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The 2006 International Research Scholars from Canada and Latin America

Luis G. Brieba de Castro, Ph.D. Center for Research and Advanced Studies, National Polytechnic Institute Mexico City, Mexico

Luis Brieba de Castro, a newly named HHMI international research scholar, is working to understand how the DNA that is found outside the nucleus of cells produces proteins. That DNA, called mitochondrial DNA, is found in small cellular structures called mitochondria. Mutations in mitochondrial DNA have been linked to several inherited medical conditions, including some forms of hearing and vision loss.

Scientists know that mitochondrial DNA is inherited only from the mother, but they do not yet fully understand the basic mechanisms of nucleic acid metabolism and how DNA damage is linked to diseases. Brieba de Castro hopes to find answers that could lead to genetic interventions to correct certain inherited disorders. Following previous studies of DNA replication in bacteriophage, a type of virus that infects bacteria, he is working in the yeast *Saccharomyces cerevisiae* to explore how DNA functions in the mitochondria.

Brieba de Castro uses a wide range of laboratory techniques to study mitochondrial DNA, including x-ray crystallography. He is investigating what happens at sites where the DNA strands have broken and is studying the processes involved in assembling large complexes of proteins during and after DNA replication.

Miguel L. Concha, M.D., Ph.D. Institute of Biomedical Sciences, University of Chile Santiago, Chile

The right and left sides of the brain process information differently, and Miguel Concha, a neuroscientist, wants to know why. The newly named HHMI international research scholar returned to his native Chile after working with Stephen Wilson, a noted neuroscientist at University College, London, to continue researching why the two sides of the brain develop differently and why it matters.

Concha uses zebrafish as a model for his research. Using embryonic tissue from the left and right sides of the zebrafish brain, he is trying to determine which genes control neuroanatomical development. He is also investigating signaling pathways to understand the role that these molecular cascades play in the development of the differing shapes of the right and left sides of the brain.

He is also studying the brains of different vertebrates to understand asymmetrical development in evolutionary terms—where and when brain development mechanisms diverged among species.

Diego de Mendoza, Ph.D. Institute of Molecular and Cellular Biology of Rosario, CONICET Rosario, Argentina

Gram-positive bacteria—which cause many human illnesses, from mild stomach upsets to fatal cases of food poisoning—have cell walls made up in part of fatty acids called lipids. Diego de Mendoza, an HHMI international research scholar since 2002, has spent several years examining how the bacteria synthesize the compounds that comprise these lipid membranes.

His current focus is on the cell signaling pathways involved in the process. He hopes that once he identifies all the steps in this molecular chain, he may be able to disrupt the process with antibiotics that target a specific step.

His lab recently reported in the *EMBO Journal* that the molecule malonyl-CA controls the function of FapR, a molecule that in turn controls the expression of many of the genes involved in lipid synthesis. De Mendoza is now working to stop FapR from doing its work in the food-borne pathogen, *Listeria monocytogenes*.

A. Beln Elgoyhen, Ph.D. Institute for Research on Genetic Engineering and Molecular Biology, CONICET Buenos Aires, Argentina

Beln Elgoyhen, an HHMI international research scholar since 1997, studies the structure and function of parts of the tiny hair cells in the inner ear that enable humans to understand speech or music. Those hair cells in the cochlea, a part of the inner ear, are actually the tips of neural receptors that transform sound waves into electrical signals that the brain can process, much like a computer decoding digital signals.

In this part of the auditory system, nerve cells relay incoming signals to the hair cells, using the chemical neurotransmitter acetylcholine. The receptors on the surface of the hair cells that detect the presence of acetylcholine are complicated molecules, composed of several subunits. Elgoyhen discovered a gene that codes for one subunit when she was a postdoctoral student with Stephen Heinemann of The Salk Institute.

As an HHMI international research scholar, she has continued to characterize the various subunits of these receptors genetically. By studying the cochlear hair cells in genetically modified mice, she hopes to learn how these receptors contribute to hearing and the sense of balance.

A. Carlos Frasch, Ph.D. Institute for Research in Biotechnology, National University of General San Martin Buenos Aires, Argentina

Carlos Frasch is part of the scientific team that published the genome sequences of three major species of trypanosomes in a special issue of the journal *Science* published in July 2005. These single-celled parasites are responsible for several debilitating and sometimes fatal human illnesses, such as sleeping sickness and Chagas disease, prevalent in tropical countries. Their genomes are of interest to scientists as a path to possible cures, and also as a way to explore genetic diversity.

Trypanosomes have evolved elaborate schemes to evade the immune systems of their hosts. Frasch is examining one of these schemes: the parasite's mechanism for expressing a large repertoire of diverse surface molecules, a trick that may account for its chameleon-like ability to evade a host's defenses.

An HHMI international research scholar since 1997, Frasch is currently exploring this and other mechanisms for modulating gene expression in trypanosomes. He hopes that understanding the parasite's genetic tricks will lead to new ways to treat or prevent the disease.

Fernando A. Goldbaum, Ph.D. Leloir Institute Foundation Buenos Aires, Argentina

Fernando Goldbaum wants to unlock the secrets of brucellosis, a bacterial infection that causes a debilitating fever that affects humans who can be infected by drinking unpasteurized milk. The organism infects many species of animals that graze. In Goldbaum's native Argentina, brucellosis infects nearly 10 percent of cattle, and it is widespread among bison in Yellowstone National Park.

