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Emerging Therapies for Diseases of the Retina and Optic Nerve

Emerging Therapies for Diseases of the Retina and Optic Nerve

Summary of a Workshop on Implementing Eye Disease Research

October 13–14, 2003
Rancho Valencia, California

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Acronyms

AAV	adeno-associated virus
AMD	age-related macular degeneration
AREDS	Age-Related Eye Disease Study
BDNF	brain-derived neurotrophic factor
CNTF	ciliary neurotrophic factor
CNV	choroidal neovascularization
COX-2	cyclooxygenase-2
DME	diabetic macular edema
DNA	deoxyribonucleic acid
DRCR.net	Diabetic Retinopathy Clinical Research Network
ERG	electroretinography
FDA	Food and Drug Administration
FGF	fibroblast growth factor
HSP-70	human heat shock protein
IGF	insulin-like growth factor
iNOS	inducible nitric oxide synthase
IOP	intraocular pressure
LCPUFA	long-chain polyunsaturated fatty acid
mRNA	messenger ribonucleic acid
NEI	National Eye Institute (of NIH)
NIH	National Institutes of Health
NSAID	nonsteroidal anti-inflammatory drug
OCT	optical coherence tomography
PDGF	platelet-derived growth factor
PEDF	pigment epithelium–derived factor
PKC	protein kinase C
RD	retinal degenerative
RGC	retinal ganglion cell
RPE	retinal pigment epithelium
RP	retinitis pigmentosa
VEGF	vascular endothelial growth factor

Preface

The third in a series of workshops on accelerating the implementation of research results on eye disease was held on October 13–14, 2003, at Rancho Valencia, California. The medical theme of this workshop was "Emerging Therapies for Diseases of the Retina and Optic Nerve." The task set for its 16 participants (listed in appendix A) was to explore the opportunities for and identify obstacles to translating the recent successful research on these therapies into improved patient care. Like the prior workshops on glaucoma and age-related macular degeneration (1, 2), this workshop was suggested by the UCLA Support Group of the Jules Stein Eye Institute of Los Angeles, California, and Mr. Robert Drabkin of Los Angeles. It was organized by the Washington Advisory Group.

The workshop began with a day and a half of presentations and discussions on pharmaceutical therapies, antineovascular therapies, gene therapies, prostheses, stem cell (progenitor cell) and nerve regeneration therapies, drug delivery, and nutrition. The workshop agenda is in appendix B. On the second day, Dr. Paul Sieving, Director of the National Eye Institute, provided his views on the status of implementing ocular therapies. This presentation opened a general discussion of near-term and longer term opportunities for progress, as well as issues and obstacles confronting these opportunities. The discussion focused on general strategies that could aid the work on a number of specific diseases or multiple therapeutic options.

Shortly before the October workshop, Dr. Elias Zerhouni, Director of the National Institutes of Health (NIH), announced a new NIH Roadmap for efforts that no single institute or center, even a small group, could conduct by itself (3, 4). Dr. Sieving described the NIH Roadmap briefly during his presentation. At its core is a set of initiatives, organized under the three themes of New Pathways to Discovery, Research Teams of the Future, and Re-engineering the Clinical Research Enterprise. (Appendix C contains NIH synopses of the initiatives, as of November 2003.) As the concluding workshop discus-

sion was being summarized for this report, strong parallels became evident between strategies favored by the workshop participants and a number of the NIH Roadmap initiatives. As co-chairs of the workshop and authors of record for the workshop report, we decided to organize our summary of the overarching strategies and issues, in section 2 of this report, to reflect these connections. As in the reports from the first two workshops in the series, section 3 contains synopses of the individual presentations from the participants.

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Executive Summary

In October 2003, 16 biomedical researchers and clinicians participated in a workshop on emerging therapies for diseases of the retina and optic nerve. As in two previous workshops on eye diseases (glaucoma and advanced macular degeneration) conducted by the Washington Advisory Group, this workshop's purpose was to explore the opportunities for, and identify obstacles to, accelerating the results of research on eye disease into better care for patients. Twelve invited presentations reviewed the state of research and promising directions in the following fields: pharmacological therapies for retinal degenerative conditions and optic nerve protection (in glaucoma); antineovascular agents to address choroidal, retinal, or corneal neovascularization; retinal and neural regeneration strategies; gene-based therapies; new approaches to delivery of drugs and therapeutic agents; nutritional approaches to reducing chronic eye disease progression; and new devices for biomimetic implants and surgical interventions. These presentations are summarized in section 3.

The final sessions of the workshop were devoted to selecting the most promising near-term and long-term opportunities in each field, as well as crosscutting issues that could help or hinder realization of their potential. The emphasis was on moving successful proofs of therapeutic principle—many of which had been described in the earlier presentations—through the stages of testing for safety and efficacy essential to delivering improved care to patients. These discussions, as well as many of the discussions in response to the individual presentations, raised a number of themes that cut across specific therapeutic approaches and present issues that address the processes for translating promising research into clinical practice. Most of these themes correspond well with initiatives included in the National Institutes of Health (NIH) Roadmap for Medical Research in the 21st Century. This NIH Roadmap was first publicly announced just before the workshop, and the participants heard a high-level summary of it in the final sessions. Two of the Roadmap's themes, Re-engineering the Clinical Research Enterprise and Re-

search Teams of the Future, resonate strongly with issues and themes from the workshop's discussions. Section 2 of this report uses the NIH Roadmap structure as a foundation for presenting these key overarching themes, which contain the workshop's recommendations on how to move these emerging therapies for eye disease into clinical practice that benefits patients.

1 Introduction

In October 2003, a small group of biomedical researchers and clinicians met in an informal workshop setting to discuss emerging therapies for a range of ocular diseases. For the 12 invited presentations, each speaker was asked to review the state of the art in a particular therapy-related research area or to provide a broad perspective on the status of and future directions for emerging ocular therapies. The agenda left ample time for discussion between presentations, as well as a more extensive discussion on the final day to consider crosscutting strategies and issues.[1] Those reviewing a particular therapeutic approach were asked to note the eye diseases to which that approach was relevant and offer a "best guess" about the prospects for future therapy (prevention and/or treatment) using that approach. All the speakers were asked to emphasize (a) potential commonalities in disease mechanisms or contributing factors and (b) potential applicability to multiple eye diseases.

Overall, the presentations and discussions supported a general point: There has been an unprecedented increase in the number of potential therapeutic *proofs of principle*, resulting from research funded by the National Eye Institute (NEI) and others. Examples of these proofs of principle discussed at the workshop included gene therapy approaches, pharmaceutical therapy, use of devices implanted in the eye, surgical treatments, and transplantation of photoreceptor or retinal pigment epithelium cells. What can, and should, be done to accelerate the rate at which these potential therapeutic approaches are evaluated for safety and effectiveness and, if successful, translated into patient treatments? In his summation, Dr. Gerald Chader suggested that the group concentrate on the following implementation strategies:

- Critically examine all the current opportunities for treating ocular diseases where proof of principle has already been established. Include those potential therapies shown to be useful in other disease processes (e.g., cancer or neural degenerations outside the eye).

[1]Appendix A lists the participants and their affiliations. Appendix B is the workshop agenda.

- Separate the near-term opportunities (best possibilities for success) from the long-term, more visionary prospects. While still supporting visionary, high-payoff but riskier research, push the immediate opportunities for clinical trials and therapies in the hope that "success breeds success."
- Seek synergies across approaches such as the use of proven neuroprotective agents in different disease processes (e.g., retinitis pigmentosa [RP] and glaucoma) and use of the same delivery systems for different indications (e.g., encapsulated cell therapy for RP, advanced macular degeneration, and glaucoma).
- Make sure that the proper infrastructure is available for clinical trials so that basic proof-of-principle findings can successfully be translated into human therapies. Services that might be provided through this infrastructure include proper animal models for efficacy and safety testing, genotyping facilities and patient registries, and clinical centers and networks for conducting clinical trials and seeking active involvement for biotechnology and pharmaceutical companies in mounting the trials.

Many of the solutions the workshop participants suggested to address issues in implementing research results involved the mechanisms, processes, and supporting infrastructure by which proof-of-principle results from biomedical research become tested, approved, and accepted for treating patients. In his presentation prior to the concluding discussions, Dr. Paul Sieving, Director of the NEI, described the themes of the National Institutes of Health (NIH) Roadmap, which had been announced several weeks earlier (3, 4). Many of the workshop participants' suggestions tie directly to one or more of the initiatives planned for implementing the NIH Roadmap. In section 2, the themes and initiatives of the NIH Roadmap provide an organizing framework for presenting the suggestions from this workshop on how to improve *translational research*: the processes by which scientific discoveries are translated into practical applications—from the laboratory bench to the patient's bedside.

The aim in applying the NIH Roadmap structure to the workshop discussions is twofold. First, if the suggestions made at this workshop can be caught up with the much larger currents of activity represented by each Roadmap initiative, their prospects for realization are improved. Second, ideas developed through our discussions may in some measure aid in supporting and defining content for the Roadmap initiatives, at least with respect to their relevance to implementing research on diseases of the eye.

2 Translating Research on Emerging Ocular Therapies into Patient Treatments

The first three parts of this section—Research Teams of the Future, Re-engineering the Clinical Research Enterprise, and New Pathways of Discovery—reflect the three thematic areas of the NIH Roadmap as announced in September 2003. (The order of the themes has been changed to reflect the emphases of the workshop discussions; presentations of the NIH Roadmap typically begin with the New Pathways to Discovery theme.) Each heading under a theme notes which NIH Roadmap initiatives are relevant to the workshop suggestions and discussions summarized under that heading. Descriptions of all the initiatives, taken from NIH documents on the Roadmap, are provided in appendix C. The appendix also includes a numbering scheme for the initiatives to facilitate cross-reference with this section.

The concluding part of this section—Deciding on Society's Need for Translational Research—raises an issue of importance not just for the therapies discussed at the workshop but also for any public expenditure on the scale of the NIH Roadmap. Who should determine which translational research on emerging therapies is of greatest value to society?

Research Teams of the Future

The NIH Roadmap envisions research teams of the future as more interdisciplinary than in the past, often involving public-private partnerships. An NIH background document on this theme states, "the traditional divisions within biomedical research may in some instances impede the pace of scientific discovery" (6). Beyond just the discovery phase, the workshop discussions illustrate the critical importance of interdisciplinary teams for bringing together the range of specialized skills and knowledge needed to advance from initial proof-of-principle results to the further stages of testing, refining, and evaluating a potential therapy. The participants also stressed the necessity of interagency cooperation at the Federal level, as well as Federal agency partner-

ships with private foundations and the pharmaceutical industry, to overcome obstacles to progress in moving emerging therapies toward implementation.

Interdisciplinary Research Centers

The participants in the emerging therapies workshop discussed the limited options in the research community for supporting cross-disciplinary teams needed to prepare for and conduct clinical trials of promising therapeutic approaches. As an example, ciliary neurotrophic factor (CNTF) and other growth factors are being tested for RP, but they should also be tested for age-related macular degeneration (AMD), glaucoma, and other retinal degenerative (RD) diseases. Institutes with a focus on ocular diseases could, like today's cancer research institutes and hospitals, support the multidisciplinary teams needed to test growth factors and other therapeutic possibilities on multiple diseases. These teams, large by traditional standards, will require access to animal facilities and to physicians and patients.

Parallel recommendations came from the first two workshops in this series on implementing eye disease research. In the first workshop, held in July 2000 to discuss approaches for moving glaucoma research results into clinical practice, the participants recommended establishing one or more cross-disciplinary centers for glaucoma research. Their action plan stated that "a research context is needed in which those investigating genetic factors, pathogenesis, and therapeutic targets and approaches have frequent interactions and ample opportunity for collaboration" (1, p. 1). In February 2002, the participants in the second workshop, which dealt with AMD research, agreed that a more coordinated, integrated research effort could make substantial advances in pursuing many of the objectives the participants identified for translational research on this disease. This approach would complement, rather than replace, individual investigator research. The intent would be to develop a consortium of investigators whose work collectively articulated larger aims in AMD research than could be undertaken as a single-investigator grant. This group favored virtual centers, rather than the traditional, physically centralized research center, as the vehicle for emphasizing multidisciplinary, integrated programs (2, p. 17).

These recommendations from the three workshops on implementing eye disease research relate to two of the NIH Roadmap initiatives: Interdisciplinary Research Centers (initiative 2-2.1 in appendix C) and the Interdisciplinary Research Training Initiative (initiative 2-2.2). Under the first initiative, NIH intends to award planning grants to begin interdisciplinary research programs to overcome traditional institutional (disciplinary) barriers, particularly for addressing biomedical problems that have resisted more traditional

research approaches. The planning activities under these grants would lay the foundations for subsequent application to NIH for support as an Interdisciplinary Research Consortium. The second initiative is meant to create a new model of funding for training scientists in interdisciplinary strategies. It will allow several NIH institutes or centers to combine in supporting an Interdisciplinary Research Consortium.

The participants at the emerging therapies workshop discussed two concepts that illustrate how interdisciplinary research centers could accelerate progress in translational research. The first illustration was in the field of gene therapy. A disease such as RP, glaucoma, or AMD is often described as being a family of diseases. Medical researchers are learning that there are distinct genotypes, or genetic variants, of the disease. Although these genotypes have important subtle differences in their physiological pathways, they share a common functional outcome, which has led to the same name, such as "retinitis pigmentosa," being applied to all of them. Success in treating one well-understood genetic variant of RP, although it might provide successful therapy for only a few thousand patients, could "prime the pump" of public support. Increased funding could enable pursuit of related gene therapy approaches for genetic variants of RP that affect many more individuals but might be more difficult applications of the therapeutic approach. Dr. William Hauswirth described his plan for using this strategy to follow up on his work with one RP genotype, the RPE65 mutation. He noted that a similar pump-priming approach could be applied to glaucoma and AMD subtypes.

However, sustaining an effective research program across several types of a disease at once will require a concerted effort that draws on the expertise of many individual researchers. Capability to share facilities, techniques, and supporting personnel from diverse disciplinary backgrounds, in an environment favoring routine and informal interactions, would help ensure a coherent strategy across parallel efforts. All these considerations point to some form of interdisciplinary research center focused on a disease family like RP, once the pump has been primed. Indeed, the first two workshops on implementing eye disease research arrived at their recommendations for interdisciplinary research centers from discussions of how best to pursue the genetic basis of glaucoma and AMD as "disease families" (1, 2).

The second illustration of the value of interdisciplinary research centers came from the potential use of progenitor cells, including stem cells, to deliver neurotrophic factors to target precise locations within the eye, such as the retina. Dr. Michael Young described work in transplanting progenitor cells in animal models of glaucoma. As part of the response to the injured ganglion

cells (the glaucoma-like condition in this model), the transplanted cells take up residence in the layer where ganglion cell death is occurring. Transplanted cells that grow near ganglion cells preserve them to some degree. But the real therapeutic innovation would be to bioengineer a progenitor cell line to overproduce growth factors or other factors that protect ganglion cells. These protective factor-expressing cells could then be delivered to within microns of their ganglion cell targets. A concerted effort on this therapeutic approach would require interdisciplinary teams composed of individuals with expertise in progenitor cell transplantation, gene transfer, protective factors, and the physiological pathways of the targeted disease condition.

Interdisciplinary Research across NIH Institutes

Several times during the emerging therapies discussions, participants noted research areas where coordination across several NIH institutes would be fruitful. Translational research on antineovascular agents for ocular diseases, such as wet AMD, could leverage from clinical trials of these agents as anticancer agents. Retinal neurodegenerations, such as ganglion cell and optic nerve disease (glaucoma), and photoreceptor degenerations such as RP and AMD are areas where the NEI could work productively with other NIH institutes in funding research in neurodegeneration and neuroprotection. For stem cell research and neural regeneration, the experts at the workshop suggested that the potential retinal applications could benefit from results of work on a number of other (non-ocular) neurodegenerative diseases.

The NIH Roadmap recognizes the value of improved coordination across the NIH institutes. One initiative will use the NIH Intramural Research Program as a laboratory to demonstrate feasibility, benefits, and successes in establishing interdisciplinary research teams (initiative 2-2.5). Another initiative aims at changing NIH business practices, such as grant application requirements, that may act as structural barriers to interdisciplinary research (initiative 2-2.4).

Public-Private Partnerships

The emerging therapies participants agreed on the necessity of partnering among government agencies supporting research, the academic research community, and the private sector. To breach substantial resource obstacles to translating research into patient treatments, the types of partnering needed go substantially beyond current practices.

One workshop participant, who had recently moved from academic research to a pharmaceutical company, then back to a university position, asked where the private sector should fit into the group's discussion of interdisci-

plinary research centers. Another participant posed the complementary question of where the NEI (and by extension, the entire NIH) should fit in the growing and evolving world of public-private partnerships. A significant factor, noted by a third participant, is that the common, serious eye diseases discussed at the workshop tend to be chronic, slow-developing diseases (figure 1). Rather than a one-year phase 2 or phase 3 trial, therapeutic approaches for these diseases might require trials as long as 5 or 10 years.[1] Trials of that length are beyond the resources and investment profile sought by the pharmaceutical industry.

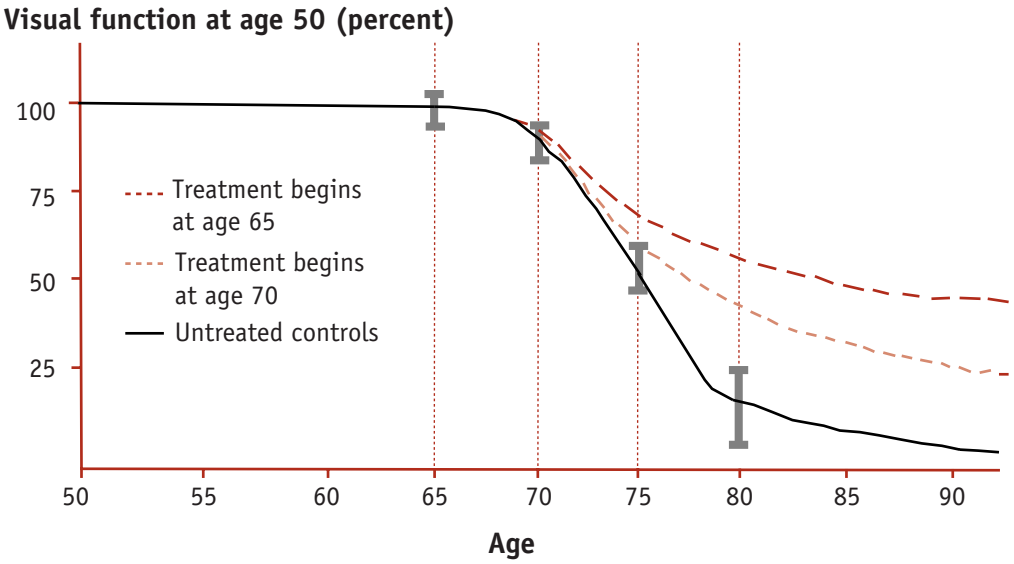

FIGURE 1. Concept of optimal timing in drug intervention studies of a slowly developing disease such as AMD. In this hypothetical example, if treatment begins at age 70 and effect is measured after 5 years, the difference from controls may be too small to be significant against normal population variability (represented by error bars on control curve). Even if treatment begins at age 65, measurement of effect at age 70 may not be significant against controls. In both cases, however, continued treatment significantly reduces loss of visual function in old age. *Source:* Reference 2, p. 7.

