National Eye Institute

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What Was My Background?

- Electrical engineering → medical school
- Met a classmate who became a pediatrician...
- Neuroscience → ophthalmology → pediatric ophthalmology
- Applications of biomedical informatics to clinical care & research
- Telehealth (retinopathy of prematurity: leading cause of childhood blindness worldwide) → validation → standard of care
What Was My Background?

- Artificial intelligence (ROP): FDA Breakthrough Status
- Genotype-phenotype correlation in ROP, risk models for ROP
- Collaborators in neonatology & pediatrics
- Data science & “big data”:
  - Research program involving EHR implementation, design, efficiency
  - American Academy of Ophthalmology Medical Information Technology Committee: leadership role in national EHR implementation plan
  - AAO IRIS Registry: leadership role in development & implementation (now ~500M eye exams from ~80M unique patients)
Why Does Vision Work Matter?

- **Impact on quality of life**: blindness is among conditions that Americans fear most, work that matters
  - Daily living: driving, recognizing people, reading
  - How we experience the world, link to emotion
  - Risk of isolation, depression, acceleration of dementia

- **Impact on science**: enormous, broad
  - NEI: 8 Nobel Prize winners (initially Hubel & Wiesel)
  - Many seminal innovations occurred first in eye & visual system → accessible setting for generalizable research
Public Health Challenges of Vision & Eye Care

- How many people & children are affected by vision disease?
  - **USA**: 150M with vision limitation, 7.1M with low vision (≤20/40), 1.1M with blindness (≤20/200), annual economic burden $50B
  - **Global**: 250M with low vision (≤20/40) or blindness (≤20/200)
  - **Children globally (age 0-14)**: 1.4M blind (including uncorrected refractive error), 22.2M with moderate-severe vision impairment, 44.6M with mild vision impairment

- **Public health & economic impact**: educational performance, gender equity, depression, accelerated dementia

- Eye disease: ranked 9th in **global disease** burden (after perinatal conditions, lower respiratory infections, HIV/AIDS...)

Some of What We’ve Done: Pediatric Ophthalmology & Development
Innovation: Gene Therapy

- Infants with Leber Congenital Amaurosis (20 years ago): “we can provide supportive care”

- **First FDA-approved gene therapy for an inherited disease** → precision medicine (LCA – RPE65)

- **First in-human CRISPR gene editing** (CEP290-driven LCA)

- **Accessibility of eye for exam, outcome measures, surgery**

Video courtesy of Jean Bennett, MD, PhD (University of Pennsylvania)
Gene Therapy Era

- ABCA4 – Stargardt disease
- CHM – X-linked choroideremia
- CNGA3 – Achromatopsia
- CNGB3 – Achromatopsia
- GUCY2D – Leber congenital amaurosis
- MERTK – Retinitis pigmentosa
- MYO7A – Usher syndrome
- PDE6B – Retinitis pigmentosa
- RLBP1 – Retinitis pigmentosa
- RPGR – X-Linked RP
- RPGRIP1 – Leber congenital amaurosis
- RS1 – X-linked retinoschisis

2021
RPE65 added to the ACMG 3.0 secondary findings genes

- USH2A – Usher syndrome (Dual vector, ASO)
- CEP290 – Leber congenital amaurosis (ASO, CRISPR)
Innovation: Artificial Intelligence for Medicine

- **First FDA-cleared autonomous AI system in any medical field** (Abramoff et al, NPJ Digit Med 2018)

- Knowledge discovery regarding systemic health (Poplin et al, Nat Biomed Eng 2018)

- Prediction of AMD progression (Yim et al, Nat Med 2020)
Eye as a Model System: Imaging

- **Retinal photography** (e.g. ETDRS: standardized diabetic retinopathy reading centers, in use since 1968)
- **OCT**: revolution in research & clinical care, **qualitative to quantitative**
- High-speed Fourier-domain OCT → to 3D volumetric imaging
- **OCT Angiography**: noninvasively detect flow & motion, capillary-level resolution, potential to generalize across other fields (structure & function)

Image and video courtesy of David Huang, MD, PhD, and Yali Jia, PhD (OHSU Casey Eye Institute)

Eye as a Model System: Functional Data & Accessibility

- Functional outcome measures (quantitative, validated):
  - Visual acuity
  - Perimetry & microperimetry (retinal function & vision loss in periphery), contrast & color sensitivity
  - Maze tests

- Accessibility for study
  - Retina as part of the brain: neurodegenerative diseases like Alzheimer’s can be detected in the eye
  - Vasculature in choroid & retina: changes in vasculature from diseases like diabetes can be measured
  - Immunology in the eye: noninfectious uveitis (form of immunity)
  - Cell-based and gene-based therapies: complex tissues are accessible & trackable
Where We’re Heading: Strategic Plan, Potential Collaborations with NHGRI
Revised NEI Mission Statement: First Since 1968

