### Speaker Presentation Abstracts by Page Number

<table>
<thead>
<tr>
<th>Page</th>
<th>Presenter</th>
<th>Presentation Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Murphy, Christopher</td>
<td>The Function Morphology of the Vertebrate Eye</td>
</tr>
<tr>
<td>3</td>
<td>Ver Hoeve, Jim</td>
<td>Electroretinography in Preclinical Studies</td>
</tr>
<tr>
<td>3</td>
<td>Twa, Michael</td>
<td>State-of-the-Art Ocular Imaging Techniques</td>
</tr>
<tr>
<td>4</td>
<td>Lorget, Florence</td>
<td>Nonclinical Safety Assessment of Lucentis® and Clinical Translatability</td>
</tr>
<tr>
<td>4</td>
<td>Gupta, Swati &amp; Zhou, Joe</td>
<td>In Vitro Tools to Control Product Quality Attributes Related Risk Assessments for Ocular Biologic Drugs</td>
</tr>
<tr>
<td>5</td>
<td>Thackaberry, Evan</td>
<td>Unexpected Toxicity with a Novel Bispecific Fab for Intravitreal Administration: Pharmacology or Immunogenicity?</td>
</tr>
<tr>
<td>5</td>
<td>Barney, Neal</td>
<td>Immunomodulation of Diseases at Ocular Surfaces</td>
</tr>
<tr>
<td>6</td>
<td>Sivak, Jeremy</td>
<td>Glial Reactivity: Key Roles in Inner Retinal Neurovascular Disease</td>
</tr>
<tr>
<td>6</td>
<td>Brandt, Curtis</td>
<td>Toll-Like Receptors and Ocular Immunotoxicology</td>
</tr>
<tr>
<td>7</td>
<td>Fox, Donald</td>
<td>Retinal Toxicology Resulting from Off-Target Effects of Drugs and Occupational Exposures</td>
</tr>
<tr>
<td>7</td>
<td>Attar, Mayssa</td>
<td>Translation of Ocular Drug Disposition from Animals to Humans</td>
</tr>
<tr>
<td>8</td>
<td>Rittenhouse, Kay</td>
<td>Species Differences in Ocular PK and Drug Molecular Characteristics</td>
</tr>
<tr>
<td>8</td>
<td>Vezina, Mark</td>
<td>Regulatory Considerations for Preclinical Ocular Programs in Support of Clinical Trials</td>
</tr>
<tr>
<td>8</td>
<td>Novack, Gary</td>
<td>Regulatory Challenges for Novel Ophthalmic Drug Delivery</td>
</tr>
<tr>
<td>9</td>
<td>Peng, Qinqhai</td>
<td>MiRNAs As Potential Predictors of Retinal Toxicity</td>
</tr>
<tr>
<td>9</td>
<td>Nakano, Kyoko</td>
<td>E2012-Induced Cataract and Its Predictive Biomarkers</td>
</tr>
<tr>
<td>10</td>
<td>Kompella, Uday</td>
<td>Drug Delivery to the Eye Overview</td>
</tr>
<tr>
<td>10</td>
<td>Sasseville, Vito</td>
<td>Slow-Release Formulations and Ocular Immunology: Microscopic Observations</td>
</tr>
<tr>
<td>11</td>
<td>Collins, Margaret</td>
<td>Vitreal/Peptide Deposits As a Slow Release Formulation</td>
</tr>
<tr>
<td>11</td>
<td>Chastain, James</td>
<td>Challenges of Slow-Release Intravitreal Therapeutics for Age-Related Macular Degeneration</td>
</tr>
<tr>
<td>12</td>
<td>Bharti, Kapil</td>
<td>IND-Enabling Preclinical Toxicity and Efficacy Studies for an RPE-Patch Developed from AMD-Patient-Specific iPS Cells</td>
</tr>
<tr>
<td>12</td>
<td>Milton, Mark</td>
<td>Development of Subretinal Gene Therapies for Retinitis Pigmentosa</td>
</tr>
<tr>
<td>13</td>
<td>Budzynski, Ewa</td>
<td>Safety and Efficacy of an AAV-Vector Following Subretinal Injection in Mouse Model of Achromatopsia</td>
</tr>
</tbody>
</table>

To access meeting material, please visit: www.toxicology.org/ocular
Session I: Ocular Toxicology: Preclinical Models and Specialized Endpoints

Presentation No: 01
The Function Morphology of the Vertebrate Eye
C. Murphy
University of California Davis, Davis, CA

An overview of the basic design of the vertebrate eye will be presented highlighting the terminology, structure, and function most relevant to ocular drug development programs.

