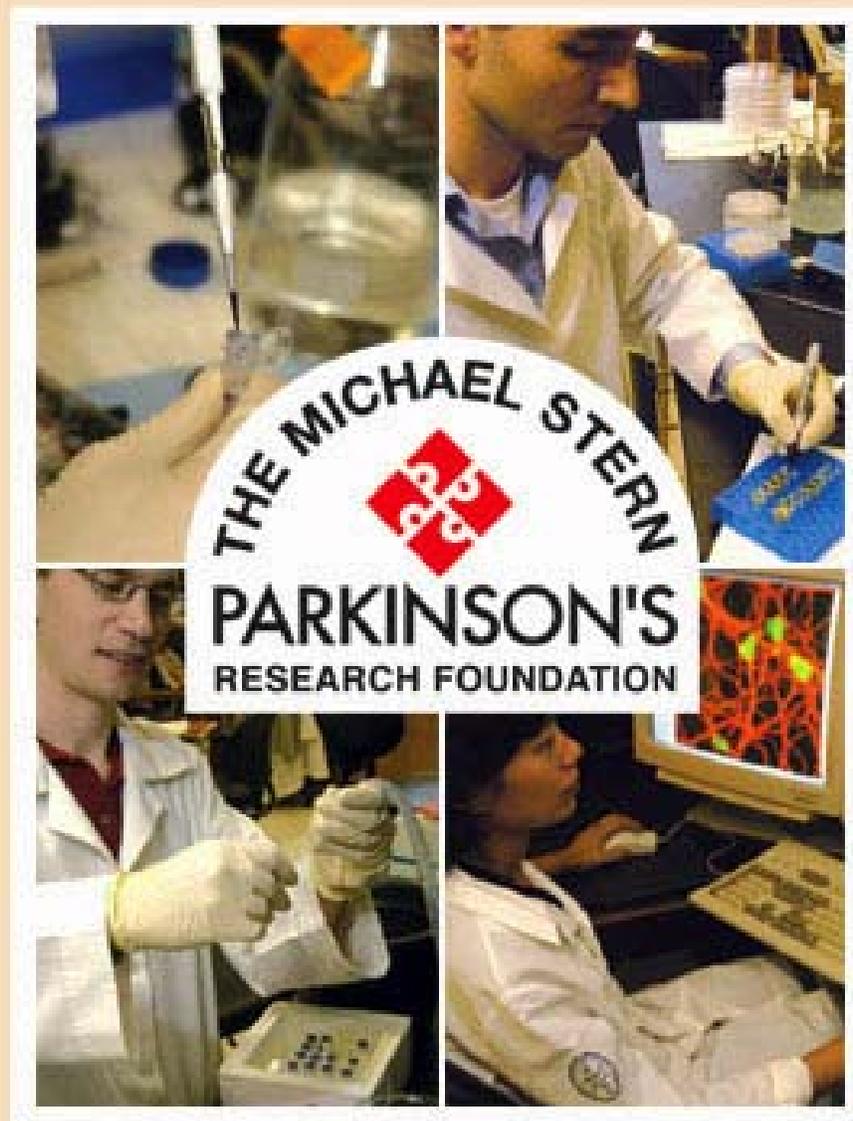


THE MICHAEL STERN PARKINSON'S RESEARCH FOUNDATION

Program in Molecular and Cellular Neuroscience at The Rockefeller University



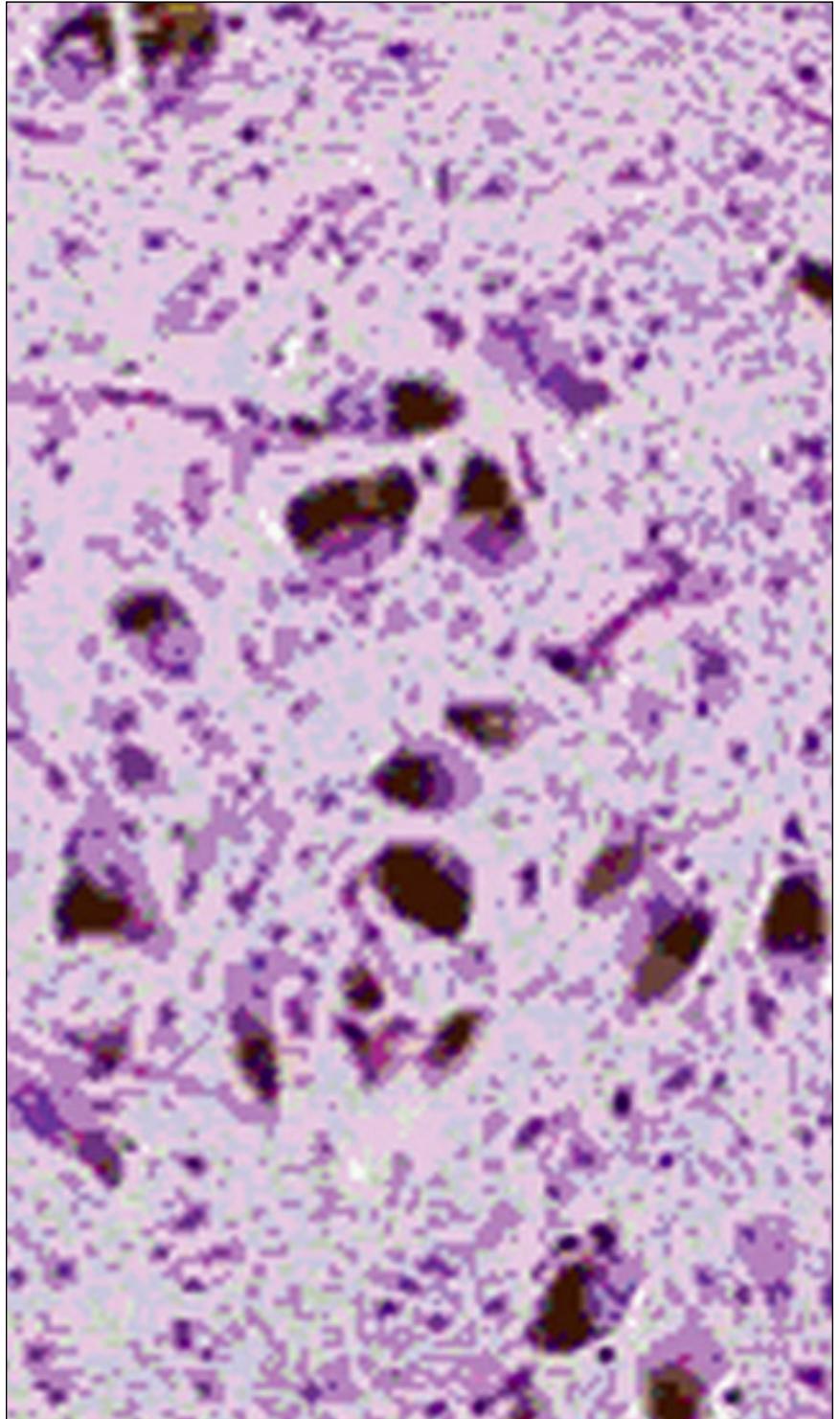
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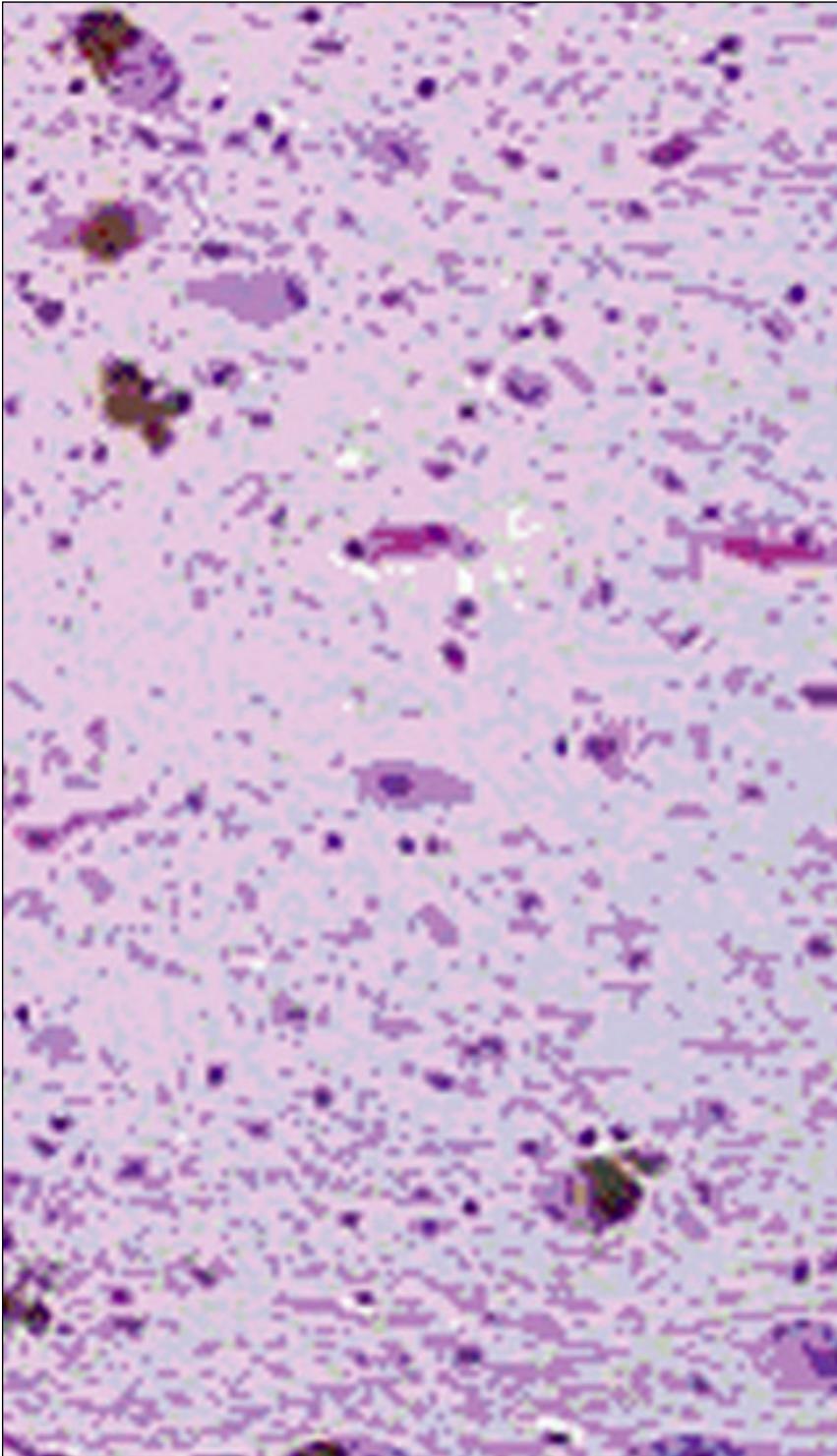
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The debilitating symptoms of Parkinson's disease (PD) can be traced to a tiny group of nerve cells deep in a brain region called the substantia nigra (shown at right). Though it is no larger than the end of your thumb, the death of neurons in this region has catastrophic results because they house the brain's manufacturing plant for dopamine, a chemical messenger critical to muscle control. As the cells degenerate and die, dopamine production falls. The result is a progressive loss of the ability to direct or control movements in a normal manner.

