Research Opportunities in Vision: A Report of the U.S.-Indo Workshops on Collaborative Research

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This article reports on two workshops in 2005, one in India and the other in the United States, to promote international research in vision and ophthalmology. The workshops were held in February and April and spanned a total of 7 days. They were sponsored by the Association for Research in Vision and Ophthalmology (ARVO) and funded through a cooperative agreement with the NationalEye Institute (NEI) of the National Institutes of Health (NIH) and by the Department of Biotechnology (DBT), Government of India.

The goal of the workshops, attended by leaders in eye and vision research from the two nations, was to identify and promote U.S.-Indo collaborations and research opportunities to accelerate the ability to understand, prevent, treat, and cure vision disorders. Five core research areas were considered: molecular genetics of eye disease; clinical aspects of genetic eye disease; harmonization of clinical measurement techniques and terminology; translational physiology; and identification, development, and exchange of research resources. It is hoped that, by providing information about the workshops with the larger eye and vision research community, additional ideas and collaborations will emerge.

A rapid outcome of the workshops was the signing, on August 24, 2005, of a United States-India Statement of Intent for collaboration on expansion of vision research. The agreement was signed by India’s Secretary of the DBT, Maharaj K. Bhan, and the NIH’s director, Elias A. Zerhouni. Quite simply, the countries officially agreed to combine their vast biomedical and clinical expertise and resources in ophthalmology, for reducing the burden of vision disability and blindness.

In addition to joint research projects, the parties foresee opportunities for research training, workshops, and exchanges of scientists, scientific information, and biological materials.

The agreement marks a more than 20-year history of successful teamwork between Indian and U.S. scientists and institutions in the prevention of blindness. One of the first collaborations was an evaluation of cryoblation and argon laser photocoagulation for Eales’ disease, in which early photocoagulation was found to help prevent vitreous hemorrhage.

Several collaborations have since occurred between Johns Hopkins University and Indian researchers. These include studies of the role of low doses of vitamin A on infant blindness and mortality; the effect of vitamin A in the perinatal period; the dose-response and adverse effects of mitomycin C as an adjunctive agent in glaucoma filtration surgery; the learning curve of physicians training in phakoeulisisfication for treatment of cataract; and the Andra Pradesh and Aravind Comprehensive Eye Survey (1994) evaluating the causes of blindness, prevalence of various eye diseases, and utilization of eye care in southern India. In addition, the University of Iowa helped develop a human genetics laboratory in India about 5 years ago and the Proctor Foundation for Research in Ophthalmology began collaborations in India in 1998 for evaluating the role of antioxidants in retarding or preventing cataract.

Other collaborations have occurred in the fields of lens biochemistry (Venkat Reddy of Oakland University, Rochester, MI, and Seetarama Bhat of the National Institute of Nutrition [NIN], Hyderabad); night blindness (Barbara Underwood of NIH and the staff of NIN); clinical ophthalmology (between L. V. Prasad Eye Institute [LVP], Hyderabad and NEI); and cataract biology (between D. Balasubramanian and Mohan Rao of the Centre for Cellular and Molecular Biology [CCMB], Hyderabad and J. S. Zigler of NEI). Contacts have also been established between two centers in India (Sankara Nethralaya [SN] in Chennai and the Aravind Eye Hospital [AEH] in Madurai) and colleagues in the United States. In the late 1980s, a bilateral United States-India case-control study of age-related cataracts was initiated between NEI and the R. P. Centre for Ophthalmic Sciences (RPC), All India Institute of Medical Sciences, New Delhi, leading to two important publications.1,2

We believe that with the formalization of this expanded vision health alliance between the United States and India, the future of eye health worldwide takes a major step forward. What follows is a brief overview of research and clinical resources in vision in the United States and India, background information about the workshops and its participants, reports on the five core research areas discussed at the workshops, summaries of opportunities for collaboration, additional details about assets in ophthalmology in India and the United States, and information for others who would like to become involved. Readers who are interested mainly in the five core research areas will find them in the section, “Structuring the Workshops.”

Overview of Resources

India has nearly 12,000 ophthalmologists and more than 20 basic biology research institutions where ophthalmic research...
is performed. Four of India’s major eye centers are LVPEI in Hyderabad, AEH in Madurai, SN and its Vision Research Foundation in Chennai, and the federally assisted RPC for Ophthalmic Sciences in New Delhi. The first workshop in this current event on collaborative research was held at LVPEI, which, along with several others, is described in more detail later in this report.

Vision disorders affect more than 22 million of India’s population of more than 1 billion. The World Health Organization, in its recent publication on global data on visual impairment in the year 2002, estimates that more than 7 million Indians are blind (visual acuity of less than 3/60). In addition, approximately 15 million people have low vision (visual acuity of less than 6/18 but equal to or better than 3/60). Cataract accounts for a major portion (approximately 60%) of the blindness burden in the country, followed by glaucoma, age-related macular degeneration, corneal opacity, diabetic retinopathy, and trachoma, in that order. Childhood blindness accounts for approximately 4% of the total. Corneal dystrophies are also common.

Hundreds of eye surgeries are performed at the various eye centers in India each day. Detailed medical and social histories are maintained on each patient. In many cases, pathologic specimens of eye tissue or whole globes are obtained and stored. Analysis of the records and tissues is likely to provide a fount of new leads and directions for research.

Unique to India is an unusually large number of people whose vision impairment can be traced to genetic or environmental causes, largely owing to India’s hundreds of tribes and communities where intracommunity and consanguineous marriages are common. India is also home to several eye conditions that exist in a small number of people in the United States, including forms of corneal dystrophy and glaucoma and, as

The first meeting of the U.S.-Indo Workshop on Collaborative Research was held from February 10–15, 2005, at the L. V. Prasad Eye Institute in Hyderabad, India, followed by site visits to the Avarind Eye Hospital in Madurai and the Sankara Nethralaya in Chennai. Attendees were selected to represent major areas of eye and vision research.

The signing of a U.S.-India Statement of Intent for collaboration on expansion of vision research attests to a strong commitment for combating vision disability and blindness. The agreement was signed by India’s Secretary of the Department of Biotechnology, Maharaj K. Bhan (right), and NIH director Elias A. Zerhouni (left). Photo courtesy of NEI/NIH.
such, will be a good source for learning more about their pathogenesis and treatments.

Many scientists and clinicians from India have a proven track record of biomedical accomplishment (see online supplement for list of publications by Indian researchers, 2000–2004; http://www.iovs.org/cgi/content/full/47/5/1717/DC1). Many have experience in collaborating with U.S. researchers. Many have extensive experience in rural outreach—an important asset considering the need for comprehensive epidemiologic data. One such program, founded in 1998, is the International Centre for Advancement of Rural Eye Care (ICARE) at LVPEI. Another major program is the vast initiative taken on cataract (and more recently diabetic retinopathy) across the state of Tamil Nadu (population 6.1 million) by the AEH system. Another is the Chennai Urban Rural Epidemiology Study, or CURES, from the Madras Diabetes Research Institute, to identify diabetic retinopathy among city residents and rural dwellers. Over the years, many American vision researchers and clinical fellows and surgeons have come to these eye centers in India for training, enhancing surgical skills, joint clinical trials, and other research. The U.S. scientists stand to gain enormously from access to the patients and expertise of their Indian collaborators. Additional areas in which India has special expertise are genetics, basic biology of the eye, and informatics.

Eye disease in the United States is estimated by the NEI to affect more than 38 million Americans aged 40 and older. This statistic includes blindness, low vision, and age-related diseases such as age-related macular degeneration, glaucoma, diabetic retinopathy, and cataract. It is projected that by 2020, 50 million Americans will be living with vision disorders. (It is quite possible that, by using methods similar to the NEI’s for assessing and counting people with eye disease, the Indian statistics for low vision and blindness would be considerably higher.)

The primary U.S. agency for eye and vision research is the NEI, in Bethesda, Maryland. The following quotation from the National Plan for Eye and Vision Research represents the mission and vision of the NEI:

The National Eye Institute will continue to protect and improve the visual health of the nation through the support and performance of the highest quality laboratory and clinical research aimed at increasing our understanding of the eye and visual system in health and disease and developing the most appropriate and effective means of prevention, treatment, and rehabilitation, and through the timely dissemination of research findings and information that will promote visual health.

The fiscal year 2005 budget for the NEI is more than $660 million. The majority of the funding (~86%) goes for vision research in universities, hospitals, medical centers, and corporations throughout the United States and internationally. The remainder goes to NEI intramural research laboratories and to educational outreach through programs such as the National Eye Health Education Program (NEHEP). The total number of extramural awards made by the NEI in fiscal year 2004 was 1649 (see Table 8 for 25 of the top-funded departments of ophthalmology and vision research centers).

Among the areas in which the United States will add unique expertise to the U.S.-Indo collaboration is in genomics and the execution of large-scale clinical research trials and epidemiologic studies. Examples of past U.S. trials involving a large number of subjects are the Beaver Dam Eye Study, Age-Related Eye Disease Study (AREDS), Baltimore Eye Survey, Salisbury Eye Evaluation Project, and Los Angeles Latino Eye Study (LALES). Already, several U.S.-sponsored multicenter clinical trials are being conducted in India. These include trials of contact lenses and intraocular lenses, antibiotic formulations, and enzymatic sclerotomy.

New collaborations based on the new agreement will take full advantage of the number and diversity of eye diseases and the varied skills and resources of the participants. Some collaborations will be extensions of previous and ongoing projects between researchers and clinicians of the two nations; many will be new.

**BACKGROUND OF THE WORKSHOPS**

Although India and the United States have been engaged in important collaborations in vision research in the past, the full potential of the collaborations has not been realized. It was with this in mind that one of the authors of this article (DB) had earlier assessed the interest of colleagues from India and the United States at an ad hoc meeting he called at the 2002 ARVO annual meeting. He sent out an informal e-mail inviting people to attend and was rewarded with more than 80 participants, including Paul Sieving, Leon Ellwein, and Edward McManus of NEI. After this, when Dr. Sieving, Director of NEI, visited India in April 2003, he was told about important vision research activities at Indian centers and began considering opportunities for expanding the earlier research collaborations.

