Immunome Research

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Short Communication

Immune Modulation: New Treatment for Heart Failure

Jordan J Lancaster[1], Ambar Grijalva[1], John Fink[1,2], David Benson[1], Jacob Ref[1], Kathryn Fox[1,3], Massimo Mangiola[4], Amitabh C Pandey[5], Michael R Zile[6], Douglas L Mann[7], Emerson C Perin[8], Sonal Singh[1], Talal Moukabary[1], Jennifer W Koevary[1,9], Steven Goldman[1*]

[1]Department of Medicine, University of Arizona, Arizona, USA; [2]Department of Pediatrics, University of Minnesota, Minnesota, USA; [3]Department of Surgery, University of Arizona, Arizona, USA; [4]Department of Pathology, NYU Grossman School of Medicine, New York, USA; [5]Department of Medicine, Tulane University, Louisiana, USA; [6]Department of Cardiology, Medical University of South Carolina, South Carolina, USA; [7]Department of Cardiology, Washington University, Missouri, USA; [8]Department of Cardiology, University of Texas, Texas, USA; [9]Department of Biomedical Engineering, University of Arizona, Arizona, USA

INTRODUCTION

There is a complex interplay among inflammation, fibrosis, and immune cell activation in patients with ischemic heart failure. While this concept is well appreciated, the immune-mediated mechanisms by which the progression occurs from an initial ischemic event to the development of Heart Failure with reduced Ejection Fraction (HFrEF) are still being studied. While current Guideline Directed Medical Therapy (GDMT) for HFrEF will reduce myocardial inflammation, none of these therapies is directly immunomodulatory [1]. The principal action of GDMT is directed towards reducing congestion and volume overload which drive recurrent hospitalizations however, it is the activated adaptive immune response in heart failure that is responsible for the persistence of inflammation [2]. The development of therapeutics that can re-direct the immune system towards reparative pathways may offer new ways of treating heart failure. Lancaster et al. have described a biological platform that can repair damaged myocardium and improve Left Ventricular (LV) function in preclinical animal models of ischemic heart failure [3,4]. The mechanism of action of this biologic platform is to modulate the body's immune response to increase the prevalence of M2 reparative macrophages in the damaged myocardium [4].

This biologically active platform is composed of human induced pluripotent stem cell-derived cardiomyocytes and human neonatal fibroblasts co-cultured on a bioresorbable matrix and implanted on the epicardial surface of immune competent Yucatan mini swine 1 month after myocardial infarction. After 6 months of treatment, the biologic platform improved Left Ventricular (LV) structural pathology, restored LV contractility without any constrictive effect on LV filling, partially reversed maladaptive LV and right ventricular remodeling, increased exercise tolerance, and caused no ventricular dysrhythmias. Myocardial oxygen consumption and the rate-pressure product did not change indicating no change in myocardial energy requirements and no pathologic hypertrophy [4]. Using spatial transcriptomics, in a murine model of HFrEF, the biologic platform induced a $CD45^{pos}$ immune cell response that resulted in an infiltration of dendritic cells and macrophages. The influx of inflammatory macrophages recruited to the damaged heart were polarized to an M2 state and developed a reparative phenotype after treatment. The biologic does not persist long term and is believed to work through paracrine signaling that down regulated pro-inflammatory M1-like macrophage polarization while simultaneously up-regulating M2 anti-inflammatory, pro-reparative pathways. *In vivo* M2 polarization was confirmed through the increase in transcriptomic expression of anti-inflammatory M2 markers such as Resistin-Like Alpha (Retnla) and Mannose Receptor C-type 1 (MRC1). The increased presence of M2 markers in the biological treated zone of the chronically infarcted heart suggests that the biologic provides signals that polarize monocytic derived macrophages to their M2 phenotype as shown in Figure 1.

Graphic illustration of how a biologically active platform improved Left Ventricular (LV) function after 6 months of treatment, in Yucatan mini swine with ischemic heart failure. The left side shows the progression of ischemic heart failure untreated with progressive LV and Right Ventricular (RV) dilatation. The right side shows that treatment with an active biologic platform improved LV structural pathology, restored LV contractility without any constrictive effect on LV filling, partially reversed maladaptive LV and RV remodeling, increased exercise tolerance, and caused no ventricular dysrhythmias. Myocardial oxygen consumption and the rate-pressure product did not

Correspondence to: Steven Goldman, Department of Medicine, University of Arizona, Arizona, USA, E-mail: goldmans@shc.arizona.edu

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change indicating no change in myocardial energy requirements and no pathologic hypertrophy. In a murine model of ischemic heart failure, the biologic induced a CD45^{pos} immune cell response that resulted in M2 macrophage polarization that is believed to work through paracrine signaling that down regulated pro-inflammatory M1-like macrophage polarization while simultaneously up-regulating M2 anti-inflammatory, pro-reparative pathways [4].

