( ) R1 ( ) R2 ( ) R3 (X) PG0 ( ) PG1 ( ) Estagiário ( ) Tecnólogo ( ) PIBIC Last Name - Borges First Name - Leonardo Middle - Pereira

Service (sector) Pharmacology - Immunology Nº CEP

Local macrophage depletion improves survival of corneal xenografts in mice by blocking antigen presentation and inhibiting hem- and lymphangiogenesis

Leonardo P. Borges, Claus Cursiefen, J. Wayne Streilein **Abstract** **Purpose:** BALB/c mice reject orthotopic guinea pig corneas acutely by a macrophage-dependent process triggered by specific CD4+ Th1 effector cells. We wished to determine which aspect(s) of macrophage function is (are) responsible for graft rejection. **Methods**: At the time that guinea pig corneas were grafted orthotopically into eyes of BALB/c mice, liposomes containing clodronate or PBS were injected subconjunctivally. Groups of recipients were examined subsequently as follows: at 12 hrs, grafted eyes were enucleated from euthanized mice and the corneas stained for CD11b+, GR-1+ and F4/80+ cells; at 6 days, corneas of grafted eyes of euthanized mice were stained for LYVE-1 and CD31 (markers of new blood and lymph vessels); and for the first 21 days postoperatively, xenografts were evaluated clinically via slitlamp for evidence of immunological rejection. **Results:** Few F4/80+ (but many CD11b+/GR1+) cells were detected in the clodronate-treated xenograft beds within 12 hrs of grafting, and few, if any, CD31+ and/or LYVE-1+ endothelial cells were detected in these beds at day 6 postoperatively. In contrast, there was strong hem- and lymphangiogenesis as well as recruitment of F4/80+ cells into PBS-treated control corneas ($p<0.0001$). Corneal xenografts in clodronate-treated eyes displayed opacity scores indicative of rejection between 18 and 23 days post grafting, a significant improvement in comparison to an average graft survival of 10 days in the PBS liposome-treated control group ($p<0.0001$). **Conclusions:** Elimination of recruited macrophages suppresses hem- and lymphangiogenesis and inhibits recipient sensitization to xenoantigens on cornea grafts. Together, these macrophage-inhibitory effects significantly promote the survival of corneal xenografts.