The Role of Host Cellular Response on Bioprosthetic Heart Valve Calcification

Hobey Tam[1], Joshua Van Swol[1], Nathaniel Parchment[1], Narendra Vyavahare[1]
[1]Department of Bioengineering, Clemson University, Clemson, South Carolina

Bioprosthetic Heart Valves

On average, about 300,000 defective heart valves are replaced every year [1]. The most common replacement for stenotic or regurgitant heart valves are glutaraldehyde (GLUT) crosslinked bioprosthetic heart valves (BHVs). **These implants fail due to structural degeneration and/or calcification in 10-15 years after implantation** [1].

Mechanisms of calcification

Underlying factors

Devitalized Cells - - - **Host response** - - - **Degraded ECM**

- **Unstable, Reversible GLUT Crosslinking Chemistry**
- **Devitalized Cells/Tissue Degradation/Exposed Collagen**
- **Nucleation site formation at high affinity regions**
- **Mineral aggregation at nucleation sites**
- **Calcification nodule formation**

Host Cellular Response exacerbates calcification

Hypothesis: Preventing interactions of host cells with BHV implant will suppress calcification.

We implanted glutaraldehyde treated bovine pericardium (GLUT-BP) subdermally in rats, either directly or enclosed in dialysis bags (MW cutoff at 12.5kDa to prevent interactions of host cells with implant), and newly developed TRI chemistry [2] (irreversible crosslinking chemistry) for 1, 3, 5, 7, or 30 days to investigate the progression of calcification and how it correlates with cellular interaction.

Acknowledgments:
Thank you to Clemson University, the NIH (R01HL108330, and P20RR021949), as well as the NSF GRFP.

[1] Schoen FJ. Annu Rev Pathol Mech Dis 2012; 7: 161 – 83., [2] Tam H et al. Biomaterials 2015; 66: 83 – 91.

Investigating the Role of Host Cellular Response

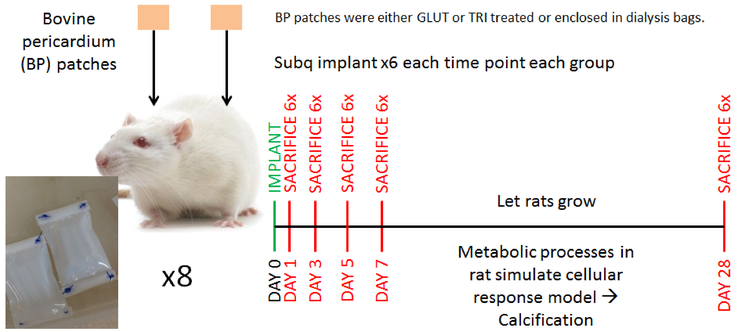

Figure 1: Experimental design to test dependence of calcification on host cellular response. (Lower left) Dialysis bags with sham sample inside.

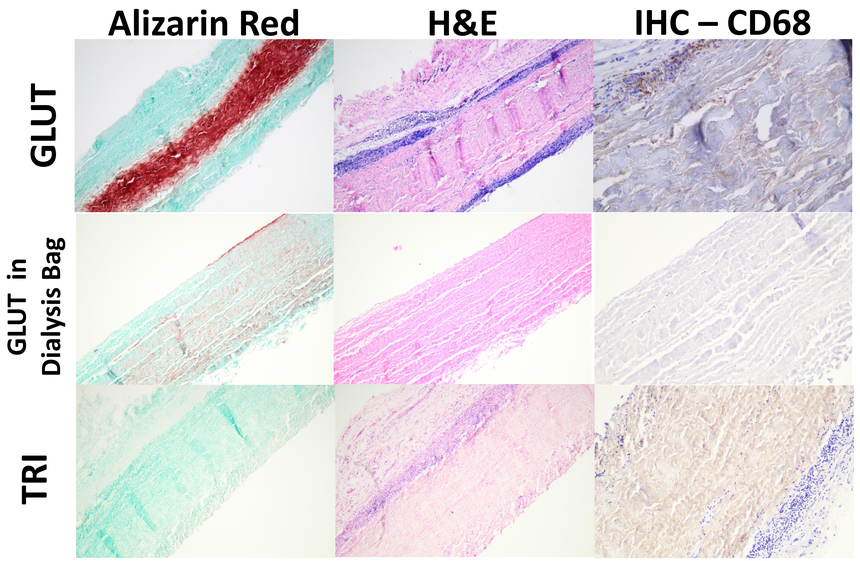

Figure 2: Histological evaluation of calcification and host cellular response at 7 days. GLUT and TRI both showed cellular infiltration but dialysis bag trials showed suppressed cellular infiltration. GLUT samples calcified heavily. Dialysis bag samples showed less calcification and TRI samples showed no calcification.

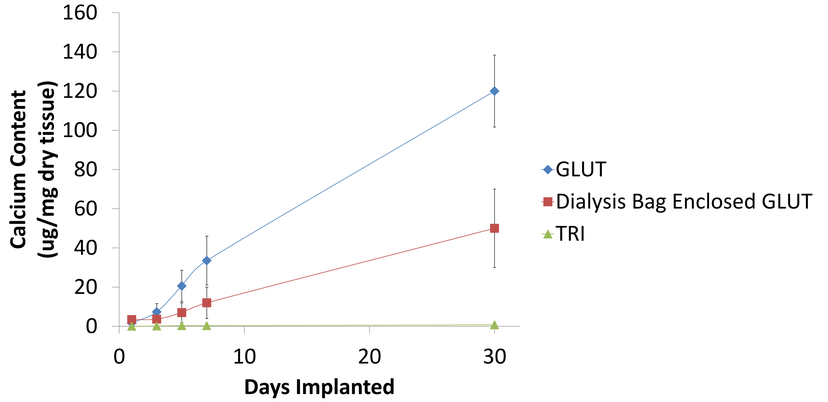

Figure 3: Mineralization content from explanted samples. Results were consistent with histology. GLUT samples calcified heavily and enclosing in dialysis bags only seemed to decrease the calcification. The ramp up in calcification formation seems to happen at the 3-7 day period. TRI samples showed minimal calcification throughout 30 days.

Conclusions

- GLUT BP calcified heavily. CD-68 IHC showed macrophage infiltration into implant.
- Enclosing the GLUT BP off from the host cellular response slowed calcification but samples still showed signs of calcification.
- Using an alternative chemistry that is more irreversible does not calcify even in the presence of host cellular response.
- Host cellular response seems to exacerbate and accelerate calcification but may not be necessarily pivotal.
    - Could be degrading matrix faster to provide higher affinity sites for calcification.
    - Host cells could also be dying inside implant and providing more nucleation sites as these are now devitalized cells.
- TEM imaging is underway to truly evaluate different calcification patterns → How do host cells participate in formation of mineral deposits? Do first deposits occur in BHV devitalized cells or infiltrating host cells? Do host cells degrade ECM and cause acceleration?