Walking, talking, writing, even smiling become



Dopamine producing cells in healthy brain tissue



Dopamine producing cells are lost in Parkinson's disease

d i f f i c u l t .
Eventually the disease robs sufferers of the ability to care for themselves, rendering them prisoners in their own bodies.

Parkinson's is one of the most baffling and complex of the brain disorders, but it also may be the most curable, according to experts. While we still don't know what causes Parkinson's, great progress has been made in understanding how dopamine is produced and processed by the brain and how it regulates the activity of nerve cells that control movement — progress that will lead to new treatments as well as ways to prevent and possibly cure the



photo by: Guy Kloppenburg

The Rockefeller University, home to the Stern Center laboratory, is located on New York's East Side.

Creating Hope Through Scientific Discovery

Finding the cause, finding more effective treatments and discovering the cure for Parkinson's is the focus of the Michael Stern Parkinson's Research Foundation, an IRS registered non-profit foundation that was established in 2001 to support and expand the pioneering research of Dr. Paul Greengard's laboratory at The Rockefeller University. Dr. Greengard discovered the fundamental rules by which neurons in the brain and spinal cord interact with one another — work that earned him medicine's highest honor, the Nobel Prize. He did this largely by examining the effects of the neurotransmitter dopamine, a chemical messenger that is progressively lost in Parkinson's disease. By teasing apart the intricate pathways and “second messengers” by which dopamine exerts its array of effects on neurons, Dr. Greengard and his team of scientists are laying the groundwork for a new generation of Parkinson's medications that act at the molecular level to stop the disease in its tracks — or prevent it altogether.

(Please see page 17 for more on Dr. Greengard's research.)

Dr. Greengard has assembled a close knit group of more than 25 outstanding scientists who are focused on translating the fundamental understandings about the dopamine system into new treatments for Parkinson's. The core team of researchers based at the Stern Foundation laboratory on the campus of The Rockefeller University interacts continually with collaborators from the United Kingdom, France, Sweden, Italy, Japan and Korea. This global presence ensures that no promising research lead is overlooked, and that progress can be made on multiple fronts simultaneously.

State-of-the Art Facility

The Stern Center shares a state-of-the-art laboratory at The Rockefeller University with the Fisher Center for Alzheimer's Research, a synergistic arrangement that capitalizes on the similar scientific questions that drive research aimed at curing these two different brain dis-

“We are in a stage in basic scientific research into Parkinson’s disease where we expect to make meaningful advances in treating this scourge in a matter of months, rather than years.”

-- Michael Stern, Chairman

eases. (For more information about the Fisher Center for Alzheimer’s Research, please see the companion brochure, “A Window on Alzheimer’s Research.”)

The laboratory is equipped with the most advanced technology available to scientists engaged in the fight against these neurodegenerative disorders. These cutting edge instruments include all the essential tools of molecular biology, such as “gene chips” that permit scientists to monitor hundreds of genes as they are turned on and off during nerve-cell function, and sophisticated equipment that enables researchers to peer inside nerve cells and eavesdrop on their inner workings. Another research tool created specifically for the lab is the “transgenic” mouse model, a mouse in which certain genes thought to be involved in PD are removed, inserted or are

abnormally over-expressed. These animal models are critical to pre-clinical research aimed at developing and testing potential drug candidates.

In addition, an integrated computer complex at the Stern Center facilitates data analysis and expedites worldwide exchange of information, while an adjoining conference center brings together top scientists from around the world. Informal collaborations among researchers augment annual symposia at The Rockefeller University on related subjects.

With its unmatched combination of advanced technology and brilliant scientific minds, the Stern Foundation is uniquely equipped to lead the search for a cure for Parkinson’s and, indeed, has already made outstanding progress toward this critical goal.



photo by: Guy Kloppenburg

Dr. Paul Greengard (left of center) is surrounded by Stern Center scientists. The Stern Center is one of the largest interdisciplinary efforts engaged in Parkinson’s disease research.

PARKINSON'S DISEASE

What is it?

Parkinson's disease is a brain disorder that affects the motor system, the system that initiates and controls skeletal muscle movements. Parkinson's is chronic and progressive, meaning that it gets worse over time. The disease progresses at different rates in different people and affects each person uniquely

— some people may suffer incapacitating movement problems while others may experience only minor impairments for some time.

It is impossible to predict which symptoms will affect any one person, but the primary symptoms of Parkinson's are:

- * Tremor, trembling in the hands, arms, legs, jaw and face;

- * Rigidity, stiffness of the limbs and trunk;

- * Bradykinesia, slowness of movement;

- * Akinesia, difficulty in initiating movement;
- * Postural instability, impaired balance and coordination.

A number of other symptoms may also accompany Parkinson's disease, some minor and some that can be debilitating. These may include depression, changes in emotions or cognitive

(thinking) abilities, difficulty in swallowing and chewing, speech changes, urinary problems or constipation, skin problems such as very oily or very dry skin, or excessive sweating, and sleep problems. Not all these symptoms occur in everyone with Parkinson's disease.