The mission of the National Eye Institute is to eliminate vision loss and improve quality of life through vision research. To achieve this mission, NEI provides leadership to:

- Drive innovative research to understand the eye and visual system, prevent and treat vision diseases, and expand opportunities for people who are blind or require vision rehabilitation

- Foster collaboration in vision research and clinical care to develop new ideas and share knowledge across other fields

- Recruit, inspire, and train a talented and diverse new generation of individuals to expand and strengthen the vision workforce

- Educate health care providers, scientists, policymakers, and the public about advances in vision research and their impact on health and quality of life.
NEI Strategic Plan (11/2021)
Opportunity: Large-Scale Curated Databases

- Understanding complex systems interactions: need **research networks & databases**

- **NIH Data Sharing Policy (Jan 2023):** need explicit plan

- Need: curate databases to **publicly share data** & establish **standard data representations**
  - Multi-omics analysis: help understand disease mechanisms
  - Combine results from multiple smaller studies

- **Other incentives** for data sharing ("carrot")
  - **New publication type:** academic credit, citations, findable
  - How to effect gradual culture shift in community? Promotion & tenure? Other ways to promote value to data sharing & harmonization?
**Opportunity: Neurodevelopment & Plasticity**

- Ability of neurons to reconnect after injury or disease
  - **Infants:** brain & visual system with high plasticity
  - **Adults:** loss of stable neuronal connections is challenging to repair
  - Adaptive (learning & memory) vs. maladaptive

- **Harness adaptive plasticity for neuro-regenerative therapy?**
  - Study developmental vs. adult plasticity: normal retina, disease (e.g. glaucoma, AMD), brain-based visual disease (e.g. amblyopia, CVI)

- **Study disease from maladaptive plasticity** (e.g. amblyopia)
  - Understand visual subsystems & circuits → treatments based on plasticity mechanisms
  - Project Prakash (New Delhi, Pawan Sinha): screening & treatment of children with blinding conditions (e.g. cataract, corneal opacity) → many cases improved over time, plasticity in visual development
Opportunity: CVI & Brain-Based Visual Impairment

- **Cerebral visual impairment (CVI):** leading cause of childhood blindness
  - Causes/associations: prematurity, perinatal brain damage, oxygen deprivation...
  - Visual acuity & field deficits, higher-order deficits (e.g. attention & recognition)

- Need understanding of **neural basis** (applications to TBI/stroke)

- Need **tools & guidelines** for diagnosis, classification (quantitative biomarkers), management

- Different rehabilitation needs of **brain-based vs. ocular impairment**

- Need interdisciplinary approach (pediatrics, developmental specialists, structural & functional imaging, neuroscience, PT/OT, educators)
Opportunity: Cellular Mechanisms of Refractive Error

Problems:

• Refractive Error (RE) involves Genes & Environment, with prevalence varying across populations (e.g., myopia “epidemic” in East Asia with 70-90% prevalence). GWAS of myopia has identified 200 loci, yet genes can’t explain exponential rise in rates.

• Controversy regarding role of environmental mechanisms (e.g. near work, screen time, broad-spectrum sunlight vs. dim light, time outdoors, diet, air pollution, etc.)

• Need: characterize interacting roles of gene/environment factors on incidence, progression, and stabilization of RE across population and age disparities.

• Need: understand cellular mechanisms of eye growth, impact of refractive error on development & education, multidisciplinary work between pediatrics + genetics + animal models + epidemiology.

Potential solution: workshop, new consortium bringing together interdisciplinary expertise (pediatrics; cell bio; retinal physiology/neuro; animal models; optics; development) and recruit new talent to decode mechanisms controlling ocular growth during development.

(Subgroup Members: Shefa Gordon, Cheri Wiggs, Chuck Wright)
PEDIG: Pediatric Clinical Trials Network

- Funded by NEI since 1997: multi-center studies in strabismus, amblyopia, other pediatric eye disease
- 123 current sites (US/Mexico/Canada), 49 studies (6 current), 117 manuscripts
- Potential translational impact of other NEI-funded work in visual development: changes in visibility of visual targets as motor skills improve (Linda Smith), models to predict eye movement during infant development (Lisa Oakes)
- **Possible collaborations**: impact of vision & refractive error on education & development, approaches to vision screening
- Potential role for integrating findings into real-world pediatric or ophthalmic care (e.g. EHRs)
Summary: Areas for Potential Collaboration

- Gene therapy for pediatric ophthalmology & pediatric disease
- Artificial intelligence: multiple data types (e.g., imaging, -omics, ophthalmic & clinical data for phenotyping, genotype-phenotype correlation)
- Data sharing: incentives (e.g., publications, P&T, team science, new metrics)
- Vision screening: integration into pediatric care, new technologies
- Plasticity, amblyopia, multidisciplinary CVI research
- Relationship between systemic development & ocular development (e.g., refractive error, education, cognitive development)