NEI Audacious Goals Initiative in Vision Research and Blindness Rehabilitation

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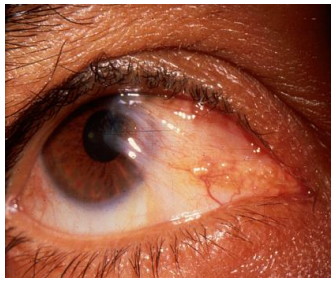
National Eye Institute

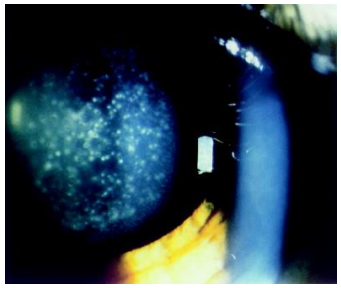
No financial interest in the subject matter of this presentation.

Focus of Eye Health National Summit
Prevent Blindness America
June 18, 2013

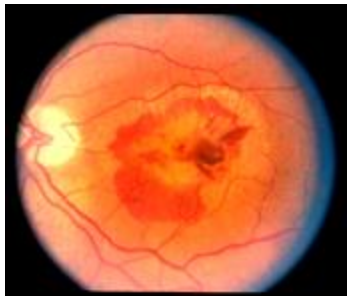
Eye Disorders Rank in the Top 10 Worldwide



Pterygium



Cataract



Macular degeneration

Rank	*Condition*
1.	*Perinatal conditions*
2.	*Lower respiratory infections*
3.	*HIV / AIDs*
4.	*Unipolar depressive disorders*
5.	*Diarrheal diseases*
6.	*Ischemic heart disease*
7.	*Cerebrovascular disease*
8.	*Malaria*
9.	***EYE DISORDERS (all types)***
10.	*Road traffic injuries*

List of 200 conditions from WHO "The World Health Report," 2003.

U.S. Public Health Challenge: Vision & Eye Care

- 38 million in the U.S. suffer vision impairment from diseases and conditions, many of which have a genetic basis or genetic risk.
- By 2020, age-related eye disease will increase 40% among Americans 40 years and older
- Eye diseases and disorders cost $60 billion annually in the U.S.

The National Eye Institute created the Audacious Goals Initiative to fundamentally advance vision research and ultimately vision care.

Audacious Accomplishments

What's next?

Decade of Remarkable Biology

Gene Therapy Returns

GENE THERAPY—REPAIRING MALFUNCTIONING cells by mending their DNA—offers an elegant solution to diseases caused by a single flawed gene. Since the first human study began in 1990, however, the field has struggled with technical challenges and setbacks such as the death of a volunteer in a trial. But this year, gene therapy turned a corner, as researchers reported success in treating several devastating diseases:

• **Leber's congenital amaurosis (LCA)**, a rare form of inherited blindness that strikes in infancy. Researchers in the United States and the United Kingdom injected one eye of LCA patients with a harmless virus carrying a gene coding for an enzyme needed to make a light-sensing pigment. In the first completed trial, the light sensitivity of all 12 partially blind patients improved. Four children gained enough vision to play sports and stop using learning aids at school. (Another team using a similar approach gave full color vision to squirrel monkeys born with red-green colorblindness.)

SCIENCE 2009

Success. Blind patients regained some vision after treatment to repair an enzyme-making gene.

2001 - Human genome sequence

2002 - Small interfering RNA (siRNA)

2002 - MicroRNA (miRNA)

2005 - Genetics of common complex diseases: *CFH* for AMD

2006 - Induced pluripotent stem cells (iPS cells)

2008 - Human gene therapy: *RPE65* replacement for LCA

2011 - 3D organogenesis: mouse eyecup from embryonic stem cells

2012 - Human embryonic stem cell therapy: for AMD / Stargardt

NEI Audacious Goals Initiative

- Presented to Nat'l Advisory Eye Council, February 2012.
- NAEC embraces the idea and incorporates "Challenge Prizes."
- Launch Audacious Goals Challenge, August 2012.
- 548 submissions received, November 2012
- Reviewed by 81 scientists with broad expertise, November 2012.
- Federal Judging Panel selects winners, January 2013.
- Hold Audacious Goals Development Meeting, February 2013.
- Develop goals further through targeted conferences.
- Implementation & facilitation by National Eye Institute & NAEC.

