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PARKINSON'S DISEASE RESEARCH

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Table of Contents

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Executive Summary

In Senate report No. 109-103, the Senate Committee on Appropriations requested that the National Institutes of Health (NIH) provide a final analysis of the Parkinson's Disease Research Agenda and report the results of the Parkinson's disease (PD) Summit held in June 2005, an analysis of the PD portfolio, an identification of shortcomings and opportunities for PD therapeutics, and recommendations for future research goals. The Committee also urged the NIH to work in conjunction with the Centers for Disease Control and Prevention (CDC) to document geographic population clusters of PD.

The NIH has orchestrated a vigorous planning effort in PD research. In January of 2000, the National Institute of Neurological Disorders and Stroke (NINDS) organized the first meeting in this effort, which included all components of the scientific and patient community. Designed to maximize brainstorming, the meeting provided participants with the opportunity to explore all possible avenues that might advance our understanding of the disease and, ultimately, the development of improved therapies. Their recommendations formed the basis of a five-year PD Research Agenda, a broad plan for managing the opportunities in four major areas of PD research: understanding PD, treating PD, creating new research resources, and enhancing the research process. The NIH has implemented the Agenda aggressively, has analyzed its progress and grant portfolio on a regular basis, and has modified its planning to incorporate new opportunities.

As an example, the NIH organized a Summit meeting in July 2002 to examine the ongoing science, explore progress in the context of the international research community, and identify roadblocks still impeding PD research. One important result of this Summit was the development of a Matrix of low-to-high risk and short-to-long term goals to help overcome these roadblocks. In June 2005, the NIH assembled a second Summit, which involved representatives from both the research and patient communities like the meeting in 2000. Participants considered progress in and goals for multiple areas of PD therapeutic research, including drug therapy; cell replacement and gene therapy; and deep brain stimulation (DBS, the targeted electrical stimulation of specific areas of the brain for therapeutic purposes). The discussions also focused on non-motor complications of PD, aspects of PD (e.g., speech) that do not respond to therapy like other motor symptoms of the disease, non-invasive therapies, risk factors, and

the prevention of PD. During the Summit, the participants developed a large number of recommendations in each of these areas, which they later prioritized.

The highest priority goals identified by the 2005 Summit participants were consistent with a number of the needs identified at past PD meetings and in analyses of the NIH grant portfolio, illustrating the importance of many of the NIH's ongoing efforts. Biomarkers – biological markers of disease onset and progress, improved animals models of PD (including models that reproduce its non-motor features), basic studies on PD gene function and dopaminergic neurons, cellular targets for therapies, clinical trials in DBS and non-motor complications, and studies of individuals at risk for inherited forms of PD all emerged as important topics for future study.

With respect to the epidemiology of PD, the CDC obtains information on PD prevalence, health care utilization, and mortality through its National Center for Health Statistics. Several programs at the NIH complement these efforts, including a California PD registry and several large-scale epidemiologic investigations, among others. The NIH believes that there is a great need for reliable incidence and prevalence estimates for PD to allow investigation of variation over time and/or geography, and will work with the CDC to combine research efforts in this area as opportunities arise.

NIH organized the 2005 PD Summit to provide guidance for the PD community in outlining the next steps necessary to develop new therapies and move experimental therapies closer to clinical evaluation and practice. The meeting was very effective in meeting that goal, and the NIH believes this input will be extremely helpful to refine future programmatic actions, and ultimately, in moving PD research into an era of effective treatments and an improved quality of life for people at all stages of PD. All of the Institutes and Centers that participate in PD research are committed to ensuring that the highest priority recommendations from this Summit are implemented quickly and effectively. As part of this process, the NIH is developing a revised PD Research Plan, which will integrate the recommendations made at the 2005 meeting with goals from previous planning meetings that remain unmet or have evolved over time. The NIH hoped that this Plan could incorporate the results of its first two neuroprotection clinical trials, because of the critical importance of therapeutics and the need to have better approaches for designing and managing trials, and an assessment of the utility and success of the World Parkinson Congress. The Congress took place in February 2006, and the clinical trial results became public in March 2006; thus the NIH is now positioned well to complete the PD Plan. The NIH will also hold additional workshops as necessary to help address specific

recommendations, and will convene larger planning meetings every other year in order to refine this Plan on a regular basis.

PARKINSON'S DISEASE RESEARCH

Introduction

In its report for the Fiscal Year 2006 budget for the Department of Health and Human Services (HHS), the Senate Committee on Appropriations stated:

"Parkinson's Disease – The Committee understands that the Director, in accordance with the Udall Act, convened a research conference in June 2005. The Committee strongly urges the Director to report back to the Committee by May 1, 2006 to address current and ongoing Parkinson's disease research including the final analysis of the Parkinson's Disease Research Agenda that expired this year, the goals and conclusions from the summit held in June 2005, a thorough examination of the existing Parkinson's research portfolio, identification of shortcomings and opportunities for more effective treatments and a cure for Parkinson's, and recommendations of research goals for the next 3 years to help scientists better understand the causes, more quickly diagnose, and develop better treatments and a cure for Parkinson's disease.

The Committee strongly urges the NIH to work in conjunction with the Centers for Disease Control and Prevention to investigate and report on geographic population clusters of incidence of Parkinson's disease. It is estimated that more than 1 million Americans are fighting Parkinson's disease and 60,000 cases are newly diagnosed each year. However, these figures are only estimates. Further, it is believed that there are increasing numbers of Americans who are diagnosed with young onset Parkinson's disease. With a stronger understanding of who is impacted by this devastating disease, the NIH will be better able to better target critical research funds that will find treatments or cures for the more than 1 million Americans who have this progressive, neurodegenerative disease." (Senate report No. 109-103, p. 172)

The following report has been prepared by the National Institutes of Health (NIH) of the HHS in response to this request.