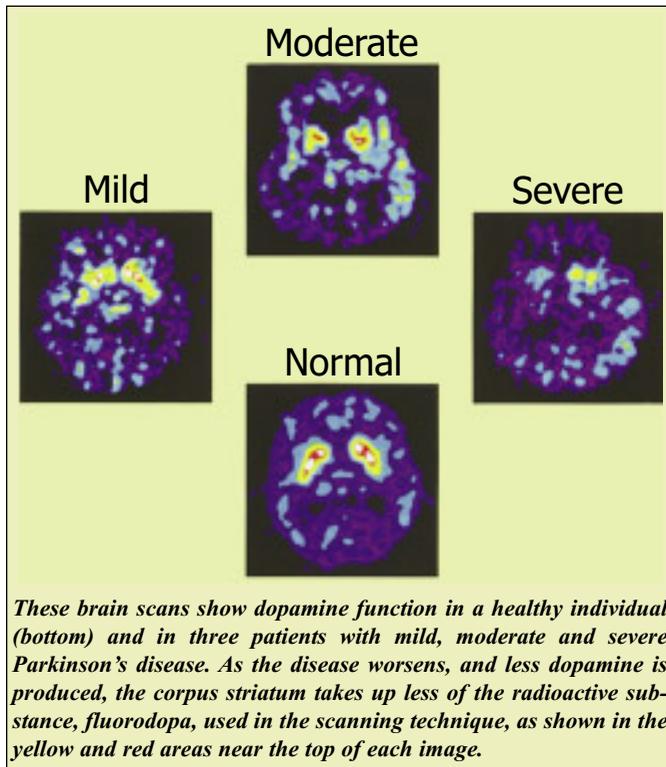


Image courtesy of National Institute of Neurological Disorders and Stroke

Parkinson's disease is classified as a neurodegenerative disease, which means that it is marked by the progressive degeneration and death of certain groups of nerve cells, or neurons. (Other neurodegenerative disorders include Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis, or Lou Gehrig's disease.) In the case of Parkinson's, the neurons that die produce dopamine, an important brain

chemical that is critical to the initiation and control of skeletal muscle movements.

What Causes Parkinson's?

While scientists don't yet know what triggers Parkinson's disease, they do know that the symptoms are the result of the progressive death or

impairment of a discrete group of nerve cells in an area of the brain called the substantia nigra. Normally, these neurons produce dopamine, a neurotransmitter that acts as a chemical messenger to relay signals between the substantia nigra and another part of the brain called the striatum, which is part of the basal ganglia (see right). As the dopamine neurons die, the level of dopamine decreases, which causes nerve cells to fire abnormally and excessively. This disrupts the brain's ability to initiate and control muscle movements, causing the classic symptoms of Parkinson's disease.

Dopamine neurons die gradually, sometimes over the course of many years. Parkinson's symptoms begin when the loss of dopamine reaches a critical point — typically when between 50 percent and 80 percent of dopamine neurons have died.

The question of why dopamine neurons begin to degenerate is being intensely investigated by scientists around the world. It is widely accepted that there is no single “cause” that triggers the disease; rather Parkinson's likely results from a confluence of inherited (genetic) and environmental factors that interact in complex, poorly understood ways to set disease processes in motion. While Parkinson's is not hereditary in the classic sense — that if one of your parents has it, you too will get it — individuals may inherit a degree of susceptibil-

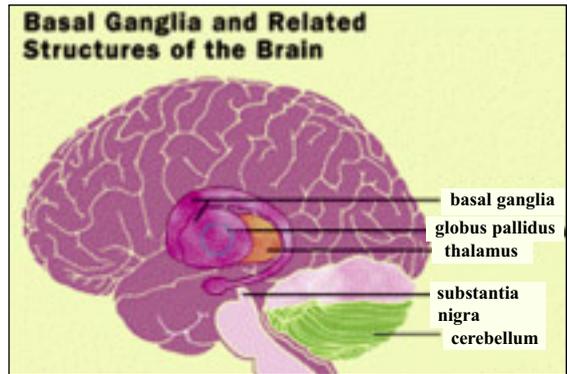


Image courtesy of the National Parkinson's Foundation, Inc.

ity to the disease. This may not be enough to cause Parkinson's, but if a genetically predisposed individual is also exposed to certain toxic environmental substances or possibly to a particular virus or bacteria, that individual may then develop the disease.

Current Theories on the Cause of Parkinson's

In recent years, science has made great strides in understanding the potential triggers for Parkinson's disease and there are a number of interrelated hypotheses about the mechanisms and pathways that lead to the disease. These include, but are not limited to:

- * abnormalities in the way certain proteins (e.g., alpha-synuclein) are processed in the brain;
- * cellular damage resulting from oxidative stress, which is sometimes described as the biological equivalent of metal rusting;
- * impairments in mitochondria, the tiny vesicles inside cells that act as energy factories to fuel cellular functions;
- * excitotoxicity, toxicity to neurons caused by neurotransmitters that get out of balance;
- * loss of so-called trophic factors, naturally occurring chemicals in the brain that nurture and support nerve cells;
- * inflammatory processes that may result when a subset of brain cells called microglial cells become inappropriately activated and release toxic substances that can damage nerve cells;
- * overactive or misdirected apoptosis (programmed cell death), a natural process in which



photo by: Gay Kloppenburg

A scientist prepares cultures to grow neurons.

The Economic Impact of Parkinson's Disease

Parkinson's disease has been called the biological opposite of Alzheimer's: While Alzheimer's destroys the mind and generally leaves the body functioning, Parkinson's robs its victims of normal physical movement, leaving the mind a prisoner in the body. People with Parkinson's live with physical incapacitation for years or decades and eventually may require complete care. The impact on individuals and their families is enormous.

The financial burden on families is also immense: according to the Parkinson's Action Network, drugs commonly used to treat Parkinson's cost between \$1,000 and \$6,000 per year, per patient. Annual medical care, including doctors' visits, physical therapies and treatment for co-occurring illnesses (such as depression) is estimated at \$2,000 to \$7,000 for people in early stages of the disease, and is perhaps much higher for advanced stages. Surgical treatments for Parkinson's can cost \$25,000 or more. As the disease progresses, institutional care at an assisted-living facility or nursing home may be required, and these costs can exceed \$100,000 annually, per person.

With about a million people affected in the U.S., it is clear that Parkinson's exacts a tremendous economic burden on the nation. Forty percent of people affected are under the age of 60, placing them squarely in the workforce. Experts say that about a third of employed individuals will lose their jobs within a year of a Parkinson's diagnosis, making lost productivity a major factor in the societal impact of the disease. Moreover, the direct

neurons in effect commit suicide.

Each of these possible mechanisms of disease onset and progression are being intensely investigated, but it is important to understand that Parkinson's disease is likely to involve more than one of these mechanisms, and possibly elements of them all. Each may interact in complex ways with the others, as well as with other factors still unknown.

Among all of these hypothetical pathways to Parkinson's disease, there is one common denominator: all result in the loss of dopamine. This basic fact is what drives scientific discovery at the Michael Stern Parkinson's research laboratory at The Rockefeller University.

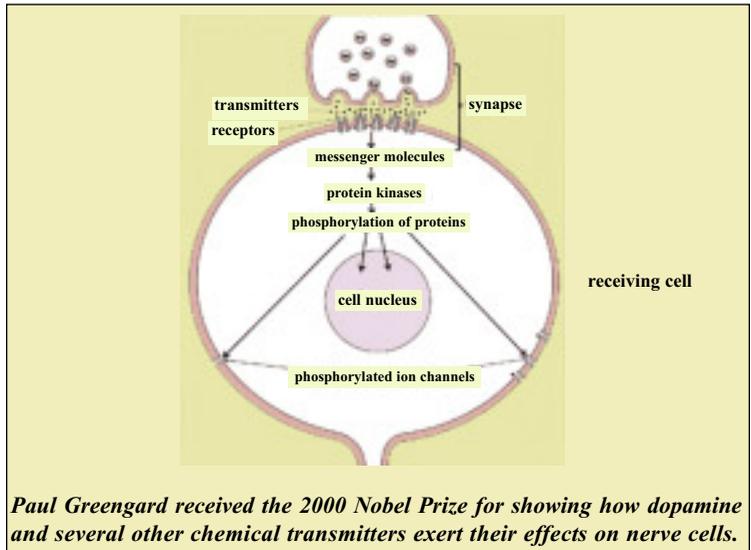


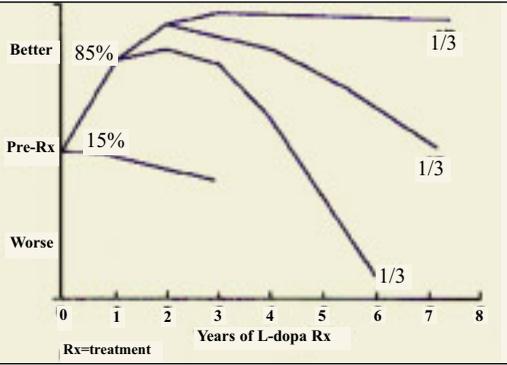
Image courtesy of the Nobel Assembly at the Karolinska Institute.