In animals, brucellosis can cause infertility and miscarriages. According to the U.S. Department of Agriculture, eradication efforts and livestock losses have cost billions of dollars worldwide. Goldbaum, head of the structural and molecular immunology laboratory of the Leloir Institute Foundation in Buenos Aires, is trying to better understand how *Brucella*, the bacteria that cause brucellosis, function.

An HHMI international research scholar since 2002, he studies the process of riboflavin metabolism in *Brucella* to determine how it is connected to the bacteria's virulence. Riboflavin is a molecule essential for catalytic activity; many enzymes rely on it to work properly. Goldbaum recently characterized the structure of one of these enzymes. Goldbaum hopes a thorough understanding of *Brucella* metabolism will lead to new ways to prevent the spread of brucellosis.

Lea Harrington, Ph.D. Ontario Cancer Institute Toronto, Canada

Lea Harrington, a newly named HHMI international research scholar, is working to understand how the length of telomeres—sequences of DNA at

the tips of chromosomes—influences susceptibility to cancer. Without a means to replace them, telomeres shorten with each cell division, exposing the chromosome to potential degradation.

The enzyme telomerase replenishes telomeres; however, it is almost completely shut off in normal adult cells. Many cancer cells have figured out a way to reactivate telomerase, allowing tumors to keep growing. As a result, telomere/telomerase interactions have become a focus of cancer researchers.

In her lab at the Ontario Cancer Institute, Harrington investigates telomere maintenance and its effects on genome stability and cancer susceptibility. Working in mice, her lab has identified two of the protein components of mammalian telomerase. They are testing the interaction of these components within cells, trying to determine at what stage each helps to perpetuate cell growth. They are also working in yeast to identify novel genes whose deletion exacerbates the loss of telomerase activity. Harrington hopes to determine if these genes play a role in the maintenance of telomere integrity and length in mammals.

Luis R. Herrera Estrella, Ph.D. Center for Research and Advanced Studies, National Polytechnic Institute Irapuato, Mexico

Plants are stuck wherever they take root. This simple fact presents a developmental challenge: How do plants flourish if they have the misfortune to be rooted in less than optimal environments?

Luis Herrera Estrella, a foreign associate of the National Academy of Sciences in the United States, has shown that scarce phosphate, an essential nutrient, triggers changes in cell division and cell differentiation. It helps modify the structure of roots so they are better able to scavenge this nutrient from the soil. But little is known about how plants detect phosphate availability and regulate their own development accordingly.

Continuing the work he has done since 1991 as an HHMI international research scholar, Herrera Estrella is seeking the genes involved in the phosphate-sensing system and the signaling pathways that control the development of the root system in *Arabidopsis thaliana*, a small flowering plant. Part of the mustard family, *Arabidopsis* has no agricultural purpose, but its small genome, already sequenced, has made it an ideal scientific model for studying plants. Herrera Estrella has identified mutant forms of *Arabidopsis* that are unable to detect phosphate availability.

Philip Hieter, Ph.D. University of British Columbia Vancouver, Canada

"Synthetic lethality" is the molecular biology equivalent of drinking and driving: Mutations in two different genes individually may cause no harm, but in combination, may be fatal. Philip Hieter, a yeast expert and newly named HHMI international research scholar, plans to use the concept of synthetic lethality to fight cancer. He is looking for gene mutations that might lethally pair with the gene mutations found in tumor cells, causing the tumors to die. Nearby healthy cells, which lack mutations in one of the "partner"

genes, would be unharmed.

Hieter will study genetic mutations in yeast to find the pairs he seeks. The principle of evolutionary conservation means that humans and yeast have genes in common, and the same mutations that can lead to human cancers can be studied more easily in yeast.

Using a technique called RNA interference (RNAi), which allows researchers to selectively turn off genes in human cells by duping them into destroying the gene's messenger RNA before it can produce a protein, Hieter will systematically combine and shut off the various pairs of genes first discovered in yeast, seeking to distinguish lethal and nonlethal pairings that might be used to selectively kill cancer cells.

Timothy R. Hughes, Ph.D. University of Toronto Toronto, Canada

A newly named HHMI international research scholar, Timothy Hughes likens genomes to a software program that contains its own instructions for installation. The challenge for scientists is to understand those instructions.

The instructions on a strand of DNA include not only genes, but also regulatory elements that tell the cell when to turn those genes on. Fortunately, many of those instructions are conserved, meaning they are the same in different species, so by comparing genomes, it is possible to narrow down the possible combinations of genes and regulatory mechanisms.

Taking advantage of that evolutionary fact, Hughes is comparing vertebrate genomes in search of regulatory elements. He will place genes on chips called microarrays that can contain hundreds of different pieces of DNA. Then he will test hundreds of regulatory elements on the genes to see which ones turn on gene expression. Using computational data analysis to analyze the results, Hughes hopes to create evolutionary trees of genes and regulatory elements that show conserved and divergent gene expression "instructions." His work should enhance understanding of how vertebrate transcriptional regulatory networks work and how they have evolved.