Informal discussion between U.S. and Indian agencies and researchers followed to assess how, by expanding collaborations, eye and vision research could be advanced. Dr. Ellwein, associate director of NEI, and Charles Gardner, then health attache at the United States embassy in New Delhi, met with Indian officials. Manju Sharma and T. S. Rao, Secretary and Director of the DBT of the Government of India, respectively, agreed that their agency would be the piloting agency in India for joint expansion of an India-U.S. eye research collaborative effort.

As a result of these early steps, it became evident that a planning workshop was needed to identify the extent and nature of the unique opportunities of an Indo-U.S. vision research collaboration. It was thought that ARVO, with its extensive experience in planning and conducting scientific meetings, would offer the most appropriate organizational framework on which to proceed. When approached, the ARVO Board of Trustees formally approved the development of a conference grant application to be submitted to the NEI for support of not one but two planning workshops, one in India and the other in the United States.

Progress in planning was rapid. After the next ARVO annual meeting, a group met to finalize the workshop grant application. One of the authors of this article (PK), as executive vice-president of ARVO, agreed to serve as the principal investigator of the workshop grant and also as U.S. co-chair of the program committee. The other author (DB), as research director of the LVPEI, agreed to be India’s co-chair.

Preliminary activities included the formation of a program committee (Table 1) to plan for the workshop topics and presenters. The first workshop was slated for February 10–15, 2005, at the LVPEI in Hyderabad. To be included in the schedule were site visits to the SN in Chennai; the Aravind Eye Hospital in Madurai; the CCMB in Hyderabad; and a world-class information technology firm called Satyam, also in Hyderabad. The second workshop was slated for April 29–30, 2005, and was held before the annual ARVO meeting, in Fort Lauderdale, Florida.

Five core research areas were selected for discussion. Thought leaders and keynote speakers were invited. The Indian leadership called for applications from potential attendees by placing advertisements in the Indian Journal of Ophthalmology, through emails to the Indian Eye Research Group, and through notices in IOVS and on the ARVO Web site. The U.S.
group called for applications through the ARVO Web site. Selection was conducted in a fair and transparent manner based on several criteria, including publication record, research interests of relevance to the proposed areas of collaboration, and, for U.S. participants, established NEI funding. NEI guidelines were followed with respect to gender balance, inclusion of minorities, and other criteria. Contact information for each participant (Table 2) is provided in the online supplement at http://www.iovs.org/cgi/content/full/47/5/1717/DC1 to facilitate additional collaborations. The list of contacts also includes participants from the NEI and ARVO.

Areas of Emphasis

From the beginning, it was clear that the workshops would not follow a classic presentation format. They would be catalytic in nature and would emphasize specific thoughts or themes where bilateral research collaboration would be most fruitful, such as ophthalmic genetics, clinical research, resources, standardization of definitions and criteria, and novel themes that might go beyond center-to-center partnerships.

The reason for holding the workshop in India was not only to bring the partners face-to-face for discussion, but also for U.S. participants to see the eye care facilities in India, innovations, and country-specific solutions; to become familiar with the types of problems that could arise; and to look for commonalities and differences. Most of the participants from India were already familiar with U.S. capabilities.

Structuring the Workshops

As mentioned above, five themes were chosen by the planning committee to be the main focus of the workshops:

- Molecular Genetics of Eye Disease
- Clinical Aspects of Eye Disease
- Harmonization of Clinical Measurement Techniques and Terminology
- Translational Physiology: Bench to Bedside Applications
- Identification, Development, and Exchange of Research Resources

Each theme was assigned two thought leaders, one from India and the other from the United States (Table 3). In India, in the first half hour of each workshop session, the two thought leaders presented the most salient points with regard to their topic. This was followed by an hour-long group discussion. The thought leaders were tasked with compiling and summarizing, in a report, the consensus of the group about possible areas for collaboration. Discussions that began at the February workshop continued a few weeks later at the second workshop, at the 2005 ARVO meeting.

The workshop in India opened with addresses by representatives from the principal Indian governmental bodies funding biomedical research: India's DBT and the Indian Council of Medical Research (ICMR). The speakers emphasized the timeliness of the workshop and its historical importance. ICMR General Director N. K. Ganguly referred to...
the significance for India of predictive testing and counseling, DNA chips, ophthalmic infections, and community-based databases to enhance blindness study programs. DBT Secretary M. K. Bhan discussed funding to boost vision research in India, as the Government of India considers the study of eye disease a high priority. Both officials emphasized the need for translational research for eradicating blindness in India.

Among several additional dignitaries at the opening of the India workshop was Altaf Lal, health attaché and U.S. Department of Health and Human Services (DHHS) regional representative for South Asia, Embassy of the United States. Dr. Lal voiced a commitment from DHHS for a successful program. Dr. Sieving spoke of the relevance of the plan to the NEI mission, the historic nature of the workshop, and its ultimate benefit to visually impaired people all over the world.

**The Five U.S.-Indo Workshop Themes: Reports from the Thought Leaders**

**Molecular Genetics of Eye Disease: Thought Leaders, Janey L. Wiggs and G. Kumaramanickavel**

The overall goal of ocular molecular genetic studies is to identify the genes that contribute to inherited ocular conditions. The characterization of genes responsible for ocular diseases will help define the molecular etiologies of the conditions and will lead to new methods of diagnosis and treatment, including DNA-based diagnostic tests. The availability of predictive and prognostic tests can provide a mechanism for early detection and treatment. People at risk who are identified early in the course of a disease and who begin appropriate and

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<td>Iqbal Ahmad</td>
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<td>Wallace Alward*</td>
<td>University of Iowa College of Medicine</td>
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<td>Karla Zadinick</td>
<td>The Ohio State University College of Optometry</td>
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*Session moderator.

**Table 2. U.S.-Indo Workshop on Collaborative Research: Additional Participants**

**Table 3. U.S.-Indo Workshop on Collaborative Research: Thought Leaders**

**Molecular Genetics of Eye Disease**

Janey L. Wiggs, Harvard Medical School
G. Kumaramanickavel, Sankara Nethralaya Vision Research Foundation

**Clinical Aspects of Eye Disease**

Anil K. Mandal, L. V. Prasad Eye Institute
Irene H. Maumenee, Johns Hopkins University School of Medicine

**Harmonization of Clinical Measurement Techniques and Terminology for Targeted Diseases and Structures**

Praveen K. Nirmalan, L. V. Prasad Eye Institute
David S. Friedman, Johns Hopkins University School of Medicine

**Translational Physiology: Bench to Bedside Applications**

Jyotirmay Biswas, Sankara Nethralaya Vision Research Foundation
Paul L. Kaufman, University of Wisconsin Medical School

**Identification, Development, and Exchange of Research Resources**

Gullappalli N. Rao, L. V. Prasad Eye Institute
Donald Zack, Johns Hopkins University School of Medicine
timely therapy will have the best chance of maintaining useful sight.

Both Mendelian (single-gene) and complex inherited ocular disorders are important causes of blindness in the United States and India. Among the single gene disorders that are especially common in India because of the practice of consanguineous marriage in the southern Indian states are autosomal recessive forms of retinitis pigmentosa and congenital glaucoma. Common age-related disorders, such as glaucoma, cataract, diabetic retinopathy and macular degeneration, also have considerable heritability and are prevalent in the United States and India. Age-related disorders are costly to treat, threaten the ability of older adults to live independently and, in India, increase the risk of mortality. A better understanding of the underlying etiologies of these disorders is critically important if we are to develop more effective means to diagnose and treat them before irreversible blindness occurs.

What follows is a review of the recent advances in ocular molecular genetics, a discussion of the current needs and challenges for ocular molecular genetic research, and a description of opportunities through collaborations among U.S. and Indian vision scientists.

Recent Advances. Mendelian disorders have a predictable inheritance pattern, which makes it possible to study them using standard linkage and molecular genetic approaches. This has led to the identification of many of the gene mutations that cause ocular conditions.

Congenital glaucoma is one example. Inherited as an autosomal recessive trait, congenital glaucoma has been associated with mutations in the CYP1B1 gene in many population groups, including in the United States and India. Another is juvenile open-angle glaucoma. Juvenile glaucoma is inherited as an autosomal dominant trait, and, in 10% to 20% of affected families, mutations in the gene that encodes the protein myocilin are responsible for the disease. In India, however, it has been shown that some families with the condition demonstrate a variation in disease expression that may be caused by differences in genetic background compared with Western populations.

In anterior segment dysgenesis, four genes have recently been identified that contribute to autosomal dominant forms of the condition. They are PITX2 (Axenfeld-Rieger syndrome), FOXC1 (Axenfeld-Rieger syndrome), LMX1B (glaucoma associated with nail patella syndrome), and PAX6 (aniridia). Although mutations in each of these genes have been found in different ethnic populations, genotype-phenotype correlations have been examined only in some instances. Genetic linkage approaches have identified more than 50 genes responsible for corneal dystrophies; more than 50 genes for inherited forms of cataract; and more than 50 genes for retinitis pigmentosa and other forms of retinal degenerations. In general the distribution of genetic defects responsible for these conditions appears to be similar in affected populations worldwide; however, the phenotypic expression of particular mutations or specific gene defects may vary. For example, a homozgyous form of granular corneal dystrophy with a phenotype more severe than patients with disease caused by heterozygous mutations was recently described in a consanguinous Indian pedigree. In addition, isolated or founder populations may have significant variations in gene frequencies and disease prevalence.

Genes have also been identified for Mendelian forms of optic atrophy and disorders of ocular motility.

Genome-wide scans have recently been completed for common inherited disorders with complex inheritance, including primary open-angle glaucoma (POAG), age-related macular degeneration, and myopia. Genome scans for adult-onset complex disorders are largely dependent on sibling pairs, and typically result in the identification of several large genetic intervals containing many possible candidate genes. Fine mapping studies including haplotype mapping, ordered subset analysis with phenotype stratification and linkage disequilibrium analysis are necessary to reduce the genetic interval size. Linkage disequilibrium analysis has lead to the recent identification of complement factor H as a major genetic risk factor for macular degeneration. Environmental factors such as cigarette smoking have also been recognized as contributing to macular degeneration.

Current Challenges and Needs. The opportunities for gains to be made in ocular health through molecular genetics are vast. To make the most of these opportunities, it is necessary to meet several important challenges. Among these challenges are identifying and managing large patient populations for genetic studies; making genotype-phenotype correlations; identifying genetic and environmental interactions; developing biomarkers to monitor disease status; and managing of enormous amounts of data from whole genome analyses.