Background

For many decades, the NIH has supported fundamental research that has contributed to important advances in understanding and treating Parkinson's disease (PD), including early studies of levodopa – the mainstay of current drug therapy – and the characterization of the brain circuitry affected by PD and the

engineering of neural prosthetic components, which were critical first steps in the development of deep brain stimulation (DBS) and other surgical strategies for treating the disease. In addition, technological breakthroughs that occurred in the mid-1990's opened up additional opportunities in many areas of the neurosciences. For the PD research community, advances such as the discovery of mutations in α-synuclein – the first gene implicated in PD – played an important role in this transformation. Because of these unprecedented scientific opportunities and the pressing needs of patients with debilitating disease, the NIH initiated a series of planning efforts to hasten discoveries in PD research that would lead to better treatments and a cure.

In FY 2000 report language, the Senate Committee on Appropriations asked the NIH to develop a coordinated effort to address the most pressing needs of and opportunities for PD researchers and the patient community. In January of 2000, the National Institute of Neurological Disorders and Stroke (NINDS) held the first Parkinson's planning meeting in this series, which included all components of the PD community: basic research scientists, clinicians, pharmaceutical company representatives, ethicists, and representatives of non-governmental organizations (NGOs). Designed as a large brainstorming effort, the meeting provided participants with the opportunity to discuss the many areas of research that could contribute to progress in PD, exploring all possible avenues that might advance our understanding of the disease and ultimately, the development of improved therapies. Their recommendations formed the basis of a five-year PD Research Agenda, a broad plan for managing the opportunities in four major areas of PD research: 1) understanding PD (basic studies of genetics, epidemiology, cell biology, and circuitry); 2) treating PD (clinical trials of drug therapies, cell- or gene-based therapies, and surgical interventions); 3) creating new research resources (infrastructure needed to assist research); and 4) enhancing the research process (the use of special mechanisms to accelerate research). In response to the PD Research Agenda, staff from the NINDS and other NIH Institutes and Centers (ICs) developed more than thirty grant and contract solicitations relevant to PD, organized more than thirty workshops, funded nine supplement programs, and established several significant resources to complement the investigator-initiated awards that make up the core of NIH grant programs. The scientific community responded enthusiastically to these actions, and as a result, the NIH invested nearly $1 billion to implement the PD Research Agenda from FY 2000 through FY 2004. In its FY 2005 Report to the Committee, the NIH provided a detailed analysis of many scientific achievements made during the years covered by the PD Research Agenda; highlights of these achievements are included in the relevant sections below.

Over the course of the Agenda's implementation, the NIH has regularly analyzed its progress and has modified it to incorporate new opportunities. In January 2002, the NIH organized a PD Agenda Implementation Review meeting; at this meeting, the scientific and PD community representatives confirmed that many of the Institutes' and Centers' efforts were on track, but identified several research areas that warranted additional research effort. In July 2002, the NIH also held a major PD Coordination Summit in order to examine the ongoing science, explore progress in the context of the international research community, and identify roadblocks still impeding PD research. The meeting resulted in the development of a PD Matrix of low-to-high risk and short-to-long term goals to help overcome these roadblocks. Since the development of this Matrix in December 2002, NIH has made considerable progress on several of its goals, including improvements in shared resources, better integration and enhancement of clinical studies at PD research centers, and acceleration of therapeutics discovery and translational research.

In addition to leading these efforts, the NINDS assesses needs and opportunities on a regular basis through a variety of focused workshops, such as the annual meeting of the Morris K. Udall Centers for Excellence in PD Research, and conducts an extensive annual analysis of the federal and non-federal PD portfolio of research. This portfolio includes research funded by other NIH ICs, the Department of Defense (DoD), the Department of Veterans Affairs (VA), non-governmental supporters of PD research, and to the extent possible, international organizations. NINDS uses this analysis to identify trends, to understand the changing scientific landscape as the field moves forward, and to capitalize on new opportunities as they arise.

To reduce redundancies in effort across the federal government, the NIH has also established a Parkinson's Disease Coordinating Committee (PDCC). Composed of representatives from twelve NIH institutes, the DoD, and the VA, the PDCC meets twice annually to coordinate planning and funding efforts across all federal agencies invested in PD research.

The 2005 Parkinson's Disease Summit

As alluded to above, the research landscape has evolved considerably in the past 5-10 years. The NIH recognizes that advances in basic and translational research bring researchers closer to new treatments for patients with PD, but this progress also highlights both old and new challenges that remain unsolved. To explore the current status and future promise of the many different approaches to preventing

and treating PD, the NIH sponsored a second PD Summit in June 2005. This meeting brought together academic researchers, industry scientists, clinicians, and members of multiple NGOs to assess progress on the Agenda, and importantly, to engage in a dialogue focused on the advances that have been made in prevention and therapeutics research and the translation of these findings into effective interventions. This second Summit differed considerably from the first, in that the first Summit focused primarily on the identification of research roadblocks and management tools to overcome them. By contrast, the second PD summit focused exclusively on the progress made in PD therapeutics research, and the development of next steps for this field. Specifically, participants at the second Summit identified a number of gaps across multiple therapeutics approaches and generated more than fifty specific recommendations for moving patient-oriented research forward. Many of these recommendations are well-suited for implementation by the NIH, while others are appropriate for other government agencies or NGOs to address. Furthermore, while the scientific advances made in the past several years have resulted in the achievement of some past goals, they have also led to the emergence of new ones. The NIH staff is currently analyzing the recommendations discussed below, as well as previous planning efforts, to integrate both into a revised PD Research Plan that will help guide programmatic activities in the coming years. NIH hoped that this Plan could also incorporate the results of the first phase of its Neuroprotection Exploratory Trials in PD (NET-PD) program (see below for more details), as these studies form the core of the NIH strategy for the development of protective neurotherapeutics, and an assessment of the utility and success of the World Parkinson Congress. The Congress took place in February 2006, and the NET-PD investigators published their results in March 2006, thus positioning the NIH well to complete the PD Plan.