Who is Affected?

Since physicians are not required to report incidences of Parkinson's in their patients, it is difficult to precisely define the number of people in the U.S. who have the disease. Estimates range from 500,000 to 1.5 million, with about 50,000 to 60,000 new diagnoses each year.

Experts say the number of people with Parkinson's is on the rise, due in large part to our aging population. The average age of onset is 60, and the disease is relatively common after age 50, affecting perhaps 1 percent to 2 percent of people in that age group. Still, Parkinson's is not only a disease of aging: 5 percent to 10 percent of patients are diagnosed before age 40, about 15 percent are under age 50 and 40 percent are under 60. The incidence appears to be increasing among younger people, for unknown reasons.

Figure 3: 1/3 of PD patients started on L-dopa have a marked response and maintain it for as long as 10 years. 2/3 of PD patients started on L-dopa have a moderate to marked response and maintain it for 2 - 5 years. 15% of people do not respond to L-dopa. Most of them do not have PD.



Men and women are affected in almost equal numbers, while Asians and African-Americans are less likely to get Parkinson's than are whites. The disease knows no social, economic or geographic boundaries, although there is some evidence that people who live in rural areas are at greater risk, as are people who drink well water, and those who are exposed to pesticides.

How is Parkinson's Disease Treated?

Ever since scientists discovered that people with Parkinson's have decreased levels of dopamine, therapy for the disease has focused on replacing brain stores of this neurotransmitter. While current therapies do not stop the progression of the disease, they can be used effectively to control the major symptoms in many people, and can dramatically improve quality of life, often for several years. Unfortunately, these treatments are not perfect — their effectiveness often diminishes over time, and they can cause debilitating side effects. Novel therapies that can stop the loss of dopamine neurons or improve the effectiveness of current medications are desperately needed, and this is a major focus of research at the Michael Stern research laboratory at The Rockefeller University.

Drug Treatment

For decades, the mainstay of drug therapy for Parkinson's has been levodopa (also called L-dopa), a naturally occurring biochemical that neurons use to make dopamine. Once it enters the brain, levodopa is chemically converted into dopamine. The drug is usually given in combination with another medication called carbidopa, which delays the conversion of levodopa until it reaches the brain. This strategy maximizes the amount of dopamine available to the neurons in the basal ganglia that rely upon it, and also minimizes some of the side effects associated with levodopa use, such as nausea and vomiting.

Levodopa has been called a triumph of modern medicine because

costs of treating and caring for people with Parkinson's are placing a growing burden on healthcare systems — a burden certain to rise as Baby Boomers age.

Estimates of the overall cost of Parkinson's are widely disparate: the National Institute of Neurological Disorders and Stroke (NINDS) puts the figure in excess of \$5.6 billion, including both direct medical expenses and indirect costs such as lost income and disability payments. But many experts say the number is much higher — as much as \$25 billion or more.

What is clear is that investment in medical research that leads to better treatments for Parkinson's can save millions of dollars each year. Studies have shown that for every dollar spent on research, \$13 could be saved in direct and indirect costs of illnesses. If new therapies could be found that could produce even a modest 10 percent slowing in the progression of Parkinson's, hundreds of millions of dollars could be saved every year.

Despite these promising projections, Parkinson's continues to receive far less federal research support than most other disorders, according to the Parkinson's Action Network. The NINDS, the lead federal agency responsible for biomedical research on neurological disorders, will commit \$215 million to Parkinson's research in 2003. While that may seem like a lot, in reality it is less than one percent — 1/100th — of the estimated yearly cost of the disease.

Privately funded research must fill these huge gaps in federal funding. At the Michael Stern Parkinson's Research Foundation, at least 96 percent of contributions go directly to research aimed at finding a cure. Donations of any amount can help us make a difference for the millions of people affected by Parkinson's directly or through a family member.

it vastly improves the quality of life for people with Parkinson's and delays the onset of debilitating symptoms. It helps at least 75 percent of patients, dramatically extending the time during which they can lead relatively normal lives. Despite these important benefits, levodopa has its limitations — notably that its effectiveness often wears off over time. It can also cause unacceptable side effects, including involuntary movements (dyskinesias) such as twitching, nodding and jerking. These adverse effects develop most commonly in people who have been taking the drug for an extended period of time and/or are taking high doses. *(Please see page 16 for a summary of our research aimed at preventing levodopa-induced dyskinesias.)*

Other medications used in Parkinson's treatment include a class of drugs called dopamine agonists (e.g., bromocriptine, pergolide, pramipexole and ropinirole), which mimic the role of dopamine in the brain. They are often given before levodopa because studies indicate that they can delay or decrease the occurrence of levodopa-related complications. Selegiline (also known as deprenyl), a drug that blocks an enzyme that breaks down dopamine in the brain, may also be used to delay the need for levodopa. Amantadine, an antiviral drug, has been shown to be effective in reducing Parkinson's symptoms as well as the troublesome involuntary movements sometimes caused by levodopa treatment. While these drugs are all important components of treatment, none are without

side effects, and none can stop the loss of naturally occurring dopamine.

Surgical Therapy

In recent years, there has been a growing interest in surgical approaches to treating Parkinson's. Brain surgery, however, is not to be taken lightly, and surgical treatment is usually reserved for people who have not been provided with relief by drug therapies. Two types of surgery are most commonly used -- thalamotomy and pallidotomy -- both of which aim to interrupt the aberrant brain signals that impair movement. In thalamotomy, surgeons destroy a small section of the thalamus, a structure deep in the brain that acts as "relay station" for nerve impulses and is thought to be the source of Parkinsonian tremors. Pallidotomy targets a portion of the globus pallidus, a brain region within the basal ganglia that seems to be a critical point along the dopamine pathway. Any neurosurgical intervention carries a risk of injury to adjacent brain structures, but many people with Parkinson's have experienced dramatic relief from symptoms after surgery.

Deep brain stimulation is another surgical technique that is being increasingly used for patients who no longer respond to drug treatment. It involves the placement of an electrode into a specific region of the brain (usually either the thalamus or globus pallidus, though studies are underway to determine which location is best), combined with a pacemaker-like device, called a neurostimulator, which is implanted under the skin of the chest. The neurostimulator is used to send a tiny electrical current to the electrode, which interferes with the faulty brain signals that produce tremor. Deep brain stimulation is being intensely investigated in government-funded studies, and has been approved by the U.S. Food and Drug Administration as a treatment for advanced PD.

Investigational Treatments

A number of therapeutic strategies are being investigated as possible treatments for Parkinson's, including new drugs and novel therapies such as cell transplantation, stem cells and growth factors:



photo by: Gay Kloppenburg

Hundreds of nerve cell lines are stored frozen at the Center.



photo by: Gray Kloppenburg

Dr. Yong Kim fractionates cellular molecules.

* The search for a true neuroprotective drug — one that prevents dopamine neurons from dying — is being aggressively pursued through government-funded clinical trials as well as basic research, but results are still several years away.

* Transplantation, which entails grafting neurons from other sources into a person with advanced Parkinson's, has proven to be a feasible strategy. However, in the largest clinical trial to date of this therapy, a small number of treated patients developed severe side effects, and scientists have taken a step back to understand why the problems developed and to better refine this approach.

* Various groups of scientists have shown that it is possible to induce embryonic stem cells to develop into dopamine-producing neurons in laboratory settings. Many experts believe Parkinson's may be the brain disease that is most amenable to treatment with stem cells, but it may be years before the science has developed enough to use stem cells clinically.

* Growth factors are naturally occurring chemicals that support the development and survival of neurons. One growth factor, called GDNF (glial cell line-derived neurotrophic factor), has been recently shown to significantly improve symptoms of advanced Parkinson's in a small, uncontrolled clinical trial. Experts are cautiously optimistic about this therapeutic strategy; more and better-controlled studies are needed to demonstrate its benefit.