Alberto R. Kornblihtt, Ph.D. University of Buenos Aires Buenos Aires, Argentina

One gene does not equal one protein. In fact, a variety of molecular processes, including a phenomenon known as alternative splicing, can make one gene encode a diverse array of proteins.

Alberto Kornblihtt, twice the recipient of an HHMI international research scholar award, is working to understand pathways that regulate both alternative splicing and the conversion of DNA into RNA (the first step in building a protein from its genetic blueprint), and how those pathways can mutate to cause human disease. His previous work showed that approximately 25 percent of human genes contain multiple alternative splicing regions. Further inspection showed that these regions can talk to each other to produce proteins with specific combinations of sequence building

blocks known as exons.

Kornblihtt now will focus on the cross-talk mechanism or mechanisms and what they cause to happen in human cells. He will also investigate how cells change alternative splicing patterns in response to DNA damage caused by ultraviolet irradiation.

M. Fatima Leite, Ph.D. Federal University of Minas Gerais Belo Horizonte, Brazil

Calcium is necessary not just to build strong bones and teeth: it is crucial for cellular signaling as well. Fatima Leite, a newly named HHMI international research scholar, wants to find out to what degree cell growth is stimulated by calcium signals in the nucleus, and how that growth is regulated.

Calcium signals respond to hormones, growth factors, neurotransmitters, and sensory systems, all of which are important for organ development and carcinogenesis. Leite plans to capitalize on her experience regenerating liver cells to test whether the calcium signaling pathway in the nucleus is necessary for organ development.

Using small interfering RNAs to silence genes, she will determine whether growth factors induce the release of the calcium ion in the nucleus. Then she plans to use microarrays, which are large sets of DNA molecules spotted onto a solid matrix (such as a microscope slide), to screen for any resulting alterations in protein expression.

Freda D. Miller, Ph.D. Hospital for Sick Children Toronto, Canada

In the ever-changing landscape of stem cell research, scientists have discovered a more accessible source of cells that may be equally useful for studying neurodegenerative diseases. Freda Miller, a newly named HHMI international research scholar, discovered the cells, called skin-derived precursors (SKPs).

Isolated from rodent and human skin, SKPs exhibit properties similar to embryonic neural crest stem cells, those able to differentiate into a host of nervous system cells. But, while neural crest stem cells only differentiate in early development, Miller found that SKPs maintain the ability to differentiate into adulthood.

A senior scientist at the Hospital for Sick Children in Toronto, Miller plans to characterize the physiological role of SKPs in skin maintenance and repair. She also wants to assess the potential of these cells as therapies for neurological diseases. Using cultured SKPs transplanted into the skin and the neural crest of embryonic chicks, she will map the fate of progeny cells. By isolating SKPs from two patient populations, she hopes to determine whether human SKPs can be used to identify the causes and potential therapies for many neurological diseases.

Pedro L. Oliveira, Ph.D. Federal University of Rio de Janeiro Rio de Janeiro, Brazil

Bloodletting is no longer common medical practice, but blood-sucking organisms are still important to science. Pedro Oliveira hopes they will provide a window into the evolution of defenses against oxidative stress, which occurs when free radicals produced by normal biochemical processes damage cells. Understanding how bloodsuckers such as mosquitoes, ticks, and the so-called kissing bug evolved to avoid oxidative stress, researchers will be one step closer to understanding how a species becomes a vector for disease.

Heme, the iron-containing component of hemoglobin, is a compound that can hurt as well as help cells. It regulates protein function by controlling stress-related gene expression, but it also promotes oxidative damage. With his second HHMI international research award, Oliveira wants to learn how blood-feeders such as mosquitoes or ticks avoid oxidative damage while ingesting large amounts of heme. He recently identified a unique heme-degradation pathway in the kissing bug *Rhodnius prolixus*, a blood-sucking insect that transmits Chagas disease.

Oliveira, who first won an HHMI international research award in 2000, now plans to characterize the defenses against heme toxicity for four blood-sucking organisms: the kissing bug, mosquitoes, ticks, and a worm called *Schistosoma mansoni*. Understanding how heme controls gene expression and antioxidant production will enable researchers to determine how these defenses are regulated.

Raúl A. Padrón, Ph.D. Venezuelan Institute for Scientific Research Caracas, Venezuela

As researchers discover the molecular mechanisms controlling muscle contraction, they are getting closer to treatments for genetic cardiac disorders such as familial hypertrophic cardiomyopathy (FHC), which often causes premature death. Raúl Padrón, an HHMI international research scholar since 1997, is among those leading the charge to elucidate the molecular mechanisms at work in both healthy and ailing cardiac muscle.

Cardiac muscle is made up of thick and thin filaments that slide against each other to produce a contraction of the cell. In earlier studies, Padrón and colleagues reconstructed the dozens of myosin protein molecules that make up the surface of a muscle cell's thick filaments. After he and colleagues determined their structure, they were able to show how thick filaments are switched off in the relaxed muscle, opening the way to understanding how calcium activates muscle movements at the molecular level, a question that he and his lab will explore in the next five years.

