Cardiac valve diseases are common clinical problems that affect from 4 to 10 % of the human population, increasing with age. For many valve problems, there are few options other than surgery, adding to the more than 16,000 surgical cases occurring each year. While surgical techniques continue to improve, the number of surgical cases and associated mortality rates still continue to increase. Secondary complications such as arrhythmias, heart failure, aortic dissection, myocardial hypertrophy, and sudden cardiac death exacerbate primary effects upon blood flow and hemodynamics, indicating the importance of identifying remedial etiologies which remain poorly understood.

Discovery of mutations in patients with congenital heart defects or valve diseases which display progressive (age related) forms of matrix degeneration (e.g., a myxomatous or a calcification phenotype) is currently providing a useful approach for uncovering mechanisms that impact heart valve development and provide candidate targets for therapy. One example of this was the discovery in 2007 by Profs. Herve Le Marec and Jean-Jacques Schott (Nantes, France) of a point mutation in patients with a non-syndromic form of mitral valve prolapse (MVP) that is characterized by progressive, degenerative changes in the extracellular matrix. The mutation occurred in the actin-binding region of a multifunctional cytoskeletal protein, filamin A (FLNA). In mice models, loss of cytoskeletal FLNA function revealed a similar phenotype to MVP resulting in hypertrophied valves with reduced mechanical properties. Further studies indicated that
downstream kinase pathways associated with increased canonical and noncanonical TGFβ signaling were associated with the FLNA mutation. How this information might be used to help patients with valve diseases like MVP is an opportunity for basic scientists and clinicians to come together to achieve remedial therapies. In this instance, the finding of altered TGFβ signaling in MVP patients evokes the question of whether similar pharmacological approaches currently being used to treat Marfan patients who also have elevated TGFβ signaling could be used to treat patients with a myxomatous valve phenotype.

The FLNA gene is normally expressed in the mesenchymal progenitors of valve or ventricular interstitial fibroblasts and is downregulated during neonatal life as shown by Russell Norris and his colleagues (Developmental Dynamics 2010). This has two important implications: (i) the roots of adult valve defects and diseases can extend back into embryonic life and (ii) heart valve development does not end at birth but is completed postnatally in neonatal life. The expression of the FLNA gene only in mesenchyme progenitors of valve or ventricular fibroblasts points to yet another important implication for valve development: lineage.

In addition to endothelial-derived, progenitor cells, extracardiac mesenchymal cells of neural crest origin or epicardial origin migrate into the heart adding to the mesenchymal population of future valve cells in the outflow track and AV inlets, respectively. Why multiple lineages of progenitor cells are needed for valvulogenesis, especially those derived from outside the heart, is an important unresolved question in heart development and a subject touched upon by three papers presented in Part IV. Dr. Andy Wessels and his collaborators indicate in their chapter that epicardial-derived cells specifically migrate into the lateral (future parietal) AV cushions and uniquely contribute to the posterior leaflets of the left and right AV valve. He then discusses the role of Bmp signaling, through the Bmp receptor BmpR1A/Alk3, in regulating the migration of epicardial-derived cells or EPDCs initially as an epithelial sheet under the endocardium of the AV mitral valve and later as free cells within the matrix. In another paper presented in Part IV, Dr. Scott Baldwin utilizes tissue-specific Cre lineage drivers in mice to differentially assess whether Tie1 is expressed in the endocardium vs. the prevalvular mesenchyme of the AV junction or outflow tract. Dr. Baldwin’s lineage-tracing studies revealed that a non-cell autonomous form of cross talk occurs between the endocardial epithelium and subjacent valve interstitial cells that affects the secretion of extracellular matrix and the normal formation and the differential remodeling of the valves of the AV junction and outflow tract in late gestation and postnatal life. His work also provides in vivo support for the in vitro observations presented in the chapter by Drs. Kei Inai and Yukiko Sugi and their collaborators that valvular endocardial cells can regulate the migration and differentiation of valve interstitial cells. Similarly, in another chapter in Part IV, Mizuta et al. demonstrate that if Tmem100, a novel, endothelial-specific, membrane protein that is a downstream of BMP9/BMP10-ALK1 signaling, is genetically deleted, the resulting Tmem100 null embryos exhibit an atrioventricular defect. The authors suggest that the atrioventricular septal defect is the result of disrupting an active
dialogue or cross talk between the AV endocardial endothelial cells and the subjacent AV prevalvular mesenchyme.

Whether this putative cross talk between endocardium and prevalvular mesenchyme involves the secretion of a paracrine signal into the extracellular matrix, transport of developmental cues within membrane-enclosed exosomes (or adherons) or direct cell contact (e.g., gap junctions) remains another important developmental heart question to be resolved. The answer to this question could provide more candidate targets for developing or engineering remedial therapies, especially if the signal requires extracellular processing or specific receptors and downstream signaling pathways.

Cross talk does not have to be unidirectional from the endocardium to the mesenchyme but may also originate from the mesenchyme and induce changes in the endocardium. One frequently suggested function for the EPDCs is that they somehow signal the termination of the transformation of AV endothelial cells into new valve progenitor mesenchyme. If correct, this could serve as a mechanism for regulating the normal size or shape of lateral AV cushions and their future parietal leaflets. Whether the neural crest plays a similar instructive “cross-talk” role in determining the size, shape, or fate of the semilunar valves derived from the outflow tract cushions also remains to be determined. Understanding how lineage and “cross talk” may intersect to shape and model inlet and outlet valve development is likely to be one of the more exciting and promising future directions for research into the mechanisms of cardiac valvuloseptal morphogenesis. Already, there are emerging clues and new insights that point to primary (non-motile) cilia as specialized structures on the surfaces of embryonic epithelial and/or mesenchymal cells that may potentially act as sites for sending or receiving developmental signals between interactive cells.

Finally, valve development – be it AV or semilunar – is largely a story about the extracellular matrix and the progenitor cells that normally differentiate into valve interstitial fibroblasts. Like all fibroblasts, they can be “friend or foe.” During normal development, they secrete a collagenous matrix which they organize and compact into mature cusps and leaflets. In disease states, they may transdifferentiate into myofibroblasts that secrete metalloproteinases and proteoglycans that disrupt the matrix resulting in a myxomatous phenotype in the AV valves, or, in the outflow tract, they may abnormally enter osteogenic lineages resulting in calcified aortic valves. In her chapter, Dr. Katherine Yutzey and her colleagues review positive and negative changes in the extracellular matrix that precede normal or pathological remodeling and dissect some of the candidate transcriptional regulatory mechanisms that regulate lineage progression and organization of valve extracellular matrix.