Stern Center Scientific Achievements in Parkinson's Research

The Stern research laboratory at The Rockefeller University is a world leader in advancing scientific understanding of the fundamental mechanisms by which neurons in the brain communicate with one another — and how these processes can go wrong in neurological conditions such as Parkinson's disease. Some of the laboratory's achievements related to Parkinson's are summarized below:

* **Discovered and described in elegant detail how neurons communicate with one another via slow synaptic transmission.**

* **Elucidated numerous signaling pathways inside neurons by which dopamine produces its effects on target neurons.**

* **Discovered the "master molecule" DARPP-32, a critical regulatory protein whose actions change the function of a large number of signalling proteins inside neurons.**

* **Characterized several signaling pathways that interact with dopamine signaling in positive or negative ways.**

* **Identified naturally occurring biochemicals that amplify the effects of dopamine, fueling hope for developing a drug that could allow even small amounts of dopamine remaining in the brains of people with Parkinson's to be used to maximum advantage.**

* **Analyzed the interactions of dopamine signaling pathways with the antidepressant drug Prozac and other compounds that affect brain levels of the neurotransmitter serotonin. This has led to a possible biochemical explanation for the high incidence of co-occurring depression in people with Parkinson's.**

* **Traced the molecular pathways through which the neurotransmitters glutamate and acetylcholine interact with the dopamine pathway to counteract or enhance dopamine's effects.**

Leading the Charge for Novel Treatments

While current Parkinson's treatments have helped many people with the disease overcome debilitating symptoms and lead relatively normal lives, available treatments have significant limitations.

Investigational therapies such as neuronal transplantation, though promising, still have significant hurdles to clear before they can be integrated into clinical practice to treat Parkinson's. As research continues to refine these dopamine-replacement therapies, the need for novel therapeutic approaches is highlighted. Better understanding of how dopamine exerts its effects in the brain paves the way for new approaches.

The scientists affiliated with the Michael Stern Parkinson's Foundation are leading the charge to develop new and better Parkinson's treatments. Led by Dr. Paul Greengard, who won the 2000 Nobel Prize for his research on how nerve cells communicate, researchers at the Stern-supported laboratory are meticulously teasing apart the dynamics of dopamine neurotransmission to reveal the secrets that will lead to therapeutic interventions.

Tracing the Dopamine Pathway

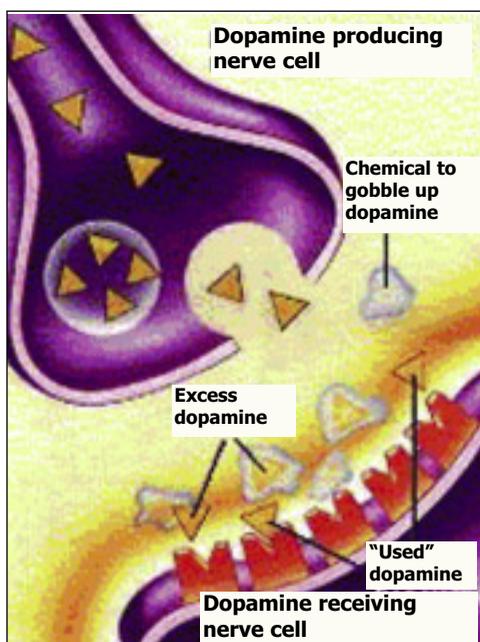
It is now well established that the symptoms of Parkinson's are attributable to degeneration of neurons that originate in a particular region deep in the brain (the substantia nigra). These

cells send their axons, the antenna-like projections that neurons use to communicate with other neurons, to another part of the brain intimately involved in the control of movement (the striatum). Over the course of numerous years, Dr. Greengard and his colleagues have discovered many components of the so-called signaling pathways by which dopamine (as well as other neurotransmitters) produce their effects on these target neurons.

These brain pathways are incredibly complex, multi-step systems involving biochemical interactions among proteins, enzymes, "second messengers," and other molecular entities that exist

inside each minute nerve cell. Taken as a whole, these systems comprise a model for how the brain functions at the molecular level.

It all starts at the synapse, the tiny gap between neurons (see figure). When a message is to be sent from one neuron to another, an



Dopamine produced at the synapse between neurons. Dopamine is a neurotransmitter that carries information between neurons.

Image courtesy of the National Parkinson's Foundation, Inc.

electrical impulse travels across the cell body and down the axon of one nerve cell (the pre-synaptic neuron) to the nerve terminal. There the signal triggers the release of packets of a neurotransmitter — in this case dopamine — which act as chemical messengers. The released dopamine diffuses across the synapse and locks on to receptors on the surface of the receiving neuron (the post-synaptic neuron), triggering a cascade of events inside the cell.

Beyond the Dopamine Receptor

What happens beyond the dopamine receptor has been the focus of Paul Greengard's outstanding scientific career for several decades. He tackled the question at a time when other scientists dismissed it as a deep mystery that might well never be solved. As a graduate student in biophysics, Dr. Greengard not only dared to ask the question, but went on to answer it in exacting detail.

There are two primary classes of dopamine receptors, known as D1 and D2 receptors, and each class exerts different effects inside the post-synaptic nerve cells. Dr. Greengard and his collaborators worked through the cascade of biochemical steps initiated by each class of receptors. The figure on page 8 summarizes some of the critical steps in this highly complex cascade, which is known as slow synaptic trans-



Michael Stern (left) chats with Dr. Paul Greengard.

photo by: Guy Kloppenburg

mission.

The cascade that is set off when dopamine locks onto a D1 receptor begins with the activation of an enzyme called adenylylase, which makes the “second messenger” cyclic AMP (or cAMP). cAMP then activates an enzyme known as protein kinase A, which in turn produces a chemical reaction called protein phosphorylation. (See sidebar page 14) This reaction — basically the addition of a phosphate group to a protein in such a way that the form and function of the protein is altered — orchestrates a wide spectrum of events within the neuron. These changes profoundly affect the action of the cell by, for example, modifying other neurotransmitter receptors, as well as ion channels and ion pumps (mechanisms neurons use to adjust their chemical make-up), or by generating transcription factors that mediate functioning of the cell's genes.

Painstakingly following this pathway to its conclusion, Dr. Greengard's team discovered a protein — dubbed DARPP-32 — that plays a central role in the actions of dopamine and has proven to be enormously useful for better understanding dopamine's effects in normal brain function and in disease. DARPP-32 acts as a “master molecule,” regulating the func-

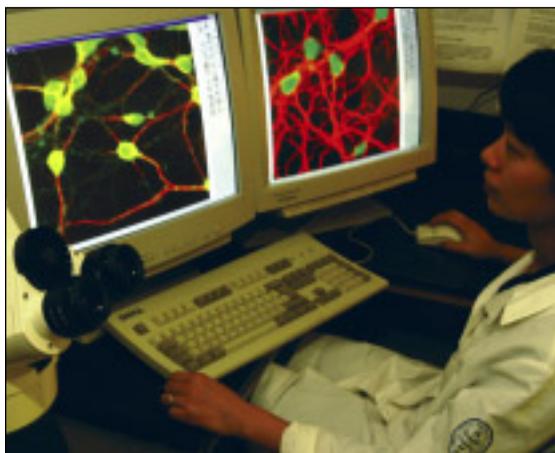


photo by: Guy Kloppenburg

At a confocal microscope, Dr. Xiao Ryan maps molecules.

Protein What?

A Primer on Phosphorylation

What is protein phosphorylation?

Many proteins encoded by our genes are components of a vast communications network that functions inside cells, connecting them to their environments. This network is composed of signaling pathways that allow cells to respond to one another and to chemical messages from hormones and neurotransmitters. Protein phosphorylation is one of the main currencies used within cells to expedite this flow of information. In short, phosphorylation is the addition of a phosphate molecule to a protein. It's been described as a sort of "on-off switch" for proteins and is often a critical step in determining what the cell machinery does next.

How does it work?

Proteins inside cells are constantly interacting with enzymes and chemical messengers in a kind of molecular Pac Man game. In phosphorylation, a phosphate group is added to a protein, which often has the effect of transforming the protein's shape, thereby changing the protein's function. This regulates its activity and/or impacts how it interacts with other cellular components. These changes in turn, affect the "river of communication" causing "downstream" effects in the cell, such as opening or shutting certain gates and pumps in the cell's outer membrane, modifying the expression of genes in the cell's nucleus, or relaying signals to a group of other signaling proteins. The on-off switch endowed by protein phosphorylation is not complete without the reverse event — dephosphorylation, which occurs when a phosphate group is removed from a protein. This returns

tion of a large number of other proteins that direct how brain cells transmit nerve impulses. Dr. Greengard calls DARPP-32 a sort of Rosetta Stone for understanding the mechanism of action of dopamine and its interactions with other chemical messengers, with therapeutic drugs such as levodopa and with drugs of abuse.