One approach to partnering on the resource investments needed for these diseases is Federal support (e.g., through the NEI for chronic ocular diseases) for establishing a clinical research network. An example is the Diabetic Retinopathy Clinical Research Network (DRCR.net), which is supported by the NEI and is evaluating new approaches to treating diabetic macular edema. This network includes a large number of participating clinics, a photographic

[1]A similar point was elaborated by Dr. Edwin M. Stone, as the issue of optimal timing of intervention and testing for effect, at the second workshop on implementing eye disease research (2, pp. 7, 21–23).

reading center, and a coordinating center. A pharmaceutical company interested in evaluating a biomolecule (e.g., a protective factor) or drug for safety and therapeutic effect can use the network to begin testing quickly.

A second approach has been developed by the Foundation Fighting Blindness, a nonprofit foundation focusing on obtaining therapies for inherited RD diseases. The Foundation Fighting Blindness has set up a number of university-based Medical Therapy Assessment Centers, which can quickly and efficiently screen a pharmaceutical agent or technique for safety and efficacy in an animal model for an RD disease. But additional resource contributions from the NEI will probably be required to sustain trials for the necessary durations. Workshop participants reported that the NEI and the Foundation Fighting Blindness are seeking innovative ways to partner with pharmaceutical companies in these evaluations. (Clinical research networks are discussed again later in this section.)

Workshop participants voiced concerns that a large number of promising candidates for therapeutic approaches, such as antineovascular agents or neuroprotective factors, are simply "sitting on the shelf." This means the company that has secured exclusive rights to the compound may have little interest in evaluating it, perhaps because the perceived return for treating one rare form of a diverse disease is too low. A solution is needed that addresses the intellectual property issues involved (discussed further below), without tying up inordinate amounts of either public or private financial resources. The DRCR.net, for example, will begin with a laser treatment trial, then evaluate a steroid that is no longer under patent (although being tested in a new formulation). However, several other potential therapeutic candidates for diabetic macular edema are proprietary. Bringing them to trial will require some form of government-industry collaboration.

Innovative approaches to delivering therapeutic agents to the retina or other specific locations inside the eye were an area of translational research discussed several times at this workshop. Most of the blinding diseases addressed by the presentations are retinal conditions for which therapeutic agents must reach the site of the pathology to be effective. If there were proven means for targeted delivery to these locations, many of the therapies discussed at the workshop could be delivered in effective doses with decreased risk of systemic side effects. After initial testing of a new drug delivery method with one candidate agent, national core facilities could acquire and make available the techniques and technology for that delivery method. It could thus be made readily available to clinical research networks for testing with other agents or for other diseases or disease variants.

The participants agreed that a partnering approach will probably be necessary to establish new paradigms for targeted drug delivery. The technology or the initial therapeutic candidates that might be tested with it often have proprietary aspects, which means the patent holder needs to be involved and the holder's intellectual property interest protected. At the same time, early involvement of the U.S. Food and Drug Administration (FDA) is essential to establish, and perhaps modify, the regulatory steps facing a new drug delivery technique or technology. Another suggestion was that drug delivery would be a fruitful area for NEI partnerships with the Association for Research in Vision and Ophthalmology, the American Physiological Society, and other societies, to arouse interest from multiple disciplines. For example, the NEI and one or more of these societies could sponsor joint workshops on drug delivery methods. Support from this direction could help overcome resistance from the pharmaceutical companies, which for business reasons are risk-averse to taking a new delivery technique into clinical trials.

The NIH Roadmap stresses that NIH already has mechanisms in place to encourage partnerships among researchers in academia, government, and the private sector (7). The initial component of Roadmap activities in this area focuses on a new office to be created, the Public-Private Sector Liaison, to facilitate collaborative efforts (initiatives 2-3.1 and 2-3.2). The partnering opportunities discussed at the emerging therapies workshop reach beyond the immediate objectives for partnering stated in the NIH Roadmap. They offer a challenging vision for a new, collaborative approach to translational research, combining the resource strengths of the Federal Government, the private sector, and the academic research community.

Intellectual Property Issues

The workshop participants identified several intellectual property barriers to testing known factors or active compounds for efficacy with a disease other than the one for which they were first developed and tested. If, as noted above, the owner or licensee of the patent for a new agent decides not to pursue clinical testing, the agent is unavailable for testing, even for other conditions, unless the intellectual property owner can be persuaded otherwise. Universities often own the intellectual property resulting from government-funded grants to university-based biomedical researchers. The workshop participants agreed that university technology transfer offices, as owners of intellectual property, have been especially resistant to making their property available for other testing once it has been licensed. Private companies are often more willing to make available their own compounds (drugs or factors for which they own the patents) than are university technology offices.

One source of the problem appears to be a lack of interest or breadth of knowledge in university technology transfer offices. To address this barrier, the participants recommended that the NIH and other Federal funders of biomedical research modify and harmonize their policies to exercise the interest they retain under current law in intellectual property created with Federal research funding.[2] At the least, agencies should pressure the owners of this intellectual property to make the potential therapeutic agents available for testing.

Intellectual property issues are not directly addressed by any one Roadmap initiative, but they are mentioned in, or are relevant to, several of them. Dealing with intellectual property issues is one of the tasks for the proposed Public-Private Sector Liaison (initiatives 2-3.1 and 2-3.2). Harmonizing policy and procedures across agencies to maintain and exploit government interest in intellectual property created with government funding support could be an objective of Roadmap initiative 3-1.1. As detailed below, the workshop participants described several intellectual property barriers to evaluating potential therapeutic agents. Dealing more effectively with these barriers will be essential if the NIH is to realize stated objectives of the Protein Production Facilities initiative (1-3.1) and provide the data content for the National Centers for Biomedical Computing (initiative 1-4.1).

Innovator Awards for High-Risk Research

A topic discussed at the emerging therapies workshop was the conflict between what a biomedical researcher can *safely* do (because it will be successful in the typical competitions for grant awards) and higher risk research that *needs to be done* to meet societal needs for treatment of blinding diseases. The latter may be perceived as too risky to be selected—for example, in the current NIH peer review process for selecting R01 (individual investigator) grants. As a partial solution to this risk aversion in the current grant process, a workshop participant suggested that introducing a new category of grants for high-risk but high-payoff research might help.

The rationale for the NIH Director's Innovator Awards (initiative 2-1.1) is to provide a mechanism by which the NIH can support more speculative, or "high risk," research proposals, while maintaining a rigorous nomination and review process. The intent is to select creative, "outside the box" thinkers whose ideas have the potential for high-impact benefits to medical research and who have demonstrated abilities to pursue them. Thus, the workshop

[2]Under the Bayh-Dole Act (35 U.S.C. §§ 200–211), Federal funding agencies retain "march-in" rights for patentable inventions made with support from Federal funds. The agency can exercise this right if the recipient of funding elects to take title to the invention but fails to seek commercialization opportunities for it.

discussion on this point parallels the rationale for a new category of Innovator Awards. An unresolved question is whether the selection process suggested in the NIH Roadmap documents (8, 5) will in fact enable the areas of high-risk research that the workshop participants had in mind. This issue is probed further in the concluding portion of this section, Deciding on Society's Need for Translational Research.

Re-engineering the Clinical Research Enterprise

According to the NIH Roadmap documents, clinical research has become more difficult. If the clinical research enterprise is to remain as successful as it has been in the past, the United States must reconfigure its system of clinical research. At the same time that this research system strives to become more efficient and contribute more effectively to basic research in the biomedical sciences, exciting discoveries in those sciences demand that clinical research not only continue but expand (9).

The NIH vision for re-engineering the clinical research enterprise begins with developing new partnerships among organized patient communities, community-based physicians, and academic researchers (9). This vision therefore expands the concept of public-private sector partnering described above.

Through the initiatives under this Roadmap theme, the NIH intends to promote the creation of better integrated *networks* of academic centers. The centers in a network will collaborate on clinical trials. These clinical trial networks will include community-based physicians, who will link the network with sufficiently large groups of well-characterized patients to carry out complex trials efficiently. The *information resources* to support these multicenter networks will be enhanced by new ways of recording clinical research data, new standards for clinical research protocols, and modern information technology. The *human resources* to support the re-engineered enterprise will be enhanced by new models of cooperation between the NIH and patient advocacy alliances and by new strategies to re-energize the clinical research workforce (9).

Clinical Research Networks

An illustrative example of a multicenter, community-based clinical research network discussed at the workshop is the network for evaluating new treatments of diabetic macular edema, DRCR.net, which is being started with NEI support. The structure and operation of DRCR.net incorporates experience gained from other research networks, such as an existing network of pediatric ophthalmologists, which has already undertaken at least a half-dozen clinical trials on pediatric eye diseases. The DRCR.net would not have been

fostered by the pharmaceutical industry alone. But once it is established with NEI support, companies will be encouraged to use it for trials of therapeutic agents whose safety and efficacy are supported by pretrial laboratory studies. The DRCR.net will be able to conduct trials on prevention, as well as on treatments of existing disease.

Specifically with respect to the NEI and eye diseases, communities and alliances are formed by patients and families of patients with a particular disease. Some of these alliances can be as narrowly defined as a particular phenotype or genotype (where a genetic basis has been established) of a disease family. These alliances become organized, vocal advocates for research targeted to "their" disease. They communicate effectively with their congressional delegations, as well as with NEI officials. Because these self-forming communities represent significant target populations for translational research (e.g., pretrial studies and phase 1 and 2 clinical trials) on a specific disease condition, the NEI and the research community need to work with them.

The timeliness of this network infrastructure for attacking chronic, complex eye diseases was emphasized at the emerging therapies workshop by Dr. Sieving's review of the pace of discovery of monogenic forms of inherited retinal and other ocular diseases. (A monogenic disease is one caused by a mutational defect at a single gene locus, such as the form of RP caused by the RPE65 mutation.) After an upward trend in discoveries of monogenic diseases during the early 1990s, the pace of discovery is now tapering off (figure 2). Perhaps, Dr. Sieving suggested, this means that the majority of mono-

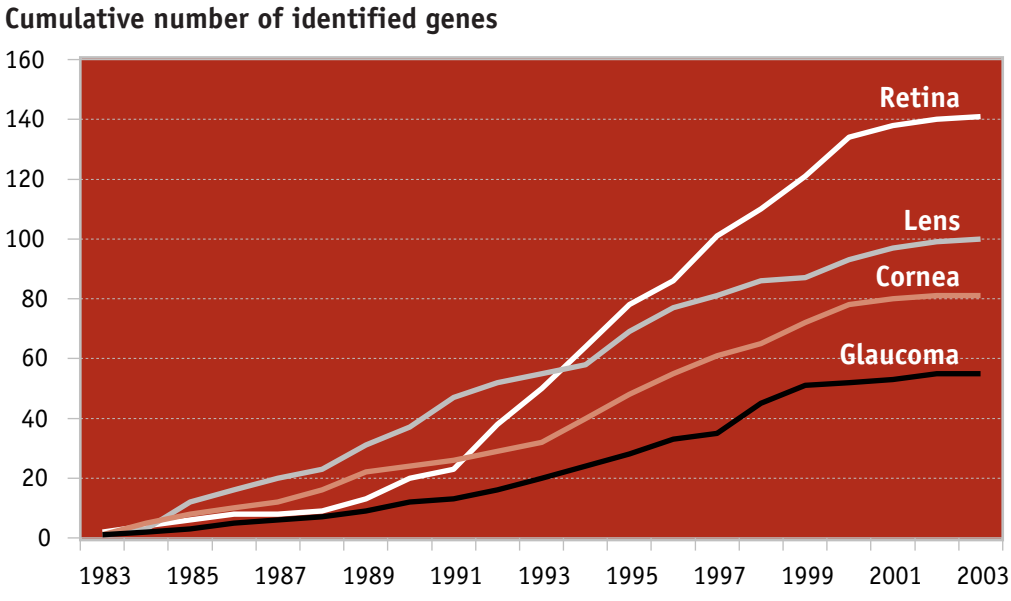

FIGURE 2. Is discovery of monogenic ocular genes plateauing? Each gene identified is counted once. *Source:* OMIN and RetNet.

genic forms have been discovered. If so, the remaining variants of the serious, common, diseases that blind or severely impair vision over time and that appear to have a substantial genetic component are likely to involve complex genetically based traits involving multiple genes. Indeed, the first two workshops on implementing eye disease research came to this same conclusion with respect to the common forms of glaucoma (1) and the more prevalent forms of AMD (2). Work with RP supports the same conclusion for the more common forms of that disease family. To pursue these complex disease variants with the tools of genetic research, investigators will need the support of community-based ophthalmologists in private practice and even optometrists and other eye care providers in the community. They can also benefit from cooperation with the self-forming alliances of those affected by a disease.

With respect to population genetics research, another suggestion from the workshop was to increase the international search for disease forms with a strong family-associated or ethnically specific prevalence. Pakistan was mentioned as an example of a country with a high prevalence of consanguineous eye maladies (blood relatives with the same disease condition). Identification and study of such patient groupings will greatly facilitate identification of both the genes and the environmental factors involved in gene expression.

The participants discussed one potential downside to NIH-led clinical research networks. In the past, the academic research community has sometimes resisted organizing a focused research effort, based on the perception that all or most of the available funding for that research area would be channeled into that one activity. The participants agreed that there was a potential handicap on innovation and unexpected discoveries if research efforts are too focused in narrow channels or restricted to only a few participating investigators.[3]

However, participants also agreed on the importance of an improved infrastructure to support higher levels of more efficient translational research (in effect, the same arguments made in the NIH Roadmap for re-engineering the clinical research enterprise). Multicenter, multidisciplinary clinical research networks as envisioned in the Roadmap initiatives are just one of the key ele-

[3]The participants in the second workshop expressed similar concerns with respect to one or more centers focusing on multidisciplinary research on AMD and other variants of macular degeneration. They recommended "virtual centers," which would not be physically located at one university in terms of active participating investigators and infrastructure, as a solution. That recommendation appears to parallel the integrated network concept, involving multiple university centers, in the NIH Roadmap.

ments in this infrastructure. Other elements are *national core facilities*, to provide resources essential for translational research more efficiently, and *harmonization of regulations* on clinical research, to lessen barriers that obstruct translation needlessly, while ensuring the safety and efficacy of new therapies.

These discussions about multicenter research networks at the emerging therapies workshop are directly relevant to three initiatives central to this NIH vision for re-engineering the system for clinical trials in the United States. These initiatives are Integration of Clinical Research Networks (initiative 3-1.2), Enhance Clinical Research Workforce Training (initiative 3-1.3), and Clinical Research Informatics: National Electronic Clinical Trials and Research Network (NECTAR) (initiative 3-1.4). The workforce training initiative embodies two programs to provide sufficient clinical professionals trained to work in the new multicenter, multidisciplinary networks. The Multidisciplinary Clinical Research Workforce Training Program will be an NIH-wide effort to train predoctoral and postdoctoral candidates in interdisciplinary and collaborative clinical research settings. The clinical disciplines to be included span medicine, nursing, dentistry, pharmacy, and allied health professions. The second program, NIH Clinical Research Associates, will give specialized training in clinical research to a cadre of community-based practitioners. The roles of Clinical Research Associates will include disseminating research findings to the patient and health care provider community, as well as participating in the discovery process (clinical research trials). NECTAR, a standardized data system, will allow the Clinical Research Associates to participate in national trials, facilitate sharing of data and resources among investigators and participating practitioners in a research network, and augment clinical research performance and analysis (5).

On the subject of enhancing the clinical research workforce, the workshop consensus was that inadequate numbers of new clinical researchers were moving into work on RD diseases. The Multidisciplinary Clinical Research Workforce Training Program, if it covered clinical research on ocular diseases, could help attract new people to the field, particularly if it were combined with establishment of multidisciplinary centers dedicated to translational research on emerging therapies for ocular diseases (initiative 3-1.6, discussed below). Support for these centers and for interdisciplinary research teams would encourage predoctoral and postdoctoral fellows to consider work on such teams, in connection with the translational research centers, as a viable career path.

National Core Facilities and Infrastructure for Clinical Trial Support

Multicenter, multidisciplinary clinical research networks as envisioned in the Roadmap initiatives are just one of the key elements in an improved infrastructure for translational research. Other elements are *national core facilities*, to provide resources essential for translational research more efficiently, and *information networks*, to share clinical research data among investigators and across programs and projects. The emerging therapies workshop participants were strong advocates of Federal support for the kinds of national core services and facilities envisioned in the Roadmap. Examples mentioned during their discussions included one or more facilities for producing high-quality standard reagents that are not yet viable as commercial products (GMP reagents), a center for conducting laboratory-based studies of ocular and systemic toxicity (required prior to phase 1 clinical trials), and facilities to maintain and enhance the range of animal models.

For emerging therapies for eye diseases, bioengineered animal models as analogues of human retinal and optic nerve degenerations, early glaucoma (high intraocular pressure), and other pathological conditions are critical to the next steps in moving from proof-of-principle research results toward clinical trials and eventual clinical care. The broad range of potential protective factors (e.g., neuroprotective or antineovascular agents) cited during the workshop presentations need to be tested in multiple animal models, to assess the relative efficacy of these candidates across the range of relevant precursor conditions and disease end states. (Additional candidate factors for such testing were discussed in the first two workshops on implementing eye disease research.) Testing in animal models also plays a key role in developing gene therapy approaches (2, pp. 11, 17, 22–23; 1, p. 7). In the emerging therapies workshop, as in the earlier AMD workshop, participants stressed the importance of using multiple animal models to test candidate agents for different aspects of RD disease, such as pathology in the retinal pigment epithelium versus effects directly on photoreceptor cells. Also, new models are needed for conditions such as geographic atrophy in macular degeneration, for which there are not yet generally accepted animal models.

Another point of agreement was the value of regional centers for supporting interdisciplinary research teams with a range of facilities and capabilities, ranging from animal facilities and expertise with primate toxicity testing to access to clinicians and patients. Few U.S. academic centers, except some of the major cancer research centers, can currently provide a full range of these core services for researchers. For basic research in areas such as structural biology, there are some recent additions, such as the multi-institutional, multidisciplinary Structural Biology Center funded by the Michigan Life Sci-

ences Corridor. Dr. Albert Aguayo described how Canada has funded centers of excellence to provide a range of services and support for translational research. Participants discussed ways in which joint Federal, industry, academic, and private nonprofit (foundation) resources might contribute to establishing and sustaining regional centers in the United States. Such centers would focus on supporting the translational research necessary to bridge the gap from proof of principle to viable candidates for commercialization.

Several Roadmap initiatives are aimed at establishing the national core facilities and information networks required to reinvigorate the clinical research system and enhance translational research. The Roadmap initiatives for Translational Research Core Services (3-1.5) and Regional Translational Research Centers (3-1.6) will provide cost-effective core services needed to support translational research in both laboratory and clinical settings. The NECTAR clinical research data network (initiative 3-1.4) will facilitate sharing of data and resources—a major factor in augmenting the capacity to do clinical research and analyze the results. Related to the initiative for enhancing the clinical research workforce, which was described above (initiative 3-1.3), NECTAR will enable community-based clinicians such as the NIH Clinical Research Associates to participate directly and actively in national trials and other major translational research activities.

Treatment-Relevant, Practical Endpoints for Clinical Trials

An essential part of preclinical testing, as well as the phase 2 clinical trial, is establishing the efficacy of a candidate therapy. Throughout the history of science, including the biomedical sciences, a major issue has been reconciling the properties we know how to measure well with the properties that are worth measuring. For example, electroretinography (ERG) has been used as a measure of efficacy in clinical research on RP. Dr. Sieving described an RP patient with negligible ERG responses who could drive a car and read books. The participants also struggled with the issue of measurable endpoints for neuroprotection, macular edema, or geographic atrophy in AMD. For these conditions, what endpoints would be decisive without requiring 20 years of follow-up and would not require control subjects to forego potentially ameliorative treatments (such as glaucoma treatments that lower intraocular pressure)?

