The 2006 Parkinson's Disease Research Plan

Developed by the National Institutes of Health

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*<u>*Notation Key for Goals*</u>

<u>*New Priority:*</u> *These were voted as top priorities at the most recent Summit but were not raised as specific recommendations at previous planning meetings*

<u>*Highest Priority:*</u> *Goals that received the most votes by participants at the Summit and that were also raised at previous PD planning meetings (including the PD Agenda meeting, the PD consortium meeting in 1/02, and the first PD Summit (in 7/02) and remain unmet.*

<u>*Priority:*</u> *Existing goals from previous planning meetings that remain unmet, but were not raised at the most recent Summit meeting.*

Parkinson's Disease Research Plan 2006

Introduction

Background

For several decades, fundamental research supported by the National Institutes of Health (NIH) has contributed to important advances in understanding and treating Parkinson's disease (PD). Early studies of L-dopa contributed to its use as the mainstay of current drug therapy, and characterization of the brain circuitry affected by PD was critical in the development of deep brain stimulation (DBS; the delivery of electrical stimulation to specific cellular targets in the brain). In the mid-1990's, technological and scientific breakthroughs opened new opportunities in many areas of the neurosciences. For the PD research community, the discovery of α-synuclein – the first gene implicated in PD – played an important role in this transformation. Because of these unprecedented scientific opportunities and pressing needs of patients, the NIH initiated a series of planning efforts to hasten discoveries in PD research that would lead to better treatments and ultimately, a cure.

In FY2000 report language the Senate Committee on Appropriations asked the NIH to develop a coordinated effort to take advantage of promising opportunities for PD research. In response, the National Institutes of Neurological Disorders and Stroke (NINDS) held a major PD planning meeting in January 2000. This meeting included all components of the PD community: basic research scientists, clinicians, pharmaceutical company representatives, ethicists, and the representatives of non-governmental organizations (NGOs). Brainstorming sessions allowed participants to discuss research critical to progress in PD, and to explore all possible research directions that could advance the understanding of the disease and thus lead to improved therapies. Their recommendations formed the basis of a five-year PD Research Agenda to manage opportunities in four major research areas: 1) understanding PD (basic studies of genetics, epidemiology, cell biology, and circuitry); 2) treating PD (clinical trials of drug therapies, cell- and 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, the NINDS and other NIH Institutes and Centers (ICs) issued more than thirty grant and contract solicitations relevant to PD, organized more than thirty workshops, funded nine supplement programs, and established important resources to complement the investigator-initiated awards that make up the core of NIH grant programs. The scientific community responded enthusiastically to these opportunities, and as a result, the NIH invested nearly $1 billion to implement the PD Research Agenda from FY 2000 through FY 2004.

During the Agenda's implementation, the NIH regularly assessed progress through annual analyses and coordination of the PD research portfolio, and modified the Agenda to incorporate new opportunities. At the midpoint of the PD research Agenda, the NIH held two additional planning meetings: an Agenda Implementation Review meeting in January 2002, and a PD Coordination Summit in July 2002. The Implementation Review meeting explored progress on the Agenda and involved participants from the scientific/clinical communities and NGOs. While

it was recognized that the NIH had made substantial progress in several areas, participants identified additional areas that warranted attention, including the non-motor aspects of PD and focused translational research for PD. The subsequent Summit meeting involved a much smaller group of scientists and clinicians, and focused on the identification of roadblocks impeding PD research within the context of the international PD research portfolio. The resulting recommendations highlighted the scientific management efforts needed to overcome these roadblocks, and were formulated by NIH into a Matrix of low-to-high risk (of success) and short-to-long term goals. Since the completion of this Matrix in December 2002, the NIH has already achieved many of its goals, including improvements in shared resources, better integration and enhancement of clinical studies at Udall and other PD research centers, and acceleration of therapeutics discovery and translational research.

Development of a New PD Research Plan

When the PD Research Agenda reached the end of its 5-year span, the NINDS sponsored a second PD Summit, held in June 2005. It brought together academic researchers, industry scientists, clinicians, and members of NGOs to assess progress made over the last 5 years, and develop future directions for PD research based upon the state of the field. Breakout groups were asked to assess progress in prevention and treatment research and the translation of these findings into therapies. There were five PD research topics of focus: Risk Factors and Prevention, Cell Implantation and Gene Therapy, Pharmacological Approaches, DBS, and Non-motor aspects of PD. At the conclusion of the Summit, the participants generated more than fifty specific recommendations for moving patient-oriented research forward in these areas. The NIH asked the participants to prioritize these recommendations to produce a comprehensive, revised PD Plan. NIH leadership and staff considered these suggestions and priorities, along with unmet goals from previous planning efforts, and developed the three-year Plan for the Federal and non-Federal PD community that follows. This Plan retains some of the outline of the original Agenda, as Summit participants agreed that many of these topical areas were important to continue to pursue, with the modifications suggested by the Summit recommendations as the field has advanced.

In addition, since the Summit meeting, the NIH has also developed a "Neuroscience Blueprint" – a plan for neuroscience research being developed by a number of NIH neuroscience-focused Institutes and Centers. The first topic of interest the "Blueprint" will pursue is neurodegeneration, and a meeting was held in March, 2006 to discuss goals and resources to accelerate discoveries in this area. While this latter meeting was broader in context, some of the goals articulated by the participants in the neurodegeneration research meeting were extremely relevant to those suggested for PD. Blueprint overlap is thus noted throughout the Plan, as this related planning process gives added weight to several PD priorities.

The PD Plan is outlined below, prefaced by a brief description of the current scientific status of each area, providing the scientific context for this updated set of goals and priorities. An Appendix of significant advances in PD relevant to the PD Research Agenda is also provided at the end of the document.

Parkinson's Disease Research Plan

Understanding Parkinson's Disease

Basic PD research over the last several decades, including genetics, molecular and cellular biology, characterization of neural circuitry, brain anatomy, and neurochemistry, has formed the basis of therapeutic research being currently pursued for PD. While the causes of PD are still not fully understood, the most prevalent theories suggest that toxic accumulation of protein in cells, dysfunctional protein clearance, and oxidative stress that leads to cell death are primary causal pathways. There is now genetic evidence for each of these pathways, and a prevailing research strategy is to identify points in these pathways that could be exploited for therapeutic benefit.

Today's basic science research continues to span a diverse array of fields, from genes and molecules, through cells and physiological systems, to the role of the environment and its interaction with genetic susceptibility. It is expected that these studies will continue to inform preventive strategies and better treatments for PD in the future.

The Genetics and Cell Biology of Parkinson's Disease

One of the most remarkable transformations in PD research over the last decade was the identification of the first gene to be associated with PD, α-synuclein. The discovery that genetic mutations could cause PD brought a sea change to a field that had previously focused only on environmental causes of the disease. Since the discovery of alpha synuclein in 1997, six genes have been linked to PD, including α-synuclein, parkin, UCH-L1, DJ-1, PINK-1, and dardarin/LRRK2 – and evidence suggests the existence of additional, as yet unidentified genes.

Gene discovery and gene characterization continue to be pivotal to clinical progress. Genetic mutations can provide a direct window into the cellular causes of disease, not only for individuals with hereditary disease, but for those with sporadic disease as well. Moreover, genetic mutations and single nucleotide polymorphisms (SNPs) – subtle variations in the genetic code that occurs across a population – can help clinicians identify who is at risk for the disease. Once neuroprotective and preventative therapies are developed, it will be crucial to target at risk patients early in disease for these therapies to have impact.

Since the discovery of α-synuclein, subsequent research has shown that synuclein plays a role in protein aggregation in dopaminergic neurons in both inherited and sporadic PD, generating translational research on aggregation inhibitors and synuclein knock-down strategies (such as small interfering RNAs, or siRNAs) as potential new treatments. Many studies suggest that protein accumulation is neurotoxic, in particular, studies showing triplication or duplication of synuclein genes, and thus synuclein protein, causes PD. However, other studies have demonstrated that the aggregation process may be a protective response to insult, and it still remains unclear as to which forms of synuclein during the aggregation process are toxic. Understanding the role of α-synuclein may enable strategies to selectively block the harmful effects associated with this protein as a novel approach to treatment of PD.

Other studies of proteins genetically implicated in PD continue to reveal potential therapeutic points of intervention - for example, mutant parkin may interfere with the disposal of misfolded proteins, leading to their subsequent aggregation, and may also adversely affect mitochondrial function; DJ-1 and PINK1 genes encode for proteins associated with mitochondria in neurons that may confer neuroprotection, thus when these genes are mutated, the loss of the normal function of these proteins leads to oxidative stress and development of the disease. Targeted manipulation of these proteins or their interacting partners will be important in modulating disease progression.

