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## PD-Ligand Blockade Decreases IRBP-Induced Uveitis in Mice

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**Purpose:** Uveitis is potentially blinding, immune mediated, intraocular inflammatory disease. Activation of the programmed death 1 (PD-1) pathway through PD-1 binding to one of its two receptors, is believed to contribute to downregulation of T cell responses. We tested the effect of the absence or blockade of PD-ligand in experimental autoimmune uveitis (EAU).

**Methods:** Uveitis was induced in C57Bl/6 mice or PD-ligand double knock out animals on the C57Bl/6 background (PD-L DKO) using the appropriate IRBP peptide according to published protocols. All experiments were carried out in strict accordance with ARVO guidelines and the Guide for the Care and Use of Laboratory Animals. For antibody studies, C57BI/6 and B10.RIII animals were treated weekly with anti-PD-L1 antibody (BioXCell), starting 3 days after IRBP exposure. Masked clinical assessment by funduscopic examination was performed on day 20 post EAU induction for C57BI/6, and day 13 for B10.RIII animals. At 3 weeks (C57BI/6) and 2 weeks (B10.RIII) following immunization, the eyes were enucleated, fixed tissues were stained, and the histological severity graded by masked observers.

**Results:** Using the PD-L DKO showed a protective effect in EAU. Significant abrogation of uveitis was observed in animals that received anti-PD-L1 antibody treatment. The percent of C57BI/6 mice that developed uveitis following treatment with anti-PD-L1 antibody was 15% and 14% for B10.RIII, whereas 100% of animals in the IgG control or no treatment group developed intraocular inflammation ($P<0.0001$).

**Conclusions:** Decreased uveitis susceptibility in the C57Bl/6 PD-L DKO animals was an unexpected result. Similar findings were confirmed following treatment with anti-PD-L1 antibody. First, this observation may lead to a new understanding of uveitis pathogenesis. Second, the availability of blocking antibodies for PD-1 and PD-ligands, recently approved for use in cancer immunotherapy, allows for the potential feasibility of blocking the PD-1 system as a possible therapeutic target in ocular inflammation.

## Clinical, histological and biochemical aspects of corneal wound healing

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Wound healing in the cornea is different from that of other tissues for these three reasons: 1) the cornea does not have blood vessels/ has no blood supply/ it is avascular; 2) it has immune privilege/ it is an immune privileged tissue/immunologic privilege makes it a very special tissue; 3) it has a very slow metabolism. Corneal wound healing can be examined when the injury is vertical to the surface; horizontal cuts will not elicit reactions provoked by vertical incisions (see superficial horizontal wound in different types of refractive surgery or lamellar keratoplasty). Wound healing in the various layers of the cornea induces various processes, the most important of which being epithelial injuries/abrasions that release cytokines. They trigger such processes such as the degradation of extracellular matrix, apoptosis of keratocytes or chemotaxis of different inflammatory cells. The restoration of the epithelium is performed through the process of re-epithelialization in which the limbal stem cells play an active role. During the reparation the keratocytes become fibroblast, later on myofibroblasts. These cells can produce new collagen fibers and glycosaminoglycan/ glycoproteins. These are different from that of normal, transparent corneas. The characteristics of the newly generated scar tissue are not transparent, its strength being 50% less. In cases of pathologic wound healing retrocorneal membrane and pannus-like tissue may develop. Corneal scarring can impair vision. It can only be managed by surgery.