The Roadmap initiative for Enabling Technologies for Improved Assessment of Clinical Outcomes (initiative 3-1.7) stresses objective techniques to measure clinically important outcomes and symptoms—such as pain, fatigue, and quality of life—that accepted clinical trial endpoints often fail to assess. In addition to this issue of new measures for clinically recognized symptoms

and outcomes, the participants in the emerging therapies workshop questioned whether ERG responses and other current or proposed measures are truly relevant to patients' well-being and quality of life.

The need for better measures of efficacy arises even before the clinical trial phase. As one participant noted, research is needed on surrogate biomarkers, as substitutes for long-term outcomes in lengthy clinical trials, to assess quickly whether a formulation is likely to be effective. For example, the current "gold standard" for cell survival in assays of neuroprotective efficacy uses sympathetic nerve ganglia in chicks. The assay is accepted because it is reproducible and gives a response proportional to administered dose. However, the response of a different neural tissue, such as retinal ganglion or photoreceptor cells, may be different. Also, the pathology of direct interest may be not simply cell death but a more specific change, such as axon degeneration (prior to death of the cell body) or loss of functionality in a photoreceptor. Are there standard cell culture assays that could be used to screen candidate agents reliably for effects on specific changes such as these?

Harmonization of Clinical Research Regulatory Requirements

The workshop discussions support the importance of lessening barriers that needlessly obstruct translation of research into practice, while continuing to ensure the safety and efficacy of new therapies. Participants with years of experience in trying to move candidate therapeutic approaches beyond the proof-of-principle phase expressed frustration with regulators' apparent resistance to adapt—even when change was justified by new understanding.

In contrast to this frustration, several participants expressed optimism about regulatory change. They had recently attended a meeting sponsored by the Foundation Fighting Blindness, with both NEI and FDA support, to discuss emerging opportunities in RD gene therapy and how to move them forward into clinical trials. A key feature of the meeting was that the clinical and patient communities, as well as academic researchers, industry, the NEI, and the FDA, were represented. In this context, the FDA, as the principal regulator, was willing to discuss and consider novel measures for endpoints and the use of multiple endpoints. Learning occurred in both directions, as those advocating more rapid translation were educated on the value of working with the FDA early in the process.

Through the Roadmap initiative for Harmonization of Clinical Research Regulatory Requirements (3-1.1), the NIH will work with other Federal agencies such as the FDA and the Centers for Disease Control and Prevention to coordinate, standardize, and streamline regulatory policies and requirements

pertaining to clinical research. The discussion at the emerging therapies workshop suggests that this regulatory reform initiative should be closely tied with the public-private partnering initiatives discussed above, with the FDA included from the onset as a key partner.

New Pathways of Discovery

The five implementation groups and 11 initiatives within the New Pathways of Discovery theme of the NIH Roadmap address areas of primary importance to foundational research. In addition, the research-supporting infrastructure of facilities and capabilities resulting from the New Pathways of Discovery initiatives will contribute in diverse ways to translational research.

The summation below connects just three of these initiatives to the workshop's concluding discussions. As explained in section 1, the concluding discussions at the emerging therapies workshop were explicitly directed to the opportunities and obstacles for translating current proof-of-principle research results into therapies available to patients, rather than on the needs and directions for new discoveries. The participants agreed that this focus was justified for a short workshop, given the substantial progress made over the past several years in research demonstrating underlying principles of new therapeutic approaches for treating ocular diseases. Because the general discussions focused on translational research, there is less to summarize in this section that is relevant to the New Pathways of Discovery theme. However, the individual presentations at the workshop emphasized promising trends in areas of basic research relevant to understanding RD diseases and emerging therapeutic approaches for them. There are, therefore, many more links between research areas highlighted in section 3 and initiatives under this Roadmap theme. For the interested reader, appendix C includes descriptions for all the New Pathways of Discovery initiatives.

Bioinformatics and Clinical Research Informatics

Participants at the workshop described plans at the NIH to develop a resource depository of genetic data. This resource depository would include information not only from NIH-conducted studies but also from studies not conducted by NIH but for which clinical information on genetics can be obtained. To increase the value of a national genetic data depository as a research resource, particularly for translational research, the mapping between well-characterized genetic variants (genotypes) to recognizable and standardized clinical descriptions of physical conditions in patients (phenotypes) must be established. The iterative, two-way process necessary to achieve a valid and useful mapping for disease families such as glaucoma and AMD

was a major topic of discussions at, and a major recommendation resulting from, both of the previous workshops (1, 2). At the emerging therapies workshop, participants described recent efforts to establish consensus on AMD phenotypes. Because published clinical descriptions of phenotypes are not uniform, the research groups involved met together to work out a standard set of phenotype definitions.

In the area of bioinformatics[4] and computational biology, the NIH Roadmap has an initiative to establish a set of National Centers for Biomedical Computing (initiative 1-4.1). The centers, some of which will begin in fiscal year 2004, will generate software and data management tools that investigators from many disciplines can use to share techniques and analytic results, as well as the raw data (5). The NECTAR data network for clinical research (initiative 3-1.4) can provide a national shared data resource through which clinical investigators and community-based practitioners will be able to employ these tools. The NEI is working on a national network for descriptive genotyping of ophthalmic diseases. Patient approval will be sought to develop a national database of genotype information, to be linked with phenotype information. The workshop participants agreed that these and similar efforts to link genotypes with phenotypes should be coordinated with, if not subsumed under and supported by, the NIH Roadmap initiatives in bioinformatics and clinical research informatics.

Bioactive Small Molecule Library and Cheminformatics

The NIH Roadmap initiative for Creation of NIH Bioactive Small Molecule Library and Screening Centers (initiative 1-2.1) will support centers for screening biologically active small molecules. The resulting data will be accessible to researchers through a national depository, the small molecule library. The closely related initiative for Cheminformatics (initiative 1-2.2) will establish a database of chemical structures, properties, and activities. Data retrieval and analysis tools will link this chemical information database to the data produced by the Small Molecule Screening Centers and to other chemical information bases and the chemical technical literature (5).

These research resources will enhance what Dr. Arthur Neufeld has called the "search for serendipitous drugs." At both the implementation workshop

[4]The NIH Roadmap documents lack a definition of "bioinformatics" of general utility to non-specialist audiences. However, the report from the second workshop drew on other NIH website documents to define "bioinformatics" as "research, development, or application of computational tools and approaches for expanding the use of biological, medical, behavioral or health data, including those computational tools and approaches to acquire, store, organize, archive, analyze, or visualize such data" (2, pp. 11–12).

on glaucoma (1, p. 6) and the emerging therapies workshop, he stressed the value of "data mining" to identify known or likely effects on eye diseases or disease preconditions of drugs that were being tested for other therapeutic targets. Dr. Frederick Ferris of the NEI added that some work in this direction is being done; for example, data from NIH-conducted trials on patients with diabetic macular edema or AMD were examined for potential beneficial effects of nonsteroidal anti-inflammatory drugs (NSAIDs). A preliminary analysis has indicated a reduced risk of progression to dry AMD (geographic atrophy) for patients in the Age-Related Eye Disease Study who were taking NSAIDs. Although initial indications such as these are tentative pending further analysis, they illustrate the potential value of data mining for selecting among candidate hypotheses to be more rigorously tested. The bioinformatics and chemical informatics resources to be created by these two Roadmap initiatives would make such data-mining efforts many times more effective and efficient. These new resources will greatly expand the range of biologically active compounds and prior clinical trials that can be investigated rapidly.

Deciding on Society's Need for Translational Research

As noted above, the workshop participants often spoke about the need for core facilities to support translational research and the broad range of candidate biomolecules and small-molecule drugs that might have therapeutic effects for specific disease or precursor conditions. During one of these discussions, the cost in both investigator time and funding resources was noted as a constraint on doing all the translational research that could be worth doing. Dr. Bronwyn Bateman, who is both a clinical practitioner and a biomedical researcher, said that a linkage must be maintained between therapeutic research results and outcomes that the American public—society at large—wants to pursue. For example, there are highly effective early treatments for diabetic retinopathy, but what society needs is a useful way to identify individuals who could benefit from these treatments. More generally, fears of losing functional vision—going blind—are high on the public's list of concerns about health and aging. Societal support for biomedical research, which translates into acceptable public funding levels, depends on sustaining and enhancing the connection between what the public values and what researchers achieve, over time, with the resources they receive.

These comments engendered a broad discussion of the role societal importance should play in biomedical research and development. The workshop participants agreed with the current system, in which researchers can make their own decisions about what they want to do but also consider where

there are resources to support work of interest. This approach was viewed as more productive of new discoveries than having researchers directed to work on particular diseases or therapeutic options in order to receive support. Nevertheless, the competitive award system does produce a tension, as one participant described it, between "the things we *can do* [as researchers, because there is funding available to support them] and the things we *need to do* [because they would produce results of real value to patients]." In other words, the current system for allocating research funds does not always distribute research resources efficiently with respect to meeting societal needs. For the workshop participants, this tension becomes most problematic when support is needed for research that carries higher risks (primarily risks of failing to produce desirable outcomes) but has far higher potential payoff to society if successful. The participants agreed that improvements are needed to the current system for recognizing and funding difficult but socially significant problems.[5]

This problem is partially addressed in the NIH Roadmap by the NIH Director's Innovator Awards (initiative 2-1.1). From the perspective raised at the emerging therapies workshop, the question is whether the Innovator Awards alone will suffice to ensure that "the things researchers *need to do*" in fact get done.

A complementary approach with broad applicability is to establish conditions that reduce the risk of a research effort failing while also reducing the cost of taking on a high-need challenge. Indeed, to the co-chairs of the workshop, this approach seems to be characteristic of the NIH Roadmap as a whole. The facilities, networks, and capabilities to be established and maintained through the Roadmap initiatives share the cost of taking on the challenges in moving beyond an individual investigator's proof-of-principle results to therapeutic options that have been proven both safe and useful. By providing essential inputs to the research conducted by many individual researchers, and by coordinating their efforts in interdisciplinary teams, the Roadmap initiatives also improve the chances of success in tackling difficult but socially important problems.

One way, therefore, to view and assess the Roadmap initiatives is through their potential to improve the efficiency and effectiveness of competitively awarded research funding to select and pursue the best opportunities for emerging therapies.

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[5]A study committee of the National Research Council and Institute of Medicine recently came to similar conclusions in *Enhancing the Vitality of the National Institutes of Health: Organizational Changes to Meet New Challenges* (16).

3 Workshop Presentations

The individual presentations during the first day and a half of the workshop are summarized below in the order they were given. Each of the first 12 presentations focused on a particular field of emerging ocular therapies. The final two presentations provided a transition to the crosscutting discussions summarized in section 2.

Pharmaceutical Therapies for Retinal Degenerations

Matthew M. LaVail, Ph.D.

Dr. LaVail focused on the emergence of neurotrophic factors as therapeutic agents for RD (retinal degenerative) disease. As context for the importance of expanding the range of therapies for these diseases, he cited incidence statistics for RP (retinitis pigmentosa) and AMD (age-related macular degeneration). RP affects 1 in every 3,500 persons worldwide. As of October 2003, 146 RP-related genes have been identified, of which 96 have been cloned. AMD is the leading cause of blindness in Americans over 55 years of age. There are estimated to be 6 million seniors in the United States who currently suffer vision loss due to AMD. This number is projected to rise sharply in the future, as the population over 60 years of age doubles by 2030.

RD disease includes conditions that damage retinal ganglion cells (RGCs), as in glaucoma, and photoreceptor cells, as in RP and AMD. In many of the photoreceptor diseases, the retinal pigment epithelium (RPE) is also affected. While many research groups around the country have contributed to the work he summarized, the effort in Dr. LaVail's group began with the discovery that basic fibroblast growth factor (FGF-2) would slow the degeneration of photoreceptors in RCS rats (a rodent model for photoreceptor RD disease) (20). From this initial result, the group went on to test other neurotrophic factors and found that many of them, including brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), interleuken-1ß, insulin-like growth factor (IGF-II), and other forms of FGF, improve the survival of photoreceptor cells in RCS rats. The mechanism by which they promote survival

remains unknown. However, because the factors studied interact with different classes of receptor sites on a cell's membrane, a reasonable hypothesis is that they work on some common point in the degeneration pathway, such as cell apoptosis (programmed cell death).

Dr. LaVail discussed five key issues in assessing these factors or others as potential therapeutic agents for a particular RD condition:

- Efficacy (does it work for the cells of interest, e.g., photoreceptors?)
- Delivery (how can the agent be delivered to the target site?)
- Specificity (do certain factors work better for certain diseases?)
- Targets (which cells—photoreceptors, RGCs, RPE, intermediate cells, etc.—are being acted upon?)
- Toxicity (does the agent have toxic effects at either excess or therapeutic levels?).

Using constant light as the degeneration-inducing challenge, Dr. LaVail's group found that certain factors have efficacy in some rat or mouse models for RD conditions, but none worked in all the models tested. CNTF has received particular attention because it has some efficacy in almost all of the rodent RD models, as well as some dog and cat models.

Much research effort has been devoted to the problem of delivering a factor to the target retinal tissue. These biomolecules are too large to cross the blood–retina barrier, so intraocular injection has typically been used in the animal experiments, rather than delivery through the circulation. However, intraocular injection in clinical therapy raises issues of patient acceptance and compliance; as many as 250 injections could be required over a patient's lifetime. One option is to look for a smaller molecule that has protective activity, but many of these candidates appear to have negative systemic effects. Another option is to find a way to sustain release of the agent after delivering it to the eye. Three delivery approaches using some form of the latter alternative have been investigated: biodegradable polymers in which a neurotrophic factor is embedded, encapsulated cells that have been bioengineered to produce the factor in therapeutically useful amounts, and gene-based delivery of the factor.

Success in protecting photoreceptor cells in a number of different animal models has been demonstrated for gene-based delivery with both modified adenoviruses and adeno-associated viruses. These experiments have also demonstrated relatively long-term expression of the factor. With respect to

specificity, many more of the factors work when gene-based delivery is used than when the same factor is delivered as a bolus by intraocular injection. Another reason for the interest in CNTF is that, with continuous delivery, it has shown to be protective in every RD animal model in which it has been examined. Dr. LaVail described additional work by his group showing that some of the neurotrophic factors affect only specific retinal degenerations.

Target cell identification is an important consideration because many of the neurotrophic factors seem to affect the photoreceptor cells indirectly. In gene expression studies with CNTF and BDNF, active receptors for the factor being expressed resided only on Müller cells or ganglion cells (21). These cells may act as intermediaries, responding to the neurotrophic factor by releasing another factor, such as FGF-2, for which the photoreceptor cells have receptors. Because the RPE has receptors for a number of neurotrophic factor families, releases a number of factors, and is involved in the movement of molecules to and from the photoreceptors, Dr. LaVail expects that RPE cells also act as intermediaries for some neurotrophic agents.

Toxicity and side effects are issues for local delivery of neurotrophic factors to the eye, as well as for systemic delivery. Dr. LaVail described negative effects that occurred occasionally when injecting FGF-2 into the eye (20). CNTF appears to decrease the ERG (electroretinography) response in mouse models with adeno-associated virus (AAV) transduction. Histologic changes in photoreceptor cell nuclei were also observed. AAV transduction of CNTF in mice (normal C57BL/6J) and in transgenic rat models (P23H rhodopsin transgenic and others) showed decreased degeneration of photoreceptors (22, 23). When data from multiple studies are compiled and compared, there appears to be dose dependence for these cell rescue effects, but negative changes also increased at higher doses. Thus, the goal is to find a delivery method or concentration that protects or rescues photoreceptors while avoiding or minimizing the negative effects. In assessing toxicity, the steps are to first identify potential negative effects, determine the impact on retinal cells and vision, and then develop the means to regulate the negative effects while sustaining a therapeutic concentration at the target tissue. In closing, Dr. LaVail expressed hope that direct application of neurotrophic factors will prove useful for various ocular and retinal diseases, either when used alone or in combination with other therapeutic agents. In some cases, a neurotrophic factor might be useful in promoting cell survival, as an adjunct to increase the overall efficacy of other courses of treatment.

During the question period, Dr. LaVail described work by his group indicating that the duration of the rescue effect after a single bolus injection of a

neurotrophic factor depends on the factor injected and the type of cell targeted for rescue.[1] With respect to behavioral indicators of negative effects, he said that he only knew of structural changes having been reported to date, but he is planning to conduct studies using behavioral tests with rodent models. Dr. Peter Campochiaro described work by his group on the ability of rats to perform visual tracking after intraocular injection of interleuken-1ß. Dr. William Hauswirth noted some reports of CNTF morphologic rescue without functional rescue. The participants discussed the body of work on efficacy and safety of neurotrophic factors. Dr. LaVail summarized the discussion as showing the need for a broader spectrum of animal models to be tested with continuous delivery of an agent by sustained release or gene-based approaches. The participants also discussed the need for standard, well-grounded measures of functional efficacy in both animal models and clinical studies. Although ERG is often used as an indicator of functional performance, there is no definitive body of work relating ERG response amplitudes to visual performance, either for animal models or humans. Both of these topics were addressed further in the discussions on the second day, summarized in section 2.

Emerging Pharmacological Therapies for Glaucoma

Arthur H. Neufeld, Ph.D.

Dr. Neufeld began his presentation with three position statements intended to evoke discussion. First, he believes that pharmacological lowering of intraocular pressure (IOP) using small-molecule drugs (less than 300 daltons) has achieved about as much as can be expected. Very good drugs for IOP lowering have been introduced in the past decade or so, capping 125 years of work on the problem; Latanaprost and other prostaglandin-like compounds now provide a once-a-day treatment with minimal side effects. Second, serendipitous findings of useful therapeutic agents can be very informative. Drugs that were initially developed and tested for one purpose, such as treating hypertension, cardiovascular disease, or cancer, may have significant benefits for other conditions such as RD disease. Third, research on pharmacological neuroprotection must be aimed at causative factors, rather than preserving cells that may have already lost functionality.

In his own work, Dr. Neufeld has moved from working on IOP-lowering drugs to neuroprotective agents that prevent the loss of RGCs in later-stage glaucoma. An ideal neuroprotective drug for glaucoma would do the following:

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[1]Dr. LaVail's response to this question was based on unpublished studies.

- Prevent or treat optic neuropathy
- Provide a complementary, adjunct therapy to lowering IOP (e.g., in primary open angle glaucoma) or an alternative (e.g., in normal pressure glaucomas)
- Slow progression of visual field changes
- Not interfere with or alter aqueous humor dynamics
- Treat patients who do not respond to, or are unable to take, IOP-lowering drugs.

The type of drug could be a small molecule, a larger biomolecule (such as a protein or growth factor), or a gene-targeting drug. The delivery approach might be local (topical, intraocular, or periocular) or systemic. To achieve practical, usable results in the near term, Dr. Neufeld believes the best prospects for glaucoma neuroprotection lie with a small-molecule drug delivered systemically.

Part of the problem in developing a neuroprotective drug is that the slow, progressive course of adult-onset glaucomas increases the difficulty and cost of clinical studies. Even if a drug seemed to be an excellent candidate for a large, multicenter trial, deciding on appropriate endpoints to test its effect clinically would be difficult. The endpoints should be clinically relevant, easily determined in the clinical setting, readily standardized, and acceptable to government agencies (regulators and funding sources). Because Dr. Neufeld suspects that onset and progression of glaucoma involve different sets of biological events, a critical question for designing a trial and selecting endpoints is whether to test for onset or progression.

