

**Stony Brook University
The Graduate School**

Doctoral Defense Announcement

Abstract

Regenerating the Mammalian Heart: Potential Roles for Cardiomyocyte Proliferation,
Cardiac Stem Cells, and Fibroblasts

By

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The human heart has long been considered a postmitotic organ which is unable to regenerate contractile cells. Recent evidence has challenged this notion, indicating that the heart does regenerate cardiomyocytes, but at a rate too slow to be therapeutic in a setting of heart disease. A large body of recent work has aimed to increase the rate of cardiomyocyte replacement to therapeutic levels. Most of this research has focused on the potential of various types of stem cells to reconstitute the diseased heart, with some evidence even suggesting the existence of resident cardiac stem cells. However, a second source of cardiac regeneration may reside in the proliferation of adult cardiomyocytes. The present body of work represents investigations into both of these approaches. Our laboratory has shown that human mesenchymal stem cells (hMSCs) can stimulate adult cardiomyocytes to proliferate *in vitro*. Based on our results and the work of others, we hypothesized that paracrine factors from the stem cells may permit cardiomyocyte re-entry into the cell cycle. Co-cultures of adult canine cardiomyocytes and hMSCs or hMSCs transfected with the genes that encode proteins relevant to cardiomyocyte proliferation were employed to investigate the role of paracrine signaling. The use of transfected hMSCs and growth factor supplementation was shown to augment the rate of colony formation in cardiomyocyte cultures. However, while the rate of cardiomyocyte proliferation may have increased, it still remained below the levels of detection using time-lapse microscopy.

Stemming from our research on colony formation, the source of cells described by others as resident cardiac progenitor cells and implicated in the formation of three-dimensional aggregates termed “cardiospheres” was investigated. Our results suggest that the cardiospheres are comprised primarily of fibroblasts, rather than a population of rapidly proliferating resident cardiac stem cells. Further experiments showed that similar spheroid structures could be created from fibroblasts derived from other tissue sources. *In vitro* differentiation protocols confirm that cells from these spheres can differentiate along a cardiac lineage, as well as other mesenchymal cell types including adipose, bone, and cartilage.

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Place: Basic Science Tower, T-5, Room 140

Program: Biomedical Engineering

Dissertation Advisor: Ira Cohen, MD, PhD