Course Description

Cataracts are caused by the improper folding and aggregation of crystallin proteins in the lens. This lecture will cover the basics of lens structure, describe why the conformations of proteins are important for lens clarity, and show how proteins undergo misfolding and aggregation with aging. I will describe our approach to discovering and optimizing potential drugs that can bind and correct the conformations of crystallin proteins to help correct lens transparency in models of cataracts. The lecture will also include a discussion of the competitive landscape as well as historical attempts to treat cataracts medically, an update on the current status of the potential therapy, a discussion of which patient populations might eventually benefit from an approved drug that works by this mechanism of action, and ideas on how such a treatment might fit into the current surgical paradigm.

Learning Objectives

• Refresh understanding of lens structure and age related pathophysiology
• Understand that crystallin protein aggregation is an important component of cataractogenesis and is reversible
• Understand current and historical attempts to treat cataracts medically
• Participate in a discussion of which patient populations might eventually benefit from an approved drug targeting crystallin proteins and how such a potential treatment fits in the current surgical paradigm

Course Outline

1. Introduction
   a. Structure and function of the crystallin lens
      i. Tissue organization
         1. Capsule
         2. Fiber cells
         3. Organelle-free zone
         4. Growth and differentiation patterns
      ii. Refractive index and transparency
         1. Protein gradient
         2. Water gradient
      iii. Biomechanical properties
      iv. Lens mechanism of accommodation
         1. Helmholtz theory
         2. Other theories and contributing factors
b. Crystallin proteins
   i. Alpha crystallins
      1. Known functions
      2. Structural biology
      3. Disease relevance
   ii. Beta crystallins
      1. Known functions
      2. Structural biology
      3. Disease relevance
   iii. Gamma crystallins
      1. Known functions
      2. Structural biology
      3. Disease relevance

2. Protein misfolding in cataracts and presbyopia
   a. Brief introduction to general protein folding thermodynamics
      i. Protein structure
      ii. Protein homeostasis
      iii. Lens requirements for protein homeostasis
   b. Changes to crystallin protein folding with aging
      i. Effects on lens stiffness
      ii. Effects on lens transparency
   c. Genetic mutations in crystallin proteins
      i. Disease relevance
      ii. Stability and phenotypes
      iii. Association with congenital cataracts
      iv. Association with systemic syndromes

3. The discovery of pharmacological chaperones for crystallin proteins
   a. Mutations in α-crystallins induce protein aggregation
      i. Defects in protein stability
      ii. Phenotypes associated with mutations
      iii. Types of cataracts
   b. High throughput differential scanning fluorimetry as a screening tool
      i. Thermodynamics
      ii. Technique and practical utility
      iii. Application to alpha crystallin mutants
   c. VP1-001 prevents and reverses protein aggregation in vitro
      i. Electron microscopy
      ii. Protein solubility
   d. VP1-001 reverses protein aggregation in mouse models
      i. Description of genetic mouse models
      ii. Slit lamp biomicroscopy and video
iii. Protein solubility as a biomarker  
iv. Electron micrographs of cell structure  
v. Description of age related cataract model  
e. Mechanism of action of VP1-001  
i. VP1-001 binds to dimer  
ii. Proposed mechanism of action  
iii. Experimental support  
iv. Alternative hypotheses  

4. Hereditary versus age-related cataracts  
a. Age-related cataracts are a multifactorial disease  
i. Role of posttranslational modifications  
ii. Endogenous protective mechanisms  
b. Known modifications related to aging  
c. Trends in protein solubility with aging  
d. VP1-001 reverses protein aggregation in aged human lenses  

5. Current and historical attempts to treat cataracts medically  
a. Aldose reductase inhibitors  
i. Theory  
ii. Application to diabetic cataract  
iii. Limitations  
b. Antioxidants and/or metal chelators  
i. Theory  
ii. Applications in preventing cataract progression  
c. Catalin for selenite-induced cataract  
i. Clinical utility in Japan, China and role in standard of care  
ii. Efficacy in double-blind clinical studies  
d. Carnosine or N-acetylcarnosine  
i. Theoretical basis for utility, background  
ii. Evidence supporting efficacy and lack of efficacy  
e. Preventative studies of aspirin, vitamins, and nutritional supplements  
i. Theoretical basis for utility  
ii. Past studies and results  
iii. Ongoing studies  
f. Protease inhibitors  
i. Theoretical basis for utility  
g. Pharmacological chaperones  
i. VP1-001 as a pharmacological chaperone  
ii. Lanosterol  
iii. Peptide and aptamer approaches  
iv. Reversibility of disease
6. A potential role for endogenous oxysterols in maintaining lens transparency
   a. Metabolites in cholesterol + vitamin D biosynthetic pathways
   b. Genetic disorders and epidemiological evidence
   c. Sterol biosynthesis genes
   d. Analogous protective mechanisms (gamma crystallins, glutathione)
   e. Hypothesis

7. Outlook on commercial development of a medical treatment for cataracts
   a. Areas of unmet medical need
      i. Pediatric cataract
         1. Current standard of care
         2. Current outcomes
      ii. Patients contraindicated for surgery
      iii. Patients with ocular comorbidities
      iv. Patients at high risk for complications or poor visual outcomes
      v. Global health opportunity
      vi. Other
   b. Potential future indications
      i. Preventative use
      ii. Delay to need for surgery
      iii. Clinical trial structures
   c. Potential clinical trial endpoints
      i. Dynamic light scattering
      ii. Pentacam imaging
   d. Current status of VP1-001 development and future steps
      i. Topical route of administration
      ii. Intraocular route of administration
      iii. Outlook

8. Parting thoughts on development path: How does a medical treatment for cataracts fit into the
   standard of care?
   a. Optometry practice
   b. Ophthalmology practice