The heart is the first crucial functioning organ in a developing embryo. The cell essential for the pumping of the blood through the vascular system is the cardiomyocyte. Cardiomyocyte precursors (CPCs) develop in the mesoderm of the embryo in close association with the endoderm. Recent advances in our knowledge on CPC show that during the initial formation of the heart tube, the so-called first heart field (FHF) progenitors are important. These primarily form the left ventricle of the mature heart. Thereafter, second heart field (SHF) CPCs add the right ventricle and outflow tract as well as part of the inflow tract to the looping heart tube. During the process of addition and looping, septation and valve formation take place. The resultant is a four-chambered heart with a unidirectional flow from the right and left atria to the right and left ventricles and respective pulmonary trunk and ascending aorta. This complex remodeling process is highly dependent on instructive and cellular contribution from various surrounding cell populations. These comprise in the early embryo the endoderm as well as later on the endocardium and the epicardium with its epicardium-derived cells (EPDCs). These cell populations are essential in their interaction with the immature myocardial cells for their proper differentiation and the eventual myocardial architecture. Last but not least, the development of a coronary vascular system with endothelial cells and EPDC-derived smooth muscle cells completes the demands of the oxygenation of the cardiomyocytes. Whether the differentiation of a specific population of the
cardiomyocytes into the cardiac conduction system requires an interaction with surrounding cells is still unresolved.

Interest in cardiomyocyte origin and maturation has been highly augmented by the use of cardiac stem cells and inducible progenitor cells (iPCs) for therapeutic aims in life-threatening myocardial pathology and possibly in the future congenital heart disease.

In this section, many aspects of cardiomyocyte (patho-)biology are addressed. For the possible use in the future of CPCs, it is essential to know whether there are differences between FHF- and SHF-derived CPCs as they have their specific contributions to the right and left ventricle with again their specific cardiac failure problems. Single cell transcriptome analysis might be a novel technique to unravel this question. In early development, the inductive role of the endoderm with several important molecular factors like FGFs including the importance of the related thyroid hormone system should be considered with a possible impact on cardiac disease.

Intriguing is the question of cardiomyocyte regeneration capacities in the mature heart not only by reactivation of the dormant CPC population but also by understanding the molecular mechanism underlying the normal cardiomyocyte cell cycle. Cardiomyocyte proliferation is highly active in the prenatal heart and stops postnatally. Understanding of the mechanism underlying this process and the possibility to extend or to reactivate cardiomyocyte proliferation, in which Meis1 is reported to have a role, might be of great clinical value.

Of similar interest are aspects of formation of the architecture of the myocardial wall consisting of 30% cardiomyocytes and 70% cardiac fibroblasts. The myocardial wall develops from a simple two-layered structure into a trabecular layer on the inside and a compact layer on the outside. During development, the relative contributions vary in which the compact layer increases in thickness and the trabecular layer through compaction diminishes. A proper balance of trabecular and compact layer formation seems to be regulated by the Notch pathway-mediated endocardial to myocardial interaction. Disturbance of this pathway in mice may result in a phenotype that resembles a left ventricular non-compaction cardiomyopathy (LVNC) also observed in human familial mutations in this pathway. Likewise, epicardial to myocardial interaction is essential for compact myocardial layer formation as well as ventricular septation. A role of the epicardium in the formation of an anterior-folding ventricular septum is described, shedding new light on the development of ventricular septal defects.

In conclusion, understanding of myocardial pathology and resultant therapeutic and preventive measures, in CHD as well as adult cardiovascular disease, deserves a highly diverse research approach as is elegantly highlighted in this section.