More recently, scientists have begun characterization of the LRRK2 gene, which may account for a high percentage of familial and idiopathic PD. To date, 20 *LRRK2* mutations have been linked to PD, accounting for approximately 7% of familial PD and for a significant fraction of sporadic PD cases. The most prevalent LRRK2 mutation is responsible for perhaps 40% of familial and sporadic PD in North African Arab populations, 30% of familial PD in Ashkenazi Jewish populations, up to 6% of familial cases in Europe, and up to 3% of apparently sporadic PD in Europe and North America. The clinical symptoms associated with *LRRK2* mutations are frequently indistinguishable from idiopathic PD, suggesting that a therapeutic strategy directed against LRRK2 might be a key target in the treatment of PD.

In addition, NINDS intramural and extramural researchers have also identified important genetic links between PD and Gaucher disease. Specifically, they now recognize that mutations in the glucocerebrosidase gene can contribute to the development of both disorders. This finding not only expands our understanding of the cellular biology of both diseases, but it also illustrates the surprising relationships that sometimes emerge between seemingly unrelated disorders.

In addition to these successes, the NINDS Human Genetics Repository has banked over 10,000 samples, (5436 from PD and 5271 control subjects) with known causal genes including parkin, LRRK2, and synuclein triplication. Publicly available samples and data exist at http://locus.umdnj.edu/ninds for 1351 subjects with PD and approximately 100 with other forms of parkinsonism. A whole genome study (SNP based analyses) is currently underway in the intramural program using these samples in PD to identify risk factors for sporadic disease. The NINDS has publicly posted clinical data and a whole genome SNP analysis from this study so far, for close to 300 control subjects, which has already been accessed by over 50 researchers to date.

Environmental Influences

Until the discovery that mutations in the α-synuclein gene can cause hereditary PD, a substantial number of researchers believed that PD was caused primarily by exposure to environmental agents. Several discoveries since the initiation of the PD Agenda have shed considerable light on the extent to which toxic exposures may contribute to PD, and the pathways through which these agents may act. Environmental toxicants and pesticides, such as rotenone, can directly and specifically damage dopaminergic neurons in PD animal models. These compounds poison neurons via oxidative stress pathways in mitochondria - the toxin MPTP causes PD in humans through the same mechanism. For many years, there remained a significant disconnect between the protein aggregation theory as a causative pathology in PD versus the oxidative stress pathway

and the implication of mitochondrial dysfunction as suggested by environmental exposures like MPTP. However, recent genetic evidence in the form of DJ-1 and PINK-1 have given additional weight to the oxidative stress pathway , and an understanding of the relationships between genetic risk factors and toxin exposures might help clarify how these disparate pathways may interact. Today, most scientists believe that genetic predisposition and environmental exposures act together to cause most sporadic cases of the disease.

Important goals for this area are 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. Though not focused on any one disease, the NIH is planning to invest more than $60 million in FY 2007 to launch the Genes, Environment and Health Initiative. The NIH expects this project to accelerate discovery of the major genetic and environmental factors for diseases that have a substantial public health impact.

Risk Factors and Prevention: Goals for Understanding Parkinson's disease

With tremendous advances made in our understanding of PD through genetic discovery, Summit participants agreed that gene discovery efforts should continue; they also emphasized that links between genetics and environmental factors will a critical area for future study.

The following represent the most important goals to pursue in the areas of genetics and epidemiology:

- *Studies of PD patients, at-risk, and not at-risk family members for clinical course, risk factors, and biomarkers.* (Highest Priority)

  Studies of PD patients and their family members without PD, but perhaps carrying genetic mutations, can yield valuable information about the early stages of disease. This can help identify early diagnostic features, or risk factors that may predispose to disease. In addition, this may reveal potential biomarkers of disease for use in clinical studies. It was agreed that LRRK2 families offer the best option for consortium study, as these appear to be the most commonly occurring genetic mutations in both familial and sporadic disease.

- *Carry out a systematic survey of control populations to identify common variants not already known from SNP databases.* (Highest Priority)

  Surveys of unaffected "control" populations to identify subtle variations in genes that might influence the susceptibility to PD could be an extremely valuable contribution to the understanding of disease causation, particularly for sporadic PD. Intramural investigators from the National Institute on Aging (NIA) are currently conducting a whole genome screen for susceptibility genes associated with PD, and importantly, will make their data available to the public. This project and similar studies will provide valuable information for researchers to conduct explorative studies of susceptibility genes in unaffected control populations.

Environmental information should also be captured in these studies; this would inform a better understanding of the relationship between genetics and environmental exposures.

- *Develop a resequencing chip for all exons and noncoding conserved elements of genes implicated in familial PD, and continuously update as new genes are found.* (New Priority)

A critical need in PD genetics is an exploration for novel genetic mutations and variations that may impact both inherited and sporadic forms of PD. The availability of a specific microarray chip containing all of the known genes for PD (and their surrounding and non-coding regions) would allow the identification of additional genetic sequences that may contribute to disease risk.

- *Expand and improve studies of gene function in PD*. (Priority)

There is much more to be learned about genetic mutations and more subtle genetic variations (such as SNPs) that may impact the risk of inherited and sporadic forms of the disease. Genetic variability in genes involved in risk or protection from disease should be a priority. Researchers can make advances in this field through traditional approaches, or through more novel studies utilizing gene therapy, RNAi, or gene repair. They must also consider cellular follow up studies to assess the impact of known genetic mutations, and to ensure that genetic findings do not outpace the cellular studies required to understand their role in disease.

- *Evaluate the clinical validity and utility of testing for mutations in genes associated with PD. Foster the development of guidelines for testing for gene alterations in individuals with PD by appropriate professional groups.* (Priority)

With the advent of genetic contributions to this disease, genetic testing has emerged as an increasingly important issue both to the patient and research communities. It will be important, as genetic tests become more mainstream for PD, that the clinical validity and utility of each test is evaluated. In addition, patients or those who believe themselves at risk for disease will need to understand the ramifications of their genetic status. Summit participants urged the involvement of appropriate professional groups in this effort, such as the Movement Disorders Society, the Parkinson's Study Group, the American College of Medical Genetics, etc.

- *Additional genetics/epidemiology studies.* (Priority)

Participants at the first PD Summit identified a number of epidemiology studies for future consideration. These studies would likely be useful both to geneticists and to researchers studying the environmental causes of PD, and include:

  - A sibling pair study,
  - Short-term case control studies,
  - Risk factor studies in individuals without a family history of PD,

- Resampling of large pre-existing cohorts (e.g., Nurses' Health Study, etc.), to compare the development of PD to exposure histories, and
- Genotype-phenotype studies.

Neural Circuits

Studies of the brain circuits that control movement, specifically those involving the basal ganglia, continue to be important to our understanding of PD, and have led to important advances that laid some of the critical groundwork for the success of DBS. Despite this progress, we still do not fully understand how disease-related changes in neural circuitry lead to the abnormal movements that accompany PD, or fully grasp why electrical stimulation or destruction of tissue can lead to symptomatic relief. The NIH portfolio has a large component of its basic research dedicated to the neuronal circuitry involved in PD, and research applications in this area continue to be received. Researchers continue to explore a range of topics related to neural circuitry, including receptor function in the basal ganglia, the role of parkin in synaptic function, the dopamine transporter, striatal plasticity, and dysregulation of dopaminergic transmission. Summit participants agreed that studies in this area should continue to progress.

Translating Discoveries into PD Therapeutics

A critical gap in generating new treatments for any disease remains the translational of basic scientific discoveries into relevant therapeutic treatments that can proceed to clinical trials in patients. Different fields may be at varied stages of readiness for translation depending on their maturity, how much is known about the disease process, and whether or not feasible, "drug-able targets" have been validated. It can be noted that the PD research field appears to be at the stage where translational research is an important next step toward goals for feasible new drug treatments. While the NIH has a long history of support for basic science research, the development of programs to facilitate translational research has occurred much more recently. At NINDS in particular, the development of an institute-wide translational program was, in part, stimulated by PD researchers who needed relevant mechanisms to perform the preclinical research required to escalate their therapeutics to clinical trials. Many applications that come into these programs are focused on neurodegenerative disease, and specifically, PD. It is important to note that participants in the recently held NIH Blueprint meeting on neurodegeneration lauded the efforts of NIH in creating translational programs, and recommended that NIH provide coordinated guidance to the community regarding the existence of these programs and how they might be best utilized by the community (see goals listed below).

Areas at the PD Summit considered most important for focused translation to the clinic included Gene Therapy and Cell Transplantation.

