475 The bench and the bedside: Who is the instructor? - Minisymposium
Wednesday, May 10, 2017 3:45 PM–5:30 PM
Room 310 Minisymposium
Program #/Board # Range: 4767–4771
Organizing Section: Immunology/Microbiology
Contributing Section(s): Cornea, Retina, Visual Psychophysics/ Physiological Optics

Program Number: 4767
Presentation Time: 3:50 PM–4:10 PM
The genetic architecture of Behçet's disease provides new insights into therapy
Dan Kastner. National Human Genome Research Institute, NIH, Bethesda, MD.
Presentation Description: This presentation will provide a state-of-the-art overview on the genetics of Behçet's disease (BD) and a discussion of how recent findings inform targeted therapies. This will begin with a summary of the role of HLA in BD susceptibility, including the seven relevant *MHC Class I* alleles, and the localization of the BD association to six residues in the peptide-binding groove of the Class I molecule. Genome-wide association studies (GWAS) have identified common polymorphisms in a number of immunologically relevant genes that confer susceptibility to BD, including variants in *IL10, IL23R, ERAP1, CCR1, STAT4,* and *KLRC4*. Epistasis between *HLA-B*51* and *ERAP1* implicates antigen presentation and other shared pathogenic pathways between BD and the spondyloarthropathies. Deep resequencing has further identified rare and low-frequency variants of *IL23R* and *TLR4*, as well as a familial Mediterranean fever-associated mutation in *MEFV,* that confer BD risk. Finally, whole-exome sequencing has led to the discovery of a new monogenic Behçet's-like disease ('HA20') caused by haploinsufficiency in the ubiquitin-regulatory A20 protein, encoded by *TNFAIP3*. These findings shed new light on the role of therapies targeting IL-1 and TNF in the treatment of BD, and suggest the possibility of novel biologic therapies targeting other cytokine pathways in BD.
Commercial Relationships: Dan Kastner, None
Support: This work was supported by the Intramural Research Program of the National Human Genome Research Institute.

Program Number: 4768
Presentation Time: 4:10 PM–4:30 PM
Immunotherapy targeting IL-2 and IL-15 cytokine receptors
Thomas Waldmann. NIH, Bethesda, MD.
Presentation Description: Disorders of IL-2 and IL-15, cytokine receptors and signaling pathways play a role in the pathogenesis of many autoimmune diseases and lymphoid malignancies. To address these disorders a series of agents have been developed targeting IL-2 and IL-15, cytokine receptors and signaling pathways. In a major collaboration with Dr. Robert Nussenblatt it was shown that daclizumab was of value in treatment of noninfectious intermediate or posterior uveitis. Furthermore, Waldmann and his collaborators demonstrated that daclizumab led to a 78% reduction in gadolinium-enhanced MRI lesions in patients with multiple sclerosis failing interferon beta therapy. These studies were extended by industry and daclizumab (Zinbryta) was approved by the FDA for treatment of patients with multiple sclerosis.
In preclinical animal models Dr. Waldmann demonstrated that an abnormality of IL-15/IL-15R plays a role in type 1 diabetes and celiac disease. Waldmann introduced an antibody, Hu Mik-Beta-1 directed to the IL-2/IL-15R beta receptor (CD122) shared by IL-2 and IL-15 that blocks IL-15 action in the treatment of patients with T-LGL leukemia, HTLV-1 associated HAM/TSP and refractory celiac disease. While IL-2 and IL-15 have been shown to be valid therapeutic targets, there are certain failed approaches with a monoclonal antibody identifying a single cytokine receptor.
In HTLV-1 associated adult T-cell leukemia the HTLV-1 Tax transactivates both IL-2 and IL-15 and their receptors. Therefore, a strategy in which multiple cytokines are blocked simultaneously is desired. We have evaluated two small molecule agents, BNZ-1 that reacts with γc (CD132) but not IL-2/IL-15R beta (CD122) and H9-RETR that binds tightly to IL-2/IL-15R beta (CD122) but not to γc. These two agents block the access of IL-2 and IL-15 to their receptors and thereby prevent the dimerization of CD122 with γc that is required for signaling. These two agents are being evaluated in preclinical models of T-cell leukemia. Finally, disordered IL-2 and IL-15 actions are being targeted using JAK kinase inhibitors, these include ruxolitinib, a JAK1/2 inhibitor as well as JAK1 and JAK3 specific inhibitors.
Commercial Relationships: Thomas Waldmann, None
Clinical Trial: NCT01893775