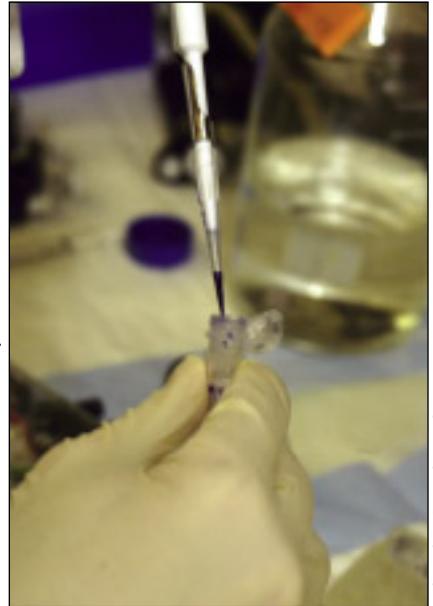


photo by: Guy Kloppenburg

While these findings were initially greeted, Dr. Greengard recalls, with "enormous skepticism, at times down-right hostility by some in the scientific community," they are now accepted as scientific dogma — and in fact earned Dr. Greengard the Nobel Prize. Not only did the discoveries change the playing field for neuroscientists and open up an entire new branch of research — that of "signal transduction" — but they also identified an array of potential targets for the development of pharmaceutical compounds that could regulate the actions of dopamine.

A molecular biologist analyzes genes.

New Drug Targets

By elucidating this complex intracellular interplay that is triggered when dopamine binds to its receptor, Dr. Greengard and his team have accumulated a textbook's worth of data on the biology of dopamine's target cells. In the process, they have discovered a number of other types of signaling pathways that interact with dopamine in various ways, both positively and negatively.

For example, two pathways that interact with dopamine in a positive manner involve two types of protein kinases that are known as casein kinase 1 and casein kinase 2 (CK1 and CK2). These enzymes increase the phosphorylation of DARPP-32 and enhance dopamine processing. Stern Center scientists have recently identified chemicals pres-

ent normally in the brain that can activate these pathways, which should make it possible to design drugs that potentiate the effects of dopamine on target cells. This would maximize the effects of even small amounts of dopamine remaining in the brains of people with Parkinson's, so that symptoms would be minimized.

Other pathways — such as those involving the proteins cyclin dependent kinase 5 (CDK5) and protein phosphatase 2C (PP2C) — interact with dopamine signaling in a negative, or inhibitory, fashion, working in coordination with the protein kinases but via a different, opposite mechanism. Chemical substances that modify the actions of these proteins would eliminate their inhibitory effects on dopamine signaling and thereby potentiate dopamine — the equivalent of blocking a tackle so the running back can move downfield. The Stern laboratory and its international team of collaborators are currently studying these and other pathways to identify substances that inhibit or enhance their actions, and to characterize the mechanisms by which they alter dopamine signaling.

Other neurotransmitters — notably glutamate and acetylcholine — also interact with the dopamine pathway, and altering their effects with drugs may present an alternative approach to Parkinson's treatment.

For example, studies led by Japanese researcher Akinori Nishi, M.D., Ph.D., have identified pathways through which



Dr. Marc Flajolet completes a study.

photo by: Guy Kloppenburg

the protein to its pre-phosphorylation state. Hence, a protein can be activated or deactivated by the addition or deletion of a phosphate.

Who are the players?

Certain enzymes called protein kinases pick up a single phosphate molecule from a compound in the cell called ATP (adenosine triphosphate) and present it to a selected protein at a specific site along the protein's chain of amino acids. Other enzymes, known as protein phosphatases, take away phosphate molecules from the protein, returning it to a dephosphorylated state. Either way, the protein's shape and activity is fundamentally transformed. Kinases and phosphatases operate in continuous feedback loops and other regulatory networks to fine-tune the cell's activity, like nature's version of checks and balances.

What does it have to do with Parkinson's?

In the subset of nerve cells that respond to dopamine, the phosphorylation of a protein called DARPP-32 is the central mechanism by which dopamine exerts its effects on neurons. DARPP-32 is more like a communications hub, able to be phosphorylated on multiple distinct sites in various combinations so that it transmits signals to a variety of pathways. The key to solving Parkinson's disease may lie in the ability to "tweak" the balance of "on" vs. "off" settings for DARPP-32, thereby altering its signaling behavior to favor relief of Parkinsonian symptoms while discouraging pathways that may lead to unwanted side effects. By understanding the pathways through which dopamine associated kinases and phosphatases act on DARPP-32 and the pathways that DARPP-32 subsequently acts on, it should be possible to design pharmaceutical compounds that interact with either the kinases or phosphatases to potentiate or block their effects. In this way, the downstream effects that dopamine normally exerts on the cell could be enhanced, mimicked or tailored, even when little or no dopamine is available.

TOWARD NEW THERAPIES FOR DYSKINESIA

Dyskinesia (abnormal involuntary movements) represents one of the major obstacles in the current drug therapy for Parkinson's disease. A complication of prolonged administration of levodopa (L-dopa), dyskinesia is thought to derive from changes in the molecular machinery of neurons in the striatum that receive dopamine inputs.

Genetically modified mice — an essential tool of clinical research — may offer an opportunity to identify the primary determinants of cellular changes underlying dyskinesia. However, a valid model of levodopa-induced dyskinesia in the mouse has thus far not been available. For this reason, Parkinson's researchers led by Gilberto Fisone, Ph.D., of the Karolinska Institute in Sweden, are developing and validating a mouse model of dyskinesia.

Fisone and his colleagues have previously found that, in the rat, dyskinesia is accompanied by abnormally high levels of phosphorylated DARPP-32, the "master molecule" through which dopamine signals. The researchers will use the newly developed mouse model of dyskinesia to examine how abnormal DARPP-32 phosphorylation is involved. They will also identify any changes at the level of specific signaling pathways and/or neurotransmitter systems that might be responsible for the aberrant phosphorylation of DARPP-32 associated with dyskinesia. This information will be used to select a number of candidate drugs that will be screened for efficacy in laboratory tests, thereby providing a basis for the design of novel pharmacological treatments for Parkinson's disease. The battery of tests the researchers have designed will serve as a paradigm for future studies aimed at screening novel Parkinson's treatments in mice.

glutamate counteracts dopamine signaling and regulates phosphorylation of DARPP-32. Similarly, acetylcholine has been shown to modulate dopamine signaling, and drugs that increase acetylcholine levels (cholinergic agents, such as those currently used to treat Alzheimer's disease) have shown some benefit in lessening Parkinson's-like involuntary movements. Elucidating the molecular mechanisms through which acetylcholine acts will reveal new targets for developing drugs that regulate these processes.

To take this vast reservoir of knowledge to the next step in the process of developing new therapies, our laboratories are producing genetically altered mice -i.e., mice that either express or fail to express genes that encode proteins of interest. A mouse that has been genetically altered to carry a new gene is said to be "transgenic." A mouse that has been genetically altered so that one of its own genes has been deleted (and can no longer be expressed) is called a "knockout." By then analyzing the biochemistry and behavior of these transgenic and knock-out mice Stern Center researchers are better able to understand how specific proteins interact with the dopamine system, and what role each plays in the development of parkinsonian symptoms.

Solutions Within Reach

These are just a few of the many lines of research our Center is pursuing in its quest to identify novel proteins and substances that can be used to develop drug therapies in the battle against Parkinson's disease. These investigations capitalize on the team's vast knowledge of dopamine signaling systems in the brain, and employ a multidisciplinary approach that advances the research in the most efficient ways possible. New drug targets are months, not years, away.

Clearly, this outstanding team of scientists has the right stuff to make the dream of effective new Parkinson's treatments a reality. With the right resources supporting them, the dream will become a reality sooner rather than later.

Scientific Leadership

Paul Greengard, Ph.D.

Dr. Paul Greengard's pioneering work in delineating how neurons communicate with one another in the brain earned him the 2000 Nobel Prize in Medicine or Physiology. During a half-century of research, he has arguably contributed more than any other single scientist to our understanding of the complex signaling processes that occur within each of the 100 billion or more nerve cells in the human brain. Collectively, these cells orchestrate every aspect of our being — from walking and talking to thinking and feeling emotion to having a unique personality. Understanding these processes enables us to comprehend not only the fundamental nature of brain function, but also what goes wrong in brain diseases such as Parkinson's. The ultimate goal, of course, is to develop effective treatments for this and other devastating disorders of the brain.

Dr. Greengard's work has focused largely on cells that process dopamine, one of the brain's most important neurotransmitters (biochemical messengers that relay signals from one neuron to another). Dr. Greengard and his team have worked out in exquisite detail the biological chain of events that occurs when a cell is activated by dopamine and other neurotransmitters, and helped establish phosphorylation as the major mechanism by which every cell in the body regulates bodily functions.