Past Progress and Development of Future Goals

At the 2005 Summit, attendees participated in a plenary session and discussion regarding the status of PD research, with special emphasis on the progress in therapeutics development. Subsequently, the group divided into five breakout sessions, each focused on one of the broad areas of therapeutics development for PD outlined in the original Research Agenda. Topics of these sessions included pharmacological (or drug) approaches, cell replacement and gene therapy, deep brain stimulation, non-motor aspects of PD and non-invasive therapeutic approaches, and risk factors and prevention. Participants in the groups discussed these topics and developed a number of very focused recommendations for the

entire PD community, including the NIH, industry, and non-governmental supporters of PD research.

This section of the report highlights these specific recommendations in the context of the scientific successes made and new programs initiated in support of the PD Research Agenda. The goals are broad and are not assigned to any specific agency or organization for formal implementation. These latter assignments will be a key topic of additional planning discussions across the NIH, and with other federal partners, representatives of the pharmaceutical and biotechnology industries, and the PD patient community.

Pharmacological Approaches for PD

Advances and Analysis

Pharmacological treatment, or drug therapy, has been the mainstay of treatment for PD for several decades. However, the standard drugs used today treat symptoms such as tremor and rigidity, but do not alter the underlying course of the disease and often have debilitating side effects such as dyskinesias. Moreover, recent studies have shown that dopamine agonist therapies may also be associated with the emergence of compulsive behaviors, such as addiction to the medication itself or pathological gambling. When facing decisions about future investments in these therapies, consideration must be given both to the potential promise of therapeutics that can treat disease symptoms and those that may be neuroprotective or disease-modifying. While neuroprotective therapy is the ideal, symptomatic therapy remains essential until protective strategies become available.

The NIH recognizes the importance of both avenues of research, and has supported a number of approaches to drug therapy in PD that have shown success in preclinical models of the disease and, in some cases, clinical studies as well (though not all supported by the NIH). These include growth factors like brain-derived growth factor (BDNF) and glial cell line-derived growth factor (GDNF), antioxidants, and drugs that block selective neurotransmitters. NINDS-funded researchers have also explored the effects of the use and timing of initiation of levodopa therapy on the progression of PD, and the Institute is currently supporting trials of drugs that may affect dopaminergic sprouting, slow the loss of dopamine terminals in the striatum, and/or inhibit the dopamine transporter. While some of these approaches have clear potential benefit for early-stage patients, others – like drugs that block receptors for excitatory neural chemicals like glutamate – may help to reduce the complications of dopaminergic therapy in

more advanced patients. In addition, a variety of NIH ICs are exploring pharmacologic approaches to treating the non-motor features of PD – which are problematic for people at all stages of PD. Some of these approaches are described in the section on non-motor complications below.

As a step toward making new neuroprotective therapies available to patients and in direct response to a need for Phase II clinical trials identified in the PD Research Agenda, the NINDS has also invested substantially in a novel series of cooperative clinical studies designed to evaluate drug therapies that have the potential to slow the progression of PD. Launched in April 2003, the Neuroprotection Exploratory Trials in PD (NET-PD) involved an extensive process of planning, infrastructure development, and rigorous review of candidate therapies. Specifically, a team of pharmacologists, clinicians, and clinical trial experts – including NINDS staff – developed specific criteria for the evaluation of potential therapies, including scientific rationale, blood-brain barrier penetration, safety and tolerability, and evidence of efficacy in animal models or humans. The team of reviewers solicited suggestions from scientists and clinicians in academia and industry, as well as patient and foundation groups, in order to identify as many potential therapies as possible. A Steering Committee selected a small number of compounds to be evaluated in pilot clinical trials, and NINDS-funded researchers have published the results on the first two compounds in March 2006. These data indicate that both creatine and minocycline warrant further consideration in a large Phase III trial; however, minocycline was not as well-tolerated as was creatine. The NINDS is now working with trial investigators to plan a Phase III trial of creatine. To prepare for this scale-up of the project, NINDS has already funded additional clinical sites in order to enhance recruitment, especially for minorities. In addition to helping the NINDS plan for Phase III trials of one of the first round of neuroprotectants tested, these trials also informed the PD research and the neurology communities about critical considerations for identifying the most promising drugs for large-scale clinical trials (and eliminating less promising compounds from future consideration), and for involving groups of untreated control participants in these kinds of studies. Furthermore, the drug evaluation team described above is assessing additional promising compounds on a regular basis, and the NINDS is planning to award a contract soon that will help fill important gaps in preclinical data on promising drugs, needed for consideration for future NET-PD trials.

Discussions at the first PD Summit strongly indicated that for researchers testing pharmacological, as well as other therapies, access to a broad range of consistently collected clinical data and pathological samples will clearly be needed. To address this concern, NINDS has worked with the research

community to develop recommendations for minimum sets of clinical and pathological data for researchers to collect, and has funded a Parkinson's Disease Data Organizing Center to collect and make available clinical data (using these minimum data sets) across the Morris K. Udall Centers for Excellence in PD Research, the Collaborative Centers for Parkinson's Disease Environmental Research [CCPDERs; funded by the National Institute of Environmental Health Sciences (NIEHS)], and other PD research centers around the country. In addition to these efforts, the NINDS has also expanded the ceiling for Udall Center funding, enabling all of the Centers to expand their clinical research efforts.

Although much of this progress is encouraging, recent assessments by the NINDS in its portfolio analysis confirm a lack of biomarkers for PD. This need continues to hinder the advancement of early diagnosis and once available, treatment (with pharmacological and other therapies), as well as the design of more effective clinical trial outcomes. The NGOs in the PD research community have also recognized this need, and have provided initial funds to several research teams to pursue promising PD biomarkers. The NINDS is monitoring the results of these studies closely, and will engage the NGOs and successful investigators in discussions regarding next steps, in the event that any of these biomarkers warrant confirmation in larger clinical trials.