Dr. Neufeld sees two reasonable research paths to finding a neuroprotective agent for glaucoma or other RD conditions. The "hard work" option is research based on understanding and targeting causative factors. This is a high-risk, expensive approach that has a long time frame for achieving success. He summarized recent work and the current scientific evidence for nine approaches, including current IOP-lowering drugs, antioxidants, agents that block a step in the pathway to cell toxicity, and neurotrophic factors.

However, Dr. Neufeld hopes that a good neuroprotective agent can be found by the alternate pathway, which relies on "good luck" in finding informative observations already made during testing of therapeutic agents for other purposes. These *serendipitous findings* can be far less expensive and risky than the more standard research on causative factors to find a new agent. Familiar examples of drugs found through serendipity include minoxidil, which was be-

ing tested for hypertension when the association with hair growth in some subjects was observed, and sildenafil (marketed as Viagra®). Among ophthalmic examples, the use of acetazolamide as a diuretic to treat systemic hypertension was the basis for testing it in topical formulation for lowering IOP. The use of timolol for lowering IOP originated in observations that patients taking beta blockers for systemic hypertension had lowered IOP. The lesson from these serendipitous findings is that some of the drugs that patients are taking for a systemic disease may be helping their optic neuropathy associated with glaucoma or another RD disease. An analogy is the National Cancer Institute's program for screening a wide variety of drugs, used or tested for other purposes, for positive effects in treating cancers.

With respect to the hard work option of biomedical research on causative factors, Dr. Neufeld discussed the rationale and results to date in his own work on inhibiting nitric oxide toxicity. From his detective work on how RGCs are being killed in the optic nerve head during later stages of glaucoma, a key culprit (causative factor) appears to be inducible nitric oxide synthase (iNOS) (42). This enzyme, which can be produced by glial cells, mediates production of nitric oxide, which attacks RGC axons. In glaucomatous optic nerves, he has observed many more glial cells and increased presence of iNOS, particularly bordering the nerve bundle regions.

Dr. Neufeld's hypothesis is that excessive nitric oxide, produced by iNOS in reactive astrocytes (glial cells) in the optic nerve head, causes glaucomatous optic neuropathy. Increasing the hydrostatic pressure on human astrocytes cultured in vitro from the optic nerve head increases iNOS production. In a rat model, iNOS is readily detected in the optic nerve head after 4 days of exposure to elevated IOP in one eye (with the other eye used as the control) (43). Subsequently, progressive loss of RGCs occurs in areas showing increased iNOS. In pharmacological studies using this rat model for glaucoma, a treatment group was administered aminoguanidine, an iNOS inhibitor. Whereas fundus photographs of the untreated group clearly display cupping at the optic nerve head characteristic of neural degeneration in advanced glaucoma, the treatment group shows no degeneration (44). A protective effect (negligible further loss of RGCs) from treatment with another iNOS inhibitor was observed even when treatment began 3 months after the start of elevated IOP exposure (figure 3). This drug is entering a clinical trial now, but not for glaucoma treatment.

Dr. Neufeld next discussed the effects of aging on RGC loss. From literature data on age-related RGC loss in monkeys and humans, together with his laboratory results on mice and rats, he found that each species loses on aver-

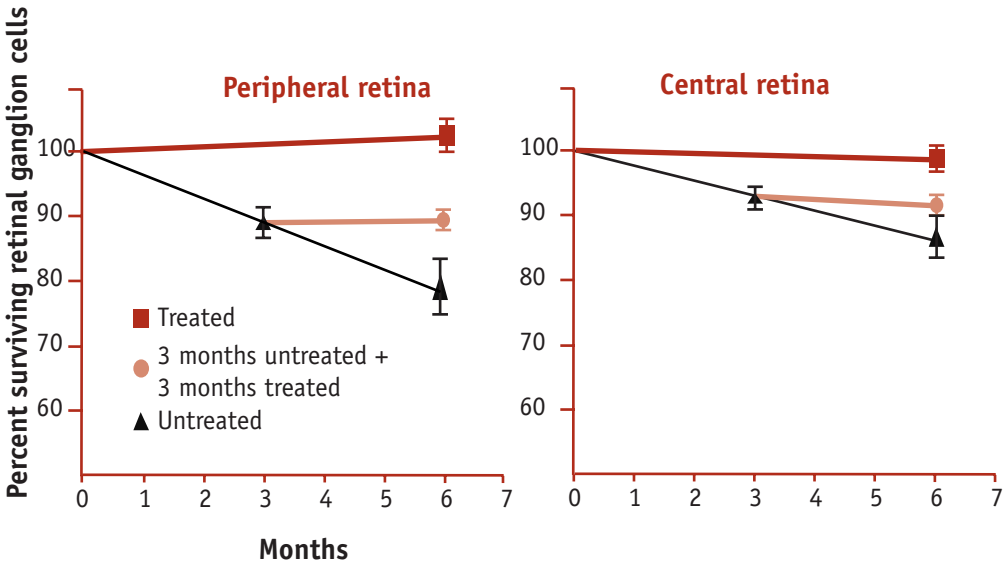

FIGURE 3. Effects of iNOS inhibitor on loss of RGCs in rat glaucoma model.

age about 40 percent of its RGCs during its full life span (from 36 percent in rats to 43 percent in monkeys). To test his hypothesis that the RGCs in older animals might be more resistant to neurotoxic effects, he exposed groups of both young and old animals to elevated IOP. The effect observed was opposite the effect hypothesized. When rats at 3 months and 24 months received a single retinal ischemia/reperfusion treatment, in which the ocular pressure was raised above systolic pressure for 75 minutes, the RGC cell loss 7 days later in the older animals was twice that of the younger group (40 percent loss versus 20 percent) (45).

Interesting results were also obtained with rats and mice on caloric-restriction diets (fed 3 days a week only) versus controls fed ad libitum (46). In rats, caloric restriction is known to be cardioprotective and neuroprotective, to decrease cancer tumors, and to increase life span. In both rats and mice, age-related RGC loss was less for the groups on caloric restriction all their lives. In addition, rats on caloric restriction for 3 months prior to a single retina ischemia/reperfusion exposure had decreased loss of RGCs and displaced amacrine cells, compared with controls. Histologic examination showed that older animals on the control diet had more intensive staining (indicating activation) of glial elements than either younger rats or older rats on caloric restriction. The ischemia/reperfusion treatment increased activation, but caloric restriction lessened the increase. In preliminary work on how caloric restriction provides neuroprotection, Dr. Neufeld has found that it may induce human heat shock protein (HSP-70). One day after one ischemia/reperfusion exposure, young animals increase the production in RGCs of BDNF, a neuroprotective factor. Old animals do not show increased BDNF af-

ter 1 day, but do after 5 days. This increase is greater in older rats on caloric restriction.

During the discussion, participants asked about the effects of other drugs and antioxidants on nitric oxide concentration in the optic nerve head. Prospects were discussed for a drug that would both protect the RGCs in the optic nerve head and lower IOP by protecting cells in the trabecular meshwork (which mediates outflow from the atreous chamber of the eye). Dr. Neufeld agreed that such an agent would be a good candidate for trial, since the FDA would accept IOP lowering as a clinical endpoint. But he doubted that inhibiting nitric oxide would be relevant to typical pathways leading to blockage in the trabecular meshwork. This led to discussion of the lack of clinical evidence for marketing claims that some IOP-lowering drugs are also neuroprotective. Dr. Neufeld noted the importance of being able to measure progression of neurodegeneration in a clinical trial and emphasized that this measurement will be key to assessing the efficacy of a neuroprotective agent for chronic conditions like glaucoma.

Another question concerned the mechanism of neurodegeneration in normal-tension glaucoma (glaucoma not associated with above-normal IOP). Dr. Neufeld has only been able to study optic nerve and retinal tissue from two patients who had well-documented normal-tension glaucoma, but both cases showed that iNOS was present.[2] He therefore suspects that iNOS induction and nitric oxide toxicity occur in this form of glaucoma, as well as in forms associated with elevated IOP. He agreed with a suggestion that glial cells in glaucoma may also perform less of their normal caretaking functions for RGCs. However, his work indicates that increased production of destructive molecules such as nitric oxide is actively killing the RGCs by destroying their axons. Other issues discussed were the best quantitative measures for neuroprotection in laboratory experiments and the potential importance of changing the paradigm for RD laboratory tests on animal models to include older animals. Dr. Neufeld believes that old animals have a background of susceptibility to retinal and neural damage that may give very different responses than are found with young animals.

Development of New Treatments for Choroidal Neovascularization

Peter A. Campochiaro, M.D.

Dr. Campochiaro distinguished retinal neovascularization, for which diabetic retinopathy is the paradigm, from choroidal neovascularization (CNV),

[2]Unpublished observation.

which occurs in diseases such as AMD or diabetic macular edema (DME) that cause abnormalities in the interface between Bruch's membrane and the RPE. In CNV, abnormal blood vessels originating in the choroid grow under the retina. These blood vessels are prone to bleeding (leakage), which causes scarring. These effects eventually lead to irreparable loss of central vision due to scarring of the macula, the small area on the human retina that provides sharpest vision. The use of a laser for photocoagulation of CNV has been the standard treatment since clinical trials demonstrated that this treatment is better than no treatment at all. However, CNV recurs within a year in 40 percent of patients who receive the "hot" laser treatment. In 5 years, it recurs in 55 percent of treated patients (17). Recurrence typically leaves the patient with very poor vision.

As one of several animal models for CNV, Dr. Campochiaro's group uses an adaptation of the monkey model developed by Dr. Steven Ryan, in which a laser is used to rupture Bruch's membrane (50). A second model the group uses is a transgenic mouse, in which a gene for vascular endothelial growth factor (VEGF) is driven by the rhodopsin promoter. This hVEGF transgene increases expression of VEGF by photoreceptors enough to cause neovascularization. Although these blood vessels originate in the deep capillary bed of the retina, rather than from the choroid, they grow into the subretinal space and act like the CNV blood vessels that grow there through an abnormality in Bruch's membrane. Because VEGF promotion alone is sufficient to cause this neovascularization, the group studied VEGF antagonists as potential anti-CNV agents. The first agent studied was protein kinase C-412 (PKC412), which inhibits VEGF receptors, as well as other receptors. PKC412 inhibited retinal neovascularization in a mouse model (retinal neovascularization from oxygen-induced ischemia) and inhibited neovascularization essentially completely in a CNV mouse model (laser rupture of Bruch's membrane) (51, 52). To determine if the blocking of VEGF receptors was solely responsible for the effects observed, the group studied other receptor kinase inhibitors. The VEGF receptor kinase inhibitors suppress CNV in the mouse model, but inhibitors of the receptors for platelet-derived growth factor (PDGF) do not.

PKC412 also suppresses VEGF-induced leakage, which the group hypothesized was a major factor in DME. (The details of the resulting multicenter clinical study of PKC412 [49] were described by Dr. Robert Frank in the next presentation.) Retinal thickening (a sign of DME), as measured by optical coherence tomography (OCT), was markedly decreased in the PKC412 treatment group. One of the three dose groups also had improved visual acuity during the treatment. Although oral administration of PKC412 benefited

some DME patients in this trial, some patients had nausea and vomiting and a few had elevated liver enzymes, indicating liver toxicity. So the next approach tried in animal studies was local delivery of PKC412. Microspheres containing the PKC412 were injected under the conjunctiva in a pig model for CNV. The sustained release from the microspheres resulted in sustained levels of PKC412 in the eye. Both of the concentrations tested decreased the area of CNV relative to controls injected with vehicle only, although the concentration at the retina was only beginning to build at the time selected for testing efficacy (10 days after injection).

Selectivity is a problem with using any VEGF receptor kinase inhibitor because of similarities in the receptors for various growth factors. Another approach that Dr. Campochiaro's group studied is the use of an antibody, or another similarly highly specific antagonist, to either VEGF or its receptors on cell membranes. In collaboration with scientists from Regeneron, they used a fusion protein that combined elements of the ligand-binding domains of two VEGF receptors (receptor 1 and receptor 2) with a very small antibody. This agent, VEGF-TRAP$_{R1R2}$, was tested using subcutaneous injection in a laser-induced mouse model for CNV and in the rhodopsin-hVEGF transgenic mouse. From the positive results, the group concluded that increased expression of VEGF is sufficient to cause neovascularization originating from the deep capillary bed and that interruption of VEGF signaling provides a good target for treatment of CNV.

Dr. Campochiaro described two clinical trials in progress in which VEGF antagonists are being administered by intravitreal injections to patients with subfoveal CNV. In the phase 1/2 trials, most patients receiving the candidate agents were stable or improved, with about a fourth of them having visual acuity improved by three lines or more (in reading a standard eye chart). The phase 3 or phase 2/3 trials are in progress now.

A candidate anti-CNV agent that works by a completely different mechanism is a tubulin-binding agent, combretastatin A-4 phosphate (53). In cell culture, it alters the shape of endothelial cells. In animal models, it specifically affects immature blood vessels and promotes thrombosis (formation of a fibrous clot). In the laser-induced mouse model of CNV, neovascularization in the group treated with combretastatin A-4 phosphate regressed after 2 weeks. This ability to cause regression of the CNV is a potential advantage over the VEGF antagonists. The best approach may be to use combretastatin first, to cause regression, followed by VEGF antagonists to prevent recurrence. A phase 1/2 trial of combretastatin for patients with neovascular AMD has just begun. Treatment is by four intravascular injections delivered a week apart.

Dr. Campochiaro reviewed work with adenoviral vectors for gene transfer of endogenous CNV inhibitors, including agents as large as pigment epithelium–derived factor (PEDF), a protein of about 50,000 daltons. Although this vector type does not persist as long as the AAV vectors, he sees it as valuable initially, when the long-term effects of administering agents in this way are still being studied. Animal studies with intravitreous adenoviral-gene transduction to express PEDF showed efficacy in suppressing CNV, even causing regression (figure 4). GenVec has a phase 1 dose-estimating trial of an adenoviral PEDF vector in progress on patients with subfoveal CNV due to AMD.

Alcon is now in clinical trials with an angiostatic steroid, anecortave acetate, as an antineovascular agent. Alcon's phase 2 trial of anecortave acetate demonstrated some benefit compared with untreated controls, but the effects were not as good as with some of the anti-VEGF agents. A phase 3 trial will test injection of anecortave acetate versus photodynamic therapy in patients with high risk of CNV. The hope is that it will prove to be a good preventative agent for suppressing neovascularization, as it can be delivered outside the eye and no systemic toxicity has been observed.

In concluding, Dr. Campochiaro said that VEGF is known to play an important role in CNV. There is mounting evidence that it is important in DME as

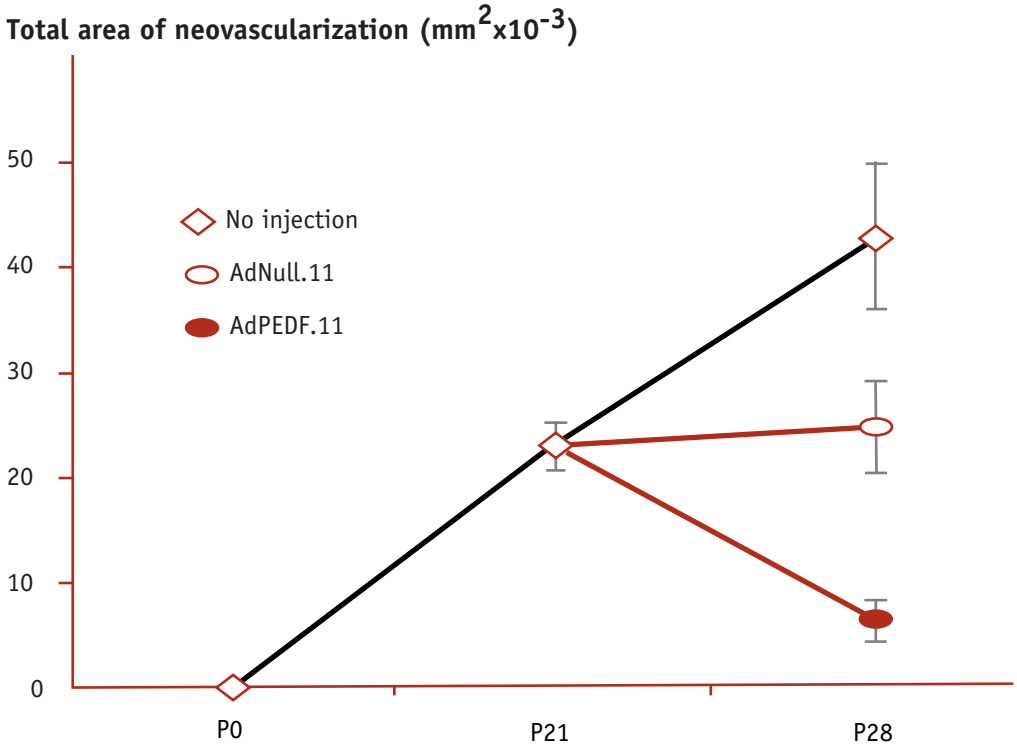

FIGURE 4. Intravitreous injection of AdPEDF.11 causes regression of subretinal neovascularization in rhodopsin/VEGF transgenics. *Source:* Peter A. Campochiaro.

well, and trials of anti-VEGF agents for DME are being planned. He thinks that intraocular injection will continue to be used as long as it is efficacious and until a less invasive but equally effective means of delivery is proven. Still unknown are the long-term consequences of treatment using anti-VEGF agents. He expects a number of pharmacological agents will go to clinical trial over the next several years, potentially including gene therapy approaches. Gene transfer of endogenous inhibitors is a promising approach that can combine local delivery, sustained release, and CNV regression as well as simple suppression of new growth.

Dr. Campochiaro agreed with a discussion comment about the potential for periocular delivery of antineovascular agents, including those as large as PEDF. Adenoviral vectors for PEDF expression have been used to transduce cells outside the eye. The PEDF produced by these cells reaches the choroid and inhibits CNV, with substantial CNV regression. Dr. Campochiaro described his work with Dr. Hauswirth on sustained delivery using a viral vector and periocular delivery. GenVec is planning a trial for periocular injection of a PEDF vector. For periocular delivery of small molecules, a useful complement is sustained release, as in the microspheres used for delivery of PKC412. From a practical standpoint, sustained release is important for small-molecule therapy. Dr. Ferris added that good results in getting therapeutic agents to the retina have also been obtained with subconjunctival implants. Because of the difficulty in getting agents across Bruch's membrane, transport via the sclera and the vitreous may be easier than transport via the choroidal circulation. Dr. Campochiaro replied that smaller agents such as PKC412 can reach the retina in therapeutic concentrations via the choroid. Periocular delivery of adenoviral vectors has produced high retinal concentrations of a PEDF recombinant protein. The participants discussed an ongoing trial in Mexico of another small-molecule antineovascular agent, the aminosterol squalamine, which causes regression of CNV membrane. Because this agent is delivered systemically, it protects both eyes from CNV. The potential for systemic toxicity of anti-VEGF agents was discussed. Earlier concerns about the risk of ischemic heart disease do not appear to be confirmed in clinical trials.

Prevention of Neovascularization in Diabetic Retinopathy and Corneal Disease

Robert N. Frank, M.D.