Gene Therapy

Gene therapy has now become a mainstream area of translational research for PD. By stripping viral DNA of the genes that produce damaging viral proteins, and replacing them with genes producing proteins known to be beneficial in PD, researchers hope to deliver these proteins for therapeutic benefit to the neurons affected by the disease. Proteins which may be relevant to PD include glial cell-derived neurotrophic factor (GDNF) and a related protein, neurturin. Research in this area has grown tremendously, and viral delivery vectors being currently pursued include adenoviruses, herpesvirus, lentivirus, and others – in addition, researchers are engineering these delivery molecules to have "on-off" switches, so that in the event of an adverse response, the vector can be shut down. Determining the location, amount, and duration of expression of these proteins in the brain, as well as assessing any potential inflammatory response, are critical preclinical studies underway.

Multiple researchers are planning or are already engaged in small pilot clinical trials – these include studies underway using adeno-associated virus to deliver a key enzyme in the production of dopamine to the striatum, the trophic factor neurturin to the striatum, and a different neurotransmitter enzyme, (GAD,) to the STN. To date, no serious adverse effects have been noted, but researchers have only assessed these vectors in small number of patients. Ongoing preclinical and clinical studies in this area will be crucial to the development of gene therapy as a rational treatment for PD.

Cell Implantation

For people with advanced PD, replacing the dopamine producing brain cells destroyed by the disease may be the best hope. Fundamental experiments in animal models of PD are progressing toward that goal and have shown promise using a variety of cell types. Researchers have successfully derived dopaminergic cells from mouse embryonic stem (ES) cells and Federally-approved human ES cells in culture, and in separate studies, have observed beneficial behavioral effects following transplants of these 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 the major cell types of the brain, both nerve cells and supporting cells.

Given the potentially negative consequences of unrestrained stem cell growth, and the unexpected dyskinesias observed in two major NINDS-funded fetal transplant trials for PD, researchers in the stem cell field are proceeding cautiously toward the translation of basic findings into human testing. NINDS is currently funding a large cooperative agreement on the development and non-human primate testing of Federally-approved human ES cells to treat PD, and the NIH has also sponsored a number of initiatives to expand research on stem cells across neurological diseases and provide the advanced training needed to and conduct experiments using these cells.

Although research is progressing on many fronts in the stem cell community, the distribution and testing of these cells have been raised as priority issues at past PD planning meetings. 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, and 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/).

Gene Therapy and Cell Implantation: Goals for Translating Discoveries into PD Therapeutics

After discussing the current status of cell replacement and gene therapy as rational therapeutics for PD, Summit participants considered the future of these areas and what would be needed to accelerate these potential therapies to the clinic; the following are the priority recommendations.

- *Expand and improve studies of gene function in PD*. (Priority)

  Along with the Risk Factors breakout group, this group also recognized the need to continue to study genetic mutations and more subtle genetic variations (such as SNPs) that may impact the risk of inherited and sporadic forms of the disease. Researchers could achieve advances in this field through traditional approaches, or through more novel studies utilizing gene therapy, RNAi, or gene repair.

- *Genetics and basic neurobiology in determination and differentiation of dopaminergic neurons*. (Priority)

  Despite advances in the field, one of the ongoing needs of stem cell researchers is a more complete characterization of the cellular environments that promote survival and normal function of dopamine neurons. 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 therapeutic development.

Drug Development for PD

Pharmacological, or drug therapy, has been the mainstay of treatment for PD for many decades. It is widely recognized that the discovery of new and better drug treatments for PD will require classical drug screening efforts. Although this has traditionally been within the realm of pharmaceutical companies, the academic setting is becoming a more common arena for mechanized rapid output, or high-throughput drug screening (HTS). NINDS and NIH have supported this trend for a variety of reasons. First, industry cannot typically invest in drug screening for extremely rare diseases that desperately need treatments. While PD is not a rare or orphan disease, other more prevalent diseases such as stroke, obesity and diabetes offer considerably larger “markets” for drug therapies than does PD. Thus, pharmaceutical companies have primarily focused on medicinal chemistry and alterations of existing PD or other neurological drugs (e.g., dopamine agonists) rather than investing in new drugs. New drug development in academia thus would produce the preclinical data necessary to make new PD drugs more attractive for industry to pursue. Second, industry invests considerable time and money on the development of broad chemical libraries to discover new drugs; drugs that they

have studied extensively for a more common disease may be 'shelved' – the potential of these drugs for PD could be further studied by the academic community. Third, compounds which are already approved by the FDA for human use may be neuroprotective for PD; many of these drugs are no longer on patents, making them less attractive for industry investment. Similarly, common, over-the-counter medications (like aspirin use in protection from cardiovascular disease) may be neuroprotective in PD – again, it is unlikely that industry would pursue these opportunities for financial reasons.

At previous PD planning meetings, participants emphasized the benefits of drug development and high-throughput screening in academia, for many of the reasons enumerated above; many of their recommendations involved making resources available for drug screening to interested investigators. These would include access to chemical libraries, facilities for performing screens, and the ability to convert scientific research assays into validated drug screening assays. NINDS has provided these resources over the last few years through several mechanisms: the availability of supplemental funds for HTS; the creation of a library of FDA-approved and other bioactive compounds; the establishment of a facility to adapt standard assays into HTS assays; and a the creation of a second supplement program (cofunded by the Michael J. Fox Foundation) to take promising therapies into rodent models of neurodegenerative disease**.** The NINDS also announced in October 2003 that it will also provide supplements to investigators for small, focused projects that will accelerate preclinical therapeutics development. Under this announcement, the highest funding priority will be given to studies that are specifically designed to support an Investigational New Drug (IND) application for clinical testing, and that form part of a well-developed plan for pursuing an IND.

In addition to these programs, the NINDS is supporting two drug screening projects at the Brigham and Women's Hospital in Boston. Investigators at the Brigham and Women's Udall Center are screening compounds with the potential to interfere with protein aggregation and testing the most promising compounds in *in vitro* and *in vivo* models of PD. In addition, the Laboratory for Drug Discovery in Neurodegeneration is staffed by scientists with experience in assay development, automation, informatics and medicinal chemistry, and serves as a facility through which investigators in the neurodegeneration field can work to screen potential therapies for PD and other neurodegenerative diseases.

It should be noted that drug screening efforts are being pursued for many different areas of science across NIH. In addition to planning for the PD community, the NIH Roadmap has identified chemical libraries as an important research resource and has funded a network of nine centers throughout the country to provide researchers with small molecules that can be used as research tools, or to screen as potential therapeutics. The NINDS has also funded five assay development grants relevant to PD under the Molecular Libraries and Imaging Roadmap Initiative. The NIH Blueprint meeting on neurodegeneration highlighted the continued support of these resources for investigators studying neurodegenerative disease, including PD, giving further contemporaneous support of these efforts at NIH.

In addition to specific aspects of drug development articulated thus far, Summit participants recognized that a critical gap in the preclinical testing of drugs, once they have been validated through high-throughput assays, is the ability to test them in PD animal models. The prevailing

research literature on testing of potential drug treatments varies widely in terms of animal model testing; a variety of animal models and species are utilized including both transgenic and chemically-lesioned mice, rats, and non-human primates. Drugs are delivered through different means at various dosages, and the tests performed to assess their effects range from chemical and molecular assays to pathological findings and behavioral studies. Moreover, participants at this Summit and at the subsequent NIH Blueprint meeting agreed that animal models which more accurately recapitulate the chronic disease process in humans are critically needed for drug validation for neurodegenerative diseases and PD.

Pharmacological Approaches: Goals for drug discovery in PD

- *Continue the development of animal models that are predictive of human PD with respect to progression of disease and response to treatment.* (Highest Priority)

Despite the usefulness of animal models of PD based on genetic manipulation or exposure to environmental toxicants, Summit participants agreed there remains a clear need for further development and refinement of models that better recapitulate the chronic and progressive nature of human PD pathology. It was suggested that a variety of models may be needed to address specific disease and treatment questions.

- *Validate drug targets for PD.* (New Priority)

In an effort to work more closely with the pharmaceutical community, it was agreed that the academic research community could focus on the validation of drug targets for PD, based on their basic bench discoveries. The validation of intracellular targets would aid and encourage pharmaceutical companies to utilize their larger chemical libraries to develop therapeutics to these targets.

- *Create a board of representatives of pharmaceutical companies to provide advice and feedback to the NIH on a regular basis.* (New Priority)

A key problem facing the field of drug development for PD (and many other neurological diseases) is that it is still not clear how to best bridge the gap between promising basic science findings and industry research and development. The development of a more open line of communication between the NIH and representatives from pharmaceutical companies, potentially including the establishment of a group of pharmaceutical staff who could provide advice and feedback to the NIH on translational projects, could facilitate the overall translational research activities in PD.

- *Develop approaches to the delivery of treatment agents to the brain.* (New Priority)

As researchers identify promising therapeutic agents for treating PD, it will be equally important to ensure that these agents can be safely and effectively delivered to the targeted brain regions. While delivery may be achieved surgically (through implanted cells or devices), surgery is not a mainstream option for preventative treatment of PD; thus strategies to help compounds cross the blood-brain barrier will ultimately be required.