Summit Recommendations

Based on this assessment of recent advances and ongoing program initiatives, the NIH asked the pharmacological therapy breakout group to examine the current status of drug therapies for PD and the needs associated with developing better pharmacologic treatments. The group considered progress made by both the academic and industry communities and generated several recommendations aimed at accelerating the discovery and testing of new therapies for PD. Their recommendations spanned both preclinical and clinical research, and recognized the emerging need to build some aspects of the pharmaceutical industry's approach to therapeutic development into the academic research community. For example, one of the key problems facing the field of drug development for PD is that it is still not clear how to best bridge the gap between promising basic science findings, industry research and development, and clinical care. The breakout group made a number of recommendations to address this problem, several of which were ranked as a high priority by the full group of Summit participants. The first of these priority recommendations highlighted the continued need for simple and reliable biomarkers of PD – comparable to the prostate-specific antigen (PSA) test for cancer prediction. As discussed above, biomarkers would

be a tremendously valuable tool for academic and pharmaceutical researchers exploring pharmacological treatments for PD, as well as researchers exploring other therapeutic approaches. Specifically, biomarkers that are sensitive in predicting clinical outcomes (e.g., gadolinium-enhancing lesions for multiple sclerosis) could help researchers screen promising therapeutics with much smaller numbers of participants. The second priority recommendation was for more "validation of drug targets," in essence, the confirmation that interference with a particular cellular process can be used as an approach for treating PD. The third priority recommendation involved the development of animal models that better mimic the numerous clinical features of PD (including non-motor features) and are predictive for therapeutics testing. This recommendation echoes those made at several past PD meetings, and highlights the difficulties in accurately modeling the diverse clinical features of a chronic neurodegenerative disease in an animal. To address the paucity of adequate animal models, the National Institute on Drug Abuse (NIDA) Intramural Research Program (IRP), together with NINDS-supported investigators in Sweden, developed a chronic mouse model of PD in which dopamine neurodegeneration takes one year to manifest, i.e. the equivalent of 40 human years. Lastly, the fourth priority recommendation involved developing a more open line of communication between NINDS and representatives from pharmaceutical companies in order to facilitate translational research activities (e.g. those that bridge basic science to clinical trials).

In addition to these priority suggestions, the group also recommended the facilitation of drug screening efforts across the academic community and increased support for medicinal chemistry – the development and refinement of chemical compounds to more effectively treat disease – to bolster the search for therapeutics directly targeted to PD. The NIH is already undertaking broad efforts to manage the medicinal chemistry problem through its Molecular Libraries Screening component of the Roadmap project; the NINDS is also supporting a pilot program for spinal muscular atrophy that contains support for medicinal chemistry. The group also noted that in the coming years, it will be extremely important to develop a means to overcome the intellectual property issues that are currently hindering the sharing of therapeutics "shelved" by pharmaceutical companies with the academic research community for further exploration. For example, NIDA is already screening thousands of compounds to identify novel chemical entities that interact with the dopamine transporter and the dopamine D1 receptor, which may have significant therapeutic and diagnostic implications for PD. This approach could be expanded to the "shelved" compounds as well. Lastly, participants in this session suggested it would be important in the future to establish a mechanism for educating researchers, including those focused primarily on basic science research, about the

requirements of the U.S. Food and Drug Administration for clinical testing of potential treatments. While NINDS is already involved in educating investigators about these requirements as part of its broad translational research program, participants believed that better communication about these requirements would enable them to be taken into consideration at the earliest stages of preclinical research.

Cell Replacement and Gene Therapy

Advances and Analysis

In addition to drug therapies, cell replacement and gene therapy are also promising strategies for providing therapies in individuals with PD at various stages. Early-stage patients may benefit, since it is believed that clinical presentation of PD occurs when more than 50 percent of a person's dopaminergic neurons in the substantia nigra – a region of the brain critical for coordination of movement – have deteriorated. Cell replacement via transplantation may be able to effectively reconstruct the lost neuronal circuitry. Gene therapy might also help these individuals as well, if neuroprotective therapies were available that could be delivered with this technique. Gene therapy also has the potential to deliver compounds to later-stage patients that would provide symptomatic relief.

Fundamental experiments in animal models of PD are making impressive progress toward the goal of cell replacement, and NIH-supported extramural and intramural studies have shown promise using a variety of cell types. For example, research teams have been successful in deriving dopamine cells from mouse embryonic stem (ES) cells and federally-approved human ES cells in culture, and in separate studies, producing beneficial behavioral effects following transplants of these types of dopaminergic cells into rodent models of PD. Researchers are also exploring the potential of adult stem cells, and have isolated cells from the white matter of human brain (removed for therapeutic surgery) that can multiply and specialize to form both major cell types of the brain, nerve cells and supporting cells.

Although these studies and others are making headway, the distribution and testing of these cells have been raised as priority issues at past PD planning meetings, and remain issues of concern across the PD research community. In order to compare the properties of the federally-approved stem cell lines and to define general strategies that allow these cells to be widely and confidently used in research, the NIH established a Stem Cell Characterization Unit in April 2003. In addition, NIH announced in October 2005 that it is funding a National Stem

Cell Bank at the WiCell Research Institute in Wisconsin. This bank will consolidate many of the federally funded eligible human ES cell lines in one location, reduce the costs that researchers have to pay for the cells, and maintain quality control over the cells. The Bank will also provide technical support that will make it easier for scientists to obtain the cell lines currently listed on the NIH Human Embryonic Stem Cell Registry (http://stemcells.nih.gov/research/registry/).