What is an "Audacious Goal"?

Big, important and inspiring, and when reached will fundamentally advance vision research or vision care.

Not about an R01, nor even two R01's.
An R01 application focuses on individual research goals.

An audacious goal:

- "…. will be on the edge of and even beyond current technology."
- "…. will push boundaries as far out as we can imagine."
- "…. will have major implications when it comes to fruition."

Audacious Goals Challenge Submissions

Total Received: 548

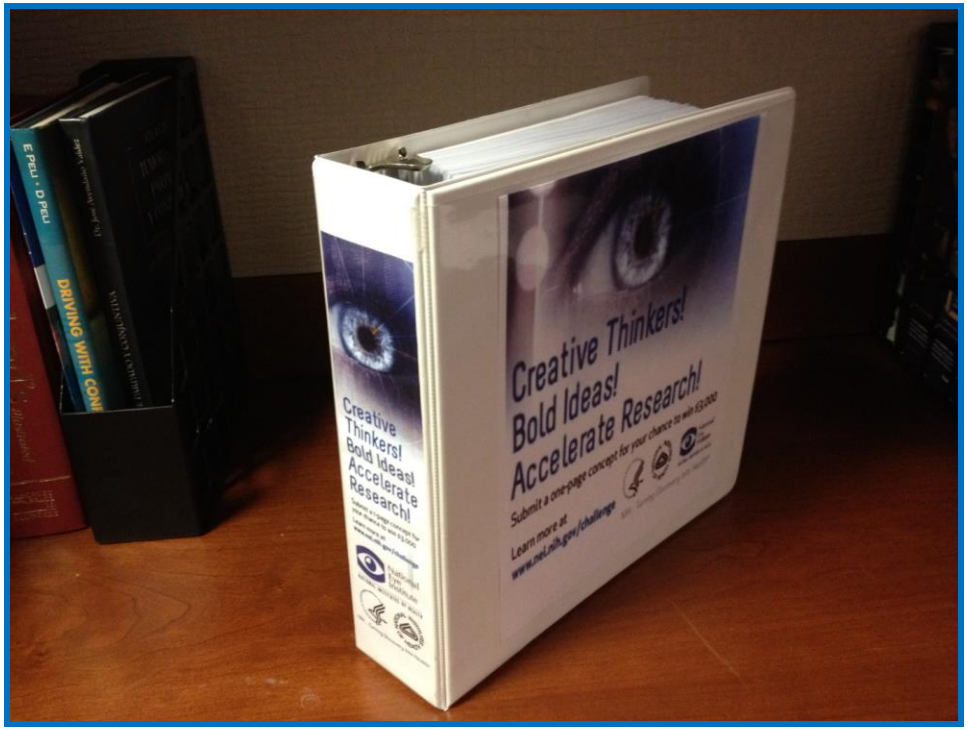
Foreign/Overseas Submissions: 33

No previous NIH grant experience: 308 (56%)

All submissions were de-identified before judging.

The submissions were winnowed by 81 readers, with 5-7 fold coverage.

Final decision by a “Federal Judging Panel,” required for federal prize money.



AG Prize Winners

Dennis Clegg. *Regenerative Therapy for Retinal Disease*

Robert Duvoisin. *Restoration of Vision by Opto-electronic Stimulation*

Yingbin Fu. *Precise Gene Editing In Vivo*

Steven Pittler. *Molecular Scissors Genome Editing to Cure Ocular Genetic Disease*

Rajesh Rao. *An Audacious Goal: Reprogramming the Retina*

Tonia Rex. *Functional and Structural Neuroregeneration*

Julia Richards. *Fountains of Youth for the Eye*

Jeffrey Stern. *Endogenous Retinal Repair: Releasing our Inner Salamander*

Russell Van Gelder. *Reversing Retinal Blindness Using Small Molecules*

Janey Wiggs. *Vision BioBank - Network of Ocular Phenotyping Centers Using Genomic and Epidemiologic Data to Promote Personalized Ophthalmology*