As you read this, these processes are occurring perhaps thousands of times a moment inside the



His Majesty, the King of Sweden, presents Dr. Paul Greengard (left) with the 2000 Nobel Prize in Medicine.

Photo: Hans Mehtlin, Nobel e-museum

neurons in your brain. Many of the most devastating brain disorders — including Parkinson's disease — are thought to arise when something goes wrong at one step or another along these signaling pathways. Each step therefore presents a potential target for developing a drug that might halt, reverse, or compensate for the “missteps” in the path that lead to disease. Fueled by the groundbreaking work of Paul Greengard and his research team, scientists worldwide are well on the way to developing rational treatments for a range of diseases based on these fundamental new understandings of brain function.

Biography of a Nobel Laureate

Paul Greengard, Ph.D., Director of the Michael Stern Parkinson's Research Foundation, is the Vincent Astor Professor and head of The Rockefeller University's



Laboratory of Molecular and Cellular Neuroscience. He is also a Vice President with the Fisher Center for Alzheimer's Research Foundation. An internationally acclaimed neuroscientist, Dr. Greengard's discoveries have provided a conceptual framework for understanding how the nervous system functions at the molecular level — work that earned him the 2000 Nobel Prize in Physiology or Medicine, the highest honor paid to medical researchers.

Dr. Greengard is a member of The National Academy of Science and has received more than fifty major awards and honors for his groundbreaking research, including the Society for Neuroscience's Ralph W. Gerard Prize in Neuroscience; the National Academy of Sciences Award in Neuroscience; the 1997 Dana Award for Pioneering Achievement in Health; the 1996 Lieber Prize for Outstanding Achievement in Schizophrenia Research, and numerous named lectures and visiting professorships. He received his Ph.D. from Johns Hopkins University and carried out postdoctoral studies at the University of London, Cambridge University and the National Institute for Medical Research in London. He was the Henry Bronson Professor of Pharmacology and Psychiatry at Yale University prior to joining The Rockefeller University in 1983 to assume his present position. Dr. Greengard was named the Founding Director of the Zachary and Elizabeth M. Fisher Center for Research on Alzheimer's Disease in 1994.

Angus C. Nairn, Ph.D.

Dr. Angus C. Nairn is Adjunct Professor in the Laboratory of Molecular and Cellular Neuroscience at The Rockefeller University and Professor of Psychiatry at Yale University's Combined Program in the Biological and Biomedical Sciences. Dr. Nairn



received his Ph.D. in Biochemistry from the University of Birmingham, England, and did postdoctoral studies in Pharmacology at Yale University School of Medicine. He has been at The Rockefeller University since 1983, first as an assistant professor, and since 1989 as an adjunct professor. Dr. Nairn serves on the editorial boards of several publications, including *Advances in Second Messenger and Phosphoprotein Research*, *Journal of Biological Chemistry* and *Journal of General Physiology*.

His current studies focus on dopamine signaling pathways and the regulation of protein phosphatases. For example, recent studies have established that phosphorylation of DARPP-32 and the inhibition of protein phosphatase-1 (PP1) are essential components in mediating the actions of dopamine in the basal ganglia. The discovery and characterization of proteins in the basal ganglia, particularly DARPP-32, provides a rational new approach to developing drugs that specifically affect these proteins or their targets. Dr. Nairn's future studies are continuing to focus on the biochemical characterization of DARPP-32 and PP1 pathways and regulators and the biochemical mechanism(s) involved in the phosphorylation of DARPP-32 by cyclin-dependent kinase 5 (CDK5).

Per Svenningsson, Ph.D.

Dr. Svenningsson is a professor in the Department of Pharmacology and Physiology at Karolinska Institute, Stockholm, Sweden and a Research Assistant Professor in the Laboratory of Molecular and Cellular Neuroscience at The



Rockefeller University.

Dr. Svenningsson received his Ph.D. in 1998 and his M.D. in 1996 both from the Karolinska Institute. He joined the Laboratory of Molecular and Cellular Neuroscience at The Rockefeller University in 1999 to undertake post doctoral studies and was promoted to the faculty position of Research Assistant Professor in 2001. His research focuses on dopamine signaling and DARPP-32 and how certain drugs alter dopamine signaling. He has also discovered a connection between dopamine and the neurotransmitter, serotonin, which is involved in depression and mood.

Dr. Svenningsson's work bridges the gap between schizophrenia and PD in that it relates abnormal dopamine signaling to the production of psychotic states and to the hallucinations suffered by some PD patients from L-dopa use. Therefore, one outcome of his research may be the ability to design new drugs that hit very specific targets, so that dopamine signaling can be restored without the unwanted side effects that sometimes result from L-dopa.

Yong Kim, Ph.D.

Dr. Yong Kim is a post-doctoral fellow in the Laboratory of Molecular and Cellular Neuroscience at The Rockefeller University. Dr. Kim received his Ph.D. in



Biochemistry from Pohang University of Science and Technology (POSTECH), Korea.

His current studies focus on the molecular mechanism of spine formation by Cdk5. Recently he has found a multi-protein complex as a downstream target of Cdk5. The complex is highly implicated in de novo synthesis of actin filaments which is a fundamental process

required for spine formation. Dr. Kim's future studies will focus on the biochemical characterization of the protein complex and elucidation of the role of the protein complex in spine formation of dopamine sensitive neurons, especially after administration of addictive drugs. Because Cdk5 is known to be involved in PD and other neurodegenerative diseases, Dr. Yong's study could uncover the factors that cause the death of dopamine producing neurons in PD, and thus to the discovery of drugs that prevent destruction of these neurons.

Marc Flajolet, Ph.D.

Dr. Marc Flajolet is a young scientist who accomplished his studies in France at the University of Paris VII where he got his Ph.D. with the highest honors.



During his Ph.D., he was working at the Pasteur Institute in Dr. Tiollais' laboratory, a world famous scientist well known for his work on the Hepatitis B virus vaccine. After his Ph.D., Marc Flajolet worked one more year at the Pasteur Institute where he was awarded the most honorific fellowship of the Institute. During his Ph.D. and for the year after, Marc Flajolet's work was focusing more and more on protein-protein interaction identification. After deciding to apply his knowledge to the new field of neurodegenerative diseases, he joined Dr. Greengard's laboratory. Now his goals are to find and study new putative drug targets for Parkinson's disease. The main aspect of his work is to search for protein-protein interactions that are crucial for the development and symptoms of Parkinson's disease and to screen for molecules that modulate those interactions, hoping that molecules will slow down, stop or reverse the pathological symptoms of PD.

Allen A. Fienberg, Ph.D.

Dr. Allen Fienberg is adjunct Assistant Professor at The Rockefeller University and former staff scientist at the Genomics Institute of the Novartis Research Foundation, a Swiss-based foundation. After starting out as an undergraduate researcher, and then research associate, at the University of California, Berkeley in the late 1970's and early 1980's, Dr. Fienberg received his Ph.D. from Yale University in 1991. Following Yale, he joined Paul Greengard at The Rockefeller University in New York City, where he has remained for more than a decade.



Dr. Fienberg describes himself as a neuroscientist, primarily trained as a geneticist. During his time in Dr. Greengard's lab, he has worked mostly on questions related to dopamine signaling systems. One of his greatest achievements there was the creation of a knockout mouse lacking one of the key dopamine-signaling proteins, DARPP-32.

Akinori Nishi, M.D., Ph.D.

Dr. Akinori Nishi, M.D., Ph.D., is an Adjunct Professor in the Laboratory of Molecular and Cellular Neuroscience at The Rockefeller University and Assistant Professor



of Physiology at Kurume University School of Medicine in Fukuoka, Japan. He pursued a Ph.D. at the Karolinska Institute in Stockholm, Sweden. He was a post-doctoral fellow at Dr. Paul Greengard's laboratory at The Rockefeller University from 1995 to 1997, and has been an adjunct faculty member with the University ever

since. He joined the Department of Physiology at Kurume in 1998.

Dr. Nishi has been studying the dopamine/DARPP-32 signaling pathway in the neostriatum, the receiving end of nerve fiber projections from dopamine neurons in the substantia nigra. He has specifically focused on how dopamine regulates the phosphorylation of the protein DARPP-32, and how the neurotransmitters glutamate and acetylcholine impact this signaling cascade. His findings in collaboration with the Greengard lab have been published in major scientific journals, including *Science*, *Nature* and PNAS.

Gilberto Fisone, Ph.D.