Patient Populations. Genetic approaches for gene identification are dependent on large, well-characterized patient cohorts. Studies designed to identify genes responsible for Mendelian single gene disorders are dependent on large, multigenerational affected pedigrees. Genome scans for complex ocular disorders require very large pedigree sets with detailed and consistent phenotypic characterization. Association studies require large populations of affected individuals and carefully matched control patient populations.

Genotype–Phenotype Correlations. Although many gene defects have been associated with a large number of inherited ocular conditions, for most of the mutations, diagnostic and prognostic information is not available. This is because detailed correlations between specific genotypes and disease outcomes have not yet been made. Correlations of phenotype with genotypes are necessary before clinicians can offer diagnostic or prognostic information to patients.

Studies of variation in phenotypic expression of specific gene defects can also identify important modifier genes that may be useful targets for novel therapies. Descriptions of phenotypes in patients carrying the same genetic defects and comparisons of phenotype between patient populations with specific gene defects are necessary to establish these important genotype phenotype correlations.

Gene–Environment Studies. The common age-related ocular disorders have a considerable degree of heritability, and the identification of the susceptibility genes that contribute to these conditions could help define the underlying molecular events that cause them. However, the genetic contributions to these disorders are complex because of an interaction of multiple genetic factors and also because of the influence of environmental exposures.

Future studies designed to identify the gene–environment interactions that underlie common complex disorders are needed to help define the relative contributions of specific genetic risk factors and environmental exposures. Evaluation of gene–environment interactions requires a large number of affected patients, analysis of distribution of specific gene defects, and methods to collect and analyze environmental exposures.

Biomarkers for Chronic Disease. Many common ocular disorders are chronic and slowly progressive and have variable clinical outcomes. Clinical trials for finding new therapies are difficult because they take a long time and are very expensive. The development and validation of biomarkers would provide new methods to monitor progression and treatment of chronic ocular diseases. Because biomarkers are likely to respond to changes in disease progression in a shorter time frame than typical clinical measurements, these bioassays would make timely therapeutic modifications possible.

Bioinformatics. Genome analysis is increasingly dependent on thousands of single nucleotide polymorphism (SNP)
markers rather than hundreds of microsatellite markers. With thousands of patients and genotypes involved in genome-wide analytical procedures,\textsuperscript{53} data management presents a major challenge.

**Opportunities.** India’s large population, number of consanguineous marriages, differences in genetic background within the population, variability in environmental exposures, and technical expertise among clinicians and researchers are among the features that present themselves as opportunities in this collaboration.

**Large Patient Population.** India has more than 1 billion people. Although all genetic approaches would benefit from access to such a large patient population, it would be especially so for association studies using case–control approaches designed to identify susceptibility genes for complex traits. Common, complex ocular disorders in India that stand to gain from this approach are cataract, glaucoma, diabetic retinopathy, and age-related macular degeneration.\textsuperscript{54}

Access to large patient populations would also be useful for gene mapping studies and genotype–phenotype correlation studies of Mendelian disorders. Although these disorders are typically rare, the large population of India makes it possible to collect a cohort of affected pedigrees in a relatively short time. This large population would be useful for studying all forms of single gene disorders, including autosomal dominant, autosomal recessive, X-linked, and mitochondrial disorders. Many such ocular gene disorders have been identified in Indian pedigrees.\textsuperscript{18,35–37}

Another opportunity for genetic mapping studies arises from the higher prevalence of certain disorders in India than elsewhere. For example, angle-closure glaucoma is more common in India than Western Europe or the United States.\textsuperscript{38} The large number of cases in India makes collecting a substantial number of pedigrees affected with these disorders feasible over a relatively short time.

**Consanguineous Pedigrees.** Consanguineous marriages (predominantly uncle–niece and first-cousin marriages) are common in India, especially in the southern states of Andhra Pradesh and Tamil Nadu,\textsuperscript{39,40} although industrialization has caused something of a decline in the practice.\textsuperscript{41} It has been documented that consanguineous marriages have contributed to a lower gene flow in some regions of India, making frequent allelic homozygosity\textsuperscript{7} and a higher incidence of recessive disorders likely in pedigrees there. The large population of India combined with the increased prevalence of consanguinity makes it likely that a sufficiently large number of inbred pedigrees, appropriate for gene mapping studies of recessive traits, could be collected fairly easily.

Studies of consanguineous families may also help identify genes responsible for ocular quantitative trait loci that are predisposing factors for ocular complex traits. Factors exerting recessive or additive effects on susceptibility to complex traits are expected to be overrepresented in such groups. Compared with nonconsanguineous families, consanguineous families are more likely to demonstrate broader variation in the magnitude of a quantitative trait because of the greater chance that siblings will inherit two copies of the same allele that contribute to the trait (assuming additive effects of the allele). Because of founder effects, inbreeding also reduces the population gene pool, which reduces the trait’s underlying genetic heterogeneity. For these reasons, it is expected that inbreeding will aid the identification of quantitative trait loci. Recent studies have shown that inbreeding loops can greatly increase statistical power for gene mapping of a quantitative trait.\textsuperscript{42}

**Genotype–Phenotype Correlations.** In addition to the opportunity to observe genotype–phenotype correlations for known gene defects and clinical traits, an opportunity also exists to observe differences in genotype–phenotype correlations influenced by differences in genetic backgrounds as identified by differences in the chromosome haplotype that carries the gene defect. Haplotypes are a group of SNPs (or other genetic markers) that are commonly inherited together in a particular population. A specific haplotype may be associated with modification of disease gene expression because it includes a variant form of a collection of SNPs that may have altered biological activity as a group but not independently. In this way, haplotypes may confer variation in gene expression that individual SNPs do not. The U.S.-funded HapMap Project is designed to identify haplotype blocks and representative SNPs in four populations: Utah residents with ancestry from northern and western Europe, Han Chinese, Japanese, and Nigerian. The HapMap Project does not currently include an Indian population, which is being undertaken by the Indian Genome Mapping Collaborative Consortium. Consanguineous marriages, phenotypic expression and background genetic haplotypes among Indian patients and between the Indian population and other populations worldwide will provide useful information about the modifying effects of specific haplotypes.

**Gene–Environment Interactions.** Environmental influences are expected to contribute substantially to common complex human disorders. In India there are considerable differences between the environmental exposures of rural and urban dwelling in matters such as nutrition (diet), living conditions (hygiene, disease exposure), and climatic conditions (UV light exposure, smoke exposure). Comparisons between Indian patients with the same gene defects but different environmental exposures would help define the gene–environment interactions that predispose people to many complex disorders.

**Plasma–Small Molecular Characterization.** Many common complex disorders are chronic and slowly progressive, with variable clinical outcomes. For these diseases, clinical trials for new therapies are difficult because they take a long time to conduct and are very expensive. The development and validation of biomarkers for chronic ocular diseases would provide new methods to monitor disease progression and treatment. Because biomarkers would respond to changes in disease progression in a shorter time frame than typical clinical measurements, such bioassays would make timely therapeutic modifications possible. The large number of patients in India affected with chronic ocular disease would make it possible to collect and archive biological fluid for identification of biomarkers.

**Technical Expertise.** The eye hospitals in India are well equipped with state-of-the-art instrumentation. They have excellent molecular genetic capabilities, which can make efficient patient collection, pedigree analysis, DNA analysis, and candidate gene analysis possible. Ophthalmologists at these centers have substantial experience delivering healthcare to rural communities and in recruiting patients and family members for clinical studies.

India is becoming a worldwide center of biotechnology expertise.\textsuperscript{43–45} Resources there include computer systems that can manage the vast amount of genetic and clinical data that are generated in genomic studies of human disease. Evidence of biotechnology expertise in India is provided by a recent initiative by Indian scientists to develop a network on predictive medicine using genomic variation among the various tribes and cultural groups in India.\textsuperscript{50} One goal of the Indian Genome Variation (IGV) consortium is to provide data on validated SNPs in more than a thousand genes in 15,000 individuals drawn from Indian subpopulations. The methods and approaches that are used in the study will be applicable to future genomic studies in the Indian population.

**Summary.** By identifying, through ocular molecular genetic studies, the genes and the genetic modifiers that contribute to inherited ocular conditions, it will become easier to predict, prevent, diagnosis, and treat ocular conditions. Impor-
tant advances in the molecular genetics of ocular single-gene and complex disorders have recently been made; however, several challenges remain that limit progress, including access to large, well-characterized patient populations; opportunities to perform genotype–phenotype correlations and gene–environment studies; collection and validation of biomarkers for chronic disease; and the development of a bioinformatics infrastructure for managing data. Special opportunities exist in India for research collaborations that address these challenges. The Indian population is large, making it possible to engage the numbers of patients and families needed for a variety of genetic approaches. Consanguineous pedigrees are ideal for mapping recessive traits (see Fig. 1). Different Indian cultural groups with different genetic backgrounds make it possible to study genotype–phenotype correlations and modifier effects of background haplotypes. The large population and varied environmental conditions will be useful for studies of gene–environment interactions. India has excellent technical expertise in areas required for these studies, including in ophthalmology, molecular genetics, and bioinformatics. The collaboration with Indian physicians and scientists and the use of their plentiful resources will lead to discoveries that will help define the underlying etiologies of blinding disorders.

Clinical Aspects of Genetic Disease: Thought Leaders, Anil Mandal and Irene Maumenee

A reasonable estimate of the number of human diseases with ocular involvement is between 2000 and 4000. Many are systemic, whereas others are purely eye related. Most that involve the eye have a genetic component.

Linking eye disease to genetic abnormalities is not new. Researchers and clinicians have been making such connections for decades. The first human eye disorder ever linked to a chromosomal defect was congenital cataract. In 1963, researchers described the cosegregation of inherited cataract with the Duffy blood group locus. Then, in 1968, the Duffy locus was assigned to chromosome 1, giving congenital cataract a place in the medical history books as the first autosomal disease to be genetically linked.

As our understanding of the molecular genetics of eye diseases grows, a body of knowledge emerges for informing discussions among clinicians, researchers, patients, and families about the prognosis, treatment, and heritability of vision disorders. Over the past decade, we have seen an exponential increase in our knowledge of heritable eye conditions. Concurrently, our ability to provide genetic counseling to our patients has improved.