Now Padrón hopes to get to the heart of the causes of a specific cardiomyopathy. He wants to determine how specific mutations cause the molecular mechanisms of muscle activation to malfunction, leading to the mid-ventricular hypertrophy type of FHC. Padrón will exchange normal

muscle tissue filaments for filaments mutated in the lab, to explore the structural and functional fallout of the mutations.

Javier F. Palatnik, Ph.D. Institute of Molecular and Cellular Biology of Rosario, CONICET Rosario, Argentina

Arabidopsis thaliana is the botanical equivalent of the lab mouse. Despite having only 5 chromosomes, the genome of the mustard-like plant contains 25,000 genes, approximately the number estimated in the human genome. Also like the human genome, *Arabidopsis* contains small bits of DNA that code for microRNAs—long thought to be genetic junk—that actually turn out to be important regulators of gene expression. So, like the mouse, *Arabidopsis* is an excellent model for studying genetics.

Using *Arabidopsis*, plant developmental biologist Javier Palatnik recently discovered how microRNAs control plant shape by inactivating larger messenger RNAs. Palatnik is a newly named HHMI international research scholar.

He now plans to probe the function of *Arabidopsis* microRNAs that have survived thousands of years, while also searching for microRNAs with newly specialized functions. His goal is to determine how microRNAs regulate a host of plant functions. Palatnik will inactivate and overexpress microRNAs to get a better understanding of how these short RNA sequences exert such remarkable control over gene expression.

Armando J. Parodi, Ph.D. Leloir Institute Foundation Buenos Aires, Argentina

Protein folding may resemble a complex, biochemical form of origami, but mistakes can have serious consequences. More than 20 neurodegenerative diseases, including Alzheimer's and prion diseases, are a direct result of misfolded proteins deposited in abnormal forms, such as plaques.

How these proteins become malformed remains poorly understood. Proteins have an inherent tendency to aggregate, but specific quality control measures have evolved in the endoplasmic reticulum, the initial intracellular location of material that will eventually be secreted, to protect newly synthesized proteins from this natural stickiness. Armando Parodi, a foreign associate of the National Academy of Sciences of the United States, recently identified the mechanism that prevents improperly folded glycoproteins from exiting the endoplasmic reticulum.

Continuing his work as an HHMI international research scholar since 1997, Parodi now wants to characterize proteins that elude the endoplasmic reticulum's quality control devices and form dangerous aggregates anyway. In addition, he hopes to determine how concentrations of calcium ions in the endoplasmic reticulum affect quality control efficiency.

Alexandre A. Peixoto, Ph.D. Oswaldo Cruz Foundation Rio de Janeiro, Brazil

Mosquitoes and other blood-sucking insects are deadly disease vectors that infect more than 700 million people worldwide each year. Molecular biologist Alexandre Peixoto, an HHMI international research scholar since 2002, conducts research into the genetics behind these insects' circadian rhythms, in hopes that what he learns will lead to the development of new and more effective control measures.

Peixoto previously studied circadian rhythms in the sand fly species primarily responsible for spreading leishmaniasis, a debilitating disease affecting thousands of people in South America. Peixoto now will focus his research on the genetics of the mosquito's circadian clock. He will compare diurnal and nocturnal species to examine the molecular basis of their behavioral differences. He will also study the effects of blood-feeding and infection on the regulation of the mosquito circadian clock.

Using gene-silencing tools such as RNA interference (RNAi), he will then examine what happens to circadian rhythms once clock genes are turned off. By combining evolutionary and behavioral analyses of closely related mosquito species, he hopes to be able to investigate the genetic basis of differences in the circadian clocks of related species.

Dana J. Philpott, Ph.D. University of Toronto Toronto, Canada

Human cells are equipped with an enviable surveillance system. If bacteria and viruses breach the barriers erected to prevent them from entering the body, the pathogenic invaders are often recognized by their telltale cellular components—called pathogen-associated molecular patterns. Honed through evolution, the ability of cellular receptors to recognize such patterns is the core of the body's innate immune system.

There are two primary types of pattern recognition receptors: toll-like receptors, anchored in the membrane, and nod-like receptors, found in the cell's cytoplasm. Dana Philpott recently discovered a string of amino acids that two of the nod-like receptors recognize as components of the bacterial cell walls—cluing them in to the presence of an intruder.

As a new HHMI international research scholar, Philpott hopes to determine how these receptors inside the cell are activated by these cell wall patterns. She hopes to understand the role of these two receptors by linking the mechanisms that activate them to the signaling necessary for immune response to infection.

Richard A. Rachubinski, Ph.D. University of Alberta Edmonton, Canada

Richard Rachubinski has recently identified some of the proteins that enable cells to pass on their peroxisomes when they replicate. Peroxisomes are specialized organelles that help metabolize lipids and rid cells of toxic substances such as hydrogen peroxide.

Eukaryotic cells, which are cells that have a membrane-bound nucleus, have evolved molecular mechanisms that permit the efficient transmission of the

individual types of organelles from mother cell to daughter cell at the time of cell division. While the molecular mechanisms underlying the inheritance of organelles such as the Golgi apparatus, endoplasmic reticulum, mitochondria, and vacuoles have become more clearly defined and better understood, little is known about the inheritance of peroxisomes. Approximately half of the mother cell's organelles must also be inherited by the daughter cell, because organelles cannot be synthesized anew.