Presentation No: 02
Electroretinography in Preclinical Studies
J. Ver Hoeve
University of Wisconsin, Madison, WI

The electroretinogram (ERG) is used widely in clinical medicine for the diagnosis of hereditary eye disease and for monitoring drug toxicity. It is used in various universities and small R&D laboratories to demonstrate efficacy of experimental therapies using animal models of ocular diseases. The ERG is increasingly used as an endpoint in large preclinical safety and efficacy studies due to the recognition that the ERG provides an important complement to anatomical and histological assessment of both ocular and non-ocular target drugs. This talk will review the physiologic basis of the ERG, outline its role in diagnosing ocular disorders, provide examples of the application of electrodiagnostic testing in preclinical safety studies, and discuss the role of the ERG in translational medicine. Limitations in interpretation of the ERG and ancillary tests (multifocal ERG, cortical evoked potentials) will also be addressed.

Presentation No: 03
State-of-the-Art Ocular Imaging Techniques
M. Twa
University of Alabama Birmingham, Birmingham, AL

Ocular imaging has evolved rapidly over the last 10 years. Three technologies have driven most of the recent innovations: confocal microscopy, optical coherence tomography, and adaptive optics. Each of these imaging techniques have spawned novel capabilities that extend our ability to see and understand the structure and function of ocular tissues. This presentation will focus on current developments in ocular imaging for humans and animal models of disease and will also provide a look at emerging developments in ocular imaging and their possible applications.
Session II: Advances in the Development of Protein-Based Intravitreal Therapies

Presentation No: 04

**Nonclinical Safety Assessment of Lucentis® and Clinical Translatability**

*F. Lorget*  
Genentech, South San Francisco, CA

Lucentis® is an anti-VEGF humanized fragment antibody that was first approved in 2006 for the treatment of age-related macular degeneration. The nonclinical package supporting its registration used the cynomolgus monkey as the relevant animal species. In this animal, repeat intravitreal administrations of Lucentis® led to a severe dose-related ocular inflammatory reaction that challenged the conduct of the studies. This adverse effect was attributed to the administration of a foreign protein to an animal and, as expected, did not translate into the clinical population. This presentation focuses on the safety findings observed in the pivotal nonclinical studies supporting Lucentis® development, the attempted strategies for mitigation and the lack of clinical translatability.

Presentation No: 05

**In Vitro Tools to Control Product Quality Attributes Related Risk Assessments for Ocular Biologic Drugs**

*S. Gupta, Q. Zhou*  
Allergan, Irvine, CA

Intravitreal (IVT) administration of Biologics is becoming a popular approach to deliver drugs to treat disease conditions in posterior segments of the eye. This route of ocular delivery results in better ocular bioavailability to retina/choroid compared to topical ocular eyedrop but is associated with other challenges, including a very stringent impurity profile. Acute ocular inflammation can be easily provoked by trace amounts of innate immune response modulating impurities (IIRMI) derived from manufacturing process and/or product degradation/aggregation. There is still insufficient understanding on how much of these impurities can be biologically relevant in triggering an immune response. In addition to traditional analytical methods to monitor the levels of endotoxin and host cell proteins, a wide variety of *in vitro* cell based assays have emerged to assess the risk of immunogenicity derived from the IIRMI in Biotherapeutics. Peripheral blood mononuclear cell (PBMC) and THP-1 cytokine release assays are generally accepted tools now to assess the potential IIRMI induced acute inflammation. Mechanism of specific TLR pathway activation can be evaluated by using hTLR transfected cell lines. Dendritic cell phenotyping and T-cell proliferation are some of the tools used for protein aggregation and formulation assessment. Hence proper application of these *in vitro* tools is useful for teasing out the key detrimental quality attributes and can contribute to guide process development to set thresholds for clinically relevant risks.
Presentation No: 06

Unexpected Toxicity with a Novel Bispecific Fab for Intravitreal Administration: Pharmacology or Immunogenicity?