Six Topics for Audacious Goals Development

1. **Aging and mechanisms of disease development and progression, from molecules to cells to people.**
   Co-Chairs: Martin Friedlander and John Dowling

2. **Molecular therapy at the gene level.**
   Co-Chairs: Stephen Sugrue and Eric Pierce

3. **Systems approaches to disease analysis.**
   Co-Chairs: Donald Zack and Jonathan Haines

4. **Molecular and functional analysis and imaging of ocular tissues *in vitro & in vivo*.**
   Co-Chairs: Joshua Sanes and David Williams

5. **Regenerative therapies for ocular disease**
   Co-Chairs: David Gamm and Sally Temple

6. **Vision restoration by optogenetics, small molecules & prosthetics.**
   Co-Chairs: Connie Cepko and Ione Fine

Audacious Goals Development Meeting

Bolger Center; Potomac, MD.
February 24-26, 2013

National Eye Institute

Developing Audacious Ideas

Create a broad national research initiative to accelerate science discovery, to prevent & treat eye and vision disorders

People & Institutions

- Scientists
- Clinicians
- Patients
- Engineers
- Inventors
- Entrepreneurs

- Academia
- Professional Societies
- Other NIH Institutes
- Other Gov. agencies
- Pharma
- Bio-industry
- Private philanthropies

Broad science coverage

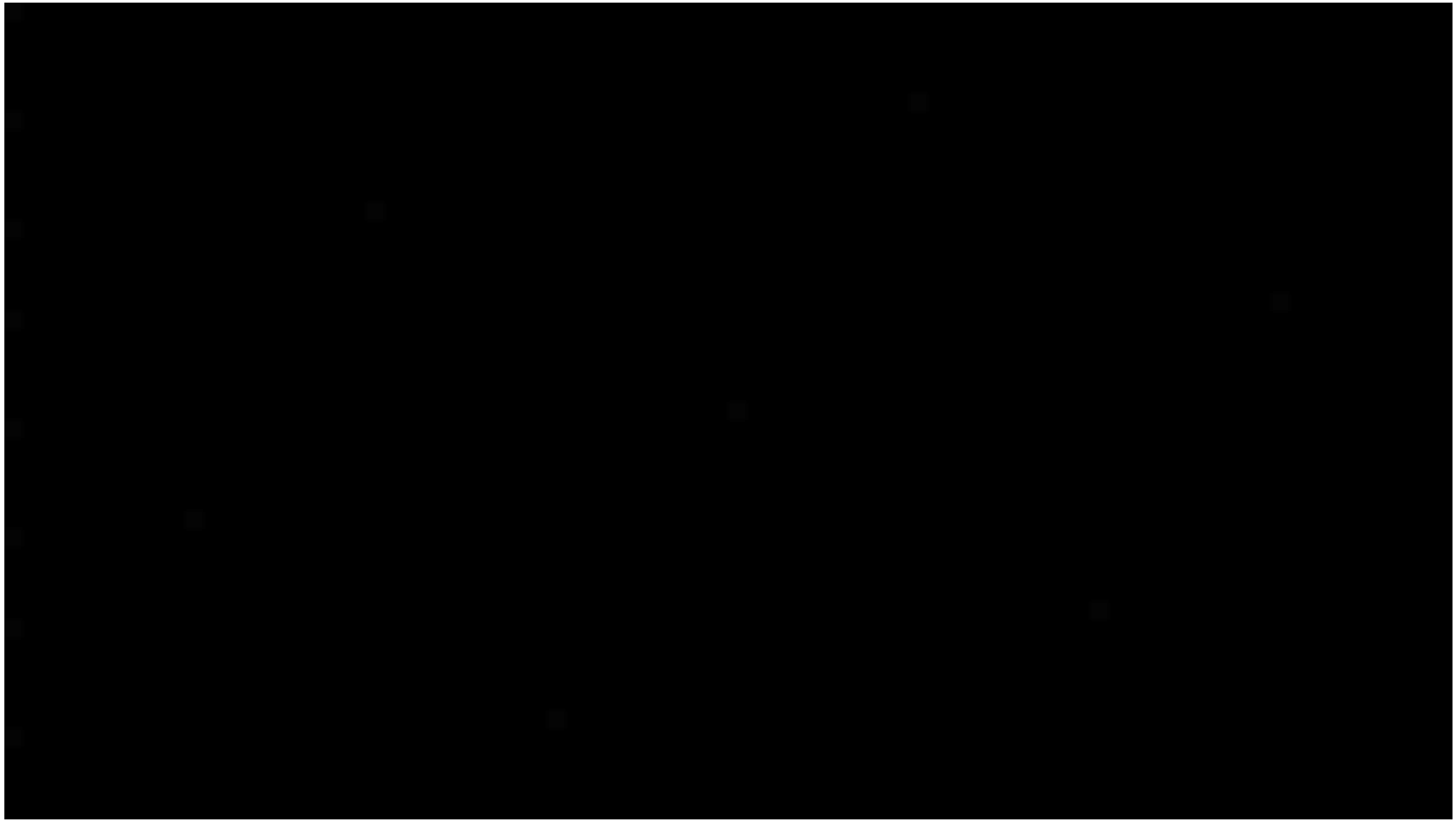
- Medicine
- Developmental biology
- Neuroscience
- Immunology
- Physiology
- Pharmacology
- Pathology
- Genetics
- Biochemistry
- Physics
- Engineering
- Nanotechnology
- Information technology
- Public Health & Epidemiology

