Ophthalmology – a great place to do translational medicine
Disclaimer and conflict of interest statement

• Employee of Pfizer, Inc.
• None of the products mentioned are marketed or currently in active development by Pfizer
• Many thanks to those who have shared their slides for this presentation including Pete Coffey and Ted Danse
Translational medicine is particularly important in ophthalmology

- Disease mechanisms in ophthalmology are often linked to previously studied pathways
  - Angiogenesis
  - Inflammation
  - Fluid balance
  - Infection

- Therapeutics are often available or translatable from other areas
  - $\beta$ (adrenergic) antagonists – IOP (timolol)
  - Anti-VEGF – neovascular AMD (bevacizumab)
  - steroids – Diabetic retinopathy – triamcinolone, fluocinolone
Can we demonstrate that the intervention impacts the biological process of disease?
The Retina
Macula

1.5mm
Macula

1.5mm
Macula

Macula

Fovea

1.5mm
The Retina
Macula

- CHOROID
- RPE
- RETINA
Macula

RPE

RETINA
High resolution OCT
Photoreceptor mosaic using AO
Age-related Macular Degeneration

Normal Eye

Optic nerve head

Macula

Normal Vision

Age-related Macular Degeneration

Dry AMD

Wet AMD
Photoreceptors and RPE are a coupled unit
Macular Translocation.
Where to find good RPE?
RPE Transplantation
Functional RPE

A

B

6 months
Fixing vision on transplant region
Pharmacological approach to restoring RPE and photoreceptors

• Provide trophic support to RPE and photoreceptors

• Ciliary Neurotrophic Factor (CNTF)
  – Upregulated in many retinal injury models
  – Photoreceptors and RPE have CNTF receptors
  – CNTF induces RPE to secrete other trophic factors that may be supportive to photoreceptors
  – CNTF has been shown in animal models to be protective against retinal degeneration
Drug delivery in the eye
Retinitis Pigmentosa

- Hereditary degeneration of the retina
- Impacts the photoreceptor cells primarily – other retinal layers less so
- Photoreceptors degenerate, generally rods first followed by cones
- Almost all patients go blind
- Mutations in both photoreceptor and RPE specific genes
  - Opsin mutations common
ECT: An “Implantable Bioreactor”
Clinical Trials

Longitudinal Study of Cone Photoreceptors during Retinal Degeneration and in Response to Ciliary Neurotrophic Factor Treatment

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Purpose. To study cone photoreceptor structure and function in patients with inherited retinal degenerations treated with sustained-release ciliary neurotrophic factor (CNTF).

Methods. Two patients with retinitis pigmentosa and one with Usher syndrome type 2 who participated in a phase 2 clinical trial received CNTF delivered by an encapsulated cell technology implant in one eye and sham surgery in the contralateral eye. Patients were followed longitudinally over 30 to 35 months. Adaptive optics scanning laser ophthalmoscopy (AOSLO) provided high-resolution images at baseline and at 3, 6, 12, 18, and 24 months. AOSLO measures of cone spacing and density and optical coherence tomography measures of retinal thickness were correlated with visual function, including visual acuity (VA), visual field sensitivity, and full-field electroretinography (ERG).

Results. No significant changes in VA, visual field sensitivity, or ERG responses were observed in either eye of the three patients over 24 months. Outer retinal layers were significantly thicker in CNTF-treated eyes than in sham-treated eyes (P < 0.005). Cone spacing increased by 2.9% more per year in sham treated eyes than in CNTF-treated eyes (P < 0.001, linear mixed model), and cone density decreased by 9.1%, or 223 cones/degree2 more per year in sham-treated than in CNTF-treated eyes (P = 0.002, linear mixed model).

Conclusions. AOSLO images provided a sensitive measure of disease progression and treatment response in patients with inherited retinal degenerations. Larger studies of cone structure using high-resolution imaging techniques are urgently needed to evaluate the effect of CNTF treatment in patients with inherited retinal degenerations. (ClinicalTrials.gov number, NCT00147881) (Invest Ophthalmol Vis Sci. 2011;52:000–000) DOI:10.1167/IOVS.10-6479

Inherited retinal degenerations represent a genetically heterogeneous group of diseases that include retinitis pigmentosa (RP) and Usher syndrome type 2. Retinal degenerations are characterized by slowly progressive death of rod and cone photoreceptors and relentless vision loss. One of the challenges that has hampered the development of treatments that may slow vision loss in retinal degeneration is the lack of sensitive outcome measures of disease progression. Objective, sensitive measures of photoreceptor survival may reduce the time required to identify a treatment effect of an experimental therapy.

Neurotrophic factors such as ciliary neurotrophic factor (CNTF) have shown promise in slowing the progression of retinal degenerations.
Sham Treated Eye, Inferonasal to Fixation

~2115 c/deg²

~1751 c/deg²

~1693 c/deg²

~20% drop in cone density from baseline
No change in cone density from baseline

**CNTF Treated Eye, Inferotemporal**

- Baseline: ~2131 c/deg²
- 15 months later: ~2162 c/deg²
- 35 months later: ~2225 c/deg²
Cone Density Decreased More in Sham-treated Eyes Compared with CNTF-treated Eyes

- Normal: gray region
- Pt 1: solid lines
- Pt 2: long dashed lines
- Pt 3: thin solid lines
- CNTF-treated: Blue
- Sham-treated: Red
- Gray region: Estimated measurement error range (+6.3%)
Summary

- Translational research in ophthalmology is facilitated by
  - The ability to image the retina and visualize the target organ at the tissue and cellular level
  - Local delivery of therapy
Why the eye?

• Drugs can be applied directly to the affected tissue
  – No worries about oral bioavailability, liver metabolism, or crossing the blood-brain barrier
  – Very high concentrations can be achieved for short times

• Systemic toxicity issues can be avoided
  – High doses to the eye do not drive biologically active doses systemically
  – Many drugs active in the eye are undetectable in systemic circulation

• Tissue can be directly observed

• Ocular manifestations are common