Role of Transforming Growth Factor *Beta2* in Congenital Heart Disease

Gracelyn Bose, Abu Ahmed, Li Huang, Kirti Sarangdhar and Mohamad Azhar
Herman B Wells Center for Pediatric Research, Indiana University School of Medicine.

Congenital heart disease (CHD) represents the largest class of birth defects in the US and affects about 0.8% of all babies born. As a result of remarkable advances in the medical and surgical management of CHD, more than 75% of children born with CHD now live into adulthood. As such, discovery of the causes for CHD is not only a fundamental research endeavor, but is vital to the health care of this growing community. Inherited genetic mutations in Transforming Growth Factor *Beta* (*TGFB*) gene are found in the patients of Loeys-Dietz syndrome. Several cardiac (endocardial, myocardial) and extra-cardiac (second heart field, neural crest) cell lineages that express *Tgfb2* contribute to heart development. To study the role of *Tgfb2* in different cell types involved in heart development, we have generated *Tgfb2* conditional knockout mice. These mice harbor *Tgfb2* LacZ-tagged conditional-ready allele (also called tm1a). By using long range PCR (LR-PCR) we have confirmed the germline transmission of $Tgfb2^{tm1a}$ allele. Histological examination shows that $Tgfb2^{tm1a/tm1a}$ embryos develop several congenital heart defects. This indicates that $Tgfb2^{tm1a}$ allele is a knockout-first allele, which is consistent with the original design of our conditional gene targeting scheme. Next, by crossing to Flp recombinase mice we can generate mice with a *Tgfb2* conditional-ready allele (also called tm1c). The presence of $Tgfb2^{tm1c}$ allele in the mice is confirmed by genomic PCR. In the future, we plan to use $Tgfb2^{tm1c}$ mice to conditionally delete *Tgfb2* in different cardiac or extra-cardiac cell types using well-characterized Cre recombinase transgenic mice. Collectively, we have produced, generated, and validated mice harboring the *Tgfb2* LacZ tagged knockout-first and conditional-ready allele. Our results from embryos carrying homozygous $Tgfb2^{tm1a}$ allele indicate that TGFβ2 is required for heart development. Future research will be crucial in expanding knowledge of the unknown cellular etiology of cardiac malformations in patients with *TGFB2* mutations.

Mentors: Mohamad Azhar, Herman B Wells Center for Pediatric Research, Indiana University School of Medicine, Department of Pediatrics.