Dr. Frank began by emphasizing that the best way to prevent retinal neovascularization is to prevent the preceding retinopathy. Diabetic retinopathy can be prevented by maintaining blood sugar at near-normal levels (near-

normoglycemia) and, at least in type 2 diabetes, maintaining blood pressure in the normal range. Dr. Frank noted some anecdotal evidence that there may be a point after which progression of retinopathy cannot be halted or reversed even if glycemia is controlled. Other participants agreed that vitreous hemorrhages after photocoagulation are not uncommon. However, an unsettled question is whether there is a point after which disease progression is inevitable, despite apparently optimal glycemic control.

Dr. Frank reviewed results from the Diabetes Control and Complications Trial on controlling glycemia to prevent diabetic retinopathy (47). Intensive treatment to maintain normoglycemia had a substantial effect over time (eight or nine years), whether as primary prevention or secondary intervention, but the difference from the control group does not begin to emerge until two to three years after treatment begins. The results indicate a long delay from onset of normoglycemia to a clearly beneficial effect. In the United Kingdom Prospective Diabetes Study, although the difference in glycemia levels with intensive control and conventional control was small in subjects with type 2 diabetes, there was a large difference in the relative risk of a two-step progression to retinopathy or of requiring retinal photocoagulation. Similarly, tighter control of blood pressure cut the risk in half of a two-step deterioration or a three-line loss of visual acuity, even though the blood pressure reductions were modest.

When proliferative diabetic retinopathy has progressed to retinal neovascularization, pan-retinal photocoagulation is the best current treatment. It reduces the occurrence of severe vision loss by 50 percent 5 years after treatment (48). Attempts to treat diabetic retinopathy by interfering with pituitary growth hormone dates back to surgical pituitary ablation in the 1950s. Now, drugs that block the action of growth hormone offer a more selective approach. A clinical trial of one such drug, octreotide, is in progress. Dr. Frank suggested that a combination of hormone blockers might provide greater efficacy with less risk of complications. Antioxidants are of interest as a treatment for many complications of diabetic retinopathy but have not yet been tested in an appropriate population. Among drugs tested that were unsuccessful have been aldose reductase inhibitors (those tested by systemic administration were unable to cross the blood–retina barrier and were ineffective). Another is aminoguanidine, which was withdrawn from clinical trial for diabetic nephropathy. One form of protein kinase C inhibitor also was unsuccessful.

Blockers of VEGF receptors are of interest because of VEGF's role in angiogenesis and the view that VEGF induces macular edema by increasing leak-

age as well as vascularization. A trial of one anti-VEGF agent was halted because of toxicity, but others may be effective. For example, cyclooxygenase-2 (COX-2) inhibitors have been suggested because COX-2 increases VEGF production. The workshop participants commented that suppression of VEGF by this route would likely be modest. Dr. Frank reviewed the results from the DME trial with PKC412, which Dr. Campochiaro had also discussed, and said the results support a linkage between vascular leakage and neovascularization (49).

A promising new treatment for macular edema in diabetic retinopathy and other conditions is intravitreal injection of steroids. Some patients seem to have recovered visual acuity after treatment, and their macular edema was decreased. One steroid, triamcinolone, will be the therapeutic agent under consideration in a DME trial (part of the DRCR.net program discussed in section 2).

New diagnostic modalities, particularly OCT for measuring macular thickness, are emerging as methods for quantifying outcomes, evaluating putative mechanisms, and testing efficacy of therapies. Others include videoangiography and scanning Doppler laser for evaluating retinal blood flow, as well as magnetic resonance measurements of retinal oxygenation. Functional magnetic resonance imaging of oxygenation is important because of the putative role of ischemia and hypoxia in neovascularization.

Turning from retinal to corneal neovascularization, Dr. Frank noted that neovascularization is a serious problem in inflammations of the front of the eye. It can make the cornea opaque, and, together with increased antibody presence, it makes corneal transplantation to treat the opacity more difficult. The mechanisms of corneal neovascularization appear to be similar to those in the retina or choroid, so a similar range of strategies to treat it has been proposed. These strategies include topical application of steroids (already used to block rejection of corneal transplants), photodynamic therapy (tested in animal models for corneal transplant), an anti-angiogenesis aptamer (a modified fragment of ribonucleic acid that binds to the VEGF molecule and inactivates it), and gene therapy to transduce an antiplasminogen agent.

In his summary, Dr. Frank pulled together the threads common to investigations of, and proposed therapeutic strategies for, neovascularization behind the retina, at the retina, and in the cornea. Because the mechanisms of neovascularization in the choroid, retina, and cornea are likely to be similar, a unified theory of ocular neovascularization is a reasonable prospect. Similar therapeutic modalities, grounded in this common explanatory framework, may well be effective in all three locations.

During the question period, Dr. Frank agreed with the suggestion that OCT should replace manual grading of stereoscopic fundus photographs as the gold standard for macular edema in clinical trials. He is convinced that OCT gives reproducible results and is safe, efficacious, and easy and simple to use in a clinical setting. The PKC412 trial for DME, for example, showed that improvement in visual acuity correlated with decreased edema as measured by OCT. He expects the upcoming trials of intravitreal steroids to confirm this linkage. However, as another participant noted, the FDA has been reluctant to accept reduction of retinal thickening as an outcome variable, preferring a functional endpoint (currently, a change in visual acuity by three lines on a standard eye chart). To gain approval of OCT as a clinical endpoint, he said, a sustained campaign of careful studies is needed to establish the association of visual function with edema as measured by fundus photography and by OCT.

The participants discussed the suitability of animal models for human diabetic retinopathy. Dr. Frank said that the dog models are the closest to human diabetic retinopathy, but studies with large numbers of dogs are difficult and expensive. A good mouse model would be useful, for example, particularly if it allowed transgenic and knockout studies. There are reasonably good models for retinopathy of prematurity, but no good models for macular edema because most species, other than humans and higher primates, lack a macula.[3]

On a related but different issue, the participants discussed the need to improve societal delivery of accepted therapies to the population at risk, in terms of getting patients that need treatment to an ophthalmologist for care. Once a patient is under care and the condition is recognized, laser photocoagulation to treat proliferative diabetic retinopathy is simple and generally well tolerated by the patient.

Stem Cells and Retinal Transplantation

Michael Young, Ph.D.

For purposes of his presentation, Dr. Young characterized a stem cell, or progenitor cell, as a primitive cell in the body that is both *pluripotent* (it can differentiate into many specialized cell types) and *self-renewing* (when a stem cell divides, it produces more stem cells). Stem cells may come from a blasto-

[3]The need for better animal models for diseases of the macula was addressed in the workshop on implementing AMD research (2). The summary from that workshop includes a basic discussion of the important roles for animal models in understanding complex ocular diseases with a strong genetic component and testing therapeutic approaches for them, including gene therapies.

cyst (embryos at approximately 5 days) or from embryonic germ cells (from the urogenital ridge at 5 to 9 weeks). Tissue-specific stem cells can be isolated from differentiated tissues, such as neural tissue (the central nervous system and retina, for example), bone marrow, or skin. These tissue-specific stem cells can be isolated from postnatal or adult animals, as well as from embryos. They are pluripotent only for cell types that compose the source tissue type. Although researchers have had only limited success in controlling the differentiation of embryonic stem cells or germ cells, control of differentiation in tissue-specific stem cell lines has been more successful.

The work done by Dr. Young's group has focused on transplanting stem cells derived from neural or retinal tissue into the retina of animal models of RD diseases. The aim has been to replace damaged or lost photoreceptors, not the entire retina. Replacing photoreceptors could have substantial therapeutic value because RGCs often retain their functional connections to the visual cortex well after all the photoreceptors are lost. The secondary cortical structures are not damaged. Once all the photoreceptors die, Dr. Young said, the retina loses its remaining functional structure over time and eventually can resemble a glial scar. But before that point, the retina is receptive to input of stem cells, and visual function could be saved.

In the late 1980s, studies were performed and published in which an entire retina was transplanted in the brain close to the ganglion cells' neural targets in the brain stem (24). RGCs in the graft grew axons that established functional connections with their midbrain targets. Grafts of healthy retinal tissue placed into the retina itself have not succeeded, in large part because the grafted neurons fail to integrate functionally with the host retinal tissue. By using stem cell grafts, Dr. Young's group has shown that this particular obstacle can be overcome. However, the work has presented a new set of obstacles, most of which revolve around achieving the desired differentiation of immature grafts into healthy, functional photoreceptor cells.

Neural stem cells are isolated from central nervous system tissue by their proliferation in response to high levels of growth factors and can be greatly expanded through multiple subcultures (passages). After isolation, these stem cells can form neurons, oligodendrocytes, and astrocytes (25). A seminal study by Dr. Young's group, in collaboration with Dr. Fred Gage's group at the Salk Institute, was to see if neural stem cells could be used to replace dead retinal cells (26). Stem cells from the adult rat hippocampus were transplanted into one eye of adult normal and RCS rats, a model of RD disease. The grafted cells colocalized with neurons in the outer plexiform layer and sent neurites into the optic nerve (where RCS rats lose their RGCs). When a

lesion was made in the retina of normal rats at the time of transplantation, the grafts grew into the ganglion cell layer, internuclear layer, and photoreceptor layer. Although the cells that grew in the photoreceptor layer looked like photoreceptor cells, they did not express photoreceptor-specific proteins. The only markers found were those also expressed in the rat hippocampus.

Next, the group tried exposing the stem cell grafts to developmental cues by transplanting into a host retina still in an early developmental stage (27). This approach has been most successful with mouse brain stem cells transplanted into postnatal South American opossums. There is a much higher level of morphological differentiation than in the transplants into adult retinas. However, only in models for very early development (such as the postnatal opossum model) have photoreceptor markers been found. These results led Dr. Young's group to concentrate on isolating and transplanting retinal stem cells. They have succeeded in isolating stem cells from developing neurosensory retinal tissue in one-day-old rodents (28). These retinal stem cells self-renew in vitro and are capable of differentiation into at least partially differentiated cells. For example, they develop into neuron-like and astrocyte-like cells when exposed to serum in vitro. With specific treatments, they can be induced to demonstrate characteristics seen in other retinal cell types. When grafted to the subretinal space of adult retina in a model for an RD or retinal injury condition, the differentiated cells resemble photoreceptors morphologically. They also produce recoverin and rhodopsin (photoreceptor markers).

Dr. Young's group has studied transplantation of retinal stem cells into pig retinas because the pig eye is much like that of a 12-year-old human, except that it lacks a true macula (29). Mouse retinal stem cells were tried first, but the immune response rejection of the foreign tissue, although delayed, eventually destroys the graft. In the interim, the transplanted cells grew into the laser-induced lesion in the host retina and integrated within the RPE layer and nuclear layers. Neurites from the integrated cells grew into the plexiform layer. Members of the collaborative team working with Dr. Young are now isolating pig retinal stem cells, using the same technique used to isolate tissue-specific cells from rodents. The source of neuroretinal tissue is 60-day embryos (about the middle of gestation). When the growth factors are removed and the isolated cells are cultured with serum on laminin, they express recoverin and rhodopsin. This leads Dr. Young to hypothesize that the isolated cells are predominantly progenitor cells for rod photoreceptors. These progenitor cells survive grafting into the subretinal space of mature pigs with laser-induced lesions (the host model). They develop into cells having characteristics of photoreceptors and glial cells, and they send neurite-

like projections into the host retina. Recently, retinal progenitor cells from transgenic pigs that express green fluorescent protein have been isolated (30). Using these cells in grafts will increase the researchers' ability to track the grafted cells and their neurites as they differentiate and incorporate into the host tissue.

Dr. Young concluded with a set of questions still to be answered about retinal stem cell transplants. What are the limits to stem cell expansion by culturing with growth factors, and are the stem cells expanded in this way truly normal? For example, will their differentiated progeny be normal, or will they form tumors eventually because the cell cycle control mechanisms have been transformed? Another approach might be to initiate and control in vivo self-repair, as occurs in fish, if these stem cells occur naturally in the body. Can any of these approaches restore or preserve functional vision in animal models of RD disease? These questions and more relate to the ultimate question: Is stem cell therapy safe and effective?

During the discussion, Dr. Neufeld asked if cells from passages earlier than passage 6 to 8, which Dr. Young uses, could be used and, if so, would they differentiate more successfully. Dr. Young said that the problem with early-passage cells is immune rejection of the graft because of contaminating cells that remain in the culture. More passages are also needed to acquire cells with sufficient plasticity to adapt to a new environment. Dr. de Juan asked whether transplants of retinal stem cells might induce proliferation by the host tissue of its own stem cell population. Dr. Young said that signs of this had never been observed in his group's work, but both participants agreed that finding evidence of it would be complicated and difficult.

Capacities of Retinal Neurons to Regenerate Injured Axons

Albert J. Aguayo, M.D.

Dr. Aguayo began with an overview of work in regenerating axons in the mammalian central nervous system. Understanding what happens in the spinal cord and brain, he said, has implications for any strategy for growing axons from the eye up to the appropriate cortical and subcortical structures to restore visual function. Five general requisites for recovery after a neuronal injury—whether to the brain or the eye—are cell survival, regrowth of the axons, long-range pathfinding of the growing axons, appropriate connectivity to their targets, and useful function after these connections are made. In development, a number of strategies are used to meet this complicated set of requirements, including retraction of neural branches, elimination of neuronal projections, and even selective cell death. For many axonal trajectories,

including those from the retina, the growth sequence and spatial pattern must be defined accurately with respect to crossing sequences. An interesting point about the eye is that some animals are able to regenerate these connections naturally. Fish, amphibians, and even newborn rodents can recover some degree of visual function, measured by behavior, after an optic nerve is cut (55). In certain reptiles, axons will also grow massively after transection of the optic nerve, but there is little restoration of function because appropriate connections are not made at the tectum. In most species, when peripheral nerves are cut, the axons will grow, but they make anomalous connections with their sensory and motor targets (56).

A condition for injured peripheral nerve axons to extend over long distances is the presence of sheath cells (Schwann cells) and a rich extracellular matrix along their course. Sheath cells facilitate axon elongation during regrowth but do not appear to provide the guiding clues that can lead them back to their precise targets. As an axon grows, it induces many Schwann cells to differentiate and form the myelin sheath or adopt the configuration of non-myelinated fibers (Remak fibers). Dr. Aguayo noted some of the known genes that express proteins involved in the interaction between the advancing neuronal growth cone, nearby Schwann cells, and the extracellular matrices.

A molecular gradient of neurotrophic factors may also help propel and guide the growth cone. By expressing specific receptors, different classes of neurons may respond only to certain growth factors in this process. For example, mammalian RGCs predominantly express the trkC receptor for BDNF and NT4. The formation of myelin by mature Schwann cells is associated with the expression of growth-inhibiting proteins such as myelin-associated glycoprotein, but in the peripheral nervous system this effect is likely to be neutralized by the presence of many growth-promoting molecules. On the other hand, the non-neuronal environment of the adult mammalian central nervous system (including that of the optic nerve) is rich in inhibitory molecules that block axonal extension after injury. Damaged astrocytes and the myelin produced by oligodendrocytes appear to be the main source of these growth-inhibiting factors (57–61). The number of known neuronal growth inhibitors is rapidly increasing. Many of them may play a role in guiding development, such as signaling when and in what direction a growing axon should turn. In mature animals, some of these molecules may inhibit axonal extension after axons are cut. In short, the response of the nerve fibers to injury represents a balance of interactions involving growth inhibitors and promoters.

Dr. Aguayo summarized results that he and his colleagues obtained in experiments to investigate the intrinsic capacity for regeneration and

reconnection of RGC axons cut in the optic nerve of adult rodents. It is well known that mammalian RGCs may regrow within the retina but do not extend down the optic nerve. A massive die-off of RGCs occurs after the optic nerve is cut near the eye. If the transection is very close to the optic nerve head in the retina, the majority of RGCs (90 percent) will die within two weeks. If the nerve is cut further down, the neurons die more slowly. The team has been able to delay this die-off with neurotrophic factors delivered directly or by viral vectors, but only by a few days at most (62).

In these experiments, changing the environment of the RGC axons from what is normally present in the optic nerve to an environment similar to peripheral nerves allowed the axons to regrow long distances and reconnect with neurons in the superior colliculus of these animals. This change was achieved by introducing a bridging graft of sciatic nerve tissue that contains denervated Schwann cells but no neurons, to serve as a substitute path for axon regrowth. Similarly, transplants of olfactory ensheathing glia have been shown to provide a substrate that permits the regrowth of axons in the central nervous system (63). However, those experiments were done in the spinal cord and not in the optic nerve. The sciatic nerve bridge extended mostly extracranially from the transection point in the optic nerve to the superior colliculus in the midbrain. The RGC axons that normally do not regenerate after injury grew a long distance within this peripheral nerve graft. In adult rats, the normal distance from the back of the retina to the superior colliculus is only about 2 cm. The RGC axons regenerated through bridges that were 4 to 12 cm long. In these experiments, as many as 12 percent of the RGCs extended through the bridge and made synapses in the colliculus, although the usual number was around 3 to 4 percent (64). Dr. Aguayo thinks that massive apoptosis of the other RGCs limits the number available for this lengthy regrowth of axons. It remains unproven, however, whether all RGCs are capable of regenerating in a similar way to that shown in these experiments.

In the targeted superior colliculus, the axons that grow through the bridge graft of sheath cells extend only 1–2 mm beyond the end of the bridge before they stop growing within the environment of the central nervous system. However, within the short course they cover within the central nervous system, they make synapses that are anatomically indistinguishable from normal connections. These synapses are formed whether or not the superior colliculus is denervated. Electrophysiological and behavioral studies of animals that have had their optic nerve axons regenerated through a bridge graft show that these connections can be functional and elicit transynaptic activity in collicular neurons when the retina is stimulated by light (65). These animals have been reported to show a slow pupillary response to light

and to exhibit light-avoidance behavior (indicating ability to discriminate light from dark).

From these results, Dr. Aguayo concludes that, in the adult mammalian retina, some of the RGCs appear capable of replicating growth capacities normally expressed during central nervous system development or in regenerating peripheral nerves. This capacity is unleashed when the environment at the neural growth cone permits, and perhaps stimulates, growth, rather than inhibiting it. In summary, Dr. Aguayo said, the field of optic nerve regeneration has advanced a great deal, but major problems remain. Severe loss of nerve cells occurs in a relatively short time, and there is limited regrowth even in the best of cases. If regrowth can be achieved, how can the axons be guided to the appropriate synaptic targets? Long-range pathfinding (directing the growing axon to the right target) is a research field that will have major implications for future efforts to reconstruct neuronal circuitries capable of yielding a predictable and beneficial recovery of function.

During the discussion, Dr. Aguayo answered questions on the state of knowledge about the multiple proteins that inhibit or facilitate growth in the context of axon extension. Dr. Aguayo also addressed the difficulties and dysfunctional consequences of attempting to stimulate axon regrowth in the retina by placing Schwann cells in the subretinal space. He stressed the need for additional basic research as a key element in laying the foundation for future therapies in humans.

Drug Delivery: On the Threshold of an Adventure

Vincent H. L. Lee, Ph.D.

Although the drug delivery process is important to a therapeutic approach, Dr. Lee said it is too often treated as an afterthought. The goal of drug delivery is all about *location*, *timing*, and *duration*. On timing, a common assumption is that all therapies benefit from maintaining a constant concentration of the active agent at the target site. This is not always true. For example, in their normal mode of action, many of the growth factors are not present at one site for long.

In conducting research on drug delivery, the key factors fall into three groups: (1) the delivery package, which consists of the drug or agent, platform, and biomaterials; (2) the microenvironment and the disease state; and (3) the use of animal models or other testing methodology. The second group tends to be underappreciated in designing drug delivery. For instance, timing delivery of the drug for the disease state can greatly influence the therapeutic outcome.

