**GLYCOSAMINOGLYCANS (GAGS) IN CARDIOVASCULAR DISEASE: SEARCHING FOR THE SWEET SPOT**

**A. Lucas**

Divisions of Cardiovascular Medicine and Rheumatologym, University of Florida, Gainesville, FL, USA

The endothelial glycocalyx alters immune reactions. Among other functions, glycosaminoglycans (GAGs) in the glycocalyx bind chemokines that attract immune cell invasion. Modifying donor graft sugars can reduce complement mediated xenotransplant rejection form swine to primate. In prior work we investigated the effects of conditional deficiency of the primary heparin sulfate modifying enzyme (N-deacetylase-N-sulfotransferase-1, Ndst1-/-) in donor artery allografts demonstrated reduced vascular inflammation and plaque. We have extended this work, examining acute immune rejection in donor renal allograft transplants in Ndst1-/- mice (C57Bl/6 background), after implant into BALB/c mice with normal Ndst1 expression (Ndst1+/+). Rejection was assessed in saline treated wild type C57Bl/6 and Ndst1-/- donor allografts, with comparison to treatment with M-T7, a chemokine inhibitor that blocks chemokine/GAG interaction. Ndst1-/- donor organs treated with only saline had significantly reduced acute rejection when compared to C57Bl/6 donor organs given saline treatments. Saline treated Ndst1-/- donors had equal reductions in acute rejection when compared to M-T7 treated C57Bl/6 donors. Analysis of heparan (HS) and chondroitin sulfate (CS) disaccharide content demonstrated significant correlations with suppressed rejection. M-T7 and M-T7 point mutations were then assessed and found to have variable efficacy in reducing acute renal allograft rejection in treatment of WT and Ndst1-/- donor allografts. M-T7, E209I and M-T R171E retained anti-rejection activity while R134D was inactive. Analysis of HS GAG and disaccharide extracts again demonstrated significant correlation between altered whole organ GAG content and capacity to reduce allograft rejection. CD3+ T cell invasion in transplanted kidneys and TH17 splenocytes were reduced in Ndst1-/- grafts and with M-T7 treatment. Ndst1-/- and M-T7 treatment altered gene expression in NFB and JAK STAT pathways. In summary, modifying donor organ GAGs and inhibition of GAG/ chemokine interactions are equally effective at inhibiting early rejection. Modifying HS content in donor organs represents a new therapeutic approach for the prevention of allograft rejection.