We are also in possession of a growing body of information about the effect of environmental influences on many eye conditions, and have learned with certainty that with any particular genetic defect many people are unaffected or less affected than others, even their own siblings. Obviously, influences from other genes and cofactors, such as diet, sunlight, and smoking, play a role in gene expression.

For some disorders, we will develop genetic treatments. For others, a manipulation of environmental factors will be effective. To start, patients with gene mutations that cause ocular conditions must be identified early on. Newborn testing for a variety of disorders that involve the eye is already performed in many regions of the United States and India. Testing for homo-cystinuria and methylmalonic aciduria, which are metabolic disorders with identified genetic causes, are two examples. Symptoms of both include serious eye disease, but, when a diagnosis is made in a newborn, special dietary regimens can be introduced to ameliorate the effect. Symptoms of homocystinuria include nearsightedness, a dislocated lens, and frequently cataracts, glaucoma, and retinal detachment. Fortunately, a low-methionine diet, started promptly and strictly followed, prevents many of the complications. In methylmalonic aciduria, in which eye findings include retinopathy, nystagmus, and reduced visual acuity, treatment to reduce symptoms includes an extremely low-protein diet. The frequency of these two diseases is low in most populations, but more common in regions with increased rates of consanguinity.

We have no doubt that the economic and social burden of vision loss can be reduced if diagnosis is made early. Genetic counseling is another effective route for reducing the risk of transmission of many blinding eye disorders.

Advances. Advances in understanding the molecular genetics of eye disorders are numerous, as described in the foregoing section on “Molecular Genetics of Eye Disease.” In retinal degenerative disorders, for example, the number of mapped and identified retinal disease genes has grown from fewer than 20 in 1990 to approximately 160 today. Leber’s congenital amaurosis (LCA) is one example of the how gene discovery is leading to potential therapies. LCA is inherited mainly as an autosomal recessive disorder. Although it is an extremely rare condition, it is the most common genetically caused congenital visual impairment in infants and children. Moderate to severe visual impairment is detected at birth or shortly afterward. The child displays nystagmus and a variety of abnormal visual responses to stimulation. The retina may initially appear normal but it ultimately develops changes similar to retinitis pigmentosa.

At least eight genes have been associated with LCA, and more are likely to be discovered. The loss of vision in LCA is caused by degeneration and deformity of photoreceptor cells related to genetic defects that affect proteins involved in the cells’ energy production and maintenance.

Gene therapy to treat LCA is moving into a human clinical trial based on discoveries made in Briard dogs, a breed that carries a defect in the RPE65 gene, which is one of the genes associated with LCA. Gene therapy restored functional vision in these dogs. More recently, researchers have reported on successful gene-replacement therapy in mice lacking the RPEGRIP gene. (An absence of RPEGRIP also leads to LCA.) The RPEGRIP gene normally codes for a protein that is involved in the function of the cilia of photoreceptor cells. Using an adenovirus-associated virus, the scientists delivered a normal RPEGRIP gene to the mouse photoreceptors. Electroretinograms detected normal retinal function in the animals and microscopy showed that photoreceptors were preserved. With these advances, we are witnessing progress. Practices such as prenatal diagnosis, preimplantation diagnosis, population screening, and heterozygote detection are also important for preventing pediatric blindness, 50% of which is genetic.
Summary. Information about clinical aspects of genetic eye disease has grown considerably in the past decade or more, and with it has come an emerging body of knowledge about eye disease treatment and prevention. The information is not just about the genetics of eye disease but also about the influence of environmental cofactors. Discoveries that have led to clinical trials of gene therapy for Leber’s congenital amaurosis are a stunning representation of advances in our understanding of the molecular cases of eye disorders.

Clinical data about eye disease and genetic and environmental factors are represented on several open or commercially available databases: Mendelian Inheritance in Man (OMIM), RetNet, POSSUM, and London Medical Databases (LMD) (see the online supplement for additional information about these databases http://www.iovs.org/cgi/content/full/47/5/1717/DC1). By developing standards for terminology and data entry for the United States-Indo collaboration, we will enhance the usefulness of these and other databases.

Harmonization of Clinical Measures Techniques and Terminology: Thought Leaders, Praveen K. Nirmalan and David Friedman

In all fields, whether it is science, medicine, business, or philosophy, a valid conversation among participants can take place only when all the parties use established definitions, standards, and measures for framing their concepts, arguments, and data. In the current collaboration between the United States and India for advancing eye care, all participants have agreed on a need to establish and standardize technologies, terminology, and grading systems for the various disorders and also databases for sharing information in a clear, useful, and secure fashion. Consistent approaches to phenotyping and data management will increase the efficiency of data sharing across centers and between the two countries.

This section presents background information and the major recommendations for harmonization of clinical measures, techniques, and terminology.

Recent Advances. A large amount of data on eye disorders is already on hand in the United States and India, or is being collected, or is waiting to be collected and analyzed. Whenever possible, Indian and U.S. scientists will use standardized techniques for data collection and analysis. Agreed upon techniques, in general, will have been published previously and will have a long track record of use.

Examples of prior use of ocular disease grading schemes are published, including reports by Indian researchers who used slit lamp grading of lens opacities,57 retinal photography for diabetic retinopathy,58.59 and automated visual fields for the diagnosis of glaucoma.58.60.61

The workshop group agreed that, for high-quality research studies, photographic documentation of ocular findings is essential. Photographic documentation will allow for prospective assessment of change over time and will allow for centralized grading of findings, which will increase the reproducibility of these findings by other investigators. However, the group agreed that clinical grading systems should also be published for cases where photography is not possible.

Current Challenges and Opportunities. Three major areas for harmonizing collaboration between U.S. and Indian scientists were established: one for technologies for assessing disease; another for grading techniques; and the third regarding databases to store clinical and genetic data.


1. Determine standard technologies for assessment of cataract.
2. Determine standard technologies for assessment of age-related macular degeneration.
3. Determine standard technologies for assessment of glaucoma.
5. Determine standard technologies for collecting refractive error data.
6. Identify uniform instruments for collecting other data (e.g., age, smoking history, sunlight exposure, diet).

To facilitate grant writing and sharing of data, it will be necessary to create publicly available documents outlining data collection methods and their justification.

Collaboration Opportunity 2: Standardize grading techniques (for data that need additional review once collected).

1. Agree on a standard grading technique for cataract studies.
2. Determine standard grading techniques for macular degeneration.

Collaboration Opportunity 3: Develop databases for storing clinical and genetic data.

1. Determine a platform for databases, one that allows easy transfer of data. Establish a common data vocabulary to allow for seamless sharing of data across studies. Publish these terms in a publicly available form.
2. Determine a system for security and access to the database. In particular, it should be able to track all edits and contain multiple levels of security to protect patient privacy.

Databases emerged as an issue in several workshop sessions. Work must be undertaken to establish a platform that can support large amounts of data (including visual images obtained by various devices), that can export and import data easily, that is accessible to all participants, and that can support security of data. An additional need is for a standard approach for addressing intellectual property rights, recognizing that participating institutions may require modifications based on their internal policies.

To facilitate harmonization of clinical measures techniques and terminology for targeted diseases, ARVO will establish an email list serv so that working groups can interact openly as they develop their common approaches.

Summary. Better determination of clinical phenotypes for various eye diseases, using standards of assessment and grading, will add value to genotype information. A classification of the genetic and environmental basis of eye diseases in India and the United States will provide a strong foundation for understanding eye diseases worldwide.

Further efforts are needed to harmonize clinical measurement techniques and definitions of the clinical phenotypes. A central resource may be needed for the validation of data and techniques, and a need for collaboration on the use of technical approaches, particularly digital photography, has been recognized. Databases must be established, and intellectual property rights must be addressed.

Translational Physiology—Bench to Bedside Applications: Thought leaders, Paul L. Kaufman and Jyotirmay Biswas

The NEI defines “translational physiology” as the application of fundamental scientific discoveries and novel technologies to the development and testing of methods leading to the prevention, diagnosis, and treatment of eye disease. Similarly, the American Physiological Society defines it as the transfer of knowledge gained from basic research to new and improved methods of preventing, diagnosing, or treating disease, as well as the transfer of clinical insights into hypotheses that can be
tested and validated in the basic research laboratory. Translational physiology in ophthalmology is a broad field. It includes studies of the whole organ, of tissues of the eye and brain, and of animals whose pathophysiology and response to therapy resembles that in the human.

The focus of translational physiology is the bridging of the gap between basic research and patient care, and between basic scientists and clinicians. However, it may be better characterized, instead of as bench-to-bedside, as bedside-to-bench-to-bedside (Table 4). Clinicians and clinical scientists have an understanding of disease mechanisms. They identify problems and develop questions that basic research can help elucidate. Basic research scientists narrow the search for answers and identify specific targets of therapeutic interest. Further research can help characterize components of the system, moving from cell-based systems to organ culture systems to animal models, and ultimately back to the patient. The diverse, complex nature of translational research is evident in the wide variety of fields that are brought together in productive collaborations.

The following sections provide highlights from the workshop session on translational physiology in ophthalmology, describing recent advances and specific challenges and opportunities that exist.

**Recent Advances.** Numerous areas in ophthalmology have progressed because of gains based on translational research. This includes advances in genomic technologies, tissue engineering, stem cell research, electrophysiological testing, and use of animal models.

The advancement of technologies for identifying and studying genes related to specific eye disorders has resulted in important clinical genetic research progress. For example, more than a dozen glaucoma genetic loci have been mapped and over half a dozen glaucoma genes have been cloned. Alleles have been identified that may play a role in primary open angle glaucoma (POAG), a complex disease affecting many millions of people. The database of genes and proteins expressed in various anterior segment tissues has grown, leading to new avenues of exploration for understanding the etiology of the disease and for developing new treatment strategies.

