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Adenoviral Gene Painting for Use in Cardiovascular Tissue Engineering

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In sick sinus syndrome, the heart's pacemaker does not function properly which often leads to implantation of a mechanical pacemaker to restore a normal heart rate. Current mechanical pacemakers have limited ability to change their rates based on physiological needs and do not accommodate growth, motivating the development of a biological pacemaker to address both of these issues. Recent studies in a porcine model have shown that Tbx18, a transcription factor normally expressed during development, induces a sinus nodal phenotype evidenced by increased heart rate and decreased dependence on a backup mechanical pacemaker. Studies from our laboratory have demonstrated that β-catenin, a component of the Wnt signaling pathway, induces certain nodal properties in mice. The goal of this work is to locally transduce mouse atrial cardiomyocytes with adenoviruses expressing transcription factors with the goal of reprogramming atrial cardiomyocytes into sinus nodal-like cells. Gene painting was used to apply a virus/polymer mixture to the left atrium of the mouse. Wild-type and immunocompromised NOD/SCID mice were painted with adenovirus expressing GFP and luciferase, and long-term expression of virally-delivered luciferase was monitored using bioluminescent imaging. The photon flux differed significantly between the NOD/SCID and wild-type mice at three days, with an even greater 893-fold difference at 23 days post-gene painting. This comparison suggests that the immune system is likely involved in clearance of viral particles or virally-transduced cells in wild-type mice. NOD/SCID hearts were evaluated for GFP expression and co-stained with α-actinin to identify localized expression in cardiomyocytes. The NOD/SCID hearts showed GFP expression in left atrial myocytes as expected, with additional regions of GFP expression observed in various regions of the left and right ventricles. Future experiments will utilize genetically-engineered adenoviruses with different backbones designed to specifically target the atria and improve local transduction.