

5th International Conference on **Clinical & Experimental Cardiology**

April 27-29, 2015 Philadelphia, USA

Impact of age and myocardial infarction on efficacy of patient-specific bone marrow cells for autologous therapy

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Delivery of bone marrow cells (BMCs) to the heart has substantially improved cardiac function in most rodent models of myocardial infarction (MI), but clinical trials of BMC therapy around the world have led to only modest improvements. Rodent models typically involve intra-myocardial injection of BMCs from distinct donor individuals that are young and healthy, unlike autologous BMCs used for clinical trials that are from post-MI individuals who are also typically of advanced age. We hypothesized that the age and post-MI status of the patient could impair the therapeutic efficacy of the BMCs in an autologous cell therapy treatment. Using BMCs from post-MI donor mice, and from old mice, we discovered that both recent donor MI and donor age impaired BMC therapeutic efficacy. In particular, MI led to myocardial inflammation and an increased inflammatory state in the bone marrow, changing the BMC composition and reducing their efficacy. Injection of a general anti-inflammatory drug or a specific interleukin-1 inhibitor to post-MI donor mice prevented this impairment, suggesting intramyocardial injection of post-MI BMCs is equivalent to the delivery of an active inflammatory re-sponse that may attack the already-injured myocardium that the therapy is designed to treat. Our findings offer one explanation of why human trials have not matched the success of rodent experiments, and suggest potential strategies to improve the success of clinical autologous BMC therapy. These results also underscore the influence of patient-specific characteristics on the efficacy of their own cells for autologous therapies.

Biography

Matthew L. Springer received his Bachelor's degree from the University of California, Berkeley in 1985 and his Ph.D. from Stanford University in 1992. He remained at Stanford for his postdoctoral research and continued his research there as a senior scientist. In 2003, he joined the faculty of the University of California, San Francisco, where he is currently one of two non-clinicians on the faculty of the Division of Cardiology. He has published extensively about cell and gene therapy approaches to the treatment of cardiovascular disease, as well as the influence of environmental factors including secondhand smoke on vascular endothelial function.

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