Harnessing immune privilege in the eye to combat autoimmune uveitis

Dr Andrew Taylor, Boston University School of Medicine, investigates how we can manipulate the immune system of the eye to treat autoimmune uveitis. Understanding the molecular mechanisms underlying autoimmune uveitis will provide potential opportunities to use naturally produced molecules to suppress the disease, instead of drugs with unpleasant side effects. His findings could be extrapolated to other autoimmune diseases.

Dr Taylor believes that understanding factors which suppress and regulate immune responses, and having the means to regulate immune cells is vital to preventing autoimmune diseases, hypersensitivity and graft rejection. The healthy ocular microenvironment can regulate immune cell activity through a process called immune privilege. Once there is improved understanding of this process, there will be a paradigm shift in approaches to immunotherapy for autoimmune diseases, such as autoimmune uveitis.

AUTOIMMUNE UVEITIS

Uveitis is a general term for inflammation inside the eye, and chronic uveitis is the third leading cause of blindness in the US. The disease can be caused by trauma or by an immune reaction to self-antigens. In either case, there is an infiltration of immune cells that can damage the light-gathering cells of the retina. This damage leads to impaired vision and can result in blindness. Uveitis can present as an isolated problem or be associated with a systemic autoimmune disease. Dr Taylor is particularly interested in autoimmune uveitis.

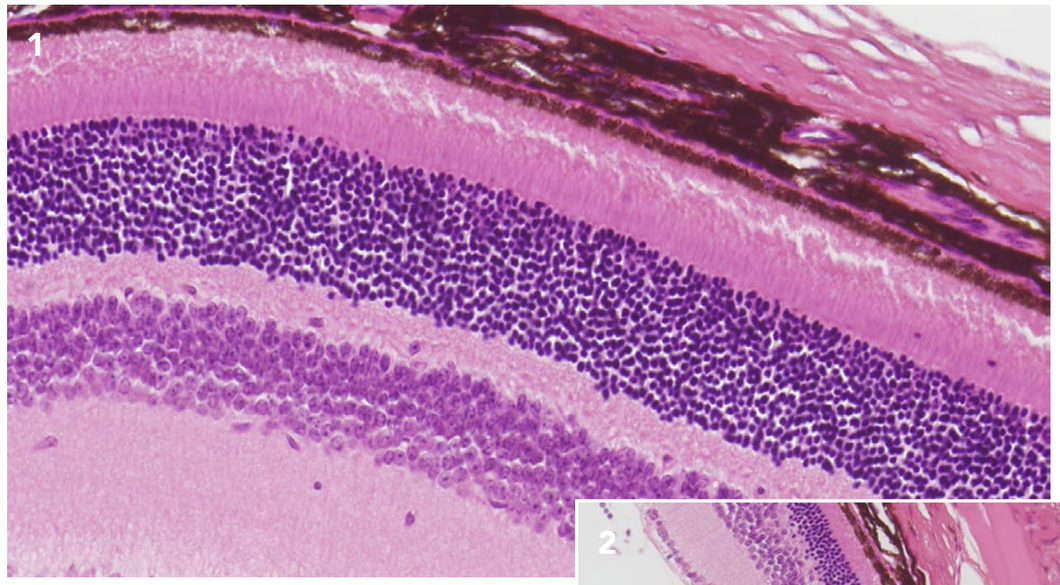
Currently, treatment options for autoimmune uveitis are based on a 60-year-old paradigm. The goal is to suppress inflammation, providing the opportunity for the patient's immune system to re-balance its own regulatory pathways and continue to use these, as yet undefined, mechanisms to continue to suppress inflammation once the drugs are withdrawn. This is normally achieved through the administration of steroids. However, the undesirable side effects of steroids are well known and, in the eye, can include increased likelihood of developing cataracts or glaucoma and increased susceptibility to infection. Furthermore, approximately 60% of uveitis patients will have at least another episode of uveitis within five years, and about 18% will continue to suffer chronic uveitis.

Therapeutics which target specific cytokines or cytokine receptors, called biologics, are the next generation of treatment option with their own set of serious side effects. In addition, they hold their own challenges and it is often difficult for clinicians to find a dose which is both effective and tolerated for each individual patient.

IMMUNE PRIVILEGE IN THE EYE

The phrase immune privilege was first used by Sir Peter Medawar to describe the lack of an immune response against allografts (a transplant between genetically different individuals of the same species) placed into the ocular microenvironment. Now, the term refers to the ability of an organ to supress responses against what would normally be considered a foreign antigen. This occurs through physical barriers, such as the blood-ocular barrier, and through biochemical signals.

