The Role of Autologous Mesenchymal Stem Cell Recellularization in Rescuing the Xenoreactive Immune Response

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INTRODUCTION

In industrialized countries, the prevalence of valvular heart disease (VHD) is estimated at 2.5%[1-4]. Accordingly, valve replacement surgery is one of the most common procedures to be performed in cardiac surgery with over 250,000 replacements performed worldwide in a give year[5]. Today, there are 3 replacement options, each with limitations.

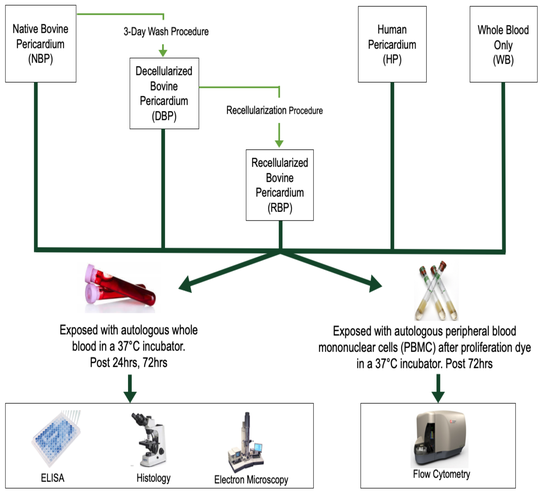
Mechanical	Bioprosthetic (tissue)	Auto/Homograft
		
- Pyrolytic carbon - Thrombogenic - Requires warfarin	- Bovine pericardium - Results in structural valve deterioration (SVD) [6-7].	- From self or cadavers - Limited Availability

AIM

We have previously shown that xenograft tissue heart valves (XTHVs) (bioprosthetic valves made of bovine pericardium) used in cardiac surgery provoke cell-mediated and humoral immune responses that are believed to contribute to time-dependent SVD.

We aim to determine if recellularization of XTHVs with human autologous cells represents one potential strategy to prevent this xenoreactive immune response and mitigate SVD.

METHODS



RESULTS

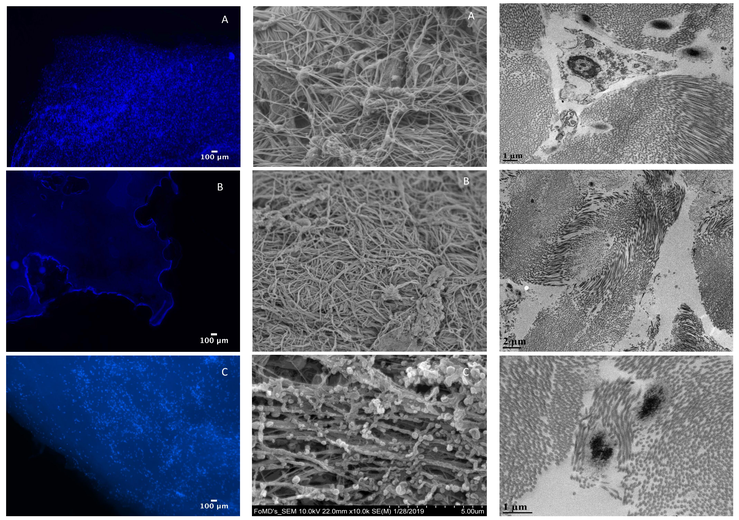
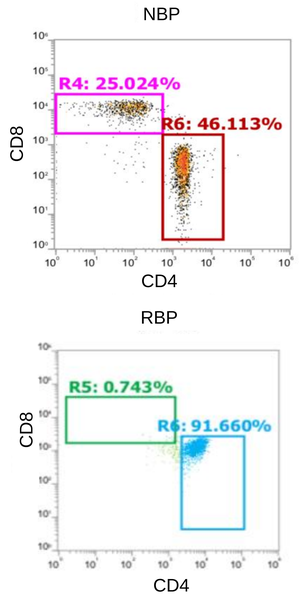
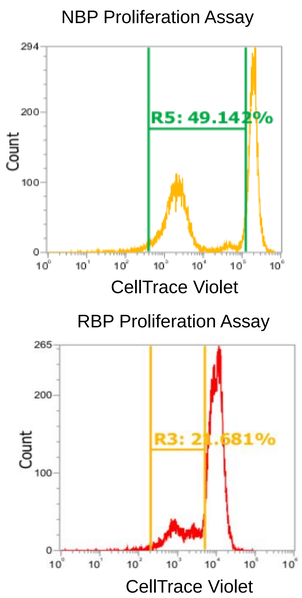


