

1. Le Blanc, K. et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. *Lancet* 371, 1579-1586 (2008).
2. Karussis, D. et al. Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. *Archives of neurology* 67, 1187-1194 (2010).
3. Sanina, C. & Hare, J.M. Mesenchymal Stem Cells as a Biological Drug for Heart Disease: Where Are We With Cardiac Cell-Based Therapy? *Circ Res* 117, 229-233 (2015).
4. Lee, S. et al. Activated mesenchymal stem cells increase wound tensile strength in aged mouse model via macrophages. *J Surg Res* (2012).
5. Polchert, D. et al. IFN-gamma activation of mesenchymal stem cells for treatment and prevention of graft versus host disease. *Eur J Immunol* 38, 1745-1755 (2008).