The mechanisms of ocular immune privilege include a blood-ocular barrier, a lack of direct lymphatic drainage, the development of a form of tolerance to foreign antigens placed in the ocular microenvironment and a specific repertoire of immunosuppressive molecules. Breakdown of one or more of these mechanisms can make an eye susceptible to uveitis.



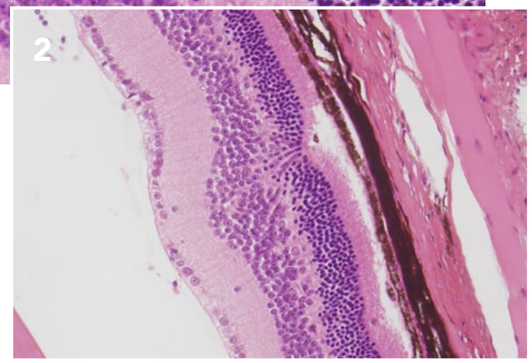


Image 1 is a healthy mouse retina. Image 2 is a retina from a mouse that recovered from experimental autoimmune uveitis. Comparing image 1 to 2, you can see that there are layers of the retina missing and the retina as a whole is thinner in image 2.

The process of immune privilege prevents the activation of proinflammatory activities of immune cells. In the eye, immune privilege can prevent antigen presenting cells from activating self-antigen responsive T-cells, which in turn prevents the T-cells from mounting an autoimmune response. Although the mechanisms of immune privilege in the eye are not fully understood, it is thought that the presence of soluble factors produced within the eye may play a role in supressing the expression of inflammatory cytokines by immune cells. These soluble factors promote the activation and expansion of T-cells with regulatory activity (Treg cells), while suppressing effector T-cells, which are involved in active immune responses and inflammation.

The current therapies for autoimmune uveitis suppress the symptoms and block the key cytokines involved in inflammation, but do not directly alter the behaviour of the immune cells responsible for causing disease. In contrast, harnessing mechanisms of immune privilege would provide the potential to change the programming of the immune cells to promote anti-inflammatory and self-regulating activity.

NEUROPEPTIDES AS POTENTIAL THERAPEUTICS

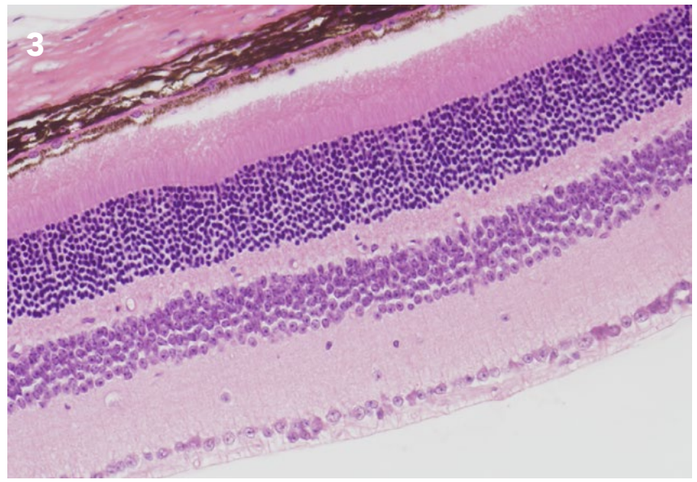
The ideal therapeutic approach must activate immune regulation within the eye, actively promote immune tolerance, and re-establish ocular immune privilege, and this is the aim of Dr Taylor's research.

The endogenous neuropeptide α-Melanocyte Stimulating Hormone (α-MSH), a member of the highly conserved melanocortin family of peptides and receptors, is a potent suppressor of inflammation. In 1992, Taylor, Cousins and Streilein first reported that α-MSH suppresses inflammation in the aqueous humour of the eye and holds an important role in maintaining ocular immune privilege in healthy eyes. It is likely that α-MSH represents just one of many immunosuppressive factors in the aqueous humour and identifying further molecules would both further understanding about immune privilege in the eye and provide novel therapeutic drugs. These molecules target a range of different immune cells at different stages during the induction of an immune response.

The sources of α-MSH in the eye are not fully known, although it has been documented that several types of cell in the eye, such as retinal pigment epithelial cells, as well as cells of the iris and ciliary body, may be sources of the neuropeptide. Evidence suggests that there is a loss of α-MSH in autoimmune disorders of the eye, or damaged

Any new therapeutic approach must activate immune regulation within the eye, actively promote immune tolerance, and re-establish ocular immune privilege.