During his second term as an HHMI international research scholar, Rachubinski will continue his search for novel proteins involved in peroxisome inheritance, using multidimensional live-cell video microscopy. Working in yeast, he will screen libraries of fluorescently tagged proteins to identify novel peroxisome proteins. He also plans to use genetic and biochemical approaches to search for and isolate protein complexes from the peroxisome membrane controlling peroxisome division and inheritance.

Ranulfo Romo, M.D., D.Sc. Institute of Cellular Physiology, National Autonomous University of Mexico Mexico City, Mexico

Ranulfo Romo, a neuroscientist and foreign associate of the National Academy of Sciences in the United States, wants to understand how the brain translates sensory information to help make decisions. To find out, he studies sensory processing in monkeys.

During a previous HHMI international research grant, Romo showed that touching a monkey's skin with a vibrating object caused specialized neurons in the brain to fire. The firing of those neurons—located in a region of the brain known as the primary somatosensory cortex—was directly related to the animal's ability to tell how fast the object was vibrating. His study, published in the December 2005 issue of the journal *Nature Neuroscience*, indicated that the brain interprets sensory signals differently, as an animal's attention span changes over time.

Now, Romo wants to understand the dynamics the brain uses to transform sensory information into decision-making actions. As he strives to determine the precise operations within circuits of the brain necessary for perception, he will continue testing the monkeys with vibrating objects. Romo plans to investigate how this sensory input triggers activity in the areas of the brain responsible for processing information from the skin and muscles, as well as those involved in reasoning and problem-solving.

Marcelo Rubinstein, Ph.D. Institute for Research on Genetic Engineering and Molecular Biology, CONICET Buenos Aires, Argentina

The chemical receptors in the brain that respond to the neurotransmitter dopamine help regulate movement, emotion, motivation, and pleasure. When these receptors do not function properly, they can lead to the development of Parkinson's disease, schizophrenia, attention-deficit hyperactivity disorder (ADHD), and drug addiction. However, little is known about the specific roles they play in the regions of the brain that process pleasure and rewards.

Marcelo Rubinstein's laboratory at the Institute for Research on Genetic Engineering and Molecular Biology, part of the National Council for Science and Technology (CONICET), studies how the dopamine D2 and D4 receptors contribute to purposeful movement, learning, emotional behaviors, and responses to drugs that stimulate the central nervous system.

Using genetically altered mice and a series of behavioral tests, he now plans to investigate the D2 and D4 receptors' role in complex behaviors such as attention, impulsivity, time perception, and reward. Rubinstein has been an HHMI international research scholar since 1997.

Michael A. Rudnicki, Ph.D. Ottawa Health Research Institute Ottawa, Canada

The stem cells of adult skeletal muscle, known as satellite cells, normally lie quietly, awaiting their instructions. But once called to action, they quickly respond to stress or injury, forming muscle precursor cells that help regenerate damaged tissue.

Michael Rudnicki is interested in the molecular mechanisms that regulate these stem cells during embryonic development and tissue regeneration. An HHMI international research scholar since 2002, Rudnicki has conducted extensive studies into embryonic muscle development and the function of stem cells in adult skeletal muscle. His laboratory identified a protein produced by the gene Pax7 as the one responsible for copying DNA information to help define the outcome of satellite cells.

Rudnicki now believes that PAX7 molecularly enforces these outcomes by chemically marking the sites of later gene expression in muscle tissue. By studying PAX7'S behavior in muscle cell precursors in mice, he hopes to further tease out the molecular functions of this gene.

Michael W. Salter, M.D., Ph.D. Hospital for Sick Children Toronto, Canada

Chronic pain is a common condition once considered a simple response to injury or disease. Scientists such as Michael Salter now recognize that chronic pain is actually a group of nervous system disorders produced and maintained by a variety of abnormal cell-signaling processes. The kinds of cell signaling that cause us to feel chronic pain can occur not only in nerve cells in the brain and spinal cord, but also in the glial cells that are interwoven with the nerve cells. Pain can also arise from abnormal interactions between these two types of cell.

Salter, a professor of physiology, plans to use his first HHMI international research award to better understand these processes and to develop tools that could interfere with or correct abnormal signaling. He will employ molecular, biochemical, electrophysiological, behavioral, and genetic techniques.

The tools he hopes to develop to regulate pain signaling could form the basis for new chronic pain medications. And, because these cell-signaling pathways are fundamental to several processes within the central nervous

system, the findings could have implications beyond chronic pain, to broad areas of central nervous system function and dysfunction.

Alejandro F. Schinder, Ph.D.Leloir Institute Foundation Buenos Aires, Argentina

The mechanisms that explain how cells mature and integrate in the adult brain remain poorly understood. Neuroscientist Alejandro Schinder plans to test the hypothesis that neurotransmitters—chemicals that send messages from one nerve cell to another—regulate how nerve cells mature. He will also examine whether the messages sent by adult-born nerve cells exhibit distinct functional properties, marking them as different from nerve cells formed during early development.

By applying retroviruses to newborn nerve cells, he plans to manipulate their genes to study how neurotransmitters affect their maturation in the adult brain. He will also measure the output of the cells that mature in the adult brain, which has never been studied before.