Audacious Goals Development Mtg, February 2013

"It's often, it seems to me, that vision research is a couple of steps in front of things that are happening in biomedical research. It's clear that vision research has played a disproportionately large share in scientific breakthroughs."

Francis S. Collins
NIH Director

NEI Audacious Goals Initiative



Outcome of Audacious Goals Meeting

One Audacious Goal,

and Two High Priority Areas

Given the remarkable, new tools of biology developed during the last decade, we have an opportunity to leverage our collective action to accomplish something big and remarkable over the next 10-15 years.

Audacious Goal

Regenerate Neurons and Neural Connections in the Eye and Visual System

- Establishing functional neural connections would be a pinnacle achievement for regenerative medicine in the eye.
- Paradigm shift to create a new understanding of plasticity and regeneration.
- Addresses the pathogenesis of many ocular and vision diseases.
- Provide a model for regenerative therapies beyond vision, for treating CNS disease and spinal cord injury.

Why Now?

New Enabling Biology: Builds on the biological discoveries, advances and tools of the last decade

- Stem cell biology: ESC, iPSC
- Cell & systems and pathophysiology of disease
- Neurotrophic factors, glial biology, neural plasticity, comprehensive signaling pathways
- Production of 3-D organized neural retina tissue in culture

Enabling Technologies

- Optogenetics
- Multiphoton microscopy
- Single cell functional imaging
- Multi-unit electrophysiology techniques
- Nanotechnology

Ocular Disease Implications

- Neurodegenerative diseases (Glaucoma, AMD, etc)
  - Regrow and reconnect functional axons in the optic nerve targeted to specific location in the brain
  - Regenerate photoreceptors with functional integration with RPE and connectivity to bipolar cells.
  - Corneal neuropathy: regrow and reconnect corneal nerves after LASIK, wounding, or ocular surface disease

- Neural Plasticity
  - Develop and translate the basic science of plasticity into effective treatments for strabismus, amblyopia, and other disorders involving central visual processes.

What will we need to know?

- What trophic factors will stimulate and guide axons to specific targets in the brain?
- How do synapses form in an adult?
- What steps are required for exogenous repair?
- Can we activate latent endogenous cells to replace lost host neurons?
- How do we control immune responses and ensure safety and efficacy?
- How do we monitor *in vivo* for functional success?

Two High Priority Research Areas

Molecular Therapy for Eye Disease

Intersection of Aging & Biological Mechanisms of Eye Disease

High Priority Research Area #1

Molecular Therapies for Eye Disease

- Develop treatments through the control, modification and delivery of genetic information.

- Use small molecules and optogenetics approaches to treat eye disease and restore sight.

Why Now?