Combining research innovations in the areas of stem cell biology, gene therapy, and cell–biomaterial interactions, has led to advances in the study of tissue engineering and replacement (Niklason LE. *IOVS* 2005;46:ARVO E-Abstract; Program #9). Stem cell research is an avenue of study that has great potential. One recent example is the finding that embryonic stem cell-derived retinal pigment epithelial (RPE) cells in nonhuman primates have the morphologic and physiological properties of normal RPE cells. These cells may provide an unlimited source of primate cells to be used for the study of pathogenesis, drug development, and cell-replacement therapy in eyes with retinal degenerative diseases due to primary RPE dysfunction. The availability of these cells and the use of animals models to elucidate these mechanisms may expedite these avenues of research. Neural progenitor cells (NPCs) capable of differentiating into multiple neural components have been found in the retinas of several species. Adult human retinas contain NPCs, which may turn out to have the potential to replace neurons and photoreceptors (van der Kooy D. *IOVS* 2005;46:ARVO E-Abstract; Program #5).

New applications of technologies are leading to noninvasive, real-time, in situ evaluation of eye disease. Objective assessment of inner and outer retina function, in nonhuman animal models and humans, is being achieved with flash and multifocal electroretinogram and multifocal visual evoked potential tests. Histopathology has validated the findings of these tests. Geometric quantification of the retina, retinal nerve fiber layer, and optic nerve head surface—thanks to development of new and existing instrumentation for screening and detecting change—is leading to substantial improvement in the clinical detection of structural damage. Again, the availability of histopathology data from experimental models allows validation of these instruments.

The use of animal models has expanded investigations at the molecular and systems levels. In studies of congenital glaucoma, we have recently seen that tyrosinase modifies the glaucoma phenotype in the *CYP1B1*-knockout mouse and that modifier genes play a role in the etiology of congenital glaucoma in children. The rodent model has also been used for evaluation of pharmacological approaches that target neurodegenerative processes; an example is gene therapy in which brain-derived neurotrophic factor is tested. Nonhuman primates are plentiful and inexpensive in India, compared with the United States, and may present a real opportunity for advancing research. Of the various animal models, their visual system most closely resembles that of humans. They are extremely valuable for both in vivo and in vitro studies in areas such as aqueous humor dynamics, corneal physiology, retinal vascular physiology, retinal electrophysiology, and aging, to name a few.

**Current Challenges.** A major challenge and limiting factor for U.S. eye and vision researchers is a lack of availability of fresh ocular tissue, including whole donor eyes. Fresh tissue is used for cell and organ culture, experimental manipulations, study of normal and diseased states, and clinicopathological correlation. In India, in contrast, both normal and diseased fresh tissue is generally much more available, especially for certain conditions such as AIDS. Eyes can be readied very quickly for research, which is critical for many experiments. The technology for preparing the tissues would need to be in place in India, but there are already facilities in that country capable of doing the work. Training and validation could be achieved in conjunction with U.S. groups. As with all studies, conditions and specimens would have to be defined carefully and precisely.

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**Table 4. Translational Research in Ophthalmology: The Bedside-to-Bench-to-Bedside Route, with Glaucoma as an Example**

| Step 1. Clinical research, to identify disease mechanisms (e.g. increased outflow resistance in glaucoma) |
| Step 2. Basic research, to identify tissues for targeting (e.g. trabecular meshwork) |
| Step 3. Basic research, to identify cellular sites for targeting (e.g. actin cytoskeleton) |
| Step 4. Chemical/cell biological research, to search for specific classes of therapeutic compounds (e.g., actin disrupting agents) |
| Step 5. Compound optimization (e.g. latrunculins, myosin light chain kinase/Rho kinase inhibitors) |
| Step 6. Testing of active compounds (e.g., cell and organ culture experiments) |
| Step 7. Preclinical testing |
| Step 8. Clinical trials |
| Step 9. Approval process |

Note: Dr. Kaufman acknowledges a proprietary interest in this area.
Needs and Opportunities. The type and number of studies that could be conducted with an adequate supply of ocular tissue is nearly limitless. Experimental protocols are already in place that would benefit from greater availability of whole and fractional parts of globes. Anterior segment organ culture has become widely used in aqueous outflow studies for evaluating the effects of pharmacologic interventions, gene therapy, and physical devices such as stents. Ussing-type chambers can be used to study corneal and ciliary body transport, physiology, and altered gene expression under various conditions. Anterior segment tissue can also be used for studies of ciliary muscle function, corneal physiology, and trabecular meshwork physiology. Posterior segment organ culture has been used to study retinal pharmacology, electrophysiology testing paradigms, and cell migration. Use of posterior segment tissue has led to development of the function of retinal ganglion cells and of ocular tissue imaging technologies. Experiments have been designed to explore enhancement of complete lens epithelial removal by adhesion-disrupting pharmacological agents to prevent posterior capsule opacification.

Matching up the research skills and needs of various researchers and laboratories with available tissues and other resources will be a challenge, but one that is by no means insurmountable. An online clearinghouse, perhaps similar to the National Disease Research Interchange (NDRI; Philadelphia, PA), could be set up to support the many ocular research projects and to make the best use of the available resources. NDRI provides human cells, tissues, and organs to scientific researchers who are investigating disease pathophysiology and therapies.

Frozen cells and tissue can be shipped, but for more complex tissue preparations, only fresh tissue can be used. Because fresh tissue can degrade quickly, it is necessary to perform the experiments as close to the tissue source as possible. With facilities now in place in India, it would be feasible to bring Indian researchers to the United States to train with U.S. scientists. With a focus on building research programs, sending young researchers to make use of training opportunities could provide important long-term benefits. If a specialized apparatus is needed, it can be fabricated (or detailed blueprints can be made), and the trainee and apparatus can then be sent back to India to establish the technology at the location of the fresh tissue. A U.S. expert can be sent to provide further training and initial oversight, quality control, and “alignment” between the laboratories, as needed. This strategy will foster true collaborative efforts, benefiting scientific research in both countries.

The cross-disciplinary nature of translational physiology often requires that multiple sites be involved in complex experimental designs. Logistic issues for collaborators should be anticipated and prepared for in advance. If travel is required for training, the appropriate type of visa (e.g., student) must be requested. Time limits must be respected and the mechanism for extending stays, if the need arises, should be investigated ahead of time. If tissue is to be shipped, permits must be obtained and the passage of time required in the process fully understood. In the United States, the process can take 3 to 6 months, making advance planning crucial. Import/export laws (which include intellectual property issues) must be followed. Some institutions require that biosafety protocols be established before there is any exchange of potentially hazardous tissue or compounds. Collaborators may have to develop material transfer and research agreements that are subject to institutional approval. U.S. and Indian requirements for human subject approvals for use of such tissues must be carefully aligned.

Clarity of experimental design is crucial to the success of prospective collaborations. Having defined goals, individual tasks, and specific outcomes with a set timeline and phased deadlines helps to establish accountability and follow-through among all participants. Researchers should have realistic expectations and understand the strengths each collaborator brings to the project.

Summary. Translational physiology unites the clinical and research communities. The collaboration of scientists and clinicians can result in major advances in the prevention, diagnosis, and treatment of ocular disease. The diversity of scientific areas where research is taking place means that opportunities exist for collaborations across many disciplines. U.S.-Indo collaborations will expand research capabilities by employing expertise, facilities, and other resources that are uniquely available in one nation or the other. This will provide unique opportunities to blend complementary skills and to develop novel approaches to eye and vision research. Such collaborations are increasingly important to securing the best outcomes for patients worldwide.

Identification, Development, and Exchange of Research Resources: Thought leaders, Gullapalli Rao and Don Zack

In building a cooperative relationship like the one envisioned by participants of the U.S.-Indo Workshop on Collaborative Research, it is necessary to identify the resources needed by the parties involved. This refers to personnel, equipment, facilities, patients, databases, and other “tangibles.” Naturally, political support and funding are also required.

This section looks generally at what may be needed and how an exchange of resources can accomplish a greater good for improving eye care and eyesight than either the United States or India could achieve by working alone.

Patient DNA Database. A goal of ophthalmology research is to establish the genetic contribution to eye disorders, and to coordinate these facts with disease phenotypes and epidemiologic factors. This requires a large number of patients and family members who are willing to provide blood samples for DNA testing, to answer a variety of health and lifestyle questions, and to undergo comprehensive eye examinations. Collecting data is just one step in a process which, to maximize the amount of useful information that could be extracted, requires a large amount of coordination in the handling of the samples and the management of the information. Issues include:

- transporting samples;
- standardizing laboratories;
- entering patient, family, and demographic data;
- developing software to manage data;
- coordinating access to the data;
- standardizing statistical analysis methods; and
- addressing patient privacy and governmental regulations.

Which genetic eye disorders would be included in the database? Only the most common or all conditions? Where, and how, would blood samples be stored for later study? Would cell lines be developed (where possible) to have an unlimited sample source?

Some researchers would access the database purely to study gene data. Others would be looking at relationships between phenotype and genotype. Yet others would be examining demographic data to assess the role of environment factors in genetic eye disease. As the project evolves, how would new data—raw and published—be entered and tracked? How would authorship of published works be attributed and how would discoveries be assigned? How would intellectual property rights be preserved, and how would they be shared among parties in complex collaborations? As a potentially even more controversial question, should they be preserved, or would eye research and patients be better served if they became part of the public domain?
These many questions dovetail with the NIH roadmap for medical research in the 21st century, to identify major opportunities that no single group could tackle alone. The NIH roadmap recognizes that, to accelerate the translation of research from the bench to the bedside, research teams must be interdisciplinary, creative, and willing to take on new challenges.

**Summary.** It is essential to identify and address the current capabilities and shortcomings in India and the United States in facilities, research subjects, knowledge, equipment, technology, funding, and administration, among other areas. It is also important to develop a way for researchers to identify opportunities to enhance their skills. Already discussed in earlier sections of this report are the merits of a well-managed eye bank and access to animal models of eye disease.

**SUMMARIZING THE OPPORTUNITIES**

Collaborative ideas emerged during the workshops and in the weeks between the first workshop and the second. Several ideas have been presented herein. One, the Human Ocular Phenome/Genome Evaluation (HOPE) project, is described in detail. Several others are briefly summarized.

**HOPE Project**

One outcome of the U.S.-Indo Workshop was the initiation of a collaborative research project (the Human Ocular Phenome/Genome Evaluation, or HOPE, project) between the United States and Indian vision research communities to create a database resource that would provide a mechanism for novel experimental approaches to help define the underlying molecular defects and pathophysiology of common complex blinding disorders.

