Ocular immunology: Fundamentals, disease entities, and future therapeutic opportunities

An on-demand course

Course organizers
Organizers: Reza Dana, MD, Mass. Eye & Ear Infirmary / Harvard Medical School, (Lead), Sunil Chauhan, PhD, Harvard Medical School and Daniel Saban, PhD, Duke University School of Medicine

Description
This education course will introduce the principles of immunology and immunological privilege as it pertains to eye physiology and disease. Key aspects covered in this course include cellular and molecular factors that maintain immune homeostasis in different ocular compartments, and how breakdown of these pathways gives rise to disease etiologies, such as infection, allergy, alloimmunity, autoimmunity, and aging. Basics of immune modulation and immune-based targeted therapies will also be discussed. This course will give an update on current areas of research and future opportunities for targeted immune-based therapies to increase the clinical knowledge, competence, and performance of learners.

The content of this course is suitable for basic and clinician scientists new to the study of ocular immunology.

Learning objectives
After attending this educational course, the participant will be able to:

- Describe the components of the immune system and immunologic privilege as it pertains to the eye.
- Recognize key cellular and molecular factors driving pathology in ocular immune/inflammatory conditions.
- Evaluate current areas of research on immune modulation and future opportunities for targeted immune-based therapies.

Presentations

Introduction- Spectrum of Ocular Immunopathologies
Reza Dana, MD, Mass. Eye & Ear Infirmary / Harvard Medical School

The spectrum of ocular immunopathologies include a wide range of conditions that encompass both the globe as well as adnexal structures (e.g. lacrimal gland and eyelids) that provide critical support for the functioning of the eye and visual system. These conditions include the various ocular atopic (allergic) disorders, dry eye disease, immune-mediated glaucoma syndromes, various uveitic disorders and some retinopathies, among others. This introductory lecture will provide the audience with a high-level overview of ocular immune mediated disorders and describe the areas of highest unmet medical need and relevant therapeutic strategies.
Ocular Immune Privilege
Jerry Niederkorn, PhD, University of Texas Southwestern Medical Center
This presentation will review the concept of ocular immune privilege – a condition in which immune responses that occur at extraocular sites are either blocked or suppressed within the eye. Studies in mice have revealed that multiple anatomical, physiological, and immunoregulatory processes conspire to tightly regulate immune-mediated inflammation in the eye. Corneal transplants are beneficiaries of ocular immune privilege and enjoy a success rate that is unrivaled in the field of organ transplantation. This presentation will also briefly discuss the major strategies that protect ocular tissues from immune-mediated inflammation and coincidentally promote the survival of corneal transplants. The presentation will describe conditions in which immune privilege is terminated in order to protect the host from life-threatening infections even at the risk of blindness.

Corneal Transplantation and Beyond
Victor Perez, MD, Foster Center for Ocular Immunology at Duke Eye Center
Transplantation and acceptance of allogeneic tissue in the eye is what every transplant immunologist and surgeon wants to understand. In fact, corneal transplantation is the most common solid organ transplant performed in the United States and immune response to these can lead to new discovery in tolerance induction and immune-modulatory approaches to other allogeneic transplanted tissue as well. In contrast to other solid organ transplants, the eye provides a unique opportunity to have access to the transplanted tissue and assess readily clinically survival end-points, develop novels way of visualizing immune responses to allo-antigens, build pre-clinical models to understand immune mechanisms of rejection and deliver novel immune-therapies to prevent these and induce tolerance. In this session, we will exploit our models to visualize immune responses in vivo, which we have used to understand mechanisms of immune responses to allo-antigens in the eye, especially in the context of high risk corneal vascularized corneal transplant, which represent a model to other solid organ transplants. Moreover, in the context of other allotransplants performed in the eye, that include stem cells, understanding inflammatory responses will also be reviewed. In total, we believe that the development of novel approaches to regulate specific local immune-early after transplantation is an innovative approach to regulate ocular allo-immune responses and prevent long-termed rejection by exploiting the immune-regulatory responses of the eye to induce immune-tolerance to transplant rejection reactions.

Development of inflammatory hypoxia and the prevalence of glycolysis in herpes simplex virus-induced stromal keratitis
Susmit Suvas, PhD, Wayne State University School of Medicine
Herpes stromal keratitis (HSK) is a chronic immunoinflammatory condition, which develops in response to recurrent corneal infection with herpes simplex virus (HSV). Immune cell influx, neovascularization, loss of corneal sensation, and the stromal opacity in HSV-1 infected cornea are the hallmarks of HSK. In United States, HSK is a major cause of infection-induced blindness and the current treatments involve long-term use of anti-virals and the topical application of corticosteroids. Considering the importance of immune cell influx in the development of HSK, the focus of this presentation will be to highlight the novel role of neutrophils and altered cellular metabolism in pathogenesis of HSK.

Interplay between adaptive and innate immune responses in chronic allergic eye disease (AED) and Meibomian gland dysfunction (MGD)
Daniel Saban, PhD, Duke University School of Medicine
The two major branches of the immune system are the 1) innate and 2) adaptive responses. In general terms, the former is fast-acting and nonspecific, whereas the latter is antigen-specific and long-lasting.
While these two branches are considered distinct, functionally they can act in an inter-dependent fashion to carry out an immune process in disease states, which will be the focus of the current presentation. Additionally, I will show recent work from our lab demonstrating that the T helper cell compartment (adaptive) can orchestrate recruitment of neutrophils (innate) to drive ocular surface inflammation. Importantly, this coordinated response causes MGD in the ‘chronic-like’ AED model in mice. Similarly, MGD severity in patients is positively correlated with tear neutrophil quantity (Reyes NJ. 2018, Science Translational Medicine). Hence, the interplay between adaptive and innate immunity is an important area of study in ocular surface disease and may be key to better understanding the unresolved clinical problem of MGD in patients.

**Ocular Immune Modulation by Adult Stem Cells**
Sunil Chauhan, PhD, Harvard Medical School
Mesenchymal stem cells are adult stem cells that possess extraordinary capacity to modulate tissue inflammation and regeneration. The objective of this educational talk is to discuss the mechanisms and factors by which adult stem cells regulate the immune response in inflamed ocular tissues.

**Innate Immunity and Uveitis**
James Rosenbaum, MD, Devers & Casey Eye Institutes
The innate immune system is strongly implicated in uveitis. Observations that support a major role for the innate immune system include: 1) uveitis is a manifestation of several autoinflammatory syndromes including Blau syndrome; 2) activation of TLR4 by bacterial endotoxin is a standard rodent model for anterior uveitis; and 3) an adjuvant that activates the innate immune system is generally required in most animal models of T cell dependent uveitis. The intestinal microbiome is an obvious potential source for ligands that could potentially activate the innate immune system within the eye.

**Type II cytokines, immune activation and regulation of metabolism**
Andrew Dick, MD, University of Bristol, UCL-Institute of Ophthalmology
The outer retina and choroid are rich in traditional and non-traditional immune cells. We are increasingly understanding that their role is extending beyond response to sterile inflammation or infection. The interaction of Type II cytokines (IL4, 13) as well as other inflammasome enabled cytokines (IL-33), are in consort with myeloid cells (Microglia and monocytes) to in turn inhibit Type II cytokine responses, such as fibrosis or angiogenesis. An emerging notion is that intracellular cytokine activation regulates and acts as a checkpoint inhibiting aerobic glycolysis and maintaining mitochondrial health and thus cell survival. This is pertinent to chronic insidious degenerative conditions such as AMD where immune activation is a positive response to ensure cell survival.