- *Translational Programs/Facilitating Translational Research in the Future*

The validation of drug targets, screening of chemical libraries to find modulating drugs for these targets, medicinal chemistry, and the subsequent drug toxicity studies have typically been a function of the pharmaceutical industry. However, Summit participants agreed that the Federal government could be contributing to this area of research as well. At this Summit, and also at the recent NIH Blueprint meeting focused on neurodegeneration, it was suggested that NIH provide more coordinated information and guidance to academia regarding the various translational research programs available and their application requirements, to encourage better participation in these programs.

Treating Parkinson's Disease

Pharmacological Approaches

As noted above, pharmacological therapy has been the mainstay of treatment for PD for many decades. Studies continue to focus on improving dopamine replacement, reducing the side effects, and smoothing out the cyclical, uneven response to dopamine replacement that causes the "on and off" periods experienced by patients. Another goal continues to be the development of drugs which can address more advanced forms of disease. However, the standard drugs used today are primarily symptomatic, treating tremor and rigidity, and do not stop the underlying progression of the disease. When facing decisions about future investments in research or trials of pharmacological therapies, consideration must be given to potential therapeutics that may be neuroprotective and disease modifying. It has been estimated that the cost of PD is more than $6 billion per year, and that slowing its progression for even as little as 5 years could provide significant savings to the country in terms of reduced medical expenses and increased productivity.

As a step toward making neuroprotective therapies available to patients, the NINDS has created Neuroprotection Exploratory Trials in PD (NET-PD), a large scale clinical trial network designed to assess potential neuroprotective agents for use in PD. The initial phase II trial design used in NET-PD are termed "futility" studies, designed to determine if the drugs warrant further consideration for testing in large, Phase III trials. Through this process, only drugs with the greatest chance of success are selected to proceed, reducing the risk of investing in trials which are considerably more expensive. Specifically, a team of pharmacologists, clinicians, clinical trial experts, including NINDS staff, solicited suggestions from the community for drugs to be considered, and subjected those to stringent criteria for evaluation. The trial leadership then selected drugs for the NET-PD futility studies, based on this review, which included assessments of accessibility to the BBB and preliminary tolerability in humans. Investigators have completed the first futility studies in individuals with early, untreated PD, and a large study of creatine in PD will begin in late 2006. Other NINDS-funded neuroprotectant trials include a planned Phase III study of CoEnzyme Q-10 ("QE3"). It is expected that the drug selection process will continue, and that further futility studies will be pursued as new neuroprotectant drugs emerge.

In addition to providing a structured approach to the identification and testing of potential neuroprotectants, the NET-PD infrastructure has provided the framework for exploring questions critical to the conduct of all future clinical trials in PD, including an examination of the futility trial design for PD trials, the potential use of patient advocates as part of the recruitment process, the difficulties in enrolling minorities into clinical trials, the health service utilization levels of study participants, and the challenges related to informed consent. The development of the drug selection process described above has also helped the NINDS to recognize the need for a more standardized approach to drug testing in preclinical settings. To make this evaluation more consistent, and to provide NINDS with a mechanism for completing batteries of tests on specific drugs that may be promising but have not been fully or consistently tested, the NINDS will support a contract facility that can provide resources and capabilities to help select the most promising drugs for PD clinical trials.

Other NIH studies of pharmacological treatments for PD include whether treatment with L-dopa accelerates the progression of PD, and trials of a variety of other drugs. These drugs may affect dopaminergic sprouting and slow the loss of dopamine terminals in the striatum, inhibit the dopamine transporter, or treat PD-related depression. Exploratory studies focus on therapies to treat the cognitive effects and mood disorders that can accompany PD, as well as complementary and alternative medicine approaches to treat PD and its accompanying complications, including depression and sleep disturbances.

The PD community confirmed at the Summit that disease-modifying trials should continue to be a high priority, and recommended that individuals with very early PD be included, once appropriate biomarkers to identify these people become available. It has been recognized at all PD planning meetings to date that a significant roadblock to the advancement of better treatments for PD remains the lack of an adequate biomarker of the disease. A valid PD biomarker would 1) allow for the identification of patients at earlier stages of disease, or identification of presymptomatic/at-risk individuals, 2) reveal the natural history of the disease, or 3) allow assessment of disease progression, including the response to therapeutic treatment.

Interestingly, the recent NIH Neuroscience Blueprint meeting focused on the identification of the most promising goals to pursue for all neurodegenerative diseases, and also highlighted the identification of biomarkers as a top priority. It was also suggested that a biomarker, or "biosignature," should not only meet some of the criteria listed above, but should also exhibit consistency across species. That is, a biosignature that could be measured in flies, rodents, non-human primates, etc as well as humans, could allow for the most rapid preclinical assessment of the best therapeutics. Delivering therapeutics across the blood-brain barrier was also noted as another top priority for therapeutics development.

Pharmacological Approaches: Goals for Treating PD

- *Develop biomarkers of PD presence, progression, and response to treatment.* (Highest Priority)

  As noted above, availability of biomarkers would serve as a tremendously valuable tool for developing more effective treatments for PD across all areas of therapeutics research.

(NINDS has already supported an assessment of imaging tools for use as biomarkers, and has found them to be inadequate at present.) This need could be addressed through focused short-term, high risk solicitations, as suggested at the most recent Blueprint meeting. Another useful strategy could be the systematic screening of genetic samples from PD patients and controls available through the NINDS repository (this includes samples collected via the NET-PD trial), and the use of clinical information on PD patients and controls available through the PD Data Organizing Center (PD-DOC; see below for more information). It can be noted that the PD repository and PD-DOC linked resource of genetic and clinical information will be used as part of a NET-PD substudy exploring the influence of common genetic variants on the risk of PD, the rate of progression, and the response to drug therapy, which may be useful in the development of biomarkers.

- *Enroll individuals with inherited (highly penetrant) forms of PD and their at-risk and non at-risk relatives for detailed longitudinal studies.* (Highest Priority)

The NINDS has already been addressing this need through support of a study assessing more than 400 families with PD including more than 500 sibling pairs. The study is designed to explore the role of the parkin gene in familial PD, to detect and isolate other PD susceptibility genes, and to test the role of putative candidate genes for inherited PD in a sample of sporadic PD cases and unaffected controls. It is expected that these investigators will expand the number of families in the study to facilitate these efforts. These and similar clinical investigations, highlighted at this and other planning meetings, are particularly valuable for characterizing the clinical course of PD, for biomarker discovery efforts in presymptomatic, at-risk patients, and for understanding the influence of environmental exposures on the development of disease.

- *Continue disease-modifying trials of agents that seem most promising based on an improving understanding of PD pathophysiology (including data from animal studies). Consider subjects with very early PD prodromes.* (Priority)

Although the PD patient community has indicated the importance of clinical trials that provide symptomatic relief to people with advanced PD, participants at all PD planning meetings to date have emphasized that clinical trials of therapies that slow or stop the progression of PD are still critical. When future trials are designed, the organizers should try to include all possible at-risk individuals, including those with clear genetic risk factors, and those without these risks but who are in the very earliest stages of PD. The development of predictive biomarkers will be essential to including the latter group of participants.

Deep Brain Stimulation

In 2002, the U.S. Food and Drug Administration approved the use of DBS for advanced PD, and to date, thousands of people worldwide have undergone this procedure. In successful cases, the improvement in mobility can be dramatic – enabling people whose disease had advanced significantly to return to many normal activities. Although the FDA has approved DBS for PD, basic science research is still warranted, including the development of better electrodes and a better understanding of the mechanisms underlying the success of DBS.

These topics were the focus of several RFAs on DBS issued by the NIH. Subsequent to these solicitations, the NIH has supported meetings of a DBS Consortium for several years. The long-term objective of the ongoing consortium is to develop better and more broadly applicable therapies through a greater understanding of mechanisms of action as validated by rigorous clinical trials.

Clinical questions regarding DBS also remain, the answers to which will be critical to making further improvements in this therapy; examples include how to optimally use DBS, and the effectiveness of DBS in different target regions. To address these issues, the NINDS has been collaborating with the Department of Veterans Affairs 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. NINDS is also supporting three additional trials of DBS for PD. The first is a phase III trial exploring the effects of DBS on motor, neuropsychological, psychiatric function, and 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 neural activity that controls movement and posture. As trials progress on this relatively new treatment for PD, the Summit participants recognized specific needs as DBS becomes more of a mainstream therapy for PD.