The collaborative project would rely on the high prevalence of consanguineous families in southern India. With data from willing members of these families, a database is proposed that will include phenotype information, measurements of ocular quantitative traits (including but not limited to intraocular pressure, axial length, corneal thickness, overall optic nerve size, optic cup size, refractive errors, number of macular drusen), whole genome genotypes, plasma protein/small molecule information, and environmental exposure data. The backbone of the database resource is high density SNP-based genetic mapping of quantitative trait loci in the collected pedigrees. The underlying hypothesis of this proposal is that consanguineous pedigrees can provide more information for mapping genes responsible for quantitative traits than families without a consanguineous loop. Genetic loci for ocular quantitative traits, defined as SNPs and haplotypes, will be identified.

The proposed database resource would be freely available to investigators through a Web-based mechanism. It will be possible to query the database to allow retrieval of information regarding the relationships between genotypes, quantitative traits, phenotypes, environmental influences, and biomarkers. Investigators performing whole genome analyses for complex disease will be able to use the database to determine whether a SNP or gene located within a mapped interval has been associated with a particular ocular quantitative trait or phenotype. Genome scans for complex diseases result in multiple chromosomal regions showing evidence for linkage. Investigators will be able to use the database to retrieve phenotypic information linked to the SNPs and genes located within such putative loci to help prioritize candidate gene evaluation. The database would also provide information for investigators who discover a novel ocular protein by providing phenotypic information about the SNPs/gene that codes for the protein. Because the entire genome will be genotyped for all individuals entered into the study, gene–gene interactions can be evaluated from the collective information. Environmental exposure information will be collected from all participants providing an opportunity for gene environment evaluations. Blood plasma samples will be collected for further analysis for proteins and small molecules that could lead to the identification of biomarkers for chronic ocular disease.

A planning grant for this project has been submitted for funding. It has two immediate goals: to perform a pilot study to generate the preliminary information required for the full-scale project and to develop a detailed scientific and administrative plan for the full-scale project that includes selection of the full scale SNP genotyping platform, methods to collect data on environmental exposure, database design, power calculations, and identification of key personnel and sites in India.

**Other Proposals for Collaborative Research**

Many additional ideas for research collaboration were presented at the workshops. Descriptions of several of the proposed projects and names and locations of collaborators are listed herein. Contact information for the collaborators is available in the online supplement at http://www.iovs.org/cgi/content/full/47/5/1717/DC1.

**Organ Culture of Human Anterior Ocular Segment for the Study of the Trabecular Meshwork (Indian venue: Aravind Eye Hospital; U.S. venue: University of Wisconsin).** Results of physiological, pharmacological, morphologic, and cell biological studies of primate and human trabecular network have not shown the expected degree of quantitative similarity. A possible explanation is the absence in the United States of consistently fresh human tissue. This collaboration proposes to have scientists from Aravind Eye Hospital in Madurai come to laboratories at the University of Wisconsin in Madison to train on a perfusion apparatus for studying the trabecular network, after which they will return to India and continue a collaboration using a replica of the apparatus and readily available fresh human trabecular tissue.

**Pharmacologic Prevention of Posterior Capsule Opacification in Cultured Human Lenses (Indian venue: Aravind Eye Hospital; U.S. venue: University of Wisconsin).** The most frequent complication of extracapsular cataract extraction and intraocular lens (IOL) implantation is posterior capsule opacification (PCO) caused by proliferation of lens epithelial cells. Improved design of IOLs, better surgical technique, and pharmacological agents (e.g., cytoskeletal drugs) have helped reduce the incidence of PCO. Although the rabbit eye is used for studying prevention of PCO, cell growth dynamics is species specific and, therefore, the rabbit is a substandard model compared with human tissue. Using tissue from whole globe enucleations, particularly from Indian donors, researchers propose to establish a human lens capsular bag culture system as a model for cytoskeletal drug-PCO studies. Such a model is necessary for development of pharmacological PCO prevention strategies, which will be necessary to enable the next generation of accommodating IOLs.

**Genome Studies in Glaucoma (Indian investigators: Subhabrata Chakrabarti, D. Balasubramanian; U.S. investigators: Elizabeth Fini, Jayanti Pandey, J. Fielding Heitmancik, David Beebe, Janey Wiggs).** Some genotype and phenotype data for primary open angle glaucoma, posterior capsule glaucoma, and anterior segment dysgenesis are available. This collaboration proposes to greatly expand the current knowledge. One aspect of the project is to functionally characterize the mutant proteins in glaucoma and to understand their role in biochemical pathways. An extensive genotype-phenotype correlation would be undertaken.

**Family Studies and Inheritance of Primary Open Angle Glaucoma (Indian investigators: Ramaswami Krishnadas, Periasamy Sundaresan; U.S. investigator: Wallace...**
A Blood Test for Risk Management of POAG (Indian investigators: Ramaswami Krishnadas, Periasamy Sundaresan; U.S. investigator: John Crabb). There is compelling evidence that biomarkers exist in plasma that would indicate a susceptibility to POAG. Researchers in this study propose to develop a blood test for POAG that will ultimately become a routine clinical test for predicting the condition and monitoring the efficacy of therapies and preventive measures. Subjects will be from centers in the United States and India.

Protein Truncation Test for Detection of Germ Line Retinoblastoma Gene Mutations in Indian Retinoblastoma Patients (Indian investigator: Subramanian Krishnakumar; U.S. investigator: Joan O’Brien). Germ line retinoblastoma usually results in a truncated retinoblastoma susceptibility gene product. Protein truncation testing (PTT) offers a rapid and sensitive method for detecting mutations that result in truncated gene products. Preliminary studies indicate that PTT may have diagnostic value in patients with germ line retinoblastoma. The objectives of this collaboration are to develop a rapid diagnostic test for retinoblastoma, to perform focused DNA sequencing to characterize RB1 mutations detected by PTT, and to determine whether mutation analysis can be used to predict disease expression.


Factors Influencing the Severity of Retinopathy of Prematurity (Indian investigators: Lingam Gopal, Angayarkanni Shanmugasundaram; U.S. investigator: Dharmapuri Vidyasagar). This research collaboration is to identify early markers of oxidative stress in blood and urine of very-low-birth-weight neonates in India to develop interventions for preventing retinopathy of prematurity (ROP). In addition, it proposes to screen for vascular endothelial growth factor (VEGF) polymorphism as a possible contributor to ROP and to determine whether the Norrie disease (NDP) gene mutation may be a factor that influences the severity of ROP.

PEDF and VEGF in Controlling Angiogenesis in Eales Disease (Indian investigators: Jyotirmay Biswas, Angayarkanni Shanmugasundaram; U.S. investigators: Joyce Tombran-Tink, Colin Barnstable). The progression of angiogenesis in various eye conditions may be dependent on the ratio of the proteins pigment epithelium-derived factor (PEDF) and VEGF. PEDF has been shown to halt angiogenesis while VEGF has the opposite effect. This collaboration seeks to examine the relationship of these growth factors and their therapeutic potential in the context of Eales’ disease, an inflammation-mediated proliferative retinopathy that is much more common in India than in the United States.

Studies of the Genetic and Molecular Mechanisms of CYP1B1-Mediated Forms of Glaucoma (Indian investigator: Subhabrata Chakrabarti; U.S. investigator: Jayanti Pande). Emerging evidence indicates that mutations in the CYP1B1 gene are associated with some forms of POAG. However, the disease mechanisms at the protein level are currently unknown. Through a collaborative effort, these researchers propose to investigate the genetic and molecular mechanisms by which mutations in the CYP1B1 gene alters such aspects as protein structure, enzymatic activity, and heme-protein interactions.

Other collaborations have been proposed to study infectious keratitis, ophthalmic changes in a genetically obese rat model, genetics of various retinal and macular dystrophies, and oxidative damage resulting in protein modifications in age-related macular degeneration.

### ADDITIONAL INFORMATION ON INDIA’S ASSETS IN EYE CARE, VISION RESEARCH, AND INFORMATION TECHNOLOGY

In addition to its 12,000 qualified ophthalmologists, India has several schools that grant graduate degrees and diplomas in optometry and vision technology, and numerous eye care centers and basic and clinical vision research facilities. It is also a global power in the area of information technology. Numerous governmental and nongovernmental comprehensive eye care centers are spread across India (Table 5). Their services include not only clinical treatment of the eye, but also clinical and basic research in epidemiology, molecular biology, biochemistry, cell biology, and related areas. The connection between basic research, clinical research, and clinical practice is robust in a few institutions in the country. Quite apart from eye care centers, India also has nearly two dozen basic biological research centers spread across the country in such cities as New Delhi, Manesar, Chandigarh, Amritsar, Ahmedabad, Mumbai, Pune, Hyderabad, Bangalore, Chennai, Madurai, and Kolkata (see the following section). Several of these are engaged in research programs with the eye care centers.

Of the eye centers in Table 5, AECS, LVPEI, RPC, and SN have access to data and patient populations through their rural
connections, satellite centers, and branches. This is a valuable resource, since each of these rural districts has a large and reasonably homogenous (genetic, nutritional, lifestyle) population base, making it realistic to conduct comparative studies of eye diseases and treatments.

Researchers from several of these centers have published valuable epidemiologic studies on eye diseases in India. Examples of studies are the India-U.S. Case Control Study of Age-related Cataracts (1989), conducted by the NEI and RPC; the Andhra Pradesh Eye Disease Study (APEDS) over the 1995 to 2000 period, conducted by researchers at LVPEI; and the glaucoma prevalence studies (1998–2003), by scientists at CMCV. Several centers devoted to related diseases have conducted relevant epidemiologic studies. An example of such a study is the Chennai Urban Population Study (CUPS) on diabetes, by the Madras Diabetes Research Foundation, Chennai.

In addition to the above clinical centers, several other institutions have engaged in clinical research and trials. These include the Aditya-Jyot Eye Centre in Mumbai, the Retina Foundation in Ahmedabad, and the Schroff Eye Centre in New Delhi.

In terms of delivery of quality eye care to its extensive rural population, India has developed several noteworthy models. The AEHS in Madurai delivers high-quality cataract surgery all across the southern Indian peninsula. They not only send teams of doctors to perform the surgery, but also they arrange patient follow-up to assure the best possible satisfactory outcomes. In many instances, the doctors and staff use telemedicine to coordinate care and to consult on cases. For example, eye care specialists in the small agricultural trading center of Tirunelveli can send detailed images of their patients’ eyes to the headquarters in Madurai and get expert consultation and opinion, all in real time.