E. Thackaberry  
Genentech, South San Francisco, CA

The development of intravitreal biologics is often complicated by immunogenicity and inflammation in nonclinical species. Depending on the severity, immunogenicity and/or inflammation may have a profound impact on the outcome of the study, up to and including a cessation of dosing. In order to assess the relevance of these non-clinical findings for human safety, it is critical to understand the mechanisms involved. This presentation will focus on unexpected ocular toxicity observed with a novel bispecific molecule being developed for the treatment of AMD. In a repeat-dose toxicology study in nonhuman primates, a dose-related increase in intraocular pressure was observed, resulting in severe glaucomatous effects. Investigative studies demonstrated that the finding observed was related to unanticipated pharmacology and was not associated with immunogenicity or inflammation. These results provided insight into a novel biology of the target and ultimately led to the termination of the program.

Session III: The Emerging Role of Ocular Immunology and Immunomodulation in Ocular Disease and Drug Development

Presentation No: 07

Immunomodulation of Diseases at Ocular Surfaces

N. Barney  
University of Wisconsin, Madison, WI

Hypersensitivity responses typically involve normal adaptive protective mechanisms that because of increased antigenic exposure and/or heightened immune status become amplified and lead to tissue pathology. Most clinically relevant ocular surface problems are not defined exclusively as a single hypersensitivity type. In ophthalmology, we may classify these four types of hypersensitivity reactions as vision threatening or non-vision threatening. If only a Type I or immediate hypersensitivity reaction of the ocular surface occurs, this is not sight threatening. The ocular surface recovers normal architecture and resident cellular compliment following an allergic reaction such as exposure to a seasonal allergen in a patient who is sensitized. Type IV hypersensitivity reactions or cell mediated hypersensitivity, uncommonly threaten vision. As such, contact dermatitis of the ocular surface may arise from the use of a number of different topical medications. Types I and IV are most commonly treated with avoidance of offending agent or topically applied medications with little need for systemic use of immunomodulating agents. Type II hypersensitivity reactions involve antibody attachment directly to the cell surface initiating complement activation or directing inflammatory cells to the target cell for recognition by a receptor to the antibody. Ocular Cicatricial Pemphigoid is such a destructive process and requires systemic use of immunomodulating agents to reduce the ocular surface damage. Type III reactions are initiated by immune complex deposition of complement fixing antibodies which triggers neutrophil infiltration and attack of normal tissue cells. As an example, scleritis, the destructive inflammatory process of the outer sclera, requires at minimum, oral steroids.
**Presentation No: 08**

**Glial Reactivity: Key Roles in Inner Retinal Neurovascular Disease**

J. Sivak  
Toronto Western Research Institute, Toronto, ON, Canada

Reactive gliosis is an early pathological feature common to nearly all neurodegenerative diseases, yet its regulation and impact remain poorly understood. In the healthy inner retina astrocytes and related Müller glia maintain a critical homeostatic and oxidative balance through interactions with neighboring neurons and vasculature. After stress or injury these astrocytes undergo rapid parainflammatory activation, accompanied by characteristic changes in intermediate filaments and morphology, and altered cytokine secretions, antioxidant activity, and vasoregulation. My lab has been studying this system to investigate the molecular mechanisms regulating these responses and their impact on the inner retina, and to therapeutically target specific components of the reactive switch.