The NIH has also supported a number of advances that promise to accelerate the use of gene transfer and other genetic approaches to treat PD. For example, NINDS has funded a large, multi-center, multidisciplinary, preclinical investigation of both dopaminergic enzyme gene therapy and neurotrophic gene therapy in non-human primate models of PD. The leaders of this project, the Parkinson's Disease Gene Therapy Study Group, are studying the different genes and gene delivery approaches and are conducting safety and toxicity assessments. Now more than three years into the project, the Study Group has developed a delivery method that can turn on and off gene expression in a controlled fashion, and has characterized the immune response to both the delivery vehicle and the treatment that is delivered. The NIH believes that by supporting this rational, coordinated and integrated approach to the development of gene therapy treatments for PD, researchers can achieve the ultimate goal of laying the groundwork for an Investigational New Drug application to the U.S. Food and Drug Administration, necessary to proceed to clinical trials in humans. This research also lays critical groundwork for development of a gene delivery scaffold that may be useful for other therapeutic molecules as well.

In addition to this large effort, the NIH has also supported a number of individual laboratories in their efforts to use gene transfer approaches to reduce the impact of parkinsonian symptoms in animal models of the disease. These researchers have already achieved some successes, including improvements in function and dopamine levels with transfer of genes that aid in the production and transport of dopamine. This approach may be especially promising for preventing the side effects of oral levodopa administration, such as dyskinesias. Other researchers are looking to more novel but also more complex approaches, such as the delivery of genes that activate neuroprotective mechanisms. In addition, taking a cue from a number of other neurodegenerative disease fields, NINDS-supported researchers have recently used gene transfer to interfere with the production of abnormal α-synuclein in cultured cells and in an animal model of the disease.

Summit Recommendations

With this background in mind, NIH asked this breakout group to assess the future of cell replacement and gene therapy as rational therapeutics for treating PD and the advances that would be needed to accelerate these potential therapies to the clinic. As a result of their discussion, the group made a number of recommendations, two of which were listed among the top priorities by the full group of Summit participants. The first priority recommendation focused on expanding our understanding of gene function in PD, in order to enhance the ability of researchers to use genetic strategies (including but not limited to gene therapy) to reduce the effects of the disease. The second priority recommendation involved the expansion of our understanding of the genetics and basic biology of the development of dopaminergic neurons. Although NIH-supported researchers have made significant progress in this area, important questions remain unanswered. Both of these recommendations highlight needs that have existed since the development of the original PD Research Agenda. Specifically, this information would help researchers understand how dopaminergic neurons specialize and make connections with other neurons, and would aid in the creation of more useful lines of dopaminergic cells for further study.

Regarding stem cell research, the participants in this breakout group also recommended the development of a more complete characterization of the cellular environments that promote survival and normal function of dopamine neurons, and the continued exploration of cells that can survive in the brain and act as drug delivery pumps. This latter recommendation could include an expanded investigation of the potential cell types that lack the ethical concerns of human embryonic stem cells (e.g., fat cells, cells from the retinal or olfactory systems, etc.); the potential combination of these cells with man-made devices for drug delivery; the consideration of stem cells for delivery of gene therapy; and the use of genetic information on PD and stem cell model systems to create even more relevant tools for preclinical therapeutics testing.

The group also acknowledged that more could be done to prepare the PD research community for the evaluation of grafted (e.g., implanted into the brain) cells in the future. Some specific goals included better methods for assuring graft quality, including optimization of cell preparation, graft location, and immunosuppression regimen; agreement on the best targets for grafts; and better measures of successful implants or grafts. In addition, the group recommended more preliminary assessments in non-human primates and more standardized measures for participant selection and assessment of outcomes.

With respect to gene therapy, the group also expressed an interest in further exploration of research designed to correct the genetic mutations that occur in some people with inherited PD. This could involve the production of additional animal models and/or the potential targeting of therapeutic molecules to specific cell types.

As a means for propelling the field forward in these areas, the participants recommended the development of a number of resources, including access to high quality gene therapy vectors (the cellular delivery vehicles); a coordinated effort to create standardized dopaminergic neurons; and recognition for investigators in the field who are developing novel PD therapies. They also suggested workshops in several areas, including stem cell standardization and transplantation techniques and the genetics of PD, as a basis for developing novel therapies.

Deep Brain Stimulation

Advances and Analysis

Deep brain stimulation (DBS) – the delivery of electrical stimulation to specific cellular targets in the brain – is becoming an increasingly common and effective therapeutic option for people with PD. In 2002, the U.S. Food and Drug Administration approved the use of deep brain stimulation (DBS) for advanced Parkinson's, and to date, thousands of people worldwide have undergone this procedure. In successful cases, the improvement in a person's mobility can be dramatic – enabling people whose disease had advanced significantly to return to a number of normal activities. The use of surgical approaches, including DBS and the targeted destruction of brain tissue used for many years prior to DBS to treat PD, has evolved over many decades through the work of clinicians both in the U.S. and overseas. However, NIH-supported studies of the brain circuits that control movement, specifically those involving a group of structures in the brain called the basal ganglia that play an important role in the clinical manifestations of PD, were particularly critical to this advance. In addition, NIH funding was also instrumental in enabling researchers to study how interference with these circuits could improve parkinsonian symptoms in non-human primate models of the disease. This body of knowledge, coupled with advances from the NIH-supported Neural Prosthesis Program – which supported the development and refinement of electrodes to stimulate brain tissue – laid the critical groundwork for the ultimate success of DBS, and for the continued basic science and clinical studies of this approach.

DBS is now performed frequently to treat advanced PD. However, the research and clinical communities still do not fully understand how it works at the level of brain circuitry. For example, DBS can effectively reduce symptoms such as tremor when applied to the subthalamic nucleus (STN), part of the brain's movement control circuitry. Previously, researchers believed that DBS worked by producing a "reversible lesion" in the STN, and preventing its output to other brain structures. However, more recent findings suggest that DBS may work by interfering with the abnormal firing patterns of the targets of STN neurons, and not by simply silencing the STN itself.