Dr. Gilberto Fisone is Adjunct Professor in the Laboratory of Molecular and Cellular Neuroscience at The Rockefeller University and



Laboratory Head and Associate Professor at the Karolinska Institute in Stockholm, Sweden. He trained in biology at the University of Pavia, Italy, and specialized in pharmacology at the "Mario Negri" Institute in Milan, Italy, studying neurotransmission in the basal ganglia. In 1986, he went to the University of Stockholm, Sweden, where he obtained a Ph.D. in neurochemistry, working on the role of neuropeptides in neurodegenerative diseases. In 1990, Dr. Fisone obtained a post-doctoral fellowship from the Swedish Research Council and joined the Laboratory of Molecular and Cellular Neuroscience, led by Dr. Paul Greengard at The Rockefeller University. Recently, he has started investigating the molecular basis of the abnormal involuntary movements (dyskinesia) occurring in parkinsonian patients after prolonged treatment with the drug levodopa (L-dopa).

Congresswoman Carolyn B. Maloney:

Stalwart Advocate for Parkinson's Research

Congresswoman Carolyn B. Maloney (D-NY), a board member of the Michael Stern Parkinson's Research Foundation, is a shining example of the difference that one dedicated person can make in the battle to find a cure for Parkinson's disease. Congresswoman Maloney's father suffered with Parkinson's for many years, so she knows first-hand the devastation that the disease can wreak on individuals and their families. Through her position in Congress, she has worked tirelessly to increase government funding for Parkinson's research, and has been instrumental in the Stern Foundation's ability to raise private funds to continue the groundbreaking research of Paul Greengard and his team of scientists.

In 1999, in conjunction with Representatives Fred Upton (R-MI), Lane Evans (D-IL), Joe Skeen (R-NM), Mark Udall (D-CO), Tom Udall (D-NM) and Henry Waxman (D-CA), Congresswoman Maloney founded the Congressional Working Group on Parkinson's Disease. This bipartisan group works to increase awareness among members of Congress on issues related to Parkinson's, including improving the state of Parkinson's-related research. The Working Group's mission is to ensure that the needs of those with the disease are considered in congressional decision-making and to meet together to pursue this common goal through public debate and legislation.

One of the central focuses of the Working Group is to ensure that the National Institutes of Health fully implements the Parkinson's Disease Research Agenda, a five-year plan developed in 1999 at the direction of Congress. The Research Agenda has as its primary goals improving understanding of Parkinson's disease, developing new treatments,



Rep. Maloney consults with Dr. Greengard at the lab.

increasing NIH's research investment through innovative funding mechanisms and public-private partnerships, and enhancing the research process by addressing ethical and social issues presented by clinical trials and emerging therapies.

"Leading scientists have described Parkinson's as the most curable neurological disorder, and recent advances in Parkinson's research have given us great hope that a cure is imminent," says Congresswoman Maloney. "The science regarding Parkinson's has advanced to a stage where greater management and coordination of the federally funded research effort will accelerate the pace of scientific progress dramatically. We must remain vigilant and keep the pressure on the NIH to stay true to the Parkinson's Research Agenda."

At the same time, the Congresswoman continues, "Federally funded research alone cannot fill the gaps that must be filled if we are to cure this disease quickly. Private contributions to support promising research, such as that being pursued by Paul Greengard and his team of scientists, are critical."

You can learn more about the Congressional Working Group on Parkinson's Disease by visiting Congresswoman Maloney's web site: www.house.gov/maloney. If your Congressional Representative is not a member of the Working Group, please call or write to them and ask them to become one, and to support increased federal funding for Parkinson's research.

BOARD OF TRUSTEES



Michael Stern – Founder, Chairman. President and CEO of The Fisher Center for Alzheimer’s Research; trustee of the AMA Foundation, Vice Chairman of the Intrepid Museum and Fisher House Foundation. Famed war correspondent; author of seven books, producer of five motion pictures, graduate of Syracuse University.



Betsy Gotbaum – serves as Public Advocate for the City of New York. Formerly Commissioner of the Department of Parks & Recreation, President of The New York Historical Society and advisor to three New York mayors. She holds a Master’s Degree in Education from Columbia University Teacher’s College.



Dr. Paul Greengard – Vice President of the Foundation. The recipient of the year 2000 Nobel Prize in Physiology and Medicine, Dr. Greengard is the Vincent Astor Professor at The Rockefeller University, Director of the Fisher Center lab and a member of the National Academy of Sciences.



Harold Gray – a noted attorney, he is personal legal counsel to members of the du Pont family and serves as a Special Master in the So. Florida District Court. He served in the U.S. Army Air Corps in WW II and has a degree in Economics and a Juris Doctor from Valparaiso University in Indiana.



Dr. Alvin Freiman – A cardiologist and Attending Physician at Memorial Sloan-Kettering Cancer Center. Professor of Clinical Medicine at Cornell University. A fellow of the American College of Cardiology and the Vice President of The Fisher Center for Alzheimer’s Research Foundation.



Hon. Henry Hyde – serves as Chairman of the U.S. House International Relations Committee and is a member of the House Judiciary Committee. A combat veteran of WW II having served with the Navy in the Pacific, Rep. Hyde holds a Juris Doctorate degree from Loyola University.



Mary Asta – With her extensive experience in government and the entertainment industry, she has been instrumental in raising millions through creative-marketing programs, grant petitions and fundraising. She is also the Foundation Director for education and resource programs at The Fisher Center Foundation for Alzheimer’s Research.



Kent Karosen – is President and Managing member of Karosen Strategic Partners, LLC. He spent 14 years with Cantor Fitzgerald, serving in the office of the Chairman as a Managing Director and Partner. He is a trustee of the Intrepid Museum Foundation, and was named an Honorary Commodore in the United States Coast Guard in 2001.



Princessa Grazia Borghese – is an active participant in the religious foundation of Nostra Signora del Buon Consiglio for the construction of hospitals for the poor. She is organizer and co-president of the Hanover Charities, Jamaica, West Indies. She is also an expert in marketing and public relations.



Hon. Carolyn Maloney – served New York City first on the City Council, and as of 1992, in the U.S. House of Representatives. Some of her top priorities include campaign finance reform and support of women and families. Rep. Maloney also founded the Congressional Working Group on PD.

Chief Administrative Officer: Mary Ann Sallas

Finance Officer: Fekadu Taddese



Lila Prounis – was the first woman elected to the all-male Greek Orthodox Archdiocesan Council and has been its United Nations Representative since 1979. From 1991-2000, she was the President of the Women’s National Republican Club and is currently

its President Emeritus.



Maria Razumich-Zec – is the General Manager of The Peninsula Chicago, recently named the Top Hotel in the U.S. by Zagat. She serves on the boards of several organizations including The Waterbor Burn and Cancer Foundation and The Nic Zec

Foundation for Lupus.



Dr. Paul Russo – is a urologist and an Associate Attending Surgeon for Cancer and Allied Diseases at Memorial Sloan Kettering. He is also an Associate Professor of Urology at Cornell University and a fellow at the American College of Surgeons. Dr. Russo received his M.D. from the College of

Physicians and Surgeons at Columbia University.



Richard Salem – is the founder of the law firm of Salem, Saxon, P.A. located in Tampa, Florida. He recently formed Enable America!, a political action committee dedicated to reducing the unemployment rate among people with disabilities. Mr. Salem received a

Juris Doctorate from Duke Law School.



Richard Shortway – served as a 1st Lieutenant with the US Air Force in WW II and flew thirty-one missions over Germany. After the war, he started at Conde Nast Publications and became Publisher of Vogue and eventually, Vice President in charge of Vogue and

Vanity Fair magazines.

HOW YOU CAN HELP

Your contributions to the Michael Stern Parkinson’s Research Foundation will directly support the pioneering research of Nobel Prize winner Paul Greengard, Ph.D. and the team of scientists at the Stern facility at The Rockefeller University, who are working every day to find solutions to Parkinson’s. Donations of any size will advance our mission of finding a cure.

These are just a few of the ways your contribution can help:

- * Identify chemical compounds that can be developed into new treatments for Parkinson’s.**

- * Make current therapies more effective by tracing the pathways of dopamine signaling in the brain so that new ways can be discovered for increasing the effectiveness of dwindling supplies of dopamine in the brains of people with Parkinson’s.**

- * Advance preclinical research of potential new therapies in animal models of Parkinson’s disease, an early step in new drug development.**

- * Start clinical trials of promising new therapies developed in our laboratory.**

Simply put, your donation can help us cure Parkinson’s — and there is every reason to believe that we can cure Parkinson’s in years, not decades. Please help us help the people and families who suffer from this devastating disease.

disease.

