Title: A Multiscale Modeling Approach to Determine Optimal Mechanical Conditions for Myocardial Cell Delivery and Contracting Band Generation: Improving Pulmonary Valve Replacement Surgery Outcome

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Right ventricular (RV) dysfunction is a common cause of heart failure in patients with congenital heart defects and often leads to impaired functional capacity and premature death. Patients with repaired Tetralogy of Fallot (ToF), a congenital heart defect which includes a ventricular septal defect and severe right ventricular outflow obstruction, account for the majority of cases with late-onset RV failure. Current therapy by surgical or catheter based pulmonary valve replacement (PVR) to treat pulmonary regurgitation and RV outflow patch reduction has proven inadequate to restore RV function in most patients. A new surgical option placing a contracting band in the right ventricle is proposed to improve RV function measured by ejection fraction (EF). An interdisciplinary multiscale multiphysics modeling approach is proposed to combine cardiac magnetic resonance (CMR) imaging, modeling, tissue engineering and mechanical engineering techniques to construct ventricle models, perform virtual surgery, demonstrate feasibility of the new surgical procedure with band insertion, and identify optimal mechanical conditions under which optimal surgical outcome and cell-seeded contracting band myocardium tissue regeneration could be achieved. 3D multiscale CMR-based RV/LV/Patch/Band models will be introduced to provide assessment for RV mechanical conditions and cardiac function with different band options. The models will include: band insertion with various design options; fluid-structure interactions (FSI) and active contraction; isotropic and anisotropic tissue (macro) and microthread (micro) material properties; two-layer RV/LV construction with myocardial fiber orientation; and models at organ, bundle and cell levels interacting with and informing each other. The organ-level models will provide global flow and mechanical conditions the band would be subjected to using real patient ventricle geometry and pressure conditions. Fibrin microthreads seeded with stem-cell-derived myocytes will be used to form microthread bundles (contracting bands) for the new surgical procedure. The thread-level models with exact dimension and geometries of the microthread bundles will be constructed to quantify flow shear stress and structural stress conditions to determine optimal thread bundle design. The cell-level models will use individual cell morphologies on a microthread surface obtained by confocal mapping to determine the actual mechanical forces those cells are subjected to. The information will provide guidance about how cells should be distributed on microthreads for optimal delivery and survival. Quantifying mechanical conditions under patient-specific and cell-specific conditions are of vital importance for success of cell delivery, survival, and the eventual

myocardium regeneration and band construction. Feasibility of PVR with band insertion will be demonstrated by organ-level RV/LV models with various band designs and properties.

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