Program Number: 4769
Presentation Time: 4:30 PM–4:50 PM
Bench to Bedside (and back): How basic research instructs clinical practice and vice versa – Gene Therapy for X-Linked Retinoschisis
Paul A. Sieving. National Eye Institute, NIH, Bethesda, MD.
Presentation Description: Developing a gene therapy program for human X-linked juvenile retinoschisis (XLRS) is the culmination of 10 years effort. Discovering the underlying pathobiology of the disease required murine studies at the bench and human studies in the clinic. Our XLRS trial is the first in vivo human gene therapy program developed within the NIH intramural program and NIH Clinical Center and illuminates a translational and regulatory pathway for other NEI investigators.
XLRS is a substantial cause of genetic macular degeneration in young males and has higher population frequency than hemophilia B. It is characterized by structural retinal failure of macular cystic schisis cavities and by functional deficits from synaptic failure that interrupts normal visual neurosignaling. There currently are no effective therapies for XLRS.
The path to initiating human gene therapy was highly interactive between bench and bedside. It required generating a transgenic XLRS mouse model and conducting basic studies of the murine pathology, designing the therapeutic gene vector, conducting pre-clinical toxicity and efficacy studies, and developing a clinical trial protocol. Following IND approval in November, 2014, we injected the first human patient in February, 2015 and are well along in the program (ClinicalTrials.Gov #NCT02317887).
Commercial Relationships: Paul A. Sieving, None
Clinical Trial: NCT02317887

Program Number: 4770
Presentation Time: 4:50 PM–5:10 PM
Human Embryonic Stem Cell derived Retinal Pigment Epithelium transplantation in severe exudative Age-Related Macular Degeneration: so far so visual
Peter Coffey[1,2]. [1]ORBIT, UCL Institute of Ophthalmology, London, United Kingdom; [2]NRI, UC Santa Barbara, Santa Barbara, CA.
Presentation Description: I will present the first two cases of the London Project in which a patch of hES-derived RPE was implanted into severe exudative AMD. We used a bespoke surgical tool to deliver the cells to the subretinal space in diseased eyes with severe vision loss. I will report the successful delivery, survival and

function of hES-derived RPE at 12 and 9 months post-implantation respectively. Visual improvement in both patients was observed and improved over the 12month period.
Commercial Relationships: Peter Coffey, Pfizer Inc (P)
Clinical Trial: NCT01691261

Program Number: 4771
Presentation Time: 5:10 PM–5:30 PM
Development of stem cell-based therapy for cornea -from tissue stem cell to iPS cell
Kohji Nishida. Ophthalmology, Osaka University, Suita, Japan.
Presentation Description: Complete loss of corneal epithelial stem cells because of severe eye disease leads to limbal stem-cell deficiency (LSCD) with corneal vascularization and opacification with severe visual loss. We previously developed a unique method with tissue-engineered epithelial cell sheets using the patient's autologous corneal or oral mucosal stem cells. Ocular surface reconstruction using autologous epithelial cell sheets containing stem cells has drastically changed the treatment of LSCD because it can prevent potential problems associated with limbal transplantation, including immune rejection and donor tissue shortages. Although the effectiveness and safety of this surgical approach have been confirmed to some extent by our past clinical research, efforts to make its use more widespread are required; the clinical trials using GMP-grade products are now on going.

More recently, we have been developing a stem cell-based therapy using autologous oral mucoal epithelium. More recently, we also have been challenging to develop iPS cell-based therapy. In the past, there were no techniques to induce human iPS cells to differentiate into corneal epithelial cells and to then isolate those cells to create functional corneal epithelium. We first succeeded in induction of corneal epithelium from human iPS cells. In fact, we developed a 2D culture system to promote cell-autonomous differentiation of human iPS cells. The culture system developed in this study can use human iPS cells to generate a 2-dimensional structure (a self-formed ectodermal autonomous multi-zone (SEAM)) consisting of 4 concentric zones of cells. Major groups of cells that comprise the eye during development (e.g. corneal epithelium, the retina, and the epithelium of the lens) are produced at specific locations in the SEAM. The current study successfully isolated corneal epithelial progenitor cells from the 3rd zone of the SEAM, and this study also successfully generated functional corneal epithelium. Corneal epithelium produced from human iPS cells was transplanted in an animal model, where that corneal epithelium was therapeutically effective. These results greatly help to start the first-in-human clinical trial of iPS cell-derived corneal epithelium for LSCD.
Commercial Relationships: Kohji Nishida, None