Heart disease remains the leading cause of death worldwide. Adult cardiomyocytes (CMs) have limited regenerative capabilities; the loss of CMs due to diseases, such as myocardial infarction (MI), often results in chronic heart failure. Recently, our and other labs had reported a novel therapeutic approach that mouse cardiac fibroblasts could be directly reprogrammed into induced CM-like cells (iCMs) by a combination of developmental cardiac transcription factors—GMT (Gata4, Mef2c, and Tbx5) or GHMT (Gata4, Hand2, Mef2c, and Tbx5) in vitro. More importantly, directly introducing those transcription factors into mouse heart after acute MI reprogrammed cardiac fibroblasts into functional iCMs in vivo and attenuated the malfunction of damaged heart.

Noticeably, cardiac reprogramming in vivo generated higher yield and better quality of iCMs than in vitro reprogramming. More than 80% of iCMs were fully reprogrammed into beating cells within the mouse heart, and half of these in-vivo iCMs were rod-shaped and bi-nucleated, closely resembling endogenous adult CMs. However, in vitro, most reprogrammed cells were partially reprogrammed without contractile activity by the same factors, and very few of them were fully reprogrammed into immature beating iCMs. This suggests that some endogenous factors in the heart with acute MI promote direct cardiac reprogramming.

In this study, we focus on the inflammatory factor caused by acute ischemic injury, because this inflammatory response is required for heart regeneration in neonatal mice after MI. We hypothesize that inflammatory cytokines, produced in the acute inflammatory response, might play a critical role to enhance direct cardiac reprogramming. We first screen those cytokines that were reported having effects on cardiac protection and regeneration, including TNF-a, IF-g, IL-6, and IL-13. We currently investigate if some cytokines can improve reprogramming efficiency and facilitate maturity of iCMs, and understand the mechanism how those effective cytokines promote direct cardiac reprogramming.