Deep Brain Stimulation: Goals for DBS

- *Extend follow-up for participants in DBS clinical trials, and expand participant numbers and standardized procedures in future trials.* (Priority)

  Since its approval in 2002 for advanced PD, the use of DBS in medical practice has expanded tremendously, nearly outpacing the research community's ability to resolve many issues critical to the long-term safety and optimization of this therapy. These include:

  - The standardization of lead location, the collection of imaging data on lead location, and the collection of data on the most appropriate stimulation parameters;
  - Future trials should incorporate more standardized approaches, and should include larger numbers of participants when possible, and follow these participants for longer periods of time than have been used in previous trials;
  - Future studies should include assessments of the non-motor effects of DBS, such as the effects on mood, speech, etc, neuroprotection, and speech.

Non-motor and Other Complications of Parkinson's Disease

It is recognized non-motor symptoms of PD are frequently more troubling to patients in terms of quality of life; improving the quality of life for people with advanced PD must include better rehabilitative therapies and treatments for these debilitating complications, in addition to the strategies to treat disease progression and motor effects. Non-motor symptoms vary from person

to person, but can include sleep abnormalities, fatigue, behavioral and cognitive impairments, anxiety, depression, autonomic dysfunction, gastrointestinal problems, and pain. Speech, which is a motor function, is often included in the context of non-motor manifestations, since it responds differently than limb movement to pharmacologic and/or neurosurgical intervention. The clinical community also recognizes psychosis as a non-motor complication of PD, although it is believed to be a complication of PD medications, rather than of the disease itself.

The NIH and other organizations have issued a variety of solicitations for basic and clinical research on the non-motor aspects of PD, most specifically for cognitive sequelae, sleep, and the creation of animal models and behavioral assays that would allow more in-depth study of these symptoms. The response to these solicitations has been marginal and the portfolio requires more development in this area. The clinical community has recognized the need for more attention to non-motor symptoms, as evidenced by an ongoing clinical trial of depression in PD, the initiation of diagnostic criteria for psychosis and depression in PD in collaboration with NINDS, and the incorporation of non-motor outcome measures into phase 3 trials such as NET-PD, and QE3.

In light of this portfolio assessment, Summit participants recommended additional research on all non-motor impairments in PD, and highlighted sleep, fatigue, behavioral/cognitive impairments, psychosis, and anxiety/depression, as areas of particular need. The participants also suggested that the generation of animal models that recapitulate these impairments was one way to reach this overall goal. It was also agreed that monitoring of non-motor aspects should continue to expand within PD trials, longitudinal studies, or other clinical research on PD patients.

Non-Motor Aspects of PD: Goals for Treating Non-Motor Symptoms

- *Incorporate non-motor manifestations of PD into clinical trials.* (Highest Priority)

  Participants at the most recent Summit and at past planning meetings have agreed that expanding clinical trials to include these complications would accelerate the discovery of both pharmacological and non-pharmacological interventions. This broad but important goal could include the initiation of new clinical trials for treatment of complications; the inclusion of non-motor outcomes in clinical trials focused on motor effects; the exploration of the impact of these impairments on PD-related disability; and the development of risk factor criteria for incipient or presymptomatic PD.

- *Improve methods for testing non-motor manifestations, uniform scales for MDS, etc.* (New Priority)

  The NINDS has already begun to work with the PD research community to develop standard diagnostic criteria for PD-related depression and psychosis, and will collaborate with the Movement Disorder Society on the development of a scale that can be used for psychosis. However, these collaborative working groups should examine many more non-motor manifestations as well.

- *Achieve a better understanding of non-motor manifestations in PD.* (Priority)

Discussions at this and previous planning meetings have highlighted the need to better understand the wide range of non-motor complications in PD, as well as motor effects (such as speech impairments) that do not respond well to traditional therapies. Effective treatments for these complications are a critical need, and an improved base of knowledge would be a substantial contribution to therapeutics development. For example, additional studies could be designed to explore the impact of PD on dopaminergic neurons outside the nigro-striatal pathway and to examine the effects of PD on non-dopaminergic neurons and circuits.

- *Develop animal models that recapitulate non-motor impairments of PD for research and drug discovery.* (Priority)

Many past PD planning meetings have emphasized the need for animal models that more specifically recapitulate the non-motor aspects of PD, however, as noted, the response to solicitations for research in this area have not been substantial. At this Summit, participants again articulated the need to generate models that reproduce the non-motor complications of the disease, as well as the development of standardized assays which measure non-motor symptoms in animals.

Rehabilitation and Quality of Life Issues

Rehabilitation and quality of life issues have been important areas of concern since the creation of the original research agenda. As evidenced by well-attended sessions devoted to exercise, music and creativity at the recent World Parkinson's Congress, non-invasive approaches to quality of life are extremely important to individuals living with PD. As discussed in a previous section, researchers are increasingly recognizing the importance of treating the many non-motor and other complications of PD, and rehabilitation techniques are playing an increasingly important role in these efforts. Currently, the NIH grant portfolio includes studies of rehabilitation, including multiple clinical trials and investigations of complementary and alternative medicine therapies. Investigators are currently exploring exercise and tai chi in individuals with PD, to determine if it aids them in improving the efficiency of their movements, and are exploring contributors to long-term disability in people with PD. Other research studies focus on promoting quality of life and quality of care in those with chronic illnesses, including PD, and caring for individuals at the end of life. Trials are ongoing which explore therapies to improve limb function, to reduce the "masked" facial expressions that often accompany PD, and to treat PD-associated depression. Summit participants agreed that non-invasive approaches, with particular emphasis on improving the quality of life for those suffering from PD, should be continued.

At the recent World Parkinson's Congress, the role of the PD caregiver was explored, as patients and their caregivers were active participants in the Congress. It was suggested by many attendees, echoing that suggested by other neurodegenerative disease communities such as that for Alzheimer's disease, that issues facing caregivers are important not only for the success of rehabilitative strategies in PD patients, but also for quality of life issues for patients and their families. Where possible, the role of the caregiver in PD related studies such as those described above, should be considered.

Outcomes Research

Although the NIH does not support a formal program of outcomes research – research on the status of participants after care or on the process of care itself – the NIH ICs do incorporate assessments of particular outcome measures when possible in clinical trials. For example, as part of the NET-PD infrastructure, researchers are developing a global statistical test that may be useful for other studies in PD, and are utilizing a standardized outcome measure (the PDQ39) that will hopefully prove more inclusive in terms of Quality of Life and non-motor aspects than the standard Unified Parkinson's Disease Rating Scale. The NINDS has also issued a contract solicitation for improving "Quality of Life Outcomes in Neurological Disorders," designed to encourage the development of innovative approaches to measuring health-related quality of life in research studies.

Diagnosis and Treatment

While the NIH mission is focused on reducing the burden of disease through research and the development of therapies, one of the natural concerns of the PD patient community is the current standard of medical care. Other Federal agencies such as the Agency for Healthcare Research and Quality (AHRQ) have long been invested in the development of clinical practice guidelines and in May 2003, AHRQ issued an Evidence Report/Technology Assessment entitled "Diagnosis and Treatment of Parkinson's Disease: A Systematic Review of the Literature." Other clinicians (many of whom are NIH grantees) have also contributed their expertise by developing clinical guidelines, with a publication on diagnosis and initial management of PD having been published as recently as September 2005 in the *New England Journal of Medicine*.

In addition, as mentioned above, the NIH has led workshop-based discussions of the diagnosis of depression and psychosis 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. 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 publication on the diagnosis and management of DLB following a jointly-sponsored meeting on clinical-pathological correlations for DLB in September 2004.

The American Academy of Neurology has also been invested in the development of guidance for practicing neurologists, and published four practice parameters on PD in April 2006, including: "Neuroprotective Strategies and Alternative Therapies for Parkinson Disease," "Diagnosis and Prognosis of New Onset Parkinson Disease," "Evaluation and Treatment of Depression, Psychosis, and Dementia in Parkinson Disease," and "Treatment of Parkinson Disease with Motor Fluctuations and Dyskinesia."

Tools and Resources

Array Technology

Array technology, which was not readily available at the start of the original PD research agenda, is now more accessible to researchers, in part due to the Neuroscience Blueprint-funded Microarray Consortium of four centers, including the Translational Genomics Research Institute, Duke, UCLA, and Yale. These centers help to further basic and translational research through the acquisition and dissemination of high quality gene expression data. To date, researchers using the Consortium have completed six projects on PD, and a seventh is in progress. The data from experiments performed by this Consortium are also shared publicly via a website (http://arrayconsortium.tgen.org) six months after a study is completed.

In addition, the NINDS has provided administrative supplements to PD researchers to access microarray technology through two separate program solicitations, and joint NINDS/NIA collaborative study on Lewy Body dementia features extensive use of microarrays.

Through the programs described above, and as microarrays have become more generally available to the research community, this resource is a less urgent need than at the start of the PD Research Agenda. However, the participants did identify a need for a resequencing chip for the genes already implicated in inherited forms of PD (see page 9 of this document for details.)