Schinder, who is a chief of laboratory at the privately funded Leloir Institute Foundation, is a first-time recipient of an HHMI international research scholar award.

Erwin Schurr, Ph.D.McGill University Montreal, Canada

Tuberculosis and leprosy are mycobacterial infections that affect and kill millions of people each year. Erwin Schurr, a newly appointed HHMI international research scholar, wants to identify the genetic factors that predispose people to these infections.

Schurr will look for the genetic determinants that govern a person's tendency to develop a beneficial immune response against tuberculosis and leprosy by measuring the extent of protective skin lesions following injection of heat-killed bacilli. He also will investigate the genetics of reversal reaction type1 (RR1)—a spontaneous reaction that can increase immunity to disease but also causes nerve damage. RR1 is the main cause of nerve damage in leprosy.

Schurr will study patients from countries where tuberculosis and leprosy are highly prevalent to determine the genetic risk factors for insufficient immunity against these diseases. The genetic risk factors for RR1 will be tested using data collected from two study populations from India and Vietnam.

Eric Alan Shoubridge, Ph.D.McGill University Montreal, Canada

Mitochondria are the tiny powerhouses that fuel cells by converting nutrients to energy and performing other specialized tasks. Human geneticist Eric Shoubridge is interested in what happens when the powerhouse breaks down.

An HHMI international research scholar since 2002, Shoubridge, and colleagues in his laboratory, have obtained the first evidence in a mouse model suggesting that genes within the cell nucleus control how variants of mitochondrial DNA segregate in reproductive and tissue cells. He now plans to clone the genes involved. His research suggests that the organization of mitochondrial DNA plays a key role in the process, and he has found that a protein called Tfam serves as the primary organizer of mitochondrial DNA.

Now, using genetic mapping techniques, he plans to identify potential genes whose expression directs the segregation of mitochondrial DNA. Then he wants to investigate their function in a mouse model. In addition, using biochemical approaches, he will investigate the details of the structural and functional organization of the mitochondrial genome. He hopes these two approaches will intersect, leading to a fundamental understanding of the molecular determinants of mitochondrial DNA organization, segregation, and expression.

Nahum Sonenberg, Ph.D. McGill University Montreal, Canada

Long-lasting memory requires messenger RNA (mRNA) translation—the process by which a cell's protein-making machinery reads mRNA and translates it into the amino acid sequence of the protein.

Nahum Sonenberg, an HHMI international research scholar since 1997, has been investigating the role of translation in cancer, learning, and memory. His laboratory has demonstrated that two regulators involved in translation—the repressor 4E-binding protein 2 and the enzyme GCN2—play important roles in the brain's ability to learn and to store memory.

He now wants to understand the mechanism by which translation affects or controls the plasticity of the synapse, which is the junction between nerve cells. He will study the enzyme mTOR—a protein kinase that regulates translation and cell division—by creating mice that lack mTOR in the part of the brain responsible for learning and memory. Similar experiments will be conducted on the translation protein eIF2. He also plans to study the roles of mTOR and eIF2 in the development of neurodegenerative diseases such as Alzheimer's disease.

Peter St George-Hyslop, M.D., D.Sc. University of Toronto Toronto, Canada

Humans have two distinct genes that code for presenilin proteins. Mutated forms of these genes can lead to early-onset Alzheimer's. Peter St George-Hyslop, an HHMI international research scholar since 1997, is focusing on how these mutations lead to neurodegeneration in Alzheimer's disease. He has recently shown that the presenilin proteins interact with several other cellular proteins to form a high-molecular-weight protein complex, and that presenilin protein mutations alter the function of this complex.

St George-Hyslop thinks that this alteration may be central to the mechanism by which presenilin mutations cause Alzheimer's disease. He also is searching for additional genes that cause susceptibility to Alzheimer's. In a paper published in the April 27, 2006, issue of the journal *Nature*, St George-Hyslop identified a protein called TMP21 that reins in the activity of molecules that make another protein that prevents normal brain function in people with Alzheimer's disease.

Now, he wants to better define the molecular structure of active and precursor presenilin complexes, to help determine the most effective ways to intervene and prevent the damage they do. St George-Hyslop will use a combination of laboratory tools and cell biology to find the parts of the protein complexes that interact and identify the areas where chemical reactions occur.

Natalie C.J. Strynadka, Ph.D. University of British Columbia Vancouver, Canada

Antibiotic resistance has become a major clinical problem worldwide. Natalie Strynadka, an HHMI international research scholar since 2000, uses x-ray techniques to identify the crystal structure of bacterial proteins, as well as other biophysical analysis tools, to study the structure and function of proteins that play key roles in antibiotic resistance and the ability of bacteria to cause disease.

She has made significant progress in understanding the structure and function of the type III secretion system (T3SS)—a needle-like apparatus of approximately 20 proteins that bacteria use to penetrate human host cell walls and cause infection. Strynadka recently determined the high-resolution crystal structures of a number of proteins constituting the T3SS.

Building on this work, she plans to further examine the protein-protein interactions that drive bacterial infection, utilizing the high-resolution x-ray structures of these complexes as a template to design novel antimicrobial agents.