**Presentation No: 09**

**Toll-Like Receptors and Ocular Immunotoxicology**

C. Brandt  
University of Wisconsin, Madison, WI

Ocular biologics and gene delivery vectors consisting of proteins, nucleic acids, or both have the potential to act as Pathogen Associated Molecular Patterns (PAMPs) and trigger inflammatory responses when injected into the eye. Acute transient uveitis has been reported following delivery of ocular biologics and we have previously shown that viral gene delivery vectors engender a similar response in non-human primate eyes. One important system for sensing PAMPs are the Toll-like Receptors (TLR) of which there are 10 in humans and it is likely that these sensors are involved in the transient uveitis. HSV based vectors induce the expression of IL6 and IL10 in NHP neural retina but the mechanism is unknown. Numerous TLRs have been identified in cultured retinal pigment epithelial cells but less is known about neural retina which is directly exposed to biologics and vectors. We have been characterizing the TLRs present in neural retina cells and have found little to no TLR3 or TLR4 and abundant TLR9 and TLR2. In addition, TLR6 is up-regulated upon exposure to a HSV vector. These results will be presented and discussed in the context of inflammatory responses to vectors and biologics.
Session IV: Drug and Toxicant-Induced Retinal Toxicity, Drug Metabolism, and Translation across Species

Presentation No: 10

Retinal Toxicology Resulting from Off-Target Effects of Drugs and Occupational Exposures

D. Fox
University of Houston, Houston, TX

Half of all neuroactive/neurotoxic chemicals adversely affect sensory functions. Of these, the initial and most frequent alterations following chemical exposure occur in the retina, suggesting that the retina is especially vulnerable to chemical insult. Several distinct tissue-, layer-, and cell-specific anatomical/structural, biochemical, metabolic and physiological characteristics underlie this vulnerability. The aim of this talk is to provide a comprehensive understanding of toxicity to photoreceptor and associated cells and framework for predictive retinotoxicity of toxicants and new drugs. To accomplish this goal, four important areas will be discussed. First, the talk will address the cellular and compartmental differences in the retina as relates to bioenergetics. Second, the mechanistic basis of well-known compartmental and cellular retinotoxicants such as lead, chloroquine, and methanol will be addressed. Third, off-target retinal sites and possible mechanisms of pharmaceuticals developed to treat different central/peripheral nervous system diseases such as Alzheimer’s, depression, schizophrenia, and seizures will be discussed. Fourth, the retinal effects of environmental and occupational neurotoxicants will be discussed. The talk will synthesize results from these areas to examine possible common sites and mechanisms such as neurotransmitter enzyme/transport, synapses, calcium regulation, mitochondrial metabolism, and phospholipidosis. The talk should be of interest to basic scientists, clinicians, researchers engaged in drug development and testing, epidemiologists and those in risk assessment/management.

Presentation No: 11

Translation of Ocular Drug Disposition from Animals to Humans

M. Attar
Allergan, Irvine, CA

An understanding of drug pharmacokinetics and disposition following administration via the intended clinical route of administration is an important component of any ocular safety program. The pharmacokinetic processes of absorption, distribution, metabolism, and elimination determine the concentration of drug delivered to the site of pharmacodynamic and/or toxicodynamic action. Drug exposure in ocular tissues and the systemic compartment are key parameters in developing an understanding of the relationship between dose level, dose regimen, dose route, and the time course of toxicological findings. Application of a systems biology approach that considers the physiological differences in animal and human eyes is a key component for translation across species. In silico, in vitro, and in vivo tools are being developed to integrate these data to aid in the interpretation of toxicology findings relative to their implications for clinical safety and use. This talk will present current approaches in this emerging scientific area.
Presentation No: 12

Species Differences in Ocular PK and Drug Molecular Characteristics
K. Rittenhouse
Bayer, New York, NY

Many in drug research and development have asked the following common question, “Why did our clinical study of an exciting, novel, and apparently potent drug, fail?” This perplexing question has been extensively discussed and a number of vital answers that may seem somewhat intuitive rise to the top of most lists: Animal to human exposure vs. response relationships. Pharmacokinetics studies are important, and are, in general, the gatekeeper or first step to advancing promising drug candidates to become licensed innovative and life saving or transforming therapies. Ocular drug disposition introduces yet another layer of complexity in elucidating these relationships. Key studies will be presented and discussed that highlight the intersection of species related differences in ocular PK with the structural and molecular make up of drug candidates and their unique attributes that may introduce further obstacles to the successful implementation of drug development for ophthalmic therapeutics.