Modulating the body's immune response to treat diseases of inflammation and fibrosis is a new approach, which, in heart failure, aims to modify the mechanisms that maintain persistent inflammation [5]. The inflammatory component of heart failure has been recognized and described but only recently has there been the target of therapeutic interventions [6]. The ability to increase the prevalence of M2 macrophages may be integral to the repair process in the damaged myocardium. Understanding how the immune response leads to repair is an opportunity for further investigation and understanding on how to further optimize the treatment and apply it to other diseases. Importantly, this is an allogeneic approach with a xenograft implant in immune competent animal models. Thus, as opposed to blocking the immune response, we are modulating it to leverage the host's native immune system. This immune modulatory approach has been postulated to be a mechanism of action in a recent clinical trial where mesenchymal precursor cells address inflammation as a major contributor to heart failure and demonstrated local cardiac as well as systemic vascular effects [6].

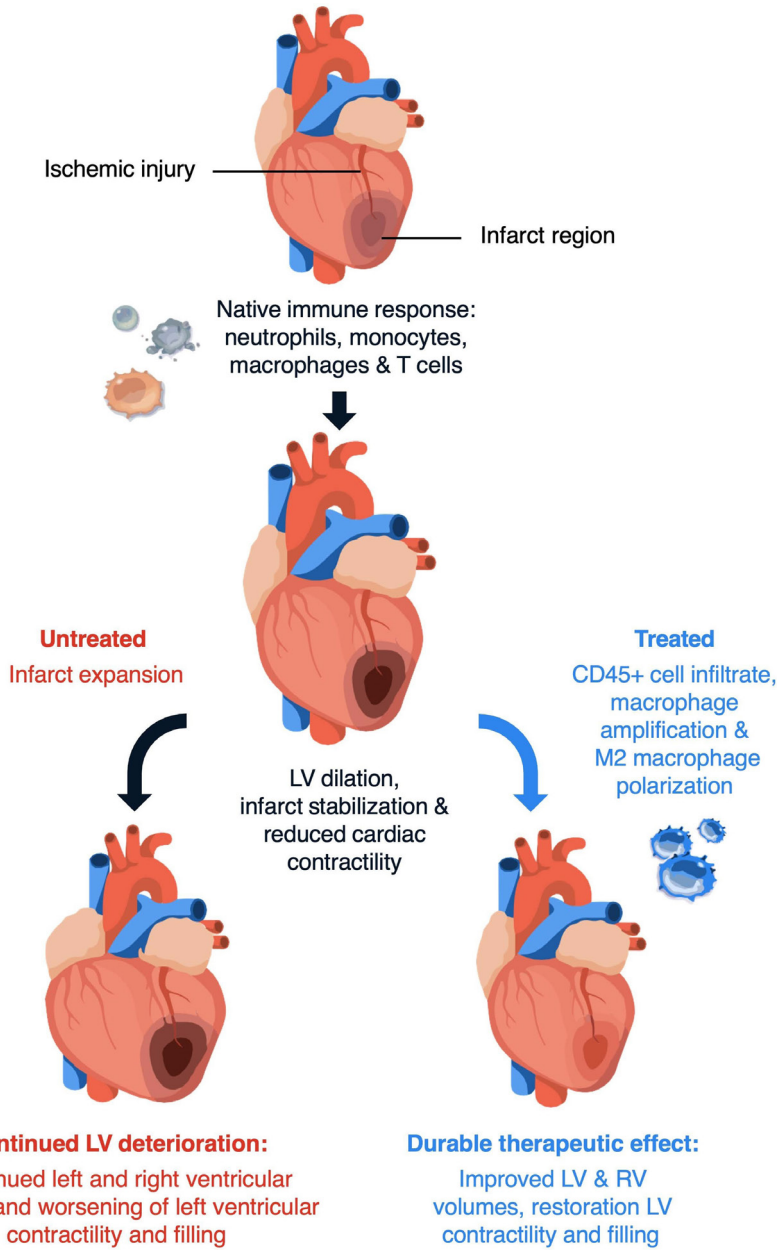

Figure 1: Biologic platform using immune modulation to treat ischemic heart failure.

CONCLUSION

The biologic delivery system in the report is a bioresorbable matrix, but this biologic platform could be delivered as an aerosol, a hydrogel or other form depending on the targeted tissue. This endogenous tissue repair response is not cardiac specific, thus providing the potential to expand this treatment to any damaged tissue or organ in the body that results in inflammation, fibrosis, and loss of functioning cells including trauma, burns, diabetes, lung disease, and liver disease.

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CONFLICTS OF INTEREST

Drs. Lancaster, Koevary, and Goldman have disclosed a financial interest in Avery Therapeutics, Inc. to the University of Arizona, which has a financial interest in Avery Therapeutics, Inc. These interests have been reviewed and are being managed by the University of Arizona in accordance with its policies on outside interests.

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