Animal Models

With remarkable developments in PD genetics and cell biology, the past five years have been a period of explosive growth in the development of animal models of PD. In addition the creation of genetic animal models based on genes implicated in PD, investigators have also used environmental toxicants in novel ways to produce more chronic and slowly progressing models of PD. Researchers have also developed models through manipulation of intracellular mechanisms of disease. For example, a new mouse model was created by using genetic engineering to disrupt mitochondrial function in dopamine neurons. Researchers have also achieved success in reproducing the cellular and behavioral effects of PD in even simpler animal models such as fruit flies and roundworms.

Access to animal models has improved, due to the NIH-wide mandates on sharing of research resources; in addition, the NINDS created a PD animal model facility at the UCLA Udall center while also providing supplemental awards for the sharing of animal models. Most recently, the institute plans to support a contract facility that will house standardized PD animal models for standardized drug testing – this facility will provide important preclinical information on drugs under consideration for clinical trials.

The National Center for Research Resources (NCRR) also continues to actively facilitate the sharing of rodent and other animal model resources, through the Induced Mouse Resources Program, Mutant Mouse Regional Resource Centers, and its National Primate Research Centers. The NCRR expects to expand these efforts further by developing a comprehensive web-based

searchable engine to make it easier for researchers to find and to use animal specific animal models.

Despite these successes, the research community is still strongly supportive of additional refinement and development of new models – especially those that can recapitulate the natural history of PD in humans more accurately.

- *Continue the development of animal models that are predictive of human PD with respect to progression of disease and response to treatment.* (Highest Priority)

  Despite the usefulness of animal models of PD based on genetic manipulation or exposure to environmental toxicants, Summit participants agreed there remains a clear need for further development and refinement of models that better recapitulate the chronic and progressive nature of human PD pathology. It was suggested that a variety of models may be needed to address specific disease and treatment questions.

Breakout groups also identified the development of animal models that that reproduce non-motor impairments as critical needs (see page 20 of this document for more details.)

Brain Banks and Repositories

Brain banking is also a continued need of the PD research community, but at present, no coordinated system of brain banks exists. In March 2002, NINDS (along with the National Institute on Drug Abuse, the NIH Office of Rare Diseases, and the NIA) sponsored an International Workshop on Brain Banking, and its staff subsequently published a summary of the brain banking issues relevant for neurodegenerative diseases that were made at this workshop. As discussed in more detail below, the NINDS has also worked with the community to develop minimum clinical and pathological data sets that can be used with the collection of tissues to be banked; having consistently used criteria will aid researchers that access these resources in the future. In addition, NINDS has also offered competitive supplements to Udall Centers that can be used to establish or expand brain banking resources. These supplements are available as part of a broader program - announced in July 2003 - in which NINDS raised the funding ceiling that may be awarded to Centers in order to encourage investigators to expand their clinical research efforts. Most recently, the NINDS has held a discussion at the 2004 Udall Centers meeting, to determine how the PD Data Organizing Center (PD-DOC) – a center developed by NINDS to coordinate the clinical data collection across the Udall Centers (described in more detail below) – may best facilitate their coordination. Investigators with existing brain banks outside of the Udall program participated, and international brain banks were represented. Participants in the breakout session focused on the needs for coordination and infrastructure. Suggestions were made as to how the NIH could help by building an informational webpage that could serve the needs of both patients/families and physicians/researchers, and NINDS is well underway in the development of this site, beginning with an informational page on brain banks currently available. It was agreed that standards, as developed in the minimum data set for PD, should be utilized and that the PD-DOC would be an appropriate venue for coordination. It was also

suggested that groups outside of the Udall Centers that have successful PD brain banking programs should also be included.

With respect to the collection of genetic samples, NINDS recognized several years ago that for many neurological conditions, a repository of DNA samples, immortalized cell lines, and accompanying clinical and pedigree data would be an invaluable resource. Beginning with a contract award in September 2002, the NINDS has supported a Human Genetics Repository (already mentioned above) for DNA and genetic material at the Coriell Institute for Medical Research in Camden, New Jersey. Although the Repository is currently storing samples from individuals with parkinsonian conditions, stroke, epilepsy, and motor neuron diseases, the contributions of the PD research community have been the highlight of the resource to date. Of more than 8900 samples submitted, 3444 are from Parkinson's submitters, including 2038 from individuals with PD. There are a total of 1140 PD samples available for sharing now, and approximately 750 control subject samples. Additionally, NINDS has recently made plates (or panels) of DNA samples available to researchers, which will allow them to perform rapid screens for validating known genes and/or for discovering new genes.

- *Facilitation of Brain Banking Efforts* (Priority)

  The coordination of brain banks with PD and control tissues available for research use continues to be a priority. It was suggested that the PD-DOC, in collaboration with the Udall centers, the National Alzheimer's Coordinating Center (NACC), and NINDS, can best coordinate these efforts.

Ethics

Since the initial discovery of synuclein, there are now a multitude of genes and genetic loci associated with familial PD in addition to synuclein - such as parkin, UCHL-1, DJ-1, PINK-1, and the most recently discovered LRRK-2, encoding the protein dardarin. With the advent of these genetic discoveries, genetic testing has emerged as an increasingly important issue both to the patient and research communities. Currently, available genetic tests are not comprehensive and may not predict disease, particularly for rarely occurring recessive genes. In addition, patients do not typically receive genetic counseling during office visits and may not understand the ramifications of their test results. Because of these concerns expressed by the community during previous planning meetings, the NINDS sponsored a workshop on the ethics of genetic testing in Parkinson's disease as a satellite to the American Society for Experimental Neurotherapeutics meeting in 2004. The recent World Parkinson's Congress included several sessions on this topic, and patients, caregivers and researchers expressed concerns about the increasing impact of genetic contributions to patients with PD and their families.

In addition to managing the ethics issues raised by genetic testing for PD, the examination of ethical questions has also been part of the Gene Therapy Working Group mentioned above. Investigators in this Group have conducted a survey to examine patient attitudes regarding volunteering in early-phase gene therapy trials, and results suggest that patients' attitudes about risk, their optimism about the promise of scientific research, and their orientation towards "action" are likely to influence their participation in these trials. NIH-funded investigators have

also published recently on the ethics of sham surgery – finding that the majority of researchers surveyed believed in the need for sham surgery controls for the testing of neurosurgical treatments, such as gene transfer for PD.

The "Risk Factors" breakout session discussed ethical issues, and as discussed in that section of the report (see page 9), recommended an evaluation of the clinical validity and utility of testing for mutations in genes associated with PD.

Training

At the start of the PD research agenda, scientists expressed concern that special efforts should be taken to train new scientists to pursue careers in PD research. NIH has a robust training program, and over the past 5 years, new investigators continue to receive training grants and begin new R01s focused on PD. In FY 2005, NINDS alone provided individual grants for 50 trainees (through the K and F mechanisms) on a diverse range of topics in PD research, including neural circuitry, the protective effects of exercise, the cell biology of the disease process, the role of neurotransmitter receptors in PD, the modeling of cellular mechanisms of PD in simple animal models (such as roundworms), the role of mitochondria, genetics, and treatments, such as DBS.

Today, issues remain regarding training – Summit participants recognized the need for specific training neuropathologists , a crucial aspect to the development of successful brain banks for PD research. In addition, at the recently held NIH Blueprint meeting on neurodegeneration, participants expressed that basic researchers should be trained in clinical disease areas. It is hoped that his can be achieved through special program announcements utilizing existing NIH training mechanisms.

- *Enhance training of individuals in PD research.* (Priority)

  As is the case across neuroscience research, the PD community is eager to see more researchers recruited to this field. Training of neuropathologists is a particularly pressing need, as is the training of new basic research scientists in the clinical aspects of disease.

Innovative Funding

At the start of the PD research agenda, strong recommendations were made to utilize innovative funding mechanisms throughout NIH to accelerate the pace of research in PD. Over the past 5 years, NIH has created fast-track funding programs, supplemental programs and a variety of other awards to address this need.

At the recently held NIH Blueprint meeting for Neurodegeneration, participants echoed this need, specifically emphasizing the need for additional high-risk, fast-track mechanisms in neurodegeneration research. The NIH plans to respond to this need via use of its R21 program, tailoring the announcement to neurodegenerative diseases, including PD.

Public-Private Partnerships

In May 2001, multiple NIH Institutes and Centers, along with several NGOs joined together to support a "R21 Fast Track Grants for Parkinson's Disease Research." Designed to stimulate novel, innovative, or high impact approaches to the field of PD research, the group of organizations made a total of 30 awards.