Session V: Regulatory Challenges for Developing Novel Ocular Therapies

Presentation No: 13

Regulatory Considerations for Preclinical Ocular Programs in Support of Clinical Trials
M. Vezina
Charles River, Senneville, QC, Canada

The eye is a complex organ system with functionally distinct tissue types. Individual ocular tissues may be subject to specific diseases or conditions that are potential targets for therapeutic intervention. In general, as a therapeutic area, there are relatively few approved ocular drugs compared to other indications and as a result there are many opportunities to develop novel therapies targeting specific ocular tissues/diseases. However, developing a novel ocular therapy in a regulatory environment can pose a number of challenges depending on the complexity of the product. Challenges within a specific study or program could include test article characterization, formulation, administration, involvement of a device, or development of novel endpoints, for example. Furthermore, within the general development program the nature of the product and its indication will determine the range of studies necessary to support the intended clinical trial. The goal of this presentation is to provide guidance on how to help identify these challenges in the context of the development of novel ocular therapies in a preclinical regulatory environment.

Presentation No: 14

Regulatory Challenges for Novel Ophthalmic Drug Delivery
G. Novack,1,2 E. Moyer3
1PharmaLogic Development, Inc., San Rafael, CA, 2University of California, Davis, CA, 3M/P Biomedical Consultants LLC

Quality vision is highly valued by the medical community and patients. Since the founding of ophthalmic specialty pharmaceutical firms in the mid-20th century, we have seen a continuum from ocular formulations of systemic medicines, to molecules developed initially for ocular treatment, to biologics and drug delivery systems. These novel therapies require innovative and often long-term clinical trials. In turn, conduct of these clinical trials requires appropriate nonclinical safety studies. The highly valued products have led to venture-funded start-up companies, for which financial considerations are paramount in planning nonclinical development. We will present issues in planning and conducting nonclinical safety studies for ocular therapies, including coordination of effort with pharmaceutics researchers on drug substance and drug product.
Session VI: Next Generation Biomarkers to Assess Ocular Injury

Presentation No: 15

MiRNAs As Potential Predictors of Retinal Toxicity

Q. Peng
Pfizer, San Diego, CA

De-risking strategies with early identification of retinal injury utilizing a predictive retinal miRNA biomarker would greatly benefit decision-making in drug discovery and reducing attrition due to retinal toxicity. ~330 miRs were profiled using the RT-qPCR technique, in which miR-124 and miR-183 cluster (miR-183, 182 and 96) were the top four expressed miRNAs in rat retina. These miRNAs were much less expressed in other tissues/organs. Cellular expressions of these miRNAs by Laser Capture Microdissection (LCM) displayed a distinctive and overlapping expression pattern in different retinal layers. To evaluate their potential as miRNA biomarkers, these retina-enriched miRNAs were investigated in three retinal toxicity models: intravitreal injection induced toxicity by retinal toxicants; systemic NaIO$_3$ induced retinal injury and laser-induced choroidal neovascularization (CNV) injury. MiR-183 cluster and miR-124 in plasma were significantly increased when compared with baseline/control (P<0.05). ERG and histopathology were also assessed in the studies for retina injury evaluation.

Presentation No: 16

E2012-Induced Cataract and Its Predictive Biomarkers

K. Nakano
Eisai, Tsukuba, Japan

E2012, a gamma secretase modulator aimed at Alzheimer’s disease induced cataract following repeated doses in the rat. Cataract appeared first at week 10–11 of treatment as a posterior subcapsular area. It was associated with prolonged and sustained elevation of lenticular desmosterol (24-dehydrocholesterol), the final precursor of cholesterol, and decrease in lenticular cholesterol. In vitro studies demonstrated that E2012 inhibits 3β-hydroxysterol Δ24-reductase (DHCR24) at the final step in the cholesterol biosynthesis. The elevation of desmosterol and decreased cholesterol levels were also seen in the liver and plasma, and preceded those in the lens. These results demonstrate that E2012 induces cataract in the rat by inhibiting DHCR24 at the final step of cholesterol synthesis with associated elevation in desmosterol within the lens, preceded by desmosterol changes which would serve as a predictive safety biomarker for lenticular opacity.
Session VII: Toxicology Assessment of Novel Slow Release Ophthalmologic Formulations