Similarly, LVPEI in Hyderabad has a four-tiered model that serves several districts in the state of Andhra Pradesh. This involves, first, the services of “vision guardians,” each of whom is responsible for a group of five thousand people in a given set of villages. Patients who need additional treatment are referred to a secondary eye care center. Each of the latter cares for approximately 100,000 people, performing cataract surgeries and delivering additional ophthalmic care. More complicated cases are referred to the next tier, or district hospitals, each of which serves more than a million people. The final tier is an excellent eye care center serving approximately 50 million people. With such a spread and a tiered structure, comprehensive and quality eye care is delivered to a large portion of the population, both urban and rural.

India is also involved in the “Vision 2020—The Right to Sight” worldwide initiative. Vision 2020 is a partnership between the World Health Organization (WHO) and the International Agency for Prevention of Blindness (IAPB). The IAPB Secretariat (or the Central Office as they call it in India) for Vision 2020 and the office of the president of the IAPB are located in Hyderabad at the LVPEI.

India can also boast of assets in basic and clinical research, animal experimentation facilities, and facilities dealing with information technology and bioinformatics. The country has formalized regulations regarding material transfer and provision of grants for international collaborations. Many of the hundreds of papers by Indian eye researchers published in professional journals during the years 2002 to 2004 are listed in the online supplement at http://www.iovs.org/cgi/content/full/47/5/1717/DC1.

Basic Research Resources

Basic biological research is conducted in laboratories across India (Table 6). Resources available in these centers, such as DNA sequencers, genomics and proteomics facilities, structural and cellular biology, ultramicroscopy, stem cell research, cell collections, transgenic and knockout strains, and the like, are used or can be used of by eye researchers through collaborative agreements.

Already researchers in several of these centers are engaged in eye research. Some have forged collaborations with eye care centers. In addition, the Indian Council of Scientific and Industrial Research (CSIR) supports an all-India program that screens for gene mutations associated with glaucoma, cataract, and corneal dystrophies, which can be used for diagnostics. CSIR hopes to develop a similar diagnostic method for infection (bacterial, fungal and viral) and also to develop specific low-vision aids such as wavelength/intensity tunable light sources for the visually handicapped.

<table>
<thead>
<tr>
<th>City in India</th>
<th>Biological Research Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amritsar</td>
<td>Centre for Genetic Disorders, Guru Nanak Dev University</td>
</tr>
<tr>
<td>Bangalore</td>
<td>Indian Institute of Science (IISc)</td>
</tr>
<tr>
<td></td>
<td>National Centre of Biological Sciences (NCBS)</td>
</tr>
<tr>
<td></td>
<td>Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR)</td>
</tr>
<tr>
<td></td>
<td>Centre for Human Genetics (CHG)</td>
</tr>
<tr>
<td>Chandigarh</td>
<td>Institute of Microbial Technology (IMTECH)</td>
</tr>
<tr>
<td></td>
<td>National Institute of Pharmaceutical Education and Research (NIPER)</td>
</tr>
<tr>
<td>Chennai</td>
<td>Indian Institute of Technology Madras (IITM)</td>
</tr>
<tr>
<td></td>
<td>ALMPG Institute of Basic Medical Sciences</td>
</tr>
<tr>
<td>Hyderabad</td>
<td>Centre for Cellular and Molecular Biology (CCMB)</td>
</tr>
<tr>
<td></td>
<td>Centre for DNA Fingerprinting and Diagnostics (CDFD)</td>
</tr>
<tr>
<td></td>
<td>National Institute of Nutrition (NIN)</td>
</tr>
<tr>
<td></td>
<td>Osmania University</td>
</tr>
<tr>
<td></td>
<td>University of Hyderabad</td>
</tr>
<tr>
<td>Kolkata</td>
<td>Indian Institute of Chemical Biology (IICB)</td>
</tr>
<tr>
<td></td>
<td>Bose Institute</td>
</tr>
<tr>
<td></td>
<td>Indian Statistical Institute (ISI)</td>
</tr>
<tr>
<td>Manesar</td>
<td>National Brain Research Centre (NBRC)</td>
</tr>
<tr>
<td>Mumbai</td>
<td>Tata Institute of Fundamental Research (TIFR)</td>
</tr>
<tr>
<td>New Delhi</td>
<td>Indian Institute of Technology Bombay (IITB)</td>
</tr>
<tr>
<td></td>
<td>National Institute of Immunology (NIIm)</td>
</tr>
<tr>
<td></td>
<td>International Centre for Genetic Engineering &amp; Biotechnology (ICGEB)</td>
</tr>
<tr>
<td>Pune</td>
<td>National Centre for Cell Sciences (NCSS)</td>
</tr>
<tr>
<td></td>
<td>University of Pune</td>
</tr>
</tbody>
</table>

Table 6. Basic Biological Research Centers in India

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human tissue. India has a well-articulated policy on this issue,
involve transfer and exchange of research tissue, particularly
Regulations Regarding Material Transfer

<table>
<thead>
<tr>
<th>City in India</th>
<th>Animal Facility Location</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmedabad</td>
<td>Ilaevi Cataract Centre</td>
<td>Houses small animals</td>
</tr>
<tr>
<td>Bangalore</td>
<td>Indian Institute of Science</td>
<td>Houses small animals and primates</td>
</tr>
<tr>
<td>Hyderabad</td>
<td>Centre for Cellular and Molecular Biology (CCMB)</td>
<td>Produces transgenic and knockout animals</td>
</tr>
<tr>
<td>Hyderabad</td>
<td>National Institute of Nutrition (NIN)</td>
<td>Houses large animals</td>
</tr>
<tr>
<td>Manesar</td>
<td>National Brain Research Centre (NBRC)</td>
<td>Houses large animals</td>
</tr>
<tr>
<td>New Delhi</td>
<td>National Institute of Immunology (NII)</td>
<td>Houses large animals; produces transgenic and knockout animals</td>
</tr>
<tr>
<td>New Delhi</td>
<td>RP Centre</td>
<td>Uses campus animal facilities of parent institute</td>
</tr>
<tr>
<td>Pune</td>
<td>National Centre for Cell Sciences (NCCS)</td>
<td>Produces cell lines</td>
</tr>
</tbody>
</table>

Animal Experimentation Facilities

Other than the RPC (which uses the animal facilities of its parent institute, the All India Institute of Medical Sciences, CMCV) and the Ilaevi Cataract Centre at Ahmedabad (which has a small intramural animal house for rats, rabbits, guinea pigs, and mice), all eye centers depend on collaborators for the housing of their research animals (Table 7). Some basic research centers with animal facilities that are available to eye researchers are the National Institute of Nutrition (NIN) in Hyderabad, the National Brain Research Centre (NBRC) in Manesar, and the National Institute of Immunology (NII) in New Delhi. In addition to small animals, some also house sheep, goats, dogs, and monkeys. NII and CCMB Hyderabad house transgenic and knockout animals. Each center that operates an animal facility has its own institutional animal welfare and ethics committee and follows the rules of India’s Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Eye research is also performed in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Visual Research.

The National Centre for Cell Sciences (NCCS) in Pune is home to an extensive collection of animal cell lines, which they make available to researchers from other institutions. The service is very useful, in that whole-animal experimentation can be replaced by cell studies. This program is particularly relevant to current practice with respect to the use of animals in experimental research, namely the three R’s (reduce, refine, replace).

Information Technology and Bioinformatics Facilities

Almost all eye care centers in India have their own Web site where clients/patients can obtain information, make appointments, and even interact with their physicians.

Professional IT services are available for data handling, data mining, data analysis, special programs and algorithms, statistics, gene and homology searches, microarray data analysis, and molecular modeling. National laboratories such as IGIB, CCMB, TIFR, and CDFD, as well as commercial agencies such as Strand Genomics in Bangalore, Oicimun Biosolutions, and Tata Consultancy Services, both in Hyderabad, offer these services in India and also to customers in the United States and Europe.

Mentioned earlier was telemedicine, which connects rural medical clinics to major eye centers. The Indian Space Research Organization (ISRO, the equivalent of NASA in India) has extended its satellite communication facilities to parties interested in the use of telemedicine.

Regulations Regarding Material Transfer

International collaboration in eye research would necessarily involve transfer and exchange of research tissue, particularly human tissue. India has a well-articulated policy on this issue, which conforms to all international guidelines and practices. It addresses the Declaration of Helsinki on the ethical principles for medical research using human subjects, the NIH guidelines, and other topics related to confidentiality and transfer of human tissue research purposes. The policy, ‘Guidance for International Collaboration for Research in Biomedical Sciences,’ is available at http://icmr.nic.in/guide.htm. It describes the procedures for collaboration between India and specific countries. In essence, there is no difference between rules that are followed in India and elsewhere (e.g., the United Kingdom, Germany, France, the United States, Japan). A material transfer agreement must be signed ahead of time and approved by national agencies from the countries involved.

Grants Available from Indian Sources

Governmental agencies in India that offer competitive research grants are the DBT, the Department of Science and Technology (DST), the Department of Atomic Energy’s Bureau of Research in Natural Sciences (DAE-BRNS), the CSIR, the ICMR, and the Defense Research and Development Organization (DRDO). The grants are available only for Indian researchers working in India. Little or no extramural funding from private foundations or industry is available.

A typical research grant for an eye researcher in India runs for a period of 3 years and supports a graduate student and/or postdoctoral associate. It allows for consumable chemicals and plastic ware, equipment purchases, and contingencies such as (domestic) travel and office expenses. It also covers institutional overhead (<15% of the grant). A typical 3-year grant may provide about Rs. 25 to 80 lakhs ($50,000 to $160,000 U.S.). A large portion goes to the purchase of equipment and chemicals, which cost slightly more in India than in the United States. Workforce costs are less than in the United States. A PhD student is paid about $3000 per year and a postdoctoral research associate, about $4500.

Turning to funding for international collaborative projects, several of the mentioned agencies have set up bilateral research agreements with various countries (e.g., the United Kingdom, France, Germany, Japan, the United States). Details of collaborative arrangements with DBT, ICMR, CSIR, and DST are available on their Web sites: www.dbtindia.nic.in, www.icmr.nic.in, www.csir.res.in, and www.dst.gov.in, respectively.

