A Combined Cell Therapy and In Situ Tissue Engineering Approach for Myocardial Repair

Manhal Habib [1], Keren Shapira [2], Oren Caspi [1], Gil Arbel [1], Amira Gepstein [1], Dror Seliktar [2], Lior Gepstein [1]

[1] *Sohnis Family Research Laboratory for Cardiac Electrophysiology and Regenerative Medicine, Bruce Rappaport Faculty of Medicine,* [2] *Faculty of Biomedical Engineering, Technion- Israel Institute of Technology, Haifa, Israel*

Myocardial cell replacement and tissue engineering strategies are emerging as novel therapeutic paradigms for myocardial repair. Here we tested the hypothesis that a combined *in situ* tissue engineering and cell delivery strategy utilizing transplantable hydrogel-embedded cardiomyocytes [either neonatal rat ventricular cardiomyocytes (NRVCMs) or human embryonic stem cell-derived cardiomyocytes (hESC-CMs)] will improve functional performance in the rat recent infarction model.

Methods and results: A novel liquid biodegradable PEGylated fibrinogen was developed, which was proved to be compatible with cardiomyocyte survival and maturation *in vitro*. Photopolymerization using UV beam results in a rapid liquid to hydrogel transformation. To determine the functional consequences of the combined *in situ* cell/tissue engineering strategy, animals were randomized to injection of saline, NRVCMs alone, the biopolymer alone, or the combined delivery of the biopolymer and the NRVCMs. Histological studies demonstrated the presence of the hydrogel-embedded cardiomyocytes within the scar tissue. The biopolymer was fully absorbed one month following delivery. Echocardiographic measurements revealed typical post-infarction remodeling in the control group (saline injection) as manifested by the deterioration of ejection fraction (EF) by 28±3% (from 43±2% at post-injury baseline to 30±2% at 4 weeks). Injection of the biopolymer or NRVCMs alone prevented this remodeling process (39±2% to 39±2% and 43±3% to 43±2% respectively; $p<0.05$ when compared to controls). Co-injection of the biopolymer and NRVCMs resulted in the best functional outcome with EF improving by 22±8% from 40±4% to 48±4% ($p<0.05$ when compared to the saline or biopolymer groups and $p=0.07$ when compared to NRVCM group). Finally, initial studies also demonstrated a favorable effect following the co-injection of the biopolymer together with hESC-CMs (from a baseline value of 45±1% to 47±1%). Similar improvements in all groups were also noted for other remodeling parameters (LV diastolic area and wall motion score).

Conclusions: We describe a novel injectable in-situ-forming hydrogel that functions as an efficient cardiomyocyte carrier for both NRVCM and hESC-CMs and acts synergistically with the grafted cells to prevent the unfavorable post-infarction cardiac remodeling and improve ventricular function in rats.