SELECTED TALK:

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Engineering the endothelial glycocalyx using glycopolymer mimics to prevent organ rejection

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Immunomodulation, the ability to alter the immune response of a cell to a desired level, can significantly enhance organ transplantation. The endothelial glycocalyx (eGcx), made up of membrane-bound glycoproteins, is of particular interest due to its ability to control cell to cell communication and the activation of immune response through cell recognition. During organ transplantation, inflammation and oxidative damage occurs and can lead to the shedding and damage of the eGcx layer, thereby affecting its health and structural integrity; this has been linked to organ failure and rejection. Taking inspiration from cell surface glycoproteins for their immunoevassive, antioxidant and anti-inflammatory properties, we developed an enzymatic approach to modify the surface of the endothelium with synthetic polymeric mimics. Pairing cell surface engineering (CSE) with our lead compound (sialic acid containing linear polyglycerol), immobilized on the lumen of organ vessels can improve hyperacute, acute and chronic transplant outcomes. Namely disrupting the interaction and recognition by immune cells.

Sialic acid presenting polymers modified on Ea.hy.926 endothelial cell surface was able to reduce leukocyte adhesion and leukocyte-mediated toxicity. Moreover, using chimeric antigen receptor (CAR) T cells expressing HLA-A antigens to mimic rejection of an allogeneic transplant, we investigated the effects of CAR-T/Ea.hy926 co-cultures. The polymer treatment was able to significantly evade CAR-T cell recognition and reduced endothelial cell cytotoxicity. Allogeneic transplants were done using Balb/C donor mice C57BL/6 recipient mice. In arterial transplants, reduced early inflammation in vessel transplants was exhibited through reduced medial thickening and pro-inflammatory markers in serum. Furthermore, de novo generation of donor-specific antibody after 42 days was reduced in polymer-treated grafts compared to untreated. Finally in renal grafts, histological analysis of polymer-treated renal grafts revealed less infiltration and mesangial expansion relating to a healthier graft after 30 days.

In summary, we demonstrate the use of an immune suppressive polymer-mediated organ engineering approach that leads to vascular protection and localized immune suppression that prevents immune-mediated rejection of organ transplants. Namely, the presentation of immunoevassive sialic acid in a multivalent manner on polymers may be key for immunomodulation, thus the exact mechanism of action is currently being investigated.

The protocol developed is simple and easy to deliver in clinic, thereby enhancing its potential translation. We envision that this *ex vivo* intervention that engineers the blood vessel lumen using an existing organ preservation/perfusion protocol with added organ engineering components could act as localized immune therapy and may be easily translated to clinics for use in other surgical procedures where tissue is restricted from blood flow for an extended period of time.