UPDATE ON NEI/NIH ASSETS IN EYE CARE

According to the NEI, the most common eye diseases in U.S. residents older then 40 years are age-related macular degeneration (AMD), glaucoma, diabetic retinopathy, and cataract. AMD in its most advanced form affects an estimated 1.8 million people; another 7.3 million have milder disease and are at substantial risk for vision loss. Glaucoma affects 2.2 million people in the United States, is the most common cause of blindness among Hispanics, and the most common cause of irreversible vision loss among African Americans. Diabetic retinopathy is estimated to affect 4.1 million people, many of whom are African American. Cataract is estimated to affect
TABLE 8. Top 25 Departments of Ophthalmology and Vision Research Centers Receiving National Eye Institute Extramural Grant and Contract Support for Research in Fiscal Year 2004

- Schepens Eye Research Institute, Boston, MA
- Johns Hopkins University, Baltimore, MD
- Washington University, St. Louis, MO
- University of Southern California/Doheny Institute, Los Angeles, CA
- Harvard University and Affiliates, Boston, MA
- University of Wisconsin, Madison, WI
- University of Pennsylvania, Philadelphia, PA
- University of Michigan, Ann Arbor, MI
- Smith-Kettlewell Eye Research Institute, San Francisco, CA
- Duke University, Durham, NC
- University of Utah, Salt Lake City, UT
- University of California, San Diego, CA
- University of Florida, Gainesville, FL
- UCLA/Jules Stein Institute, Los Angeles, CA
- University of Pittsburgh, Pittsburgh, PA
- University of Texas Health Science Center, Houston, TX
- Oregon Health & Science University, Portland, OR
- University of Illinois, Chicago, IL
- University of California, San Francisco, CA
- University of Miami Medical Center, Miami, FL
- Louisiana State University Health Sciences Center, New Orleans, LA
- University of Washington, St. Louis, MO
- Emory University, Atlanta, GA
- University of Louisville, Louisville, KY
- University of Oklahoma Health Sciences Center, Oklahoma City, OK

20.5 million Americans; cataract is the leading cause of low vision among Americans and is responsible for approximately 50% of cases.

The United States has approximately 18,500 ophthalmologists and 115 medical residency programs in ophthalmology. Subspecialties among ophthalmologists include mainly anterior segment surgery, corneal external disease, glaucoma, neuro-ophthalmology, ocular-plastic surgery, ophthalmic pathology, pediatric ophthalmology, retina-vitreous, and uveitis immunology.

Optometry is also well represented in the United States. Optometrists are often the first to encounter a patient’s eye disorder. There are currently 17 schools and colleges of optometry in the United States and Puerto Rico, according to the Association of Schools and Colleges of Optometry (ASCO). Subspecialties in optometry include binocular vision, perception and pediatrics, cornea and contact lenses, low vision, optometric education, primary care optometry, public health, and visual science.

Areas of concentration by the NEI are retinal disease, corneal disease, lens and cataract, glaucoma and optic neuropathies, strabismus, amblyopia and visual processing, and low vision and blindness rehabilitation.

Table 8 shows the 25 departments of ophthalmology and vision research centers that received the highest amount of funding from the NEI in 2004. The list starts with the center receiving the highest level of funding.

Through a combined support of clinical and basic research, NEI funding has led to many important discoveries that have changed the thinking about eye disease and the practice of eye care. Support of basic research has led to the discovery of genes associated with major eye diseases such as glaucoma, AMD, and retinitis pigmentosa. Results from several multicenter clinical trials have altered clinical practices. For example, the recently completed Ocular Hypertension Treatment Trial demonstrated the efficacy of intracocular pressure-lowering drugs in preventing the onset of glaucoma in people at risk and in delaying disease progress in those who already have glaucoma. Results from the AREDS have revealed that the use of certain antioxidant- and zinc-containing nutritional supplements can decrease the risk of vision loss in people who are at high risk for advanced AMD. Other recent NEI-funded research has studied the prevalence of vision disorders in Latino populations in Los Angeles, the efficacy of laser treatments in diabetic retinopathy, anti-VEGF therapies to inhibit abnormal blood vessel formation (neovascularization) in certain vision disorders, noninvasive imaging for diabetic retinopathy, bone marrow-derived stem cells for rescue of photoreceptors for retinitis pigmentosa, and gene therapy for Leber’s congenital amaurosis. Most recently, NEI-funded DNA sequencing of the complement factor H gene revealed a coding variant (Y402H) that is a strong indicator of markedly increased risk of developing AMD.

The NEI, as part of the larger NIH scientific community, engages in collaborations with other NIH institutes, such as the National Institute for Diabetes and Digestive and Kidney Disorders (NIDDK), National Institute of Neurologic Disorders and Stroke (NINDS), National Heart, Lung and Blood Institute (NHLBI), National Institute of Biomedical Imaging and Bioengineering, and the National Cancer Institute (NCI), to further its mission to improve eye health and eye care outcomes.

NEI is also an active participant in the NIH roadmap for accelerating medical discoveries to improve health. The roadmap, introduced by NIH director Elias A. Zerhouni, advocates for public-private partnerships and interdisciplinary research with a strong focus on translational research. Another NIH/NEI initiative is the National Eye Disease Genotyping Network and Resource (EyeGENE). With hundreds of gene mutations now linked to inherited eye diseases, we have the potential to detect conditions early and employ gene-based therapies. The network will assist in developing public and professional awareness of genotyping resources that are available to people with various ocular genetic diseases, their clinicians, and scientists studying these diseases. It will enroll patients interested in participating in future therapeutic clinical trials to treat or prevent genetic eye diseases. By having large datasets of people with shared genetic mutations, it will be possible to draw phenotype-genotype relations, identify risk factors, and develop targeted therapies for unique gene-based disorders. The goal of the Ophthalmic Genotyping Network is to augment existing university-based and commercial genotyping ventures.

Yet another initiative involving the NEI is the NIH’s Neuroscience Blueprint. According to Dr. Zerhouni, who has involved all 15 NIH Institutes and Centers in the project, the Neuroscience Blueprint is intended to reduce the impact of diseases of the nervous system, including eye diseases, which account for six of the top 10 causes of death in the United States. The Blueprint project focuses on neural development, plasticity, neurodegeneration, and behavior. NEI is participating in every component of the Neuroscience Blueprint, including the Blueprint Microarray Consortium and the Gene Expression Nervous System Atlas (GENSAT). The Microarray Consortium allows researchers to access advanced technologies for gene expression profiling and single nucleotide polymorphism genotyping. The GENSAT project is mapping the expression of thousands of genes of the central nervous system.

The NEI is the primary resource for U.S. scientists who are seeking funding for research and collaborative activity for advancing vision and eye care. The NEI works closely with ARVO to keep vision researchers informed of NIH funding opportunities. Scientists can also seek funding from other public and private agencies, organizations, private industry, and elsewhere. Examples are the Foundation Fighting Blindness, Prevent Blindness America, Fight for Sight, Research to Prevent Blindness, and the Lions Clubs.

Investigators from outside the United States are eligible for NIH research project grants. The NEI participates in a unique program in which foreign investigators who train in an NIH intramural program and return to their country of origin to
continue their work have the opportunity to apply for funding from the NIH Fogarty International Center’s Global Health Research Initiative Program for New Foreign Investigators (GRIIP).

Additionally, the Fogarty International Center has the Fogarty International Research Collaboration Award (FIRCA) for NIH grantees to foster international research partnerships between NIH-supported U.S. scientists and their collaborators in various countries, including India.

**THE NEXT STEPS**

The alliances fostered by the U.S.-Indo Workshops on Collaborative Research and NIH funding opportunities will advance research in many areas of ophthalmology. Indian and U.S. eye and vision researchers will exchange techniques, technologies, resources, and other assets. The research enterprises from both nations will be enhanced, with patients as the ultimate beneficiaries.

The next step is to institute collaborations. Scientists will continue to identify research areas that make use of each other’s vast resources. Researchers plan to identify counterparts who have complementary interests, expertise, and facilities, and to develop detailed research plans. Funding sources will be identified and arrangements will be made for exchange and training of personnel. Indian and U.S. funding agencies are developing a mechanism for joint proposal applications and funding. Information about the funding will be widely disseminated when it is available.

Some forward movement has already occurred. One example is in cataract studies using an anterior segment organ culture perfusion system. U.S. scientists have contacted Indian researchers who have an established interest in this field, experiments using fresh whole globes have been proposed, and work is under way to find funding sources. The experiments will test the effects of various molecules and viral vectors on anterior segment outflow. The U.S. laboratory will lead with equipment fabrication and initial training of Indian researchers. Once equipment is installed in the laboratories in India of the collaborators, the scope of experiments will be expanded.

From the workshops in India and the United States, to advance collaborations that accelerate the ability to understand, prevent, treat, and cure vision disorders, we expect to see important gains in clinical and basic vision research. We invite questions (U.S.-Indo@arvo.org, or through direct contact with workshop participants) and involvement from researchers, clinicians, and policymakers elsewhere.

**APPENDIX: U.S.-INDO COLLABORATIVE RESEARCH WORKSHOPS GROUP**

Jyotirmay Biswas (Sankara Nethralaya Vision Research Foundation), David S. Friedman (Johns Hopkins University School of Medicine), G. Kumaramanickavel (Sankara Nethralaya Vision Research Foundation), Anil K. Mandal (L. V. Prasad Eye Institute), Irene H. Maumenee (Johns Hopkins University School of Medicine), Praveen K. Nirmalan (L. V. Prasad Eye Institute), Gullapalli N. Rao (L. V. Prasad Eye Institute), Janey L. Wiggs (Harvard Medical School), and Donald Zack (Johns Hopkins University School of Medicine).

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The authors thank the DBT, Government of India, for its continuing role as India’s piloting agency for the U.S.-India initiative and its financial assistance; M. K. Bhan, B. M. Gandhi, and T. S. Rao of the DBT for their help in formulating the Statement of Intent of collaboration between the DBT and NIH; N. K. Ganguly of the Indian Council of Medical Research, I. V. Subba Rao, Health Secretary of the state of Andhra Pradesh, and Ramalinga Raju, chairman of Satyam Computers, Hyderabad, for help and participation in the first workshop; and special thanks to Kanakaraj Jaiganesh, Junior Administrator, LVPEI for help in organizing the workshops.

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**References**