Other questions persist regarding the optimal clinical use of DBS. As just one example, clinicians do not have information from well-designed, controlled clinical trials to use in selecting the optimal target for brain stimulation. To resolve this specific question, the NINDS has been collaborating with the VA since January 2002 on the largest trial to date of DBS in individuals with PD. The trial is designed in two phases – the first to compare DBS and best medical management, and the second to evaluate the effects of DBS in two different brain locations. The NINDS is providing substantial support for this project, primarily to enhance the enrollment of women and minorities.

In addition to this collaborative study, the NINDS is also supporting three additional trials of DBS for PD, which are designed to explore a series of other unresolved questions. The first such study is a phase III trial exploring the effects of DBS on motor, neuropsychological, and psychiatric function, as well as quality of life. The second study is a phase II trial that will explore the impact of DBS on mood and cognition, and the third is a phase I study that will begin to explore how DBS affects the underlying neural activity that controls movement and posture. The National Center for Research Resources (NCRR) has also supported studies of this approach, specifically the effects of DBS in the thalamus and globus pallidus on both functional rating scales and imaging outcomes.

Summit Recommendations

Despite the advances that have been made in DBS research and the trials that NINDS has initiated, the PD community still needs more information on long-term follow-up of patients, and tools to help guide clinicians in identifying not only the appropriate stimulation parameters for individual patients but also the optimal target and stimulation guidelines. Given these issues, the NIH asked this Summit breakout group to discuss the role of DBS as a standard of surgical therapy for PD, and how it could be improved to the benefit of PD patients. The group developed several recommendations, one of which – the participation of

larger numbers of appropriately-selected subjects in clinical trials, and longer subject tracking – was highlighted as a priority by the full group of Summit participants. In addition to this priority recommendation, the breakout group also suggested the continuation of improvements in the technology for DBS, including improved electrode design; standardization of electrode placement; improved imaging of the electrodes; improved understanding of the mechanism of DBS; expansion of data on appropriate stimulation parameters; and the banking of brain samples from individuals with DBS stimulators. The group also emphasized the need for other improvements in DBS clinical trials, including the creation of a database to capture clinical information on trials; refinements in subject selection and guidelines for placement and stimulation of electrodes; and the standardization of procedures.

Non-motor Aspects of PD and Non-Invasive Therapeutic Approaches

Advances and Analysis

One of the most debilitating aspects of PD is that in addition to the motor complications of the disease, multiple non-motor features can develop which can severely impact a person's quality of life. These complications vary from person to person, but can include sleep abnormalities, fatigue, behavioral and cognitive impairments, anxiety, depression, autonomic dysfunction, gastrointestinal problems, pain and psychosis. While psychosis is a non-motor complication of PD, it may be caused by PD medications, rather than from the disease itself. Speech problems are often included in this group of complications as well. Although speech is a motor function, it responds differently than limb movement after pharmacologic and/or neurosurgical intervention.

Over the past several years, NIH-funded researchers have increasingly recognized the need to study these aspects of PD, and have targeted their research to address their impact. For example, the National Institute on Deafness and Other Communication Disorders (NIDCD) has long been interested in the swallowing and speech problems that accompany PD, and to address the first of these problems, is supporting a randomized study of two interventions for liquid aspiration in individuals with PD. Liquid aspiration is the most common type of aspiration in older populations, and it can lead to pneumonia in these individuals. The National Institute of Child Health and Human Development (NICHD) is also interested in improvement of quality of life, and supports a wide range of rehabilitation studies to this end. With respect to PD, the NICHD is currently exploring exercise in individuals with PD, to determine if it aids them in improving the efficiency of their movements, and is exploring contributors to

long-term disability in people with PD. The National Institute of Mental Health (NIMH) fosters research on PD, including studies on understanding relevant brain mechanisms, developing new animal models and diagnostic tools, and improving diagnosis and treatment of co-morbid mood disorders. Furthermore, the National Center for Complementary and Alternative Medicine (NCCAM) continues to explore complementary and alternative medicine practices to treat PD and its accompanying complications, including depression and sleep disturbances.

The NCRR has also supported investigators studying the effects of transcranial magnetic stimulation on depression related to PD. The NIDA and NINDS IRPs are also collaborating on a new transcranial magnetic stimulation coil design that will allow non-invasive stimulation of deeper brain areas. The National Institute of Nursing Research (NINR) is supporting research into improving the quality of life and easing the burden of family caregivers of patients with PD. NINR research priorities related to PD have included understanding and easing symptoms, delaying the onset of disability, slowing disease progression, and caring for individuals at the end of life. Lastly, the NINDS is also funding a number of clinical studies that are directed to improved quality of life; these trials are exploring therapies to improve limb function, to reduce the "masked" facial expressions that often accompany PD, and to treat PD-associated depression.

The NIH grant portfolio now includes additional ongoing studies of these complications, including clinical trials and investigations of several complementary and alternative medicine therapies, and the NIH, DoD and foundation groups have sponsored workshops and meetings to develop diagnostic criteria for important complications such as depression, psychosis, and dementia related to PD. Diagnostic criteria are extremely important for the inclusion of appropriate subjects in clinical research studies, for linking clinical symptoms to the cellular changes in the disease, and ultimately, for the earliest possible identification and treatment of affected individuals. To explore the diagnosis of depression, the NINDS funded a meeting in December 2003 to begin development of diagnostic criteria; NINDS staff and participants published a set of initial criteria in October 2005. In November 2005, NINDS held a second criteria development workshop focused on psychosis and PD. Again, participants are working with NINDS staff to follow the meeting with the development of clinical criteria and scales – and a working group of the Movement Disorders Society will likely take part in this project as it proceeds. The NIA and NINDS have also supported the development of clinical criteria for diagnosing dementia with Lewy bodies (DLB), with the publication of a December 2005 paper on the diagnosis and management of DLB following a jointly-sponsored meeting on clinical-pathological correlations for DLB in September 2004. While these

groups have made substantial progress on the clarification of the diagnoses, the clinical research community has not yet adopted these initial criteria on dementia and depression. In addition, studies to find a wider array of treatments for these and other non-motor symptoms are still needed.