Michael D. Tyers, Ph.D. Samuel Lunenfeld Research Institute Toronto, Canada

Researchers can now explore what actually happens inside a cell when disease strikes, and they can search for the genes that cause disease—cancer, for example. Michael Tyers, a first-time HHMI international research scholar, will use this new knowledge to create a large collection of small molecules, or drugs, that alter gene functions, providing a means to control the behavior of normal and diseased cells. He will make these small molecules available to scientists around the world, to use in looking for ways to alter the genetic mutations that cause illness or in trying to find agents to combat viral, bacterial, and fungal infections.

Tyers will begin by testing the effect of 5,000 selected bioactive small molecules on *Saccharomyces cerevisiae*, or baker's yeast. Small molecules that can either change normal cellular functions or kill cells that have specific

genetic mutations will be collected in a comprehensive "Chemical Genetic Matrix" of drug-gene interactions. Tyers will then test the effects of selected combinations of these small molecules on yeast and human cells to identify cocktails that kill infective agents or cancer cells, but not human host cells.

Baker's yeast is an ideal model organism for these studies because its genes can be manipulated and screened against compound libraries far more easily and cost-effectively than in human cells. Also, this yeast is related to pathogenic yeast, so toxic combinations of compounds may provide a basis for novel anti-infective agents. The principles discovered in these studies should help forge new approaches to drug discovery.

André Veillette, Ph.D. Clinical Research Institute of Montreal Montreal, Canada

Rheumatoid arthritis, multiple sclerosis, type 1 (insulin-dependent) diabetes, and HIV/AIDS are all disorders of the immune system. Like many immune system diseases, even when they aren't fatal, these conditions can destroy a person's quality of life.

André Veillette, a first-time HHMI international research scholar, is exploring the role of a family of molecules called serum amyloid P (SAP), which are found in normal immune cells, such as T and B lymphocytes in the blood. Veillette's research has revealed that SAP family molecules regulate the immune system by playing matchmaker and helping molecules called signaling lymphocyte activating molecules produce chemical reactions inside the cell that turn lymphocyte immune activities on and off.

He will use mice and state-of-the-art biochemical techniques to increase his understanding of the way the immune system keeps itself in balance. Along the way, he hopes to learn more about immune system dysfunctions, including autoimmune diseases and immunodeficiency diseases, and identify new ways to treat these disorders.

Jean-Philippe Vielle-Calzada, Ph.D. Center for Research and Advanced Studies, National Polytechnic Institute Irapuato, Mexico

Jean-Philippe Vielle-Calzada is trying to understand how a flowering plant can form seeds in the absence of sexual reproduction.

Reproductive cells, such as the sperm and egg in mammals, are also called gametes. Normally, male and female gametes in flowering plants combine to form a seed that develops into a new plant, but sometimes cells that do not have a reproductive identity— called somatic cells—create seeds on their own without being fertilized by male gametes.

Vielle-Calzada, an HHMI international research scholar since 2002, wants to find out how a somatic cell gives rise to a plant embryo without undergoing gamete formation or fertilization. He believes that small RNAs and chromatin-remodeling factors play an important role in this process. Chromatin is a combination of proteins that packages and compacts DNA

within the cell nucleus. Before the cell can divide, the chromatin shell around its DNA must be opened, or remodeled, so the DNA can send its instructions to the rest of the cell.

Vielle-Calzada will analyze the effects that different chromatin-remodeling factors have on the ability of female plant gametes to produce seeds by themselves. He also plans to study the genetic structure of gametes before and after they start dividing to create a seed. He will use this information to determine whether plant embryos develop differently if they inherit their genes from a female gamete alone or from a combination of female and male genetic material. The researcher believes that the answer to this question has a unique potential to impact biological areas such as animal cloning or limb regeneration.

Alejandro J. Vila, Ph.D. Institute of Molecular and Cellular Biology of Rosario, CONICET Rosario, Argentina

Antibiotic resistance is becoming an increasing problem in the control of infectious disease. Public health crises are emerging around the world as antibiotics fail to kill dangerous strains of bacteria. Alejandro Vila, an HHMI international research scholar since 2002, is investigating resistance mechanisms to a family of antibiotics called beta-lactam antibiotics, which include penicillins, cephalosporins, and carbapenems.

Despite much progress in antibiotic design throughout six decades since the introduction of penicillin, resistance to beta-lactams is now a serious clinical problem, particularly in after surgery and in hospital-acquired infections and immunosuppressed patients. The most prevalent resistance mechanism is the generation of beta-lactamases, bacterial enzymes that destroy these antibiotics. The metallo-beta-lactamases (MBLs) are one of the most recent forms of beta-lactamase. They are zinc-containing enzymes that are extremely active against all beta-lactam antibiotics, and they cannot be stopped by any current drug.

Vila is an expert on metalloprotein structure and function. Now he plans to analyze the structure of each subclass of MBLs and identify the mechanism they use to break down antibiotics. He will look for common features in MBLs that could help scientists create drugs to inhibit them. He also will explore how they evolved, which could help predict and disable future resistance mechanisms.