Drug delivery presents options we are just beginning to explore and exploit in ocular therapy. Delivery alternatives being studied include topical, systemic, intravitreal, and transcleral routes (figure 5). Until recently, the lens was as far into the eye as we attempted to deliver a therapeutic agent locally. More ways are needed to bring a therapeutic agent inside the eye and target specific locations within it, such as the retina. To implement effective neuroprotection, for example, the agent must reach the back of the eye. The bioavailability of ocular drugs delivered by eye drops ranges from 0.1 to 10

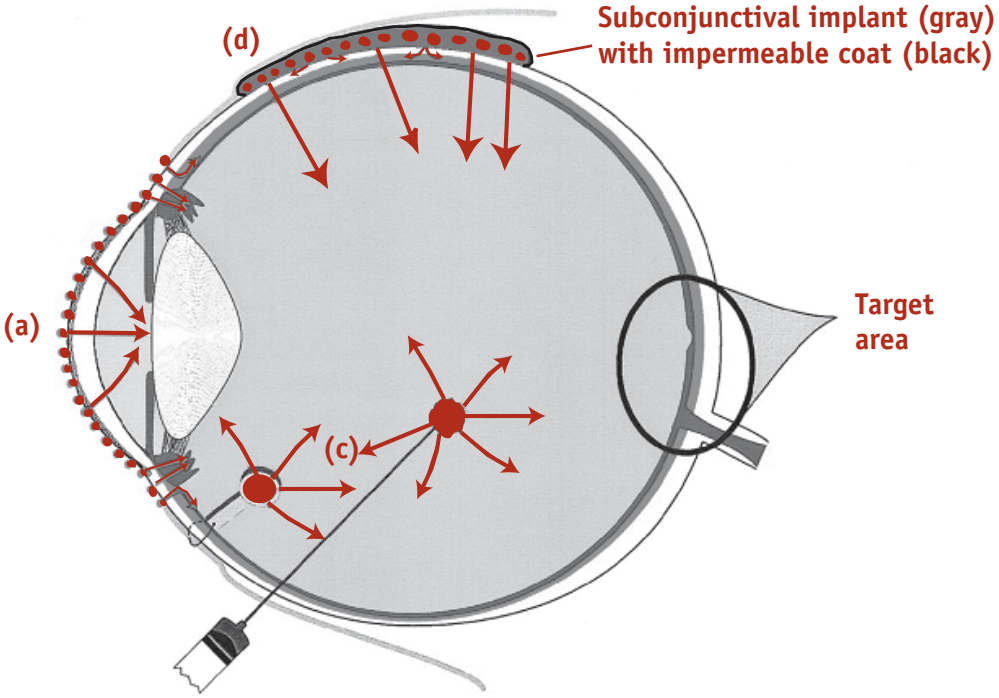

FIGURE 5. Delivery options: (a) topical, (b) systemic (not shown), (c) intravitreal (anchored capsule or injected bolus), and (d) trans-scleral.

percent, with only 1 percent typically reaching the target site. Because of this low level of bioavailability for many targets inside the eye, Dr. Lee believes eye drops will be replaced by more effective alternatives for these targets within 10 years. This may be the right time for a change in the paradigms for ocular therapy, going beyond the accepted options of either topical delivery at the front of the eye or systemic delivery.

Dr. Lee suggested thinking about the eye as a small cavity with different points of access. His own research on topical application at the front of the eye has compared corneal and conjunctival access. The conjunctiva can be an

efficient pathway for delivering some agents to the back of the eye. Penetration rates for some beta blockers, for example, are higher for conjunctival/scleral pathways than for corneal access. For systemic delivery of a therapeutic agent, Dr. Lee said that, since viruses can cross the blood–retina barrier, researchers should think about novel ways to move macromolecules across this barrier.

Distribution of potentially therapeutic agents inside the eye has not been well studied. For example, the half-life of an agent is likely to affect its distribution within the eye over time. It may make sense to design some delivery packages (as defined above) to give the therapeutic agent a much longer half-life at the target location. An example is inserting a wafer package in the subconjunctival space.

At present, many ocular drug candidates were initially developed and selected for oral administration and systemic delivery, with 100 percent bioavailability to the circulation as a preference. When these drugs are considered for ocular applications, the typical delivery platform is topical administration. But if only 1 percent of an eye drop reaches the inside of the eye, what happens to the rest, which may have systemic activities apart from the intended effect on an ocular condition? For Dr. Lee, this approach is asking for trouble, in terms of undesirable systemic effects. He favors reassessing the rejects from the paradigm of oral administration and systemic availability, seeking agents whose characteristics fit well with the drug delivery system and the local environment to which it is delivered. In the next decade, he would like ocular drug delivery techniques to embrace multiple points of access, a library of delivery platforms, an expanded definition of what counts as a drug (to include everything from small molecules to macromolecules), and d*elivery-savvy drugs*. A delivery-savvy drug is one designed to make use of the biology specific to tissues in its delivery location and target environments. Examples include target-seeking agents, which would be designed with sufficient information to find a specific target site via the circulation, and drugs that select specific cells in need of therapeutic intervention.

As an illustration to indicate the potential for delivery-savvy drugs, Dr. Lee discussed drug transporters in tissues that an agent must penetrate to reach its target cells. Transporters in the conjunctival tissue increase the penetration of Brimonidine, a neuroprotective agent, to the retina. After 5 days of topical administration in a monkey model, Brimonidine concentrations at the cornea, ciliary body, iris, and choroid/retina were two to four orders of magnitude higher than in whole blood or plasma. Dr. Lee foresees drugs that take advantage of transporters in tissues to provide pathways to a target site in

the eye, as well as responding to specific receptors at the target cell locations. Although drugs are now designed for a specific receptor, the receptor may differ in different environments.

Biomaterials tailored for a drug package can provide selectivity via pathway and target characteristics, as well as controlled release of active agent at the target. New options for biomaterials in the ocular environment must be biocompatible and generally biodegradable. Many protein agents could benefit from a polymeric substrate that maintains their biologically active conformation. Although many of these desirable features of biomaterials are obvious, pharmaceutical companies will not take the first steps in introducing a new delivery paradigm because of regulatory obstacles. Dr. Lee suggested that this impasse might be overcome through a concerted effort, in which several companies collaborate with Federal agencies and the academic community.

Dr. Lee's closing points were that our increasing understanding of ocular disease conditions should be used to improve methods of drug administration. We need to design drugs that will not have a high toxicity profile (systemic side effects), but many of the drugs in use today were not developed with that in mind. We need to consider new biomaterials for use in the delivery package, based on how these materials interact with target cells and with the various tissues in the path from delivery site to target cell. Surprisingly, bioavailabilities of 1 percent or less for topical ocular administration are currently accepted, even though 100 percent bioavailability is the norm for oral administration and systemic absorption.

During the discussion, Dr. Lee addressed questions on iontopheresis as a local delivery method, topical delivery as a way to avoid high systemic toxicity, and issues with the inflammatory response to polymers in delivery packages. Some large biodegradable polymers can alter the microenvironment in their vicinity, such as changing the pH. On the latter issue, Dr. Lee thought that it would be worthwhile to first investigate how the currently used polymers could be better tolerated by surrounding tissues, before concluding that the polymers should be modified or that entirely different polymers are needed. When nanotechnology, which is currently in the spotlight, proves successful as a drug delivery approach, biomaterials are likely to be the backbone of the enabling drug delivery platform. The tolerability of these materials by cells that would otherwise be sheltered from making contact with foreign materials can be a pivotal factor in determining the therapeutic outcome. Success with this challenging problem will require an integrated, multidisciplinary approach.

Applying Nutritional Findings to Research and Clinical Practice

Frederick L. Ferris III, M.D.

Dr. Ferris discussed the use of epidemiologic studies and clinical trials for studying the relationship between dietary nutrients and progression of chronic eye diseases. Almost all the clinical information on these relationships comes from observational studies, including the dietary association component of the Age-Related Eye Disease Study (AREDS) and five other large epidemiologic studies. Dr. Ferris began with the AREDS findings on the association of dietary lutein and omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) with AMD progression. The multivariate regression analyses of the data included adjustments for a list of factors known to affect AMD outcomes, including age, gender, smoking, and others. Despite the imprecision inherent in defining dietary intake quintiles (five levels of intake of the nutrient of interest, from no intake to highest) and the uncertainties in the statistics, Dr. Ferris said that the trend across all quintiles provides a reasonably good indication of the strength of an association. Diets with high levels of these nutrients were associated with about a 50 percent decreased risk of progression to neovascular AMD, compared with no intake (table 1) (37). The results indicate that eating a diet high in lutein/zeaxanthin and high in omega-3 LCPUFAs can reduce the risk of AMD. Overall, the results from AREDS and other observational studies suggest that there may be a dose dependence at these dietary levels, so that diets higher in these nutrients are better.

Dr. Ferris also summarized the part of AREDS that provided a controlled clinical trial for the effect of nutritional supplements on AMD progression (19). This trial covered 3,640 AREDS subjects. Half had few or no drusen deposits under the retina (low risk groups); the other half had either large drusen (intermediate risk group) or had already developed advanced wet or dry AMD in one eye as an indicator for developing AMD in the other eye

Table 1. Neovascular AMD versus Controls (No Drusen)

	Lutein/Zeaxanthin		Total Omega-3 LCPUFAs	
Quintile*	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
2	0.74	0.5–1.0	0.91	0.7–1.3
3	0.54	0.4–0.8	0.72	0.5–1.0
4	0.68	0.5–1.0	0.77	0.5–1.1
5	0.65	0.5–0.9	0.60	0.4–0.9

*Compared with Quintile 1.

P trend ≤ 0.01.

(the highest risk group). For the two groups whose starting condition indicated a higher risk of progressing to advanced AMD, treatment with zinc and antioxidants as a nutritional supplement decreased the risk of progression from 28 percent (with no supplement) to 20 percent. No benefit from supplements was observed in the low-risk groups. Dr. Ferris summarized the rationale followed by the study investigators in adopting their analytical approach and the issues raised after publication, in response to their approach.

Dr. Ferris's main point, however, was that results from observational studies should be viewed only as *generating hypotheses*, not testing them. Clinical trials are the best method to test these hypotheses. Although confounding factors, bias, and chance can still affect the results, clinical trials (such as the clinical trial portion of the AREDS) can be carefully designed to avoid them. Uncontrolled confounders and bias are major problems for observational studies. As an example, whereas observational studies had suggested that beta-carotene reduced the risk of lung cancer (38, 39), in two subsequent clinical trials beta-carotene given as a supplement had been associated with an increased risk of lung cancer (40, 41). However, observational studies can be useful in pointing out potentially significant associations. Because there are not enough resources to test every possible nutritional factor, there should be a high probability of an effect to make a controlled clinical trial worthwhile. Lutein and zeaxanthin, for example, are likely to have important roles in the health of the eye, given their levels in normal retinal tissue and the metabolic roles that can reasonably be hypothesized for them as light filters and antioxidants. The AREDS designers wanted to include lutein in the clinical trial, but there was no commercial source for it at that time.

Dr. Ferris addressed questions from the other workshop participants on the time required to gather several years of data for a full study population, the evaluation of statistical findings, and generalizing results from clinical trials to socioeconomic sectors that are not well represented in the study population. He used the AREDS results as they accumulated over time to illustrate the importance of having a data monitoring committee from the research community to provide flexibility in looking for important emerging results of an ongoing clinical trial and adjusting the study analyses accordingly. He agreed with a comment that the AREDS results for antioxidants and zinc could mean that their effect is predominantly as neovascularization antagonists, rather than in arresting progression of AMD generally (e.g., in early stages of stress on the RPE and photoreceptors).

Gene Therapy for Retinal Disease

William W. Hauswirth, Ph.D.

Dr. Hauswirth reviewed gene therapy approaches that have been successful in animal models for retinal diseases. To illustrate what he believes will be the future of gene therapy approaches, he discussed in more detail the status of a current clinical trial. He rated a range of gene delivery technologies (six varieties of viral vectors plus naked DNA and lipofectin approaches) with respect to biological characteristics such as their ease of manufacture, the maximum gene size, the range of host cells that could be targeted, their efficiency in gene delivery to the host cell population, and duration of gene expression after transduction (table 2). For example, because gene expression from transduction with an adenovirus vector is relatively short-lived, this vector type

Table 2. Gene Delivery Alternatives: Biological Issues

Technology	Ease of manufacturing	Max. gene size (kb)	Host cell range	Gene delivery efficiency	Gene expression
Adenovirus	Medium	8	Broad	Good	Transient
Adenovirus-gutless	Very difficult	37	Broad	Good	Long term
Retroviral	Medium	8	Narrow	Good	Long term
Lentivirus	Medium	9	Broad	Good	Long term
AAV	Medium	4.9	Broad	Good	Long term
HSV	Medium	12	Broad	Good	Long term
Naked DNA	Easy	No limit	Narrow	Variable	Transient, low
Lipofectin	Easy	No limit	Narrow	Low	Transient, high

has a disadvantage for treating chronic conditions. So-called "gutless" adenovirus vector has a much longer duration of expression, but it is difficult to manufacture (31). Retrovirus vectors, naked DNA, and lipofectin require cells that routinely divide (undergo mitosis) and are therefore inappropriate for the retina. He then discussed his ratings of the same range of technologies with respect to safety and regulatory issues, such as immunogenicity, pathogenicity, and characteristics of their use to date in clinical trials (table 3). Both lentivirus and herpes simplex virus vectors raise difficult regulatory issues because of their long duration in the body and their potential for pathogenic and immunogenic effects. When these two sets of constraints are meshed, Dr. Hauswirth believes that AAV (adeno-associated virus) vectors stand out as the most promising candidate for a gene therapy approach to treating chronic retinal diseases.

In Dr. Hauswirth's work with AAV vectors to transfer genes into retinal cells, he has found them to be nonpathogenic, evoking only a modest immune re-

Table 3. Gene Delivery Alternatives: Safety, Regulatory Issues

Technology	Immunogenicity	Pathogenicity	Trials	Patients	Regulatory issues	Adverse events
Adenovirus	Moderate/high	Moderate/high	171	644	Moderate	1 death
Adenovirus-gutless	Moderate	Low	Increasing	Increasing	Moderate	
Retroviral	Moderate/high	Moderate/high	217	1,755	Moderate	2 cancer
Lentivirus	Moderate/high	Moderate/high	1	0	Difficult	
AAV	Low	Very low	15	102	Moderate	
HSV	Moderate	Moderate/high	5	21	Difficult	
Naked DNA	Very low	Very low	Low	Low	Standard	
Lipofectin	Very low	Very low	77	619	Standard	

sponse. By varying the promoter with the gene, the injection site, and the vector serotype, Dr. Hauswirth's group can target whether rod, cone, RPE, or RGC cells are preferentially transduced. From 25 percent to 95 percent of the targeted cell type can be transduced in human-size eyes (e.g., pig eyes). Duration of gene expression in the retina has been 30 months in rodents (full life span). Gene expression in transduced retinal cells has continued for 38 months and counting in dogs exhibiting an early-onset type of RP (32).

As an example of a gene therapy approach for a dominant gene defect, Dr. Hauswirth described ribozyme therapy in the P23H rat, which has a genetic defect resulting presumably in accumulation of a toxic metabolic byproduct in the retina. His group has been interested in designing ribozymes targeted to a specific mutant messenger ribonucleic acid (mRNA) for rhodopsin. When that mRNA is removed from the translatable pool of mRNA, the toxic byproduct (mutant rhodopsin) is no longer produced. An untreated P23H rat develops a phenotypical retinal degeneration of rod photoreceptors dying off first, after which the cones die. The model is of medical interest because this progression is typical of the disease progression in RP. The gene vector used in treatment is a serotype 2 or 5 AAV vector carrying the ribozyme targeting the P23H mRNA and a mouse opsin promoter. With one subretinal injection at about two weeks after birth, the treated eye at age 4 months retains six rows of nuclei in the outer nuclear layer of the retina, versus two rows for the control eye and nine rows in rats without the gene defect (33). At age 6 months, the treated eyes have four rows versus one in the control eyes. Even if treatment is delayed until 40 percent or more of the rods have been lost, there is substantial preservation of the remaining rods 3 months after treatment (34). A constraint on the treatment method is that the reagent (i.e., the gene vector) is probably reaching only half the target cell population. The group is now preparing to start transductions in a mouse model carrying the

human version of the P23H opsin gene. In this transgenic version of a heterozygous rhodopsin knockout mouse, the half-life of photoreceptors without treatment is about 6 weeks, which is analogous to the photoreceptor loss rate in human patients (adjusted for the life span difference). A highly active ribozyme with high specificity for the mutant P23H allele has been developed for this experiment.

Dr. Hauswirth's second example was treatment for a recessive gene defect. In this situation, the disease phenotype can be changed if just one copy of the wild-type gene (without the recessive defect) can be transduced into the affected cell. In the RPE65 mutant Briard dogs that have been used as an animal model for this recessive form of RP in humans, vision is affected even more severely than in humans with the defect. Because of the defect, which apparently prevents *trans* retinal esters from being converted to the physiologically active *cis* conformation, nonrecyclable retinoids accumulate in the RPE cells as lipid bodies. In time, the outer segments of photoreceptors are lost and the RPE and photoreceptor layers become disorganized.

For the treatment reagent, the group developed an AAV vector targeted to the RPE cells because the gene of interest, RPE65, is specific to RPE cells (35). In the first experiment, the dogs were treated by subretinal injection at age 4 months, but the response to treatment at times later than this has been the same and very successful. In this model, an important consideration is that, although the dogs are born with a flat ERG and profound visual defect, the RPE and photoreceptor cells are present and retain their morphology. Therefore, rescue of functionality is possible. Unfortunately, only the RPE directly below the injection bleb appears to be rescued, and intravitreous injection is ineffective in delivering the reagent to the RPE. As the purity of the reagent has been improved, inflammatory response to the treatment has been eliminated.

The third gene therapy approach Dr. Hauswirth discussed is what is called *gene-based pharmaceutical therapy*. It can be used to treat any genetic defect (either Mendelian dominant or recessive) or one in which the genes involved are unknown. The therapeutic approach applies to glaucoma, the retinal diseases involving neovascularization, and some of the more common forms of RP. The general strategy here is to up-regulate production of a protective factor—for example, an antineovascular agent, if neovascularization is to be prevented, or a neuroprotective agent in the case of RP or glaucoma. The animal model for this approach that Dr. Hauswirth's group has studied is a mouse model for retinopathy of prematurity, produced by placing newborn mice in a chamber with supranormal oxygen tension. When they are later removed

from the chamber, the shift to normal oxygen is experienced as an hypoxic ischemic event. Blood vessels proliferate above the retina and penetrate into the retina and the vitreous, frequently leading to leakage and scarring. The condition produced is also a partial model for proliferative diabetic retinopathy.

The treatment reagent for this model is an AAV vector carrying a transgene for an antineovascular agent. Five different antineovascular agents were tested in this way. In each case, the amount of new blood vessel formation (measured by the average number of proliferated endothelial cell nuclei) in the treated eye was reduced to 10 percent to 25 percent of vessel formation in the untreated eye (36).