One of the deficiencies recognized at the 2002 PD Coordination Summit was the absence of a truly integrated and international basic science/clinical/patient community meeting for PD. The NGOs have worked continuously with the NIH for three years to address this need, organizing the World Parkinson Congress, "a nonprofit organization dedicated to providing an international forum for the best scientific discoveries, medical practices and caregiver initiatives related to Parkinson's disease." The Congress held this meeting in February 2006 in Washington, DC, and it brought together both the basic science and clinical research communities to discuss research findings at the international level; provided a forum for members of the PD patient community to learn about recent scientific findings and discuss quality of life and other issues of interest; and encouraged a productive dialogue between these different groups.

More recently, the NINDS is undertaking a public-private partnership as part of the expansion of the PD-DOC. In collaboration with the DoD, the National Parkinson Foundation, and Cephalon, Inc., the NINDS is working with the leaders of PD-DOC to add data from a cohort of 800 participants from Cephalon's previous PRECEPT clinical trial. This data will serve as a valuable source of clinical descriptions, imaging information and the natural histories of the individuals who participated in this trial.

Udall Centers Program

For the past eight years, the Morris K. Udall Centers of Excellence in PD Research have been a core component of the NINDS PD research portfolio. In fact, advances in many research areas, including PD genetics, environmental studies, stem cell research, drug screening, and the understanding of α-synuclein toxicity – would not have been possible without contributions from Udall researchers. As this program has grown to include 13 Centers, and as investigators have incorporated more clinical studies into their projects, it became clear that additional coordination of these efforts was needed. Specifically, in July 2002, mid-way through the PD Research Agenda, NIH held a PD Coordination Summit with leading scientists and clinicians to explore roadblocks that were impeding PD research. Participants suggested that better integration of the Udall Center program could accelerate their progress. Accordingly, the group suggested that formal coordination of Centers' data was needed, with a focus on the capture of clinical information.

To define the specific needs of the Udall and other PD research centers, and to develop a minimum data set for both the clinical and pathological diagnosis of PD, NINDS sponsored a workshop in March 2003. Outside researchers, Udall center directors, and NIH staff discussed ways in which PD research centers could be more collaborative, and how the collection of PD data and resources could be streamlined. To address the first need, NINDS worked with

extramural researchers to develop the minimum data sets and has made them freely available on the NINDS PD website. To address the issue of coordination of data collection across the Centers, NINDS solicited applications for the first PD-DOC, and awarded this cooperative agreement to the University of Rochester in September 2004. The Center serves as a "data clearinghouse" for the Udall Centers program and other Parkinson's research centers. The PD-DOC will collect clinical data on PD patients for research use and sharing by the community, as well as create virtual catalogs of biological materials of interest to PD.

Since the award was made, the PD-DOC has explored ways to dovetail the University of Rochester's databasing efforts with the existing NINDS genetics repository, and has begun to create patient confidentiality forms to ensure the protection of PD patients whose data will be collected. Udall representatives and others from the previous working group continue to evaluate and revise the set of clinical data elements previously developed by the Institute. The PD-DOC investigators have also begun initial contacts with the VA to determine if any commonalities could be taken advantage of, given their similar efforts on data banking. In December 2004, the PD-DOC investigators presented their strategy and plans at the 6th annual Udall Centers meeting, to collect additional feedback from the Center Directors and Staff.

Conclusions

NIH organized the 2005 PD Summit to provide guidance for the PD community in outlining a revised plan for PD research, one that will help guide researchers closer to prevention and better treatment for individuals at all stages of disease. The meeting was very effective in identifying new priorities for the field, and in providing perspective to a number of goals from previous planning meetings that have already been achieved. However, it is clear that several recommendations made at previous meetings – including biomarker development and improvement of animal models of PD – have not been fully met, highlighting the difficulties inherent in many areas of PD research. In some cases, the participants also 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 has utilized this input, along with recommendations made at previous planning meetings, to develop the series of goals outlined above. The NIH ICs believe that these goals can be effectively addressed in the coming three years, although it is not possible to predict precisely what scientific progress can be achieved by that time, particularly in terms of the development of therapeutics. However, all of the ICs that participate in PD research are committed to ensuring that these recommendations are implemented quickly and effectively. The NIH will hold additional workshops as necessary to help address specific recommendations, and will convene a larger planning meeting in two years, in order to revise this Plan further.

Appendix

Scientific Advances Linked to the Parkinson's Disease Research Agenda
*(*Indicates those advances that were supported in part by the NIH)*

I. Understanding Parkinson's disease

Using genetics to understand Parkinson's disease

- New genes discovered:
  - *SNCA (PARK4; also related to the earlier discovery of PARK1, the original mutation discovered in α -synuclein)
  - *PARK6 (PINK1; discovered through collaborative effort between European genetics and NHGRI and community.
  - PARK7 (DJ-1)
  - *PARK8 (LRRK2) – LRRK2 is the most common genetic cause of PD found to date, and may account for 7% of familial PD and for a significant fraction of sporadic PD cases.
- *Variations in the UCHL1 gene appear to protect against PD
- *Variations in specific, less-common genetic regions of mitochondrial DNA may be associated with a reduced risk of PD, including Complex I, a component of the mitochondria that is already known to be vulnerable to environmental toxicants
- *Variations in a gene involved in the breakdown of dopamine appear to influence the cognitive changes that can occur in people with PD; PD medications can worsen these effects
- *BDNF genetic variants are associated with onset age of familial PD.
- *Variations in the apolipoprotein E gene control the risk and age at onset of PD
- *Variations in the tau gene may confer susceptibility to PD
- *In men, the protective effect of smoking against PD appears linked to the presence of a specific variation in the MAO-A gene (involved in the breakdown of dopamine)
- The Nurr1 gene, crucial to the development of dopaminergic neurons, may also act as a risk factor for the disease.
- Variations in synphilin 1 have been associated with PD, and synphilin may play a role in the toxic aggregation of proteins, may adversely affect their degradation, and may contribute to apoptosis and formation of Lewy bodies.
- A gene involved in male differentiation during development, Sry, was found to be expressed in rat substantia nigra, and is linked to dopaminergic degeneration in male rats.
- *The NINDS repository has banked over 10K samples, (5436 from Parkinson's disease and 5271 control subjects) with known causal genes including parkin, LRRK2, and synuclein triplication. Publicly available samples and data exist at http://locus.umdnj.edu/ninds for 1351 subjects with Parkinson's disease and approximately 100 with other forms of parkinsonism. A whole genome study (SNP based analysesis underway in the NIA intramural program using these samples in Parkinson's disease to identify risk factors for sporadic disease. The NINDS has publicly posted clinical data and a whole genome SNP analysis from this study's progress thus far, for close to 300 control subjects, which has been accessed by over 50 researchers to date.

Epidemiology to determine risk factors for Parkinson's disease

- *Chronic systemic exposure to the pesticide rotenone reproduces features of PD in an animal model
- *Rotenone produced cellular toxicity through increases in oxidative stress
- *Neurotoxicants appear to interact with one another to enhance their cellular effects
- *The nervous system may be able to survive some levels of neurotoxicant exposure unless additional environmental or genetic risk factors provide another "hit" to the system
- *Higher levels of physical activity may lower the risk of PD in men or men predisposed to PD tend to avoid strenuous physical activity in their early adult years
- *Moderate doses of caffeine may have a protective effect on the risk of developing PD in men and women
- *Postmenopausal estrogen therapy appears associated with a reduced risk of PD in women who have not had hysterectomies.
- *Women who *combine* hormone replacement therapy with heavy caffeine use may be *more* likely to develop PD
- *Even a single incident of moderate to severe head trauma may increase the risk of developing PD
- *Milk intake may be associated with an increased risk of PD
- *Welding may be linked to a higher incidence of PD
- Excessive daytime sleepiness has been linked to men who go on to develop PD.

Life and death of neurons involved in Parkinson's disease

- *Disturbances of the ubiquitin-proteosome system may play a role in the development of hereditary and sporadic PD
- *An intermediate form of α-synuclein fibrils may play a key role in neurodegeneration and dopamine may stabilize this form
- *Increased expression of mutant α-synuclein causes abnormal cellular function
- *α -synuclein may serve a protective function in PD
- *Normal parkin protein may play a role in the targeting of misfolded proteins for destruction and may also serve additional neuroprotective functions
- *Individuals with PD exhibit a reduced number of norepinephrine-producing nerve endings in the heart (2000)
- *DJ-1 and PINK-1 appear to interact via mitochondria to serve a neuroprotective function in the cell
- A novel technique enables researchers to show that one of two previously undistinguishable types of nerve cells is selectively vulnerable in PD, illustrating how brain movement control circuits malfunction, revealing the molecular mechanism that kills those cells, and identifying a potential new target for drugs to slow PD.