Image 3 is a retina from a mouse that recovered from experimental autoimmune uveitis by alpha-MSH treatment. In contrast to Image 2 on the previous page, in this alpha-MSH treated mouse, the retina looks nearly normal (as in Image 1).



retinas. Therefore, administering α-MSH therapeutically may offer a novel approach for treatment.

Indeed, preliminary studies done by Taylor and his group using α-MSH peptide therapy have shown that this treatment does suppress rodent models of autoimmune uveitis. Alpha-MSH treatment also appeared to lead to retinal pigment epithelial cells regaining their immune regulating activity.

A previous study by Taylor and Lee demonstrated that α-MSH is capable of inducing conversion of effector T-cells into Treg cells. Interestingly, α-MSH did not induce regulatory behaviour in T-cells which have not been exposed to antigens: this phenomenon was confined to the effector T-cell population, demonstrating that α-MSH mediates action of inducible Treg cells. Recently, Taylor and Lee found that α-MSH takes effect through inducing antigen presenting cells to mediate contra-conversion of effector T-cells into inducible Treg cells.

Further data from Taylor's lab suggest that receptor-specific agonists to melanocortin 1 and 5 receptors (MC1r and MC5r) both suppress an experimental model of autoimmune uveitis. Out of the two, it appears that it is through MC5r that α-MSH mediates immune regulation. They concluded that this suggests a strong possibility that MC5r stimulation is necessary for α-MSH suppression of experimental autoimmune uveitis, and the possibility of reactivating ocular immune privilege.

Dr Taylor also hypothesises that there is a role for ocular neuropeptides in the regulation of macrophage activity in the healthy eye, particularly in promoting suppressive and anti-inflammatory activity. These macrophages respond to pathogens without mediating inflammation or activating T cells. Moreover, the macrophages produce anti-inflammatory cytokines, and suppress and possibly induce death in activated T-cells. Taylor has evidence that this is mediated by the neuropeptides neuropeptide Y and α-MSH produced within the eye.

Ultimately, there is the potential to develop a new approach to uveitis therapy that would use the body's own natural anti-inflammatory activities, mediated by the neuropeptide α-MSH, to combat the disease.

PUBLIC HEALTH RELEVANCE
Examining the mechanisms of ocular immune privilege promotes the importance of interactions between the nervous and the immune systems and may provide opportunities to use these interactions to beneficially manipulate immune responses.

The work of Dr Taylor's lab has demonstrated that the melanocortin pathway, which acts through the neuropeptide α-melanocyte stimulating hormone and its melanocortin receptors, is essential for ocular immune privilege. Therefore, as the group has shown, it is possible to stimulate the melanocortin pathway to provide a therapeutic option for suppressing inflammation and autoimmune disease. Ultimately, there is the potential to develop a new approach to uveitis therapy that would use the body's own natural anti-inflammatory activities, mediated by the neuropeptide α-MSH, to combat the disease.

Behind the Research
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Research Objectives

Dr Taylor's work focuses on how we can manipulate the immune system to treat chronic uveitis, an autoimmune disease that attacks the light-gathering tissues of the eye and leads to vision loss and blindness.

Detail

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Bio
Dr Taylor received his PhD from The Ohio State University, and completed a postdoctoral fellowship with Scott Cousins, MD and J. Wayne Streilein, MD at the University of Miami School of Medicine. In 1993, he joined the Schepens Eye Research Institute and Harvard Medical School. In 2010, Dr Taylor joined the Boston University School of Medicine where, in 2015, he was appointed Associate Dean of Research. Dr Taylor has served on several NIH, DOD, and other domestic and international review panels, and he is currently finishing a rotation on the Diseases and Pathology of the Visual System NIH review panel.

Funding
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Personal Response

What are the next steps required to investigate whether α-MSH presents a feasible therapeutic option for treating autoimmune uveitis in humans?

"While therapies and drug trials using melanocortins are shown to suppress inflammation in patients needing steroid-sparing therapies, the potential of inducing regulatory immunity that would further suppress and help prevent recurrence of autoimmune disease has not been assayed in humans. Such a finding would demonstrate that α-MSH is a different type of drug therapy: that α-MSH is more than anti-inflammatory it is a behavioural modifier of immune cells changing them from harmful to beneficial in action."