Dr. Hauswirth summarized the results from his studies in three points. First, with the appropriate serotype, promoter, and injection site, AAV vectors can efficiently target cargo genes to a variety of retinal cell types. Second, AAV vectors show therapeutic proof of principle in a variety of animal models of retinal disease. Third, although rodent and canine models demonstrate the relative safety of AAV gene therapy, whether AAV vectors are safe vehicles to deliver genes to the retina *in primates* remains to be formally proven. With respect to his third point, Dr. Hauswirth described the time line for a phase 1 clinical trial of the RPE65 treatment for Leber Congenital Amaurosis, a form of RP in which children are born with severe visual impairment. This trial will include a primate toxicity and biodistribution study during the spring and summer of 2004. He hopes to be able to proceed with treating a first set of human patients (the phase 1 clinical trial) early in 2005. The discussion questions related to details of this trial, including issues in meeting FDA requirements for use of a viral vector in human subjects and appropriate outcome measures. The hope is that this trial will lead to similar trials for most if not all forms of RP, whether dominant, recessive, or X-linked.

Biomimetic Systems for Ocular Disease

Eugene de Juan, Jr., M.D.

Dr. de Juan began his presentation on biomimetic systems and devices by suggesting the breadth of applications conceivable with current or emerging technology. He has been working with both retinal prostheses and passive-release drug delivery devices. Other potential applications for biomimetic systems include IOP regulation; drug delivery systems that use a micropump to deliver a therapeutic agent to treat retinal conditions, glaucoma, or inflammation; accommodating lens prostheses for cataract; and artificial lids (blinking function).

The University of Southern California's Doheny Retina Institute, with which Dr. de Juan is associated, is developing an *epiretinal* implant for a retinal prosthesis (54). The implant sits on the vitreal surface of the retina (figure 6). Several other groups are working on *subretinal* implants, where the implant is placed in the interphotoreceptor space between the retina and RPE cell layers. Epiretinal placement has advantages in being less disruptive to the retina and allowing more flexibility in component placement, but it requires more complex algorithms to process a stimulus. Subretinal implants are in the natural position of the photoreceptors, but they disrupt the retina structurally and, if they rely on incident light for power, may not be able to generate an effective stimulus.

The investment in developing a retinal prosthesis is substantial. For the implant work at the Doheny Institute, the major sources of funding have been Second Sight (a private company) with $20 million invested, the National Science Foundation with $10 million ($1 million annually to support an Engineering Research Center at the University of Southern California for 10 years), the U.S. Department of Energy with $ 9 million ($3 million per year for three years), and the NIH with $12 million ($2 million per year for six years). Cumulative foundation support has been $500,000. Dr. de Juan be-

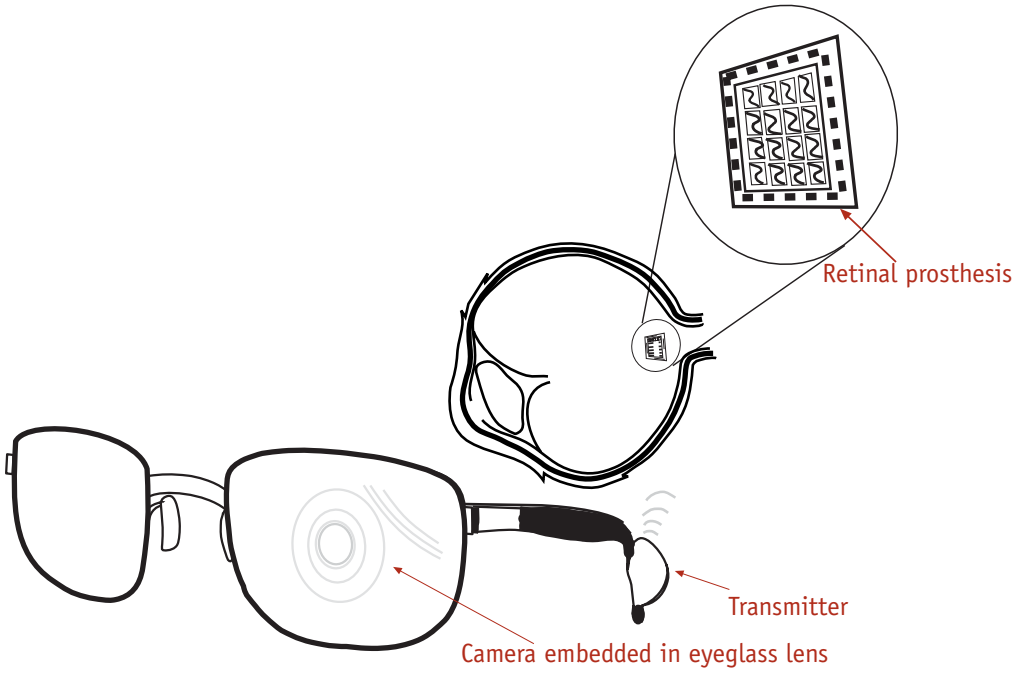

FIGURE 6. The epiretinal implant system developed by the Doheny Retina Institute as a retinal prosthesis. A camera embedded in the eyeglass lens sends image data to the transmitter attached to the ear piece of the glasses. The image data are transmitted to the array of microelectrodes on the implant. The microelectrodes stimulate the retinal cells beneath the implant.

lieves multiple investment and funding sources, covering several sectors as in the case of his group's support, are probably necessary for a project of this scope and risk. Multiple sources of support have been involved since the program's beginning. Some separation of activities and roles has been needed to avoid conflicts of interest, but the presence of a commercial entity has been valuable in pushing the research team toward useful applications.

The prototype Doheny prosthesis has a camera embedded in the lens of a pair of dark eyeglasses worn by the subject. A transmitter behind the ear transmits image data from the camera wirelessly to a 4x4 array of microelectrodes in the implant. The array stimulates retinal cells (probably bipolar cells), which in turn stimulate the RGCs that send the image to the brain. The implanted array is held in place with a retinal tack.

The patients tested thus far have been adults who lacked even light perception for a number of years. Beyond just perceiving light, at least two of these patients are now able to recognize single letters and differentiate familiar objects, such as a cup or plate. Their visual behavior includes scanning movements of the head, which apparently builds up the amount of visual data to be integrated beyond the implant, resulting in a perceived image. The subjects can detect motion (of other objects) and locate and identify objects by using scanning motions. Another significant finding is that the thresholds for retinal stimulation by the implant array decrease with time, rather than increasing. This finding suggests that the stimulated area becomes more sensitive to the input signal over time.

Electrophysiological responses to the retinal prosthetic have been recorded. OCT (optical coherence tomography) has been used to image the implant-retinal interface and collect quantitative data about the interface. Dr. de Juan described the stimulus pattern tests used to determine how well patients can spatially locate a signal in their visual field when different electrodes in the array are stimulated in sequence or concurrently. These tests show that spatial distribution of perceived light is reliable. Performance on the tests is better when the camera is moving (subject makes head movements). The impedances and thresholds are largely stable to chronic stimulation.

Future directions include increasing the resolution to a 32x32 array in the implant. Dr. de Juan commented that the stimulator implant was a high-risk research area when he and others on the team began working on it. The successes to date are generating enthusiasm for other biomimetic systems that use microelectronic and microprocessor technology. He anticipates that these systems will be as revolutionary and effective in ocular therapy as any of the other emerging therapeutic approaches described at the workshop.

Dr. de Juan next described devices he has been developing for drug delivery to the vitreous or subretinal space. One device is a special needle for penetrating the retina to inject an antineovascular agent, such as a steroid, directly on a CNV membrane at the RPE. This delivery technique is already being used on patients. Needles of different lengths are used to target the vitreous, subretinal space, subconjunctival space, or other locations inside the eye.

Another delivery device he is testing in animals (rabbits) is a helical coil that can be screwed through the sclera into the vitreous. The coil can be coated with a therapeutic agent embedded in a matrix or under a solid coating, from which the agent is released continuously over an extended period (up to 2 years). In test animals, the coil has been left in place for 6 months with no reaction to the materials used, all of which are approved for biocompatibility. Important points for therapeutic application are that the coil can be inserted and removed in the clinic (hospitalization is not needed) and the procedure does not require suturing. The general point of these examples, Dr. de Juan said, is that surgical approaches can be combined with pharmabiology to contribute new solutions for treating ocular diseases. He emphasized Dr. Lee's point that there are huge benefits, in terms of effective concentration and avoidance of systemic toxicity, in delivering a therapeutic dose directly to the target tissue.

During the question period, Dr. de Juan said that the prosthetic implant had originally been designed to stimulate RGCs, which were thought then to be the last cells to degenerate. In fact, the bipolar cells appear to be the last to go. When prototypes were placed on patients' retinas and simulated, the patients reported seeing a point of light rather than an elongated streak of light, as one would expect from RGC stimulation. This and other evidence indicated that the easiest retinal neural cells to stimulate, after the photoreceptors, are bipolar cells. If very high currents are used, the RGCs are stimulated and patients report a streak perception.

Emerging Strategies for Ocular Therapies

Paul Sieving, M.D., Ph.D.

Dr. Sieving began with an overview of the design for the phase 1 clinical trial of Neurotech-501, a pharmaceutical therapeutic approach for treating RP with a novel encapsulated cell therapy (ECT). He then led off the general discussion session of the workshop by introducing a set of topics that he, as NEI Director, views as important to moving emerging therapies toward safe and effective implementation in treating patients.

Fundamental to the clinical pathobiology of RP is that it is a diverse "family" of hereditary disorders affecting the photoreceptors. In a typical RP case, the death of rod photoreceptors, followed by the cones, causes progressive visual loss, often leading to blindness. Retinal degeneration from the various forms of RP affects more than 100,000 patients in the United States, and no effective therapy is currently available.

To illustrate some of the issues for an RP clinical trial, Dr. Sieving described the peripheral vision loss in one of his own RP patients. This woman, 41 years old, has substantial loss of peripheral vision due to RP from the P23H rhodopsin mutation. Her responses in a clinical ERG test are nearly flat. Yet, she can still drive a car and has 20/20 visual acuity. This patient's mother, who died at age 73, had severe tunnel vision due to loss of peripheral photoreceptors. On postmortem examination, her retina had no rods and fewer than 40 percent of the cones. There were no organized outer segments, and the inner segments were collapsed. Yet, her visual acuity was 20/70 when last tested. For Dr. Sieving, these cases reflect the realities of patients living with RD diseases. If the clinician can effect even some degree of photoreceptor rescue, or slow the progressive cell loss that results in blindness, whether in global or macular retinal degeneration, the clinical outcome could greatly benefit the patient. Clinical trial targets need to better reflect these therapeutic realities, he said, however difficult they may be to represent in observable and quantitatively reproducible outcome measures.

In the older of these two patients, the peripheral retina was nearly completely disorganized, with no photoreceptors and few neural cells identifiable by morphology. Jones et al. recently described the extensive negative remodeling of the retina in late-stage retinal degenerations (15). This remodeling and rewiring of the retina changes the remaining neural structure, regardless of which cells were affected by the degenerative condition initially. For Dr. Sieving, this negative remodeling in late-stage RD disease raises the question of what rescue strategy—an implanted prosthetic device, trophic factors, cell transplants, or stem cell replacement—might benefit the patient, once this stage has been reached. If, as Dr. Robert Marc and others have suggested, the remodeling results from lack of neural input from photoreceptors, a strategy for neural stimulation of the bipolar cells before this extensive reorganization occurs might preserve the retinal architecture.

These and other clinical realities raise a number of challenges and opportunities for a long-term program of improving therapeutic approaches to RD diseases:

- What is the relationship of observed outcomes in animal models to human visual function? For example, how does a decrease in the number of outer nuclear layers in a P23H rhodopsin transgenic rat correlate with visual acuity?
- The disease state typically varies across the retina. Could the location of the margin between the clinically dead region and the still viable region be a useful clinical endpoint for trials?
- What should the clinical endpoints be? For example, it is not clear what an ERG means in terms of daily-life visual function. What are the useful correlates, in animal studies and clinical trials, for visual fields, acuity, and sensitivity?
- Clinical endpoints of significance for retinal degeneration may develop slowly. For example, in a clinical trial of an IOP-lowering agent to treat glaucoma, the lowered IOP is observable within days after treatment. However, in a neuroprotective strategy for glaucoma, when should the clinical endpoint be measured?[4]
- What ratio of risks to potential benefits warrants a rescue effort?
- Which diseases should grab the attention of medical research? Where are the biological opportunities to make a significant difference for a patient population? When is an opportunity ripe for concerted effort?
- Under what circumstances is it worthwhile—even essential—to invest public resources in extensive research, including clinical trial, on treatment for a very rare monogenic disease (i.e., an orphan disease)?

Next, Dr. Sieving discussed the NeuroTech-501 trial, which is a clinical collaboration of the NEI with NeuroTech USA, in light of these broader questions. This clinical trial uses human RPE cells that have been transfected for chronic release of CNTF. The cells are sequestered in a capsule, which is implanted in the patient's vitreous. Dr. Sieving described the trial as both a test of CNTF as a neurotrophic factor and a test of the NeuroTech device for ECT. He reviewed the extensive laboratory studies that have been done on CNTF, including tests in 12 animal models of Huntington's disease, amyotrophic lateral sclerosis, and RP.

The ECT approach using the NeuroTech technology with cells transfected to produce CNTF has been tested in the rcd1 dog model for RP. The histology

[4]Figure 1 (p. 7) illustrates this issue graphically.

shows that the treated eye has more photoreceptors than the untreated control eye. The ECT device is 11 mm long and 1 mm in diameter. It is inserted through the sclera into the vitreous chamber, where an anchor loop on one end is sutured to the inner scleral wall. Because ECT allows sustained intraocular delivery of large proteins, it is an alternative to either repeated direct intraocular injections of a macromolecular agent or gene transfer approaches using intraocular injection of viral vector. The dog study showed that CNTF was delivered to the vitreous from the NeuroTech device for at least 1 year in vivo. Devices that were removed at that time still contained viable cells, and repeated emplacement of the devices was well tolerated. Dose-dependent photoreceptor rescue was demonstrated using rows of nuclei in the outer nuclear layer of the retina as the output measure.

Dr. Sieving described the design of the clinical trial, which will use ECT devices that yield two different levels of CNTF ("low" and "high" doses). Each level will be tested in five patients. This first trial is designed to evaluate potential inflammatory response, screen for catastrophic outcome, prepare for a phase 2 study, and test the ECT technology as a platform for delivering other large protein agents. If the NeuroTech-501 approach to ECT, or another approach, proves successful in delivering a macromolecule like CNTF in effective concentrations at the retina for an extended time, the technology could be tested for other RD diseases. It could, for example, be used to deliver an antineovascular or neurotrophic agent to the macula of patients with advanced AMD, which affects at least 1.7 million Americans.

In response to questions, Dr. Sieving said that knowing the genotype of patients in the trial would be useful, but he expects no more than half to have an identifiable RP genotype. The participants discussed other issues related to the trial design and protocol and other studies of CNTF delivery.

As an introduction to the general discussion session later in the day, Dr. Sieving suggested a list of general topics relevant to the emerging therapies that had been discussed throughout the workshop.

- What are meaningful patient selection parameters for a clinical trial of an emerging therapy?
- What outcome parameters are meaningful for clinical documentation of efficacy? In the RP field, the ERG is used clinically, and the FDA is beginning to consider it as an outcome measure for efficacy. However, what do changes in ERG mean for a patient who can drive and read books but has a negligible ERG before treatment?

- When is the opportunity for clinical trial ripe? The advisory group Dr. Sieving assembled to consider the NeuroTech-501 phase 1 trial concluded that the opportunity to do that trial was appropriate, in terms of the balance of risks and benefits to the patients and to the field.
- What determines the appropriateness of testing a therapy for a very rare monogenic disease? The category of orphan drugs will expand as more is learned about the molecular basis of these diseases. On the order of 3,000 individuals have retinal degeneration from the form of RP caused by the P23H rhodopsin mutation. For some other monogenic diseases, fewer than a hundred individuals in the United States are known to be affected.
- Is it time to think about some national-scale facilities to advance emerging therapies? The pace of discovery of monogenic genes picked up during the 1990s but now appears to be tapering off (figure 2, p. 12). Are investigators moving to more-complex genetic traits to understand the remaining forms of chronic RD disease?
- Are there more families to find and study for genetic factors in diseases? Do we need to look at diverse ethnic communities, perhaps in other countries, to find high incidences of consanguineous disease conditions, indicative of a strong genetic component in the disease pathogenesis? Do treatment opportunities need to be assessed on a worldwide scale, not just domestically?
- The NIH Director has proposed a long-term Roadmap for the next set of opportunities to address. The Roadmap includes multiple initiatives under three broad themes: New Pathways to Discovery, Research Teams of the Future, and the Clinical Research Enterprise. What is the relation of these themes to what should be done to encourage translational research on the emerging therapies that have been discussed in this workshop? Where and by whom will the clinical trials for translational research be conducted?

Dr. Sieving summarized the activities being planned under the three themes of the NIH Roadmap. He then expanded on the range of innovations being considered by a Roadmap implementation group he is leading on nanotechnoology, including nanobiotechnology and nanomedicine.

For the NEI, Dr. Sieving sees opportunities in visual and retinal neurobiology to work with other NIH institutes with joint research teams and collaborative

approaches. Retinal degenerations will continue to be important in NEI programs, including research on ganglion cell and optic nerve diseases, such as glaucoma, and photoreceptor diseases such as AMD. Work in genetics will include studies of monogenic forms within a disease family, as well as more complex forms of those diseases. Two upcoming events are an AMD phenotype consensus meeting and a meeting to establish standards for a national network for ophthalmic genotyping. The workshop discussion in response to Dr. Sieving's list of topics is reflected in section 2 of this report.

Emerging Strategies and Future Directions

Gerald J. Chader, Ph.D.

Dr. Chader led the discussion of future directions for the emerging therapies presented and discussed during the previous sessions of the workshop. He suggested the following framework as a way to bring together the workshop's range of ocular diseases and the therapeutic approaches emerging to treat them:

- **The need has been established.** For each of the RD and other disease conditions discussed, there is a need for therapeutic approaches beneficial to the patient in limiting or avoiding the possibility of blindness.
- **The opportunity is at hand.** Why is it important to do something about these needs now? There is a heightened possibility now of being able to make significant advances in treatment because of unprecedented increases in our understanding of disease conditions and progression.
- **Therapeutic proof of principle has been established.** An important portion of these advances in understanding has been research, funded by the NEI and others, establishing the biological proof of principle that an agent or technique has a desirable effect on conditions, such as animal models, that are usefully similar to ocular disease conditions in human patients. Examples include the gene therapy approaches described by several presenters, the prosthetic microarray implant for total blindness, pharmaceutical treatments, and surgical treatments. Other proofs of principle that were not covered in the presentations include photoreceptor or RPE transplants. Which of these successful initial steps represent near-term opportunities that should be moved forward quickly? Which have potentially high payoffs in terms of benefiting patients, but will need further preparation before proceeding to clinical trials?

- **Clinical trials are the next step toward implementation.** As presenters have mentioned, some of these emerging therapies are proceeding to clinical trials. Many more could go to trial, if resources were available and remaining issues were addressed. What can this group say about accelerating the movement of the most promising of these emerging therapies into and through the clinical phases of testing for safety and efficacy?
- **Initial success in treating, curing, or preventing one disease can enable further, wider successes.** An initial step in treating a chronic RD condition may work for only one form of a disease family, and perhaps only a few thousand or a few hundred patients may be helped immediately. However, if that first small step establishes a pathway to treating more prevalent forms, then it may be worthwhile for the support it engenders to carry the research further.

Before he polled each of the workshop participants for their thoughts on their own areas of expertise and those presented by others, Dr. Chader suggested the four implementation strategies listed in section 1. The resulting discussion, along with the discussion following Dr. Sieving's presentation, was the basis for the section 2 summary of workshop themes.