Neural circuits in Parkinson's disease

- FDA approved DBS for use in advanced PD
- *DBS may reduce symptoms of PD by interfering with the abnormal firing patterns of the targets of STN neurons, and not by simply silencing the STN itself
- *The beneficial effects of the Lee Silverman Voice Treatment for PD are accompanied by a normalization of brain activity in regions of the brain associated with speech control

- Calcium channels act as pacemaker cells in the nigra, and sodium channels are associated with a loss of connectivity of striatal spiny neurons in dopamine depletion PD models, suggesting potential drug targets for PD.

II. Developing New Treatments for Parkinson's Disease

Pharmacological approaches

- *Creatine is found to be a promising neuroprotective agent to test in Phase III trials for PD.
- *High-dose Coenzyme Q10 appears to slow the progression of functional loss in a phase II clinical trial
- Apomorphine, an injectable drug, is now approved for use to rapidly treat “off” periods commonly associated with long-term l-dopa use. Patients experience a return to movement within 20 minutes.
- Rasagiline, a potent MAO inhibitor, was shown to be safe and effective as monotherapy in PD and as adjunctive therapy for patients receiving levodopa; 1-year trials have suggested that rasagiline may be neuroprotective and may slow the progression of PD.
- Gambling was associated with the use of dopamine agonists, patients and clinicians are now aware of this potential side effect.
- *Vaccination with copolymer-1 appears as a promising therapeutic approach in an animal model of PD
- *COX-2 is involved in PD-related neurodegeneration, and COX-2 inhibitors appear promising in an animal model as a potential treatment for PD
- Clinical trials of glial cell line-derived neurotrophic factor (GDNF) have not shown consistent results
- *Brain images from participants in industry-funded GDNF trials do not exhibit cerebellar damage suspected based on preliminary findings in animal models
- *GDNF is effective in improving motor function in aging primates and in a primate model of PD
- *The use of nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) may delay or prevent the onset of PD.
- *Levodopa either slows the progression of Parkinson's disease or has a prolonged effect on the symptoms of the disease

Deep brain stimulation and other surgical approaches

- Unilateral pallidotomy does not produce overall neuropsychological or psychiatric changes in patients with PD.
- After a 5 year follow up, study of patients who had received DBS showed no incidence of cognitive decline.

Cell implantation

- *Fetal tissue transplants appear to have minimal beneficial effects in treating advanced PD and are accompanied by difficult-to-control dyskinesias.
- *Dopamine neurons can be developed in culture from Federally-approved human embryonic stem (ES) cells

- *Neural cells derived from human and mouse ES cells can integrate into an animal host and reduce parkinsonian symptoms; adult human stem cells (removed during therapeutic surgery) also have similar potential
- *Transplantation of dopamine nerve cells derived from somatic cell nuclear transfer can help treat parkinsonian symptoms in mice
- Human neural progenitors can deliver GDNF to parkinsonian rodents and aged primates
- *Intrastriatal implantation of human retinal pigment epithelial cells attached to microcarriers reduce motor deficits in animal models of PD and are safe and well-tolerated in humans
- Novel genes have been identified which are up- or down-regulated in survival of different types of dopaminergic neurons, suggesting a basis for selective vulnerability. These genes may also be important in the generation and survival of dopaminergic stem cells used therapeutically.

Gene therapy

- *Researchers can generate regulated viral vectors for delivering therapeutic genes for treating PD.
- *Gene transfer of interfering RNAs can reduce the expression of mutant alpha-synuclein in an animal model of PD
- *Gene therapy that combines delivery of the enzyme that synthesizes L-dopa, along with a necessary co-factor, can produce long-lasting reductions in parkinsonian behaviors in a rodent model
- *Gene therapy that delivers GDNF can prevent neurodegeneration in primate models of PD
- PET and MRI have been successfully used together in the non-invasive assessment of gene transfer and gene therapy in humans.
- Sustained, regulated expression of AAV vector proteins was shown, even in the presence of an immune response in animals, suggesting that AAV would likely be successful in humans, most of whom possess antibodies to AAV naturally.
- Preclinical studies have demonstrated that infusion of neurturin, a protein similar to GDNF, improved symptoms in primate animal models of PD within 3 months; a small pilot trial of gene therapy for neurturin has begun in 12 PD patients.
- GAD, a protein involved in synthesis of inhibitory neurotransmitter, was shown to improve PD symptoms in a rat model; a pilot trial of GAD gene therapy is being pursued in 12 PD patients. Interim results have been positive thus far, with patients showing a statistically significant improvement in motor symptoms on the side of the body correlated with the side of the brain that received gene therapy.
- Four patients have now been treated with dopaminergic enzyme (AADC) gene therapy in an open label unblinded study; preliminary analysis at 6 months show that 3 of 4 patients improved on their motor scores.

Non Motor Aspects of PD

- Diagnostic criteria for depression in PD have been developed, and clinical scales for fatigue, as well as Activities of Daily Living (ADL) have been validated in PD patients.

Rehabilitation

- Exercise improves social interactions and physical abilities in PD patients, and studies suggest that taichi may improve balance.

- Acupuncture is safe and well tolerated in PD; pilot studies show that it does not improve motor symptoms, but may improve non-motor symptoms and overall quality of life.
- An educational program has been developed for use by PD patients and their caregivers to address the psychosocial challenges of PD.

Outcomes research and evidence based medicine

- Practice parameters have been developed by the American Academy of Neurology for:
    - A Neuroprotective and alternative therapies in PD;
    - B Treatment of motor fluctuations and dyskinesias
    - C Depression, psychosis and dementia
    - D Diagnosis and prognosis of new onset PD
    - E Initiation of treatment in PD
- Depression in PD is associated with difficulties in Activities of Daily Living (ADL) rather than motor problems.

III. Creating new research capabilities

High throughput drug screening

Array technologies

- NINDS has established four Microarray Consortium centers to further basic and translational research through the acquisition and dissemination of high quality gene expression data.

Models of Parkinson's disease

- *Exposure to rotenone can be used to create a new rodent model of PD (see above), as well as fruit fly model of PD
- Transgenic and knock-out models have been created for many of the genes associated with PD to date, including synuclein, parkin, PINK1, DJ1, UCHL-1, and nurr1.
- Fly models, which offer rapid and inexpensive means to screen drugs for PD, have been created with synuclein, parkin, and DJ-1. Similarly, worm models have been created for synuclein, parkin and DJ-1.
- *Use of the combined application of the neurotoxicants paraquat and maneb can generate a rodent model of PD
- Expression of the c-terminal truncated form of alpha synuclein generates a mouse model with lewy body-like inclusions.
- *Over-expression of normal or mutant human alpha-synuclein via gene therapy can induce progressive parkinsonian neurodegeneration and motor impairment in marmosets
- *Researchers have used genetic engineering to disrupt mitochondrial function in the dopamine neurons of mice to produce a new mouse model of PD. A transgenic mouse model of synuclein has been generated which exhibits similar pathology to that seen in humans, an important preclinical animal model that may be useful for testing PD therapeutics.
- Animal models of PD can be created by using proteasomal inhibitors, implicating the involvement of this cellular process in the pathology of the disease – these models may provide a useful tool for the evaluation of therapeutics.

Biomarkers

- Levels of alpha synuclein, homocysteine, and other molecules in blood plasma may correlate with PD; studies are underway to test these finding in larger PD populations.

Neuroimaging

- *Current imaging modalities are insufficient to be used alone in diagnosing PD or as a biomarker for disease progression
- *Magnetic resonance imaging may be useful as an early marker for detecting dementia associated with PD

Brain banks and other repositories

- *1140 PD genetic samples are now available in the NINDS Human Genetics Repository for use by the research community, along with approximately 750 control samples
- Update on Udall banks to date.

IV. Enhancing the research process

Ethical issues

- *Individuals' decisions about whether to participate in an early clinical trial of gene therapy for PD will likely depend more on their attitudes towards and tolerance to risk, their perceived benefit of science to society, and a personal tendency toward action, and not on their clinical, functional, or demographic status.
- *PD clinical researchers believe that sham surgeries should be included to show efficacy in clinical trials of neurosurgical approaches to treating PD

Innovative funding mechanisms

The NIH continues to explore the best ways to fund research that enables the translation of basic bench findings into potential therapeutics for degenerative diseases. The Translational Neuroscience program, a milestone-driven research program, continues to receive and fund research that will provide the preclinical data necessary to submit INDs to the FDA for Parkinson's Therapeutics. Studies ongoing in the program include those on stem cells, gene therapy, and drug therapeutics for neurodegenerative diseases.

Public-private partnerships

NIH continues to develop public private partnerships to enhance PD research, creating novel requests for applications with voluntary organizations and supporting a large international meeting on PD with the entire research, clinical, public, and private PD communities. Given that public private partnerships continue to be a priority for the Roadmap and other large NIH-wide initiatives, that activities in this area will continue to develop.