Presentation No: 17

Drug Delivery to the Eye Overview

U. Kompella
University of Colorado, Denver, CO

Although the eye is readily accessible for topical drug application, less than ten percent of the applied drug reaches intraocular tissues, due to the presence of static and dynamic ocular barriers that prevent entry of foreign agents. Drug entry from an eye drop is primarily confined to the anterior segment of the eye, since therapeutic quantities of drugs are typically not attained in the back of the eye following topical dosing. Therefore, ophthalmic drugs applied topically as conventional solution, suspension, or ointment dosage forms are indicated for treating diseases of the anterior segment only. With advances in ocular pharmacology, a few drug products indicated for the back of the eye are also in the clinic. These products are administered through invasive means to the vitreous space. Since repeated invasion of the eye could be toxic by itself, several slow release products have been developed for treating back of the eye diseases. Overall, the field of ophthalmology has seen several innovative drug delivery systems to date. Additionally, novel routes of drug administration (e.g., transscleral, suprachoroidal, and subretinal) as well as new delivery systems (e.g., nanoparticles, injectable slow release implants, encapsulated cells, and viral vectors) are being explored for drug and gene delivery to the eye. The safety of a given drug product depends on several factors including route of administration, amount administered, properties of the materials employed, pathophysiology of the eye, and the interaction and clearance of the materials in the biological space. The purpose of this presentation is to provide an overview of barriers, drug delivery routes, and delivery systems for treating eye diseases.

Presentation No: 18

Slow-Release Formulations and Ocular Immunology: Microscopic Observations

V. Sasseville
Novartis, Cambridge, MA

The ocular administration of biotherapeutics to preclinical species, notably the rabbit and cynomolgus monkey, has shown an unusual and diverse range of ophthalmologic and microscopic findings ranging from an acute mild transient anterior inflammation to a delayed onset and persistent inflammatory response. This latter phenomenon will be the focus of this presentation. In addition to implanted devices, novel formulations have been employed in recent years to extend the residence time of intravitreal administered biotherapeutics. These approaches have greatly enhanced the efficacy in various preclinical models, but long term safety remains an unknown. It is important to differentiate findings in preclinical species associated with an anti-drug antibody response to intravitreal injection of human or humanized proteins versus a response to vehicle component(s). The role of ocular immunology and the translatability of the anti-drug antibody response to this process remain poorly understood. Specific case examples will be given to show the range of inflammatory responses observed with the intravitreal administration of biotherapeutics in the preclinical setting.
Presentation No: 19

**Vitreal/Peptide Deposits As a Slow Release Formulation**

M. Collins  
Charles River, Reno, NV

Following a single intravitreal injection of a complement inhibitor that was provided as a preformulated, aqueous solution, cynomolgus monkeys were evaluated via standard ocular endpoints on Days 2 and 15. Necropsy was conducted for ocular PK sampling of high-dose animals on Day 1 at 4 timepoints. Terminal necropsy was conducted for all groups on Day 2, and Recovery necropsy was conducted on Day 15. At the time of necropsy, spheroidal deposits were noted in the vitreous of some animals, and these deposits were collected separately. The initial response was to consider that formation of deposits in the vitreous was an adverse outcome. Subsequently, a decision was made to analyze these deposits. Small amounts of test article were still present in the deposit collected at Day 15. On the basis of these analyses, the Sponsor continued the development program for this test article.

