

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Fiscal Year 2007 Budget Request

Witness appearing before the
House Subcommittee on Labor-HHS-Education Appropriations

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Mr. Richard Turman, Deputy Assistant Secretary, Budget

Mr. Chairman and Members of the Committee:

I am pleased to present the Fiscal Year (FY) 2007 President's budget request for the National Eye Institute (NEI). The FY 2007 budget includes \$661,358,000, which reflects a decrease of \$5,398,000 under the FY 2006 enacted level of \$666,756,000 comparable for transfers proposed in the President's request.

As the Director of the NEI it is my privilege to report on the progress laboratory and clinical scientists are making in combating blindness and visual impairment and about the unique opportunities that exist in the field of vision research.

RETINAL DISEASES

Retinal diseases are a diverse set of sight-threatening conditions that include age-related macular degeneration (AMD), diabetic retinopathy, retinopathy of prematurity, retinitis pigmentosa, Usher's syndrome, ocular albinism, retinal detachment, uveitis (inflammation) and cancer (choroidal melanoma and retinoblastoma).

Of these diseases, AMD is the most frequent cause of vision loss and legal blindness in older-age Americans, making it a research priority for the NEI. AMD causes degeneration of the macula, the central part of the retina that gives us fine, sharp visual detail. AMD is thought to result from the confluence of genetic predisposition and chronic exposure to environmental risk factors.

On the genetic side of the equation, identifying subtle alterations in a gene or

genes in AMD and other late onset diseases has been complicated by the fact that traditional genetic research strategies and tools are either inadequate or too cumbersome in their application. The development of more sophisticated genetic tools has enabled scientists to scan the entire human genome more quickly and efficiently. Using data from the Human Genome Project and the International HapMap Project, four different NEI supported laboratories identified a common variation in a gene called complement factor H (*CFH*) that accounts for an estimated 50 percent of the risk of developing AMD.

The *CFH* protein regulates an inflammatory response that is typically triggered by infectious microbes. Alterations in the *CFH* gene are postulated to poorly regulate this response, leading to chronic, localized inflammation and ensuing damage to cells in the center of the retina, the macula, and its neighboring tissues. Inflammation is thought to play a role in many other common diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, kidney disease, stroke, and atherosclerosis. Although the cells, tissues, and molecular events in these diseases are diverse, they may share some common disease mechanisms that present an opportunity to cross pollinate findings from diverse research areas.

The discovery of the *CFH* gene will allow researchers to create animal models and evaluate therapies that control chronic inflammation. The *CFH* gene also illustrates the potential of a new paradigm for medicine in the 21st century. This new paradigm holds that the practice of medicine should be preemptive, personal and predictive. The

CFH gene presents the possibility to one day identify at-risk patients and intervene well before pathology is clinically detectable.

STRABISMUS, AMBLYOPIA AND VISUAL PROCESSING

Developmental disorders such as strabismus (misalignment of the eyes) and amblyopia (commonly known as "lazy eye") are among the most common eye conditions that affect the vision of children. It is estimated that 20 percent of preschool children ages 3-4 have these and other treatable eye conditions¹.

In an effort to identify children with treatable eye conditions, many states are developing guidelines for preschool screening programs. However, none of the commonly used vision tests have been evaluated in a research-based environment to establish their effectiveness. To address this issue, the NEI supported a large, multi-center study called the Vision in Preschoolers (VIP) Study to determine which tests and test conditions can effectively identify preschoolers in need of a comprehensive eye exam. Previously VIP Study researchers found that in the hands of licensed eye care professionals, the best performing tests were able to detect 90 percent of children with the most severe visual impairments. This year, VIP Study investigators found that specially trained nurses and lay people can achieve results that are comparable to screenings performed by licensed eye care professionals. Given that most eye screening programs rely on lay people and nurses, this finding validates the effectiveness of this approach.

¹ Comparison of preschool vision screening tests as administered by licensed eye care professionals in the Vision in Preschoolers Study. *Ophthalmology* 111(4): 637-50, 2004.

GLAUCOMA AND OPTIC NEUROPATHIES

Glaucoma is a group of eye disorders that causes optic nerve damage that can lead to severe visual impairment or blindness. Elevated intraocular pressure (IOP) is frequently, but not always, associated with glaucoma. Glaucoma is a major public health problem and published studies find that the disease is three times higher in African Americans than in non-Hispanic whites².

The defining event that leads to vision loss in all forms of glaucoma is the degeneration of retinal ganglion cells (RGC) in the back of the eye. These cells relay visual information to the brain through the optic nerve and their loss effectively severs the neural network that allows us to process visual information. However, little is known about the molecular events that result in RGC degeneration. Using high dose radiation and bone marrow rescue to explore inflammatory responses in an animal model of glaucoma, researchers unexpectedly discovered that this procedure prevents the loss of RGCs. The neuroprotection offered by this procedure was complete, highly reproducible, and lasting. Normally, by 12-14 months, these glaucoma susceptible mice have complete RGC loss. At 14 months, treated mice had no detectable signs of disease. Although the mechanism that offers neuroprotection is not yet known, researchers speculate that it is due to radiation, because the transferred bone marrow was genetically identical to the original bone marrow the mice were born with. This highly novel treatment protocol offers a tool to understand neurodegeneration and, with

² The Eye Diseases Prevalence Research Group: Prevalence of open-angle glaucoma among adults in the United States. *Arch Ophthalmol* 122:532-538, 2004.

refinement, could have important implications for the treatment and prevention of neurodegenerative diseases.