Figure 1. DAPI nuclei stain of native bovine pericardium (a), decellularized bovine pericardium (b), and recellularized bovine pericardium (c)

Figure 2. Scanning electron microscopy (SEM) image of native bovine pericardium (a), decellularized bovine pericardium (b) and recellularized bovine pericardium (c)

Figure 3. Transmission electron microscopy (TEM) image of native bovine pericardium (a), decellularized bovine pericardium (b) and recellularized bovine pericardium (c)





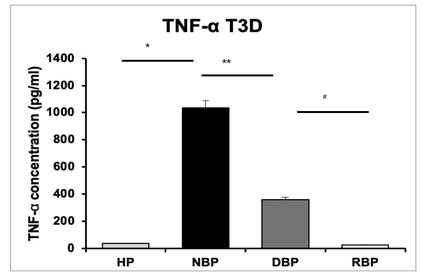


Figure 4. Tumor necrosis factor alpha concentration at 3-day after autologous whole blood exposures (n=8).

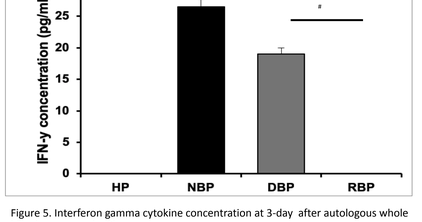


Figure 5. Interferon gamma cytokine concentration at 3-day after autologous whole blood exposures (n=8).

CONCLUSIONS

- Autologous human mesenchymal stem cell recellularized of xenogenic tissue rescues the xenoreactive immune response with a reduction in pro-inflammatory cytokines and T-cell proliferation
- Autologous human mesenchymal stem cell recellularization may be an effective approach to develop a novel tissue engineered heart valve, thus decreasing the progression of structural valve

FUTURE DIRECTIONS

- Examine expression of other proinflammatory cytokines and antibodies such as IL1b, IgG and decrease in expression of anti-inflammatory cytokines such as IL12.
- Determine whether recellularization of a decellularized xenograft matrix with autologous cells can limit the cellular and humoral immune response to recellularized xenograft tissue in a small animal, *in-vivo* model.

REFERENCES

1 **Lung B.** A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *European Heart Journal. 2003;24(13):1231-1243.*

2. **Nkomo V, Gardin J, Skelton T, Gottdiener J, Scott C, Enriquez-Sarano M.** Burden of valvular heart diseases: a population-based study. *The Lancet. 2006;368(9540):1005-1011.*

3. **Lung B, Vahanian A.** Epidemiology of valvular heart disease in the adult. *Nature Reviews Cardiology. 2011;8(3):162-172.*

4. **Lung B, Vahanian A.** Epidemiology of Acquired Valvular Heart Disease. *Canadian Journal of Cardiology. 2014;30(9):962-970*

5. **Manji R, Ekser B, Menkis A, Cooper D.** Bioprosthetic heart valves of the future. *Xenotransplantation. 2014;21(1):1-10.*

6. **Manji R, Lee W, Cooper D.** Xenograft bioprosthetic heart valves: Past, present and future. *International Journal of Surgery. 2015;23:280-284.*

7. **O'Keefe K, Cohle S, McNamara J, Hooker R.** Early Catastrophic Stentless Valve Failure Secondary to Possible Immune Reaction. *The Annals of Thoracic Surgery. 2011;91(4):1269-1272.*

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DISCLOSURES

Bovine pericardium was provided by LivaNova