- Genetic and cellular bases of many eye diseases are rapidly becoming understood.
- Proof of concept demonstrated for ocular gene therapy.
- New and promising technologies are coming on line for precise gene correction *in vivo*.
- Molecular design and biology of light-sensitive molecules is feasible.

What will we need to know next?

- Define and prioritize among disease targets.
- Explore *in vivo* gene editing and correction tools for the eye.
- Define unique markers on a large scale for specific ocular cell types.
- Provide targeted reagents for specific cell types, and demonstrate regulatable, high-efficiency therapy.

High Priority Research Area #2

Intersection of Aging & Biological Mechanisms of Eye Disease

- Understand how the biology of aging contributes to disease and the course of disease.
- Evaluate how the failure of homeostatic processes causes or allows the transition from aging to early disease.
- Define biological staging of disease to understand pathophysiology toward therapy.

Why Now?

- Genetic and epigenetic risk factors are already identified for ocular diseases of aging.
- Longevity field has provided proof of concept that murine life span can be extended.
- New technologies allow earlier detection of disease.

How do we define success?

Demonstrate prevention or delay of disease progression.

Possible Interim Steps.

- Elucidate normal homeostasis of ocular tissues and deviations that contribute to disease.
- Identify biological predictors of early onset disease.
- Engineer drugs to target pathophysiology of disease.
- How do we map the biological pathways and "zones of transition" from normal aging to disease?

Implementation: Audacious Goals Initiative

Starting this summer, convene expert workshops to define needs and approaches to move the projects forward.

Charge:

- Build on the new biology.
- Identify and prioritize the first steps to set direction.
- Anticipate challenges and potential roadblocks.
- Consider measures of successful outcomes.

Guiding Principles for Implementation

Support the science trajectory, evaluate progress toward goals yearly and make course adjustments as the science evolves.

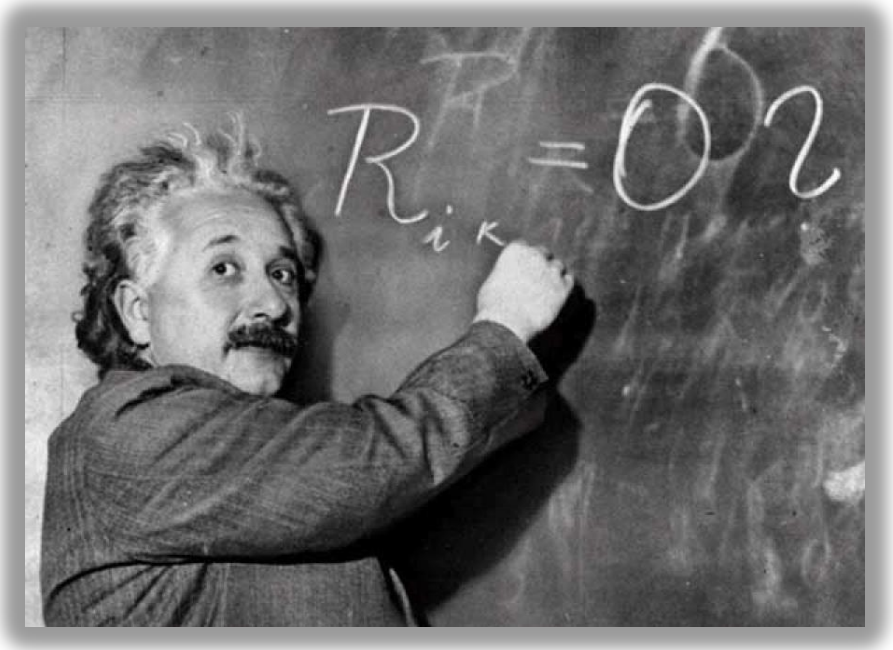
- Form an independent scientific leadership committee with rotating membership using the broad community base.
- Use open processes throughout.
- Remain flexible as science changes.
- Close participation with NAEC, and involve the vision community as a whole.

How do we approach a bold new frontier?

Albert Einstein:

"Logic will get you from A to B.

Imagination will take you everywhere."



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National Eye Institute

Prevent Blindness America®

Our Vision Is Vision®