Presentation No: 20

**Challenges of Slow-Release Intravitreal Therapeutics for Age-Related Macular Degeneration**

J. Chastain  
Alcon, Fort Worth, TX

Current approved treatment of neovascular age-related macular degeneration (nAMD) involves intravitreal (IVT) injection of a monoclonal antibody or fusion protein targeting vascular endothelial growth factor (VEGF). While highly effective, these drugs require frequent injections (every 4 or 8 weeks), resulting in inconvenience to the patient and increased potential for injection-related complications. As a result, a variety of novel drug delivery approaches are under development, involving slow or sustained release formulations or devices. These follow in the footsteps of drug implants for treating CMV (ganciclovir), uveitis (fluocinolone acetonide) and macular edema (dexamethasone). More recent approaches to slow-release include use of microparticles, nanotechnology, lipid polymer matrices, thermal gels, protein pegylation, and implantable drug delivery systems, including refillable devices and encapsulated cell technology. The unique challenges with regard to ocular safety and pharmacokinetics will be discussed along with selected examples.
Session VIII: Developing the Future: Safety Assessment of Gene and Stem Cell Therapies

Presentation No: 21
IND-Enabling Preclinical Toxicity and Efficacy Studies for an RPE-Patch Developed from AMD-Patient-Specific iPS Cells

K. Bharti
National Eye Institute-NIH, Bethesda, MD

Induced pluripotent stem (iPS) cells are a promising source of personalized cell therapy. iPS cells can provide immune-compatible autologous replacement tissue for the treatment of potentially all degenerative diseases. National Eye Institute (NEI) is preparing for the first phase I clinical trial using iPS cell derived ocular tissue to treat age-related macular degeneration (AMD), one of the leading blinding diseases in the US. AMD is caused by the progressive degeneration of retinal pigment epithelium (RPE), a monolayer tissue that maintains vision by maintaining photoreceptor function and survival. Combining developmental biology with tissue engineering NEI team has developed protocols for manufacturing a clinical-grade iPS cell derived RPE patch on a degradable scaffold. This patch performs key RPE functions like phagocytosis of photoreceptor outer segments, ability to transport water from apical to basal side, and the ability to secrete cytokines in a polarized fashion. Currently, the NEI team is testing the delivery, safety, and the efficacy of this replacement patch in animal models as part of a Phase I Investigational New Drug (IND)-application. Approval of this IND application will lead to transplantation of autologous iPS cell derived RPE patch in patients with the advanced stage of AMD. Success of NEI autologous cell therapy project will help leverage other iPS cell-based trials making personalized cell therapy a common medical practice.

Presentation No: 22
Development of Subretinal Gene Therapies for Retinitis Pigmentosa

M. Milton
Novartis, Cambridge, MA

Retinitis pigmentosa is a group of inherited diseases causing retinal degeneration. There are many forms of RP including Leber’s congenital amaurosis, Newfoundland Rod-Cone Dystrophy and Bothnia Dystrophy. These diseases are candidates for treatment by gene therapies that can be administered close to the tissues that need to be treated. The development path for gene therapies can be complicated and long, with many challenges along the way. These challenges range from the design and production of the gene therapy, the “proof of concept” in animal species, the design and conduct of the toxicology and bio-distribution studies, the route of administration and the existence of pre-existing antiviral vector antibodies. This presentation will highlight some of these challenges that need to be overcome both nonclinically and clinically for the successful development of such therapies.
Presentation No: 23

Safety and Efficacy of an AAV-Vector Following Subretinal Injection in Mouse Model of Achromatopsia

E. Budzynski
Covance, Madison, WI

Achromatopsia is an inherited retinal disorder characterized by markedly reduced visual acuity, nystagmus, intolerance of bright light, and severe loss of color discrimination. Approximately 50% of cases are caused by mutations in the cone photoreceptor-specific cyclic nucleotide-gated channel beta subunit (CNGB3) gene. Cone photoreceptor function is absent in patients with these mutations and in animal models with mutations in the homologous genes. AGTC is developing a rAAV vector expressing CNGB3, to be delivered by subretinal injection, as a potential therapy. Studies using appropriate animal disease models for development of gene therapies are encouraged by the FDA because they offer the potential to better define relationships between dose, bioactivity and safety, and hence better inform clinical dose setting. This presentation will describe the practical considerations and results of a toxicology, biodistribution, and efficacy study conducted in the CNGB3-deficient mouse model of achromatopsia.