CORNEAL DISEASES

The cornea is the transparent tissue at the front of the eye. Corneal disease and injuries are the leading cause of visits to eye care professionals, and are some of the most painful ocular disorders. In addition, approximately 25 percent of Americans have a refractive error known as myopia or nearsightedness that requires correction to achieve sharp vision; many others are far-sighted or have astigmatism³.

Inflammation is a common immune response to injury and infection in the body. In the cornea, however, inflammation can cause extreme discomfort and result in vision loss. Nonetheless, the cornea retains a remarkable capacity for wound repair while actively suppressing an inflammatory response. Scientists have recently discovered that two lipids, lipoxin A₄ (LXA₄) and docosahexaenoic acid-derived neuroprotectin D1 (NPD1), are formed in the cornea and act as anti-inflammatory agents during corneal infection and wound healing. Topical treatment with LXA₄ and NPD1 in mice with corneal injuries increased the rate of tissue repair and inhibited inflammation without impairing the recruitment of key immune leukocytes, which are normally associated with inflammation, into the wounded tissue. Moreover, a transgenic mouse that lacks these lipids exhibited delayed wound healing and attenuated leukocyte recruitment. The identification of these anti-inflammatory lipids in the cornea and their enhancement of

³ The Eye Diseases Prevalence Research Group: The prevalence of refractive errors among adults in the United States, Western Europe, and Australia. *Arch Ophthalmol.* 122:495-505, 2004.

wound healing by topical application suggest their use as therapeutic agents to overcome aberrant and damaging inflammatory responses in the eye.

CATARACT

Cataract, an opacity of the lens of the eye, interferes with vision and is the leading cause of blindness in developing countries. In the U.S., cataract is also a major public health problem. The enormous economic burden of cataract will worsen significantly in coming decades as the American population ages.

The lens is a dense, compact structure containing two cell types: metabolically active epithelial cells and quiescent fiber cells. Throughout the life-time of an individual, the lens carries out a process of continued growth with epithelial cells dividing and differentiating into fiber cells. During this process, the emerging fiber cells become denuded of organelles such as the nucleus and mitochondria. This process in part helps the lens achieve the high transparency needed for clear vision. Scientists have previously found that the lens uses proteins involved in a biological process called programmed cell death or apoptosis to rid lens fiber cells of their organelles. This past year, vision researchers have discovered the biologic process that regulates apoptosis such that it allows for the elimination of organelles without resulting in cell death.

The process is termed Apoptosis-related Bcl-2 and Caspase-dependent (ABC) differentiation. In this process, a number of proteins that normally lead to cell death such as caspases—proteins that break-down internal cellular structures—are expressed

to denude organelles. The caspase proteins are balanced by the simultaneous induction of pro-survival molecules such as bcl-2, a protein that binds to cell death proteins and inhibits further damage or death to fiber cells. The discovery of ABC differentiation in the lens will allow researchers to better understand lens cell renewal and determine whether faulty mechanisms in this process might lead to cataract formation.

NIH ROADMAP

A goal of the NIH Roadmap Nanomedicine Initiative is to characterize quantitatively the molecular scale components or nanomachinery of cells and to precisely control and manipulate these molecules and supramolecular assemblies in living cells to improve human health. The NEI has a leadership role in implementing the NIH Roadmap Nanomedicine Initiative. Under this initiative, a Request for Applications (RFA) was prepared to award Nanomedicine Center Concept Development Awards. These concept development awards were created to allow applicants time and resources to develop the concept for a Nanomedicine Center that would address various issues in nanomedicine including, biomolecular dynamics, intracellular transport, and protein-protein interactions. Understanding these fundamental biologic processes at the nanoscale level will allow scientists to engineer molecular structures, assemblies, and organelles for treating diseased or damaged cells and tissues. Of the applications, four Nanomedicine Centers were awarded in FY 2005. The Centers will be dedicated to understanding the nanobiology that underlies protein folding machinery; ion channels and ion transport proteins; synthetic signaling and motility systems; and mechanical biology. The NIH expects to fund additional Nanomedicine Centers in FY 2006. The

Nanomedicine Initiative will also benefit eye research in a more direct way. Current NEI grantees are exploring the use of nanotechnology to assist in corneal wound healing and drug delivery to the retina. Increased support of nanomedicine through the NIH Roadmap will undoubtedly speed progress in these areas.

NIH NEUROSCIENCE BLUEPRINT

The NIH Neuroscience Blueprint is a collaborative effort among 15 NIH institutes and centers to accelerate the pace of discovery and understanding in neurosciences research. In an effort to better understand all elements of the nervous system, the Blueprint will focus on the development of tools and resources that will facilitate research on the processes of development, neurodegeneration, and plasticity that underlie the health and disorders of the nervous system. One of the approaches to develop these tools and resources is a cellular level approach to discovering the key molecules involved in nervous system function. There is still a need to identify the location, the developmental timing, and the cellular function of most of the genes and proteins expressed in the brain. Mapping of the neurogenome is being conducted by creating and analyzing transgenic mice to map gene expression and activity to different cell types and regions of the mouse central nervous system. The NEI component of this effort will be to ensure that the genes involved in neurons of the complete visual system are included in the neurogenome map.

Mr. Chairman, this concludes my prepared statement. I would be pleased to respond to any questions you or other members of the committee may have.