Summit Recommendations

Based on the growth in this research field, the NIH asked this breakout group to examine the many significant non-motor aspects of PD, and to also consider the status and potential promise of non-invasive treatments for PD, including exercise, speech-language intervention, and other behavioral rehabilitation techniques. The group discussed a wide range of non-motor aspects of PD, and identified sleep dysregulation, fatigue, behavioral and cognitive impairment, psychosis, and anxiety/depression as particularly important for future research studies. This group also developed numerous broad recommendations, and several were confirmed by all of the Summit participants as being of high priority. The first of these priority recommendations involves expanding our understanding of the non-motor manifestations in PD. The portfolio analysis illustrates that more treatments for these features are needed, and an improved base of knowledge would be a substantial contribution to therapeutics development. A second priority recommendation was the development of animal models that reproduce non-motor features of PD for research, drug discovery, and testing. Past PD planning meetings have emphasized the need for improved animal models, but this is the first formal recommendation to expand these efforts to encompass models that reproduce the non-motor complications of the disease as well. A third priority recommendation was the incorporation of evaluations of the non-motor manifestations of PD into clinical trials, which the group agreed would aid in the testing of both pharmacological and non-pharmacological interventions for these complications. The last priority recommendation involves the development of improved methods for characterizing the non-motor complications, including standardized methods for clinical assessment. As discussed above, the NIH has already taken important steps forward in developing diagnostic criteria for PD-associated dementia and depression, but it is clear that the community needs similar efforts for other complications of the disease.

In addition to these priority recommendations, the group also suggested a number of other strategies to move this field forward, including studies of how the cellular changes in PD lead to non-motor symptoms; the incorporation of studies of non-motor manifestations into the development of risk factor criteria; and further studies of the impact of these aspects of the disease on disability.

Risk Factors and Prevention

Advances and Analysis

Several different risk factors may impact a person's susceptibility to developing PD. Age is the most significant risk factor, with most cases of PD occurring in individuals over fifty. In addition, mutations in specific genes (described in more detail below) are believed to cause PD in rare families around the world. Subtle genetic changes called single nucleotide polymorphisms (SNPs) can also be harbored by larger groups of people. While SNPs may not cause disease in everyone affected, they may increase a person's susceptibility. Lastly, researchers have implicated exposures to various environmental toxicants – including agricultural pesticides and heavy metals – as risk factors for PD. The effectiveness of future prevention efforts may hinge both on our ability to identify and understand the impact of genetic and environmental risk factors, and to develop ways to track the very earliest signs of PD in affected individuals.

As described in a previous section, the basic science studies of the underlying causes of PD form a robust part of the NIH research portfolio, and they have made significant contributions to our understanding of the risk factors for PD. Genetic studies have flourished in recent years, beginning with the discovery by NIH investigators and international collaborators of mutations in the α-synuclein gene as the first gene defects associated with PD. The discovery that genetic mutations could cause PD brought a dramatic shift to a field that had previously focused primarily on environmental causes of the disease. When the NIH drafted the PD Agenda several years later, one additional gene – parkin – was also linked to PD. Now, six genes have recognized links to PD, including α-synuclein, parkin, UCHL-1, DJ-1, PINK1, and LRRK2 – and evidence suggests the existence of at least five other as yet unidentified genes. These discoveries have helped expand the overall number of genetic and molecular studies being pursued and have enabled researchers to better understand how genetic mutations can cause downstream changes that lead to problems with dopaminergic function. Importantly, the genetic advances have also enabled the development of new animal models of PD. However, recent advances and the NINDS portfolio analysis suggest that as more genes and proteins are implicated in PD, subsequent cell biological studies will be needed.

In addition to gene discovery efforts, the NIH is also supporting a genome-wide screen for additional mutations or genetic variations that may contribute to inherited and more common forms of the disease. The NIH hopes to complete this first publicly-shared screen for PD early in 2006. NINDS has also made a number of resources available to investigators – including a large repository of DNA samples from individuals with PD (and controls) and microarrays (gene chips, or glass slides containing minute amounts of genetic material arranged in a pattern that facilitates rapid examination) – that are accelerating genetic studies in a number of laboratories.

Although the NIH has been extremely successful in characterizing genetic contributors to PD, a significant gap exists in our understanding of how these genetic changes interact with environmental factors to alter disease risk. The NIEHS and other ICs have supported several important research advances in this area, including the discovery that chronic administration of the botanical pesticide rotenone to rats causes anatomical and behavioral changes that mimic PD. Importantly, these changes include the development of cellular structures that mimic Lewy bodies, intracellular protein accumulations that are characteristic of PD-affected neurons. This model has already been extended successfully into non-rodent species that have important experimental advantages. The NIEHS and other NIH ICs have also supported a wide range of related research projects, including studies of the intracellular effects of rotenone and other agricultural toxicants; the synergistic effects of combined toxicants; the enhanced sensitivity of the aging dopaminergic neurons to pesticides; other risk factors, including occupational and dietary heavy metal exposures; and other environmental events that may predispose people to develop PD (e.g., head trauma). To complement these research studies, the NIEHS established three CCPDERs in 2002. The primary research objectives of CCPDER Consortium Program were to identify genetic and environmental factor interactions that contribute to PD; to understand how gene-environment interactions trigger the cellular processes that ultimately produce PD; and to develop the knowledge required to translate research findings into rational prevention and intervention strategies for PD.

While these programs and advances illustrate the NIH commitment to understanding the genetic and environmental contributors to PD, more work will be needed as our genetic knowledge continues to grow. In addition, and as described above, the lack of reliable biomarkers presents a significant challenge to prevention efforts in the future. Furthermore, as gene discovery efforts continue, it will be increasingly important to recognize the effects of these findings on people with PD and their families. As a result, researchers and clinicians must

address the ethical and moral issues regarding genetic testing as their studies progress.