Yu Tian Wang, Ph.D. University of British Columbia Vancouver, Canada

As people age, short- and long-term memory loss and difficulty learning can interfere with employment and social functioning and herald the beginning of old age. Yu Tian Wang, an HHMI international research scholar since 2002, may have found one of the keys to preserving memory and learning for people as they age, as well as those with brain diseases that cause impairment of thinking and memory.

Since good brain function depends on how efficiently nerve impulses can travel between brain cells, Wang studies the chemical receptors on brain cell surfaces that receive these impulses and pass them through the tiny gap between nerve cells called the synapse. He discovered that several molecules in the brain help the AMPA-type glutamate receptor to efficiently deliver and securely anchor into the membrane that covers the surface of neurons. This increases the number of receptors available to catch and relay nerve impulses and thereby to strengthen their transmission.

Wang, who holds the Heart and Stroke Foundation of British Columbia and Yukon Chair in Stroke Research at the University of British Columbia, is using a combination of molecular biology and electrophysiology techniques to explore this process. He hopes his work will lead to new therapies to improve memory and learning.

Pablo Wappner, Ph.D. Leloir Institute Foundation Buenos Aires, Argentina

Poor oxygen usage can interfere with the body's ability to develop properly and repair itself, and it may lead to strokes, other oxygen-deprivation (ischemic) diseases, and even cancer.

Pablo Wappner, a first-time HHMI international research scholar, has been looking at the way oxygen controls gene expression in cells. He has discovered that a protein called hypoxia-inducible factor-1 (HIF-1), which relays gene instructions from the nucleus to the rest of the cell, plays a major role in oxygen metabolism. HIF-1 activity is regulated by a number of cell mechanisms, and Wappner is exploring some of these.

He plans to investigate how HIF-1 affects development, using the fruit fly *Drosophila* as a model. The fly is a perfect model for such studies because it reproduces quickly, enabling scientists to observe several generations of gene transmission in a short time.

Richard W. Wozniak, Ph.D. University of Alberta Edmonton, Canada

Understanding how cells divide and grow is central to the work of every scientist in biology, biochemistry, microbiology, and medicine. Richard Wozniak, a newly named HHMI international research scholar, is trying to learn more about this process by examining the ways molecular traffic through the nuclear envelope (NE)—the membrane around the cell nucleus—regulates events in the cell's life cycle.

The NE keeps the genes and chromosomes of the nucleus separate from the cytoplasm in the body of the cell. It is honeycombed by nuclear pore complexes (NPCs), which are holes in the membrane that allow the vast array of molecules necessary for healthy cellular metabolism to pass through the membrane in both directions. To exercise some control over this process, the NPCs employ traffic cops called karyopherins, or kaps. Kaps escort multiple cargos backward and forward through the NPCs, including molecules from the cytoplasm that tell genes in the nucleus that it is time to replicate and begin the process of cell division, and RNA messengers from the genes that

tell the cytoplasm how to manufacture proteins and other essential molecules.

Wozniak is planning to study the NPCs of yeast cells to learn more about how changes inside the NPCs control the transport of molecules into and out of the nucleus, and how this transport process regulates cell division and growth.

Jeffrey L. Wrana, Ph.D. Samuel Lunenfeld Research Institute Toronto, Canada

Signaling mechanisms tell our cells when to divide and when to stop dividing, and if they don't function properly, cancer can develop. Jeffrey Wrana, an HHMI international research scholar since 2002, believes that much can be learned about how cancer and other diseases develop by studying larger signaling networks outside the cell.

Researchers have studied extensively local signaling pathways, such as Wnt and TGF β , two molecules that orchestrate development, but little is known about the structure and properties of the larger networks. Wrana is investigating the global networks that affect morphogens, molecules that tell developing organs what size and shape they should become. Wnt and TGF β pathways send signals to morphogens, and since those pathways intersect at several points, Wrana thinks they are probably part of a global network.

He will use computational tools to identify the global networks that regulate the Wnt and TGF β pathways and discover how they regulate cell behavior through morphogens. He will also look at how alterations in local signaling pathways and a global signaling network associated with breast cancer contribute to the development of this disease.

Marcelo J. Yanovsky, Ph.D. Institute for Agricultural Plant Physiology and Ecology, CONICET Buenos Aires, Argentina

All living organisms, from bacteria to human beings, have an internal clock that prompts them to wake, become active, feed, and sleep on a fixed, 24-hour schedule called a circadian rhythm. Although circadian rhythms respond and adapt to light and temperature, Marcelo Yanovsky, a first-time HHMI international research scholar, is particularly interested in organisms' internal control mechanisms for circadian rhythms, molecular feedback loops called endogenous circadian oscillators.

Circadian rhythms produce clear patterns of brain wave activity, hormone production, cell regeneration, and other critical biological activities. Disrupting them can have significant adverse effects on health, from jet lag to bipolar disorder and cardiovascular disease.

Yanovsky wants to understand how internal circadian oscillators regulate the physiological processes they control and how those regulators interact with the light and temperature cycles that adjust circadian rhythms daily. He is using plants for his studies because they depend on sunlight for growth and development—and a great deal is known about how they process and use

light as a source of information to synchronize physiological processes with daily and seasonal changes in their environment. Yanovsky is studying both specific "clock" genes and the broader patterns in genomes that produce circadian rhythms.