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Appendix B Conference Agenda

Sunday, October 12, 2003

6:00–9:00 p.m. Reception and dinner for participants and guests

Monday, October 13, 2003

Session Chair: James Wyngaarden

8:15–8:30 a.m. **Welcoming Remarks:** Robert White

8:30–10:00 a.m. **Pharmaceutical Therapies**
- 8:30–8:50 Matthew LaVail (Retina)
- 8:50–9:15 Discussion
- 9:15–9:35 Arthur Neufeld (Glaucoma)
- 9:35–10:00 Discussion

10:00–10:30 a.m. Break

10:30 a.m.–12:00 p.m. **Antineovascular Therapies**
- 10:30–10:50 Peter Campochiaro (AMD)
- 10:50–11:15 Discussion
- 11:15–11:35 Robert Frank (Diabetic Retinopathy and Cornea)
- 11:35–12:00 Discussion

12:00–1:15 p.m. Lunch

Session Chair: Jack Hetherington

1:15–2:45 p.m. **Stem Cell and Regeneration Therapies**
- 1:15–1:35 Michael Young (Stem Cell Research)
- 1:35–1:55 Discussion
- 1:55–2:15 Albert Aguayo (Nerve Regeneration)
- 2:15–2:45 Discussion

2:45–3:00 p.m. Break

3:00–4:30 p.m. **Drug Delivery and Nutrition**
- 3:00–3:20 Vincent Lee (Drug Delivery)
- 3:20–3:45 Discussion
- 3:45–4:05 Frederick Ferris (Nutrition)
- 4:05–4:30 Discussion

4:30–5:00 p.m. **Introduction to a Final Report:** Robert White, Robert Katt

5:00–6:00 p.m. Break

6:00–8:00 p.m. Dinner for participants and guests

Tuesday, October 14, 2003

Session Chair: Bronwyn Bateman

8:15–9:45 a.m. **Gene Therapy and Prostheses**
- 8:15–8:35 William Hauswirth (Gene Therapy)
- 8:35–9:00 Discussion
- 9:00–9:20 Eugene de Juan (Prostheses)
- 9:20–9:25 Discussion

9:45–10:00 a.m. Break

10:00–10:30 a.m. **Ocular Therapies: A Director's Perspective:** Paul Sieving

10:30 a.m.–12:00 p.m. Discussion

12:00–1:15 p.m. Lunch

Session Chair: Gerald Chader

1:15–2:45 p.m. **Emerging Strategies: General Discussion and Future Directions**

2:45–3:00 p.m. Break

3:00–5:00 p.m. Emerging Strategies: General Discussion and Future Directions (continued)

5:00 p.m. Workshop adjourned

Appendix C The NIH Roadmap Initiatives: An Overview

The NIH Roadmap initiatives are organized according to three major themes. Each theme is divided into Implementation Groups, under which the individual initiatives are arrayed. The titles of themes, implementation groups, and initiatives in this overview are from a summary document on all the initiatives (5), which is available on the NIH Roadmap website, www.nihroadmap.gov. The text descriptions of the initiatives come from that summary document or from NIH Backgrounder documents, also available at the website. The numbering of implementation groups and initiatives in this summary is not from the NIH source documents. It has been added for ease of reference from the workshop report.

Only those initiatives most relevant to discussions at the emerging therapies workshop (the third Drabkin conference) are cited in section 2 of the workshop report. However, all of the Roadmap initiatives, as of November 2003, are included in the summary below. The NIH Roadmap is intended to be a living plan: initiatives and their scope and objectives are likely to evolve over time. Readers interested in the most current information on the Roadmap or a specific initiative should consult the NIH Roadmap website.

Theme 1: New Pathways to Discovery

1-1 Building Blocks, Pathways, and Networks Implementation Group

In this set of NIH Roadmap initiatives, researchers will focus on the development of new technologies to accelerate discovery and facilitate comprehensive study of biological pathways and networks (10).

1-1.1 Initiative: National Technology Centers for Networks and Pathways

To better understand the proteome, innovative tools must be developed that will enable researchers to determine in real time the amounts, locations, and interactions of large numbers of individual proteins within a single cell. NIH will establish a series of National Technology Centers for Networks and Pathways to promote the development of new proteomic technologies. Such capability is crucial to expanding the identification of biological pathways and developing treatments for diseases involving such pathways (10).

This network of research centers will create new tools to describe the dynamics of protein interactions. The centers will develop instruments, methods, and reagents for quantitative measurements at subcellular resolution and very short timescales (5).

1-1.2 Initiative: Metabolomics Technology Development

This initiative will promote development of novel technologies to study cellular metabolites, such as lipids, carbohydrates, and amino acids. Knowledge gained from these studies will be used to understand more precisely the role of metabolites in the context of cellular pathways and networks (5).

1-1.3 Initiative: Standards for Proteomics and Metabolomics/Assessment of Critical Reagents for Proteomics

Workshops will be convened to address these two important areas. The "Standards" workshops will engage the scientific community in the establishment of quality and data standards for proteomics and metabolomics. The "Reagents" workshops will seek advice from extramural and intramural scientists and program staff regarding critical reagents required to enhance future research in proteomics (5).

1-2 Molecular Libraries and Imaging Implementation Group

1-2.1 Initiative: Creation of NIH Bioactive Small Molecule Library and Screening Centers

These NIH-funded centers will provide a public collection of chemically diverse small molecules, high-throughput screening to identify compounds active in target- and phenotype-based assays, medicinal chemistry to transform hits into chemical probes, implementation of novel technologies, and deposition of screening data into a freely accessible public database (5).

1-2.2 Initiative: Cheminformatics

A database of chemical structures, properties, and activities will be established at the NIH National Center for Biotechnology Information, which will be integrated with other databases and the literature, and will link to data produced by the screening centers. Research-focused cheminformatics tools and funding for the development of improved tools will also be made available (5).

1-2.3 Initiative: Technology Development

Bottlenecks in the development of compounds as basic research tools and drugs will be targeted, including improvement of chemical diversity, assay flexibility, screening instrumentation/robotics, and prospective characterization of compounds' metabolism and toxicology properties (5).

1-2.4 Initiative: Development of High Specificity/High Sensitivity Probes to Improve Detection

This technology development program seeks to ultimately achieve a 1,000-fold improvement in imaging probe detection sensitivity and optimal specificity for basic research and clinical applications (5).

1-2.5 Initiative: Comprehensive Trans-NIH Imaging Probe Database

This comprehensive database of imaging probes, with their specificities, activities, and applications, will be integrated with the Molecular Libraries Cheminformatics database (5).

1-2.6 Initiative: Core Synthesis Facility to Produce Imaging Probes

This facility will produce known imaging agents for which there is no commercial supply, and generate novel imaging probes, for use in both basic research and clinical applications. The facility will draw from, and contribute to, the Molecular Libraries compound repository and screening activities (5).

1-3 Structural Biology Implementation Group

1-3.1 Initiative: Protein Production Facilities

This initiative will focus on the long-standing challenge of membrane-bound protein structure through the development of rapid, efficient, and dependable methods to produce protein samples that scientists can use to determine the three-dimensional structure, or shape, of a protein (5).

The NIH will begin by funding interdisciplinary groups of scientists to develop innovative methods for producing large quantities of membrane proteins, those proteins that are wedged tightly within the wrappings of our cells. Project planners expect that the development of new, protein-producing methods will lead to the creation of specialized facilities that will be capable of quickly and efficiently manufacturing large quantities of research-grade membrane protein samples. Once scientists have access to sufficient quantities of proteins for their experiments, they can determine a protein's shape using standard methods involving X-rays or extremely powerful magnets (12).

1-4 Bioinformatics and Computational Biology Implementation Group

1-4.1 Initiative: National Centers for Biomedical Computing

This initiative will create a national software engineering system in which biologists, chemists, physicists, and computer scientists anywhere in the country will be able to tap into a supercomputing network to share and analyze data, using a common set of software tools (5).

A central focus of the initiative will be a set of National Centers for Biomedical Computing, the first few of which will be funded next year. As the centers begin to generate the software and data management tools to serve as fundamental building blocks for 21st century medical research, individual scientists will be funded to work together with the centers (13).

1-5 Nanomedicine Implementation Group

1-5.1 Initiative: Planning for Nanomedicine Centers

In FY 2004, a series of workshops will be held to plan for the launch of Nanomedicine Centers in FY 2005. These centers will focus on quantitative measurement of biological processes at the nanoscale and the engineering of new tools to intervene at the nanoscale or molecular level. This research will help scientists construct synthetic biological devices, such as miniature, implantable pumps for drug delivery or tiny sensors to scan for the presence of infectious agents or metabolic imbalances that could signify disease (5).

Theme 2: Research Teams of the Future

2-1 High-Risk Research Implementation Group

The past two decades have brought tremendous advances to biology, from PCR and microarray technologies to bioinformatics and detailed disease progression models. At the same time, major strides continue to be made in computer science, telecommunications, physics, engineering, materials science, chemistry, and many other areas of study that can vastly benefit medical research.

While this unprecedented era of progress will continue into the foreseeable future, there is also a great need to accelerate the current pace of discovery. One approach is to encourage the world's most innovative thinkers to consider the major challenges of 21st century biology and medicine. By bringing their unique perspectives and creativity to bear on key research questions, they may develop seminal theories or technologies that will propel fields forward and translate the promise of molecular medicine into improved human health.

Historically, however, the NIH has almost exclusively supported research projects, not individual scientists or thinkers. Moreover, the NIH peer-review process is oriented to fund so-called "low risk" proposals that advance well-established areas of science. This leaves many more speculative, or "high risk," proposals without an obvious mechanism of NIH support. To change this, the NIH Roadmap has created a new funding award to encourage creative, outside-the-box thinkers to pursue exciting and innovative ideas about biomedical research. Given the unique nature of this award, applicants will undergo a rigorous nomination process to establish the potential "high impact" benefits of their idea to medical research and their likely abilities to pursue their proposal. Applicants will not have to provide a detailed scientific plan. They will have the intellectual freedom to pursue their ideas and follow them in expected or even unexpected directions (8).

2-1.1 Initiative: NIH Director's Innovator Awards

These awards will provide support to a highly select group of individuals who have the potential to make extraordinary contributions to medical research. Evaluation criteria will include exceptional creative abilities, potential for ground-breaking discovery, evidence of focused and skillful habits of mind

that predict perseverance and thorough exploration of the investigator's ideas, and prospects for making seminal biomedical research advances (5).

2-2 Interdisciplinary Research Implementation Group

2-2.1 Initiative: Interdisciplinary Research (IR) Centers

Planning grants will be awarded to begin IR programs that will address significant and complex biomedical problems, particularly those that have been resistant to more traditional approaches. Planning activities will include approaches to overcoming traditional institutional barriers to IR, which are intended to lay the foundation and prepare investigators for submitting a subsequent application for support through an IR consortium (5).

As currently planned, the first awards will be made in FY 2004 to establish 15 planning grants for interdisciplinary research centers. In addition, Requests for Application, or RFAs, will also be issued in FY 2004 to provide training to scientists in this emerging area of science (6).

2-2.2 Initiative: Interdisciplinary Research Training Initiative

This new model of funding will address key issues critical to IR team science. Also, as IR will likely cross the borders of two or more NIH institutes and centers, the new model of support will allow each institute and center to support wholly components of a consortium that are relevant to its mission, even when the preponderance of research in a given consortial effort does not.

2-2.3 Initiative: Innovations in Interdisciplinary Technology and Methods (Meetings)

The goal of [this initiative] is to facilitate interdisciplinary research, which includes the behavioral and social sciences, by developing and improving methods and measurement.

2-2.4 Initiative: Removing Structural Barriers to Interdisciplinary Research

This initiative will help the NIH remove business practice barriers that impede IR. For example, the NIH only recognizes one principal investigator, and this minimizes the contributions of coinvestigators. NIH program officials run focused programs within their area of scientific expertise, and this may not serve IR grant applications and grants well when the research involves areas outside of a single program official's area of specialized expertise (5).

2-2.5 Initiative: NIH Intramural Program as a Model for Interdisciplinary Research

As a corollary to the extramural IR Centers, this initiative will utilize the NIH Intramural Research Program (IRP) as a laboratory to demonstrate the feasibility, benefits, and successes of establishing IR teams. Specifically, the IRP will serve as an excellent model for (1) providing Ph.D.s with training and education in interdisciplinary translational research, and (2) building programs that bring interdisciplinary research teams together (5).

2-2.6 Initiative: Interagency Conference on the Interface of Life Sciences and Physical Sciences

In response to FY 2004 House Appropriations report language for the NIH and for the National Science Foundation, an interagency conference will be convened "to discuss what needs to be done to encourage progress in the physical sciences that will provide support and underpinning in the future for advances in the life sciences" (5).

2-3 Public-Private Partnerships Implementation Group

Partnerships between government agencies and private industry already have extended and accelerated NIH research, research training, and the dissemination of information in diverse and creative ways. For example, the Osteoarthritis Initiative partnership is poised to do something that neither government nor private industry could accomplish alone—establish a database of radiological images, biomarkers, and physical exams as objective and measurable standards for the progression of this painful and disabling disease. Currently, there is no effective treatment for osteoarthritis, so new therapies are acutely needed by the millions of Americans affected by this disorder. The seven-year project to recruit 5,000 men and women age 50 and older at high risk for developing osteoarthritis of the knee is funded by several NIH institutes, along with the pharmaceutical companies Merck, Novartis Pharmaceuticals Corp., and Pfizer. The data collected through the initiative will be available to researchers to quicken the pace of scientific studies and to speed progress toward better treatments (7).

2-3.1 Initiative: Designation of a Public-Private Sector Liaison

Public-Private partnerships enhance NIH research, training, and information activities. To expand such collaborations, the Public-Private Sector Liaison will serve as a resource to NIH staff on such partnerships, share best practices across the NIH by developing training and policies and procedures, and chair an internal Public-Private Partnerships Coordinating Committee (5).

With an eye toward keeping pace with changes in the business sector and dealing with concerns about intellectual property, patents, and licensing rights, the liaison working with the Coordinating Committee will regularly review existing partnership mechanisms and recommend any necessary changes in policies, regulations, or legal authorities to achieve the NIH's objectives (7).

2-3.2 Initiative: High-Level Science-Driven Partnership Meetings

The Public-Private Sector Liaison, working with the Public-Private Partnerships Coordinating Committee, will identify scientific initiatives that could be accelerated, improved upon, or facilitated by public-private partnerships and that warrant a high-level meeting. The NIH Director will meet with senior officials in potential partner organizations to explore partnership opportunities (5).

Theme 3: Re-engineering the Clinical Research Enterprise

Clinical research is the linchpin of the Nation's biomedical research enterprise. Before a therapy is approved for general use, it must be studied carefully in the laboratory to understand its mechanism of action, effectiveness, and potential risks. The safety and benefits for human beings are then proven through an orderly series of tests in people. While clinical research helps ensure that new products and techniques that ultimately are made available to doctors and their patients are safe and effective, it is a lengthy and sometimes inefficient process (9).

To accelerate and strengthen the clinical research process, this set of initiatives will re-engineer the clinical research enterprise by adopting a systematic infrastructure that will better serve the evolving field of scientific discovery (9).

3-1 Clinical Research Implementation Group

To improve human health, scientific discoveries must be translated into practical applications. Such discoveries typically begin at "the bench" with basic research—where scientists study the mechanisms and pathogenesis of a disease at a molecular or cellular level—then progress to the clinical level, or the patient's "bedside."

Scientists have become increasingly aware that this bench-to-bedside approach to translational research is really a two-way street. Not only do basic scientists deliver to clinicians new tools to examine in patients, clinical researchers also make novel observations about the nature and progression of disease that can stimulate basic investigations (9).

Key to building a strong infrastructure will be to increase interactions between basic and clinical scientists, and ease the movement of powerful new tools from the laboratory into the clinic. In one approach aimed at accomplishing this, the NIH is exploring development of regional translational research centers. These centers would provide sophisticated advice and resources to better enable scientists to master the many steps involved in bringing a new product from the bench to clinical use. Such steps involve laboratory studies to understand a therapy's mechanisms of action and animal studies to determine how well a therapeutic agent is absorbed into the body, how it is distributed to target tissues, how effective it is, and how likely it may be to cause unanticipated side effects (9).

3-1.1 Initiative: Harmonization of Clinical Research Regulatory Requirements

This initiative is intended to enhance the leadership and coordination of efforts to harmonize, standardize, and streamline Federal policies and requirements pertaining to clinical research, while emphasizing the integrity and effectiveness of Federal and institutional systems of oversight. As part of its stewardship responsibilities, the NIH is responsible for taking steps to foster the responsible conduct of high-quality clinical research (5).

3-1.2 Initiative: Integration of Clinical Research Networks

The efficiency and productivity of the Nation's clinical research enterprise will be enhanced by promoting clinical research networks capable of rapidly conducting high-quality clinical studies and trials where multiple research questions can be addressed (5).

3-1.3 Initiative: Enhance Clinical Research Workforce Training

This NIH Roadmap effort envisions two major programs to expand, enhance, and empower the clinical research workforce: the establishment of an agency-wide Multidisciplinary Clinical Research Workforce Training Program and a cadre of NIH Clinical Research Associates. The Multidisciplinary Clinical Research Workforce Training Program will be an NIH-wide effort to train pre- and postdoctoral candidates in clinical research settings that are interdisciplinary and collaborative. The emphasis will be on new strategies and curricula with training opportunities that span a variety of disease areas; a broad range of clinical disciplines, including medicine, nursing, dentistry, pharmacy, and other allied health professions; and a wide array of research areas, including biostatistics, behavioral medicine, clinical pharmacology, and epidemiology (9).

In addition, a cadre of NIH National Clinical Research Associates will be established. This group will be composed of community-based practitioners who will receive specialized training in clinical research. These Research Associates will play a critical role both in advancing the discovery process and in disseminating research findings to the community (5).

3-1.4 Initiative: Clinical Research Informatics: National Electronic Clinical Trials and Research Network (NECTAR)

A standardized data system, the National Electronic Clinical Trials and Research Network, will be developed through a phased planning and development process. The network will allow community-

based clinicians from the NIH Clinical Research Associates to participate in important national studies, facilitate the sharing of data and resources, and augment clinical research performance and analysis (5).

3-1.5 Initiative: Translational Research Core Services

This effort will facilitate the translation of basic discoveries to early phase clinical testing. It will provide bench and clinical investigators with cost-effective core services, including the expertise needed to move projects through complex logistical and regulatory barriers, and the technical services to synthesize chemical and biological agents for early phase clinical studies (5).

3-1.6 Initiative: Regional Translational Research Centers

These centers will increase interactions between basic and clinical scientists and accelerate the translational development of new drugs, biomarkers, and treatment strategies from the laboratory bench to clinical testing. New centers will provide essential core infrastructure and support, including specialized cores that provide expertise in biostatistics, clinical pharmacology, pharmacogenetics, and genetics (5).

3-1.7 Initiative: Enabling Technologies for Improved Assessment of Clinical Outcomes

There is a pressing need to better quantify clinically important symptoms and outcomes, including pain, fatigue, and quality of life that are now difficult to measure. Through this effort, new technologies will be developed and tested to measure these self-reported health states and outcomes across a wide range of illnesses and disease severities (5).

Many of the most debilitating chronic illnesses gradually erode patients' quality of life because of the associated fatigue, pain, and mood changes. Currently, these critical symptoms cannot be objectively measured in the same way, for example, as blood sugar levels or blood cell counts. More sensitive, well-validated tools need to be developed to improve measurements of these types of symptoms (9).

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