Summit Recommendations

With these advances and needs as the context, NIH asked this group to develop goals related to the identification and validation of risk factors for PD, which will ultimately enable the prevention of the disease. In response, the group recommended a wide range of additional research studies, five of which were confirmed as high priorities by the other Summit participants. The first priority recommendation was the expansion of studies of people at-risk for inherited forms of PD. These clinical investigations are particularly valuable for characterizing the clinical course of the disease, and for biomarker discovery efforts in presymptomatic at-risk patients. A second priority was the development of a gene chip that would allow for further in-depth analysis of the genes implicated in inherited forms of PD. A third priority recommendation was the continuation of prevention/disease-modifying clinical trials in at-risk populations, and again, using these trials to extend biomarker discovery efforts. In identifying subject criteria for these studies, participants believed that multiple potential risk factors or early indicators of PD should be considered, including genetic mutations that have been linked to PD; imaging findings consistent with PD; and sleep disorders. A fourth priority involved surveys of "control" populations to identify subtle variations in genes that might influence the susceptibility to PD. These studies will be critical to revealing information on the complex role of genetics in individuals that may develop typical, non-inherited forms of PD. Lastly, the fifth priority recommendation was to foster the development of genetic testing guidelines with appropriate professional groups.

In addition to these priorities, the group also recommended two goals for the epidemiology community, as they continue to explore the causes of PD across populations. First, the group urged them to develop standardized instruments for the collection of data and to require that NIH-funded instruments be shared among all researchers in the epidemiology community. Genetic analyses should also be included as a component of these studies. Second, the group suggested that epidemiologists try to combine and analyze data from existing studies, even though different data collection instruments may have been used.

Additional recommendations on the prevention of PD included searching for biomarkers in groups of "control" subjects recruited for clinical trials (to explore early indicators of sporadic PD in the general population), and expanding prevention trials to include individuals at risk for non-genetic forms of PD as well

– once biomarker or complex genetic profiles are available to help identify these individuals.

Lastly, in addition to the concerns raised above about genetic testing, the group also urged an evaluation of the clinical usefulness of testing for genetic mutations believed to be linked to PD, and clarification of the regulations that govern the ethical and privacy aspects of this research, to ensure that misunderstandings regarding policy issues are not unduly hampering the research process.

Parkinson's Disease Incidence and Geographic Clusters

The Centers for Disease Control and Prevention (CDC) obtains information on PD prevalence, health care utilization, and mortality through its National Center for Health Statistics; specific data collection mechanisms include the National Health Interview Survey, the National Vital Statistics System, the National Hospital Discharge Survey, and the National Nursing Home Survey. Several programs at the NIH compliment these efforts. For example, the NIEHS has provided modest support, along with the Michael J. Fox Foundation, for the piloting of a California PD registry. This registry will be of great value to PD research in light of the significant variation in race/ethnicity, geography, and environmental exposures in California. Moreover, the NIEHS is supporting a number of large-scale epidemiologic investigations that are incorporating thorough characterization of PD cases in various locales and these will be of benefit for understanding the current clinical variation in PD. The NIEHS is also supporting the use of international registries (in Denmark and Sweden) that are population-based and can provide some insight into disease trends, and the development of epidemiologic instruments that can be shared with investigators in other countries who wish to initiate research on PD and potential risk factors. The NINDS has also provided leadership with its PD-DOC efforts to standardize clinical and pathological criteria for data collection; these efforts are crucial for comparing potential differences in PD incidence over time. The NIH believes that there is a great need for reliable incidence and prevalence estimates for PD to allow investigation of variation over time and/or geography, and will work with the CDC to combine their respective research efforts in this area as opportunities arise. In particular, the various epidemiology studies should provide information on the location of obvious geographic clusters in the regions being studied.

Conclusions

NIH organized the 2005 PD Summit to provide guidance for the PD community in outlining the next steps necessary to move therapies closer to clinical evaluation and practice. The meeting was very effective in identifying new priorities for the field, and in providing closure to goals from previous planning meetings that have already been met. In addition, some recommendations, such as the significant need for biomarkers, improvement of animal models of PD, and an increased focus on therapeutics development, reiterate suggestions made at previous PD planning meetings and needs identified in previous NIH portfolio analyses. These findings highlight the difficulties inherent in many areas of Parkinson's research. In several of these cases, the participants provided greater specificity to these previous recommendations, such as emphasizing the need for animal models of the non-motor complications of PD and the critical importance of drug target validation.

The NIH believes this input will be extremely helpful to refine future programmatic actions, and ultimately, in moving PD research into an era of effective treatments and an improved quality of life for people at all stages of PD. To this end, NIH staff is already utilizing the recommendations developed at the Summit to guide its short-term program plans, and some workshops and initiatives currently under development address the priority goals listed above. As the NIH ICs identify the steps necessary to implement the highest priority recommendations for the next three years, Institute leaders and staff will engage in further discussions with other governmental and non-governmental supporters of PD research, in order to determine which organization is best suited to lead each effort. In addition, the NIH expects to develop a revised PD Research Plan, which integrates the recommendations made at the most recent meeting with goals from previous planning meetings that remain unmet or have evolved over time. All of the ICs that participate in PD research are committed to ensuring that the highest priority recommendations from the 2005 meeting are implemented quickly and effectively. The NIH hoped that this plan could incorporate the results of its first two neuroprotection clinical trials, because of the critical importance of therapeutics and the need to have better approaches for designing and managing trials, and an assessment of the utility and success of the World Parkinson Congress. The Congress took place in February 2006, and the clinical trial results became public in March 2006; thus the NIH is now positioned well to complete the PD Plan. The NIH will hold additional workshops as necessary to help address specific recommendations, and will convene larger planning meetings every other year in order to refine this Plan on a regular basis.