Heart disease is the leading cause of death worldwide. Cell transplantation therapy is emerging as a method for regeneration of the heart muscle cells (cardiomyocytes) lost during disease. Despite several advances in cell transplantation field, there is no consensus on the type of donor cell or optimal conditions required for myocardial repair. Cardiac progenitor cells (CPC) present in mid-gestation ventricles exhibit unique attributes such as the ability to rapidly divide and subsequently differentiate into mature cardiomyocytes. The present study examined the effects of β-adrenergic receptor (β-AR) agonists and antagonists on proliferation and differentiation of mid-gestation ventricular cells in vitro as well as on intracardiac graft formation in vivo. Results showed that primary cultured or transplanted ventricular cells underwent a reduction in cell cycle activity following exposure to non-selective β-adrenergic stimulation via Isoproterenol (ISO). Further, administration of β-AR blocker Metoprolol rescued deleterious cell cycle effects associated with ISO treatment in vitro and in vivo. While β-AR stimulation increased the differentiation of CPCs into cardiomyocytes, β-AR blockers exhibited the opposite effect on CPC differentiation.

This study also tested the hypothesis that developmental stage and differentiation status of ventricular cells could impact on their engraftment potential in vivo. Results showed that mid-gestation ventricular cells could form larger intracardiac grafts when compared to ventricular cells from later developmental stages. Notably, mid-gestation ventricular cells can migrate to the injured myocardium and improve cardiac function more efficiently compared to cells from a later developmental stage. Further, this work also evaluated the potential of a novel mitochondrial dye (TMRM) based method to fractionate CPCs from cardiomyocytes. Results from TMRM based fractionation studies demonstrated that CPCs could be efficiently separated from cardiomyocytes and the fractionated CPCs have the potential to differentiate into cardiomyocytes with or without cardiomyogenic factors. Collectively, results from this thesis increased our current understanding of the mechanisms regulating proliferation and differentiation of cardiomyogenic donor cells. These findings could bridge the gap between the basic research and clinical use of myocardial cells derived from pluripotent stem cells and possibly aid in the development of new cell-based therapies for treating patients with severe heart disease.